An Expert System For Development of Powder Filled Hard Gelatin Capsule Formulations

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by

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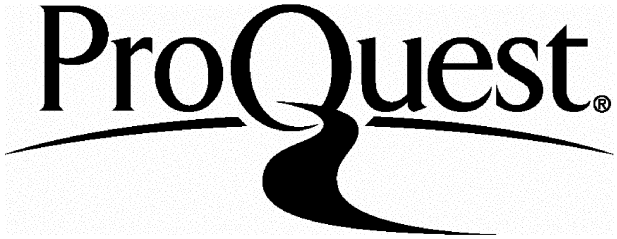

Dedicated to my Father

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I would like to dedicate this thesis to my father, without whom I would not be able to achieve this PhD. My sister, Esther and my boyfriend, Eric were also very understanding and have been most supportive throughout my 'ups and downs'.

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ABSTRACT

The aim of my PhD project is to build up an expert system for development of formulation for powder filled hard gelatin capsules. An expert system is a program that attempts to capture the knowledge and experience from experts in the field.

It is very often a time consuming process to develop formulations for drugs particularly new drugs. With the aid of an expert system, a logically devised formula can be recommended more efficiently. It can also be used as a training tool.

C and DbaseIV computer languages were used to develop the expert system. Relevant information such as dose; drug properties, for example, solubility and particle size; and incompatibility data of drug with gelatin and excipients were fed into the system and the output would include the recommended formula.

This system was made up of three major components : the databases, the main program and the 'learning package'. The **databases** formed the knowledge base and the foundation of the system. The databases contained knowledge of marketed formulations, drugs and excipients; bibliography and expert knowledge in the subject; and results of statistical analysis of experiments carried out to derive missing information. Based on this knowledge base, rules and facts of developing formulations in powder filled hard gelatin capsules were derived. Decision trees of the **main program** were developed. After the initial trial which tested the logic of these rules, the decision trees were translated into programming language. The **'Learning package'** is an important feature in the system. When the expert system is used for a longer period of time, there may be new knowledge in the subject. Some of the current rules may need to be changed or replaced. The lists of default excipients used may be updated using the learning package.

In conclusion, the expert system is a learning system. It provides an efficient way to develop formulations for powder filled hard gelatin capsules.

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Abbreviations

AAPS	:	American Association of Pharmaceutical Scientists
AI	:	Artificial Intelligence
AUC	:	Area Under Curve
BAN	:	British Approved Name
BP	:	British Pharmacopoeia
CG	:	Centre of Gravity
CGD	:	Centre of Gravity Design
CRS	:	Controlled Release Society
DSC	:	Differential Scanning Calorimetry
DT	:	Disintegration time
EMC	:	Equilibrium Moisture Content
EP	:	European Pharmacopoeia
ESS	:	Expert System Shells
EU	:	European Union
FDA	:	Food and Drug Administration
FT-IR	:	Fourier Transform Infrared Spectroscopy
HPC	:	hydroxypropylcellulose
HPLC	:	High Performance Liquid chromatography
HPMC	:	hydroxypropyl methylcellulose
ICH	:	International Conference on Harmonisation
IPEC	:	International Pharmaceutical Excipient Councils
JP	:	Japanese Pharmacopoeia
MCC	:	microcrystalline cellulose
MDT	:	Mean Dissolution Time
MgSt	:	magnesium stearate
Na st glycol	:	sodium starch glycolate
PEG	:	polyethylene glycol
PFES	:	Product Formulation Expert System
ppm	:	part per million
preg starch	:	pregelatinised starch
PVP	:	polyvidone

RH	:	relative humidity
SEM	:	Scanning Electron Microscopy
STVF	:	Surface Tension Viscous Flow
SUPAC	:	Scale-UP and Post Approval Changes
UK	:	United Kingdom
USA	:	United States of America
USP/NF	:	United States Pharmacopoeia / The National Formulary
UV	:	Ultraviolet
VDT	:	Variance of Dissolution Time

List of Symbols

θ	=	contact angle
γ	=	liquid surface tension
η	=	liquid viscosity
σ	=	major normal stress
δ	=	step length
σ_α	=	unconfined yield stress
γ_{LV}	=	equilibrium free energies / unit area of liquid / vapour
γ_{SL}	=	equilibrium free energies / unit area of solid / liquid
γ_{SV}	=	equilibrium free energies / unit area of solid / vapour
ψ	=	sphericity
A	=	aerated bulk density
A'	=	interfacial surface area
A_n	=	Fourier coefficient
a	=	constant
b	=	constant
B	=	constant depending on particle shape
C	=	shape coefficient
Carr	=	Carr's compressibility index
C_R	=	Degree of volume reduction
Cs	=	concentration of drug in the saturated diffusing layer
Ct	=	concentration of drug in the dissolution medium at time t
c.s.	=	compression setting of filling machine
cv	=	coefficient of variation
D	=	irregularity of the particle surface
D'	=	diffusion coefficient of the solute
d	=	volume/surface mean diameter
$\frac{dc}{dt}$	=	dissolution rate of drug
Dmax	=	maximum bulk density
Dmin	=	minimum bulk density
dose	=	dose of drug

dsgq = disintegrant level

dsgt = disintegrant type

dsol = solubility of drug

dvs = mean particle size based on volume distribution

f = shape coefficient

fq = filler level

ft = filler type

gliq = glidant level

H = Hausner's ratio

h = high dose

h_D = thickness of the diffusion boundary layer

k = constant

k = shape coefficient

k_e = shape coefficient

L = length of liquid penetration

L_δ = perimeter estimated with step length

L_D = thickness of the diffusion boundary

l = low dose

lubq = lubricant level

m = medium dose

m = ratio of breath to thickness of particles

mfw = mean fill weight

N = number of taps

n = shear index

n = ratio of length to breath of particles

P = applied pressure

P' = packed bulk density

R = capillary radius

sd = standard deviation

t = time

t_1 = tapped density of the disintegrant

t_2 = tapped density of the lubricant

t_3 = tapped density of the glidant

t_4 = tapped density of the wetting agent

t_5 = tapped density of the binder

tc = predicted bulk density of drug after compression

td = tapped density of the drug

tf = tapped density of the diluent

V = total volume

V' = volume of dissolution medium

V_0 = initial volume

v_1 = volume occupied by the disintegrant

v_2 = volume occupied by the lubricant

v_3 = volume occupied by the glidant

v_4 = volume occupied by the wetting agent

v_5 = volume occupied by the binder

vd = volume occupied by the drug

Ve = volume of particular capsule size

vf = volume occupied by the diluent

V_N = volume of drug after N taps

V_P = volume of a powder column under applied pressure P

W = total weight

x_1 = %w/w of the disintegrant

x_2 = %w/w of the lubricant

x_3 = %w/w of the glidant

x_4 = %w/w of the wetting agent

x_5 = %w/w of the binder

xd = %w/w of the drug

xf = %w/w of the diluent

Chapter 1

Introduction

1. Introduction

1.1 Expert system as an aid in pharmaceutical formulation

For decades, scientists have been looking at the possibility of transferring human "intelligence" into a machine. This leadsto the development of an area of research called "Artificial Intelligence". Expert systems are one of the results of such an aspiration. They are computer programs that attempt to capture the knowledge and experience of the human experts and to solve problems, in a specific area, by simulating the problem solving process of these experts (Doukidis and Whitley, 1988a). There are several ways of which Expert Systems are described. Sell (1985) mentioned that an Expert System is "a knowledge based system that emulates expert thought to solve significant problems in a particular domain of expertise". Weiss & Kulikowski (1984) described that it "handles real-world problems requiring an expert's interpretation" and "solves these problems using a computer based model of expert human reasoning, reaching the same conclusions that the human expert would reach if faced with a comparable problem".

1.1.1 Use of an Expert System in pharmaceutical industry

In the pharmaceutical industry, the use of Expert Systems is not novel. Lai (1992) described the use of Expert Systems in pharmaceutical technology whereas Rowe (1993b) reviewed the use of Expert Systems in the development of solid dosage forms. Hohne and Houghton (1985) designed an Expert System for formulation of agricultural products which can be utilized for pharmaceutical products. Lai (1988) described a prototype Expert System for selecting pharmaceutical powder mixers. An Expert System , based on PFES (Product Formulation Expert System) shell (Skingle, 1990), for formulation of pharmaceutical tablets was initiated in Zeneca Pharmaceuticals (Rowe, 1993a). Application of an Expert System for troubleshooting and diagnostics of a Korsch high-speed rotary tablet press was developed by Murray (1989). A knowledge based system in pharmaceutical quality control environments was described by Tsuji and Jenkins (1990). Podczeck (1992) described the knowledge acquisition process in developing an Expert System for tablet formulations which is based on fundamental

research into the relationships between the physico-chemical and mechanical properties of fifteen model drugs and their behaviour in powder mixtures with excipients. Ramani et al (1992) designed an Expert System to investigate the drug's physical, chemical and biological properties alone and in combination with excipients which were used to aid drug preformulation for Cadila Laboratories. An Expert System for the identification and solution of film coating defects has also been developed (Rowe and Upjohn, 1993). It was also believed that a computer system which simulate crack propagation in pigmented tablet film coatings can be easily combined with such an Expert System (Rowe et al, 1995). Stricker et al (1994) developed a knowledge-based system for the development of the most important dosage forms including sterile products (such as injections and infusions), solutions, tablets and powders for capsules. The selection of excipients for formulation of oral solid dosage forms formulation using a database was also described by Taudou et al (1994). Bateman et al (1996) described the use of a knowledge based system in capsule formulation for a company, developed using a PFES shell by the 'in-house' formulators.

1.1.2 Advantages of Expert System

The use of Expert Systems in pharmaceutical formulation was claimed to have significant benefits (Lai, 1988; Ramani et al, 1992; Rowe, 1993a) The Expert System is a time saving tool, which increases efficiency and decreases cost. According to Wood (1991), The Boots Company developed a prototype Expert System using PFES to aid formulations of lotions and creams. It was found that "in twenty minutes formulators using PFES could complete tasks that previously took two days" and that "the system has cut material costs" (Wood, 1991). Expert Systems preserve and accumulate human knowledge. Pharmaceutical formulations depend heavily on the knowledge and experience of the formulator. When an experienced formulator leaves a company, a large and often irreplaceable amount of knowledge may be lost. Experts, therefore, spend considerable amounts of their time in training new personnel, to pass on their expertise and knowledge. An Expert System can preserve the knowledge of one or more experts and can also be used as an effective training tool for the "next generation". Personal preferences can often result in an inconsistent approach in pharmaceutical formulation. An expert system is consistent in its decision process which can be

documented and updated. The feature of documentation of the decision making process is particularly useful, not only in terms of training new formulators, but also in terms of making the regulatory process more efficient before the drug can be marketed in different countries.

1.1.3 Disadvantages of Expert System

Some people regard Expert Systems as a means of automating knowledge-base offering the possibility for huge cost savings and profits, while others hold that these programs are dangerous concepts, thought to be more powerful than they actually are and a poor model of the human expertise they aim to automate. There are indeed some limitations with expert systems.

Compared to human experts, Expert Systems are less creative and less adaptive. Common sense knowledge is often used by human experts but the Expert System often lacks this kind of knowledge. In addition, human experts use knowledge at a higher level. This knowledge makes use of patterns of characteristics that cannot be explicitly defined. The testing of the system is a critical and crucial stage in developing the system (Doukidis and Whitley, 1988a). The knowledge of the Expert Systems is captured from human experts and therefore they can only provide maximum benefits if they are used by experts.

In addition, there may be unrealistic user expectations that all problems in constructing Expert Systems are solved and that any type of expertise can be turned into an expert system with little effort. However, expert systems do not always fulfill such expectations. Expert systems do, in many cases, provide explanations for the deducted results. However, the explanations are often weak, in the sense that they can only report back the rules that have been used. More adequate explanation would require the system to understand the rationale behind the rules which is not always easily achievable (Steels, 1989).

1.1.4 Expert System technology

Expert Systems were developed from a field called Artificial Intelligence (AI). The antecedents of Artificial Intelligence can be dated back to the Ancient Greeks (Gardner, 1986), but the ideas that sparked the research into human intelligence and formal reasoning were conducted by various groups in the United States and Europe in the years prior to and following World War II. In 1956, AI was officially born in a Summer Research Project held at Dartmouth College where the ideas of many active researchers in areas of cybernetics and computer reasoning were consolidated. The term "Artificial Intelligence" was invented by John McCarthy in the process of naming the meeting (Parsaye and Chignell, 1988a). AI subsumed a range of topics that involve the replication of the functionality of the human mind and even the attempts to replicate the internal structure of the brain. In the 1970s, the Expert System was born and instead of trying to discover a few very powerful and very general problem-solving heuristics, the focus was narrowed down to specific problems (Forsyth, 1984). Problem-solving strategies were employed to be tailored to specific classes of problems (Bench-Capon, 1990a). Examples of the early Expert Systems are DENDRAL, the mass-spectrogram interpreter (Feigenbaum et al, 1971); MYCIN, for diagnoses of bacterial infections of the blood and to prescribe suitable drug therapy (Shortliffe, 1976); XCON for configuration of DEC (Digital Equipment Corporation) minicomputers (McDermott, 1979); and INTERNIST for diagnosis of internal medicine on the basis of observable symptoms (Pople et al, 1975).

The idea of an Expert System was to develop a system that imitated experts, in that they operate on a substantial problem in a limited area and in a consultative style of which they operated (Bench-Capon, 1990a). Steels (1989) proposed that Expert Systems are designed to assist the human expert in a limited but difficult 'real-world domain' and are modeled after the reasoning of a human expert. Generally, Expert Systems are interactive. They tend to use heuristics rather than determinated rules. A heuristic is a rule of thumb which make problem solving easier. The knowledge domain is often composed by extraction of knowledge from the human experts. There are areas that the human experts could not give a certain answer and sometimes the information

may simply be unavailable. The ability to handle uncertain or incomplete information is often a feature of an Expert System (Bench-Capon, 1990a).

Knowledge acquisition

Knowledge acquisition is usually one of the primary stages in building up an Expert System. "Knowledge acquisition is the transfer and transformation of problem-solving expertise from some knowledge source to a program. " (Buchanan and Shortliffe, 1985). Knowledge can be acquired from different resources such as from the public domain (e.g. publications), interviews with human experts, and by performing experimental studies. Acquisition of the knowledge from the human experts is the most essential but yet this process is the most complicated. Human experts do not normally analyse the contents of their thoughts and the intermediate steps in their reasoning may seem obvious to them but these decisions may not eloquently provide an overall account required by a machine reasoning process. Usually the 'knowledge engineer' would work with the experts to map the knowledge into a form suitable for an Expert System (Parsaye and Chignell, 1988c). In addition, Rowe (1996) also described a technology called 'case-based reasoning' to overcome this knowledge acquisition bottleneck. The acquired knowledge can also be stored in the form of databases and represented in such a way which can be encoded into a computer.

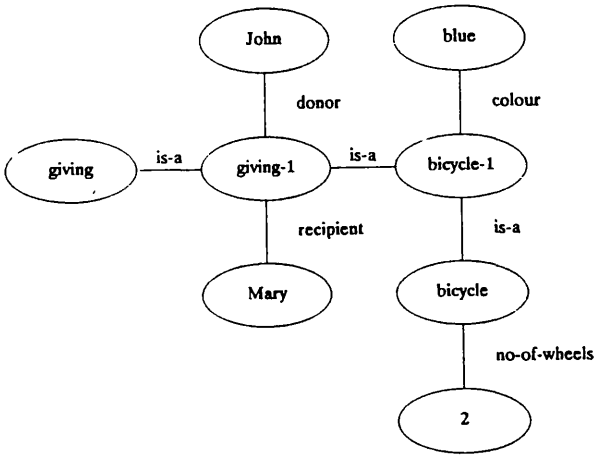
Knowledge representation

There are a number of ways of knowledge representation. Examples of the leading representation paradigms are production rules; structured objects such as semantic networks and frame; logic and predicate calculus (Bench-Capon, 1990b). Production rules have two components : condition and action. Informally they may be read as "IF conditions are satisfied, THEN perform actions." The conditions are often expressed as lists of three elements : the entity involved, the attribute of the entity under consideration, and the value of that attribute for that entity (e.g. "John age 18") (Bench-Capon, 1990b). The major advantage of the production-rule paradigm is that it provides a single uniform method of representation and is relatively easy to understand by the non-computer specialists (the experts who provide the knowledge). Structured object

representation is an alternative way to represent knowledge. One form of the structured object representation is the semantic network. Semantic network is a graph (in the mathematical sense), which comprises a number of nodes linked together by arcs, with both nodes and arcs having labels. The nodes are supposed to represent concepts denoted by the words in the subject under considerations, while the arcs denoted the relationships between these concepts (Figure 1.1).

Figure 1.1 : An example of knowledge representation by semantic nets (Bench-Capon, 1990b)

The information represented below is that John gives Mary a blue bicycle and the bicycle has 2 wheels.



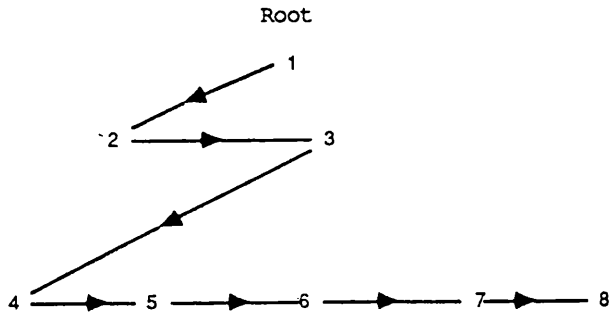
Frames (Minsky, 1975) represent another form of structure object representation which can be seen as a development from a semantic network. It involves the identification of the types of objects that will be of interest to the system, and describing these classes of objects in terms of frames (Bench-Capon, 1990b). The third knowledge representation paradigm is 'logic'. A number of logics have been developed in philosophy and mathematics to represent arguments and their conclusions. The whole enterprise of logic programming is based on the ability to produce an interpreter which will deduce consequences from a set of logical axioms (often expressed in the format of first-order predicate calculus) (Bench-Capon, 1990b). Predicate calculus expresses relations between objects, asserting and denying these relationships, and stating the logical relations between these statements. It is developed specifically in order to give a precise and unambiguous representation of statements, and it offers a clear view of how these

statements should be manipulated in its deductive proof theory. These three knowledge representation paradigms have been described in details by Bench-Capon (1990b).

The 'search' principles

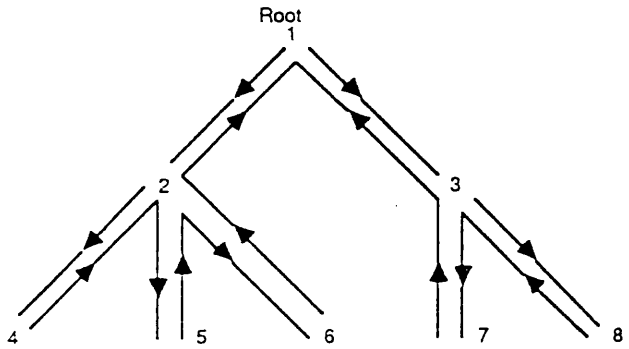
The search principle is another essential issue in designing an Expert System. The knowledge can be represented such that it is goal-driven (*backward chaining*) or data-driven (*forward chaining*). *Forward chaining* takes all the relevant facts and rules to deduce a conclusion while *backward chaining* starts with a statement of the goal to achieve and works backward through the rules to find the data that establish that goal (Buchanan and Shortliffe, 1985). As well as the direction of search, the order in which the nodes are developed in the search space should also be considered. The nodes can be expanded fully in the order in which they are encountered. There are usually two methods to develop the most recently encountered node : *breadth-first search* and *depth-first search.* In *breath-first* search, all the nodes at each level of the rules are examined before expanding any nodes to a greater depth (Bench-Capton, 1990c) (Figure 1.2).

Figure 1.2 : Breath-first search (Winstansly, 1987a)



In *depth-first* search, the highest hierarchy of rules is examined followed by the rules immediately below that rule. The system searches down a single branch of the rules until the answer is found and backtracks if the path terminates (Tsuji and Jenkins, 1990) (Figure 1.3).

Figure1.3 : Depth-first search (Winstansly, 1987a)



Basic components of an Expert System

Almost all Expert Systems can be seen as comprising three distinct components : knowledge base, inference engine and user interface. The knowledge base represents the domain knowledge elicited from the experts or from knowledge acquisition, independent of how it is to be used to solve the problems. Therefore the knowledge base is usually free from details of control and implementation and comprises a set of statements, ideally in some suitable knowledge representation formalism. The inference engine manipulates the knowledge base so as to solve the problems. It uses the information in the knowledge base and the facts relating to the case under consideration to draw conclusions. The nature of the inference engine will depend on both the representation chosen for the knowledge base and the problem-solving strategy considered appropriate by the author of the system. The third component is the user interface. The basic requirements on the user interface are to obtain information from the user so that the session can be started, to ask relevant questions of the users and to convey the information on to other parts of the expert system to the user, and to provide the explanations required by the user (Bench-Capon, 1990a).

Tools for developing Expert System

An Expert System can be built by using symbolic languages such as LISP and PROLOG or by high level computer languages such as C, Fortran and PASCAL (Lai, 1988; Doukidis and Whitley, 1988a). Recently some Expert Systems used in the pharmaceutical industry were built with the aid of an Expert System Shell (Section

1.1.1). In addition, Expert System Environments, as described below, are also known to be used in developing an Expert System.

LISP and PROLOG are examples of the more famous symbolic computer languages used in AI research. LISP was developed by John McCarthy in the United States in the late 1950s while PROLOG is a Franco-British development (Doukidis and Whitley, 1988b). They may be regarded as the most cost effective way for those who only want to learn about the issues and are prepared to spend some time to learn the languages. Many of the computation codes commonly used in development of Expert Systems are 'precoded' in a simplified form or function. They provide a relatively easy way to build up an Expert System. However, most of these languages are rather user-unfriendly and possess limited functions to perform only a restrictive range of tasks. The implementation of these languages is very often inefficient. The users do not have full control of inference, for example, in a PROLOG program, the search strategy with the PROLOG database cannot be controlled. Restrictions on type of computer used may also be applied to the use of some of these symbolic language. For example, one version of LISP (iLISP) can only operate on a 8-bit CP/M operation system but another version, IQLISP, is designed to operate under the operating systems supported on the IBM range of personal computers (Winstanley, 1987b). Lai (1988) and Ramani et al (1992), based on PROLOG, developed a prototype Expert System for selecting pharmaceutical powder mixers and an Expert System for drug preformulation respectively.

Using high level languages such as C and PASCAL would require writing all the computer codes from basics. The programmers must be well aware of the internal workings of inference engines and the constructions of the whole system. It is not the most rapid way to develop an Expert System but they have advantages over almost all other tools. They give full flexibility to create the knowledge structures and the inference engine as well as full control on the inference strategies. The compilers are usually very efficient. They could provide the most effective implementations based on current hardware (Doukidis and Whitley, 1988b).

Expert Systems Shells (ESS) can be described as Expert Systems with the knowledge base removed; which means that any sets of rules that followed the format of the original system could use the same shell. EMYCIN (Empty-MYCIN) was one of the best examples of ESS. Another example is Xi+ which is an ESS developed by the company Expertech Ltd. Users could purchase a shell and use their own expertise to supply the domain knowledge and therefore obtain an Expert System for their own purposes. Companies which had been attracted by the prospective advantages of expert systems but which had been daunted by the costs of exploring the technology, and which perhaps could not identify any application with a sufficient high prospective payback, could now acquire a shell and use in-house expertise to explore applications at a relatively small cost. Prewritten knowledge bases for certain areas, for example maternity law, are also marketed by the same company. However, these systems are not very flexible. The users do not have much control on the inference of the knowledge base that was installed for the particular domain (Doukidis and Whitely, 1988b).

The Product Formulation Expert System (PFES) (Logica, Cambridge, UK) is a reusable software tool used in the construction of expert-system decision-support tools for product formulation. It provides a framework to support the construction of new formulation systems (Skingle, 1990; Turner, 1991) and has been used to develop several Expert Systems in pharmaceutical formulation (e.g. Wood, 1991; Rowe, 1993a; Bateman, 1996). The M.1 knowledge-system shell software program (Cimflex-Teknowledge, California, USA) was also used in pharmaceutical industry, for example in pharmaceutical quality control environments (Tsuji and Jenkins, 1990).

Compared to the Expert System Shell, the Expert System Environments provide less ready-made solutions but more possibilities. They are probably the most sophisticated Expert System development tools. They are more expensive and only available on large computers. They are meant as tools for developing tools. They are not designed simply to have a knowledge base attached. An Expert System Environment is designed to be used to write a shell and then attach a knowledge base to that new shell. They support many different approaches of knowledge representations and inference strategies. There are only very few environments available and they tend to run on very expensive and dedicated machines (Doukidis and Whitley, 1988b).

Tasks to which Expert Systems can be applied

It is desirable that the problem that the Expert Systems are supposed to solve should be well understood and that the knowledge required for the task should be fairly extensive and yet readily available. If the knowledge to be encoded in the Expert System could be taught easily to some moderately able person, then an Expert System will not be justified. Usually an Expert System is designed to solve a complicated task which is usually performed by experts. The major hurdle to Expert Systems development is to uncover the tacit knowledge required to perform the tasks usually carried out by an expert - the knowledge acquisition step (Bench-Capon, 1990a).

1.1.5 Why use an Expert System in capsule formulation?

Before any drug can exert its therapeutic action, it must be formulated into a medicinal product that can be easily manufactured, handled and administered. Dosage formulation is a complex process that is controlled by a range of competing factors. The experienced formulator must amalgamate the commercial, legislative, environmental and technical factors. Factors like chemical and physical properties of the drug and excipients, regulatory requirements of the proposed market countries, patient acceptability and cost of production are all important (Section 1.3). The formulation must be capable of rapid, economical manufacture to provide a product of consistent performance and quality.

Traditionally, through trial and error, the experienced formulator will eventually achieve a formulation that can be used under defined circumstances. However, this may be a time consuming procedure and depends heavily on the experience and preference of the formulator. With the development of technology, mathematical models are often employed to perform multi-factorial statistical testing to aid formulation. Factorial design or optimisation techniques are also used. Factorial designs can be used to derive formulations (Podczeck, 1996). They allow for the detection of relationships between the dependent and independent variables in the system. Optimisation techniques use a mathematical approach to find out the most suitable combination of factors with the minimum number of experiments required (Lewis and Chariot, 1992). Integrated experimental design softwares are also available to design the formulation experiments,

analyze the data collected, and assist in interpreting results (Dobberstein, 1994). The more recent 'explorations' in computer-aided design in pharmaceutical sciences are the use of Expert Systems (Section 1.1.1) and artificial neural networks (e.g. Hussain et al, 1991; Hussain et al, 1994; Murtoniemi et al, 1994a, 1994b; Achanta et al, 1995 and Türkoglu et al, 1995).

1.2 Background to Hard Gelatin Capsules

"Capsules are solid preparations with hard or soft shells of various shapes and capacities, usually containing a single dose of active ingredient. They are intended for oral administration." (*European Pharmacopoeia*, 1980). In the pharmaceutical industry, capsules are popular oral dosage forms, second to tablets. Capsule formulations account for around 15% of the marketed formulations in the UK (Halbert, 1993).

They provide a good aid to mask unpleasant taste of some drugs. They are tasteless and easy to swallow. A wide range of colours are available for capsules, making thousands of two-colour combinations possible to enable products to be readily identified. Compared to other dosage form, capsules are described to provide better patient compliance and from surveys conducted in France and Germany, greater preference for capsule products was shown (Anonymous, 1989; Jones and Schweiger, 1990).

The gelatin capsule is a versatile dosage form that can be filled with many different types of formulation, for example, dry powders, granules, pellets, pastes and liquid (Jones et al, 1988). There are several categories of capsules e.g. hard capsules, soft capsules, gastric-resistant capsules and modified-release capsules (*European Pharmacopoeia*, 1980). Hard gelatin capsules are mainly used to deliver particulate solids for oral administration or inhalation.

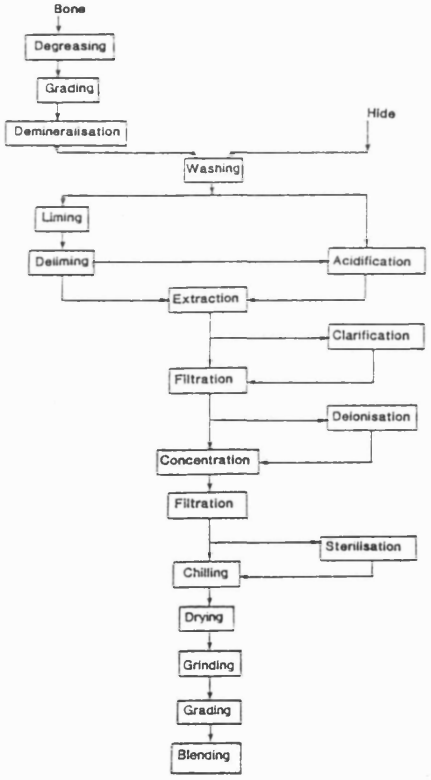
1.2.1 Brief history of gelatin capsules

Details of the history of gelatin capsules have been reviewed by Jones (1987a) and the main features are outlined as follows. The gelatin capsule has been known since 1833. It was first patented in Paris in 1834 by Mothes (the inventor of gelatin capsule) and Dublanc (French Patent 5648). Mothes was a pharmacy student, and in order to present the patent he became associated with Dublanc, who was already an established pharmacist. At this stage, capsules existed in the form of one-piece capsules. The fore-runner to the modern hard gelatin capsule is the hard two-piece capsules which were invented by Lehuby. Lehuby was granted a patent in 1846 (French Patent 4435) (Jones, 1987a). Murdoch was also granted the British Patent 11,937 in 1848 for the manufacture of two-piece capsules, and the method to make a vegetable gelatin from carragheen moss. It was also the first patent which admitted the sole use of animal gelatin in making capsules. The two-piece capsules consisted of a pair of open-ended cylinders of gelatin which fitted one inside the other. The performance of these capsules depended upon the accuracy with which the two pieces were made. In 1874, the first industrial scale manufacture of hard gelatin capsules was commenced by Hubel, a Detroit pharmacist. The capsule quickly became popular, and particularly after 1875 when the whole of Hubel's output was sold for him by another Detroit company, Parke, Davis. In the period 1877 to 1883, a large number of patents were granted for capsule-making machines. There had been a continuous improvement in machine design. By 1896, the capsule machines could be operated by one man and could produce 10,000 to 12,000 capsules per day. Each capsule had to be manually trimmed and individually joined, but this last manual step was eliminated in 1913 by the first fully-automatic capsule manufacturing machine (US Patent 1 076 459). The output capacity was about 8000 capsules per hour. Several years later, the machine was further modified to enable two-coloured capsules to be made. In 1931, Arthur Colton patented an improved version of the machine (US Patent 1 787 777 and British Patent 360 427) which could produce 30 000 capsules per hour and formed the basis of the design for nearly all modern large scale capsule manufacturing machines. The manufacturing process continued to improve and many different types of capsules (Section 1.2.4) were also developed.

1.2.2 Manufacture of gelatin capsule shells

The capsule shells are usually made of gelatin. Gelatin is the major component of the capsule mainly because it is non-toxic and is widely acceptable for use throughout the world. It is readily soluble in the body. It is relatively inert and capsule shells can be safely filled with many different materials. Its glossy appearance, ability to hold dye colour, neutral taste, and processing convenience also make gelatin a favorable material for use as the outer layer of drug formulation (Jones et al, 1988; Britten, 1992).

Figure 1.4: A flowsheet of the commercial process for the conversion of collagen to gelatin (Jones, 1987b)



Gelatin is not a naturally-occurring protein, but is derived from the fibrous protein collagen. Fibrous protein collagen is the principal constituent of animal skin, bone, sinew and connective tissue (Jones, 1987b). Since gelatin is extracted from the natural products (animal bones or skins) which may have varied properties, the commercial manufacture of

gelatin is designed with the object of achieving the maximum yield of gelatin consistent with the commercially acceptable values of properties such as gel strength, viscosity, colour, clarity and taste. The manufacture processes basically involve the removal of non-collagenous material, conversion of collagen to gelatin, purification, and then recovery of gelatin in a dry form (Figure 1.4).

The manufacturing of hard gelatin capsules using a modern high-speed capsule-manufacturing machine can be summarised as follows according to Jones (1987c). A gelatin solution is prepared, containing the gelatin itself together with colourants and various process additives such as gelatin extenders and preservatives. The capsules are made by dipping and are then dried. The dried capsules are removed from the moulds; and the caps and bodies are assembled (Jones, 1987c). The assembled capsules are sorted, printed and packaged (Jones, 1987c).

1.2.3 Properties of hard gelatin capsules

The capsules when supplied to the user should have a moisture content in the range of 13-16 %w/w. This moisture content can be affected by the atmospheric conditions to which the capsules have been exposed. When the moisture content falls below 10%, the capsules become brittle and will easily fracture on handling. When the moisture content rises above 18% the capsules soften and distort (Jones, 1987c). As reviewed by Jones (1987c), there is a change of approximately 0.5% in dimensions for each 1% change in moisture content over the range 13 - 16 % w/w.

The equilibrium moisture content (EMC) of hard gelatin capsules was also determined by several groups of workers and summarised by Jones (1987c). A capsule will have its optimum performance on high-speed filling machines if it is handled in an atmosphere with a relative humidity between 30 - 50%. If the conditions are outside this range, the capsules will be adversely affected. However, there would be no practical difficulties provided that only a minimum number of capsules are exposed for fairly a short time because the lag time to reach the EMC is several hours (Jones, 1987c).

Gelatin is readily soluble in biological fluids at body temperature. If the temperature falls much below 37°C, the rate of solution decreases (Jones, 1987c). At a temperature ranged between 35 - 39 °C, the change in the rate of solution was found to be about 30% (Jones and Cole, 1971).

The hard gelatin capsules protects the active substance against mechanical effects as well as against carbon dioxide and oxygen. The permeability of the capsule wall to oxygen and carbon dioxide was found to be dependent upon the concentration of gas external to the capsule (Czetsch-Lindenwald, 1967).

1.2.4 Types of Hard Gelatin Capsules

Different types of hard gelatin capsules have been developed. The STANDARD hard gelatin capsule consists of two cylindrical parts, a body with a hemispherical base and a corresponding cap of the same shape but shorter. The internal diameter of the cap virtually equals the external diameter of the body. When fitted, the two parts constitute a container of high dimensional constancy. In 1963 Eli Lilly developed the Lok Cap®

Figure 1.5 : Different types of capsules
(Capsugel literature, "*All about hard gelatin capsules*", 1991)

STANDARD® capsule

Preclosed SNAP-FIT® capsule

Closed SNAP-FIT® capsule

CONI-SNAP® capsule

CONI-SNAP SUPRO® capsule

which had indentations inside the capsule that provided an improved friction fit. In 1968, the SNAP-FIT® capsule was developed to ensure firm and reliable union of the

cap and body. It made it almost impossible for the capsule to be reopened during further processing. The relatively more recent innovations are CONI-SNAP® and CONI-SNAP SUPRO®. CONI-SNAP® reduces premature opening of empty capsules during both transportation and filling and ensures an almost defect free filling process on high speed filling machines. In the case of CONI-SNAP SUPRO® capsules, the cap covers so much of the body that only the rounded end of the latter is visible. This prevents manual opening of the capsule as there is no surface of the body which can be gripped to force the two halves apart (Cole, 1987d; Britten, 1992; Ansel et al, 1995a). Figure 1.5 shows the different types of hard gelatin capsules. Other newer capsule types such as the DB capsules (for double blind studies) and the press-fit gelcaps (based on techniques to encapsulate caplets) are also available.

1.2.5 Capsule size

Hard gelatin capsules are available in a range of sizes. Standard capsules are in the sizes 000 to 5; SNAP-FIT® is available from sizes 00 to 5; CONI-SNAP® from sizes 00 to 4 and CONI-SNAP SUPRO® from sizes A to E. The fill volume for different sizes of hard gelatin capsules is shown in Table 1.1; and Table 1.2 illustrates the average capacities for SNAP-FIT® and CONI-SNAP® capsules.

Table 1.1 : Fill volume for different size of hard gelatin capsule (Jones et al, 1988)

Capsule size	Volume in ml
000	1.36
00	0.95
0el	0.78
0	0.67
1	0.48
2	0.37
3	0.27
4	0.20
5	0.13

Table 1.2 : Average capacities for SNAP-FIT® / CONI-SNAP® capsules

(Capsugel literature, "*All about hard gelatin capsules*", 1991)

Average capacities
for SNAP-FIT® / CONI-SNAP® capsules

Capsule size	Volume in ml	Capacity in mg			
		Powder density			
		0.6 g/ml	0.8 g/ml	1.0 g/ml	1.2 g/ml
000	1.37	822	1096	1370	1644
00	0.95	570	760	950	1140
0 el*	0.73	468	624	780	936
0	0.68	408	544	680	816
1	0.50	300	400	500	600
2	0.37	222	296	370	444
3	0.30	180	240	300	360
4	0.21	126	168	210	252
5	0.13	78	104	130	156

*0 el = 0 elongated: size 0 with elongated body

Average capacities
for CONI-SNAP SUPRO® capsules

Capsule size	Volume in ml	Capacity in mg			
		Powder density			
		0.6 g/ml	0.8 g/ml	1.0 g/ml	1.2 g/ml
A	0.68	408	544	680	816
B	0.50	300	400	500	600
C	0.37	222	296	370	444
D	0.30	180	240	300	360
E	0.21	126	168	210	252

The most popular sizes in practice are size 0 through to 4 (Jones et al, 1988). The size selected for use is determined by the amount of material to be encapsulated. There are no strict rules for predicting the proper capsule size for a given formulation because the extent of the packing of the powder mixture into a capsule shell is largely determined by the density and compressibility of a powder mixture (Ansel et al, 1995a).

1.2.6 Storage condition

The ideal storage conditions are a relative atmospheric humidity (R.H.) of 50% and temperature of 21°C. However, according to Capsugel *literature "All about the hard gelatin capsule*" (1991), variations of relative humidity and temperature of 35-65% and 15-25°C respectively have little effect on capsule quality, especially if the original package remains intact. When the storage recommendations are followed, empty capsules remain stable for years.

1.3 Capsule formulation

When developing a capsule formulation, the goals are to ensure accurate dosage, satisfactory bioavailability characteristics and trouble-free capsule filling procedure. To achieve these goals, a capsule invariably contains the active ingredient (the drug) together with other inactive ingredients (the excipients) which improve the performance of the formulation. To produce a good formulation, the physico-chemical properties of the drug (such as particle size and shape, solubility and flowability), the use of excipients, compatibility with excipients, processing method, type of filling machine and other more practical issues such as cost and company practices must also be considered.

1.3.1 Physico-chemical properties of drug and excipients

1.3.1.1 Particle size

Description of particle size

Particle size has a strong impact on capsule formulation. Particle size can be described as a measurement that indicates the distance from one side of the particle to its opposite side (Washington, 1992). However, this description becomes inadequate if the particle is irregular shaped. The equivalent sphere and its corresponding diameter (i.e. equivalent diameter) are therefore used to quote the particle size of a non-spherical particle. There are a large number of ways to define equivalent diameters (see Table 1.3) (Allen, 1981).

The particle size measurement techniques are not within the scope of this project and are described in Allen (1981), Parrott (1986), Staniforth (1988b), Washington (1992). The "HPE laboratory methods" presented in the *Handbook of Pharmaceutical Excipients* (Wade and Weller, 1994) also provide some useful guidelines in particle size measurement. To obtain a good description of the particle system, the selected equivalent diameter, which is associated with the measurement technique, should be

Table 1.3 : Definition of particle size (Allen, 1981)

Symbol	Name	Definition
d_v	Volume diameter	Diameter of a sphere having the same volume as the particle
d_s	Surface diameter	Diameter of a sphere having the same surface as the particle
d_{sv}	Surface volume diameter	Diameter of a sphere having the same external surface to volume ratio as the particle
d_d	Drag diameter	Diameter of a sphere having the same resistance to motion as the particle in a fluid of the same viscosity and at the same velocity
d_f	Free-falling diameter	Diameter of a sphere having the same density and the same free-falling speed as the particle in a fluid of the same density and viscosity
d_{Stk}	Stokes' diameter	The free-falling diameter of a particle in the laminar flow region ($Re < 0.2$)
d_a	Projected area diameter	Diameter of a circle having the same area as the projected area of the particle resting in a stable position
d_p	Projected area diameter	Diameter of a circle having the same area as the projected area of the particle in random orientation
d_c	Perimeter diameter	Diameter of a circle having the same perimeter as the projected outline of the particle
d_A	Sieve diameter	The width of the minimum square aperture through which the particle will pass
d_F	Feret's diameter	The mean value of the distance between pairs of parallel tangents to the projected outline of the particle
d_M	Martin's diameter	The mean chord length of the projected outline of the particle
d_R	Unrolled diameter	The mean chord length through the centre of gravity of the particle

relevant to the property of the particle that one is interested in. For example, if the study concerns the sedimentation properties of the material, Stokes' diameter or free fall diameter should be selected. In relation to effect of particle size on filling performance or drug release of hard gelatin capsules, a wide range of particle size such as volume diameter, surface volume diameter, Feret's diameter can be used, as long as only one clearly defined particle diameter is employed in the study. Particle size distribution is also important because the range of size influences the properties of the powder.

Frequency and cumulative distributions are two widely used methods of depicting the particle size distribution of a sample. Frequency distribution illustrates the number particles that fall within a given size increment whereas cumulative distribution shows how much material lies above or below a particular size. The distributions can be constructed based on the number of particles counted or based on the mass or surface area of material included in each size band. To assist rapid comparison and examination of distributions, simpler but meaningful quantities are often extracted from the distribution.

The 'averages' or 'means' of a set of data are normally used to characterize a maximum in the particle size distribution. Three different quantities are often used : median, mode and mean. The median value (D_{50}) is the size which splits the distribution into two halves with 50% of the mass or particle number greater and 50% smaller than this value. Quartiles such as D_{25} and D_{75} or values like D_{10} and D_{90} are also popular measurements. The mode of a distribution is the value of the 'maximum' of the distribution. In cases where normal distribution is obtained, the mode is equal to mean and median. However, in most cases the distribution is skewed and in some cases two or more peaks (bimodal or multimodal) are obtained. The mean diameter can be defined from number, area, volume or mass distributions. The mean diameter of the number distribution is different from the volume mean diameter or mass mean diameter or surface mean diameter. Volume mean diameter and mass mean diameter are often used interchangeably as the particle density is usually independent of size (Washington, 1992).

In practice, the amount of powder mixture filled into the capsule bodies is determined by the volume of powder occupied in the space available in the capsule shells and is therefore depending on the density of the powder mixture and its packing properties. Therefore particle size based on 'volume distribution' would provide some useful information although particle size based on 'weight distribution' is also commonly used.

Effect of particle size on powder behaviour

The particle size influences the flowability of powder. Generally, fine elongated particles are more cohesive than coarse spherical particles. Farley and Valentin (1967-68) showed that a correlation appeared to exist between shear index (n) and the shapes and sizes of the particles (equation 1.1). Shear index was employed as a quantitative measure of the flowability of powders (for free flowing powder, n is in the region of unity and its value increase to approximately 2 for strongly cohesive powders), as reviewed by Pilpel (1971).

$$n = 1 + \frac{B}{d}k \quad \text{.....(1.1)}$$

where B is a constant dependent on particle shape
k is a constant in the region of 0.6-0.7 and
d is the volume/surface mean diameter

According to Staniforth (1988a), fine particles with very high surface to mass ratios are more cohesive than coarser particles. Particles greater than 250 μm are generally considered to be free-flowing. Powders become cohesive if the size falls below 100 μm; and if the particle size is less than 10 μm, the powders are usually extremely cohesive. Kristensen (1971) also proved that the flowability of powder is affected mainly by the proportion of fine particles, of which the critical size depends on the nature of the powder. By decreasing the content of fine particles within the powder mixture, the flow would improve (Kristensen, 1971).

During the filling process, in cases where a dosator nozzle filling machine is used, the drug mixture must be cohesive enough to support the powder plug within the nozzle and yet free flowing enough to be ejected from the nozzle into the shell and provide uniform powder flow to guarantee a low coefficient of variation of fill weight (Jolliffe et al, 1980; Jolliffe and Newton, 1982a & 1983b). Jolliffe and Newton (1982b) indicated that as the particle size increased, it became more difficult to retain the powder within the nozzle. As the particle size decreased, the transmission of force by the plunger from the top to the bottom of the powder bed, is less effective. Therefore an optimum conditions of particle size and pressure for powder retention is required.

Segregation of particles in the drug mixtures can cause serious problems, for example, inaccurate dosing of drug. Segregation problems are more apparent in formulations which contained a wide range of particle sizes particularly if the active drug is at one extreme of the particle size distribution (usually the finer end) (Carson, 1988) with different shape and bulk density. Smaller particles may fall through the voids between larger particles and thus settle at the bottom of the mass (Travers, 1988; Johanson, 1996). A size difference of three times or more in the mean diameter may cause significant segregation (Johanson, 1996). Segregation can also occur when superfine particles are contained in the powder mixture. The superfine particles may become airborne and migrate to the vessel walls or toward the dust collection system in the processing equipment (Johanson, 1996). Carson (1988) pointed out that one of the solutions to overcome segregation problems was to change the particle size distribution, for example, by lowering the particle diameter ratio below 1.3 : 1 (nearly uniform size distribution) or decreasing the mean particle diameter below 100 μm (Carson, 1988).

Effect of particle size on granulation process

Particle size and particle size distribution are also important in granulation process. The amount of granulating liquid used is dependent on the surface area of the powder. As reviewed by Kristensen and Schaefer (1987), decreasing the particle size (i.e. increasing the surface area) resulted in the need to use a larger amount of granulating liquid in order to keep the granule size constant or resulted in formation of smaller granule size at a constant amount of liquid. This can be explained by the fact

that agglomeration of the powder during granulation can only be achieved by availability of free surface liquid (Kristensen and Schaefer, 1987) which depends on the surface area of the particles.

Effect of particle size on drug-excipient interaction

Different particle size of individual components in the drug mixture may also contributed to drug-excipient interaction. For example, Nakagawa et al (1980) showed that magnesium stearate reduced the dissolution rate of rifampicin from hard gelatin capsules in cases where rifampicin was sieved through 42 - 80 mesh. However, if rifampicin was sieved through a 200 mesh screen, magnesium stearate accelerated the dissolution rate. For rifampicin which contained small particle size, the cohesive force between the rifampicin particles was strong and thus impeded the release of the drug from the powder bed. Magnesium stearate reduced the cohesive force between the rifampicin particles and thus accelerated the dissolution rate. However, for rifampicin that contained large particle size, the cohesive force between the drug particles was not as strong. The inhibitory effect due to formation of hydrophobic film of magnesium stearate over the surface of rifampicin particles became significant. The presence of magnesium stearate thus hindered the penetration of the dissolution medium into the powder bed.

Effect of particle size on drug release

Particle size of drug has important impacts on capsule formulations in terms of its effect on dissolution. Noyes and Whitney (1897) described the dissolution rate of drug (dc/dt) as directly proportional to the interfacial surface area, A', (the surface area of the undissolved solid in contact with solvent) and the difference between the concentration of the drug in the saturated diffusing layer (Cs) and the concentration of the drug in the dissolution medium at time t, (Cs - Ct) (equation 1.2) where D' is the diffusion coefficient of the solute and h_D denotes the thickness of the diffusion boundary layer and V' is the volume of the dissolution medium.

$$\frac{dc}{dt} = \frac{D'}{V'h_D} A'(Cs - Ct) \ldots\ldots\ldots\ldots (1.2)$$

Since particle size is inversely proportional to surface area, small particles tend to dissolve more rapidly than large ones. Generally, poorly soluble drugs showing a dissolution rate-limiting step in the absorption process exhibited improved bioavailability when administered in finer particle size with increased surface area (York, 1988; Ansel et al, 1995a). Simões et al (1996) also established a correlation between the mean dissolution time and the mean particle size of the various indomethacin fractions by using the Coulter method. It was concluded that the dissolution rate increases with a reduction in particle size. However, reduction of the particle size of drug does not always solve the bioavailability problems of capsules. In fact, Newton and Rowley (1970) demonstrated that capsules containing ethinamate, a sparingly soluble drug with a solubility of 1 in 400 in water, had a greater drug release with the largest particle size fractions with equivalent packing densities, as judged by porosity. The observation was attributed to the decrease of the permeability of the liquid medium into the powder bed as the particle size was reduced (Newton and Rowley, 1970). Newton and Bader (1980) also observed similar effects with acetylsalicylic acid. These effects were also reported by Ljungberg and Otto (1970) who studied the same drug in capsule formulation. It was later found that by incorporating a large quantity of maize starch, which ensured water penetration into the powder and thus adequate contact with the surface of the particles, will increase the dissolution rate of fine particles of benoxaprofen, a relatively water-insoluble drug (Ridolfo et al, 1979; Wolen et al, 1979). Mosharraf and Nyström (1995a) studied the effects of particle size and shape on the surface specific dissolution rate of microsized (less than 5μm) practically insoluble drugs (including griseofulvin, barium sulphate, glibenclamide and oxazepam) and also confirmed that micronization or particle size reduction did not always lead to a faster dissolution rate. On the contrary, Lindberg and Lundstedt (1994) observed no general relationships between particle-size and dissolution rate parameters with respect to prednimustine (in crystallites, aggregates and agglomerates states). This was probably attribute to the impurities which may influence the crystallite size and agglomerate size as well as the surface roughness and wettability of the particles.

Although decrease in particle size tends to increase rate of dissolution as the surface area increase, the permeability of the medium into the powder bed also has an overwhelming effect on dissolution. Therefore particle size reduction or micronisation does not always lead to a faster dissolution rate. Furthermore, impurities of the drug and their effect on the particle morphology also play an important part in the rate of drug release. The influence of particle size of drug on rate of dissolution is a complex subject and cannot be elucidated by a simple correlation.

1.3.1.2 Particle shape

Description and measurement of particle shape

A wide number of measurements for particle shape have been proposed in the past. The more commonly used qualitative terms which indicate the nature of particle shape are shown in Table 1.4. These terms are extracted from the British Standard 2955 : Glossary of Terms Relating to Powders by Allen (1981).

Table 1.4 : Definitions of particle shape (Allen, 1981)

Terms	Description
Acicular	needle-shaped
Angular	sharp-edged or having roughly polyhedral shape
Crystalline	freely developed in a fluid medium of geometric shape
Dentritic	having a branched crystalline shape
Fibrous	regularly or irregularly thread-like
Granular	having approximately an equidimensional irregular shape
Irregular	lacking any symmetry
Modular	having rounded, irregular shape
Spherical	global shape
Flaky	plate-like

A qualitative description of particle shape is not always adequate and therefore quantitative information about shape is also used. The simplest way to define particle shape is in terms of the measurements of the thickness, breadth and length of the particles (Heywood's ratio) (Heywood, 1963). These measurements are taken when the particle is resting in its position of maximum stability. Shape data is therefore often extracted from microscopic measurements. For example, Sims and Withington (1983) employed a semi-automatic system to perform particle size analysis by microscopy for acicular and non-acicular particles which included samples of Sephadex G25 (fine), spray-dried lactose and an acicular drug substance. Houghton and Amidon (1992) described a microscopic method, which belonged to a class of semiautomatic non-TV-interfaced analyzers, to measure the 3-dimensional size and texture data in order to determine the particle size and shape for two types of sand (silica and quartz), two excipients (Emdex and NuTab) and four lots of ibuprofen. Methods other than microscopy, such as the slotted sieves method, were also used by Whiteman and Ridgway (1986) to discriminate particle shape of sodium perborate tetrahydrate, a granular particles of similar size and shape to many pharmaceutical granulates. In these measurements, the thickness was the height of the particle; where the breadth was the minimum distance between two tangential planes which are perpendicular to the plane of maximum stability; and the length was the distance between two tangential planes which are perpendicular to those defining the thickness and breadth.

These measurements are often used to calculate more meaningful values such as shape coefficients or shape factors. Heywood (1963) found that the volume coefficient 'k' was related to the geometrical form of the particle (equation 1.3). Heywood (1954) also derived a relationship between a shape coefficient 'f' and the geometrical properties of large particles (equation 1.4).

$$k = k_e / m\sqrt{n} \quad \text{.....(1.3)}$$

$$f = 1.57 + C\left(\frac{k_e}{m}\right)^{4/3}\left(\frac{n+1}{n}\right) \quad \text{.....(1.4)}$$

where m = the ratio of breadth to thickness

n = the ratio of length to breadth

k, f, C and k_e are shape coefficients. Some values of the coefficients k_e and *C* for certain geometrical forms and for irregular particles were determined experimentally by Heywood (1954). Using these coefficients, it is possible by making a visual assessment of the particle shape and proportions through the microscope, to calculate the appropriate values of the coefficients *f* and *k*.

Apart from the Heywood's ratio (Heywood, 1963), different shape factors were also used in the literature to define particle shape. For example, the shape factor used by Holgado et al (1995), described the departure of the particle from a spherical form. For spherical particles, the shape factor is 1, while for all other particles, the shape factor is smaller than 1. The shape factor can be calculated from the area and perimeter of the particle (equation 1.5) (Holgado et al, 1995).

$$\text{circularity} = \frac{4\pi \times \text{area}}{\text{perimeter}^2} \quad \ldots\ldots\ldots (1.5)$$

An alternative way to obtain the shape factor of non-spherical particles is by measuring their diameters using two different techniques which usually results in two different sizes as mentioned in Washington (1992). In this case, the shape factor is the ratio of the two equivalent diameters obtained by the different methods (Washington, 1992). Sphericity (Ψ) is also used to quantitatively describe particle shape (equation 1.6) (Wadell, 1934).

$$\Psi = \frac{\text{surface area of a sphere having the same volume as the particle}}{\text{surface area of the particle}} \quad \ldots\ldots\ldots (1.6)$$

An extensive review can also be found in Hawkins (1993).

Fourier transformation analysis consists of finding the particle outline and its centre of gravity from which a polar co-ordinate system can be set up (Allen, 1981). Fourier coefficients (A_n) depend on the particle shape and that particles have 'signatures' depending on 'A_n' (Meloy, 1977a & 1977b). Beddow (1974) also showed how a number of particle silhouette shapes could be analysed and reproduced by Fourier transforms.

Another method that can be used to characterize particle morphology is fractal dimension. Fractal geometry is a mathematical tool used to describe the surface morphology of a particle and its degree of surface irregularity as reviewed by Washington (1992) and Holgado et al (1995). The perimeter of a silhouette edge is dependent on the step length which is measured. The smaller the step length, the larger is the perimeter measured, and more details of the structure are taken into account. The relationship between the fractal dimension (D), step length (δ) and the perimeter estimated with step length (L_δ) is shown in equation (1.7). 'D' represents the irregularity of the particle surface and k is a constant. The greater the value of 'D', the more irregular a substance is (Farin and Avnir, 1987).

$$L_\delta = k \times \delta^{(1-D)} \quad \text{.....(1.7)}$$

Several pharmaceutical excipients were studied using fractal geometry (Bergeron et al, 1986; Thibert et al, 1988). Cartilier and Tawashi (1993) studied lactose and Holgado et al (1995) studied coated lactoses using such a method. Fernández-Hervás et al (1994) also characterized the particle morphology of a drug, diclofenac hydroxyethyl-pyrrolidine using fractal analysis.

Effect of particle shape on powder flow

Powders with similar particle sizes but different particle shapes have markedly different flow properties due to differences in interparticle contact areas. Spherical particles has minimum interparticle contact and thus tend to be more free flowing than irregularly shaped particles (Staniforth, 1988a) while needle or plate shaped particles tend to exhibit flow problems. When rough, flat or angular particles are mixed with smooth or round particles, the different particle shapes segregate into piles due to the differences in flow properties.

Koh (1984) studied binary and ternary mixtures of Emcompress covering a range of particle sizes with different shape. The bulk density and mass flowrate (through a hopper or an orifice) decreased with an increase in particle angularity. The binary mixtures of spherical and angular particles had both flowrate (from an orifice)

and bulk density lower than predicted by linear interpolation. Generally, the angular particles disrupted the bed of spherical particles to produce the observed results. The ternary mixtures indicated complex particle shape interaction that cannot be predicted from the binary constituents. However, for both binary and ternary mixtures, the effects of particle shape on bulk density and flow were more pronounced at smaller particle size. Ho (1989) also reported similar findings for Elcema and spray-dried lactose. Irregularly shaped particles have greater resistance to shear (Whiteman and Ridgway, 1986) because they tend to interlock with each other and are more cohesive.

The combined effects of particle size and shape can be influential in powder flow and thus filling performance. As particle size decreases, the effects of particle shape become more important. When the particle size reaches around 50 μm or below, shape effects can predominate over effects exerted by particle size and this can significantly affect capsule filling operations (Whiteman and Ridgway, 1986).

Effect of particle shape on granulation

Powder mixtures are sometimes granulated before being filled into capsules. In the formation of granules, irregular particle shape will increase granule strength which is especially important where large mechanical forces are involved in the granulation processes. In cases where fluidized bed granulation method is used, needle-shaped or plate-shaped particles may be difficult to fluidize (Kristensen and Schaefer, 1987).

Effect of particle shape on drug release

The drug release from the capsule formulation can also be affected by particle shape of the powder. Mosharraf and Nyström (1995a) showed that, for particles of the same size, the dissolution rate of sparingly soluble drugs (griseofulvin, barium sulphate, oxazepam and glibenclamide) decreased as the level of flakiness and irregularity increased. The average hydrodynamic boundary layer thickness increased as the particles become more irregular; and the thickness of the hydrodynamic boundary layer is inversely proportional to dissolution rate (as indicated by Noyes-Whitney equation, Equation 1.2).

1.3.1.3 Flow properties

Determination of flowability of powders

Various methods have been used to determine the flow properties of powders. For mildly cohesive powders, some crude measurements can be provided by angular measurement (Table 1.5). A static heap of powder tends to form a conical mound. The angle of the side of this 'cone' to the horizontal cannot exceed a certain value and this is known as the 'angle of repose' (Wells and Aulton, 1988). There are a number of methods in measuring the angular characteristics of powder, such as the fixed funnel (Craik, 1957), fixed bed cone (Nelson, 1955), revolving cylinder (Franklin and Johanson, 1955) and the tilting box (Takahasi, 1934). These methods have been discussed by Train (1958), Pilpel (1966) and (Neumann, 1967). However, angular measurements have been assessed and criticized by Gold et al (1966b) and by Jones and Pilpel (1966) because the results are highly method-dependent and may be open to misinterpretation. As reviewed by Pilpel (1971), it is inadvisable to determine the flow properties or cohesiveness of powders by angular measurement, except in a qualitative manner to compare the difference in flowability of different powders measured under the same circumstances.

Table 1.5 : Angle of repose as an indication of powder flow properties (Wells and Aulton, 1988)

Angle of repose (degree)	Type of flow
< 25	Excellent
25 - 30	Good
30 - 40	Passable, may be improved by glidant
>40	Very poor

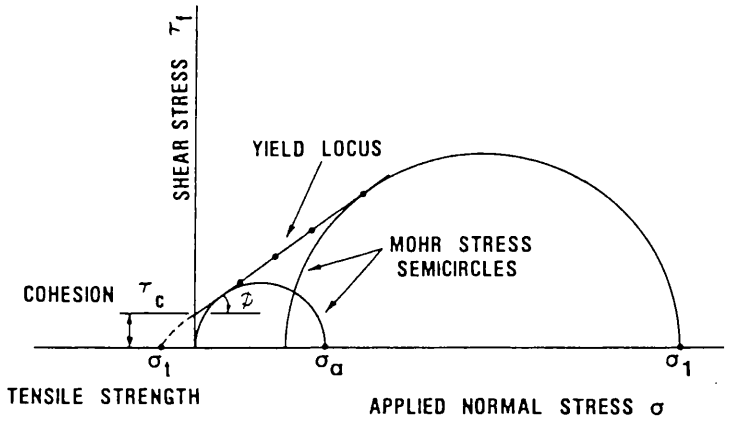
For materials with low cohesion, direct measurement of the flow rate through an aperture is possible (Brown and Richards 1959 & 1960; Cole, 1987c). The calculation of an intrinsic flowability factor by timed delivery of a specified weight or volume of powder through different orifices was proposed by Gioia (1980). Powder flowmeters

have also been used. Instrumentation and application of recording powder flowmeters were described by Gold et al (1966a and 1968a). The flow of lactose granules and effects of glidants on flow rate, measured by recording powder flowmeter, were also studied by Gold et al (1966b and 1968b). The potential uses of recording powder flowmeters in pharmaceutical applications were reported by Jordan and Rhodes(1979) and Rudnic et al (1980).

The measurements of the tensile strength and shear strength of powders which assess the cohesiveness of powder is an alternative approach to indicate the flowability. The "cohesiveness" of a powder may be defined as the tendency of its individual particles to stick together (Pilpel, 1971). Generally, the more cohesive the powder, the less free-flowing the powder. The split plate method, as described by Thouzeau and Taylor (1961), Ashton et al (1965), Fowler and Radford (1965), measures the strength of powder beds when they are being subjected to a tensile force. This method involves packing the powder into a split plate of which one half is fixed and the other half is free to move by means of small wheels or ball bearings which run in tracks in a table. The table is then tilted at an angle. At a certain angle, the powder cohesion is overcome and the mobile half plate breaks away from the stationary half. The tensile stress can then be evaluated (Staniforth, 1988a). A shear cell equipment such as Jenike shear cell (Jenike, 1961 & 1964) measures the shear stress of the powder bed at different values of normal stress. Powder is packed into two halves of the cell and weights are applied as normal stress on the lid of the assembled cell. A mechanical drive on the upper half of the cell applies a shearing stress across the two halves of the cell. A yield locus (Figure 1.6) can be constructed by plotting the normal stress against the shear stress. Mohr semicircles are then marked on the graph. Based on the shear stress on the abscissa of the graph, at which failure occurs, the radius of the Mohr semicircles are deduced. A line called the 'yield locus' which is characteristic of the powder under given conditions can then be obtained. Different properties of the powder e.g. the cohesion value, the tensile strength, angle of internal friction and flow factor can be evaluated from the Mohr diagram (Staniforth, 1988a). The cohesion value is defined as the value of shear stress at zero applied load (Gordon et al, 1990) whereas the angle of internal friction is a measure of the difficulty of maintaining a constant volume flow (Hiestand et al, 1973). The Jenike flow factor is defined as the reciprocal slope of the tangent to the

graph of unconfined yield stress (σ_α) versus major normal stress (σ_1) obtained from several yield loci (Pilpel, 1971). The details of the extraction of these values are not within the scope of this thesis but could be found in Jenike (1961 & 1964) and William and Birks (1967). These values can be used to assess the flowability of a powder, for example, the more cohesive a powder, the smaller the flow factor and the greater the angle of internal friction (Pilpel, 1971). Based on a similar principle, an annular shear cell (Kocova and Pilpel, 1972) was devised and was claimed to be more advantageous over Jenike shear cell in terms of smaller sample size, more rapid measurement and less variation in shear strain across the sample. York (1975) applied the technique of annular shear cell to assess the effects of glidants on flowability of cohesive pharmaceutical powders (alpha-lactose monohydrate and calcium hydrogen phosphate).

Figure 1.6 : Typical Mohr's shear diagram (Gordon et al, 1990)



Another method which has been devised to measure cohesion specifically for capsule filling is a 'cohesion viscometer'. The powder is stirred by the stirrer motor of the viscometer and the resistance to the rotation of the stirrer is recorded and is used as an indication of the cohesiveness of powder in the beaker (Cole, 1987c) and thus flowability of the powder.

The more compressible a material is, the less flowable it is; and the less compressible a material is, the more free flowing it is (Carr, 1965a). Therefore the flowability of a powder can also be indicated by its compressibility. Carr (1965a & 1965b) developed a simple test to evaluate flowability of powder by comparing the

packed bulk density (maximum bulk density) and the 'aerated' bulk density (minimum bulk density). The Carr's compressibility index (Table 1.6), which can be calculated using equation (1.8), provides an empirical guide for the flowability of powders.

$$\text{Carr's compressibility (\%)} = (P'-A) / P' \times 100 \quad \text{.....(1.8)}$$

where P' = packed bulk density

A = aerated bulk density

Aerated bulk density is the density of a powder which was fed into a container of known volume through a 100 mesh screen. The packed bulk density is the density of the powder subjected to five minutes of vibration (Carr, 1965a).

Neumann (1967) also studied the relationship between compressibility of powders and its flowability. Unlike Carr (1965a), the reduction of volume occupied by the powder was achieved by a compressive load acting on the surface instead of by vibration or tapping. Similarly, Chowhan and Chow (1980) described the use of consolidation ratio in predicting flow properties of powders. The consolidation of loosely packed powders was also achieved by applying a series of loads on the surface of the powder bed. It was found that compression by applying a load on the powder bed surface did not produce as great a reduction in powder bed volume as prolonged tapping without any pressure.

Table1.6: Generalized relationship between Carr's index and type of powder flow (Wells and Aulton, 1988)

Carr's Index (%)	Type of flow
5 - 10	Excellent
12 - 16	Good
18 - 21	Fair to passable
23 - 35	Poor
33 - 38	Very poor
> 40	Extremely poor

Hausner (1967) derived that the ratio of the maximum bulk density and minimum bulk density can be used as an indication of flow (equation 1.9 and Table 1.7).

Hausner ratio = maximum bulk density / minimum bulk density ..... (1.9)

Table 1.7: Hausner's ratio as an indication of powder flow
(Values from Wells and Aulton, 1988)

Hausner's ratio	Type of flow
< 1.25	good flow
1.25 - 1.5	Passible, improve by the addition of glidant
> 1.5	poor flow

Effect of powder flow on capsule formulations

Powder flow is of paramount importance in terms of provision of uniform feed in the capsule filling equipment. Both Jones (1985) and Staniforth (1988a) described that the drug mixture must be reasonably free-flowing to produce a uniformly packed powder bed. The dose is then transferred from the powder bed into the capsule bodies. Uneven flow of powder mixtures tends to produce unreproducible filling of capsule bodies and therefore increases the variability in capsule fill weight and results in inaccurate dosing of drug. The uniformity of weight of capsules is therefore strongly related to the flowability of the powder mixture. In some cases, uneven flow can result from excess fine particles which increase particle-die wall friction and cause lubrication problems (Jones, 1985; Staniforth, 1988a). The flowability of powder also plays an important role in solid/solid blending and powder homogeneity (Sadek et al, 1982) in terms of uniformity of content and accurate dosing of capsules as well as the evenly distribution of excipients within the drug mixture.

A number of studies have been performed to investigate the relationship between the flowability of powder and variability of capsule fill weight. Reier et al

(1968) developed a mathematical model to correlate the machine speed, capsule size, presence or absence of glidant (talc) and powder properties such as specific volume and flowability; with mean gross capsule weight, standard deviation of capsule weight and capsule weight coefficient of variation the fill-weight variation using a semi-automatic filling machine. From these equations, it was revealed that mean capsule fill weight was dependent on specific volume, flowability, machine speed and capsule size. Irwin et al (1970) obtained a correlation of 0.96 between the flow properties of clomacran phosphate powder blends and the capsule fill weight variation existed based on a Zanasi automatic capsule-filling machine. Later Chowhan and Chow (1980) indicated a direct relationship existed between powder flow, powder consolidation ratio and variation in capsule fill weight filled on a Zanasai automatic capsule filling machine. The powder consolidation ratio was suggested to be a useful tool in predicting flow properties of powder mixture. Tan and Newton (1990a & 1990b) also indicated, with the aid of a simulated dosator nozzle machine, that powder flowability could be used as an indication of capsule filling performance and the influence of compression setting ratio on capsule fill weight and weight variability for pharmaceutical excipients such as microcrystalline cellulose, maize starch, lactose, calcium carbonate and pregelatinised starch.

If a dosator nozzle filling machine is used, the powder mixture must be free-flowing to enable uniform filling of the powder mixture and yet also exhibits a degree of cohesiveness to allow retention within a dosator nozzle system and thus completely transferred from the nozzle into the capsule bodies (Jolliffe and Newton, 1982a). Hauer et al (1993a) also pointed out that formulations, which are very free flowing, can be difficult to compress to a strong powder plug and have greater weight variation. In a symposium, Neumaier (1991) stated the importance of having optimum flow properties for the filling materials.

'Free flowing' is a common characteristic of most highly segregating materials of which particles of different size are easily separated from each other (Carson, 1988). Therefore one of the solutions to ensure a decrease in segregation is to increase its cohesiveness. However, it is important that the cohesiveness is not increased too much as highly cohesive powders often cause problems in filling. The Johanson Indices,

derived from the flow properties of basic bulk solids (Johanson, 1996), were described to provide a quantitative means in predicting segregation and flow behavior of compound components and have the potential to quickly identify troublesome formulations using bench-scale tests.

Another area where a cohesive powder may be counter-productive is granulation. The choice of granulator may be more limited for cohesive powders. Cohesive powders are difficult or impossible to fluidise and therefore fluidised bed granulation may not be appropriate. If a high shear mixer is used instead, the densification of the powder mixture will be very much dependent on the impeller speed and wet massing time and therefore the amount to granulating liquid used becomes critical. (Kristensen and Schaefer, 1987)

1.3.1.4 Bulk Density, compressibility, packing

Determination of bulk density and compressibility

Density, the general term, is the weight to volume ratio of a substance. The true density is the weight to volume ratio of only the solid portion of the powder particles. It can be determined by degassing an accurately weighed sample of the powder in a known volume container and admitting a fluid which wets but does not dissolve the powder. The volume of the void spaces occupied between the particles can be calculated from the weight of the fluid used to occupy these void spaces and the density of this fluid. A pycnometer is often used to measure the true density of particles (Lantz, 1990). The apparent density is the weight to volume ratio of particle including the intraparticulate pores. The porosity of the particle is the ratio of volume of intraparticulate pore space to total volume of particle and can be determined from the apparent density and true density (equation 1.10) (Rees, 1977).

$$\text{Porosity of the particle} = 1 - \text{apparent density/true density} \quad \ldots\ldots\ldots (1.10)$$

Bulk density also provides important information about the drug or drug mixture. Bulk density is the ratio of weight of powder to the volume it occupies at a

particular packing condition. It accounts for the volume of the solid portion of the particles as well as the void space within each particle and between the particles. It is therefore essential to describe the packing condition (Lantz, 1990). The minimum bulk density can be described as the density of a known weight of powder gently poured into a container (usually a 100 ml graduated cylinder) without vibration, tapping or compression. The maximum bulk density is the density of the same powder mass in the same container which is vibrated or tapped until no further decrease in the volume occurs. The porosity of the powder column can be calculated by subtracting the reciprocal of the true density from that of the bulk density (Lantz, 1990). Carr (1965a) evaluated an index of compressibility of a powder from the minimum and maximum bulk densities (equation 1.8) which can be related to the flowability of the powder (Section 1.3.1.3).

There are also numerous mathematical models that describe the change in the relative density of the powder (in a powder column) as a function of the applied pressure. Some of these models were applied widely in the pharmaceutical research, for example, in areas related to the compression processes (Paronen and Iikka, 1996). One of these is the Kawakita equations (Kawakita and Tsutsumi, 1966) (equation 1.11 and 1.12).

$$C_R = V_0 - V_P / V_0 \quad \text{..... (1.11)}$$

$$\frac{P}{C_R} = \frac{P}{a} + \frac{1}{ab} \quad \text{.....(1.12)}$$

where C_R = degree of volume reduction

V_P = volume of a powder column under the applied pressure P

V_0 = initial volume

a, b = constants characteristic to powder being compressed

By plotting a graph of P/C_R versus P, the constants 'a' and 'b' can be calculated. The gradient of the plot is the reciprocal of constant 'a' whereas the y-intercept represents the value 1/ab. The constant 'a' gives an indication of the maximum volume reduction available and is considered to describe the compressibility of a powder while 'b' is considered to describe an inclination toward volume reduction. Kawakita and co-

workers (Lüdde and Kawakita, 1966; Kawakita and Lüdde, 1970/71; Yamachiro et al, 1983) also applied the equation to describe the relationship between the volume reduction and tapping process at small tapping numbers. In this case, the pressure P in equation (1.12) was replaced by N (tapping number). The properties relating to the fluidity, cohesion and compressibility of various powder solids (e.g. starch, magnesium stearate, calcium stearate, talc and aluminium stearate) were also investigated by Yamachiro et al (1983).

Effect on capsule formulations

The bulk density or compressibility of the powder is important not only because of its indirect relationship with the flow properties of the powder but also due to its effect on the filling procedure. Information regarding the bulk densities of the drug mixture and individual ingredients in the formulation are needed to determine the volume which a unit dose weight will occupy in a capsule. Newton and Bader (1981) predicted the maximum bulk density of a two-component mixture (acetylsalicylic acid and lactose) from measuring the properties of the individual components. From the predicted maximum bulk density, the expected fill was calculated. The relationship between these predicted values and the filling performance of hard gelatin capsules (mean fill weight) was also evaluated. However, the method was less satisfactory for the prediction of the bulk density and capsule fill weight when compression was involved in the filling process. Varthalis and Pilpel (1976) showed that the packing arrangements of particles of a powder mixture may give rise to anomalies in some properties of the mixtures. The mean particle sizes, tensile strengths and flow properties of the mixtures of lactose and paracetamol and of lactose and oxytetracycline were not proportionally intermediate between those of the constituents. Since the interaction forces between two lactose particles were different from that between two oxytetracycline particles and different from that between an oxytetracycline and a lactose particle, the strength of the packing may also change and this could account for the anomalies observed (Varthalis and Pilpel, 1976). Höfliger and Karg powder-plug estimator was therefore designed to determine the volume occupied by a formulation under a known pressure and relating the data to a required capsule size (Cole, 1987c).

Chowhan and Chow (1980) found a direct relationship between the powder consolidation ratio and the variation of fill weight in capsules filled by an automatic capsule filling machine (Zanasi). The consolidation ratio is the intercept of a plot of the logarithm of the ratio of change of volume in the powder bed against the pressure acting on the powder bed surface for a given powder. This ratio can also be used to predict flowability of the powder (see Section 1.3.1.3). As the consolidation ratio increased, the coefficient of variation of capsule fill weight also increased.

The porosity of the powder bed also reflects the compressibility of the powders. Woodhead et al (1979) developed a method using γ-ray attenuation to establish the influence of powder bed porosity variation on the capsule fill-weight. However, Woodhead (1980) later concluded that the degree of powder bed porosity did not appear to be related to the reproducibility of the capsule fill weight.

According to Neumaier (1991), it is mainly the compressing properties of the formulation that determine its suitability for filling. With dosing-disc filling machines, it is particularly important to be able to compress the material with varying forces because the dosage can only be set by changing the density of the plug or by changing the dosing-disc.

The filling performance of capsules can be related to the compression settings of the filling machine. Jolliffe and Newton (1982a, 1982b) investigated the effect of compression on the capsule filling properties on an instrumented mG2 G36 capsule filling machine simulator. It was shown that an increase in the degree of compression applied resulted in an increase in the interaction between the powder and the nozzle wall. This interaction, in some cases e.g. when the drug mixture is free-flowing, is necessary to ensure powder retention in the nozzle during the transfer of the drug mixture into the capsule bodies. However, excessive compression may cause excessive coating of the nozzle wall which may lead to large fill weight variation or even a complete seizure of the nozzle within the piston. Tan and Newton (1990b) studied the influence of compression setting ratio of dosator nozzle filling machine (represented by an instrumented mG2 G36 capsule filling machine simulator) and the capsule fill weight and weight variability for a range of pharmaceutical excipients. It was shown

that for most powder systems, the most uniform weights were achieved when no compression was applied to the powder during the filling process. Powders with fine particle size fraction required some compression to aid powder retention but for larger particle size fraction, high compression settings could induce the piston to jam in the nozzle and failure to fill a capsule. Hauer et al (1993a) showed that good compressibility (indicated by degree of reduction in volume) as well as strength of binding were important in provision of non-problematic filling with uniform fill weights using an intermittent operated dosator nozzle filling machine.

1.3.1.5 Solubility

Determination of solubility

Qualitative descriptions of the solubility are sometimes used. For example, the *British Pharmacopoeia* (1993) described the solubility by expressions such as "insoluble" and "very slightly soluble" which are defined quantitatively in terms of solubility of the solute in parts per parts of solvent. However, qualitative descriptions are considered to be imprecise (Florence and Attwood, 1988). Other quantitative expressions such as milligram per milliliters or parts per million (ppm) are also used. Standard methods to determine the solubility quantitatively are described in the literature such as the *Handbook of Pharmaceutical Excipients* "HPE Laboratory Methods" and will not be included in this thesis.

Determination of solubility for relatively insoluble drugs (less than 100μg /ml) can be problematic. Long equilibration time, the presence of impurities (Higuchi et al, 1979) and existence of a more soluble amorphous layer around the less soluble crystalline core of the particles (Elamin et al, 1994) contribute to the complicated interpretation of solubility data. Coulter counter was suggested to be an alternative method to determine the solubility of sparingly soluble drugs as reviewed by Mosharraf and Nyström (1995a). Both the measurements of solubility and dissolution rate of sparingly soluble compounds (griseofulvin and felodipine) were determined, at the same time, by suspending the drug in micellar solutions (Nyström and Bisrat, 1986).

This technique was later improved by Mosharraf and Nyström (1995b) for determination of drugs with a solubility even less than 5 μg/ml.

The degree of ionization varies with the pH of the medium and thus the solubility of acidic and basic drug is also pH-dependent. For example, chlorpromazine, a basic drug, is more soluble in acidic solution and acidic drugs like nitrofurantoin are more soluble in alkaline solutions (Florence and Attwood, 1988). Aqueous solubility of drug could serve as a useful biopharmaceutical parameter if the solubility of the drug is to be determined as a function of pH over the physiological pH range of 1 to 8 (Wadke et al, 1989). In the SUPAC (Scale-Up and Post-Approval Changes) guidelines for immediate-release oral dosage forms issued by the FDA (Centre for Drug Evaluation and Research, 1995), the changes involved in the scale-up procedure are predicted based on aqueous solubility over pH range of 1 to 8 and permeability of drug into the gastrointestinal tract. The solubility-pH profiles of acidic or basic substances have been described extensively in a number of textbook including Florence and Attwood (1988), Abdou (1989a), Wadke et al (1989), Cartensen (1990b) and is not within the scope of this thesis. The measurement of the solubility of drug would therefore depend on a number of variables such as pH of the solvent and the precision of the method used.

Effect of solubility and capsule formulation

Prior to the absorption of drug into the body, the drug must be dissolved in the gastrointestinal fluids. Therefore the dissolution of drugs in gastrointestinal fluids could influence the rate and extent of their absorption. According to the Noyes-Whitney (1897) equation (equation 1.2), the dissolution of drugs is a function of solubility of drug in the dissolution medium. For insoluble drugs, the solubility of these drugs will play a paramount effect in its absorption. Aguiar et al (1968) stated that when a drug has a relatively low solubility, the rate of absorption is governed by the effective concentration at the absorption site, in the other words, the solubility of the drug at the absorption site. Newton and Razzo (1977b) also expressed a mathematical model which indicated that the *in vitro* drug release of capsule formulation was directly related to the logarithm of the solubility of the drug. As a general rule, drug mixtures

with an aqueous solubility of less than 1% w/v may present a potential dissolution-related absorption problem (Wadke et al, 1989; Abdou, 1989d).

In a joint FDA-AAPS workshop on scale-up of immediate-release solid dosage forms (Skelly et al, 1993), the importance of the relationship between solubility and particle size of drug in the development of solid dosage forms, mainly in the scale-up procedure, was stressed. It was concluded that "for drug substances with an aqueous solubility of ≤ 5 mg/ml, a change greater than 10% in mean particle size (distribution remaining the same), surface area, or intrinsic dissolution rate - or for drug substances with an aqueous solubility of ≥ 5 mg/ml, a change greater than 25% in particle size (distribution remaining approximately the same), surface area, or intrinsic dissolution - is viewed as a major change, unless justified by appropriate scientific rationale". Although Chowhan (1994) did not support the general guideline laid out in the FDA-AAPS workshop, the importance of the aqueous solubility of drug product as determined by the effects of physical properties such as particle size and shape in developing solid dosage forms was confirmed.

The 'dissolution stability' of the formulations can be affected by the type of diluent used, capsule size, storage condition and solubility of the formulation (Desai et al, 1994b). During storage, the moisture liberated from the excipients and the capsule shells may cause significant caking of the capsule contents and thus retard the dissolution rate. However, it was shown that if the formulation had high aqueous solubility, the caking of the contents had no discernible effect on dissolution.

In the granulation process, the solubility of the material (mainly the drug and diluent) is also important. As reviewed by Kristensen and Schaefer (1987), if the material is soluble in the binder solution, the growth rate of the granules is higher; whereas if it is insoluble and poorly wettable, the growth rate of the granules is lower. When the powder is semisoluble in the binder solution, the amount of solution needed decreased compared to poorly soluble drug mixtures. In the review, it was also mentioned that recrystallization of dissolved material during drying will also increase the strength of the granules. On the other hand, recrystallization of dissolved powder may sometimes cause formation of practically insoluble crystals and thus prohibit the

release of drug. A binder is often needed in the granulation process to keep the granules together by formation of solid bridges after drying and these solid bridges are formed by recrystallization. Therefore if the material (drug and diluent) is semisoluble in the granulating liquid (water in many cases), solid bridges can be formed, possibly without the need of a binder (Kristensen and Schaefer, 1987).

1.3.1.6 Moisture content

The moisture content of a drug or material is very often accounted by its *equilibrium moisture content.* The equilibrium moisture content can be described as the amount of moisture adsorbed by a fixed weight of anhydrous sample in equilibrium with the moisture in the air at a given temperature (Wadke et al, 1989). The equilibrium moisture content for the hard gelatin capsule shell is between 13-16% w/w in an atmosphere with a relative humidity between 30-50% (Jones, 1987c). However, if the moisture content between the capsule shell and its content differs, it is possible that the moisture may transfer between the capsule shell and its contents or vice versa, affecting the stability of the product. If the moisture content of the capsule shell drops below 10% w/w, the gelatin become brittle and if the moisture content raises above 18% w/w, the gelatin shell will be softened and distorted (Jones, 1987c). If the moisture is transferred into the capsule content, there may be problems with the stability of moisture sensitive drug. The decomposition of the drug may be caused by available moisture which enable a reaction (for example, hydrolysis) to take place or provide a sorbed moisture layer (Carstensen, 1990a). The drug may dissolve in the presence of the sorbed moisture layer, and decompose. This moisture layer may also dissolve oxygen and lead to oxidation of the drug. The drug may also chemically bind with the moisture and the resulting pseudomorph of the active drug may present a bioavailability problem. The excipients may affect the stability of the active drug by interacting with the drug or act as a surface catalyst. The acidity and basicity properties of the excipient may also alter the pH of the sorbed moisture layer and thus lead to decomposition of the active drug (Umprayn and Mendes, 1987). Tingsted and Dudzinski (1973) provided a more detailed discussion on the effect of moisture content on stability of drug substances in solid pharmaceutical dosage systems in their review. Ito et al (1969a) showed that to prevent moisture from passing either to or from the capsule shell or

contents on storage, each component should be used at its equilibrium moisture content as determined by the storage conditions of the capsule products. Bond et al (1970) produced similar findings when preparing a stable formulation for cephalexin capsules. In their work, the equilibrium moisture content values of hard gelatin capsules and of cephalexin were also used to predict both the best starting moisture contents for the raw materials and the probable stability of the finished product. The effect of powder moisture content on drug release from hard gelatin capsules filled with 50:50 maize starch : barbitone and 50:50 maize starch : sodium barbitone was also studied by York (1980). The moisture sorption and desorption isotherms for gelatin capsules, maize starch, maize starch : barbitone mixture and maize starch : sodium barbitone mixture all exhibit hysteresis (York, 1980) and the moisture sorption hysteresis was analyzed in York (1981).

Moisture also modifies the flow and mechanical properties such as compressibility of many powders (Pilpel, 1971). Craik and Miller (1958) studied the flow properties of maize starch, sucrose and sodium chloride under humid conditions. It was concluded that when the moisture content is increased, the powders showed increased adhesion, and became less free-flowing. This effect can be overcome by a small concentrations of magnesium oxide. A quantitative explanation was also given for both the effects of moisture on the flow properties and the effects of the added magnesium oxide in maintaining the ease of flow of moist powders (Craik and Miller, 1958). Harwood (1969) found that the cohesion and tensile strength of loosely packed starch, lactose and griseofulvin rose as their moisture contents were increased. Dawoodbhai and Rhodes (1989) explained the mechanism of the effect of moisture on the flow of powders. Moisture significantly influenced the tensile strength of powders by formation of liquid bridges (Eaves and Jones, 1972a, 1972b, 1972c). When moisture content increases, the number of liquid bridges between particles and particles also increased which can result in increased cohesion and aggregation of powders and ultimately the formation of a hard cake.

Dissolution stability of capsule formulations is affected by the presence of the moisture liberated from the excipients and capsule shells. Desai et al (1994b) showed that the decrease in dissolution rate of sorivudine and hydrochlorothiazide capsules

after 6 months storage at 50 °C, 40 °C/75% RH, and 40 °C was contributed by the type of lactose (Fast-Flo lactose, hydrous lactose or anhydrous lactose) used. It was hypothesized that water liberated from Fast-Flo or hydrous lactose tended to bind the capsule contents together and resulted in aggregation of the drug mixture and thus reduced the penetration of the dissolution medium. Ampicillin trihydrate capsules which were subjected to 4 months' storage under varying humidities (between 50-90%) also had significant retardation in dissolution rates. The reduction in dissolution rate was attributed to the agglomeration and subsequent caking of the capsule contents due to moisture transfer from the shell (Georgarakis et al, 1988). The release rate of phenytoin sodium from capsules was also monitored as a function of storage time (2-8 weeks), humidity (11 and 67% RH) and excipient-to-drug ratio. The excipients were calcium sulphate and lactose. Capsules containing calcium sulphate dissolved more rapidly after ageing whereas formulations containing lactose dissolved more slowly after aging when compared with the corresponding initial values. Increased excipient-to-drug ratio caused prolonged *in-vitro* after storage and changes were more evident at higher humidity level (Rubino et al, 1985).

Hygroscopic drugs may prove to be a problem when formulated into hard gelatin capsules (Jones, 1985). Hygroscopic drugs tend to adsorb moisture and draw the moisture from the capsule shells and the surroundings. Carstensen et al (1993) stated that when a substance is subjected to a moist atmosphere, then it may take up moisture and the moisture uptake rate is proportional to the difference between the moisture vapor pressure in the atmosphere and the equilibrium pressure over the solid. However, there is no accepted definition for hygroscopicity since there are both thermodynamic and kinetic components in the term (Carstensen, 1977) and there is no unique method to determine the hygroscopicity of a substance. As reviewed in Umprayn and Mendes (1987), Admirat and Grenier (1975) defined critical relative humidity as the relative humidity of a substance in equilibrium with a saturated solution of the substance and this value was used to determine its hygroscopicity. If a drug is stored at a atmosphere with relative humidity greater than the critical relative humidity, the substance will start to adsorb moisture and become hygroscopic. Czetsch-Lindenwald (1963) classified degree of hygroscopicity into 3 classes : softening substances, substances retaining moisture and 'antistatica'. Modrezejewski and Pokora-

Bartyzel (1966) proposed a description of hygroscopicity of a substance using the term "hygroscopic point" which was defined as the relative humidity in the atmosphere at which the powder can take up approximately 1% of moisture within 24 hours and thus determine the limit of the relative humidity at which the material would begin to take up moisture. Callahan et al (1982) classified hygroscopicity of a number of pharmaceutical excipients into 4 classes : non-hygroscopic, slightly-hygroscopic, moderately-hygroscopic and very hygroscopic; based on the increase in moisture content under different defined storage conditions.

Water absorbing materials such as starches can have effect on the processes which may be involved in capsule formulation, for example in wet granulation process (Kristensen and Schaefer, 1987). In addition, water absorbing materials require greater amount of granulation liquid to wet the surface of the materials completely as reviewed in Kristensen and Schaefer (1987). However, the water content of starches varies from different sources and therefore it is unsuitable to use a constant amount of binder solution when granulating starches or drug mixtures that contains a high content of starch. The granule size distribution may also be affected if the amount of binder solution used is not controlled properly.

Other studies between the relative humidity at various temperature and stability of pharmaceutical products were also performed. Genton and Kesselring (1977) showed a linear relationship between the decomposition constant of nitrazepam and relative humidity at various temperature. Aspirin is a well-known moisture sensitive drug and the effect of relative humidity on the stability of aspirin was studied by Leeson and Mattocks (1958), Yang and Brooke (1982) and Carstensen et al (1985). Pharmaceutical products such as ascorbic acid, streptomycin, noradrenaline, acetaminophen, hydrochlorothiazides and nystatin (as outlined in Umprayn and Mendes, 1987) were also studied. However, the definition of 'moisture sensitive' drugs remains unclear. A moisture sensitive drug can be generally described as a drug that is prone to decomposition subject to exposure of moisture but the degree of decomposition and the degree of exposure of moisture are, so far, not clearly defined and is very much subjected to the experience of the formulator. A drug, which may be described as moisture sensitive in hard gelatin capsules, does not necessary mean that

the drug is also moisture sensitive when undergoing wet granulation. It also depends on the type of granulator used. For example, the extent of moisture exposure to the drug will be smaller in a fluidised bed granulator than in a high shear mixer. The stability of a moisture sensitive drug may not be affected using the former granulator but the reverse may be true if the latter granulator is used. Guidelines for stability testing, for example, the ICH Tripartitie Guideline (Grimm and Thomae, 1995) issued the requirements for stability testing of drug substances and drug products (for all Registration Applications with EU, Japan and USA) and the duration, temperature and relative humidity of the stability test to be performed and the limits of the allowed degree of degradation of drug substance or product in order to pass the test were also stated. These guidelines may provide some ideas to help defining moisture sensitivity of drug substances but it certainly does not provide a definition for the subject.

1.3.1.7 Wettability

Determination of wettability

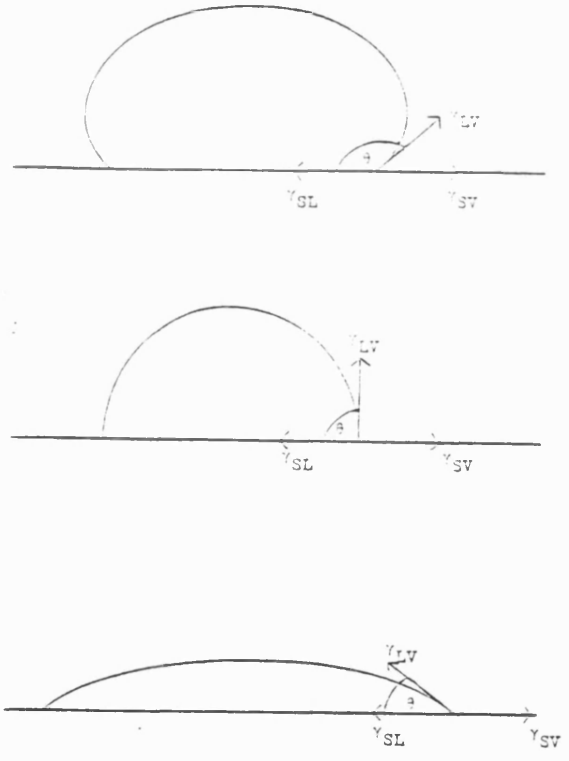
Wettability of a powder depends on the surface energy at the interface (interfacial energy) between the solid and the liquid (Abdou, 1989b). The surface energy of a solid is the best measure of wettability and can be derived from measurements of the contact angle. Contact angle (θ) represents an equilibrium of energies at a three phase interface (solid, liquid and vapour) and the equilibrium free energies per unit area of the liquid/vapour (γ_{LV}), solid/liquid (γ_{SL}) and solid/vapour (γ_{SV}) interfaces may be resolved horizontally to give the Young's equation (1805) (equation 1.13 and Figure 1.7).

$$\gamma_{SV} = \gamma_{SL} + \gamma_{LV} \cos \theta \text{.....(1.13)}$$

When describing wettability, the measurement of the contact angle is most commonly used. Generally, if the wetting is complete, then the contact angle is 0°. If the contact angle is greater than 90°, the powder is not wetted.

Insoluble powders often have a low affinity for aqueous fluid and hence has poor wettability with high contact angle (Lerk et al, 1977b). However, this is not always true. For example, kaolin has low solubility but is highly wettable (with contact angle of 0°) (Jaiyeoba and Spring, 1980). Lippold and Ohm (1986) indicated that the complete wetting of the surface of drugs may be achieved at a contact angle greater than the commonly accepted value of 0° - the critical contact angle. A value of 40° was found. However, variation in critical angle was expected to be dependent on experimental conditions (Heertjes and Witvoet, 1970).

Figure1.7 : Configurations of a drop of liquid on a solid surface (Cook, 1978)



There are various methods to measure the contact angle. Contact angles can be obtained by direct measurement of the height and the width of the drop of liquid on the flat surface by use of a telemicroscope (Harder, 1970). Sessile drop (Fox and Zisman, 1950), tilting plate (Adam and Jessop, 1925) and plate rise (Neumann and Tanner, 1970) methods have also been used. Rough solid surfaces would produce variations in

the measurement of contact angles (Wenzel, 1936) and therefore in cases where there is no continuous smooth surface on which to work i.e. powders which exist as finely divided irregular porous solids, direct measurement is not possible. Indirect determination of the contact angle can be performed. There are generally two approaches : to measure the liquid penetration through the powder bed or to obtain a smooth flat surface by preparing compressed discs of powder. The Washburn method (Washburn, 1921) based on a cylindrical tube model measured the rates of liquid penetration into the powder beds and thus calculated the contact angle using the Washburn equation (equation 1.14).

$$L^2 = \frac{R \cdot \gamma \cdot \cos\theta \cdot t}{2 \cdot \eta} \quad \text{.....(1.14)}$$

where L = length of liquid penetration

R = capillary radius of the bed

γ = liquid surface tension

θ = the contact angle

η = the liquid viscosity

However, penetration of liquid is only spontaneous when the contact angle is less than 90° (Cook, 1978). Studebaker and Snow (1955) later modified the method such that the contact angle can be determined by comparing the time necessary for a perfect and a non perfect wetting liquid to penetrate a given length into the powder bed. Apart from the cylindrical tube model, the surface tension viscous flow (STVF) model was also used (Miller and Miller, 1956). Odidi and Newton (1993) compared the two models and questioned the validity of the universal application of the STVF model.

Other indirect methods include measurements performed on compressed discs of powder (e.g. Heertjes and Kossen, 1967; Zografi and Tam, 1976). To obtain wettability data which can be applied in capsule formulation i.e. for loosely packed powders rather than for compact, the method involving compressed surfaces would be inaccurate and the liquid penetration method would be more preferential as reviewed by Buckton and Newton (1985). The size of the contact angle changes with time, particularly for water absorbing materials and therefore the measurement must be made

instantaneously but such measurement can be difficult. A photographic method, which measures the contact angle instantaneously, was described by Neumann and Good (1979) and Stamm et al (1984).

Effect of wettability on capsule formulation

The wettability of a solid is important when considering the manufacturing process such as wet granulation and dissolution rate of the capsule formulation. The wetting of the powder mixture by the granulation liquid is usually the first stage involved in the wet granulation process. The uniformity of moisture distribution will influence properties such as granules size and strength of the final granules. Jaiyeoba and Spring (1980) studied the effect of wettability of the third component in a ternary powder mixture on granule sizes and granule strength. Lactose, boric acid and either sulphanilamide, heavy kaolin or salicylic acid were used to prepare the ternary mixture. The third component substituted only 10% of the lactose-boric mixture. It was shown that wettability and packing properties of the powder mixture influenced the distribution of granulation liquid (PVP solution) over their surfaces and affect the formation of liquid bridges which hold the particles together. It was concluded that by the substitution of some 10% of the granulation with an excipient with fine particle size and good wettability (such as kaolin) would result in stronger and larger granules. Buckton (1992) pointed out that the wetting process of the powders has always been recognized to play an important part in the interaction between the binder fluid and the powder. Spreading coefficient of binders which can be calculated from contact angles and surface energies has allowed the quantification of this process and to predict the optimum binder used and the granule friability (Rowe, 1990; Zajic and Buckton, 1990). This is particularly useful in prediction of tablet strength (Rowe, 1990) and susceptibility of handling of granules during production processes.

The wettability of the solid dosage form, which indicates the access of liquid to the solid surface, is very often the limiting factor in the dissolution process (Samyn and Jung, 1970). For capsule formulation, the gelatin shell is highly hydrophilic and therefore is not expected to have any wettability problem. However, the wettability of the capsule content may have great influence on the dissolution rate (Abdou, 1989b). The effects of wettability of drugs and their dissolution rates were investigated in

several studies. Increases in dissolution rate and amount of absorption of a highly lipid-soluble drug after mixing with lactose was probably also due to an increase in wettability (Allen and Davies, 1975). Newton et al (1971a) indicated that the presence of a wetting agent increased drug release and the higher level producing a greater increase. It was suggested that the mechanism was associated with the wetting of the hydrophobic drug. In addition, Rowley and Newton (1970) also indicated that for complex capsule formulations, rapid liquid penetration of the powder mixture does not necessarily ensure good dissolution of the drug from the capsules and formulations which gave poor wetting did not necessarily gave poor dissolution. However, the formulation which allowed no liquid penetration did have the lowest dissolution rate. Newton and Razzo (1974), in a detailed study on the effect of additives on the release of drugs from hard gelatin capsules, highlighted the complex influence of the additives. The addition of sodium lauryl sulphate (wetting agent) was not shown to provide a major enhancement of drug release and in certain cases can be detrimental.

The wettability of the capsule content tends to decrease with the incorporation of a hydrophobic ingredient, for example, hydrophobic lubricants such as talc or magnesium stearate, or tends to decrease with an increase in compressibility of capsule content, for example, by using a smaller capsule size (Abdou, 1989b). By incorporation of a hydrophilic material such as starch or lactose, the wettability of a capsule formulation can be increased (Newton, 1987a). Large proportions (up to 80%) of the diluent may be needed to be effective and do not always guarantee complete drug release, especially of highly insoluble drugs (Newton and Razzo, 1974). Lerk et al (1978) also showed that the release of poorly soluble hydrophobic drug (hexobarbitone) from capsules can be improved by intensively mixing the drug with a small amount of a solution of a hydrophilic excipient (hydroxymethyl or hydroxyethyl cellulose) which produced microgranules after drying. A reduction in the contact angle and marked improvement in dissolution rate were achieved.

1.3.1.8 Adhesion

Determination of adhesion of powders

Adhesion forces are the attraction forces between faces of different materials (Molerus, 1980; Martin et al, 1983). As reviewed by Böehme et al (1962), weighing method, pendulum method, aerodynamic method and the centrifuge methods could be used to measure the adhesion forces of powder particles. However, the centrifuge method was described to be more advantageous in providing 'direct evidence on the adhesive forces between particles and between single particles and a substrate (Böehme et al, 1962). In the same study, centrifuge method was employed to measure the adhesive forces in starch-starch and iron-iron oxide systems. Booth and Newton (1987) modified the technique to determine the adhesive forces between pharmaceutical powders (polyethylene glycol 4000 (PEG 4000) and Sta-Rx 1500) and substrates of various materials including mild steel, stainless steel, dural, brass, perspex, PTFE. A similar method was later employed by Lam and Newton (1991, 1992a, 1992b, 1993) in the study of factors affecting adhesion of powder particles for pharmaceutical excipients on metal substrate. Schmidt and Walter (1994) investigated the cohesion behavior of powders and their adhesion to a carrier by an electronic tensiometer. Podczeck and Newton (1995) employed an ultracentrifuge technique to determine the adhesion and friction force of starch microspheres to flat compacted microcrystalline cellulose powder surfaces. The obtained results indicated the possible use of starch microspheres in powder mixtures with microcrystalline cellulose for tableting or capsule filling (Podczeck and Newton, 1995).

A more practical approach was employed by Tan and Newton (1990c, 1990d) in which they recorded the amount of powder adhering to a nozzle after use in capsule filling. This approach was used to study the influence of dosator wall texture during capsule filling process. In addition, a grading method was described by Patel and Podczeck (1996) to describe the observation of adhesion of powder coating on the nozzles during the filling process. Grade 0.0 for no coating, 0.5 for slight coating and 1.0 for strong coating.

Effect of adhesion and capsule formulation

The flowability of powders is related to the adhesion forces between the particles. The measurement of the adhesion forces between particles (e.g. by methods such as a modified annular shear cell) are often used as an indication of flow (Section 1.3.1.3). The knowledge of the autoadhesion forces between particles was also shown to be an indication of the flow properties of the powder (Podczeck et al, 1994). The adhesion forces between powder particles also affect the mixing properties of powders (Hersey, 1975; Schmidt and Walter, 1994; Podczeck et al, 1995). Adhesional force is one of the important element in order to achieve ordered mixing (Hersey, 1979). The lubrication effect of a lubricant is attributed by the reduction of friction between the particles and particles of the host powder and also between the host particles and metal surfaces as described by Staniforth et al (1993). Increasing conductance by incorporation of excipients such as Aerosil which aid to discharge the electrostatic adhesion between particles also improves powder flow (Gold and Palermo, 1965; Führer, 1996).

The adhesion between particles and metal surfaces such as the nozzle wall should also be emphasized. Neumaier (1991) pointed out that sticky powder mixtures and high compression force of the filling machine (dosing disc type) can cause deposits of filling material on the dosing and transfer pins of the filling machine and thus cause variation in capsule fill weight. In extreme cases, mechanical damage of the filling machine may have resulted.

Tan and Newton (1990b, 1990c, 1990d) studied the adhesion of powders to the nozzle wall of a capsule filling simulator and its effect on the capsule filling performance (represented by fill weight and weight variation). Both particle size and wall roughness of the nozzle have influences on the angle of wall friction and powder-wall adhesion. In cases where the ratio of the particle size to wall roughness is less than 1, the fine particles tend to be trapped in the surface irregularities. Therefore, both powder-wall and powder-powder friction contributed to the 'stickiness' of the powder at the nozzle wall. With increasing powder build-up at the nozzle wall, the angle of wall friction approaches the angle of effective friction of the powder. An increase in particle

size or having smoother wall would tend to decrease the angle of wall friction (Tan and Newton, 1990c). For powders which have little affinity to adhere to the nozzle wall (Starch 1500 and Avicel PH101), wall texture exerts only a minor influence on the capsule-filling performance (Tan and Newton, 1990d). Powder coatings and their losses behind the piston tip are main reasons for decreased fill weights and these problems are more pronounced with fine powders (Tan and Newton, 1990e). In the case of lactose, the nozzle and piston may also be jammed due to powder-wall adhesion. Jolliffe and Newton (1983a and 1983b) also highlighted the importance of dosator nozzle wall texture to the filling performance of lactose powders. By using a resurfaced nozzle, the capsule filling performance can be improved and an optimum surface texture exists for capsule filling. The correlation between powder retention ability within the nozzle and interaction with a wall surface was also studied by Jolliffe and Newton (1982a).

The adhesion of several pharmaceutical excipients to metal surfaces were studied by Booth and Newton (1987). It was shown that adhesion between polyethylene glycol 4000 (PEG 4000) or pregelatinised starch (Sta-Rx 1500) and metal increased when an external force was applied (by spinning in a centrifuge). The extent of increase was greater with PEG 4000 and therefore PEG 4000 was expected to be more liable to adhere to a surface than Sta-Rx 1500 (Booth and Newton, 1987). In another study, PEG 4000, starch 1500 (pregelatinised starch), spray-dried lactose, calcium carbonate was found to be the descending order of adherence onto stainless steel substrates among these four excipients (Lam and Newton, 1991).

1.3.2 Use of excipients

To formulate a drug substance into hard gelatin capsules, excipients are very often included such that the formulation would provide accurate dosage, good bioavailability characteristics and ease of capsule filling during production. Traditionally, excipients are considered to be the inert ingredients in the formulation which should not exert any therapeutic or biological action or modify the biological action of the drug present in the dosage form (Proudfoot, 1988). However, it is also recognized that excipient can potentially influence the rate and / or extent of absorption

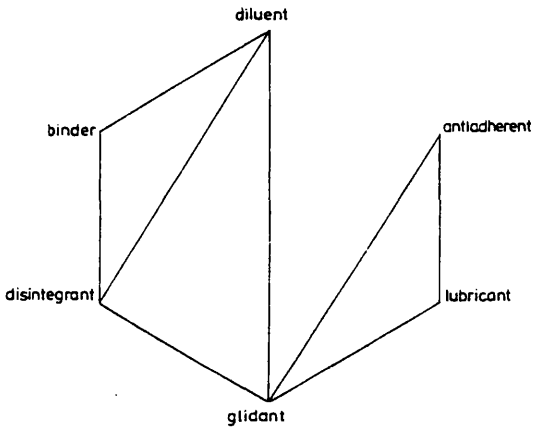
of the drug (Whithey and Mainville, 1969; Samyn and Jung, 1970; Newton et al, 1971a, 1971b; Newton, 1972; Newton and Razzo, 1974, 1977a, 1977b). IPEC-America produced another definition of an excipient. "Pharmaceutical excipients are any substance other than the active drug or prodrug which has been appropriately evaluated for safety and is included in a drug delivery to either : 1) aid processing of the system during manufacture, or 2) protect, support or enhance stability, bioavailability or patient acceptability, or 3) assist in product identification, or 4. enhance any other attribute of the overall safety and effectiveness of the drug product during storage or use." (Blecher, 1995). According to Blecher (1991), pharmaceutical excipients are the components of a formulation other than the active drug.

Generally, the types of excipients commonly incorporated in a powder or granule filled capsule formulation are diluent, disintegrant, lubricant, glidant, antiadherents, binder and wetting agent. Other excipients included antioxidant, preservatives, buffers stabilizers and absorption enhancers. Colourant is often found in the gelatin capsule shell but seldom included in the capsule content. A diluent is usually inert and is used as a filler to create the desired bulk, flow properties and compression characteristics in the preparation of capsules (Ansel et al, 1995b). A disintegrant promotes the disruption of the solid mass into smaller particles which are more readily dispersed or dissolved (Ansel et al, 1995b). A lubricant reduces the friction between powders and the metal components of machines during the capsule filling process and anti-adherent reduces powder metal adhesion and thus prevent the powder adhering to the dosing tube and piston, and the dosing disc and tamping finger. A glidant improves the flow properties of the powder mixture while a wetting agent improves the water penetration into the powder mass (Jones, 1994). A binder is used to cause agglomeration of powder particles in the granulation process (Ansel et al , 1995b) and thus formation of handling resistant granules. Stabilizers improve product stability. Buffers such as acidifying and alkalizing agents are used to provide a suitable pH level for product stability. Both an antioxidant and a preservative are sometimes included to prevent deterioration of the product due to oxidation process and growth of microorganisms or fungi (Ansel, 1995b). A review on antioxidant and preservative was also published recently (McEvoy et al, 1996). An absorption enhancer improves the

absorption of drugs which are usually practically insoluble and / or of low permeability in the gastrointestinal tract.

Newton et al (1971a and 1971b) indicated that the relationship between excipients were complex in terms of drug release. The effects of a diluent (lactose), a lubricant (magnesium stearate) and a wetting agent (sodium lauryl sulphate) on the formulation of ethinamate (a drug of solubility of 1 part of drug in 500 parts of water) was studied and it was found that the effect of one excipient was very often dependent on the presence and the level of the other two components. Jones (1977) also pointed out that the functions of excipients are often interrelated (Figure 1.8). For example, microcrystalline cellulose could be used as a diluent but also possesses disintegrant properties and some degree of lubricating effect (Omray and Omray, 1986).

Figure 1.8 : Interrelated excipient functions (Jones, 1977)



1.3.2.1 Diluent

The diluent for capsule formulations is chosen based on three criteria : the ability to form plugs at low compression pressures; the flow properties and solubility of diluent and drug (Jones, 1995). Numerous studies have also been performed for diluent in tableting and in some cases, the criteria of diluent chosen can also be applied to capsule formulations. Staniforth (1993) pointed out that tablet diluent should be strong

enough to withstand further processing and handling but yet able to deaggregate sufficiently quickly in contact with gastrointestinal fluid and release the drug into solution promptly and reproducibly and this would also be applicable to capsule formulation.

The powder mixture must provide the type of flow characteristics required by the filling equipment. Hostetler (1986) mentioned that for the Lilly, Parke-Davis, Höfliger and Karg, Osaka and Perry machines, powders must be free flowing and in the case of Zanasi, Macofar, Farmatic and mG2 equipment, the powder must have sufficient cohesiveness to retain its slug form during delivery to the capsule bodies. Hauer (1993b) also showed that powders, which can be filled with a dosator nozzle type of filling machine such as Zanasi machine, should be able to be filled in a tamp filling machine such as Höfliger and Karg machine. Therefore, if the drug is formulated such that it is fit to be filled by a dosator nozzle filling machine, a tamp filling machine can also be used. As described by Jolliffe and Newton (1982a), if a dosator nozzle type filling machine is used, the powder must be cohesive enough to be retained in the nozzle during the transference of the powder into the capsule bodies and yet free flowing enough to allow reproducible powder bed to ensure that the uniformity of weight and contents can be achieved. The diluents which can be incorporated to increase the cohesiveness of the powder mixture are microcrystalline cellulose, lactose and pregelatinised starch (Jones, 1985; Hostetler, 1986). Starch 1500 (pregelatinised starch) is also known to reduce the coating of a nozzle with consequential improvement in capsule filling performance as reviewed in Newton (1987b).

Unless the dose of drug is high, the particle size of the diluent often determines the flowability of the drug mixture. The relationship between particle size and flowability of drug mixture was described in Section 1.3.1.1. In most cases, the smaller the particle size, the more cohesive the powder is and poorer the powder flow is. Patel and Podczeck (1996) showed that the fine grade of microcrystalline cellulose (Avicel Ph105) should be avoided in capsule filling because of unsatisfactory flow properties. However, medium and coarse grade microcrystalline cellulose can be classified as a good capsule filling excipient. Lactose is also a commonly used diluent. Spray-dried

lactose is more free flowing than lactose monohydrate and anhydrous lactose (Banaker, 1994a).

Newton and Bader (1980) showed that there is an optimum combination of particle size fraction of drug (acetylsalicylic acid) and diluent (lactose) for maximum drug release. An increase in the level of lactose increased the dissolution rate and the extent of the increase depended on the proportion of lactose added and the particle size of lactose. This was probably due to the effect of particle size of the drug mixture on the powder packing. For example, for the larger and the smallest particle size fractions of acetylsalicylic acid (430, 330 and 64μm), 20% of 125μm lactose or 40% of 90 μm lactose gave optimum results whereas for intermediate drug particle size (250, 170 and 117 μm), it appeared preferable to incorporate the 94 μm or 65 μm fraction of lactose. Capsules containing 80% of lactose had a value of t_{50} (time to reach 50% of drug release) which was independent of particle size of drug or diluent.

The rate and / or extent of drug release can be greatly affected by the type of diluent used. A classic example is the outbreak of toxicity of phenytoin capsules in Australia (Tyrer et al, 1970; Bochner et al, 1972) due to the change of diluent from calcium sulphate dihydrate to lactose. Lactose is a soluble diluent while calcium sulphate dihydrate is insoluble. The rate of drug release was greatly enhanced by using lactose as a diluent. A more complex explanation was later found. It was shown that in presence of calcium sulphate, there is an increased faecal phenytoin excretion (Tyrer et al, 1970), in the other words, phenytoin is incompletely absorbed. Calcium sulphate may have been involved in suppressing the toxicity of the drug or reducing absorption by formation of insoluble calcium salt with phenytoin (Bastami and Groves, 1978). Replacement of lactose by maize starch increased the disintegration rate but reduced the drug dissolution (Bastami and Groves, 1978). The solubility of diluent and the possibility of the formation of an insoluble salt between the drug and diluent can therefore be influential in drug release of capsule formulation.

Samyn and Jung (1970) studied the influence of different excipients on the disintegration and dissolution of the capsules containing a drug of moderate solubility and no dominant hydrophobic or hydrophilic characteristics. It was shown that the

lubricant (magnesium stearate) and the filler (lactose or dibasic calcium phosphate dihydrate) had the greatest influence on the disintegration of the capsules. Slow dissolution of drug was obtained for formulations containing the insoluble dibasic calcium phosphate dihydrate and 2% magnesium stearate. The dissolution rate of drug increased if calcium phosphate dihydrate was replaced by the soluble lactose. Calcium phosphate dihydrate is insoluble and magnesium stearate is hydrophobic and therefore the water penetration into the powder mass is retarded, resulting in a reduction in dissolution rate.

In a study on the effect of additives on the release of drug from ethanimate capsules (Newton et al, 1971b), it was shown that 10% diluent (lactose) reduced drug release whereas inclusion of 50% lactose increased the release of drug. Later, Newton and Razzo (1974) performed a study on the *in vitro* release of drug from hard gelatin capsules as a function of drug (nitrofurantoin, nitrofurazone, oxytetracycline dihydrate and tetracycline hydrochloride), diluent (lactose, Primojel and Dry-Flow starch), level of diluent (20% or 80%), presence or absence of lubricant (magnesium stearate) and wetting agent (sodium lauryl sulphate). It was shown that a high level of diluent increased the drug release in many cases but not by a constant ratio even when lubricant and wetting agent were present. However, formulations containing tetracycline, a soluble drug, showed a decrease in drug release at higher level of lactose. Reduction of drug release of chloramphenicol capsule was also observed if the lactose content increased (Withey and Mainville, 1969). Frömming and Gröbler (1983) found that the addition of 80% of lactose to a hydrophilic drug (sodium salicylate) delayed drug release, compared to formulations containing a lower amount of lactose. This is probably due to the formation of viscous areas at the surface of the powder mass and thus impeding the release of drug (Frömming and Gröbler, 1983). For highly soluble drugs, larger percentage of starch (80% w/w/), could also decrease drug release (Newton and Razzo, 1977b). Therefore starch or Primojel should not be used for low dose, highly soluble drug. Increasing the level of lactose in the same capsule size, increased the density of the content and decreased the pore size between the particles. The ease of access of the dissolution medium to the powder mass was therefore reduced and resulted in a decrease in the dissolution, for example, the phenytoin capsules (Bastami and Groves, 1978). In contrast, Davies and Fell (1973), showed that the

presence of large quantities of diluent (50% w/w of lactose or maize starch) did not inhibit the release of the water soluble phenobarbitone sodium. Although a high level of lactose did not necessarily increase the drug release for a hydrophilic drug, a high level of lactose (> 50% w/w) did enhance drug release of the hydrophobic drug (phenobaribtone). A high level of maize starch also enhance release of the hydrophobic drug but not to the same extent as lactose. A high level of hydrophilic diluent such as lactose was considered to alter the hydrophobic nature of the powder bed and thus enhance drug release (Davies and Fell, 1973). Petrovick et al (1991), on the other hand, showed that replacing the diluent, microcrystalline cellulose, by lactose decreased the dissolution efficiency of capsules containing hydrochlorothiazide, a poorly soluble drug. Dissolution efficiency was defined as the area under the dissolution curve up to a certain time *t*, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time (Kahn, 1975). Although both fillers are hydrophilic, lactose is soluble in aqueous medium and microcrystalline cellulose is not. However, microcrystalline cellulose has good wicking action and a great capacity to incorporate water and thus increase the exposure of drug to the dissolution fluid. When lactose dissolved in the liquid medium, the presence of new molecules could influence the 'solubility product' of hydrochlorothiazide and resulted in a decrease in the dissolution rate (Petrovick et al, 1991). Daniel et al (1989) also obtained similar results. Capsule formulations of a slightly soluble drug (designated by a coded name, A^4, with a solubility of 0.8 mg/ml at 20°C), containing diluent of 100% lactose or 2:1 lactose : microcrystalline cellulose or 2 : 3 lactose : microcrystalline cellulose or 100% microcrystalline cellulose were compared. A formulation containing 100% lactose gave poor dissolution results at a slower paddle speed but the dissolution rate increased at faster paddle speeds. A formulation containing 100% microcrystalline cellulose provided a faster dissolution rate. Hannula et al (1989b) studied the effect of excipients on release of ibuprofen capsules. Spray dried lactose and dicalcium phosphate dihydrate, as the only excipients, were suitable for machine filling of the ibuprofen capsules, judged by good weight and content uniformity and rapid dissolution. However, in automatic filling, the use of 5% talc as a glidant together with dicalcium phosphate dihydrate or spray dried lactose would form permanent plugs and reduce content uniformity (Hannula et al, 1989b). The effectiveness of diluent was shown to be influenced by the drug, presence of lubricant and level of diluent. These

complicated relationships between the type and level of diluent, drug, lubricant and wetting agent were discussed by Newton and Razzo (1974).

Stewart et al (1979) studied the release of a low-dose (less than 1% w/w) drug (riboflavine) from hard gelatin capsules. The choice of diluent was shown to be fundamental for formulation of this drug. A hydrophobic diluent would hinder penetration of fluid into the powder mass but even with hydrophilic diluent which allowed penetration of fluid, subsequent deaggregation cannot always be completely assured. The interactive effect between diluents and hydrophobic lubricant (magnesium stearate) was obvious. A hydrophilic soluble diluent such as lactose, Primojel, sodium bicarbonate was not affected by the level of magnesium stearate present and can counter the hydrophobic nature of magnesium stearate. The average effectiveness of the diluents in that study, irrespective to level of magnesium stearate used was shown to be Primojel > sodium bicarbonate > Avicel PH 101≈ Dri-flo starch ≈ lactose >Emcompress ≈ kaolin >starch (Stewart et al, 1979).

The type of diluent used is also important in moisture sensitive drug. Desai et al (1994a) studied the effect of different types of lactose on the formulation of hydrochlorothiazide capsules. Hydrochlorothiazide is a moisture sensitive drug. The maximum decrease of drug release was found if Fast-flo lactose is used, followed by hydrous lactose (lactose monohydrate) and anhydrous lactose. Compared to hydrous lactose and anhydrous lactose, Fast-flo lactose contains the highest level of moisture. In the presence of moisture form the gelatin shell and excipient, hydrochlorothiazide underwent hydrolysis and formaldehyde was formed. The subsequent interaction of the formaldehyde with gelatin capsule shells and corn starch presented in the formulation led to formation of insoluble compounds. The amount of formaldehyde formed was found to be dependent on the type of lactose used. Banaker (1994a) also suggested that lactose monohydrate, which contains approximately 5% moisture, is a potential source of instability for moisture sensitive drugs. Maize starch contains up to 10% moisture (Banaker, 1994a) and is a moderately hygroscopic excipient (Callahan et al, 1982). The incorporation of maize starch should be avoided in formulation of moisture sensitive or hygroscopic drug. Since maize starch also exhibits hysteresis effects in its sorption cycle and the free surface moisture in maize starch may have a significant effect on

flowability of powder mixture, Jones (1977) emphasized the importance of drying starch excipients immediately prior to blending and filling, to ensure that subsequent storage did not permit resorption of surface moisture. York (1980) also suggested that for capsule formulations, starch must be equilibrated under specified humidity conditions, otherwise, moisture partitioning between capsule and content may occur. Sorbitol is very hygroscopic (Banaker, 1994a) and therefore should also be avoided in formulation of moisture sensitive or hygroscopic drug. To formulate a moisture sensitive drug, transfer of moisture into the capsule contents can be reduced if the moisture content of both capsule content and the capsule shells are at equilibrium (Section 1.3.1.6). The diluents chosen should also have minimum water uptake characteristics, for example, dicalcium phosphate or microcrystalline cellulose (Jones, 1985). The moisture content of microcrystalline cellulose is typically less than 5% w/w but varies with grade. It is, however, classified as a hygroscopic compound according to the Handbook of Pharmaceutical Excipients (Mathur, 1994; Callahan, 1982). Mannitol is a non-hygroscopic diluent (Banaker, 1994a) and can be offered as an alternative choice of diluent for moisture sensitive or hygroscopic drug. However, if the drug is deliquescent or strongly hygroscopic, Jones (1985) suggested that the drug should not be formulated as powder mixtures to avoid moisture transfer to and from the capsule shell which would result in a detrimental effect on the integrity of the capsule shells.

The type of diluent used can have a significant effect on the drug release from capsule formulations. However, the source of even the same type of diluent may also contribute to the difference in the filling performance and dissolution profile of the capsule product. Patel and Podczeck (1996) studied the interchangeability of different sources of microcrystalline cellulose in capsule formulation. Three groups of microcrystalline cellulose of different sources were identified. One group contained Avicel PH 102, Microcel, Emcocel; while Avicel PH 103, Avicel PH 101, Unimac MG-100 belonged to the second group with the last group containing Unimac MG-200. The first group has the lowest coefficient of fill weight variation, followed by the second group and then the third group. The performances of microcrystalline cellulose in different groups were not interchangeable. Diluent obtained from natural sources

such as maize starch also have variations in their properties (Farhadieth, 1994) and may affect the performance of capsule products.

Surveys of excipients used in marketed products and in industry have been performed by Jones (1995) and Shangraw and Demarest (1993) respectively. The survey performed by Shangraw and Demarest (1993) was in a form of questionnaires directed to 64 industrial companies whereas the one performed by Jones (1995) was from publications which contained information of marketed formulations from France, Germany and Italy. From the study performed by Shangraw and Demarest (1993), lactose monohydrate was the top choice of diluent in most companies (22 responses) in capsules. When lactose monohydrate is combined with anhydrous lactose, the preference for lactose as a diluent was even greater. Both microcrystalline cellulose and pregelatinised starch were preferred over maize starch. Jones (1995) categorized the diluents into sugar, starch, inorganic salts and organic compounds. Similar to the findings of Shangraw and Demarest (1993), Jones (1995) also observed that lactose was the most 'popular' diluent in the sugar group. Other diluents in the sugar group included mannitol, icing sugar, sucrose and glucose. The most widely used starch was pregelatinized maize starch. Inorganic salts including carbonates, phosphates, and silicates were also used but silicates (principally talc) were most frequently used. Organic salts (chiefly the celluloses), with microcrystalline cellulose being the most 'popular'. Combinations such as lactose and starch were also found. Correlation between the choice of diluent solubility and the solubility of drug was not observed. The proportion of insoluble diluents used with active drugs of low solubility was approximately the same as that for soluble drugs.

1.3.2.2 Disintegrant

Formerly, disintegrants were not included in capsule formulation because traditional disintegrant (normally used in tablet) are not effective for loosely compacted powder found in capsules. However, the situation changed with the introduction of newer disintegrants (super-disintegrant) which have the capacity to expand their volume to a much greater extent when wetted and are thus able to disrupt the loosely packed powder mass inside the capsule (Jones, 1995). Common disintegrants include starch,

modified starch such as sodium starch glycolate, modified cellulose such as croscarmellose sodium, microcrystalline cellulose, pregelatinised starch and alginates (Bandelin, 1989).

A number of studies were performed to study the effect of disintegrant on capsule formulations. According to Botzolakis et al (1982), some of these reports (for example Shah and Moore, 1970; Samyn and Jung, 1970; Goodhart et al, 1973) produced negative or mixed results and this was probably due to the fact that hand-filled capsules were involved. Hand-filled capsule are more porous than machine filled capsules and provided little compression of the content. Compressibility of the powder will affect the effectiveness of disintegrants. The porosity of the powder mass decreases as the compression increases. As the disintegrant particles swell, the reduction of porosity would increase the disruptive action of disintegrant. Therefore more studies were later performed using capsules which were filled using dosator-type automatic capsule filling machine, of which the capsule contents were actually compressed as in the practical situation (Botzolakis et al, 1982; Botzolakis and Augsburger, 1984; Botzolakis and Augsburger, 1988a, 1988b).

Higher levels of disintegrants are required in capsule formulations, compare to those commonly used in tableting. This is probably related to the high porosity of the powder mass and that a relatively larger proportion of the swelling of the disintegrant is necessary to accommodate for the voids in the powder mass before disintegration occurs. A minimum concentration is necessary to produce primary particles upon disintegration and significantly affect dissolution (Botzolakis and Augsburger, 1988a). 2% of sodium carboxymethyl cellulose (AcDiSol and CLD-2), sodium carboxymethyl starch (Explotab and Primojel) and cross-linked Polyvinylpyrrolidone (Polyplasdone XL) did not appreciably increase the dissolution of capsules containing hydrochlorothiazide (an insoluble drug). A concentration of 4% of AcDiSol dramatically enhanced dissolution whereas 4% Explotab appeared ineffective, however 6% Explotab did enhance dissolution (Botzolakis et al, 1982).

Cross-linked sodium carboxymethyl cellulose (croscarmellose) such as AcDiSol are more effective than sodium starch glycolate such as Primojel or Explotab. Cross-

linked Polyvinylpyrrolidone (crospovidone) such as Polyplasdone XL is relatively less effective and so is maize starch. Botzolakis and Augsburger (1984), Botzolakis and Augsburger (1988a and 1988b) showed that croscarmellose sodium was a more effective disintegrant than sodium starch glycolate, followed by Polyplasdone XL. DeBeukelaer et al (1985) also showed that 50% w/w of sodium starch glycolate is a more effective disintegrant than 50% w/w potato starch in the release of a model drug (phenacetin) in capsule formulation. These findings appeared to be in excess of the usual disintegrant levels and there may be other factors involved. Hannula et al (1989a) investigated the effect of disintegrants in drug release of ibuprofen from hard gelatin capsule and again croscarmellose sodium and sodium starch glycolate were found to be most effective. Explotab was comparatively less effective than Primojel, although both disintegrants are chemically the same (i.e. sodium starch glycolate). The difference in their performance may be due to difference in the raw-material starch or to differences in various manufacturing steps (Shangraw et al, 1980). The use of 10% of maize starch improved the dissolution of hydrochlorothiazide capsules by about two-fold (Botzolakis et al, 1982) but in some cases, it was reported that maize starch delayed the disintegration of capsules as well as the dissolution rate of the drug substance (Hannula et al, 1989b; Hauer, 1993b).

The mechanism by which these disintegrants produce their effect is complex and factors such as swelling, wetting and liquid penetration may also be involved (Botzolakis et al, 1982). It was observed that extensive swelling of disintegrant particles, rather than wicking action, was of primary importance for a disintegrant to be effective (De Beukelaer et al, 1985; Botzolakis and Augsburger, 1988a). Compacts containing AcDiSol (the most effective disintegrant) swell the most, and at a faster rate, followed by Primojel, Polyplasdone-XL and maize starch. However, the rate of wicking action was a possible limiting step in the rate and the extent of swelling of a disintegrant and hence hinder its efficacy in hard gelatin capsules (Botzolakis and Augsburger, 1988b). Maize starch compacts were found to wet completely and rapidly but only swell minimally. In addition, maize starch lost part of its wicking efficacy when included in an insoluble and hydrophobic matrix (Botzolakis and Augsburger, 1988b). Therefore, other mechanisms such as capillary action and / or slug softening

may contribute to its disintegration activity (Patel and Hopponen, 1966) and also mentioned by Rawlins (1977).

Other factors affecting the efficiency of disintegrants include compression force applied by the filling machine, level of lubricants, solubility of diluent and drug. As compression force increases, the porosity of the system decreased and, as the disintegrant particles swell, they will exert a more powerful disruptive action (Botzolakis and Augsburger, 1984). El-Shaboury et al (1993) also showed that the maximum effectiveness of disintegrants was obtained at higher compression pressure. At low compression pressure, higher levels of disintegrant were required to accelerate the disintegration and drug release. Correlation between effectiveness of disintegrant and porosity was also proposed by Couvreur et al (1974). According to Couvreur et al (1974), a disintegrant should be effective if the linear growth of the disintegrant particles during swelling is greater than the mean pore diameter in the powder bed. However, De Beukelaer et al (1985) showed that this theory does not seem to hold in the case of hard gelatin capsules, although marked swelling was observed for potato starch (disintegrant), and was more pronounced in powder beds with lower porosity. None of the capsules, with different porosities, containing potato starch, disintegrate within 120 minutes (De Beukelaer et al, 1985). Hauer (1993b) also pointed out that the experience of the disintegration process cannot be transferred from tablets to capsules because of the higher porosity of the capsule content.

Hydrophobic lubricants such as magnesium stearate often has deleterious effect on dissolution rate as mentioned in Section 1.3.2.3. Disintegrants appear to help to overcome the problem of poor wetting of powder mass at high lubricant concentration. However, at low lubricant level, the differences between various types and concentrations of disintegrants are minimized (Botzolakis and Augsburger, 1984). 2% and 4% AcDiSol levels in the 0.5% lubricant (magnesium stearate) system give similar dissolution profiles as found with 4% and 6% of AcDiSol in the 1% lubricant system. A lower disintegrant concentrations appeared to be effective when lower lubricant levels were used (Botzolakis et al, 1982).

The efficiencies of disintegrants decreased as the hydrophilicity of the capsule content increased. The efficiency of disintegrants was greater with capsules containing dicalcium phosphate (a less soluble diluent) than lactose (a more soluble diluent) (Botzolakis and Augsburger, 1984; Hannula et al, 1989a). However, when anhydrous lactose was used, the diluent tended to dissolve partially upon liquid penetration and increased the viscosity of the penetrating liquid and impeded release of drug. Disintegrants counteract this effect by promoting wicking and opening up the structure (Botzolakis and Augsburger, 1988a). Capsules containing a less soluble drug (hydrochlorothiazide) required a lower level of AcDiSol to exert similar increase in dissolution rate as capsules containing a more soluble drug (acetaminophen). The efficiency of disintegrant increased with decrease in solubility of drug (Botzolakis et al, 1982).

The pH of the dissolution medium also affects the efficiencies of disintegrants. The efficiency of Primojel, judged by liquid penetration and swelling, decreased in acid environment and therefore it may affect the *in-vivo* availability of drug. AcDiSol, however, had a faster disintegration rate in low pH whereas Polyplasdone-XL and starch showed no difference (Botzolakis and Augsburger, 1988b). However, in tableting, Gordon et al (1993) found that the superdisintegrant, regardless of the type used, usually facilitated faster dissolution in a neutral pH dissolution medium than in acidic pH medium.

Another area where the presence of disintegrant may play a role is its effect on dissolution rate of capsule products subject to exposure of increased humidity or temperature. Dahl et al (1991) studied the influence of disintegrant level and capsule size on dissolution of hard gelatin capsules stored in high humidity conditions. It was concluded that capsules of larger capsule size, containing 10 % or more of AcDiSol can withstand the stress of a high humidity storage condition. It was hypothesized that a water layer formed at the gelatin-powder blend interface may inactivate the disintegrant if the powder blend is highly compacted. In cases where a larger capsule size is used (no compaction and high porosity), the disintegrant may still be functional enough to aid in breaking up any agglomerates which may have formed, due to the high humidity exposure. Desai et al (1994a) also demonstrated the effects of different types of

disintegrants on dissolution stability of hydrochlorothiazide capsule formulations. Dissolution of hydrochlorothiazide capsules decreased after 6 months storage at 50°C, except in cases where crospovidone (Polyplasdone XL) was used as a disintegrant. The decrease in dissolution was due to the formation of a trace amount of formaldehyde from the hydrolysis of hydrochlorothiazide in the presence of moisture liberated from the excipients and the capsule shells. Polyplasdone XL improved the dissolution stability of the hydrochlorothiazide capsules owing to its moisture scavenging ability, which prevented the formation of formaldehyde and to some extent, its non-reactivity with formaldehyde.

Granulation processes are often employed in capsule formulation. The mode of incorporation of disintegrant in wet granulation process may influence drug release from capsules. An extragranular addition of a superdisintegrant (croscarmellose sodium) was shown to improve the dissolution rate of capsules containing a low dose water soluble drug (Katdare et al, 1990). Croscarmellose sodium was added just before lubrication. Several extensive studies which compare the effectiveness of varied lubricants have also been performed in the tableting area. Gordon et al (1993) investigated the effect of the mode of super disintegrants (sodium starch glycolate, crospovidone and croscarmellose sodium) on the dissolution of wet granulated tablets. The disintegrants were incorporated extragranularly or intragranularly or distributed equally between the two phases. Extragranular incorporation of disintegrants resulted in faster dissolution, compared to tablets containing disintegrants that were incorporated with equal distribution of intragranularly and extragranularly. Intragranular incorporation of disintegrant was found to be the least effective.

In terms of practical use of the different types of disintegrants, a clear preference for either starch or sodium starch glycolate or croscarmellose was shown in a survey performed by Shangraw and Demarest (1993). Similarly, Jones (1995) also indicated that sodium starch glycolate was one of the principal disintegrant used in the marketed formulations in France, Germany and Italy. Other substances including alginic acid, croscarmellose and crospovidone were also used. The range of level of sodium starch glycolate used in Italy varied from 1.9% to 22.3% with a median value of 3.6%.

The optimum concentration of disintegrants used in capsule formulation are not as widely documented as for tablet formulation. To provide a wide base of data, information concerning common concentrations of disintegrants incorporated in capsules as well as tablets are described. Higher levels of disintegrant are usually needed in capsule formulations (Botzolakis and Augsburger, 1988a). From the *Handbook of Pharmaceutical Excipients,* maize starch can be used as a tablet disintegrant at 3 - 15% (Farhadieh, 1994). In Bandelin (1989), 5 - 20% of starch USP can be used as a disintegrant in tablet granulation; whereas in Rawlins (1977), 2 - 10% is quoted. For sodium starch glycolate, concentration of 2 - 8% is usually employed in a formulation as suggested in the *Handbook of Pharmaceutical Excipients* (Banaker, 1994b) and Bandelin (1989). Croscarmellose sodium can be used as a disintegrant in capsules at concentration of 10 - 25% (0.5 - 5% in tablets) as quoted in the *Handbook of Pharmaceutical Excipients* (Weller, 1994). However, this level is relatively high compared to the results obtained by Botzolakis et al (1982) of which 4% and 6% were shown to be effective for hydrochlorothiazide capsules filled by an automatic filling machine. Crospovidone is quoted as a tablet disintegrant in the *Handbook of Pharmaceutical Excipients* for which a concentration of 2 - 5% was suggested (Strom, 1994). Similarly, 7 % of crospovidone was shown to improve the dissolution rate of hydrochlorothiazide capsules (Botzolakis and Augsburger, 1988a). Alginic acid can be used as a disintegrant (not specified for dosage form) at concentrations between 1 - 5 % (Haase and McGinity, 1994); whereas pregelatinised starch can be used as a tablet disintegrant at 5 - 10% (Lordi, 1994) as suggested in the *Handbook of Pharmaceutical Excipients.*

1.3.2.3 Lubricant

A lubricant is used in capsule formulation to reduce adhesion and friction between the dosing surfaces (the dosator piston or tamping finger tip) and other parts of the filling machines such as dosing walls or walls of the powder hopper (Jones, 1985). Many lubricants may also possess anti-adherant and glidant properties such as talc (Gold and Palmero, 1965; Dawoodbhai and Rhodes, 1990) and thus facilitate reproducible filling performance (Newton and Razzo, 1977a) and to minimize fill weight variation (Cole, 1987b).

Generally, lubricants can be described as hydrophobic lubricants and hydrophilic lubricants. The more common hydrophobic lubricants include stearates such as magnesium stearate, calcium stearate; stearic acid, talc and waxes. However, the use of talc is not as favourable due to the possibility of contamination with asbestos according to International Agency for Research on Cancer/World Health Organisation (1987). Asbestos is carcinogenic in humans. Sodium lauryl sulphate, magnesium lauryl sulphate, sodium stearyl fumerate, polyethylene glycol 4000 are examples of hydrophilic lubricants. Hydrophobic lubricants are usually more effective in reducing friction between host particles and metal surfaces than hydrophilic lubricant (Hölzer and Sjögren,1981; Abdou, 1989c). However, the incorporation of these lubricants will generally increase of hydrophobicity of the powder mass and could often decrease the disintegration and dissolution (Samyn and Jung, 1970; Newton and Razzo, 1974; Newton and Razzo, 1977b; Bastami and Groves, 1978; Petrovick et al, 1991) and slug hardness (Mehta and Augsburger, 1981) of capsule formulations. Desai et al (1993) replaced magnesium stearate with other hydrophobic lubricants such as calcium stearate and zinc stearate in capsule and tablet formulations of various drugs. Retardation of dissolution rate remained and similar results in dissolution rate were obtained. However, replacement of magnesium stearate by hydrophilic lubricants such as sodium stearyl fumarate did not slow dissolution. Similarly, Chowhan and Chi (1986b) showed that, compared to 0.5% magnesium stearate, 0.5% of sodium starch fumerate did not affect dissolution.

A lubricant can be considered to function by two mechanisms : fluid (or hydrodynamic) and boundary lubrication as described in Peck et al (1989) and Staniforth et al (1993). In the case of fluid lubrication, the two moving surfaces are viewed as being separated by a finite and continuous layer of fluid lubricants (lubricants of low melting point) such as oils or waxes, for example, paraffin and beeswax (Peck et al, 1989; Staniforth et al, 1993). Boundary-type lubrication is facilitated by solid lubricants which form "a uniform surface-adsorbed film in a manner similar to a Langmuir-type adsorption" (Shah and Mlodozeniec, 1977) on the granule or particle surface as proposed by Strickland (1956). The polar portions of the lubricant molecule with long carbon chains adhered to the metal surfaces of die wall (Peck et al, 1989).

Boundary-type lubricants are therefore more readily and firmly adhered to the interacting surface than fluid-type lubricants (Freeman, 1962) and are more effective (Peck et al, 1989). Magnesium stearate and sodium stearyl fumarate are examples of boundary-type lubricants (Bolhuis and Hölzer, 1996). Shah and Mlodozeniec (1977) also described that there are three different mechanisms of which the degree and extent of surface coverage of a substrate particle can be described, namely adsorption or surface contact adhesions; diffusion or solids penetration; and delamination or deagglomeration of lubricants to form a film coating on the substrate particles.

As mentioned in Bolhuis and Hölzer (1996), the powdered lubricant, submitted to a mixing action will either distribute as a free fraction or, when deagglomeration and delamination take place, as a surface film on the substrate. Prolonged mixing time will transfer more lubricant from the free fraction to the surface film. The degree of mixing and its effect on the formation of the hydrophobic lubricant film were reported by Bolhuis et al (1975) and further studies were performed by Lerk et al (1977a) and Lerk and Bolhuis (1977). Khalil and Ali (1972) mentioned that the difference between talc and magnesium stearate in their effect on dissolution rate of chloramphenicol capsules may be ascribed to a difference in the nature of the lubricant film formed around drug particles. Talc has insignificant effect on dissolution rate of chloramphenicol capsules whereas magnesium stearate has significantly suppressive effect, especially at a high concentration. Talc favours the formation of a discontinuous film compared with that produced by magnesium stearate (Khalil and Ali, 1972). In addition, in a review presented by Dawoodbhai and Rhodes (1990), the mechanism of talc to function as a lubricant was described to be based on its loosely bound lattice layers sliding over each other when placed between moving surfaces. An extensive review in the subject is also provided by Bolhuis and Hölzer (1996).

The effectiveness of various lubricants have been evaluated in a number of studies. Hauer (1993b) showed that magnesium stearate and Precirol (glycerol palmitostearate) were more effective lubricants than stearic acid in terms of filling and dissolution performance of caffeine capsules. Small and Augsburger (1978) also compared the effectiveness of different types of lubricants (magnesium stearate, stearic acid and magnesium lauryl sulphate) and their effects on the formulation by measuring

the ejection forces of an instrumented automatic capsule filling machine (Zanasi LZ 64) during the filling process. Three diluents (compressible starch, microcrystalline cellulose, and anhydrous lactose) were used. Compressible starch and microcrystalline cellulose required relatively low levels of magnesium stearate as compared to anhydrous lactose. In compressible starch , the performance of stearic acid and magnesium lauryl sulphate compared favorably with magnesium stearate. Studies performed relating to tableting also provide some indication of the effectiveness of lubricants. Eight lubricants were compared with magnesium stearate and stearic acid, by determination of the friction coefficients during tableting in a study performed by Hölzer and Sjögren (1981). Magnesium stearate was the most effective lubricant with lowest friction coefficients followed by sodium stearyl fumerate. Triglycerides and sugar ester which include microcrystalline stearic acid triglycerides (Dynasan 118), hydrogenated castor oil (Cutina HR), glyceryl palmitostearate (Precirol) and stearic palmitic sugar ester (Ryoto) and together with stearic acid formed the intermediate group. Sodium lauryl sulphate and magnesium lauryl sulphate followed behind but polytetrafluoroethylene (Teflon) was not effective. Sodium lauryl sulphate was more effective than magnesium lauryl sulphate. The deleterious effect in dissolution with prolonged mixing duration was most pronounced for magnesium stearate and triglycerides and the least for stearic acid, glyceryl palmitostearate (Precirol) and sodium stearyl fumerate (Hölzer and Sjögren, 1981). Delacourte et al (1993) investigated the use of various lubricants with lactose (Fast Flo lactose) or dibasic calcium phosphate dihydrate (Emcompress) as diluent based on determination of the upper punch force that could produce the 'jamming' of tableting machines. In both diluent systems, magnesium stearate was the most effective, followed by Precirol (glyceryl palmito-stearate) and Compritol 888 (glyceryl behenate) and Lubritab (hydrogenated cottonseed oil). Talc and then polyethylene glycol 4000 were less effective.

An optimum level of lubricant which provides the maximum efficiency and minimum deleterious effects would be ideal. Mehta and Augsburger (1981) observed that as the lubricant (magnesium stearate) level was increased from 0.05% to 1.5%, the t_{60} values first decreased to a minimum at about 1% concentration and then increased. The initial increase in dissolution with increasing lubricant level (from 0.05% to 1%)

may be due to reduced slug hardness, which could promote deaggregation and wetting of the capsule contents. However, in the presence of higher concentrations of magnesium stearate, the retarding effect exerted by the hydrophobicity of the lubricant eventually superseded the softening effect on capsule content (Mehta and Augsburger, 1981). In addition, the inclusion of a high level of lubricant may also prevent plug formation (Hauer, 1993b). As explained previously, plug formation is important during the filling process for a dosator nozzle filling machine in retaining the drug mixture in the nozzle when transferring into the capsule bodies. In addition, the drug release from the capsule formulations can also be affected by the concentration of the lubricant used. Samyn and Jung (1970) used 2% and 5% of magnesium stearate and found that 2% of magnesium stearate retarded dissolution of capsules. The drug release of chloramphenicol capsules was studied by Khalil and Ali (1972). At low concentrations, (0 - 3%) magnesium stearate produced a negligible change in dissolution as determined by speed 30 strokes/min. At speed 20 strokes/min, reduction of drug release from capsules containing 2 and 3% of magnesium stearate became more obvious. At 7.5 and 15%, magnesium stearate decreased the dissolution rate significantly. In another study, the *in vitro* diffusion rate of oxytetracycline hydrochloride from hard gelatin capsules was reduced at the presence of 1.4% of magnesium stearate and this effect was especially pronounced when 23% of magnesium stearate was incorporated (Mura et al, 1984). The retardation of dissolution rate in presence of several lubricants was studied using disks of equimolar mixture of aspirin and salicylic acid (Iranloye and Parrott 1978). It was found that increased in the concentrations of magnesium stearate, calcium stearate, glycerol monostearate or stearic acid decreased dissolution of the disks of an aspirin and salicylic acid mixtures. However the dissolution rates of these disks were independent of talc concentration, up to 5 %. Similar findings were reported by Khalil and Ali (1972). The incorporation of 0 - 15% of talc had insignificant effect on the dissolution of chloramphenicol capsules.

The presence of other excipients in the formulations should also be taken into considerations. Concentrations of 0%, 1% and 5% of magnesium stearate were employed in the study of drug release from ethanimate capsules (Newton et al, 1971b). If magnesium stearate was the only additive , the drug release was retarded; but in the presence of a wetting agent and a diluent, the effect of magnesium stearate was not

always predictable. These findings were again observed in a further study performed by Newton and Razzo (1994). In this study, 0% or 1% of magnesium stearate were used. The more usual effect of addition of magnesium stearate would be a decrease in drug release. However, in some cases, in the presence of high level of diluent, even when lubricant and / or wetting agents were incorporated, the drug release from capsules containing the insoluble drugs nitrofurazone and nitrofurantoin were actually greater. Petrovick et al (1991) also showed that hydrochlorothiazide capsule formulations containing 1% of magnesium stearate with no wetting agent (Polysorbate 80) resulted in the least favorable dissolution rate with depressed drug release. Formulations containing both magnesium stearate and wetting agent showed better dissolution efficiency. Wang and Chowhan (1990) revealed that addition of sodium lauryl sulphate in the solid state to magnesium stearate in 1 : 5 ratio can offset the deleterious effects of the lubricant in hand filled, uncompacted ketorolac tromethamine capsules. The formulation also contained crospovidone and spray dried lactose. Subject to prolonged mixing, drug-excipient interaction between magnesium stearate, starch, lactose and ketorolac tromethamine particles resulted in formation of drug-excipient agglomerates and caused retardation in drug release (Chowhan and Chi, 1985a & 1985b). The strong physical interaction between magnesium stearate and sodium lauryl sulphate during mixing, however liberated the magnesium stearate from the drug-excipient agglomerates and thus the capsule disintegrant and dissolution were not adversely affected (Wang and Chowhan, 1990).

In addition to the wetting agent, the diluent type and level should also be taken into consideration when determining the effect of lubricant on formulation performance. Samyn and Jung (1970) showed that capsules containing 2% of magnesium stearate and an insoluble diluent (dibasic calcium dihydrate) produced a slower dissolution rate compared to capsules containing same amount of lubricant and a soluble diluent (lactose). Newton and Razzo (1977b) showed that the addition of 1% magnesium stearate in the presence of 20% diluents (lactose, Primojel or starch), generally decreased drug release below the overall average. In the presence of 80% diluents, the presence of 1% magnesium stearate did not always reduce drug release. In formulations containing starch and nitrofurazone, the presence of 1% magnesium stearate produced a marked improvement (Newton and Razzo, 1977b). In some cases,

if a high level of diluent such as microcrystalline cellulose of good lubricity (Mathur, 1994) was used, it will not be necessary to include a lubricant in the formulation. Augsburger and Shangraw (1966) pointed out that microcrystalline cellulose flow sufficiently well by itself to allow the production of uniform tablets without lubricant. Similar practice should be able to be applied in capsule formulations which is compressed to a much lesser extent than tablet.

From the marketed formulations in several European countries, Jones (1995) pointed out that 80% of capsule products contain a lubricant. Magnesium stearate being the most frequently used lubricant. Other stearates such as calcium stearate, stearic acid, glyceryl monostearate, glyceryl palmitostearate and sodium stearate are also used. Dimethicone, hydrogenated vegetable oils, liquid paraffin, polyethylene glycol, sodium stearyl fumarate were also found by Jones (1995).

Lubricants are often used in both tablets and capsules. The data concerning common lubricant level used in both dosage forms are collected. In *the "Handbook of Pharmaceutical Excipients"*, magnesium stearate is used as a lubricant in capsule and tablet at 0.25% - 5% (Allen and Luner, 1994). However, Rawlins (1977) mentioned that 0.1-1% magnesium stearate can be used as external tablet lubricant while a concentration of 0.25% - 1% was quoted by Rubinstein (1988). Jones (1995) reported that the Italian capsule products contained 1.6% of magnesium stearate (median value) with a lower quartile of 1% and upper quartile of 2.7%. A concentration of 0.5-5% of glyceryl palmitostearate is reported to be used as tablet lubricant in the "*Handbook of Pharmaceutical Excipients*" (Armstrong, 1994). Delacourte et al (1993) showed that at concentrations of exceeding 1.25% and 1.5% of Precirol were needed for lactose and Emcompress systems respectively in tablets. Talc at a level of 1 to 10% was mentioned in "*Handbook of Pharmaceutical Excipients*" (Schirmer, 1994) as glidant or tablet lubricant but a much lower level (1 - 2%) was quoted by Rubinstein (1988), as tablet glidant or lubricant. Rawlins (1977) quoted 1 - 5% talc as an external lubricant for tablet and glidant. Delacourte et al (1993) pointed out that concentration exceeding 5% for lactose and Emcompress system tablets. Stearic acid of 1 - 3% and 0.1% - 2% can be used as tablet lubricant as mentioned in the "*Handbook of Pharmaceutical Excipients*" (Allen, 1994) and Rawlins (1977) respectively. Sodium stearyl fumerate is

used as a lubricant in capsule and tablet formulations at 0.5 -2 % (Surén, 1971; Hölzer and Sjögren, 1979, 1981 as reviewed in "*Handbook of Pharmaceutical Excipients*" (Davies, 1994)). Polyethylene glycol was mentioned to be used as tablet lubricant at 2 - 15% (Rawlins, 1977).

According to Jones (1995), some marketed formulations in Europe contained more than one lubricant but the details were not mentioned in the report. Magnesium stearate and talc are sometimes used in combination. Studies involving the use of both magnesium stearate and talc in tableting would provide some indication of their use in capsule formulation. Addition of talc has a positive effect to increase the lubrication of the powder mixture (Mechtersheimer and Sucker, 1986) and this was reviewed by Peck et al (1989) and Dawoodbhai and Rhodes (1990). However, magnesium stearate and talc would interact with each other if they are added together. Addition of small amounts of talc forces magnesium stearate out of cavities of material during the mixing process and hence promotes the film formation of magnesium stearate. This reduces the available amount of magnesium stearate and decreases the lubricating effect (Lerk and Sucker, 1988a & 1988b). It is therefore better to add magnesium stearate after talc is dispersed (Mechdtersheimer and Sucker, 1986). Mechtersheimer and Sucker (1986) also suggested by increasing talc concentration beyond 1% would also increase the lubricating effect by using 0.3% of magnesium stearate alone.

The sequence of mixing between magnesium stearate and colloidal silica is also important. The interaction between magnesium and colloidal silica (Aerosil) was reported in Lerk and Bolhuis (1977), Ragnarsson et al (1979), Johansson and Nicklasson (1986), Schrank-Junghäni et al (1984) as quoted in a review by Bolhuis and Hölzer (1996). In tableting, when the concentration of colloidal silica is equal to that of magnesium stearate or even higher, the glidant will have a significant effect on the lubrication properties. A well covered system between particles prevents particles from sticking together. Therefore there will be less bonding between the particles and thus resulting in weaker tablets. However, the positive effect is that the ejection force and the wall friction will also be decreased. These effects can be altered by changing the mixing time, sequence of mixing and concentration of magnesium stearate and colloidal silicon dioxide used. For example, mixing 0.1% magnesium stearate and 0.5%

colloidal silica simultaneously or mixing with 0.1% magnesium stearate after previously mixing with 0.5% colloidal silica, restored the bonding properties but increased of the ejection force as compared to tablets containing only 0.1% of magnesium stearate (Ragnarsson et al, 1979). Although these studies were based on the formulation of tablets, the implication that the strength of a slug will also decrease in capsule formulations containing high colloidal silicon dioxide added to magnesium stearate may apply.

The granulation process is often employed in capsule formulation. The lubricants are often incorporated extra-granularly in order to exhibit its functions i.e. to reduce friction between granules and dosing surface. According to Peck et al (1989), lubricants should be 200 mesh or finer and are passed through a 100-mesh screen before addition to the granulation (Abdou, 1989c; Peck et al 1989). This is due to the fact the lubricants function by coating, as mentioned before, with their effectiveness relating to their surface area (Peck et al 1989). The mixing of one minute would probably be adequate to distribute the magnesium stearate among the granules (Bolhuis and Hölzer, 1996).

1.3.2.4 Glidant or Anti-adherant

Glidants are often incorporated to improve flow characteristics of powders or granulations and tend to be used mainly in formulations that contain high dose of the drug (Jones, 1995). Münzel (1959) was believed to be the first person to employ the term "glidant" to designate agents which improve flow characteristics of granulation at low concentrations (Gold et al, 1966b). A glidant very often possesses lubricant (Danish and Parrott, 1971) and anti-adherent properties (Gold and Palermo, 1965) as well. However, it was also pointed out that materials which are good glidants are generally poor lubricants (Peck et al, 1989). The commonly used glidants include silica such as colloidal silicon dioxide, metallic stearate such as magnesium stearate, talc and others include starch, magnesia and calcium phosphate (Cooper, 1971; Pilpel, 1971).

The efficiency of different glidants were studied by a number of researchers. Gold et al (1966b) studied the effect of fumed silicon dioxide, magnesium stearate, maize starch and talc by using angle of repose method and by a recording powder flowmeter. Talc was shown to be a poor glidant which decreased the flow rate of calcium sulphate and aspirin crystals at all concentrations (0 - 5%). Maize starch increased the flow rate of both types of crystals at low concentrations (0.25%); but at higher concentrations of maize starch, the flow rate decreased. Magnesium stearate and fumed silicon dioxide increased the flow of both crystals. In contrast, Rudnic (1980) showed that magnesium stearate (0.5, 1 and 2 %) is a poor glidant by using a recording powder flowmeter. Although Gold et al (1966b) showed that talc decreased the flow rates of calcium sulphate and aspirin crystals, Reirer et al (1968) showed that the presence of talc acts to decrease the filled capsule weight variation, possibly by providing a more uniform powder flow. York (1975) applied powder failure methods to assess the effect of glidants on flowability of cohesive powders. It was shown that both magnesium stearate and talc were not as effective as colloidal silicon dioxide (Aerosil), judged by the flow factor and in terms of concentrations required to achieve maximum improvement in flowability, and that talc was the least effective among the three glidants. Augsburger and Shangraw (1966), investigated the effectiveness of glidant based on tablet weight and weight variation. It was found that all silica-type glidant (including pyrogenic silica, hydrated sodium silico-aluminate, amorphous non-gelled precipitated silica and silica hydrogel) improved the flow properties of microcrystalline cellulose as reflected in increased tablet weights and decreased weight variations. Pyrogenic silica and hydrated sodium silico-aluminate were the most effective while silica hydrogel was the least effective.

There are several mechanisms by which glidant improves the flowability of powders. The small glidant particles adhere to the surfaces of the larger host particles, smoothing out the irregularities and thus reducing the tendency to interlock during movement of flow (Pilpel, 1971). The reduction of interparticular friction and surface rugosity by glidant particles adhering to the surface of the host particles were also reported in Peleg and Mannheim (1972). The other mechanism, described by Bandelin (1989), was based on the ball bearing effect produced by glidant. Glidant particles rolled under shear stress and produced a ball bearing effect which caused the granules

to roll over one another and thus improve flow. Peleg and Mannheim (1972) also mentioned that removal of electrostatic charges on the surface of the host powder being another possible mechanism of glidants. Some glidants such as magnesium stearate and talc have anti-static properties but not all glidants do (Gold and Palmero, 1965). For example, fumed silicon dioxide has no antistatic properties (Gold and Palmero, 1965). In a study performed by York (1975), the possible mechanism of fine silica particles, magnesium stearate and talc were described. Fine silica particles adsorbed onto host particles and smoothed out the surfaces of the host particles, thus decreasing both friction and mechanical interlocking of particles during flow and replacing the host-host interactions at particle contact points by weaker glidant-glidant forces (York, 1975). Magnesium stearate functions as a glidant by accumulating in voids between hydrophilic host particles (Pilpel, 1970), thereby reducing interparticular friction and attractive forces between host particles. The mode of action for talc was proposed to be due to its laminar crystalline structure which rolls up into a spherical structure when subjected to the low shearing force (Train and Hersey, 1960).

The effectiveness of glidants is therefore dependent on the physical and chemical affinity between the glidant and host particles. As described above, glidants may exert their action by coating the host powder completely and smoothing out irregularities in their shape, therefore physical properties such as size, shape of both the glidants and host particles, the distribution of glidants and formulation components are of paramount importance (Pilpel, 1971). It has also been mentioned that the smaller the particle size of glidant, the lower the concentration of glidant is required to produce an increase in flow (Bandelin, 1989). A number of studies showed that glidant that exhibited excellent effectiveness are of very small particle size (Augsburger and Shangraw, 1966; Sadek, 1982). Bandelin (1989) also mentioned that silica type glidant is the most effective due to their small particle size. Owing to different propensities to coat the particles of the host powders, Varthalis and Pilpel (1977) also found that silica aerogels which act as a glidant for some powders (lactose and paracetamol) can also act as an antiglidant for others (oxytetracycline). Other physical factors including moisture content and electrostatic charge of the powder mixture, which affect the flow properties of powder mixture (Section 1.3.1.3) may also influence the effectiveness of glidants as described by Pilpel (1971) and Sadek (1982). In addition Burak (1966) also proposed

that hydrophilic glidant was more effective on hydrophobic powder and the opposite is true for hydrophobic glidants.

In a number of studies, it has been shown that glidants function at an optimum concentration above which it ceases to be effective and in some cases may act as an antiglidant (Pilpel, 1964; Gold et al, 1966b; Sadek, 1982). Gold et al (1966b) proposed that the optimum concentrations of glidants were 1% or lower. The glidants examined were fumed silicon dioxide, magnesium stearate, cornstarch and talc. Ito et al (1969) studied the effects of glidant (Aerosil) on lactose and maize starch capsules filled by a semi-automatic filling machine. Deviations of dose for capsules containing Aerosil decreased and the maximum effect of Aerosil was obtained between 0.1 -2 % whereas the maximum filled weights were observed at 0.1 - 0.5%. Augsburger and Shangraw (1966) showed that the more effective silica-type glidants (pyrogenic silica and hydrated sodium silico-aluminate) were effective at concentrations as low as 0.1% when added to plain microcrystalline cellulose and no increase in glidant activity was observed with concentrations greater than 0.5%. Danish and Parrott (1971) showed that maximum flow rate of lactose granules was obtained at 1% stearic acid, 0.7% hydgrogenated castor oil and 0.5% polyethylene glycol 4000 which can also act as a lubricant and even lower levels of glidant/lubricant were needed for sodium chloride particles. Sadek (1982) pointed out that including an excessive amount of glidant would cause extremely high surface energy of glidant particles. The force of interparticulate attraction may supersede the frictional force between host particles and thus decrease the flowability of the powder mixture. In addition, Hannula et al (1989b) showed that, the incorporation of 5% of talc as a glidant worsened the content uniformity and that combining talc with dicalcium phosphate dihydrate and spray dried lactose would result in the formation of permanent plugs. The optimal talc concentration to improve flow was reported to be about 0.5% (Gold et al, 1968b) based on powder flow study using recorded powder flowmeter and 2% (Hammerness and Thompson, 1958; Kristensen and Jensen, 1969; York, 1975) using shear cell studies. Mathematical derivations, for example proposed by Jones and Pilpel (1965) and Sadek (1982), were also used to estimate the optimum glidant concentration which would provide maximum flow. The equations proposed by Jones and Pilpel (1965) were based on diameters of glidant and host particles while the one proposed by Sadek were

based on diameters and bulk densities of glidant and host particles. Both equations assumed spherical particles.

In practice, the two main glidants being used in Europe (France, Germany and Italy) are colloidal silicon dioxide and talc (Jones, 1995). The other materials used are silicates which include calcium silicate, magnesium silicate and magnesium trisilicate. In Italian formulations, 0.9% and 3% are the median amount of colloidal silicon dioxide and talc used respectively.

The common levels of glidants used in capsules and tablets are widely available in the literature. In the *Handbook of Pharmaceutical Excipients*, a concentration range between 0.1 - 0.5% of colloidal silicon dioxide can be used as glidant (Harpaz, 1994). The same concentration range is also quoted by Rawlins (1977) and Rubinstein (1988) as a glidant in tablet formulations. However, a slightly higher concentration (1-3%) was suggested by Peck et al (1989), as glidant in tablet formulations. Compare to colloidal silicon dioxide, talc is used at a higher concentration as glidant. In the *Handbook of Pharmaceutical Excipients*, a concentration range between 1 - 10% is suggested (Schirmer, 1994). A concentration of 5% of talc is recommended by Peck et al (1989); 1-2% by Rubinstein (1988) and 1-5% by Rawlins (1977) as tablet glidant.

1.3.2.5 Wetting agent

Wetting agents can be described as surfactants that are adsorbed at the liquid / vapour and solid / liquid interfaces and function by reducing the interfacial tension (Kayes, 1988) and thus improving liquid penetration into the powder mass contained in capsules. They are very often included in capsule formulations to overcome the deleterious effect exerted by hydrophobic compounds included in the formulations (Jones et al, 1988). The non-ionic surfactant, polysorbate 80 and the anionic surfactant, sodium lauryl sulphate are examples of commonly used wetting agents. However, polysorbate 80 is less popular for capsule formulations because of autoxidation of polysorbate 80 which results in formation of formaldehyde and denaturation of inner surface of the capsule (Chafetz et al, 1984). In addition, sodium lauryl sulphate is also

toxic with acute toxic effects including irritation to the skin, eyes, mucous membranes, upper respiratory tract and stomach (Behn, 1994).

Aguiar et al (1967) showed that incorporation of 0.5% of "polyol surfactant" in tightly packed capsules containing benzoic acid greatly improved their dissolution rate by increasing the deaggregation rate of the powder mass. Benzoic acid is a poorly soluble compound. Daniel et al (1989) showed that incorporation of a wetting agent (sodium lauryl sulphate) increased the dissolution rate of capsules containing a slightly soluble drug. The observation was explained to be attributed to the increase in the rate at which the solvent penetrated the solid mass in presence of the wetting agent, thereby increased its effective surface area and ultimately the dissolution rate. Petrovick (1991) demonstrated that capsule formulations containing magnesium stearate (hydrophobic lubricant) and no surfactant had poor dissolution rate while formulations that contained a surfactant (polysorbate 80) had a relatively high dissolution rate.

As described by Samyn and Jung (1970), liquid penetration is very often the limiting factor in the dissolution process. Formulations that allows no liquid penetration have poor dissolution (Rowley and Newton, 1970). However, Rowely and Newton (1970) suggested that wetting may not be the controlling feature of the drug release from capsules. Khalil and Ali (1972) also agreed that evaluation of liquid penetration through powder bed was not a good measurement of dissolution, although a qualitative correlation between the two measurements did exist. Rowley and Newton (1970) also emphasised that the presence of a wetting agent readily promoted liquid penetration but not necessarily assist dissolution. The liquid penetration test can help in the screening of wetting agents but its extension to the prediction of drug release from capsules may not be possible. Newton et al (1971a) showed that the release of ethinamate, a poorly soluble drug, was improved in the presence of a wetting agent and the higher level of wetting agent produced a higher increase. Nevertheless, Newton and Razzo (1974) also showed that addition of 1% of sodium lauryl sulphate did not provide a major enhancement of drug release from capsules containing poorly soluble drugs (nitrofurantoin or nitrofurazone) and in some cases can be detrimental. The addition of sodium lauryl sulphate actually reduces drug release from capsules containing water-soluble drugs (oxytetracycline or tetracycline) (Newton and Razzo,

1974). Newton (1987b) also explained that sodium lauryl sulphate dissolves with swelling and thus may retard penetration in the 'wetting test' but aid disruption of capsules in the dissolution test. Newton and Razzo (1977a and 1977b) highlighted that the effect of the wetting agent may also be influenced by the level of diluent and the presence of other excipients such as hydrophobic lubricants in the formulation. The interaction between sodium lauryl sulphate and magnesium stearate which resulted in increase in drug release from ketorolac tromethamine capsules (Wang and Chowhan, 1990) were described in Section 1.3.2.3. Newton and Razzo (1977a) showed that the effect of diluent on drug release was greater than wetting agent. The hydrophilic nature of lactose appeared to promote greater dissolution of drug than the wetting effect of sodium lauryl sulphate. For formulations containing 0 - 40% of lactose, the presence of sodium lauryl sulphate was detrimental to drug release (Newton and Razzo, 1977a).

In cases where the addition of wetting agent is advantageous, a low concentration of the adjuvant would be adequate. Newton et al (1971b) showed that 1% of sodium lauryl sulphate is sufficient to enhance the drug release of ethinamate capsules. Jones et al (1988) suggested that the deleterious effect on drug release caused by the presence of the hydrophobic compounds can be overcome by an addition of 0.1 - 0.5% of wetting agents (type not specified). Daniel et al (1989) showed that the addition of 0.75% of sodium lauryl sulphate to Fitzmilled drug, increased the dissolution of capsules containing a slightly soluble drug. However, a 1% level caused a significant decrease in dissolution, probably due to the fact that the critical micelle concentration of sodium lauryl sulphate had been exceeded. In such case, the excess sodium lauryl sulphate would not be adsorbed at the interfacial surface, but remained in the liquid where these molecules aggregated to form micelles and thus resulted in an increase in the percentage of undissolved drug. A similar effect was observed with micronized drugs. However, a slightly higher level of sodium lauryl sulphate was needed to produce similar observations. A level of 1% of sodium lauryl sulphate produced an improvement of drug release in this case and 1.5% of the wetting agent was detrimental to drug release (Daniel et al, 1989). In the *Handbook of Pharmaceutical Excipients*, a concentration of 1-2% of sodium lauryl sulphate was quoted to be used as wetting agent in dentrifices (Behn, 1994). In the marketed capsule formulations in Italy, a range of 0.05% - 5% (median value 0.26%) of sodium lauryl

sulphate was used (Jones, 1995). In the case of polysorbate 80, a concentration of 0.1 - 3% is suggested in the *Handbook of Pharmaceutical Excipients* (Leyland, 1994).

In practice, less than 20% of marketed formulations in Europe (France, Germany and Italy) contain a wetting agent (Jones, 1995). The main wetting agent used is sodium lauryl sulphate but others such as lecithin, polysorbate 80, polyoxyethylene stearate and sorbitan mono-oleate are also found to be used as wetting agents. Polyethylene glycol 6000 is believed to be used in some of these formulations as both a wetting agent and a lubricant (Jones, 1995).

1.3.2.6 Binders

Capsules can be filled not only by powders but also by granules. Binders are often used as adhesives to hold particles together in the production of granules and are most widely used in the process of wet granulation (Drummond, 1996). Binders are intended to function in the 'particulate binding' giving the granule its strength (Symecko and Rhodes, 1995).

Binders are either sugars or polymeric materials (Bandelin, 1989). One of the most common way to classify binders is by their chemical origin (Symecko and Rhodes, 1995). Based on this classification, Symecko and Rhodes (1995) divided the binders into three different categories: natural, semisynthetic or synthetic. Natural binders include acacia, alginic acid, gelatin, guar gum, magnesium aluminium silicate, sodium alginate and Zein. Pregelatinised starch, dextrin, liquid glucose and cellulose byproducts such as carboxymethylcellulose, ethylcellulose, hydroxypropylcellulose (HPC), hydroxypropyl methylcellulose (HPMC), methylcellulose are examples of semisynthetic binders and synthetic binders include polymethacrylates, polyethylene glycol and polyvidone (PVP) (Symecko and Rhodes, 1995). In addition, Drummond (1996) suggested that an ideal binder should be a good adhesive and be easy to handle; should be free-flowing and easily dispersible in the granulating liquid.

The method of binder addition may influence the wet granulation process (Symecko and Rhodes, 1995). As reviewed in Kristensen and Schaefer (1987),

distribution of the binder into the drug mixture in a dry state before wetting may reduce the granule size and increase the content of lumps due to the possibility of inhomogeneous distribution of the binder. Therefore, binders are normally dissolved in the granulating liquid before the granulation process begins (Kristensen and Schaefer, 1987). However, granulation can proceed without the inclusion of binders into the granulating liquid (Symecko and Rhodes, 1995).

According to Drummond (1996) the type of binders used, the solubility of binders and properties of binder solution such as its surface tension and viscosity as well as type of mixers and granulators used would also affect the size and strength of the granules. Drummond (1996) also described that the viscosity of aqueous solution of PVP was highly dependent on the molecular weight of the polymer. With lower molecular weight of PVP such as Plasdone K25 and Plasdone K29/32, a drastic increase in the viscosity of the binder solution was not observed until concentration of the polymer exceeded 40% w/w whereas with higher molecular weight of PVP such as Plasdone K90, an increase in the viscosity of the binder solution was observed at concentration greater than 10% w/w. Ritala et al (1986) compared different binders (Kollidon VA 64(PVP), Methocel E 5 (HPC), Methocel E 15 (HPC) and Kollidon 90 (PVP) and Protein S (hydrolysed gelatin)) in a high shear mixer. Kollidon 90 has high surface tension and stronger mobile liquid bonds than other binders and thus resulted in decrease in intergranular porosity, higher liquid saturation and therefore less granulation liquid was required. Compared to other binders, the use of hydrolysed gelatin gave rise to granule growth at a lower liquid saturation and this was probably due to gelation of the solution (Ritala et al, 1986). As reviewed in Kristensen and Schaefer (1987), gelatin also gave rise to larger granule size than low molecular types of PVP; and in cases where fluidised bed granulators were used, the growth rate of granules was dependent upon the droplet size of the binder solution. The surface tension and viscosity of the binder solution would affect its droplet size. In a high speed mixer, the type of binder and the viscosity of binder solution seem to be of less importance (Kristensen and Schaefer, 1987).

The dissolution of drugs from capsules can also be increased by intimate mixing of the drug with a solution of the hydrophilic material, following by drying to give

minigranules, which in turn reduce the contact angle of the drug mixture (Newton, 1987a). By granulating griseofulvin with a solution of HPC, the drug release (assessed by dissolution and urinary excretion of the major metabolite) was increased (Fell et al, 1978). Kwong et al (1994) showed that PVP-granulated solid had a superior absorption when compared with dry, ungranulated filled capsules containing a poorly water soluble drug. In tableting, it was reviewed by Drummond (1996) that acetaminophen tablets granulated in a high-shear mixer with PVP (Plasdone K90) had faster disintegration and dissolution compared to tablets containing HPC and gelatin as binder.

Polyvinylpyrrolidone (PVP) is a versatile polymeric binder. PVP is usually used in either an aqueous solution or alcohol but it can also act as a dry binder (Banker and Anderson, 1986). As suggested by Bandelin (1989), generally it is better to granulate insoluble powders with aqueous or hydroalcoholic solutions of PVP and to granulate soluble powders with PVP in alcoholic solution. Anhydrous ethanol should be used to prepare the alcoholic solution and anhydrous isopropanol should not be used as a trace of its odor would remain in the granules for a long time (Bandelin, 1989). According to the *Handbook of Pharmaceutical Excipients*, a concentration of 0.5 - 5% of PVP was a common level of binder used in granulation process (Walkling, 1994). However, a level of 2-10% in granulation fluid and 5 -20% aqueous, alcoholic or hydroalcoholic solution have been quoted by Rubinstein (1988) and Bandelin (1989) respectively.

Gelatin solutions have been extensively used in the past as a binder but they have been replaced by various synthetic polymers such as PVP. In addition, the gelatin solutions also serve as culture media for bacteria and moulds unless a preservative is incorporated (Bandelin, 1989). Generally, 2 - 10% of aqueous solution of gelatin can be used as a binder in wet granulation (Bandelin, 1989). A similar suggestion of 5-20% of gelatin in granulating fluid was quoted in Rubinstein (1988).

Methylcellulose can be used to granulate both soluble and insoluble powders although it is a better binder for soluble excipients such as lactose, mannitol and other sugars (Bandelin, 1989). The concentration of binding solutions would depend on the viscosity grade of methylcellulose. A concentration of 2 - 10% aqueous solution is

quoted in Bandelin (1989) while a similar concentration of 2 - 6% is suggested in the *Handbook of Pharmaceutical Excipients.*

Hydroxypropyl methylcellulose (HPMC) is also available in various grades which vary in viscosity and extent of substitution. A concentration of 2 - 5 % may be used as a binder in either wet or dry granulation processes (Harwood and Johnson, 1994). Hydroxypropyl cellulose (HPC) can also be used as a binder in either wet granulation or dry compaction. Generally a concentration between 2-6% is used (Harwood and Johnson, 1994). In general, modified celluloses provide binder capabilities when used dry and can be used as adhesive in their aqueous solutions (Banker and Anderson, 1986).

Traditionally, starch in the form of starch paste was the most frequently used binder (Banker and Anderson, 1986). A concentration of 5-10% of aqueous pastes is usually incorporated (Bandelin, 1989). Pregelatinised starch 5-10% in aqueous solution is recommended by Bandelin (1989) and Lordi (1994) as binder in wet granulation. According to the *Handbook of Pharmaceutical Excipients*, alginic acid can be used as a binder for tablet and capsule formulation at a concentration of 1-5% (Haase and McGinity, 1994).

1.3.3 Incompatibilities : drug, excipients and gelatin

According to Racz (1989), incompatibilities are "undesired physical, chemical, colloidal or biopharmaceutical processes which take place during the preparation, storage or administration of the drug product resulting in an undesirable or unfavorable effect on the organoleptic properties or efficacy of the drug preparation." There are several techniques by which interactions between drug and excipients, can be detected. Techniques such as diffuse reflectance (Lach and Bornstein, 1965; Pope and Lach, 1975), thin-layer chromatography and infrared spectrometric techniques (Kassem et al, 1979), thermal analysis including differential thermal analysis (DTA) (Jacobson and Reier, 1969) and differential scanning calorimetry (DSC) (Botha et al, 1986b) can be applied to study solid state stability and provide information about possible interactions (Botha and Lötter, 1989b). In addition, fluorescence spectroscopy and high

performance liquid chromatography (HPLC) methods were employed by Lessen and Zhao (1996) to study the interactions between hydralazine hydrochloride and starch. Hartauer and Guillory (1991) compared the DSC method and diffuse reflectance Fourier transform infrared spectroscopy (FT-IR) in the study of interaction between aminophylline and lactose. It was found that DSC thermograms could be used to predict the occurrence of interaction between the two compounds but FT-IR could provide more insight into the nature of the interaction. Isotherm stress testing together with thermal analysis (DSC) were performed by Dürig and Fassihi (1993) in their study of stabilizing and destabilizing effects of drug-excipient interaction of pyridoxal hydrochloride. Routine drug-excipient interaction studies by DSC and isothermal stress test and guidelines in interpreting the thermograms were also presented by Dooren (1983). Based on the results obtained from the DSC and the isothermal stress test, excipients that showed no indications for incompatibilities with the drug are the first choice in the design of a tablet or capsule formulation (Dooren, 1983). However, in formulation of hard gelatin capsules, compatibilities between the capsule content and gelatin shells are as important as compatibilities between the different ingredients contained in the capsules.

1.3.3.1 Crosslinking of gelatin capsules

The potential of crosslinking between capsule content and gelatin is a possible cause for problems in *in vitro* or *in vivo* performance of capsules (Carstensen and Rhodes, 1993; Digenis et al, 1994). The chemistry of gelatin crosslinking is described in details in Digenis et al (1994). The reactive side-chain groups of gelatin consist of amino, carboxyl, and hydroxyl groups, of which the amino groups such as lysine have the most reactivity (Jones, 1987d). There are two common ways of which crosslinking within the gelatin polypeptide occur : by bridging within the same polypeptide strand (intramolecular crosslinking) or between the amino acid residues from two neighboring peptide strands (intermolecular crosslinking) (Digenis et al, 1994). Gelatin is known to cross-link with aldehydes, imines and ketones and at times give rise to the formation of a water-insoluble gelatin film, referred to as a pellicule, during dissolution test. This thin, tough film does not disrupt easily by gentle agitation and can act as a barrier in drug release and result in reduction in dissolution rate of capsule formulations

(Carstensen and Rhodes, 1993). However, the film can be rapidly digested by pepsin and hence presents no problem in enzyme-containing dissolution medium (Carstensen and Rhodes, 1993). Digenis et al (1994) suggested that for *in vitro* dissolution tests of hard gelatin capsules should be performed in two stages prior to *in vivo* evaluation. These two stages are first, dissolution in a medium without enzymes and secondly dissolution in a media containing enzymes (pepsin at pH 1.2 and pancreatin at pH 7.2, representing gastric and intestinal media respectively).

The presence of particular drugs or excipients in the capsule formulation may lead to crosslinking with the gelatin shell. Murthy et al (1989) showed that gemfibrozil, hydrochlorothiazide and diphenhydramine hydrochloride when stored under high humidity underwent conformational change and crosslinked with gelatin. However, Chafetz et al (1984) showed that the film-forming gemfibrozil capsules (where crosslinking occur) were bioequivalent to the readily dissolving gemfibrozil capsules even though the former showed a significant decrease in dissolution rate in the *in vitro* test. Dahl et al (1991) showed that gelatin-coated acetaminophen tablets when stored at high humidity for 3.5 and 7 months showed significant reduction in *in vitro* drug release in cases where the dissolution medium is deionized water. However, such reduction in drug release was not observed when 1% aqueous pancreatin solution was used as dissolution medium. Mohamad et al (1986, 1987) showed that the *in vitro* dissolution of hard gelatin capsules containing tetracycline hydrochloride subsequent to storage of 42 months at ambient temperature was decreased while no differences in the bioavailability of the antibiotic were observed *in vivo.* Hard gelatin capsules that contained etodolac and stored at high temperature (40°C) and high humidity (75% RH) failed the dissolution tests in phosphate buffer (pH 7.5) but met the dissolution specifications (not less than 85% drug release in 30 minutes) when tested in phosphate buffer (pH 7.5) containing 1% w/v pancreatin (Dey et al, 1993).

In terms of excipients, as reviewed in Digenis et al (1994), maize starch may contain traces of the stabilizer hexamethylenetetramine which decomposes under humid conditions to form ammonia and formaldehyde. The formaldehyde may thus crosslink with gelatin and retard *in vitro* dissolution rate. The presence of polysorbate 80 decreased the *in vitro* dissolution rate of gemfibrozil capsules stored under high-

humidity conditions (Chafetz et al, 1984). This was probably due to the formation of formaldehye resulting from autoxidation of Polysorbate 80. Autoxidation of polyethylene glycols, some plasticizers and preservatives can also lead to formation of aldehydes and reaction with gelatin to form insoluble crosslinked products resulting in reduction of dissolution rate (Carstensen and Rhodes, 1993; Digenis et al, 1994). The interaction of gelatin with four monosulfonated or monocarboxylated azo dyes (acid azo dyes) and the effects on properties of gelatin in the solution, gel and solid states were also investigated by Gautam and Schott (1994). In addition, gelatin capsules packaged in bottles containing rayon coilers which contained aldehyde furfural also lead to reduction in dissolution rate (Hartauer et al, 1993).

In vitro drug release can be significantly influenced by the possibility of crosslinking between capsules content and gelatin shells and also by the type of dissolution medium used. Therefore in capsule formulation, special attention should be paid to the purity and chemical reactivity of the excipients that are to be encapsulated in a gelatin shell.

1.3.3.2 Drug-excipient and / or excipient -excipient interactions

The compatibility data of existing drugs are very often recorded in the monographs in publications such as *European Pharmacopoeia* or *Merck Index.* The *Handbook of Pharmaceutical Excipients* also provides a good review on incompatibilities for different excipients. According to the *Handbook of Pharmaceutical Excipients*, amorphous lactose (including spray-dried lactose but not crystalline lactose) would react with a primary amine group to form brown-colored products (Castello and Mattocks, 1962). This reaction can be accelerated in the presence of alkaline lubricants (Goodhart, 1994). Lactose is incompatible with amino acids, aminophylline (Hartauer and Guillory, 1991) and amphetamines (Blaug and Huang, 1972). Oxprenolol hydrochloride was also shown to interact with lactose (type not specified) (Botha and Lötter, 1989b). Dürig and Fassihi (1993) also showed that pyridoxal hydrochloride was not compatible with anhydrous lactose. Microcrystalline cellulose is incompatible with strong oxidizing agents (Mathur, 1994). Starch and pregelatinised starch have no recorded incompatibilities according to the *Handbook of*

Pharmaceutical Excipients (Farhadieh, 1994; Lordi, 1994) but maize starch was shown to be incompatible with pyridoxal hydrochloride by Dürig and Fassihi (1993). Desai et al (1994c) showed that under storage conditions of high humidity, hydrochlorothiazide may undergo hydrolysis which lead to formation of formaldehyde. Indeed, formaldehyde is a very reactive substance which can cross-link with starch or starch derived compounds (*Merck Index*, 1976). Interaction between hydralazine hydrochloride and starch (type not specified) in tablet formulations was also studied by Lessen and Zhao (1996). According to the *Handbook of Pharmaceutical Excipients*, there is no reported incompatibilities with mannitol in the dry state. However, Dürig and Fassihi (1993) showed that mannitol would interact with pyridoxal hydrochloride.

In terms of the more commonly used disintegrants, croscarmellose sodium was found to be less effective if wet granulated in presence of hygroscopic excipients such as sorbitol (Johnson et al, 1991). Hollenbeck (1988) also showed that the drug-excipient interaction between croscarmellose sodium and a weakly basic drug (phenylpropanolamine hydrochloride) was observed in *in vitro* dissolution test where distilled water is the dissolution medium. This interaction, however, did not adversely influence the bioavailability of phenylpropanolamine hydrochloride from a solid dosage form containing croscarmellose sodium (Hollenbeck, 1988). Sodium starch glycolate is incompatible with ascorbic acid (Botha et al, 1987). Desai et al (1994c) also showed that formation of formaldehyde, due to hydrolysis of hydrochlorothiazide subjected to storage under high humidity, may lead to subsequent reaction with Primojel (sodium starch glycolate). This resulted in formation of an insoluble product and thus caused reduction in disintegration power of Primojel and decrease drug release from the formulation (Desai et al, 1994c). Alginic acid is incompatible with strong oxidizing agents and would form insoluble alginate salts in presence of alkaline earth metal and group III metals (except magnesium) (Haase and McGinity, 1994).

Magnesium stearate is not compatible with strong acids, alkalis and iron salts and should not be mixed with strong oxidizing materials (Allen and Luner, 1994). Therefore it is inappropriate to place magnesium stearate and alginic acid (disintegrant) in the same formulation even though alginic acid is not a strong acid. Combination of magnesium stearate and stearic acid (lubricant) should also be avoided for the same

reason. Magnesium stearate was also shown to be incompatible with oxprenolol hydrochloride (Botha and Lötter, 1989b). Talc is incompatible with quaternary ammonium compounds (Schirmer, 1994). Stearic acid was found to be incompatible with most metal hydroxides and probably with oxidizing agents (Allen, 1994). Botha and Lötter (1989b), by the use of DSC, showed that stearic acid would interact with oxprenolol hydrochloride and later, by employing the same method, the same excipient is also incompatible with naproxen (Botha and Lötter, 1990). Glyceryl palmitostearate was found to be incompatible with ketoprofen (Botha and Lötter, 1989a) and naproxen (Botha and Lötter, 1990). Glyceryl monostearate is incompatible with acidic substances (Pagliocca, 1994) and again care should be taken if used together with alginic acid or stearic acid.

Colloidal silicon dioxide is incompatible with diethylstilbestrol preparation (Johansen and Møller, 1977). Sodium lauryl sulphate, being an anionic surfactants, reacts with cationic surfactants and is not compatible with some alkaloidal salts and precipitate with lead and potassium salts (Behn, 1994). Polysorbates may precipitates and / or discolors with various substances such as phenols, tannin, tars and / or tar-like materials (Leyland, 1994). The antimicrobial activity of paraben preservatives is also reduced in presence of polysorbates (Allen et al, 1981).

Povidone (PVP) may form complex in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin and iodine. The efficacy of some preservatives such as thimerosal may also be reduced due to complex formation with povidone (Walking, 1994). Interaction of povidone with oxprenolol (Botha and Lötter, 1989b) and with pyridoxal hydrochloride (Dürig and Fassihi, 1993) have also been studied. Hydroxypropyl methylcellulose is incompatible with some oxidizing agents (Harwood and Johnson, 1994) whereas sodium carboxymethyl cellulose, can form precipitates with promazine hydrochloride, reserpine, veratrine sulphate, chlorpomazine hydrochloride, quinine hydrochloride, acridine dyes, neomycin sulphate, methacrine hydrochloride, streptomycin sulphate, cinchocaine chloride, hyoscyamine hydrochloride (Racz, 1989).

Drug-excipient and /or excipient-excipient interaction resulting from powder mixing involving magnesium stearate and different disintegrants may also affect the rate and / or extent of drug release. In tableting, Bolhuis et al (1981) showed that 0.5% magnesium stearate could interact with starch (potato starch) and starch derivatives (sodium starch glycolate) after 5 minutes mixing in tablets containing aspirin or dibasic calcium phosphate dihydrate or lactose. The interaction led to formation of a hydrophobic lubricant film which exerted a strong negative effect on the binding properties of tablets judged by the decrease in crushing strength of tablets and also by the increase in disintegration time. It was observed that less pronounced increase in disintegration time was exhibited by tablets containing sodium starch glycolate, probably because sodium starch glycolate swells more extensively than potato starch and manages to disrupt the hydrophobic film. Lerk et al (1982) extended the study to investigate the effect of such interaction on dissolution rate. It was found that the dissolution rate for tablets containing potato starch depended both on the compression force and on mixing time with magnesium stearate whereas the dissolution rate for tablets containing sodium starch glycolate was independent of both factors. Later, Chowhan and Chi (1985a, 1985b) also investigated the similar aspect of drug-excipient interaction between the drug (ketorolac tromethamine), magnesium stearate, maize starch (disintegrant), pregelatinised starch (disintegrant / filler), spray-dried lactose (filler), resulting from powder mixing in capsule formulations. The drug and disintegrant with or without lactose were mixed for 25 minutes before mixing with magnesium stearate for 2, 5, 10, 20 and 28 minutes. Scanning electron microscopy (SEM) was also employed to provide a better understanding of the interaction. Agglomeration of maize starch grains were revealed by SEM when drug, maize starch and lactose were mixed together, without magnesium stearate. During mixing with magnesium stearate, flakes of magnesium stearate and agglomeration of maize starch were readily visible. Magnesium stearate flakes were shown to adhere to the drug particles and to the maize starch agglomerate. Such phenomenon was caused by interactions that are specific to the drug-excipient combination i.e. ketorolac tormethamine with lactose, corn starch and magnesium stearate. As a result of prolonged mixing with magnesium stearate, the dissolution rate of drug was decreased (Chowhan and Chi, 1985a). It was also shown that machine-filled capsules exhibited a much slower dissolution rate than did the hand-filled capsules. Powder compaction

probably magnified the deleterious effects of prolonged mixing with magnesium stearate significantly (Chowhan and Chi, 1985a). By replacing maize starch and lactose by pregelatinised starch, the previously observed interactions between drug and excipients were essentially absent. There was no cohesion of the pregelatinised starch or flaking and subsequent adhesion of magnesium stearate flakes to the drug and/or excipient particles. The dissolution behaviour of capsule formulations containing pregelatinised starch was not adversely affected by mixing with magnesium stearate (Chowhan and Chi, 1985a). In cases where crospovidone was employed as disintegrant, drug-excipient and / or excipient-excipient also occurred (Chowhan and Chi, 1985b). Ketorolac tromethamine were observed to fit into the voids of the crospovidone particles and formed drug-crospovidone agglomerates, in the absence of magnesium stearate, and thus led to a low level of drug recovery during dissolution test. The amount of drug entrapment was higher in the case of larger drug particles. Mixing had caused the magnesium stearate to flake and the flakes adhere to the drug-crospovidone agglomerates and subsequently decreased the dissolution rate. Chowhan and Chi (1986a) extended the study by using micronized prednisone as the drug and dibasic calcium phosphate dihydrate as the filler. Potato starch or sodium starch glycolate was used as disintegrant, pregelatinised starch as a disintegrant / filler and magnesium stearate being the lubricant. This study confirmed that drug-excipient interactions were the major factor influencing disintegration time and dissolution rate of capsule formulations (hand-filled and uncompacted). When prednisone, dibasic calcium phosphate dihydrate and maize starch or sodium starch glycolate were mixed thoroughly, only about 70% of the drug was released in 30 minutes. This was explained to be largely due to drug-excipient interaction (between prednisone and dibasic calcium phosphate dihyrate) and adhesion of magnesium stearate flakes to the drug particles and agglomerates. Drug mixtures containing pregelatinised starch and magnesium stearate did not exhibit decreased dissolution rate. Chowhan and Chi (1986b) compared the role of magnesium stearate and sodium stearyl fumarate in drug-excipients interaction for ketorolac tromethamine capsules. It was shown that, in contrast to magnesium stearate, sodium stearyl fumarate did not interact with the drug (ketorolac tromethamine) or excipients (crospovidone and spray dried lactose) and that the disintegration time and drug dissolution rate from hand-filled, uncompacted capsules were not adversely affected.

Drug-excipient and / or excipient-excipient interaction resulting from powder mixing involving magnesium stearate and other excipients such as colloidal silicon and sodium lauryl sulphate has also been studied and can be found in Section 1.3.2.3.

Nevertheless, some excipients have been found to have stabilising effects on the drug. For example, pyridoxal hydrochloride has strong stabilising effect with various cellulose (Avicel PH101, methylcellulose, ethylcellulose) and colloidal silicon dioxide (Aerosil 380) which function as moisture scavengers and decreased the amount of free water available for interaction (Dürig and Fassihi, 1993). Desai (1994a) also showed that success of crospovidone (Polyplasdone XL) in improving dissolution stability of hydrochlorothiazide capsules and attributed the effect mainly to its moisture scavenging ability, which prevented the formation of formaldehyde and also its non-reactivity with formaldehyde.

Occasionally, the drug-additive interaction carried out in a controlled manner can also be favorable for formulation of hydrophobic, insoluble drug. Precipitation of hydrophobic drugs and povidone could increase the dissolution rate of the formulation (Racz, 1989). Co-precipitation of digitoxin and povidone (1:9 ratio), reserpine and povidone (1:5 ratio) or sulphathiazole and povidone (1:4 ratio) are examples where dissolution rate of the co-precipitate increased the dissolution rate of drug as reviewed by Racz (1989).

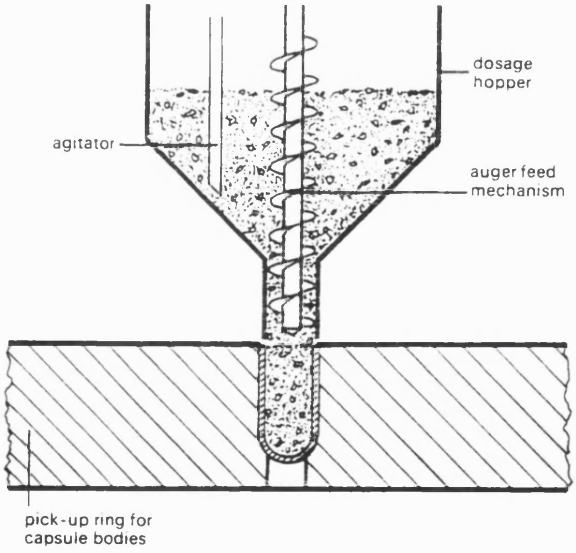
1.3.4 Filling machine

Capsules can be filled with a high degree of filling accuracy if the drug mixture is well-formulated. Reier et al (1968) showed that machine speed was one of the factors affecting the mean fill weight of capsules filled by semi-automatic filling equipment (Lilly model 8 capsule filling machine). Botzolakis et al (1982) also pointed out the difference in effectiveness of disintegrants may be attributed to the method of filling. Hand-filled capsules are generally uncompacted whereas capsules filled by filling machines are compacted. The effect of compressibility of capsule content on the performance of the formulation is mentioned in Section 1.3.1.4. In capsule formulations, it should be taken into considerations that there are several mechanisms by which different filling machines functions.

The mechanical operations of filling hard gelatin capsules have been reviewed by Cole (1987b) and Jones (1988 and 1994) and different models of different types of filling machines have also been described in details in Cole (1987a). Jones (1994) distinguished between the type of filling machines that use the capsule body to measure the dose of material (the "dependent fillers") and those which do not use the capsule body to measure the dose (the "independent fillers").

Both auger or fluidiser type of filling machine belongs to the group "dependent fillers" (Jones, 1994). The former type of machine (auger) fill the capsules by an auger feed system (Figure 1.9). The powder hopper is positioned above the capsule body and the weight of powder filled is controlled by the rotation of the auger and the length of time that the capsule body is positioned beneath the powder hopper (Cole, 1987b; Jones, 1994). The fluidiser type machine uses a vibrating plate to cause the powder to flow into the body. The weight of powder filled is controlled by the amplitude of vibration of the plate and by the position of the body beneath the powder hopper (Jones, 1994).

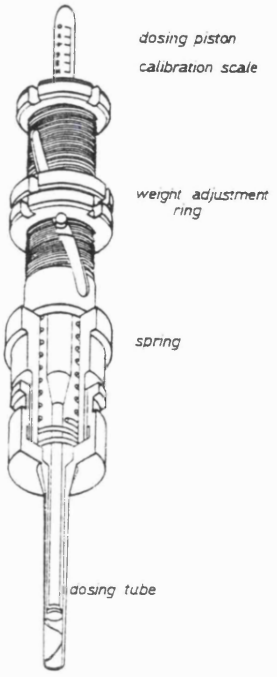
Figure 1.9 : Filling capsules by the auger feed system (Cole, 1987b)



According to Jones (1994), the majority of machines used in Europe and USA is of the "independent fillers" type. The "independent fillers" form a plug from the amount of powder to be filled into each capsule and can be divided up into two groups depending on the method of plug formation. The first group contains machines that form plug inside a dosing tube or dosator nozzle and the second group of filling machines form plugs inside a hole in the dosage disc by means of a tamping finger (Jones, 1988 and 1994).

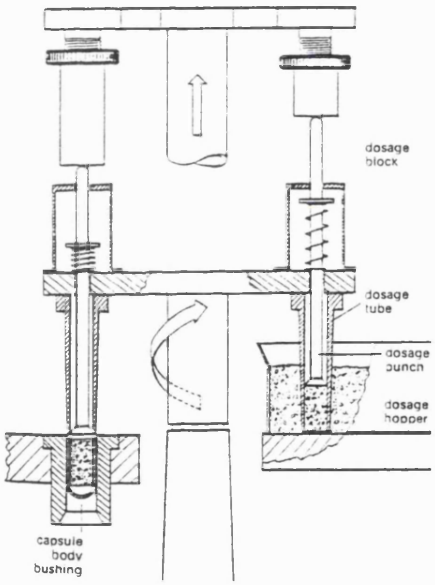
In the dosator nozzle type of filling machine, the powder is fed into the dosage hopper and the level of the powder bed is adjusted to about twice the depth of the compressed plug. The dosage tube is inserted into the powder bed the powder inside the dosator is then pressed by the dosage punch (inside the dosator) just sufficiently to form a coherent plug that can be lifted by the dosator and carried to the capsule body. The assembly of a typical Zanasi dosator is shown in Figure 1.10. The powder plug is then ejected into the capsule body by the piston. The compression force used should be just sufficient to allow clean transfer to the capsule body and to ensure that the plug does not break up on ejection from the dosage tube. The plug should also fit into the capsule body without protruding too far above the top (Cole, 1987b). The dose of the capsules is therefore dependent on the formation of the powder plug. The weight of the plug is controlled by the initial position of the piston in the dosator and by the height of the powder bed (Jones, 1994). Britten et al (1995), with the use of an intermittent-motion capsule filling machine simulator (Macofar 13/2 dosator type machine), collected information about plug weight, plug density, plug length and powder bed density and related these information with pressure and displacement data of the filling machine. For capsules filled by this type of filling machine, it is also important that the formulation must be free-flowing but yet possesses some cohesiveness (Jolliffe and Newton, 1982a).

Figure 1.10 : The assembly of a typical Zanasi dosator (Cole, 1987b)



These type of machines can be operated by intermittent or continuous compression filling. The intermittent compression filling of capsules of a Zanasi LZ-64 intermittent machine is shown in Figure 1.11. The use of continuous compression filling was first developed by the mG2 Company (Cole, 1987b). Essentially there is little difference between the application and the principle for a continuous machine and an intermittent machine. However, the dosage trough in a continuous machine is annular, rotates and is fed from a bulk hopper. The dosators dip into the dosage trough whilst it is in motion (Cole, 1987b). The dosage accuracy can be affected by the speed of the machine, the level of fill and the uniformity of density of the powder mixture (Cole, 1987b).

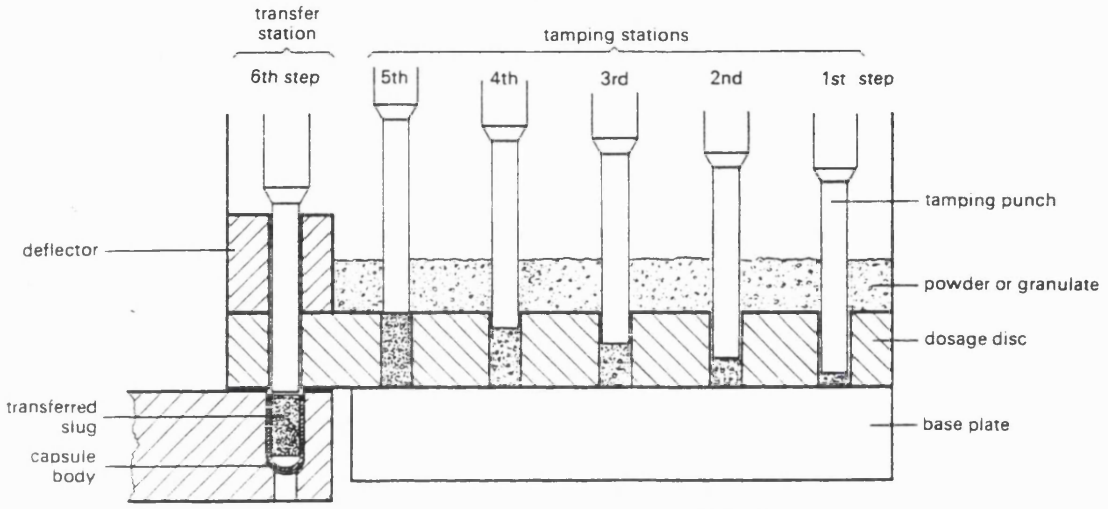
Figure 1.11 : Intermittent compression filling of capsules (Cole, 1987b)



The other type of "independent fillers" machines is based on the use of dosing disc and tamping fingers, for example, Bosch (Höfliger and Karg) GKF 2400 (Jones, 1994). Powder is transferred from a feed tray by tamping pins into the holes in a dosing disc, which is machined to the thickness to provide a certain fill-weight in the capsule. A tamping punch compresses the powder against the base plate and then rises. Filling and retamping takes place in five successive stages. After the fifth stage the dosage hole moves off the base plate and the plug of powder is ejected into the capsule body (Figure 1.12) (Cole, 1987b). The dose is controlled primarily by the thickness of the

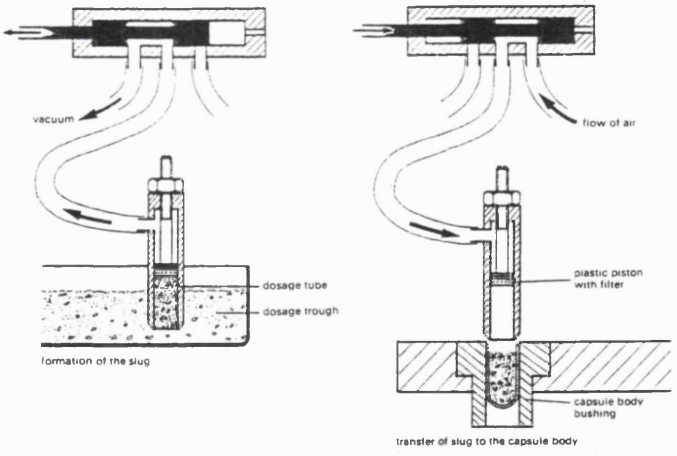
transfer disk, the adjustment of the tamping punches and the depth of powder in the dosage hopper (Cole, 1987b).

Figure 1.12 : Filling capsules by the tamping method (Cole, 1987b)



The powder plugs, formed on both types of "indirect fillers" filling machines, are formed by pressure applied at the top end of the plug and the way in which the forces are transmitted through the powder mass are dependent upon several factors such as flow, internal friction and compressibility (Jones, 1994).

Figure 1.13 : Filling capsules by the vacuum method (Cole, 1987b)

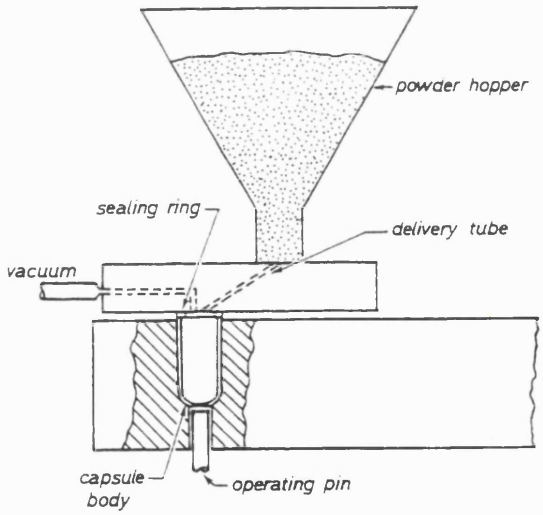


Another method of filling, vacuum filling, was developed by Perry Industries Inc and was also described by Cole (1987b). The principle is to draw the powder into the dosator by suction, applied through a filter pad. Some compression takes place but not as much as in the Zanasi dosator machine. The material is held in place by the vacuum until the dosage tube is in position over the capsule body. The powder is

ejected by releasing the vacuum and applying positive pressure (Figure 1.13). This method does not rely on the movement of mechanical parts during the filling operation and therefore lubricants are not needed in the formulation.

Alternatively, in the Drugpack system, as illustrated in Figure 1.14, a vacuum is used to remove the air from the capsule body through an exhaust passage. The pressure difference causes the powder to flow from the hopper down into the capsule body. When normal atmospheric pressure is reached, the flow of the drug mixture ceases. The amount of powder to be dispensed into the capsule can be adjusted by adjusting the vacuum system. The advantage of this type of filling machine is to allow filling of single substances which reduces the amount of formulation work required and eliminates the need for powder lubricants (Cole, 1987b).

Figure 1.14 : Filling capsules by the Drugpack system (Cole, 1987b)



A number of studies was performed, with the help of instrumented capsule filling machine, to provide a better understanding in factors affecting performance of capsule formulation. Cole and May (1972 and 1975) recorded the forces involved in plug formation and ejection during a capsule filling operation by the use of an instrumented Zanasi LZ-64 intermittent capsule filling machine. Such data was also used in the evaluation of the effect of lubrication of powder mixtures involved in the study. Indication of the true lubricant requirement of automatic capsule filling machine was also provided with the aid of an instrumented Zanasi LZ-64 filling machine (Small and Augsburger, 1978). It was shown that a small percentage of magnesium stearate

can dramatically reduce the ejection force of compressible starch as compared to the unlubricated powder. Hauer et al (1993a) also used an instrumented LZ 64 filling machine to investigate the influence of the filling material and machine parameters in rational development and optimization of capsule formulations. It was found that for non-problematic filling, with uniform fill weights, good compressibility and strength of binding of powder mixture are important. Powder with extremely good flow properties can be difficult to be densified and weight variations may increase (Hauer et al, 1993a). El-Shaboury et al (1993) used an instrumented Zanasi AZ-20 automatic (dosator type) filling machine to study the effect of various levels of effervescent salt on release of fenopropfen calcium and ketoprofen from hard gelatin capsules. It was found that maximum effectiveness, judged by decrease in disintegration time and increase in dissolution rate of capsules, was obtained at low compression pressure. Mony et al (1977) measured the compression and ejection forces during capsule filling using various excipients with and without lubricants by an instrumented Zanasi RZ-59 machine. Joliffe et al (1982) described the instrumentation of a mG2 G36 (dosator type) capsule filling machine simulator. It was later used to study the effect of powder coating on dosator nozzle, amount of compression (compression ratio), particle size of lactose and wall surface at the nozzle outlet on capsule fill weight uniformity by measuring the compression and ejection stresses (Jolliffe and Newton, 1982a, 1982b, 1983b) and these studies were extended by Tan and Newton (1990 a -f) with the same simulator.

1.3.5 Other factors

1.3.5.1 Dose and capsule size

Generally, hard gelatin capsules are used to encapsulate between 65 mg and 1 g of powder, depending on the bulk density of the mixture (Ansel et al, 1995a). If the dose for the active ingredients is low, there is more space available for excipients and provide greater flexibility in choices of excipients. In such cases, the final formulation will be governed by the nature of the excipients (Jones, 1994). If the dose of the active ingredients is high, the choice of capsule size will be more limited compare to low dose drug and there will be less space available for excipients. The physical properties of the

mixture will tend to be governed by the drug (Jones, 1994). However, the drug does not necessary possess ideal properties to provide a good capsule formulation.

The amount of filling material fill inside a capsule and the capsule size chosen may influence the packing density and the performance of the capsules. Aguiar et al (1968) emptied some commercial chloramphenicol capsules (labeled 250 mg dose) and packed the content into a larger capsule size (No. 1). It was found that packing into a larger capsule increased the initial dispersion. However, further deaggregation was slow which indicated that the nature of the excipients contained in the capsules was more important than the packing density in terms of deaggregation and dissolution rates (Aguiar et al, 1968). Reier et al (1968) developed a model which defined and quantified the factors affecting the encapsulation of powders in hard gelatin capsules using a semi-automatic capsule filling equipment and capsule size was one of these factors. The variation of fill weight, judged by the standard deviation, is a function of capsule size, machine speed, specific volume, flowability and the presence of glidant (Reier et al, 1968). Samyn and Jung (1970) showed that packing density (355 mg / No.2 capsule and 400 mg / No.2 capsule), in absence of magnesium stearate, did not influence dissolution rate of capsules containing either calcium phosphate or lactose as filler. However, in presence of 5% of magnesium stearate, increased packing density increased the dissolution rate for capsules containing either calcium phosphate or lactose. The impact of packing density was found to be greater with the calcium phosphate system (Samyn and Jung, 1970). Irwin et al (1970) showed that as the dose of drug (Clomacran phosphate) increased (25mg, 50mg and 100mg), the weight variation of capsules (No.4 capsules) containing powder blends of the drug mixture also increased. Khalil & Ali (1972) showed that dissolution and disintegration of formulations of chloramphenicol capsules (250 mg dose) were dependent on the capsule size, diluents, lubricants and method of filling. Dissolution rate from No. 1 hand-filled capsules was higher than No. 2 machine-filled capsules. It was shown that an increase in compaction, in the case of No. 2 machine-filled capsules, would result in a decrease of drug release through hindered permeability of the dissolution medium to the powder mass and therefore has a lower dissolution rate. On the other hand, Newton et al (1971b) indicated that the additive effects are independent of capsule packing density. Capsules were filled into size 0 capsule shells to give a series of capsules of

low fill weight and high fill weight. It was found that similar quantities of drug were released from both low and high capsule filling densities (Newton et al, 1971b).

The packing density of drug mixture could affect the performance of capsules such as dissolution rate and weight variation of capsules. For low dose drug, the performance of the capsules can be adjusted by the use of excipients. However, such flexibility is not possible with high dose drug (Jones, 1994).

1.3.5.2 Regulatory restrictions · Company practices · Cost

Kruss (1989) discussed the toxicological and legal aspects in excipient design. It was described that "choosing suitable formulation excipients is like walking a high-wire between toxicological and legal aspects on the one hand and their pharmaceutical suitability on the other" (Kruss, 1989). For approval of a new drug product, evidence must be presented by way of scientific data to show that the preparation will have no adverse effects when used as specified. However, most of the excipients in common use today have never undergone formal approval procedures. On the other hand, it can be argued that the safety of these excipients has been more than adequately demonstrated by years of practical use (Kruss, 1989).

The regulatory guidelines for toxicology studies for excipients are different from country to country (Table 1.8).

Table 1.8 : Regulatory guidelines for toxicology studies (Kruss, 1989)

Germany	Arzneimittelprüfrichtlinien Federal Republic of Germany Draft Dec 12, 1986, effective from Jan 1, 1990
EC	EEC-Council Directive 83/570 Official Journal of the European Community L 332 Nov 28, 1983
USA	Guideline for the Format and Content of the Nonclinical/ Pharmacology/Toxicology Section of an Application. U.S. Department of Health and Human Services FDA, February 1987
Japan	Toxicity Test Guideline 1984. Collection of Notifications Related to the Pharmaceutical Affairs Law (IV)

For a multinational pharmaceutical company, the most stringent international standards must be met if data is to be used all over the world. The cost of such tests could be immense. This explains why most companies are often reluctant to use new excipients or excipients for which limited toxicological data is available. In addition, the justification of the choice of a particular excipient is now being requested by some regulatory authorities (Moreton, 1996).

Official and non-official lists of excipients are often used. The pharmacopoeias for Europe, UK, Japan and USA) and compendia such *Martindale*, *Merck Index*, *Remington's*, *Handbook of Pharmaceutical Excipients* are examples of the standard references being referred to. In Japan, the List of Excipients (1986) compiled, based on a survey of over 160 Japanese pharmaceutical companies, provides a comprehensive overview of the excipients on the Japanese market at the time of publication. The US Code of Federal Register lists additives permitted in food for human consumption (Code of Federal Register, 1987). It lists substance that are generally recognized as safe (Code of Federal Register, 1987) and takes for granted that safe food ingredients are also safe for use in drugs (Kruss, 1989). The WHO/FAO has published the maximum tolerated daily doses for food additives (1974). Drug Master Files contain toxicological data provided by the manufacturer of an excipient also provided useful information. However, there are differences in the monographs for certain excipients between the pharmacopoeias and unnecessary amount of extra testing as specified in the pharmacopoeias can result from attempts to comply with all monographs.

To avoid unnecessary duplication of development effort and resources, many multinational pharmaceutical companies have created centralized Research and Development departments to develop new products. Over the years, there has been a trend to market the same formulation(s) of a new drug worldwide : globalization (Moreton, 1996). The International Pharmaceutical Excipient Councils (IPECs) were established in U.S. (IPEC-America), Europe (IPEC-Europe) and in Japan (Japanese Pharmaceutical Excipient Council). Harmonization of pharmaceutical excipients is one of the aims of IPECs. In view of the recognition of the differences in the monographs for excipients, there was a desire among the pharmacopoeias and regulatory agencies to harmonize monographs to simplify international registrations. The first group of

excipients selected in the harmonization process was based on the frequency of inclusion in registration applications and is listed in Table 1.9. The first excipient to complete the harmonization process was lactose (Moreton, 1996). In capsule formulation, the possibility to develop a globalized formulation for the worldwide market with harmonized excipients also prevails.

Table 1.9 : Excipients for Harmonization (Moreton, 1996)

Excipient	Lead Pharm
1 Magnesium stearate	USP
2 Microcrystalline cellulose	USP
3 Lactose	USP
4 Starch:	
Corn (maize) and tapioca	USP
Wheat and potato	Ph Eur
Rice	JP
5 Cellulose derivatives:	
Carboxymethyl cellulose calcium	USP
Carboxymethyl cellulose sodium	USP
Microcrystalline cellulose	USP
Powdered cellulose	USP
Cellulose acetate	USP
Cellulose acetate butyrate	USP
Cellulose acetate phthalate	USP
Hydroxypropyl cellulose (HPC)	USP
Low substituted HPC	USP
Hydroxypropyl methylcellulose	JP
Hydroxypropyl methylcellulose phthalate	USP
Ethyl cellulose	Ph Eur
Hydroxyethyl cellulose	Ph Eur
Methyl cellulose	JP
6 Sucrose	Ph Eur
7 Povidone	JP
8 Stearic acid	Ph Eur
9 Dibasic calcium phosphate	JP
10 Polyethylene glycol	USP
11 Hydrochloric acid	USP
12 Alcohol	Ph Eur
13 Benzyl alcohol	Ph Eur
14 Talc	Ph Eur
15 Sodium chloride	Ph Eur
16 Sodium starch glycolate	USP (Ph Eur)
17 Sodium hydroxide	Unassigned
18 Polysorbate 80	JP
19 Calcium disodium edetate	JP
20 Petrolatum	USP
21 Colloidal silicon dioxide	JP
22 Citric acid	Ph Eur
23 Methylparaben	Ph Eur
24 Sodium saccharin	USP
25 Titanium dioxide	USP (JP)

Economic factors also play a role in choice of excipients. Diluents are very often incorporated at a high level in capsule formulations. In such case, if two diluents are both effective for the particular formulation, the cheaper one would be preferred. Generally, lactose monohydrate is an inexpensive excipient. For example, lactose B.P. (standard grade) is about £1.2 / kg (Sales Dept., Borculo Whey Products UK Ltd,) compared to Starch 1500 (pregelatinised starch) of £4.3 / kg (Sales Dept., Colorcon Ltd, UK) and Avicel PH102 (microcrystalline cellulose) of £8.77 / kg (Sales Dept., Honeywill and Stein Ltd, UK) (the prices for 1995 were quoted).

1.4 Objectives

A vast amount of information about capsule formulation has been published (Section 1.3). The aim of this project is to organise this knowledge (obtained from the public domain), together with knowledge contributed by the experienced formulators from both academic and industrial background (human experts) through discussions and meetings, and observations obtained from experimental studies and analysis of the formulations on the market; to design an Expert System that would mimic an expert's thinking process to solve the complex problems in powder filled hard gelatin capsule formulations.

The System to be developed is intended to provide the best optimized formulation as early as possible for Phase I development stage with documentation of the decision making process. Ability to learn from past experience is a further feature to be included in the system and thus enable the System to serve the educational purpose. The system needs to be as flexible as possible but yet remains a "restricted" system; in a sense that its decision making process should be dominated by the logic of the system but yet company practices and the user's choice must also be accommodated and documented. Additional features, such as 'statistical design' and 'multiple dose' (Section 5), are also advantageous to aid the optimisation of the formulations during drug development, manufacturing and marketing process.

There are a number of Expert Systems available in pharmaceutical industry and many of them are developed using expert system shell based on knowledge of experts in one company (Section 1.1.1). The unique feature of this Expert System is that it will be developed with the joint efforts between the academic and industrial experts worldwide from more than thirty industrial companies in Europe, Japan and United States; as well as using the published information and information deduced from the experimental studies as the foundation of its knowledge base.

To enable the full flexibility and control in development of an Expert System in an area of great complexity (i.e. formulation of hard gelatin capsules) as indicated in Section 1.3, a high level language, C programming language (Microsoft Inc.) in

association with the software, dBASE IV (Borland Inc.) are to be used (as suggested in Section 1.1.4).

The knowledge base will be stored in three groups of database files (Chapter 2) and represented by production rules which are arranged in the form of decision trees. The inference engine will manipulate the rules and generate information by *forward chaining*, with 'depth-first' search (Section 1.1.4). These rules should be updated continuously, based on the feedback received from the experts during the regular 'Expert System Meetings'. This is intended to be a learning system.

Chapter 2

Knowledge Acquisition

2. Knowledge Acquisition

2.1 Building up the knowledge-base

Human beings make decisions based on knowledge that is accumulated through years of experience. Traditionally, knowledge is passed on from generation to generation via education and training or by publications. New knowledge can also be explored through scientific research. Similar to human beings, Expert Systems also make decisions depending on their knowledge or "knowledge-base". The knowledge-base of an Expert System is usually developed for one particular subject requiring expertise to solve the specific problems. The process of extracting knowledge from experts or other sources and formalising this knowledge for the inclusion into the knowledge-base is called knowledge acquisition (Parsaye and Chignell, 1988).

There are a number of approaches to knowledge acquisition. The three approaches that were adopted in this system were first by collecting information from publications; secondly by discussions with experts; and thirdly by performing experimental work designed to provide additional knowledge.

Discussions with a group of experienced formulators from industry in Europe (the founder group) were conducted every three months over a two-year period. During these meetings, the knowledge attained from previous meetings and other sources were discussed. Published knowledge was therefore consolidated while unpublished knowledge and experience from these experts were shared. Details of the operation of the initial version of the system were also discussed and approved during these meetings. After the initial version of the system was completed, similar meetings were also conducted with experienced formulators from both industry and academia in the United States and Japan. These meetings provided suggestions to improve the system, feedbacks for the system and guidelines to help the system to accommodate the difference in "habits" of formulation in different countries.

The foundation of the knowledge-base was built based on publications in the subject. For example, from the publications regarding formulations on the markets from selected countries (see Section 2.2), trends of excipients used in the past was observed.

Some of these trends could also be seen to be related to the dose or solubility of drugs (Section 2.2.4). Standard references such as the pharmacopoeia from various countries, the *Handbook of Pharmaceutical Excipients* (1994), *Merck Index* (1976) and *Martindale* (1993) were consulted. The information included in the database of excipients and drugs (Table 2.1) was extracted from these reference books. The format and layout of these databases can be found in Section 2.3. Textbooks and publications in capsule formulation and related areas formed the basics in developing the logic and the rules of the system. The database of bibliography (Table 2.1) captured the information of these references and the format of this database can be found in Section 2.4. The amount of published information was enormous (see Section 1.2 and 1.3) but not all the information can be incorporated in the system initially. A core system was to be built in the initial stage and only information that contributed to the construction of this 'core' was extracted. A core system, in this project, was a system that provide fundamental support for capsule formulation and only essential features were to be included.

The third approach to knowledge acquisition was to extract information derived from experimental work. The relationship between formulation variables and the performance of formulations are complex. Experimental work were therefore designed to investigate this complicated relationship to provide further understanding in the subject (see Section 2.5).

The composition of the knowledge-base could therefore be divided into three parts as shown in Table 2.1, each part was composed of a set of database files. The word 'database' was used as a general term to describe the 'reservoir' that stored the information resources. 'Database file' was the actual computer file that kept the information. Information about the formulations on the market, drugs and excipients was stored in three different database files and was classified under database group I. Database group I provides the background information for existing formulations and ingredients found in these formulations. Bibliography for capsule formulation was captured in another database file. This database file, together with the unpublished knowledge and experience from the experts participating in the meetings, were classified under database group II. The third part of the knowledge-base (database

group III) was made up of the observations and principles derived from the experimental work as mentioned before.

Table 2.1 : Composition of the knowledge-base in the system

Database Group I
Formulations on the market
drugs
excipients

Database Group II
bibliography
expert knowledge

Database Group III
data from experimental work

2.2 Database of Formulations on the Market - Trend of excipients

2.2.1 Purpose

The database of formulations on the market contains qualitative and some quantitative information about marketed formulations from five countries : Germany, France, United States, Italy and Belgium. A summary of entries for capsule products was extracted from the *Rote Liste* (1993) , *Vidal* (1993), *Physicians' Desktop Reference* (1993), *L'Informatore Farmaceutico* (1993) and *Belgium Compendium* (1993). Information was taken from only products that contained non-liquid filled hard gelatin capsules. Formulations from these five countries were used because they were the only ones found to provide qualitative information about both active ingredients and excipients in the formulations at the relevant time. Formulations from *L'Informatore Farmaceutico* (1993) also indicate the amount of each excipient used.

In addition, by statistical analysis of the data from this database, 1) the frequency of use of excipients; and 2) relationship between dose and solubility of drugs and the types of excipients used were identified.

2.2.2 Organisation of database

The data was organised using dBaseIV version 1.5 software (Borland International, Inc.). Each record contains the drug name, brand name, dose, solubility of drug, list of excipients in the formulation, reference number, storage condition (if listed) and coating materials (if present).

Drug Name

The information from each data source was recorded onto the database in the same format as stated in the source i.e. in the form of chemical names or approved names in their respective languages. Later, the drug names were converted to British approved names (BAN) where possible.

Brand Name

Brand name is exactly the same as printed in the source. If there are more than one brand that uses the same formula (see 'Duplicated records' in this Section), only one of the brands will be displayed, although all brands were recorded.

Dose

Dose is expressed in milligrams at all times unless indicated otherwise. If the formula contains more than one active ingredients, the dose of each ingredient will be displayed in the same order as the drug name. A '+' sign is used to separate the dose of each ingredient. If the drug(s) can be formulated in more than one dose, then a 'comma' is used to separate the doses.

Solubility

Solubility is expressed in terms of solubility classes as agreed by the experts during one of the meetings (Table 3.2 in Section 3.2.4.2).

Excipients

In a manner similar to the drug names, the excipient names were recorded as printed in the sources and later converted, where possible, into British Approved Names (BAN). If quantitative information was available, the amount of each excipient used will be stated after each ingredient, in milligrams.

Reference numbers

A reference number is used to indicate the source of information. The code used is shown below (x represents a numerical number) in Table 2.2 :

Table 2.2 : Format of the reference numbers of the database of marketed formulations

Source of information	**Format of the reference numbers**
Rote Liste (1993)	xx/xxx
Vidal (1993)	VIDALxxx
Physicians' Desktop Reference (1993)	xxxxPDR
L'Informatore Farmaceutico (1993)	ITALYxxx
Belgium Compendium (1993)	BELGxxxx

Storage condition :

Sometimes, particular storage conditions are required for particular drugs. This information is included if available.

Coating Materials

Coating materials, usually included in the non-active ingredients list in most sources, were stored in this particular section.

(Information about capsule size was not always available in the sources and therefore was not recorded.)

Duplicated records

This database was analysed subject to the removal of the duplicated records. Below are the assumptions used to define 'duplicated records' :

a) In cases where the same drug, the same dose, the same excipients and the same amount of excipients were used (where applicable), they are considered to be duplicate regardless whether or not they have the same or different brand names, or from the same or different countries.

b) In cases where the same drug, the same dose, the same excipients but different amount of excipients were used, they are considered to be two different formulations regardless whether or not they have the same or different brand names, or from the same or different countries.

c) In cases where the same drug, the same excipients (name and amount), the same brand name from the same country were used but a different dose, then the two were combined into one entry, using a 'comma' to separate the two doses.

d) In cases where the same drug, the same excipients (name and amount), the same brand name but different doses and marketed in different countries were found, then the two entries were combined into one entry using brackets for the additional dose.

Definitions of the family of 'starch'

Starch can be described as "being obtained from either the mature grain of corn, Zea mays or of wheat, Triticum aestivum, or from tubers of the potato Solanum tuberosum" (USP/NF, 1995) . "BP 1993 also permits starch to be produced from rice.

In tropical and subtropical countries where these starches may not be readily available, BP 1993 additionally permits the use of tapioca starch, subject to additional requirements." (*Handbook of Pharmaceutical Excipients*, 1994). Maize starch can be described as starch obtained specifically from the caryopsis of Zea mays (BP, 1993).

In the source references, maize starch or corn starch is specified in most cases. Table 2.3 illustrates the number of occurrences of different types of starch in the database of formulations on the market.

Table 2.3 : number of occurrences of different type of 'starch'

Types of starch	**number of occurrence**
maize starch	201
wheat starch	1
potato starch	2
rice starch	8
tapioca starch	0
not specified	3

(Total number of formulations : 843.)

Definition of lactose

Lactose is a generic title that describes different types of lactose including monohydrate and anhydrous forms.

There are 1182 records including duplicates and 843 records excluding duplicates in the database of marketed drugs. These entries include 462 drugs or drug combinations.

2.2.3 Method of analysis of database

To identify the popular excipients, the number of occurrences of all excipients in this database was counted. These excipients were categorised according to their accepted functions described in the *Handbook of Pharmaceutical Excipients* (1994). Generally, they can be divided into diluents, disintegrants, lubricants, glidants and wetting agents. However, some of these excipients can be multifunctional.

Categorisation of excipients

One of the typical multifunctional pharmaceutical excipients is maize starch. Maize starch is a very common diluent but it can also be used as a disintegrant depending on the quantity included. Unfortunately, this quantitative information, which is very often essential in determining the function of such ingredient, was not always available. Consequently, to overcome these limitations, no two excipients were categorised to the same function. If one of the two functions that the excipient concerned can be performed by another ingredient present in the formula, this excipient would be classified in the alternative function group, similar to a study performed by Jones (1994). For example, talc can act as both a lubricant and a glidant (Dawoodbhai and Rhodes, 1990). If talc, colloidal silicon dioxide (a typical glidant) and lactose (diluent) (*The Handbook of Pharmaceutical Excipients*, 1994) are presented in the formula, talc is classified as lubricant not glidant.

Maize starch can be used as the sole diluent, a second diluent in the formulation or as a disintegrant, depending on the quantity used. Since the quantitative information is not always available, the following assumptions were used although they did not necessary reflect cases where maize starch was used as a second diluent :

a) If no quantitative information was available and if there was another diluent present in the formulation, then starch was classified as disintegrant; if no other diluent was present, then maize starch was categorised as diluent.

b) Normally, 3 - 15% of maize starch is used as a disintegrant for tablets (*The Handbook of Pharmaceutical Excipients*, 1994). If quantitative information was available and if the content of starch was greater than 50%, then starch was categorised as diluent , otherwise, starch is classified as disintegrant.

After all excipients were categorised, the occurrence of each of these excipients was tabulated according to their functions to enable the identification of the most popular diluent, disintegrant, lubricant, glidant and wetting agents. All the excipients that have more than five occurences among the 843 unduplicated formulations are listed in Table 2.4 (in Section 2.2.4).

The next step was to identify whether there was any relationship between the dosage and solubility of drugs and the excipients used. Two approaches were used. First, by dividing all the formulations (excluding duplicates) into four dose classes as defined in Section 3.2.2 (Table 3.1) and secondly by dividing all the formulations based on the published solubility data into three solubility classes as described before (Table 3.2 (Section 3.2.4.2)). If the formulation contained more than one active ingredient, the solubility of the formulation would be determined by the least soluble ingredient and the dose of the formulation would be the sum of the dose of all the active ingredients. The classification of both the doses and solubility was defined by the experts in the Expert System Meetings. For each formulation, the diluent, disintegrant and lubricant used were noted. The relationships between dose and / or solubility of drug and the use of excipients were also observed.

2.2.4 Result

2.2.4.1 Result : To identify the popular excipients

Diluents

The three most popular diluents in the database were lactose, microcrystalline cellulose and maize starch. In this database (database of marketed formulations), only 9% of the formulations contained microcrytalline cellulose compared to 42.7% for lactose. Microcrystalline cellulose became more commonly used in capsule formulation in the 1980's. It was recorded as a tablet diluent in *The Pharmaceutical Codex* (11th edition), published in 1979; and as a tablet and capsule diluent, in The *Handbook of Pharmaceutical Excipients* (1st edition), published in 1986. Therefore the current trend

of its use cannot be accurately reflected in this database which contains marketed formulation irrespective of their date of introduction. Sugars such as saccharose and sucrose, mannitol, pregelatinised starch, carbonate salts such as magnesium carbonate, potassium carbonate, phosphate salts like calcium phosphate and chloride salts like sodium chloride, potassium chloride and kaolin were also used (see Table 2.4).

The use of lactose overwhelmed the other diluents, agreeing with the survey of Shangraw and Demarest (1993). In their survey, 22 out of 58 of their respondents preferred lactose monohydrate in various forms. Microcrystalline cellulose and pregelatinised starch were preferred over maize starch. Jones (1994) reported similar findings (Section 1.3.2.1).

Disintegrants

From information in the database of marketed formulations, maize starch, crospovidone, sodium starch glycolate, croscarmellose sodium, pregelatinised starch and alginic acid were found to be the more common disintegrants (see Table 2.4). In a similar report performed by Jones in 1994, the disintegrants identified were also similar. They were sodium starch glycolate, alginic acid, croscarmellose and crospovidone (Section 1.3.2.2).

It was, at first, surprising that maize starch should be the most common disintegrant used because, in capsule formulation, maize starch functions as a disintegrant using a different mechanism as in tablets. It only swells by 5-10% and is insufficient to disrupt the less compacted powder mass in capsule formulations (Jones, 1994). Maize starch is therefore not always considered as the choice of disintegrant in capsule formulations (Expert System Meeting - communicated). However, if the assumptions used in 'Categorisation of the excipients' are considered (i.e. maize starch is classified as a disintegrant if another diluent is present in the formulation, unless quantitative information was available to prove that maize starch functions as a second diluent), the episode of a high occurence of maize starch used as a disintegrant can be explained. In addition, many formulations in the database were marketed before the

introduction of the newer disintegrants (or super disintegrants) (Section 1.3.2.2) were available.

The use of sodium starch glycolate and croscarmellose sodium were found to be 4.4% and 1.2% which were less frequent than one would expect. In the survey performed by Shangraw and Demarest (1993), it was found that more than 60% of the respondents used disintegrating agents, other than starch, with a clear preference for either sodium starch glycolate or croscarmellose, then crospovidone and pregelatinised starch. Sodium starch glycolate or croscarmellose only became more commonly used in the 1980's. The 'technical literature' of croscarmellose sodium (Ac-Di-sol) was only published in 1988 by FMC Corporation and croscarmellose sodium is included in the second edition of the *Handbook of pharmaceutical excipients* published in 1994 but not in the first edition published in 1986. Such trends were therefore not able to be reflected in this database, as explained previously (see Table 2.4).

Lubricants and glidants

From Table 2.4, magnesium stearate is by far the most popular lubricant, confirming the findings in a study preformed by Jones (1994). Talc, a lubricant and a glidant, was very popular in the past. It was used as lubricant in conjunction with magnesium stearate as glidant (Mechtersheimer and Sucker, 1986). Nowadays, talc is not used as first choice because of the possibility of contamination with asbestos which is carcinogenic in humans (Section 1.3.2.3). The high percentage of presence of talc in the database can be explained by the fact that some of these formulations were, indeed, marketed for a long time. Other lubricants used are stearic acid, dimethicone, stearate salts e.g. calcium stearate, sodium stearate, aluminium stearate; stearic palmitic acid, glycerol palmito stearate and glycerol monstearate. Polyethylene glycol grades with molecular weights of 6000 and above, which can also be used as lubricant in tablet and capsule formulations, were also found. Regarding glidant, colloidal silicon dioxide and talc were both popular (see Table 2.4).

Wetting agents

The choice of wetting agents in capsule formulation is more limited. Sodium lauryl sulphate was identified as the most popular wetting agent from our results (see Table 2.4), again similar to the findings of Jones (1994). Polyoxyethylene sorbitan fatty acid ester such as polysorbate 80 was also used (see Table 2.4). Other wetting agents such as dioctyl sodium sulphosuccinate were also found but were not frequently used.

2.2.4.2 Result : to identify any relationship between solubility and dosage of drug and the use of excipients

a) Dosage of drug and the use of diluents

Among the 843 formulations in the database, 80, 262 and 536 formulations were identified in the low dose, medium dose and high dose categories. Only one formulation was found in the very low dose group. Some of these formulations were used for several doses for the same drug and therefore were present in more than one dose catagory. 0.2%, 2.8% and 20.8% of the formulations in the low, medium and high dose groups respectively contain no diluent (see Table 2.5). A clear trend of not including a diluent in the formulations exists as the dose increases. The higher the dose, the more likely is the absence of diluent.

The pattern of diluents used in the other formulations appears to be very complex. Lactose was the main diluent used covering more than 50% of the formulations in each dose-class. The use of maize starch increased with dose, and it appears that maize starch is much more likely to work in high dose drug capsule formulations. In this class, it changes position with microcrystalline cellulose. The use of microcrystalline cellulose slightly decreased with increased dose, but on the whole it appears that microcrystalline cellulose can generally be used with drugs of any dose. The use of pregelatinised starch also decreased with increase in dose. It is used more often in the low dose class. These trends are shown in Figure 2.1.

Table 2.4 : Number and percentage of formulations (in the database of formulations on the market) containing the listed excipients

The data for excipients that have occurence more than five times out of a total of 843 formulations on the market are shown. Some of the formulations may contain more than one excipient in the same class of 'excipient type'. For example, a formulation may contain both lactose and sucrose.

Excipient Type	**No. of formulations containing the excipient**	**percentage of formulations containing the excipient**
DILUENT		
lactose	360	42.7
microcrystalline cellulose	81	9.6
*maize starch	61	7.2
saccharose	49	5.8
mannitol	15	1.8
sucrose	12	1.4
calcium phosphate	9	1.1
magnesium carbonate	8	0.9
rice starch	8	0.9
pregelatinised starch	7	0.9
others	16	1.9
nil	261	31.0

* Please refer to assumptions made in Section 2.2.3.

[1] In the past, talc and magnesium stearate were incorporated in the formulation to act as lubricant and glidant respectively (see 'Lubricant and Glidant' in this Section).

.....Continue Table 2.4

Excipient Type	**No. of formulations containing the excipient**	**percentage of formulations containing the excipient**
DISINTEGRANTS		
*maize starch	140	16.6
crospovidone	67	7.9
sodium starch glycolate	37	4.4
croscarmellose sodium	10	1.2
pregelatinised starch	7	0.8
alginic acid	6	0.7
others	24	2.8
nil	574	68.1
LUBRICANTS		
magnesium stearate	365	43.3
*talc[1]	201	23.8
*talc	101	12.0
stearic acid	51	6.0
polyethylene glycol	18	2.1
dimethicone	13	1.5
glycerol monostearate	5	0.6
others	33	3.9
nil	74	8.8
GLIDANTS		
*magnesium stearate[1]	201	23.8
*talc	39	4.6
colloidal silicon dioxide	181	21.5
others	2	0.24
nil	500	59.3

.....Continue Table 2.4

Excipient Type	**No. of formulations containing excipient**	**percentage of formulations containing excipient**
WETTING AGENTS		
sodium lauryl sulphate	100	11.9
polyoxyethylene sorbitan fatty acid ester, polysorbate 80	12	1.4
others	4	0.5
nil	731	86.7

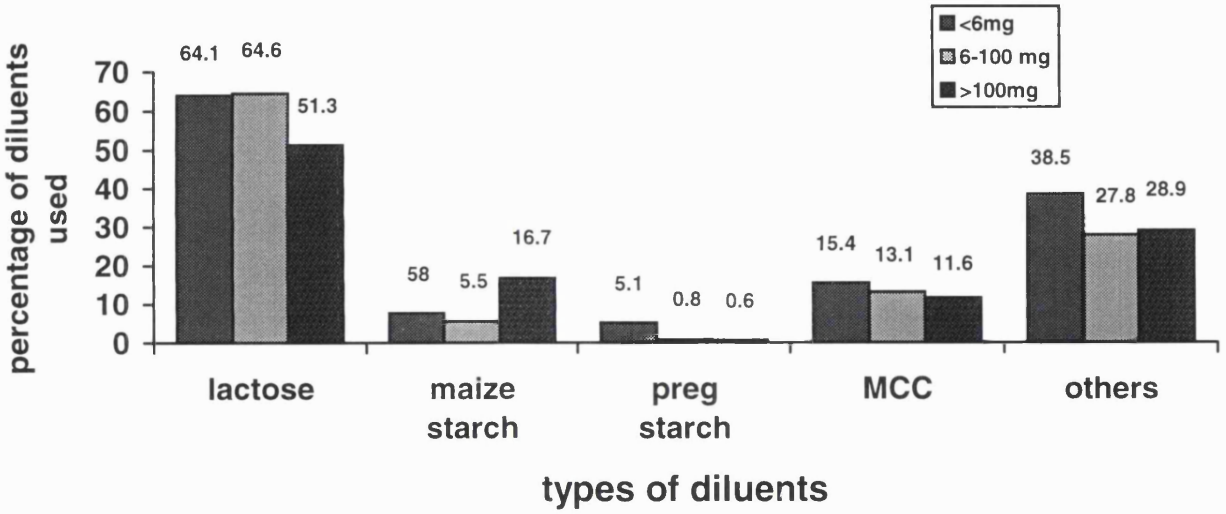
Table 2.5 : Percentage of the use of diluents in formulations of different dose range

	low	medium	high
lactose	64.1	64.6	51.3
maize starch	7.7	5.5	16.7
preg starch	5.1	0.8	0.6
MCC	15.4	13.1	11.6
others	38.5	27.8	28.9
Total number of formulations that contain diluent	78	237	353
Number of formulations that contain no diluent	2 (0.2%)	25 (2.8%)	183 (20.8%)
Gross total number of formulations	80	262	536

'preg starch' is pregelatinised starch.

'MCC' is microcrystalline cellulose.

Figure 2.1 : The effect of dosage of drugs on the type of diluents



b) Solubility of drug and the use of disintegrants

The formulations were separated into three solubility classes as desribed in Section 2.2.3. There were 475 formulations, with known solubility data. There were 130, 96 and 249 formulations in soluble, medium soluble and insoluble classes respectively (see Table 2.6).

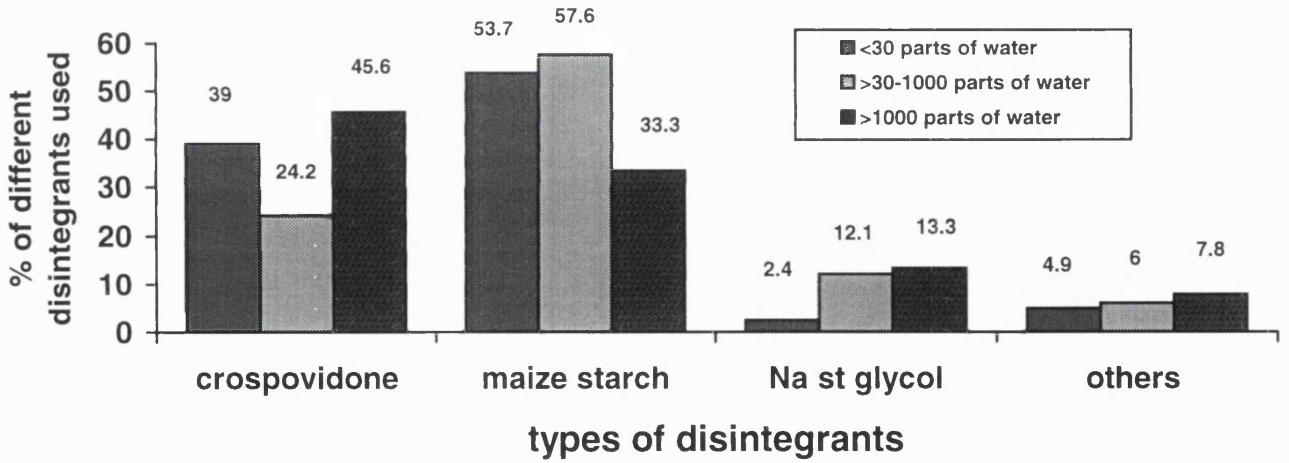
More than 60% of the formulations in each solubility group did not contain any disintegrant (see also Section 2.2.4.2 (c)). The increase in the use of super disintegrants and, at the same time the decrease of the use of low strength disintegrants (in the statistics represented by maize starch) with decreased solubility is an obvious trend (see Figure 2.2).

Table 2.6: percentage of the use of disintegrants in formulations of different solubility classes

	class 1	class 2	class 3
crospovidone	39.0	24.2	45.6
maize starch	53.7	57.6	33.3
Na st glycol	2.4	6.1	8.9
others	19.5	24.2	7.7
Total number of formulations	41	33	90
Number of formulation that contain no disintegrant	89 (68%)	63 (65%)	159 (64%)
Gross total number of formulations	130	96	249

Na st glycol = sodium starch glycolate

Figure 2.2 : The effect of solubility of drugs on the type of disintegrants



By further dividing the 475 formulations used in (b) into low, medium and high dose groups, the effect of both solubility and dose of drug on the use of different excipients were investigated as described in Sections (c) to (f) below.

c) Solubility and dosage of drugs and the use of disintegrants

Table 2.7 : percentage of the use of disintegrants in formulations of different dose/solubility classes

	soluble			medium soluble			insoluble		
	l	m	h	l	m	h	l	m	h
crospovidone	0	22.7	58.6	0	22.2	25.0	31.8	33.3	53.1
croscarmellose	0	0	6.9	0	0	5.0	0	1.6	3.1
Na st glycol	0	0	3.4	0	0	20.0	4.5	6.3	14.1
maize starch	0	68.2	41.4	100	66.7	30.0	36.4	31.7	35.9
alginic acid	0	0	3.4	0	0	0	0	0	1.6
others	0	13.6	17.2	0	22.2	10.0	54.5	30.2	15.6
Total no. of formulations	0	22	29	6	9	20	22	63	64
% with no disintegrants	100	61.5	73.9	40	62.5	71.8	37.1	39.4	66.3
Gross no. of formulations	9	52	111	10	24	71	35	104	190

(l = low dose; m = medium dose; h = high dose; Na st glycol = sodium starch glycolate)

In all solubility classes, as the dose increased, the use of disintegrant decreased but the degree of reduction decreased with the decrease in solubility (see Table 2.7). This can be explained by the fact that as solubility decreased, the need to incorporate a disintegrant increased. However, as the dose increased, the space available for the excipients also decreased. 66.3% of the high dose insoluble formulations contained no disintegrant, compare to 71.8% in the high dose medium soluble group and 73.9% in the high dose soluble group. One would expect that a higher proportion of formulations in the high dose insoluble class would contain a disintegrant. However, the concept of including a disintegrant in capsule formulation for insoluble drug was only patented by Newton and Rowley in 1975 and it is only after this that their use in capsule formulations increased.

From Table 2.7, it was obvious that no disintegrant was needed for low dose, soluble drug. On average, almost 80% of the formulations containing soluble drug did not contain any disintegrant. For medium soluble drug, the use of maize starch decreased as the dose increased but its use was still greater than a super disintegrant e.g. crospovidone.

The use of a strong disintegrant increased with decreased solubility and increased dose. The opposite was observed for the use of low strength disintegrant such as maize starch.

d) Solubility and dosage of drug and the use of diluents

In addition to the trend that was identified in part (a), it was also obvious that in all dose/solubility groups, lactose was the most used diluent (Table 2.8). However, as solubility decreases, the use of maize starch as a diluent decreased while the use of microcrystalline cellulose increased (except in the case of medium soluble, low dose drug). About 20% of the formulations contained a combination of lactose and maize starch. In cases where quantitative information was available, it was found that the more common lactose : maize starch ratios used were 2:1, 1:2, 3:1. The incorporation of the combination of lactose and maize starch did not seem to be affected by dose or solubility of drug and was believed to be based on habits of formulators or company practices (Expert System Meeting - communicated). 30% of the formulations in the high dose group, independent of solubility, contained no diluent which was not surprising because the space available for excipients decreased.

e) Solubility and dosage of drug and the use of lubricants and glidants

Lubricant and/or glidant was included in over 90% of formulations in all dose/solubility groups. Magnesium stearate, being the most popular lubricant, was included in over 50% of all the formulations even in the low dose groups (see Table 2.9). Although magnesium stearate is known to decrease dissolution rate for insoluble drugs, it has the greatest lubricity (Section 1.3.2.3). This may explain the reason why the trend to decrease the use of magnesium stearate was not obvious for insoluble drug. In

addition, neither the dose nor solubility seems to have any effect on the use of magnesium stearate.

Table 2.8 : percentage of the use of diluents in formulations of different dose/solubility classes

	soluble			medium soluble			insoluble		
	l	m	h	l	m	h	l	m	h
lactose	33.3	48.0	44.4	60.0	47.6	41.3	67.7	70.8	54.4
maize starch as sole diluent	22.2	10.0	19.4	0	9.5	15.2	0	9.4	14.4
lactose + maize starch	0	16.0	6.9	6.0	19.0	13.1	19.4	21.9	14.4
pregelatinised starch	33.3	2.0	4.2	0	9.5	2.2	0	0	0
microcrystalline cellulose	0	4.0	7.0	30.0	4.8	19.6	16.1	13.5	10.4
others	22.2	32.0	20.8	40.0	28.6	17.4	35.5	21.9	16.0
Total no. of formulations	9	50	72	10	21	46	31	96	125
with no diluents (%)	0	3.8	35.1	0	12.5	35.2	11.4	7.7	34.2
Gross no. of formulations	9	52	111	10	24	71	35	104	190

(l = low dose; m = medium dose; h = high dose)

About an average of 20% of the formulations contain a combination of magnesium stearate and talc (see Table 2.9). This phenomenon reflects the past 'habits' of using these two excipients in conjuntion to improve flow (see Section 2.2.4.1, 'Lubricants and glidants'). The incorporation of other lubricants such as stearic acid, dimethicone, glycerol monostearate and polyethylenglycol was relatively infrequent and was independent of dose and solubility of drug.

As the dose increased, the use of aerosil, a glidant, also increased, independently of the solubility of drug (see Table 2.9). For low dose soluble drugs, no formulation was found to contain colloidal silicon dioxide. This can be explained by the fact that as the dose increases, the properties of drug would have greater influence on the formulation and therefore the use of glidant becomes necessary for cases like high dose, poor flow drug. The use of talc which acts as both a lubricant and a glidant, decreased with increased dose and decreased solubility.

Table 2.9 : percentage of the use of luricant and glidant in formulations of different dose/solubility classes

	soluble			medium soluble			insoluble		
	l	m	h	l	m	h	l	m	h
magnesium stearate	50.0	55.1	70.5	70.0	52.6	68.2	67.6	79.8	73.7
talc	0	59.2	34.3	70.0	42.1	36.4	52.9	48.9	39.4
magnesium stearate + talc	0	22.4	16.2	40.0	10.5	16.7	26.5	29.8	23.4
stearic acid	0	8.2	6.7	10.0	5.3	7.6	2.9	6.4	6.9
dimethicone	0	6.1	7.6	0	0	15.2	0	1.1	1.7
glyceryl monostearate	25.0	2.0	0	0	5.3	3.0	0	0	2.9
polyethylene glycol	0	0	1.0	0	15.8	1.5	2.9	3.2	2.9
aerosil	0	16.3	20.0	10.0	21.1	25.8	20.6	17.0	24.6
others	50.0	0	1.0	0	0	4.5	0	1.1	0.6
Total no. of formulations	4	49	105	10	19	66	34	94	175
with no lubricant (%)	55.6	5.8	5.4	0	20.8	7.0	2.9	9.6	7.9
Gross no. of formulations	9	52	111	10	24	71	35	104	190

(l = low dose; m = medium dose; h = high dose)

f) Solubility and dosage of drug and the use of wetting agent

Generally speaking, about 20% of the formulations contained a wetting agent. A trend to increase the use of wetting agent with decreased solubility and increased dose was observed (Table 2.10). As the dose increases, the effect of solubility on the formulation will be more significant. If the drug is insoluble, there is a greater chance of the drug being non-wetting and, therefore, a wetting agent was used in a higher proportion in the high dose, insoluble drug groups.

Sodium lauryl sulphate was used more often than polysorbate in all dose/solubility group.

Table 2.10 : percentage of the use of wetting agents in formulations of different dose/solubility classes

	soluble			medium soluble			insoluble		
	l	m	h	l	m	h	l	m	h
sodium lauryl sulphate	0	11.5	9.0	0	20.8	9.9	17.1	16.3	14.7
polysorbate	0	0	0	0	4.2	0	2.9	1.9	2.1
Gross no. of formulations	9	52	111	10	24	71	35	104	190

(l = low dose; m = medium dose; h = high dose)

2.2.5 Conclusion and Rules deduced

The data of formulations on the market used in the analysis can be marketed for a number of years. However, the year of registration of a formulation was not always available. The trend towards using relatively new excipients, for example, microcrystalline cellulose, sodium starch glycolate and croscarmellose sodium cannot, therefore, be reflected accurately in the results as explained before (Section 2.2.4.1). On the other hand, 'old habits' in the formulation, for example, the use of talc and magnesium stearate in a combination to aid the flow of powders, can be shown (see Section 2.2.4.1 under 'Lubricant and Glidant'). Nevertheless, these results can provide some guidelines on the recommendation of excipients for different drugs of varying doses and solubility levels.

From the result in Section 2.2.4.1, 2.2.4.2 (a) and 2.2.4.2 (d), it can be concluded that lactose (form not specified) is the most popular and is used in all dose/solubility groups. Microcrystalline cellulose also appears to be used with drugs of any dose but more often in insoluble drugs. The inclusion of maize starch in all dose/solubility group is evident but the use of maize starch as a sole diluent decreased as the solubility of drug decreases, although it can also be found in the 'insoluble drug' group classified as a disintegrant. Lactose and maize starch were found in combination in all dose/solubility groups except in the low dose, soluble drug group. The use of pregelatinised starch also decreased as dose increased. About 30 % of formulations in the high dose group, independent of solubility, did not contain a diluent. The following observations were

deduced from the data and they may provide guidelines for choice of diluent in the system :

Observation 1 : Lactose was the first choice diluent.

Observation 2 : Microcrystalline cellulose was also used in many cases but not as a first choice.

Observation 3 : Maize starch was recommended as a diluent but not preferred with insoluble drugs.

Observation 4 : If the dose was high, a diluent might not be included, depending on the drug.

As far as disintegrant is concerned, it can be concluded that no disintegrant is needed for soluble drug and definitely not for low dose soluble drug (Section 2.2.4.2 (b) and (c)). For medium soluble drug, a less powerful disintegrant such as maize starch can be used whereas a more powerful disintegrant should be used as solubility decreased and dose increased. From this database, the most popular disintegrants are maize starch for soluble to medium soluble drug whereas crospovidone was the more frequently used super disintegrant for insoluble drugs (see Section 2.2.4.2 (b) and (c)). These observations contributed to the deduction of the rules in recommendation of disintegrants in the system :

Observation 5 : A disintegrant was not needed for soluble drugs.

Observation 6 : A more powerful disintegrant was needed for insoluble drugs.

Observation 7 : Crospovidone could be suggested for high dose, insoluble drugs.

Observation 8 : For a medium soluble drug, a medium strength disintegrant such as maize starch could be recommended.

From the results mentioned in Section 2.2.4.2 (e), it can be concluded that over 90% of all formulations contain either a lubricant or a glidant to aid flow and, among those formulations, 50% contained magnesium stearate, independently of the solubility of the drug. Aerosil was one of the most recommended glidant (see also Section 2.2.4.1) and was contained in about 20% of the formulations independent of dose or solubility of drug (Section 2.2.4.2 (e)). Hence, the observations deduced are :

Observation 9 : A lubricant was recommended in most of the formulations in the database.

Observation 10 : Magnesium stearate was the first choice lubricant.

Observation 11 : Stearic acid and talc could also be recommended as a lubricant but as not first choice.

Observation 12 : Aerosil was the first choice glidant.

Observation 13 : Talc could be recommended as a second choice glidant.

Under 20% of the formulations contained a wetting agent depending on dose and solubility (see Section 2.2.4.2 (f)). Sodium lauryl sulphate was more popular than polysorbate (see also Section 2.2.4.1). The following observations were derived :

Observation 14 : Increased use of wetting agent was observed with decrease solubility and increase in dose of drug.

Observation 15 : Sodium lauryl sulphate was the first choice wetting agent followed by polysorbate.

The incorporation of a particular excipient was very often based on the 'habits' of individual formulators or restrictions in the company policies (Section 2.2.4.2 (a)). The analysis of the use of different excipients based on dose and solubility only reflect a general trend of the use excipients. It does not necessary mean that the more popular excipients give a more superior performance than the less popular ones. Information from the experimental work (see Section 2.5) and published data (see Section 1.2 and 1.3) are both essential.

2.3 Databases of Drugs and excipients

In addition to the information regarding formulations on the market in five different countries (Section 2.2), qualitative information about the drugs and excipients in these formulations were also obtained. This information was assembled from a variety of international sources and standard references such as the pharmacopoeia from various countries, the *Handbook of Pharmaceutical Excipients* (1994), *Merck Index* (1989), *Martindale* (1993) and *Physicians' Desktop Reference* (1993).

The database was organised using dBaseIV version 1.5 software (Borland International, Inc.). Each entry for either a drug or an excipient contained the following details :

Non-proprietary names - with preference being given to British Approved Names (BAN). If unavailable, United States Adopted Names and other International Nonproprietary Names were adopted.

Alias names - In the database of drugs, alias names including commonly used abbreviated names; English/American/Latin synonyms; names used in other languages when these may not be readily identifiable. In the database of excipients, alias names included trade names used by suppliers.

Solubility - The solubility of drugs and excipients at 'ordinary room temperature' is considered to be about 20 - 25 °C as outlined in Martindale (1993), the major pharmacopoeias and Merck Index (1989). It was recorded in number of parts of water per part of drug (if known), otherwise the solubilities were suggested in words as defined in the British Pharmacopoeia (1993).

Incompatibility data - substances reported to be incompatible, physically and chemically with the drugs or excipients.

Storage - Conditions of which the substances and preparations should be stored to prevent contamination and diminish deterioration was recorded. The term ' a cool place' described a place in which the temperature does not exceed 15 °C.

The main pharmaceutical functions of each excipients, as described in the *Handbook of Pharmaceutical Excipients* (1994) were also captured.

At this stage, there is information of about 76 excipients and 256 drugs in the two databases.

2.4 Database of bibliography

A significant amount of knowledge contained in the Expert System was extracted from publications and references in the subject. The database of bibliography captured the sources of publications and references in capsule formulation. This database was constructed by information from two main sources, first from a bibliography organised by Jones and Newton in 1987 in the area of powder filled hard gelatin capsules which mainly covers the period between 1960 and up to the second half

of 1986 and secondly by systematically searching through the more recently published references which goes up to early 1994.

The data was again organised by the same computer software (Borland International, Inc.) as the database of drugs and excipients. Each record contains the information about author, source, title and keywords.

Author - the name of the authors and the year of the publication were recorded in this section.

Source - the source of the reference is recorded. If the source of information is a journal , then the name of the journal, the volume number and the page number will be given. If the source of information is a book, then the title of the book, the name of the editor, publisher and country of publication will be recorded.

Title - the title of the paper or the title of a particular section in a book are presented.

Keywords - this section briefly describes the content of the publication in simple words or phrases.

There are 1036 records in the database of bibliography of which 735 were from the bibliography edited by Jones and Newton (1987) and 301 were from the other sources.

2.5 Using data obtained from experiments to derive information

2.5.1 Background

The relationship between the formulation variables and their effect on the formulation are complex and cannot be predicted in simple terms. Investigations of these complex relationships would provide a better understanding of capsule formulation and help to improve the predictability of the system in recommending different types and amount of excipients for a particular drug. Rules or principles in capsule formulation can also be identified and incorporated in the process of construction of the decision tree.

Part of the observations or rules deduced in this Section was based on the observations published in Hogan et al (1996). Two multivariate statistical methods (parametric and non-parametric canonical analysis) were employed to investigate the influence factors on performance of capsule formulations for five drugs (phenytoin, theophylline, paracetamol, propranolol hydrochloride and aminophylline) (Hogan et al, 1996). A total of 33 formulations of different combinations of drug and excipients were studied (Table 2.11). These 33 formulations were formulated, based on a statistical design ("Centre of Gravity Design" deduced by Podczeck, 1986). Formula 15 (Table 2.11) is composed of formulation variables which constitutes the "centre" of the design. The influence variables or independent variables studied were the types of drugs (represented by the solubility and particle size of drug), level of drug or drug content, types and amount of diluent, types and amount of disintegrant, concentration of lubricant and concentration of glidant. The response variables or dependent variables were the flow properties of the drug mixture (represented by Hausner's ratio and Carr's compressibility index), filling performance (represented by the mean fill weight, standard deviation of fill weight and coefficient of variation of the fill weight), results of the dissolution test (represented by the area under the curve (AUC), the mean dissolution time (MDT) and the variance of dissolution time (VDT)) and results of the disintegration test (Table 2.12 and Table 2.13). These reponse variables provided an indication on the performance of the formulations.

Hogan et al (1996) showed that the major influence factors were the particle size of the drug, the amount of glidant used and the type of filler and disintegrant incoporated into the formulation. The concentration of the drug was also one of the important factors to be monitored. It was suggested that calcium phosphate should be excluded from capsule filling as the coefficient of fill weight variation for formulations that contained calcium phosphate were exceptionally high (Hogan et al, 1996). A requirement of a minimum amount of glidant of 0.5% and the optimum concentration of 1.0% were also mentioned (Hogan et al, 1996). The solubility of the drug was shown to dominate the disintegration and dissolution process and that the type of disintegrant and, in some cases, the type of the filler incorporated were also important influence factors. It was observed that the disintegration time tended to increase with increase in solubility of drug. It was explained that particles of the highly soluble drug competed with the disintegrant particles and thus impede the effectiveness of the disintegrants which

function mostly by their swelling properties (Hogan et al, 1996). The disintegration mechanism for starch was described to be by "redeformation of the starch particles into their original shape after contact with water causing a weakening of the plug structure". Hence, maize starch, the least swelling disintegrant, can also cause fast dissolution (Hogan et al, 1996). Solubility and particle size of drug were also found to be interacting factors affecting the mean dissolution time (Hogan et al, 1996).

In addition to the canonical analysis employed as described in Hogan et al (1996), cluster analysis were also applied, to the same data for influence and response variables, to study the relationship between the influence variables and the filling performance of these formulations. Additional observations concerning factors affecting drug release of capsule formulations might be obtained.

2.5.2 Cluster Analysis

Cluster analysis is a tool for detecting similarities in data (Hartung and Elpelt 1984). Each set of data was characterised by a combination of different influence and reponsive variables. The influence variables employed in cluster analysis must reflect a "property" of the subject under investigation. Therefore drug level, disintegrant level, lubricant level and glidant level could not be used. The response variables included maximum and minimum bulk densities, mean fill weight of capsules, standard deviation of fill weight and coefficient of variation of fill weight.

The aim of this analysis was to group these data into clusters or classes of similar objects. There are different types of classification in use, for example, partitioning and hierarchical classification. The clusters were classified by "partitioning with average linkage". Two types of indices were used : indices of homogeneity and indices of heterogeneity. By calculating the distance between each member of the cluster, the indices of homogeneity quantify the similarity between these members. According to Podczeck (1996), the indices of heterogeneity measured the distance between pairs of cluster by taking the average distance of all members of each cluster into account. Depending on these indices, the clusters were grouped in such a way that members in the same cluster have similar distances from each other (the most homogenic) and the distance between clusters and clusters were also optimised, in the other words, the most heterogenic to each other (Podczeck, 1996).

Table 2.11 : The 33 formulations of different combinations of drugs and excipients used in the Cluster analysis (Data from Hogan et al, 1996)

Formulation number (No.); mean particle size of drug (dvs, μm); solubility of drug (dsol, g/l); drug level (dq, %w/w); filler type (ft) (represented by an ordinal value : 5 for calcium phosphate, 4 for microcrystalline cellulose, 3 for maize starch, 2 for pregelatinised starch and 1 for lactose monohydarate); filler level (fq, %w/w); disintegrant type (dsgt) (determined by the relative swelling volume, sodium starch glycolate (1680%), croscarmellose sodium (600%), polacrillin potassium or Amberlite (190%), crospovidone (150%), maize starch (110%), Hogan et al, 1996); disintegrant level (dsgq, %w/w); lubricant (magnesium stearate) level (lubq, %w/w) and glidant (colloidal silicon dioxide or Aerosil) level (gliq, %w/w).

No.	dvs	dsol	dq	ft	fq	dsgt	dsgq	lubq	gliq
1	26.0	15.0	50.0	2.0	44.0	1680	5.0	1.0	0.0
2	26.0	15.0	50.0	2.0	43.5	1680	5.0	1.0	0.5
3	26.0	15.0	50.0	2.0	42.5	1680	5.0	1.0	1.5
4	26.0	15.0	50.0	2.0	42.0	1680	5.0	1.0	2.0
5	26.0	15.0	50.0	2.0	44.0	1680	5.0	0.0	1.0
6	26.0	15.0	50.0	2.0	43.5	1680	5.0	0.5	1.0
7	26.0	15.0	50.0	2.0	42.5	1680	5.0	1.5	1.0
8	26.0	15.0	50.0	2.0	42.0	1680	5.0	2.0	1.0
9	26.0	15.0	50.0	2.0	48.0	1680	0.0	1.0	1.0
10	26.0	15.0	50.0	2.0	45.5	1680	2.5	1.0	1.0
11	26.0	15.0	50.0	2.0	41.5	1680	7.5	1.0	1.0
12	26.0	15.0	50.0	2.0	38.0	1680	10.0	1.0	1.0
13	65.0	0.2	50.0	2.0	43.0	1680	5.0	1.0	1.0
14	57.0	8.0	50.0	2.0	43.0	1680	5.0	1.0	1.0
15	26.0	15.0	50.0	2.0	43.0	1680	5.0	1.0	1.0
16	122.0	50.0	50.0	2.0	43.0	1680	5.0	1.0	1.0
17	26.0	200.0	50.0	2.0	43.0	1680	5.0	1.0	1.0
18	26.0	15.0	20.0	2.0	73.0	1680	5.0	1.0	1.0
19	26.0	15.0	35.0	2.0	58.0	1680	5.0	1.0	1.0
20	26.0	15.0	65.0	2.0	28.0	1680	5.0	1.0	1.0
21	26.0	15.0	80.0	2.0	13.0	1680	5.0	1.0	1.0
22	26.0	15.0	50.0	1.0	43.0	1680	5.0	1.0	1.0
23	26.0	15.0	50.0	3.0	43.0	1680	5.0	1.0	1.0
24	26.0	15.0	50.0	4.0	43.0	1680	5.0	1.0	1.0
25	26.0	15.0	50.0	5.0	43.0	1680	5.0	1.0	1.0
26	26.0	15.0	50.0	2.0	43.0	600	5.0	1.0	1.0
27	26.0	15.0	50.0	2.0	43.0	190	5.0	1.0	1.0
28	26.0	15.0	50.0	2.0	43.0	150	5.0	1.0	1.0
29	26.0	15.0	50.0	2.0	43.0	110	5.0	1.0	1.0
30	26.0	15.0	50.0	1.0	48.0	1680	0.0	1.0	1.0
31	26.0	15.0	50.0	1.0	38.0	1680	10.0	1.0	1.0
32	26.0	15.0	50.0	5.0	48.0	1680	0.0	1.0	1.0
33	26.0	15.0	50.0	5.0	38.0	1680	10.0	1.0	1.0

Table 2.12 : Results obtained for the response variables in terms of packing and filling performace

(Data from Hogan et al, 1996)

Formulation number (No.), Minimum bulk density (Dmin), maximum bulk density (Dmax), Hausner's ratio (H), Carr's compressibility index (Carr), mean fill weight (mfw) (not published), standard deviation of fill weight (sd) (not published) and coefficient of variation of fill weight (cv).

No.	Dmin g/cm	Dmax g/cm	H	Carr (%)	mfw (mg)	sd	cv (%)
1	0.505	0.825	1.63	38.79	491.4	74.16	15.09
2	0.500	0.790	1.58	36.71	527.1	6.29	1.19
3	0.455	0.720	1.58	36.81	478.5	11.47	2.40
4	0.430	0.680	1.58	36.76	452.7	5.80	1.28
5	0.500	0.760	1.52	34.21	506.7	12.73	2.51
6	0.500	0.720	1.44	30.56	476.1	8.85	1.86
7	0.480	0.710	1.48	32.39	478.5	6.53	1.36
8	0.470	0.700	1.49	32.86	470.3	5.57	1.18
9	0.490	0.720	1.47	31.94	479.0	4.56	0.95
10	0.495	0.740	1.49	33.11	494.4	3.90	0.79
11	0.495	0.710	1.43	30.28	474.4	6.83	1.44
12	0.485	0.745	1.54	34.90	503.4	20.45	4.06
13	0.545	0.785	1.44	30.57	524.9	7.36	1.40
14	0.555	0.795	1.43	30.19	530.1	3.84	0.72
15	0.490	0.740	1.51	33.78	495.3	3.71	0.75
16	0.625	0.830	1.33	24.70	552.6	10.51	1.90
17	0.530	0.800	1.51	33.75	538.3	4.82	0.90
18	0.550	0.780	1.42	29.49	521.3	4.19	0.80
19	0.515	0.755	1.47	31.79	502.8	4.94	0.98
20	0.445	0.670	1.51	33.58	443.8	10.57	2.38
21	0.405	0.620	1.53	34.68	416.5	14.87	3.57
22	0.540	0.800	1.48	32.50	533.0	4.52	0.85
23	0.455	0.725	1.59	37.24	483.2	6.03	1.25
24	0.395	0.575	1.46	31.30	382.1	6.26	1.64
25	0.385	0.640	1.66	39.84	355.3	65.80	18.52
26	0.445	0.730	1.64	39.04	490.3	4.10	0.84
27	0.460	0.720	1.57	36.11	485.2	5.42	1.12
28	0.435	0.685	1.57	36.50	458.9	5.04	1.10
29	0.460	0.730	1.59	36.99	488.0	4.67	0.96
30	0.545	0.830	1.52	34.34	557.1	13.46	2.42
31	0.530	0.805	1.52	34.16	534.9	7.04	1.32
32	0.395	0.610	1.54	35.25	288.4	59.61	20.67
33	0.415	0.650	1.57	36.15	424.2	25.21	5.94

Table 2.13 : Results obtained for the response variables in terms of drug release (Data from Hogan et al, 1996)

Formulation number (No.), Disintegration time (DT), area under dissolution curve (AUC), mean dissolution time (MDT) and variance of dissolution time (VDT).

	Disintegration test	Dissolution test		
No.	DT (min)	AUC (%.min)	MDT (min.)	VDT (min.min)
1	10.5	2480.2	28.6	106.6
2	8.6	1268.4	15.1	23.1
3	8.2	956.8	12.5	14.0
4	7.5	1906.7	19.0	42.4
5	6.9	1994.0	18.1	54.9
6	7.2	1733.3	17.4	33.0
7	8.4	1869.4	18.8	49.5
8	10.4	1774.6	17.3	45.5
9	9.0	1069.3	11.0	16.3
10	8.2	2087.5	20.8	72.4
11	7.7	2719.2	25.5	111.4
12	7.9	1833.7	19.7	55.9
13	6.6	200000.0	2000.0	200000.0
14	8.2	1979.6	19.1	70.6
15	9.9	706.3	9.0	7.8
16	7.6	2992.8	28.3	128.4
17	11.5	1571.0	22.3	41.3
18	7.5	1361.5	16.4	31.2
19	7.7	1592.7	16.9	45.6
20	7.4	2486.0	22.6	98.7
21	11.4	2032.2	18.8	74.8
22	10.8	2044.3	19.0	68.1
23	7.4	3080.9	28.1	147.8
24	7.0	1260.9	12.7	27.3
25	7.6	2011.5	19.9	56.6
26	7.7	1546.0	16.3	40.0
27	9.3	3356.4	29.1	172.8
28	9.8	3682.8	29.6	229.3
29	7.6	1335.5	14.5	29.4
30	12.1	7121.4	70.4	840.5
31	8.9	2797.5	25.0	117.1
32	10.0	82318.8	760.1	117068.5
33	7.3	2467.31	25.1	86.3

Five combinations of influence variables and response variables were investigated (Table 2.14). In each of these combinations, one influence variables and several response variables were involved in order to magnify the effect of the influence variable on the response variables. The data in each of these combinations were then split into four, six and eight clusters. Formation of six clusters provided an optimum. In this study, only the results obtained by grouping the data into six clusters are reported.

Table 2.14 : Combinations of variables used in clusters analysis

Solubility of drug (dsol), mean particle size (volume distribution) of drug (dvs), type of filler (ft), type of disintegrant (dsgt), minimum bulk density (Dmin), maximum bulk density (Dmax), mean fill weight (mfw), coefficient of variation of fill weight (cv).

combination no.	variables	purposes
1	dsol, Dmin, Dmax, mfw, cv	effect of drug solubility on filling factors
2	dvs, Dmin, Dmax, mfw, cv	effect of particle size-volume distribution of drug on filling factors
3	ft, Dmin, Dmax, mfw, cv	effect of types of fillers on filling factors
4	dsgt, Dmin, Dmax, mfw, cv	effect of types of disintegrants on filling factors
5	dsol, Dmin, Dmax, cv	effect of drug solubility on filling factors (without mean fill weight)

Results

In combination 1 (Table 2.14), the variables involved were drug solubility, minimum and maximum bulk density, mean fill weight and coefficient of variation of fill weight. The 33 formulations were grouped into six clusters based on the data obtained for these variables (Table 2.11 and Table 2.12). The mean value of each variable in each cluster and the member of these clusters were shown in Table 2.15 (a)

and (b) respectively. Most of the formulations were grouped in cluster 5. Cluster 5 could be described as the cluster that represented the 'average performance'. Cluster 2 had high mean value of solubility of drug variable (200 g/l) and high average value of mean fill weight variables (538 mg) (Table 2.15 (a)) and contained only one member (formula 17) (Table 2.15 (b)). The excipients in formula 17 were similar to most other formulations but the drug was different. Therefore the properties of drug were thought to contribute to the cause of the separation of formulation 17. This formulation contained aminophylline which has solubility of 200 g/l (the same as the mean value of soluble variable (dsol) in cluster 2) and it produced a mean fill weight of 538.3 mg (Table 2.12), similar to the average value of the mean fill weight (mfw) variable of cluster 2. The maximum bulk density of this formulation was also high (0.8 g/cm^3) and therefore it was not surprising that the mean fill weight of the capsules would be greater than other formulations. This indicated the importance of solubility and bulk density of the drug in formulation design. Formulation 32 was isolated in cluster 4 (Table 2.15 (b)). Cluster 4 had a high coefficient of variation of the fill weight (20.6%). Formula 32 contained calcium phosphate (48% w/w) as a filler and the other ingredients were similar to ingredients in other formulations. Calcium phosphate was therefore thought to be the cause of the high coefficient of variation of fill weight. The Carr's compressibility index of this formula was 35.25 % (Table 2.12) and from this value it was predicted that the drug mixture of formula 32 has poor flow properties and this may explain the phenomenon of the increase variation in fill weight. Formulation 24 and 25 were grouped in cluster 1 which also had high coefficient of variation of fill weight (mean value of 15%) and low mean fill weight (mean value of 360 mg) (Table 2.15 (a)). Formulation 24 and 25 contained microcrystalline cellulose and calcium phosphate as fillers respectively. Both formulations had low mean fill weight of 382.1 mg and 355.3 mg respectively (Table 2.12) but the coefficient of variation of fill weight for formulation 24 and 25 were 1.64% and 18.52% respectively (Table 2.12). It was surprising that formula 24 was classified in cluster 1. The coefficient of variation for formula 24 was quite different from the mean value of this cluster (15%) (Table 2.15 (a)). It was thought that the mean fill weight of the formulation may influence the classification of the data. The mean fill weight of formula 24 (382.1 mg) was very similar to the average value of the mean fill weight of cluster 1 (360 mg). The classification of formula 24 into this cluster may be dominated by its mean fill weight. Therefore in combination 5 (Table 2.14), the analysis was carried out without the mean

fill weight variable. Cluster 3 had relatively high mean fill weight (553 mg), low coefficient of variation of the fill weight (1.9 %) and mean solubility of 45 g/l. This cluster contained two members, formulation 16 and 30. Formula 16 contained propranolol with a solubility of 50 g/l and formula 30 contained paracetamol (solubility of 15 g/l). Unlike most other formulations, formula 30 contained no disintegrant. Formula 16 and 30 produced mean fill weight of 552.6 mg and 557.1 mg with coefficient of variation of fill weight of 1.9% and 2.42% respectively. Compared to formula 15 (the centre of the design) (Section 2.5.1) which had coefficient of variation of fill weight of 0.75% (almost the lowest), formulae 16 and 30 had higher variation in fill weight. Although the solubility of the drug was used to represent the type of drug being used, particle size of drug may play a more important role in the filling performance of the formulations. Indeed, the mean particle size (volume distribution) of propranolol was 122 μm (the greatest among the five drugs) compared to 26 μm (paracetamol) in formula 15. Similar to the observation obtained in canonical analysis (Hogan et al, 1996), particle size of drug may affect the filling performance of the drug mixture. Formulations 4, 8 20, 21, 28 and 33 showed a trend of increasing coefficient of variation of fill weight and were all classified in cluster 6. Formula 4 and 8 contained a high level of glidant (2% w/w of Aerosil) and a high level of lubricant (2% w/w of magnesium stearate) respectively. It was observed that optimum levels of lubricant and glidant are needed. In formula 15 (the centre of the design) where 1% of Aerosil and 1% of magnesium stearate were used, the coefficient of variation of fill weight was almost the lowest (0.75%) (Table 2.12). In formulations that contained more or less than 1% w/w of Aerosil or magnesium stearate (formulation 1 - 8), the coefficient of variation of fill weight increased. The level of drug content is also important. Formula 15 contained 50% w/w of paracetamol. Formula 20 and 21 contained 65% w/w and 80% w/w of the same drug and had increased variation in the mean fill weight with coefficient of variation of fill weight of 2.38% and 3.57% respectively (Table 2.12). Compared to formula 15 (the centre of the design), formula 28 contained 5% w/w of crospovidone as disintegrant and pregelatinised starch as diluent and formula 33 contained 10% w/w of sodium starch glycolate as disintegrant and calcium phosphate as diluent. Formula 28 and 33 had coefficient of variation of fill weight of 1.1% and 5.94% respectively (Table 2.12). Formula 15 contained 5% of sodium starch glycolate as disintegrant and pregelatinised starch as diluent produced a coefficient of variation of fill weight of only 0.75%. Calcium phosphate may increase coefficient of variation of

fill weight in formula 33. It was therefore implied that by changing the type and amount of disintegrant used or by changing the type of diluent used, the variation of filling performance was also affected.

The intention of using combinations 1- 4 (Table 2.14) was to focus on the effect of the one influence variable on the four response variables in each combination, as mentioned before. Interestingly, the members of the six clusters obtained from these four combinations were the same. This was probably due to the fact that the response variables subjected to the analysis were identical and therefore the outcome of the way these six clusters were classified were also similar. The result obtained from combination 2 to 4 which were similar to combination 1 were therefore not repeated in this report.

Combination 5, however, was analysed again with one influence factor with only three response variables (represented minimum and maximum bulk densities and coefficient of variation of fill weight). The mean fill weight was not included as one of the response variables because there was evidence to support the hypothesis that this variable may affect the way the clusters were grouped (as explained before, for the classification of formula 24 in cluster 1 for variables in combination 1 (Table 2.14)). The influence factor employed in this combination was the solubility of the drug. In Table 2.16, the average value of the variables in each of the six clusters and members in each cluster were shown. Formulation 1, 25 and 32 were classified together in cluster 1 which had high coefficient of variation of fill weight (19.3%) (Table 2.16 (a)). Formulation 1 contained no glidant and this could be the reason why this formula has coefficient of variation of fill weight of as high as 15.09% (Table 2.12). Similar to the result obtained in combination 1, formula 25 and 32, both contained calcium phosphate as diluent were grouped together in a cluster of high coefficient of variation in fill weight. Formulation 13, 17, 16 and 14 were isolated in cluster 2, 3, 5 and 6 respectively. Each of these formulations contained a different drug. The classification of these formulations seemed to be dominated by the solubility of the drugs. The mean value of solubility of drug (dsol) variable in clusters 2, 3, 5 and 6 were 2 g/l, 200 g/l, 50 g/l and 8 g/l (Table 2.16 (a)) whereas the drug contained in the formula 13, 17, 16 and 14 were 0.2, 200, 50 and 8 g/l respectively. Extra information, however, was not demonstrated by the results obtained from combination 5.

Table 2.15 : Results for combination 1 - average value of the variables in each of the six clusters and members in each cluster

a) Average value of the variables in each clusters					
cluster no.	dsol	Dmin	Dmax	mfw	cv
1	15	0.39	0.63	360	15
2	200	0.53	0.8	538	0.9
3	45	0.63	0.83	553	1.9
4	15	0.4	0.61	288	20.6
5	10.7	0.51	0.78	510	2.81
6	15	0.42	0.66	434	4.51

b) Members in each cluster (represented by the formulation number shown in Table 2.11) :	
1	24, 25
2	17
3	16, 30
4	32
5	1, 2, 3, 5, 6, 7, 9, 10, 11, 12, 13, 14, 15, 18, 19, 22, 23, 26, 27, 29, 31
6	4, 8, 20, 21, 28, 33

For abbreviations, see Table 2.11 and 2.12.

2.5.3 Other Observations

From the results obtained from the disintegration test and dissolution test (Table 2.13), trends between formulation factors and drug release could be observed. From the canonical analysis (Hogan et al, 1996), some of these observations were mentioned in Section 2.5.1. Other observations relating to the fillers, disintegrants and lubricant employed were also made.

Table 2.16 : Results for combination 5 - average value of the variables in each of the six clusters and members in each cluster

a) Average value for variables in each cluster				
cluster no.	dsol	Dmin	Dmax	cv
1	15	0.44	0.67	19.3
2	2	0.55	0.79	1.40
3	200	0.53	0.80	0.89
4	15	0.47	0.71	3.20
5	50	0.50	0.83	1.90
6	8	0.55	0.80	0.72

b) Members in each cluster (represented by the formulation number shown in Table 2.11) :	
1	1, 25, 32
2	13
3	17
4	2,3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15, 18,19,20,21,22,23,24,26,27,28,29,30,31,33
5	16
6	14

For abbreviations, see Table 2.11 and 2.12.

a) Disintegrant level

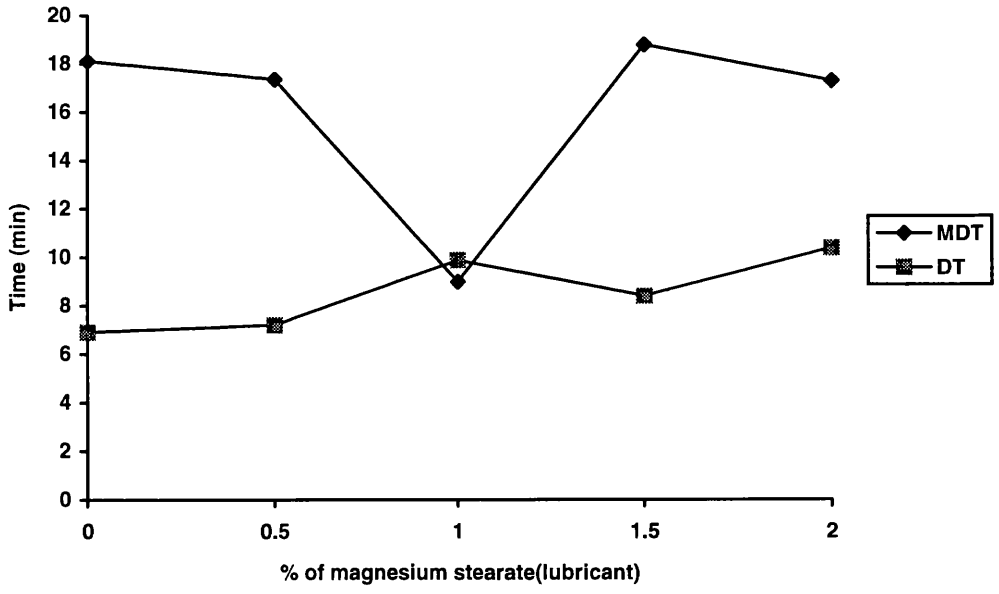
There was an optimum concentration at which the disintegrant was the most effective for drug release. Sodium starch glycolate was used in most formulations (Tabe 2.11). Formula 9 - 12 (Table 2.11) employed sodium starch glycolate of a range between 0 - 10% w/w (0%, 2.5%, 7.5% and 10%) whereas formula 15 contained 5% of sodium starch glycolate. The mean dissolution time for the formula containing 5% of sodium starch glycolate was the shortest (9.04 mins). The mean dissolution time increased as the content of sodium starch glycolate increased or decreased. The mean dissolution time for formulae containing 0%, 2.5%, 7.5% and 10% of sodium starch

glycolate were 10.95 mins, 20.76 mins, 25.49 mins and 19.72 mins (Table 2.13). The observation that 5% w/w of sodium starch glycolate being the optimum concentration of disintegrant is also supported by Botzolakis and Augsburger (1988a). Botzolakis and Augsburger (1988a) found that both 5% and 7% of sodium starch glycolate had significant influence on the release of drug. At a lower concentration, the swelling was insufficient whereas at a higher concentration, the penetration of the dissolution medium was impeded by the thicker gel formed (Botzolakis and Augsburger (1988a).

b) Lubricant level

In formula 5 - 8, a range of lubricant level was used (0%, 0.5%, 1.5% and 2% Table 2.11) and formula 15 employed 1% of magnesium stearate. The mean dissolution time was the lowest when 1% of magnesium stearate was used and as the concentration of magnesium stearate increased or decreased, the mean dissolution time also increased (Table 2.13, Figure 2.3). The optimum level of lubricant, in terms of formulation performance based on drug release, was 1%.

Figure 2.3 : The effect of lubricant level on mean dissolution time (MDT) and disintegration time (DT) for paracetamol capsules



c) Filler type

Fillers such as pregelatinised starch and microcrystalline cellulose, which are reported to have a disintegration effect (*The Handbook of Pharmaceutical Excipients*, 1994), were found to have shorter mean dissolution time (9.04 mins for formula 15 and 12.68 mins for formula 24) compared to formulations contained lactose monohydrate (formula 22) and calcium phosphate (formula 25) as fillers (about 19 mins for both formula 22 and 25) (Table 2.13). Pregelatinised starch and microcrystalline cellulose are the fillers for formula 15 and 24 respectively and both formulae contained 5% of sodium starch glycolate as disintegrant. For formulations that contained pregelatinised starch as filler, it was indicated that the inclusion of a disintegrant did not necessary make a significant difference in the mean dissolution time. In fact, formula 9 containing pregelatinised starch and no disintegrant, had a mean dissolution time of 10.95 mins (compare to 9.04 mins for formula 15). On the contrary, this may not be the case with maize starch which is also a disintegrant. Formulation 23, which contained 43% of maize starch as filler with 5% of sodium starch glycolate (Table 2.11), produced a relatively high mean dissolution time of 28.06 mins (Table 2.13). Although the mean dissolution time may be decreased by inclusion of a filler with disintegration effect such as pregelatinised starch and microcrystalline cellulose, decrease of mean dissolution time was not observed for formulations containing maize starch as the filler.

d) Disintegrant type

Hogan et al (1996) mentioned that maize starch as a disintegrant caused fast dissolution. Formula 29 which contained 5% of maize starch had mean dissolution time of 14.5 mins and disintegration time of 7.6 mins (Table 2.13). From Table 2.13, the result of the disintegration and dissolution test also suggested that 5% w/w croscarmellose sodium (formula 26) and 5% w/w sodium starch glycolate (formula 15) were also effective. The mean dissolution time and disintegration time of formula 26 were 16.3 mins and 7.7 mins respectively while formula 15 also has a relatively short mean dissolution time (9.0 mins) and disintegration time of 9.9 mins (Table 2.13).

e) Combination effects of disintegrant and filler

When no disintegrant was used, the solubility of the filler in the formulation affects the dissolution markedly. In the absence of a disintegrant, the mean dissolution time for formulation containing a soluble diluent (lactose) (formula 30) was ten fold faster than the formulation containing an insoluble filler (calcium phosphate) (formula 32) (Table 2.13). However, when a disintegrant was included in the formulation, the difference between the mean dissolution time was less obvious. In formula 22 and 25, the filler was lactose and calcium phosphate respectively together with an addition of 5% sodium starch glycolate acting as a disintegrant. The mean dissolution time for both formulations were similar (about 19 mins,Table 2.13). In the cases of an addition of 10% sodium starch glycolate (formula 31 and 33), the mean dissolution time were about 25 mins in both cases. This suggested that the solubility of filler, present in a significant level (in this study, filler level is greater than 40%), does influence the dissolution of the drug. However, the impediment caused by an insoluble filler could be compensated by the inclusion of an adequate level of an effective disintegrant.

2.5.4 Observations deduced for the decision trees

The relationship between the formulation design factors and performance of the formulations were complicated. Although considerable amount of information were extracted by the analysis described in this section and contributed considerably to the building of the decision tree, only a small part of the knowledge in capsule formulation could be captured. The following provides a brief recapitulation of the observations obtained in this study :

Observation 1 : Calcium phosphate should be avoided in capsule formulation due to high coefficient of variation of fill weight obtained in all formulations containing calcium phosphate (Section 2.5.1 and 2.5.2).

Observation 2 : Fillers such as lactose, maize starch, microcrystalline cellulose and pregelatinised starch gave reasonable filling performance as formulations contained these fillers were not isolated in clusters with poor filling performance (Section 2.5.2).

Observation 3 : Powder formulation, in absence of glidant, may have high variation in fill weight (Section 2.5.2).

Observation 4 : Solubility and particle size of drug were shown to affect the dissolution rate and the filling performance. If the particle size of the drug is too large, the coefficient of variation of fill weight may increase (Section 2.5.2). Increased solubility of drug also tends to increase disintegration time of drug due to competition with water between the drug and disintegrant (Section 2.5.1). The dissolution rate was found to be related to the combined effect of both the solubility and the particle size of drug (Section 2.5.1).

Observation 5 : A high level of drug or any type of excipients except filler may cause problems (Section 2.5.2).

Observation 6: The optimum level of magnesium stearate (lubricant), in terms of filling performance and drug release, was 1% (Section 2.5.2 and 2.5.3 (b)).

Observation 7 : The optimum level of sodium starch glycolate (disintegrant) is 5% (Section 2.5.3 (a)).

Observation 8 : There was an optimum Aerosil (glidant) level in order to achieve good filling performance. This level was shown to be 1% in this study (Section 2.5.1 and Section 2.5.2).

Observation 9 : The impediment to the dissolution process caused by an insoluble filler could be compensated by an inclusion of an adequate level of an effective disintegrant (5% sodium starch glycolate) (Section 2.5.3 (e)).

Observation 10 : Among the five disintegrants under investigation, croscarmellose sodium, sodium starch glycolate and maize starch were effective. (Section 2.5.3 (d)).

Observation 11 : Maize starch, if incorporated as a disintegrant, produces fast dissolution (Section 2.5.1) but for formulations containing 43% of maize starch (act as filler), a slow dissolution was observed (Section 2.5.3 (c)).

Note : observations described in Section 2.5.1 were published in Hogan et al (1996).

2.6 Summary of the chapter

Databases which stored information related to capsule formulation were constructed. Theses databases included a database of formulations on the market (Section 2.2), a database of drugs and excipients (format shown in Section 2.3) and database of bibliography (published references) (format shown in Section 2.4). Information that was deduced from practical experiments also formed part of the databases (Section 2.5). In this chapter, the construction of these databases was described and the observations deduced from the database of marketed formulations and the practical experiments were also reported.

From the database of marketed formulations, the trend of the use of different types of excipients were identified (Section 2.2). The commonly used diluents, disintegrants, lubricants, glidants and wetting agents were recognised. The trend between between the incorporation of these excipients and dose / solubility of drugs were also evaluated. The system contained default lists of different types of excipients which was built partially by using this information.

Nevertheless, the above-mentioned analysis only reflected a general trend in the use of excipients and it did not relate the different types and level of these excipients and the types of drugs to the performance of the formulations. Practical experiments, as described in Section 2.5, were considered to investigate such relationships and the observations derived were also available to aid the construction of the decesion tree.

The knowledge captured in these databases coupled with those collected from the published literature (Section 1.2 and 1.3), together with the help of the experienced expert formulators, were available for organisation in the form of a decision tree. It is the decision tree which controlled the operation of the system. Its organisation will be described in the next chapter.

Chapter 3

Rules and Decision Tree

3. Rules and Decision Tree

3.1 Introduction

Bearing in mind that the main aim of this program is the possibility to generate a robust formulation for a drug at an early formulation development stage with only limited information about the drug, crucial factors affecting capsule formulations are identified to create a "sound" foundation in the subject and to allow the more complicated branches to be built on in the future.

In view of the complicated factors affecting capsule formulation as discussed in Section 1.3, Section 2.2 and Section 2.5, the knowledge captured so far must be organized in a logical order, for example in the form of a decision tree, such that all the information can be programmed in a lucid manner. The decision tree can be arranged in the form of a "tree" with a "tree trunk", "main branches" and "minor branches". The "tree trunk" act as the backbone of the program and is made up of the "main branches". The program, like the "tree" can be divided into smaller parts called routines i.e. the "main branches". These routines can be divided into sub-routines i.e. the "minor branches". The system is programmed according to the way the decision tree is built. However, the building of the decision can be complicated. The factors involved in capsule formulations are not only complicated, in many cases, they interact or counteract each other. For example, magnesium stearate is an effective lubricant that helps to decrease variation in fill weight but its hydrophobicity may also cause problems in drug release (Section 1.3.2.3); the dissolution rate of capsule formulations was found to be affected by the interactions of solubility and particle size of drug (Section 2.5.4, Observation 4). To achieve the balance, the contributions by the experienced formulators in the building of the decision tree also played an important role.

In this chapter, the interpretation of the information captured in the database into the decision tree is described. Each routine that made up the decision tree will be described individually but these routines, if arranged in appropriate order, can build up a picture of the whole "tree" (Appendix IV).

3.2 Construction of the decision tree

3.2.1 Suitability for hard gelatin capsules

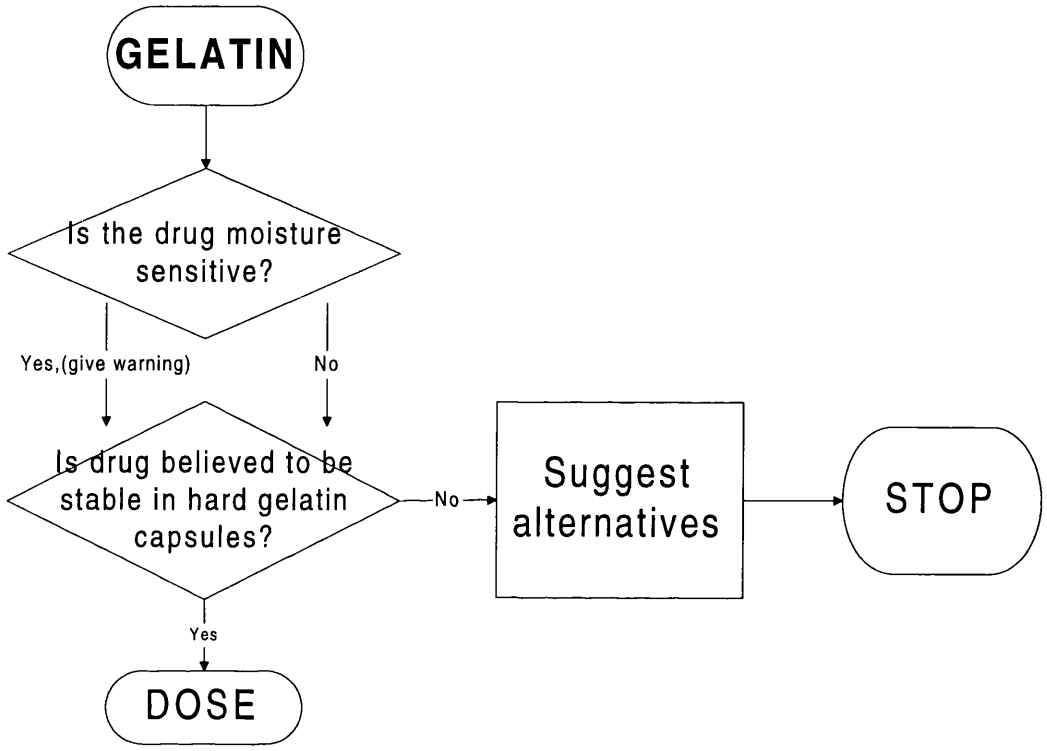
The first step in considering whether a drug can be formulated into hard gelatin capsules would be based on the stability issue, for example, moisture sensitivity of drug and compatibility of the drug with gelatin capsules.

The possibility of the transfer of moisture between gelatin capsule shell and capsule content if their moisture content is not in equilibrium may affect both the integrity of the capsule shell and the drug (Section 1.3.1.6). It was also stressed that the definition of moisture sensitivity may depend on the processes such as type of granulation it undergoes and condition of storage. A definite description of moisture sensitivity is not available, although the result obtained from stability testing may provide some guidelines (Section 1.3.1.6). The equilibrium moisture content values of the gelatin shells and the drugs may also help to predict both the best starting moisture contents for the raw materials and the probable stability of the finished product (Section 1.3.1.6). Great care should be taken if a potentially moisture sensitive drug is to be encapsulated. However, even if the drug is not moisture sensitive, it may crosslink with the gelatin capsule shell and lead to formation of an insoluble pellicule film (Section 1.3.3.1) and thus affect the dissolution stability of the capsule formulation. The drug may also interact with the gelatin capsules (Section 1.3.3.1) and affect the stability of the capsule formulation. In such case, where the drug is not compatible with gelatin capsule shell, formulation as powder mixture into hard gelatin capsules is not a suitable oral dosage form for the drug. Alternative suggestions such as to fill the capsules with coated drug are made. However, the system is only aiming to formulate powder or granule filled hard gelatin capsule at this stage and further advice in areas such as coating is not available. It will be meaningless to proceed with the system any further.

If the drug is potentially moisture sensitive but it is compatible with hard gelatin capsules, then the possibility of formulating into hard gelatin capsules should not be denied. However, a remark that the drug is moisture sensitive and that the moisture content contained in the gelatin shells may affect the stability of the drug is provided.

The above decisions is summarized in the 'GELATIN' routine of the system and a diagrammatic representation can be found in Figure 3.1.

Figure 3.1 : 'GELATIN' routine of the system



'DOSE' is the next routine in the system.

3.2.2 Dosage of drug

If the drug is suitable for capsule formulation, the dosage of drug could be another restraint in formulation into hard gelatin capsules. According to the experience of the formulators, if the dose is greater than 1000 mg, it is not likely that the drug can be fitted into the capsules. Such proposed suggestion can be confirmed by a simple calculation. For example, the volume of a capsule shell of size 00 is 0.95 cm^3 (Section 1.2) and assuming that the average maximum bulk density of a drug is 0.7 g/cm^3, the maximum amount of drug that can be fitted into the capsule shell is 665 mg. Therefore, if the dosage of drug is greater than 500 mg, the possibility of having problems to fit the

drug into the capsule shells increases and if the dose is greater than 1000 mg, such problem is probably unavoidable and unless the dose can be reduced, there is little meaning to proceed to formulate a drug which cannot be filled into the capsule shell. If the dose cannot be altered, other possibilities such as to compact or densify the drug prior to formulation would be advisable but information about the densified product is needed before the system can proceed.

Dosage of drug is generally not a restraint for capsule formulation if the dose is smaller than 500 mg but it would have important effects on the choice of excipients. For example, if the dose of drug is low, there is more space available for excipients and provide greater flexibility in choice of excipients and if the dose is high, the choice of capsule size will be more limited and the physical properties of the drug mixture will tend to be governed by the drug (Section 1.3.5.1). With the experience of the formulators who participated in the process of construction of the decision tree, it was agreed, based on debate of the known practices, to divide the dosage of drug into five different classes (Table).

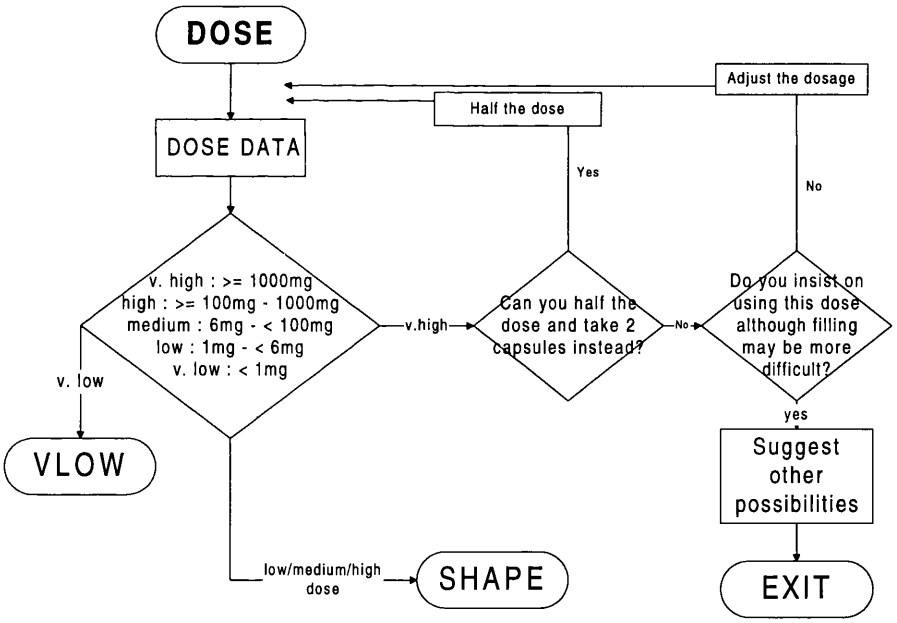
Table 3.1 : Classification of the dosage of drug by the system

Dose	Description of category
greater than 1000 mg	very high dose
between 100 mg and 1000 mg	high
between 6 mg and 100 mg	medium
between 1 mg and 6mg	low
less than 1 mg	very low

A dose of greater than 1000 mg is very high and merely packing the drug into the capsule size will be difficult and unless the dose is reduced, the system would not proceed. Dose of drug of greater than 99 mg to 1000mg can be described as high dose and for dose smaller than or equal to 500mg, it is likely that the drug would fit into the capsules without reducing the dose although not much space would be available for the excipients. A dose of 6 mg to 100 mg is categorized in the class of a medium dose

whereas a dose of 1 mg to less than 6 mg is in the class of a low dose drug. As the dose decreases, the flexibility in the choice of excipients increases. More information about the drug and excipients are required. In most cases, the dose of drug will be classified in the low, medium or high dose category. However, cases where the dose of drug is less than 1 mg are not impossible for the more potent drugs. For a dose of such small quantity, it becomes difficult to distribute the drug evenly throughout the drug mixture and the uniformity of drug content becomes crucial for the formulation process. The properties of the excipients would dominate the nature of the formulation. Special treatments may thus be needed for a dose of less than 1 mg strength (Section 3.2.3). The schematic flow chart diagram in Figure 3.2, 'DOSE' routine, summarized the decisions discussed so far.

Figure 3.2 : 'DOSE' routine of the system



'SHAPE' is the next routine in the system for high, medium and low dose drug.

'VLOW' is the next routine in the system for very low dose drug.

3.2.3 Formulation for very low dose drug (less than 1 mg)

The challenge of formulating a drug of such a small quantity (less than 1 mg) lies in the uniform distribution of the drug and thus the provision of the uniformity of drug content for the capsules. The use of different techniques and equipments in mixing plays an important role when preparing the drug mixture. An Expert System called POMM in powder mixing at Laurentian University was described by Kaye (1991b). The mixing process, being a complicated subject as reviewed in Kaye (1991a), is not an area the system covers at this stage. For the time being, the system focuses on the formulation aspect of the drug.

Another method to improve the distribution of the minor component (the drug in this case) in the powder mixture and to prevent segregation of the constituents in the powder mixture is the use of wet granulation (Jones et al, 1988). Since the system, at this stage, only focuses on the formulation aspect of the drug, the details of the granulation techniqnes and method will not be covered. However, the use of binder (one of the component in the formula) will be included (Section 3.4).

According to Stewart et al (1979), the possible retardation of drug release by the diluent is also an area of concern for formulation of very low dose drug (Section 1.3.2.1). The major ingredient of a formulation containing drug of such a low dose is the diluent. In Section 1.3.2.1, the choice of diluent was shown to be fundamental for formulation of low dose drug and that the interactive effect between diluent and hydrophobic lubricant (magnesium stearate) was obvious. Hydrophilic soluble diluent such as lactose can counteract the hydrophobic nature of magnesium stearate (Section 1.3.2.1). According to the information extracted from the database of formulations on the market Section 2.2.4, lactose, microcrystalline cellulose and maize starch were found to be used quite extensively in capsule formulations. Since a high level of diluent is usually incorporated for formulation of very low dose drug, the economic factor becomes more prominent. Microcrystalline cellulose is relatively expensive (Section 1.3.5.2) and therefore is not as favourable as lactose and maize starch. Lactose and then maize starch were agreed, by the experienced formulators who participated in the construction of decision tree, to be the choice of diluent for very low dose drug.

In the system, the choice of diluent agreed by the experienced formulators would become the default by the system i.e. the system would recommend the diluent for the formulations following the order in which the default diluents are arranged although the possibility to override the suggestions recommended by the system is also provided. There are several lists of default diluents in the system. The one that concerns the formulation of very low dose drug is called 'DILUENT L' which contains lactose and then maize starch as the choice of diluent for very low dose drug (also see Section 3.3.2).

Other excipients such as disintegrant and lubricant are also included in the basic mixture for very low dose drug. A lubricant is incorporated to reduce friction between granules and thus to ensure good flow of the granules (Section 1.3.2.3). A disintegrant is included to ensure disruption of granules and thus drug release (Section 1.3.2.2). The use of disintegrant such as sodium starch glycolate can also counteract the deleterious effect, in terms of drug release, of the hydrophobic lubricant (Section 1.3.2.2). The choice of type and amount of lubricant and disintegrant used are described in Section 3.3.4 and Section 3.3.3 respectively.

A glidant is normally incorporated to improve the flow of powder mixture and can also act as an anti-static agent Section 1.3.2.4). For formulation of very low dose drug where granulation is employed, the incorporation of a glidant is probably unnecessary because granules generally have improved flow properties, provided that the size of the granules is not too fine (Section 1.3.1.1).

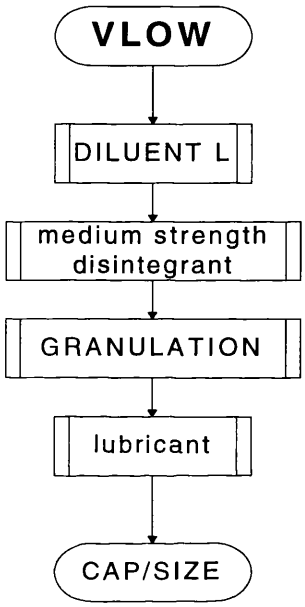
Wetting agents are generally used to promote fluid penetration into the powder mass (Section 1.3.2.5). However, granulation with a hydrophilic diluent provides a mean to aid penetration of water into the powder mass and thus improve drug release. Therefore a wetting agent is not required in the basic mixture to formulate a very low dose drug.

For a dose of such a small quantity (less than 1 mg), the properties of drug play a minimal role in the formulation and therefore the knowledge of drug properties are less critical. The filler is the main ingredient in the formulation for a very low dose drug

with small amount of disintegrant, lubricant and binder. Once the information of capsule size is available, the quantitative information of each components included in the formula can be calculated.

A simplified flow chart diagram, 'VLOW' (Figure 3.3), summarizes the decisions made for formulation of very low dose drug.

Figure 3.3 : 'VLOW' routine of the system



'DILUENT L', 'medium strength disintegrant', 'GRANULATION' and 'lubricant' are sub-routines of which the details can be found in Sections 3.3.2, 3.3.4, 3.4 and 3.3.5 respectively. 'CAP/SIZE' is the next routine in the system.

3.2.4 Formulation of high, medium, low dose drug

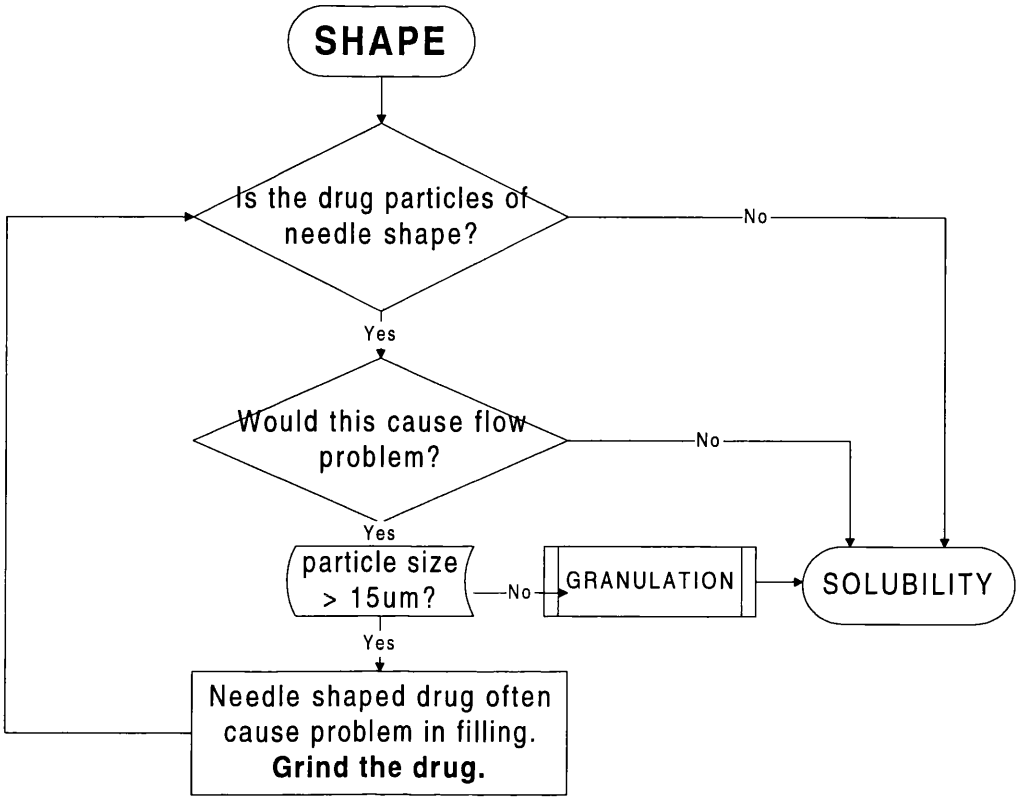
Generally, the formulation of a drug of high, medium or low dose (Table 3.1) would require more knowledge about the properties of drug such as particle size and shape, solubility and flow properties. The effect of properties of drug on capsule formulations is described in Section 1.3.1.

3.2.4.1 Particle shape

The description and measurement of particle shape is summarized in Section 1.3.1.2. When particle size reaches to about 50 μm or below, the shape effects can predominate over effects exerted by particle size and can significantly affect the flow properties of drug and thus affect capsule filling operations (Section 1.3.1.2). Spherical particles tend to be more free flowing than irregularly shaped particles (Section 1.3.1.2) and for needle-shaped particles, it is more likely to exhibit flow problems. The dissolution rate of sparingly soluble drugs also decreases as the level of flakiness and irregularity of the particles increases (Section 1.3.1.2). If the drug mixture is to be granulated, there may be some limitation for needle-shaped or plate-shaped particles. Fluidized bed granulation method may not be suitable as needle-shaped or plate-shaped particles may be difficult to fluidize (Section 1.3.1.2). On the other hand, not all needle-shaped particles would exhibit problems in flow. It also depends on other factors such as particle size. Coarse particles usually flow better than fine particles (Section 1.3.1.1). However, in cases where the particles are of needle-shape and cause flow problems, modification of the particle shape provides a solution. It is easier to formulate a drug with spherical shape. By grinding the drug, it is possible to obtain particles of more equidimensional shape. However, for fine particles, further size reduction is not ideal because fine particles are more cohesive and may cause flow problems (Section 1.3.1.1). Based on known practice by the experienced formulators, wet granulation would be a more appropriate process to improve the flow properties of drug particles of a size smaller than 15μm.

The decisions discussed above are summarized in the flow chart for 'SHAPE' routine (Figure 3.4).

Figure 3.4 : 'SHAPE' routine



'GRANULATION' is a sub-routine in the system. The details can found in Section 3.4. 'SOLUBILITY' is the next routine in the system.

3.2.4.2 Solubility of drug

The solubility of a drug plays an important role in drug release from the capsule formulations and thus absorption of drug. The effect of solubility on formulation is described in Section 1.3.1.5. As a general rule, drug mixtures with an aqueous solubility of less than 10 g/l may represent a potential dissolution-related absorption problem (Section 1.3.1.5). However, at an early development stage, the solubility of drug mixture or even the constituents in the drug mixture are unknown but if the solubility of the drug is poor and is formulated in high dose, the likelihood of having problem in drug absorption is high. Based on the debate of known practices by the experienced formulators, the drugs can be classified according to their solubility into 3 classes (Table 3.2).

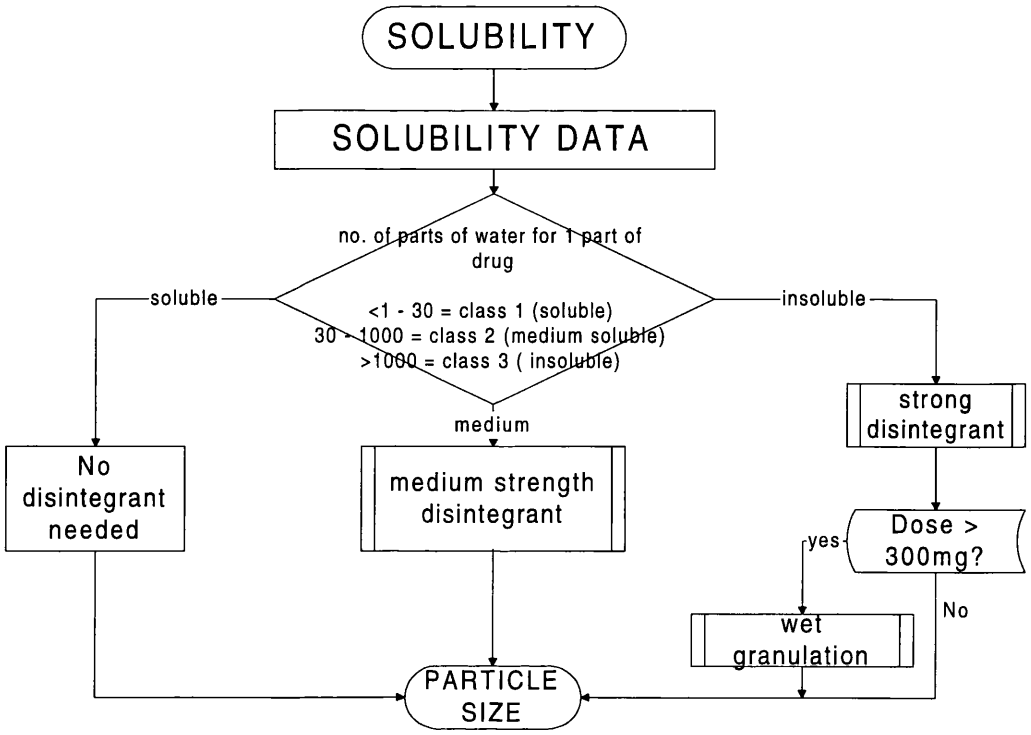
Table 3.2 : Classification of the solubility of drug by the system

Solubility Classes	Solubility (part of water per part of drug)	Solubility (g/l)
Class 1 (soluble)	less than 30	> 1000 - 33
Class 2 (medium soluble)	from 30 to 1000	< 33 - 1
Class 3 (insoluble)	greater than 1000	< 1

Since the unit, part of water per part of drug, is used in the British Pharmacopoeia, the system also stored the data for solubility of drug in the same unit although the unit, g/l, is probably more widely used these days. Soluble drugs which dissolve in less than 1 to 30 parts of water per part of drug belong to Class 1; drugs which dissolve in more than 30 to 1000 parts of water per part of drug belong to Class 2 and drugs which require more than 1000 parts of water per part of drug to dissolve belong to Class 3.

The use of a 'strong disintegrant' i.e. a disintegrant with extensive swelling properties (the list of 'strong disintegrant' is described in Section 3.3.3) were shown to improve the dissolution profile of the capsule formulations containing poorly soluble drug (Section 1.3.2.2). Therefore to formulate a drug of 'Class 3' solubility, a strong disintegrant is preferred. From the analysis of the marketed formulations, a more powerful disintegrant is used for insoluble drug (Section 2.2.5). However, if a high dose of insoluble drug is to be formulated, it is necessary to provide a mean to further increase the liquid penetration into the insoluble powder mass to ensure release of drug from the capsules. Methods such as wet granulation would be advisable. Doses of greater than 99 mg to 1000 mg are classified as high dose in the system (Section 3.2.2). However, based on the experience of the formulators who participated in the construction of the decision tree, only for insoluble drug (Class 3) for which the dose exceeds 300 mg require application of a granulation process.

Figure 3.5 : 'SOLUBILITY' routine of the system



'medium strength disintegrant' and 'strong disintegrant' are sub-routines of which the details can be found in Section 3.3.4. 'PARTICLE SIZE' is the next routine in the system.

Formulation of medium soluble and soluble drugs is slightly different. The efficiencies of disintegrant decreases as the hydrophilicity of the capsule content increases (Section 1.3.2.2). Therefore it is unnecessary to incorporate a disintegrant for formulation of soluble drug (Class 1) unless a hydrophobic diluent is used. This decision is also supported by the observations made with the marketed formulations (Section 2.2.5). The commonly used diluents in the system are mostly hydrophilic (Section 3.3.2). However, should a hydrophobic diluent be used in the formulation, and the quantity of the diluent incorporated exceeds 50% w/w, then the drug mixture would be treated as in the case of medium soluble drug (as agreed by the experienced formulators). For medium soluble drug (Class 2), the use of a disintegrant would ensure the disruption of powder mass and thus good drug release. However, a 'medium strength ' disintegrant (described in Section 3.3.3) of smaller swelling capacity (compared to the strong disintegrant) is probably adequate.

For highly soluble drugs, large percentage of starch (80% w/w) such as maize starch would decrease drug release (Section 1.3.2.1) and therefore should be avoided in formulation of low dose, soluble drug. In many cases, the diluent recommended by the system is stored in the default list of diluent called 'DILUENT N' (described in Section 3.3.2). To avoid this adverse effect, maize starch is not included as one of the default diluents in 'DILUENT N'.

The decisions made relating solubility of drug and use of disintegrants can be summarized in a simplified flow chart diagram in Figure 3.5.

3.2.4.3 Particle size of drug

The particle size of a drug has a strong impact on the filling performance and drug release of capsule formulation as described in Section 1.3.1.1. The description of particle size are often method-dependent. The mean, median or quartile values are sometimes used and the implications of these values also may vary depending on the particle size distribution (Section 1.3.1.1). To simplify the description of size and provide a core foundation for future development, the definition of 'particle size' of drugs used in the system is the 'mean' particle size of drug based on 'weight distribution'. Based on discussions with the experience formulators, the particle size of the drugs is divided into five categories (Table 3.3).

Table 3.3 : Classification of the particle size of drugs by the system

Particle size	Description
< 10 μm	very fine
10 - 50 μm	fine
> 50 - 100 μm	medium
> 100 - 150 μm	large
>150 μm	coarse

'Coarse' particles are generally very free flowing and 'very fine' particles are cohesive (Section 1.3.1.1). The flowability of the fine, medium and large particles may also depend on other properties of drugs such as particle shape.

It is difficult to formulate a 'high' dose drug (Table 3.1) with coarse particles because firstly segregation is likely to occur; secondly the drug particles would also be so free-flowing that the powder mixture would have difficulties being retained in the dosator nozzle if dosator nozzle filling machine is used (Section 1.3.1.1); thirdly if tamp filling machine is used, the powder mixture is usually of limited compressibility and spillage of powders over the dosing disc may occur (communicated). As mentioned in Section 1.3.1.1, the reduction of the mean particle diameter to smaller than 100 μm would reduce the chance of segregation. Therefore, in formulation of 'high' dose drug, size reduction of coarse particles, for example by grinding is advisable. The new particle size of the ground drug is therefore needed before the system proceeds. However, in cases where only 'low' or 'medium' dose drug is involved, the use of suitable diluent would overcome the deletorious effect caused by the coarse particle size. Coarse grade of lactose monohydrate, microcrystalline cellulose (e.g. Avicel PH 102) and pregelatinised starch are examples of suitable diluents. ('DILUENT N', Section 3.3.2).

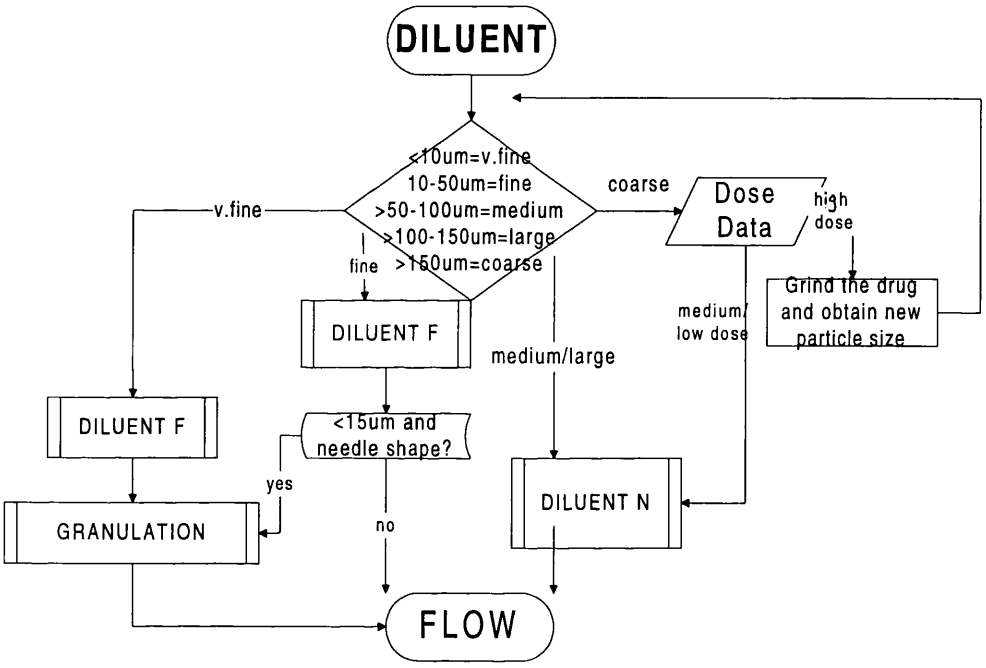
Formulation of drugs with very fine particle size also requires special attention. The chance of having segregation and flow problems is relatively high (Section 1.3.1.1). By incorporating a diluent of similar particle size (of particle diameter ratio below 1.3 : 1 as suggested in Section 1.3.1.1) would reduce the segregation problem. The granulation process could be an efficient way to improve the flow properties and also to prevent segregation. Examples of diluents with fine particles size are maize starch (2 - 32 μm, Wade and Weller 1994) and the fine grade lactose monohydrate such as the *Microfine* lactose which contains 99.9 % of 10 μm particles (Wade and Weller, 1994). Other diluents with fine particle size such as pregelatinised starch can also serve as the alternatives to maize starch or fine grade lactose. The list of default diluent that the system used for drugs of fine particle size is 'DILUENT F' (Section 3.3.2).

The formulation of drugs with 'fine' particle size (10 - 50 μm) would be similar to formulation of drugs with 'very fine' particles, although the flowability of the drug will not be as cohesive as with drugs of 'very fine' particles but the use of diluents with fine particles ('DILUENT F') are preferred. However, other factors such as particle

shape would also influence the flowability of the drug. Based on the debate of known practices, if the particle size is less than 15 μm and is of a needle shape, flow problems often occur. A granulation process would be recommended to alleviate this problem.

Figure 3.6 : 'DILUENT' routine

'DILUENT F', 'DILUENT N' and 'GRANULATION' are sub-routines in the system. The details of 'DILUENT F' and 'DILUENT N' can be found in Section 3.3.2 while details of 'GRANULATION' can be found in Section 3.4. 'FLOW' is the next routine in the System.



Drugs with a 'medium' or 'large' size particles (Table 3.3) usually have reasonable flow properties. It is not necessary to undergo granulation process (to improve performance in flow). Diluent of particle size similar to the drug can be used. Maize starch is too fine for drugs of this particle size range. Lactose monohydrate (medium or large grade), microcrystalline cellulose such as Avicel PH 102 for large particles and Avecel PH 101 for medium particles and pregelatinised starch are suitable fillers and will be contained in the default list of diluent called 'DILUENT N' in the system (Section 3.3.2).

The decisions discussed are summarised in the flow chart 'DILUENT' routine as shown in Figure 3.6.

3.2.4.4 Flow properties of drug

The flowability of the drug mixture plays an important role in provision of uniform feed in the capsule filling equipment and the effect of powder flow of drug mixture on capsule formulation is described in Section 1.3.1.3. There are a number of ways by which the flow properties of drug can be determined and the use of Carr's compressibility index is one of the methods (Section 1.3.1.3). Carr's compressibility index, which is employed by the system, provides information about both compressibility and flow of the drug (Section 1.3.1.3 and 1.3.1.4). To provide a comprehenisve classification in flow properties, Table 1.6 (Section 1.3.1.3) which shows the relationship of Carr's index and powder flow, is modified as agreed by the experienced formulators (Table 3.4).

Table 3.4 : Generalized relationship between Carr's compressibility index and type of powder flow defined in the system

Carr's Compressibility Index (%)	Description of flow properties
<15	very good
15-28	good
28-35	fairly good
>35	bad

The impact of flow properties of drug is insignificant if the dose is less than 5 mg ('low' dose, Table). Based on discussion with the experienced formulators, the knowledge of flow properties of drug will not be required. However, for dose greater than 5 mg but smaller than 50 mg, the knowledge of bulk densities and flow properties of drug is preferred. However, should the data be unavailable at the time of the development, it is reasonable to use a value of 0.6 g/cm^3 (approximate tapped density, based on experience of experts), in the calculation of the volume of the drug (i.e. for

dose less than 50 mg). It is also logical to assume that the flow properties of the drug do not affect the flowability of drug mixture.

For doses greater than 50 mg, the information about the maximum and minimum bulk densities is crucial. The volume that the drug occupies is calculated from the maximum bulk density. Flowability of the drug, predicted from the Carr's compressibility index, also has a significant influence on the capsule filling performance (Section 1.3.1.3). If the data of maximum and minimum bulk densities is not available, an estimation of these data based on methods such as the one suggested in the system in the 'BENCH' routine (as described below), would enable the system to generate a provisional formulation for the drug before the accurate measurements can be obtained.

If the drug is predicted to have 'poor' or 'fairly good' flow (Table 3.4), the flowablility of the drug mixture can be improved by a granulation process. If the drug is predicted to have 'good' or 'very good' flow, granulation of the drug mixture is thus not required to improve the flowability of the drug (Figure 3.7).

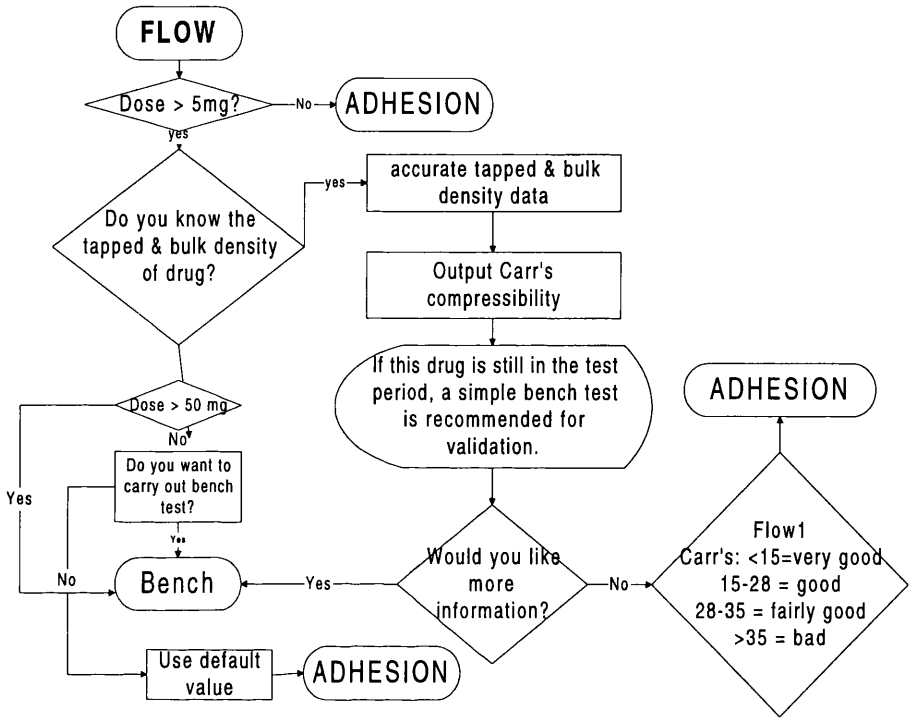
The decisions on the incorporation of lubricant and glidant depend on the knowledge of the flowability of drug and other properties of drug such as adhesion of drug towards the metal surfaces. These aspects will be described in Section 3.2.4.5. So far, the decisions discussed relating classification of flowability of the drug and dose are summarised in the flow chart 'FLOW' routine (Figure 3.7).

In cases where the dose is greater than 50 mg and that the minimum and maximum bulk density of the drug is not available, a simple bench test can be performed to provide the estimated data for the system to generate a provisional formulation for the drug at the early development stage. The simple bench test that the system suggests ('BENCH' routine, Figure 3.8) is based on the change of volume of a sample drug (contained in a small container of known weight) subject to tapping action. Since both the maximum and minimum bulk densities data are not accurately measured, the prediction of flowability of drug, which is based on Carr's compressibility index derived from these values, would also change. According to the experience of the

experts, the Carr's compressibility index calculated from estimated values of bulk densities is generally higher. Therefore the relationship between Carr's compressibility index and flowability of drug would be altered

(Table 3.5).

Figure 3.7 : 'FLOW' routine

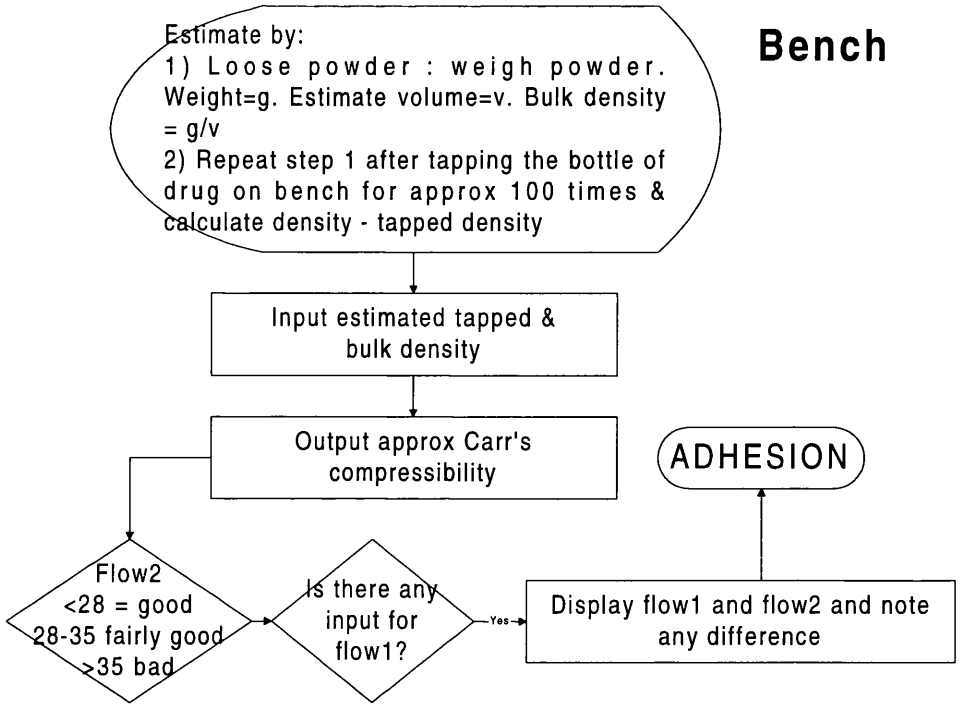


'Bench' is the next routine in cases where the tapped and bulk densities data are not available. In other cases, 'ADHESION' will be the next routine.

Table 3.5 : Generalized relationship between Carr's index (derived from **estimated** maximum and minimum bulk densities) and type of powder flow defined in the system

Carr's Compressibility Index (%)	Description of flow properties
<28	good
28 - 35	fairly good
>35	bad

Figure 3.8 : 'BENCH' routine



'ADHESION' is the next routine.

3.2.4.5 Adhesion of drug towards metal surfaces

The adhesion of the drug towards metal surfaces may cause problems during the capsule filling procedure (Section 1.3.1.8). Most of the methods described, in the literature, to measure the adhesion force between particles and surfaces do not apply directly in the measurement of powder adhesion to the dosator wall during capsule filling process (Section 1.3.1.8). Adhesion to nozzle was an alternative measure of assessment of the amount of adhesion, and therefore a grading method can be used to describe the observation of adhesion of powder coating on the nozzles during the filling process (Section 1.3.1.8). However, the result of the observation would be judged solely by the perception and experience of the formulator.

Glidants are often employed to improve the flow characteristics of powders as well as acting as an anti-adherent agent (Section 1.3.2.4). The adhesion between the drug and metal surfaces of the filling machine can be reduced by the incorporation of a glidant (Section 1.3.2.4). For drugs with 'poor' or 'fairly good' flow (Table) and where granulation is not incoporated, problems in flowability of the drug mixture is expected.

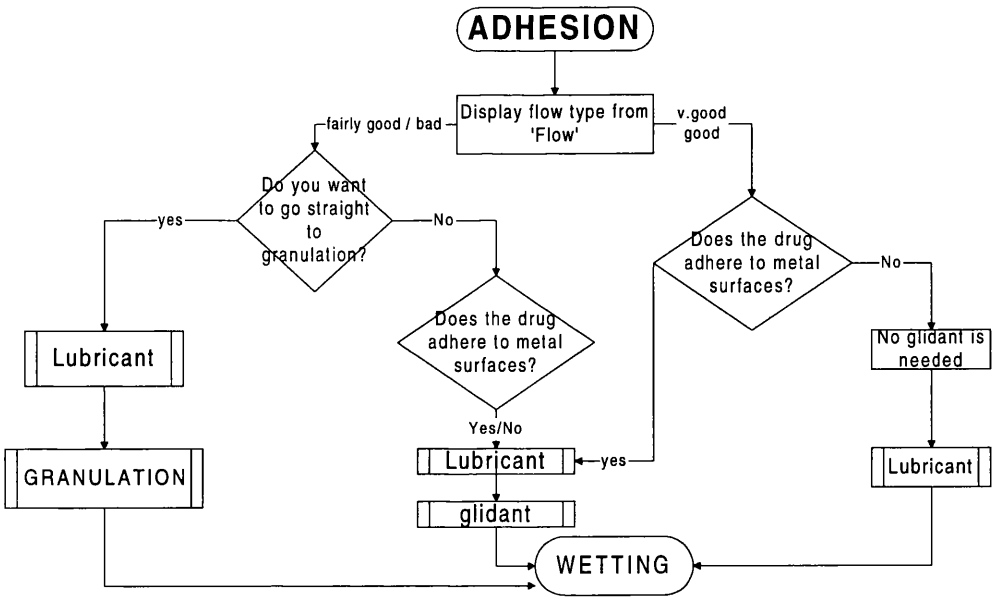
Therefore, the incorporation of a glidant is advisable to alleviate the flow problems. However, for drugs that undergo granulations, it is generally unnecessary to employ a glidant because, in the form of granules, the adhesion between the drug and the metal surfaces of the filling machine is reduced. The choice of type and amount of glidant to be used is described in Section 3.3.5.

Based on debate of known practices expressed by the experienced formulator participated in the construction of the decision tree, a lubricant is generally incorporated in capsules filled by powders or granules to ensure good flow of the filling materials. In the system, a lubricant is recommended in most cases and in Section 3.3.4 the type and amount of lubricant used is described.

The decisions made concerning drugs with different flowability as well as drugs of different tendency to adhere to metal surfaces of the filling machines are summarised in the flow chart for 'ADHESION' routine in Figure 3.9.

Figure 3.9 : 'ADHESION' routine

'Lubricant', 'glidant' and 'GRANULATION' are sub-routines of which the details can be found in Sections 3.3.5, 3.3.6, and 3.4 respectively. 'WETTING' is the next routine in the system..



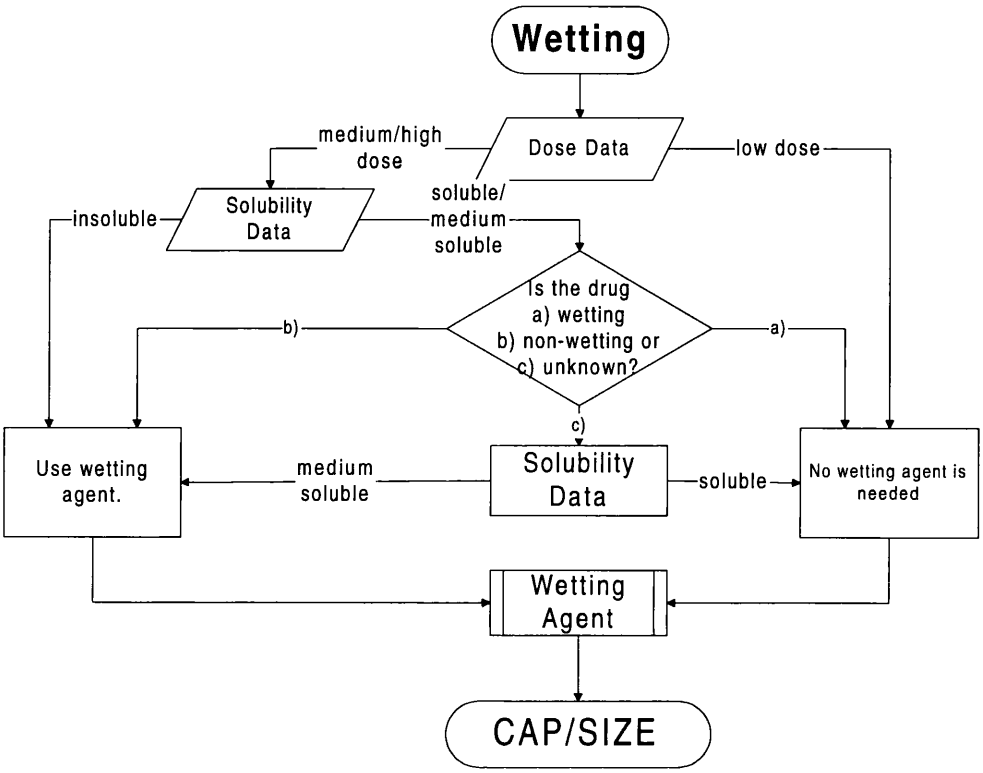
3.2.4.6 Wettability of drug

The wettability of the drug is often the limiting factor in the dissolution process and is important when considering the manufacturing process such as wet granulation (Section 1.3.1.7). The contact angle is very often used to indicate the wettability of a powder. A number of methods of measuring the contact angle were described in the literature (Section 1.3.1.8). To measure the contact angle of a drug, indirect measurement such as the Washburn method is often used (Section 1.3.1.8). If the wetting is complete, the contact angle is 0° and if the contact angle is greater than 90°, the powder is not wetted. However, according to the experience of the experts, the amount of drug available at early development stage is often not sufficient for such measurement. Other simple visual methods can be used to estimate the wettability of drug. For example, by sprinkling some powder particles on top of a beaker of water. If the drug floats on the top of the water, the drug is probably non-wetting. If the drug sinks, it wets with water. Another test described is by packing a capillary tube with the drug and place one end of the capillary tube (the end with the drug) into the water. If the drug wets with water, the water will rapidly rise in the capillary tube. It the water only rises very slowly or does not rise in the capillary tube, the drug is described as non-wetting.

The dissolution process of a non-wettable drug can be improved by the incorporation of a wetting agent (Section 1.3.2.5). If the drug is of 'low' dose (less than 6 mg, Table 3.1), the effect of the wettability of the drug on capsule formulation is minimal and therefore a wetting agent is not needed. However, if the dose of the drug is 'medium' or 'high' (Table 3.1), the use of a wetting agent would depend on both the solubility of the drug as well as its wettability. Based on debate of known practices, it was agreed that if the drug is insoluble, whether the drug is wettable or not, the use of wetting agent would be preferred to ensure penetration of the dissolution medium into the capsules. If the drug is soluble or medium soluble (Table 3.2) and if the the drug is non-wetting, incorporation of a wetting agent is also preferred. However, for a wettable, soluble or medium soluble drug, it is reasonable not to employ a wetting agent. In cases where the wettability of the drug is unknown, the incorporation of a wetting agent would again depend on the solubility of the drug. For a soluble drug, the wetting agent is not needed whereas for a medium soluble drug, the incorporation of a wetting agent would

become advisable. The choice of type and amount of wetting agent to be used is described in Section 3.3.6. These decisions are summarised in the flow chart of 'WETTING' routine (Figure 3.10).

Figure 3.10 : 'WETTING' routine



'Wetting agent' is a sub-routine in the system and the details can be found in Section 3.3.7. 'CAP/SIZE' is the next routine.

3.2.5 Tapped density of excipients

In the previous parts of the system, the recommendation of certain excipients are established. To predict the volume of the drug mixture occupied, the knowledge of the tapped density of the excipients such as the diluent and disintegrant is crucial. The tapped density of the excipients varied from manufacturer to manufacturer and batch to batch. It is possible that a substantial part of the drug mixture is constituted by the diluent and / or the disintegrant and therefore the information about the tapped density

of the diluent and disintegrant of the batch to be used for formulating the particular drug is preferred. In the case where such information is not available, assumptions are made based on a default value set by the system. The default tapped density values are evaluated from the data available in the *Handbook of Pharmaceutical Excipients* (1994) and the data collected in database III (Section 2.1). For excipients (such as lubricant, glidant, wetting and binder) which are usually included in a relatively small quantity in each capsule, the use of a default tapped density should not affect the prediction of the volume of the drug mixture.

3.2.6 Calculation of the volume of the drug mixture

The prediction of the volume of the drug mixture is complicated. In Section 1.3.1.4, Newton and Bader (1981) predicted the maximum bulk density and capsule fill weight of two component mixtures from the measurements of the properties of individual components. However, the prediction of the bulk density and capsule fill weight was less satisfactory when compression is involved. Unless the capsules are filled manually, the capsule content will be compressed to a certain extent (Section 1.3.1.4). The amount of reduction in volume due to compression is not always predictable. In addition, packing of the drug mixture also makes the deduction of the total volume occupied by the drug mixture difficult to be predicted. The packing of the powder bed often depends on the particle size and shape of each individual component and the interaction between them. The smaller particles would fill the void space between the larger particles. For example, the function of magnesium stearate (an effective lubricant) would depend on the degree and extent of surface coverage of a substrate particle (Section 1.3.2.3) and therefore the amount of magnesium stearate required is minimal. Therefore the volume of the drug mixture is often smaller than the total sum of volume of each individual components. Moreover, if the drug mixture undergoes granulation (wet or dry granulation), the change of bulk density of the granules (compare to powder) would depend on a number of other factors such as particle size (Section 1.3.1.1), the granulation method and amount of granulating liquid used. However, inadequate amount of information is available in the literature to enable prediction of the change of bulk density of powder mixture subject to granulation process.

To build up the core foundation of the system, it was generally agreed by the participating experts to simplify the complicated matter by calculating the volume of the drug mixture based on individual volume of each constituents and its relative proportion in the mixture at this stage. The advantage of using this method is that the chance of overfilling the capsules is minimal. If the capsules are underfilled, addition of diluent to the formula is usually not too difficult. Since the system aims to provide a starting point in formulation of a drug in early development stages, the recommended formula can be fine-tuned when more information is available. The following assumptions are thus taken when calculating the volume of the drug mixture :

a) The drug mixture is filled at tapped bulk density.

b) The volume of the drug mixture is assumed to be equal to the total sum of volume of each individual component.

c) The compression of the drug mixture during the filling process is minimal.

d) Change of bulk densities of drug mixture due to granulation process is minimal.

The volume occupied by the drug mixture can be a critical factor in the choice of capsule size. The dose and tapped density of the drug is known and thus the volume of the drug can be calculated. The quantity (in terms of %w/w) of each excipients (except diluent) and their tapped densities are also known. Therefore the volume occupied by each of these excipients (except diluent) can also be worked out. The amount of diluent required often depends on the capsule size chosen. Therefore, if the volume occupied by merely the drug and other excipients i.e. with no diluent (the minium capsule volume) is calculated, then the smallest capsule size (size X, Figure 3.11) that is required to fill this volume can thus be determined (Section 3.2.7). If the formulator choose a larger size capsules, the diluent is added to the formulation to fill the capsules to 80 - 90% level (as agreed by the experienced experts). The final volume occupied by the drug mixture can thus be calculated as described above. In this system, the volume of the drug mixture is calculated in two stages : before the capsule size is chosen (the predicted minimum volume of the drug mixture is calculated without the inclusion of a diluent); and after the capsule size is decided (the predicted final volume of the drug mixture is calculated with the inclusion of a diluent).

Mathematical derivation of the volume of drug mixture

Notations :

xd	=	%w/w of the the drug
xf	=	%w/w of the diluent
$^{\dagger}*x_1$	=	%w/w of the disintegrant
$^{\dagger}*x_2$	=	%w/w of the lubricant
$^{\dagger}*x_3$	=	%w/w of the glidant
$^{\dagger}*x_4$	=	%w/w of the wetting agent
$^{\dagger}*x_5$	=	%w/w of the binder
*td	=	tapped density of the drug (g/cm^3)
‡*tf	=	tapped density of the diluent
‡*t_1	=	tapped density of the disintegrant (g/cm^3)
‡*t_2	=	tapped density of the lubricant (g/cm^3)
‡*t_3	=	tapped density of the glidant (g/cm^3)
‡*t_4	=	tapped density of the wetting agent (g/cm^3)
‡*t_5	=	tapped density of the binder (g/cm^3)
vd	=	volume occupied by the drug (cm^3)
vf	=	volume occupied by the diluent (cm^3)
v_1	=	volume occupied by the disintegrant (cm^3)
v_2	=	volume occupied by the lubricant (cm^3)
v_3	=	volume occupied by the glidant (cm^3)
v_4	=	volume occupied by the wetting agent (cm^3)
v_5	=	volume occupied by the binder (cm^3)
*dose	=	dose of drug (g)
V	=	total volume (cm^3)
*Ve	=	volume of particular capsule size (cm^3)
W	=	total weight (g)

* The variable has fixed value as determined by the system.

† The variable is equal to 0 if the corresponding excipient is not needed in the formula.

‡ To avoid the occurrence of assigning a zero value in the denominator, a default of 999 is used when the corresponding excipient is not needed in the formula.

Calculations :

Two basic concepts are used (equation 3.1 and equation 3.2) in the calculations.

$$\text{mass of substance A} = \frac{\%\text{w/w of substance A} \times \text{total weight}}{100} \quad \text{.....(3.1)}$$

$$\text{volume of substance A} = \frac{\text{mass of substance A}}{\text{maximum bulk density of substance A}} \quad \text{.....(3.2)}$$

From equation 3.1 and equation 3.2,

$$\text{volume of substance A} = \frac{\%\text{w/w of substance A} \times \text{total weight}}{100 \times \text{maximum bulk density of substance A}} \quad \text{.....(3.3)}$$

From equation 3.1,

$$\text{dose} = \frac{xd \times W}{100}$$

$$W = \frac{\text{dose} \times 100}{xd} \quad \text{.....(3.4)}$$

From equation 3.3,

$$v_1 = \frac{x_1 \times W}{100 \times t_1} \quad \text{.....(3.5)}$$

$$v_2 = \frac{x_2 \times W}{100 \times t_2} \quad \text{.....(3.6)}$$

$$v_3 = \frac{x_3 \times W}{100 \times t_3} \quad \text{.....(3.7)}$$

$$v_4 = \frac{x_4 \times W}{100 \times t_4} \quad \text{.....(3.8)}$$

$$v_5 = \frac{x_5 \times W}{100 \times t_5} \quad \text{.....(3.9)}$$

$$v_f = \frac{x_f \times W}{100 \times t_f} \quad \text{.....(3.11)}$$

$$v_d = \frac{x_d \times W}{100 \times t_d} \quad \text{.....(3.12)}$$

And,

$$V = vd + vf + v_1 + v_2 + v_3 + v_4 + v_5$$

Combining equations 3.5 to 3.12,

$$V = \frac{W}{100}\left(\frac{xd}{td} + \frac{xf}{tf} + \frac{x_1}{t_1} + \frac{x_2}{t_2} + \frac{x_3}{t_3} + \frac{x_4}{t_4} + \frac{x_5}{t_5}\right) \quad \text{.....(3.13)}$$

From equation 3.4,

$$V = \frac{\text{Dose}}{100 \times xd \times 100}\left(\frac{xd}{td} + \frac{xf}{tf} + \frac{x_1}{t_1} + \frac{x_2}{t_2} + \frac{x_3}{t_3} + \frac{x_4}{t_4} + \frac{x_5}{t_5}\right) \quad \text{.....(3.14)}$$

To predict the minimum volume of the drug mixture i.e. with no diluent,

$$xf = 0$$

and therefore,

$$xd = 100 - x_1 - x_2 - x_3 - x_4 - x_5$$

'V' can be calculated by substituting xd into equation 3.14. After the capsule size is selected, the amount of diluent required to fill the capsules (to 80 - 90% level) is to be calculated as shown below :

Assume that initally,

$$xf = 50$$

$$xd = 100 - 50 - x_1 - x_2 - x_3 - x_4 - x_5$$

By substituting xd into equation 3.14, the volume of drug mixture (V) at xf = 50 % w/w is calculated. The value of V is then compare with the volume of the capsule shells of chosen size (Ve). The value xf may need to be adjusted accordingly as shown below such that the volume of the drug mixture (V) is between 80 - 90% of the volume of the capsule shell (Ve) :

if $V > 0.9\ Ve$

xf is decreased and the new drug volume (V) is calculated.

if $V < 0.8\ Ve$

xf is increased and the new drug volume (V) is calculated.

Several adjustments may be needed before the 'V' is between 80 - 90% of Ve (the optimum 'V'). The total weight (W) of the drug mixture can be calculated by equation 3.4 using the xd value at which the optimum value of 'V' is achieved. The mass of diluent required per capsule is calculated from the xf values at which the optimum value of 'V' is achieved (equation 3.15).

From equation 3.1,

$$\text{mass of diluent (per capsule)} = \frac{xf \times W}{100} \quad \text{.....(3.15)}$$

The mass of the disintegrant, lubricant, glidant, wetting agent and binder can also be calculated in the same manner. As a whole, the dose of drug, the type and amount (in mg and %w/w) of each excipients, the total fill weight and the total fill volume are all available at this stage - the formula is thus deduced.

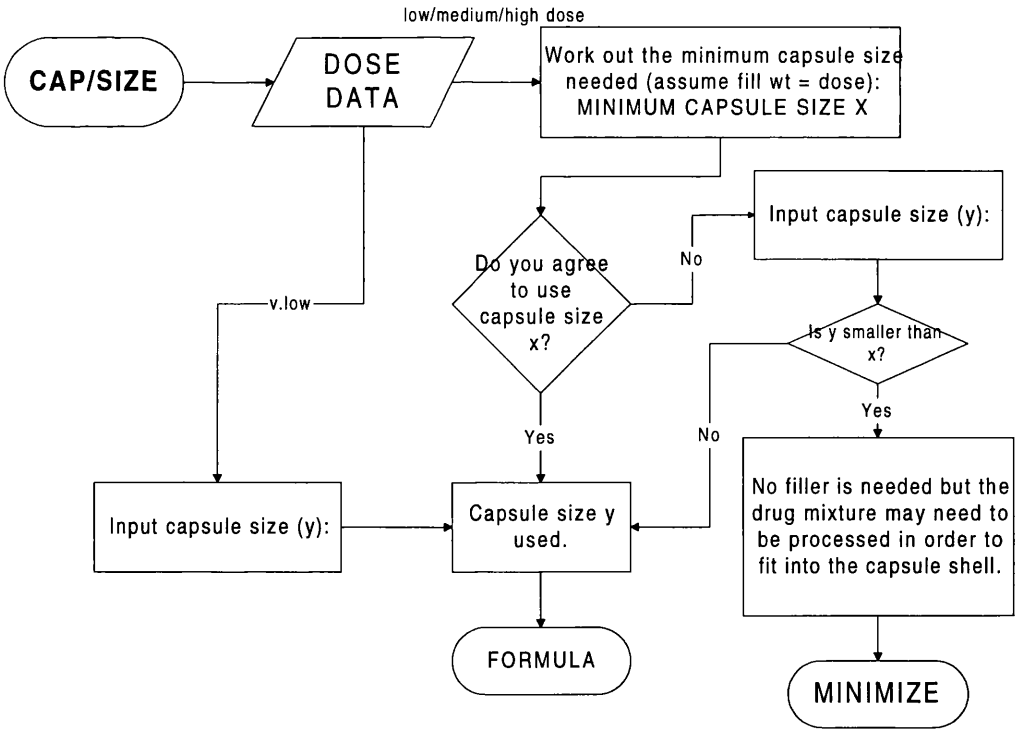
3.2.7 Determination of the capsule size

In the case of formulation for high dose drug, the selection of the capsule size can be affected by the volume occupied merely by the drug. The calculation of the minimum volume of the drug mixture (i.e. with no diluent) is shown in Section 3.2.6. The smallest capsule size (size X in figure 3.11) required to fit such drug mixture can be

worked out from the known volume of the different capsule size (Table 1.1, Section 1.2). If the formulator chooses a smaller capsule size (smaller than size X), then it is logical to assume that the drug mixture would need to be densified before it can be fitted into the capsules. The densification process will be considered in Section 3.2.8. In such case, only relatively small amount (sometimes none) of diluent, depending on the capsule size, would be able to fit into the capsule shells. However, if the formulator decides to choose a bigger capsule size, adequate amount of diluent will be added to the formulation and the drug mixture can usually be filled into the chosen capsule size comfortably.

Figure 3. 11 : 'CAP/SIZE' routine

Depending on the Input data, the next routine in the system can be 'FORMULA' or 'MINIMIZE'.



For dose of less than 6 mg ('low' dose drug,Table 3.1), the volume occupied by the drug would be small and does not usually exert any restriction on the choice of capsule size. A diluent will be required almost in all cases to fill up the capsules.

Based on the calculations shown in Section 3.2.6, the formula for the particular drug can be deducted. The decisions discussed in this Section are summarised in the flow chart for 'CAP/SIZE' routine (Figure 3.11).

3.2.8 Densification of the drug mixture

In cases where the dose of the drug is high, the choice of capsule size may be restricted (Section 3.2.6) by the volume of the drug. However, other restrictions in areas such as patient compliance, marketing and clinical trial may mean that formulators sometimes have no choice but to use a relativly small capsule size which requires densification of the drug mixture to a smaller volume to fit the capsule shells.

The Kawakita's mathematical model (Section 1.3.1.4) described the change of the density of powder as a function of the applied pressure and can be used as an indication of the maximum volume reduction of the powder. To predict whether densification of the dry powder mixture by compression (with filling machine) provides the adequate volume reduction, the constant 'a' of the Kawakita's equation (equation 1.13, 1.14 in Section 1.3.1.4) is evaluated. Equation 1.13 and 1.14 can be written as below in equation 3.16 :

$$\frac{N}{\frac{(V_0 - V_N)}{V_0}} = \frac{N}{a} + \frac{1}{ab} \quad \text{.....(3.16)}$$

where N = number of taps

V_N = volume of drug after N taps

V_0 = initial volume of drug

The predicted bulk density of the drug after compression (tc) can be calculated from the maximum bulk density of the drug (td) and the constant 'a' from the Kawakita's equation (equation 3.17).

$$tc = td \times (1 + \frac{a}{100}) \quad \text{.....(3.17)}$$

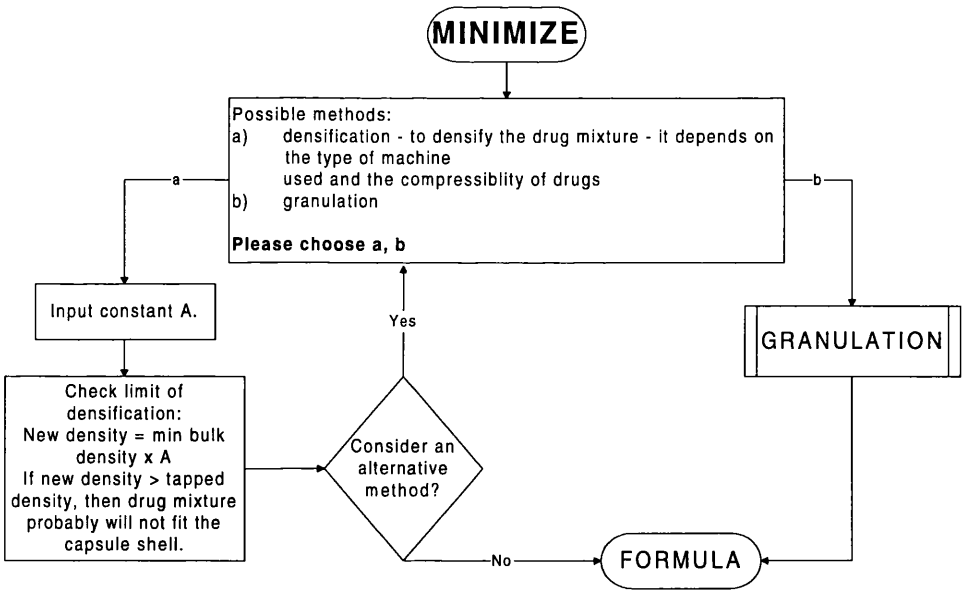
The volume of the drug mixture subjected to the compression can then be evaluated from the 'tc'. If the evaluated volume is greater than the volume of the capusle size, it is

likely that the densification by compression is not a practical method to reduce the volume of the drug mixture.

Dry compaction or dry granulation can offer an alternate route to densify the drug mixture. The use of wet granulation may also reduce the volume of the drug mixture (to a smaller extent compared to dry compaction) but this also depends on the granulation method used. The use of some granulation methods such as fluidised bed may increase the drug volume and cause more problems. If wet granulation has to be employed (may be for other reasons such as to improve bioavailability of drug mixture), the use of high shear mixer is more beneficial. As mentioned before, the system focuses mainly on the formulation aspect in capsule formulation and therefore the technical details of granulation process (dry or wet) are not covered (also see Section 3.4).

Figure 3.12 : 'MINIMIZE' routine

'GRANULATION' is the sub-routine (see Section 3.4) where 'FORMULA' is the next routine in the system.



The system offers two choices to densify the drug mixture : the use of compression and granulation. In the case of compression, if the result of the calculations (equation 3.16, 3.17) indicates that to use such method is not adequate to densify the drug mixture to the required extent, the use of granulation can be an

alternative. The flow chart of 'MINIMIZE' routine summarised the decisions made in this Section (Figure 3.12).

3.2.9 Display of the formula

The content of the formula can be calculated as described in Section 3.2.6. To present the formula in a more meaningful and more practical way, the content of each of the ingredient and the calculated capsule fill weight are rounded up to 1 decimal place and to whole number respectively. A systematic approach is adopted for the rounding up procedure. The amount of diluent is normally used to adjust the difference in fill weight generated by the rounding up procedure. For a formula that does not contain diluent, the amount of disintegrant would be used for the adjustment. If neither the diluent and disintegrant are present in the formulation, the lubricant content would be adjusted. If diluent, disintegrant and lubricant are not present, then the quantity of glidant included would be changed to accomodate the alterations and if diluent, disintegrant, lubricant and wetting agent are not present, the level of binder would be adjusted. In the rare case where the only ingredient in the formula is the drug, no adjustment in the rounding up procedures would be necessary. In addition to the requirement of the adjustment of actual content of the excipient, the %w/w of each ingredients are also adjusted.

The amount of some of these excipients used can be very small. For example, only 1% w/w of magnesium stearate is often used. An adjustment of, say the lubricant content, can lead to a significant change in the proportion (%w/w) of the formulation. Therefore, if the change of content of any excipient (except diluent) is greater than 25%, a remark would be provided by the system.

The formula is displayed in a 'Summary' format of which the qualitative and quantitative information of each ingredient in the formula (per capsule), the expected filled volume, fill weight and capsule size are provided. The scale up of the formula to a batch of 1 kg is also generated.

3.2.10 Other Options

Although the main object of the system is to provide a formulation for the particular drug, other options such as 'statistical design' which help to optimise the suggested formula; the 'multiple-dose' option which help the formulator to develop a formula for several doses at a time; are also provided. These options are described in greater details in Chapter 5.

3.3 Excipients

Following the decision trees, discussed in Section 3.2, the recommendation to incorporate particular types of excipient in the formulation of particular drugs are established. Different groups of the more commonly used excipients are stored in the system. These default excipients are stored in order of preferences based on formulation factors such as effectiveness of the excipients, properties of drug, cost and experiences of the experts. Sometimes, more than one default list are prepared for excipients belonging to the same functionality group. For example, there are three default lists of diluents in the system (Section 3.3.2). Different lists of default diluents are used for formulation of different types of drug. In this Section, the composition of the default lists of excipients in the system and the systemic approach of which the system follows in recommendation of excipients will be described.

3.3.1 Compatibility with excipients • Company practices

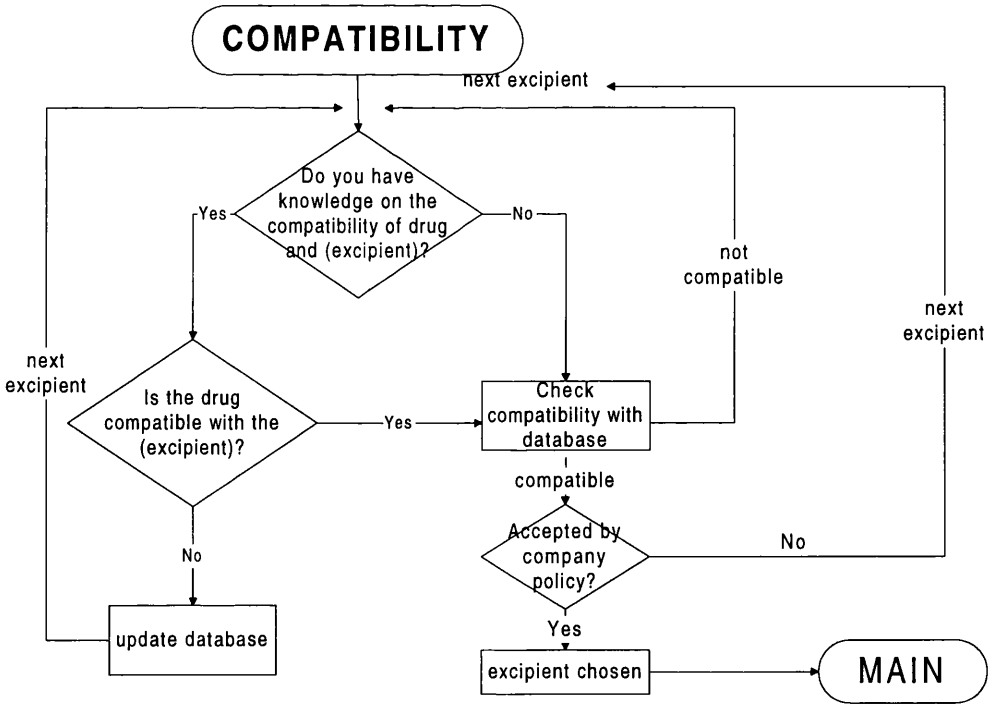
The incompatibilities between drugs and excipients very often affect the stability and the rate and / or extent of drug release (Section 1.3.3). Some of the examples of the known incompatibilities between the drugs, excipients and gelatin are also described in Section 1.3.3. To make the most effective use of these knowledge, for each default excipients in the system, a file ('incompatible' file) is created to store the name of the incompatible drugs, chemicals or chemical functional groups (e.g. amines). Information about cross-linking with gelatin is also stored in a similar manner. During the selection process of each excipient, the information in the 'incompatibility' file of the corresponding excipient is retrieved. If the name of the formulated drug is found in this file, a warning about the possibility of incompatibility between the drug and the

particular excipient will be provided and if the formulator agrees with the findings, this excipient will be rejected. On the other hand, if new information concerning incompatibilities between the drug and excipient are provided by the formulator, the system will store the information in a format which can be retrieved in the future (automatic 'learning') (Section 5.3.5). The excipient with known incompatibilities will be rejected by the system and the next default excipient on the list will be pointed and the same procedure will be repeated.

Company practices also have important impact on the recommendation of the excipients (Section 1.3.5.2). It is meaningless to recommend an excipient which is not acceptable to the company practices. The system would point to the next default excipient in the list and repeat the similar procedure to examine the incompatibility and company practice on this excipient.

Figure 3.13 : 'COMPATIBILITY' routine

'MAIN' represents the section in the main program where this routine is triggered.



In cases where all the default excipients in the system failed to pass through the tests on 'compatibility' and the 'company practices', the possibility to use a 'user's choice'

(or non-default) excipient should not be denied. However, the system may not have much information about this excipient and therefore it is necessary for the user to confirm that the drug is compatible with such excipient; the excipient is acceptable in the country where the drug will be marketed; the amount of excipient needed (% w/w) to be effective (except if the excipient is used as a diluent); and the tapped density of the excipient if it is used as a diluent or a disintegrant. To aid the future development, some of these data acquired from the users will be stored in the system (Section 5.3.2.4 (a)).

A diagramatical representation of the procedures described in this Section can be found in the flow chart of 'COMPATIBILITY' routine (Figure 3.13).

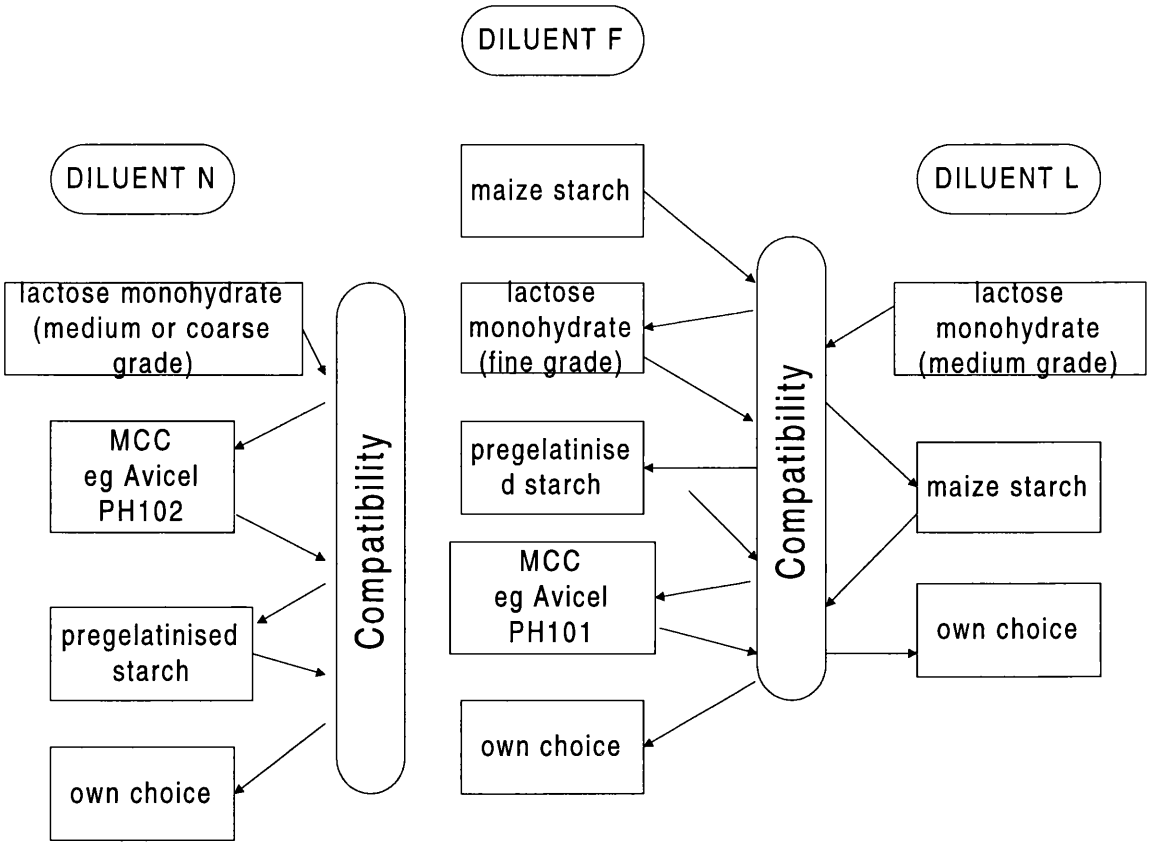
3.3.2 Default diluents

The use of the diluents and the factors affecting the choice of diluents is described in Section 1.3.2.1. The diluent must provide the type of flow characteristics required by the filling equipment. For example, for dosing disc filling machine, the powder mixture must be free flowing; whereas for dosator nozzle filling machines, the powder mixture need to have sufficient cohesiveness to retain its slug form during deliver to the capsule bodies (Section 1.3.2.1). The powders which can be filled with a dosator nozzle type of filling machine should also be able to be filled in a dosing disc filling machine (Section 1.3.2.1). The diluent which can be incorporated to increase the cohesiveness of the powder mixture are microcrystalline cellulose, lactose monohydrate and pregelatinised starch (Section 1.3.2.1). This is one of reasons why these three diluents are chosen in the default lists of diluents used in the system (Figure 3.14). There are three default lists of diluent in the system : 'DILUENT N' (used in most cases), 'DILUENT F' (for drugs with 'fine' or 'very fine' particles, Table 3.3) and 'DILUENT L' (for 'very low' dose drug, Table 3.1).

Lactose monohydrate was shown to be the most frequently used diluent in the marketed formulations (Section 1.3.2.1 and Section 2.2.5) and is an inexpensive excipient (Section 1.3.5.2). Lactose monohydrate was also described to improve drug release for some insoluble drugs (Section 1.3.2.1). Therefore is placed as the first choice diluent in 'DILUENT N' and 'DILUENT L'.

Microcrystalline cellulose is shown to be a better diluent for hydrochlorothiazide (a poorly soluble drug) compared to lactose (Section 1.3.2.1). However, it is more expensive (Section 1.3.5.2) and is not as frequently used as lactose monohydrate (Section 1.3.2.1 and Section 2.2.5). The formulator must also be aware of the variation in the effectiveness of different brands of microcrystalline cellulose (Section 1.3.2.1). Therefore microcrystalline cellulose is placed behind lactose monohydrate in 'DILUENT N' and 'DILUENT F' (Figure 3.14). Fine grade microcrystalline cellulose (Avicel PH 105) and calcium phosphate were found to cause problem in capsule filling in Section 1.3.2.1 and Section 2.5.4 respectively and therefore both are not included in the default list.

Figure 3.14 : Lists of default diluents



Maize starch has fine particle size and is inexpensive, therefore it is listed as first choice diluent for formulation of drug with a fine particle size ('DILUENT F'). Economic reason also dominates the reason behind the choice of diluent for low dose drug ('DILUENT L') since the effect exerted by the drug is minimal and the formulations is predominantly occupied by the diluent (Section 1.3.5.1). One of the

reason why maize starch is placed behind lactose monohydrate is because maize starch is not used as frequently as lactose monohydrate (Section 1.3.2.1 and Section 2.3.4.1) and that the free surface moisture in maize starch may have a significant effect on flowability of powder mixture (Section 1.3.2.1). Maize starch is not preferred to be used in formulation of low dose, soluble drug because this may decrease the rate of drug release (Section 1.3.2.1 and Section 2.5.3). In addition, from the analysis of the marketed formulations (Section 2.2.5), it was also shown that maize starch is not preferred with insoluble drugs. The fine maize starch particles may also segregate with larger drug particles (Section 1.3.1.1). It is therefore reasonable not to include maize starch in 'DILUENT N' (list of default diluents that are used in most cases).

Formulations filled with pregelatinised starch which is also known to have disintegration action (Section 1.3.2.2) were found to have good drug release in presence or absence of disintegrant (Section 2.5.3) and reasonable filling performance (Section 2.5.4). It is included as last choice in the 'DILUENT N' list.

3.3.3 Default disintegrants

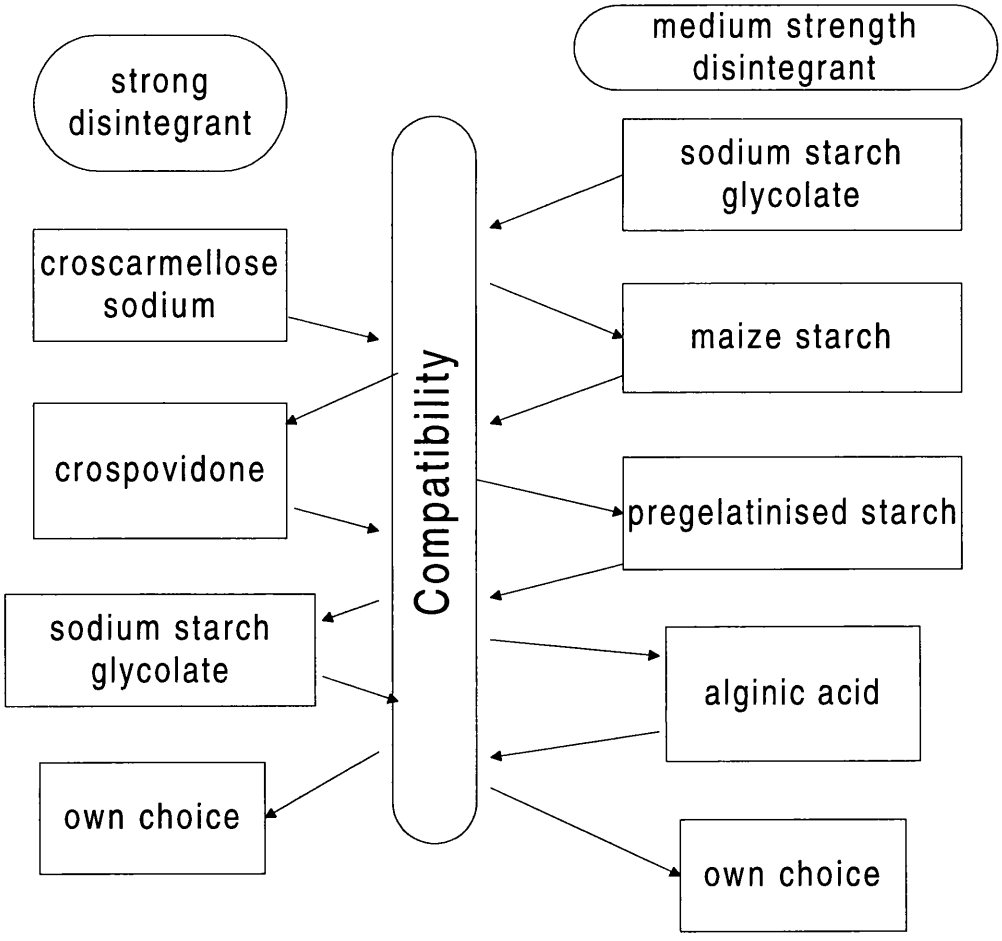
The use, types and mechanism of disintegrants are discussed in Section 1.3.2.2. The efficiencies of different disintegrants are also compared as described in Section 1.3.2.2. In the system, there are two lists of default disintegrants : 'strong disintegrant' and 'medium strength disintegrant' (Figure 3.15), designed for drugs with different solubilities (Section 3.2.4.2).

From Section 1.3.2.2, the super disintegrants have strong capacity to swell and are generally the more effective than the traditional disintegrants such as maize starch or pregelatinised starch. Examples of super disintegrants are croscarmellose sodium, crospovidone and sodium starch glycolate (Section 1.3.2.2). Croscarmellose sodium was shown to be the most efficient followed by sodium starch glycolate and crospovidone (Section 1.3.2.2). Therefore, croscarmellose sodium is the first choice 'strong disintegrant'. It was also found that a minimum concentration of these disintegrant was necessary to produce significant improvement in dissolution (Section 1.3.2.2). The range of croscarmellose sodium used as recorded in the literature can be

found in Section 1.3.2.2 but based on debate on known practices by the experts, 2%w/w of croscarmellose sodium is set as default. Similarly, 3% of crospovidone is also set as default. From Section 2.5.4, the optimum level of sodium starch glycolate used is shown to be 5% which also agrees with the findings in the literature (Section 1.3.2.2). A concentration of 5% sodium starch glycolate is therefore set as default.

From the literature (Section 1.3.2.2), disintegrants with smaller swelling capacity (compare to the 'strong disintegrant') are also used. Based the discussion with the experts, the medium strength disintegrants were identified to be 5% w/w sodium starch glycolate, 10% w/w maize starch, 10% pregelatinised starch and 8% w/w alginic acid. Sodium starch glycolate is the most effective among the four disintegrants and are therefore listed as the first choice (Section 1.3.2.2). Alginic acid is the least used out of the four (Section 2.2.4.1) and therefore is used as the last choice.

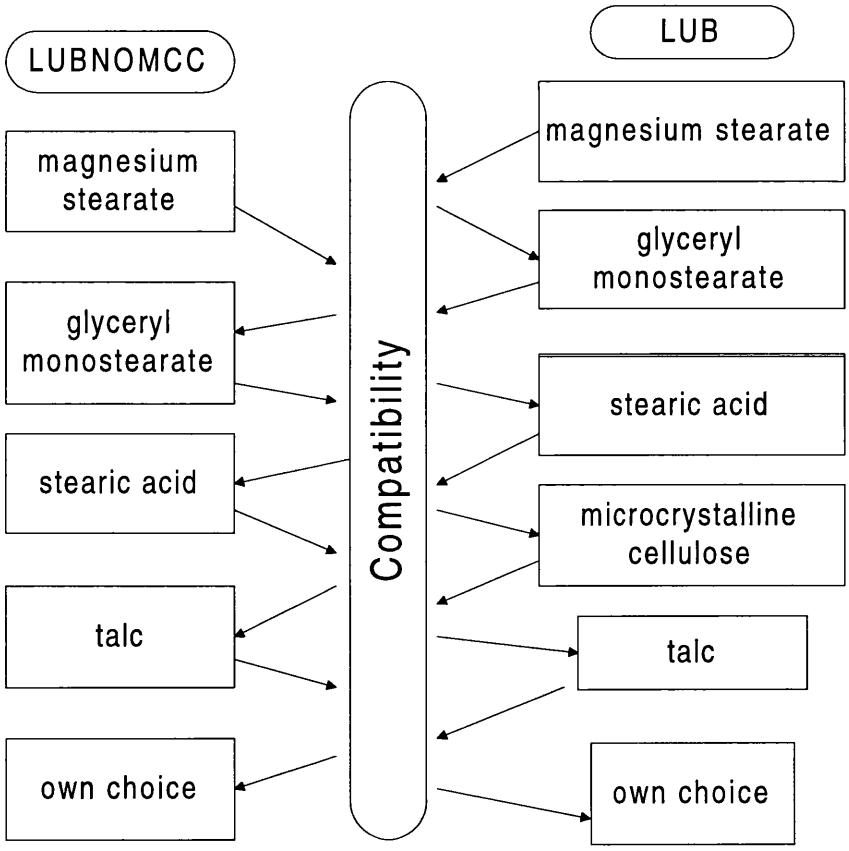
Figure 3.15 : Lists of default disintegrants



3.3.4 Default lubricants

The use of lubricants in capsule formulation (including types and concentration of lubricants incorporated) are discussed in Section 1.3.2.3. In the system there are two lists of default lubricants : 'LUBNOMCC' and 'LUB' (Figure 3.16). The 'LUB' list is used for 'low' dose drug (< 6 mg) (Table 3.1) whereas the 'LUBNOMCC' list is used for drugs of higher dose. The difference between the two default lists of lubricants is that microcystalline cellulose is included in the 'LUB' list but not in the 'LUBNOMCC' list. For low dose drug, the lubricity of microcrystalline cellulose (if chosen as diluent) would provide adequate lubrication for the drug mixture. Microcrystalline cellulose is known to have some degree of lubricating effect (Section 1.3.2). If the chosen diluent is not microcrystalline cellulose, then the addition of 10% of microcrystalline cellulose would help to lubricate the drug mixture.

Figure 3.16 : Lists of default lubricants

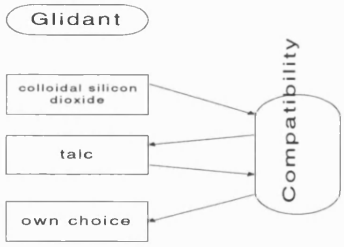


Magnesium stearate is the most effective lubricant (Section 1.3.2.3) and is the most frequently used (Section 2.2.5 and Section 1.3.2.3). Therefore it is chosen as the first choice lubricant in the system. A concentration of 1% w/w of magnesium stearate is shown to be the optimum (Section 2.5.4) and is within the range of usual levels quoted in the literature (Section 1.3.2.3). A number of studies were performed to investigate the efficiency of different lubricants (Section 1.3.2.3). From the analysis of the marketed formulations, the use of talc and stearic acid in capsules was evident (Section 2.2.5). The other default lubricants are 2% glyceryl monostearate, 0.5% of stearic acid and 5% of talc (in decrease order of preferences).

3.3.5 Default glidants

Glidants are often incorporated in capsule formulations to improve flow characteristics of powders or granules and can also be used as an anti-adhesive (Section 1.3.2.4). The effectiveness and mechanisms of the more commonly used glidants are described in Section 1.3.2.4. The two main glidants being used in Europe are colloidal silicon dioxide and talc (Jones, 1995). Similar findings were also observed from the analysis of the database of marketed formulations (Section 2.2.5). Therefore both colloidal silicon dioxide and talc are set as the default glidant. Colloidal silicon dioxide is more effective than talc (Section 1.3.2.4) and is used as the first choice glidants (Figure 3.17). A concentration of 1% was observed to be the optimum level of colloidal silicon dioxide in capsule formulations (Section 2.5.4) and Jones (1995) also showed that a median value of 0.9% is used in the marketed capsule formulations in Europe. However, many of the findings in the literature (mostly based on tablet formulations) quoted a smaller concentration (0.1 - 0.5%) (Section 1.3.2.4). Bearing in mind that the smaller the particle size of the glidant, the lower the concentration of glidant is required to produce an increase in flow (Bandelin, 1989) (Section 1.3.2.4), the optimum level of colloidal silicon dioxide may decrease subject to sieving or other means which reduce the size of the agglomerates. A level of 1% colloidal silicon dioxide is set as default unless sieved colloidal silicon dioxide is used. However, in cases where sieved colloidal silicon dioxide is used, a level of 0.5% of the glidant may be adequate. From the literature (Section 1.3.2.4), the use of 5% of talc as the second choice glidant is also reasonable.

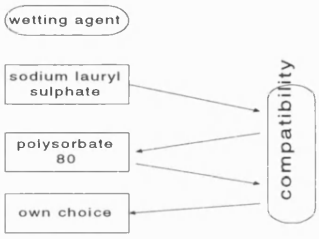
Figure 3.17 : List of default glidant



3.3.6 Default wetting agents

Wetting agents are used to improve the penetration of water into the drug mixture and thus improve the release of drug from capsules. The use of wetting agents in capsule formulations is described in Section 1.3.2.5. From the analysis of the marketed formulations, sodium lauryl sulphate is the most frequently used wetting agent followed by polysorbate (Section 2.2.5). From the literature search, 1% of sodium lauryl sulphate were used in a number of studies (Section 1.3.2.5) although a median value of 0.26% was quoted to be used in marketed capsule formulations in Italy (Jones, 1995). Based on discussion with the experts, a level of 1% sodium lauryl sulphate is set as the first choice wetting agent in the system. From literature (Section 1.3.2.5), a level of 0.1 to 3% of polysorbates is usually used. Based on debate of known practices, a level of 1% of polysorbate 80 is decided to be the second choice wetting agent. The list of default wetting agent is shown in Figure 3.18.

Figure 3.18 : List of default wetting agents



3.3.7 Default binders

Binders are often used as adhesives to hold particles together, for example in granulation process. The use of different binders (including type and level of binders) is discussed in Section 1.3.2.6. However, information about the relative effectiveness of these binders are not clear from the literature search. The granulation process has always been an area that demand a great deal of experience from the formulators. The order of preference of the default binders of the system is decided mainly by discussion with the experts. Together with information extracted from the literature (Section 1.3.2.6), 2% Povidone (PVP), 10% pregelatinised starch, 5% gelatin, 3% hydroxypropyl methylcellulose, 2% alginic acid and 1.5% of ultra-amylopectin were set as default binders in the system (in decreasing order of preference).

The amount of binder required is calculated in terms of weight of dry powder. It is not possible to estimate the amount of water or granulating liquid used because it varies tremendously depending on the granulating method used. For example, if the granulating liquid is sprayed onto the drug mixture in the fluidising bed, the concentration of granulating liquid is used is low (i.e. thin solution). If the granulating liquid is to be poured onto the powder bed, then the solution needs to be thick and the concentration of the granulating liquid can be high. However, after drying, the amount of binder (mg) in the mixture is assumed to be the same.

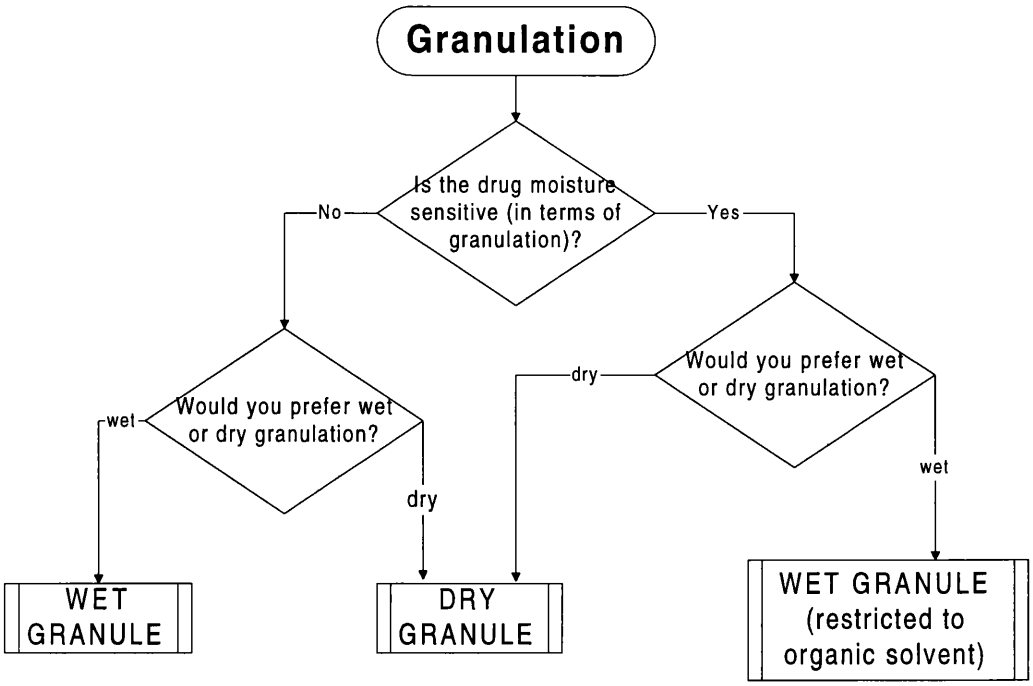
3.4 The Granulation Process

The granulation process is a complicated subject which can be affected by a number of factors such as method of granulations, properties of drug and binders, level of granulating liquid, drying time and condition, condition of the process (temperature and relative humidity of the surrounding). The system focus on the formulation aspect of capsule formulation and therefore will not cover the technical details involved in granulation process.

In the system, recommendation of either wet or dry granulation (dry compaction) are possible (Figure 3.19). However, moisture sensitivity of the drug could be a restriction on the choice of granulation methods. As described in Section 1.3.1.6, it is often difficult to define 'moisture sensitivity'. For example, a drug which is moisture sensitive under storage in a hard gelatin capsules does not necessary mean that the drug is moisture sensitive in terms of granulation because the drug is exposed to moisture in a much shorter duration during granulation than under storage. The system therefore addresses this differences and confirms that the drug is not moisture sensitive in terms of granulation. If the drug is moisture sensitive in terms of granulation, then it can only be processed by dry granulation (Section 3.4.2) or wet granulation with organic solvent (Section 3.4.1). The decisions made are summarised in the flow chart of 'Granulation' routine (Figure 3.19).

Figure 3.19 : 'Granulation' routine

'WET GRANULE' and 'DRY GRANULE' are the sub-routines (Sections 3.4.1 and 3.4.2).



3.4.1 Wet Granulation

For a drug that undergoes a wet granulation process, granulating liquid and binder are needed. Unless the drug is moisture sensitive (in terms of granulation), water is normally used as granulating liquid. However, in some cases, the formulator may prefer to use another granulating liquid. Based on debate of known practices, ethanol, methanol, isopropyl alcohol and acetone are the default organic solvents in the system. Binder is generally needed to form strong granules (Section 1.3.1.6). The selection of a binder is described in Section 3.3.7. Sometimes a suitable type of diluent can also act as a binder. Based on the experience of the experts, if the diluent is from a 'sugar' family and is soluble (i.e. would become sticky on contact with water) and where the drug is soluble, the binder is not needed. If the drug is 'medium soluble' or 'insoluble' drug and where the soluble binder is presented in more than 10%w/w, the binder is probably not needed either.

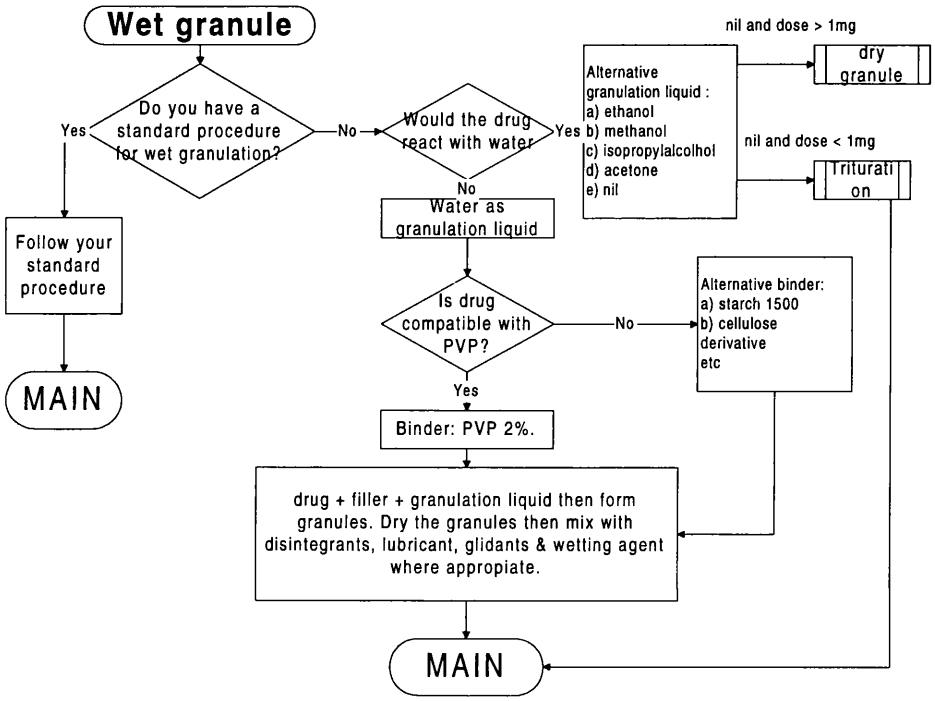
The use of wet granulation can be restricted by the moisture sensitivity (in terms of granulation) of the drug. For a moisture sensitive drug, an organic solvent will be used as granulating liquid. If organic solvent cannot be used (e.g. due to compatibility reason, company practices) and the drug is moisture sensitive, only dry granulation can be used (Section 3.4.2). Special treatment would be needed for 'very low' dose (less than 1mg) as described in Section 3.4.3.

Although the system does not cover the technical details involved in granulation process, a brief outline on the granulation procedure is provided, if the user does not have a standard procedure of his own. Generally, the drug and the diluent (and wetting agent where needed) are mixed together. Disintegrant, depending on its mechanism and the user's preference, may be added intragranularly or extragranularly. Strong disintegrants (Section 3.3.3) which function by their powerful swelling effect in contact with water, are more effective when added extragranularly. Intragranular incorporation of these disintegrants is the least effective (Section 1.3.2.2). The granulating liquid is mixed together with the binder and then added to the drug mixture to form granules. Wetting agent can also be added into the granulating liquid. The granules are then dried

and then mixed with disintegrant (if needed), lubricant, glidant where appropriate. Figure 3.20 illustrates the brief outline of the 'Wet granulation' routine.

Figure 3.20 : 'Wet granulation' routine

'MAIN' represents the section in the main program where this routine is triggered.

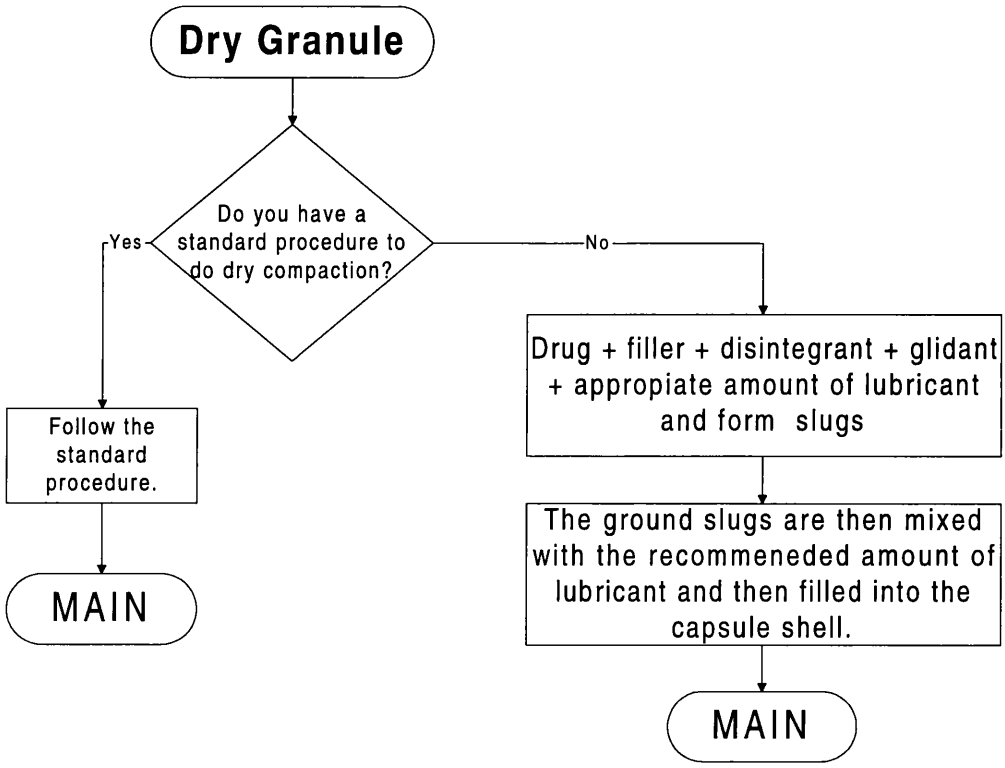


3.4.2 *Dry granulation*

Generally, the drug, diluent, disintegrant, glidant and appropriate amount of lubricant are mixed together and slugs are formed. These slugs are then ground and mixed with the recommended amount of lubricant, and filled into the capsule shell. However, different companies may have different procedures in dry granulation, although the principle should be similar. The amount of lubricant required to form slugs varies depending on the method used and on the type of drug used. Therefore the quantity of lubricant required for the formation of slugs is not included in the recommended formula. Figure 3.21 illustrates the outline of the 'Dry granulation' procedure.

Figure 3.21 : 'Dry granule' routine

'MAIN' represents the section in the main program where this routine is triggered.

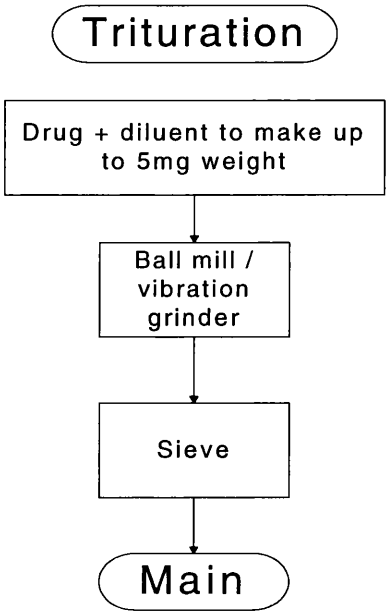


3.4.3 Trituration of the drug for very low dose drug (< 1 mg)

This routine is designed for drugs of a dose of less than 1 mg where a wet granulation process is recommended but neither water nor organic solvents can be used. Wet granulation of such a small amount of drug would be difficult. As suggested by the experience experts, triturating (dilute) the drug to a bigger volume with diluent would be one of the methods to tackle the problem. Figure 3.22 shows the outline of the trituration procedure. Basically the drug is mixed with some diluent. This mixture of drug and diluent should weigh 5mg and will then be processed by a ball mill or a vibration grinder and later be sieved to deagglomerate aggregates formed during milling. This primary drug mixture can then be mixed with the other ingredients in the formula with reduced risk of uneven mixing of the low dose drug.

Figure 3.22 : 'Trituration' Routine

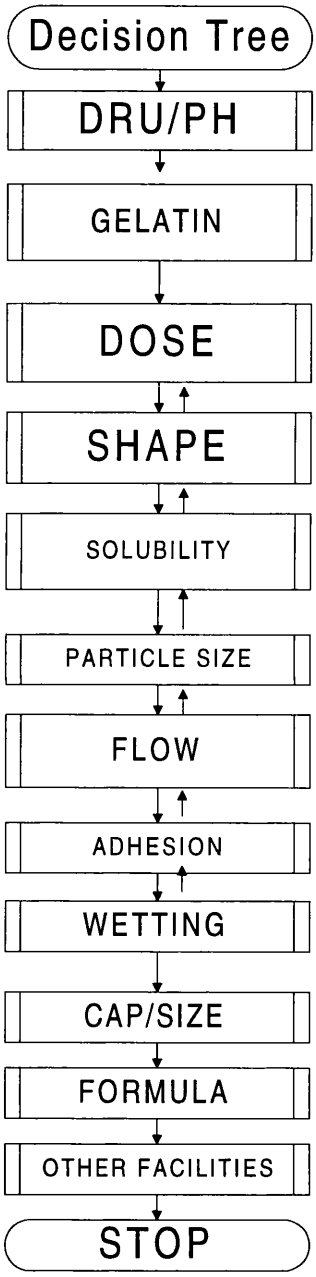
'MAIN' represents the section in the main program where this routine is triggered.



3.5 Summary

The knowledge accumulated and stored in the three databases (Chapters 1 and 2) are transformed into the form of a decision tree. The way the system is programmed depended on the way the decision tree were contructed. The area of knowledge that the system covers is rather extensive and the judgement by the experts who partipated in the 'decision tree contruction' plays an important role in extracting the essential information from the knowledge base to build up the core system and the contributions of their 'unpublished' knowledge in the form of 'team effort' is also a unique feature for this system. The major branches of the decision tree are described in this Chapter. A 'skeletal' structure of the system can be built by these branches as shown in Figure 3.23. As a result of the processing of these routines, a robust formula (based on logic) can be produced for the particular drug.

Figure 3.23 : Skeletal structure of the system



'DRU/PH' captures the name of the drug and the specification required for the product. Details of 'OTHER FACILITIES' can be found in Section 5.2.

Chapter 4

Practical Experiments

4. Practical Experiments

Practical experiments were carried out in two stages to test the viability of the system - before and after the decision tree was programmed in computer language. Before the decision tree was programmed, the routes were tested by formulating two drugs, paracetamol and diltiazem, using the recommendations of the decision tree. After the decision tree was transformed into computer programming language, acetylsalicylic acid was formulated based on the recommendation in the 'output' of the program.

In this chapter, the formulation of the three model drugs paracetamol, diltiazem (Section 4.1) and acetylsalicylic acid (Section 4.3) are described. The performance of these formulations, in terms of filling, disintegration and dissolution are reported. A set of experiments was also carried out to investigate the correlation between coefficient of variation of the fill weight against running time between sample collections and the flow properties of the powder mixture concerned. The purpose of this set of experiments is to confirm the hypothesis (which was deduced after formulation of paracetamol and diltiazem) that insufficient running time between sample collections may cause an apparently higher value of the coefficient of variation of the fill weight.

4.1 The use of the System in the formulation of diltiazem and paracetamol capsules in a stage one trial

4.1.1 Aim :

The aim of this study was to verify the practicability of the decision tree before it was programmed in computer language. Two drugs, diltiazem and paracetamol, were formulated based on the recommendations the decision tree provided. Diltiazem is a soluble drug and belonged to solubility class 1 while paracetamol belonged to solubility class 2 as defined in the Expert System (Table 3.2, Section 3.2.4.2). The drugs were formulated into different doses : 500mg (high dose), 50 mg (medium dose), 2 mg (low dose) and 0.05 mg (very low dose) (Table 3.1, Section 3.2.2).

4.1.2 Materials :

Paracetamol (HN Norton & Co Ltd, UK) and Diltiazem (Fermion, Orion Corporation Ltd, Finland) were used. The excipients used have been recommended by the system and they included maize starch (Reed Medway Sacks Ltd, UK), lactose monohydrate (Whey Products, UK), Explotab (sodium starch glycolate) (Forum Chemical Ltd, UK), magnesium stearate (British Drug Houses, UK) and Aerosil 200 (colloidal silicon dioxide) (Degussa, Belgium).

4.1.3 Methods of determination of the properties of drugs :

Information about properties of drugs, tapped densities of some excipients and compatibility data of drugs and excipients must be entered into the system before any recommended formulations for the drugs can be suggested. The format and detail of the input data required can be found in the sample Input Package in Appendix I.

Determination of the bulk densities of the drugs and some excipients

In the System, the calculation of the formulation is based on the accurate measurements of the bulk densities of drug, diluent and disintegrant (Section 3.2.5). The bulk densities of these ingredients were measured by a mechanical tapping device, consisting of a 100 ml measuring cylinder containing the corresponding powder sample, which was tapped by means of a constant velocity rotating cam. The rotating cam displaced the cylinder at a distance of 1 cm at a rate of 3 taps per minute. Hausner's ratio (1967) and Carr's compressibility index (Carr, 1965a & b) were then calculated to indicate the flow properties of the drugs.

Determination of other physico-chemical properties of the drugs

The particle size and shape were determined by an image analyser (Seescan Solitaire 512, Cambridge, UK). The tip of a pointed spatula was used to remove a tiny sample of the drug. The drug particles were dispersed in a drop of liquid paraffin on a microscope slide. The slide (together with a coverslip) was then placed under the

microscope of the image analyser. The image observed under the microscope was analysed by the computer (a component of the image analyser) and the Ferret's diameter (Section 1.3.1.1) was determined by the computer based on the measurement of more than 200 particles. The shape of the particles was also observed.

The wettability of the drug was determined by observations, so that practical situation, where only very limited amount of drug is available, can be mimicked (Section 3.2.4.6). A droplet of water was placed carefully on a glass slide using a small pipette. A very small amount of drug was sprinkled on top of the droplet of water. If the drug remained floating on the top of the water droplet after 5 minutes, it was classified as 'not wettable' and if it sinks, it was considered to be 'wettable'.

The adhesion of the drug towards metal surfaces was determined using a grading method. The dosator nozzle (dissembled from the filling machine) was dipped into the powder beds of paracetamol or diltiazem and the amount of drug attached to the nozzle was observed after withdrawal. If a significant amount of drug was attached to the nozzle, the drug was considered to be adhesive; otherwise, it was considered as non-adhesive.

The solubility data for paracetamol and diltiazem were extracted from the published domain. Paracetamol has solubility of 1 in 70 of water (British Pharmacopeoia, 1993). From Table 3.2 (Section 3.2.4.2), paracetamol was considered to be medium soluble (Class 2 solubility). Diltiazem is described to be 'freely soluble' in water according to *Merck Index* (1976) and is 'soluble' according to *Physician Desktop Reference* (1993) and therefore is classified as soluble (Class1 solubility) drug by the system.

4.1.4 Input Information :

4.1.4.1 Bulk densities and flow properties of drugs

Tables 4.1 and 4.2 show the flow properties of drugs and tapped densities of excipients respectively. The description of the flow type is defined with reference to the

Carr's compressibility index (Section 1.3.1.3) and can be found in Table 3.1 (Section 3.2.2).

Table 4.1 : Flow properties of paracetamol and diltiazem

	Dmax (g/cm^3)	Dmin (g/cm^3)	H	Carr (%)	Flow type
paracetamol	0.50	0.28	1.79	44.2	poor
diltiazem	0.71	0.52	1.36	26.4	good

Dmax = tapped density

Dmin = bulk density

H = Hausner's ratio

Carr = Carr's compressibility

4.1.4.2 Tapped densities of excipients

The following table shows the tapped densities for the diluents and disintegrants used in this study.

Table 4.2 : Tapped densities of diluent and disintegrant used in the study

Excipients	**Dmax(g/cm^3)**
maize starch	0.82
lactose	0.96
sodium starch glycolate	0.3

4.1.4.3 Compatibility of paracetamol, diltiazem and excipients

As yet, no interactions have been reported in the official references, such as *The Handbook of Pharmaceutical Excipients* (1994) and *Martindale* (1993), between paracetamol or diltiazem and of the default excipients recommended in the System (i.e.

maize starch, lactose, sodium starch glycolate, magnesium stearate and colloidal silicon dioxide).

4.1.4.4 Other properties of paracetamol and diltiazem

Using the methods described in Section 4.1.3, results obtained for particle size and shape, wettability and adhesiveness of drugs on metal surfaces are shown in Table 4.3. Additional information concerning moisture sensitivity, solubility and stability of drugs were extracted from publications. The stability of drug in gelatin capsules were judged by the moisture sensitivity of drug, possibility of chemical reactions between drugs and gelatin and possibility of crosslinking between drugs and gelatin. Both paracetamol and diltiazem were found to be not moisture sensitive. Records of chemical reaction or crosslinking between paracetamol or diltiazem and gelatin could not be found. Therefore both drugs were considered to be 'stable' in gelatin capsules in this study.

Table 4.3 : Other properties of paracetamol and diltiazem

	Paracetamol	**Diltiazem**
*moisture sensitive	No	No
*stable in gelatin capsules	Yes	Yes
mean particle size (Ferret's diameter)	25 μm (fine)	22 μm (fine)
Needle shape	no	no
*Solubility	Class 2 (medium soluble)	Class 1 (soluble)
Wettability with water	yes	yes
Coating on metal surface	yes	yes

*Source of information : *Merck Index* (1976); *British Pharmacopoeia* (1993); *Martindale* (1993); *Physicians' Desk Reference* (1993).

4.1.5 Derivation of the formulations for paracetamol and diltiazem from the decision tree

Paracetamol and diltiazem were formulated into high dose (500mg), medium dose (50mg), low dose (2mg) and very low dose (0.05mg) following the recommendation suggested by the flow charts of the System (Chapter 3).

4.1.5.1 Paracetamol (high, medium and low dose) - Derivation of the recommended formulations from the decision tree

From the skeletal structure of the decision tree shown in Figure 3.23 (Section 3.5), the first routine 'DRU/PH' required the name of the drug and the specifications of the drug, excipients and product. The specifications required should follow the standards listed in British Pharmacopoeia. In 'GELATIN' routine (Section 3.2.1), it was established from the literature that paracetamol is not moisture sensitive and is stable in gelatin capsules (Table 4.3).

The doses of paracetamol used are 500 mg, 50 mg and 2 mg (classified as high, medium and low dose) and this information was processed in the 'Dose' routine (Section 3.2.2). For high, medium or low dose drugs, the next routine is 'SHAPE' (Section 3.2.4.1). The particles of paracetamol are not needle shaped (Table 4.3) and therefore the 'SOLUBILITY' routine will follow (Figure 3.4, Section 3.2.4.1). Paracetamol is a medium soluble drug (class 2 solubility) and therefore a medium strength disintegrant was deduced to be used (Figure 3.5, Section 3.2.4.2). From Section 3.3.3 'Default disintegrant', the first choice medium strength disintegrant is sodium starch glycolate with a default concentration of 5% w/w. Since there is no indication of incompatibility between paracetamol and sodium starch glycolate, the first choice disintegrant recommended by the System, 5% w/w sodium starch glycolate was agreed to be used.

The next routine is 'Particle size' (Figure 3.5, Section 3.2.4.2). From the samples examined, paracetamol has a mean particle size of 25 μm, thus a fine particle size (see Table 4.3). Following the 'DILUENT' routine (Figure 3.6, Section 3.2.4.3), a diluent

from the 'DILUENT F' list (Section 3.3.2) was recommended. From Section 3.3.2 ('Default diluent'), the first choice in this list is maize starch. There is no indication of incompatibility between maize starch and paracetamol. Maize starch was agreed to be included in the formula. Following the same routine (Figure 3.6), the drug has a particle size greater than 15 μm and is not of needle shaped, therefore no granulation is needed and the information was then passed onto the next routine, 'Flow'. In the 'Flow' routine (Section 3.2.4.4), from the maximum bulk density (0.5 g/cm^3) and minimum bulk density of (0.279 g/cm^3), paracetamol was expected to flow poorly (based on Carr's compressibility index) (Table 4.1). This information was passed onto the 'Adhesion' routine (Figure 3.9, Section 3.2.4.5). For poor flow drug, some user may prefer to go straight to granulation process and thus improve the flow rate of drug. However, if granulation is not adopted, the system would recommend the use of both lubricant and glidant. In this study, the latter sub-routine was tested. The first choice lubricant (Section 3.3.4 'Default lubricant') is magnesium stearate 1% w/w and the first choice glidant (Section 3.3.5 'Default glidant') is colloidal silicon dioxide 1% w/w. Since no interaction was found reported in the literature, both magnesium stearate and colloidal silicon dioxide were agreed to be employed in the formula. The use of wetting agent was determined in the 'Wet' routine (Figure 3.10, Section 3.2.4.6). From this routine, it was suggested that no wetting agent was needed for the 2 mg dose paracetamol formulation. For the 50 mg and 500 mg formulations, since paracetamol is a medium soluble drug that wets with water (Table 4.3), no wetting agent was suggested.

All these information as well as the information about the tapped densities of the diluent and the disintegrant (Table 4.2) would be used to calculate the volume of the drug mixture (Section 3.2.6) and passed onto the next routine, 'Cap/Size' routine (Figure 3.11, Section 3.2.7). From the calculation, the minimum capsule size for formulating 500 mg (high dose) paracetamol is size 00 and there is no restriction on capsule size used for both the 50mg (medium dose) and 2mg (low dose) paracetamol. Based on common practice, for medium dose formulations, size 1 capsules are often employed whereas for the low dose formulations, size 3 capsules are used. Size 00 capsule is not commonly used because the size of the capsule is relatively large to swallow. A size 0 capsule was chosen for 500 mg paracetamol capsule. Since the chosen capsule size for 500 mg formulation (size 0) was smaller than the calculated minimum capsule size (size

00), the 'Minimize' routine was triggered. From the 'Minimize' routine (Section 3.2.8), granulation method or densification by compression were suggested to be possible methods to densify the drug mixture. The granulation method was chosen and followed was the 'Granulation' routine (Section 3.4). Since the paracetamol is not moisture sensitive drug, it was believed that the drug would not be moisture sensitive in terms of granulation either. A choice of wet or dry granulation were offered by the system (Figure 3.19, Section 3.4). The dry granulation or dry compaction method usually densifies the drug mixture to a greater extent compared to wet granulation. Dry granulation was chosen. The 'Dry granule' routine was shown in Figure 3.21 (Section 3.4.2). The quantitative content of each ingredient was then calculated and displayed (Section 3.2.9). For the 500 mg dose, where the agreed capsule size is smaller than the calculated minimum capsule size, there is only minimal space for the incorporation of a diluent and in this particular case, no diluent is included. In other cases (i.e. for 50 mg and 2 mg paracetamol formulations), the choice of size 1 and size 3 capsules respectively will not trigger the 'Minimize' routine. The formulations were calculated as described in Section 3.2.6. Table 4.4 shows the recommended formulations for high, medium and low dose paracetamol.

Table 4.4 : The recommended formulations for paracetamol

	*High Dose		Medium Dose		Low Dose	
	%w/w	wt(mg)	%w/w	wt(mg)	%w/w	wt(mg)
Paracetamol	93	500	19.2	50	0.012	2
maize starch	0	0	73.8	205	92.99	154
sodium starch glycolate	5	27	5	14	5	8
magnesium stearate	1	5	1	3	1	2
Aerosil	1	5	1	3	1	2
smallest capsule size required	00		-		-	
agreed capsule size used	0		1		3	

* Process : Dry granulation

The powder mixture is dry compacted first in order to fit into size 0 capsule shells.

4.1.5.2 Diltiazem (high, medium and low dose) - Derivation of the recommended formulations from the decision tree

The derivation of the formulations for diltiazem follows the same sequences of routines set out in the flow charts as described in Chapter 3. From the 'Gelatin' routine (Section 3.2.1), the fact that diltiazem is not moisture sensitive and is stable in gelatin capsules are noted (Table 4.3). From the 'Dose' routine' (Section 3.2.2), for high, medium and low dose diltiazem, the information would pass onto the next routine which is the 'Shape' routine (Section 3.2.4.1). The particles of diltiazem are not of needle shape (Table 4.3) and the information would pass onto the next routine, the 'Solubility' routine (Section 3.2.4.2). In the 'Solubility' routine, it was deduced that no disintegrant is needed because diltiazem is a soluble drug. In the 'DILUENT' routine (the next routine) (Figure 3.6, Section 3.2.4.3), the particle size of 22 μm (Table 4.3) would lead to the use of the first choice diluent (maize starch) from the 'DILUENT F' list (Section 3.3.1). Since the particle size of the drug is greater than 15μm and not of needle shaped, the information will be passed to the next routine, 'Flow' (see Fgiure 3.5). From Table 4.1, diltiazem has maximum bulk density of 0.71 g/cm^3 and minimum bulk density of 0.522 g/cm^3 and would flow relatively well. This information was passed from the 'Flow' routine onto the 'Adhesion' routine (Figure 3.9, Section 3.2.4.5). For drugs that have a good flow, the use of a glidant depends on whether the drug would adhere to the metal surfaces. Diltiazem does coat the metal surface (Table 4.3). Following the recommendations deduced from the 'Adhesion' routine, both lubricant and glidant are included in the formulation. The first choice lubricant (Section 3.3.4 'Default lubricant') is magnesium stearate 1% w/w and the first choice glidant (Section 3.3.5 'Default glidant') is colloidal silicon dioxide 1% w/w. Since no incompatibility between diltiazem and magnesium stearate or colloidal silicon dioxide were found to be reported in the literature (Section 4.1.4.3), both excipients were agreed to be used. From the 'Wet' routine (Figure 3.10, Section 3.2.4.6), similar to paracetamol, no wetting agent was suggested for a soluble drug (which wets with water) of high, medium or low dose (Table 4.3).

Table 4.5 : The recommended formulations for diltiazem

The powder mixture is dry compacted first in order to fit into size 0 capsule shells.

	*High Dose		Medium Dose		Low Dose	
	%w/w	wt(mg)	%w/w	wt(mg)	%w/w	wt(mg)
Diltiazem	98	500	19	50	0.008	2
maize starch	0	0	79	209	97.99	161
magnesium stearate	1	5	1	3	1	2
Aerosil	1	5	1	3	1	2
smallest capsule size required	00		-		-	
agreed capsule size used	0		1		3	

* Process : Dry granulation

In the 'Cap/Size' routine (Section 3.2.12), the minimum capsule size calculated for the 500 mg dose of diltiazem is 00 and there is no restriction in the capsule size used for the 50 mg and 2 mg doses of the same drug. Capsule size 1 was chosen for the 50 mg dose and capsule size 3 was chosen for 2 mg dose of diltiazem (similar to the case of paracetamol, Section 4.1.5.1). For the 500 mg dose, the capsule size chosen (size 0) is smaller than the minimum capsule size determined. The 'Minimize' routine (Section 3.2.8) was triggered and, similar to the case of paracetamol, the dry granulation method was chosen to densify the drug mixture such that the capsules will not be overfilled.

In the 'Formula' routine (Section 3.2.9), the quantitative content of each ingredient in the formulations suggested for high, medium and low dose diltiazem was calculated and displayed. The calculation would also require information about tapped density of maize starch, the diluent, as shown in Table 4.2. For the 500 mg dose, where the agreed capsule size is smaller than the smallest required capsule size, there is only

minimal space for the incorporation of a diluent and in this particular case, no diluent is included. The results are shown below in Table 4.5.

4.1.5.3 Very low dose formulations for paracetamol and diltiazem - Derivation of the recommended formulations from the decision tree

Since the drug content for very low dose (0.05mg) was so small that the effect of drug properties was minimal, a basic formulation was used as long as the drug was compatible with all the excipients. The formulations were derived from the same flow charts but branching to a different sub-routine in 'Dose routine' (Figure 3.2, Section 3.2.2). The 'VLOW' routine (Figure 3.3, Section 3.2.3) was designed for a dose of less than 1 mg. The reasoning for the following decisions can be found in Section 3.2.3. In the 'VLOW' routine, the first choice diluent, lactose monohydrate, from the 'DILUENT L' list (Section 3.3.1) was chosen and a medium strength disintegrant was recommended. From Section 3.3.2, 'Default disintegrant', the first choice medium strength disintegrant is sodium starch glycolate 5% w/w. Both lactose monohydrate and sodium starch glycolate were indicated to be compatible with both paracetamol and diltiazem (Section 4.1.4.3). Therefore both excipients were agreed to be included in the formulations for both drugs.

A granulation process is recommended based on the 'VLOW' routine (Section 3.2.3). The Wet Granulation process (Section 3.4.1) is commonly used if the drug is of very low dose and is not moisture sensitive. Water being the most popular granulating liquid and polyvidone (PVP) 2% w/w is the default binder in the System. Since PVP is not found to be reported as incompatible with the drugs, it was chosen as the binder for the formulation. A lubricant was also recommended. Magnesium stearate 1% w/w being the first choice lubricant (Section 3.3.4).

For a dose of 0.05mg, there will be no restriction on the capsule size used and capsule size 3 was common size used for low dose drug. Therefore the formula was calculated based on the use of capsule size 3. Together with the information about the tapped density of the diluent, lactose (Table 4.2), the quantitative content of each ingredient in the formula was calculated and the formula is shown below in Table 4.6.

Table 4.6 : Formulation for very low dose drug

Drug (diltiazem / paracetamol)	0.05mg
lactose	187mg
sodium starch glycolate (5%)	10mg
magnesium stearate (1%)	2mg
polyvidone (2%)	4mg
capsule size	3

Process : Wet granulation

4.1.6 Procedures involved in the formulation of paracetamol and diltiazem

4.1.6.1 Powder mix

Once the formulations were deduced, the drug and the excipients were mixed together using a Turbula System (Schatz, Willy A Bachofen AG Maschinenfabrik, Switzerland) at a speed of 30 rpm. The drug and disintegrants (where appropriate) were mixed for 15 minutes and then the lubricant and glidant were added and mixed for a further 5 minutes.

The mixtures were then filled into size 0 hard gelatin capsules using the Zanasi AZ5 (IMA, Italy), an intermittent-motion dosator nozzle filling machine. Since the parts of the filling machine was only adjusted for the filling of size 0 capsules, a size 0 capsule shell was used in all cases, even though a different capsule size was used in the formulation generated by the Expert System. The targeted weight was adjusted accordingly by calculating from the tapped density of the drug mixture (Table 4.7 and Table 4.8, Section 4.1.8.1).

4.1.6.2 Wet granulation

In cases where wet granulation was recommended (e.g. for very low dose formulations), the drug was mixed with the diluent (lactose) and the disintegrant

(sodium starch glycolate) using a mixer (Kenwood, UK). The binder (polyvidone) was dissolved in the granulation liquid (water). The solution was heated up gently until the polyvidone was dissolved in the water. A small amount of the cooled binder solution was added slowly into the drug mixture. The drug mixture was then mixed with a small amount of the binder solution by the Kenwood mixer. This process was repeated until all the binder solution was added.

The subsequent drug mixture was then placed into an Erweka AR400 (Copley, UK) oscillating granulator where the wet drug mixture was oscillated and pressed through a size 1mm sieve. The granules formed were dried at 60 °C for about 1 hour and a 1200 microns sieve was used to remove any large granules. Magnesium stearate was then mixed with the dried granules for 5 minutes in a Tubula mixer System (Schatz, Willy A Bachofen AG Maschinenfabrik, Switzerland). The mixture was then filled into size 0 hard gelatin capsules using a Zanasi AZ5 (IMA, Italy) filling machine.

4.1.6.3 Dry granulation / dry compaction

Dry granulation was recommended for the 500 mg dose of paracetamol and diltiazem. In this study, the powder mixture consisting of drug, diluent (maize starch), disintegrant (where required) and 0.5%w/w of lubricant was slugged initially using a single punch eccentric tableting machine (Manesty F3, UK) with 7mm diameter flat faced die. Minimal amount of lubricant was added in order to facilitate the slugging process. The quantity of lubricant needed depending on the granulating equipment and was not included in the formula generated by the system. These slugs were then ground down to granules using mortar and pestle and were sieved using a 1200 microns sieve. For paracetamol and diltiazem mixtures, extra lubricant of 0.5% and 1.5%w/w respectively was added at the slugging stage. The recommended amount of lubricant (1% w/w of magnesium stearate) and glidant (1% w/w of aerosil) were added to the granules before filling them into size 0 capsule using a Zanasi AZ5 filling machine (IMA, Italy).

4.1.7 Sample collection and tests performed on the formulations

The machine settings of the filling machine were adjusted. Dosator heights 1.9 and 1.8 units with a compression setting of grade 2 were used. The drug mixture was poured into the powder feed in the filling hopper. The empty size 0 capsule shells (Capsugel AG, France) were also fed into the corresponding hopper. The filling machine was allowed to run until the powder bed was settled (about 50 capsules were filled) before any sample was collected. For each formulation, 40 to 50 sample capsules were then collected. Tests for uniformity of weight, disintegration and dissolution as described in the British Pharmacopoeia 1993 were carried out.

4.1.7.1 Uniformity of weight test (BP)

Twenty capsules were weighed individually. The contents of each of these capsules were emptied and the weight of each capsule shell was obtained. The fill weight of each capsule was then calculated and subsequently the mean fill weight, standard deviation and coefficient of variation of the fill weight were determined. To pass the BP standard, the fill weight variation should not be more than 7.5% if the dose is greater than 300 mg and less than 10% if the dose is less than 300 mg.

4.1.7.2 Disintegration Test (BP)

Disintegration test (BP) was carried out for six capsules from each formulation. One capsule was introduced into each of the six tubes in the disintegration test apparatus (as specified in BP). The apparatus was suspended in a 1000ml beaker containing water at 36 - 38 °C. A disc was used for each capsule to prevent the capsule from floating on top of the water. The apparatus was operated for 30 minutes. "The capsules pass the test if no residue remains on the screen of the apparatus or, if a residue remains, it consists of fragments of shell or is a soft mass with no palpable core" (British Pharmacopoeia, 1993). Any residue remaining on the lower surface of the discs consisted only of fragments of shell.

4.1.7.3 Dissolution Test (BP)

The dissolution apparatus, apparatus II (paddle apparatus), consisting of a dissolution tester (Pharma Test type, PTWS), fraction collector (Pharma Test, type PTCI) and a pump (ISMATEC IPS) was used. An ultraviolet spectrometer was used to measure the concentration of drug in the sample solution collected from the dissolution medium. For paracetamol, the wavelength used was 239nm while for diltiazem, the wavelength used was 230 nm.

A capsule was placed in each of the six beakers using a capsule holder. The speed of rotation of the paddles of the dissolution tester was 50 rpm. The dissolution medium for both paracetamol and diltiazem was 1000 ml of distilled water at 37 °C. To pass the BP standard, 70% of the drug content must be released into the dissolution medium within 45 minutes.

4.1.8 Results : Performance of the recommended formulations

4.1.8.1 Uniformity of weight test (BP)

The maximum and minimum bulk densities, Hausner's ratio, Carr's compressibility, mean fill weight, standard deviation of fill weight and coefficient of variation of the fill weight would provide some information about the filling performance. Tables 4.7 and 4.8 illustrate the filling performance of paracetamol and diltiazem capsules respectively.

Table 4.7 : Filling performance of paracetamol formulations

	Dmax g/cm	Dmin g/cm	H	Carr's (%)	† targeted fill wt. (mg)	mean fill wt (mg)	stand dev	coef. of variation of the fill weight (%)	*settings of machine	BP test for weight uniformity
compacted high dose (500mg)	0.876	0.682	1.28	22.15	536	488.6	10.08	2.06	1.9 cs 2	Pass
						477.57	20.53	4.30	1.8 cs 2	Pass
medium dose (50 mg)	0.735	0.534	1.38	27.50	450	470.3	7.11	1.51	1.9 cs 2	Pass
						407.9	18.72	4.59	1.8 cs 2	Pass
low dose (2 mg)	0.781	0.588	1.33	24.70	478	458.2	26.78	5.84	1.9 cs 2	Pass
						418.4	20.88	4.99	1.8 cs 2	Pass
very low dose (0.05 mg)	0.680	0.591	1.15	13.09	416	436.7	9.77	2.24	1.8 cs 2	Pass
						478.9	9.90	2.07	1.9 cs 2	Pass

* The settings of the filling machine is represented by the compression setting (cs) of grade 2 preceded by a number which represent the dosator height (per unit)

- capsules used for dissolution and disintegration tests

† The targeted fill weight is assumed to be 90% of the capsule volume (for size 0) (Table 1.1) multiplied by the tapped density of the drug mixture (Dmax).

Table 4.8 : Filling performance of diltiazem formulations

	Dmax g/cm	Dmin g/cm	H	Carr's (%)	† targeted fill wt. (mg)	mean fill wt (mg)	stand dev	coef. of variation of fill weight (%)	settings of machine	BP test for weight uniformity
compacted high dose (500 mg)	0.847	0.660	1.28	22.10	518	506.2	6.88	1.36	1.8 cs 2	Pass
						581.7	19.21	3.30	1.9 cs 2	Pass
medium dose (50 mg)	0.767	0.555	1.38	27.60	469	426.6	18.43	4.32	1.8 cs 2	Pass
						459.8	17.64	3.84	1.9 cs 2	Pass
low dose (2 mg)	0.785	0.571	1.37	27.26	480	415.2	15.01	3.62	1.8 cs 2	Pass
						474.0	11.92	2.51	1.9 cs 2	Pass
very low dose (0.05 mg)	0.718	0.609	1.18	14.82	439	436.8	11.05	2.53	1.8 cs 2	Pass
						496.2	11.05	2.23	1.9 cs 2	Pass

* The settings of the filling machine is represented by the compression setting (cs) of grade 2 preceded by a number which represent the dosator height (per unit)

- capsules used for dissolution and disintegration tests

† The targeted fill weight is assumed to be 90% of the capsule volume (for size 0) (Table 1.1) multiplied by the tapped density of the drug mixture (Dmax).

4.1.8.2 Disintegration Test (BP)

Tables 4.9 and 4.10 show the results of the disintegration tests for paracetamol and diltiazem formulations respectively.

Table 4.9 : The results of disintegration tests for paracetamol formulations

	disintegration time for last capsule	BP test result
compacted high dose	4 min 10 secs	Pass
medium dose	6 min 10 secs	Pass
low dose	5 min 20 secs	Pass
very low dose	4 min 40 secs	Pass

Table 4.10 : The results of disintegration tests for diltiazem formulations

	disintegration time for last capsule	BP test
compacted high dose	3 min 10 secs	Pass
medium dose	5 min 30secs	Pass
low dose	4 min 45 secs	Pass
very low dose	3 min 40 secs	Pass

4.1.8.3 Dissolution Test (BP)

The results obtained from the dissolution tests for paracetamol and diltiazem are presented in Table 4.11 and 4.12 respectively and the dissolution profiles for paracetamol and diltiazem are shown in Figure 4.1 and Figure 4.2.

Table 4.11 : The result of dissolution test for paracetamol formulations

	percentage of drug dissolved at 45 min.	BP test result
compacted high dose	99.2	Pass
medium dose	97.8	Pass
low dose	97.2	Pass
very low dose	97.5	Pass

Table 4.12 : The result of dissolution tests for diltiazem formulations

	percentage of drug dissolved at 45 min.	BP test
compacted high dose	99.5	Pass
medium dose	99.2	Pass
low dose	98.3	Pass
very low dose	98.7	Pass

Figure 4.1 : Dissolution curves for paracetamol formulations

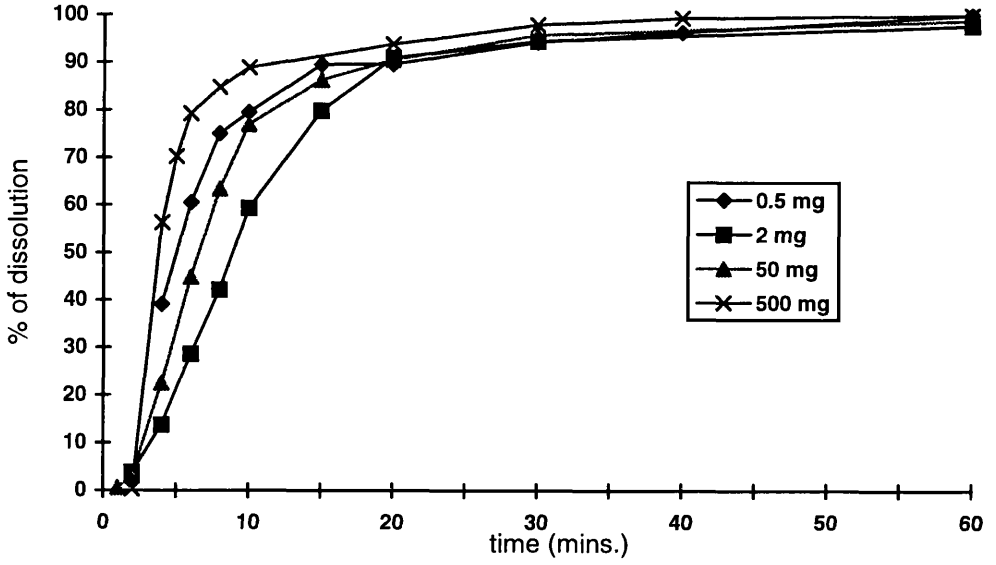
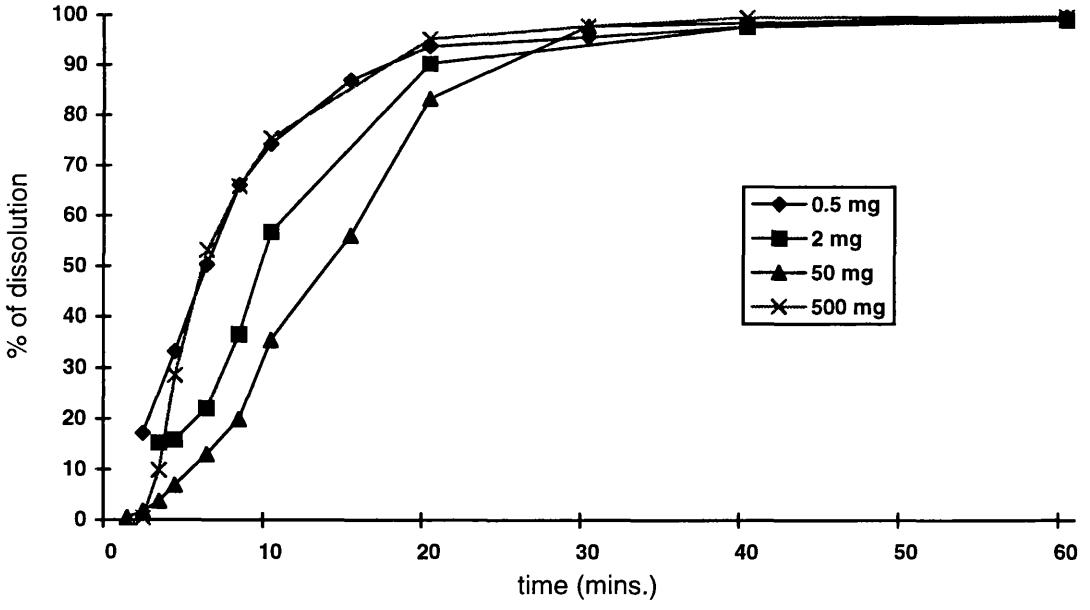


Figure 4.2 : Dissolution Curves for diltiazem formulations



4.1.9 Conclusion and Discussion

With respect to the BP standards, for uniformity of weight, the disintegration and dissolution, all the formulations deduced from the flow chart of the Expert System passed the required standards. The Carr's compressibility index of the formulations for paracetamol varied from 13.09% to 27.5%. The coefficient of variation of the fill weight of these formulations vary from 1.51% to 5.84% and passed the uniformity of weight test (BP). All the four diltiazem formulations seems to have fairly good flow with Carr's compressibility between 14% to 28%, and all these formulations passed the uniformity of weight test (BP) with coefficients of fill weight variation of 1.5% to 2.5%. However, the coefficient of variation of the fill weight of these formulations was high in terms of industrial standards. In some industrial companies, a coefficient of variation of the fill weight of greater than 3% is classified as "failed". The concern over the relatively high coefficient of variation of the fill weight experienced may be explained by an insufficient running time between sample collections since the samples were collected after about fifty capsules were produced i.e. soon after the powder bed settled. This problem was further investigated in Section 4.2.

The results from the disintegration tests and the dissolution tests showed that all the ten formulations could dissolve in water (37 °C) within the limits set out in the British Pharmacopoeia. These gave a positive indication of the bioavailability of drugs although *in vivo* tests would be required to give a better picture of the uptake of drugs by the body.

In conclusion, the recommended formulations deduced from the flow charts of the Expert System (for different doses of paracetamol and diltiazem) have been successful in terms of the standards set by the British Pharmacopoeia.

4.2 Correlation between coefficient of variation of the fill weight against running time between sample collections and powders (excipients) of different flow properties

4.2.1 Aim :

During our discussion over the performance of the diltiazem and paracetamol formulae, concerns were expressed over the relatively high coefficient of variation of the fill weight in terms of industrial standards. This was believed to be caused by insufficient running time between sample collections. This study was therefore designed initially to confirm the hypothesis and to find out the minimum running time between sample collections. By performing this study with excipients of a range of different properties, the correlation between filling performance and flow properties of excipients can also be obtained. Six common excipients were used. They are lactose, maize starch, magnesium stearate and three different grades of microcrystalline cellulose.

4.2.2 Material :

Microcrystalline cellulose : Avicel PH101, PH102, PH105 (FMC, USA); medium grade lactose (Unigate, UK); maize starch (Reed Medway, UK) and magnesium stearate (British Drug Houses, UK) were used.

4.2.3 Method :

Avicel PH101, Avicel PH102, maize starch - without additives together with Avicel PH105 with 1% magnesium stearate, and lactose with 0.5% magnesium stearate - 5 different combinations of excipients were studied.

The flow properties for each combination of excipients were measured. A mechanical tapping device was used to determine both the maximum and minimum densities. Values for Hausner's ratio, Carr's compressibility index and Kawakita's constant were calculated. Kawakita's constant, '*a*', can be used to express the

compressibility of the drug mixture (Section 1.3.1.4). Static angles of repose measured by fixed bed cone method (Nelson, 1955) were also measured.

Each combination of excipients was then filled into size 0 hard gelatin capsules using the Zanasi AZ5 (IMA, Italy), an intermittent-motion dosator nozzle filling machine. The filling machine was set at a compression setting of grade 2 and a dosator height 1.8 units throughout the study. The first ten capsules were discarded. The next forty capsules were then collected (Lot 1). The second collection of 40 capsules (Lot 2) was made after 100 capsules were filled. After 200 capsules, another forty capsules were collected (Lot 3) and the last collection of 40 capsules was made after 500 capsules were filled (Lot 4). Uniformity of weight test (BP) for each batch of capsules was carried out.

4.2.4 Result :

1) **Flow properties of different excipients or combinations of excipients**

Flow properties of the 5 combinations of excipients are shown below in Table 4.13 :

Table 4.13 : Flow properties of the five combinations of excipients in the study

	Dmax	Dmin	H	Carr	*a* (%)	angle of repose
Avicel PH102	0.4061	0.3317	1.22	18.32	18.81	42.18°
Avicel PH101	0.4313	0.339	1.27	21.40	22.21	47.65°
maize starch	0.7894	0.5938	1.33	24.78	27.88	----------
Avicel PH105+MgSt	0.4178	0.2771	1.51	33.68	37.24	59.68°
lactose+MgSt	0.7528	0.4587	1.64	39.07	42.09	----------

Dmax : Maximum bulk density (g/cm^3)

Dmin : Minimum bulk density (g/cm^3)

MgSt : Magnesium Stearate

H : Hausner's ratio

Carr : Carr's Compressibility index (%)

'a' : constant in Kawakita's equation

------: powder mixtures were too cohesive to flow through the funnel and therefore no value can be obtained.

2) **Coefficient of variation of the fill weight and number of capsules filled**

From the uniformity of weight test (BP), the mean fill weight of the twenty sample capsules were determined (see Section 4.1.7). The coefficient of variation of the fill weight of these capsules were also calculated and were used as an indication of the capsule filling performance. In order to determine a) the correlation between coefficient of variation of fill weight and running time between sample collections of different combinations of excipients and b) any correlation between coefficient of variation of fill weight and flow properties of excipients or combinations of excipients, the result of the coefficient of variation of fill weight for the five powders or powder mixtures against number of capsules filled are tabulated as follow in Table 4.14 :

Table 4.14 : Coefficient of variation of fill weight of different batches of samples collected

no. of capsules filled	10	100	200	500
Avicel PH102	75.07	2.42	2.08	1.57
Avicel PH101	2.62	2.50	2.11	1.46
maize starch	2.94	1.80	1.39	0.91
Avicel PH105+MgSt	3.19	5.77	4.96	5.50
lactose+MgSt	28.05	51.45	53.82	51.95

4.2.5 Discussion :

1) **Correlation between coefficient of variation of the fill weight and running time between sample collection of different combinations of excipients :**

At least 200 capsules must be filled before the coefficient of the variation of fill weight becomes stable. As described in Section 4.1, only 50 capsules were filled before samples of paracetamol and diltiazem capsules were collected for the uniformity of weight test (BP). The coefficients of variation of the fill weight for the paracetamol and diltiazem capsules were therefore not surprised to be relatively high in terms of industrial standards even though all the formulations can be described as 'successful' in term of the standards set by the BP (Section 4.1.9). In the second stage of the validation process of the system i.e. to formulate acetylsalicylic acid based on the recommend formulation suggested by the program (Section 4.3), each sample was collected after at least 200 capsules were filled.

2) **Correlation between coefficient of variation of the fill weight and flow properties of excipients or combinations of excipients :**

Order of flow properties (expressed in terms of Carr's compressibility index) of excipients or combinations of excipients :

From low to high : Avicel PH102 > Avicel PH101 > Maize Starch > Avicel PH105+magnesium stearate > lactose+magnesium stearate.

Avicel PH102 is the most free flowing whereas mixture of lactose and magnesium stearate is the least free flowing. The lower the Carr's compressibility index, the more free flowing the powder mixture is.

Order of coefficient of variation of the fill weight after 200 capsules were filled :

From low to high : Maize Starch < Avicel PH101 < Avicel PH102 < Avicel PH105+magnesium stearate < lactose+magnesium stearate.

It was shown that if the powder mixture has poor flow properties (Carr's compressibility index of greater than 30), the coefficient of variation of the fill weight was high even after 500 capsules were filled. In other words, the filling performance for poor flow powder mixture will not improve by the increase of running time.

If the powder mixture is free flowing, the coefficient of variation of the fill weight decreases, significantly in some cases, with increase of running time. However, the ease of the powder flow does not necessary reflect the extent of the reduction in the coefficient of variation of the fill weight. For example, Avicel PH102 has a Carr's compressibility index of 18.32 which is the lowest and thus the powder is the most free flowing where the Carr's compressibility index of maize starch is 24.78. The coefficient of variation of the fill weight of maize starch is actually lower than Avicel PH102. The powder must possess a certain degree of cohesiveness in order to be retained in the dosator nozzle during the transference of the powder from the powder bed into the capsule bodies. If the powder is too free-flowing and is unable to be retained in the nozzle during the capsule filling process, the coefficient of variation of fill weight may also increased (Section 1.3.1.3).

3) Throughout this study, a nozzle with rough surface was used in place of a good nozzle as the latter was not available at the time of the study. Since the study was performed on a comparative basis, the order of the trend of performance should not be affected. However, the coefficient of variation of the fill weight can be expected to be lower if a good nozzle was used.

4.3 The use of the Expert System in formulation of acetylsalicylic acid in the stage two trial

4.3.1 Aim :

The aim of this study was to validate the programmed system using a model drug, acetylsalicylic acid. First of all, the required information about the drug and excipients were deduced, and filled into an Input Package (Appendix I, also see Section 5.3.1). The system will process the information based on the decision tree described in Chapter 3. The output was documented in the Output Package (Appendix II, also see Section 5.3.3). The performance of the suggested formulation was also established by carrying out the uniformity of weight test, disintegration test and dissolution test as laid out in the BP (1993). The results of these tests were filled into the feedback report

(Appendix III, also see Section 5.3.4) which is designed to capture the knowledge acquired from the validation test.

From BP (1993), it was mentioned that acetylsalicylic acid may gradually hydrolysed to acetic and salicylic acids in contact with moisture. However, the extent of water sensitivity in gelatin capsules is not established. Acetylsalicylic acid (aspirin) is actually marketed in capsule dosage form. Examples of the marketed formulations containing acetylsalicylic acid can be found in Figure 5.7 (Chapter 5). Acetylsalicylic acid is a medium soluble drug, with a solubility of 1 in 300 parts of water at room temperature, belonging to solubility class 2 (Table 3.2 (Section 3.2.4.2)). It possesses needle shaped particles and is incompatible with magnesium stearate and therefore an alternative lubricant have to be used. By formulating acetylsalicylic acid, other aspects of the system can then be tested.

4.3.2 Material :

Acetylsalicylic acid (PhEur 7016 crystals) (Monsanto, UK); Explotab (sodium starch glycolate) (Forum Chemical Ltd, UK), glyceryl monostearate (Hul, UK) and Aerosil 200 (colloidal silicon dioxide) (Degussa, Belgium) were used.

4.3.3 Methods in determination of properties of drugs :

The input information like the maximum and minimum bulk densities of the drug and excipients, particle size and shape, wettability of drug and the adhesiveness of the drug to metal surfaces were determined as described in Section 4.1.3.

4.3.4 Input Information :

The input information was filled into the Input Package which captures all the information required for the system in order to suggest a recommended formulation for acetylsalicylic acid. The Input Package for acetylsalicylic acid can be found in Appendix I.

4.3.4.1 Bulk densities and flow properties of acetylsalicylic acid

The bulk densities of acetylsalicylic acid were determined using the method described in Section 4.1.3 and the results are shown as follow :

Maximum bulk density	:	0.788 g/cm^3
Minimum bulk density	:	0.702 g/cm^3
Hausner's ratio	:	1.122
Carr's compressibility	:	10.91 %

4.3.4.2 Tapped densities of diluent and disintegrant

Excipients	g/cm^3
lactose	0.96
sodium starch glycolate	0.3

4.3.4.3 Compatibility data of acetylsalicylic acid

As mentioned in Section 1.3.3.2, magnesium stearate is known to interact with acidic substances. Therefore acetylsalicylic acid may interact with magnesium stearate. However, no other known incompatibility was found between acetylsalicylic acid and other excipients used in this study (*Martindale*, 1993; *Handbook of Pharmaceutical Excipients*, 1994).

4.3.4.4 Other properties of acetylsalicylic acid

Using the methods described in Section 4.1.3, results obtained for particle size and shape, wettability and adhesiveness of drug on metal surfaces of acetylsalicylic acid are shown in Table 4.15. Additional information concerning moisture sensitivity, solubility and stability of drug in gelatin capsules are extracted from publications as mentioned in Section 4.3.1 and Section 4.1.4.4.

Table 4.15 : Other properties of acetylsalicylic acid

‡moisture sensitive	*Yes
‡stable in gelatin capsules	*Yes
Particle size	113 μm (large)
Needle shape	yes
‡Solubility	Class 2 (medium soluble), 1 part of drug in 300 parts of water
Wettability with water	yes
Coating on metal surface	yes

* Although acetylsalicylic acid is moisture sensitive , the extent of water sensitivity in gelatin capsules is not established. Since acetylsalicylic acid was marketed in hard gelatin capsules (Figure 5.7, Chapter 5), it was decided that, for the purpose of this study, the water content in the capsule shell will not affect the short-term stability of the capsule product.

‡ Information extracted from the *Martindale* (1993) & *British Pharmacopoeia* (1993).

4.3.5 Derivation of the recommended formulation for 500 mg acetylsalicylic acid from the decision tree

Similar to paracetamol and diltiazem, the derivation of the formulations for acetylsalicylic also depended on the same sequences of routines laid out in the flow charts as described in Chapter 3. From the 'Gelatin' routine (Section 3.2.1), it was noted that acetylsalicylic acid is moisture sensitive but is stable in gelatin capsules as described above (Table 4.15). From the 'Dose' routine' (Section 3.2.2), the dose of 500 mg was entered. Following the 'high dose' branch in the 'Dose' routine, the next routine is 'Shape' (Section 3.2.4.1). The 'Shape' routine captured the particle shape of acetylsalicylic acid (i.e. needle shape) (Table 4.15) and noted that the particle shape did not seem to cause any flow problems (Section 4.3.4.1). In the next routine, the 'Solubility' routine (Section 3.2.4.2), it was determined that a medium strength disintegrant is needed because acetylsalicylic acid is a medium soluble drug. The first

choice medium strength disintegrant is sodium starch glycolate 5% w/w (Section 3.3.2). From the 'Particle size' routine (Section 3.2.4.3), the first choice diluents, lactose monohydrate (medium grade), taken from the 'DILUENT N' list (Section 3.3.1) was chosen because acetylsalicylic acid is of large particle size (Table 4.15). The next routine followed is 'Flow' (Section3.2.4.4). In Section 4.3.4.1, it was shown that acetylsalicylic acid has a maximum bulk density of 0.788 g/cm^3 and minimum bulk density of 0.702 g/cm^3 and would flow very well. This information was passed onto the 'Adhesion' routine (Section 3.2.4.5). For a drug that has good flow, the use of glidant depends on whether the drug would adhere to metal surfaces. From Table 4.15, acetylsalicylic acid does adhere to metal surfaces and therefore both lubricant and glidant should be used. Since acetylsalicylic acid may interact with magnesium stearate (the first choice lubricant in most cases, Section 3.3.4 'Default lubricant'), the first choice lubricant for acetylsalicylic acid was glycerol monostearate 2% w/w (second choice in the 'Default lubricant' list, Section 3.3.4). The first choice glidant (Section 3.3.5 'Default glidant') was colloidal silicon dioxide 1% w/w. The use of wetting agent was determined in the 'Wet' routine (Section 3.2.4.6). For a high dose, medium soluble drug that wet with water (see Table 4.15), no wetting agent is needed.

In the 'Cap/Size' routine (Section 3.2.7), the minimum capsule size calculated for was 00. However, the agreed capsule size is size 0 i.e. smaller than the minimum capsule size determined. 'Minimize' routine (Section 3.2.8) was called and dry granulation method was chosen to densify the drug mixture in order to fit into size 0 capsules (similar to the case of formulation of paracetamol, Section 4.1.5.1). In cases where granulation process is performed, the incorporation of a glidant in the formulation would become redundant (because granulation alone would decrease the adhesiveness of the drug towards metal surfaces and thus a glidant is not needed). The previous decision of including colloidal silicon dioxide was therefore overturned by the system. Colloidal silicon dioxide was indeed incorporated in the formulations of paracetamol and diltiazem (Section 4.1) when the stage one trial was carried out. However, the rules involved in incorporation of glidant were reviewed since then, before the stage two trial.

In the 'Formula' routine (Section 3.2.9), the quantitative content of each ingredient in the recommended formulation was calculated. The capsule size agreed

(capsule size 0) is smaller than the minimum capsule size required. There is only minimal space for the incorporation of a diluent and in this particular case, no diluent is included. The summary of the recommended formulation is shown in Table 4.16. The output of the system is kept in a document called 'Output Package'. The Output Package for this drug can be found in Appendix II.

Table 4.16 : Recommended formulation for 500 mg acetylsalicylic acid

	High	Dose
	%w/w	weight (mg)
acetylsalicylic acid	93	500
sodium starch glycolate	5	27
*glycerol monostearate	2	11
minimum capsule size	00	
agreed capsule size	0	

Process : Dry granulation

* As explained in Section 3.4.2, the amount of lubricant suggested in the recommended formula does not include the amount of lubricant required in the slugging process. As described in Section 4.3.6, an amount of 0.5%w/w of lubricant was used in the slugging process and therefore the total amount of lubricant used was 2.5% w/w.

4.3.6 Procedures involved in formulation of acetylsalicylic acid capsules

In this study, the powder mixture consisting of drug, disintegrant (sodium starch glycolate 5% w/w) and 0.5%w/w of lubricant (glycerol monostearate) was mixed together in the Turbula mixer (Schatz by Willy A Bachofen AG Maschinenfabrik, Switzerland) for about 2 minutes. This mixture was then slugged initially using a single punch tableting machine (Manesty F3, UK) with a flat face die of 7 mm diameter. These slugs were then ground down to granules using mortar and pestle and were sieved using a 1200 microns sieve. The recommended amount of lubricant (2%w/w of

glycerol monostearate) was added to the granules and mixed for a further two minutes. The mixtures were then filled into size 0 hard gelatin capsules as described in Section 4.1.6.

4.3.7 Sample collection and tests performed on the acetylsalicylic acid 500 mg formulation

The filling machine was adjusted to a range of commonly used machine settings. Dosator heights from 1.7 to 1.9 units with compression settings of 1 or 2 were used. The drug mixture was poured into the powder feed hopper in the filling machine. The filling machine was allowed to run until the powder bed was settled. Samples were collected after at least 200 capsules were filled (see Section 4.2). For each formulation, forty to fifty sample capsules were collected. Tests for uniformity of weight, disintegration and dissolution as described in Section 4.1.7 were performed.

4.3.8 Result : Performance of the acetylsalicylic acid formulation

The results obtained below are required in the feedback report (Section 5.3.4). An example of the feedback report for acetylsalicylic acid can be found in Appendix III.

4.3.8.1 Uniformity of weight test (BP)

The results obtained in the uniformity of weight test is summarised in Table 4.17.

Table 4.17 : Result of uniformity of weight test for acetylsalicylic acid formulation

Target fill wt of the formula : 538 mg

machine setting	mean fill wt (mg)	s. d. (mg)	c.v. (%)	BP test in uniformity of weight
1.7 c.s. 2	456.7	6.8	1.50	pass
1.8 c.s. 2	520.4	10.1	1.95	pass
1.9 c.s.2	547.4	9.8	1.79	pass
1.9 c.s.1	519.7	10.7	2.05	pass

s.d. : standard deviation of fill weight; c.v. : coefficient of variation of the fill weight
The settings of the filling machine is represented by the compression setting (c.s.) of grade 1 or 2 preceded by a number which represents the dosator height (per unit).

4.3.8.2 Disintegration test (BP)

Table 4.18 summarised the results obtained in the disintegration test for the acetylsalicylic acid formulation.

Table 4.18 :Result of disintegration test for acetylsalicylic acid formulation

machine setting	disintegration time for the last capsule	BP standard
1.7 c.s. 2	6 min 25 secs	pass
1.8 c.s. 2	7 min 20 secs	pass
1.9 c.s.2	6min 10 secs	pass
1.9 c.s.1	6 min 40 secs	pass

4.3.8.3 Results from Dissolution test (BP)

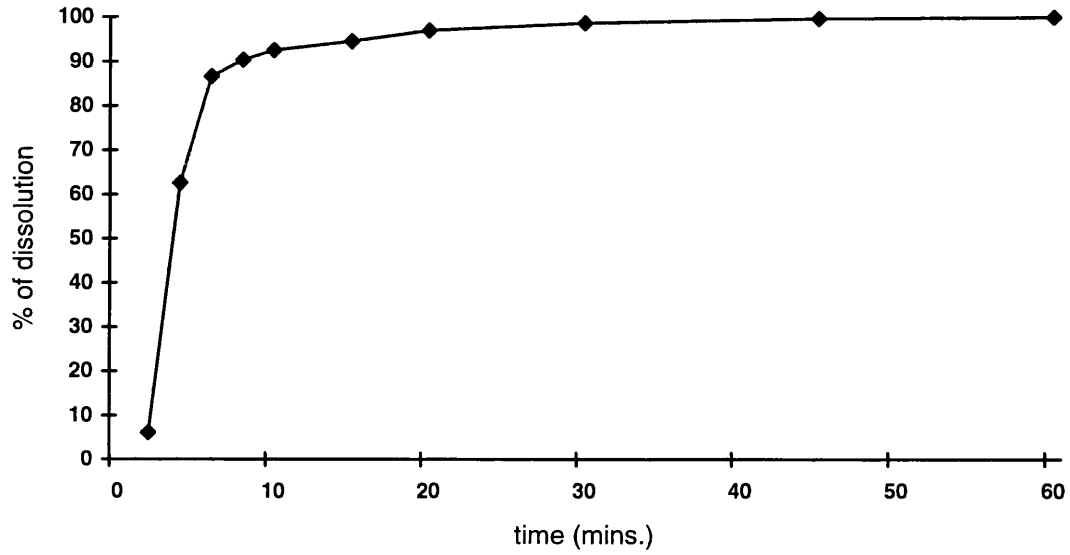
The concentration of acetylsalicylic acid was measured at wavelength of 271nm by a UV spectrometer. The details of the dissolution medium and conditions of the dissolution test were described in Section 4.1.7.3 and the results obtained from the dissolution test for the acetylsalicylic acid formulation are illustrated in Table 4.19.

Table 4.19 : Result of dissolution test for acetylsalicylic acid formulation

machine setting	percentage of drug dissolved at 45 min	BP standard
1.7 c.s. 2	98.16	pass
1.8 c.s. 2	99.71	pass
1.9 c.s.2	99.54	pass
1.9 c.s.1	99.94	pass

Figure 4.3 shows the dissolution profile for 500 mg acetylsalicylic acid capsules which were filled by filling machine settings of dosator height 1.8 units and compression setting of 2.

Figure 4.3 : Dissolution Curve for 500 mg acetylsalicylic acid capsule formulation (machine setting : dosator height 1.8 units, compression setting 2)



4.3.9 Conclusion

From the above results, the recommended formula passed the uniformity of weight test, disintegration test and the dissolution test specified in the British Pharmacopoeia (1993) and therefore the formulation suggested by the system for acetylsalicylic acid is considered to be successful.

4.4 Overall Conclusion

The validation process can be regarded as an important procedure in developing a computer software of a nature which involved incorporation of rules 'translated' from human experts or from a vast amount of literature. It is important to make sure that the rules are indeed robust rules and that they were accurately interpreted into computer

languages. One of the methods to validate the system is to test the performance of the recommended formulations provided by the system (the 'Expert System' formulations), as described in this chapter. However, the best validation procedure would be, if possible, to compare the 'Expert System' formulation and the marketed formulation of the same drug.

The formulations suggested by the system, before and after the decision tree was programmed, for paracetamol, diltiazem and acetylsalicylic acid were all successful based on standards laid out in BP. In addition, the validation process of the system also involves the participation of industrial companies using drugs which are still undergoing a development stage or are marketed drugs. The result of the validation process carried by eight Japanes companies can found in Section 6.3.1.

Chapter 5

Features and Structure of the Expert System

5. Features and Structure of the Expert System

5.1 Introduction

The main feature of this system is to enable the user to obtain a robust formulation for a new drug entity at the earliest possible stage in development. Apart from this feature, the system also provides other optional facilities to help the user to optimise the formulation, to provide the user with more information and to aid further development of the system (i.e. the learning procedure).

In this chapter, these facilities will be described followed by the outline of the overall composition of this system.

5.2 Facilities in the Expert System

5.2.1 Statistical Design

The 'statistical design' feature is useful if the suggested formula which did not pass some or all of the Pharmacopoeia tests, or if it did not satisfy the standards set in the user's company. Optimisation is a mathematical method used to identify the most advantageous combination of variables influencing the properties of a dosage form. The use of optimisation techniques requires a set of experiments which are logically related to each other. Usually such experiments can be organised in a statistical design.

Although factorial designs of the type n^2 or n^3 (where n is the number of variables) and composite designs are commonly used, all the experiments have to be performed before a judgment can be made. In cases where it is known that only the level of one excipient out of a set of excipients needs to be varied, a design which can be fractionated according to the formulation purpose will be desirable, for example the Centre of Gravity Design (CGD) (a type of Composite Design) (Podczeck, 1996). Other designs such as the response-surface experimental design have also been used (e.g. Gustavo Gonzál, 1993).

In this system, the provision of the 'Statistical Design' facility is based on the Centre of Gravity Design (CGD). The aim of this design is to offer suggestions of sets of experiments which are logically related to each other so that the optimum can be found. The setup of a full CGD depends on the recommended formula being the Centre of Gravity (CG) of the design. The recommended formula is used as the CG because the Expert System uses a default concentration for any excipient, which is equivalent to the commonly used concentration according to the knowledge-base (database I, II and III). The effects of excipients to be considered can be both linear and non-linear, and hence several concentrations will be assigned around the CG. Thus, the system calculates excipient concentrations two levels above and below the CG level. In total there will be five main levels per excipient, including the CG level. Furthermore, interactions between the excipients may occur, and therefore interaction terms on two levels will be additionally proposed by the system.

The common types of excipients used in capsule formulations are the diluent, the disintegrant, the lubricant, the glidant and the wetting agent and sometimes the binder if a granulation process is required. Among these excipients, the amount of diluent used is always adjusted to meet the requirements to fill the formula in a certain capsule shell size and hence does not play a role in the statistical design. Binder is used during the granulation process and therefore the amount of binder included should be kept constant all the time. Consequently, the concentration of binder used does not play a role in the statistical design either. As such, the concentrations of disintegrant, lubricant, glidant and wetting agent, if present in the formulation, should be varied.

An example based on the recommended formulation generated by the system for acetylsalicylic acid (Section 4.3) is used to demonstrate the 'statistical design' facility generated by the system (Table 5.1). This formulation, suggested by the system, contains acetylsalicylic acid, lactose being the diluent, as well as a disintegrant (5%w/w sodium starch glycolate) and a lubricant (2%w/w glycerol monostearate); and is set as the CG of the design. The system also calculates the excipient levels for both the disintegrant (D) and lubricant (L) of two levels above and two levels below the CG level. Each of the suggested changes in the formulations (in terms of %w/w) shown in Table 5.1 are logically related to each other and thus the use of an optimization

technique to determine the optimal formula is possible. In the Output Package (Appendix II), the details expressed in terms of weight per capsules of each excipients, are also available.

Table 5.1 : Example of a 'Centre of Gravity Design' provided by the system

To aid optimization of the suggested formulation which contains acetylsalicylic acid, diluent (lactose), a disintegrant D (5%w/w sodium starch glycolate) and a lubricant L (2%w/w glycerol monostearate) [see Ouput Package for Acetylsalicylic acid (Appendix II)].

Design code	level of D (%w/w)	level of L (%w/w)
suggested change for disintegrant level :		
D1	2	2
D2	3.5	2
[D_{CG}	5	2 (suggested formula)]
D3	6.5	2
D4	8	2
suggested change for lubricant level :		
L1	5	1.0
L2	5	1.5
[L_{CG}	5	2(suggested formula)]
L3	5	2.5
L4	5	3
suggested change for both disintegrant and lubricant level (interaction terms) :		
DL1	3.5	1.5
DL2	3.5	2.5
DL3	6.5	2.5
DL4	6.5	1.5

Generally, there are two ways to proceed with the CGD suggested by the system:

1) to perform all experiments of the design and to use an optimisation package afterwards to calculate the optimal formula - this is the more mathematical and sophisticated way.

2) alternatively, for example, if the formulation has shown flow problems resulting in a non-uniformity of fill weight whereas all the other Pharmacopoeia tests gave satisfactory results, the CGD should be fractionated. This special design allows such a fractionation to be performed easily. If only the level of L needs to be optimized, then only the experiments where L is varied are carried out. There are in fact four variations suggested (see L1, L2, L3 and L4 in Table 5.1). Provision of these four variations together with the Centre of Gravity point (CG) would fulfil the requirement of having a minimum number of 5 points in the mathematical optimization. If the level of diluent and lubricant used are believed to have an interaction effect on the flow properties of the formulation, experiments DL1, DL2, DL3 and DL4 may be performed as well. The optimum can then be found either by using a simple diagram to illustrate the relationship between L and the formulation properties, or by using an optimization software can be used.

5.2.2 Setting maximum fill weight

In some companies, the facility to set a maximum fill weight of capsules is preferable (as discussed in the Expert System Meetings). This facility is designed solely to accommodate the needs of such companies.

Conditions under which this option is offered

To fulfill the restriction of the fill weight set by the user, the amount of diluent included in the formulation is manipulated. Therefore this option is only available when the drug is of medium or low dose and that the chosen capsule size is greater than the smallest capsule size required i.e. the formulation would contain a reasonable amount of diluent.

Application

This option would only exert an effect on the formulation if the maximum fill weight required is smaller than the predicted fill weight of the formula. In these cases, the amount of diluent included is reduced to adjust the fill weight down to the limit required by the user. However, if the maximum fill weight required is greater than the predicted fill weight of the suggested formula, the suggested formula would be accepted.

This particular facility can sometimes be useful for formulation of drugs available in different strengths. In clinical trials, different doses of the tested drug are very often formulated into capsules of the same size. For example in double blinded studies, the use of capsules of the same size and the same fill weight would be preferred. By adjusting the maximum fill weight, the targeted fill weight can probably be achieved.

Another example for using this option is, say, related to the batch-size / capsule number relationship. For example, if 100,000 capsules are to be produced per batch, and the drug mixture can be stored in containers holding 10kg each, it would be better to have a 100 mg capsule instead of 110 mg capsule, because in the former case, exactly one container would be needed (as discussed in an Expert System Meeting).

Reminder

The System assumes that capsules are generally filled up to about 80 - 90% of the capsule shell volume. However, if the user has decided to set the maximum fill weight to a relatively low level, it is possible that the capsules are underfilled. In such cases, the system will inform the user at what level the capsules may be filled.

5.2.3 Possibility of Single formula for 'multiple-dose' drug

During the early development stage (e.g. Phase I) in formulation, the therapeutic dose of a drug is often not firmly established. Therefore, a range of doses is very often formulated at this stage. It would be more cost-effective to use the same formula for

more than one dose of the drug in adapted capsule sizes i.e. to use a common blend where possible. For example, a drug of a dose of 100mg and 50mg can be formulated by one formula where the 100mg dose would fit in say size 3 capsules, while the 50mg dose which contains half the amount of the 100mg dose formula would probably fit into a size 4 capsule. Please refer to the example demonstrated in Appendix II 'Output Package for sample drug acetylsalicylic acid'.

At this stage, the system would provide an idea of the smallest capsule size required (if any) should the same formula be used for different doses of the same drug. The corresponding expected fill weights and fill volumes are also calculated. The calculations are based on the proportion of change in dose. However, when the dose changes, the formulation may also require adjustment quantitatively as well as qualitatively. Such change will not be taken into account in this option. This system will only provide suggestions for the formulators but it is the formulator's responsibility to make the final decisions.

5.2.4 Generation of different formulae by altering input parameters

In the early development stage, the formulator may have only a limited amount of drug and information about the drug. The formulator may not have a definite idea of the dose or even a concise measurement of, for example, the particle size of drug at the preformulation stage. One of the advantages of the system is that more than one formulation can be deduced in a very short time (within minutes) with low cost by adjusting the input parameters of the drug. It is therefore possible for the formulator to simulate a variety of formulations for a new drug at the pre-formulation stage using the system. However, one must bear in mind that the quality of the recommended formulations depends heavily on the accuracy of the input parameters.

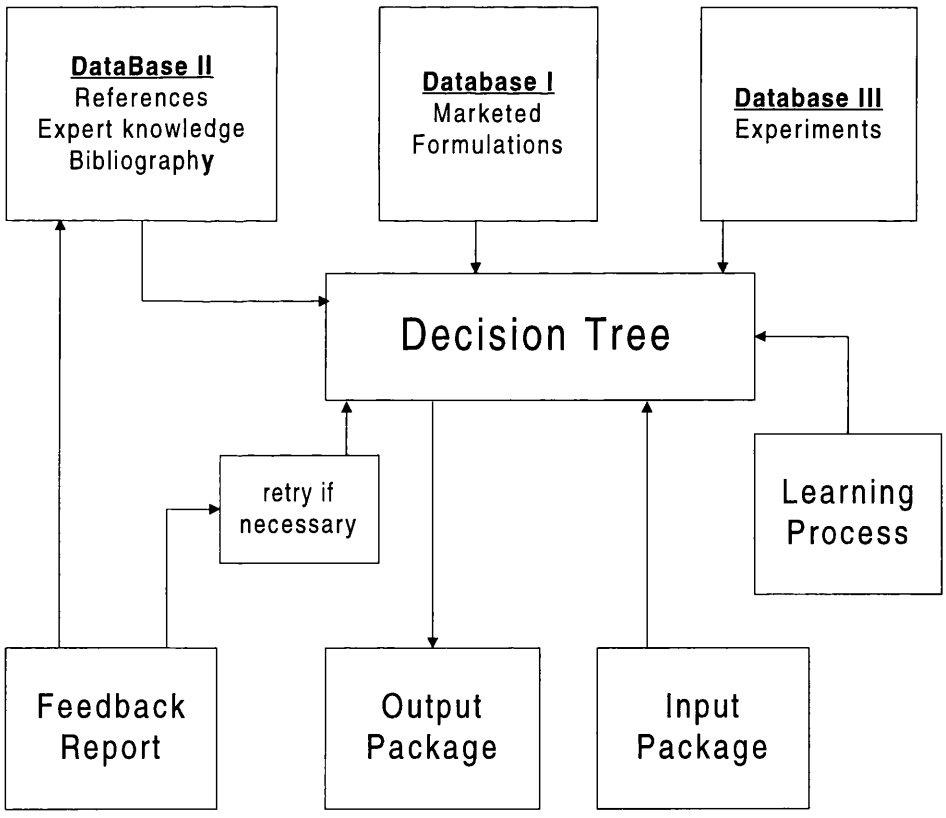
This option provides the user the possibility of altering one or more input parameters at a time. The input parameters in this system are divided into two levels. The change of capsule size and / or choice of excipients can be described as the more superficial change because these changes will not affect the 'root' level of the decision making process whereas changes of the more fundamental input parameters such as the

dose or other drug properties will. In the latter case, the system would again determine the necessity of a granulation process, the choice of each type of excipient and the capsule size to be used.

5.3 Structure of the Complete Expert System

Similar to human experts, the Expert System must first extract some information about the subject and based on the knowledge, provides useful recommendations to the users. The Input Package, Output Package and Feedback report would therefore serve as an interface between the user and the program.

Figure 5.1 : The overall layout of the System



The user would be required to input the data into the program through the Input Package. The program would then process these data and the result would be transferred to the output device. The Output Package summarises the output in a documentation form. The recommended formulation is then tested and the comments of the formulator about the results of the tests are captured in the feedback report. The knowledge in formulating the particular drug is therefore collected. The system learns from past experience. The program will be updated and sometimes the format of the information required in the Input Package will also change. Figure 5.1 represents the cycle between the input, the program, the output, the feedback and the learning stages.

5.3.1 Input Package

An Input Package (Appendix I) is used to extract and collect information from the user. The recommendations suggested by the system would heavily depend on the quality and accuracy of these information.

The input package inquires the information about the following :

- name or coded name of drug
- specification for drugs, excipients and product
- dosage of drug
- drug properties like particle size
  particle shape
  solubility of drug
  wettability of drug
  adhesiveness of drug towards metal surfaces
  tapped and bulk densities of drug
- incompatibility of drug with gelatin capsules and excipients
- company policy about use of certain excipients and procedures
- capsule size
- information about granulation procedure if required
- information about method to densify the drug mixture should such procedure be required

The relevant data is extracted during the execution of different stages or routines in the program as described in Chapter 3.

5.3.2 Program

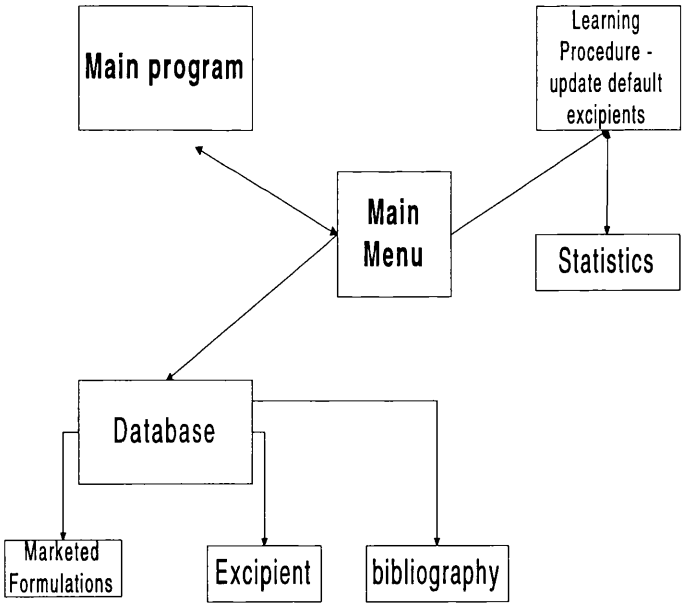
The program can be described as the 'nerve centre' of the computer system. It performs all the arithmetic and logical processes to be applied to data. The complete program in this system contains several smaller programs and the databases.

The complete program contains three major parts :

1. the main program - to deduce a formulation for a particular drug
2. databases - to provide information
3. learning procedures - to update default excipients recommended in the system

These components are connected by the main menu. Figure 5.2 shows the assembly of these individual programs / structures.

Figure 5.2 : Assembly of individual programs / structures into the Expert System



5.3.2.1 Main Menu

The main menu links up the individual programs together. From the main menu, the user can access the main program, the databases and part of the learning procedures. Figure 5.3 shows the display of the main menu in the system.

5.3.2.2 Main Program - to develop a formulation

The main program (option 'a') can be described as the 'soul' of the expert system. The emphasis of this project is to develop this main program. The details of the development of this main program are described in Chapter 2, 3 and 4. The user interacts with the system via the computer screen. For example, Figure 5.4 shows the computer screens which displayed some drug properties of a model drug (acetylsalicylic acid) based on the answer the user input before. Figure 5.5 shows the screen which displays a remark about the interaction found between the acetylsalicylic acid and magnesium stearate. Figure 5.6 shows the computer screen of which the subsequent formulation for the same drug was suggested. These outputs on the computer display were also documented in the Output Package (Appendix II).

5.3.2.3 Search and Update databases

The three main databases which are directly accessible to the users are :

1) Database 1 which contains qualitative and some quantitative information about marketed formulations in Belgium, France, Germany, Italy and United States.
2) Database 3 which contains the bibliography of capsule formulations.
3) Database 2 which contains information about common excipients employed in capsule formulation. To this date, information for 72 excipients is available

As shown in Figure 5.3, Options 'b' - 'h' (except option 'd') allow the users to search and update the above databases. Figures 5.7, 5.8 and 5.9 show examples of the results obtained by searching through Databases 1, 2 and 3 respectively. This option is particular useful in development of formulations for generic drugs in hard gelatin capsules. In this database, the branded name of the drugs and the type of excipients used (with quantity, if available) are provided.

Figure 5.3 Main Menu of the system

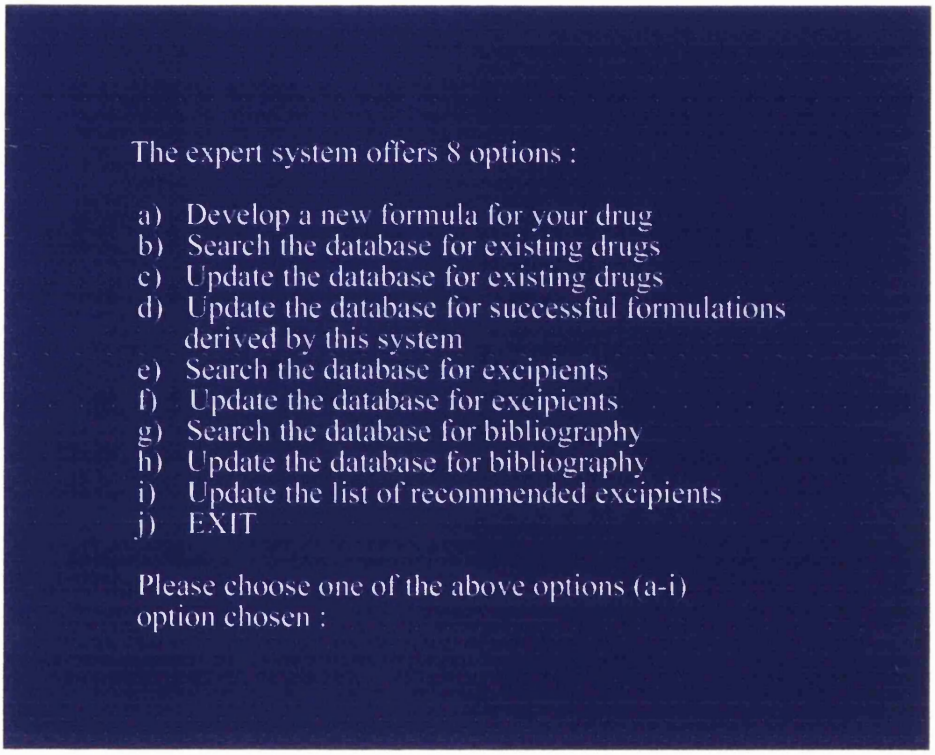


Figure 5.4
Basic properties of acetylsalicylic acid,
as displayed by the Expert System

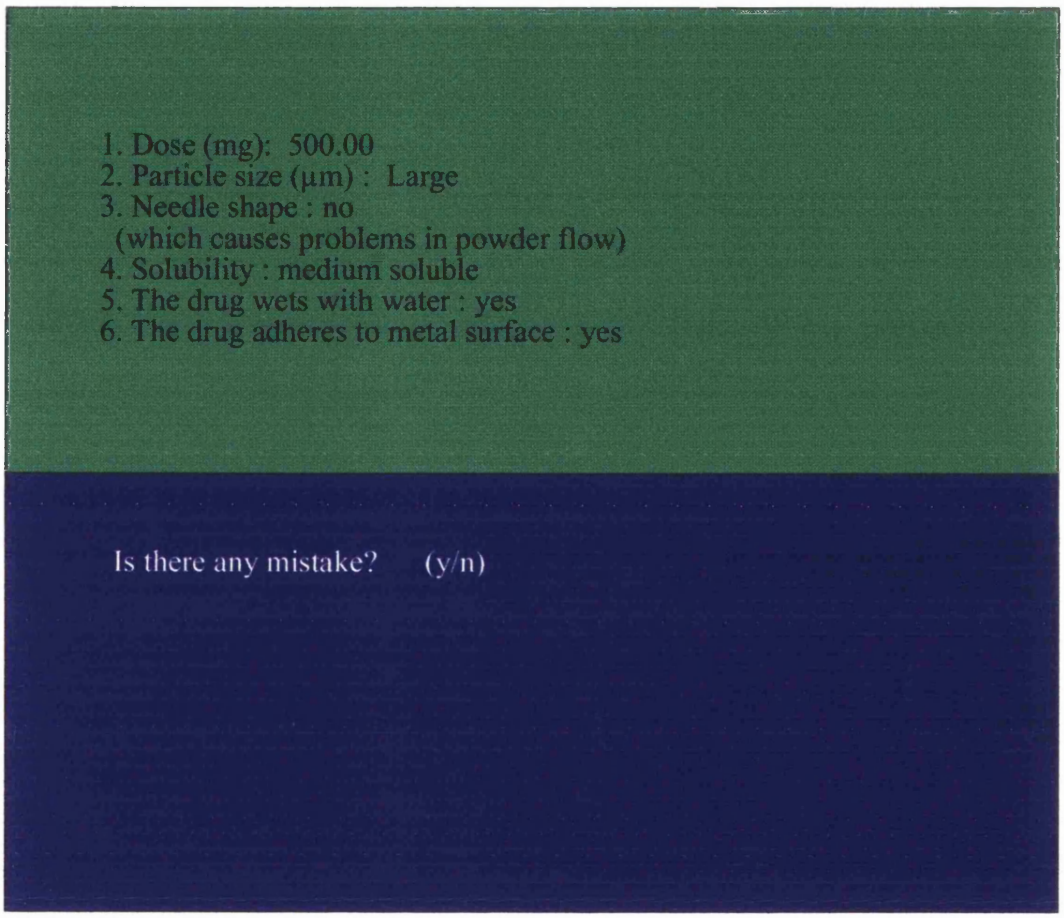


Figure 5.5
Recommendation of excipients for acetylsalicylic acid
Interaction between acetylsalicylic acid and magnesium stearate is detected

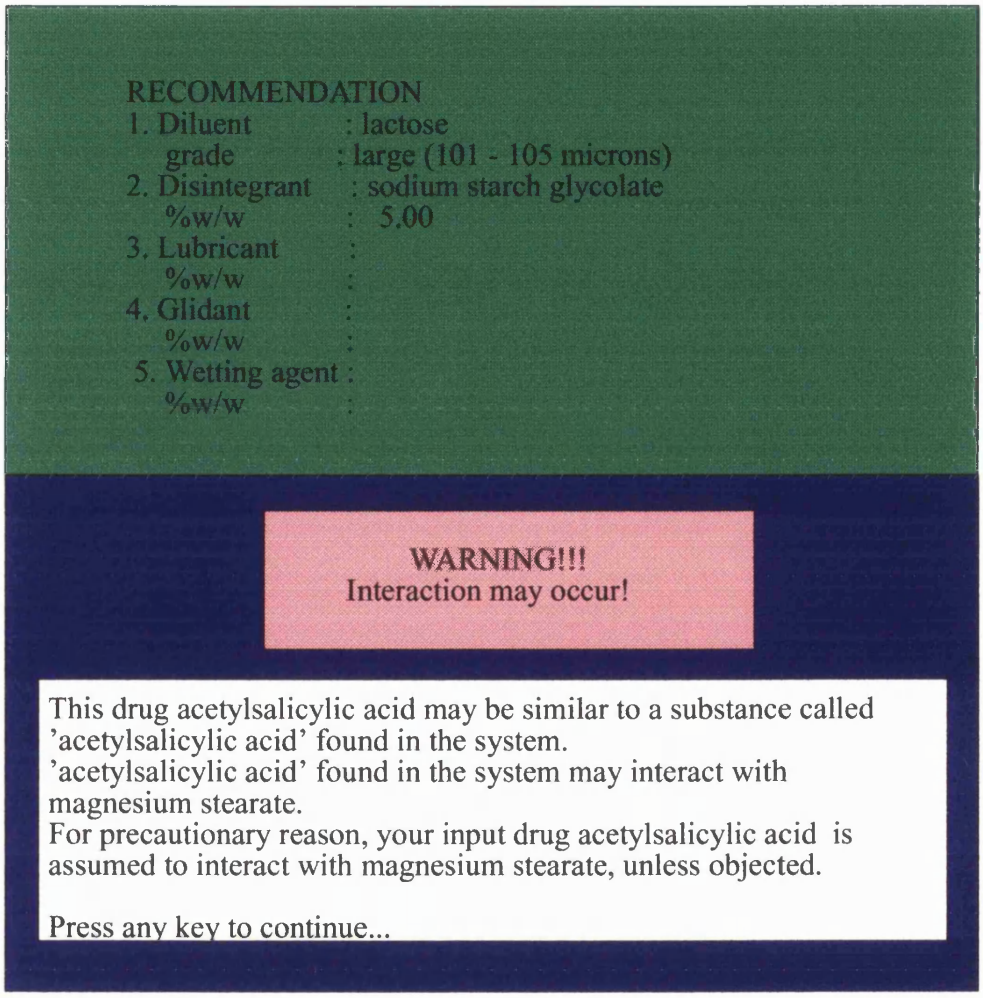


Figure 5.6
Proposed formula for acetylsalicylic acid as displayed by the system
(Also see Appendix II 'Output Package' for acetylsalicylic acid)

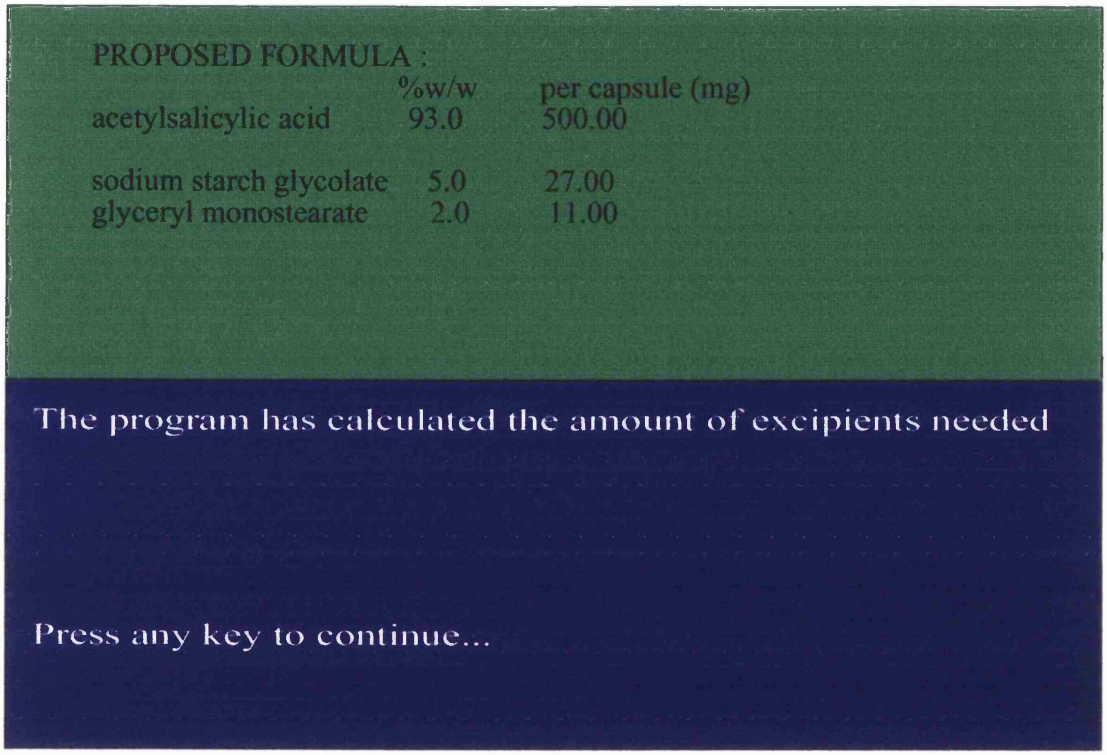


Figure 5.7 : An example of the search in the database of marketed drugs : for aspirin.

Option 'b' in the main menu (Figure 5.3)

Aspirin (acetylsalicylic acid) is marketed in hard gelatin capsules as a single drug or combined with other active ingredients.

```
drug        : aspirin

brand_name : monobeltin magensaftresistente
dose        : 350mg
solubility class :  0
excipients : sodium lauryl sulphate, polysorbate 80, talc, (dimethicon emulsion
2-acetyl-citric acid triethylester are probably buffering agent for aspirin)

reference no. : 78/004
storage :
coating material : poly(ethylacrylat,methacryl acid)


drug        : butalbital + aspirin + caffeine

brand_name : fiorinal
dose        : 50+325+40 mg
solubility class :  3
excipients : microcrystalline cellulose, sodium lauryl sulphate, starch, talc


reference no. : 2102 PDR
storage : store below 25C, tight container
coating material :
```

```
NOTE :

Solubility Class :
soluble              <1 - 30 parts of water per part of drug
medium soluble       >30 - 1000
insoluble            >1000


Index no : 12/345       German Rotelist 1993
           VIDAL123     French Vidal 1993
           1234 PDR     Physician's Desktop Reference (USA) 1993
           ITALY123     L'Informatore Farmaceutico 1993
           BELG1234     Belgium Compendium 1993
```

Figure 5.8 : An example of the search in the database of bibliography : for author named 'NEWTON'. Option 'g' in the main menu (Figure 5.3)

author : JOLLIFFE, I.G., NEWTON, J.M. AND WALTERS, J.K.(1979)

reference : J.Pharm. Pharmac.,31, Suppl., 70P

tittle : A theoretical approach to optimising capsule filling by a dosator nozzle

keywords : filling machine, dosing tube mechanism; powder properties,relationship to machine

author : WOODHEAD, P.I., NEWTON, J.M., HARDY, J.G. AND JACK- SON, S.A.(197

reference : J. Pharm. Pharmac.,31, Suppl., 72P

tittle : A gamma-ray attenuation technique for assessing the distribution porosity in powder beds

keywords : filling machine, dosing tube mechanism; powder properties.bulk density measurement, non-disruptive technique with gamma source

author : JOLLIFFE, I.G., NEWTON, J.M. AND WALTERS, J.K.(1980)

reference : Powder Technol.,27, 189-95

tittle : Theoretical considerations of the filling of pharmaceutical hard gelatin capsules

keywords : filling machine, dosing tube mechanism;powder plug formation,powd properties, arch formation, relationship angle of powder/wall friction and machine compressive force

Figure 5.9 : An example of the search in the database of excipients : for magnesium stearate. Option 'e' in the main menu (Figure 5.3)

```
name            : magnesium stearate
other_name      : estearato de magnesio, mag stear, magnesii stearas

use             : lubricant, glidant

solubility      : >10,000
compatible      : acidic/alkaline substance, iron salts. avoid mixing with stro
oxidizing materials. use with caution with drugs which are incompatible with
alkali.
stability       : stable, non self polymerizable. store in cool dry place in a
well-closed container
```

Option 'd' (Figure 5.3) allows the update of the database of successful formulations. The aim of this database is to store information about formulations which have been successfully developed by the system and are likely to go through further development stages. Further discussions with the Expert System Development Team is expected regarding the confidentiality in this area. However, at this early stage, no further conclusion is drawn on the matter.

5.3.2.4 Learning procedure - to update default excipients

This is option 'i' available in the main menu (Figure 5.3) which contains a sub-program that is designed to update the excipients recommended by the system.

The inclusion of some of the existing default excipients and their order of preference may require update in the future. In order to increase the flexibility of the system, a learning procedure is designed to help the user to decide whether to add or to

delete a particular excipient, or to alter the order of preference of the existing default excipients. As mentioned in Section 3.3.1 before, some information about the non-default excipients (excipients which the system encounters but which are not recommended by the system at this stage) are stored.

5.3.2.4 (a) 'Non-default Excipient Files'

Each time a non-default excipient is encountered by the system, the following information is collected :

name of excipient
use of excipient
type of excipient file
amount of excipient used
number of occurrences

Name of excipients

At this stage, the name of excipients recorded depends on the name the user entered i.e. it could be the British approved name or United States approved name, or even a short form. What the system learns depends on the quality of the input information.

Functionality of excipients

The functionality of an excipient recorded depends on the function it had in the particular formulation that the system recommended during data entrance.

'Excipient Files Types'

There are nine types of excipient files in the system :

i)	'DILUTE F' file	- diluents for drugs with fine particle size
ii)	'DILUTE L' file	- diluents for low dose formulations
iii)	'DILUTE N' file	- diluents for general cases
iv)	'medium strength disintegrant' file	- medium strength disintegrants

v)	'strong disintegrant' file	- strong disintegrants
vi)	'LUB' file	- lubricants for dose of less than 6 mg
vii)	'LUBNOMCC' file	- lubricants for dose of 6mg or above
viii)	glidant	
xi)	wetting agent	

The type of excipients file recorded depends on the file that was called during data entrance.

Amount of excipients used (%w/w)

The amount being incorporated in the formulation would be used as a guideline for future reference. The quantity used may also differ for a multi-functional excipient.

Number of occurrences

The system also keeps a record of the number of occurrences of each non-default excipient entered in the file. This would provide some guidelines about the trend of excipients used in capsule formulation and thus may provide evidence for the inclusion of these excipients in the default lists.

5.3.2.4 (b) Options

There are four options available in this sub-program :

1) to look at the statistical count of the non-default excipients data collected
2) to add new excipients to the existing lists of default excipients
3) to delete excipients from the existing lists of default excipients
4) to alter the order of preference of the existing lists of default excipients

Each of these options can be applied to the nine types of excipient files listed above. Therefore the first step is to determine which 'Excipient File Type' one would like to update e.g. 'DILUTE F' file.

Option 1 - to look at the statistical count of data collected so far

The name and number of occurrences of non-default excipients recorded in the 'Non-default Excipient File' for the particular 'Excipient Files Type' is displayed.

Option 2 - to add new excipients onto the existing excipient files

From Option 1, if there is a non-default excipient which is encountered by the system frequently, one may decide to add this new excipient onto the existing list of the default excipient file. For example, by performing a statistical count of the excipients included in the 'Non-default Excipients File', carmellose calcium was found to be a preferable disintegrant suggested by some users (more frequently used in Japan than in Europe). The count of the 'Non-default Excipient File', the number of occurrences of the particular excipient in the database of marketed formulations are combined to give the total count However, the few encounters of carmellose calcium may not justify its addition to the list of default disintegrants at this time. To prevent adding new excipients onto the list of default excipients without adequate evidence, the program is devised so that only non-default excipients which have been encountered for more than 30 times in the past, can be considered to be added onto the default excipient list. The number of '30' is only an arbitrary number set at this stage and may be adjusted to a more practical value after further validation of the system. Furthermore, the Expert System Development Team must also be consulted. The ranking position of the excipient in the default list is also decided by the members of the Expert System Development Team.

Once an excipient is selected for addition onto the list of default excipients, the recommended amount (%w/w) of this new excipient must also be defined. Useful guidelines are available by looking at the 'Non-default Excipient File' which also stores the information about quantity included by the users in the past.

Option 3 - to delete excipients from existing excipient files

Some of the default excipients chosen at this stage may be out-dated in the future. This option provides an easier way to remove out-dated default excipients based on the experience of the Expert System Development Team.

Option 4 - to alter the order of preference of excipients in the existing files

Similar to Option 3, this option allows changes of order of preference of the default excipients in the existing files. At the initial stage, for example, excipient 'A' may have a higher rank of order compared to excipient 'B' in the 'strong disintegrant' list. However, with more experience and more validation tests performed, evidence may be available to prove otherwise. This option would provide an easier approach to perform the alteration by the Expert System Development Team.

5.3.3 Output Package

The output may be presented in different forms, for example visual display, in the floppy disk and printout. The Output Package is stored on a floppy disk and can be printed out as a document.

The Output Package contains the following standard features :

- summary of drug properties
- information about capsule size
- recommended formula presented in
  weight per capsule, %w/w and weight per kilogram of drug mixture
- specification of drugs, excipients and product
- documentation of the decision process
- filling conditions
- tests to be used to study the performance of the recommended formula

The results or suggestions produced by other facilities e.g. statistical design will also be included when requested. An example of an 'output package' for a sample drug (acetylsalicylic acid) can be found in Appendix II.

5.3.4 Feedback Report

The experts who participated in the Expert System development team are encouraged to perform the Uniformity of weight test, Disintegration test and Dissolution test (if available for the particular drugs in the formulations) on the formulations suggested by the system.

The feedback report is designed to capture the knowledge acquired from the validation tests of the formula. The results from the above tests e.g. the coefficient of variation of the fill weight and the dissolution profile of the formulations are recorded. Information about the capsule filling machine used, machinability and batch size tested are also needed.

As mentioned in Section 3.2.6, the granulation factor was not taken into the account in the prediction of the fill weight and fill volume of the formulation. In order to find out more information about the effect of granulation on the prediction of the calculated fill weight and fill volume of the recommended formulation, details about the bulk densities and size distribution of granules, as well as the granulation procedures are also needed to improve the system. Moreover, the comments from the experts also form an important part in the feedback and are invaluable to fine-tune the system. The feedback report of acetylsalicylic acid can be found in Appendix III.

5.3.5 Learning process

The fact that this system is a 'learning' system is one of its unique feature. The system can learn in three different ways :

a) automatic learning / knowledge accumulation in two areas :

First the compatibility of drugs and excipients and secondly the information about non-default excipients, are accumulated automatically when the main program is

used (Section 3.3.1).The information will be triggered where necessary in the future encounter.

b) semi-automatic learning procedure

Building on the knowledge accumulated for the non-default excipients and the knowledge of the experts, a sub-program is available to aid the update of the lists of default excipients the system uses. The details of how this procedure functions were described in Section 5.3.2.4 The sub-program is available to make the process easier and faster. The learning procedure also relies on the interpretation and decision making by human experts and therefore is a semi-automatic learning procedure.

c) manual learning procedure

In the light of experience and development of new technologies, the executive instructions of the program and probably the information required in the input or Input Package might change. From the result of the feedback reports and from the comments the experts expressed after their encounter with the expert system, the system will be refined and constantly updated. This is, however, a complicated procedure and cannot be handled directly by the computer program. In addition, the computer program will not be able to distinguish between genuine knowledge and "gabbage" data (e.g. for testing) that was entered beforehand. 'Human effort' has got to be involved for the update of the decision tree.

5.3.6 Update of decision tree

The update of the decision tree involves the combinations of knowledge collected from the feedback report, the Input Package and discussions with experts from the Expert System Development Team. Apart from published knowledge, unpublished knowledge is also revealed during the course of discussion. Different practices from different countries are also exchanged. This knowledge is invaluable for the development of the system and is accumulated in Database II which contains also the expert knowledge, published and unpublished. The decision tree will then be updated accordingly. The next version of the system would again go through the same cycle : validation, feedback, discussion, accumulation of knowledge and update plus refinement. This is an ongoing process - a learning process.

5.4 Limitations of the system

Under no circumstances is the system perfect yet. There are indeed some limitations within the system. First of all, this is a single drug system i.e. it can only work for ONE drug at a time. If a binary drug system is involved, the users would have to find out the combined properties of the mixture. Secondly, it is designed for filling of powders or granules for hard gelatin capsules aimed for internal use. It is not to be used for filling liquids, semi-solids or pellets. It is not suitable for capsules used for inhalation purpose. Thirdly the knowledge base does not include too much details about *in-vivo* information on the subject. The users will have to take into consideration the absorption of drug from the gastro-intestinal tract. Fourthly, the capsule filling machine used in the experiments carried out (in database III) is a dosator nozzle filling machine. Therefore, we must bear in mind that some of the rules used in this system are based on this particular type of machine. Fifthly, the drug mixture is assumed to be filled at the tapped density of the mixture, except in cases where a relatively small capsule size is used and densification of the drug mixture is required during the filling process (see 'MINIMIZE' routine in Section 3.2.13). Sixthly, the effect of granulation on drug mixture in terms of reduction in volume and also details of granulation procedures are not provided at this stage.

5.5 Conclusion

This chapter has outlined the features available in the main program followed by the structure of the complete system which includes the Input and Output Packages, the Feedback Report and the databases. The learning features of the system were also described.

Chapter 6

Summary

Present Position

Future Plan

6. Summary . Present Position . Future Plan

6.1 Introduction

To date, a number of in-house Expert Systems for tabletting and other pharmaceutical-related areas have already been incorporated in different pharmaceutical industrial companies. However, not many of these Expert Systems are able to be extended to their full potential as most of them are used 'in-house' and only in-house knowledge and experience can be accumulated. The update of such systems would sometimes require referral back to the computer company which initially provide a software and this can be time consuming and expensive. In view of the situation, this Expert System is developed together with united effort by groups of experts in academia and pharmaceutical industry globally from United States, Europe and Japan and is used specifically for formulation of hard gelatin capsules. This is not an 'in-house' system and can be used by different companies of different backgroud (e.g. generic companies or multi-national companies) in different part of the world.

In this chapter, a summary of this system is outlined followed by the review of the validation tests performed by the Japanese Expert Group. The reflection of the present position of the system and the plans for future development are also included.

6.2 Summary

This Expert System was developed to aid the formulation of powder filled hard gelatin capsules. Knowledge was accumulated from experts in the subject and is kept into three groups of databases. The first set of databases contains information about marketed formulations, excipients and drugs. The second set of databases was constructed from published references associated with the formulation of capsules and knowledge obtained from experts in the pharmaceutical industry and academia. Results from a statistically designed experiment which identified factors influencing the filling and *in vitro* release performance of model drugs were used to enhance the current knowledge and were stored into the third database. Some of the databases are accessible to the formulators and provide them with information about qualitative and quantitative

(where available) information about excipients used in the marketed formulations and information about excipients in general. The database containing the bibliography in capsule formulation is also available.

The information from these sources was combined to provide a logical set of rules. These rules that represented the knowledge in the Expert System were expressed in the form of decision trees and constituted the major part of the system. Each rule is a conditional statement that specifies an action to be executed, under a certain set of conditions. Sets of default excipients were also defined. Given a set of information about a drug, these rules provide a systematic approach to deduce a recommended formulation for the drug. An initial trial was performed to test the validity of these rules. Paracetamol (sparingly soluble drug) and Diltiazem (soluble drug) were formulated at high dose (500mg), medium dose (50mg), low dose (2 mg) and very low dose (0.05mg) using the recommended formulations derived from these rules. BP tests for uniformity of weight, dissolution and disintegration were carried out to test the performance of these formulations and satisfactory results were obtained. The rules were translated into C programming language. Further tests were performed using acetylsalicylic acid (500 mg) to confirm the validity of the program. Acetylsalicylic acid was formulated based on the Output Package provided by the program. Reasons for the choice of excipients and processes and information about capsule size are also included in the document. The performance of this formula was tested similarly as described in the initial trial. Again, satisfactory results were obtained.

In addition, other facilities are also available e.g. learning routines and statistical design. The statistical design is an option that provides aid to the formulators to design experiments in order to further optimize the proportion of excipients used. Two learning routines were programmed. An automatic learning routine was designed to accumulate knowledge of compatibility between drugs and excipients and the trend of non-default excipient used. A 'learning package' or a semi-automatic learning routine was also incorporated to help to modify choice and order of preference of default excipients in the system. In addition, the decision tree of the system was kept updated manually based on the validation tests and the feedback from the experts.

6.3 Present Position

The system was built initially with experts from Europe and six meetings were held at a three months intervals for a period of eighteen months to discuss the development of the system. Thereafter, two focus group meetings were held in United States and two in Japan to further update the system.

At this stage, the present version of the system is undergoing validation tests by the industrial experts worldwide. In Japan, nine formulations were provided by the system for eight drugs from eight different companies. Two formulations were produced for the same drug of different doses. Some of these are marketed drugs where comparisons between the marketed formulation and the Expert System formulation can be made.

Out of the eight drugs, wet granulation was suggested to be used for six drugs, where dry granulation was suggested to be used for the remaining two drugs. Out of these formulations, three formulations obtained a different fill weight compared to the fill weight predicted by the system but all of them passed the Uniformity of Weight tests under the specification of Japanese Pharmacopoeia. The difference of the fill weight achieved and the predicted fill weight, as explained in Section 3.2.6, is one of the limitations of the system at this stage. Two of the formulations were shown to have a problem in the wet granulation process. As mentioned in Section 3.4, the system will only give a simple guideline about the subject and in this respect an improvement will be implemented in the next development stage. The overall results were : four 'perfect' formulations; one formulation was excluded because there is no equipment available in the company involved to carry out dry granulation and four formulations require further modifications (three formulations passed all the specification of Japanese Pharmacopoeia but the fill weight achieved is different from the predicted fill weight and two formulations failed to pass all the tests probably due to problems in the granulation process).

These results were kindly provided and presented by Dr Kashihara, the team leader of the Japan expert team.

6.4 Future Plan

The future plan is to improve and refine the present system and to build up new branches to the system. This system which is built up using C and dBase IV computer languages is flexible enough to incorporate a wide range of additional facilities.

To refine the present system

Unpublished information and common practices are collected globally and areas that require more attentions are also noted via the feedback from the experts using the system. Some of these refinements are listed below :

1) update the status of the decision trees
2) refine the granulation process
3) refine the prediction of fill weight and fill volume of the suggested formulation
4) include more reminders and 'hints' for the formulator based on the unpublished information and common practices
5) enable utilisation of global pharmacopoeial specifications
6) provide more detail about grades of excipients
7) possibilities to 're-enter' the system and obtain an improved formula based on the test results from the first recommended formulation

To build up new branches

New branches can be connected to the present ones to make the system more sophisticated. Some of the proposed branches are listed below :

1) to incorporate capsule shell compositions like dyes and preservatives
2) to expand other functional types of excipients like buffers and antioxidants
3) to handle secondary or tertiary interactions between drugs and excipients or excipients and excipients in 'multi-component' system
4) looking at aspects related to stability and bioavailability of the formulations
5) incorporate manufacturability or mechanical aspects such as 'dosing disc' type as well as 'dosator' type machine factors

6.5 Conclusion

In this project, an Expert System for the formulation of hard gelation capsules has been successfully developed with considerable success and acceptability as demonstrated when the System was presented at several international conferences such as the AAPS Conference (1995) in United States, the Pharmaceutical Technology Conference (1996) in United Kingdom and the CRS Conference (1996) in Japan.

In conclusion, what has been achieved in this project is an initial but considerable contribution to introduce a unique and novel system in the complex field of capsule formulation with the kind support from international pharmaceutical and academic collegues. In addition, prospects regarding the potentials for the system to expand and to evolve are described to be excellent and the possibilities for it to be offered as a training tool for new formulators are also highlighted by the participants who have tested the system.

Ultimately, it is hoped that the Expert System will continue to collect and to built on existing experience to develop a novel and functional system benefitting both the pharmaceutical and academic communities.

References

References

Abdou, H.M., Dissolution, Bioavailability & Bioequivalence. Mack, Easton 1989a, pp.267-269.

Abdou, H.M., Dissolution, Bioavailability & Bioequivalence. Mack, Easton, 1989b, pp.37- 40.

Abdou, H.M., Dissolution, Bioavailability & Bioequivalence. Mack, Easton, 1989c, pp.73-80.

Abdou, H.M., Dissolution, Bioavailability & Bioequivalence. Mack, Easton, 1989d, pp.367-369.

Achanta, A.S., Kowalski, J.G. and Rhodes, C.T., Artificial neural networks : implications for pharmaceutical sciences . Drug Dev. Ind. Pharm. 21 (1995) 119 - 155.

Adam, N.K. and Jessop, G. J., CCL - Angle of contact and polarity of solid surfaces. Chem. Soc. 127 (1925) 1863 - 1868.

Admirat, P., Grenier, J.C. and Rech, J. Atmos. 9 (1975) 97 through Umprayn and Mendes (1987).

Aguiar, A.J., Wheeler, L.M., Fusari, L.M. and Zelmer, J.E., Evaluation of physical and pharmaceutical factors involved in drug release and availability from chloramphenicol capsules . J. Pharm.Sci. 57 (1968) 1844 - 1850.

Aguiar, A.J., Zelmar, L.E. and Kinkel, A.W., Deaggregation behaviour of a relatively insoluble substituted benzoic acid and its sodium salt. J. Pharm. Sci. 56 (1967) 1243 - 1252.

Allens, J.G. and Davies, C.A., The effect of lactose on the oral absorption of a highly lipid soluble drug. J. Pharm. Pharmacol. 27 (1975) 50 -51.

Allen, L.V., Stearic acid. In : Handbook of Pharmaceutical Excipients. (Wade, A. and Weller, P.J., Eds.) 2nd ed., The Pharmaceutical Press, London, 1994, pp.494 - 497.

Allen, L.V. and Luner, P.E., Magnesium stearate. In : Handbook of Pharmaceutical Excipients. (Wade, A. and Weller, P.J., Eds.) 2nd ed., The Pharmaceutical Press, London, 1994, pp.280 - 282.

Allen, L.V., Levinson, R.S., Robinson, C. and Lau, A., Effect of surfactant on tetracycline absorption across everted rat intestine . J. Pharm. Sci. 70 (1981) 269 - 271 through Leyland (1994).

Allen, T., Particle Size Measurement. Powder Technology Series. 3rd ed., Chapman and Hall, London, 1981, pp.103- 119.

Anonymous., Can the appearance of medication improve compliance? Pharm. J. 242 (1989) 98

Ansel, H.C. Popovich, N.G. and Allen, L.V.J., Pharmaceutical Dosage Forms and Drug Delivery Systems. 6th Ed., Williams & Wilkins, Baltimore, 1995a, pp.155-176.

Ansel, H.C., Popovich, N.G. and Allen, L.V.J., Pharmaceutical Dosage Forms and Drug Delivery Systems. 6th ed., Williams & Wilkins, Baltimore, 1995b, pp.110 - 116.

Armstrong, N.A., Glyceryl palmitostearate. In : Handbook of Pharmaceutical Excipients. (Wade, A. and Weller, P.J., Eds.) 2nd ed., The Pharmaceutical Press, London, 1994, pp.211- 212.

Ashton, M.D., Cheng, D.C.H., Farley, R. and Valentin, F.H.H., Some investigations into the strength and flow properties of powders. Rheol. Acta 4(3) (1965) 206 - 217 through Pilpel (1971).

Augsburger, L., Instrumented capsule-filling machines : development and application . Pharm. Tech. 6 (9) (1982) 111 - 119.

Augsburger, L.L. and Shangraw, R.F., Effect of glidants in tableting . J. Pharm. Sci. 55 (1966) 418 - 423.

Banaker, U.V., Role of ingredients and excipients in developing pharmaceuticals . Manuf. Chem. 59 (4) (1994a) 32 - 35.

Banakar, U.V., Sodium starch glycolate. In : Handbook of Pharmaceutical Excipients. (Wade, A. and Weller, P.J., Eds.) 2nd ed., The Pharmaceutical Press, London, 1994b, pp.462- 466.

Bandelin, F.J., Compressed tablets by wet granulation. In : Pharmaceutical Dosage Forms : Tablets. Volume 1. (Lieberman, H. Lachman, L. and Schwartz, J., Eds.) 2nd ed., Marcel Dekker, Inc., New York, 1989, pp.151- 179.

Banker, G.S. and Anderson, N.R., Tablets. In : The Theory and Practice of Industrial Pharmacy. (Lachman, L. Lieberman, H. and Kanig, J., Eds.) 3rd ed., Lea & Febiger, Philadelphia, 1986, pp.327- 328.

Bastami, S.M. and Groves, M.J., Some factors influencing the in vitro release of phenytoin from formulations. Int. J. Pharm. 1 (1978) 151 - 164.

Bateman, S.D., Verlin, J., Russo, M., Guillot,M. and Laughlin, S.M., The development and validation of a capsule formulation knowledge-based system. Pharm. Tech. 20(3) (1996) 174-184.

Beddow, J.K., Report A390-CLME-74-007. University of Iowa, 52242, 1974 through Allen (1981).

Behn, S., Sodium lauryl sulphate. In : Handbook of Pharmaceutical Excipients. (Wade, A. and Weller, P.J., Eds.) 2nd ed., The Pharmaceutical Press, London, 1994, pp.448-450.

Belgium Compendium. 13thed, Association generale de I'industrie du medicament, Bruxelles, Belgium, 1993.

Bench-Capon, T.J.M., Knowledge representation. An approach to artificial intelligence. Academic Press, London, 1990a, pp. 141 - 169.

Bench-Capon, T.J.M., Knowledge representation. An approach to artificial intelligence. Academic Press, London, 1990b, pp. vi, 63 - 121.

Bench-Capon, T.J.M., Knowledge representation. An approach to artificial intelligence. Academic Press, London, 1990c, pp. 41 - 59.

Bergeron, M., Laurin, P. and Tawashi, R., Effects of particle morphology in selecting pharmaceutical excipients . Drug Dev. Ind. Pharm. 12 (1986) 915 - 926.

Blaug, S.M. and Huang, W., Interaction of dextroamphetamine sulphate with spray-dried lactose . J. Pharm. Sci. 61 (1972) 1770 - 1775.

Blecher, L., Formation of the International Pharmaceutical Excipient Council. Pharm. Tech. 15 (6) 1991 54 - 60.

Blecher, L., Pharm. Process 12(1) (1995) 6 through Moreton (1996).

Bochner, F., Hooper, W.D., Tyrer, J.H. and Eadie, M.J., Factors involved in an outbreak of phenytoin intoxication . J. Neurol. Sci. 16 (1972) 481 - 487.

Böhme, I.G., Krupp, H., Rabenhorst, H. and Sandstede, G., Adhesion measurements involving small particles. Trans. Inst. Chem. Eng. (London) 40 (1962) 252 - 259.

Bolhuis, G.K. and Hölzer, A.W., Lubricant sensitivity. In : Pharmaceutical Powder Compaction Technology. (Alderborn, G. and Nyström, C., Eds.) Marcel Dekker, Inc., New York, 1996, pp.517- 560.

Bolhuis, G.K., Arends-Scholte, A.W., Stuut, G.J. and De Vries, J.A., Disintegration efficiency of sodium starch glycolate, prepared from different native starches . Eur. J. Pharm.Biopharm. 40 (1994) 317 - 320.

Bolhuis, G.K., Lerk, C.F., Zijlstra, H.T. and De Boer, A.H., Film formation by magnesium stearate during mixing and its effect on tabletting . Pharm. Weekbl. 110 (1975) 317 - 325.

Bolhuis, G.K., Smallenbroek, A.J. and Lerk, C.F., Interaction of tablet disintegrants and magnesium stearate during mixing I : Effect on tablet disintegration . J. Pharm. Sci. 70 (1981) 1328 - 1329.

Bond, C.M., Lees, K.A. and Lorna Packington, J., Cephalexin : A new oral broad-spectrum antibiotic . Pharm. J. 205 (1970) 210 - 214.

Booth, S.W. and Newton, J.M., Experimental investigation of adhesion between powders and surfaces . J. Pharm. Pharmacol. 39 (1987) 679 - 684.

Botha, S.A., du Preez, J.L. and Lötter, A.P., DSC screening for drug-drug and drug excipient interactions in polypharmaceutical intended fro the alleviation of the symptoms of colds and flu I. Drug Dev. Ind. Pharm. 12 (1986) 811

Botha, S.A., Lötter, A.P. and du Preez, J.L., DSC screening for drug-excipient and excipient-excipient interactions in polypharmaceuticals intended for the alleviation of the symptoms of colds and flu III . Drug Dev. Ind. Pharm. 13 (1987) 1197 - 1215.

Botha, S.A. and Lötter, A.P., Compatibility study between ketoprofen and tablet excipients using differential scanning calorimetry . Drug Dev. Ind. Pharm. 15 (1989a) 415 - 426.

Botha, S.A. and Lötter, A.P., Compatibility study between oxprenolol hydrochloride and tablet excipients using differential scanning calorimetry . Drug Dev. Ind. Pharm. 15 (1989b) 1843 - 1853.

Botha, S.A. and Lötter, A.P., Compatibility study between naproxen and tablet excipients using differential scanning calorimetry . Drug Dev. Ind. Pharm. 16 (1990) 673 - 683.

Botzolakis, J.E. and Augsburger, L.L., Role of disintegrants in hard gelatin capsules . J. Pharm. Pharmacol. 36 (1984) 77 - 84.

Botzolakis, J.E. and Augsburger, L.L., Disintegrating agents in hard gelatin capsules. Part 1. Mechanism of action . Drug Dev. Ind. Pharm. 14 (1988a) 29 - 41.

Botzolakis, J.E. and Augsburger, L.L., Disintegrating agents in hard gelatin capsules. Part 2. Swelling efficiency . Drug Dev. Ind. Pharm. 14 (1988b) 1235 - 1248.

Botzolakis, J.E., Small, L.E. and Augsburger, L.L., Effect of disintegrants on drug dissolution from capsules filled on a dosator-type automatic capsule-filling machine . Int. J. Pharm. 12 (1982) 341 - 349.

British Pharmacopoeia. 13th ed., Volume 1 and 2, Her Majesty's Stationery Office, London, 1993.

Britten, J.R., PhD Thesis, University of Wales : The Design, Validation, and Use of a Capsule Filling Machine Simulator. Parke Davis & Co Ltd., 1992, p.4.

Britten, J.R., Barnett, M.I. and Armstrong, N.A., Construction of an intermittent-motion capsule filling machine simulator . Pharm. Res. 12 (1995) 196 - 200.

Brown, R.L. and Richards, J.C., Exploratory study of the flow of granules through aperatures. Trans. Instn. Chem. Engrs. 37 (1959) 108 - 119.

Brown, R.L. and Richards, J.C., Profile of flow of granules through aperatures. Trans. Instn. Chem. Engrs. 38 (1960) 243 - 256.

Buchanan, B. and Shortliffe, E., RuleBased Expert Systems. "The MYCIN Experiments of the Stanford Heuristic Programming Project". Addison-Wesley, 1985.

Buckton, G., The assessment, and pharmaceutical importance of the solid/liquid and the solid/vapour interface : a review with respect to powders . Int. J. Pharm. 44 (1988) 1 - 8.

Buckton, G., The estimation and application of surface energy data for powdered systems . Drug Dev. Ind. Pharm. 18 (1992) 1149-1167.

Buckton, G. and Newton, J.M., Assessment of the wettability and surface energy of a pharmaceutical powder by liquid penetration . J. Pharm. Pharmacol. 37 (1985) 605-609.

Burak, N., Chemicals for improving the flow properties of powders . Chem. Ind. 21 (1966) 844 - 850.

Callahan, J.C., Cleary, G.W., Elefant, M., Kaplen, G., Densler, T. and Nash, R.A., Equilibrium moisture content of pharmaceutical excipients . Drug Dev. Ind. Pharm. 8 (1982) 355 - 369.

Capsugel, Company Literature : All About The Hard Gelatin Capsule. 1991, pp. 6 - 24.

Capsugel Library, Expert System for formulation support, Capsugel/Warner Lambert 1996 p.34.

Carr, R.L., Evaluating flow properties of solids . Chem. Engr. 72 (1965a) 163 - 169.

Carr, R.L., Classify flow properties of solids . Chem. Engr. 72 (1965b) 69-72.

Carson, J.W., Overcoming particle segregation in the pharmaceutical and cosmetic industries . Drug Dev. Ind. Pharm. 14 (1988) 2749 - 2758.

Carstensen, J.T., Pharmaceutics of Solids and Solid Dosage Forms. Wiley, New York, 1977, pp.11- 15.

Carstensen, J.T., Effect of Moisture on the stability of solid dosage forms. In : Drug Stability. Principles and Practices. Drugs and The Pharmaceutical Sciences Volume 43. (Carstensen, J.T. Eds.) Marcel Dekker, New York, 1990a, pp.165- 207.

Carstensen, J.T., Preformulation. In : Drug Stability. Principles and Practices. Drugs and the Pharmaceutical Sciences. Volume 43. (Carstensen, J.T. Eds.) Marcel Dekker, New York, 1990b, pp.263- 276.

Carstensen, J.T., Attarchi, F. and Hou, X., Decomposition of aspirin in the solid state in the presence of limited amounts of moisture. J. Pharm. Sci. 74 (1985) 741 -745.

Carstensen, J.T., Ertell, C. and Geoffroy, J., Physico-chemical properties of particulate matter . Drug Dev. Ind. Pharm. 19 (1993) 195 - 219.

Carstensen, J.T. and Rhodes, C.T., Pellicule Formation in Gelatin Capsules . Drug Dev. Ind. Pharm. 19 (1993) 2709 - 2712.

Cartilier, L.H. and Tawashi, R., Effect of particle morphology on the flow and packing properties of lactose . S.T.P. Pharma Sci. 3 (1993) 213 - 220.

Castello, R.A. and Mattocks, A.M., Discoloration of tablets containing amines and lactose . J. Pharm. Sci. 51 (1962) 106 - 108.

Chafetz, L., Hong, W., Tsilitonis, D.C., Taylor, A.K. and Philip, J., Decrease in the rate of capsule dissolution due to formaldehyde from polysorbate 80 autoxidation. J. Pharm. Sci. 73 (1984) 1186 - 1187.

Chowhan, Z.T., Excipients and their functionality in drug product development . Pharm. Tech. 17(9) (1993) 72 - 82.

Chowhan, Z.T., Drug substance physical properties and their relationship to the performance of solid dosage forms . Pharm. Tech. 18(3) (1994) 44 - 60.

Chowhan, Z.T. and Chi, L., Drug-excipient interactions resulting from powder mixing, I : possible mechanism of interaction with starch and its effect on drug dissolution . Pharm. Tech. 9 (3) (1985a) 84 - 97.

Chowhan, Z.T. and Chi, L., Drug-excipient interactions resulting from powder mixing, II : possible mechanism of interaction with crospovidone and its effect on drug dissolution . Pharm. Tech. 9 (4) (1985b) 28 - 41.

Chowhan, Z.T. and Chi, L., Drug-excipient interactions resulting from powder mixing III : Solid state properties and their effect on drug dissolution. J. Pharm. Sci. 75 (1986a) 534 - 541.

Chowhan, Z.T. and Chi, L., Drug-excipient interactions resulting from powder mixing IV : Role of lubricants and their effect on in vitro dissolution . J. Pharm. Sci. 75 (1986b) 542 - 545.

Chowhan, Z.T. and Chow, Y.P., Powder flow studies I. Powder consolidation ratio and its relationship to capsule-filling - weight variation . Int. J. Pharm. 4 (1980) 317 - 326.

Cole, G.C., Capsule-filling machinery. In : Hard Capsules. Development and Technology. (Ridway, K. Eds.) The Pharmaceutical Press, London, 1987a, pp.104- 164.

Cole, G.C., The mechanical operations of filling hard capsules. In : Hard Capsules. Development and Technology. (Ridway, K. Eds.) The Pharmaceutical Press, London, 1987b, pp.92- 103.

Cole, G.C., Powder characteristics for capsule filling. In : Hard Capsules. (Ridway, K. Eds.) The Pharmaceutics Press, London, 1987c, pp.80- 86.

Cole, G.C., Capsule types, filling tests and formulation in hard capsules. In : Hard Capsules. (Ridway, K. Eds.) The Pharmaceutics Press, London, 1987d, pp.165 - 175.

Cole, G.C. and May, G., Instrumentation of a hard shell encapsulation machine . J. Pharm. Pharmacol. 24 (1972) 122P - 123P.

Cole, G.C. and May, G., The intrumentation of a Zanasi LZ/64 capsule filling machine . J. Pharm. Pharmacol. 27 (1975) 353 - 358.

Cook, D.T., PhD Thesis : A study of the wetting properties of a hydrophobic powder. University of Nottingham, 1978, pp.1- 28.

Cooper, J., Recent advances in tablet technology. In : Advances in Pharmaceutical Sciences. Volume 3. (Bean, H.S. Beckett,A.H. and Carless, J.E., Eds.) Academic Press, London, 1971, pp.3- 18.

Couvreur, P., Gillard, J., van den, H.G.S. and Roland, M., Mécanisme de désintégration des comprimés à base d'amidon. J. Pharm. Belg. 29 (1974) 399 - 414.

Craik, D.J., The flow properties of starch powders and mixtures . J. Pharm. Pharmacol. 9 (1957) 73 - 79.

Craik, D.J. and Miller, B.F., The flow properties of powders under humid conditions . J. Pharm. Pharmacol. 10 (1958) 136T - 144T.

Czetsch-Lindenwald, H., Oesterr. Apoth. Ztg. 17 (1963) 553 through Umprayn and Mendes (1987).

Czetsch-Lindenwald, H., Sinn und Grenzen der 'in vitro' - Versuche. Pharm. Ind. 29 (1967) 145-149 through Jones (1987c).

Dahl, T.C., Sue, I.T. and Yum, A., The influence of disintegrant level and capsule size on dissolution of hard gelatin capsules in high humidity conditions. Drug Dev. Ind. Pharm. 22 (1991) 1001 - 1016.

Daniel, J.E., Draper, J.R. and Simon, T.H., Development of a clinical capsule formulation containing a marginally water soluble drug . Drug Dev. Ind. Pharm. 15 (1989) 585 - 607.

Danish, F.Q. and Parrott, E.L., Effect of concentration and size of lubricant on flow rate of granules . J. Pharm. Sci. 60 (1971) 752 - 754.

Davies, J.E. and Fell, J.T., The influence of starch and lactose on the release rates of durgs from hard gelatin capsules. J. Pharm. Pharmacol. 25 (1973) 431 - 432.

Davies, P.N., Sodium stearyl fumarate. In : Handbook of Pharmaceutical Excipients. (Wade, A. and Weller, P.J., Eds.) 2nd ed., The Pharmaceutical Press, London, 1994, pp.467- 469.

Dawoodbhai, S. and Rhodes, C.T., The effect of moisture on powder flow and on compaction and physical stability of tablets . Drug Dev. Ind. Pharm. 15 (1989) 1577 - 1600.

Dawoodbhai, S. and Rhodes, C., Pharmaceutical and cosmetic uses of talc . Drug Dev. Ind. Pharm. 16 (1990) 2409 - 2429.

DeBeukelaer, P. and Ooteghem, M., Influence of powder bed porosity and wettability on liquid penetration and on drug release of powder mixtures filled into hard gelatin capsules . S. T. P. Pharma 1 (1985) 956 - 961.

DeBeukelaer, P., Van Ooteghem, M. and Ludwig, A., The influence of the swelling characterisitics of starch and starch derivates on the disintegration of powders, packed in hard gelatin capsules . Drug Dev. Ind. Pharm. 11 (1985) 431 - 439.

Delacourte, A., Guyot, J.C., Colombo, P. and Catellani, P.L., Effectiveness of lubricants and lubrication mechanism in tablet technology . Drug Dev. Ind. Pharm. 21 (1995) 2187 - 2199.

Delacourte, A., Predella, P., Leterme, P., Provasi, D., Colombo, P., Coute, U., Catellani, P.L. and Guyot, J.C., A method for quantitative evaluation of the effectiveness of the lubricants used in tablet technology . Drug Dev. Ind. Pharm. 19 (1993) 1047 - 1060.

Desai, D.S., Rubitski, B.A., Varia, S.A. and Newman, A.W., Physical Interactions of magnesium stearate with starch-derived disintegrant and their effects on capsule and tablet dissolution . Int. J. Pharm. 91 (1993) 217 - 226.

Desai, D.S., Rubitski, B.A., Bergum, J.S. and Varia, S.A., Effects of different types of lactose and disintegrants on dissolution stability of hydrochlorothiazide capsule formulations . Int. J. Pharm. 110 (1994a) 257 - 265.

Desai, D.S., Rubitski, B.A., Bergum, J.S. and Varia, S.A., Effects of various formulation factors on dissolution stability of aztreonam, hydrochlorothiazide and sorivudine capsules. Int. J. Pharm. 110 (1994b) 249 - 255.

Desai, D.S., Rubitski, B.A., Varia and Huang, M.H., Effect of formaldehyde formation on dissolution stability of hydrochlorothiazide bead formulations . Int. J. Pharm. 107 (1994c) 141 - 147.

Dey, M., Enever, R., Kraml, M., Prue, D.G., Smith, D. and Weierstall, R., The dissolution and bioavailability of etodolac from capsules exposed to conditions of high relative humidity and temperatures . Pharm. Res. 10 (1993) 1295 - 1300.

Dictionnaire Vidal. 71th ed, Editions du Vidal, Paris, 1993.

Digenis, G.A., Gold, T.B. and Shah, V.P., Crosslinking of gelatin cpausles and its relevance to their in vitro - in vivo performance . J. Pharm. Sci. 83 (1994) 3 - 11.

Dobberstein, R.H., Computer-assisted experimental design . Pharm. Tech. 18(3) (1994) 84 - 94.

Dooren, A.A., Design for drug-excipient interaction studies . Drug Dev. Ind. Pharm. 9 (1983) 43 - 55.

Doukidis, G.I. and Whitley, E.A., Introduction to Expert Systems. In : Developing Expert System. Chartwell-Bratt, 1988a, pp.1-17.

Doukidis, G.I. and Whitley, E.A., Tools for developing Expert Systems. In : Developing Expert System. Chartwell-Bratt, 1988b, pp.50-77.

Drummond, J.N., Binders for granules and tablets . Pharmaceutical manufacturing review 8(1) (1996) S2 - S4.

Dürig, T. and Fassihi, A.R., Identification of stabilizing and destabilizing effects of excipient-drug interactions in solid dosage form design . Int. J. Pharm. 97 (1993) 161 - 170.

Eaves, T. and Jones, T.M., Effect of moisture on tensile strength of bulk solids I : sodium chloride and effect of particle size. J. Pharm. Sci. 61 (1972a) 256-261.

Eaves, T. and Jones, T.M., Effect of moisture on tensile strength of bulk solids II : fine particle-size materials with varying inherent coherence. J. Pharm. Sci. 61 (1972b) 342-348.

Eaves, T. and Jones, T.M., Effects of surface tension on the tensile strength of beds of moist bulk solids. Pharm. Acta Helv. 47 (1972c) 537 - 545.

El-Shaboury, M.H., Abd El-Gawad, A.H., Gabr, K.E. and Hashem, F.M., Effect of effervescent salt on the dissolution and bioavailability of drugs from capsules filled on a dosator-type capsule fillingmachine . Pharm. Ind. 55 (1993) 176 - 179.

Elamin, A.A., Ahlneck, C., Alderborn, G. and Nyström, C., Increased metastable solubility of milled griseofulvin, depending on the formation of a disordered surface structure . Int. J. Pharm. 111 (1994) 159 - 170.

European Pharmacopoeia. 2nd ed. Published under the direction of the Council of Europe, Maisonneuve, Sainte-Ruffine, France, 1980.

Farhadieh, B., Starch. In : Handbook of Pharmaceutical Excipients. (Wade, A. and Weller, P.J., Eds.) 2nd ed., The Pharmaceutical Press, London, 1994, pp.483- 488.

Farin, D. and Avnir, D., Reactive fractal surfaces. J. Phys. Chem. 91 (1987) 5517 - 5521.

Farley, R. and Valentin, F.H.H., Effect of particle size upon the strength of powders. Powder Technol. 1 (1967-68) 344 -354.

Faroongsarng, D. and Peck, G.E., The role of liquid water-uptake by an insoluble tablet containing a disintegrant . Drug Dev. Ind. Pharm. 20 (1994) 1777 - 1794.

Feigenbaum, E.A., Buchanan, B.G. and Lederberg, J., On generality and problem solving : a case study using the DENDRAL program. In : Machine Intelligence. American Elsevier, New York (1971) pp. 165 - 190 through Steels (1989).

Fell, J.T., Calvert, R.T., Riley-Bentham, P., Bioavailability of griseofulvin from a novel capsule formulation. J. Pharm. Pharmacol. 30 (1978) 479 - 482.

Fernández-Hervás, M.J., Holgado, M.A., Rabasco, A.M. and Fini, A., Use of fractal geometry on the characterization of particles morphology. Application to the diclofenac hydroxyethylpirrolidine salt . Int. J. Pharm. 108 (1994) 187 - 194.

Florence, A.T. and Attwood, D., Physiochemical Principles of Pharmacy. 2nd ed., The Macmillan Press Ltd, London, 1988, pp.131 - 171.

Forsyth, R., Expert Systems, Principles And Case Studies. London, 1984, pp.3- 9.

Fowler, R.T. and Radford, C.D., Preliminary studies into the cohesion of granular particles. Mech. & Chem. Eng. Trans. Inst. Engrs Australia May (1965) 129-134.

Fox, H.W. and Zisman, W.A., The spreading of liquids on low energy surfaces I. Polytetrafluoroethylene. J. Colloid. Sci. 5 (1950) 514 - 531.

Franklin, F.C. and Johanson, L.N., Flow of granular material through a circular orifice. Chem. engn. Sci. 4 (1955) 119 -134.

Freeman, P., Lubrication and Friction. Pitman, London, 1962, pp.136 through Staniforth et al (1993).

Frömming, K. and Gröbler, S., Influence of fillers and of magnesium stearate on drug liberation from hard gelatin capsules . Pharm. Ztg. 128 (1983) 786 - 793.

Führer, C., Interparticulate attraction mechanisms. In : Pharmaceutical Powder Compaction Technology. (Alderborn,G. and Nyström, C., Eds.) Marcel Dekker,Inc., New York, 1996, pp.1- 16.

Gardner, H., The Mind's New Science. Basic Books, New York, 1986 through Parsaye and Chignell (1995a).

Gautam, J. and Schott, H., Interaction of anioic compounds with gelatin. II : Effect on some physicochemical properties of gelatin . J. Pharm. Sci. 83 (1994) 316 - 321.

Genton, D. and Kesselring, U.W., Effect of temperature and relative humidity on nitrazepam stability in solid state. J. Pharm. Sci. 66 (1977) 676 - 680.

Georgarakis, M., Hatzipantou, P. and Kountourelis, J.E., Effect of particle size, content in lubricant, mixing time and storage relative humidity on drug release from hard gelatin ampicillin capsules. Drug Dev. Ind. Pharm. 14 (1988) 915-923.

Gioia, A., Intrinsic flowability : A new technology for powder-flowability classification. Pharm. Tech. 4(2) (1980) 65 - 68.

Gold, G. and Palmero, B.T., Hopper flow electrostatics of tabletting material. II. Tablet lubricants . J. Pharm. Sci. 54 (1965) 1517 -1519.

Gold, G., Duvall, R.N. and Palmero, B.T., Powde r flow studies I : Instrumentation and applications . J. Pharm. Sci. 55 (1966a) 1133 - 1136.

Gold, G., Duvall, R.N., Palmers, B.T. and Slater, J.G., Powder flow studies II - effect of glidants on flow rate and angle of repose . J. Pharm. Sci. 55 (1966b) 1291 - 1295.

Gold, G., Duvall, R.N., Palmero, B.T. and Slater, J.G., Powder flow studies IV. Uniformity of flow : Instrumentation and applications . J. Pharm. Sci. 57 (1968a) 2153 - 2157.

Gold, G., Duvall, R.N., Palmero, B.T. and Slater, J.G., Powder flow studies III. Factors affecting the flow of lactose granules . J. Pharm. Sci. 57 (1968b) 667 - 671.

Goodhart, F.W., McCoy, R.H. and Ninger, F.C., New in vitro disintegration and dissolution test method for tablets and capsules . J. Pharm. Sci. 62 (1973) 304 - 310.

Goodhart, F.W., Lactose. In : Handbook of Pharmaceutical Excipients. (Wade, A. and Weller, P.J., Eds.) 2nd ed., The Pharmaceutical Press, London, 1994, pp.252 - 261.

Gordon, M.S., Rudraraju, V.S., Dani, K. and Chowhan, Z.T., Effect of the mode of super disintegrant incoporation on dissolution in wet granulated tablets . J. Pharm. Sci. 82 (1993) 220 - 226.

Gordon, R.E. Rosanske, T.W. and Fonner, D.E., Granulation technology and tablet characterization. In : Pharmaceutical Dosage Forms : Tablets Volume 2. (Lieberman, H.A. Lachman, L. and Schwartz, J., Eds.) 2nd ed., Marcel Dekker, New York, 1990, pp.303- 305.

Graf, J.C., The importance of resolution limits to the interpretation of fractal descriptions of fine particles . Powder Technol. 67 (1991) 83 - 85.

Grimm, W. and Thomae, K., International harmonization of stability tests for pharmaceuticals. The ICH tripartite guideline for stability testing of new drug substances and products . Eur. J. Pharm. Biopharm. 41 (1995) 194 - 195.

Gustavo González, A., Optimization of pharmaceutical formulations based on response-surface experimental designs. Int. J. Pharm. 97 (1993) 149 - 159.

Haase, M. and McGinity, J.W., Alginic acid. In : Handbook of Pharmaceutical Excipients. (Wade, A. and Weller, P.J., Eds.) 2nd ed., The Pharmaceutical Press, London, 1994, pp.10- 11.

Halbert, G.W., Pharmaceutical development. In : The Textbook Of Pharmaceutical Medicine. (Griffin, J.P. O'Grally, J. and Wells, F.O., Eds.) Greystone, Belfast, 1993, p.39.

Hammerness, F.C. and Thompson, H.O., A study of the effect of lubricant and fines on a tablet granulation . J. Pharm. Assoc. Sci. Ed. 47 (1958) 58 - 61.

Hannula, A.M., Marvola, M. and Jons, M., Release of ibuprofen from hard gelatin capsule formulations : effect of modern disintegrants . Acta Pharm. Fenn. 98 (1989a) 189 - 196 (through I.P.A. 27(22) (1990) 27-14142).

Hannula, A.M., Marvola, M. and Kopra, T., Release of ibuprofen from hard gelatin capsule formulations : effect of various additives and filling method . Acta Pharm. Fenn. 98 (1989b) 11 - 20 (through I.P.A. 27(10) (1990) 27-05666).

Harder, S.W., Zuck, D.A. and Wood, J.A., Characterisation of tablet surfaces by their initial surface-tension value. J. Pharm. Sci. 59 (1970) 1787-1792.

Harpaz, D., Colloidal Silicon Dioxide. In : Handbook of Pharmaceutical Excipients. (Wade, A. and Weller, P.J., Eds.) 2nd ed., The Pharmaceutical Press, London, 1994, pp.424- 427.

Hartauer, K.J. and Guillory, J.K., A comparison of diffuse reflectance FT-IR spectroscopy and DSC in the characterization of a drug-excipient interaction . Drug Dev. Ind. Pharm. 17 (1991) 617 - 630.

Hartauer, K.J., Bucko, J.H., Cooke, G.G., Mayer, R.F., Schwier, J.R. and Sullivan, G.R., The effect of rayon coiler on the dissolution stability of hard-shell gelatin capsules. Pharm. Tech. 17(6) (1993) 76 - 83.

Hartung, J. and Elpelt, B.R., Multivariate Statistik, R. Oldenbourg Verlag, Munich, Vienna, 1984, pp.174,443 through Podczeck (1996).

Harwood, C.F., PhD Thesis. University of London, 1969 through Pilpel (1971).

Harwood, R.J. and Johnson, J.L., Hydroxypropyl cellulose. In : Handbook of Pharmaceutical Excipients. (Wade, A. and Weller, P.J., Eds.) 2nd ed., The Pharmaceutical Press, London, 1994, pp.223- 228.

Hasse, M. and McGinity, J.W., Alginic acid. In : Handbook of Pharmaceutical Excipients. (Wade, A. and Weller, P.J., Eds.) 2nd ed., The Pharmaceutical Press, London, 1994, pp.10- 11.

Hauer, B., Remmele, T., Züger, O. and Sucker, H., The rational development and optimisation of capsule formulations with an instrumental dosator capsule filling machine. 1. Instrumentation and influence of the filling material and the machine. Pharm. Ind. 55 (1993a) 509 - 515.

Hauer, B., Remmele, T. and Sucker, H., The rational development and optimization of capsule formulations with an instrumented dosator capsule filling machine. 2. Fundamentals of the optimisation strategy. Pharm. Ind. 55 (1993b) 780 - 786.

Hausner, H.H. Int. J. powd. Metall. 3 (1967) 7 through Wells and Aulton (1988).

Hawkins, A.E., The shape of powder-particle outlines. Research Studies Press Ltd., Taunton, 1993, pp.42 - 52.

Heertjes, P.M. and Kossen, N.W.F., Measuring the contact angle of powder liquid systems . Powder Technol. 1 (1967) 33 - 42.

Heertjes, P.M. and Witvoet, W.C., Some aspects of the wetting of powders. Powder Technol. 3 (1969/70) 339 - 343.

Hersey, J.A., Ordered mixing : a new concept in powder mixing practice. Powder Technol. 11 (1975) 41 - 44.

Hersey, J.A., Seminar on Bulk Solids andling : Powder Mixing. Philadelphia, 1979 through Lantz and Schwartz (1990).

Heywood, H. J., Imp. Coll. Chem. Engng. Soc. 8 (1954) 25 - 33 through Heywood (1963).

Heywood, H., Techniques for the evaluation of powders. I. Fundamental properties of particles and methods of sizing analysis . Powder Metall. 7 (1961) 1 - 28.

Heywood, H., The evaluation of powders . J. Pharm. Pharmacol. 15 (1963) 56T - 74T.

Hiestand, E.N., Valvani, S.C., Peot, C.B., Strzelinski, E.P. and Glasscock, J.F.J., Shear cell measurements of powders : determination of yield loci . J. Pharm. Sci. 62 (1973) 1513 - 1517.

Higuchi, T., Shih, F.L., Kimura, T. and Rytting, J.H., Solubility determination of barely aqueous-soluble organic solids . J. Pharm. Sci. 68 (1979) 1267 - 1272.

Ho, K.L., The effect of particle shape on bulk properties of some tablet excipients. PhD Thesis. University of London, London, 1989, pp.290-291.

Hogan, J., Shue, P.I., Podczeck, F., Newton, J.M., Investigations into the relationship between drug properties, filling and the release of drugs from hard gelatin capsules using multivariate statistical analysis. Pharm. Res. 13 (1996) 945 - 950.

Hohne, B.A. and Houghton, R.D., An Expert System for the formulation of agricultural chemicals. In : Artificial Intelligence Applications in Chemist. (Pierce, T.H. and Hohne, B.A., Eds.) ACS Symposium Series 306, Chicago, 1985, pp.87- 97.

Holgado, M.A., Fernández-Hervás, M.J., Fernández-Arávalo, M. and Rabasco, A.M., Use of fractal dimensions in the study of excipients : application to the characterization of modified lactose . Int. J. Pharm. 121 (1995) 187 - 193.

Hollenbeck, R.G., Bioavailability of phenylpropanolamine HCl from tablet dosage forms containing croscarmellose sodium . Int. J. Pharm. 47 (1988) 89 - 93.

Hölzer, A.W. and Sjögren, J., Evaluation of sodium stearyl fumarate as a tablet lubricant. Int. J. Pharm. 2 (1979) 145-153.

Hölzer, A.W. and Sjögren, J., Evaluation of some lubricants by the comparison of friction coefficients and tablet properties . Acta Pharm. Suec. 18 (1981) 139 - 148.

Hostetler, V.B., Hard Capsules. In : The Theory and Practice of Industrial Pharmacy. (Lachman, L. Lieberman, H.A. and Kanig,J., Eds.) 3rd ed., Lea & Febiger, Philadelphi, 1986, pp.389-392.

Houghton, M.E. and Amidon, G., Microscopic characterization of particle size and shape : an inexpensive and versatile method . Pharm. Res. 9 (1992) 856 - 859.

Hussain, A., Shivanand, P. and Johnson, R.D., Application of neural computing in pharmaceutical product development : computer aided formulation design . Drug Dev. Ind. Pharm. 20 (1994) 1739 - 1752.

Hussain, A.S., Yu, X. and Johnson, R.D., Application of neural computing in pharmaceutical product development . Pharm. Res. 8 (1991) 1248 - 1252.

Ingram, J.T. and Lowenthal, W., Mechanism of action of starch as tablet disintegrant I : factors that affect the swelling of starch grains at 37° . J. Pharm. Sci. 55 (1966) 614 - 617.

International Agency for Research on Cancer / World Health Organisation., Silica and some silicates. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans 42 (1987) through Schirmer (1994).

Iranloye, T. and Parrott, E., Effect of compression force, particle size, and lubricants on dissolution rates . J. Pharm. Sci. 67 (1978) 535 - 539.

Irwin, G., Dodson, G. and Ravin, L., Encapsulation of clomacran phosphate {2-Chloro-9[3-(dimethylamino) propyl] acridan phosphate} I : Effect of flowability of powder blends, lot-to-lot variability, and concentration of active ingredient on weight variation of capsules filled on an automatic capsule-filling machine . J. Pharm. Sci. 59 (1970) 547 - 549.

Ito, K., Kaga, S.-I. and Takeya, Y., Studies on hard gelatin capsules I. Water vapor transfer between capsules and powders . Chem. Pharm. Bull. 17 (1969a) 1134 - 1137.

Ito, K., Hitomi, M., Kaga, S. and Takeya, Y., Studies on hard gelatin capsules II. The capsule filling powders and effects of glidants by ring filling method-machine . Chem. Pharm. Bull. 17 (1969b) 1138 - 1145.

Jacobson, H. and Reier, G., Application of differential thermal analysis to compatibility and stability problems in Penicillin-stearic acid mixtures. J. Pharm. Sci. 58 (1969) 631 - 633.

Jaiyeoba, K.T. and Spring, M.S., The granulation of ternary mixtures : the effect of the wettability of the powders . J. Pharm. Pharmacol. 32 (1980) 386 - 388.

Jenike, A.W. Utah Engineering Experimental Station. Bulletins (1961) 108 through Pipel (1971).

Jenike, A.W., Storage and flow of solids. In : Utah Engineering Experimental Station Bulletin No. 123. University of Utah, 1964 through Pipel (1971).

Johansson, M.E. and Nicklasson, M., Investigation of the film formation of magnesium stearate by applying a flow through dissolution technique. J. Pharm. Pharmacol. 38 (1986) 51 - 54.

Johansen, H. and Møllen, N., Solvent deposition of drugs on excipients II : interpretation of dissolution, adsorption and absorption characteristics of drugs. Arch. Pharm. Chem. (Sci) 5 (1977) 33-42 through Harpaz (1994).

Johanson, J.R., Predicting segregation of bimodal particle mixtures using the flow properties of bulk solids. Pharm. Tech. Eur. 8(1) (1996) 38-44.

Johnson, J.R., Wang, L., Gordon, M.S. and Chowhan, Z.T., Effect of formulation stability and hygroscopicity on disintegrant efficiency in tablets prepared by wet granulatoin, in terms of dissolution . J. Pharm. Sci. 80 (1991) 469 - 471.

Jolliffe, I.G. and Newton, J.M., The effect of powder coating on capsule filling with a dosator nozzle . Acta Pharm Technol. 26 (1980) 324 - 326.

Jolliffe, I.G., Newton, J.M. and Walters, J.K., Theoretical considerations of the filling of pharmaceutical hard gelatin capsules . Powder Technol. 27 (1980) 189-195.

Jolliffe, I.G. and Newton, J.M., Practical implications of theoretical consideration of capsule filling by the dosator nozzle system . J. Pharm. Pharmacol. 34 (1982a) 293 - 298.

Jolliffe, I.G. and Newton, J.M., An investigation of the relationship between particle size and compression during capsule filling with an instrumented mG2 simulator . J. Pharm. Pharmacol. 34 (1982b) 415 - 419.

Jolliffe, I.G., Newton, J.M. and Cooper, D., The design and use of an instrumented MG2 capsule filling machine simulator . J. Pharm. Pharmacol. 34 (1982) 230 - 235.

Jolliffe, I.G. and Newton, J.M., The effect of dosator nozzle wall texture on capsule filling with the mG2 simulator . J. Pharm. Pharmacol. 35 (1983a) 7 - 11.

Jolliffe, I.G. and Newton, J.M., Capsule filling studies using an mG2 production machine. J. Pharm. Pharmacol. 35 (1983b) 74 - 78.

Jones, B.E., Hard gelatin capsules and the pharmaceutical formulator . Pharm. Tech. 9 (9) (1985) 106 - 112.

Jones, B.E., The History of the gelatin capsule. In : Hard Capsules. (Ridway, K. Eds.) Pharmaceutical Press, London (1987a) pp. 1 - 12.

Jones, B.E., The manufacture of hard gelatin capsules. In : Hard Capsules. (Ridway, K. Eds.) Pharmaceutical Press, London (1987c) pp. 68 - 79.

Jones, B.E., Factors affecting drug release from powder formulations in hard gelatin capsules . S. T. P. Pharma 3 (1987e) 777 - 783.

Jones, B.E., Powder formulations for capsule filling . Manuf. Chem. 59 (7) (1988) 28 - 33.

Jones, B.E., The two-piece gelatin capsule : The role of excipients in formulation. In : Current and Novel Applications of Excipients in Pharmaceutical Dosage Forms : The Challenge of the Global Market. 24-25 Nov 1994. International Pharmaceutical Excipients Council, Nice (France), pp.42- 56.

Jones, B.E., Two-piece gelatin capsules : Excipients for powder products, European practice . Pharm. Tech. Eur. 7 (11) (1995) 25 - 34.

Jones, B. E. and Cole, W.V.J., The influence of test conditions on the disintegration time of gelatin capsules. J. Pharm. Pharmacol. 23 (1971) 438 - 443.

Jones, B.E. and Newton, J.M., Bibliography of capsules. In : Hard Capsules. Development and Technology. (Ridway, K. Eds.) The Pharmaceutical Press, London, 1987, pp.205 - 300.

Jones, B.E. and Schweiger, B., Patient preference for oral dosage forms : survey of medical practitioners and consumers . Pharm. Ind. 52 (1990) 630 - 634.

Jones, B.E. Seager, H. Aulton, M.E. and Morton, F.S.S., Capsules. In : Pharmaceutics - The Science of Dosage Form Design. (Aulton, M.E. Eds.) Churchill Livingstone, Edinburgh, 1988, pp.322- 340.

Jones, B.E. and Turner, T.S., Century of commercial hard gelatin capsules . Pharm. J. 213 (1975) 614 - 616.

Jones, R.T., Gelatin : structure and manufacture. In : Hard Capsules. (Ridway, K. Eds.) Pharmaceutical Press, London (1987b) pp. 13 - 29.

Jones, R.T., Gelatin : physical and chemical properties. In : Hard Capsules. (Ridgway, K. Eds.) The Pharmaceutical Press, London, 1987d, pp.42- 44.

Jones, T.M. and Pilpel, N. Some physical properties of magnesia and their relevance to material handling. J. Pharm. Pharmacol. 17 (1965) 440 - 448.

Jones, T.M. and Pilpel, N. Some angular properties of magnesia and their relevance to material handling. J. Pharm. Pharmacol. 18 (1966) 182S - 189S.

Jones, T.M., Effects of excipients on the characteristics of oral dosage forms . Pharm. Ind. 39 (1977) 469 - 476.

Jordan, R.P. and Rhodes, C.T., Recording powder flow meters and their use in pharmaceutical technology . Drug Dev. Ind. Pharm. 5 (1979) 151 - 167.

Kahn, K.A., The concept of dissolution efficiency . J. Pharm. Pharmacol. 27 (1975) 48 - 49.

Kassem, A.A., Zaki, S.A., Mursi, N.M. and Tayel, S.A., T.L.C. and I.R. studies of interaction between macromolecular polymers and chloramphenicol in solid dispersions. Pharm. Ind. 41 (1979) 1220 - 1223.

Katdare, A.V., Keller, K.O., Christoff, J.J. and Bavitz, J.F., Evaluation of dissolution characteristics of an encapsulated water soluble tablet granulation . Drug Dev. Ind. Pharm. 16 (1990) 1109 - 1119.

Kawakita, K. and Tsutsumi, Y. Bull. Chem. Soc. Japan 39 (1966) 1364 through Paronen and Ilkka (1996).

Kawakita, K. and Lüdde. K.H., Some considerations on powder compression equations. Powder Tech. 4 (1970/1971) 61 - 68.

Kayes, J.B., Disperse systems. In : Pharmaceutics - The Science of Dosage Form Design. (Aulton, M.E. Eds.) Churchill Livingstone, Edinburgh, 1988, p 109.

Kaye, B.H., Powder mixing review. Pharm Tech. 15 (9) (1991a) 62 -70.

Kaye, B.H., Using an Expert System to monitor mixer performance. Powder and Bulk Engineering, January (1991b) 36 - 40 through Kaye (1991a).

Khalil, S.A. and Ali, L.M.M., Some formulation factors affecting disintegration and dissolution of chloramphenicol capsules . Acta Pharm. Suec. 9 (1972) 563 - 572.

Kocova, S. and Pilpel, N. The failure of lactose and calcium carbonate powders. Powder Technol. 5 (1972) 329 - 343.

Koh, C.K., The bulk and flow properties of binary and ternary mixtures of particles of different shape. PhD Thesis. University of London, London, 1984, pp.216- 219.

Kristensen, H., Studies on flow properties of powders VI. Some physical properties of crystalline and spray dried lactose . Dansk Tidsskr. Farm. 45 (1971) 114 - 124.

Kristensen, H. and Jensen, V.G., Studies on flow properties of powders III : The influence of glidants on the technical properties of tablet granulation. Dansk Tidsskr. Farm. 43 (1969) 205 - 211.

Kristensen, H. and Schaefer, T., Granulation. A review on pharmaceutical wet-granulation . Drug Dev. Ind. Pharm. 13 (1987) 803 - 872.

Kruss, B., Developments in excipient design - toxicological and legal aspects. In : Topics in Pharmaceutical Sciences 1989. Proceedings of the 49th International Congress of Pharmaceutical Sciences of F.I.P., held in Munich, Germany, 4 - 9 September 1989.

(Breimer, D.D., Crommelin, D.J.A. and Midha, K.K., Eds) Fédération Internationale Pharmaceutique (F.I.P.) (International Pharmaceutical Federation), The Hague, 1989, pp.223- 234.

Kwong, E.C., Lamarche, P.L., Down, G.R.B., McClintock, S.A., Vada, E.B. and Cotton, M.L., Formulation assessment of MK-886, a poorly watersoluble drug, in the beagle dog. Int. J. Pharm. 103 (1994) 259 - 265.

L'Informatore Farmceutico. Medicinali 1. Annuario Italiano dei Medicinali E Dei Laboratori (Italian Directory of medines and manufacturers). 55th., Organizzazione Editoriale Medico Farmaceutica, Milano, Italy, 1993.

Lach, J.L. and Bornstein, M., Diffuse reflectance studies of solid-solid interactions. Interactions of oxytetracycline, phenothiazine, anthracene, and salicylic acid with various adjuvants. J. Pharm. Sci. 54 (1965) 1730 - 1736.

Lai, F.K.Y., A prototype Expert System for selecting pharmaceutical powder mixers . Pharm. Tech. 12 (8) (1988) 22 - 31.

Lai, F.K.Y., Expert Systems as applied to Pharmaceutical Technology. In : Encyclopedia of Pharmaceutical Technology. Vol 15.. (Swarbrick, J. and Boylan, J.C., Eds.) Marcel Dekker Inc., New York, 1992, pp.361- 378.

Lam, K.K. and Newton, J.M., Investigation of applied compression on the adhesion of powders to a substrate surface . Powder Technol. 65 (1991) 167 - 175.

Lam, K.K. and Newton, J.M., Influence of particle size on the adhesion behaviour of powders, after application of an initial press on force . Powder Technol. 73 (1992a) 117 - 125.

Lam, K.K. and Newton, J.M., Effect of temperature on particulate solid adhesion to a substrate surface . Powder Technol. 73 (1992b) 267 -274.

Lam, K.K. and Newton, J.M., The influence of the time of application of contact pressure on particle adhesion to a substrate surface . Powder Technol. 76 (1993) 149 - 154.

Lantz, R.J., Size Reduction. In : Pharmaceutical Dosage Forms : Tablets. Volume 2. (Lieberman, H.A. Lachman, L. and Schwartz, J., Eds.) 2nd ed., Marcel Dekker,Inc., New York, 1990, pp.162- 167.

Lantz, R.J., Schwartz, J.B., Mixing. In : Pharmaceutical Dosage Forms : Tablets. Volume 2. (Lieberman, H.A. Lachman, L. and Schwartz, J., Eds.) 2nd ed., Marcel Dekker,Inc., New York, 1990, p. 15.

Leeson, L. and Mattocks, Decomposition of aspirin in the solid state. A. J. Amer. Pharm. Ass. Sci. Ed. 47 (1958) 329 - 333.

Lerk, C.F. and Bolhuis, G.K. Interaction of lubriacnts and colloidal silica during mixing with excipients. Pharm. Acta Helv. 52 (1977) 39 - 44.

Lerk, C.F., Bolhuis, G.K., Smallenbroek, A.J. and Zuurman, K., Interaction of tablet disintegrants and magnesium stearate during mixing II. Effect on dissolution rate . Pharm. Acta Helv. 57 (1982) 282 - 286.

Lerk, C.F., Bolhuis,G.K. and Smedema, S.S., Interaction of tablet disintegrants and magnesium stearate during mixing II. Effect on dissolution rate . Pharm. Acta. Helv. 52 (1977a) 33 - 39.

Lerk, C.F., Lagas, M., Boelstra, J.P. and Broersma, P., Contact angles of pharmaceutical powders. J. Pharm. Sci. 66 (1977b) 1480 - 1481.

Lerk, C.F., Lagas, M., Fell, J.T. and Nauta, P., Effect of hydrophilization of hydrophobic drugs on release rate from capsules . J. Pharm. Sci. 67 (1978) 935 - 939.

Lerk, P.C. and Sucker, H., Interaction of magnesium stearate and talc upon tabletting mixtures, I : Effect on ejection force after compaction. Acta Pharm. Technol. 34 (1988a) 68 - 71.

Lerk, P.C. and Sucker, H., Interaction of magnesium stearate and talc upon tableting mixutres, II : Effect on wettability of powder blends. Acta Pharm. Technol. 34 (1988b) 72 - 76.

Lessen, T. and Zhao, D., Interactions between drug substances and excipients. 1. Fluorescence and HPLC Studies of Triazolophthalazine derivatives from hydralazine hydrochloride and starch . J. Pharm. Sci. 85 (1996) 326 - 329.

Lewis, G.A. and Chariot, M., Flexible Experimental Design in pharmaceutical development : optimal designs for formulation and process optimisation . Pharm. Tech. Int. 16(9) (1992) 46 - 51.

Leyland, R.L., Polyoxyethylene sorbitan fatty acid esters. In : Handbook of Pharmaceutical Excipients. (Wade, A. and Weller, P.J., Eds.) 2nd ed., The Pharmaceutical Press, London, 1994, pp.375 - 378.

Lindberg, N.-O. and Lundstedt, T., The relationship between the dissolution rate and the particle size of prednimustine : a disagreement with the Noyes-Whitney equation . Drug Dev. Ind. Pharm. 20 (1994) 2547 - 2550.

Lippold, B.C. and Ohm, A., Correlation between wettability and dissolution rate of pharmaceutical powders . Int. J. Pharm. 28 (1986) 67 - 74.

Ljungberg, S. and Otto, G., Particle size and intestinal absorption of acetylsalicylic acid in dogs. Acta Pharm.Suec. 7 (1970) 449 - 456.

Lordi, N.G., Pregelatinised starch. In : Handbook of Pharmaceutical Excipients. (Wade, A. and Weller, P.J., Eds.), 2nd Ed., The Pharmaceutical Press, London, 1994, pp.491-493.

Lowenthal, W., Mechanism of action of tablet disintegrants . Pharm. Acta Helv. 48 (1973) 589 - 609.

Lüdde, K.H. and Kawakita, K., Die Pulverkompression (in German). Pharmazie 21 (1966) 393 - 403 through Capsugel Library (1996).

Martin, A. Swarbrick, J. and Cammarata, A., Interfacial Phenomena. In : Physical Pharmacy. 3 rd ed., Lea & Febiger, Philadelphia, 1983, p. 450.

Martindale The Extra Pharmcopoeia. 30th., The Pharmaceutical Press, London, 1993.

Mathur, L., Microcrystalline cellulose. Handbook of Pharmaceutical Excipients. 2nd.ed, The Pharmaceutical Press, London, 1994, pp.84 - 87.

McDermott, J., RI : A rule based configurer of computer systems. AI Magazine 1(1) (1979) through Parsaye and Chignell (1988a).

McEnvoy C., Edwards, M., and Snowden, M., An overview of antioxidant, preservative and solvent excipients used in the pharmaceutical industry. Pharm. Tech. Eur. 8(6) (1996) 36 - 40.

Mechtersheimer, B. and Sucker, H., The effects of punch-face geometry and different magnesium stearate / talc combinations on tableting properties . Pharm. Tech. 10(2) (1986) 38 - 50.

Mehta, A.M. and Augsburger, L.L., A preliminary study of the effect of slug hardness on drug dissolution from hard gelatin capsules filled on an automatic capsule-filling machine. Int. J. Pharm. 7 (1981) 327 - 334.

Meloy, T.P., A hypothesis for morphological characterisation of particle shape and physiochemical properties. Powder Technol. 16 (1977a) 233 - 254.

Meloy, T.P. , Fast fourier transforms applied to shape analysis of particle silhouettes to obtain morphological data. Powder Technol. 17 (1977b) 27 - 36.

Merck Index, An Encyclopedia of chemicals and drugs. (Windholz, M., Budavari, S., Stroumtsos, L.Y. and Fertig, M.N., Ed.) 9th ed. Merck & Co., Inc., N.J., 1976.

Miller, E.E. and Miller, R.D., Physical theory of capillary flow phenomena. J. Appl. Phys. 27 (1956) 324 - 332.

Minsky, M., A framework for representing knowledge. In : The Psychology of Computer Vision. (Winston, P.H., Ed.) McGraw-Hill, New York (1975) pp. 211 - 277 through Bench-Capon (1990b).

Modrezejewski, F. and PokoraBartyzel,O. Acta. Pol. Pharm. 23 (1966) 480 through Umprayn and Mendes (1987).

Mohamad, H., Aiache, J.-M., Renoux, R., Mougin, P. and Kantelip, J.P., Étude de la stabilté biopharmaceutique des médicaments. Application à des gélules de chlorhydrate de tétracycline IV. Étude complémentaire in vivo. S.T.P. Pharma 3 (1987) 407 - 411.

Mohamad, H., Renoux, R., Aiache, S., Aiache, J.-M. and Kantelip, J.P., Étude de la stabilté biopharmaceutique des médicaments. Application à des gélules de chlorhydrate de tétracycline II. Etude in vivo. S.T.P. Pharma 2 (1986) 630 - 635.

Molerus, O., Particle Technol. (Conference), June 3-5. Amsterdam NL, 1980, pp.932 through Führer (1996).

Mony, C. Sambeat, C. and Cousin, C., 1st Int. Conf. on Pharmaceutical Technology (Paris APGI, May 31- June2, 1977). 1977, pp.98 - 108 through Jolliffe et al (1982).

Moreton, R.C., Tablet excipients to the year 2001 : a look into the crystal ball . Drug Dev. Ind. Pharm. 22 (1996) 11 - 23.

Mosharraf, M. and Nyström, C., The effect of particle size and shape on the surface specific dissoluiton rate of microsized practically insoluble drugs . Int. J. Pharm. 122 (1995a) 35 - 47.

Mosharraf, M. and Nyström, C., Solubility characterization of practiclaly insoluble drugs using the Coulter counter principle . Int. J. Pharm. 122 (1995b) 57 - 67.

Münzel, K., The influence of glidants on the flow properties of granules. First Industrial Pharmaceutical Conference, Land O'Lakes, Wis, June 1959 through Gold et al, 1966b.

Mura, P.A., Mazzi, G., Liguori, A., Bramanti, G. and Papini, P., Influence of certain factors on the in vitro diffusion rate of oxytetracycline hydrochloride from hard gelatin capsules . Boll. Chim. Farm. 123 (1984) 344 - 351.

Murray, F.J., The application of Expert System to pharmaceutical proceeding equipment. Pharm. Tech. 3(3) (1989) 100 - 110.

Murthy, K.S., Enders, N.A. and Fawzi, M.B., Dissolution stability of hard-shell capsule products, part I : the effect of exaggerated storage conditions . Pharm. Tech. 13(3) (1989) 72 - 86.

Murtoniemi, E., Yliruusi, J., Kinnunen, P., Merkku, P. and Leiviskä, K., The advantages by the use of neural networks in modelling the fluidized bed granulation process. Int. J. Pharm. 108 (1994a) 155 - 164.

Murtoniemi, E., Merkku, P., Kinnunen, P., Leiviskä, K. and Yliruusi, J., Effect of neural network topology and training end point in modelling the fluidized bed granulation process. Int. J. Pharm. 110 (1994b) 101 - 108.

Nakagawa, H., Mohri, K., Nakashima, K. and Sugimoto, I., Effects of particle size of rifampicin and addition of magnesium stearate on release of rifampicin from hard gelatin capsules . Yakugaku Zasshi 100 (1980) 1111 - 1117.

Nelson, E.J., Measurement of the repose angle of a tablet granulation . J. Am. Pharm. Assoc. Sci. Ed. 44 (1955) 435 - 437.

Neumaier, G., Filling Suitability of various filling materials on tube-filling and dosing-disc capsule filling machines. Kapsel symposium. 24 October 1991. Waiblingen. Industrielle Lohnverpackung GmbH & Co, Waiblingen, 1991, pp.2- 12.

Neumann, A.W. and Good, R.J., Techniques of measuring contact angles. In : Surface and Colloid Science, Vol II. (Good, R.J. and Stromberg, R.R., Eds.) Plenum, New York, 1979, pp.31- 91 through Buckton (1988).

Neumann, A.W. and Tanner, W., J. Colloid Interface Sci. 34 (1970) 1 - 8 through Buckton and Newton (1985).

Neumann, B., The flow properties of powders . Advances In Pharmaceutical Sciences. Volume 2 (Bean, H.S., Beckett, A.H., and Carless, J.E., Eds) Academic Press, London, 1967, pp. 181 - 220.

Newton, J.M., The release of drugs from hard gelatin capsules . Pharm. Weekbl. Ned. 107 (1972) 485 - 498.

Newton, J.M., Drug release from capsules. In : Hard Capsules. Development and Technology. (Ridway, K. Eds.) The Pharmaceutical Press, London, 1987a, pp.195- 204.

Newton, J.M., Filling of hard gelatin capsules . S. T. P. Pharma 3 (1987b) 880 - 885.

Newton, J.M. and Bader, F., The influence of drug and diluent particle size on the in vitro release of drug from hard gelatin capsules. J. Pharm. Pharmacol. 32 (1980) 167 - 171.

Newton, J.M. and Bader, F., The prediction of the bulk densities of powder mixtures, and its relationship to the filling of hard gelatin capsules . J. Pharm. Pharmacol. 33 (1981) 621 - 626.

Newton, J.M. and Razzo, F.N., The influence of additives on the *in vitro* release of drugs from hard gelatin capsules . J. Pharm. Pharmacol. 26 (1974) 30P - 36P.

Newton, J.M. and Razzo, F.N., The influence of additives on the presentation of a drug in hard gelatin capsules . J. Pharm. Pharmacol. 29 (1977a) 294 - 297.

Newton, J.M. and Razzo, F.N., The in vitro bioavailability of various drugs formulated as hard gelatin capsules . J. Pharm. Pharmacol. 29 (1977b) 205 - 208.

Newton, J.M. and Rowley, G., On the release of drug from hard gelatin capsules . J. Pharm. Pharmacol. 22 (1970) 163S - 168S.

Newton, J.M. and Rowley, G., Drug formulations. In : U.S. Patent 3859431. Lilly Industries Ltd., 1975 through Jones and Newton (1987).

Newton, J.M., Rowley, G. and Törnblom, J.V., The effect of additives on the release of drug from hard gelatin capsules . J. Pharm. Pharmacol. 23 (1971a) 452 - 453.

Newton, J.M., Rowley, G. and Törnblom, J.V., Further studies on the effect of additives on the release of drug from hard gelatin capsules . J. Pharm. Pharmacol. 23 (1971b) 156S - 160S.

Noyes, A. and Whitney, W., The rate of solution of solid substances in their own solutions . J. Am. Chem. Soc. 19 (1897) 930- 934.

Nyström, C. and Bisrat, M., Coulter counter measurements of solubility and dissolution rate of sparingly soluble compounds using micellar solutions . J. Pharm. Pharmacol. 38 (1986) 420 - 425.

Odidi, I.O. and Newton, J.M., Cylindrical tube and surface tension viscous flow models in the assessment of capillary flow and liquid contact angles in pharmaceutical powders. Int. J. Pharm. 90 (1993) 203 - 211.

Omray, A. and Omray, P., Evaluation of microcrystalline cellulose as a glidant . Indian J. Pharm. Sci. 48 (1986) 20 -22.

Pagliocca,B., Glyceryl Monostearate. In : Handbook of Pharmaceutical Excipients. (Wade, A. and Weller, P.J., Eds.) 2nd ed., The Pharmaceutical Press, London, 1994, pp.209 - 210.

Paronen, P. and Iikka, J., Porosity - Pressure Functions. In : Pharmaceutical Powder Compaction Technology. (Alderborn, G. and Nyström, C., Eds.) Marcel Dekker, Inc., New York, 1996, pp.58- 64.

Parrott, E.L., Milling. In : The Theory and Practice of Industrial Pharmacy. (Lachman, L. Lieberman, H. and Kanig, J., Eds.), 3rd ed., Lea & Febiger, Philadephia, 1986, pp.21-29.

Parsaye, K. and Chignell, M., Expert Systems For Experts. John and Sons Inc., Wiley, New York, 1988a, pp. 7 - 18.

Parsaye, K. and Chignell, M., Expert Systems For Experts. John and Sons Inc., Wiley, New York, 1988b, pp. 136 - 148.

Parsaye, K. and Chignell, M., Expert Systems For Experts. John and Sons Inc., Wiley, New York, 1988c, pp. 327 - 378.

Patel, N.R. and Hopponen, R.E., Mechanism of action of starch as a disintegrating agent in aspirin tablets . J. Pharm. Sci. 55 (1966) 1065-1068.

Patel, R. and Podczeck, F., Investigation of the effect of type and source of microcrystalline cellulose on capsule filling . Int. J. Pharm. 128 (1996) 123 - 127.

Peck, G.E. Baley, G. McCurdy, V.E. and Banker, G.S., Tablet formulation and design. In : Pharmaceutical Dosage Forms : Tablets. Volume 1. (Lieberman, H. Lachman, L. and Schwartz, J., Eds.) 2nd ed., Marcel Dekker,Inc., New York, 1989, pp.110- 129.

Peleg, M. and Mannheim, C.H., Effect of conditioners on the flow properties of powdered sucrose. Powder Technol. 7 (1972) 45 - 50.

Petrovick, P.R., Jacob, M., Gaudy, D., Bassani, V.L. and Guterres, S.S., Influence of adjuvants on the in vitro dissolution of hydrochlorothiazide from hard gelatin capsules . Int. J. Pharm. 76 (1991) 49 - 53.

The Pharmaceutical Codex. 11th ed., Pharmaceutical Press, London, 1979.

Physician Desktop Reference. 47 th ed., Medical Economics Data, Montvale, NJ, 1993.

Pilpel, N., The flow properties of magnesia . J. Pharm. Pharmacol. 16 (1964) 705 - 716.

Pilpel, N., The flow of powders and granular solids. Br. chem. Engng. 11 (1966) 699 - 702.

Pilpel, N., Some effects of moisture on the flow and cohesiveness of powders. Mfg. Chem. Aerosol News 41(4) (1970) 19 - 23.

Pilpel, N., Cohesive pharmaceutical powders. In : Advances in Pharmaceutical Sciences. Vol 3. (Bean, H.S. Beckett, A.H. and Carless, J.E., Eds.) Academic Press, London, 1971, pp.173-219.

Podczeck, F., Beiträge zur rechnergestützten Entwicklung fester Peroralia. Thesis (Dr. rer. nat). Martin-Luther-Univ.Halle-Wittenberg, Halle/Saale, 1986, pp.54,59,113 (through communication with the author).

Podczeck, F., Knowledge based system for the development of tablets. In : Proc. 11th Pharmaceutical Technology Conf., Manchester, 1992, pp.240- 264.

Podczeck, F., The development and optimisation of tablet formulations using mathematical methods. In : Pharmaceutical Powder Compaction Technology. (Alderborn, G. and Nyström, C., Eds.) Marcel Dekker, Inc., New York, 1996, pp.561-593.

Podczeck, F. and Newton, J.M., Development of an ultracentrifuge technique to determine the adhesion and friction properties between particles and surfaces . J. Pharm. Sci. 84 (1995) 1067-1071.

Podczeck, F., Newton, J.M. and James, M.B., Assessment of adhesion and autoadhesion forces between particles and surfaces : I. The investigation of autoadhesion phenomena of salmeterol xinafoate and lactose monohydrate particles using compacted powder surfaces . J. Adhesion Sci. Technol. 8 (1994) 1459 - 1472.

Podczeck, F., Newton, J.M. and James, M.B., Assessment of adhesion and autoadhesion forces between particles and surfaces. Part II. The investigation of adhesion phenomena

of Salmeterol Xinafoate and lactose monohydrate particles in particle-on-particle and particle-on-surface contact . J. Adhesion Sci. Technol. 9 (1995) 475 - 486.

Pope, D.G. and Lach, J.L., Some aspects of solid-state stability and diffuse reflectance spectroscopy. Pharm. Acta Helv. 50 (1975) 165 - 177.

Pople, H.E. Myers, J.D. and Miller, R.A., Dialog internist : A model of diagnostic logic for internal medicine. In : Proceedings of the 4th International Joint Conference on AI. [DIALOG was an early name for INTERNIST], 1975, pp.849-855 through Bench-Capon (1990a).

Proudfoot, S.G., Factors influencing bioavailability : factors influencing drug absorption from the gastrointestinal tract. In : Pharmaceutics. The Science of Dosage Form Design. (Aulton, M.E. Eds.) Churchill Livingstone, Edinburgh, 1988, pp.162- 164.

Racz, I., Physicochemical interactions encountered in the course of drug product preparation. In : Drug Formulation. John Wiley & Sons, Brisbane, 1989, pp.176 - 243.

Ragnarrson, G., Hölzer, A.W., and Sjögren, J., The influence of mixing time and colloidal silica on the lubricating properties of magnesium stearate. Int. J. Pharm. 3 (1979) 127 - 131.

Ramani, K.V., Patel, M.R. and Patel, S.K., An Expert System for drug preformulation in a pharmaceutical company . Interfaces 22(2) (1992) 101 - 108.

Rawlins, E.A., Tablets and capsules. In : Bentley's Textbook of Pharmaceutics. (Rawlins, E.A. Eds.) 18th Ed., Baillière Tindall, London, 1977, pp.269- 316.

Rees, J.E., Characterisation of pharmaceutical particulate materials . Boll. Chim. Farm. 116 (1977) 125 - 141.

Reier, G., Cohn, R., Rock, S. and Wagenblast, F., Evaluation of factors affecting the encapsulation of powders in hard gelatin capsules I., J. Pharm. Sci. 57 (1968) 660 - 666.

Ridolfo, A.S., Thompkins, L.; Bechtol, L.D. and Carmichael, Benoxaprofen, a new-anti-inflammatory agent : particle size. Effect on dissolution rate and oral absorption in humans. J. Pharm. Sci. 68 (1979) 850 - 852.

Ritala, M. Jungersen, O., Holm, P., Schæfer, T. and Kristensen, H.G., A comparison between binders in the wet phase of granulation in a high shear mixer. Drug Dev. Ind. Pharm. 12 (1986) 1685 - 1700.

Rote Liste, Bundesverband der Pharmazeutischen Industrie., Editio Cantor, Aulendorf, 1993.

Rowe, R.C., Binder-substrate interactions in tablets : a therorectical approach based on solubility parameters . Acta Pharm Technol. 34 (1988) 144 - 146.

Rowe, R.C., An expert system for the formulation of pharmaceutical tablets . DTI Manu Intelligence Newsletter 14 (1993a) 13 - 15.

Rowe, R.C., Expert Systems in Solid Dosage Development . Pharm. Ind. 55 (1993b) 1040 - 1045.

Rowe, R.C., Using experience in product formulation. Manuf. Chem. 67 (3) (1996) 20 - 21.

Rowe, R.C., Rowe, M.D. and Roberts, R.J., Formulating film coating with the aid of computer simulations. Pharm. Tech. Eur. 7 (2) (1995) 27 -33.

Rowe, R.C. and Upjohn, N.G., An Expert System for the identification and solution of film coating defects . Pharm. Tech. Int. 5(3) (1993) 34 - 38.

Rowley, G. and Newton, J.M., Limitations of liquid penetration in predicting the release of drugs from hard gelatin capsules . J. Pharm. Pharmacol. 22 (1970) 966 - 967.

Rubino, J.T., Halterlein, L.M. and Blanchard, J., The effects of aging on the dissolution of phenytoin sodium capsule formulations. Int. J. Pharm. 26 (1985) 165 - 174.

Rubinstein, M.H., Tablets. In : Pharmaceutics. The Science of Dosage Form Design. (Aulton, M.E. Eds.) Churchill Livingstone, Edinburgh, 1988, pp.309- 315.

Rudnic, E.M., Chilamkurti, R. and Rhodes, C.T., Further studies of the potential of recording powder flow meters . Drug Dev. Ind. Pharm. 6 (1980) 279 - 289.

Rudnic, E.M., Rhodes, C.T., Welch, S. and Bernardo, P., Evaluation of the mechanism of disintegrant action . Drug Dev. Ind. Pharm. 8 (1982) 87 - 109.

Sadek, H.M., Olsen, J.L., Smith, H.L. and Onay, S., A systematic approach to glidant selection . Pharm. Tech. 6 (2) (1982) 43 - 62.

Samyn, J.C. and Jung, W.Y., In vitro dissolution from several experimental capsule formulations . J. Pharm. Sci. 59 (1970) 169 - 175.

Schirmer, J., Talc. In : Handbook of Pharmaceutical Excipients. (Wade, A. and Weller, P.J., Eds.) 2nd ed., The Pharmaceutical Press, London, 1994, pp.519- 521.

Schmidt, P.C. and Walter, R., Investigation of the cohesion behaviour of powders and their adhesion to a carrier by an electronic tensiometer . Pharmazie 49 (1994) 183 - 187.

Schrank-Junghäni, H., Bier, H.P. and Sucker, H., The measurement of die wall forces to determine the minimum concentration of lubricant needed for tablet formulations. Acta Pharm. Technol. 30 (1984) 224 - 234.

Sell, P. Expert Systems - A Practical Introduction. Camelot press, 1985 through Doukidis and Whitley (1988a).

Senderoff, R.I., Methylcellulose. In : Handbook of Pharmaceutical Excipients. (Wade, A. and Weller, P.J., Eds.) ,2nd ed., The Pharmaceutical Press, London, 1994, pp.306-309.

Shah, A.C. and Mlodozeniec, A.R., Strategies in the development of a tablet formulation of a poorly soluble drug for double-blind clinical studies . J. Pharm. Sci. 66 (1977) 1377 - 1382.

Shah, P.T. and Moore, W.E., Dissolution behavior of commercial tablets extemporaneously converted to capsules . J. Pharm. Sci. 59 (1970) 169 - 175.

Shangraw, R. and Demarest, D.J., A survey of current industrial practices in the formulation and manufacture of tablets and capsules . Pharm. Tech. 17 (1) (1993) 32 - 44.

Shangraw, R.F., Mitrevej, A. and Shah, M., A new era of tablet disintegrants . Pharm. Tech. 4(10) (1980) 49 - 57.

Shortliffe, E., Computer Based Medical Consultations : MYCIN. American Elservier, New York, 1976, through Parayne and Chignell (1988).

Shotton, E. and Leonard, G.S., Effect of intragranular and extragranular disintegrating agents on particle size of disintegrated tablets. J. Pharm. Sci. 65 (1976) 1170 - 1174.

Sims, E. and Withington, R., Description and evaluation of a semi-automatic system for particle size analysis by microscopy . Int. J. Pharm. 17 (1983) 167 - 181.

Simões, S., Sousa, A. and Figueiredo, M., Dissolution rate studies of pharmaceutical multisized powders - a practical approach using the Coulter method. Int. J. Pharm. 127 (1996) 283 - 291.

Skelly, J.P., Van Buskirk, G.A., Savello, D.R., Amidon, G.L., Arbit, H.M., Dighe, S., Fawzi, M.B., Gonalez, M.A., Malick, A.W., Malinowski, H., Nedich, R., Peck, G.E., Pearce, M., Shah, V. Shangraw, R.F., Schwartz, J.B. and Truelove, J., Workshop Report : Scale-Up of immediate release oral dosage forms . Pharm. Res. 10 (1993) 313 - 316.

Skingle, B., An Introduction to the PFES project. In : 10th Inter Workshop on Expert System and Applications. Proceed. Avingnon. 1990, pp. 907 - 921.

Small, L.E. and Augsburger, L.L., Aspects of the lubrication requirements for an automatic capsule filling machine . Drug Dev. Ind. Pharm. 4 (1978) 345 - 372.

Stamm, A., Gissinger, D. and Boymond, C., Quantitative evaluation of the wettability of powders . Drug Dev. Ind. Pharm. 10 (1984) 381 - 408.

Staniforth, J.N. and Ahmed, H.A., Influence of ternary components on lubrication of microcrystalline cellulose following blending with magnesium stearate. J. Pharm. Pharmacol. 39 (Suppl.) (1987) 68P.

Staniforth, J.N., Powder flow. In : Pharmaceutics. The Science of Dosage Form Design. (Aulton, M.E. Eds.) Churchill Livingstone, Edinburgh, 1988a, pp.600- 635.

Staniforth, J.N., Particle size analysis. In : Pharmaceutics. The Science of Dosage Form Design. (Aulton, M.E. Eds.) Churchill Livingstone, Edinburgh, 1988b, pp.564- 580.

Staniforth, J.N., The design and use of tabletting excipients . Drug Dev. Ind. Pharm. 19 (1993) 2273 - 2308.

Staniforth, J.N., Cryer, S. Ahmed, H.A. and Davies, S.P., Aspects of pharmaceutical tribology. In : Pharmaceutical Technology. Tableting Technology. Volume 2. (Compression). (Wells, J.I. and Rubinstein, M.H., Eds.) Ellis Horwood Ltd, Chichester, 1993, pp.189-205.

Steels, L., The deepening of expert systems. In : Perspectives in Artifical Intelligence. Volume 1 Expert Systems : Applications and Technical Foundations. (Campbell, J.A. and Cuena, J., Eds) Ellis Horwood Ltd, New York, 1989, pp. 17 - 23.

Stewart, A.G., Grant, D.J. and Newton, J.M.,The release of a model low-dose drug (riboflavine) from hard gelatin capusle formulations. J. Pharm. Pharmacol. 31 (1979) 1-6.

Stricker, H., Fuchs, S., Haux, R., Rößler, R., Rupprecht, B., Schmelmer, V. and Weigel, S., Das Galenische Entwicklungs-System Heidelberg. Pharm. Ind. 56 (1994) 641 - 647.

Strickland, W.A.J., Nelson, E., Busse, L.W. and Higuchi, T., The physics of tablet compression. Fundamental aspect of tablet lubricant. J. Am. Pharm. 45 (1956) 51 - 58.

Strom, J.G., Crospovidone. In : Handbook of Pharmaceutical Excipients. (Wade, A. and Weller, P.J., Eds.) , 2nd ed., The Pharmaceutical Press, London, 1994, pp.143- 144.

Studebaker, M.L. and Snow, C.W., The influence of ultimate composition upon the wettability of carbon black . J. Phys. Chem. 59 (1955) 973 - 976.

Surén, G., Evaluation of lubricants in the development of tablet formula . Dansk Tidsskr. Farm. 45 (1971) 331 - 338.

Symecko, C.W. and Rhodes, C.T., Binder functionality in tabletted systems . Drug Dev. Ind. Pharm. 21 (1995) 1091 - 1114.

Takahasi, K. Sci. Pap. , Inst. phys. chem. Res. Tokyo 540(26) (1934) 11 through Train (1958).

Tan, S.B. and Newton, J.M., Powder flowability as an indication of capsule filling performance . Int. J. Pharm. 61 (1990a) 145 - 155.

Tan, S.B. and Newton, J.M., Influence of compression setting ratio on capsule fill weight and weight variability . Int. J. Pharm. 66 (1990b) 273 - 282.

Tan, S.B. and Newton, J.M., Influence of capsule dosator wall texture and powder properties on the angle of wall friction and powder-wall adhesion . Int. J. Pharm. 64 (1990c) 227 - 234.

Tan, S.B. and Newton, J.M., Capsule filling performance of powders with dosator nozzles of different wall texture . Int. J. Pharm. 66 (1990d) 207 - 211.

Tan, S.B. and Newton, J.M., Observed and expected powder plug densities obtained by a capsule dosator nozzle system . Int. J. Pharm. 66 (1990e) 283 - 288.

Tan, S.B. and Newton, J.M., Minimum compression stress requirements for arching and powder retention within a dosator nozzle during capsule filling . Int. J. Pharm. 63 (1990f) 275 - 280.

Taudou, A.M., Patau, J.P. and Combes, A.F., Selection of excipients for oral solid forms formulation using a specific computer programme . Journal de Pharmacie de Belgique 49 (1994) 133-144.

Thibert, R., Akbarieh, M. and Tawashi, R., Application of fractal dimension to the study of the surface ruggedness of granular solids and excipients . J. Pharm. Sci. 77 (1988) 724 - 726.

Thouzeau, G. and Taylor, T.W. Safety in Mines Research Establishment Research Report 197 (1961) through Cole (1987c).

Tingsted, J. and Dudzinski, Preformulation studies II : Stability of drug substances in solid pharmaceutical systems. J. Pharm. Sci. 62 (1973) 1856 - 1860.

Train, D. and Hersey, J.A., The use of laminar lubricants in compaction process. J. Pharm. Pharmacol. 12 (1960) 97T - 104T.

Train, D., Some aspects of the property of angle of repose of powders . J. Pharm. Pharmacol. 10 (1958) 127T - 135T.

Travers, D.N., Mixing. In : Pharmceutics. The Science Of Dosage Form Design. (Aulton, M.E. Eds.) Churchill Livingstone, Edinburgh, 1988, pp.550- 563.

Tsuji, K. and Jenkins, K.M., Knowledge based Expert System in pharmaceutical quality control envoiroments . Pharm. Tech. Int. 2 (1990) 51 - 56.

Türkoglu, M., Özarslan, R. and Sakr, A., Artificial neural network analysis of a direct compression tabletting study. Eur. J. Pharm. Biopharm. 41 (1995) 315 - 322.

Turner, J., Product Formulation Expert System. DTI Manufacturing Intelligence newsletter 12 (1991) 12 - 14.

Tyrer, J.H., Eadie, M.J., Sutherland, J.M. and Hooper, W.D., Outbreak of anticonvulsant intoxication in an Australian city . Br. Med. J. 2 (1970) 217 - 273.

Umprayn, K. and Mendes, R.W., Hygroscopicity and moisture adsorption kinetics of pharmaceutical solids : A review . Drug Dev. Ind. Pharm. 13 (1987) 653 - 693.

United States Pharmacopoeia / The National Formulary (USP23/NF18). United States Pharmacopeial Convention, Inc., Rockville, MD 1994 (Official from January 1,1995).

Varthalis, S. and Pilpel, N., Anomalies in some properties of powder mixtures . J. Pharm. Pharmacol. 28 (1976) 415 - 419.

Varthalis, S. and Pilpel, N., The action of colloidal silicon dioxide as a glidant for lactose, paracetamol, oxytetracycline and their mixture . J. Pharm. Pharmacol. 29 (1977) 37 - 40.

Vidal (see Dictionnaire Vidal)

Wade, A. and Weller, P.J., Handbook of Pharmaceutical Excipients. 1st ed., The Pharmaceutical Press, London, 1986.

Wade, A. and Weller, P.J., Handbook of Pharmaceutical Excipients. 2nd ed., The Pharmaceutical Press, London, 1994.

Wade, A. and Weller, P.J., Appendix II : HPE Laboratory Methods. In : Handbook of Pharmaceutical Excipients. (Wade, A. and Weller, P.J., Eds.) 2nd Ed., The Pharmaceutical Press, London, 1994, pp.625- 632.

Wadell, H. Physics 5 (1934) 281 - 291 through Washington (1992).

Wadke, D.A. Serajuddin, A.T.M. and Jacobson, H., Preformulation testing. In : Pharmaceutical Dosage Forms : Tablets. Volume 1. (Lieberman, H.A. Lachman, L. and Schwartz, J.B., Eds.) 2nd ed., Marcel Dekker, Inc., New York, 1989, pp.1- 69.

Walking, W.D., Povidone. In : Handbook of Pharmaceutical Excipients. (Wade, A. and Weller, P.J., Eds.) 2nd ed., The Pharmaceutical Press, London, 1994, pp.392- 399.

Wang, L. and Chowhan, Z.T., Drug-excipient interactions resulting from powder mixing. V.Role of sodium lauryl sulfates . Int. J. Pharm. 60 (1990) 61 - 78.

Washburn, E.W., The dynamics of capillary flow . Phys. Rev. 17 (1921) 273 - 283.

Washington, C., Particle Size Analysis in Pharmaceutics and Other Industries. Theory And Practice. (Washington, C. Eds.) Ellis Horwood, New York, 1992, pp.9- 39.

Weiss, S.M. and Kulikowski, C.A., A practical guide to designing Expert Systems. Rowman and Allenheld, 1984 through Doukidis and Whitley (1988a).

Weller, P.J., Croscarmellos Sodium. In : Handbook of Pharmaceutical Excipients. (Wade, A. and Weller, P.J., Eds.) 2nd ed., The Pharmaceutical Press, London, 1994, pp.141- 142.

Wells, J.I. and Aulton, M.E., Preformulation. In : Pharmaceutics. The Science of Dosage Form Design. (Aulton, M.E. Eds.) Churchill Livingstone, Edinburgh, 1988, pp.223 - 253.

Wenzel, R.N. Ind. Eng. chem. 28 (1936) 988 - 994 through Cook (1978).

Whiteman, M. and Ridgway, K., Particle shape discrimination using slotted sieves . Drug Dev. Ind. Pharm. 12 (1986) 1995 - 2013.

Whithey, R.J. and Mainville, C.A., A critical analysis of a capsule dissolution test . J. Pharm.Sci. 59 (1969) 1120 - 1126.

Williams, J.C. and Birks, A.H., The comparison of the failure measurements of powders with theory. Powder Technol. 1 (1967) 199 - 206.

Winstanley, G., A rule-based problem solving approach. In : Program Design. For Knowledge Based Systems. Sigma Press, Wilmslow, 1987a, pp. 93 - 108.

Winstanley, G., LISP. In : Program Design. For Knowledge Based Systems. Sigma Press, Wilmslow, 1987b, p. 35.

Wolen, R.L., Carmichael, R.H., Ridolfo, A.S., Thompkins, L., Ziege, K.A., The effect of crystal size on bioavailability of Benoxaprofen studies utilizing Denterium labeled drug. Biomed. Mass Spectrom. 6 (1979) 173 - 178.

Wood, M., Expert systems save formulation time. Laboratory Equipment Digest, 12 (1991) 17 - 19.

Woodhead, P.J., The influence of powder bed porosity variations on the filling of hard gelatin capsules by a dosator system. PhD Thesis. University of Nottingham, 1980, pp. 307 - 315.

Woodhead, P.J., Newton, J.M., Hardy, J.G. and Jackson, S.A., A Gamma-ray attenuation technique for assessing the distribution of prosity in powder bed . J. Pharm. Pharmacol. 31 (1979) 72P.

Yamashiro, M., Yuasa, Y. and Kawakita, K., An experimental study on the relationships between compressibility, fluidity and cohesion of powder solids at small tapping numbers. Powder Technol. 34 (1983) 225 - 231.

Yang, W.H. and Brooke, D., Rate equation for solid state decomposition of aspirin in presence of moisture. Int. J. Pharm. 11 (1982) 271-276.

York, P., Application of powder failure test equipment in assessing effect of glidants on flowability of cohesive pharmaceutical powder . J. Pharm. Sci. 64 (1975) 1216-1220.

York, P., Studies of the effect of powder moisture content on drug release from hard gelatin capsules . Drug Dev. Ind. Pharm. 6 (1980) 605 - 627.

York, P., Analysis of moisture sorption hysteresis in hard gelatin capsules, maize starch, and maize starch : drug powder mixtures . J. Pharm. Pharmacol. 33 (1981) 269 - 273.

York, P., The design of dosage forms. In : Pharmaceutics. The Science of Dosage Form Design. (Aulton, M.E. Eds.) Churchill Livingstone, Edinburgh, 1988, pp.8- 9.

Young, T., An essay on the cohesion of fluids. Phil. Trans. 95 (1805) 65 through Buckton (1988).

Zajic, L. and Buckton, G., The use of surface energy values to predict optimum binder selection for granulaitons. Int. J. Pharm. 59 (1990) 155 - 164.

Zografi, G. and Tam, S.S., Wettability of pharmaceutical solids : Estimation of solid surfaces polarity. J. Pharm. Sci. 65 (1976) 1145 - 1149.

Appendix I

Input Package for acetylsalicylic acid

Please note that the Input Package enclosed is of a version that was used at the time of the study. A newer version of the Input Package is now available.

USER'S INFORMATION SHEET

Expert System for Formulation Support of Hard Gelatin Capsule

Author : *Samantha Lai
Supervised by : *Prof J M Newton and *Dr F Podczeck

Limitation of this expert system:
This system is designed for the formulation of hard gelatin capsules to be filled with powder or granules. At this stage it can only be used in formulae that contain one drug. It gives advice on how to formulate the drug into the capsules and consideration may be necessary for different types and settings of filling machines. It is your responsibility to consider any problem related to absorption of the drug from the gastrointestinal tract and the stability testing of the product.

You will require the following information about the drug

1. **Dose** or possible range of dose levels
2. Anticipated **particle size**
   The expert system uses the following definitions :

<10 μm	very fine
10 - 50 μm	fine
>50 - 100 μm	medium
>100 - 150 μm	large
>150 μm	coarse

3. **Solubility** of drug in water
   The expert system uses the following definitions :

<1 - 30 parts of water per 1 part of drug	solubility class1
<30 - 1000	solubility class2
>1000	solubility class3

4. Indication of **wetting** properties
5. Indication of **adhesion** to metal
6. Minimum and Maximum **bulk density** of drug
7. Drug **compatibility** with excipients :
   In cases, where the answer is 'don't know', the system would go through its existing records to check the possibility of incompatibility. If no record is found, the drug would be treated as 'compatible with the excipient'.

THIS SHEET SHOULD BE KEPT BY THE USER

INPUT PACKAGE

Please fill in all required information

The School of Pharmacy
Company name : .....

Samantha
Contact name : .....

University of London, 29/39 Brunswick Square, London
address : .....

tel no : ..... **fax no : .....**

Date : .....

Specifications of drugs, excipients and products

Which of the following specifications would you use for drugs, excipients and product?

√ British Pharmacopoeia (BP)
European Pharmacopoeia (EP)
United State Pharmacopoeia (USP)
Japan Pharmacopoeia (JP)

Others .....

Identification of product

In this program, information about the drug including its name, properties and proposed formula would be stored in the database which provide information associated with the continued development of the expert system. For cases where such information is confidential, please use a coded drug name and retain this coded name for future reference.

Drug name/Drug Registration number/Coded drug name :
acetylsalicylic acid
.....

Identification of properties of drug

1) ***Dosage of drug*** (mg) : ... 500...

If dose > 1000mg:

Are the capsules being swallowed? y/n

If yes: Can the dose be given as two capsules instead? y/n
If no: Do you insist on using this dose? y/n
If no: What is the new dose? Dose : .....

2) ***Particle shape of drug*** : needle ? (y)/~~n~~

If yes, do you expect this to cause problems with powder flow?
~~y~~/(n)

3) ***Mean particle size of drug*** (μm) : ....113 (large).....

(The mean particle size should be based on 'weight distribution')

For particles of needle shape, please give the mean length of the longest dimension

If the particle size is not known, it is important to **write down** the range (coarse, large, medium, fine or very fine) using the guideline in Appendix A.

4) ***Solubility of drug*** : Please answer either a) or b)

a) no. of parts of water to 1 part of drug : .....1 in 300.....

b) solubility classes : (please tick one)

√	Solubility Classes	part of water per 1 part of drug
	1	<1 - 30
√	2	>30 - 1000
	3	>1000

5) ***Does the drug wet with water?*** (y)/~~n~~ don't know

If don't know : Does the chemical structure indicate dominant hydrophobic character? y/n don't know

6) ***Does the drug adhere to metal surfaces?*** (y)/~~n~~ don't know

If don't know : Place the powder in a metal container and turn the container round and observe whether the powder adheres to the metal surface.

7) For dose greater than 50mg, it is essential to have the following information :

Minimum bulk density of drug (g/cm^3) : ....0.7022...

Tapped bulk density of drug (g/cm^3) : ....0.788....

(See Appendix A if bulk densities are not known)

8) Is it your company policy to granulate the drug mixture under all circumstances?

(~~y~~/n)

Identification of compatibility of drug with excipients

8) ***Is the drug compatible with the excipients listed below :***

If none of the following diluent / disintegrant / lubricant / glidant / wetting agent are to be used in your company, please suggest your own choice and amount used (%w/w), except for diluent, in spaces provided under 'others'. **Please also make sure that this excipient is compatible with the drug.**

*At any stage, **if the default amount is not agreed**, please write next to the excipient the amount you prefer to use in terms of %w/w.*

a) *Gelatin :*

A definite answer must be given to enable the system to proceed.
Is the drug moisture sensitive ? (y)/n
if yes : Reminder : the water content in the gelatin shell may affect the stability of drug

Is the drug stable in gelatin capsules? (y)/n

b) *Diluent :*

name	compatible with drug?	Acceptability to company
lactose	(y)/ n don't know	(y)/ n
maize starch	(y)/ n don't know	(y)/ n
pregelatinised starch	(y)/ n don't know	(y)/ n
microcrystalline cellulose	(y)/ n don't know	(y)/ n

others : name ..... - Is it soluble in water? y/n
- Does it belong to 'sugar' family? y/n

c) *Disintegrant :*

name	default amount	compatible with drug?	Acceptability to company
croscarmellose sodium	2 (%w/w)	(y)/ n don't know	y / n
crospovidone	3	(y)/ n don't know	y / n
maize starch	10	(y)/ n don't know	y / n
pregelatinised starch	10	(y)/ n don't know	y / n
sodium starch glycolate	5	(y)/ n don't know	y / n
alginic acid	8	(y)/ n don't know	y / n

others: name .....
amount .....%w/w

d) *Lubricant*

name	default amount	compatible with drug?	Acceptability to company
magnesium stearate	1 %w/w	~~y~~ / (n) don't know	(y) / ~~n~~
glycerol monostearate	2	(y) / ~~n~~ don't know	(y) / ~~n~~
stearic acid	0.5	(y) / ~~n~~ don't know	(y) / ~~n~~
microcrystalline cellulose	10	(y) / ~~n~~ don't know	(y) / ~~n~~
talc	5	(y) / ~~n~~ don't know	(y) / ~~n~~

others: name .....
amount .....%w/w

e) *Glidant*

name	default amount	compatible with drug?	Acceptability to company
colloidal silicon dioxide	1 %w/w	(y) / ~~n~~ don't know	(y) / ~~n~~
talc	5 %w/w	(y) / ~~n~~ don't know	(y) / ~~n~~

others: name .....
amount .....%w/w

f) *Wetting agent*

name	default amount	compatible with drug?	Acceptability to company
sodium lauryl sulphate	0.5 %w/w	(y) / ~~n~~ don't know	(y) / ~~n~~
Tween 80	1 %w/w	(y) / ~~n~~ don't know	~~y~~ / (n)

Please note that Tween products can only be used in wet granulation procedures. Please enter an alternative choice.

others: name .....
amount .....%w/w

If your answer is 'don't know', the system would check whether it contains any information on compatibility. However, it is still your responsibility to make sure that the drug does not interact with any of the excipient used.

Properties of excipients

9) ***Tapped density of excipients used by your company : (g/cm³)*** **:**

The properties of excipients vary from manufacturer to manufacturer. The tapped bulk density of the excipients used by your company should therefore be used. The measurement should be based on a typical batch which you would expect to use.

a) *Diluent:*

lactose	-fine	.....	or	don't know √
	-medium	...0.96...		or don't know
	-coarse	.....	or	don't know √
microcrystalline cellulose (e.g. Avicel PH101)	-medium	.....	or	don't know √
	-coarse (e.g. Avicel PH102)	.....	or	don't know √
maize starch		.....	or	don't know √
pregelatinised starch		.....	or	don't know √
others (if any)		.....	or	don't know

b) *Disintegrant:*

croscarmellose sodium	.....	or	don't know √
crospovidone	.....	or	don't know √
sodium starch glycolate	...0.3...	or	don't know √
alginic acid	.....	or	don't know √
others (if any)	.....	or	don't know √

If the value given for the tapped density of any of the excipients recommended by the system is 'don't know', a default value based on information from the database of the system would be used.

Information about the manufacturing conditions

10) ***Capsule size*** : (Please cross out the capsule size that you will not consider)

~~000~~ ~~2~~
~~00~~ ~~3~~
~~0el~~ ~~4~~
(0) ~~5~~
~~1~~

11) ***Maximum fill weight :***
Is there any restriction in capsule fill weight for this formulation? y/~~n~~

if yes : What is the maximum fill weight ? .....600.....mg

In most cases, the system would be able to deduce a formula based on the above information. However, there are also some cases where the following information is required.

12) For cases where the chosen capsule size is smaller than the calculated minimum capsule size, the drug mixture must be densified before filling into the capsule shell. Please choose one of the following method to densify the drug mixture. (Please tick one)

a) by altering compression force or dosator height of filling machine -
The system can work out whether it is feasible to compress the drug mixture by increasing the compression force of the filling machine. The value of constant a(%) in Kawakita's equation is needed.

Do you know the a (%) in Kawakita's equation? y/n
if yes : a(%) in Kawakita's equation = ...
if no : please perform the following test using a mechanical tapping device :
Measure the weight of drug. Measure the initial volume of drug. Tap the measuring cylinder containing the drug for n times and measure the volume of drug after n taps. Repeat this process until the volume of drug becomes constant.

weight of drug : .....g

no. of taps	0										
vol. of drugs (cm^3)											
no. of taps											
vol. of drugs (cm^3)											

√ b) granulation

13) For cases where ***granulation*** is required, please answer the following questions:

a) Is the drug water sensitive in terms of granulation? y/~~n~~

b) Would you prefer wet or dry granulation? wet / dry (no preference)

c) Do you have a standard granulation liquid? y/~~n~~

if yes : The standard granulation liquid is .....water.....

d) Are you able to use organic liquids as granulation liquid? ~~y~~/n

if yes : What organic granulation liquid would you prefer?

(please tick one)

√	name	Is it compatible with drug?	Is it soluble in this liquid?
	ethanol	y/n or don't know	y/n or don't know
	methanol	y/n or don't know	y/n or don't know
	isopropyl alcohol	y/n or don't know	y/n or don't know
	acetone	y/n or don't know	y/n or don't know

f) Binder : Would you use PVP as a binder? y/~~n~~

if yes : Is the drug compatible with polyvidone? y/~~n~~

if no : Which binder would you use? (write the amount to be used if the default is not agreed)

name	default amount (%w/w)	compatible with drug?	Acceptability to company
pregelatinised starch	10	y / n	y / n
gelatin	5	y / n	y / n
hydroxypropyl-methylcellulose	3	y / n	y / n
alginic acid	2	y / n	y / n
ultra-amylopectin	1.5	y / n	y / n

g) Do you have a standard procedure for:
wet granulation? ~~y~~/n
dry granulation? ~~y~~/n

If the answer is 'no' or 'don't know', the system would suggest a brief guideline for such processes.

Appendix A

Estimation of Particle Size

In cases where particle size of the drug is not known, a rough estimation may be useful :

Put a tiny sample of drug on a dark surface and do the following observation :

a) If individual particles can be seen and can be easily distinguished from each other, the particle size must be **LARGE or COARSE.**

b) If individual particles can be seen but cannot be easily distinguished from each other, the particle size would be **MEDIUM.**

c) If individual particles cannot be seen by human eyes, the particle size is **FINE.**

If the drug is produced by micronisation, the particle size is **VERY FINE.**

Bench Test for Bulk Densities of Drug

In cases where the tapped and minimum bulk density of drug is not known, the following bench test may be useful :

a) Weigh the loose powder in the container. g = weight. Estimate the volume of powder in the container. Usually the size of the container is somewhere on the bottom. By observing the approximate proportion of powder in the container, the volume can be determined. v = volume. The approximate minimum bulk density is g / v.

b) To determine the approximate tapped density, step a) is repeated after tapping the container of drug on the bench for approximately 100 times.

Thank you very much for providing the above information. This information will be fed into the

Appendix II

Output Package for acetylsalicylic acid

Contents in the Output Package

HARD GELATIN CAPSULE
Expert System

**********Pharmaceutics Department**********
*******The School of Pharmacy, University of London*******

Tel:+44 171-753-5852 Fax : +44 171-753-5942
Address : 29/39 Brunswick Square, London WC1N 1AX, UK
Contact: Miss Samantha Lai

Date : 01/04/96

Name of company : The School of Pharmacy
Name of contact for this product : Samantha

DRUG NAME/DRUG REGISTRATION NO./CODED NAME :

acetylsalicylic acid

DRUG PROPERTIES:

1. Moisture sensitive : yes
2. Compatible with gelatin capsules : yes
3. Dose (mg) : 500.00
4. Particle size (Estimate) : Large
5. Needle shape that causes problems in powder flow : no
6. Solubility : medium soluble
   (300.0 parts of water per part of drug)
7. The drug wets with water : yes
8. The drug adheres to metal surface : yes
9. Flow properties :

   Minimum bulk density (g/ccm) : 0.702
   Tapped bulk density (g/ccm) : 0.788
   Carr's Compressibility (%) : 10.888
   Carr's Classification : good

NOTE :

The volume of the drug mixture may be too large to fit into the capsule.
To reduce volume of drug mixture :

By granulation - see Summary

CAPSULE SIZE :

Minimum capsule size calculated : 00
Agreed Capsule size : 0
Volume of agreed Capsule Shell (ccm): 0.68

SUMMARY:

Formula	%w/w	per capsule(mg)
acetylsalicylic acid	92.9	500.0
sodium starch glycolate	5.1	27.2
glyceryl monostearate	2.0	10.8

Granulation:
dry granulation

capsule wt: 538.0

*** *** ***

Expected capsule fill volume (ccm): < 0.68

Capsule size = 0

SCALE UP TO 1 KG

Formula	1 kg (g)
acetylsalicylic acid	929.4
sodium starch glycolate	50.5
glyceryl monostearate	20.1

*PLEASE NOTE :

The amount of lubricant recommended in this formulation
does not include the amount needed for the granulation process.
The predicted capsule fill weight may therefore be altered
as well.

SPECIFICATION :

The specification of drugs, excipients and product in this program
is based on BP.

LIST OF EXCIPIENTS USED :

Diluent : not required for the chosen capsule size

Disintegrant : sodium starch glycolate

Reason : this is a medium soluble drug, a medium strength disintegrant is chosen

Lubricant : glyceryl monostearate
Reason : incompatibility to magnesium stearate, therefore an alternative lubricant is chosen

Glidant : nil
Reason : no glidant is required if granulation process is used

Wetting agent : nil
Reason :
drug wets with water
medium soluble drug

GRANULATION :

Type of Granulation : dry
Reason : to increase bulk density of drug mixture and to prevent decomposition by wet aqueous granulaiton

Brief Guideline of procedure :

Mix the drug, filler, disintegrant and an appropiate amount of lubricant together and form slugs.

The slugs are ground first and then mixed with the recommended amount of lubricant (see formula) and then filled into the capsule shell.

FILLING CONDITION

1. The drug mixture should be filled at the tapped bulk density of the mixture.

2. At this stage, the recommendation of this system is based on dosator nozzle filling machine.

TEST TO BE PERFORMED

The above suggested formula should be tested according to BP and should pass the following test :

1) Uniformity of weight test BP

2) Disintegration test BP

3) Dissolution test BP is recommended
if such test is developed for this drug

OPTIMIZATION TECHNIQUES

The following remarks could be interesting to you, if the suggested formula resulted in capsules which did not pass some or all of the Pharmacopoeia tests, or if it did not satisfy your own standards for a good capsule formulation.

Optimization is a mathematical method to identify the most advantageous combination of variables influencing the properties of a dosage form. The use of optimaztion techniques requires a set of experiments which are in a logical relation to each other, e.g. by variation of the variables involved in the formulation problem. Usually such experiments are organised in a statistical design, and you will find a useful introduction into this subject in the book by L. Davies 'Efficiency in research, development and production : The statistical design and analysis of chemical experiments.' (Roy. Soc. Chem. Cambridge 1993).

Factorial designs of the type n(exp 2) or n(exp 3) are very common in Pharmaceutics. Occasionally composite designs are used. However, with two or three levels per variable all the experiments have to be performed, before a judgement can be made. This appears inappropiate if e.g. it is known that only the lubricant out of a set of excipients needs to be varied to improve the dosage form. Therefore, a design which can be fractionated according to the formulation purpose will be desirable. Again, there are several designs possible, but the authors of the Expert System have had good results from the Centre of Gravity Design (CGD) (a type of Composite Design), first reported by Podczeck and Wenzel (Pharm. Ind. 52 (1990) 230). Hence the following suggestions are based on such a design. Imagine your formula suggested by the Expert System contains a disintegrant D, a lubricant L and a filler F. The setup of a full CGD would be based on the formula suggested by the Expert System as the Centre of Gravity (CG), because the Expert System used a default concentration for any excipient, which is equivalent to the commonly used concentration according to the literature (data base I and II). The filler concentration is always adjusted to meet the needs to fill the formula in a certain capsule shell size and hence does not play a role in the statistical design. Therefore, the concentrations of D and L need to be varied. Often the effects excipients produced are non-linear and hence the concentrations will be varied around the CG. Thus, the Expert System calculates excipient levels above and below the CG level. In total there will be 5 levels per excipient, including the CG level. Furthermore, interactions between the excipients may occur, and therefore interaction terms on two levels will be proposed by the Expert System.

Generally there are now two ways to proceed with the CGD suggested by the Expert System. The mathematically sophisticated way would be to perform all experiments of

the design and to use an optimization package afterwards to calculate the optimal formula. However, this might result in a series of experiments. As mentioned above there might have been just a flow problem resulting in non-uniformity of fill weight, and all the other Pharmacopoeia tests gave satisfactory results. Hence the CGD should be fractionated. This special design allows such a fractionation to be performed easily. If only the level of L needs to be optimized than one uses only the experiments where L is varied. These are in fact 4, and including the CG point the minimum number of 5 points to use mathematical optimization has been fulfilled. The optimum can then be found either using a simple diagram to illustrate the relationship between L and the formulation properties, or optimization software can be consulted. In the unlikely event that a change in L to its proposed optimal concentration results in e.g. unsatisfactory dissolution results, the same procedure can then be repeated using D, and the complete design can be used if necessary.

The following pages will list for you the CGD for your capsule formula. First the experiments along the centre axes are listed. Experiments X1, X2, X4, X5 are always listed. The missing value of X3 is the CG, i.e. your recommended formula, which you will already have tested. The first table tells you the concentraitons [%], whereas the second table gives you details about the capsule fill weight and the actual absolute amount of the excipients. Secondly the interaction terms are listed. Again you will find two tables listing the relative concentrations and the absolute amount of excipients.

If there are any queries about the CGD and how to use it, please do not hesitate to contact us for further information. We would also appreciate to hear about the optimal formula you finally obtain, because this will help us to improve the forecasting by the Expert System. Thank you very much for your assistance.

*Denote :

Wt = Capsule Fill Weight
F = Filler
D = Disintegrant
L = Lubricant
G = Glidant
W = Wetting Agent
B = Binder

STATISTICAL DESIGN :

1) Centre axes - variation of quanitiy of only one excipient

a) %w/w of excipients used :

The Recommended Formula - Centre of the design

no	D	L
D1	2.0	2.0
D2	3.5	2.0
-	Centre of Gravity	-
D4	6.5	2.0
D5	8.0	2.0
L1	5.0	1.0
L2	5.0	1.5
-	Centre of Gravity	-
L4	5.0	2.5
L5	5.0	3.0

b) Amount of excipients used (mg):

The Recommended Formula - Centre of the design

no	Wt	D	L
D1	521.0	10.6	10.4
D2	529.0	18.4	10.6
D4	546.0	35.1	10.9
D5	556.0	44.9	11.1
L1	532.0	26.7	5.3
L2	535.0	27.0	8.0
L4	541.0	27.5	13.5
L5	544.0	27.7	16.3

2) INTERACTION TERMS - variation of quantity of two excipients

a) %w/w of excipients used :

no	D	L
DL 1	3.5	1.5
DL 2	3.5	2.5
DL 3	6.5	2.5
DL 4	6.5	1.5

b) Amount of excipients used (mg):

no	Wt	D	L
DL 1	526.0	18.1	7.9
DL 2	532.0	18.7	13.3
DL 3	549.0	35.3	13.7
DL 4	544.0	35.8	8.2

MULTIPLE DOSE OPTION :

The dose is changed by a factor of 0.500
New Dose = 250.0 mg

Based on the recommended formula :
New expected fill weight = 269.0 mg
The volume of the drug mixture of this new dose is 0.34 ccm and
has minimum capsule size of 2

COMMENT :

none

The drug is moisture sensitive hence the drug may
decompose due to water content of the gelatin capsule
shell.

PART 2

YOU HAVE ATTEMPTED TO CHANGED THE FOLLOWING PARAMETER :

dose or other drug properties

THE RECOMMENDED FORMULA MAY BE CHANGED.

DRUG NAME/DRUG REGISTRATION NO./CODED NAME :

acetylsalicylic acid

DRUG PROPERTIES:

1. Moisture sensitive : yes
2. Compatible with gelatin capsules : yes
3. Dose (mg) : 250.00
4. Particle size (Estimate) : Large
5. Needle shape that causes problems in powder flow : no
6. Solubility : medium soluble
   (300.0 parts of water per part of drug)
7. The drug wets with water : yes
8. The drug adheres to metal surface : yes

9. Flow properties :

Minimum bulk density (g/ccm) : 0.702
Tapped bulk density (g/ccm) : 0.788
Carr's Compressibility (%) : 10.888
Carr's Classification : good

CAPSULE SIZE :

Minimum capsule size calculated : 1
Agreed Capsule size : 0
Volume of agreed Capsule Shell (ccm): 0.68

SUMMARY:

Formula	%w/w	per capsule(mg)
acetylsalicylic acid	59.0	250.0
lactose	33.0	140.1
sodium starch glycolate	5.0	21.2
glyceryl monostearate	2.0	8.5
aerosil	1.0	4.2

capsule wt: 424.0

*** *** ***

Expected capsule fill volume (ccm): 0.61

Capsule size = 0

SCALE UP TO 1 KG

Formula	1 kg (g)
acetylsalicylic acid	589.6
lactose	330.5
sodium starch glycolate	50.0
glyceryl monostearate	20.0
aerosil	9.9

SPECIFICATION :

The specification of drugs, excipients and product in this program is based on BP.

LIST OF EXCIPIENTS USED :

Diluent : lactose
Grade : large (101 - 150 microns)
Reason : the drug has large particle size

Disintegrant : sodium starch glycolate
Reason : this is a medium soluble drug, a medium strength disintegrant is chosen

Lubricant : glyceryl monostearate
Reason : incompatibility to magnesium stearate, therefore an alternative lubricant is chosen

Glidant : aerosil
Reason : drug adheres to metal surface
-to prevent adhesion
Aerosil must be sieved before incorporating into the drug mixture
Aerosil must be sieved before incorporating into the drug mixture

Wetting agent : nil
Reason :
drug wets with water
medium soluble drug

FILLING CONDITION

1. The drug mixture should be filled at the tapped bulk density of the mixture.

2. At this stage, the recommendation of this system is based on dosator nozzle filling machine.

TEST TO BE PERFORMED

The above suggested formula should be tested according to BP and should pass the following test :

1) Uniformity of weight test BP

2) Disintegration test BP

3) Dissolution test BP is recommended if such test is developed for this drug

COMMENT :

In the first part, a formulation is derived for 500mg of acetyl-salicylic acid in size 0 capsules. From the Multiple Dose option, it is noted that 250mg dose of the same drug can be formulated into size 2 capsules. However, if the capsule size remains constant, then two formulations will be required to formulate both 500mg and 250mg of acetylsalicylic acid. In Part 2 of this output package, a separate formulation for 250mg dose can be found.

The drug is moisture sensitive hence the drug may decompose due to water content of the gelatin capsule shell.

PLEASE DO NOT FORGET TO LET US KNOW THE RESULT OF THE TESTS PERFORMED

Appendix III

Feedback Report

Please note that the Feedback Report enclosed is of a version that was used at the time of the study. A newer version of the Input Package is now available.

Feedback Report

Expert System for Formulation Support of Hard Gelatin Capsule

Author : * Samantha Lai
Supervised by : *Prof J M Newton and *Dr F Podczeck

The School of Pharmacy

Company name : .....
Samantha
Contact name: .....

tel no : ..... **fax no : .....**

Date : .....

Please use one form for each formula

---

acetylsalicylic acid
Drug Name / Code : .....

Reference No. / Date of Output Package :.....

Results :

1) Scale of experiments : ..... **1 kg** .....

2) Equipment used for filling :

• Filling machine - Type of filling machine : .....**dosator nozzle** .....

• Others : .....

3) Machinability :

Performance : • 1 • 2 • 3 √• 4 • 5

(1 - poor 5 - excellent)

Yield : ..... (e.g. no. of capsules / hour)

Description of problem, if any : .....**no problem** .....

.....

4) Uniformity of weight test : √• pass • fail

mean fill weight : .... **511.1 (average)** .... mg

standard deviation : ..... **9.35** ..... mg

coefficient variation of fill weight : ..... **1.82** .....%

5) Uniformity of content test (if performed) • pass • fail

mean drug content : ..... mg

standard deviation : ..... mg

6) Disintegration Test : √• pass • fail

disintegration time :..**6 min 38 sec (average)**.. mins

standard deviation : ..... mins

7) Dissolution Test : √• pass • fail

method : .... **paddle apparatus (BP)** .....

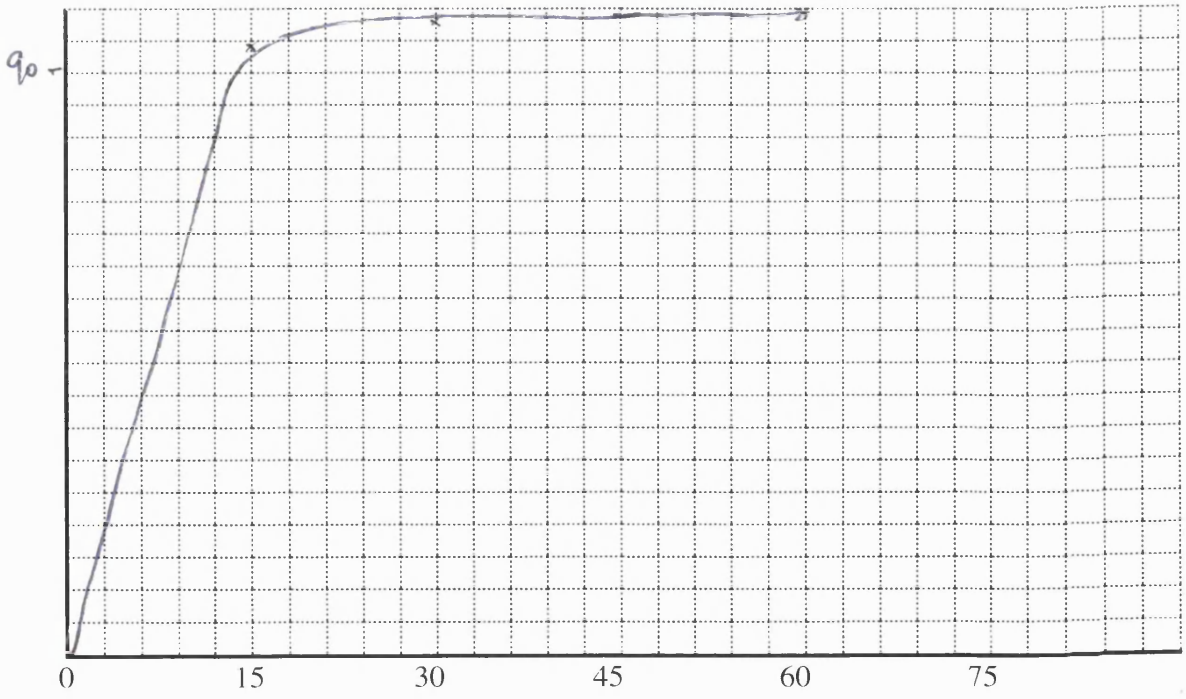
medium : .....**1000 ml distilled water** .....

temperature : .....**37 °C**.....

dissolution profile :

A dissolution curve is desirable, otherwise, please fill in the following table :

Time (mins)	mean % dissolved
0	
15	**94.54**
30	**98.64**
45	**99.66**
60	**100**



% dissolved against time (mins)

8) Granulation process :

Information about the granules :

a) minimum bulk density (g/cm^3) : ..... **0.89**.....

maximum bulk density (g/cm^3) : .....**0.98**.....

b) size distribution of granules :

size range (μm) percentages

.....**not measured** .....
....
....
....
....

c) description of granules : (e.g. compact / bulky)

relatively small granules

.....

d) description of granulation procedures used :

(including sequence of addition of different ingredients in the

formulation, mixing method, drying method and equipment involved)

.....**Dry granulation**.....

.....

.....

.....

.....

.....

9) Did you use the statistical design provided ? • yes √• no

If yes, please write down your optimal formulation :

Ingredients	% w/w	wt. per capsule (mg)
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....

10) General comment :

..... **see Section 4.3.9**.....

.....

.....

.....

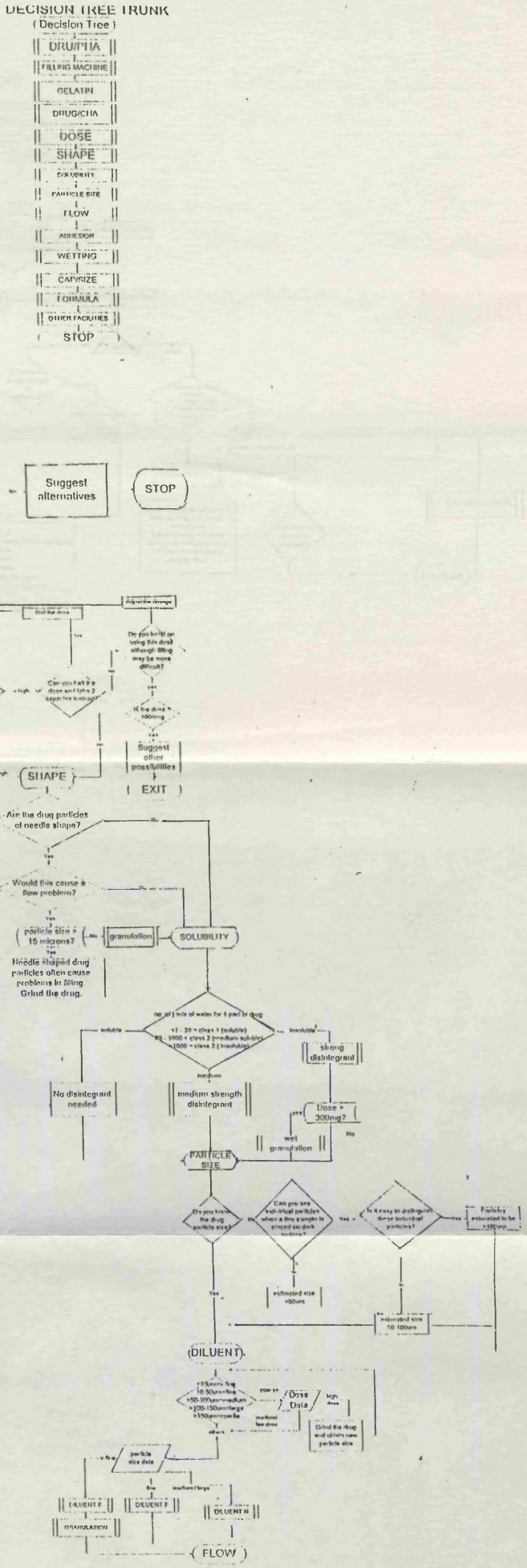
.....

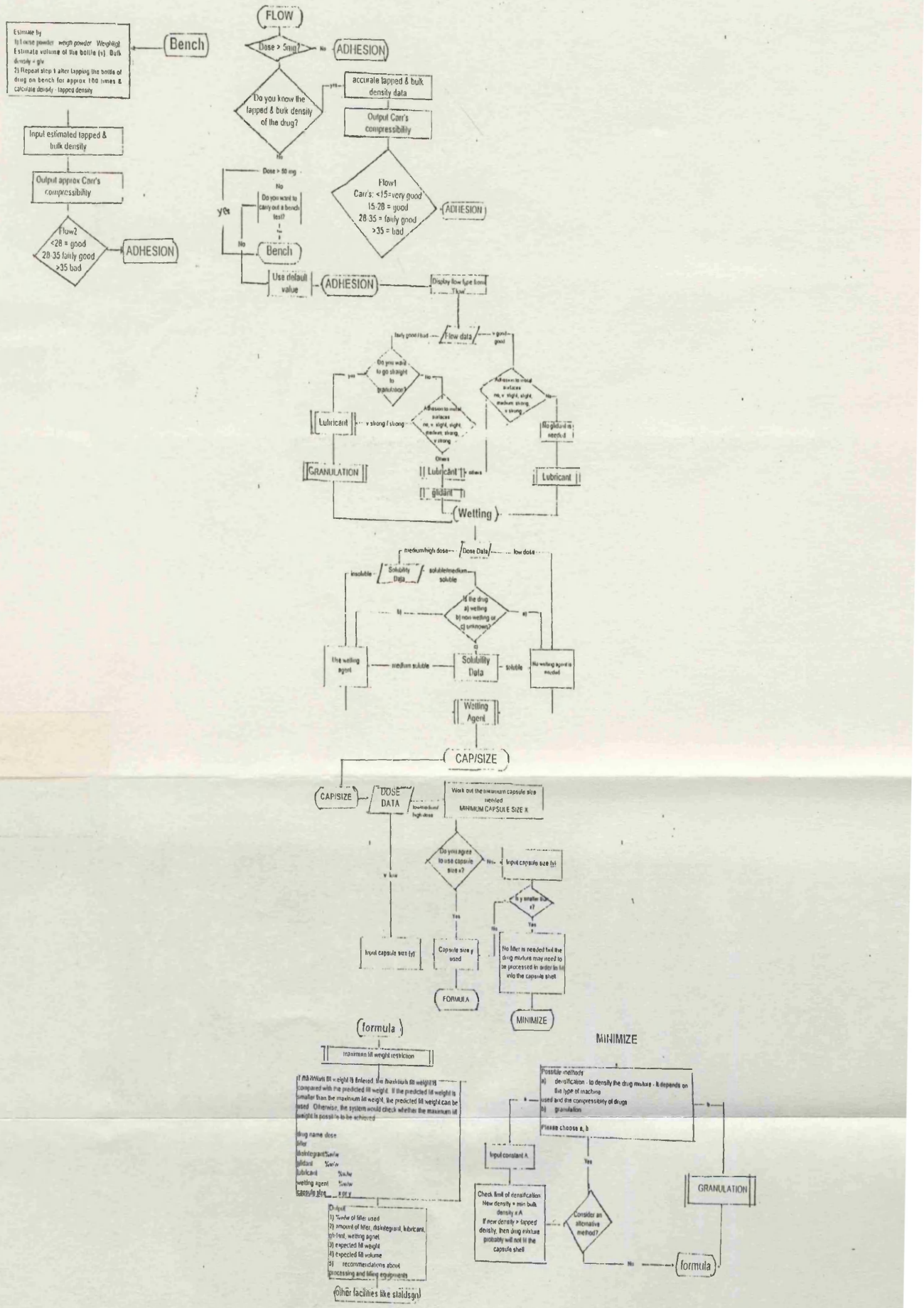
.....

Appendix IV

Overview of the decision tree

Please note that the enclosed overview of the decision tree shows how individual parts of the decision tree (Chapter 3) come together to build up the overall decision tree. The smaller branches of the decision tree is not shown. Please see details in Chapter 3.


DECISION TREE TRUNK
(Decision Tree)
DRUGTIA
FILLING MACHINE
GELATIN
DRUGICHA
DOSE
SHAPE
SOLUBILITY
PARTICLE SIZE
FLOW
ADHESION
WETTING
CAPSIZE
FORMULA
OTHER FACILITIES
STOP
(GELATIN)
Is the drug moisture sensitive?
Is drug believed to be stable in hard gelatin capsules?
Suggest alternatives
STOP
DOSE
DOSE DATA
(VLOW)
DILUENT
medium strength disintegrant
GRANULATION
lubricant
(CAPSIZE)
SHAPE
Suggest other possibilities
(EXIT)
Are the drug particles of needle shape?
Would this cause a flow problem?
particle size > 15 microns?
granulation
SOLUBILITY
Needle shaped drug particles often cause problems in filling. Grind the drug.
soluble
insoluble
strong disintegrant
No disintegrant needed
medium strength disintegrant
Dose > 300mg?
wet granulation
PARTICLE SIZE
(DILUENT)
Dose Data
Grind the drug and obtain new particle size
particle size data
DILUENT F
DILUENT F
DILUENT H
GRANULATION
(FLOW)


FLOW
Dose > 5mg?
No
ADHESION
Yes
Do you know the tapped & bulk density of the drug?
yes
accurate tapped & bulk density data
Output Carr's compressibility
Flow1
Carr's: <15=very good
15-28 = good
28-35 = fairly good
>35 = bad
ADHESION
no
Dose > 50 mg
No
Do you want to carry out a bench test?
yes
No
Bench
Use default value
ADHESION
Display flow type from Flow
Bench
Estimate by
1) Loose powder weigh powder Weight(g)
Estimate volume of the bottle (v) Bulk density = g/v
2) Repeat step 1 after tapping the bottle of drug on bench for approx 100 times & calculate density - tapped density
Input estimated tapped & bulk density
Output approx Carr's compressibility
Flow2
<28 = good
28-35 fairly good
>35 bad
ADHESION
Flow data
fairly good / bad
v good / good
Do you want to go straight to granulation?
yes
No
Lubricant
v strong / strong
Adhesion to metal surfaces no, v. slight, slight, medium, strong, v strong
Others
GRANULATION
Lubricant
glidant
Adhesion to metal surfaces no, v. slight, slight, medium, strong, v strong
No glidant is needed
Lubricant
Wetting
Dose Data
medium/high dose
low dose
Solubility Data
insoluble
soluble/medium soluble
If the drug a) wetting b) non wetting or c) unknown?
a)
b)
c)
the wetting agent
medium soluble
Solubility Data
soluble
No wetting agent is needed
Wetting Agent
CAP/SIZE
CAP/SIZE
DOSE DATA
low/medium/ high dose
Work out the minimum capsule size needed
MINIMUM CAPSULE SIZE X
Do you agree to use capsule size x?
No
Input capsule size (y)
Is y smaller than x?
Yes
No
Yes
Input capsule size (y)
Capsule size y used
No filler is needed but the drug mixture may need to be processed in order to fill into the capsule shell
FORMULA
MINIMIZE
formula
maximum fill weight restriction
If maximum fill weight is entered, the maximum fill weight is compared with the predicted fill weight. If the predicted fill weight is smaller than the maximum fill weight, the predicted fill weight can be used. Otherwise, the system would check whether the maximum fill weight is possible to be achieved
Drug name dose
filler
disintegrant %w/w
glidant %w/w
lubricant %w/w
wetting agent %w/w
Solubility data g/cm3
Output
1) %w/w of filler used
2) amount of filler, disintegrant, lubricant, glidant, wetting agnet
3) expected fill weight
4) expected fill volume
5) recommendations about processing and filling equipments
other facilities like stairs(gn)
MINIMIZE
Possible methods
a) densification - to densify the drug mixture - it depends on the type of machine used and the compressibility of drugs
b) granulation
Please choose a, b
a
b
Input constant A
Yes
Check limit of densification: New density = min bulk density x A
If new density > tapped density, then drug mixture probably will not fill the capsule shell
Consider an alternative method?
No
GRANULATION
formula