INVESTIGATIONS INTO THE FILLING PROPERTIES OF POWDER MIXTURES INTO HARD SHELL CAPSULES

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To Mum and Dad
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ABSTRACT

Powder filled hard gelatine capsules are an established dosage form. There are relatively few literature reports studying the filling behaviour of tamp filling machines due to the large variety of dosing systems available for filling capsules. The aim of the study was to investigate the effect of excipient type and levels and to identify relationships between powder flow, filling performance, disintegration and dissolution of powder mixtures using the tamp filling principle. Two studies using two model drugs were carried out. The first study used theophylline as the model drug due to its poor solubility. The second study used ibuprofen due to its low melting point. The fillers used were lactose and microfine cellulose respectively. Partially pregelatinised starch and magnesium stearate were used in both studies. A central composite factorial design was employed in order to identify and predict relationships. The bulk and tapped densities were determined and the volume as a function of the number of taps was evaluated to give the values for angle of internal flow and the compaction constant T. Carr's compressibility index was calculated from the values of the bulk and tapped densities. Further powder investigations included shear testing. The powders were filled into hard gelatine capsules (size 1) on an instrumented Bosch GKF-400S tamp filling machine with a 19.6mm dosing disk. The capsules were filled at different compression settings. For the theophylline study the tamping force was measured at tamping stations 3 and 4 and for the ibuprofen study two powder bed heights were employed. The optimal filling performance was evaluated by the fill weight, coefficient of fill weight variation, tamping force and density of capsule plug. Disintegration and dissolution tests were also carried out. These powder formulations containing the poorly flowing drug theophylline or the low melting point drug ibuprofen could be satisfactorily filled on the tamp filling capsule machine. For the theophylline study, tamping forces were always greater at tamping station 3 than at station 4, indicating that the capsules were mainly full by the time they reached the third station. The increased powder bed height for ibuprofen slightly increased the capsule fill weight and decreased the coefficient of fill weight variation. It was found that higher compression settings were associated with higher fill weights and lower coefficients of fill weight variation. The flow properties of the powder also influenced the filling of powders into capsules. By altering the concentration of the filler, it was possible to change the flow properties, which further affected the filling performance of the powder mixtures. The type and level of excipients influenced the disintegration and dissolution properties of the powder blend.
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<td>$\rho_{\text{min}}$</td>
<td>minimum (aerated) bulk density</td>
</tr>
<tr>
<td>$\rho_{\text{max}}$</td>
<td>maximum (tapped) bulk density</td>
</tr>
<tr>
<td>CCI</td>
<td>Carr's compressibility index</td>
</tr>
<tr>
<td>HR</td>
<td>Hausner's ratio</td>
</tr>
<tr>
<td>N</td>
<td>number of taps</td>
</tr>
<tr>
<td>C</td>
<td>volume reduction from Kawakita's equation</td>
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<tr>
<td>$V_0$</td>
<td>initial volume of powder</td>
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<tr>
<td>$V_T$</td>
<td>volume of powder after $N$ taps</td>
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<td>a, b</td>
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<td>$\theta$</td>
<td>angle of internal flow</td>
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<td>E</td>
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<td>K</td>
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<td>T</td>
<td>compaction constant</td>
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<td>$d_N$</td>
<td>density reached after number of taps ($N$)</td>
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<td>$d_{\text{min}}$</td>
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<td>$\delta$</td>
<td>angle of internal friction</td>
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<tr>
<td>$\tau_0$</td>
<td>cohesion coefficient</td>
</tr>
<tr>
<td>$\phi$</td>
<td>angle of effective friction</td>
</tr>
<tr>
<td>FF</td>
<td>Jenike's flow factor</td>
</tr>
<tr>
<td>$\tau$</td>
<td>shear stress</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>normal stress</td>
</tr>
<tr>
<td>$f_c$</td>
<td>unconfined yield strength</td>
</tr>
<tr>
<td>$\sigma_m$</td>
<td>major principal stress</td>
</tr>
<tr>
<td>CTD</td>
<td>cumulative tamping distance</td>
</tr>
<tr>
<td>BH</td>
<td>bed height</td>
</tr>
<tr>
<td>CFV</td>
<td>coefficient of fill weight variation</td>
</tr>
<tr>
<td>$R^2$</td>
<td>linear determinant (regression analysis)</td>
</tr>
<tr>
<td>PGS</td>
<td>pregelatinised starch</td>
</tr>
<tr>
<td>MFC</td>
<td>microfine cellulose</td>
</tr>
<tr>
<td>MS</td>
<td>magnesium stearate</td>
</tr>
</tbody>
</table>
CHAPTER 1

INTRODUCTION
Chapter 1 - Introduction

1.1 DEFINITION OF A CAPSULE

The word "capsule" originates from the Latin word "capsula" meaning a small box or container. Pharmaceutically, a capsule is used to describe a solid oral dosage form usually made from gelatine, which is filled with medicine to produce a unit dose (Jones, 1987a). Depending on the nature of the shell, capsules can be classified as either hard or soft. The hard capsule consists of two pieces, a cap and a body. The cap has a slightly larger diameter than the body, thus fitting over the body to form a sealed unit. The hard capsules are produced and filled in separate operations, unlike the soft gelatine capsules, which are manufactured and filled in one operation. The soft gelatine capsule is a one-piece container and has variable shape. Most pharmaceutical capsule products manufactured today are of the hard type (Jones, 1987a).

1.2 HISTORICAL BACKGROUND - THE INVENTION OF CAPSULES

The gelatine capsule was invented in the first half of the nineteenth century by a pharmacy student called Mothes as an attempt to mask the taste of medicinal substances (Jones and Turner, 1974). These soft capsules were formed by dipping leather sacs into gelatine solutions, which were filled with a pipette and sealed with a drop of molten gelatine (Augsburger, 1995). The patent for the gelatine capsule was filed in Paris in 1834 by Mothes and Dublanc. In the following year capsules were being manufactured as far apart as New York and Berlin (Jones, 1988; Jones, 2001).

The hard two-piece gelatine capsule was invented by J.C. Lehuby in 1846 (Jones and Turner, 1974). It consisted of two pieces, the cap and the body and resembled the modern hard gelatine capsule. In Lehuby's patent, the capsule shells were produced by dipping silver plated metal moulds into a gelatine solution. The film was then dried, cut to length and the two halves joined together. The performance of these capsules depended on the accuracy with which the cap and the body were made (Jones, 1987a).

The first manufacture of the hard two-piece gelatine capsules on a commercial scale was by F.A. Hubel in 1874 (Jones and Turner, 1974). Pieces of iron wire were set onto wooden blocks and used as moulds. The moulds were of different diameters, one for the body and one for the cap, so that the two halves obtained an accurate fit. These moulds were dipped into a gelatine solution and withdrawn to produce a film, which whilst still wet, was cut to the required length to form the capsule pieces. The capsule pieces were then allowed to dry and joined together (Jones and Turner, 1974).
The current numbering system used for the classification of capsule sizes was introduced by Hubel. In 1875, Hubel was making capsules in three standard sizes, 1, 2 and 3 (Jones, 1987a).

The only significant change in design of the hard gelatine capsule since the time of Lehuby has been the development of the self-locking capsule first introduced and patented by Eli Lilly (Jones, 1987a). Originally two methods of sealing the capsule were used, banding and dot sealing (as used by Park Davis & Co.) (Cole, 1987a), but both had the disadvantage of being time consuming, costly and spoiling the appearance of the capsule (Jones and Turner, 1974).

Hard gelatine capsules were made self-locking by introducing indentations or grooves on the inside of the cap and the external surface of the body (Cole, 1987a). Indentations formed further down the cap provided a pre-lock, which prevented the empty capsules separating during transit from the manufacturer, whilst allowing easy separation for filling. When closed together after filling, a lock was created between the cap and body portions so that there was a final holding force between the two pieces. This was to ensure that the contents did not leak during packaging or distribution (Cole, 1987a). Each company uses its own brand name to market their self-locking capsules (Cole, 1987a). The main suppliers of self-locking capsules today are Shionogi Qualicaps division of Shionogi, the Capsugel division of Pfizer Limited and to some extent R. P. Scherer.

Today, empty hard shell gelatine capsules are manufactured in a similar manner to those produced by F.A. Hubel in 1874 (Jones and Turner, 1974). The process involves dipping greased metal pin-like moulds into a molten gelatine mixture. The resultant films are dried, stripped and joined together in an automated process (Jones, 1987b).

1.3 PROPERTIES OF HARD SHELL CAPSULES

The choice of a hard capsule as a dosage form may be based on the following criteria:

1.3.1 Acceptability

Capsules are an elegant dosage form. Capsules are generally recognised as being easier to swallow compared with tablets because the tongue reflexively lines up the capsule end on for swallowing (Jones, 1987a). In addition, capsules have the advantage of their ease of use, portability and they provide a tasteless shell for drugs. This is particularly beneficial for drugs having an unpleasant taste or odour and can be produced in a wide range of colours (Hostetler, 1986). The colour of the capsule has a beneficial role in helping
patient motivation and improving compliance (Wattenwyl, 1981; Jones, 1993). In addition, the colour of the capsule enables the identification of the drug and confusion between different drugs has thus been minimised (Wattenwyl, 1981).

1.3.2 Compatibility
Gelatine is a large component of the capsule. This is due to the fact that it is non-toxic and thus widely used in foodstuffs. It is also readily soluble in biological fluids at room temperature and a strong, clear, flexible film forming material (Jones, 1987c). The exceptions are materials that react with gelatine, such as aldehydes, or those materials containing a large amount of moisture (Jones, 1985).

1.3.3 Bioavailability
The bioavailability of a capsule preparation is a very complicated process involving solution of the drug in the gastro-intestinal fluid, absorption and distribution (Newton, 1987). Usually, the bioavailability of a drug from a well formulated hard shell capsule will be better than or at least equal to that of the same drug from a compressed tablet (Ashford, 2002). This assumption is most likely derived from the fact that the gelatine shell rapidly ruptures and dissolves enabling rapid drug release. This is aided by the fact that there is a lack of compaction process comparable with tablet compression, thereby increasing the available surface area for drug dissolution (Ashford, 2002).

1.3.4 Stability
The stability of photolabile materials can be improved by filling into an appropriate colour of capsule shell (Jones, 1987c). The amount of transmission and the wavelength of UV light passing through the gelatine film depends on the type of colour of the capsule shell. Opaque coloured shells have been shown to have the lowest transmission of ultraviolet light (Jones, 1987c).

1.3.5 Clinical trials
Hard shell capsules are often used as the first dosage form for preliminary studies for new drugs in clinical trials (Jones, 1969). Capsules may also be used in bioequivalance studies of tablet formulations, which can be “blinded” by inserting the tablets into capsules so that the products may be compared for therapeutic response without the knowledge of the patient (Cole, 1987c).
1.4 SIZES OF HARD GELATINE CAPSULES

Hard shell gelatine capsules are manufactured in a range of eight sizes, (Table 1.1) from size 000 which is the largest, to size 5 which is the smallest.

Table 1.1: Sizes and volumes of eight sizes of hard gelatine capsules commercially available (Cole, 1987a)

<table>
<thead>
<tr>
<th>Capsule size</th>
<th>000</th>
<th>00</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (ml)</td>
<td>1.37</td>
<td>0.95</td>
<td>0.68</td>
<td>0.5</td>
<td>0.37</td>
<td>0.3</td>
<td>0.21</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Capsules used in the pharmaceutical industry are usually not greater than size 0 due to the difficulty for patients swallowing larger sizes (Cole, 1987a). Size 5 is rarely used due to difficulties in the automatic filling process (Cole, 1987a).

1.5 STORAGE OF EMPTY CAPSULES

Empty gelatine capsules are designed to have a moisture content of 13% to 16% (Jones, 1987b). The water acts as a plasticiser and is critical in maintaining the flexibility and the strength of the film. If the moisture content falls below the limit, the capsules will become brittle. If the moisture content rises above it, the capsules will soften (R.T. Jones, 1987). The moisture content also affects capsule dimensions. Thus, producers of empty capsules pack capsules for transport in sealed moisture proof packages (R.T. Jones, 1987).

1.6 ALTERNATIVE CAPSULE SHELL MATERIALS

For a long time, hard shell capsules were made from gelatine, as it is a material widely used in the food industry. It is readily soluble in biological fluids at body temperature and is a good film forming material. Its suitability for producing capsules is related to its ability to form a thermally reversible gel. However, gelatine capsules do have some drawbacks. Capsule shells made from gelatine become brittle when exposed to low relative humidity and when they are filled with formulations containing hygroscopic materials. It was found that exposure to tropical conditions, with high relative humidity above 60% to 70%, increased the minimum temperature for dissolution of the gelatine films from 31°C to over 50°C and even up to more than 97°C (R.T. Jones, 1987). Cross-linking between gelatine proteins due to the presence of aldehydes groups in the filling material also reduced the solubility of the capsule shells (Cartensen and Rhodes, 1993; Digenes et al., 1994). Thus, it is beneficial to be able to use different materials for manufacturing two-piece hard shell capsules (Chiwele et al., 2000).
Various materials have been evaluated to fully replace or modify the hard gelatine capsule shell. These attempts have been unsuccessful and can be attributed to the difficulties in large-scale manufacture, or because the capsules could not be used on conventional filling machines, or the capsules had \textit{in vivo} solubility problems (Chiwele et al., 2000). However, new varieties of capsule shells have been developed, which fulfil the requirements for two-piece hard shell capsules in terms of their manufacture and filling properties (Chiwele et al., 2000).

Matsuura and Yamamoto (1993) developed hydroxypropyl methylcellulose (HPMC) capsules. They achieved this by adding carrageenan and potassium chloride in small quantities to lower the thermal gelation temperature of HPMC. They found that the equilibrium moisture content of HPMC capsules was approximately one half to one third of gelatine capsules. HPMC capsules were found to have sufficient strength at 1% moisture content, compared to gelatine capsules, which were brittle below 10% moisture. Thus, HPMC capsules are useful for labile drugs, which are affected by moisture (Matsuura and Yamamoto, 1993). Matsuura and Yamamoto (1993) also compared the disintegration times of HPMC and gelatine capsules after storage of 10 days at 60°C and 75% relative humidity. They found that the disintegration of gelatine capsules was extensively prolonged, whereas the disintegration of HPMC capsules did not change. Dissolution studies showed that 75% of acetaminophen dissolved within 15 minutes from both capsules. However, the initiation time of dissolution from HPMC capsules was delayed by 3 minutes compared to the gelatine capsules (Matsuura and Yamamoto, 1993). HPMC capsules should have no incompatibility with most filling materials or powders, as the only incompatibility currently known for HPMC is the interaction with some oxidising agents (Harwood, 2000). In addition, HPMC capsules are made of plant derived materials and do not contain components of animal origin, thus eliminating problems with religious dietary restrictions (Ogura et al., 1998).

During transport and storage, gelatine capsules are subject to breakage due to their brittleness. Ogura et al., (1998) found that the percentage of broken capsules greatly increased as the moisture content of gelatine capsule shells dropped below 10%. However, they found that the degree of brittleness could be modified by the addition of polyethylene glycol (PEG) to the gelatine during manufacture. When exposed to air of low relative humidity they found that these ‘gelatine/PEG’ capsules showed a minimised brittleness and could thus be used for the filling of hydroscopic materials.
Bronsted et al., (1998) developed cross-linked dextran capsules on a laboratory scale. This was achieved by dissolving the dextran in water and adding magnesium chloride and PEG 400 to the solution. The cross-linking agent, glutaraldehyde was added afterwards and the solution was applied onto moulds to form two-piece hard shell capsules. They found that these capsules could be used for the delivery of drugs to the colon without the need to coat them with a polymer film (Bronsted et al., 1998).

Chiwele et al., (2000) studied the shell dissolution properties of gelatine, gelatine/polyethylene glycol (PEG) and HPMC hard shell capsules as a function of temperature, dissolution medium, and different storage conditions. They found that HPMC capsule shells dissolved rapidly in any dissolution medium with a pH below or equal to 5.8, and there was no difference in the time in which dissolution occurred in the tested temperature interval of 10°C to 55°C. Gelatine and gelatine/PEG capsule shells generally did not dissolve at temperatures below 30°C (Chiwele et al., 2000).

When testing the dissolution of HPMC, gelatine and gelatine/PEG capsule shells in the mixed phosphate buffer (pH 6.8), Chiwele et al. found that the dissolution time was increased and the dissolution profile was more variable. The addition of pancreatin and bile salts to any dissolution medium was found not to enhance the differences between the types of capsules investigated (Chiwele et al., 2000). Hence, their results indicated that capsule formulations should not be taken with carbonated drinks due to the large amount of phosphates. Gelatine capsules should preferably be taken with a warm drink, however, HPMC capsules may be taken with either a cold or warm drink (Chiwele et al., 2000).

When investigating the storage of capsules under hot, humid tropical conditions, Chiwele et al. (2000) found that a short storage of HPMC under such conditions affected the capsule shell matrix. They attributed changes in disintegration times and dissolution times of formulations filled using HPMC capsules to the powders incorporated rather than of the capsule shells as Matsuura and Yamamoto (1993) found. However, a short storage of gelatine containing capsules under the same conditions did not alter the dissolution properties of the shells.
1.7 FILLING OF HARD GELATINE CAPSULES

1.7.1 Materials Filled into Capsules

Hard shell capsules are mainly filled with a powder containing the active ingredient. There are a variety of materials, however, which can also be filled into capsules (Table 1.2).

Table 1.2: Materials filled into hard gelatine capsules (Jones, 2002a)

<table>
<thead>
<tr>
<th>Dry solids</th>
<th>Semisolids</th>
<th>Liquids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powders</td>
<td>Thixotropic mixtures</td>
<td>Oily liquids</td>
</tr>
<tr>
<td>Granules</td>
<td>Thermosoftening mixtures</td>
<td>Suspensions</td>
</tr>
<tr>
<td>Pellets</td>
<td>Pastes</td>
<td>Solutions</td>
</tr>
<tr>
<td>Tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsules</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There have been a number of significant developments in the use of hard shell two-piece capsules for granules, pellets, tablets, liquids, and pastes.

Granules and Pellets

Materials which are sensitive to processing conditions such as granules or modified release products such as pellets may be filled into hard shell capsules, as they can be filled without a high compression force comparable to tableting, which could affect the control release coating or even break the particles (Augsburger, 1995). The most important factors to consider are the friability of the particles, their roundness/roughness and their size distribution. This is because the dosing mechanism for filling is based on measuring chambers that have variable volumes. From these chambers, capsule ingredients are transferred to the capsule body. Hence, the fill particles should be free flowing and dust free (Jones, 1985).

Tablets

Hard gelatine capsule products have been produced in which smaller dosage forms are enclosed within the capsule. This approach was originally chosen to separate incompatible materials. In 1963, Eli Lily manufactured a capsule in which a film-coated tablet was encapsulated with other ingredients as a powder mixture. This technique was also used by Boehringer Ingelheim to produce a controlled release capsule, which contained five film-coated clonidine hydrochloride tablets of different release rates. For ease of filling, the tablets need to be smooth and preferably film coated to reduce the formation of dust. The size of the capsule must also be considered, as it has to be large enough to accommodate a given product shape, but not exceed the maximum diameter of the dosage form which can be used for each capsule size (Jones, 1985).
Semisolids and Liquids

Due to the ease of measuring small quantities of liquids, hard gelatine capsules were used as containers for oils. Liquid products sometimes leaked out of the capsule, or the capsule halves came apart during handling. This problem was overcome in the 1960s by the development of the self-locking capsule (Jones and Turner, 1974) and by maintaining the capsule contents in liquid form only during the filling process, then converting them to a solid after filling (Jones, 1985). This conversion was achieved either by using thixotropy (mixtures are liquefied by sheer stress) or thermosoftening (mixtures are liquefied by heat). A combination of both phenomena may also be used. The main difference from standard capsule filling machinery is the substitution of a dosing head for liquid products. A hopper is provided in which the formulation is liquefied by stirring or heating. A volumetric pumping system subsequently doses the liquid fill into capsules, in which the fill returns to solid form (Jones, 1985).

The important physical properties of the formulated mass are its viscosity, surface tension, and melting point, which will determine how the product will withstand handling and storage. If the thixotropic effect is low, this will result in increased problems of leakage (Francois and Jones, 1979).

Semisolid and liquid filling hard gelatine capsules reduces the problems of conventional pharmaceutical processing methods. Walker et al. (1980) found that when liquid filling hard shell capsules with a poorly soluble drug, triamterene, the dissolution rate was significantly enhanced. The uniformity of fill weight and content can also be improved for potent drugs, by using solutions and volumetric dosing pumps (Walker et al., 1980). By selecting an appropriate concentration of excipient, the release rate of a drug may be modified as Walker et al. (1980) demonstrated. They found that altering the polyvinyl acetate concentration from 2% to 6%, reduced the rate and extent of release of nomifensine hydrogen maleate capsules. Toxic drugs may be safely handled by incorporating the active drug into a base, thereby reducing cross-contamination associated with powders (Jones, 1985). In addition, materials which have low melting points or are liquid at room temperature may present difficulties when formulating as dry powders, and require high concentrations of excipient to avoid processing problems. This problem may be overcome by filling directly into capsules or formulating the material as a semi-solid. Materials which are very hygroscopic can be successfully produced as a semisolid fill because the incorporation of the compound in a semisolid matrix effectively excludes it from contact with oxygen or moisture. Bowtle et al. (1988) found that the incorporation of an unstable hygroscopic antibiotic compound into a formulation based
on polyethylene glycol 6000 was found to reduce water uptake to such an extent that a product with a one-year shelf life could be produced. This technique could also be used to reduce the access of oxygen to the active drug (Jones, 1985).

A variety of medicines, which are normally filled into soft gelatine capsules, can thus be filled into hard gelatine capsules. Table 1.3 demonstrates the range of capsule filling machinery capable of filling “non-powders” into hard shell capsules. Many filling machines are also capable of dosing more than one type of fill into a single capsule. This technique allows a large number of combinations to be produced, thereby enhancing a formulator’s ability to tailor release profiles to meet specific needs.

Table 1.3: Dosage form filled into hard shell capsules

<table>
<thead>
<tr>
<th>Machine</th>
<th>Model</th>
<th>Capsules/Hour</th>
<th>Dosage Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>MG2 (Bologna, Italy)</td>
<td>Futura</td>
<td>12,000</td>
<td>Powder/Pellets*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24,000</td>
<td>Powder/Liquids*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48,000</td>
<td>Powder/Tablets*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>96,000</td>
<td>Herbs/Pastes*</td>
</tr>
<tr>
<td></td>
<td>Suprema</td>
<td>24,000</td>
<td>Powder/Pellets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48,000</td>
<td>Powder/Pellets</td>
</tr>
<tr>
<td></td>
<td>G38/N</td>
<td>60,000</td>
<td>Powder/Pellets/Tablets*</td>
</tr>
<tr>
<td></td>
<td>G60</td>
<td>60,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>G37/N</td>
<td>100,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>G70</td>
<td>70,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>G100</td>
<td>100,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>G120/N</td>
<td>120,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>G120</td>
<td>120,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>G140</td>
<td>140,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>G250</td>
<td>200,000</td>
<td>Powder/Pellets</td>
</tr>
<tr>
<td>Macofar (Romaco, Rastignano, Italy)</td>
<td>CD5</td>
<td>6,000</td>
<td>Powder/Pellets/Tablets*</td>
</tr>
<tr>
<td></td>
<td>CD20</td>
<td>20,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>CD40</td>
<td>40,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>CD60</td>
<td>60,000</td>
<td>&quot;</td>
</tr>
<tr>
<td>Index (Romaco, Rastignano, Italy)</td>
<td>K-40</td>
<td>40,000</td>
<td>Powder/Pellets/Tablets</td>
</tr>
<tr>
<td></td>
<td>K90</td>
<td>90,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>K120</td>
<td>120,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>K150</td>
<td>150,000</td>
<td>&quot;</td>
</tr>
<tr>
<td>IMA (Bologna, Italy)</td>
<td>Zanasi 6</td>
<td>6,000</td>
<td>Powder/Pellets/Tablets/Liquids*</td>
</tr>
<tr>
<td></td>
<td>Zanasi 12</td>
<td>12,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>Zanasi 25</td>
<td>25,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>Zanasi 40</td>
<td>40,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>Zanasi Plus 8</td>
<td>8,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>Zanasi Plus 16</td>
<td>16,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>Zanasi Plus 52</td>
<td>32,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>Zanasi Plus 48</td>
<td>48,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>Zanasi Plus 70</td>
<td>70,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>Zanasi Plus 85</td>
<td>85,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>Matic 60</td>
<td>60,000</td>
<td>Powders/Pellets</td>
</tr>
<tr>
<td></td>
<td>Matic 90</td>
<td>90,000</td>
<td>Powders/Pellets</td>
</tr>
<tr>
<td></td>
<td>Matic 120</td>
<td>120,000</td>
<td>Powders/Pellets</td>
</tr>
<tr>
<td></td>
<td>Imatic 100</td>
<td>100,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>Imatic 120</td>
<td>150,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>Imatic 200</td>
<td>200,000</td>
<td>&quot;</td>
</tr>
<tr>
<td>Bosch (Wahlbingen, Germany)</td>
<td>GKF 400S</td>
<td>24,000</td>
<td>Powder/Pellets/Tablets/Liquids*</td>
</tr>
<tr>
<td></td>
<td>GKF 700S</td>
<td>42,000</td>
<td>Powders/Pellets</td>
</tr>
<tr>
<td></td>
<td>GKF 7000S</td>
<td>150,000</td>
<td>Powders/Pellets/Tablets*</td>
</tr>
<tr>
<td>Shionogi Qualcaps (Nara, Japan)</td>
<td>Liqfil super 40</td>
<td>40,000</td>
<td>Powders/Granules/Liquids/Pastes*</td>
</tr>
<tr>
<td></td>
<td>Liqfil super 80</td>
<td>80,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>Liqfil super 100</td>
<td>100,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>Liqfil super 150</td>
<td>150,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>Liqfil super JCF40</td>
<td>40,000</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>Liqfil super JCF80</td>
<td>80,000</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

*Multiple dosing of fill material possible
1.7.2 Procedure of Filling a Capsule

All capsule filling machines perform five basic operations when filling hard gelatine capsules (see Figure 1.1) (Cole, 1987b; Jones, 2002a).

1. Rectification - The capsules are positioned so that they point in the same direction, cap uppermost in the machine ready for separation.
2. Separation - The bodies are separated from the cap by suction. The open end of the body is exposed for filling.
3. Filling - The desired quantity of fill material is measured into the body.
4. Joining - The body and the cap are then vertically aligned together. Pins are used to replace the cap onto the body and the capsule is closed to the correct length.
5. Discharge - The filled capsules are ejected using pins. Compressed air may also be used.

Figure 1.1: The capsule filling process (Cole, 1987b)

1.7.3 Filling Machinery

Machines used for filling can be classified into categories by their mode of operation: manual, semi-automatic and automatic (Jones, 2002a). Automatic machines can be further divided depending on whether the movement of capsules is intermittent or continuous in operation (Jones, 2002a).

Dosing mechanisms can be divided into direct and indirect types. In the direct type, the capsule body is used to directly to measure the dose. In the indirect type, the machine measures the dose in a separate system and is filled as a plug of material (Augsburger, 1995).
The majority of formulations filled into capsules are dry powders (Augsburger, 1995). In comparison to tablet making, capsule filling has the disadvantage in that the method of placing powder into the capsules varies greatly from one manufacturer of filling equipment to another causing a variation in weight and reproducibility.

There are five main dosing mechanisms for powder filling; auger and vibratory method, which are both examples of direct filling, and the dosing disk, dosator filling and vacuum method, which are all indirect methods.

1.7.3.1 Direct Filling
Auger method

The auger fill principle involves the use of a hopper fitted with a rotating auger (Figure 1.2). The agitator feeds material into the auger, which in turn feeds it into the capsule body thus aiding powder flow and ensuring uniform powder feed (Cole, 1987b). The powder flows into the capsule bodies, which are held in a filling ring rotating under the powder hopper. This method uses the capsule body to measure the dose of material (Cole, 1987c).

The fill weight of a capsule which is filled by the auger fill principle is dependent upon the rate of rotation of the filling ring. This machine relies on the use of a single auger. Slower rates will provide a heavier fill weight because the capsule bodies have a longer dwell time underneath the powder hopper (Cole, 1987b). Other factors affecting the fill weight of the capsule are the capsule size (Deodhar, 1990) and the level of powder in the hopper (Cole, 1987c). To ensure a reproducible fill weight, the flow properties of the powder blend must be consistent so that there is a uniform flow rate from the hopper into the capsule body (Deodhar, 1990).

Figure 1.2: Auger filing system (Jones, 2002a)

(A) auger; (B) powder hopper; (C) stirrer arm; (D) pressure relief hole; (E) capsule carrying rings; (F) body ring holder
Reier et al. (1968) investigated powder properties using a semi-automatic capsule filling machine, based on the auger filling method. They derived a model relating machine settings to the powder properties of a formulation and found that the mean capsule fill weight could be calculated from the capsule size, machine speed and the particulate properties of the material.

Höfliger and Karg originally produced a machine using this kind of feed system, which filled at a rate of 3,000 capsules per hour. The machine operated only while the hopper was positioned over the capsule body and the timing on the auger drive regulated the fill weight. The hopper was fixed and the capsule bodies were moved by the plate (Cole, 1987c; Jones, 2002a).

Today, Shionogi Qualicaps (Nara, Japan), produce fully automatic capsule filling machines based on the auger filling principle. The range includes the Liqfil super JCF 40 and JCF 80, which fill capsules at a rate of 40,000 and 80,000 capsules per hour, respectively.

**Vibratory Method**

The vibratory fill method involves the use of a vibratory feed mechanism to fill the capsule body (Deodhar, 1990). The vibration causes powder to flow from the powder hopper to the capsule body. This mechanism of filling also uses the capsule body to measure the dose of the material (Cole, 1987b). The fill weight of the capsule is therefore determined by the capacity of the capsule (Deodhar, 1990). The flow properties of the powder are critical for this mechanism of powder feed as this can greatly affect the fill weight variation of the capsules (Deodhar, 1990).

The Osaka filling machine employed this principle (Cole, 1987c). This machine was a high capacity continuous motion machine. This machine is not available commercially. The Liqfil super 40 (Shionogi Qualicaps, Nara, Japan) has a rated capacity of 40,000 capsules per hour. The capsules can be filled using mechanical vibration or tamp filling. The Liqfil super 100 only uses mechanical vibration as the filling method and has a production capacity of 100,000 capsules per hour.

**1.7.3.2 Indirect Filling**

Dosing disk Machines (Tamping Finger Machines)

In this system the powder is tamped into individual powder plug doses. These are then ejected into empty capsule bodies. Höfliger and Karg first developed this method based
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on free flowing powders combined with the tamping punch (Cole, 1987b). Powder initially flows into the holes in the dosing disk, which forms the base of the powder hopper (Cole, 1987b). The dosing disk is machined to thickness to provide a certain fill weight in the capsule. The tamping pins are lowered into the sets of holes in the dosing disk of various depths, which compress the powder against the tamping ring, and then rise (Jones, 2002a) (Figure 1.3). Filling and retamping takes place at five tamping stations resulting in each plug being compressed five times per cycle (Jones, 2002a). The tamping pins can be adjusted according to the scale marked on the tamping stations. With each successive tamp, more powder finds its way into the filling cavities until the plug is complete. After five tamps excess powder is scraped off. The dosing disk moves off the tamping ring to position the plugs over the empty capsule bodies where they are ejected by transfer pins (Cole, 1987b). A degree of compactibility is required for clean efficient transfer at the ejection station. Difficulties can occur when using this method if the batch-to-batch variation in density of the powder is very wide (Cole, 1987b).

Figure 1.3: Dosing disk filling mechanism (Jones, 2002a)

(A) dosing disk; (B) tamping pin; (C) powder hopper; (D) powder bed; (E) tamping ring; (F) tamping distance adjuster; (G) over load spring relief; (H) ejection adjuster; (I) guide block; (J) transfer block; (L) capsule body in bore; (M) suction

The weight of the capsule can be adjusted by the thickness of the dosing disk, which will determine the plug dimensions, hence the capsule fill weight. The force of the tamping punches and the depth of the powder in the hopper will also affect the fill weight (Cole, 1987b; Jones, 2002a).

Formulations used in tamp filling must be adequately lubricated so that filming is prevented during plug ejection and to reduce any friction between any sliding components that may come into contact with the powder (Cole, 1987b).
Kuhihara and Ichikawa (1978) filled capsules using the Höflinger-Karg-GKF 1000 dosing disk machine. They found a relationship between the capsule fill weight variation and the angle of repose and found an optimum angle of 38° to 44° for a minimum fill weight variation. This angle was determined by the size and the speed of the dosing disk. Kuhihara and Ichikawa also filled capsules employing a vibratory filling machine, Osaka OCF-120 and found that the capsule fill weight variation is closely related to the minimum orifice diameter. They found that powders having a small minimum orifice diameter resulted in a lower fill weight variation.

Podczeck and Newton (1999) used the Bosch GKF-400S tamp filling machine to fill excipient powders. They found that a wider range of powders could be filled using this machine in comparison to a dosator machine. Increasing the powder bed height solved filling problems caused by powder flooding. They also found that if powders did not form firm plugs, this was not necessarily related to the coefficient of fill weight variation. The influence of the powder bed height on the capsule fill weight increased with decreasing powder flow. The effect of the tamping pin setting on the capsule fill weight was small and further decreased with a decrease in powder flow. When Podczeck and Newton filled capsules using a granulated material, they found that the tamping pin setting was more important than the powder bed height on the capsule fill weight. For moderately flowing powders, the coefficient of fill weight variation was almost independent of powder bed height or tamping pin setting. However, for powders with poor flow properties, filling performance could be improved by adjusting both machine settings. They found very complex relationships between the powder flow properties such as the angle of internal flow, dynamic densification profile, Carr’s compressibility index, particle size and shape and the filling behaviour.

Podczeck et al. (1999) investigated the filling behaviour of a range of herbs. The herbs were filled on the Bosch GKF-400S and the Zanasi AZ5. All the samples had poor flow properties demonstrated by the high Carr’s compressibility index and they found that the addition of magnesium stearate did not improve powder flow. All the lubricated samples of herbs could be filled on the tamp filling machine. Depending on the herb, some powders filled better with no compression and others at high compression. When filling with the dosator machine, some of the powders were not successfully filled due to the inability of forming a powder plug. Hence Podczeck et al. suggested that a tamp filling machine can handle a wider range of herbs than a dosator machine.
Höfliger and Karg and Harro Höfliger machines were based on the tamp filling principle (Cole, 1987b). Today, tamping machines are manufactured by Bosch GmbH (Waiblingen, Germany) Romaco Inc. (Rastignano, Italy), Shionogi Qualicaps (Nara, Japan) and CapPlus Technologies (Phoenix, Arizona). The tamping stations contain different numbers of tamping pins depending upon the model.

Bosch produces the GKF 400S, 700S and 2000S, which can fill at a maximum rate of 150,000 capsules per hour. The Bosch GKF-400S is a small-scale production machine utilising three tamping pins. In each station the tamping pin height can be adjusted to increase the weight of the capsule (Bosch manual). Bosch also produces the GKF 2000ASB, which processes the same number of capsules as the GKF 2000S but is also instrumented and provides feedback control.

Another manufacturer of tamp filling machinery is the Index division of Romaco. The models available include K40i, K90, K90i, K120, K120i and K150i. These machines have a filling capacity of 40,000 to 150,000 capsules per hour. The “i” represents “intelligent choice” such that there is a control system, which controls all operations of the capsule filling process.

Shionogi Qualicaps also employ the tamp filling principle and produce machines which include the Liqfil super 40, which has a rated capacity of 40,000 capsules per hour. They also produce the Liqfil super 80 and Liqfil super 150 capsule filling machines. These machines employ both tamp and auger filling, and have a filling capacity of 80,000 and 150,000 capsules per hour, respectively.

The Sejong division of CapPlus Technologies produce the SF40, SF100 and the SF135, which employ the tamp filling method and have a filling capacity of 40,000 and 100,000 and 135,000 capsules per hour, respectively.

**Dosator Machines (Dosing Tube Machines)**

The dosator machine uses a cylindrical dosing tube fitted with a moveable piston. The bottom of the dosator is exposed and the piston can be adjusted to control the height of the cylindrical chamber formed in the dosator to achieve a particular volume (Cole, 1987b; Jones, 2002a).

The mode of operation of this type of machine is as follows: The dosator is inserted into the powder bed and powder enters the dosator. The powder is compressed by a piston
forming a powder plug. The dosator is withdrawn from the powder hopper and transferred over the empty capsule body. The piston is pushed down and the powder plug is ejected (Cole, 1987b). In the dosator mechanism a powder plug is built by a single action and not a series of tamps as on tamping machines (Jones, 2002a).

Figure 1.4: Dosator system (Jones, 2002a)

(A) compression force planten; (B) piston; (C) dosing tube; (D) powder hopper; (E) plug ejection planten; (F) capsule body in bore

The height of the cylindrical chamber will control the internal volume of the dosator. This will affect the amount of powder in the dosator and thus the fill weight and strength of the plug produced. The fill weight is also affected by the depth of the powder bed into which the dosator dips (Augsburger 1995).

To ensure a minimum fill weight variation, clean transfer of the plug to the capsule body must be achieved, to ensure that it does not break up on ejection from the dosator (Cole, 1987b). The retention of powder is aided by a compression force applied to the powder bed by the piston whilst the dosator nozzle is dipping into the bed. Retention within the dosator nozzle requires that the powder is able to support itself. This requires the formation of a stable powder arch at the nozzle outlet (Jolliffe et al., 1980). Ideally the compression force should be a minimum, as higher compression forces result in difficulties in ejection. The fill weight variation can be minimised by using a lubricant such as magnesium stearate and/or a flow aid such as Aerosil. These both enable the plug not to adhere to the dosator or the end of the piston (Cole, 1987b). However, the lubricants required are often hydrophobic, thus the stronger the compact, the greater the difficulty in wetting and the bioavailability will be reduced (Cole, 1987b). Formulations for these machines also need good flow and lubrication properties (Jones, 2002a).
Dosator machines can either be intermittent or continuous. In the intermittent machines the powder bed does not rotate. The dosator instead rotates around an axis between the powder bed and capsule shell conveyor *i.e.* the capsules stop at each stage of the filling. For continuous machines the powder bed rotates together with the dosator and the capsule body is ejected without any of the processes stopping at any stage (Cole, 1987b). The speed of filling therefore increases and the dwell time (*i.e.* the time taken for the dosage tube to dip into powder and compress the plug of material) decreases (Cole, 1987b). This means that the powder must be of uniform density, easily compressible and not too elastic. It can therefore be seen that the speed of the machine, the level of fill and the density of the substance to be filled have an influence on the dosage accuracy (Cole, 1987b).

Using the Zanasi LZ64 machine, Irwin et al. (1970) investigated the relationships of powders with different flow rates. They found a significant correlation between the rate of flow and the capsule fill weight variation. They related this to the free flowing powders having the ability to reform the powder bed after the dosator had removed the powder plug.

Chowhan and Chow (1981) indicated that there is a linear relationship between the coefficient of fill weight variation and the powder consolidation ratio filled on the Zanasi dosator machine. Later, Chowhan and Yang (1981) demonstrated a linear relationship between the tensile strength of the powder bed and the consolidation pressure, prepared under different loads.

Patel and Podczeck (1996) investigated different microcrystalline cellulose samples using the Zanasi AZ5 dosator nozzle machine to fill the capsules. They found that the Kawakita constant (a) (Kawakita and Lüdde, 1970/71) and Hausner's ratio (Hausner, 1967) gave a good indication of the capsule filling performance. Hogan et al., (1996) also used the Zanasi AZ5 machine and found that the filling performance was dependent on the drug particle size, type of diluent, and concentration of drug and glidant.

Capsule filling machines using the dosator principle are of two types:

a) The intermittent motion type:

IMA (Bologna, Italy) produce the Zanasi series, which include the Zanasi 6, 6E/F, 12, 12E/F, 25, 25E/F, 40, 40E/F (E/F represents electronic devices attached to the capsule filling machine for production monitoring and automatic adjustment of processing parameters). These machines fill at a rate from 6,000 to
40,000 capsules per hour. They also produce the Zanasi PLUS series (8E/F, 16E/F, 32E/F, 48E/F, 70E/F and 85E/F). These machines have a filling capacity of up to 85,000 capsules per hour.

b) The continuous motion type:
MG2 (Bologna, Italy) produce low and high speed filling machines. The MG Futura has a filling capacity of 6,000 to 48,000 capsules per hour. The MG Suprema (24,000 capsules per hour or 48,000) enables capsules to be filled at a medium speed. The high speed models are the G38/N, G60, G70, G37/N, G100, G120/N, G120, G140, which have a filling capacity of 60,000 to 140,000 capsules per hour. Recently, the G250 has been introduced and has a filling capacity of up to 200,000 capsules per hour.

IMA (Bologna, Italy) produce the Matic range which include the Matic 60, 90 and 120. These fill at a rate of 60,000 to 120,000 capsules per hour. They also produce the Imatic series (Imatic 100, 150, 200). These are high speed continuous motion filling machines and have a filling capacity of up to 200,000 capsules per hour.

The continuous motion machine provides a greater filling capacity than the intermittent motion machine (Cole, 1987b).

Vacuum Method
The operation of the machine is continuous. The dose of material is measured in a device similar to a dosator. The powder is drawn into the dosator by suction applied through a filter where some compression takes place (Cole, 1987b) but not as much as in the dosator mechanism. The powder plug is held in place by a vacuum until the dosator is positioned over the capsule body (Cole, 1987b). The plug is then ejected into the capsule body by closing the vacuum and applying a positive pressure (Cole, 1987b; Deodhar, 1990).

Perry Industries Inc. USA developed this method of filling (Cole, 1987b). Currently, the Macofar division of Romaco (Rastignano, Italy) produces capsule filling machines, which employ this type of filling mechanism. They produce the CD-5 and CD-20 models, which are small scale machines suitable for laboratories and clinical trials and fill from 6,000 to 20,000 capsules per hour. They also produce medium speed machines, the CD-40 and the CD-60, which have a filling capacity of 40,000 and 60,000 capsules per hour,
respectively. These are intermittent motion capsule filling machines. The dosators are vacuum assisted, which enables powders with difficult flow characteristics to be handled. In addition, formulations filled using the vacuum method require no or limited lubrication as no moving part comes into contact with the powder. Hence, these machines are advantageously employed in the filling of dry powder inhalations into capsules.

1.7.4 Instrumentation of Capsule Filling Machinery

Instrumentation techniques provide the ability to monitor force during capsule filling. This information has contributed greatly to the understanding of capsule filling processes. It has also facilitated formulation development and provided a means for in-process control of manufacturing.

1.7.4.1 Dosing Disk Machines

The first dosing disk machine to be instrumented was the Höfliger and Karg model GKF 330 by Shah et al., (1983). Instrumentation of the machine was achieved by introducing resistance strain gauges, which were directly bonded to the pistons. Only two tamping stations were instrumented at any particular time. It was found that if the two successive tamping stations were adjusted so that there was the same depth of penetration in the disk cavity, fill weight gain at the second station was dependent upon the void volume left after the tamp at the preceding station.

Shah et al., (1986) later studied all five stations of the Höfliger and Karg GKF 330 and found that all compaction stations and all piston positions contributed equally to the formation of plugs except for the first station. This was due to a non-uniform powder bed over the dosing disk at tamping station 1 because of it being near to the scrape-off bar. They also calculated that the target fill weight could be achieved using three tamping stations for anhydrous lactose with 0.5% magnesium stearate. They confirmed their findings by plotting the fill weight as a function of compression force to show the effect of multiple tamping.

Using the same machinery, Shah et al., (1987) studied the effect of multiple tamping and compression on drug dissolution. They found that multiple tamping retarded drug dissolution and higher compression forces improved drug release when anhydrous lactose was the filler but adversely affected the dicalcium phosphate based capsules. The addition of a disintegrant cancelled the effects of multiple tamping on drug dissolution for both fillers and enhanced drug dissolution from the dicalcium phosphate based formulation.
Cropp et al. (1991) installed linear variable displacement transformers (LVDTs) also using the Höfliger and Karg GKF 330. This allowed force and displacement curves to be measured. They found a greater force and displacement when using a 2.0mm spring than a 1.6mm spring. The plug weight, however, did not increase greatly due to a high degree of elastic recovery after compression suggesting that there was little advantage of using the 2.0mm spring to achieve the target weight. They were able to show that the work encountered during capsule plug formation was less than that encountered during tableting and this was proven using area under the curve calculations.

Davar et al. (1997) filled various formulations at different compression forces. They calculated the size of the plug produced based on powder density. Profiles were constructed of plug strength and target density and these were related to the compression force to predict the appropriate dosing disk height to achieve a given fill weight on the Höfliger & Karg capsule-filling machine.

Podczeck (2000) instrumented the Bosch GKF-400S machine. The Bosch GKF-400S consists of five tamping blocks consisting of three pins and a plug transfer station. Conventionally springs are placed between the tamping head and the tamping pins. These springs were replaced by a chamber filled with compressed air (Figure 1.5).

Podczeck (2000) found that the use of the pneumatic tamping head was limited to control the fill weight during tamping and therefore recommended that any large adjustments of the fill weight should be carried out by altering the tamping pin settings and powder bed height at the set up stage of the machine. Podczeck (2000) also found that most of the powder that forms the plug enters the dosing disk bores during rotation of the dosing disk due to powder flow and not due
to the tamping pins pushing the powder into the dosing disk bores when space is available.

In a later study, (Podczeck, 2001) to control the capsule fill weight on tamp filling machines, Podczeck recommended installing a pneumatic tamping head at tamping station 4, as all plugs would have achieved their maximum length and density. A second pneumatic tamping head could also be installed on tamping station 3. However, this would not be instrumented. This would enable signals to be received from the instrumentation and thus the inner chamber of the second pneumatic tamping head could be controlled to adjust the capsule fill weight. In addition Podczeck suggested that the cumulative tamping distance should be large enough to produce a force reading but small enough to avoid overfilling of the capsules. Podczeck (2001) found that at each tamping station there was further compression of the plug. This contradicted the finding of Shah et al. (1983). This can be attributed to the fact that Shah et al. had used brittle materials in comparison to Podczeck who used soft ductile materials (Podczeck, 2001).

1.7.4.2 Dosator machines

Cole and May (1972) were the first to instrument an automatic capsule filling machine. They instrumented the Zanasi LZ-64 machine with strain gauges, which were mounted on the piston of a dosator nozzle. The small forces were amplified in order to be measured, as forces obtained on the Zanasi LZ-64 machine were usually 20N to 30N, in comparison to forces obtained on a tablet machine during compression, which are $3 \times 10^4$N. Due to rotation of the dosator, the machine was modified by Cole and May, (1975) by the introduction of a planetary gear system, which prevented twisting of the output cable during operation.

Cole and May were able to show that compression and ejection forces could be measured during plug formation (Cole and May, 1975). They found:

a) the development of a compaction force whilst the plug was being formed. This occurred as the dosator was inserted into the powder bed.

b) partial retention of the compaction force during rotation towards the ejection station

c) during plug transfer the development of an ejection force

d) after plug ejection the appearance of a drag force on the piston as it was being retracted

e) reduction of the ejection force with the addition of a lubricant to the material
Small and Augsburger (1977) later reported on the instrumentation of the piston of the same model of Zanasi machines with strain gauges. They employed a simpler mercury contact swivel system between the amplifier and the piston to prevent twisting of the output cable. This device was mounted over the hopper, which avoided the need for making any machine modifications. Small and Augsburger (1977) observed two stages in plug compaction, unlike Cole and May (1975). This was the precompression stage (PC), which occurred when the dosator dipped into the powder bed before actual compression. They also observed the compression stage (C), which is caused when the powder bed is compressed to a plug by tamping of the piston. Like Cole and May (1975) retention (R) and drag forces (D) after ejection (E) were also observed which could be related to the amount of lubrication in the formulation (Figure 1.6).

![Figure 1.6: Sketches of traces obtained using the Zanasi LZ-64 (Augsburger, 1988)](image)

(PC) Precompression, (C) compression, (R) retention force, (E) ejection force, (D) piston drag force

Small and Augsburger (1978) later studied the effects of the lubrication requirements of the Zanasi LZ-64. The effects of powder bed height, piston height and compression force on the ejection forces generated during the filling process were examined. Also examined were the lubricant type and concentration (Small and Augsburger, 1978).

Three fillers were studied, microcrystalline cellulose, pregelatinised starch and anhydrous lactose. Also studied were three lubricants, magnesium stearate, stearic acid and magnesium lauryl sulphate (Small and Augsburger, 1978). Small and Augsburger found that the ejection force increased by increasing the powder bed height, piston height and compression force. Compressible starch and microcrystalline cellulose required relatively low levels of magnesium stearate compared to anhydrous lactose. The performance of stearic acid and especially magnesium lauryl sulphate compared favourably with magnesium stearate in compressible starch (Small and Augsburger, 1978).
Mehta and Augsburger (1980) mounted a LVDT (linear voltage displacement transformer) on the instrumented Zanasi LZ-64 (Small and Augsburger, 1977). This allowed monitoring of force and displacement at the same time (Mehta and Augsburger, 1980).

Mehta and Augsburger (1981) studied the effect of powder plug strength on drug dissolution using the Zanasi LZ-64. They reported improved drug dissolution with increased magnesium stearate levels, accompanied by a large decrease in plug mechanical strength. Hence, the decrease in plug mechanical strength was of greater importance than the hydrophobicity of the plug.

Using the same instrumentation, Botzolakis and Augsburger (1982) studied the effect of disintegrants on drug dissolution. They found that disintegrants such as sodium starch glycolate and croscarmellose sodium enhanced drug dissolution due to liquid uptake into the powder plug and plug swelling. In a later study, Botzolakis and Augsburger (1984) found that the compression force, lubricant concentration and filler type were found to influence the effectiveness of the disintegrants.

More recently, Hauer et al. (1993a, 1993b) instrumented the Zanasi LZ 64 dosator machine. They related compressibility to the changes in bulk density of the powder (dynamic packing), which was studied using the Kawakita equation (Kawakita and Lüdde, 1970/71). They found that very free flowing powders did not maintain a uniform powder bed due to powder flooding. Improved powder flow properties resulted in difficulties in powder bed densification and thus greater fill weight variations were observed. The addition of magnesium stearate reduced the ejection force (Hauer et al., 1993b). However, as the lubricant concentration was increased, this resulted in problems with plug formation and an increase in the weight variation was observed.

1.7.5 Instrumentation of Capsule Filling Machine Simulators

Simulators have the advantage over instrumented capsule filling machines in that small amounts of substances can be tested. Also the individual stages of precompression, compression and ejection can easily be studied independently of one another. This is not possible on capsule filling machines as all the moving parts are linked so that any alteration affects all parts of the capsule filling cycle (Jolliffe et al., 1982; Britten and Barnet, 1991).
Jolliffe et al., (1982) described instrumentation of the mG2 G36 capsule filling machine simulator. They encountered difficulties when instrumenting a standard continuous motion capsule machine due to rotation of the dosator nozzles. To overcome the problem of nozzle rotation, a modified filling turret was used. This allowed the dosator nozzles to move up and down but not rotate and could therefore be instrumented in the form of a strain gauged dosator piston. This enabled the measurement of compression and ejection forces during filling. Distance transducers measured the movement of the piston relative to the nozzle and the whole dosator relative to the turret.

The system was simplified by only using one dosator nozzle. The dosator nozzle moved vertically, dipping into a rotating powder bed to pick up powder. The dosator nozzle then lifted out of the feed bed. The feed bed moved away and was replaced by a magazine of capsule bodies. When the dosator nozzle moved down again the empty capsule bodies were positioned so that powder could be ejected into the body (Jolliffe et al., 1982).

Using the mG2 capsule filling machine simulator, Jolliffe and Newton (1982b) studied the effects of the amount of compression on the capsule fill weight uniformity and measured compression and ejection stresses for four size fractions of lactose. They found that for fine adhesive powders the range of compression over which satisfactory filling was achieved was large but decreased with increasing particle size. The lower limit of filling ability was related to powder retention, and the amount of compression required to achieve retention increased with an increasing particle size. The upper limit for compression was caused by the compaction of the powder, which prevented the piston to cause retention. Large particle sizes were able to undergo only a small change in volume before compaction, in comparison to fine powders, which were more compressible and thus could be filled more satisfactorily at higher compression settings.

To test the applicability of the mG2 simulator, Jolliffe and Newton (1983a) repeated the experiments using a mG2 production machine. They found that the capsule fill weights obtained using fine, adhesive powders gave a uniform fill weight over a wide range of compression settings but as increasingly free flowing powders were used, the range decreased.

Jolliffe and Newton (1983a) found that the upper limit on compression was set by compaction of the powder producing poor fill weights. This occurred at lower compressions for coarse, free flowing powders due to their low compressibility. Resurfaced nozzles were also studied and they found that surface roughness affected the
filling properties and there was an optimum surface texture for capsule filling performance. Jolliffe and Newton (1983a) found that the results obtained with the mG2 capsule filling production machine were similar to those obtained from the simulator and thus validated the use of simulators for studying production capsule filling.

Further work by Jolliffe and Newton (1983b) studied the effect of capsule filling with resurfaced nozzles and found that there was an increase in the fill weight, improved uniformity and reduction in compression and ejection stresses compared with the untreated nozzle surface. The resurfaced nozzle showed an increased improvement in the filling performance. This showed that there was an optimum angle of wall friction to achieve good powder retention (Jolliffe and Newton, 1983b).

Tan and Newton (1990a) also used the instrumented mG2 simulator to study the capsule filling characteristics of size fractions of five pharmaceutical excipients. These excipients were ranked in order of flowability and it was found that flowability was dependent on the particle size, morphology and bulk density of the powder. Tan and Newton (1990a) found that there was a significant correlation between the value of the coefficient of fill weight variation and Carr's compressibility index, Hausner ratio, angle of repose, Kawakita's equation constant (a) and Jenike's flow factor. The coefficient of fill weight variation was also related to the powder bed bulk density and the variation in the compression stress. They found no correlation between the values of the coefficient of fill weight variation with the angle of internal flow and the angle of effective friction.

Tan and Newton (1990b) later studied the minimum stress requirements for arching and powder retention within a dosator nozzle during capsule filling for five pharmaceutical excipients. They discovered that the higher the compressive stress applied for arching at the opening of the dosator, the greater the compressive stress at the top of the powder plug. The size of these stresses depended on the size of the particles and the material (Tan and Newton, 1990b).

The influence of the surface texture of the dosator nozzle wall on the capsule filling performance was also studied by Tan and Newton (1990c). They found that changing the mean surface texture did not affect the capsule weight variability when various size fractions of Starch 1500 and Avicel were used. This contrasted with the findings of Jolliffe and Newton (1983b) who found that for lactose, the surface texture was very important due to the adhesion of powder to the nozzle wall. Hence Tan and Newton suggested that for powders which had little affinity to bind or coat the nozzle wall, the
wall texture only had a small influence on the capsule filling performance (Tan and Newton, 1990c).

The influence of the compression setting ratio on capsule fill weight and weight variability was assessed by Tan and Newton (1990d) for various excipients using the mG2 simulator. They found that the most uniform weights were achieved when no compression was applied to the powder during the filling process (Tan and Newton, 1990d).

Tan and Newton (1990e) also assessed the influence of compression settings on the observed powder plug density and its deviation from the expected plug density during filling of different size fractions of pharmaceutical excipients. They found that the observed powder plug density depended on the particle size and material. Where there were deviations in the observed and expected powder plug densities, this was caused by differences in the observed and expected fill weights. Larger deviations in the values of the observed and expected powder plug density occurred with fine powders and high compression settings.

Britten and Barnett (1991) constructed a simulator, based on the dosator mechanism using the Macofar MT13-2 capsule filling machine. The dosating system for this machine was similar to the Zanasi but was simpler as no twisting of the dosator piston occurred relative to the dosator body during the compression and ejection strokes. Due to the similarity in both of the models, the speed range of both the machines was incorporated in the simulator. The vertical movements of the bowl (equivalent to dosator movement) were tracked by two linear variable displacement transformer transducers (LVDTs). Displacement time curves were obtained and velocities calculated from them. Also force transducers were fitted to the dosator piston and due to the size of the force generated in the simulator, strain gauges were used to measure radial forces and compression forces (Britten and Barnet, 1991; Britten et al., 1995).

The simulator was set up to operate in a range of modes and various dosator and piston speeds:

Precompression simulation
- The powder plug is formed by the dosator as it descends into the powder bed
Constant displacement simulation
- The powder has been partially precompressed but an additional tamp is applied by the dosator piston

Constant pressure simulation
- The powder has been precompressed and the piston can travel as much as possible until the resistance of the powder to undergo further compression equals the applied compression pressure

Other information collected for every plug was the compression pressure, radial pressure, residual axial pressure, residual radial pressure axial, ejection pressure and radial ejection pressure (Britten et al., 1995; Britten et al., 1996). Additionally, plug weight, plug density, plug length and powder bed density was calculated and this data was related back to the pressure and displacement data (Britten et al., 1995; Britten et al., 1996).

Britten et al., (1996) found that the piston ejection speed had no effect on plug properties, but an increase in compression speed resulted in a less consolidated powder plug and therefore a reduction in the plug weight. By applying higher pressures, this reduced the plug weight changes but affected the release properties of the powder plug. When comparing the axial and radial pressures generated by the Starch 1500 plug and lubricated lactose, there were large differences due to the different consolidation and elastic properties of the two solids (Britten et al., 1996).

In a further study, using the same simulator, Tattawasart and Armstrong (1997) studied the effect of lubricant concentration, dosator pressure and piston height settings on the properties of lactose plugs. The derived factors measured were plug porosity under compression and after ejection, ejection pressure, uniformity of plug weight and length of plug after ejection. Their analysis showed that plug porosity was dependent upon piston pressure and that plug weight and length were dependent upon piston height. The ejection pressure was found to be dependent upon both piston pressure and height. They found that the lubricant concentration played little part in the analysis and concluded that 0.5% magnesium stearate provided the adequate lubrication for lactose plugs (Tattawasart and Armstrong, 1997).
1.7.6 Summary for Machinery

All powders filled into hard gelatine capsules need to have good flow properties, minimum powder-metal adhesion and minimum dustiness on filling. For automatic machines, the powders need to have sufficient interparticulate forces to form a good plug. Each type of machine has slightly different requirements. For instance, the machines with dosator nozzles normally need greater interparticulate forces than those with dosing disks. This is due to the fact that the plug has an unsupported lower surface while it is being transferred from the powder bed to the capsule body and enough material could be lost to affect the fill weight. A slower rate of filling tends to increase fill weight and increase its uniformity. Slow speed, however, may not be ideal in a production environment. Low speed may also increase stirring of the powder in the feed hopper, which can enhance lubricant dispersion over the particle surface causing an increase in hydrophobicity of the powder blends. At very high speeds it is possible for the powder plug to be incompletely or jerkily ejected from the dosator so that only a portion arrives in the capsule body (Cole, 1987b).

1.8 Capsule Standards

When filling capsules, the finished product must meet requirements such as uniformity of weight, uniformity of content, disintegration and dissolution to ensure that they contain the correct dosage and this dosage is available for absorption. These standards are tests to ensure that capsule products comply with the minimum acceptable standard.

1.8.1 Uniformity of Fill Weight

The test for uniformity of fill weight is the simplest indicator of the content of active ingredient, assuming that the contents of the capsule are homogenous (Jones, 1987d).

The uniformity of fill weight test for hard shell capsules as defined by the British Pharmacopoeia (BP) 2001 is a double limit test and carried out as follows: Twenty intact capsules are individually weighed. One capsule is weighed and the contents removed as completely as possible. The capsule shell is weighed and the weight of the contents determined. The procedure is repeated with the rest of the capsules and the average fill weight of the capsules is calculated.

For capsules greater than 300mg, no more than two capsules should be out of the ±7.5% of the mean weight limit and none are out of the ±15% mean weight limit. For capsules less than 300mg the limits are ±10% and ±20% respectively.
1.8.2 Uniformity of Content

The test for uniformity of content is described by the BP (2001) as follows: Unless otherwise justified and authorised, capsules containing less than 2mg or less than 2% w/w of an active ingredient must comply with the following test:

The content of an active ingredient in each of the ten capsules is determined by using a suitable analytical method. The capsules will comply with the test if not more than one of the individual values obtained is outside the limits of 85% to 115% and none is outside the limits of 75% to 125%. If two or three individual capsules are outside the limits of 85% to 115% but inside the 75% to 125% range another twenty capsules taken at random are analysed. Compliance is achieved if in the total of thirty capsules not more than three capsules are outside the limits of 85% to 115% of the average value and none are outside the range of 75% to 125% (BP, 2001).

1.8.3 Disintegration and Dissolution

A solid dosage form capsule must undergo disintegration and dissolution before it is absorbed. Both disintegration and dissolution tests are hence important for the formulation of the powder (Jones, 1987d).

1.8.3.1 Test for Disintegration

The disintegration test indicates whether capsules disintegrate within a specified time when placed in a liquid medium at body temperature. The conditions used in the test attempt to simulate in vivo conditions (Jones, 1987d). Most pharmacopoeias attempt to simulate movement within the stomach by the use of an oscillating tube apparatus, which consists of a vertically mounted tube, made of glass or perspex with a wire mesh base. The capsule is placed in the tube, which is then raised and lowered in the test solution at a frequency of approximately 30 strokes per minute through a specified distance. If it is found that the capsules float on the surface of the liquid, a transparent plastic disk is placed in the disintegration tube on top of the capsule. The U.S. Pharmacopoeia test, which applies to hard capsules, modifies the apparatus by the addition of a 10-mesh wire cloth on the top of each tube to prevent capsules from floating to the surface of the test medium.

The BP (2001) monograph states that six capsules taken at random are tested. Water is used as the liquid medium at a temperature of between 36°C to 38°C, which corresponds to body temperature. A disintegration time of 30 minutes for capsules is generally considered acceptable.
The first stage in drug release is disintegration of the capsule shell. When the capsule disintegrates, the shell splits by opening at the weakest point, which is either the radius or the seal (Jones and Cole, 1971). The capsule contents sometimes start to empty before all the gelatine has dissolved, leaving the empty capsule shells. The shell pieces may then agglomerate to form an adhesive mass of gelatine, which will take longer to dissolve because of its thickness. This situation is recognised and is the reason for the difficulty in determining the end point of disintegration (Jones and Cole, 1971). The BP (2001) has defined the end point as 'no residue remains on the screen or, if a residue remains it consists of soft fragments of shell or is a soft mass with no palpable core'. The rate controlling step in the majority of experiments is the effect of the final pieces of the gelatine capsule shell, except for those capsules which are filled using non-wetting insoluble materials where the contents remaining are the last to pass through the mesh (Jones and Cole, 1971). The rate of gelatine solubility is dependent upon the temperature of the solution (Jones and Cole, 1971). There is a large decrease in gelatine solubility as the temperature falls below 35°C, and below 30°C the capsules are completely insoluble and only swell and distort. Over the temperature range of 35°C to 39°C, there is a 30% change in rate of solution of empty capsules. HPMC capsules, however, have a slower but uniform solubility between 10°C and 55°C. Both types of capsules are affected by the dissolution medium, and different storage conditions (Chiwele et al., 2000).

A formulation for filling a capsule in the majority of cases is a simple powder mixture of the active ingredients together with diluents, lubricants, glidants or surfactants as required. The powder mass in the capsule should be so that it does not interfere with the dissolution of the gelatine shell and so that the mass will break up.

**1.8.3.2 Test for dissolution**

The dissolution test measures the rate at which the drug is released into solution in a specified fluid under given conditions from a dosage form and is used as an indication of the bioavailability of the product (Newton, 1987).

The apparatus used for dissolution testing varies in design, but is usually a paddle where capsules are anchored with a wire spiral (Jones, 2002a), which are immersed in a glass vessel containing the specified dissolution medium. Drug dissolution studies are widely used in both quality control and the development of the dosage forms to ensure the end product or batch-to-batch consistency and to identify acceptable formulations.
The BP (2001) states the test for drug dissolution as follows: Six capsules are subjected to the dissolution test. Individual monographs regulate the apparatus and the test procedures. The preparation will comply with the test if, for each capsule the amount of active ingredient in the solution is not less than 70% of the stated amount except that if one fails this requirement, a further six may be tested individually and all must then comply.

1.9 CAPSULE CONTENTS

1.9.1 Active Ingredient

The type and amount of active ingredient affects the size of the capsule and the excipient used in the formulation (Augsburger, 1995). If the active ingredient has a low drug solubility, the dissolution rate will also be low and therefore so will absorption (Newton and Razzo, 1977; Newton, 1987). To overcome the low rate of dissolution, the particle size can be reduced, thus increasing the surface area in contact with the solvent and improve bioavailability (Bastami and Groves, 1978). However, the smallest particles are not always ideal as Newton and Rowley (1970) showed. They found that at equivalent packing densities, a greater drug release was achieved for the larger particle size fractions. This can attributed to the smaller particle size fractions having a smaller surface area for drug dissolution due to particle agglomeration (Newton and Rowley, 1970). By granulating the formulation it is possible to increase the permeability and drug release of a non-permeable powder bed with low drug release (Newton and Rowley, 1970).

1.9.2 Diluent

Diluents or ‘bulking agents’ are excipients that are added to a formulation to increase the volume to a more manageable quantity. It is the major component after the drug and is often found in the greatest quantity (Jones, 2002b).

Newton et al., (1971a, 1971b) measured the effects of a diluent, wetting agent and lubricant with each factor at different levels of concentration. They found that the system was complex and interactions occurred between the components and for a drug of low solubility, the release was enhanced with higher levels of a soluble diluent (Newton et al., 1971a; Newton et al., 1971b).

The most common diluents used are lactose and starch. Other diluents include microcrystalline cellulose, dicalcium phosphate, dextrose, sucrose and mannitol. Modifications of these materials such as spray dried lactose and pregelatinised starch can
also be used. These substances improve the flow and compatibility and maintain the basic properties of the materials (Augsburger, 1995).

1.9.3 Lubricant

Most high speed filling machines operate by pre-forming a powder plug prior to transferring it into the capsule shell. This usually involves consolidation of the powder bed (Aiache and Beyssac, 1995). Lubricants reduce filming on pistons and adhesion of powder to metal surfaces and reduce friction between the sliding surfaces in contact with the powder and ease the ejection of plugs (Augsburger, 1995).

The most commonly used lubricants are the stearates. Magnesium stearate is the most popular lubricant used in capsule formulations (Jones, 2002b). The problem with lubricants is that they are often hydrophobic and can prevent the wetting of powders and therefore retard drug dissolution (Samyn and Jung, 1970; Newton et al., 1971a; Newton et al., 1971b). The optimum amount of lubricant thus used in capsule formulations should be the minimal quantity, which has the desired lubrication effect (Newton, 1987).

1.9.4 Disintegrants

Disintegrants are added to formulations to break up the dosage form when placed in an aqueous environment (Alderborn, 2002). The object of a disintegrant is to cause the capsule to disintegrate rapidly so as to increase the surface area of the powder plug and promote rapid release of the drug (Jones, 2002b). Disintegrants were not previously used very often in capsule formulations due to the weak nature of the powder plug. Modern capsule filling machinery involves compressing the capsule contents, which have made disintegrants more popular (Jones, 2002a). Traditionally starch was the disintegrant of choice (Botzolakis et al., 1982). Botzolakis et al., (1982) compared the new “super” disintegrants (cross-linked sodium carboxymethylcellulose, sodium carboxymethyl starch and cross-linked polyvinylprolidone) with starch, in capsules filled using the Zanasi LZ-64 dosator capsule filling machine and found enhanced drug release (Botzolakis and Augsburger, 1982). Botzolakis and Augsburger (1984) later studied the effect of disintegrants on drug dissolution from soluble (lactose) and insoluble (dicalcium phosphate) fillers at different lubricant concentrations and compression forces. They found that disintegrants enhanced drug dissolution and that the compression force, lubricant concentration and filler type influenced the effectiveness of the disintegrants (Botzolakis and Augsburger, 1984). However Lai (1991) found that there is little function for disintegrants in capsule formulations and that 60% of capsule formulations on the market do not contain a disintegrant.
1.10 POWDER FLOW

Good powder flow is vital for a uniformly filled capsule. This is because the powder bed from which the dose of the mix is measured needs to be homogenous in order to give uniform fill weights. Good packing is assisted with good powder flow and this is aided by mechanical devices on the filling machine (Aiache and Beyssac, 1995).

For hand operated, semi-automatic capsule filling machines, vibratory capsule filling machines and vacuum capsule filling machines the powders must be free flowing. In the case of the dosator type capsule filling machines, the powders must be sufficiently free flowing to flow under gravity from a reservoir down to a lower dosing hopper. The powder should permit efficient closing in of the hole left by the dosator and sufficient adhesiveness to retain the powder plug within the dosator funnel and to prevent loss of material from the end of the powder plug during delivery into the capsule body (Cole, 1987b).

Powder flow can be affected by a variety of factors including particle physical properties such as particle size, shape, density and the overall packing characteristics. The surface energy, porosity and electrostatic charges also have a great affect on the flowability of the powder as well as container shape and wall surface properties (Carr, 1970).

1.10.1 Particle Size

Particle size affects the flowability of a powder. Particles with a high surface to mass ratio are generally more adhesive than coarser particles (Staniforth, 2002). Particles greater than 250μm are usually relatively free flowing (Staniforth, 2002), but as the size drops to 50μm - 150μm powders become adhesive and flow problems are likely to occur (Pilpel 1971). However, adhesive properties up to a size range of 300μm - 400μm have been reported for substances such as carboxymethyl cellulose. This can be attributed to its irregular shape causing the particles to mechanically interlock (Pilpel, 1971). Powders having a particle size of less than 10μm are usually extremely cohesive and resist flow under gravity except as large agglomerates (Neumann, 1967). This is because surface forces are related to surface area and as the size of the particle decreases the relative surface area increases and hence the surface forces increase (Carr, 1970).

1.10.2 Particle Shape

Different flow properties are encountered with powders with similar particle sizes but different shapes. This is caused by differences in interparticulate contact areas i.e. a
A group of spheres has minimum number of interparticulate contacts and therefore generally exhibits good flow properties, whereas a group of particles which are elongated, fibrous or irregular shaped have many points of contact and therefore possess poorer flow properties (Carr 1970).

### 1.10.3 Particle Density

Powders normally flow under the influence of gravity and therefore dense particles are generally less adhesive and more free flowing than less dense particles of the same size and shape (Carr, 1970).

### 1.10.4 Packing Geometry

Particles filled into a certain volume of space produce a powder bed, which is in static equilibrium due to interaction of gravitational and adhesive forces. If the bed is slightly vibrated, the particles will be mobilised so that if the vibration is stopped, the bed is once more in static equilibrium but occupies a different spacial volume than before. By rearranging the packing geometry of the particles, the bulk volume occupied by the particles is altered causing a change from a set of particles which are loosely packed to a more tightly packed set of particles, where there is a greater adhesive force. This also means that more tightly packed powders require a higher force to produce powder flow than more loosely packed particles (Staniforth, 2002).

### 1.10.5 Flow from Hoppers

Due to the importance of producing unit doses in capsule filling machinery, the flow behaviour of particles in a hopper has been greatly studied along with the method in which the particles pass through the orifice (Podczeck, 1998).

A hopper can be considered as a tall cylinder with a closed orifice. When the orifice is opened a flow pattern develops as the powder discharges from the hopper (Neumann, 1967).

The flow of material in a hopper is shown in figure 1.7. Particles in region A slide rapidly over region B which itself is sliding slowly over the stationary region E. Region C is formed by groups of particles from regions A and B which move rapidly downwards and inwards into region D where the material flows out of the hopper (Neumann, 1967).
The consequences of this are that replenishing partly emptied hoppers may result in long
residence times in region E for particular fractions of the material. Discharge patterns
from a hopper with this form may result in segregation (Cole, 1987d).

To avoid dead spaces occurring and so that every particle is in motion and so no arches
can form over the hopper outlet and the effects of segregation are minimised, a hopper
can be designed so that ‘mass flow’ takes place (Prescott and Barnham, 2001). These
hoppers are designed so that the outlet is large enough for mass flow and the walls steep
enough (Jenike, 1961). Where uniform flow is still not achieved, small quantities of air
may be introduced into the lower hopper wall and/or a glidant may be added (Pilpel,
1965; Cole, 1987d).

1.10.6 Characterisation of Powder Flow
There are many methods to characterise powder flow, either directly using dynamic
methods, or indirectly by carrying out measurements on static beds.

Powder flow can be measured by the determination of the angle of repose (Train, 1958)
or by direct observation of the flow velocity using electrical or electronic flow meters
(Gold et al., 1966), by using a linear shear cell (Jenike, 1961) or an annular shear cell
(Carr and Walker, 1967/68), by determination of the critical orifice diameter (Walker,
1966) or by using packing properties such as minimum and maximum powder density
and derived parameters (Carr, 1965; Hausner, 1967).

Experimental methods to determine the angle of repose may be divided into two groups,
static and dynamic (Train, 1958). The static methods include the fixed funnel and the
fixed bed cone. The dynamic methods involve measurement under more dynamic conditions and thus are more realistic and include the tilting box, the rotating cylinder and drained angles of repose (Pilpel, 1965). Static methods tend to give lower values than dynamic methods caused by some degree of heap collapse (Train, 1958). The different methods for the measurement for the angle of repose have been critically assessed by various workers including Train (1958). It emerges that the value found for the angle of repose depends on the method of measurement. The angle decreases as the size of the bed and the particle size increase and also the different methods may produce different values of angle of repose for the same powder (Train 1958).

Powder flow meters (Gold et al., 1966) can only be applied to free flowing powders, where the adhesional and frictional forces are easily overcome by gravity. Thus powder flow meters are often equipped with vibrators to assist with powder flow (Podczeck, 1998).

The critical orifice diameter (Walker, 1966) is a direct measure of the ability of a powder to form an arch. Thus, it is a measure of the attractive forces between the particles in the powder bulk (Podczeck, 1998).

1.10.6.1 Bulk Density Measurements
The powder bulk density is the weight per unit volume of a material and is dependent on particle packing (Carr, 1965). Packing properties are evaluated by determining the minimum bulk density (also known as bulk, fluff or poured density) and the maximum bulk density (also known as tapped, equilibrium or consolidated bulk density) (Aiache and Beyssac, 1995).

The minimum bulk density is determined by the weight of the powder allowed to flow from a fixed height into a container, divided by the volume of the powder bulk. To obtain the maximum bulk density, the powder contained in the measuring cylinder is mechanically tapped using a mechanical tapping device. This instrument measures the change in packing volume, which occurs when the void space diminishes and consolidation occurs so that the volume decreases from the minimum bulk density to the maximum bulk density when it has attained its most stable packing arrangement (Carr, 1965).

The tapping kinetics can be estimated by recording the density after a given number of taps until no change occurs. Powder consolidation is a function of several factors,
including particle size, shape, particle density, surface properties and size distribution (Aiache and Beyssac, 1995).

1.10.6.2 Carr's Compressibility Index and Related Methods

Carr (1965) found a strong relationship between compressibility and the flowability of a powder. Carr (1965) observed the more compressible a material is, the less flowable it will be and conversely the less compressible it is, the more flowable the material would be. The compressibility $C$ was defined as follows:

$$CC\% = \left( \frac{\rho_{\text{max}} - \rho_{\text{min}}}{\rho_{\text{max}}} \right) \times 100$$

where $\rho_{\text{max}}$ is the maximum bulk density and $\rho_{\text{min}}$ is the minimum bulk density.

Carr's compressibility index gives an indirect indication of the uniformity in size and shape, deformability, surface area, adhesion and moisture content of the powder (Carr, 1965; Carr, 1970). The change from a freely flowing powder into a non-freely flowing powder is at 20% to 21% of Carr's compressibility index (Carr, 1965), (Table 1.4).

Table 1.4: Relationship between percentage compressibility and powder flow according to Carr (Carr, 1970)

<table>
<thead>
<tr>
<th>Carr's compressibility index (%)</th>
<th>Flowability</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-15</td>
<td>Free flowing granules (excellent flow)</td>
</tr>
<tr>
<td>12-16</td>
<td>Free flowing powdered granules (good flow)</td>
</tr>
<tr>
<td>18-21</td>
<td>Powdered granules (fair to passable flow)</td>
</tr>
<tr>
<td>23-28</td>
<td>Very fluid powders (poor flow)</td>
</tr>
<tr>
<td>28-35</td>
<td>Fluid cohesive powders (poor flow)</td>
</tr>
<tr>
<td>33-38</td>
<td>Fluid cohesive powders (very poor flow)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Cohesive powders (very, very poor flow)</td>
</tr>
</tbody>
</table>

Similarly, Hausner (1967) defined a compression ratio named the Hausner ratio ($HR$):

$$HR = \frac{\rho_{\text{max}}}{\rho_{\text{min}}}$$

Hausner found that the maximum bulk density and minimum bulk density ratio was related to particulate properties such as particle porosity, size and shape and the surface properties of the particles. Thus the compression ratio could be used to predict powder flow properties. Hausner (1967) found that values less than 1.25 indicate good powder flow and values above 1.25 indicate poor powder flow.
Both the Hausner ratio and Carr’s compressibility index reflect the frictional and adhesive properties of the powder. This is because at rest, those particles with high frictional and adhesive forces will have a low bulk density as gravity alone will not be able to overcome these forces (Podczeck, 1998). During tapping, particles will jump and thus lose contact with each other. At this moment there will be no frictional and adhesive forces between the particles, allowing the particles to rearrange themselves in the powder bed. Hence the greatest reduction in volume is achieved when the frictional and adhesive forces between the powder particles are large (Hausner, 1967; Podczeck, 1998).

Lüddecke and Kawakita (1966) used the Kawakita compression equation to describe the volume reduction of a powder when subjected to vibration, pressure or tapping:

\[
\frac{N}{C} = \frac{1}{ab} + \frac{N}{a}
\]

Where \(N\) is equal to the number of taps; \(a\) and \(b\) are constants which are characteristics of the powder bed; \(C\) is the volume reduction and equals to \((V_0-V_T)/V_0\) where \(V_0\) is the initial volume of the powder and \(V_T\) is the powder volume, after \(N\) taps. Lüddecke and Kawakita (1966) showed that the constant \(a\), which quantifies the maximum possible volume reduction is theoretically equal to Carr’s compressibility index for tapping experiments.

Podczeck and Lee-Amies (1996) confirmed this experimentally and found that the application of the Kawakita constant had no advantage over the use of Carr’s compressibility index. They found that an estimate of the volume reduction due to low compression could be determined by adding 5% to Carr’s compressibility index (Podczeck and Lee-Amies, 1996). The Kawakita constant \(a\) and the angle of internal friction were measured by Lüddecke and Kawakita (1966) and Tan and Newton (1990a). They found no correlation between the Kawakita constant and the angle of internal friction indicating there was no correlation between the frictional properties of the powders and Carr’s compressibility index or Hausner’s ratio. Podczeck (1998) suggested that this could be attributed to the shear cell not reflecting the frictional forces adequately, or Hausner’s theory being wrong, or the measurements being flawed. Podczeck and Sharma (1996) discussed the limitations of the accuracy with which the tapped powder density could be obtained using a mechanical tapping device. They found that at a fast tapping speed (greater than 30 taps per minute) and a low free fall distance (less than 25mm), particles could not overcome their adhesional and frictional force interactions and thus particle packing remained incomplete, even after 50,000 taps (Podczeck and Sharma, 1996). The BP (2001) requires that tapping experiments be performed at a tapping speed of 250 ± 15 taps per minute using a free fall distance of 3 ± 0.2mm. Hence,
particles with high adhesional and frictional forces, result in less reliable tapping results under BP conditions. Therefore, the lack in correlation between Kawakita constant (and therefore Carr's compressibility index) and the angle of internal flow using shear cell measurements may be attributed to flawed tapping experiments (Podczeck, 1998).

### 1.10.6.3 Angle of Internal Flow

Varthalis and Pilpel (1976) established another method to analyse data from tapping experiments. They found a relationship between the powder porosity $E$ and the number of taps $N$.

By plotting: \[ \frac{E^3 N}{1 - E} \] as a function of the number of taps $N$,

Varthalis and Pilpel found a linear relationship whose intercepts on the ordinate were defined as $K_\theta$. Plotting $(K - K_\theta)$ against $N$ gave a straight line and the slope of this line was defined as $\tan \theta$, where $\theta$ was termed the angle of internal flow.

Using a tamp filling machine simulator, Newton and Bader (1987) found that as the values for the angle of internal flow increased, the fill weight of the capsules decreased. However, when filling powders on an instrumented mG2 dosator nozzle capsule filling simulator, Tan and Newton (1990a) found no significant relationship between the coefficient of fill weight variation and the angle of internal flow. Podczeck and Newton (1999) found that when filling powders using a tamp filling machine, there was a close relationship between the angle of internal flow, the minimum coefficient of fill weight variation, the stickiness of the powder and the dynamic packing behaviour represented by the kinetics constant $k_i$ according to Hauer (1993a). The maximum plug density and the maximum coefficient of fill weight variation were also related to the same set of powder properties. They found that as the angle of internal flow increased, the minimum coefficient of fill weight variation increased. Sticky powders such as lactose, dicalcium phosphate and corn starch, were found to be less good as fillers and this influenced the values for the angle of internal flow and the filling performance. They also found that as the angle of internal flow increased, the plug density decreased. They attributed this to the frictional forces between the particles, which hindered slippage and particle rearrangement, so that upon tamping, the powders could not be densified to a large extent.
1.10.6.4 Compaction Constant
Mohammadi and Harnby (1997) explained that the minimum bulk density can only be imprecisely determined as it is subject to experimental error. They suggested that it is better to use a model of densification describing the volume reduction during tapping (rate of densification) which is less influenced by experimentally obtained minimum and maximum bulk densities.

The Cooper and Eaton equation (Cooper and Eaton, 1962) was modified and the minimum and maximum bulk densities were fitted to a non-linear relationship between the density reached \((d_N)\) after a certain number of taps \((N)\), (Mohammadi and Harnby, 1997):

\[
d_N = d_{\text{max}} - (d_{\text{max}} - d_{\text{min}}) \exp^{-N/T}
\]

The values of \(d_{\text{max}}\) and \(d_{\text{min}}\) are the theoretical maximum and minimum bulk density of the powders, respectively, and are fitted parameters instead of measured values. ‘\(T\)’ is the compaction constant and describes the ease of densification. A value of ‘\(T\)’ below 35 indicates slow densification whereas \(T\)-values greater than 35 indicate rapid densification. However, Podczeck and Newton (1999) found that for capsule filling with a tamp filling machine, the optimum value for the compaction constant \(T\) was between 20 and 25. Values below the optimum resulted in a high capsule fill weight variation caused by powder flooding and \(T\)-values above 30 resulted in major filling problems, due to poor powder flow and slow bed densification.

1.10.7 Shear Properties
Shear cell measurements are a direct reflection of the attractive forces between the particles in a powder bulk, although the assessment of the powder properties is based on a continuum approach (Podczeck, 1998). Jenike (1961) assumed that a bulk solid could be closely approximated by a rigid-plastic Coulomb solid. From soil mechanics, such a solid could be characterised by a yield locus that defines the limiting shear strength under any normal stress. Jenike (1961) found however, that shear measurements made with real bulk solids at low values of shear stress, the yield locus deviated from a straight line. He also found that the yield locus did not increase indefinitely but terminated at point \(E\) (end point). At this particular point, the powder flowed without a change in its volume and was described as the critical state. Furthermore, Jenike (1961) discovered that the position of the yield locus was not constant, but a function of the extent to which the powder was consolidated \(i.e.\) a function of its bulk density.
This principle was demonstrated using the linear shear cell (Jenike, 1961) (Figure 1.8). The powder was filled into the two halves of the shear cell and consolidated using a normal stress (normal load per cross-sectional area). A shear stress was applied across the two halves of the shear cell to result in failure of the powder bed. For a linear shear cell, fresh powder was filled into the shear cell and consolidated using the same normal load, before a reduced normal load was applied and the powder sheared. This complicated the procedure and made the outcome more variable. However, using an annular shear cell, the powder bed could be consolidated to the initial failure stress by reverting the direction of the turntable. Therefore, the procedure of shearing the powder until failure could be repeated using reduced normal loads without having to exchange the powder in the cell. This resulted in a yield locus, which defined the critical combinations of normal and shear stresses at which failure occurred for the powder sample (Podczeck, 1998).

Figure 1.8: Linear shear cell; Powder is filled into two halves of the shear cell and consolidated. At a given normal load, shear stress is applied across the two halves of the shear cell to result in failure of the powder bed (Staniforth, 2002)

1.10.7.1 Angle of Internal Friction

The slope of the yield locus for a given normal stress (Figure 1.9), i.e. \( \tan \delta \) is proportional to the kinetic coefficient of friction, while \( \delta \) is called the angle of internal friction. The value of \( \delta \) is a measure of the ease at which powder flow at constant volume can be maintained (Richards, 1966).

Figure 1.9: Evaluation of shear cell measurements to determine the angle of internal friction (\( \delta \)) and the cohesion coefficient (\( \tau_0 \)) (Podczeck, 1988)
1.10.7.2 Cohesion Coefficient

The cohesion of a powder bed is deduced from the intercept of the yield locus with the normal stress (Jenike, 1961). Hence, the shear stress at zero normal stress is equal to the cohesion of the powder and is referred to as the “cohesion coefficient” or “stickiness” of the powder. It describes the shear strength of a powder at failure for zero normal stress. For a non-cohesive powder, the intercept of the yield locus will pass through the origin, equivalent to zero normal shear stress. The value of the cohesion coefficient is related to the adhesion or autoadhesion forces acting between the particles in the powder bed (Podczeck, 1998).

1.10.7.3 Angle of Effective Friction

The effective yield locus (Jenike, 1961) operates during steady state flow (Figure 1.10). It is obtained from yield loci and is the line that links the shear stress with the origin for each consolidation stress. The angle of effective friction $\phi$ is thus the angle formed between the effective yield locus and abscissa. For free flowing powders where attractive forces in the powder bulk are small, the values for the angle of internal friction and the angle of effective friction are similar and cohesion coefficient approaches zero.

Figure 1.10: Evaluation of shear cell measurements to determine the angle of effective friction (Podczeck, 1988)

1.10.7.4 Mobility Index

The mobility of a powder can be defined as (Deluil et al., 1994) where $\phi$ is the angle of effective friction:

$$ m = \frac{1 - \sin \phi}{1 + \sin \phi} $$

The mobility index $m$ is an intrinsic property of the individual particles in the powder bulk. The value of $m$, can lie between 0.03 and 0.6. Low values of $m$ are associated if the particle shape allows interlocking, or increased friction between the particles due to rough surfaces. A value of $m$ greater than 0.35 indicates a high degree of freedom between the particles and thus an increased chance of segregation.
1.10.7.5 Jenike' Flow Factor

Jenike's flow factor \((FF)\) characterises the flowability of a solid. Jenike (1961) defined a flow factor based on the unconfined yield strength \((f_c)\) and the major principal stress \((\sigma_m)\). The unconfined yield strength is a measure of the strength required for arching to occur \(i.e.\) the largest stress that the solids can withstand at a free, unsupported surface. Hence, the adhesion or autoadhesion forces between the particles of a powder bed must exceed the force of gravity, which would cause the powder to flow. The major principal stress represents the stress along the major principal plane at zero shear stress, which consolidates the powder and acts at any point in the powder bed during gravitational flow. The flow factor is obtained by constructing two Mohr stress circles with their centres on the normal axis, tangentially to the yield locus (Figure 1.11). Jenike (1961) used a Mohr stress semicircle to identify the frictional and strength properties of the powder from the yield locus. For any stress condition represented by a Mohr semi-circle tangent to the yield locus, the bulk solids will be at yield. The first semicircle is constructed to pass through the origin and defines the unconfined yield strength \(f_c\). The second passes through the end point of the yield locus and its intercept on the abscissa gives the major principal stress \(\sigma_m\). A pair of such values is obtained from each yield locus and the results are plotted on a graph with the ordinates \(f_c\) and \(\sigma_m\). The Jenike-flow factor (Jenike, 1961) of the material is thus defined as the reciprocal slope of \(f_c\) as a linear function of \(\sigma_m\) of the resulting graph at various consolidation loads.

Figure 1.11: Mohr circle to obtain the major principal stress \(\sigma_m\) and unconfined yield stress \(f_c\) (Pilpel, 1971)

In general, free flowing powders are characterised by a \(FF > 10\), easy flowing powders have \(FF\) values between 4 and 10, and cohesive powders have a \(FF\) value between 1.6 and 4. Values less than 1.6 are characteristic of very cohesive, non-flowing powders (Jenike 1961).
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Tan and Newton (1990b) found a significant correlation between the coefficient of fill weight variation and the flow factor. However, they found no correlation between the coefficient of fill weight variation and the angle of internal friction for powder filled hard gelatine capsules using an instrumented mG2 dosator capsule filling simulator.

Podczeck and Miah (1996) studied the influence of particle size and shape on the angle of internal friction and Jenike's flow factor on lubricated and unlubricated powders. They found that for unlubricated powders, the angle of internal friction was dependent on particle size and shape. However, they found that at an optimum magnesium stearate concentration, the angle of internal friction depended only on the particle shape and asymmetry of the particles. They found that at optimal magnesium stearate concentrations for the flow factor, i.e. flow factor values were the highest; these values were slightly different to those for the angle of internal friction. Podczeck and Miah (1996) found that while the flow factor depended only on particle shape, the corresponding optimal magnesium stearate concentration only depended on particle size.

1.11 MIXING

1.11.1 Definition

Mixing is involved at some time in the preparation of practically every pharmaceutical preparation (Twitchell, 2002). Mixing is a process to obtain a distribution in which each particle of a component is near a particle of another component (Poux et al., 1991), so that each fraction randomly sampled contains all the components in the same proportion as the whole preparation (Aiache and Beyssac, 1995). The chance of obtaining this type of mixture in industrial mixers is very unlikely (Poux et al., 1991).

1.11.2 Types of Mixtures

Powder mixtures can be free flowing or adhesionless, where the particles of the powder mixture are able to move independently of each other (Fan et al., 1990). There are also interactive powder mixtures (Hersey, 1975; Egermann and Orr, 1983) where interparticulate forces are present and particles move with an associated cluster of particles (Fan et al., 1990).

1.11.2.1 Free Flowing Mixtures

If free flowing particles are identical then a random mixture can be obtained. This requires particles of the same size and weight, which are non-adhesive (Fan et al., 1990; Poux et al., 1991). If the particles, however, are not identical, then a partially randomised
final mixture will be obtained due to incomplete mixing or segregation in the blend (Fan et al., 1990).

1.11.2.2 Interactive Mixtures
In interactive or adhesive powder mixtures, the forces causing adhesion are Lifshitz-van der Waals forces, capillary forces, electrical forces and electrostatic image forces (Podczeck, 1998). The attractive forces between the particles are greater than the gravitational forces and thus mixing and segregation effects caused by gravity do not arise (Staniforth, 1981; Podczeck, 1998).

In interactive mixing, one of the powdered mixes is added in a fine form and during mixing it will adhere to the surface of the larger coarse particle or carrier particles (Yip and Hersey, 1977a). The strength of the interparticulate force will determine the properties of the powder mix (Fan et al., 1990; Podczeck, 1998). This has the effect of minimising segregation whilst maintaining good flow properties (Twitchell, 2002). This was first reported during the mixing of micronised sodium bicarbonate with sucrose crystals and was found to exhibit minimal segregation (Travers and White, 1971).

Hersey (1975) stated that the homogeneity of powder mixtures may be improved by adhesion between the particles. Yip and Hersey (1977a) found that the mixing of binary mixtures of micronised salicylic acid or fine grade crystal violet with coarse grade sucrose resulted in almost perfectly homogenous mixtures. The homogeneity of the mixtures was defined using Buslik’s concept of homogeneity (Buslik, 1973), stating that an ordered mixture cannot achieve a greater homogeneity than the size of the single ordered unit. They concluded that adhesion interactions between the particles led to an interactive powder mixture (Yip and Hersey, 1977a). When adding a third component to a powder mixture, the amount of adhesion forces between the particles will determine which component adheres to which (Podczeck, 1998). Anno and Rees (1985) found that depending on the interparticulate forces between the components of a powder mix, the sequence of mixing significantly influenced the dissolution of drug from the capsules.

1.11.2.3 Partially Ordered Mixture
Mixing of powders in the pharmaceutical industry is rarely solely free flowing in that some interaction and adhesion will occur between constituents leading to a mix which is partly interactive and partly free flowing (Poux, 1991). Johnson (1979) found that when mixing tetracycline with lactose, some of the tetracycline adhered on the surface of the lactose while some of the tetracycline remained freely distributed as primary drug
particles (i.e. mixing was achieved by both an interactive and free flowing processes) (Johnson, 1979). Hersey et al., (1979) described this as a partially ordered mixture where the adsorption sites on the carrier particles become saturated with the fine adhesive particles and the remaining adhesive material agglomerates.

1.11.3 Powder Mixing Mechanisms

1.11.3.1 Mixing in Free Flowing Mixtures
There are three mechanisms of powder mixing: convective mixing, shear mixing and diffusive mixing (Poux et al., 1991).

Convective mixing
Convective mixing occurs when groups of adjacent particles are transferred from one location to another (Lacey, 1954) i.e. when relatively large groups of particles are transferred from one part of the powder bed to another by means of blades or paddles (Twitchell, 2002).

Shear mixing
Shear mixing is caused by the setting up of slip planes within the mixture (Lacey, 1954). It occurs when a ‘layer’ of material flows over another ‘layer’. This could be due to the removal of a mass by convective mixing creating an unstable slip plane, which results in the powder bed collapsing. It can also occur in high shear mixers or tumbling mixers, where the action of the mixer results in velocity gradients within the powder bed and therefore shearing of one layer over another (Twitchell, 2002).

Diffusive mixing
Diffusive mixing occurs when there is a distribution of particles over a freshly developed surface (Lacey, 1954). For example, when a powder bed is forced to move or flow, the volume occupied by powder bed will increase. This is because the powder particles will become less tightly packed and there will be an increase in the air spaces or voids between them. Under these circumstances, there is potential for the particles to fall under gravity through the voids created. Since diffusive mixing involves individual particles, it can in time produce a truly random mix. Convective and shear mixing can quickly produce a rough mix but local groups of particles may remain unseparated unless subjected to diffusive mixing (Twitchell, 2002).
1.11.3.2 Mixing in Interactive Mixtures
Interactive mixing probably occurs to a certain extent in every pharmaceutical powder mix, due to adhesive forces acting between components in the powder mixture. It is most likely to occur when smaller particles exist, as these have a high specific surface area and so the attractive forces holding the particles to the adsorption site are likely to be greater than the gravitational forces separating the components (Fan et al., 1990). Stephenson and Thiel (1980) showed that the relative humidity influenced the formation of an interactive mixture by affecting the adhesion forces and giving rise to ordered units.

1.11.4 Segregation
Mixing and segregation are both influenced by the flow characteristics of the powder. If the particles are free flowing, they have a high degree of mobility and can flow easily. Mixing and segregation occur when the systems are subjected to motion in a mixer or handled after mixing (Chowhan, 1995).

1.11.4.1 Segregation in Free Flowing Mixtures
Segregation of the mix can occur at the same time as the blend is being mixed. Ideally to avoid segregation, it is useful to mix powders with very close characteristics. Factors which cause segregation are differences in particle size, particle size distribution, density, shape and shape distribution (Chowhan, 1995).

Particle size is the most important factor (Chowhan, 1995). Small particles can fall through the gaps between the larger particles making their way towards the bottom of the container causing the larger particles to rise to the top. Ideally, all the components should have the same particle size as the drug (Poux et al., 1991).

Particles of the same size may not have the same density and shape. The density of each component affects the stability of the mixture. The denser particles have a tendency to fall to the bottom whilst the less dense particles rise to the top of the powder bed (Train, 1960). These particles will separate whenever their motion is accelerated or decelerated such as under the influence of centrifugal force (Chowhan, 1995).

Wong and Pilpel (1990) studied the effect of particle shape on the mixing of powders. They found that the time taken to achieve an acceptable standard deviation of mixing increased with the irregularity of the particles, but mixtures containing irregular particles segregated less on vibration (Wong and Pilpel, 1990).
Good homogeneity is more difficult to obtain if the proportion of one component is small. Segregation may occur during transfer, transportation, storage or during movement of the powder mixture from the hopper or during sampling for analytical test procedures (Chowhan, 1995). In recent years equipment which can perform both mixing and other operations in the same vessel have become popular. This avoids handling the mass between operations (Twitchell, 2002).

There are three types of segregation:

**Percolation segregation**
Interparticle percolation is size, shape or density segregation in a failure zone (Chowhan, 1995). The rate of percolation is determined by the gravitational force on the particles (Fan et al., 1990) and hence does not occur for adhesive powders (Chowhan, 1995). Percolation segregation occurs when there are two powders of different sizes and the smaller particles move through the voids between the larger particles. It can also occur if the powders are similar in size and there is a high void fraction or the powder bed is mobile (Chowhan, 1995). Spherical particles exhibit the greatest flowability and are therefore more easily mixed, but they also segregate more easily than the non-spherical particles. Irregular or needle shaped particles may become interlocked, thus reducing the tendency to segregate. Non-spherical particles also have a greater surface area to weight ratio, which will tend to decrease segregation by any cohesive effects. If the components are of different density, the more dense material will have a tendency to move downwards, even if the particle sizes are similar (Twitchell, 2002).

**Trajectory segregation**
When particles are mixed and set in motion they gain kinetic energy. Larger particles gain more energy and travel a greater distance into the powder mass before they reach their “stopping distance” (Poux et al., 1991; Chowhan, 1995). This can result in preferential separation of the powder particles (Twitchell, 2002). Trajectory segregation can also occur with particles of the same size but different densities due to their differences in mass (Twitchell, 2002).

**Vibration segregation**
Differences in size, density and shape between particles may cause segregation if the mass is subject to vibration (Chowhan, 1995). This can occur in a vibratory capsule filling machine. It is found that the larger, denser particles move upwards through the mass. This may be due to the fact that vibration causes the smaller particles to move
beneath the larger particles and become slightly compacted and raise the large particles upwards in the bed (Staniforth, 1982; Chowhan, 1995).

1.11.4.2 Segregation in Interactive Powder Mixtures
Interactive powder mixtures have been shown to be mechanically stable (Egermann and Orr, 1983). The constituents in an interactive mixture tend not to segregate because of the strong adhesive forces acting among them (Yip and Hersey, 1977b). The nature and strength of these forces will determine the ease or difficulty of mixing and segregation (Fan et al., 1990). Segregation of interactive mixes can, however, still occur. To avoid segregation of interactive mixes, the type of mixer should be taken into consideration as some mixers can encourage segregation (Poux et al., 1991). Segregation can be minimised if the excipient is monodispersed (Crooks and Ho, 1976). Also if each particle has an equal number of monodispersed drug particles adhering to it (Yip and Hersey, 1977b).

“Ordered unit” segregation
Ordered units are aggregates of fine particles adhering to coarse carrier particles (Podczeck, 1998). Segregation of the material can occur if there are differences in size between the carrier particles, as they will have different surface area to weight ratios, containing different amounts of adsorbed drug per unit mass. Segregation of the carrier particles will result in areas where there are high drug concentrations, resulting in ordered unit segregation (Yip and Hersey, 1977b)

Displacement segregation
The addition of a third component to an interactive mix may result in competition for the available sites. It can replace the adhered particles on the carrier particles or remove the particles without adhering to the carrier particles (Lai and Hersey, 1979). This only occurs if the attractive forces between the fine particles and the third component are greater than those developed for the carrier particles (Podczeck, 1998). Magnesium stearate is a common lubricant added to mixes and Lai and Hersey (1979) have demonstrated that this may cause “stripping” of fine particles from carrier particles.

Saturation segregation
This occurs when there are insufficient carrier particles. Each particle can only accommodate a certain amount of adsorbed material on its surface. If there is an excessive amount of small particles which are not adsorbed onto the carrier particles, the
powder may segregate. This limits the amount of the active component that may be used in the formulation (Twitchell, 2002).

1.11.5 Powder Mixing Equipment

An ideal powder mixer should rapidly produce a complete blend and not encourage segregation. It should be easily cleaned and discharged, be dust tight and require low maintenance and low power consumption (Poux et al., 1991).

Mixer vessels operate by a predominant mode of action but all three powder mixing mechanisms, convective, shear and diffusive mixing occur together to some extent (Poux et al., 1991). Mixing can thus be considered as a random shuffling operation, involving both large and small particle groups of individual particles (Aiache and Beyssac, 1995).

1.11.5.1 Tumbling Mixers

Materials can be mixed in tumbling mixers or rotating-shell mixers, which are rotating vessels of various shapes: drum type, cubical or polyhedron shaped and double cone. The charge flows with the vessel when the angle of repose is exceeded (Aiache and Beyssac, 1995).

These mixers are used commonly and have their axis of rotation horizontal to the centre of the blender (Fan et al., 1990). The addition of baffles or inclining the drum on its axis increases the flow and increases convective mixing. The Y-cone blender is an example of a tumbler mixer (Fan et al., 1990). On rotation, the powder flows into the top two arms of the Y and then back into the third arm. When the streams overlap, mixing occurs by shear and diffusion. There is an optimum speed of rotation, which enables the mix to flow into the arms and then back into the third arm (Aiache and Beyssac, 1995).

1.11.5.2 Convective Mixers

A convective mixer, or fixed-shell mixer depends upon the motion of a blade or paddle through the blend. Groups of particles are moved from one location to another producing a high degree of convective mixing (Fan et al., 1990). The ribbon mixer is the most common type (Fan et al., 1990). The ribbon blades rotate in a hemispherical trough and the particles are relocated by the moving ribbon (Fan et al., 1990). The shearing action which develops between the moving blade and the mixer serves to break down powder agglomerates but dead spaces are difficult to eliminate (Aiache and Beyssac, 1995).
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The Nautamixer is a more recent type of convective mixer. It consists of a conical vessel fitted at the base with a rotating screw, which is fastened to the end of a rotating arm at the top (Fan et al., 1990). The screw carries material to the top of the vessel, which then falls back into the mass (Twitchell, 2002). The advantage of this type of mixer is that dead spots are avoided because the screw encompasses every part of the vessel in each revolution as the arm rotates (Twitchell, 2002). This mixer combines diffusive, shear and convective mixing (Twitchell, 2002).

1.11.6 Homogeneity

A homogenous mixture is defined as any sample taken from the mixture being identical to any other sample. As long as the samples are large enough, however, every mixture can be defined as homogenous (Poux et al., 1991).

1.11.6.1 Sampling Method

To assess the quality of a mixture, a small volume of the material can be selected from the powder mixture and analysed to calculate relative standard deviation or variation of the samples (Poux et al., 1991). Samples may be withdrawn periodically from the mixer using a samples thief or on-line during the mixing process (Poux et al., 1991).

1.11.6.2 Number of Samples

When too many samples are taken from a mixture, this can alter the structure of the mixture. If not enough samples are taken, it is not possible to determine the homogeneity of the mixture (Poux et al., 1991). Schweiger et al., (1997) used a statistical approach to determine the minimum number of samples to be drawn. See section 5.3.1.

1.11.6.3 Sample Size

Yip and Hersey (1977a) defined an interactive mixture as having a standard deviation of zero of the sample concentration at all sample sizes. This only applied as long as the sample size was greater than the size of a single ordered unit. The standard deviation for a random mixture however, decreases with increasing sample size (Poux et al., 1991). The scale of scrutiny is the sample size at which the mixture should be examined (Poux et al., 1991). In evaluation of the mixture, care must be taken such that the scale of scrutiny is appropriate. It is of little consequence how the drug is dispersed within this sample, but the size of the samples chosen must be large enough to contain sufficient particles to represent accurately the region from which they were taken, and yet not so large as to obscure important small-scale variations in composition. The selection of a scale of scrutiny of a mixture also depends on the ultimate use of the mixture (Twitchell, 2002).
Schweiger et al., (1997) demonstrated that the sample size depends on the number of particles and calculated the minimum sample size using statistical analysis.

1.11.6.4 Location of the Sample
Samples withdrawn from different areas of the mixer should give an overall view of the progress of the mixing process. This varies according to the type of mixer employed (Poux et al., 1991).

1.11.6.5 Effects of Mixing Time
The factors promoting segregation require a longer time to establish a segregation mix than is needed to produce a reasonable degree of mixing. It is counterproductive to prolong the mixing time beyond an optimum point as this may promote segregation (Cook and Hersey, 1974; Schweiger et al., 1997). Cook and Hersey (1974) studied the mixing of fenfluramine with various diluents and found that the optimal mixing time was at 10 minutes. Subsequent mixing of the components resulted in a partial segregation of the components (Cook and Hersey, 1974). Hence, it is disadvantageous to prolong the mixing beyond a certain point (Twitchell, 2002).

Schweiger et al., (1997) determined the optimum mixing time of a powder mixture of lactose and corn starch. Samples were drawn from the mixer at various time intervals and the variance of lactose concentration was measured for progress and quality of mixing.

Hence, to achieve a homogenous powder mixture, the adhesion forces between the components in the mixture must be greater than the autoadhesion forces between the particles. This will result in one component distributing over the surface of another component. However, particulate properties such as surface roughness and deformability can influence the distribution process. Particles with rough surfaces have larger clefts and these can trap fine particles in the powder mixture. Therefore, the fine particles will fill the clefts and fewer particles will be distributed. If the fine particles consist of soft deformable particles, the mixing force can enhance the area of contact between them and this will result in strong autoadhesion forces. This could result in the autoadhesion forces being greater than the adhesion forces to a second powder component. Hence the final powder mixture will contain the coarse powder component and the agglomerates of the fine powder component, and the homogeneity of the powder mixture will be comparable to that of a free flowing mixture (Podczeck, 1998).
1.12 AIMS AND OBJECTIVES

There are relatively few literature reports studying the filling behaviour of hard gelatine capsules on tamp filling machines due to the large variety of dosing systems available for filling capsules. The aim of the study was to investigate the effect of excipient type and levels and to identify relationships between powder flow, filling performance, disintegration and dissolution of powder mixtures using the Bosch GKF-400S machine tamp filling machine. Two studies using two model drugs were carried out. The first study used theophylline as the model drug due to its poor solubility. The second study used ibuprofen due to its low melting point. The fillers used were lactose and microfine cellulose respectively. Partially pregelatinised starch and magnesium stearate were used in both studies. A central composite factorial design was employed in order to identify and predict relationships. Powder characterisation was achieved through the following flow properties;

Carr's compressibility index - measures powder compressibility and flowability
Angle of internal flow - measures interparticulate friction
Compaction constant $T$ - measures ease of densification
Maximum bulk density - measures ease of densification
Angle of internal friction - measures frictional forces
Cohesion coefficient - measure of powder stickiness
Mobility Index - indication of powder segregation
Jenike's flow factor - indication of powder flow

The capsules were filled at different compression settings. For the theophylline study, a single powder bed height was employed and tamping forces were measured at tamping stations 3 and 4. For the ibuprofen study two powder bed heights were employed and tamping forces were measured at tamping station 3. The optimal filling performance was evaluated by the following parameters;

Fill weight - indication of powder densification
Coefficient of fill weight variation - indication of uniformity of filling
Closing length of the capsule - indication of powder densification
Capsule plug density - indication of powder densification
Disintegration testing - ability of the capsule plug to disintegrate
Dissolution testing - indication of drug release

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CHAPTER 2

MATERIALS & METHODS
2.1 MATERIALS

2.1.1 Pregelatinised starch

Starch 1500® is an example of a partially pregelatinised starch. Partially pregelatinised starch is prepared by subjecting corn starch to shear stress or physical compression in conditions of high moisture, which causes an increase in the temperature, and a partial pregelatinisation of some of the starch (Bolhius and Chowhan, 1996). When manufactured, some of the hydrogen bonds between the amylose and amylopectin are partially ruptured (Newman et al., 1996) such that the product contains 5% free amylose, 10% to 20% free amylopectin and 75% to 80% unmodified starch (Bolhius and Chowhan, 1996). The free amylose and unmodified starch provides the disintegration properties, whilst the amylopectin is responsible for cold-water solubility and binding properties (Bolhius and Chowhan, 1996). It has been found that partially pregelatinised starch possesses elastic properties during compression (Newman et al., 1996; Bolhius and Chowhan, 1996). Also, starch particles do not fuse together and are nearly always surrounded by a space, which contributes to its disintegration properties (Newman et al., 1996).

2.1.1.1 Appearance

Starch occurs as a fine white to pale cream powder, which is odourless and tasteless (Lordi and Rowley, 2000). It comprises of very small spherical or ovoid granules. The botanical origin of the starch material will determine the granule size and shape. However, partially pregelatinised starch exhibits an entirely different morphology. The particles are irregular and show large pores for the majority of particles (Newman et al., 1996).

2.1.1.2 Uses and Applications

Starch is widely used in the pharmaceutical industry as an excipient primarily in oral solid dosage formulations where it is utilised as a binder, diluent and disintegrant (Colorcon, 1999; Lordi and Rowley, 2000). It also possesses lubrication properties (Lordi and Rowley, 2000) and therefore can be compressed without the addition of a lubricant (Bolhius and Chowhan, 1996; Colorcon, 1999). The most common explanation for the disintegration properties is the swelling of the starch granules when exposed to water caused by the amylose. A second mechanism proposed for the disintegrating properties is the capillary action rather than swelling. The third mechanism proposed is based on the particle-particle repulsion forces between the capsule constituents when in contact with water and the hydrophilic nature of the starch (Newman et al., 1996). In addition, it is readily available, inexpensive and inert.
2.1.1.3 Supplier
Starch 1500®, Colorcon, West Point, USA. Batch number: 8090201, cold water solubility 19.6%.

2.1.2 Lactose Monohydrate
Lactose is the most widely used material in the pharmaceutical industry (Bolhius and Chowhan, 1996). It is a natural disaccharide consisting of glucose and galactose and it is obtained from milk. Lactose exhibits optical rotation. There are many lactose grades commercially available including anhydrous α-lactose, α-lactose monohydrate and to a small extent, anhydrous β-lactose. Various particle sizes are available for lactose and therefore, depending on the application, a particular size range may be used (Kibbe, 2000).

2.1.2.1 Appearance
Lactose is a white or creamy white hard soluble crystalline material, which is readily milled into a powder. It is odourless, has a slightly sweet taste and rapidly dissolves in water. Lactose monohydrate is stable in air and is unaffected by humidity at room temperature (Kibbe, 2000).

2.1.2.2 Uses and Applications
Lactose is a popular diluent used in capsules and tablets. It is used to a more limited extent in lyophilised products, infant feed formulas and sugar coating solutions (Kibbe, 2000).

2.1.2.3 Supplier
Borculo Whey Products Ltd, Saltney, UK. Batch no: 749035 “medium grade”.

2.1.3 Microfine cellulose
Microfine cellulose or powdered cellulose is manufactured by the purification and mechanical size reduction of α-cellulose obtained as a pulp from fibrous plant materials (Bolhius and Chowhan, 1996). The cellulose fibres in the starting material are composed of millions of microfibrils (Bolhius and Chowhan, 1996). There are two regions in the microfibrils; a paracrystalline region, which is amorphous consisting of a flexible mass of cellulose chains and a crystalline region, which is composed of tight bundles of cellulose chains in rigid linear arrangement. Microfine cellulose is practically insoluble in water (Aulton, 2000).
2.1.3.1 Appearance
Microfine cellulose occurs as a white or almost white, odourless and tasteless powder. The powder is composed of various particle sizes ranging from a free flowing fine powder to a fluffy non-flowing material.

2.1.3.2 Uses and Applications
Microfine cellulose is used as a diluent in hard shell gelatine capsules and as a tablet diluent. It serves as a bulking agent to increase the physical size of the dosage form in formulations containing a small amount of active substance. However, it possesses poor flow properties (Aulton, 2000). Microfine cellulose is a stable, slightly hygroscopic material. It also has disintegrant and lubricant properties (Aulton, 2000) and requires lower levels of lubricant compared to other excipients (Bolhuis and Lerk, 1973).

2.1.3.3 Supplier
Vitacel® A80, Rettenmaier & Sons, Ellwangen-Holzmühle, Germany. Batch no: 0781390324.

2.1.4 Magnesium Stearate
Magnesium stearate consists mainly of magnesium stearate with variable proportions of magnesium palmitate and magnesium oleate. It is a poorly flowing, cohesive powder (Allen and Luner, 2000). Physical properties of magnesium stearate can vary among different manufacturers because the solid state characteristics of the powder are influenced by the manufacturing variables (Miller and York, 1985). Magnesium stearate is a hydrophobic compound, which can slow the dissolution rate of a formulation by forming a film around the powder mass and therefore only the smallest quantity is used. Capsule dissolution is sensitive to both the amount of magnesium stearate in the formulation and the mixing time. This can result in the formation of hydrophobic powder beds that do not disperse even after the capsule shell has dissolved (Samyn and Jung, 1970; Murthy and Samyn, 1977).

2.1.4.1 Appearance
Magnesium Stearate is a fine, white powder of low bulk density with a characteristic taste and a faint odour of stearic acid. It is greasy to touch and readily adheres to the skin (Allen and Luner, 2000).
2.1.4.2 Uses and Applications
Magnesium stearate is widely used as a lubricant in capsule and tablet manufacture and is the most frequently listed of all excipients in capsule formulations (Allen and Luner, 2000).

2.1.4.3 Supplier
Colorcon, West Point, USA. Magnesium stearate (dihydrate). Batch number: 972065.

2.1.5 Theophylline Anhydrous
Theophylline was chosen as the model drug due to its low solubility (Pharmaceutical Codex, 1994). It is sensitive to light, with the appearance of a yellow discolouration following extended exposure (Pharmaceutical Codex, 1994).

2.1.5.1 Appearance
Theophylline occurs as a white, odourless crystalline powder with a bitter taste (Pharmaceutical Codex, 1994).

2.1.5.2 Uses and Applications
Theophylline is used as a bronchodilator used for reversible airways obstruction (BNF, 2002).

2.1.5.3 Supplier
Knoll, Harlow, UK. Batch number: 95658.

2.1.6 Ibuprofen
Ibuprofen was chosen as the model drug as it has a low melting point (75°C to 78°C) and because it is practically insoluble in water (Pharmaceutical Codex, 1994). Ibuprofen formulations currently on the market consist mainly of tablets and are complicated to manufacture.

2.1.6.1 Appearance
Ibuprofen exists as a white or almost white crystalline powder or colourless crystals with a slight characteristic odour (BP, 2001).
2.1.6.2 Uses and Applications

Ibuprofen is a non-steroidal anti-inflammatory drug. It is used in the management of mild to moderate pain and inflammation. The usual oral dose for adults is 1.2g to 1.8g daily in divided doses (BNF, 2002).

2.1.6.3 Supplier

BASF plc, Nottingham, UK. Batch no. 5511138.
2.2 METHODS

2.2.1 Experimental Design

Theophylline

Choice of Drug
Theophylline was the drug of choice with respect to its poor flow properties. In addition, it is a poorly soluble drug and consists of needle shaped particles.

Choice of Excipient
Pregelatinised starch was chosen as the prime excipient due to its multiple functionality. Lactose monohydrate was employed as the second excipient as it is widely used and forms stable plugs when in fine powder form. These plugs are rapidly disintegrating and the material promotes water uptake into the plug.

The first factor studied was the ratio between pregelatinised starch and lactose in the powder mixtures. The main factor levels tested were:

- pregelatinised starch: lactose 20:80%
- pregelatinised starch: lactose 40:60%
- pregelatinised starch: lactose 60:40%
- pregelatinised starch: lactose 80:20%
- pregelatinised starch: lactose 100:0%

For interaction terms, the factor levels were:

- pregelatinised starch: lactose 30:70%
- pregelatinised starch: lactose 90:10%

The interaction terms were set in between the two outer factor levels. For high dose drugs with poor flow properties it is important to reduce the level of excipient to a minimal level to avoid the need to use extreme capsule sizes. Thus, the second factor studied was the drug excipient ratio. The excipient ratio refers to the total amount of pregelatinised starch and lactose mixture.
The following main factor levels were tested:

- 15% theophylline
- 30% theophylline
- 45% theophylline
- 60% theophylline
- 75% theophylline

Interaction levels were:

- 22.5% theophylline
- 67.5% theophylline

To determine the optimal lubricant concentration for capsule filling, different concentrations of magnesium stearate were the third factor studied:

- 0.25% lubricant
- 0.50% lubricant
- 0.75% lubricant
- 1.00% lubricant
- 1.25% lubricant

Interaction levels were:

- 0.375% lubricant
- 1.125% lubricant

A central composite design (Box and Wilson, 1951) was expanded to a centre of gravity design (Podczeck, 1996) to identify relationships and to predict behaviour patterns, for three factors at different factor levels. Statistical analysis was used to evaluate the relationships between the influence factors and the response variables. Here five main factor levels were employed and the interaction terms were set symmetrically between two outer factor levels (Table 2.1). For three factors this resulted in 21 experiments. Table 2.2 shows the percentage of pregelatinised starch, lactose, theophylline and magnesium stearate in each of the formulations.
### Table 2.1: Centre of gravity design based on three factors; pregelatinised starch, theophylline and magnesium stearate (CG-centre of gravity, i-interaction term)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Factor 1</th>
<th>Factor 2</th>
<th>Factor 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pregelatinised starch % in excipient</td>
<td>Theophylline % in mixture</td>
<td>Magnesium stearate % in mixture</td>
</tr>
<tr>
<td>1 CG</td>
<td>60</td>
<td>45.0</td>
<td>0.750</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
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<td>45.0</td>
<td>0.750</td>
</tr>
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<td>0.750</td>
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<td>45.0</td>
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<td>13</td>
<td>100</td>
<td>45.0</td>
<td>0.750</td>
</tr>
<tr>
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<td>0.375</td>
</tr>
<tr>
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<td>0.375</td>
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<tr>
<td>17 = i</td>
<td>30</td>
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<tr>
<td>18 = i</td>
<td>90</td>
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<td>67.5</td>
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<tr>
<td>20 = i</td>
<td>90</td>
<td>22.5</td>
<td>1.125</td>
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<tr>
<td>21 = i</td>
<td>90</td>
<td>67.5</td>
<td>1.125</td>
</tr>
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</table>

### Table 2.2: Percentage of pregelatinised starch, lactose, theophylline and magnesium stearate in the 21 formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Pregelatinised starch (%)</th>
<th>Lactose (%)</th>
<th>Theophylline (%)</th>
<th>Magnesium stearate (%)</th>
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<td>21.700</td>
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<td>0.500</td>
</tr>
<tr>
<td>4</td>
<td>32.400</td>
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<td>1.000</td>
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<td>41.550</td>
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<td>0.750</td>
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<td>23.550</td>
<td>15.700</td>
<td>60.000</td>
<td>0.750</td>
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<td>75.000</td>
<td>0.750</td>
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<td>10.850</td>
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<td>45.000</td>
<td>0.750</td>
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<td>0.375</td>
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<td>28.238</td>
<td>3.138</td>
<td>67.500</td>
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</table>
Ibuprofen

Choice of Drug
Ibuprofen was the second drug chosen in the study for three reasons. Firstly, ibuprofen has very poor powder flow, which is due to the sticky nature of the material. Secondly, ibuprofen has a very low melting point of 75°C to 78°C (Moffat, 1986). This would be a challenge during filling because friction caused between the powder particles could exceed the melting point of ibuprofen, resulting in spot melting. Consequently, the powder would stick to the tamping pins and/or between the dosing disk and tamping ring, disrupting the filling process. Finally, ibuprofen is a poorly soluble drug and does not dissolve in water, thus the aim was to observe the effect of the choice and quantity of excipients on ibuprofen disintegration and dissolution.

Choice of Excipient
Pregelatinised starch was again chosen as the prime excipient. Microfine cellulose was employed as the second excipient. Microfine cellulose is a relatively new excipient on the market and there are very few literature reports. The reason why it was chosen was due to its ability to absorb moisture, which would agree with a material such as ibuprofen.

The first factor studied was the ratio between pregelatinised starch and microfine cellulose in the powder mixtures. The main factor levels tested were:

- pregelatinised starch: microfine cellulose 100:0%
- pregelatinised starch: microfine cellulose 75:25%
- pregelatinised starch: microfine cellulose 50:50%
- pregelatinised starch: microfine cellulose 25:25%
- pregelatinised starch: microfine cellulose 0:100%

For interaction terms the factor levels were:

- pregelatinised starch: microfine cellulose 10:90%
- pregelatinised starch: microfine cellulose 90:10%

Interaction terms were set 10% from the two extreme factor levels.
The second factor studied was the drug excipient ratio. The excipient ratio is the total amount of pregelatinised starch and microfine cellulose in the mixture. This was to reduce the level of excipient to a minimal level for high dose drugs with poor flow properties in order to avoid the need to use large capsule sizes.

The following factor levels were tested:

- 50% ibuprofen
- 60% ibuprofen
- 70% ibuprofen
- 80% ibuprofen
- 90% ibuprofen

Interaction levels were:

- 54% ibuprofen
- 86% ibuprofen

To test the possibility of reducing the lubricant level from the typically 1% used in a powder mixture for capsule filling, different concentrations of magnesium stearate were the third factor studied:

- 0.2% lubricant
- 0.4% lubricant
- 0.6% lubricant
- 0.8% lubricant
- 1.0% lubricant

Interaction levels were:

- 0.28% lubricant
- 0.92% lubricant

A centre of gravity design was used (Table 2.3). Five main factor levels were employed and the interaction terms were set symmetrically between the two outer factor levels. For three factors this resulted in 21 experiments. Table 2.4 shows the percentage of pregelatinised starch, microfine cellulose, ibuprofen and magnesium stearate for the 21 mixes. For a correct modeling of the relationships between the influence factors and the response variables, statistical analysis was carried out using the linear determinant.
Chapter 2 – Materials and Methods

Table 2.3: Centre of gravity design based on three factors; pregelatinised starch, ibuprofen and magnesium stearate (CG-centre of gravity, i-interaction term)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Pregelatinised starch (% in excipient)</th>
<th>Ibuprofen (% in formulation)</th>
<th>Magnesium stearate (% in formulation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 CG</td>
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<tr>
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<td>19 = i</td>
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<tr>
<td>21 = i</td>
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<td>86.0</td>
<td>0.920</td>
</tr>
</tbody>
</table>

Table 2.4: Percentage of pregelatinised starch, microfine cellulose, ibuprofen and magnesium stearate in the 21 formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Pregelatinised starch (%)</th>
<th>Microfine cellulose (%)</th>
<th>Ibuprofen (%)</th>
<th>Magnesium stearate (%)</th>
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<td>1.308</td>
<td>86.000</td>
<td>0.920</td>
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</tbody>
</table>
2.2.2 Particulate Properties of Materials

2.2.2.1 Particle Size Analysis

Particle size analysis was carried out using an air-jet sieve (Alpine, Augsberg, Germany), using sieve sizes of 32µm, 45µm and 63µm (Haver & Boecker, Westfalen, Germany). Approximately 30g of the material was initially passed through the 32µm sieve for 15 minutes. This procedure was repeated five times. The remainder of the material was then passed through the 45µm sieve using 30g of material each time. The material that remained on the 45µm sieve was passed through the 63µm sieve, again using approximately 30g of material.

The material that remained on the 63µm sieve was sieved using a vibratory shaker (Endecotts, London, UK). Seven sieve sizes were used with a progression based on a $\sqrt{2}$ change in mesh size; 90µm, 125µm, 180µm, 250µm, 355µm, 500µm and 710µm (Endecotts, London, UK). These were stacked with the smallest mesh above a collector tray, followed by meshes that were progressively coarser towards the top and the powder was sieved for a total of 10 minutes. This procedure was carried out three times for pregelatinised starch, lactose and theophylline.

Ibuprofen

When carrying out sieve analysis for ibuprofen, the particle size proved to be very small and the majority of the particles passed through the 32µm air-jet sieve. Therefore laser diffraction (Malvern Mastersizer S, Worcestershire, UK) was used. Mie theory was chosen as the optical model. The refractive index used for ibuprofen was 1.4362 (Sample Dispersion and Refractive Index Guide) and the imaginary index used was 0.01. The solvent used was deionised water. The suspension was prepared by placing a few milligrams of ibuprofen in a 10ml vial containing deionised water. The vial was manually shaken to disperse the particle agglomerates and the suspension was tested in the instrument.

2.2.2.2 Particle Density

Theophylline

The particle density of the materials was determined using an air compression pycnometer (Model 930, Beckman Scientific Instruments, Marca, Canada). The apparatus was operated by placing the material in the sample cup, which was locked in and the coupling valve closed. Both the measuring and the reference handwheel were turned simultaneously until the reference handwheel stopped and the sample volume was read
from the counter. The powder was weighed and the density of the powder was determined using the equation below:

\[ \text{density (g/cm}^3) = \frac{\text{weight (g)}}{\text{volume (cm}^3) \} } \]

This procedure was carried out three times for pregelatinised starch, lactose monohydrate, magnesium stearate and theophylline.

**Ibuprofen**

The particle densities for pregelatinised starch, microfine cellulose, ibuprofen and magnesium stearate were evaluated using the Quantachrome multipycnometer, model MVP-1, (Quantachrome Corporation, Syosset, NY, USA). This is a helium pycnometer. The particle densities were calculated using the equation in the pycnometer instruction manual.

\[ V_R(\text{micro}) = \frac{V_{\text{calc}}(\text{micro})}{\left[ \frac{P_{1(\text{micro})}}{P_{2(\text{micro})}} - 1 \right] - \left[ \frac{P_{\text{micro}}}{P_{2\text{micro}}} - 1 \right]} \]  

(1)

\[ V_C(\text{micro}) = V_{\text{calc}}(\text{micro}) + V_R(\text{micro}) \left[ \frac{P_{\text{micro}}}{P_{2\text{micro}}} - 1 \right] \]  

(2)

\[ V_p = V_C - V_R \left[ \frac{P_1}{P_2} - 1 \right] \]  

(3)

- \( V_{\text{calc}}(\text{micro}) \) = Volume of both micro calibration spheres (given)
- \( P_{1(\text{micro})} \) = Pressure in \( V_R \) micro with no spheres in cell
- \( P_{2(\text{micro})} \) = Pressure in \( V_R \) micro and the micro cell with no spheres in cell
- \( P_{\text{micro}} \) = Pressure in \( V_R \) micro with the calibration spheres in cell
- \( P_{2\text{micro}} \) = Pressure in \( V_R \) micro and the micro cell with the calibration spheres in cell
- \( V_R \) = Volume of reference cell (cm\(^3\))
- \( V_C \) = Volume of sample cell (cm\(^3\))
- \( V_p \) = Volume of powder (cm\(^3\))
- \( P_1 \) = Pressure after pressurizing the reference volume
- \( P_2 \) = Pressure reading in the reference cell after gas flow to the sample cell
After solving equations 1, 2 and 3, the volume of the powder \( V_p \) was substituted into equation 4 to calculate the particle density:

\[
\text{Particle density} = \frac{\text{sample weight (g)}}{\text{powder volume (cm}^3\text{)}}
\]  

(4)

2.2.2.3 Moisture Content
The moisture content of the materials was determined using thermogravimetric analysis (TGA 2850 Thermogravimetric Analyser, TA instruments, Surrey, UK). The mass placed on the aluminum sample pan for each material was constant (±1mg) to achieve consistent results. The usual mass of material placed onto the sample pan was 10mg to 15mg depending on the density of the material. The sample was heated at a rate of 5°C/min from ambient temperature 23°C-27°C to 200°C. The nitrogen flow connected to the “balance purge” inlet was 40ml/min and 60ml/min to the purge inlet. An analysis program (Thermal Analyst 2000, TA Instruments, Surrey, UK) was used to record and analyse the data.

2.2.2.4 Particle Shape
The particle size, shape and surface morphology of the materials was observed using scanning electron microscopy (SEM) (Philips SEM XL20, Eindhoven, Netherlands). The samples were sputter-coated with gold (Emitech K550, Ashford, UK), then examined using a SEM at 10kV voltage using the secondary electron technique.

2.2.3 Determination of the Optimal Mixing time
Theophylline
The appropriate quantities for the centre of gravity mixture were weighed; pregelatinised starch (217g), lactose (144.67g) and theophylline (300g). This was a total quantity of 666.67g, representing a one-third of the total batch volume required and these powders were placed into the Y-cone blender (Erweka Apparatebau GmbH, Heusenstamm, Germany). To assess the optimal mixing time, five samples were taken from the Y-cone blender using a sample thief (model I, GlobePharma, New Brunswick, NJ, US). The number of samples was determined using a statistical approach as described by Schweiger et al., (1987). The samples were taken at 5 minutes, 8 minutes and subsequently at every 2 minutes up to and including 40 minutes in order to assess the homogeneity of the mixture.
The sample thief was inserted at five different locations where the sampling was to take place. The sample thief was too long to match the depth of the Y-cone blender as it was only filled to 30% to ensure effective mixing. Therefore, only the first die cavity was completely inserted into the powder blend. Thus, each time a sample was taken, the sampling device had to be inserted into the powder blend. Figure 2.1 illustrates the locations from which the samples were taken from the Y-cone blender. The samples were analysed using polarimetry and UV analysis to determine the relative standard deviation of the lactose and theophylline content, respectively.

Figure 2.1: Locations from which five samples were taken from the Y-cone blender

**Polarimetry**

**Calibration**

Lactose was quantitatively measured using a polarimeter (B-S model, Bellingham and Stanley Ltd., London, UK). A stock solution of lactose was prepared by dissolving 1g lactose in 50ml deionised water. A calibration curve was produced to determine the amount of lactose in the mixture. This procedure was carried out three times (see appendix 1 for calibration curve).

**Testing of Samples**

Samples taken from the Y-cone blender were dissolved in a 25ml volumetric flask and left for 24 hours. A Whatman filter paper, grade 1 (Whatman International Ltd, Maidstone, England) was used to retain gelatinous precipitates of the undissolved starch. The samples were then analysed using the polarimeter.

**UV analysis**

**Calibration**

Initially a stock solution was made of theophylline by dissolving 100mg in 1,000ml deionised water. Various concentrations of theophylline were then made up to volume in a 100ml volumetric flask and measured using UV spectroscopy (Model 554, Perkin-Elmer, Beaconsfield, UK) at 272nm. This was carried out three times (see appendix 2 for calibration curve).
Testing of Samples

100μl of the filtered solution was measured using a pipette (P100, Gilson Pipetman®, Anacham Ltd, Luton, UK) and dissolved in a 100ml volumetric flask and analysed using UV spectroscopy. This method was also used to measure the theophylline content in the samples for the 21 formulations.

Optimal Mixing Time

The relative standard deviation of the lactose and theophylline content was determined for the five samples. These values were plotted as a function of time (Ch. 3.1.3.5). The point at which the relative standard deviation was lowest, was regarded as the optimum mixing time.

Powder Mixing

In order to fill the capsules, a 2,000g batch was required. Table 2.5 shows the quantity of each component for the 21 formulations. Mixing was carried out three times to make a total mass of 2,000g. Table 2.6 shows the quantity of each component for the formulations when placed in the Y-cone blender for a batch size of 666.67g. Pregelatinised starch, lactose and theophylline were placed into the blender and mixed for 22 minutes at 28 rpm. (see Ch. 3.1.3.5 for determination of optimal mixing time). The appropriate quantity of magnesium stearate was added and mixed for a further 5 minutes. The three portions were combined in a large plastic bag to achieve the final mass of 2,000g.
Table 2.5: Quantity of pregelatinised starch, lactose, theophylline and magnesium stearate in a 2,000g batch for the 21 formulations

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<th>Formulation</th>
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<th>Theophylline (g)</th>
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Table 2.6: Quantity of pregelatinised starch, lactose, theophylline and magnesium stearate in a 666.67g batch for the 21 formulations when placed in the Y-cone blender

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<tr>
<th>Formulation</th>
<th>Pregelatinised starch (g)</th>
<th>Lactose (g)</th>
<th>Theophylline (g)</th>
<th>Magnesium stearate (g)</th>
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Ibuprofen
To determine the optimal mixing time for the ibuprofen formulations, the appropriate quantities of the components for the centre of gravity mixture were weighed; pregelatinised starch (73.5g), microfine cellulose (73.5g), and ibuprofen (350g). This was a total quantity of 497g, representing one-quarter of the total batch volume required and these powders were placed into the Y-cone blender. To assess the optimal mixing time, five samples were taken from the Y-cone blender using a sample thief. Samples were taken every 2 minutes up to and including 40 minutes in order to assess the homogeneity of the mixture. Samples were taken from the same locations as the theophylline study and analysed using UV analysis to determine the relative standard deviation of the ibuprofen content.

UV analysis
Calibration
Initially a stock solution was made by dissolving 100mg ibuprofen in 90% alcohol in a 25ml volumetric flask. A calibration curve was prepared using different concentrations of ibuprofen solution in 90% alcohol, which were then made up to volume in a 25ml volumetric flask and measured using UV spectroscopy (Model 554, Perkin-Elmer, Beaconsfield, UK) at an optimum absorbance of 274nm (see appendix 3 for calibration curve). This was carried out three times. Fresh solutions were made every two days and the UV spectrometer was checked each time the samples were tested.

Testing of Samples
The sample was dissolved in 90% alcohol in a 25ml volumetric flask and left overnight. 1.5ml of the solution was placed in a 1.5ml epindorph vial (Anachem Ltd, Luton, UK) and centrifuged using a bench centrifuge (Micro Centaur, MSE Ltd., Crawley, UK) at high speed of 13,000 rpm. 1ml of the sample was measured using a pipette (P100, Gilson Pipetman®, Anacham Ltd, Luton, UK) then dissolved in 90% alcohol and measured using the UV spectrometer at 274nm. The relative standard deviation of the samples was calculated and plotted as a function of time to determine the optimal mixing time. UV analysis was also used to measure the ibuprofen content in the samples for the 21 formulations.

Powder Mixing
In order to fill the capsules, a 2000g batch was required. Table 2.7 shows the quantity of each component for the 21 formulations. Mixing was carried out four times to make a total mass of 2,000g. Table 2.8 shows the quantity of each component for the
formulations when placed in the Y-cone blender for a batch size of 500g. Pregelatinised starch, microfine cellulose and ibuprofen were placed into the blender and mixed for 25 minutes at 28 rpm (see Ch. 4.1.4.5 for determination of optimal mixing time). After 25 minutes, the Y-cone blender was stopped and the appropriate quantity of magnesium stearate was added and mixed for a further 5 minutes. The four portions were combined in a large plastic bag prior to use to achieve the final mass of 2,000g.

Table 2.7: Quantity of pregelatinised starch, microfine cellulose, ibuprofen and magnesium stearate in a 2,000 batch for the 21 formulations

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Table 2.8: Quantity of pregelatinised starch, microfine cellulose, ibuprofen and magnesium stearate in a 500g batch for the 21 formulations when placed in the Y-cone blender

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2.2.4 Bulk Properties of Powders

The flow and packing properties were determined using an automatic tap volumeter (Jencons Scientific Equipment, Radon Ind. Electronics Co. Ltd., Worthing, UK). The volumeter used had a 250ml measuring cylinder (graduation 2ml), a lift height of approximately 30mm and a tapping frequency of 30 taps/min. Approximately 200ml of the powder was carefully filled into the tared measuring cylinder. The powder bed was leveled with a spatula and the maximum powder volume (to give the minimum bulk density) was read. The volumeter was tapped once and the volume was read again. This procedure was repeated so that the number of taps increased between individual readings until there were three consecutive readings of the same volume after 200 taps, (i.e. the volume did not reduce any further). This volume was read and recorded as the minimum powder volume (to give the maximum bulk density). The measuring cylinder was then weighed to determine the weight of the powder. This was carried out three times for each of the powders always using fresh powder. Statistical analysis of the data was performed using commercial software (SPSS 8.0, Woking, UK). Carr’s compressibility index (Carr, 1965) was calculated from the computed minimum and maximum bulk densities. The dynamic packing profile was also used to give the angle of internal flow (Varthalis and
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Pilpel, 1976). The density of the powder was evaluated as a function of the number of taps using the model described by Mohammadi and Harnby (1997).

2.2.5 Shear Properties of Powders

The Peschl shear tester (RO-200 semi-automatic, Industrial Powder Technology, Vaduz, Liechtenstein) is a rotational split level shear tester. This was used to evaluate the shear stresses of the powder for the ibuprofen study.

A fill sieve (Industrial Powder Technology, Vaduz, Liechtenstein) was used to fill powder into the shear cell in order to prevent lumps and agglomerates and to ensure uniform filling of the shear cell. The material was scraped off the upper edge of the fill ring and a porous consolidation lid was placed on top of the powder. The shear cell was placed in the consolidation bench and a consolidation weight of 1,500g was loaded onto the shear cell. This weight corresponded to the pressure applied during the shear test. The material was consolidated for 10 minutes. The fill ring and the additional material above the top of the shear cell ring was removed and the weight of the material was determined.

A semi-automatic machine was used for the shear tests, thus the consolidation loads were placed manually. Normal loads were placed on the loading lid of 1,500g, 1,200g, 900g, 600g, 300g, and 150g. The surface area of the shear cell was 30cm²; hence the normal stress applied to the loading lid was 50g/cm², 40g/cm², 30g/cm², 20g/cm², 10g/cm², and 5g/cm² respectively. The consolidation step by applying a 1,500g weight to the loading lid occurred for two minutes followed by 2 minutes for the shear step.

The cell base was rotated against the loading lid of the shear cell. A shear plane developed between the cell base and the cell ring. The rotational movement of the shear cell allowed the development of unlimited stresses in the shear plane until plastic deformation occurred. With this development of stresses, two important stages were measured; the shear step value of stress at the beginning of shear and the stationary value of the shear stresses that occurred during plastic deformation.

Multiple shear tests could be made on the same sample to obtain the complete yield locus. The sequencing of consolidating, shearing, acquisition and evaluation of the data was controlled by a programmed microprocessor.

The following properties were derived from the measured shear values; angle of internal friction, cohesion coefficient and Jenike’s flow factor. From the angle of effective
friction, the mobility index was derived. The shear data was presented as the average value obtained from three different yield loci.

2.2.6 Capsule Filling

Theophylline

The powder was filled into hard gelatine capsules size 1 (Shionogi Qualicaps, Alcobendas, Madrid, Spain) on a Bosch GKF-400S tamp filling machine (Robert Bosch GmbH, Waiblingen, Germany), which is a small scale production machine (Figure 2.2).

![Bosch GKF-400S tamp filling machine](image)

(A) capsule hopper; (B) capsule magazine; (C) powder hopper; (D) tamping station; (E) instrumented tamping head

The advantage of using a small scale machine was that knowledge was gained about the performance of the powders when scaling up to larger production machines. A 19.6mm dosing disk was used so that the capsules would be filled completely. By using a large dosing disk it was easier to identify the filling properties of the material such as small plug instabilities and flow irregularities, as these would be reflected in the coefficient of fill weight variation.

A powder bed height of 20mm was tested at seven compression settings ranging from “no compression” to “firm compression”. No compression indicated that the tamping pin did not penetrate the dosing disk during tamping and firm compression indicated that the first four tamping pins penetrated the dosing disk during tamping (Figure 2.3).
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Figure 2.3 Tamping pin settings of no compression and firm compression (Podczeck, 2000)

For each of the formulations, the tamping pins at each tamping station were adjusted to increase the penetration depth into the dosing disk by 1mm each time. The cumulative tamping distance (CTD) is the total penetration depth of the tamping pins into the dosing disk at their lowest position during tamping (Table 2.9). The machine was taken apart after each run and carefully cleaned to remove the adhering powder particles from the tamping pins, dosing disk, tamping ring, powder bowl, hopper and auger.

Table 2.9: Cumulative tamping distance (CTD) of the tamping pins at the five tamping stations

<table>
<thead>
<tr>
<th>Tamping station 1</th>
<th>Tamping station 2</th>
<th>Tamping station 3</th>
<th>Tamping station 4</th>
<th>Tamping station 5</th>
<th>CTD (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>22</td>
</tr>
</tbody>
</table>

Ibuprofen

For ibuprofen, the capsules were filled at powder bed heights of 20mm and 25mm at nine compression settings ranging from “no compression” to “firm compression”. For each of the formulations, the tamping pins at each tamping station were adjusted to increase the penetration depth into the dosing disk by 1mm each time. Table 2.10 shows the cumulative tamping distance settings during tamping (Table 2.10).
Chapter 2 – Materials and Methods

Table 2.10: Cumulative tamping distance (CTD) of the tamping pins at the five tamping stations

<table>
<thead>
<tr>
<th>Tamping station 1</th>
<th>Tamping station 2</th>
<th>Tamping station 3</th>
<th>Tamping station 4</th>
<th>Tamping station 5</th>
<th>CTD (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>9</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td>0</td>
<td>30</td>
</tr>
</tbody>
</table>

2.2.7 Capsule Fill Weight

Theophylline

To determine the capsule fill weight and the coefficient of fill weight variation, sixty capsules were taken randomly from each of the 294 batches. These were weighed using the Bosch KKE-2000 capsule weight verification system (Robert Bosch GmbH, Waiblingen, Germany). The machine had the capacity to measure capsules within ±2mg accuracy. Each capsule was corrected for the average weight of the capsule shells (71.1mg). The mean, standard deviation and the coefficient of fill weight variation were calculated from the corrected capsule weights.

Ibuprofen

To determine the capsule fill weight and the coefficient of fill weight variation, sixty capsules were randomly obtained from each of the 378 batches. These were weighed using the QM-4B capsule weighing machine (CI Electronics Ltd, Salisbury, UK). The machine had the capacity to weigh capsules up to ±1mg accuracy. Again, the mean fill weight and variance of weight were corrected for the average weight of the empty capsule shells (71.1mg).

2.2.8 Capsule Closing Length

The closing lengths of twelve capsules from all batches of the theophylline and ibuprofen study were measured using an image analyser (Seescan Sonanta, Cambridge, UK) fitted with a black/white CCD-4 camera (Rengo, Toyohashi, Japan) and a zoom lens (18-108/2.5, Olympus Europe, Hamburg, Germany). Using the capsule size and the fill weight, this enabled the determination of the plug density.
2.2.9 Tamping force

Theophylline

The Bosch GKF-400S was instrumented and allowed recording of individual tamping forces as described by Podczeck (2000). Tamping forces were measured in Newtons (N) and calculated according to the calibration of the instrument using the equation below (Podczeck, 2000).

\[
\text{Force (N)} = \frac{mV - 2566}{38.55}
\]

The different tamping settings enabled differentiation of disturbances in filling caused by poor powder flow and those due to non-compressibility. Once the depth of the tamping pin setting was changed, the machine was run and the capsules were discarded from the first twenty tamping events, after which the tamping forces were measured for the next thirty tamping events, whereby the capsules were collected.

For theophylline, tamping forces were measured at tamping stations three and four at bed height 20mm. For ibuprofen, forces were measured at tamping station 3 at bed heights 20mm and 25mm.

2.2.10 Disintegration Studies

Theophylline

The disintegration test determines whether capsules disintegrate within a prescribed time when placed in a liquid medium under prescribed experimental conditions. The disintegration test was carried out using the Copley disintegration tester (Copley Scientific Instruments Ltd, Nottingham, England). As there were 21 formulations in total and tamping forces were measured at stations three and four, using seven compression settings, 14 batches for each formulation were tested making a total of 294 batches.

The BP (2001) states that a capsule is placed in each of the six tubes and placed in a beaker containing the specified liquid and the apparatus is operated for a prescribed period. The assembly is withdrawn and the state of the capsules examined. To pass the test all six capsules must have disintegrated within 30 minutes. However, this method does not give an indication about the variability of the individual disintegration times of the capsules. Therefore, the individual disintegration times were noted for each of the six
capsules so that a mean and standard deviation could be calculated and compared with other batches.

Only three capsules were placed in the basket rack to enable viewing of the end point for the disintegration test. The basket rack was placed in 800ml deionised water, which had a temperature of 37±1°C. The end point was timed and this was achieved when there was no residue except fragments of the undissolved capsule shell left on the screen or adhering to the lower surface of the disc.

**Ibuprofen**
The disintegration time was determined using the Copley disintegration tester (Copley Scientific Instruments Ltd, Nottingham, England) in deionised water of 37±1°C. Six capsules were tested from each of the 378 batches (21 formulations and tamping forces were measured at station three using nine compression settings at bed heights 20mm and 25mm). To enable viewing of the end point, three capsules were placed in the basket rack and the individual disintegration time was noted to determine the mean and standard deviation for the batches.

**2.2.11 Dissolution studies**

**Theophylline**
The dissolution tests were carried out according to the paddle method (BP, 2001). A dissolution apparatus (Pharmatest dissolution tester/ TPWS 2C Pharma Test, Hamburg, Germany) was employed with a stirring rate of 50rpm at a temperature of 37±0.1°C. The dissolution media was 900ml of deionised water. Dissolution testing was carried out for the centre mix (formulation 1), and the main outer factor levels (formulation 2; formulation 5; formulation 6; formulation 9; formulation 10 and formulation 13). Six capsules were taken from the batch with the highest tamping pin setting i.e. CTD 22mm. This was in order to observe the dissolution process at the optimum tamping pin setting.

The aqueous solution was filtered and continuously pumped to a flow cell in a spectrophotometer (CecilCE 2020, Cecil Instruments, Cambridge, UK) and absorbance values were recorded at the maximum wavelength of theophylline (272nm). The results were the mean of six experiments.

The dissolution profiles were evaluated by determination of statistical moments, the mean dissolution time (MDT) of theophylline and the variance of the dissolution time (VR) and
an associated parameter, the relative dispersion of the concentration-time profile (RD) described by Pinto et al., (1997).

**Ibuprofen**
The same method was employed for the ibuprofen study. However, the dissolution media was 900ml of a phosphate buffer solution at pH 7.2. Six capsules were taken from each formulation from both bed heights to observe the effect of filling at different bed heights at maximum tamping pin setting, CTD 30mm, as this was the optimum tamping pin setting. Absorbance values were recorded at a wavelength of 265nm and the results were the mean of six experiments.
CHAPTER 3

THEOPHYLLINE
3.1 POWDER FLOW PROPERTIES

In capsule production, using a tamp filling machine, the filling relies on the measurement of volume by the dosing disk, even though the doses are specified by weight. Thus, to achieve capsules with uniform fill weights, it is essential to have powders with good flow and packing properties. Hence, there is a need to accurately evaluate the flowability of powders and give an indication of capsule fill weight and coefficient of fill weight variation during filling. In addition, the powder should form good plugs, there should be minimal adhesion between the powder and the machine and minimum dustiness upon filling (Jones, 1988a).

Characterisation of powder flow properties has been achieved by numerous methods including the angle of repose, (Train, 1958; Craik and Miller, 1958; Dahlinder et al., 1982; Velasco Antequera et al., 1994), flow meters to measure the flow velocity (Gold et al., 1966; Gold et al., 1968), determination of the critical orifice diameter (Walker, 1966), flow through orifices (Irwin et al., 1970) and using packing properties such as the minimum and maximum bulk density and derived parameters (Carr, 1965; Hausner, 1967; Grey and Beddow, 1968/1969; Varthalis and Pilpel, 1976; Kostelnik and Beddow, 1970; Mohammadi and Harby, 1997).

The angle of repose is limited to measuring free flowing powders where gravity can easily overcome the adhesion and frictional forces (Podczeck, 1998). Hence, this flow parameter gives little information about the adhesion properties of the powder. Powder flow meters give an indication of powder flow, however, this has not been related to inter-particulate adhesion or friction forces in the powder bulk (Sumner et al., 1966). However, Irwin et al., (1970) found good correlation between the flow rate and the fill weight uniformity using the Zanasi LZ64 machine. Kurihara and Ichikawa (1978) found that weight uniformity correlated well with the minimum orifice diameter using the OCF-120 vibratory filling machine. They also found good correlation between the weight uniformity and the angle of repose for the Höfliger-Karg-GKF-100 tamp filling machine. An optimum range for the angle of repose between 38° to 44° was found to give the best fill weight uniformity. This can be attributed to the powder being too fluid at lower values and becoming displaced from the dosing disk bores (Kurihara and Ichikawa, 1978). Hence, a certain degree of adhesion and friction must be present between the powder particles. The packing characteristics during tap consolidation are widely used to evaluate the flow properties of powders, as both packing and flow are dependent on the friction between the particles during sliding and rearrangement (Podczeck, 1998). These tests enable the comparison of different powders in terms of their flowability. From the
packing characteristics during tapping experiments, various flow parameters such as Carr’s compressibility index, angle of internal flow and the T-value may also be derived which will be useful in differentiating the flow behaviour of the powder mixtures. Hence, more than one flow parameter may be used to evaluate powder flow.

The nature and degree of interaction occurring between the powder particles will determine the powder properties of the formulation such as the flow properties of the powder (Podczeck, 1998).

### 3.1.1 Particulate Properties of Materials

The particle sizes and densities of the materials are shown in Table 3.1. Pregelatinised starch and lactose possess similar mean sizes of 51μm and 47μm respectively. However, their particle densities vary. Pregelatinised starch had a lower particle density (1.492g/cm³) compared to lactose (1.550g/cm³), which may affect the flow and filling properties. Theophylline had a large mean particle size (114μm). However, due to its needle shaped particles it had a large surface area, which will increase the interparticulate forces between the particles.

<table>
<thead>
<tr>
<th></th>
<th>Pregelatinised starch</th>
<th>Lactose</th>
<th>Theophylline</th>
<th>Magnesium stearate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Particle size (μm)</strong></td>
<td>51 ± 2.1</td>
<td>47 ± 2.0</td>
<td>114 ± 6.5</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Particle density (g/cm³)</strong></td>
<td>1.492 ± 0.001</td>
<td>1.550 ± 0.006</td>
<td>1.475 ± 0.005</td>
<td>1.143 ± 0.009</td>
</tr>
<tr>
<td><strong>Moisture content (%)</strong></td>
<td>9.484 ± 0.04</td>
<td>5.092 ± 0.10</td>
<td>0.119 ± 0.00</td>
<td>5.224 ± 0.18</td>
</tr>
</tbody>
</table>

*The results are the arithmetic mean of three investigations

Scanning electron microscopy (SEMs) were taken to illustrate the morphology and range sizes and shapes exhibited by the materials. Pregelatinised starch particles were angular consisting of a wide range of particle sizes with a smooth surface (Figure 3.1). Lactose particles were angular in shape with a rough surface. Lactose also possessed a heterogeneous size distribution (Figure 3.2). The SEM shows that theophylline has a wide range of particle sizes which are needle shaped with a rough surface (Figure 3.3). Magnesium stearate is a very fine material and consists of agglomerated platelets (Figure 3.4). The size and shape of magnesium stearate is necessary for it to function as a lubricant to reduce interparticulate friction and aid powder flow.
Thermogravimetric analysis (TGA) was carried out to determine the moisture content for the materials. The moisture content for each of the materials is shown in Table 3.1. Figure 3.5 depicts a typical weight loss curve (TG-curve) and its derivative (DTG-curve) as a function of temperature for pregelatinised starch. There was a steady weight loss as the temperature was increased. At 150°C, the weight loss stopped and became constant in spite of increasing the temperature to 200°C. The moisture content for pregelatinised starch was 9.484%, which agrees with the value of Newman et al., (1996) who also found a moisture content of 8% to 9% using TGA. The moisture content for lactose monohydrate was 5.092%. Lactose contained very little free water as illustrated by the water loss beginning at 90°C, indicating the loss of bound water (Figure 3.6). The moisture content for lactose agreed with Berlin et al., (1971). They also found no loss of bound water at temperatures less than 90°C to 95°C, but above this temperature, found a 5% water loss. Theophylline contained no bound water and very little free moisture 0.119% (Figure 3.7). Upon visualising the moisture loss for magnesium stearate, the TGA data confirmed that the crystal structure of magnesium stearate used in this study was a dihydrate (Barra and Somma, 1996). This can be illustrated by the kink in the moisture loss curve occurring at 90°C (Figure 3.8).
3.1.2 Bulk Properties of Materials

Tap consolidation is widely used to evaluate the flow properties of powders. From the packing characteristics during tapping experiments, Carr's compressibility index, angle of internal flow and the compaction constant $T$, were derived which enabled differentiation of the flow behaviour of the powders (Table 3.2).

Table 3.2: Powder Properties of Materials

<table>
<thead>
<tr>
<th></th>
<th>Pregelatinised starch</th>
<th>Lactose</th>
<th>Theophylline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum bulk density (g/cm$^3$)</td>
<td>0.651 ± 0.004</td>
<td>0.623 ± 0.001</td>
<td>0.491 ± 0.005</td>
</tr>
<tr>
<td>Maximum bulk density (g/cm$^3$)</td>
<td>0.798 ± 0.007</td>
<td>0.894 ± 0.004</td>
<td>0.728 ± 0.012</td>
</tr>
<tr>
<td>Carr's compressibility index (%)</td>
<td>18.36 ± 0.27</td>
<td>30.32 ± 0.47</td>
<td>32.55 ± 0.57</td>
</tr>
<tr>
<td>Angle of internal flow (°)</td>
<td>20.94 ± 0.44</td>
<td>16.07 ± 0.23</td>
<td>26.02 ± 1.10</td>
</tr>
<tr>
<td>Compaction constant $T$</td>
<td>12.93 ± 1.29</td>
<td>21.87 ± 1.55</td>
<td>25.93 ± 0.63</td>
</tr>
</tbody>
</table>

* The results are the arithmetic mean and S.D. of three investigations.

3.1.2.1 Minimum and Maximum Bulk Density

Figure 3.9 compares the change in the bulk density ($\rho_b$) with the number of taps applied for the different materials. Pregelatinised starch has a higher minimum bulk density compared to lactose but as the materials were tapped, lactose particles had better packing properties resulting in higher powder densities. Additionally, comparison of the slopes of the packing profiles indicated that pregelatinised starch packed faster, which is facilitated by its smooth angular particles. It densifies quickly to its maximum bulk density as can be
seen at 600 taps. For lactose and theophylline however, it takes longer for the powder to reach its maximum bulk density; 800 taps and 1,000 taps, respectively are required.

The large increase in the maximum bulk density for lactose and theophylline can be explained by the more heterogeneous size and shape distributions of the particles. During tapping, slippage and rearrangement of the particles occur which allows closer packing such that the smaller particles tend to occupy the interparticulate voids thus increasing the packed density.

The low minimum bulk density of theophylline indicates large interparticulate forces existing between the particles. During tapping however, these forces were temporarily overcome and slippage and rearrangement of the powder particles occurred.

![Figure 3.9: Densification of materials as a function of the number of taps applied](image)

**Figure 3.9: Densification of materials as a function of the number of taps applied**

3.1.2.2 Carr’s Compressibility Index

From the tapping experiments, Carr’s compressibility index can be determined to evaluate the flowability of the materials. Results showing Carr’s compressibility index are presented in Table 3.2. Pregelatinised starch has fair to passable flow. This can be attributed to the smooth surface of the pregelatinised starch particles. Lactose and theophylline however, have a rough surface resulting in poor powder flow. Packing characteristics are further influenced by the size, shape, density and porosity of the particles (Carr, 1970).
3.1.2.3 Angle of Internal Flow
The angle of internal flow was derived by Varthalis and Pilpel (1976) who found a relationship between the particle porosity and the number of taps. Varthalis and Pilpel related the angle of internal flow to the interparticulate friction in a powder bulk during flow. High values indicate the presence of increased interparticulate forces as seen for pregelatinised starch (20.94°) and theophylline (26.02°).

3.1.2.4 Compaction Constant (T-value)
The compaction constant describes the rate of densification of a powder bulk. According to Mohammadi and Harnby (1997), a compaction constant less than 35 is related to slow densification due to the presence of small particles. However, Podczeck et al., (1999) found when filling powdered herbs into capsules using a tamp filling machine, poor powder flow and slow densification were more likely connected via high T-values. This is important, as slow densification of the fill material could be problematic especially if the powder bed does not settle into equilibrium. This may cause problems during filling and could lead to a high coefficient of fill weight variation. In a further study, Podczeck and Newton (1999) found an optimum value for the compaction constant between 20 and 25. They found that powders below this optimum were associated with rapid densification and good powder flow and resulted in a greater coefficient fill weight variation caused by “powder flooding”. They showed that T-values above 30 indicated major filling problems. This should not pose a problem for lactose and theophylline, which have T-values of 21.9 and 25.9, respectively. However, the low T-value for pregelatinised starch (12.9) suggests increased variability in the capsule fill weight.

3.1.3 Optimal Mixing Time
The experimental design (see chapter 2.1) showed 21 batches were mixed. It would have been too time consuming to optimise the mixing conditions for all of the mixtures. Thus, the optimal mixing conditions were determined for the average mixture composition i.e. the centre of gravity mixture. A three component model was used to calculate the total volume of the batch, number of samples required from the batch and the weight of each sample. To achieve this, the bulk volume of the powder was obtained (Table 3.3).

Table 3.3: Percentage, weight and volume of 2,000g of the centre of gravity mixture

<table>
<thead>
<tr>
<th>Material</th>
<th>% of Materials</th>
<th>Weight of 2,000g (g)</th>
<th>Volume of 2,000g (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregelatinised starch</td>
<td>32.55</td>
<td>651</td>
<td>1,000.0</td>
</tr>
<tr>
<td>Lactose</td>
<td>21.70</td>
<td>434</td>
<td>696.6</td>
</tr>
<tr>
<td>Theophylline</td>
<td>45.00</td>
<td>900</td>
<td>1,833.0</td>
</tr>
</tbody>
</table>
Assuming additivity, the proportional bulk volumes were used. Thus, the total loose bulk volume for a 2,000g batch was 3,529.62 cm$^3$. The Y-cone blender was chosen to allow both shear and diffusive mixing. For optimum mixing to occur, the Y-cone blender was only filled to 35% of its nominal volume. As the total volume of the mixer was 4,000cm$^3$, mixing was carried out three times. Thus, 666.67g was placed into the Y-cone blender each time to make the final 2,000g batch. The speed of the Y-cone blender was 28rpm. This enabled homogeneity of the mixture without inducing dust development.

### 3.1.3.1 Minimum Number of Samples

Calculation of the minimum number of samples did not depend upon the number of components. A statistical approach used by Schweiger et al., (1997) was used to calculate the minimum number of samples $n_c$.

$$n_c = 1 + 0.5 \left( \frac{z}{d} \right)^2$$

(1)

Where $z$ is the confidence number for a 2-sided test of normal distribution. Its value can be found in a statistical table (Geigy scientific tables). Assuming error probability 5%:

$$\alpha = 0.5$$

$$z\alpha = 1.96$$

'Precision' $(d)$ as stated in the above equation is defined as:

$$d = \left( \frac{s}{\sigma} \right) - 1$$

(2)

Where 's' is the standard deviation of the mixture estimated from randomly drawn samples and 'σ' is the theoretical standard deviation of the distribution.

The variance $s^2$, calculated from the randomly drawn samples should not be higher than three times the theoretical variance $σ^2$. Therefore, for the three components:

$$s^2 \leq 3σ^2$$

Rearranging:

$$\frac{s^2}{σ^2} \leq 3$$
Chapter 3 - Theophylline

Therefore:

\[ \frac{s}{\sigma} \leq 1.732 \]  \hspace{1cm} (3)

Thus, 'precision' \((d)\):

\[ d = 1.732 - 1 \]

\[ = 0.732 \]

Substituting into equation (1):

\[ n_s = 1 + 0.5 \left( \frac{1.96}{0.732} \right)^2 = 4.58 \]  \hspace{1cm} \text{i.e. five samples}

Using statistical methods to evaluate the homogeneity of the mixture, five samples were required, assuming the particles followed a normal distribution.

3.1.3.2 Minimum Sample Size

The minimum sample size is dependent upon the concentration of components in the mixture. The minimum number '\(z_{\text{min}}\)' of particles to allow a statistically justified statement about the composition of the sample is:

\[ z_{\text{min}} = \left( \frac{z_\alpha}{y} \right)^2 \left( \frac{1 - p}{p} \right) \]

Where '\(p\)' is the concentration of the component with the smallest quantity in the mixture. Lactose has the lowest concentration in the formulation of 21.7% and therefore '\(p\)' is 0.217.

With three components the mixing quality will not be as good as with 2 components. Therefore an arbitrary decision based on literature reports: With 99% probability \((\alpha = 0.01)\) the composition of the samples should not deviate by more than 0.5% from the specified composition \(y\). Where, \(z_\alpha = 2.576\) and \(y = 0.005\). Thus \(z_{\text{min}}\) is:

\[ z_{\text{min}} = \left( \frac{2.576}{0.005} \right)^2 \left( \frac{1 - 0.217}{0.217} \right) \]

\[ = 957,753 \text{ particles / sample} \]
3.1.3.3 Calculation of the average volume, mass and number of particles per gram of the powder mixture

The volume was estimated as a cube because the particles were not round (theophylline is needle shaped). The mean size was obtained from sieve analysis, which has a square mesh (Table 3.4).

Table 3.4: Calculation of average volume, mass, and number of particles per gram of mixture

<table>
<thead>
<tr>
<th></th>
<th>Pregelatinised starch</th>
<th>Lactose</th>
<th>Theophylline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average volume (cm$^3$)</td>
<td>$1.327 \times 10^{-3}$</td>
<td>$1.038 \times 10^{-3}$</td>
<td>$1.482 \times 10^{-6}$</td>
</tr>
<tr>
<td>Average mass of particles (g)</td>
<td>$1.979 \times 10^{-3}$</td>
<td>$1.609 \times 10^{-3}$</td>
<td>$2.185 \times 10^{-6}$</td>
</tr>
<tr>
<td>No of particles per gram of powder</td>
<td>5,052,667</td>
<td>6,214,050</td>
<td>457,608</td>
</tr>
<tr>
<td>Particles per gram of powder mixture</td>
<td>1,644,643</td>
<td>1,348,449</td>
<td>205,924</td>
</tr>
</tbody>
</table>

3.1.3.4 Weight of the Sample

Calculation of the weight of a sample of mixture

$$\frac{\text{no of particles/sample}}{\text{no of particles per gram mixture}} = \frac{957,753}{3,199,015} = 0.299 \text{g}$$

Following the statistical procedure, it was found that the sample weight should be at least 0.299g. However, according to the BP (2001), the total mass of all samples should be $\geq 0.3\%$ of the mass of the mixture.

As the total mass of the mixture was 666.67g, therefore the total mass of samples taken was 2g. Five samples were taken, hence, the mass of each sample was 0.4g. This sample mass is slightly larger than the calculated minimum sample mass of 0.299g. Hence, the scale of scrutiny chosen will represent the randomisation stage of the mixture.

3.1.3.5 Determination of the Optimal Mixing Time

The theophylline and lactose content was calculated for each of the samples using the calibration curves. This enabled the relative standard deviation (Figure 3.10) to be determined for the five samples taken from different locations from the Y-cone blender (chapter 2.2.3) at different time intervals.

There was a high relative standard deviation between the five samples up to approximately 18 minutes \textit{i.e.} when the three components, pregelatinised starch, lactose
and theophylline were not mixed. The optimum mixing time was achieved when the relative standard deviation for the drug between the five samples was the lowest. A steady increase in the relative standard deviation can be seen after the optimum mixing time has been reached which indicates that demixing and segregation may be occurring in the mixture.

The optimum mixing time was achieved for lactose at approximately 24-27 minutes, as the relative standard deviation was at its lowest. After 27 minutes of mixing, the components, the relative standard deviation increased again suggesting that segregation was occurring in the mixture.

For theophylline, the relative standard deviation was slightly more erratic compared to lactose. This is probably due to the needle shaped particles that take longer to mix compared to the angular shape of the lactose particles. The graph suggests that the optimum mixing time for theophylline was 27-30 minutes. The theophylline and lactose therefore mix at different rates and hence 27 minutes of mixing was considered to be the optimum mixing time.

Magnesium stearate would also be added to the mixture for five minutes. The total mixing time for pregelatinised starch, lactose, and theophylline was hence set to 22 minutes at which point the Y-cone blender was stopped and magnesium stearate was added to the mixture. This will be mixed for a further five minutes such that the total mixing time was 27 minutes as derived above.

Figure 3.10: Relative standard deviation as a function of mixing time for lactose and theophylline
3.1.3.6 Uniformity of Powder Mixture

The homogeneity of the samples was determined analytically to assess whether 27 minutes was a suitable mixing time for all mixtures. Five samples were taken from the Y-cone blender at 22 minutes for all twenty-one formulations.

As the theophylline concentration was increased, the content of uniformity was met up to 45% theophylline (at equal quantities of pregelatinised starch and lactose in the excipient) (Table 3.5). At high pregelatinised starch concentrations in the excipient, the expected theophylline content was more closely met. This can be explained by its improved flow properties in comparison to lactose.

The interaction mixes show that at low theophylline concentrations (22.5%), the expected theophylline content was very closely met and was not dependent on the concentration of the excipients. At higher theophylline concentrations (67.5%) and high pregelatinised starch concentrations in the excipient, the theophylline content was closely met. It must be concluded that the content uniformity of some of the mixtures was not as good as expected. However, it has to be borne in mind that the samples were taken 5 minutes before the optimum mixing time *i.e.* before addition of the lubricant, which would have interfered with the analytical procedures. Thus, during the final 5 minutes post-mixing, the content uniformity should have further improved.

Table 3.5: Observed and Expected Theophylline Concentration

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Theophylline concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
</tr>
<tr>
<td>1</td>
<td>44.06 ± 4.31</td>
</tr>
<tr>
<td>2</td>
<td>46.71 ± 5.15</td>
</tr>
<tr>
<td>3</td>
<td>38.00 ± 7.06</td>
</tr>
<tr>
<td>4</td>
<td>40.41 ± 3.36</td>
</tr>
<tr>
<td>5</td>
<td>39.54 ± 3.73</td>
</tr>
<tr>
<td>6</td>
<td>12.86 ± 1.50</td>
</tr>
<tr>
<td>7</td>
<td>24.60 ± 3.30</td>
</tr>
<tr>
<td>8</td>
<td>50.66 ± 8.56</td>
</tr>
<tr>
<td>9</td>
<td>50.58 ± 4.31</td>
</tr>
<tr>
<td>10</td>
<td>28.82 ± 3.89</td>
</tr>
<tr>
<td>11</td>
<td>29.56 ± 6.19</td>
</tr>
<tr>
<td>12</td>
<td>37.66 ± 7.09</td>
</tr>
<tr>
<td>13</td>
<td>35.30 ± 3.75</td>
</tr>
<tr>
<td>14</td>
<td>19.64 ± 2.98</td>
</tr>
<tr>
<td>15</td>
<td>57.20 ± 3.74</td>
</tr>
<tr>
<td>16</td>
<td>20.17 ± 1.00</td>
</tr>
<tr>
<td>17</td>
<td>58.51 ± 7.21</td>
</tr>
<tr>
<td>18</td>
<td>20.44 ± 1.94</td>
</tr>
<tr>
<td>19</td>
<td>64.52 ± 2.17</td>
</tr>
<tr>
<td>20</td>
<td>22.11 ± 5.45</td>
</tr>
<tr>
<td>21</td>
<td>63.72 ± 1.82</td>
</tr>
</tbody>
</table>

*Concentrations are the arithmetic mean of five samples taken from the Y-cone blender at 25 minutes*
3.1.4 Bulk Properties of Powder Mixtures

3.1.4.1 Carr's Compressibility Index

Carr's compressibility index indicates the flowability of a powder. The change from a freely flowing powder into a non-freely flowing powder is at 20% to 21% of Carr's compressibility index (Carr, 1965). However, capsules can be filled up to a Carr's compressibility index of 35-40, but filling problems occur at values greater than 30 (Podczeck et al., 1999).

Pregelatinised starch

As the pregelatinised starch concentration increased in the excipient, Carr's compressibility index decreased for the centre mix and formulations containing a low theophylline concentration (22.5%), thus indicating improved powder flow (Figure 3.11). At high theophylline concentrations (67.5%), increasing the pregelatinised starch concentration relative to lactose increased Carr's compressibility index showed a worsening of powder flow. This implies that it is preferential to have high pregelatinised starch concentrations in the excipient at low theophylline concentrations and high lactose concentrations in the excipient at high theophylline concentrations. The high magnesium stearate concentration (1.125%) further decreased Carr's compressibility index and had a greater effect at high theophylline (67.5%) and a high pregelatinised starch concentration (90%) in the excipient.

Theophylline

Increasing the theophylline concentration in the centre mix had little effect on Carr's compressibility index (Figure 3.12). This is unexpected because theophylline has a high Carr's compressibility index (32.55). A possible explanation is that the other materials in the formulation are compensating for the poor flow properties of theophylline.

At low theophylline concentrations (22.5%), it was preferable to have a high pregelatinised starch concentration in the excipient (90%), as Carr's compressibility index was lowest. As the theophylline concentration increased, Carr's compressibility index increased at low magnesium stearate concentrations (0.375%), indicating a worsening of powder flow. However, at higher magnesium stearate concentrations (1.125%), Carr's compressibility index did not increase. This suggests that there is a critical concentration of magnesium stearate required to overcome the frictional forces in the powder mixture at high theophylline and high pregelatinised starch concentrations in the excipient.
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Figure 3.11: Carr's compressibility index as a function of the pregelatinised starch concentration in the excipient

Figure 3.12: Carr's compressibility index as a function of the theophylline concentration

Figure 3.13: Carr's compressibility index as a function of the magnesium stearate concentration
This is surprising, as pregelatinised starch possesses lubrication properties of its own, which would imply that a high magnesium stearate concentration would not be necessary. Lactose, however has poor flow properties indicated by a high Carr’s compressibility index of 32.92. However, a high lactose concentration in the excipient at high theophylline concentrations resulted in an improvement in powder flow, suggesting that a low magnesium stearate concentration (0.375%) was sufficient to provide the necessary lubrication required.

**Magnesium Stearate**

Due to the lubrication properties of magnesium stearate, increasing the magnesium stearate concentration improved powder flow (Figure 3.13). The greatest improvements in flow indicated by the large decrease in Carr’s compressibility index occurred when there was a high concentration of theophylline in the formulation and a high concentration of pregelatinised starch in the excipient. There was very little improvement in powder flow at low theophylline concentrations and a high lactose concentration in the excipient, which implies that a high lubricant concentration was not essential for all formulations.

**3.1.4.2 Angle of internal flow**

The angle of internal flow should be as low as possible in order to provide satisfactory flow properties. A lack of interparticulate forces however will hinder plug formation resulting in increased coefficient of fill weight variation. Thus, the angle of internal flow should have an optimum range.

**Pregelatinised starch**

Increasing the pregelatinised starch concentration in the excipient increased the angle of internal flow due to an increase in interparticulate forces (Figure 3.14). This could be due to the smooth surface of pregelatinised starch and therefore an increased contact area between the pregelatinised starch particles. However, lactose has an irregular surface with clefts and grooves and thus the contact between the lactose particles is less and hence results in reduced interparticulate forces. The lowest value for the angle of internal flow occurred when there was a low theophylline concentration and a high magnesium stearate concentration. The angle of internal flow shows that it is essential to have a high magnesium stearate concentration in formulations containing high theophylline and high pregelatinised starch concentrations in the excipient in order to reduce interparticulate friction.
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Figure 3.14: Angle of internal flow as a function of the pregelatinised starch concentration in the excipient

Figure 3.15: Angle of internal flow as a function of the theophylline concentration

Figure 3.16: Angle of internal flow as a function of the magnesium stearate concentration
Theophylline
An increase in the theophylline concentration increased the angle of internal flow (Figure 3.15). At low theophylline concentrations, a high magnesium stearate concentration was most important for a low value for a low angle of internal flow. At higher theophylline concentrations (67.5%), it was important to have a high magnesium stearate concentration when there was a high concentration of pregelatinised starch in the excipient to achieve a low angle of internal flow. However, at high theophylline concentrations when there was a high lactose concentration in the excipient, the magnesium stearate concentration did not influence the angle of internal flow. This indicates that the magnesium stearate concentration of 0.375% is sufficient to cover both the theophylline and lactose particles. Further increasing the magnesium stearate concentration suggests that the lubricant particles are becoming trapped in the grooves and clefts of the irregular surface of lactose particles.

Magnesium Stearate
As the magnesium stearate concentration increased in the formulation, the angle of internal flow decreased (Figure 3.16). The magnesium stearate concentration had little effect at a high theophylline concentration and a low pregelatinised starch concentration in the excipient for reasons explained earlier. When increasing the magnesium stearate concentration from 0.375% to 1.125%, the greatest reduction in interparticulate forces occurred when there was a high theophylline concentration (67.5%) and high pregelatinised starch concentration (90%) in the excipient.

3.1.4.3 Compaction constant $T$
Mohammadi and Harnby (1997) explained that minimum bulk density of a powder could only be imprecisely determined. They used a model of densification describing the volume reduction during tapping as it is less influenced by the experimentally obtained maximum and minimum bulk density. An adaptation of the Cooper-Eaton equation (Cooper and Eaton, 1962) was used where the minimum and maximum bulk density were fitted to a nonlinear relationship between the density reached after a certain number of taps. The final values of the minimum and maximum bulk density of the powder were the theoretical and fitted parameters instead of measured values.

The compaction constant $T$, links flow and packing properties (Mohammadi and Harnby, 1997) by indicating the ease of densification. Mohammadi and Harnby (1997) stated a value below 35 indicated slow densification but good flow properties and a value above 35 was related to rapidly packing powders with poor flow properties.
However, according to Podczeck et al., (1999) poor powder flow and slow densification are connected by higher T-values and a value of T below 35 indicates fast densification thus an improvement in powder flow.

**Pregelatinised starch**

As the pregelatinised starch concentration increased in the excipient, there was a decrease in the T-value indicating improved powder flow and faster densification (Figure 3.17). The lowest T-value occurred when there was a low theophylline concentration, a high magnesium stearate concentration and a high pregelatinised starch concentration in the excipient. This data observed for the T-value agreed with flow data observed for Carr's compressibility index, where it was preferable to have high pregelatinised starch concentrations in the excipient at low theophylline concentrations. The highest T-value occurred when there was a low theophylline concentration, a low magnesium stearate concentration and a high lactose concentration in the excipient mix. This indicates that high lactose concentrations are responsible for increased T-values. However, by increasing the magnesium stearate concentration, there was a vast improvement in the T-value. At high theophylline concentrations, there was only a slight improvement of the T-value with increasing pregelatinised starch concentration in the excipient. Lower T-values were associated with high concentrations of magnesium stearate indicating good powder flow and faster densification, due to the lubricating properties of magnesium stearate.

**Theophylline**

An increase in the theophylline concentration effected the T-value but it was the other components in the formulation that determined whether the T-value increased or decreased (Figure 3.18). At low theophylline concentrations (22.5%), it was preferable to have a 90% pregelatinised starch concentration in the excipient. However, at low theophylline concentrations and high lactose concentrations in the excipient (70%), it was necessary to have a high magnesium stearate concentration (1.125%) in order to achieve low T-values.

At high theophylline concentrations (67.5%) it was necessary to have a high magnesium stearate concentration (1.125%) in order to obtain good flow and fast densification. A slight worsening of powder flow could be seen when there was a high theophylline concentration at high pregelatinised starch concentrations in the excipient. However, the T-value was improved when there was a high magnesium stearate concentration present.
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Figure 3.17: Compaction constant $T$ as a function of the pregelatinised starch concentration in the excipient.

Figure 3.18: Compaction constant $T$ as a function of the theophylline concentration.

Figure 3.19: Compaction constant $T$ as a function of the magnesium stearate concentration.
Magnesium Stearate
As the magnesium stearate concentration increased, the T-value decreased (Figure 3.19). This indicates an improvement in powder packing and powder flow and agrees with data obtained from Carr’s compressibility index and the angle of internal flow. The T-value data clearly shows that a high magnesium stearate concentration was required when there was a high lactose concentration present in the excipient at low theophylline concentrations. This can be seen by the vast decrease in the angle of internal flow when the magnesium stearate concentration was increased.

Good flow properties and rapid densification of the filling material are required in capsule filling because this guarantees quick settlement of the powder bed into an equilibrium state. Hence, low values of the compaction constant imply that capsule filling should be possible without major filling problems and that the coefficient of fill weight variation will be very small especially when there is a high pregelatinised starch concentration in the excipient and a high magnesium stearate concentration. The data for the T-value confirms the results obtained for Carr’s compressibility index that at low theophylline concentrations it is better to have a high pregelatinised starch concentration in the excipient as indicated by the low T-values. However, if the lactose replaces the pregelatinised starch, then it is necessary to have a high magnesium stearate concentration in order to keep the T-values low.

3.1.4.4 Maximum bulk density
Pregelatinised starch
As the pregelatinised starch concentration increased in the excipient, there was a decrease in the maximum bulk density (Figure 3.20). The maximum bulk density was greatest when there was a low theophylline concentration, a high magnesium stearate concentration and a low pregelatinised starch concentration in the excipient. High theophylline concentrations resulted in low maximum bulk densities and can be attributed to its packing properties. Magnesium stearate provided lubrication and therefore at high magnesium stearate concentrations there was an increase in the maximum bulk density.

Theophylline
As the theophylline concentration increased, the maximum bulk density decreased (Figure 3.21). Higher values for the maximum bulk density were associated with a low pregelatinised starch concentration in the excipient. A high magnesium stearate concentration further increased the maximum bulk density at low theophylline concentrations. At high theophylline concentrations when lactose was the principle excipient, the magnesium stearate concentration had little effect.
Figure 3.20: Maximum bulk density as a function of the pregelatinised starch concentration in the excipient

Figure 3.21: Maximum bulk density as a function of the theophylline concentration

Figure 3.22: Maximum bulk density as a function of the magnesium stearate concentration
Magnesium Stearate

As the magnesium stearate concentration increased, there was an increase in the maximum bulk density except when there was a high theophylline concentration and a high lactose concentration in the excipient. This suggests that generally a high magnesium stearate concentration results in improved packing (Figure 3.22).

The minimum and maximum bulk density for the different formulations depends on the powder characteristics such as the particle porosity, average particle size, particle size distribution, particle shape and particle shape distribution and the surface properties of particles (Hausner, 1967). The bulk density was at a minimum for theophylline where high adhesion and friction forces existed. For close packing to occur, these forces must be overcome, which was not achieved by the force of gravity while the powders were at rest. Thus, during tapping particles were forced to jump and lose contact between each other. At this moment no adhesion and friction forces occurred between the particles and they could rearrange their position in the powder bed (Hausner, 1967). Increased adhesion and or friction forces were related to a greater reduction in the volume a defined concentration of powder occupies. Therefore Carr's compressibility index is representative of the adhesion and friction conditions of the powder particles (Hausner, 1967; Podczeck, 1998).

The maximum bulk density of the formulation is dependent on the components and their relative proportions, whereby adding a bulky component results in a drop in the maximum bulk density of the powder mixture (Newton and Bader, 1981). Podczeck and Sharma (1996) found that by adding needle-shaped particles resulted in a lower maximum volume reduction due to packing whereas angular particles such as lactose improved the packing properties of powder mixtures. The results show that a high maximum bulk density is achieved when there is a low theophylline concentration and a high lactose concentration in the excipient.

For powders containing a high concentration of pregelatinised starch it was found that the particles packed down rapidly into their maximum bulk density. The smooth angular shape of the pregelatinised starch particles and its self-lubricating properties facilitated powder flow, which was reflected by the low Carr's compressibility index. However, pregelatinised starch particles are interspersed with a high proportion of small particles which exhibit high frictional forces and this probably also contributed to the increased angle of internal flow. These interparticulate forces were overcome during tapping and hence there was good packing demonstrated by the low T-value.
Lactose particles are dense and angular and during tapping the small particles tend to occupy the interparticulate voids resulting in high maximum bulk densities. The data indicates that lactose is a better excipient compared to pregelatinised starch due to the higher maximum bulk density it provides. A high lactose concentration, however, results in poor flow properties demonstrated by the high Carr’s compressibility index, which is most likely associated with the rough surface of the lactose particles.

As the magnesium stearate concentration increased, there was an increase in the maximum bulk density indicating a reduction in frictional and adhesive properties that facilitates particle slippage and rearrangement. This suggests that a high magnesium stearate concentration is required to achieve good packing.

Capsule filling by tamp filling involves tamping a powder plug which is subsequently ejected into the capsule body. Powder flow is very important because the powder bed needs to reform as quickly as possible after the powder has been tamped. Powders with a low Carr’s compressibility index have good flow, thus form a uniform powder bed which results in improved capsule fill weight uniformity. The Carr’s compressibility index for the formulations ranged from 22.6 to 29.4, however, according to Carr (1965), for good flow to occur the value should be between 12 and 16 and even less for excellent flow. However, according to Podczeck and Newton (1999), when filling capsules using the Bosch GKF-400S tamp filling machine, they found that an optimum range exists for Carr’s compressibility index between 15 and 30. They also found that at optimum machine settings, powders outside this range could also be filled satisfactorily.
3.1.5 Relationship between powder flow properties

To understand the relationship between the flow parameters and the materials, the linear determinant $R^2$ was calculated (Table 3.6). A relationship was observed between the lactose concentration and the maximum bulk density. As the lactose concentration increased, the maximum bulk density also increased (Figure 3.23). However, as the theophylline concentration increased, the maximum bulk density decreased (Figure 3.24). This describes the packing characteristics of these materials and gives an indication of how these materials will fill into hard gelatine capsules. Figure 3.25 shows that as the magnesium stearate concentration increased, the T-value decreased. This is not surprising as magnesium stearate lubricates the materials so that they can slide over each other and facilitate packing.

The angle of internal flow was strongly correlated with the minimum and maximum bulk densities (Figure 3.26). As the bulk densities increased, the angle on internal flow decreased. This is because a reduction in interparticulate forces results in improved powder packing. Also, as the equation used to determine the angle of internal flow is based on the relationship between the particle porosity and the number of taps and particle porosity is a function of the powder bulk density, it is not surprising that values for the angle of internal flow show similar trends to those of the minimum and maximum bulk density.

There was a slight trend between Carr’s compressibility index and the T-value. As Carr’s compressibility index decreased, the T-value also decreased. This agrees with Podczcek (1998), who suggested that lower T-values are indicative of improved powder flow and faster densification.

Table 3.6 Correlation of Materials and Bulk Characteristics (linear determinant $R^2$)

<table>
<thead>
<tr>
<th></th>
<th>PGS</th>
<th>Lactose</th>
<th>Theophylline</th>
<th>MS</th>
<th>$\rho_{min}$ (g/cm$^3$)</th>
<th>$\rho_{max}$ (g/cm$^3$)</th>
<th>CCI (%)</th>
<th>$\theta$ (°)</th>
<th>$T$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGS</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lactose</td>
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<td>1.000</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td>Theophylline</td>
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<td>$\rho_{min}$ (g/cm$^3$)</td>
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<td>$\rho_{max}$ (g/cm$^3$)</td>
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<td>0.542</td>
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<tr>
<td>CCI (%)</td>
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<td>0.377</td>
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<td>0.327</td>
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<td>0.115</td>
<td>0.194</td>
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<td>0.236</td>
<td>0.020</td>
<td>0.383</td>
<td>0.084</td>
<td>1.000</td>
</tr>
</tbody>
</table>
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Figure 3.23: Maximum bulk density as a function of the lactose concentration

Figure 3.24: Maximum bulk density as a function of the theophylline concentration

Figure 3.25: Compaction constant as a function of the magnesium stearate concentration

Figure 3.26: Bulk density as a function of the angle of internal flow
3.2 CAPSULE FILLING

3.2.1 Capsule Fill Weight

In the production of hard gelatine capsules, dose uniformity is an important requirement. A major problem in capsule manufacture is that although doses are specified by weight, the filling system measures by volume. Automatic filling machines which employ the tamp filling system require accurate dosing and ejection into the capsule body.

The capsule filling process can be influenced by machine parameters that will affect powder performance. Powder filling can be measured by the mean capsule fill weight and the coefficient of fill weight variation. Most pharmacopoeias evaluate weight uniformity by setting limits for the range of variation and the number of capsules that can exceed these limits. Different regulations exist in various pharmacopoeias for a maximum variation of the fill weight depending on capsule weight and drug content. For low dose drugs, the test for the content uniformity of fill weight is usually replaced by a test of content uniformity of dose.

The BP (2001) requires that the coefficient of fill weight variation should not exceed 6.7% for a capsule fill weight up to 300mg and 5% for capsule fill weights greater than 300mg. However, industrial standards usually apply a 1% limit for the coefficient of fill weight variation.

The present work describes the use of an instrumented Bosch GKF-400S tamp filling machine to study the capsule filling characteristics of various formulations containing different quantities of pregelatinised starch, lactose and magnesium stearate using theophylline as the model drug. Capsule filling performance was measured by capsule fill weight, coefficient of fill weight variation, plug length and plug density. Tamping forces were measured during the filling cycle to evaluate machine performance.

To investigate relationships between powder flow parameters and capsule filling performance of the powder at different machine parameters, size 1 capsules were filled under 7 different compression settings using the Bosch GKF-400S machine as described in chapter 2.2.6.

3.2.1.1 Cumulative tamping distance

The cumulative tamping distance (CTD) is the total penetration depth of the five tamping pins into the dosing disk bores. The higher the CTD, the greater the penetration depth of the tamping pins. There was an increase in the capsule fill weight as the cumulative
tamping distance was increased (Figures 3.27 to 3.29). At low tamping pin settings there was little difference in the fill weight up to a CTD 6mm. This indicates that at least a CTD of 10mm is required to have an influence on the capsule fill weight. The fill weight increased up to a CTD of 18mm, above which there was little increase in the fill weight when the tamping pin settings were further increased. Thus, the greatest effect on capsule fill weight was found between CTD 10mm and 18mm.

**Pregelatinised starch**
As the pregelatinised starch concentration increased in the excipient, the mean capsule fill weight decreased (Figure 3.27). For every 20% increase in pregelatinised starch in the excipient, there was an approximate 10mg drop in the capsule fill weight up to a pregelatinised starch concentration of 60%, after which there was only a very small decrease by a few milligrams in the fill weight. The flow properties of pregelatinised starch indicated good flow properties and this was demonstrated by the flat smooth powder bed which was similar in height at all five tamping stations.

**Theophylline**
An increase in the theophylline concentration increased the capsule fill weight (Figure 3.28). This is surprising because theophylline has poor flow properties and thus the excipients are needed to provide the necessary properties for good filling to occur. At CTD 18mm and higher, there was a greater spread in the capsule fill weight, indicating that the higher tamping pin settings had a greater effect on the fill weight. It was possible to fill capsules up to a theophylline concentration of 75%. However, an uneven powder bed was experienced at theophylline concentrations greater than 60% whereby the powder bed was highest at tamping station 5 and lowest at tamping station 1. This may lead to increased variability of capsule fill weights.

**Magnesium Stearate**
An increase in the magnesium stearate concentration from 0.25% to 1.25% (Figure 3.29), improved the capsule fill weight by 10mg. The small improvement in the fill weight may be associated with the 60% pregelatinised starch in the excipient that also possesses self-lubricating properties. As the increase in the capsule fill weight was very small, it is preferable to use a low magnesium stearate concentration such that disintegration and dissolution are not hindered.
Figure 3.27: Fill weight at different pregelatinised starch concentrations in the excipient as a function of the cumulative tamping distance.

Figure 3.28: Fill weight at different theophylline concentrations as a function of the cumulative tamping distance.

Figure 3.29: Fill weight at different magnesium stearate concentrations as a function of the cumulative tamping distance.
3.2.1.2 Concentration of materials

The capsule fill weight at CTD 22mm was plotted as a function of the concentration of the materials.

Pregelatinised starch

As the pregelatinised starch concentration increased in the excipient, the capsule fill weight decreased (Figure 3.30). The capsule fill weight decreased most when there was a low theophylline concentration and a low magnesium stearate concentration due to the large concentration of pregelatinised starch. The highest capsule fill weight was found at 60% theophylline, 0.75% magnesium stearate and only 20% pregelatinised starch in the excipient and therefore 80% lactose.

Theophylline

As the theophylline concentration increased, the fill weight increased (Figure 3.31). Higher fill weights were associated with a high lactose concentration in the excipient. At low theophylline concentrations, a high magnesium stearate concentration (1.125%) improved the capsule fill weight when there was a high pregelatinised starch concentration in the excipient. At higher theophylline concentrations, the magnesium stearate concentration only had a small effect on the capsule fill weight.

Magnesium Stearate

As the magnesium stearate concentration increased, the fill weight slightly increased (Figure 3.32). The greatest improvement in the capsule fill weight was found at a low theophylline concentration and a high pregelatinised starch concentration in the excipient. In order to produce high capsule fill weights, a high theophylline concentration can be present. It is better to have a high lactose concentration in the excipient compared to pregelatinised starch as this produces higher capsule fill weights. A high magnesium stearate concentration further increases the capsule fill weight.
Figure 3.30: Fill weight as a function of the pregelatinised starch concentration at cumulative tamping distance 22mm.

Figure 3.31: Fill weight as a function of the theophylline concentration at cumulative tamping distance 22mm.

Figure 3.32: Fill weight as a function of the magnesium stearate concentration at cumulative tamping distance 22mm.
3.2.1.3 Capsule Fill Weight Difference CTD 0mm - 22mm
The capsule fill weight difference is the difference in weight when the tamping pin setting is increased from CTD 0mm to 22mm. This can vary for different formulations depending upon the theophylline, pregelatinised starch, lactose and magnesium stearate concentration in the formulation and demonstrates the influence of machine parameters on the formulation.

**Pregelatinised starch**
As the pregelatinised starch concentration increased in the excipient, the capsule fill weight difference decreased (Figure 3.33). This indicates that as the pregelatinised starch concentration increases in the excipient, the effect of the tamping pin setting decreases. At high theophylline concentrations in the formulation, the influence of the tamping pin setting is much greater than at low theophylline concentrations.

**Theophylline**
As the theophylline concentration increased, there was a clear increase in the fill weight difference (Figure 3.34). This shows that the tamping pin setting has a large influence on the capsule fill weight when there is a high theophylline concentration. Hence poorly packing materials require higher tamping pin settings to fill.

**Magnesium Stearate**
As the magnesium stearate concentration increased, there was very little change in the capsule fill weight difference (Figure 3.35). This suggests that the small magnesium stearate concentration of 0.25% in the formulation is sufficient to provide the necessary lubrication properties required.
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Figure 3.33: Fill weight difference between CTD 0mm – CTD 22mm as a function of the pregelatinised starch concentration in the excipient.

Figure 3.34: Fill weight difference between CTD 0mm – CTD 22mm as a function of the theophylline concentration.

Figure 3.35: Fill weight difference between CTD 0mm – CTD 22mm as a function of the magnesium stearate concentration.
3.2.2 Coefficient of Fill Weight Variation

3.2.2.1 Optimal Cumulative Tamping Distance Setting

Optimum machine parameters are required to achieve uniform fill weights. To obtain the optimum tamping pin setting, the coefficient of fill weight variation at each tamping pin setting for the 21 formulations was averaged to determine the lowest coefficient of fill weight variation.

Figure 3.36 shows that up to CTD 6mm, the coefficient of fill weight variation was very similar. Thus, at low tamping pin settings, there is very little effect on the coefficient of fill weight variation. The maximum coefficient of fill weight variation is at CTD 10mm, therefore capsules should not be filled at this setting. At tamping pin settings greater than 10mm, the coefficient of fill weight variation decreases up to CTD 18mm, after which the coefficient of fill weight variation remains very similar. The lowest coefficient of fill weight variation is at CTD 22mm and thus it is best to fill at this CTD.

Figure 3.36: Mean coefficient of fill weight variation for 21 formulations at different cumulative tamping distance settings

3.2.2.2 Minimum Coefficient of Fill Weight Variation

The minimum coefficient of fill weight variation was associated with CTD 18mm and 22mm (Table 3.7). There was no clear pattern to indicate when it was better to fill at CTD 18mm or 22mm as it was difficult to determine a relationship with the concentration of materials in the formulation and the tamping pin settings. However, in general it is the higher tamping pin settings that are associated with a lower coefficient of fill weight variation.
Table 3.7: Minimum coefficient of fill weight variation (min CFV) for the 21 formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>min CFV (%)</th>
<th>CTD (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.875</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>0.641</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>0.876</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>0.850</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>0.742</td>
<td>22</td>
</tr>
<tr>
<td>6</td>
<td>0.650</td>
<td>18</td>
</tr>
<tr>
<td>7</td>
<td>0.643</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>1.173</td>
<td>18</td>
</tr>
<tr>
<td>9</td>
<td>1.451</td>
<td>18</td>
</tr>
<tr>
<td>10</td>
<td>1.005</td>
<td>22</td>
</tr>
<tr>
<td>11</td>
<td>1.044</td>
<td>18</td>
</tr>
<tr>
<td>12</td>
<td>1.017</td>
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<td>0.657</td>
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</tr>
<tr>
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</tr>
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<td>16</td>
<td>0.820</td>
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</tr>
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</tr>
<tr>
<td>21</td>
<td>0.745</td>
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</tr>
</tbody>
</table>

3.2.2.3 Cumulative Tamping Distance

Pregelatinised starch

As the pregelatinised starch concentration increased in the excipient, the coefficient of fill weight variation decreased (Figure 3.37). This indicates that pregelatinised starch is a good excipient to achieve uniform fill weights. However, a high pregelatinised starch concentration in the excipient resulted in low capsule fill weights. Thus, a balance must be sought between a high fill weight and a low coefficient of fill weight variation.

Theophylline

As the theophylline concentration increased, the coefficient of fill weight variation also increased (Figure 3.38). An increased theophylline concentration increases the capsule fill weight but it also increases the coefficient of fill weight variation. Therefore, an optimum concentration must be reached such that a high fill weight is attained yet the coefficient of fill weight variation remains low. However, the coefficient of fill weight variation for all formulations was below 2%. To achieve a coefficient of fill weight variation of less than 1% and fill the formulation at any tamping pin setting, the maximum amount of drug that can be filled is 30%. However, if the drug was filled at CTD 22mm, then it is possible to fill up to 45% drug and still achieve less than a 1% coefficient of fill weight variation.
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Figure 3.37: Coefficient of fill weight variation at different pregelatinised starch concentrations in the excipient as a function of the cumulative tamping distance

Figure 3.38: Coefficient of fill weight variation at different theophylline concentrations as a function of the cumulative tamping distance

Figure 3.39: Coefficient of fill weight variation at different magnesium stearate concentrations as a function of the cumulative tamping distance
Magnesium Stearate
An increase in the magnesium stearate concentration had very little effect on the coefficient of fill weight variation (Figure 3.39). All formulations had a coefficient of fill weight variation of less than 1.5%. When filling at CTD 22mm, the coefficient of fill weight variation was less than 1%. Carr's compressibility data indicates that an increase in the magnesium stearate concentration up to 1.25% improves powder flow, however this was not reflected in the coefficient of fill weight variation.

3.2.2.4 Concentration of Materials
The coefficient of fill weight variation at CTD 22mm was plotted as a function of the concentration of the materials.

Pregelatinised starch
An increase in the pregelatinised starch concentration in the excipient decreased the coefficient of fill weight variation (Figure 3.40). At low theophylline concentrations (22.5%), the coefficient of fill weight variation was less than 1% and the magnesium stearate concentration did not influence the coefficient of fill weight variation. However, at higher theophylline concentrations, a high magnesium stearate concentration was required to reduce the coefficient of fill weight variation when there was a high pregelatinised starch concentration in the excipient. Formulations containing high pregelatinised starch concentrations, especially formulations 6, 13, 18 and 20, which contained more than 50% pregelatinised starch in the formulation, produced uniform powder beds and resulted in an overall lower coefficient of fill weight variation. Formulations containing a high lactose concentration produced very angled powder beds resulting in higher coefficients of fill weight variation.

On visual inspection of the tamping pin faces and pin shafts, there was almost no powder build-up or stickiness when there was a high pregelatinised starch concentration in the excipient. High lactose concentrations did however produce powder build-up. Tan and Newton (1990a) found high weight variations for lactose powders due to powder binding and piston jamming during filling with the MG2 capsule filling simulator. Podczeck (1999) reported when capsules were filled with pregelatinised starch, there was no adherence to the tamping pins and powders could be filled without the addition of lubricant. However, unlubricated lactose monohydrate, caused the capsule filling machine to seize up after 25 minutes due to the powder adhering to the ejection pins of the transfer station.
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Figure 3.40: Coefficient of fill weight variation as a function of the pregelatinised starch concentration in the excipient at cumulative tamping distance 22mm

Figure 3.41: Coefficient of fill weight variation as a function of the theophylline concentration at cumulative tamping distance 22mm

Figure 3.42: Coefficient of fill weight variation as a function of the magnesium stearate concentration at cumulative tamping distance 22mm
Theophylline
An increase in the theophylline concentrations was associated with a high coefficient of fill weight variation. For the centre mix, the coefficient of fill weight variation remained less than 1% up to a theophylline concentration of 45%, but at concentrations greater than 45%, there was a large increase in the coefficient of fill weight variation (Figure 3.41). A higher coefficient of fill weight variation was related to low pregelatinised starch concentrations in the excipient and the magnesium stearate concentration did not affect the coefficient of fill weight variation. At high theophylline concentrations and high pregelatinised starch concentrations in the excipient, a high magnesium stearate concentration was required to keep the coefficient of fill weight variation low. During filling, formulations containing more than 60% theophylline in the formulation (mixtures 8, 9, 15, 17, 19 and 21) produced highly angled powder beds (Figure 3.43). The powder was overflowing from the bowl due to the strong degree of the angle of the powder bed (Figure 3.44). On visual inspection of the tamping station there was powder build-up on the tamping pin faces and shafts, which further increased the coefficient of fill weight variation. However, all tamping pins were immersed in powder at their highest position and hence, high fill weights were observed for these poor flowing powders. Therefore even poor flowing powders could be filled on a tamp filling machine.

Magnesium Stearate
An increase in magnesium stearate concentration had little effect on the coefficient of fill weight variation (Figure 3.42). Although a high magnesium stearate concentration improved powder flow indicated by Carr’s compressibility index, angle of internal flow and T-value, it did not decrease the coefficient of fill weight variation except at high theophylline concentrations and a high pregelatinised starch concentration in the excipient.
Hence, weight uniformity can be influenced by a variety of factors; powder flow properties, uniformity of the powder bed, tamping pins settings and magnitude of the tamping force during dosing. The high interparticulate friction associated with pregelatinised starch indicated by the increased angle of internal flow results in a lower coefficients of fill weight variation due to less powder loss during ejection of the powder plug. A high lactose concentration in the excipient resulted in higher mean fill weights but also produced high coefficients of fill weight variation. This is because formulations containing a high lactose concentration had a tendency to stick to the dosing disk and/or the tamping pins especially at high tamping pin settings.
3.2.3 Length of Powder Plug

3.2.3.1 Cumulative Tamping Distance

The tamping pin setting had no effect on the plug length up to a CTD 6mm (Figures 3.45 to 3.47). Increasing the tamping pin setting increased the plug length up to CTD 18mm after which there was no further increase. Hence, the plug length is influenced between CTD 10mm to 18mm.

Pregelatinised starch

The pregelatinised starch concentration had very little effect on the plug length up to CTD 6mm, but at higher tamping pin settings, the increase in the pregelatinised starch concentration decreased the plug length (Figure 3.45). This is very apparent at CTD 18mm and 22mm. The decreased plug length is due to the elastic behaviour of pregelatinised starch resulting in lower capsule fill weights.

Theophylline

At theophylline concentrations up to 45%, an increase in the tamping pin setting had very little influence on the plug length (Figure 3.46). However, at theophylline concentrations greater than 60%, a higher tamping pin setting had a greater impact on plug length. This could be associated with the poor flow properties of theophylline, which at an increased concentration would require a higher tamping pin setting in order for the dosing disk to be filled.

Magnesium Stearate

At low tamping pin settings up to CTD 6mm, there was almost no change in the plug length caused by the magnesium stearate concentration (Figure 3.47). This is associated with the fill weight also being unaffected. At higher tamping pin settings, magnesium stearate concentrations up to 0.75% decrease the plug length due to improved packing demonstrated by the capsule fill weight being unaffected. By further increasing the magnesium stearate concentration, there was very little change in the plug length. This suggests that for good packing to occur a magnesium stearate concentration of 0.75% is required.
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Figure 3.45 Plug length at different pregelatinised starch concentrations in the excipient as a function of the cumulative tamping distance

Figure 3.46: Plug length at different theophylline concentrations as a function of the cumulative tamping distance

Figure 3.47: Plug length at different magnesium stearate concentrations as a function of the cumulative tamping distance
3.2.3.2 Concentration of Materials

The coefficient of fill weight variation at CTD 22mm was plotted as a function of the concentration of the materials.

**Pregelatinised starch**

An increase in the pregelatinised starch in the excipient decreased the plug length due to its elastic behaviour (Figure 3.48). High theophylline (67.5%) concentrations were associated with higher plug lengths. This is due to the increase in capsule fill weight. A low magnesium stearate concentration (0.375%) further increased the plug length. This suggests that although a high magnesium stearate concentration increases the capsule fill weight by improving the flow properties of the powder, it also improves the packing properties of the powder and hence smaller plug lengths can be observed. This agrees with the T-value data whereby increasing the magnesium stearate concentration in the formulation improves the packing properties of the powders.

**Theophylline**

An increase in the plug length was observed at high theophylline concentrations due to the increased fill weight (Figure 3.49). The highest plug lengths were observed at low pregelatinised starch concentrations of 30% and 70% lactose in the excipient. A low magnesium stearate concentration further increased the plug length due to the poor packing properties of the powder.

**Magnesium Stearate**

An increase in the magnesium stearate concentration decreased the overall plug length (Figure 3.50). Again, this was associated with the improvement in packing as indicated by a decrease in the T-value. A high theophylline concentration resulted in increased plug lengths. The plug length was further increased by a low pregelatinised starch concentration in the excipient. The plug length gives an indication of capsule fill weight, *i.e.* the higher the plug length, the higher the fill weight. The plug length also gives an idea of the packing properties of the powder, as improved packing results in lower plug lengths. Therefore, to understand the influence of the different formulations on plug length and fill weight, the plug density was calculated.
Figure 3.48: Plug length as a function of the pregelatinised starch concentration in the excipient at cumulative tamping distance 22mm

![Graph showing plug length as a function of pregelatinised starch concentration.]

- Centre mix
- Low theophylline / low MS
- Low theophylline / high MS
- High theophylline / high MS
- High theophylline / low MS

Figure 3.49: Plug length as a function of the theophylline concentration at cumulative tamping distance 22mm

![Graph showing plug length as a function of theophylline concentration.]

- Centre mix
- Low PGS / low MS
- Low PGS / high MS
- High PGS / low MS
- High PGS / high MS

Figure 3.50: Plug length as a function of the magnesium stearate concentration at cumulative tamping distance 22mm

![Graph showing plug length as a function of magnesium stearate concentration.]

- Centre mix
- Low PGS / low theophylline
- Low PGS / high theophylline
- High PGS / high theophylline
- High PGS / low theophylline

150
3.2.4 Plug Density

The density of the powder plug was calculated by dividing the capsule fill weight by the volume of the plug (determined from the plug length and diameter). The powder plug density gives an indication of powder flow and packing. However, a balance must be sought between plug density and plug porosity, as this may result in problems with drug dissolution and bioavailability. Hence, Newton (1987) advised that capsules should not be filled such that the plug density of the powder is greater than the maximum bulk density. In all cases, for all powder formulations and at all the settings, the plug density of the powder was not more than the maximum bulk density.

3.2.4.1 Cumulative Tamping Distance

Pregelatinised starch

An increase in the tamping pin settings resulted in a linear increase in the plug density (Figure 3.51). This was due to extra powder being pushed into the dosing disk cavity by the tamping pin increasing the capsule fill weight. As the pregelatinised starch concentration increased in the excipient, there was a decrease in the powder plug density up to a pregelatinised starch concentration of 60% in the excipient, after which the powder plug density remained similar.

Theophylline

The tamping pin settings had little effect on the powder plug density up to a CTD 3mm. The plug density increased up to CTD 18mm after which there was no further increase in powder plug density (Figure 3.52). Therefore, theophylline formulations can be filled at a CTD 18mm. However, the coefficient of fill weight variation is lower at CTD 22mm and thus it is better to fill at the higher cumulative tamping distance. As the theophylline concentration increased, the powder plug density remained very similar. Therefore, the increase in the capsule fill weight associated with a high theophylline concentration was compensated by an increase in the plug length.

Magnesium Stearate

The powder plug density increased with increasing tamping pin setting up to a CTD 18mm, after which there was no more increase in the plug density (Figure 3.53). Increasing the magnesium stearate concentration increased the plug density. This is because of its lubrication properties, which improve powder flow and packing, indicated by the low Carr's compressibility index and the low T-value.
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Figure 3.51: Plug density at different pregelatinised starch concentrations in the excipient as a function of the cumulative tamping distance.

Figure 3.52: Plug density at different theophylline concentrations as a function of the cumulative tamping distance.

Figure 3.53: Plug density at different magnesium stearate concentrations as a function of the cumulative tamping distance.
3.2.4.2 Concentration of Materials

The density of the powder plugs at CTD 22mm was plotted against the concentration of each of the components.

**Pregelatinised starch**

As the pregelatinised starch concentration increased in the excipient, the powder plug density decreased (Figure 3.54). The plug density decreased most when there was a low theophylline concentration. This is because there was a greater amount of excipient and hence a higher quantity of pregelatinised starch in the capsule. A high magnesium stearate concentration increased the powder plug density most when there was a high pregelatinised starch concentration in the excipient. This is because the magnesium stearate improved the powder flow and hence more powder could be filled into the dosing disk, which increased the capsule fill weight. This supports the data that high concentrations of pregelatinised starch increase the angle of internal flow. Therefore by adding 1.125% magnesium stearate, interparticulate forces are reduced and there is improved powder packing.

**Theophylline**

An increase in the theophylline concentration increased the powder plug density at high pregelatinised starch concentrations in the excipient (Figure 3.55). This is because at low theophylline concentrations, a high pregelatinised starch concentration resulted in low plug densities. As the theophylline concentration increased, the pregelatinised starch concentration proportionately decreased and the plug density increased. At low pregelatinised starch concentrations in the excipient however, there was a slight decrease in plug density as the theophylline concentration was increased. This can be attributed to the high lactose concentration in the excipient. Thus, an increase in the theophylline concentration decreased the overall lactose concentration and the powder plug density decreased. This shows that a high lactose concentration results in high plug densities. A high magnesium stearate concentration further increases the powder plug density.

**Magnesium Stearate**

The high magnesium stearate concentration increased the density of the powder plug (Figure 3.56). This is due lubricant properties of magnesium stearate, which improve powder flow and hence facilitate capsule filling.
Figure 3.54: Plug density as a function of the pregelatinised starch concentration in the excipient at cumulative tamping distance 22mm

Figure 3.55: Plug density as a function of the theophylline concentration at cumulative tamping distance 22mm

Figure 3.56: Plug density as a function of the magnesium stearate concentration at cumulative tamping distance 22mm
3.2.5 Force Data
The tamping force was measured on tamping stations 3 and 4 during the capsule filling cycle for each of the formulations at the different tamping pin settings. The median tamping force was determined from the force data from each of the tamping events.

3.2.5.1 Comparison of Forces at Tamping Stations 3 and 4
Tamping force profiles (Figures 3.57 to 3.62) of formulation 1 show that all forces were greater at tamping station 3 compared to tamping station 4. As a greater force was required at tamping station 3, this indicates that the capsules were mainly full at tamping station 3. This suggests that the powder possessed good flow properties.

3.2.5.2 Cumulative Tamping Distance
As the tamping pin setting increased, the tamping force also increased. This is due to more powder being pushed inside the dosing disk cavity, thus increasing the tamping force.

Pregelatinised starch
A trend can be observed with the quantity of pregelatinised starch and the tamping force. As the pregelatinised starch concentration increased in the excipient, the tamping force decreased (Figure 3.63). This is most likely associated with the decrease in capsule fill weight. Also, pregelatinised starch possesses lubricant properties of its own which could further decrease the tamping force.

Theophylline
There was an increase in the tamping force as the tamping pin setting increased. However there was no clear relationship with the quantity of theophylline in the formulation and the tamping force except that at low concentrations of theophylline (15%), the tamping force was highest at both tamping stations 3 and 4 which indicates that the high tamping force is probably due to the high quantity of excipient in the formulation (Figure 3.64).

Magnesium Stearate
At tamping station 3, the magnesium stearate concentration had little influence on the tamping force (Figure 3.65). This suggests that the low magnesium stearate concentration (0.25%) was sufficient to provide the necessary lubrication. By further increasing the magnesium stearate concentration in the formulation, it did not affect the tamping force.
Figure 3.63: Median tamping force at different pregelatinised starch concentrations in the excipient as a function of the cumulative tamping distance at tamping stations 3 and 4.

Figure 3.64: Median tamping force at different theophylline concentrations as a function of the cumulative tamping distance at tamping stations 3 and 4.

Figure 3.65: Median tamping force at different magnesium stearate concentrations as a function of the cumulative tamping distance at tamping stations 3 and 4.
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At tamping station 4, the tamping forces were affected by the magnesium stearate concentration at high tamping pin settings. As the magnesium stearate concentration increased, there was a drop in the tamping force. The only exception to the trend was formulation 1. This illustrates that formulations containing a high magnesium stearate concentration produce lower tamping forces. This agrees with Podczeck and Newton (2000) who found that a high magnesium stearate concentration was favourable for machine function when using the Bosch GKF-400S tamp filling machine. However, they also found that a high magnesium stearate concentration was not the optimal concentration for powder bulk properties (Podczeck and Newton, 2000). The results illustrate that when measuring tamping forces it is not sufficient to measure the tamping forces at just one tamping station to give an indication of powder filling and machine performance.

3.2.5.3 Concentration of Materials

The optimum tamping pin setting was found to be CTD 22mm because it was associated with the lowest coefficient of fill weight variation. Therefore the median tamping force at CTD 22mm was plotted against the concentration for each of the materials.

Pregelatinised starch

There was a decrease in the tamping force as the pregelatinised starch concentration increased at tamping station 3 (Figure 3.66). The greatest decrease in force was associated with a high theophylline concentration and a low magnesium stearate concentration in the formulation. This is probably because the pregelatinised starch compensated for the low magnesium stearate concentration. At low pregelatinised starch concentrations in the excipient, the magnesium stearate concentration was an important factor in influencing the tamping force. This is because lower tamping forces were associated with high magnesium stearate concentrations but at higher pregelatinised starch concentrations in the excipient (90%) due to the self-lubricating properties of pregelatinised starch, the magnesium stearate concentration was less important.

The force data at tamping station 4 was more complicated (Figure 3.69). As with tamping station 3, the highest tamping force was associated with a high theophylline concentration, low magnesium stearate concentration and a high lactose concentration in the excipient. When the pregelatinised starch concentration increased at high theophylline concentrations, there was a large decrease in the tamping force.
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Figure 3.66: Median tamping force as a function of the pregelatinised starch concentration in the excipient at cumulative tamping distance 22mm and tamping station 3

Figure 3.67: Median tamping force as a function of the theophylline concentration at cumulative tamping distance 22mm and tamping station 3

Figure 3.68: Median tamping force as a function of the magnesium stearate concentration at cumulative tamping distance 22mm and tamping station 3
Figure 3.69: Median tamping force as a function of the pregelatinised starch concentration in the excipient at cumulative tamping distance 22mm and tamping station 4

Figure 3.70: Median tamping force as a function of the theophylline concentration at cumulative tamping distance 22mm and tamping station 4

Figure 3.71: Median tamping force as a function of the magnesium stearate concentration at cumulative tamping distance 22mm and tamping station 4
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There was however almost no effect on the tamping force when the pregelatinised starch concentration increased at high magnesium stearate concentrations. This could be due to the lower tamping forces at tamping station 4 compared to tamping station 3 and therefore the high magnesium stearate concentration (1.125%) is sufficient without the need for extra pregelatinised starch to provide the lubrication to maintain the low tamping force. This suggests that more than one tamping station should be used to measure the tamping force to give an indication of the powder properties. However, at low theophylline concentrations, due to the large amount of excipient, increasing the pregelatinised starch in the excipient increased the tamping force. This could be because the capsules are full at station 3, and due to the elastic nature of pregelatinised starch, the plug expands in the dosing disk bore and the next tamping event has hence to produce sufficient force to densify the plug again.

**Theophylline**

When measuring the tamping forces at tamping station 3 (Figure 3.67), the theophylline concentration had no effect on the tamping force, except when there was a low pregelatinised starch concentration in the excipient and a low magnesium stearate concentration. When increasing the theophylline concentration there was an increase in the tamping force due to the lack of lubrication in the formulation. As long as there was some degree of lubrication in the formulation, magnesium stearate or pregelatinised starch, the tamping force remained relatively low.

The force data at tamping station 4 showed that at a high pregelatinised starch concentration in the excipient, increasing the theophylline concentration decreased the tamping force (Figure 3.70). This reduced tamping force is probably a result of the decrease in the capsule fill weight. At a low pregelatinised starch concentration in the excipient, there was an increase in the tamping force with an increase in the theophylline concentration. A high magnesium stearate concentration reduced the tamping force and no further increase was seen when the theophylline concentration was increased.

**Magnesium Stearate**

The magnesium stearate concentration had little effect on the tamping force at tamping station 3 except when there was a high theophylline concentration and a low pregelatinised starch concentration in the excipient (Figure 3.68). This confirms that a high magnesium stearate concentration must be present if there is a large theophylline concentration and a high lactose concentration in the excipient.
At tamping station 4, a decrease in the tamping force was observed with an increase in the magnesium stearate concentration (Figure 3.71). This suggests that powders which contain a high magnesium stearate concentration are virtually full at tamping station 3 due to good flow properties. Therefore, these powders require a lower tamping force compared to formulations which have a low magnesium stearate concentration, as there is still some space for powder to be filled into the capsule. Thus, a high magnesium stearate concentration is preferable for machine operation and to achieve high capsule fill weights but it has little function to reduce the fill weight variability except when there is a high theophylline concentration and a high pregelatinised starch concentration in the excipient.

3.2.5.4 Spread of Tamping Force

The spread of the force is the difference between the minimum and maximum tamping force and gives an indication about the variability of the force. Powders that possess poor flow properties will have erratic flow and therefore the spread of the tamping force will be greater than those powders which have good flow properties.

At tamping station 3, increasing the concentration of pregelatinised starch, theophylline or magnesium stearate in the formulation had almost no affect on the tamping force spread. This can be observed in figures 3.72, 3.73, and 3.74, respectively. This is because at tamping station 3, the forces are high (Figures 3.63 to 3.65), because this is the tamping station for the main filling of the powders and hence there is little variability between the tamping forces. However, tamping station 4 is the critical tamping station, as tamping forces measured at this tamping station will differentiate between a good flowing powder and a poor flowing powder. This agrees with Podczeck (2001) indicating that the best way to control fill weight would be to place the instrumented tamping head to measure tamping forces at the tamping station 4, where the plug was formed to its final length and density.

Pregelatinised starch

An increase in the pregelatinised starch concentration in the excipient resulted in a decrease in the tamping force spread at tamping station 4 (Figure 3.75). This can be clearly seen when there is a low theophylline concentration of (22.5%) as there is more room for the pregelatinised starch. The decrease in the tamping force spread at high pregelatinised starch concentrations in the excipient suggests that pregelatinised starch does not have erratic flow. Hence, there will be little variability in the powder plug weight and this is supported by the low coefficient of fill weight variation.
Figure 3.72: Tamping force spread as a function of the pregelatinised starch concentration in the excipient at cumulative tamping distance 22mm and at tamping station 3.

Figure 3.73: Tamping force spread as a function of the theophylline concentration at cumulative tamping distance 22mm and at tamping station 3.

Figure 3.74: Tamping force spread as a function of the magnesium stearate concentration at cumulative tamping distance 22mm and at tamping station 3.
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Figure 3.75: Tamping force spread as a function of the pregelatinised starch concentration in the excipient at cumulative tamping distance 22mm and at tamping station 4

Figure 3.76: Tamping force spread as a function of the theophylline concentration at cumulative tamping distance 22mm and at tamping station 4

Figure 3.77: Tamping force spread as a function of the magnesium stearate concentration at cumulative tamping distance 22mm and at tamping station 4
Powders containing a high lactose concentration in the excipient had greater variability in
the tamping force due to the poor powder flow and this was confirmed by the high
coefficient of fill weight variation. At high theophylline concentrations (67.5%)
increasing the pregelatinised starch concentration did not influence the tamping force
spread, indicating that the pregelatinised starch concentration was too small.

Theophylline
Low variabilities in the tamping force measured at tamping station 4 were associated with
a high pregelatinised starch concentration in the excipient (Figure 3.76). Increasing the
theophylline concentration increased the tamping force spread, indicating an increase in
the variability of the tamping force. The tamping force spread was highest at a low
theophylline concentration and a high lactose concentration in the excipient. This is
supported by the high coefficient of fill weight variation associated with high lactose
concentrations in the excipient.

Magnesium Stearate
As the magnesium stearate concentration increased, there was little change in the tamping
force spread (Figure 3.77). Increased variability in the tamping force was associated with
a high lactose concentration in the excipient. This indicates that a low magnesium stearate
concentration was sufficient to lubricate the powder, however it is the other materials in
the formulation that influence the tamping force spread.

The observed differences in the tamping forces may be attributed to the different
morphology and bulk behaviour of the powders. Small and Augsburger (1978) reported
higher ejection forces for lactose compared to pregelatinised starch when filling capsules
with the Zanasi LZ-64 dosator nozzle machine. The increase in the magnitude of the
tamping force at increasing tamping pin settings for lactose and theophylline is indicative
of the readiness of these powders to consolidate into a more closely packed state during
tamping.
### 3.2.6 Relationship Between the Flow and Filling Parameters

To produce capsules with minimal fill weight variation, powders must have optimum flow and packing properties. During the capsule filling process, the powder needs to have sufficient interparticulate forces so that the plug can be successfully ejected into the capsule shell. Meanwhile, the powder bed must be free flowing to achieve a smooth powder bed that is similar in height at all five tamping stations and the powder must be able to fill the void created by the tamping pin (Jones, 1988). The powder bed must also have the ability to rapidly densify to give a similar bulk density in the powder bowl (Hauer, 1993). Therefore an evaluation of the powder flow properties is valuable to determine the suitability of the powder for the capsule filling process and to enable the prediction of capsule filling parameters. It was found that the best filling performance occurred at high tamping pin settings as this resulted in high capsule fill weights and low coefficients of fill weight variation. Therefore the tamping pin setting should be tested at various settings for the powder formulations in order to achieve the optimal filling performance.

The linear determinant $R^2$, was calculated to compare the concentration of materials and flow parameters; Carr’s compressibility index, angle of internal flow and T-value, in relation to the capsule filling characteristics such as fill weight, coefficient of fill weight variation, powder plug density and tamping force and tamping force spread. The linear determinant was compared at each of the tamping pin settings to attain whether the there was a change in the correlation at different compression settings.

There was a very strong correlation between the fill weight and the pregelatinised starch concentration at higher tamping pin settings above CTD 14mm (Table 3.8 and Figure 3.78), whereby increasing the pregelatinised starch concentration decreased the capsule fill weight. This is due to the elastic nature of pregelatinised starch resulting in further material being prevented from entering the dosing disk. The increased lactose concentration increased the capsule fill weight (Figure 3.79). There was a clear relationship at lower tamping pin settings up to CTD 6mm, however the relationship was not very clear at higher tamping pin settings. This could be due to the fact that at higher tamping pin settings lactose fragments and therefore extra lactose is forced into the dosing disk cavity.

The capsule fill weight can roughly be predicted by flow parameters such as the maximum bulk density (Figure 3.80) and the angle of internal flow (Figure 3.81) at low tamping pin settings up to CTD 6mm. As the maximum bulk density increased, the
capsule fill weight increased. This is due to good powder bed densification resulting in more powder entering the dosing disk cavity. As the angle of internal flow increased, the capsule fill weight decreased due to increased interparticulate forces. This agrees with Newton and Bader (1987), who also found that the fill weight decreased with increasing values of angle of internal flow. Both parameters can only predict capsule fill weight at low tamping pin settings. This is because the maximum bulk density and the angle of internal flow are derived from tapping experiments where the powder densifies under the force of gravity alone. Therefore at low tamping pin settings up to CTD 6mm, there is little powder plug densification. At tamping pin settings greater than 6mm, the tamping pin densifies the powder plug pushing more powder into the dosing disk cavity and therefore it is difficult to predict the capsule fill weight from this flow parameter alone. This agrees with Newton and Bader (1987) who found that when filling capsules manually, the relationship between the angle of internal flow and the fill weight was much better when tapping the powder into the cavities rather than applying compression.

There was a relationship between the concentration of the materials and the coefficient of fill weight variation (Table 3.9). As the theophylline concentration increased, the coefficient of fill weight variation increased (Figure 3.82). Therefore there would be a maximum theophylline concentration allowed in the capsule. However, theophylline concentrations up to 75% could be filled at any setting and the coefficient of fill weight variation remained less than 2.5%. To obtain the industry standard of 1%, theophylline concentrations up to 45% could be filled at CTD 22mm. As the pregelatinised starch concentration increased, the coefficient of fill weight variation decreased (Figure 3.83). A high pregelatinised starch concentration also resulted in lower capsule fill weights and therefore an optimum pregelatinised starch concentration must be sought such that the capsule fill weight remains high but does not increase the coefficient of fill weight variation. The coefficient of fill weight variation cannot be predicted by the flow characteristics of the powder formulations. However, Patel and Podczeck (1996) studied data concerning the relationship between powder bulk properties and capsule filling performance of microcrystalline powders on a dosator nozzle machine. It was found that the T-value was strongly related to the coefficient of fill weight variation (Podczeck, 1998). Using a different method of assessment, Hauer et al. (1993) observed that the velocity with which a powder bed reduces its volume was directly related to the flow properties of the powder. Patel and Podczeck (1996) found that Carr's compressibility index was less predictive in this respect, which confirms the fact its use in flow assessments should be discouraged.
The density of the powder plug was related to the pregelatinised starch concentration at high tamping pin settings (Table 3.10 and Figure 3.84). An increase in the pregelatinised starch concentration resulted in a decrease in the powder plug density. As the lactose concentration increased, the plug density increased (Figure 3.85). This is expected because there is not a large increase in the plug length and therefore trends observed for the capsule fill weight are also observed for the powder plug density. The flow characteristics such as the maximum bulk density and the angle of internal flow are also related to the powder plug density (Figures 3.86 and 3.87 respectively). This is because both characteristics are a measure of powder packing. Therefore, low values for the angle of internal flow and high maximum bulk densities result in high plug densities.

There was no correlation between the tamping force and the concentration of the materials and flow parameters (Table 3.11). This could be because many of the correlations occur at low tamping pin settings, whereas there is a threshold tamping pin setting before the tamping force can be measured. However, the tamping force spread gave an indication of the variability of the tamping force (Table 3.12). This was demonstrated by the increase in the tamping force spread as the theophylline concentration was increased (Figure 3.88). Also as the maximum bulk density increased, the tamping force spread decreased (Figure 3.89). This could be associated with rapid settlement of the powder in the dosing disk bores resulting in decreased variability of the tamping force.

On comparison of the filling parameters (Table 3.13), there was a strong correlation between the capsule fill weight and the powder plug density. This was expected, as both parameters are related. There was also a slight relationship between the coefficient of fill weight variation and the capsule fill weight at higher tamping pin settings. This could be due to the fact that at higher tamping pin settings, a firmer powder plug is formed and hence on ejection of the plug, there is little powder loss. A slight trend was also observed between the coefficient of fill weight variation and the tamping force spread at tamping station 4 and CTD 18mm.

It is clear that the results indicate that the flow parameters reflect the flow and packing behaviour of powders on a dosing disk machine. The flow parameters may also be used to predict the capsule filling parameters. The results show that the maximum bulk density and the angle of internal flow are valuable indices in predicting capsule fill weight and plug density. The flow parameters do not correlate with the coefficient of fill weight variation. This indicates that even poor flowing powders can be filled satisfactorily with
a tamp filling machine. The machine settings however, determine the coefficient of fill weight variation because lower coefficients of fill weight variation were associated with increased tamping pin settings.

### Table 3.8: Correlation of fill weight with the materials and flow parameters at different cumulative tamping distances (linear determinant $R^2$)

<table>
<thead>
<tr>
<th>CTD (mm)</th>
<th>PGS</th>
<th>Lactose</th>
<th>Theophylline</th>
<th>MS</th>
<th>$\rho_{\text{min}}$ (g/cm$^3$)</th>
<th>$\rho_{\text{max}}$ (g/cm$^3$)</th>
<th>CCI (%)</th>
<th>$\theta (\degree)$</th>
<th>$T$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.421</td>
<td>0.660</td>
<td>0.006</td>
<td>0.059</td>
<td>0.137</td>
<td>0.442</td>
<td>0.015</td>
<td>0.391</td>
<td>0.033</td>
</tr>
<tr>
<td>3</td>
<td>0.457</td>
<td>0.668</td>
<td>0.003</td>
<td>0.027</td>
<td>0.078</td>
<td>0.387</td>
<td>0.049</td>
<td>0.326</td>
<td>0.057</td>
</tr>
<tr>
<td>6</td>
<td>0.410</td>
<td>0.673</td>
<td>0.008</td>
<td>0.064</td>
<td>0.136</td>
<td>0.462</td>
<td>0.020</td>
<td>0.407</td>
<td>0.022</td>
</tr>
<tr>
<td>10</td>
<td>0.418</td>
<td>0.613</td>
<td>0.003</td>
<td>0.093</td>
<td>0.154</td>
<td>0.450</td>
<td>0.009</td>
<td>0.414</td>
<td>0.015</td>
</tr>
<tr>
<td>14</td>
<td>0.658</td>
<td>0.506</td>
<td>0.029</td>
<td>0.040</td>
<td>0.027</td>
<td>0.198</td>
<td>0.046</td>
<td>0.166</td>
<td>0.059</td>
</tr>
<tr>
<td>18</td>
<td>0.816</td>
<td>0.351</td>
<td>0.132</td>
<td>0.048</td>
<td>0.013</td>
<td>0.092</td>
<td>0.020</td>
<td>0.080</td>
<td>0.040</td>
</tr>
<tr>
<td>22</td>
<td>0.850</td>
<td>0.314</td>
<td>0.167</td>
<td>0.045</td>
<td>0.007</td>
<td>0.064</td>
<td>0.019</td>
<td>0.055</td>
<td>0.045</td>
</tr>
</tbody>
</table>

### Table 3.9: Correlation of the coefficient of fill weight variation with the materials and flow parameters at different cumulative tamping distances (linear determinant $R^2$)

<table>
<thead>
<tr>
<th>CTD (mm)</th>
<th>PGS</th>
<th>Lactose</th>
<th>Theophylline</th>
<th>MS</th>
<th>$\rho_{\text{min}}$ (g/cm$^3$)</th>
<th>$\rho_{\text{max}}$ (g/cm$^3$)</th>
<th>CCI (%)</th>
<th>$\theta (\degree)$</th>
<th>$T$</th>
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<tbody>
<tr>
<td>0</td>
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<td>0.001</td>
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<td>0.029</td>
<td>0.012</td>
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<td>0.561</td>
<td>0.015</td>
<td>0.204</td>
<td>0.159</td>
<td>0.082</td>
<td>0.152</td>
<td>0.044</td>
</tr>
<tr>
<td>6</td>
<td>0.564</td>
<td>0.000</td>
<td>0.546</td>
<td>0.010</td>
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<td>0.114</td>
<td>0.015</td>
<td>0.113</td>
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<tr>
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<td>0.000</td>
<td>0.663</td>
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<td>0.172</td>
<td>0.072</td>
<td>0.174</td>
<td>0.095</td>
</tr>
<tr>
<td>14</td>
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<td>0.598</td>
<td>0.072</td>
<td>0.134</td>
<td>0.150</td>
<td>0.025</td>
<td>0.151</td>
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</tr>
<tr>
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<td>0.002</td>
<td>0.493</td>
<td>0.017</td>
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<td>0.098</td>
<td>0.023</td>
<td>0.098</td>
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</tr>
<tr>
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<td>0.076</td>
<td>0.015</td>
<td>0.059</td>
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</table>

### Table 3.10: Correlation of plug density with the materials and flow parameters at different cumulative tamping distances (linear determinant $R^2$)

<table>
<thead>
<tr>
<th>CTD (mm)</th>
<th>PGS</th>
<th>Lactose</th>
<th>Theophylline</th>
<th>MS</th>
<th>$\rho_{\text{min}}$ (g/cm$^3$)</th>
<th>$\rho_{\text{max}}$ (g/cm$^3$)</th>
<th>CCI (%)</th>
<th>$\theta (\degree)$</th>
<th>$T$</th>
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<tbody>
<tr>
<td>0</td>
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<td>0.003</td>
<td>0.074</td>
<td>0.169</td>
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<td>0.413</td>
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</tr>
<tr>
<td>3</td>
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<td>0.005</td>
<td>0.062</td>
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<td>0.109</td>
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<td>0.467</td>
<td>0.006</td>
<td>0.434</td>
<td>0.007</td>
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<td>0.175</td>
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<td>0.001</td>
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<td>0.246</td>
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<td>0.236</td>
<td>0.003</td>
<td>0.230</td>
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### Table 3.11: Correlation of tamping force with the materials and flow parameters at different cumulative tamping distances at tamping stations 3 and 4 (linear determinant $R^2$)

<table>
<thead>
<tr>
<th>Tamping station</th>
<th>CTD (mm)</th>
<th>PGS</th>
<th>Lactose</th>
<th>Theophylline</th>
<th>MS</th>
<th>$P_{\text{min}}$ (g/cm$^2$)</th>
<th>$P_{\text{max}}$ (g/cm$^2$)</th>
<th>CCI (%)</th>
<th>$\theta$ ($^\circ$)</th>
<th>$T$</th>
</tr>
</thead>
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<td>0.002</td>
<td>0.100</td>
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<td>0.003</td>
<td>0.100</td>
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</table>

### Table 3.12: Correlation of tamping force spread with the materials and flow parameters at different cumulative tamping distances at tamping stations 3 and 4 (linear determinant $R^2$)

<table>
<thead>
<tr>
<th>Tamping station</th>
<th>CTD (mm)</th>
<th>PGS</th>
<th>Lactose</th>
<th>Theophylline</th>
<th>MS</th>
<th>$P_{\text{min}}$ (g/cm$^2$)</th>
<th>$P_{\text{max}}$ (g/cm$^2$)</th>
<th>CCI (%)</th>
<th>$\theta$ ($^\circ$)</th>
<th>$T$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>14</td>
<td>0.342</td>
<td>0.008</td>
<td>0.239</td>
<td>0.047</td>
<td>0.002</td>
<td>0.013</td>
<td>0.003</td>
<td>0.017</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>0.065</td>
<td>0.035</td>
<td>0.007</td>
<td>0.073</td>
<td>0.004</td>
<td>0.020</td>
<td>0.009</td>
<td>0.015</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>0.029</td>
<td>0.150</td>
<td>0.027</td>
<td>0.003</td>
<td>0.017</td>
<td>0.097</td>
<td>0.018</td>
<td>0.061</td>
<td>0.003</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>0.069</td>
<td>0.061</td>
<td>0.019</td>
<td>0.013</td>
<td>0.015</td>
<td>0.009</td>
<td>0.027</td>
<td>0.065</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>0.150</td>
<td>0.144</td>
<td>0.496</td>
<td>0.066</td>
<td>0.345</td>
<td>0.415</td>
<td>0.057</td>
<td>0.384</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>0.135</td>
<td>0.253</td>
<td>0.006</td>
<td>0.002</td>
<td>0.000</td>
<td>0.061</td>
<td>0.077</td>
<td>0.023</td>
<td>0.039</td>
</tr>
</tbody>
</table>

### Table 3.13: Correlation of the filling parameters at different cumulative tamping distances (linear determinant $R^2$)

<table>
<thead>
<tr>
<th>CTD (mm)</th>
<th>Fill weight</th>
<th>CFV</th>
<th>Plug density</th>
<th>Force station 3</th>
<th>Force station 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.706</td>
<td>0.103</td>
<td>0.097</td>
<td>0.120</td>
<td>0.228</td>
</tr>
<tr>
<td>3</td>
<td>0.094</td>
<td>0.363</td>
<td>0.378</td>
<td>0.913</td>
<td>0.947</td>
</tr>
<tr>
<td>6</td>
<td>0.096</td>
<td>0.098</td>
<td>0.376</td>
<td>0.937</td>
<td>0.927</td>
</tr>
<tr>
<td>9</td>
<td>0.092</td>
<td>0.927</td>
<td>0.918</td>
<td>0.918</td>
<td>0.918</td>
</tr>
<tr>
<td>12</td>
<td>0.092</td>
<td>0.927</td>
<td>0.927</td>
<td>0.927</td>
<td>0.927</td>
</tr>
<tr>
<td>15</td>
<td>0.092</td>
<td>0.927</td>
<td>0.927</td>
<td>0.927</td>
<td>0.927</td>
</tr>
<tr>
<td>18</td>
<td>0.092</td>
<td>0.927</td>
<td>0.927</td>
<td>0.927</td>
<td>0.927</td>
</tr>
<tr>
<td>21</td>
<td>0.092</td>
<td>0.927</td>
<td>0.927</td>
<td>0.927</td>
<td>0.927</td>
</tr>
<tr>
<td>24</td>
<td>0.092</td>
<td>0.927</td>
<td>0.927</td>
<td>0.927</td>
<td>0.927</td>
</tr>
</tbody>
</table>
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Figure 3.78 Fill weight as a function of the pregelatinised starch concentration at cumulative tamping distance 22mm

Figure 3.79 Fill weight as a function of the lactose concentration at cumulative tamping distance 6mm

Figure 3.80 Fill weight as a function of the maximum bulk density at cumulative tamping distance 6mm

Figure 3.81 Fill weight as a function of the angle of internal flow at cumulative tamping distance 10mm
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Figure 3.82: Coefficient of fill weight variation as a function of the theophylline concentration at cumulative tamping distance 10mm

Figure 3.83: Coefficient of fill weight variation as a function of the pregelatinised starch concentration at cumulative tamping distance 10mm

Figure 3.84: Plug density as a function of the pregelatinised starch concentration at cumulative tamping distance 10mm

Figure 3.85: Plug density as a function of the lactose concentration at cumulative tamping distance 3mm
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Figure 3.86: Plug density as a function of the maximum bulk density at cumulative tamping distance 10mm

Figure 3.87: Plug density as a function of the angle of internal flow at cumulative tamping distance 10mm

Figure 3.88: Tamping force spread as a function of the theophylline concentration at tamping station 4 and cumulative tamping distance 18mm

Figure 3.89: Tamping force spread as a function of the maximum bulk density at tamping station 4 and cumulative tamping distance 18mm
3.3 DISINTEGRATION

3.3.1 Disintegration of the Formulations

The disintegration time was determined for six capsules at each of the tamping pin settings for all mixes as described in Ch. 2.2.10. All capsules disintegrated within the specified time of 1800 seconds according to the BP (2001). It was difficult to see an immediate trend when the disintegration time was plotted against the cumulative tamping distance. To determine if the tamping pin settings influenced the disintegration times of the batches, one-way (single factor) analysis of variance was carried out using the Microsoft Excel 2000 package. At the 5% significance level, the tamping pin setting significantly affected the disintegration times for mixes 9, 10, 14 and 17. When identifying the material in these formulations, there was no clear relationship between the concentration of the materials and the effect of the tamping pin setting on the disintegration time.

As only four of the twenty-one batches had significantly different disintegration times due to an increase in the tamping pin setting at the 5% level, the average disintegration time over the different tamping pin settings was sought for each of the formulations and this was plotted against the concentration of the materials.

Pregelatinised starch

An increase in the pregelatinised starch concentration increased the disintegration time (Figure 3.90). In tabletting, pregelatinised starch functions as a disintegrant. This is because pregelatinised starch has the ability to swell in water, which pushes the particles in the tablet compact apart. This enables water to enter the compact and hence aids the disintegration process. In capsules, the plug is not as dense and therefore any swelling of the pregelatinised starch fills the voids in the plug and thus the disintegration process is retarded.

Lower disintegration times were associated with a high theophylline concentration (67.5%). The magnesium stearate concentration did not affect the disintegration time. However, at low theophylline concentrations of (22.5%) and low pregelatinised starch concentrations in the excipient, it was preferable to have a low magnesium stearate concentration in the formulation. Hence, the magnesium stearate concentration influences the disintegration process at high lactose concentrations.
Figure 3.90: Disintegration time as a function of the pregelatinised starch concentration in the excipient

Figure 3.91: Disintegration time as a function of the theophylline concentration

Figure 3.92: Disintegration time as a function of the magnesium stearate concentration
Theophylline

As the theophylline concentration increased, the disintegration times decreased (Figure 3.91). This shows that filling a hydrophobic drug does not necessarily increase the disintegration times of the capsule. Lower disintegration times were associated with a low pregelatinised starch concentration for reasons explained earlier. The disintegration times were further improved by a low magnesium stearate concentration. At high theophylline concentrations, the magnesium stearate concentration did not influence the disintegration time.

Magnesium Stearate

The increase in the magnesium stearate concentration did not have a large consequence on the disintegration time (Figure 3.92). This indicates that the five minutes post mixing of the materials was sufficient to provide lubrication in the formulation and yet prevent the particles from becoming hydrophobic. The only formulation that showed an increase in the disintegration time as the magnesium stearate concentration was increased was that having a low theophylline concentration and a low pregelatinised starch to lactose ratio. This indicates that at high lactose concentrations, only a small magnesium stearate concentration should be used to maintain a low disintegration time. This could be due to the rough surface of lactose, which traps the magnesium stearate particles in its gaps and crevices, which cause the increase in the disintegration time.

3.3.2 Relationship between the disintegration time and the flow and filling parameters

In order to determine a relationship between the mean disintegration time and the concentration of the materials, flow properties and filling properties, the linear determinant $R^2$ was determined (Tables 3.14 and 3.15). There was a very strong correlation between the pregelatinised starch concentration and the mean disintegration time. This clearly indicates that an increase in the pregelatinised starch concentration i.e. a disintegrant, results in an increase in the disintegration time. Thus, contrary to popular belief, the need for a disintegrant is not required in capsule formulations. This agrees with Newton (1987) who also found that tablet disintegrants do mostly not work in capsule formulations. Also Lai (1996) found that approximately 60% of capsule formulations on the market do not contain a disintegrant.

When comparing the filling properties with the disintegration time, strong relationships could be seen, which depended upon the tamping pin setting. As the tamping pin setting was increased, the correlation between the fill weight and the disintegration time
increased and therefore also the plug density and the disintegration time. It could be assumed this is because increasing the compression setting pushes more powder into the dosing disk and produces firmer powder plugs, which take longer to disintegrate. This was not the case as higher capsule fill weights were associated with lower disintegration times. The most reasonable explanation for this is that high concentrations of pregelatinised starch were associated with lower fill weights and high disintegration times. This indicates that formulation parameters such as materials chosen are more critical in determining the disintegration time than the density of the powder plugs.

There was a strong relationship between the coefficient of fill weight variation and the disintegration times at low tamping pin settings (CTD 0mm). As the coefficient of fill weight variation increased, the disintegration time decreased. This can be attributed to the high pregelatinised starch concentration in the formulation as a high pregelatinised starch concentration was related with a low coefficient of fill weight variation. Therefore the machine parameters have a small part to play in the overall role of the disintegration process, but the most important variable to consider is the concentration of the materials.

Table 3.14: Linear determinant $R^2$ for the relationship between the disintegration time and the materials and flow properties

<table>
<thead>
<tr>
<th>Material</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGS</td>
<td>0.852</td>
</tr>
<tr>
<td>MFC</td>
<td>0.130</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>0.343</td>
</tr>
<tr>
<td>MS</td>
<td>0.001</td>
</tr>
<tr>
<td>$\rho_{\text{min}}$ (g/cm$^3$)</td>
<td>0.016</td>
</tr>
<tr>
<td>$\rho_{\text{max}}$ (g/cm$^3$)</td>
<td>0.003</td>
</tr>
<tr>
<td>CC1(%)</td>
<td>0.020</td>
</tr>
<tr>
<td>$\theta$ (°)</td>
<td>0.006</td>
</tr>
<tr>
<td>$T$</td>
<td>0.198</td>
</tr>
</tbody>
</table>

Table 3.15: Linear relationship $R^2$ for the relationship between the disintegration time and the filling parameters

<table>
<thead>
<tr>
<th>Cumulative tamping distances (mm)</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>10</th>
<th>14</th>
<th>18</th>
<th>22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fill weight (mg)</td>
<td>0.397</td>
<td>0.401</td>
<td>0.359</td>
<td>0.366</td>
<td>0.537</td>
<td>0.713</td>
<td>0.743</td>
</tr>
<tr>
<td>CFV (%)</td>
<td>0.790</td>
<td>0.551</td>
<td>0.616</td>
<td>0.667</td>
<td>0.655</td>
<td>0.554</td>
<td>0.387</td>
</tr>
<tr>
<td>Plug density (g/cm$^3$)</td>
<td>0.382</td>
<td>0.361</td>
<td>0.342</td>
<td>0.283</td>
<td>0.378</td>
<td>0.532</td>
<td>0.514</td>
</tr>
<tr>
<td>Tamping force (N)</td>
<td>St. 3</td>
<td>0.008</td>
<td>0.045</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>St. 4</td>
<td>0.098</td>
<td>0.122</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.4 DISSOLUTION

The release characteristics of the formulations were studied by performing dissolution tests. Dissolution testing was carried out for formulation 1 (centre mix), and the main outer factor levels, formulation 2 (0.25% magnesium stearate); formulation 5 (1.25% magnesium stearate); formulation 6 (15% theophylline); formulation 9 (75% theophylline); formulation 10 (20% pregelatinised starch and 80% lactose in the excipient) and formulation 13 (100% pregelatinised starch in excipient). Capsules were taken from the batch with the highest tamping pin setting i.e. CTD 22mm. This was in order to observe the dissolution process at the optimum tamping pin setting.

The mean dissolution profile for each formulation (Figure 3.93) showed that altering the formulation influenced drug release. The centre mix possessed fast drug release characteristics. However, when altering the concentration of the excipients, it is evident that a high pregelatinised starch concentration in the excipient (100%) resulted in a lag period before dissolution of the capsules was observed. This can be associated with the swelling properties of pregelatinised starch, which fills the void spaces in the powder plug. Hence, water penetration into the powder plug was reduced and the dissolution process was retarded. A low pregelatinised starch concentration in the excipient (20% pregelatinised starch and 80% lactose) however, resulted in fast drug dissolution. This was demonstrated by 70% of the drug being released within five minutes. However, drug dissolution slowed down after 80% of the drug was released. Stewart et al., (1979) also found that the type of diluent significantly influenced the drug release of a model low dose drug (riboflavine) and the diluents could be ranked in order of effectiveness.

The lag period before dissolution was also observed at a low theophylline concentration (15%). This again is associated with the large amount of pregelatinised starch (60%) present in the excipient formulation. A high theophylline concentration (75%) resulted in fast drug dissolution up to 70% drug release, and then the dissolution process was slowed. This shows that it is possible to use high concentrations of a hydrophobic drug and still achieve fast drug release. This trend was also observed for the disintegration data.

The dissolution profile for magnesium stearate was almost the same up to 80% drug release for the low (0.25%) and high (1.25%) concentration, indicating that 5 minutes post-mixing of the lubricant was sufficient not to cause hydrophobicity of the drug. The high magnesium stearate concentration resulted in faster peak theophylline concentrations. This agrees with Nakagwu (1980) who also reported improved drug dissolution at high magnesium stearate levels for rifampicin capsules and attributed this
with reduced powder adhesiveness. Mehta and Augsburger (1981) reported improved
drug dissolution with an increased magnesium stearate concentration up to the optimum
lubricant concentration for microcrystalline cellulose and hydrochlorothiazide as a model
low dose drug for capsules filled by a dosator capsule filling machine. They attributed
this to the decrease in plug mechanical strength. They suggested that the decrease in plug
mechanical strength was of greater importance than the increase in matrix hydrophobicity
(Mehta and Augsburger, 1981).

Figure 3.93: Percentage of theophylline released for the different formulations as a function of time at
cumulative tampon distance 22mm

Analysis of the results was carried out by determination of statistical moments (Podczeck,
1993; Pinto et al., 1997) to characterise and compare the release profiles of different
formulations of theophylline. These were the mean dissolution time (MDT) of
theophylline and variance of the dissolution time (VDT) and an associated parameter, the
relative dispersion of the concentration-time profile (RD) and the area under the curve
(AUC). Figures of the calculated parameters as a function of the concentration of
pregelatinised starch, theophylline and magnesium stearate are shown in table 3.16 and
figures 3.94 to 3.97.
Chapter 3 - Theophylline

Table 3.16: Calculated parameters [area under the curve (AUC), mean dissolution time (MDT), variance of the dissolution time (VDT) and the relative dispersion coefficient (RD) for theophylline for the different formulations at cumulative tamping distance 22mm

<table>
<thead>
<tr>
<th>No.</th>
<th>AUC (% min)</th>
<th>MDT (min)</th>
<th>VDT (min^2)</th>
<th>RD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>577.9 ± 24.2</td>
<td>6.04 ± 0.23</td>
<td>13.19 ± 2.66</td>
<td>0.362 ± 0.059</td>
</tr>
<tr>
<td>2</td>
<td>710.6 ± 65.5</td>
<td>7.28 ± 0.89</td>
<td>25.34 ± 6.03</td>
<td>0.530 ± 0.042</td>
</tr>
<tr>
<td>5</td>
<td>563.2 ± 29.3</td>
<td>6.02 ± 5.72</td>
<td>10.04 ± 0.63</td>
<td>0.298 ± 0.046</td>
</tr>
<tr>
<td>6</td>
<td>747.5 ± 32.1</td>
<td>7.54 ± 0.26</td>
<td>12.44 ± 1.80</td>
<td>0.173 ± 0.034</td>
</tr>
<tr>
<td>9</td>
<td>778.6 ± 111.1</td>
<td>8.40 ± 1.19</td>
<td>76.67 ± 23.25</td>
<td>1.573 ± 0.103</td>
</tr>
<tr>
<td>10</td>
<td>624.8 ± 112.3</td>
<td>6.54 ± 1.20</td>
<td>55.98 ± 25.33</td>
<td>1.427 ± 0.049</td>
</tr>
<tr>
<td>13</td>
<td>699.0 ± 24.9</td>
<td>7.49 ± 0.21</td>
<td>11.34 ± 0.86</td>
<td>0.197 ± 0.016</td>
</tr>
</tbody>
</table>

From these parameters, it was possible to relate the release of theophylline to the dissolution mechanisms. The MDT and the AUC increased as the pregelatinised starch concentration increased. This can be attributed to the swelling properties of pregelatinised starch, which hinders drug release. There was a clear decrease in the MDT and AUC as the magnesium stearate concentration was increased, due to reasons explained previously. Theophylline showed optimum drug release for the centre mix.

The VDT values are an indication of the variation of the dissolution times and show a decrease as the pregelatinised starch concentration increased. There was an increase in the VDT as the theophylline concentration was increased, which can be attributed to the hydrophobic nature of theophylline. An increase in the magnesium stearate concentration only slightly decreased the VDT. The VDT shares a relationship with the coefficient of fill weight variation, as a high pregelatinised starch concentration in the excipient resulted in low values for the coefficient of fill weight variation; high theophylline concentrations increased the variability of the fill weight and high magnesium stearate concentrations has almost no effect on the coefficient of fill weight variation.

The values obtained for the RD were calculated and varied for the different formulations. The values achieved did not perfectly fit those for any of the traditional dissolution models and thus the closest release rate mechanism was chosen [RD = 1.0, first order release (class 1); RD = 0.8, pseudo first order release (class 2); RD = 0.6 cube root release (class 3); RD = 0.3, zero order release (class 0)] (Pinto et al., 1997). However, the data shows that as the concentration of the components formulation increased, a change in the release mechanism was observed.
Figure 3.94: Area under the curve as a function of the pregelatinised starch, theophylline and magnesium stearate concentration

Figure 3.95: Mean dissolution time as a function of the pregelatinised starch, theophylline and magnesium stearate concentration

Figure 3.96: Variance of the dissolution time as a function of the pregelatinised starch, theophylline and magnesium stearate concentration

Figure 3.97: Relative dispersion coefficient as a function of the pregelatinised starch, theophylline and magnesium stearate concentration

Note: Pregelatinised starch concentration (low, 20% in excipient; medium, 60% in excipient; high, 100% in excipient); Theophylline concentration (low, 15%; medium, 45%; high, 75%); Magnesium stearate concentration (low, 0.25%; medium, 0.75%; high, 1.25%)
The centre mix had a RD of 0.351 indicating zero order release. As the PGS concentration increased from 20% to 100% in the excipient, the release mechanism changed from first order release to zero order release. The increase in the theophylline concentration from 15% to 75% resulted in a change from zero order release to first order release. The magnesium stearate concentration resulted in a change in the release mechanism from cube root release to zero order release.
CHAPTER 4

IBUPROFEN
4.1 POWDER FLOW PROPERTIES

Powder flowability influences the manufacturing process of capsule formulations. Poor powder flow often requires changes of an otherwise satisfactory formulation.

4.1.1 Particulate Properties of Materials

The mean particle sizes of ibuprofen and microfine cellulose were 41µm and 40µm respectively (Table 4.1). Particle densities were here determined using a helium pycnometer and hence the slightly different value for pregelatinised starch compared to chapter 3. The particle densities for pregelatinised starch and microfine cellulose were very similar, which reduced the variability when comparing the two materials. Ibuprofen had a much lower density comparatively, which may influence its packing performance during powder flow tests and capsule filling.

<table>
<thead>
<tr>
<th>Material</th>
<th>Particle size (µm)</th>
<th>Particle density (g/cm³)</th>
<th>Moisture content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregelatinised starch</td>
<td>51 ± 2.1</td>
<td>1.468 ± 0.002</td>
<td>9.484 ± 0.04</td>
</tr>
<tr>
<td>Microfine cellulose</td>
<td>41 ± 1.7</td>
<td>1.516 ± 0.008</td>
<td>5.950 ± 0.05</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>40 ± 1.5</td>
<td>1.121 ± 0.007</td>
<td>n/a</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>n/a</td>
<td>1.051 ± 0.003</td>
<td>5.224 ± 0.18</td>
</tr>
</tbody>
</table>

* The results are the arithmetic mean of three investigations

Particle morphology of the materials was investigated by visual inspection using SEM (scanning electron microscopy). Figures 4.1 and 4.2 show the SEMs for ibuprofen and microfine cellulose. Ibuprofen possessed smooth rod shape particles compared to the irregular, mainly fibre-like particles of microfine cellulose. Both materials had a heterogeneous size distribution, which may increase the interparticulate forces of the materials.

Figure 4.1: SEM of Ibuprofen
Figure 4.2: SEM of Microfine Cellulose
Thermogravimetric analysis was carried out to determine the moisture content of the materials. The moisture content for each of the materials is shown in Table 4.1. Figures 4.3 and 4.4 depict a typical weight loss curve (TG-curve) and its derivative (DTG-curve) as a function of the temperature for ibuprofen and microfine cellulose. Ibuprofen contained no free water illustrated in figure 4.3. The water loss for microfine cellulose was 5.95% and mainly occurred before 100°C (Figure 4.4).

### 4.1.2 Bulk Properties of Materials

#### 4.1.2.1 Minimum and Maximum Bulk Density

When comparing the packing profile of the materials, pregelatinised starch had a much higher minimum and maximum bulk density compared to ibuprofen and microfine cellulose (Table 4.2).

<table>
<thead>
<tr>
<th></th>
<th>Pregelatinised starch</th>
<th>Microfine cellulose</th>
<th>Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum bulk density (g/cm³)</td>
<td>0.651 ± 0.004</td>
<td>0.259 ± 0.007</td>
<td>0.352 ± 0.006</td>
</tr>
<tr>
<td>Maximum bulk density (g/cm³)</td>
<td>0.798 ± 0.007</td>
<td>0.431 ± 0.005</td>
<td>0.483 ± 0.009</td>
</tr>
<tr>
<td>Carr's compressibility index (%)</td>
<td>18.36 ± 0.27</td>
<td>40.00 ± 0.70</td>
<td>27.03 ± 0.819</td>
</tr>
<tr>
<td>Angle of internal flow (°)</td>
<td>20.94 ± 0.44</td>
<td>53.56 ± 0.24</td>
<td>35.62 ± 1.30</td>
</tr>
<tr>
<td>Compaction constant T</td>
<td>12.93 ± 1.29</td>
<td>86.95 ± 2.62</td>
<td>37.01 ± 3.77</td>
</tr>
<tr>
<td>Angle of internal friction (°)</td>
<td>31.20 ± 0.10</td>
<td>41.53 ± 0.54</td>
<td>34.30 ± 1.60</td>
</tr>
<tr>
<td>Cohesion coefficient (g/cm³)</td>
<td>3.36 ± 0.35</td>
<td>3.98 ± 0.27</td>
<td>6.14 ± 0.70</td>
</tr>
<tr>
<td>Mobility index m</td>
<td>0.28</td>
<td>0.18</td>
<td>0.23</td>
</tr>
<tr>
<td>Jenike's flow factor FF</td>
<td>9.37 ± 0.95</td>
<td>8.96 ± 0.64</td>
<td>5.51 ± 0.61</td>
</tr>
</tbody>
</table>

*The results are the arithmetic mean and S.D. of three investigations*

Pregelatinised starch demonstrated faster packing and was mainly packed after 600 taps in comparison to microfine cellulose and ibuprofen, which took approximately 800 taps and 1,000 taps, respectively (Figure 4.5). The difference between the minimum and maximum bulk density was also much greater for ibuprofen and microfine cellulose. These packing characteristics can be attributed to the shape and the heterogeneous size distribution of microfine cellulose and ibuprofen, which result in high interparticulate forces. However, during tapping, particles jump and lose contact and the friction and
adhesion forces are temporarily overcome resulting in improved packing. Pregelatinised starch, however, has a smooth angular particle shape which facilitates rapid packing of the material to its maximum bulk density.

**Figure 4.5: Densification of materials as a function of the number of taps applied**

![Graph showing densification of materials](image)

### 4.1.2.2 Carr’s Compressibility Index

According to Carr’s classification for powder flowability, microfine cellulose possesses extremely poor flow and ibuprofen possesses poor flow compared to the passable flow of pregelatinised starch (Table 4.2). Podczeck et al. (1999) reported that materials could be filled up to a maximum Carr’s compressibility index of 35 to 40. Therefore, the values obtained may indicate problems when filling formulations containing high concentrations of microfine cellulose.

### 4.1.2.3 Angle of Internal Flow

The angle of internal flow describes the relationship between the powder bulk porosity and the number of taps. High values indicate the presence of increased interparticulate forces. In comparison to pregelatinised starch, microfine cellulose and ibuprofen had very high values for the angle of internal flow (Table 4.2), which may indicate problems during capsule filling.

### 4.1.2.4 Compaction Constant T

The compaction constant gives information about the rate of densification. High T-values are associated with poor powder flow and slow densification (Podczeck et al., 1999). This applies to microfine cellulose and ibuprofen, which have very high T-values of 86.95 and 37.01, respectively (Table 4.2). This suggests that the powder bed may take longer to reach an equilibrium state and therefore will result in a high coefficient of fill weight variation.
4.1.3 Shear Properties of Materials

In addition to the previous flow parameters tested, a Peschl shear cell was used to characterise the shear and failure properties of the materials. From the failure properties, flow parameters such as the angle of internal friction, cohesion coefficient, mobility index and Jenike's flow factor were derived (Table 4.2).

4.1.3.1 Angle of Internal Friction

The angle of internal friction gives an indication of the frictional properties of the material. The values for the angle of internal friction for pregelatinised starch and ibuprofen were low, i.e. 31.2° and 34.3°, respectively, in comparison to microfine cellulose, 41.53° (Table 4.2). This can be attributed to the smooth surface of pregelatinised starch and ibuprofen particles, whereas microfine cellulose consists of irregular fibrous particles with a rough surface.

4.1.3.2 Cohesion Coefficient

The cohesion coefficient of a material is a measure of the stickiness of the material. When handling ibuprofen, it felt sticky to touch and this was represented by its high cohesion coefficient value of 6.14g/cm². Pregelatinised starch and microfine cellulose were less sticky and hence the lower values for the cohesion coefficient, 3.36g/cm² and 3.98g/cm², respectively (Table 4.2).

4.1.3.3 Mobility Index

The mobility of a material measures the likeliness that a material will segregate. Higher values are associated with increased chance of segregation. Pregelatinised starch had the highest mobility index (0.28), which was probably due to its surface properties. Microfine cellulose had the lowest mobility index due to its irregular fibrous shape that allows mechanical interlocking of the particles and thus reduces the chance of segregation (Table 4.2).

4.1.3.4 Jenike's Flow Factor

According to Jenike's rough guide to the flowability of solids, pregelatinised starch was an almost free flowing powder, as demonstrated by its high Jenike’s flow factor value (9.37) (Table 4.2). This is because pregelatinised starch particles possess a smooth surface with an angular shape. Ibuprofen had a much lower Jenike’s flow factor value (5.51) compared to pregelatinised starch. This is because it possesses elongated particles and hence, there are increased frictional forces between the particles. Microfine cellulose showed good flow properties, almost similar to pregelatinised starch as seen by its
Jenike’s flow factor value (8.96). This is unexpected when considering its fibrous particle shape.

Considering all bulk properties described above, pregelatinised starch appears to be an excipient with good flow properties in general, whereas microfine cellulose shows some aspects of good and poor flow, depending on the test method employed. Ibuprofen exhibits generally poor powder flow.

### 4.1.4 Optimal Mixing Time

To determine the optimal mixing time, the optimal mixing conditions were determined for the average mixture composition *i.e.* the centre of gravity mixture. A three-component model was used to calculate the total volume of the batch, number of samples required and the weight of each sample. Initially, the bulk volume of the powder was obtained (Table 4.3).

<table>
<thead>
<tr>
<th>Material</th>
<th>% of Materials</th>
<th>Weight of 2,000g (g)</th>
<th>Volume of 2,000g (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregelatinised starch</td>
<td>14.70</td>
<td>294</td>
<td>451.6</td>
</tr>
<tr>
<td>Microfine cellulose</td>
<td>14.70</td>
<td>294</td>
<td>1,135.1</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>70.00</td>
<td>1,400</td>
<td>3,977.3</td>
</tr>
</tbody>
</table>

Assuming additivity, the proportional bulk volumes were used. Hence, the total loose bulk volume for a 2,000g batch was 5,564.02 cm³. A Y-cone blender was chosen as the mixer as it allowed both shear and diffusive mixing. The total volume of the mixer was 4,000 cm³ and for optimum mixing to occur, the Y-cone blender was only filled to 35% of its nominal volume. Thus, mixing was carried out four times and 500g of the material was placed into the Y-cone blender each time to make the 2,000g batch. The speed of the Y-cone blender was 28 rpm. This enabled homogeneity of the mixture in an acceptable time without inducing dust development.

### 4.1.4.1 Minimum Number of Samples

A statistical approach used by Schweiger et al., (1997) was used to calculate the minimum number of samples $n$. To evaluate the homogeneity of the mixture, five samples were required (Ch 3.1.3.1).
4.1.4.2 Minimum Sample Size

The minimum sample size was dependent upon the concentration of components in the mixture. The minimum number of particles \( z_{\text{min}} \), to allow a statistically justified statement about the composition of the sample was:

\[
z_{\text{min}} = \left( \frac{z_d}{y} \right)^2 \left( 1 - \frac{p}{p} \right)
\]

Where \( p \) is the concentration of the component with the smallest quantity in the mixture. Both pregelatinised starch and microfine cellulose had the lowest concentration in the blend of 14.7% and therefore \( p \) was 0.147. With 99% probability \( (\alpha = 0.01) \) the composition of the samples would not deviate by more than 0.5% from the specified composition \( y \).

\[
z_d = 2.576 \quad y = 0.005
\]

\[
z_{\text{min}} = \left( \frac{2.576}{0.005} \right)^2 \left( 1 - \frac{0.147}{0.147} \right)
\]

\[
= 1,540,222 \text{ particles/sample}
\]

Thus, 1,540,222 particles were required per sample to allow a statistically justified statement about the composition of the sample.

4.1.4.3 Calculation of the Average Volume, Mass and Number of Particles per gram of the Powder Mixture

The volume was estimated as a cube because the particles were not round as ibuprofen is rod shaped and microfine cellulose is fibrous shaped (Table 4.4).

<table>
<thead>
<tr>
<th></th>
<th>Pregelatinised starch</th>
<th>Microfine Cellulose</th>
<th>Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average volume ((cm^3))</td>
<td>(1.327 \times 10^{-7})</td>
<td>(6.892 \times 10^{-8})</td>
<td>(6.400 \times 10^{-8})</td>
</tr>
<tr>
<td>Average mass of particles ((g))</td>
<td>(1.947 \times 10^{-7})</td>
<td>(1.045 \times 10^{-7})</td>
<td>(7.174 \times 10^{-8})</td>
</tr>
<tr>
<td>No of particles per gram of powder</td>
<td>5,135,272</td>
<td>9,570,822</td>
<td>13,938,448</td>
</tr>
<tr>
<td>(\text{particles/gram} = (1/m))</td>
<td>754,885</td>
<td>1,406,911</td>
<td>9,756,913</td>
</tr>
</tbody>
</table>
4.1.4.4 Weight of the Sample

Calculation of the weight of a sample of mixture

\[
\frac{\text{no of particles / sample}}{\text{no of particles per gram mixture}} = \frac{1,540,222}{11,918,709} = 0.129 \text{g}
\]

Following the statistical procedure, it was found that the sample weight should be at least 0.129g. However, according to the BP (2001), the total mass of all samples should be \( \geq 0.3\% \) of the mass of the mixture. As the total mass of the mixture was 500g, therefore the total mass of all samples was 1.5g. Five samples were taken. Thus, the mass of each sample should be 0.3g. This sample mass is much larger than the calculated minimum sample mass of 0.129g. Hence, the scale of scrutiny chosen will represent the randomisation stage of the mixture with great certainty.

4.1.4.5 Determination of the Optimal Mixing Time

The relative standard deviation (S.D.) between the five samples taken from different locations from the Y-cone blender (chapter 2.2.3) in terms of ibuprofen concentration at each of the time intervals can be seen in Figure 4.6. The relative standard deviation between the samples was high for the first fifteen minutes, indicating that pregelatinised starch, microfine cellulose and ibuprofen were not mixed. As the mixing time increased, the relative standard deviation for the drug in the samples decreased, reaching a minimum at 30 minutes. Hence, 30 minutes was the total mixing time for 500g of the centre mixture and was used for all twenty-one formulations. At 25 minutes of mixing pregelatinised starch, microfine cellulose and ibuprofen, the Y-cone blender was stopped and magnesium stearate was added for a further five minutes. Hence, the total mixing time was kept at 30 minutes.

Figure 4.6: Relative standard deviation as a function of mixing time
4.1.4.6 Uniformity of Powder Formulation

To evaluate the homogeneity of the formulations and assess whether 30 minutes was a suitable mixing time, five samples were taken from the Y-cone blender at 25 minutes for all twenty-one formulations. It is assumed that after further post-mixing with the lubricant for 5 minutes (such that the total mixing time is 30 minutes), the homogeneity has either improved or remained the same.

Table 4.5 shows the observed and expected ibuprofen content for each of the formulations. The values match very closely thus confirming that the mixing time of 30 minutes is adequate. When evaluating the relative standard deviation between the materials and the concentration of the materials, no relationship could be seen.

Table 4.5: Observed and Expected Ibuprofen Concentration

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Ibuprofen concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
</tr>
<tr>
<td>1</td>
<td>69.58 ± 1.56</td>
</tr>
<tr>
<td>2</td>
<td>69.19 ± 0.43</td>
</tr>
<tr>
<td>3</td>
<td>69.51 ± 1.37</td>
</tr>
<tr>
<td>4</td>
<td>69.21 ± 1.38</td>
</tr>
<tr>
<td>5</td>
<td>69.89 ± 1.96</td>
</tr>
<tr>
<td>6</td>
<td>48.97 ± 0.99</td>
</tr>
<tr>
<td>7</td>
<td>62.18 ± 3.15</td>
</tr>
<tr>
<td>8</td>
<td>81.61 ± 4.44</td>
</tr>
<tr>
<td>9</td>
<td>91.11 ± 1.79</td>
</tr>
<tr>
<td>10</td>
<td>70.96 ± 2.25</td>
</tr>
<tr>
<td>11</td>
<td>70.22 ± 1.27</td>
</tr>
<tr>
<td>12</td>
<td>71.57 ± 2.30</td>
</tr>
<tr>
<td>13</td>
<td>70.51 ± 1.48</td>
</tr>
<tr>
<td>14</td>
<td>54.85 ± 1.41</td>
</tr>
<tr>
<td>15</td>
<td>86.81 ± 1.82</td>
</tr>
<tr>
<td>16</td>
<td>55.92 ± 2.69</td>
</tr>
<tr>
<td>17</td>
<td>85.25 ± 1.45</td>
</tr>
<tr>
<td>18</td>
<td>53.38 ± 0.93</td>
</tr>
<tr>
<td>19</td>
<td>84.66 ± 3.51</td>
</tr>
<tr>
<td>20</td>
<td>52.53 ± 0.83</td>
</tr>
<tr>
<td>21</td>
<td>84.78 ± 1.65</td>
</tr>
</tbody>
</table>

* Concentrations are the arithmetic mean of five samples taken from the Y-cone blender at 25 minutes
4.1.5 Bulk Properties of Powder Mixtures

4.1.5.1 Carr's Compressibility index

Pregelatinised starch

An increase in the pregelatinised starch concentration in the excipient mixture improved the flow properties of the powder blend (Figure 4.7) as illustrated by the decrease in Carr’s compressibility index (Carr, 1965). The lowest value for Carr’s compressibility index was achieved with a low ibuprofen concentration (54%) and a high magnesium stearate concentration (0.92%). A low ibuprofen concentration is preferable as there is a greater amount of excipient available and thus pregelatinised starch in the blend. Also, a high magnesium stearate concentration improves powder flow by lubricating the powder particles. When the ibuprofen concentration was high (86%) and the magnesium stearate concentration was low (0.28%), Carr’s compressibility index was high. Hence, an adjustment in the concentration of one of these materials is required in order to attain a low Carr’s compressibility index to achieve good flow properties.

Ibuprofen

An increase in the ibuprofen concentration increased Carr’s compressibility index, suggesting a worsening of the powder flow properties (Figure 4.8). This trend is expected, as ibuprofen is a poor flowing material demonstrated by the high Carr’s compressibility index of 34.13. Ibuprofen consists of rod shaped particles that have a large surface area, giving rise to higher friction and adhesion forces between the particles.

At low ibuprofen concentrations (54%), it is preferable to have a higher pregelatinised starch concentration in the excipient (90%), as the Carr’s compressibility index is lower. This can be attributed to the angular shaped pregelatinised starch particles, which have better flow properties compared to the fibrous shaped particles of microfine cellulose. The flow properties of the powder blend can be further improved by a high magnesium stearate concentration (0.92%). However, at low pregelatinised starch concentrations in the excipient (10% pregelatinised starch and 90% microfine cellulose), the Carr’s compressibility index is greatly increased and the magnesium stearate concentration has little effect on Carr’s compressibility index. This gives an indication of the self-lubricating properties of microfine cellulose.

At higher ibuprofen concentrations, the determining factor for low values of Carr’s compressibility index is the low magnesium stearate concentration. Formulations containing a high microfine cellulose concentration in the excipient are here also influenced by the magnesium stearate concentration.
Figure 4.7: Carr’s compressibility index as a function of the pregelatinised starch concentration in the excipient

Figure 4.8: Carr’s compressibility index as a function of the ibuprofen concentration

Figure 4.9: Carr’s compressibility index as a function of the magnesium stearate concentration
There is hence a critical concentration of ibuprofen when additional lubrication is required in the blend. For the centre mix, which contains a 50:50 ratio of pregelatinised starch to microfine cellulose, this threshold value is at a 70% ibuprofen concentration.

**Magnesium Stearate**

Magnesium stearate functions as a lubricant and hence improves powder flow. This can be shown by the decrease in Carr’s compressibility index as the magnesium stearate concentration is increased (Figure 4.9). At low magnesium stearate concentrations (0.28%), higher values of Carr’s compressibility index are associated with high ibuprofen concentrations (86%). This result indicates that a high magnesium stearate concentration is required to improve the lubrication properties of the powder blend. A high pregelatinised starch concentration (90%) in the excipient is responsible for further reducing Carr’s compressibility index. Formulations containing a low amount of ibuprofen (54%) and 90% microfine cellulose in the excipient show no improvement in powder flow when the magnesium stearate concentration is increased, as discussed earlier.

At high magnesium stearate concentrations (0.92%), improved powder flow is associated with high concentrations of pregelatinised starch in the excipient (90%). This result indicates that pregelatinised starch alone possesses good flow properties and when mixed with magnesium stearate, their flow and lubricating properties combined further improve powder flow. Microfine cellulose also possesses self-lubricating properties but with sufficient concentrations of microfine cellulose in the blend, no further magnesium stearate is required.

To obtain good flow properties, high pregelatinised starch concentrations must be present in the excipient. It is possible to increase ibuprofen concentrations up to 86%, but in order to achieve a Carr’s compressibility index value of 25 or less, it is recommended that a high magnesium stearate concentration is used (0.92%). When filling with microfine cellulose, it is preferable to always use a high magnesium stearate concentration so that an ibuprofen concentration of up to 86% may be used in the blend to maintain a Carr’s compressibility index of 30.
4.1.5.2 Angle of Internal Flow

Pregelatinised starch

As the pregelatinised starch concentration increased in the excipient mixture, the angle of internal flow decreased, suggesting a reduction in interparticulate forces (Figure 4.10). This result can be explained by comparing the particle morphology of pregelatinised starch and microfine cellulose. Pregelatinised starch possesses angular shaped particles, resulting in relatively low interparticulate contact compared to microfine cellulose. Microfine cellulose, however, has fibrous shaped particles, which due to the elongated nature of the particles have greater interparticulate contact.

At low pregelatinised starch concentrations in the excipient (10%), the ibuprofen concentration determined the angle of internal flow. High ibuprofen concentrations (86%) resulted in low angles of internal flow due to reduced interparticulate forces. Low ibuprofen concentrations (54%) resulted in higher angles of internal flow due to a greater concentration of microfine cellulose present in the blend. This can be explained by microfine cellulose’s high angle of internal flow (53.5°). A high magnesium stearate concentration (0.92%) further reduced the interparticulate forces when there was a high ibuprofen concentration in the blend. However, the magnesium stearate concentration had no effect at low ibuprofen concentrations with 90% microfine cellulose in the excipient. This result agrees with Carr’s compressibility data supporting the previous suggestion that microfine cellulose possesses self-lubricating properties and indicates that a low concentration of magnesium stearate (0.28%) is sufficient to provide the lubricant properties in this particular formulation.

At high pregelatinised starch concentrations in the excipient (90%), the angle of internal flow reached a minimum of approximately 35°. This can be explained by ibuprofen’s value for the angle of internal flow (35.62°). Even formulations containing a low ibuprofen concentration (54%), are largely influenced by the value for the angle of internal flow of ibuprofen. A high magnesium stearate concentration slightly reduces the angle of internal flow, indicating a further reduction in interparticulate forces.

Ibuprofen

At low ibuprofen concentrations (54%) and 10% pregelatinised starch in the excipient (90% microfine cellulose), the angle of internal flow was high, thus indicating higher interparticulate forces (Figure 4.11). As the ibuprofen concentration increased, the amount of microfine cellulose in the blend proportionately decreased, causing a decrease in the angle of internal flow.
Chapter 4 - Ibuprofen

Figure 4.10: Angle of internal flow as a function of the pregelatinised starch concentration in the excipient

![Graph showing the angle of internal flow as a function of pregelatinised starch concentration.](image)

Figure 4.11: Angle of internal flow as a function of the ibuprofen concentration

![Graph showing the angle of internal flow as a function of ibuprofen concentration.](image)

Figure 4.12: Angle of internal flow as a function of the magnesium stearate concentration

![Graph showing the angle of internal flow as a function of magnesium stearate concentration.](image)
At low ibuprofen concentrations with 90% pregelatinised starch in the excipient, the angle of internal flow was relatively low. As the ibuprofen concentration increased, the amount of excipient reduced, resulting in less pregelatinised starch in the blend and a slight increase in the angle of internal flow. The magnesium stearate concentration had little affect on the angle of internal flow.

Magnesium Stearate
As the magnesium stearate concentration increased, there was very little effect on the angle of internal flow, indicating that the low amount of magnesium stearate (0.28%) was sufficient to provide adequate lubricant properties for the powder blend (Figure 4.12).

The blend containing a low ibuprofen concentration (54%) and a low amount of pregelatinised starch in the excipient (10% pregelatinised starch and 90% microfine cellulose) had the highest angle of internal flow. Higher values for the angle of internal flow may imply problems during filling due to poor flow and may also result in very strong plugs being formed, which may not disintegrate well. The angle of internal flow improved when the ibuprofen concentration was increased because the amount of microfine cellulose in the blend reduced. Therefore, the angle of internal flow shows that for a good flowing blend it is preferable to have a small amount of microfine cellulose.

The lowest value for the angle of internal flow occurred at a low ibuprofen concentration (54%) and a high amount of pregelatinised starch in the excipient (90%) and a high magnesium stearate concentration in the blend (0.92%). Low values for the angle of internal flow were also observed at a high ibuprofen concentration (86%) and a high pregelatinised starch concentration (90%) in the excipient. Formulations with low angles of internal flow imply reduced interparticulate forces, which often suggest poor plug forming properties but good flow. The values obtained here were sufficiently high not to indicate problems during filling in terms of plug strength.
4.1.5.3 Compaction Constant $T$

Pregelatinised starch

As the pregelatinised starch concentration increased in the excipient, the $T$-value decreased, indicating improved powder flow and faster densification (Figure 4.13). Lower $T$-values were associated with high magnesium stearate concentrations (0.92%). This could be a result of magnesium stearate coating the powder particles, thus improving powder flow and densification. At low pregelatinised starch concentrations in the excipient (10% pregelatinised starch and 90% microfine cellulose), the $T$-values were high indicating poor flow and slow densification. As the pregelatinised starch concentration increased to 90% in the excipient mixture, lower $T$-values were achieved. The lowest $T$-value was observed when the ibuprofen concentration was low (54%), the magnesium stearate concentration was high (0.92%) and there was a high pregelatinised starch concentration present in the excipient (90%). Hence, high pregelatinised starch concentrations and high magnesium stearate concentrations result in good flow and packing. The good flow properties observed for pregelatinised starch are strengthened by the low value of Carr’s compressibility index and angle of internal flow. Formulations with a high microfine cellulose concentration show poor flow properties, as indicated by the high $T$-value and this is supported by the high Carr’s compressibility index and the high angle of internal flow.

Ibuprofen

Increasing the ibuprofen concentration resulted in complicated relationships with the $T$-value, depending upon the concentration of the excipients (Figure 4.14). High pregelatinised starch concentrations in the excipient lead to overall low $T$-values. The $T$-value was lowest when the ibuprofen concentration was low (54%) and the magnesium stearate concentration was high (0.92%). However as the ibuprofen concentration increased, the amount of pregelatinised starch decreased, resulting in an increase in the $T$-value.

At low ibuprofen concentrations (54%), when the pregelatinised starch concentration in the excipient was low (10%) and the magnesium stearate concentration was low (0.28%), the $T$-value was at its highest, due to the large microfine cellulose concentration. As the ibuprofen concentration increased, the $T$-value decreased. An improvement in flow and packing was observed with the inclusion 0.92% magnesium stearate. Mixtures containing a high amount of microfine cellulose showed an increase in the $T$-value and thus it appears to be better not to use an excipient such as microfine cellulose for materials that show problems with respect to flow and packing.
Figure 4.13: Compaction constant $T$ as a function of the pregelatinised starch concentration in the excipient.

Figure 4.14: Compaction constant $T$ as a function of the ibuprofen concentration.

Figure 4.15: Compaction constant $T$ as a function of the magnesium stearate concentration.
Magnesium Stearate

As the magnesium stearate concentration increased, the T-value decreased, indicating improved flow and faster densification (Figure 4.15). A high pregelatinised starch concentration in the excipient resulted in overall lower T-values. A high magnesium stearate concentration had a greater impact on the formulation at low ibuprofen concentrations and a high pregelatinised starch concentration in the excipient mixture. At a high amount of ibuprofen in the blend, increasing the magnesium stearate concentration only slightly decreased the T-value. Therefore, above a certain concentration of ibuprofen in the blend, the magnesium stearate concentration has only a small influence on the T-value.

The improvement in flow and packing demonstrated by the decrease in the T-value as the magnesium stearate concentration was increased was accompanied by the decrease in Carr's compressibility index. The angle of internal flow shows little change as the magnesium stearate concentration is increased. This indicates that the T-value measures another flow parameter compared to the angle of internal flow. However, all parameters show that the formulation with a low ibuprofen concentration and a high pregelatinised starch to microfine cellulose ratio has the best flow properties, which is further improved by a high magnesium stearate concentration.

4.1.5.4 Maximum Bulk Density

Pregelatinised starch

An increase in the pregelatinised starch concentration in the excipient increased the tapped density (Figure 4.16). This is probably due to the improved packing properties of pregelatinised starch demonstrated by the low T-value. Formulations containing a low amount of ibuprofen (54%) showed the greatest increase in tapped density when the pregelatinised starch concentration was increased in the excipient mixture. At a high ibuprofen concentration (86%) in the blend, increasing the pregelatinised starch concentration in the excipient increased the tapped density but not to the same extent as when there was a low ibuprofen concentration. This is due to the small amount of excipient and hence, less pregelatinised starch which has good packing properties. Magnesium stearate had little influence on the tapped density. This is not surprising as magnesium stearate functions as a lubricant. Comparing the results with the values for the compaction constant $\tau$, it appears that the lubricant influences the velocity with which densification occurs, but only has little effect on the final packing state reached.
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Figure 4.16: Maximum bulk density as a function of the pregelatinised starch concentration in the excipient

![Graph showing maximum bulk density as a function of pregelatinised starch concentration.]

Figure 4.17: Maximum bulk density as a function of the ibuprofen concentration

![Graph showing maximum bulk density as a function of ibuprofen concentration.]

Figure 4.18: Maximum bulk density as a function of the magnesium stearate concentration

![Graph showing maximum bulk density as a function of magnesium stearate concentration.]
Ibuprofen
As the ibuprofen concentration increased, the tapped density showed a similar trend to the T-value data (Figure 4.17). At high pregelatinised starch concentrations in the excipient, an increase in the ibuprofen concentration decreased the tapped density. However, at low concentrations of pregelatinised starch in the excipient, an increase in the ibuprofen concentration increased the tapped density. This is due to a high pregelatinised starch concentration, which is the determining factor for a high tapped density and as the ibuprofen concentration increased, there was less overall pregelatinised starch in the blend and hence the decrease in the tapped density was observed.

Magnesium Stearate
The magnesium stearate concentration had little effect on the tapped density (Figure 4.18). This is because during tapping, frictional forces between the particles are overcome mechanically, resulting in improved packing. Hence, the small amount of magnesium stearate in the blend was sufficient for good packing to occur when an external force was applied.

4.1.6 Shear Properties of Powder Mixtures
The shearing properties of any powder blend depend upon the bulk properties and the interaction of the particles within the powder bulk. The density and packing state of the powder mass will influence the shearing properties. Additionally, the powder particles at the shear plane will affect the shearing process, (Hiestand, 1966).

4.1.6.1 Angle of Internal Friction
The angle of internal friction is related to the shape and surface properties of the powder particles (Podczeck and Miah, 1996). Optimal formulations are achieved at low angles of internal friction. The value for the angle of internal friction was divided by the density of the powder bed when sheared to avoid the porosity of the sample influencing the true value for the angle of internal friction.
**Pregelatinised starch**

As the pregelatinised starch concentration increased in the excipient, there was a decrease in the angle of internal friction (Figure 4.19). This is expected as high pregelatinised starch concentrations result in improved flow properties demonstrated by the low Carr's Compressibility index, angle of internal flow and T-value. Lower values for the angle of internal friction were associated with high ibuprofen concentrations in the blend (86%), which further decreased as the pregelatinised starch concentration was increased. At low ibuprofen concentrations (54%), an increase in the pregelatinised starch concentration relative to microfme cellulose resulted in a large decrease in the angle of internal friction. Hence large concentrations of microfine cellulose result in increased friction in the blend. This can be associated with rough fibrous shaped particles of microfine cellulose and their heterogeneous size distribution. This agrees with Podczeck and Miah (1996) who found that the angle of internal friction was dependent both on particle size and shape.

Another reason for the differences in the angle of internal friction for pregelatinised starch and microfine cellulose could be due to their different elastic properties, which can be quantified by their Young's modulus of elasticity, $E$. Highly elastic, bouncing surfaces result in reduced friction. The value of $E$ for pregelatinised starch and microfine cellulose was 5.02 GPa and 8.69 GPa, respectively (Bin Baie et al., 1996). Comparing the values for the angle of internal friction at high pregelatinised starch concentrations and high microfine cellulose concentrations in the excipient, it can be seen that the higher the friction is, the larger $E$ is. This agrees with Podczeck and Miah (1996) who also found that the angle of internal friction was proportional to the elastic properties of the powders at optimum lubricant concentration.

At low ibuprofen concentrations (54%), a high magnesium stearate concentration (0.92%) decreased the angle of internal friction. However, at high ibuprofen concentrations (86%), the high magnesium stearate concentration only enhanced powder flow at 90% pregelatinised starch in the excipient. Therefore at high microfine cellulose concentrations, there is an optimal concentration of lubrication within the powder blend and the frictional properties cannot be further improved by increasing the magnesium stearate concentration.

**Ibuprofen**

Figure 4.20 shows the decrease in the angle of internal friction as the ibuprofen concentration increased. This can be attributed to the smooth surface ibuprofen possesses.
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Figure 4.19: Angle of internal friction/density as a function of the pregelatinised starch concentration in the excipient

Figure 4.20: Angle of internal friction/density as a function of the ibuprofen concentration

Figure 4.21: Angle of internal friction/density as a function of the magnesium stearate concentration
Lower values for the angle of internal friction were associated with high pregelatinised starch concentrations in the excipient (90%) and as the ibuprofen concentration increased, there was only a small decrease in the angle of internal friction. However, at low ibuprofen concentrations (54%) and low pregelatinised starch concentrations in the excipient (10% pregelatinised starch and 90% microfine cellulose), increasing the ibuprofen concentration greatly reduced the angle of internal friction. This is due to the ibuprofen replacing the microfine cellulose, which contributed to the high values of the angle of internal friction. As seen in Figure 4.20, the high magnesium stearate concentration (0.92%) further decreased the angle of internal friction and was most effective at high ibuprofen concentrations and high pregelatinised starch in the excipient.

**Magnesium Stearate**

As the magnesium stearate concentration increased, there was a slight decrease in the angle of internal friction for all formulations (Figure 4.21). However, increasing the magnesium stearate concentration was most effective for formulations containing high concentrations of ibuprofen (86%) and pregelatinised starch in the excipient (90%) as seen previously. This implies that by providing extra lubrication for this particular powder blend, its flow properties can be further improved. This could be due to a large area of contact between the pregelatinised starch and ibuprofen particles, and magnesium stearate functions by reducing the friction and adhesion forces that operate between them so that the particles can slide past one another (Pilpel, 1971).

**4.1.6.2 Cohesion Coefficient**

The cohesion coefficient of a powder is obtained by extrapolation of the yield locus towards the shear stress axis and corresponds to the shear stress when no normal stress is being applied to it (Jenike, 1961). Van der Waals forces are the most predominant interparticulate forces acting in dry powders. They contribute to the forces between adjacent particles and are of very short range. The "cohesiveness" of a powder can be defined as the tendency of its individual particles to stick together (Pilpel, 1971), or the autoadhesion or adhesion forces acting between the particles in the powder bed (Podczeczek, 1998). The cohesion coefficient was divided by the density of the powder bed during shear in order not to allow the porosity of the powder bulk in the shear cell to affect the value.
Pregelatinised starch

As the pregelatinised starch concentration increased in the excipient, formulations containing a low ibuprofen concentration (54%), showed no change in the cohesion coefficient and the magnesium stearate concentration also had no effect on this flow parameter (Figure 4.22). However, at high ibuprofen concentrations (86%), the cohesion coefficient value was much greater. This was expected, because upon visual inspection of the powder blend in the capsule filling machine, rat-holing could be seen occurring in the powder hopper and the powder bed was highly angular. As the pregelatinised starch concentration was increased, there was a slight increase in the cohesion coefficient value. This can be explained by the hygroscopic properties of microfine cellulose, which reduces some of the stickiness in the powder blend (Aulton, 2000). At high ibuprofen concentrations (86%), the high magnesium stearate concentration (0.92%) decreased the cohesion coefficient in the powder blend.

Ibuprofen

As the ibuprofen concentration increased, there was an increase in the cohesion coefficient value, which can be justified by the stickiness of the material (Figure 4.23). At low ibuprofen concentrations (54%) the concentration of the excipients and the magnesium stearate concentration did not affect the cohesion coefficient value. However, as the ibuprofen concentration was increased from 54% to 86%, the formulation containing a high pregelatinised starch concentration in the excipient and a low magnesium stearate concentration showed the largest increase in the cohesion coefficient. Hence, high pregelatinised starch concentrations are not favourable for highly sticky materials such as ibuprofen.

Magnesium Stearate

As the magnesium stearate concentration increased, it had no affect on the cohesion coefficient for formulations containing a low ibuprofen concentration (54%) and nor did the concentration of the excipient (Figure 4.24). Thus, if there is a sufficient concentration of excipient in the formulation, the cohesion coefficient value is not influenced by the magnesium stearate concentration. However, at high ibuprofen concentrations (86%), it is preferable to have a high magnesium stearate concentration (0.92%) to reduce the stickiness in the powder blend. This is particularly important for smooth running of the capsule filling machine and to avoid stickiness between the dosing disk and tamping ring and on the tamping pins.
Figure 4.22: Cohesion coefficient as a function of the pregelatinised starch concentration in the excipient

Figure 4.23: Cohesion coefficient as a function of the ibuprofen concentration

Figure 4.24: Cohesion coefficient as a function of the magnesium stearate concentration
4.1.6.3 Mobility Index

The mobility index $m$ describes the intrinsic property of the individual particles of the bulk. It gives an indication to the likelihood that a powder will segregate and is related to flow properties of the powder blend. The value of $m$ can lie between 0.03 and 0.6. Lower values indicate that the particles are less mobile and therefore the risk of segregation is reduced. Higher values of $m$ greater than 0.35, indicate a high degree of freedom between the particles resulting in increased risk of segregation. Lower values are associated with the particle shape and consequently particle interlocking, or with an increased friction between the particles due to surface roughness (Deleuil et al., 1994). None of the formulations possessed a value for the mobility index greater than 0.35 suggesting that there is little chance for the powder blends to segregate.

Pregelatinised starch

As the pregelatinised starch concentration increased, there was an increase in the mobility of the particles (Figure 4.25). This was expected as high pregelatinised starch concentrations are associated with good powder flow, demonstrated by its flow properties. The largest increase in the mobility index occurred at a low ibuprofen concentration (54%). As the pregelatinised starch concentration was increased relative to microfine cellulose, there was a large increase in the mobility index due to vast improvement of powder flowability. A high magnesium stearate concentration (0.92%) further increased the mobility index.

At high ibuprofen concentrations (86%), increasing the pregelatinised starch concentration in the excipient resulted only in a small increase in the mobility index. This is because there is less excipient available in the blend for pregelatinised starch to influence the mobility index to a large extent. A high magnesium stearate concentration (0.92%) however, resulted in a large increase in the mobility of the particles.

Ibuprofen

As the ibuprofen concentration increased, formulations containing a low pregelatinised starch concentration in the excipient (10% pregelatinised starch and 90% microfine cellulose) showed an increase in the mobility index (Figure 4.26). This can be attributed to the smooth surface of ibuprofen. This indicates that a high microfine cellulose concentration in the excipient results in poor mobility. A high magnesium stearate concentration (0.92%) further increased the mobility in the powder blend. At 90% pregelatinised starch in the excipient, increasing the ibuprofen concentration decreased the mobility of the powder blend at low magnesium stearate concentrations (0.28%).
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Figure 4.25: Mobility index as a function of the pregelatinised starch concentration in the excipient

Figure 4.26: Mobility index as a function of the ibuprofen concentration

Figure 4.27: Mobility index as a function of the magnesium stearate concentration
However, at high magnesium stearate concentrations (0.92%), increasing the ibuprofen concentration had no effect on the mobility. Hence, there was sufficient magnesium stearate to compensate for the increase in the ibuprofen concentration.

**Magnesium Stearate**

An increase in the mobility index can be observed as the magnesium stearate concentration is increased, indicating a greater mobility of the particles within the powder blend (Figure 4.27). Poor mobility is associated with a low pregelatinised starch concentration (10%) and high microfine cellulose concentration (90%) in the excipient. The formulation containing a high ibuprofen concentration (86%) and a high pregelatinised starch (90%) concentration in the excipient is most affected by increasing the magnesium stearate concentration. This has been demonstrated earlier with previous flow parameters, which also showed that a high magnesium stearate concentration (0.92%) greatly improves the flow properties of a formulation containing a high ibuprofen concentration (86%) and high pregelatinised starch concentration in the excipient (90%). A certain degree of mobility is required between particles in order to achieve good powder flow; however if the mobility is too high this can result in segregation of the powder particles and thus an optimum mobility value must be reached.

4.1.6.4 Jenike's Flow Factor

Jenike (1961) defined the flow factor based on the unconfined yield strength ($f_c$) and the major principal stress ($\sigma_m$). The unconfined yield strength is a measure of the strength required in a powder bed for arching to occur. Therefore, the adhesion or autoadhesion between the particles of a powder bed must exceed the force of gravity, which would cause the powder to flow. The major principal stress represents the stress along the major principal plane at zero shear stress. The Jenike flow factor is the reciprocal of the slope of $f_c$ as a linear function of $\sigma_m$ for different consolidation loads (Jenike, 1961). The importance of Jenike's flow factor for filling powders into hard gelatine capsules has been demonstrated by Tan and Newton (1990) who found a significant correlation between the coefficient of fill weight variation and the flow factor.

**Pregelatinised starch**

As the pregelatinised starch concentration increased in the blend, there was a slight worsening of powder flow, demonstrated by the decrease in Jenike's flow factor (Figure 4.28). This is unexpected, as pregelatinised starch alone resulted in an almost free flowing powder according to the Jenike classification for powder flow, suggesting that contrary to previous flow tests, microfine cellulose should also aid the flow of the powder mixture.
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Figure 4.28: Jenike’s flow factor as a function of the pregelatinised starch concentration in the excipient

Figure 4.29: Jenike’s flow factor as a function of the ibuprofen concentration

Figure 4.30: Jenike’s flow factor as a function of the magnesium stearate concentration
Ibuprofen
As the ibuprofen concentration increased in the formulation, there was a large decrease in Jenike’s flow factor resulting in the powder changing from an ‘easy flowing’ to a ‘cohesive’ powder (Figure 4.29). This can be related to the sticky nature of ibuprofen resulting in a worsening of the flow properties. At low ibuprofen concentrations (54%), a high pregelatinised starch concentration in the excipient resulted in slightly lower values for Jenike’s flow factor. However, as the ibuprofen concentration increased, Jenike’s flow factor achieved for the different formulations was very similar. This is due to the large quantity of ibuprofen, which determined the value for Jenike’s flow factor. The magnesium stearate concentration did not affect the value of Jenike’s flow factor.

Magnesium Stearate
As the magnesium stearate concentration increased, formulations containing a high ibuprofen concentration (86%) showed an increase in Jenike’s flow factor indicating an improvement in the flow properties (Figure 4.30). This is because magnesium stearate aids slippage of the particles and improves powder flow. However, formulations containing a low ibuprofen (54%) concentration showed no improvement in powder flow indicating that the large quantity of excipient provided the necessary lubrication in the blend. In fact, the blend containing a low ibuprofen concentration (54%) and a high microfine cellulose concentration, showed a drop in Jenike’s flow factor as the magnesium stearate concentration increased. This could be due to an excess of magnesium stearate in the powder blend.

According to Podczeck and Miah (1996), particle size and shape influence the friction and flow properties of the powders. While the friction properties depend more on the asymmetry or elongation of the particles, powder flow depends more on the geometric shape. However, at an optimal glidant concentration, needle shaped particles can provide similar flow properties to round particles. This is because the surface area of needle shaped particles is less than that of angular shaped particles (Podczeck and Miah, 1996). However, this does not explain why Jenike’s flow factor decreases as the pregelatinised starch concentration increases relative to microfine cellulose because pregelatinised starch possesses angular particles compared to the fibrous shaped particles of microfine cellulose.

The best flow properties are achieved at the lowest value for angle of internal friction, lowest value for the cohesion coefficient and the highest value of Jenike’s flow factor. Irono and Pilpel (1982) found that an improvement in the flow properties represented by Jenike’s flow factor was associated with a reduction in the angle of internal friction.
It is thus surprising that as the angle of internal friction decreases, here Jenike’s flow factor also decreases. This relationship is difficult to explain and hence these two flow parameters must assess different powder characteristics. However Jolliffe and Newton (1982) and Podczeck and Miah (1996) also found such discrepancies and showed that slight changes in the angle of internal friction were not always accompanied by slight changes in Jenike’s flow factor. The cohesion coefficient also does not represent a relationship with either of the above parameters.

4.1.7 Relationship Between the Powder Flow Properties
The $R^2$ value was sought between the concentration of the materials and the flow parameters (Table 4.6). A relationship could be seen between the pregelatinised starch concentration and the minimum and maximum bulk density. As the pregelatinised starch concentration increased, there was an increase in both of these parameters (Figure 4.31). This is expected due to the good packing properties of pregelatinised starch and thus a decrease in Carr’s compressibility index was simultaneously seen (Figure 4.32). A trend could be observed between the microfine cellulose concentration and the maximum bulk density; as the microfine cellulose concentration increased, the maximum bulk density decreased slightly (Figure 4.33). This can be attributed to the strong interparticulate forces between the microfine cellulose particles. This is confirmed by the strong correlation between microfine cellulose concentration and the angle of internal flow and angle of internal friction as figures 4.34 and 4.35 show. Due to the irregular surface properties of microfine cellulose, a high microfine cellulose concentration resulted in decreased mobility of the particles (Figure 4.36). This is probably due to particle interlocking which prevented segregation of the material. An anomalous and less strong relationship exists between the microfine cellulose concentration and Jenike’s flow factor (Figure 4.37). The increase in Jenike’s flow factor with increasing concentration in microfine cellulose is surprising because the data so far implied that microfine cellulose possesses poor flow due to its high interparticulate forces. Therefore, Jenike’s flow factor clearly measures a different flow parameter. The high correlation between the ibuprofen concentration and the cohesion coefficient value confirms the stickiness of the material (Table 4.6).

Relationships were also observed between the individual flow parameters. A similar trend i.e. decrease of the parameter with increasing value of minimum bulk density could be seen for Carr’s compressibility index, angle of internal flow and the T-value (Figures 4.38 to 4.40). This can be explained because the angle of internal flow is a measure of the interparticulate forces and the T-value is a measure the powder packing properties and the
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minimum bulk density is a result of these forces. A slight but opposite trend was observed between the mobility and the minimum bulk density (Figure 4.41). As the minimum bulk density increased, the mobility of the particles increased. Hence, measuring powder flow using a simple technique such as tap density measurements can give an indication of powder segregation. The maximum bulk density showed correlation with the angle of internal flow and the angle of internal friction (Figures 4.42 and 4.43). Both parameters are a measure of the frictional forces occurring between the particles and therefore the extent of particle packing is a result of these forces occurring between the particles. Hence, during tapping even though a certain degree of friction and adhesion forces are overcome, the final tapped value is governed by these interparticulate interactions. The mobility of the particles is related to the maximum bulk density (Figure 4.44) and the higher the tapped density, the greater the chance of segregation. Carr's compressibility index was found to be related to the T-value (Figure 4.45). This is not surprising because Carr’s compressibility index is a parameter derived from the minimum and maximum bulk density and is a measure of powder flow compared to particle packing, which the T-value is a function of. Interestingly, there seems to be a plateau when Carr’s compressibility index reaches approximately 27% i.e. the T-value becomes more or less constant. This suggests that the velocity with which the powder can pack is directly related to the flow properties, and all powders with poor flow properties also pack slowly. There was a very strong correlation between the angle of internal flow and the angle of internal friction (Figure 4.46). As these values increase, there is a decrease in the mobility of the material (Figure 4.47 and 4.48). The angle of internal friction was also related to Jenike’s flow factor (Figure 4.49). However, these results are contradictory, because as the angle of internal friction increases, Jenike’s flow factor increases. This is surprising as the flow factor is a measure of particle flow and increasing the frictional forces between the particles would hinder powder flow and not enhance it. Therefore Jenike’s flow factor appears not to measure frictional forces. There was a very strong relationship between Jenike’s flow factor and the cohesion coefficient value (Figure 4.50). As the interparticulate forces between the particles increased, Jenike’s flow factor decreased.
Table 4.6: Correlation of materials and bulk characteristics (linear determinant $R^2$)

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<th>Ibuprofen</th>
<th>MS</th>
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<th>$\rho_{\text{max}}$ (g/cm$^3$)</th>
<th>CCI (%)</th>
<th>$\theta$ (°)</th>
<th>$T$</th>
<th>$\delta$ (°)</th>
<th>Cohesion (g/cm$^3$)</th>
<th>Mobility</th>
<th>FF</th>
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215
Figure 4.31: Bulk density as a function of the pregelatinised starch concentration

Figure 4.32: Carr's compressibility index as a function of the pregelatinised starch concentration

Figure 4.33: Maximum bulk density as a function of the microfine cellulose concentration

Figure 4.34: Angle of internal flow as a function of the microfine cellulose concentration
Figure 4.35: Angle of internal friction as a function of the microfine cellulose concentration

Figure 4.36: Mobility index as a function of the microfine cellulose concentration

Figure 4.37: Jenike's flow factor as a function of the microfine cellulose concentration

Figure 4.38: Carr's compressibility index as a function of the minimum bulk density
Figure 4.39: Angle of internal flow as a function of the minimum bulk density

Figure 4.40: Compaction constant as a function of the minimum bulk density

Figure 4.41: Mobility index as a function of the minimum bulk density

Figure 4.42: Angle of internal flow as a function of the maximum bulk density
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Figure 4.43: Angle of internal friction as a function of the maximum bulk density

Figure 4.44: Mobility index as a function of the maximum bulk density

Figure 4.45: Compaction constant as a function of Carr's compressibility index

Figure 4.46: Angle of internal friction as a function of the angle of internal flow
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Figure 4.47: Mobility index as a function of the angle of internal flow

Figure 4.48: Mobility index as a function of the angle of internal friction

Figure 4.49: Jenike's flow factor as a function of the angle of internal friction

Figure 4.50: Jenike's flow factor as a function of the cohesion coefficient
4.2 CAPSULE FILLING

4.2.1 Capsule Fill Weight
The instrumented Bosch GKF-400S was used to study the capsule filling characteristics of twenty-one formulations containing different concentrations of pregelatinised starch, microfine cellulose, ibuprofen and magnesium stearate. The capsule filling performance was measured by the capsule fill weight, coefficient of fill weight variation, plug length, plug density and tamping forces measured during the filling cycle.

The relationship between the flow parameters and the capsule filling performance was sought at different machine parameters. In comparison to the first study, which measured forces at tamping station 3 and 4, this study utilised 2 bed heights of 20mm and 25mm at 9 different compression settings, measuring forces at tamping station 3 only.

4.2.1.1 Cumulative Tamping Distance
The cumulative tamping distance (CTD) is the total penetration depth of the tamping pins into the dosing disk bores and gives an indication of the compression applied to the powder plug which influences the capsule fill weight. Figures 4.51 to 4.56 show that as the tamping pin setting increased, the fill weight increased. There was very little change in the capsule fill weight up to CTD 6mm. Hence, a certain degree of penetration of the tamping pins into the dosing disk bores is required to exert an effect on the capsule fill weight. From CTD 10mm to CTD 22mm, there was an increase in the capsule fill weight. At tamping pin settings greater than CTD 22mm, the fill weight reached equilibrium and there was almost no further increase. Therefore, to control the capsule fill weight by adjusting machine parameters, the most important tamping pin settings are between CTD 10mm and 22mm.

Pregelatinised starch
As the pregelatinised starch concentration increased in the excipient, the capsule fill weight increased. At bed height 20mm, when there was no pregelatinised starch in the excipient and 100% microfine cellulose, the capsule fill weight was only 231.6mg at CTD 0mm, increasing to 314.8mg at CTD 30mm (Figure 4.51). However, when there was 100% pregelatinised starch in the excipient, the capsule fill weight was much higher with 274.9mg at CTD 0mm and 361.8mg at CTD 30mm. For every 25% increase in the pregelatinised starch concentration in the excipient, there was an 11.3mg increase in the capsule fill weight. Similarly at bed height 25mm, the increase in the capsule fill weight was 11.5mg (Figure 4.54).
Increasing the bed height from 20mm to 25mm also increased the overall fill weight of the capsules. The increase in the bed height had a greater influence on the capsule fill weight at lower tamping pin settings. On average, there was a 9.5mg increase in the capsule fill weight by increasing the bed height at CTD 0mm compared to only a 3.4mg increase at CTD 30mm. This can be explained by the fact that at lower tamping pin settings, the powder flows into the dosing disk bores and does not depend upon external forces. Increasing the bed height means there is a greater quantity of powder available in the powder bed bowl, which results in more powder in the dosing disk. However, at higher tamping pin settings, powder is pushed into the bores by the tamping pins and hence the effect of increasing the bed height is less clearly observed.

**Ibuprofen**

As the ibuprofen concentration increased, there was a decrease in the capsule fill weight. At bed height 20mm and 50% ibuprofen in the blend, the mean capsule fill weight at CTD 0mm was 250.2mg and 338.4mg at CTD 30mm (Figure 4.52). When the ibuprofen concentration increased to 90%, the fill weight of the capsules decreased to 241.1mg at CTD 0mm and 328.4mg at CTD 30mm. Increasing the bed height increased the capsule fill weight and exerted a greater influence at lower tamping pin settings (Figure 4.55). At CTD 0mm, there was on average an 8.1mg increase in the capsule fill weight compared to only a 2.7mg at CTD 30mm for reasons explained earlier.

During filling it was found that formulations which contained less than 30% of any combination of pregelatinised starch and microfine cellulose (formulations 8, 9, 15, 17, 19 and 21) could not be readily filled at any powder bed height or compression setting. Even the addition of 0.92% magnesium stearate did not prevent excessive powder stickiness to the tamping pins and between the dosing disk and tamping ring. On visual inspection of the powder bed bowl, the powder bed was highly angled being highest at tamping station 5 and lowest at tamping station 1.

**Magnesium Stearate**

Increasing the magnesium stearate concentration from 0.2% to 1% had virtually no effect on the capsule fill weight. This can be demonstrated by comparing the fill weights at magnesium stearate concentrations of 0.2% and 1.0%. The fill weight of the capsules at a magnesium stearate concentration of 0.2% at bed height 20mm and CTD 0mm was 252.8mg and 337.9mg at CTD 30mm (Figure 4.53). When the magnesium stearate concentration was increased to 1%, the fill weight was 253.6mg at CTD 0mm and 332.6mg at CTD 30mm.
Figure 4.51: Fill weight at different pregelatinised starch concentrations in the excipient as a function of the cumulative tamping distance at bed height 20mm

Figure 4.52: Fill weight at different ibuprofen concentrations as a function of the cumulative tamping distance at bed height 20mm

Figure 4.53: Fill weight at different magnesium stearate concentrations as a function of the cumulative tamping distance at bed height 20mm
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Figure 4.54: Fill weight at different pregelatinised starch concentrations in the excipient as a function of the cumulative tamping distance at bed height 25mm

Figure 4.55: Fill weight at different ibuprofen concentrations as a function of the cumulative tamping distance at bed height 25mm

Figure 4.56: Fill weight at different magnesium stearate concentrations as a function of the cumulative tamping distance at bed height 25mm
This implies that a 0.2% magnesium stearate concentration was sufficient to achieve the maximum capsule fill weight. However, when running the capsule-filling machine for longer periods of time, it may be necessary to use a higher concentration of magnesium stearate to supply the machine with lubricant. However, this may be problematic during capsule disintegration as magnesium stearate makes formulations hydrophobic. Hence, there is a discrepancy between the magnesium stearate concentration required to fill and to lubricate the machine. This was also reported by Podczeck and Newton (2000) who found that filling properties were better at lower magnesium stearate concentrations, whereas machine performance improved with an increase in the magnesium stearate concentration up to 0.8%.

4.2.1.2 Concentration of Materials

Pregelatinised starch

The capsule fill weight was plotted against the concentration of the materials at CTD 30mm at bed heights 20mm and 25mm (Figures 4.57 and 4.60). The trends for pregelatinised starch at the two bed heights were almost identical. Both figures showed that as the pregelatinised starch concentration increased in the excipient, the capsule fill weight increased. This can be attributed to the good flow properties of pregelatinised starch. The figure shows that formulations containing a low ibuprofen concentration (54%) and a low pregelatinised starch concentration in the excipient (10% pregelatinised starch and 90% microfine cellulose) had the lowest capsule fill weights. At high ibuprofen concentrations (86%), increasing the pregelatinised starch concentration relative to microfine cellulose only slightly increased in the capsule fill weight due to the low amount of excipient (14%). The magnesium stearate concentration had almost no effect on the capsule fill weight. This indicates that a low amount of magnesium stearate (0.28%) is sufficient to provide adequate lubricant properties. This was also indicated by the angle of internal flow where there was almost no change when the magnesium stearate concentration was increased.

Ibuprofen

When comparing the figures for ibuprofen at powder bed heights 20mm and 25mm, the figures looked very similar indicating no change in trend with increasing bed height (Figures 4.58 and 4.61). Lower capsule fill weights were associated with low ibuprofen concentrations (54%) and low pregelatinised starch concentrations in the excipient (10%). As the ibuprofen concentration increased, there was a slight increase in the capsule fill weight due to a decrease in the microfine cellulose concentration in the excipient.
Figure 4.57: Fill weight as a function of the pregelatinised starch concentration at cumulative tamping distance 30mm and bed height 20mm.

Figure 4.58: Fill weight as a function of the ibuprofen concentration at cumulative tamping distance 30mm and bed height 20mm.

Figure 4.59: Fill weight as a function of the magnesium stearate concentration at cumulative tamping distance 30mm and bed height 20mm.
Figure 4.60: Fill weight as a function of the pregelatinised starch concentration at cumulative tamping distance 30mm and bed height 25mm.

Figure 4.61: Fill weight as a function of the ibuprofen concentration at cumulative tamping distance 30mm and bed height 25mm.

Figure 4.62: Fill weight as a function of the magnesium stearate concentration at cumulative tamping distance 30mm and bed height 25mm.
The highest capsule fill weights were related to a low ibuprofen concentration and a high pregelatinised starch to microfine cellulose ratio. As the ibuprofen concentration increased, the excipient concentration decreased, resulting in a decrease in the amount of pregelatinised starch and causing the capsule fill weight to drop.

**Magnesium Stearate**

The figure clearly demonstrates that an increase in the magnesium stearate concentration has little effect on the capsule fill weight (Figures 4.59 and 4.62). As discussed previously, the highest capsule fill weights were associated with a low ibuprofen concentration (54%) and a high pregelatinised starch concentration in the excipient (90%).

### 4.2.1.3 Capsule fill weight difference CTD 0mm – CTD 30mm

The influence of tamping pin settings can be measured by determining the difference between the capsule fill weight at CTD 0mm and CTD 30mm and comparing this to the concentration of the materials at a particular bed height.

Comparison of the capsule fill weight difference at bed heights 20mm and 25mm demonstrated that the tamping pin settings had a greater influence at bed height 20mm compared to bed height 25mm. This can be attributed to the fact that at the lower bed height the capsules were not completely full at CTD 0mm. This is because there was not enough material in the powder bed bowl for the powder to flow into the dosing disks. Hence, by increasing the tamping pin setting to CTD 30mm, more powder was pushed into the dosing disk, which increased the capsule fill weight. However, at bed height 25mm there was more powder in the powder bed bowl and at CTD 0mm, powder was filled into the dosing disk also due to simple flow. Increasing the tamping pin setting to CTD 30mm did not affect the fill weight to the same extent as when there was a lower bed height of 20mm (Figures 4.63 and 4.68).

**Pregelatinised starch**

At bed height 20mm, increasing the pregelatinised starch concentration in the excipient had little effect on the capsule fill weight difference when compared to a bed height of 25mm (Figures 4.63 and 4.66). At bed height 25mm, the capsule weight difference was lowest at a high ibuprofen concentration (86%), low pregelatinised starch concentration in the excipient (10%) and a low magnesium stearate concentration (0.28%). As the pregelatinised starch to microfine cellulose ratio increased, the fill weight difference increased due to improved powder flow properties.
Figure 4.63: Fill weight difference between CTD 0mm – CTD 30mm as a function of the pregelatinised starch concentration in the excipient at bed height 20mm

Figure 4.64: Fill weight difference between CTD 0mm – CTD 30mm as a function of the ibuprofen concentration at bed height 20mm

Figure 4.65: Fill weight difference between CTD 0mm – CTD 30mm as a function of the magnesium stearate concentration at bed height 20mm
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Figure 4.66: Fill weight difference between CTD 0mm – CTD 30mm as a function of the pregelatinised starch concentration in the excipient at bed height 25mm

Figure 4.67: Fill weight difference between CTD 0mm – CTD 30mm as a function of the ibuprofen concentration at bed height 25mm

Figure 4.68: Fill weight difference between CTD 0mm – CTD 30mm as a function of the magnesium stearate concentration at bed height 25mm

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At low ibuprofen concentrations (56%) and low pregelatinised starch in the excipient (10% pregelatinised starch and 90% microfine cellulose), the fill weight difference was generally high. This can be associated with the poor flow properties of microfine cellulose, which require higher tamping pin settings in order to successfully fill. As the pregelatinised starch concentration was increased in the excipient, there was a decrease in the capsule fill weight difference. This is due to the good flow properties of pregelatinised starch whereby a high tamping pin setting was not required to successfully fill at low ibuprofen concentrations.

A high magnesium stearate concentration increased the capsule fill weight difference by improving powder flow. The figure shows that the increase in the pregelatinised starch concentration when comparing low and high magnesium stearate concentrations at high ibuprofen concentrations resulted in parallel lines. The same with opposite trend was also true for the low ibuprofen concentrations, indicating additivity of the two factors.

Ibuprofen
At bed height 20mm, an increase in the ibuprofen concentration had almost no effect on the capsule fill weight difference (Figure 4.64). At bed height 25mm, increasing the ibuprofen concentration from 54% to 86%, decreased the capsule fill weight difference for formulations containing a low amount of pregelatinised starch (10%) (Figure 4.67). This can be attributed to the “sticky” nature of ibuprofen, which probably adhered to the tamping pin faces at high tamping pin settings.

At high pregelatinised starch concentrations in the excipient, increasing the ibuprofen concentration increased the capsule fill weight difference. This can be to the improved flow of pregelatinised starch enabling a greater amount of powder being pushed into dosing disk. A high magnesium stearate concentration further increases the capsule fill weight difference.

Magnesium Stearate
At the lower bed height of 20mm, the magnesium stearate concentration did not influence the capsule fill weight difference (Figure 4.65). However, at the higher bed height of 25mm, an increase in the capsule fill weight difference was observed (Figure 4.68). This is due to improved lubrication of the powder blend such that at higher tamping pin settings, more powder could be filled into the dosing disk bores.
At bed height 20mm, a high tamping pin setting was required to fill the dosing disk bores. However, at the higher bed height of 25mm, a high tamping pin setting did not necessarily result in large increases in the fill weight. Thus, an increased bed height can be used at lower tamping pin settings resulting in softer powder plugs being formed, which have faster disintegration and also reduced ware and tare of the machine.

4.2.1.4 Capsule fill weight difference between bed height 20mm and 25mm

Pregelatinised starch
When comparing the differences in the fill weight between the two bed heights, the figures showed that generally higher fill weights were observed at bed height 25mm (Figure 4.69). The greatest difference between the two bed heights was at low ibuprofen concentrations (54%) and low pregelatinised starch in the excipient (10% pregelatinised starch and 90% microfme cellulose). As the pregelatinised starch concentration was increased, the influence of the bed height decreased. Hence, a higher bed height is more important for poor flowing materials such as microfine cellulose. There was also not a large difference in the fill weight when increasing the bed height from 20mm to 25mm for formulations containing a high amount of ibuprofen. This can be associated with its sticky nature and therefore a certain degree of powder flow is required to observe an improvement in the fill weight.

Ibuprofen
A higher fill weight was observed at an increased bed height of 25mm (Figure 4.70). As the ibuprofen concentration increased, the capsule fill weight difference between the two bed heights decreased. The lowest difference by increasing the bed height from 20mm to 25mm occurred at a high ibuprofen concentration (86%), a low pregelatinised starch concentration in the excipient and a high magnesium stearate concentration. This can be associated with the amount of ibuprofen in the blend for reasons explained earlier.

Magnesium Stearate
Increasing the magnesium stearate concentration increased the difference between the two bed heights (Figure 4.71). The only exception to the trend, which cannot be explained, occurred at a low ibuprofen concentration (56%) and a low pregelatinised starch concentration in the excipient (10%).
Figure 4.69: Fill weight difference between bed height 20mm and 25mm at cumulative tamping distance 30mm as a function of the pregelatinised starch concentration in the excipient

Figure 4.70: Fill weight difference between bed height 20mm and 25mm at cumulative tamping distance 30mm as a function of the ibuprofen concentration

Figure 4.71: Fill weight difference between bed height 20mm and 25mm at cumulative tamping distance 30mm as a function of the magnesium stearate concentration
4.2.2 Coefficient of Fill Weight Variation

4.2.2.1 Optimal Cumulative Tamping Distance Setting

Optimal filling performance is required to achieve high fill weights and uniform filling. The determination of the optimal tamping pin settings enables the most favourable parameters to be used during filling. To calculate this parameter, the coefficient of fill weight variation for all twenty-one formulations was averaged at each of the tamping pin settings for both bed heights. This resulted in the optimal tamping pin settings at bed heights 20mm and 25mm. Figure 4.72 shows that the coefficient of fill weight variation is lower at bed height 25mm compared to 20mm, indicating that it is better to fill at the higher bed height to minimise variability between the capsule fill weights.

The lowest coefficient of fill weight variation at bed height 20mm occurred at CTD 30mm and this is therefore the optimal tamping pin setting. For the higher bed height of 25mm, figure 4.72 suggests it is slightly better to fill at a CTD 26mm, as this setting is accompanied by the lowest coefficient of fill weight variation. For both bed heights, the highest coefficient of fill weight variation was found at a CTD of 14mm. This is therefore the worst tamping pin setting to fill the capsules and the coefficient of fill weight variation is more than doubled compared to the optimum setting. Hence, it is important to carry out a preliminary trial to determine the optimal tamping pin setting so that machine parameters can be optimised and poor filling can be avoided.

Figure 4.72: Mean coefficient of fill weight variation for 21 formulations at different cumulative tamping distance settings

4.2.2.2 Minimum Coefficient of Fill Weight Variation

Due to the bell shape of the optimal CTD curve (Figure 4.72), the optimal tamping pin setting occurs either at very low tamping settings (CTD 0mm and CTD 3mm) or very high tamping pin settings (CTD 26mm and CTD 30mm). When comparing the concentrations of the materials, it was difficult to determine a relationship between the
minimum coefficient of fill weight variation and the optimal tamping pin setting (Table 4.7). It is clear however, that for each of the formulations, the optimal tamping pin setting is generally the same at both bed heights. Generally, it is preferable to fill at higher tamping pin settings because in many cases the minimum coefficient of fill weight variation at low tamping pin settings is comparable to the coefficient of fill weight variation at the higher tamping pin settings. However, in those cases where the coefficient of fill weight variation is lowest at a higher compression setting, the value at low compression settings is much larger. Also, high tamping pin settings result in increased capsule fill weights.

<table>
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<th>Bed height 25mm</th>
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<tr>
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4.2.2.3 Cumulative Tamping Distance

Figures 4.73 to 4.78 demonstrate the change in the coefficient of fill weight variation against the tamping pin settings with different concentrations of materials in the formulation. Low tamping pin settings (CTD 0mm - CTD 6mm) are associated with low coefficients of fill weight variation. As the tamping pin setting increases, there is an increase in the coefficient of fill weight variation between CTD 10mm - CTD 22mm after which a decrease in the coefficient of fill weight variation can be seen. Filling capsules in a tamp filling machine is a complicated process. At low tamping pin settings, filling mainly occurs via powder flow into the dosing bores, whereas at high tamping pin settings filling is a result of applying a compression force. The results suggest that this transition where filling occurs due to powder flow and/or a compression force results in high coefficients of fill weight variation.
Pregelatinised starch
At 100% pregelatinised starch in the excipient, the overall coefficient of fill weight variation was lowest. As the pregelatinised starch concentration decreased in the excipient and the microfine cellulose concentration increased, an increase in the coefficient of fill weight variation was observed (Figures 4.73 and 4.76). In comparison to microfine cellulose, pregelatinised starch is the superior excipient, as it results in improved powder flow, higher fill weights and a lower coefficient of fill weight variation.

Ibuprofen
At low tamping pin settings, the coefficient of fill weight variation for ibuprofen concentrations less than 70% was erratic. For higher ibuprofen concentrations, the coefficient of fill weight variation was less than 3%. This can be associated with its high angle of internal flow resulting in firm powder plugs being formed. Hence, upon transfer of the plug into the capsule body, very little powder was lost and a low coefficient of fill weight variation was observed. This agrees with Newton and Bader (1987) who also found that powders with a high angle of internal flow resulted in a low coefficient of fill weight variation. Increasing the tamping pin setting increased the coefficient of fill weight variation but at CTD 26mm, the coefficient of fill weight variation fell below 3.5% at bed height 20mm and 3% at bed height 25mm (Figures 4.74 and 4.77). This is due to the good plug forming properties of ibuprofen. Thus, it is possible to fill high concentrations of ibuprofen with a minimum amount of excipient and yet achieve a relatively low coefficient of fill weight variation. This does not meet the industry standards of 1% at any ibuprofen concentration or bed height, however the BP standards have been met.

Magnesium Stearate
The higher bed height of 25mm showed improved filling as it resulted in a lower and more consistent coefficients of fill weight variation and thus more predictable filling. At both bed heights a lower coefficient of fill weight variation was observed between CTD 0mm – CTD 6mm and CTD 22mm – CTD 30mm. At bed height 20mm, it was difficult to see a relationship between the magnesium stearate concentration and the coefficient of fill weight variation (Figures 4.75). However at bed height 25mm, at low tamping pin settings (CTD 0mm – CTD 6mm), higher magnesium stearate concentrations were associated with lower coefficients of fill weight variation (Figure 4.78). This supports the fact that at low tamping pin settings, filling is mainly due to powder flow. This improved powder flow results in improved filling and hence a lower coefficient of fill weight variation is observed.
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Figure 4.73: Coefficient of fill weight variation at different pregelatinised starch concentrations in the excipient as a function of the cumulative tamping distance at bed height 20mm

Figure 4.74: Coefficient of fill weight variation at different ibuprofen concentrations as a function of the cumulative tamping distance at bed height 20mm

Figure 4.75: Coefficient of fill weight variation at different magnesium stearate concentrations as a function of the cumulative tamping distance at bed height 20mm
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Figure 4.76: Coefficient of fill weight variation at different pregelatinised starch concentrations in the excipient as a function of the cumulative tamping distance at bed height 25mm

Figure 4.77: Coefficient of fill weight variation at different ibuprofen concentrations as a function of the cumulative tamping distance at bed height 25mm

Figure 4.78: Coefficient of fill weight variation at different magnesium stearate concentrations as a function of the cumulative tamping distance at bed height 25mm
As the tamping pin setting increases, filling via compression becomes more dominant and therefore the magnesium stearate concentration has little influence on the coefficient of fill weight variation.

### 4.2.2.4 Concentration of Materials

The coefficient of fill weight variation at CTD 30mm was plotted against the concentration of the materials (Figures 4.79 to 4.84). CTD 30mm was chosen as the optimal setting as overall this resulted in the lowest coefficient of fill weight variation. For all formulations the coefficient of fill weight variation at CTD 30mm was always less than 3% but never less than 1%.

**Pregelatinised starch**

As the pregelatinised starch concentration increased in the excipient, there was a general decrease in the coefficient of fill weight variation at both bed heights. However, it was more noticeable at the higher bed height (Figures 4.79 and 4.82). This could be associated with the greater amount of powder in the powder bed bowl, which resulted in improved filling especially at high pregelatinised starch concentrations in the excipient.

**Ibuprofen**

Both figures at the two bed heights show a similar trend (Figures 4.80 and 4.83). The coefficient of fill weight variation was lowest at a low ibuprofen concentration (54%), high pregelatinised starch concentration in the excipient (90%) and a low magnesium stearate concentration (0.28%). As the ibuprofen concentration increased, which was accompanied by a reduction in the amount of pregelatinised starch in the excipient, an increase in the coefficient of fill weight variation was observed. However, when there was a high magnesium stearate concentration (0.92%), the coefficient of fill weight variation dropped as the ibuprofen concentration was increased. This could be due to the high magnesium stearate concentration providing sufficient lubrication for the powder to successfully fill. Formulations containing 90% microfine cellulose in the excipient had the highest coefficient of fill weight variation. As the ibuprofen concentration increased, there was a further increase in the coefficient of fill weight variation. Hence, microfine cellulose does not improve the filling performance of ibuprofen.
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Figure 4.79: Coefficient of fill weight variation as a function of the pregelatinised starch concentration in the excipient at cumulative tamping distance 30mm and bed height 20mm

Figure 4.80: Coefficient of fill weight variation as a function of the ibuprofen concentration at cumulative tamping distance 30mm and bed height 20mm

Figure 4.81: Coefficient of fill weight variation as a function of the magnesium stearate concentration at cumulative tamping distance 30mm and bed height 20mm
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Figure 4.82: Coefficient of fill weight variation as a function of the pregelatinised starch concentration in the excipient at cumulative tamping distance 30mm and bed height 25mm

Figure 4.83: Coefficient of fill weight variation as a function of the ibuprofen concentration at cumulative tamping distance 30mm and bed height 25mm

Figure 4.84: Coefficient of fill weight variation as a function of the magnesium stearate concentration at cumulative tamping distance 30mm and bed height 25mm
During filling, problems were encountered with formulations containing high concentrations of ibuprofen (70% and greater). On visual inspection of the machine, rat-holing had occurred in the hopper and the powder bed was highly angled due to the sticky nature of ibuprofen (Figure 4.85). Therefore, it was not surprising to have found a high coefficient of fill weight variation when ibuprofen concentrations of 70% and greater were filled.

**Figure 4.85**: Highly angled powder bed resulting in overflowing from powder bowl

**Magnesium Stearate**

The influence of magnesium stearate was the same at both bed heights (Figures 4.81 and 4.84). High ibuprofen concentrations (86%) and low pregelatinised starch concentrations in the excipient (10% pregelatinised starch and 90% microfine cellulose) were associated with a high coefficient of fill weight variation. As the magnesium stearate concentration increased, there was no change in the coefficient of fill weight variation. At high ibuprofen concentrations (86%) and high pregelatinised starch in the excipient (90%) increasing the magnesium stearate concentration decreased the coefficient of fill weight variation. This is because ibuprofen is a sticky material and therefore the addition of magnesium stearate resulted in an improvement of the flow properties.

At low magnesium stearate concentrations, the lowest coefficient of fill weight variation was associated with a low ibuprofen concentration. This can be explained due to the large amount of pregelatinised starch in the blend. However, as the magnesium stearate concentration increased, the coefficient of fill weight variation increased. A possibility for this to occur could be over lubrication of the formulation making the powder flow “too well” and resulting in “flooding”. Hauer (1993) also reported an increase in the coefficient of fill weight variation with formulations having very good powder flow.
4.2.3 Length of the powder plug

4.2.3.1 Cumulative Tamping Distance

The length of the powder plug was measured as a function of the CTD to determine the packing properties of the formulations. Due to the increase in the capsule fill weight with increasing tamping pin settings, it would be expected that the length of the powder plug would also increase.

Pregelatinised starch

The figures for plug length as a function of the CTD were almost identical at bed heights 20mm and 25mm (Figures 4.86 and 4.89). As the tamping pin setting increased, there was no change in plug length up to CTD 14mm for the formulations. However, high plug lengths were associated with high pregelatinised starch concentrations in the excipient. At CTD 14mm, a critical point was reached where formulations previously having high plug lengths due to a large amount of pregelatinised starch in the excipient now had smaller plug lengths. This change in the plug length can be explained by the change in the filling behaviour of the capsules. At tamping pin settings below CTD 14mm, filling of the capsules was mainly achieved by flow due to the low compression caused by the tamping pin settings. Hence, capsules containing a high amount of pregelatinised starch had higher plug lengths due to its good flow properties. At CTD 14mm, there was a transition in the filling mechanism. Due to a greater compression force achieved by the tamping pins, filling was mainly due to the application of a tamping force. Therefore, powder plug lengths were determined by the packing properties of the materials. As the tamping pin setting increased, capsules with a high amount of pregelatinised starch in the excipient resulted in smaller plug lengths, due to improved powder packing. Formulations containing no pregelatinised starch in the excipient (100% microfine cellulose) increased in plug length due to poor packing.

Ibuprofen

At low tamping pin settings (below CTD 10mm), high plug lengths were associated with high ibuprofen concentrations. This was associated with the poor packing of ibuprofen and is demonstrated by its high compaction constant. As the tamping pin setting increased, filling via compression became more dominant. This resulted in smaller plug lengths at ibuprofen concentrations greater than 80%, due to the strong plug forming properties of ibuprofen. The transition where filling via compression takes over from filling via flow is more defined at bed height 25mm than at bed height 20mm. At bed height 25mm this takes place at CTD 18mm, whereas at bed height 20mm, it is between CTD 10mm and CTD 22mm (Figures 4.87 and 4.90).
Figure 4.86: Plug length at different pregelatinised starch concentrations in the excipient as a function of the cumulative tamping distance at bed height 20mm

Figure 4.87: Plug length at different ibuprofen concentrations as a function of the cumulative tamping distance at bed height 20mm

Figure 4.88: Plug length at different magnesium stearate concentrations as a function of the cumulative tamping distance at bed height 20mm
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Figure 4.89: Plug length at different pregelatinised starch concentrations in the excipient as a function of the cumulative tamping distance at bed height 25mm

Figure 4.90: Plug length at different ibuprofen concentrations as a function of the cumulative tamping distance at bed height 25mm

Figure 4.91: Plug length at different magnesium stearate concentrations as a function of the cumulative tamping distance at bed height 25mm
Figure 4.92 shows two capsules filled at maximum compression. The capsule on the left is formulation 6 and contains a low amount of ibuprofen (50%). The capsule on the right is formulation 9 and contains a large ibuprofen concentration (86%). The figure clearly demonstrates the strong plug forming capability of ibuprofen at high concentrations as a gap can be seen at the top of the capsule where the plug has not filled the void. However this firm plug formed may have implications during disintegration and dissolution of the powder plug.

Magnesium Stearate

At magnesium stearate concentrations between 0.2% and 0.6%, there was a slight increase in plug length as the tamping pin setting increased. However, at magnesium stearate concentrations of 0.8% and greater, the plug length remained almost the same. This could be because at lower magnesium stearate concentrations, there was poor powder flow and hence a high tamping pin setting had a greater effect on the capsule fill weight, which influenced the plug length (Figures 4.88 and 4.91).
4.2.3.2 Concentration of Materials

The plug length was plotted against the concentration of each of the materials at CTD 30mm for bed heights of 20mm and 25mm.

Pregelatinised starch

As the pregelatinised starch concentration increased, the length of the plugs decreased (Figures 4.93 and 4.96). Smaller plug lengths either indicate poor powder flow properties, resulting in low capsule fill weights or good powder flow and packing, resulting in high capsule fill weights. All flow properties indicate pregelatinised starch has good flow properties and this supported by high capsule fill weights. Therefore, the decrease in the plug length is a result of good packing.

Lower plug lengths were associated with high ibuprofen concentrations. This is because of the good plug forming properties of ibuprofen when tamped at high tamping pin settings. At high ibuprofen concentrations and high magnesium stearate concentrations (0.92%), there was no change in the plug length when the pregelatinised starch concentration was increased in the excipient. This indicates that there was sufficient lubricant in the powder blend for good packing to be achieved. However, at low magnesium stearate concentrations (0.28%), increasing the pregelatinised starch concentration decreased the plug length due to insufficient magnesium stearate in the formulation.

Capsules filled with a low amount of ibuprofen and a low pregelatinised starch concentration in the excipient (10% pregelatinised starch and 90% microfine cellulose) had the highest plug lengths. The magnesium stearate concentration did not affect the plug length. This indicates that when there is a large concentration of microfine cellulose in the excipient, a high magnesium stearate concentration is not useful. This was demonstrated previously for the capsule fill weight data. As the pregelatinised starch concentration increased in the excipient relative to microfine cellulose, there was a drop in the plug length. This is due to an improvement in packing, which was further improved by a high magnesium stearate concentration (0.92%). This trend was observed at both bed heights of 20mm and 25mm.
Figure 4.93: Plug length as a function of the pregelatinised starch concentration in the excipient at cumulative tamping distance 30mm and bed height 20mm.

Figure 4.94: Plug length as a function of the ibuprofen concentration at cumulative tamping distance 30mm and bed height 20mm.

Figure 4.95: Plug length as a function of the magnesium stearate concentration at cumulative tamping distance 30mm and bed height 20mm.
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Figure 4.96: Plug length as a function of the pregelatinised starch concentration in the excipient at cumulative tamping distance 30mm and bed height 25mm

Figure 4.97: Plug length as a function of the ibuprofen concentration at cumulative tamping distance 30mm and bed height 25mm

Figure 4.98: Plug length as a function of the magnesium stearate concentration at cumulative tamping distance 30mm and bed height 25mm
Ibuprofen
As the ibuprofen concentration increased, the length of the powder plugs decreased (Figures 4.94 and 4.97). At low ibuprofen concentrations (54%), smaller plug lengths were associated with high pregelatinised starch concentrations in the excipient, which further decreased at high magnesium stearate concentrations (0.92%). The largest plug lengths were associated with low pregelatinised starch concentrations in the excipient (10% pregelatinised starch and 90% microfine cellulose), and a low ibuprofen concentration (54%) and were not influenced by the magnesium stearate concentration. As the ibuprofen concentration increased, the formulation containing a high pregelatinised starch concentration and a high magnesium stearate concentration possessed the lowest plug length. This implies that at high ibuprofen concentrations (86%), a high magnesium stearate concentration (0.92%) results in good packing. This trend occurred at both bed heights of 20mm and 25mm.

Magnesium Stearate
Increasing the magnesium stearate concentration decreased the plug length for all formulations (Figures 4.95 and 4.98). The only exception where no further improvement in packing was observed was at a low ibuprofen concentration (54%) and a high microfine cellulose concentration in the excipient (90%) for reasons explained earlier.
4.2.4 Plug Density
The plug density of the capsule was determined by dividing the capsule fill weight by the volume of the capsule. According to Newton (1987), capsules should not be filled such that the plug density of the powder is greater than the maximum bulk density, as this could be problematic during dissolution. However, all formulations showed a greater plug density than the maximum bulk density. This could be indicative of poor dissolution, as the powder plug is less permeable to liquid.

4.2.4.1 Cumulative Tamping Distance
Increasing the tamping pin setting increased the plug density of the capsule. There was little change in the plug density at low tamping pin settings (CTD 0mm – CTD 6mm). This is because the compression force was insufficient to result in an increase in the capsule fill weight. As the tamping pin setting was increased above CTD 6mm, it resulted in an increase in the plug density.

Pregelatinised starch
An increase in the pregelatinised starch concentration increased the plug density at both bed heights (Figures 4.99 and 4.102). The affect of the pregelatinised starch concentration on the plug density was almost the same at both bed heights, but applying maximum compression had a greater influence on plug density compared to when no compression was applied. Increasing the bed to height from 20mm to 25mm increased the overall plug density of the capsules due to a greater quantity of powder in the powder bed bowl and had a greater influence at lower tamping pin settings. This is because at low tamping pin settings, the powder flows into the dosing disk bore and does not depend upon compression. However, at higher tamping pin settings, a compression force aids powder flow hence, the effect of the increased bed height is less clearly observed.

Ibuprofen
As the ibuprofen concentration increased, a decrease in plug density was observed (Figures 4.100 and 4.103). This could be associated with the increase in the pregelatinised starch concentration, which has a higher bulk density compared to ibuprofen. Increasing the ibuprofen concentration in the formulation affected the plug density to virtually the same extent at both bed heights. An increase in the bed height increased the plug density but only slightly and was only observed at low tamping pin settings.
Figure 4.99: Plug density at different pregelatinised starch concentrations in the excipient as a function of the cumulative tamping distance at bed height 20mm

Figure 4.100: Plug density at different ibuprofen concentrations as a function of the cumulative tamping distance at bed height 20mm

Figure 4.101: Plug density at different magnesium stearate concentrations as a function of the cumulative tamping distance at bed height 20mm
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Figure 4.102: Plug density at different pregelatinised starch concentrations in the excipient as a function of the cumulative tamping distance at bed height 25mm

Figure 4.103: Plug density at different ibuprofen concentrations as a function of the cumulative tamping distance at bed height 25mm

Figure 4.104: Plug density at different magnesium stearate concentrations as a function of the cumulative tamping distance at bed height 25mm
Magnesium Stearate
As the magnesium stearate concentration increased from 0.2% to 1%, it had no effect on the plug density (Figures 4.101 and 4.104). This suggests a 0.2% magnesium stearate concentration was adequate to achieve the maximum plug density. However, increasing the bed height from 20mm to 25mm increased the plug density especially at low tamping pin settings as seen earlier. Hence, plug density gives some indication to the filling properties. However, without understanding the change in the capsule fill weight and plug length, it is difficult to determine a true picture because plug length could compensate for the change in the fill weight.

4.2.4.2 Concentration of Materials
Pregelatinised starch
As the pregelatinised starch concentration increased in the excipient, there was an increase in the plug density. Both bed heights showed identical trends (Figures 4.105 and 4.108). The lowest plug densities were associated with low ibuprofen concentrations (54%) and low pregelatinised starch concentrations in the excipient (10% pregelatinised starch and 90% microfine cellulose). As the pregelatinised starch concentration increased relative to microfine cellulose, there was a large increase in the plug density. At high ibuprofen concentrations (86%), increasing the pregelatinised starch concentration increased the plug density but not to the same extent as when there was a low ibuprofen concentration. This is due to the low amount of excipient available for pregelatinised starch to make a substantial difference in the plug density. Increasing the magnesium stearate concentration further increased the plug density.

Ibuprofen
As the ibuprofen concentration increased, the plug density decreased for formulations containing a high pregelatinised starch concentration (90%) in the excipient. However, the plug density increased for formulations containing a high microfine cellulose concentration in the excipient (90%). This occurred at both bed heights 20mm and 25mm (Figures 4.106 and 4.109).

The trend observed for the plug density was also seen when measuring flow and filling properties such as tapped density and capsule fill weight. The similarity between the plug density and the tapped density was because both parameters measured the ease of densification of the formulation. The relationship between the plug density and the capsule fill weight is not surprising as the plug density is a function of the capsule fill weight.
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Figure 4.105: Plug density as a function of the pregelatinised starch concentration in the excipient at cumulative tamping distance 30mm and bed height 20mm

Figure 4.106: Plug density as a function of the ibuprofen concentration at cumulative tamping distance 30mm and bed height 20mm

Figure 4.107: Plug density as a function of the magnesium stearate concentration at cumulative tamping distance 30mm and bed height 20mm

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Figure 4.108: Plug density as a function of the pregelatinised starch concentration in the excipient at cumulative tamping distance 30mm and bed height 25mm

Figure 4.109: Plug density as a function of the ibuprofen concentration at cumulative tamping distance 30mm and bed height 25mm

Figure 4.110: Plug density as a function of the magnesium stearate concentration at cumulative tamping distance 30mm and bed height 25mm
The trend for the plug density mirrors the angle of internal flow and T-value data because these parameters describe the frictional properties of the powder and the higher these values, the worse the powder flows, resulting in low plug densities. Therefore, the angle of internal flow and the T-value may be used to some extent to predict the plug density of the capsule.

**Magnesium Stearate**

As the magnesium stearate concentration increased, there was a slight increase in the plug density. This is due to improved packing of the powder blend resulting in higher plug densities. The highest plug densities were associated with a high pregelatinised starch concentration in the excipient (Figures 4.107 and 4.110).
4.2.5 Force Data

Tamping forces were measured at tamping station 3 for bed heights 20mm and 25mm during the capsule filling cycle. The median tamping force and spread of the tamping force was determined from the force data for each of the tamping events for all formulations at different tamping pin settings.

4.2.5.1 Comparison of Median Forces at Bed Heights 20mm and 25mm

Tamping force profiles (Figures 4.111 to 4.118) for formulation 1 illustrate that all forces were greater at bed height 25mm compared to bed height 20mm. This can be associated with extra powder in the powder bed bowl, which increases the pressure exerted on the tamping pins.

4.2.5.2 Cumulative Tamping Distance

No tamping forces were measured below CTD 14 because of a threshold force of approximately 58N known as a baseline force. Increasing the tamping pin settings increased the tamping force due to more powder being pushed inside the dosing disk cavity.

Pregelatinised starch

Increasing the pregelatinised starch concentration increased the tamping force (Figure 4.119). This is because high pregelatinised starch concentrations improve powder flow properties and thus produce higher fill weights resulting in an increase in the tamping force.

Ibuprofen

As the ibuprofen concentration increased, there was a general decrease in the tamping force when the CTD was increased (Figure 4.120). This is surprising, because during the filling process, the capsule filling machine produced loud “crunching” noises for formulations containing high ibuprofen concentrations (greater than 70%). This is due to powder stickiness indicating a difficulty in the filling process. The explanation for the decrease in the tamping force as the ibuprofen concentration was increased is due to the drop in the capsule fill weight because of the low pregelatinised starch concentration in the formulation.

Magnesium Stearate

An increase in the tamping force was observed as the magnesium stearate concentration increased (Figure 4.121). A possible explanation for the higher tamping forces could be an improvement in powder properties resulting in higher capsule fill weights.
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Figure 4.111: Tamping force profile of formulation 1 at CTD 18mm measured at bed height 20mm

Figure 4.112: Tamping force profile of formulation 1 at CTD 22mm measured at bed height 20mm

Figure 4.113: Tamping force profile of formulation 1 at CTD 26mm measured at bed height 20mm

Figure 4.114: Tamping force profile of formulation 1 at CTD 30mm measured at bed height 25mm

Figure 4.115: Tamping force profile of formulation 1 at CTD 18mm measured at bed height 20mm

Figure 4.116: Tamping force profile of formulation 1 at CTD 22mm measured at bed height 25mm

Figure 4.117: Tamping force profile of formulation 1 at CTD 26mm measured at bed height 25mm

Figure 4.118: Tamping force profile of formulation 1 at CTD 30mm measured at bed height 25mm
Figure 4.119: Median tamping force at different pregelatinised starch concentrations in the excipient as a function of the cumulative tamping distance at bed heights 20mm and 25mm.

Figure 4.120: Median tamping force at different ibuprofen concentrations as a function of the cumulative tamping distance at bed heights 20mm and 25mm.

Figure 4.121: Median tamping force at different magnesium stearate concentrations as a function of the cumulative tamping distance at bed heights 20mm and 25mm.
However, when comparing the capsule fill weight data, it does not support this theory. Another explanation could be that the maximum fill weight has already been achieved at the low magnesium stearate concentration. As the magnesium stearate concentration further increases, the powder flow also improves. This leads to a better distribution of the powder in the powder bed bowl, which results in increased tamping forces i.e. a similar effect to increasing the powder bed height.

4.2.5.3 Concentration of Materials
The median force was plotted against the concentration for each of the materials at CTD 30mm as this was the overall optimal tamping pin setting for bed heights 20mm and 25mm (Figures 4.122 to 4.127). Both bed heights show similar trends for the tamping force profiles.

Pregelatinised starch
As the pregelatinised starch concentration increased, there was an increase in the tamping force (Figures 4.122 and 4.125). At low ibuprofen concentrations (54%), there was a big increase in the tamping force when the pregelatinised starch concentration was increased. This is due to the large quantity of excipient in the formulation and as the pregelatinised starch concentration in the excipient increased from 10% to 90%, this produced high capsule fill weights. At high ibuprofen concentrations (86%), there was only a slight increase in the tamping force. This is due to less excipient and therefore less pregelatinised starch, resulting in lower tamping forces. At high ibuprofen concentrations, a high magnesium stearate concentration further increased the tamping force due to improved powder flow.

Ibuprofen
At low ibuprofen concentrations (54%), the pregelatinised starch concentration determined the magnitude of the force (Figure 4.123). Lower forces were associated with low pregelatinised starch concentrations in the excipient (10% pregelatinised starch and 90% microfine cellulose). This is due to the poor flow and filling properties of microfine cellulose, which result in low capsule fill weights and produce low tamping forces. Increasing the ibuprofen concentrations for the formulation containing a high magnesium stearate concentration increased the tamping force. This can be attributed to an improvement of the flow properties, which produces higher capsule fill weights. When the magnesium stearate concentration was low, there was very little change in the tamping force.
Figure 4.122: Median tamping force as a function of the pregelatinised starch concentration in the excipient at cumulative tamping distance 30mm and bed height 20mm

Figure 4.123: Median tamping force as a function of the ibuprofen concentration at cumulative tamping distance 30mm and bed height 20mm

Figure 4.124: Median tamping force as a function of the magnesium stearate concentration at cumulative tamping distance 30mm and bed height 20mm
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Figure 4.125: Median tamping force as a function of the pregelatinised starch concentration in the excipient at cumulative tamping distance 30mm and bed height 25mm

Figure 4.126: Median tamping force as a function of the ibuprofen concentration at cumulative tamping distance 30mm and bed height 25mm

Figure 4.127: Median tamping force as a function of the magnesium stearate concentration at cumulative tamping distance 30mm and bed height 25mm
At high pregelatinised starch concentrations in the excipient (90%) and high magnesium stearate concentrations (0.92%), there was no change in the tamping force when the ibuprofen concentration was increased at bed height 25mm (Figure 4.126). This could be due to the fact that there was sufficient magnesium stearate in the formulation to maintain good filling. However, at low magnesium stearate concentrations (0.28%), a decrease in the tamping force was observed, probably due to a worsening of the filling properties.

**Magnesium Stearate**

Magnesium stearate functions as a lubricant by improving the flow properties of the material and enhancing the filling performance of the powder. It also serves to provide lubrication for the machine and therefore high magnesium stearate concentrations should result in low tamping forces. However, figures 4.124 and 4.127 demonstrate that as the magnesium stearate concentration increased, the tamping force also increased. This is due to reasons explained earlier. The only formulation that did not follow this trend was that containing a low ibuprofen concentration (54%) and a high pregelatinised starch concentration in the excipient (90%).

Thus, the tamping force is a measure of the flow and filling properties of the material. High tamping forces are a result of either poor filling properties due to insufficient lubricant in the formulation or a result of high capsule fill weights associated with high pregelatinised starch concentrations.

**4.2.5.4 Spread of Tamping Force**

The spread of the tamping force describes the variability of the force and is the difference between the minimum and the maximum tamping force observed during the filling process. Powders which possess poor flow properties will have erratic flow and therefore the spread of the tamping force will be greater than those powders with good flow properties. Both bed heights showed similar trends as the concentration of the materials was increased (Figures 4.128 to 4.133).

**Pregelatinised starch**

A decrease in the tamping force spread was seen as the pregelatinised starch concentration increased, for formulations containing a low ibuprofen concentration (Figures 4.128 and 4.131). This indicates that high pregelatinised starch concentrations in the excipient (90%) reduce the variability of the filling performance.
Figure 4.128: Tamping force spread as a function of the pregelatinised starch concentration in the excipient at cumulative tamping distance 30mm and bed height 20mm

Figure 4.129: Tamping force spread as a function of the ibuprofen concentration at cumulative tamping distance 30mm and bed height 20mm

Figure 4.130: Tamping force spread as a function of the magnesium stearate concentration at cumulative tamping distance 30mm and bed height 20mm
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Figure 4.131: Tamping force spread as a function of the pregelatinised starch concentration in the excipient at cumulative tamping distance 30mm and bed height 25mm

Figure 4.132: Tamping force spread as a function of the ibuprofen concentration at cumulative tamping distance 30mm and bed height 25mm

Figure 4.133: Tamping force spread as a function of the magnesium stearate concentration at cumulative tamping distance 30mm and bed height 25mm
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However, formulations containing a high ibuprofen concentration (86%) an increase in the variability of the tamping force was observed as the pregelatinised starch concentration was increased in the excipient. At 70% ibuprofen as seen for the centre mix there was a reduction in the tamping force. Therefore, ibuprofen concentrations greater than 70% appear critical for the increase in the variability of the tamping force. The high magnesium stearate concentration further improved powder flow, which can be demonstrated by the reduction in the tamping force spread.

**Ibuprofen**

As the ibuprofen concentration increased, an increase in the tamping force spread was observed due to its poor flowing and sticky nature. This became very apparent when the ibuprofen concentration was increased at high pregelatinised starch concentrations in the excipient (90%). Therefore, pregelatinised starch can only provide the necessary lubrication at low ibuprofen concentrations (54%). Formulations containing a low pregelatinised starch concentration in the excipient (10% pregelatinised starch and 90% microfine cellulose) possess a much higher tamping force spread especially at low ibuprofen concentrations. As the ibuprofen concentration increases, there is an improvement in the tamping force spread when there is a high magnesium stearate concentration (Figures 4.129 and 4.132).

**Magnesium Stearate**

At bed height 20mm, as the magnesium stearate concentration increased, there was a decrease in the tamping force spread for formulations containing a low pregelatinised starch concentration in the excipient, indicating a reduction in the variability of the tamping force. However, at high pregelatinised starch concentrations in the excipient, there was a slight increase in the tamping force spread. At bed height 25mm, the tamping force decreased with increasing magnesium stearate concentrations. This indicates that a high magnesium stearate concentration is required to provide the necessary lubrication in the powder. The only exception was found at a low ibuprofen concentration (54%) and a 90% pregelatinised starch concentration in the excipient (Figures 4.130 and 4.133).
4.2.6 Relationship Between the Flow and Filling Parameters

The linear determinant \( R^2 \) was calculated to evaluate the capsule filling performance with the concentration of the materials and the flow parameters. The correlation coefficient was determined at both bed heights for the different compression settings.

Figure 4.134 shows that high pregelatinised starch concentrations resulted in higher capsule fill weights due to improved powder flow and packing of the powder. Also, higher compression settings further increased the correlation between the pregelatinised starch concentration and the capsule fill weight (Table 4.8).

There was a very high correlation between the minimum bulk density and the capsule fill weight, whereby an increase in the minimum bulk density increased the capsule fill weight. As the compression setting increased there was no change in the correlation at bed height 20mm. However at the higher bed height, increasing the compression setting further increased the correlation. This was the same for the maximum bulk density (Figure 4.135). The strong relationship of minimum tapped density and the maximum tapped density with the capsule fill weight can be attributed to the fact that these parameters measure the packing characteristics of the powder and are representative of how the powder will behave when filled into capsules.

A trend was observed between the fill weight and the angle of internal flow (Figure 4.136). An increase in the angle of internal flow decreased the capsule fill weight. This was also observed by Newton and Bader (1987) who found that capsules filled on a dosator capsule filling machine decreased in fill weight as the angle of internal flow increased. At bed height 20mm increasing the compression setting decreased the correlation between these two parameters. However at bed height 25mm, the compression setting had no affect. Trends were also observed between the fill weight and flow parameters such as Carr’s compressibility index, T-value and the mobility index.

A step-wise relationship could be seen between the coefficient of fill weight variation and the microfine cellulose content at low compression settings (Table 4.9 and Figure 4.137). The figure suggests that concentrations below approximately 15% have no detrimental effect on the filling performance of the formulations, whereas concentrations above this threshold level should be avoided.

The angle of internal flow and the angle of internal friction were both related to the coefficient of fill weight variation at low tamping pin settings (Figures 4.138 and 4.139).
Formulations with a high angle of internal flow resulted in high coefficients of fill weight variation. This disagrees with Tan and Newton (1990a) who found, when filling with a dosator capsule machine simulator, that a low coefficient of fill weight variation was observed with high angles of internal flow. The data shows that as the compression settings increased, the relationship between the coefficient of fill weight variation and these parameters decreased. This is because both parameters measure the frictional properties of a material and this is required for good plug forming properties. However at high compression settings, high interparticulate forces are not necessary due to the application of a high compression force. Therefore the angle of internal flow is only indicative of the coefficient of fill weight variation at low compression settings and this relationship only applied up to CTD 18mm at both bed heights.

A trend was observed between the mobility index \( m \) and the coefficient of fill weight variation (Figure 4.140). As the mobility between the particles increased, the coefficient of fill weight variation decreased. An explanation for this relationship is that the mobility index is indicative of powder flow and if the material flows well, this results in a low coefficient of fill weight variation. This relationship was only valid at low compression settings; CTD 10mm at bed height 20mm and CTD 18mm at bed height 25mm.

A slight trend was also observed between the Jenike's flow factor and the coefficient of fill weight variation. As Jenike’s flow factor increased, the coefficient of fill weight variation also increased. Jenike’s flow factor was found to be an unreliable method of measurement for powder flow (see chapter 4.1.6.4) and had shown contradicting relationships with other flow parameters. Also, Jenike’s flow factor describes microfine cellulose as an almost free flowing material. This is contradictory to all flow parameters, which found that microfine cellulose was a poor flowing material. Thus, Jenike’s flow factor must measure a powder characteristic that is not described by other flow parameters. This relationship again is only valid at low compression settings of up to CTD 10mm for both bed heights.

All the relationships between the coefficients of fill weight variation and the flow parameters were greater at the lower bed height. This is due to less powder in the powder bed bowl at the lower bed height and therefore the powder plugs are not tamped to the same extent as at the higher bed height. This lower bed height has the same effect as applying a low compression setting. This is because relationships with the flow parameters are generally valid at lower compression settings.
The plug density is a characteristic of the packing performance of the powder. There is a very high correlation between the pregelatinised starch concentration and the plug density due to the good packing performance of pregelatinised starch (Table 4.10 and Figure 4.141). Hence, there is also a strong correlation between the minimum and maximum bulk density with the powder plug density (Figure 4.142). As the compression settings increased, the correlation strengthened between these parameters and the plug density. This also applied for the angle of internal flow, however, the relationship with the plug density was not as strong (Figure 4.143). Another trend mainly observed at high compression settings was a relationship with the mobility index (Figure 4.144). As the mobility index increased, the plug density also increased. This suggests that the mobility index is an indirect measure of powder flow and packing. Filling parameters such as the plug density and the capsule fill weight generally show a higher correlation at increased compression settings. Other flow parameters that showed trends with the plug density were Carr’s compressibility index and the T-value.

Due to a threshold force, tamping forces could only be measured at compression settings greater than CTD 18mm (Table 4.11). Generally the correlation between the flow parameters and the tamping forces were stronger at the lower bed height due to reasons explained earlier. There was a strong relationship between the pregelatinised starch concentration and the median tamping force, which can be associated with the increase in the capsule fill weight at higher pregelatinised starch concentrations (4.145). There was also a correlation between the minimum and maximum bulk density and the tamping force (4.146) and increasing the compression force strengthened this relationship. This is because higher minimum and maximum bulk densities were responsible for increased plug densities due to improved packing properties of the powder. Hence, a relationship was also observed between Carr’s compressibility index and the median tamping force (Figure 4.147).

The angle of internal flow and T-value also showed trends with the tamping force, whereby a decrease in both these parameters increased the tamping force. This can be attributed to a reduction in the interparticulate forces and an improvement in the packing characteristics of the powder. A slight trend was observed between the mobility index and the tamping force; an increase in the mobility of the particles resulted in an increase in the tamping force.

Another parameter obtained from the force measurements was the spread of the tamping force (Table 4.11). This did not show any relationships with the flow parameters. This is
surprising, as poor powder flow would contribute to an increase in variability of the tamping force and an increase in the tamping force spread. It could be that the spread is more influenced by the stickiness of the powder to the tamping pins, which could not be quantified during the experiments.

When evaluating the relationships between the filling parameters at the different compression settings (Table 4.12 and 4.13), there was a very strong correlation between the fill weight and the plug density. This is not surprising as the plug density is a function of the capsule fill weight. These parameters also showed a trend with the tamping force, whereby an increase in the fill weight and plug density increased the tamping force. This relationship was stronger at higher compression settings and at the lower bed height.
### Table 4.8: Correlation of fill weight against the materials and flow parameters at different cumulative tamping distances at bed heights 20mm and 25mm (linear determinant $R^2$)

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<th>Bed Height</th>
<th>CTD (mm)</th>
<th>PGS (g/cm³)</th>
<th>MFC (g/cm³)</th>
<th>Ibuprofen (g/cm³)</th>
<th>MS (g/cm³)</th>
<th>Pmc.x (g/cm²)</th>
<th>CCI (%)</th>
<th>$\theta$ (%)</th>
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<td>0.000</td>
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<td>0.916</td>
<td>0.382</td>
<td>0.103</td>
<td>0.000</td>
<td>0.852</td>
<td>0.849</td>
<td>0.425</td>
<td>0.548</td>
<td>0.383</td>
<td>0.367</td>
</tr>
</tbody>
</table>

### Table 4.9: Correlation of the coefficient of fill weight variation against the materials and flow parameters at different cumulative tamping distances at bed heights 20mm and 25mm (linear determinant $R^2$)

<table>
<thead>
<tr>
<th>Bed Height</th>
<th>CTD (mm)</th>
<th>PGS (g/cm³)</th>
<th>MFC (g/cm³)</th>
<th>Ibuprofen (g/cm³)</th>
<th>MS (g/cm³)</th>
<th>Pmc.x (g/cm²)</th>
<th>CCI (%)</th>
<th>$\delta$ (%)</th>
<th>Cohesion (g/cm²)</th>
<th>Mobility</th>
<th>FF</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>0.039</td>
<td>0.695</td>
<td>0.363</td>
<td>0.004</td>
<td>0.138</td>
<td>0.258</td>
<td>0.003</td>
<td>0.544</td>
<td>0.085</td>
<td>0.594</td>
<td>0.267</td>
</tr>
<tr>
<td>3</td>
<td>0.068</td>
<td>0.703</td>
<td>0.299</td>
<td>0.001</td>
<td>0.130</td>
<td>0.308</td>
<td>0.006</td>
<td>0.569</td>
<td>0.122</td>
<td>0.641</td>
<td>0.257</td>
</tr>
<tr>
<td>6</td>
<td>0.015</td>
<td>0.700</td>
<td>0.459</td>
<td>0.000</td>
<td>0.084</td>
<td>0.211</td>
<td>0.003</td>
<td>0.515</td>
<td>0.053</td>
<td>0.633</td>
<td>0.343</td>
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<tr>
<td>10</td>
<td>0.006</td>
<td>0.573</td>
<td>0.417</td>
<td>0.016</td>
<td>0.038</td>
<td>0.131</td>
<td>0.009</td>
<td>0.378</td>
<td>0.003</td>
<td>0.491</td>
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<td>0.084</td>
<td>0.401</td>
<td>0.108</td>
<td>0.031</td>
<td>0.125</td>
<td>0.320</td>
<td>0.004</td>
<td>0.341</td>
<td>0.029</td>
<td>0.423</td>
<td>0.108</td>
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<td>18</td>
<td>0.384</td>
<td>0.343</td>
<td>0.001</td>
<td>0.031</td>
<td>0.507</td>
<td>0.468</td>
<td>0.295</td>
<td>0.420</td>
<td>0.365</td>
<td>0.329</td>
<td>0.004</td>
</tr>
<tr>
<td>22</td>
<td>0.403</td>
<td>0.135</td>
<td>0.058</td>
<td>0.016</td>
<td>0.503</td>
<td>0.296</td>
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<tr>
<td>26</td>
<td>0.167</td>
<td>0.029</td>
<td>0.052</td>
<td>0.020</td>
<td>0.170</td>
<td>0.071</td>
<td>0.291</td>
<td>0.225</td>
<td>0.014</td>
<td>0.124</td>
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<tr>
<td>30</td>
<td>0.105</td>
<td>0.036</td>
<td>0.016</td>
<td>0.005</td>
<td>0.089</td>
<td>0.042</td>
<td>0.137</td>
<td>0.022</td>
<td>0.072</td>
<td>0.048</td>
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</tbody>
</table>

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Table 4.10: Correlation of plug density against the materials and flow parameters at different cumulative tamping distances at bed heights 20mm and 25mm (linear determinant $R^2$)

<table>
<thead>
<tr>
<th>Bed Height (mm)</th>
<th>CTD (mm)</th>
<th>PGS (g/cm³)</th>
<th>MFC Ibuprofen</th>
<th>MS</th>
<th>$P_{min}$ (g/cm³)</th>
<th>$P_{max}$ (g/cm³)</th>
<th>CCI (%)</th>
<th>$\theta$ (%)</th>
<th>$\delta$ (%)</th>
<th>Cohesion (g/cm²)</th>
<th>Mobility</th>
<th>FF</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>0</td>
<td>0.880 0.393 0.048 0.001 0.856 0.857 0.423 0.573 0.408 0.363 0.043 0.462 0.004</td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td>0.900 0.359 0.110 0.000 0.845 0.849 0.413 0.542 0.407 0.336 0.050 0.420 0.002</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>6</td>
<td>0.889 0.322 0.128 0.006 0.833 0.789 0.642 0.481 0.442 0.299 0.076 0.411 0.000</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>10</td>
<td>0.924 0.237 0.203 0.004 0.838 0.763 0.495 0.412 0.424 0.229 0.117 0.320 0.009</td>
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<td></td>
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<td>14</td>
<td>0.936 0.313 0.149 0.000 0.846 0.827 0.437 0.496 0.395 0.310 0.061 0.377 0.000</td>
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</tr>
<tr>
<td>18</td>
<td>0.921 0.335 0.119 0.001 0.884 0.829 0.502 0.517 0.415 0.346 0.056 0.465 0.000</td>
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</tr>
<tr>
<td>22</td>
<td>0.977 0.362 0.121 0.000 0.887 0.857 0.474 0.540 0.405 0.348 0.055 0.444 0.001</td>
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<tr>
<td>25</td>
<td>0.897 0.446 0.070 0.000 0.904 0.911 0.428 0.636 0.422 0.440 0.019 0.518 0.016</td>
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<td></td>
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</tr>
<tr>
<td>26</td>
<td>0.900 0.429 0.080 0.000 0.898 0.908 0.437 0.625 0.424 0.429 0.022 0.522 0.015</td>
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</table>

Table 4.11: Correlation of tamping force and spread against the materials and flow parameters at different cumulative tamping distances at bed heights 20mm and 25mm (linear determinant $R^2$)

<table>
<thead>
<tr>
<th>Bed Height (mm)</th>
<th>CTD (mm)</th>
<th>PGS (g/cm³)</th>
<th>MFC Ibuprofen</th>
<th>MS</th>
<th>$P_{min}$ (g/cm³)</th>
<th>$P_{max}$ (g/cm³)</th>
<th>CCI (%)</th>
<th>$\theta$ (%)</th>
<th>$\delta$ (%)</th>
<th>Cohesion (g/cm²)</th>
<th>Mobility</th>
<th>FF</th>
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<tr>
<td>Tamping Force</td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>18</td>
<td>0.714 0.122 0.215 0.001 0.646 0.585 0.384 0.300 0.352 0.158 0.087 0.219 0.005</td>
<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>22</td>
<td>0.738 0.282 0.101 0.088 0.860 0.718 0.601 0.466 0.614 0.316 0.053 0.453 0.000</td>
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</tr>
<tr>
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<td>0.813 0.352 0.089 0.070 0.920 0.803 0.611 0.543 0.595 0.368 0.041 0.499 0.001</td>
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<td></td>
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<tr>
<td>30</td>
<td>0.747 0.365 0.055 0.070 0.850 0.761 0.573 0.526 0.533 0.380 0.032 0.517 0.004</td>
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</tr>
<tr>
<td>25</td>
<td>18</td>
<td>0.632 0.078 0.244 0.055 0.599 0.444 0.508 0.190 0.39° 0.102 0.146 0.100 0.038</td>
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<td>0.628 0.358 0.09° 0.156 0.783 0.636 0.509 0.474 0.552 0.351 0.023 0.532 0.006</td>
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<td>26</td>
<td>0.744 0.363 0.064 0.117 0.903 0.780 0.604 0.565 0.645 0.385 0.022 0.490 0.004</td>
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</tr>
<tr>
<td>30</td>
<td>0.792 0.355 0.105 0.090 0.864 0.703 0.688 0.466 0.455 0.299 0.072 0.477 0.000</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

| Spread        |          |             |                |     |                 |                 |        |            |           |                 |          |     |
| 20  | 18       | 0.275 0.506 0.039 0.059 0.473 0.517 0.173 0.577 0.404 0.595 0.119 0.514 0.228 |
| 22  | 0.063 0.162 0.382 0.002 0.002 0.000 0.005 0.064 0.001 0.173 0.328 0.106 0.309 |
| 26  | 0.349 0.154 0.454 0.000 0.179 0.086 0.231 0.000 0.006 0.016 0.461 0.000 0.265 |
| 30  | 0.288 0.021 0.143 0.103 0.266 0.138 0.346 0.044 0.287 0.010 0.173 0.068 0.066 |
| 25  | 18       | 0.456 0.392 0.003 0.084 0.639 0.506 0.508 0.427 0.399 0.371 0.005 0.580 0.025 |
| 22  | 0.042 0.193 0.370 0.014 0.022 0.006 0.035 0.112 0.011 0.178 0.388 0.092 0.343 |
| 26  | 0.002 0.003 0.000 0.004 0.000 0.003 0.014 0.001 0.018 0.000 0.013 0.014 0.005 |
| 30  | 0.275 0.095 0.044 0.117 0.320 0.198 0.331 0.114 0.207 0.085 0.120 0.296 0.004 |
Table 4.12: Correlation of the filling parameters at different cumulative tamping distances at bed height 20mm (linear determinant \( R^2 \))

| CTD (mm) | 0  | 3  | 6  | 10 | 14 | 18 | 22 | 26 | 30 | 18 | 22 | 26 | 30 | 18 | 22 | 26 | 30 |
|----------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| CFV      | 0  | 0.233 | 0.154 | 0.086 | 0.173 | 0.477 | 0.646 | 0.202 | 0.216 | 0.389 | 0.228 | 0.216 | 0.202 | 0.389 | 0.228 | 0.216 | 0.389 |
| Plug density | 0  | 0.956 | 0.961 | 0.967 | 0.967 | 0.967 | 0.967 | 0.967 | 0.967 | 0.967 | 0.967 | 0.967 | 0.967 | 0.967 | 0.967 | 0.967 | 0.967 |
| Tamping force | 0  | 0.810 | 0.733 | 0.794 | 0.794 | 0.794 | 0.794 | 0.794 | 0.794 | 0.794 | 0.794 | 0.794 | 0.794 | 0.794 | 0.794 | 0.794 | 0.794 |
| Tamping spread | 0  | 0.382 | 0.383 | 0.384 | 0.384 | 0.384 | 0.384 | 0.384 | 0.384 | 0.384 | 0.384 | 0.384 | 0.384 | 0.384 | 0.384 | 0.384 | 0.384 |

Table 4.13: Correlation of the filling parameters at different cumulative tamping distances at bed height 25mm (linear determinant \( R^2 \))

| CTD (mm) | 0  | 3  | 6  | 10 | 14 | 18 | 22 | 26 | 30 | 18 | 22 | 26 | 30 | 18 | 22 | 26 | 30 |
|----------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| CFV      | 0  | 0.317 | 0.157 | 0.067 | 0.208 | 0.231 | 0.208 | 0.067 | 0.208 | 0.231 | 0.208 | 0.067 | 0.208 | 0.231 | 0.208 | 0.067 | 0.208 |
| Plug density | 0  | 0.991 | 0.989 | 0.993 | 0.993 | 0.993 | 0.993 | 0.993 | 0.993 | 0.993 | 0.993 | 0.993 | 0.993 | 0.993 | 0.993 | 0.993 | 0.993 |
| Tamping force | 0  | 0.762 | 0.619 | 0.742 | 0.742 | 0.742 | 0.742 | 0.742 | 0.742 | 0.742 | 0.742 | 0.742 | 0.742 | 0.742 | 0.742 | 0.742 | 0.742 |
| Tamping spread | 0  | 0.023 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
Figure 4.134: Fill weight as a function of the pregelatinised starch concentration at cumulative tamping distance 30mm and bed height 20mm

Figure 4.135: Fill weight as a function of the bulk density at cumulative tamping distance 30mm and bed height 20mm

Figure 4.136: Fill weight as a function of the angle of internal flow at cumulative tamping distance 30mm and bed height 20mm

Figure 4.137: Coefficient of fill weight variation as a function of the microfine cellulose concentration at cumulative tamping distance 0mm and bed height 20mm
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Figure 4.138: Coefficient of fill weight variation as a function of the angle of internal flow at cumulative tamping distance 0mm and bed height 20mm

Figure 4.139: Coefficient of fill weight variation as a function of the angle of internal friction at cumulative tamping distance 0mm and bed height 20mm

Figure 4.140: Coefficient of fill weight variation as a function of the mobility at cumulative tamping distance 0mm and bed height 20mm

Figure 4.141: Plug density as a function of the pregelatinised starch concentration at cumulative tamping distance 30mm and bed height 20mm
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Figure 4.142: Plug density as a function of the bulk density at cumulative tamping distance 30mm and bed height 20mm

Figure 4.143: Plug density as a function of the angle of internal flow at cumulative tamping distance 30mm and bed height 20mm

Figure 4.144: Plug density as a function of the mobility at cumulative tamping distance 30mm and bed height 20mm

Figure 4.145: Tamping force as a function of the pregelatinised starch concentration at cumulative tamping distance 30mm and bed height 20mm

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Figure 4.146: Tamping force as a function of the bulk density at cumulative tamping distance 30mm and bed height 20mm

Figure 4.147: Tamping force as a function of the Carr's compressibility index at cumulative tamping distance 30mm and bed height 20mm
4.3 DISINTEGRATION

4.3.1 Disintegration of Formulations

The mean disintegration time was determined for six capsules at each of the compression settings. All capsules disintegrated well within the specified time of 1800 seconds according to BP (2001). The shortest disintegration time was 87 seconds and the longest disintegration time was 229 seconds. Hence, the overall disintegration for all the formulations was relatively low.

To determine whether the compression settings affected the disintegration times of the formulations, single factor analysis was applied using the Microsoft Excel 2000 package. At the 5% significance level, the compression settings significantly affected the disintegrations times for formulations as 5, 7-9, 11, 12, 14, 16, 18 and 19 at bed height 20mm and formulations 5, 6, 8-10, 14 and 18 at bed height 15mm. As there was no clear relationship between the concentration of the materials and those formulations that showed a significant difference at the 5% level between the tamping pin settings at either bed height, the mean value was sought for the formulations at both bed heights. This value was plotted against the concentration of the materials.

Pregelatinised starch

As the pregelatinised starch concentration increased in the excipient, there was an increase in the disintegration time of the capsules. This is because pregelatinised starch swells on contact with water. This characteristic is useful in tabletting as it pushes the powder particles apart and this aids the disintegration process. However, in capsules, the powder plug is not as compact compared to tablets. Therefore, swelling of the pregelatinised starch particles fills the voids in the plug only, which hinders the disintegration process. There was a large increase in the disintegration time when the ibuprofen concentration was low (54%). This is due to the large amount of pregelatinised starch in the formulation. However, at high ibuprofen concentrations (86%), as the pregelatinised starch concentration increased, there was only a slight increase in the disintegration time. This is due to the small amount of excipient available for pregelatinised starch to make a substantial difference. The magnesium stearate concentration did not affect the disintegration process at high ibuprofen concentrations. The trend observed was the same for both bed heights (Figures 4.148 and 4.151).
Figure 4.148: Disintegration time as a function of the pregelatinised starch concentration in the excipient at bed height 20mm

Figure 4.149: Disintegration time as a function of the ibuprofen concentration at bed height 20mm

Figure 4.150: Disintegration time as a function of the magnesium stearate concentration at bed height 20mm
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Figure 4.151: Disintegration time as a function of the pregelatinised starch concentration in the excipient at bed height 25mm

![Graph showing disintegration time as a function of pregelatinised starch concentration.]

Figure 4.152: Disintegration time as a function of the ibuprofen concentration at bed height 25mm

![Graph showing disintegration time as a function of ibuprofen concentration.]

Figure 4.153: Disintegration time as a function of the magnesium stearate concentration at bed height 25mm

![Graph showing disintegration time as a function of magnesium stearate concentration.]

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The trend observed for the disintegration time was very similar to the trend observed for the plug density. This is not surprising, as the density of the powder plug would have a direct effect on the disintegration time making it more difficult for the disintegration medium to penetrate the powder plug.

**Ibuprofen**

As the ibuprofen concentration increased, there was no change in the disintegration time when there was a low pregelatinised starch concentration in the excipient (10% pregelatinised starch and 90% MFC). Hence, the disintegration properties of ibuprofen and MFC are similar. However, when there was a high pregelatinised starch concentration in the excipient, increasing the ibuprofen concentration caused a large decrease in the disintegration time. This is because of the decrease in the excipient, which decreased the total amount of pregelatinised starch in the formulation. Again the magnesium stearate concentration had no effect on the disintegration properties of the formulations. The trends observed as the ibuprofen concentration was increased were the same at both bed heights (Figures 4.149 and 4.152).

**Magnesium Stearate**

The longest disintegration times were associated with a low ibuprofen concentration and a high pregelatinised starch concentration in the excipient due to reasons explained earlier. As the magnesium stearate concentration was increased for this particular formulation, there was a slight increase in the disintegration time. This could be because, at high pregelatinised starch concentrations in the formulation, water penetration is retarded due to the swelling of the excipient and a high magnesium stearate concentration causes hydrophobicity of the particles, which further hinders plug disintegration. However, for the rest of the formulations there was very little change in the disintegration times as the magnesium stearate concentration increased. This indicates that five minutes mixing time was sufficiently short to prevent the particles from becoming hydrophobic (Figures 4.150 and 4.153).
4.3.2 Relationship Between the Disintegration Time and the Flow and Filling Parameters

The linear determinant $R^2$ was determined for the disintegration data with the concentration of the materials and the flow and filling parameters (Tables 4.14 and 4.15). There was a very high correlation between the disintegration times and the pregelatinised starch concentration. The data proves that pregelatinised starch possesses a retarding effect on the disintegration process of the capsules.

On comparison of the flow parameters with the pregelatinised starch concentration both the minimum and maximum bulk density had a strong relationship with the disintegration times. As the minimum and maximum bulk densities increased, there was an increase in the disintegration time. This can be explained by the fact that increased packing of the powder results in denser powder plugs, which slows the disintegration of the capsules. A slight trend was observed between the disintegration times and the angle of internal flow, whereby an increase in the angle of internal flow decreased the disintegration time of the capsules. This result is not surprising as the angle of internal flow is a measure of the interparticulate forces in the powder bulk which results in lower capsule fill weights and lower plug densities.

On comparison of the disintegration data with the filling parameters, many relationships were observed. There was a very high correlation between the capsule fill weight and the disintegration of the capsules. Thus, there was also a strong relationship with the plug density. This is expected as a denser plug makes it more difficult for the water to penetrate the plug to disintegrate it.

The median tamping force was also related to the disintegration time of the capsules. This is because high fill weights resulted in higher tamping forces.
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Table 4.14: Linear determinant $R^2$ for the relationship between the disintegration time and the concentration of the materials and the flow properties

<table>
<thead>
<tr>
<th>Material</th>
<th>Bed height 20mm</th>
<th>Bed height 25mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGS</td>
<td>0.884</td>
<td>0.876</td>
</tr>
<tr>
<td>MFC</td>
<td>0.236</td>
<td>0.228</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>0.184</td>
<td>0.188</td>
</tr>
<tr>
<td>MgSt</td>
<td>0.005</td>
<td>0.001</td>
</tr>
<tr>
<td>$\rho_{min}$ (g/cm$^3$)</td>
<td>0.761</td>
<td>0.768</td>
</tr>
<tr>
<td>$\rho_{max}$ (g/cm$^3$)</td>
<td>0.786</td>
<td>0.779</td>
</tr>
<tr>
<td>CCI(%)</td>
<td>0.337</td>
<td>0.355</td>
</tr>
<tr>
<td>$\theta$ (°)</td>
<td>0.449</td>
<td>0.444</td>
</tr>
<tr>
<td>$\tau$</td>
<td>0.333</td>
<td>0.352</td>
</tr>
<tr>
<td>$\delta$ (°)</td>
<td>0.251</td>
<td>0.246</td>
</tr>
<tr>
<td>Cohesion (g/cm$^3$)</td>
<td>0.059</td>
<td>0.060</td>
</tr>
<tr>
<td>Mobility</td>
<td>0.305</td>
<td>0.292</td>
</tr>
<tr>
<td>FF</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table 4.15: Linear determinant $R^2$ for the relationship between the disintegration time and the filling parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bed height (mm)</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>10</th>
<th>14</th>
<th>18</th>
<th>22</th>
<th>26</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fill weight (mg)</td>
<td>20</td>
<td>0.837</td>
<td>0.867</td>
<td>0.851</td>
<td>0.877</td>
<td>0.884</td>
<td>0.862</td>
<td>0.902</td>
<td>0.900</td>
<td>0.884</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>0.836</td>
<td>0.912</td>
<td>0.897</td>
<td>0.918</td>
<td>0.917</td>
<td>0.909</td>
<td>0.892</td>
<td>0.899</td>
<td>0.889</td>
</tr>
<tr>
<td>CFV (%)</td>
<td>20</td>
<td>0.083</td>
<td>0.137</td>
<td>0.070</td>
<td>0.012</td>
<td>0.179</td>
<td>0.460</td>
<td>0.334</td>
<td>0.081</td>
<td>0.079</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>0.174</td>
<td>0.113</td>
<td>0.122</td>
<td>0.042</td>
<td>0.293</td>
<td>0.410</td>
<td>0.202</td>
<td>0.083</td>
<td>0.102</td>
</tr>
<tr>
<td>Plug density (g/cm$^3$)</td>
<td>20</td>
<td>0.858</td>
<td>0.882</td>
<td>0.870</td>
<td>0.883</td>
<td>0.893</td>
<td>0.848</td>
<td>0.901</td>
<td>0.875</td>
<td>0.850</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>0.848</td>
<td>0.908</td>
<td>0.894</td>
<td>0.918</td>
<td>0.923</td>
<td>0.920</td>
<td>0.896</td>
<td>0.883</td>
<td>0.873</td>
</tr>
<tr>
<td>Tamping force (N)</td>
<td>20</td>
<td>0.787</td>
<td>0.719</td>
<td>0.739</td>
<td>0.644</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>0.607</td>
<td>0.592</td>
<td>0.682</td>
<td>0.648</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chapter 4 - Ibuprofen

4.4 DISSOLUTION

The release characteristics of the formulations were studied by performing dissolution tests. Dissolution testing was carried out for the centre mix (formulation 1), and the main outer factor levels i.e. formulation 2 (0.2% magnesium stearate); formulation 5 (1% magnesium stearate); formulation 6 (50% ibuprofen); formulation 9 (90% ibuprofen); formulation 10 (100% pregelatinised starch in excipient) and formulation 13 (0% pregelatinised starch in excipient and 100% microfine cellulose in the excipient). Six capsules were taken from each formulation from both bed heights 20mm and 25mm to observe the effect of filling at different bed heights at maximum tamping pin setting, CTD 30mm, as this was the optimum tamping pin setting.

The mean dissolution profile for each formulation at bed heights 20mm and 25mm (Figures 4.154 and 4.155) showed that altering the formulations influenced the amount of drug released. However, the release characteristics of ibuprofen were virtually the same at both bed heights. A high pregelatinised starch concentration in the excipient (100%) was again preferable to a high microfine cellulose concentration (100%) as faster drug release profiles were observed. At a high microfine cellulose concentration, ibuprofen release was severely retarded and resulted in the B.P. specification not being met, as 70% of the drug was not released within 45 minutes. Thus, microfine cellulose is not an excipient of choice for ibuprofen as it results in lower fill weights, higher coefficients of fill weight variation and slower release profiles. At low ibuprofen concentrations (50%) fast drug release was observed as opposed to a high ibuprofen concentration (90%). At high ibuprofen concentrations, BP specifications were not met. Therefore as well as filling being problematic, drug dissolution was also affected. Increasing the magnesium stearate concentration from 0.2% to 1% had almost no influence on the release characteristics of ibuprofen. Therefore a high magnesium stearate concentration can be used without drug dissolution being affected, if the mixing conditions employed are optimised.

Analysis of the results was carried out by determination of statistical moments (Podczeck, 1993; Pinto et al., 1997) to characterise and compare the release profiles of different formulations of ibuprofen. These were the mean dissolution time (MDT) of theophylline and variance of the dissolution time (VDT) and an associated parameter, the relative dispersion of the concentration-time profile (RD) and the area under the curve (AUC).
Figure 4.154: Percentage of ibuprofen released for the different formulations as a function of time at CTD 30mm and bed height 20mm

Figure 4.155: Percentage of ibuprofen released for the different formulations as a function of time at CTD 30mm and bed height 25mm
Calculated parameters as a function of the concentration of pregelatinised starch, ibuprofen and magnesium stearate for bed heights 20mm and 25mm are shown in Table 4.16 and 4.17 and Figures 4.156 to 4.163.

Table 4.16: Calculated parameters [area under the curve (AUC), mean dissolution time (MDT), variance of the dissolution time (VDT) and the relative dispersion coefficient (RD)] for ibuprofen at cumulative tamping distance 30mm and bed height 20mm for the different formulations

<table>
<thead>
<tr>
<th>No.</th>
<th>AUC (% min)</th>
<th>MDT (min)</th>
<th>VDT (min²)</th>
<th>RD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1206 ± 154</td>
<td>12.80 ± 1.62</td>
<td>192.6 ± 23.1</td>
<td>1.199 ± 0.211</td>
</tr>
<tr>
<td>2</td>
<td>1043 ± 93</td>
<td>11.12 ± 1.33</td>
<td>151.6 ± 35.1</td>
<td>1.225 ± 0.173</td>
</tr>
<tr>
<td>5</td>
<td>1045 ± 45</td>
<td>10.86 ± 0.39</td>
<td>144.9 ± 13.4</td>
<td>1.178 ± 0.069</td>
</tr>
<tr>
<td>6</td>
<td>626 ± 80</td>
<td>6.34 ± 0.81</td>
<td>56.6 ± 30.3</td>
<td>1.326 ± 0.449</td>
</tr>
<tr>
<td>9</td>
<td>1435 ± 76</td>
<td>18.81 ± 0.60</td>
<td>269.9 ± 10.8</td>
<td>0.765 ± 0.055</td>
</tr>
<tr>
<td>10</td>
<td>1001 ± 132</td>
<td>9.81 ± 1.51</td>
<td>130.9 ± 18.7</td>
<td>1.087 ± 0.149</td>
</tr>
<tr>
<td>13</td>
<td>1423 ± 133</td>
<td>19.94 ± 3.25</td>
<td>275.6 ± 36.1</td>
<td>0.768 ± 0.109</td>
</tr>
</tbody>
</table>

Table 4.17: Calculated parameters [area under the curve (AUC), mean dissolution time (MDT), variance of the dissolution time (VDT) and the relative dispersion coefficient (RD)] for ibuprofen at cumulative tamping distance 30mm and bed height 25mm for the different formulations

<table>
<thead>
<tr>
<th>No.</th>
<th>AUC (% min)</th>
<th>MDT (min)</th>
<th>VDT (min²)</th>
<th>RD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>991 ± 202</td>
<td>10.37 ± 2.22</td>
<td>123.8 ± 46.5</td>
<td>1.063 ± 0.126</td>
</tr>
<tr>
<td>2</td>
<td>1035 ± 120</td>
<td>10.86 ± 1.27</td>
<td>171.1 ± 14.6</td>
<td>1.486 ± 0.303</td>
</tr>
<tr>
<td>5</td>
<td>966 ± 59</td>
<td>9.90 ± 0.72</td>
<td>129.1 ± 44.0</td>
<td>1.177 ± 0.206</td>
</tr>
<tr>
<td>6</td>
<td>557 ± 71</td>
<td>5.55 ± 0.72</td>
<td>32.80 ± 12.4</td>
<td>0.907 ± 0.250</td>
</tr>
<tr>
<td>9</td>
<td>1340 ± 90</td>
<td>18.16 ± 1.13</td>
<td>268.9 ± 19.4</td>
<td>0.814 ± 0.048</td>
</tr>
<tr>
<td>10</td>
<td>976 ± 150</td>
<td>10.96 ± 1.16</td>
<td>138.9 ± 25.0</td>
<td>1.087 ± 0.087</td>
</tr>
<tr>
<td>13</td>
<td>1437 ± 150</td>
<td>19.55 ± 2.06</td>
<td>280.2 ± 30.5</td>
<td>0.724 ± 0.118</td>
</tr>
</tbody>
</table>

Employing these parameters, it was possible to relate the release of ibuprofen to the dissolution mechanisms. At bed height 20mm, the MDT and the AUC increased as the pregelatinised starch concentration increased. This is due to the swelling properties of pregelatinised starch, which hinders drug release. However, at the increased bed height of 25mm, the increase in the dissolution time only occurred at a PGS concentration greater than 50% in the excipient. This could be because at the higher bed height, the plug density is higher compared to the lower bed height and therefore up to 50% PGS in the excipient can be used without posing a problem for drug dissolution. There was a large increase in the AUC and MDT as the ibuprofen concentration increased. Thus, when filling high dose drugs, the dissolution time may be prolonged and therefore very high concentrations should not be used. As the magnesium stearate concentration increased, the AUC and MDT were highest at 0.6% magnesium stearate concentration at bed height 20mm. This is difficult to explain, as the magnesium stearate concentration had almost no effect on the plug density. However, at the higher bed height, as expected there was no change in the AUC and MDT as the magnesium stearate concentration increased.
Figure 4.156: Area under the curve as a function of the pregelatinised starch, ibuprofen and magnesium stearate concentration at bed height 20mm

Figure 4.157: Mean dissolution time as a function of the pregelatinised starch, ibuprofen and magnesium stearate concentration at bed height 20mm

Figure 4.158: Variance of the dissolution time as a function of the pregelatinised starch, ibuprofen and magnesium stearate concentration at bed height 20mm

Figure 4.159: Relative dispersion coefficient as a function of the pregelatinised starch, ibuprofen and magnesium stearate concentration at bed height 20mm

Note: Pregelatinised starch concentration (low, 0% in excipient; medium, 50% in excipient; high, 100% in excipient); ibuprofen concentration (low, 50%; medium, 70%; high, 90%); Magnesium stearate concentration (low, 0.2%; medium, 0.6%; high, 1%)
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Figure 4.160: Area under the curve as a function of the pregelatinised starch, ibuprofen and magnesium stearate concentration at bed height 25mm

Figure 4.161: Mean dissolution time as a function of the pregelatinised starch, ibuprofen and magnesium stearate concentration at bed height 25mm

Figure 4.162: Variance of the dissolution time as a function of the pregelatinised starch, ibuprofen and magnesium stearate concentration at bed height 25mm

Figure 4.163: Relative dispersion coefficient as a function of the pregelatinised starch, ibuprofen and magnesium stearate concentration at bed height 25mm

Note: Pregelatinised starch concentration (low, 0% in excipient; medium, 50% in excipient; high, 100% in excipient); Ibuprofen concentration (low, 50%; medium, 70%; high, 90%); Magnesium stearate concentration (low, 0.2%; medium, 0.6%; high, 1%)
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The variance of the dissolution times increased as the ibuprofen concentration increased and the PGS concentration increased in the excipient. This can be attributed to the increase in the AUC and MDT. An increase in the magnesium stearate concentration also resulted in a similar change in the value of VDT, AUC and MDT. Hence the variance of the dissolution time is directly related to the change in the values of AUC and MDT.

The values obtained for the relative dispersion coefficient were calculated and varied for the different formulations. The values achieved did not perfectly fit those for any of the traditional dissolution models and thus the closest release rate mechanism was chosen [RD = 1.0, first order release (class 1); RD = 0.8, pseudo first order release (class 2); RD = 0.6, cube root release (class 3); RD = 0.3, zero order release (class 0)] (Pinto et al., 1997). However, the data shows as the concentration of the components formulation increased, a change in the release mechanism was observed.

The centre mix had a RD of 1.199 and 1.063 at bed heights 20mm and 25mm respectively indicating first order release. As the PGS concentration increased from 0% to 100% in the excipient, the release mechanism changed from first order release to pseudo first order release. The increase in the ibuprofen concentration from 50% to 90% also resulted in a change from first order release to pseudo first order release. The magnesium stearate concentration had no effect on the release mechanism and remained first order release.
CHAPTER 5

CONCLUSIONS

&

FUTURE WORK
5.1 Conclusions

- Relationships were observed between powder flow parameters for both the theophylline and ibuprofen study:
  - Low values for the minimum and maximum bulk density resulted in high values for the angle of internal flow caused by increased interparticulate forces.
  - Low values for Carr's compressibility index were associated with low T-values as a result of good flow and packing.

- Further relationships were found in the ibuprofen study:
  - An increase in the minimum bulk density resulted in a decrease in Carr's compressibility index and the T-value.
  - High minimum and maximum bulk densities resulted in increased mobility between the particles.
  - The angle of internal flow and the angle of internal friction were very closely related and both these parameters were related to the mobility index.

- Hence, bulk property tests used in this study such as the minimum and maximum tapped density, Carr's compressibility index, angle of internal flow and the compaction constant T were valuable parameters to give an indication of powder flow. These tests can give information about particle flow, particle packing and an indirect measure of interparticulate forces and thus the mobility of the particles.

- Shear property tests are less useful as information gained is similar to that of bulk property tests i.e. angle of internal friction provides similar information to the angle of internal flow; the mobility index and the maximum bulk density are very closely related. However, the cohesion coefficient does provide different measure of a different powder flow characteristic. The Jenike's flow factor was found to be slightly misleading and contradicted other flow parameters.

- Capsule filling investigations demonstrated that optimum machine parameters were at high compression settings and high bed heights, as these resulted in high capsule fill weights and low coefficients of fill weight variation. Therefore, a preliminary study should be carried out to obtain optimum machine settings.
Chapter 5 - Conclusions and Future Work

- Poor flowing materials such as theophylline and ibuprofen fill better i.e. produce higher fill weights and lower coefficients of fill weight variation at high compression settings. However, for good flowing materials such as pregelatinised starch, the influence of increased tamping pin settings is not so obvious.

- Powder plug lengths and plug density provide valuable information about the packing characteristics of the powder formulation. For example, the role of magnesium stearate was identified as not to increase the capsule fill weight of the material, but in fact to improve packing of the material.

- Tamping forces should be measured at tamping stations 3 and 4, as good flowing powders are mainly packed by station 3 resulting in higher tamping forces at tamping station 3 compared to tamping station 4. Therefore, the magnitude of the forces measured at tamping station 4 is a reflection of powder flow properties.

- For ibuprofen, higher capsule fill weights observed at bed height 25mm compared to bed height 20mm resulted in greater tamping forces at station 3. An improvement in powder flow properties resulted in a decrease in the tamping force spread at both bed heights.

- Formulations filled such that the powder plug density is greater than the maximum bulk density did not pose problems during disintegration or dissolution when using ibuprofen and pregelatinised starch and microfine cellulose as excipients.

- The study has shown that poor flowing powders such as theophylline and ibuprofen can be satisfactorily be filled on a tamp filling machine at high compression settings, resulting in high capsule fill weights and low coefficients of fill weight variation.

- Low melting point drugs such as ibuprofen may be filled on a tamp filling machine, as long as the correct excipients are chosen.

- From the excipients tested, pregelatinised starch was an effective excipient to result in good powder flow demonstrated by low values of Carr's compressibility index and low T-values. High pregelatinised starch concentrations also resulted in low coefficients of fill weight variation, however, problems were incurred.
during capsule disintegration where the material was more a hindrance compared to theophylline, which is a hydrophobic drug.

- Lactose (average particle size 47μm) possessed improved packing properties compared to pregelatinised starch indicated by lower values for the angle of internal flow and resulted in higher capsule fill weights. However, the flow properties of lactose resulted in a highly angled powder bed causing an increase in the coefficient of fill weight variation.

- Microfine cellulose (average particle size 41μm) was not an effective excipient, as it resulted in poor powder flow, however, it was preferable in comparison to pregelatinised starch to reduce the cohesion coefficient. Therefore, for sticky materials, such as ibuprofen, a small quantity of microfine cellulose may be favoured. Mixtures containing a large quantity of microfine cellulose in the excipient performed poorly during capsule filling and resulted in lower capsule fill weights and high coefficients of fill weight variation in comparison to pregelatinised starch.

- The optimum lubricant concentration varied for good powder flow and optimum machine performance. High magnesium stearate concentrations were important for good powder flow. However, the magnesium stearate concentration was less important to achieve high capsule fill weights and low coefficients of fill weight variation. The magnesium stearate concentration had no effect of the capsule disintegration time, indicating high magnesium stearate concentrations may be used as long as the powder blend is not overmixed.
5.2 FUTURE WORK

- Further tests could be carried out to investigate the powder flow characteristics described by Jenike’s flow factor and this parameter could be compared with bulk property tests.

- The formulations could be filled using different capsule sizes to identify the limits of the formulations in terms of powder flow.

- These formulations could be filled using a dosator capsule filling machine to evaluate how these filling methods compare and whether one method is better than the other to fill a range of formulations with different powder flow characteristics.

- Alternative diluents and lubricants could be tested to identify a ranking of materials.

- Alternative drugs with poor powder flow and/or low melting points could be tested to confirm that these findings are universally applicable.
REFERENCES
References


References


Bosch manual. Robert Bosch GmbH. Waiblingen, Germany, pp.5-8


299


References


302


References


References


307


References


References


Appendix 1: Lactose calibration line

Rotation
0.0 0.5 1.0 1.5 2.0 2.5

Concentration (mg/ml)
0 5 10 15 20 25

R^2 = 0.99987

- Lactose
- Regression line for lactose
Appendix 2: Theophylline calibration line

R² = 0.99998
Appendix 3: Ibuprofen calibration line

Concentration (µg/ml)

Absorbance

R² = 0.99973

Ibuprofen
Regression line for ibuprofen