THE EXTRUSION OF VARIOUS FORMULATIONS
OF MICROCRYSTALLINE CELLULOSES

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A B S T R A C T

The process of extrusion is fundamental to many of the dosage forms produced by modern pharmaceutical industry. Often, the excipient of first choice in pharmaceutical extrusion is microcrystalline cellulose. The work described indicates that the extrusion behaviour of formulations based on microcrystalline cellulose can be studied and compared effectively using various techniques to assess the relationship between force and displacement during ram extrusion through a single-holed die.

The results show that the grade of microcrystalline cellulose upon which a formulation is based affects its extrusion in terms of the rheological parameters measured and the quality of the extrudate produced. The differences appear to be due to physical differences in the powders themselves (e.g., particle size) and to physico-chemical differences in the interaction of the microcrystalline cellulose with the continuous phase.

The work demonstrates that microcrystalline cellulose formulations are able to respond to shear rate by the formation of a lubricating layer at the die wall, which facilitates stable flow and yields a product with a smoother surface. There is an optimum quantity of water required to lubricate flow.

The origin of imperfections in the flow of these systems is identified. Declining or uneven Steady State Flow Stages are indicative of barrel wall interaction and unstable flow respectively. Pressure overshoot is indicative of difficulty in overcoming capillary resistance at the yield stage, but is not necessarily related to ease of flow after yield has occurred. Forced Flow is shown to arise at the entrance to the die, whereas extrudate surface impairment is seen to originate downstream of the die-entry region.
This Thesis is Dedicated in Loving Memory of My Mother.
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NOTATION

A  Cross-sectional area of the die
A₀  Cross-sectional area of the barrel
A'  Constant
α  Die entry yield stress velocity factor
β  Die land velocity factor
β*  Modified power law constant
c  Constant
D  Diameter of the die
D₀  Diameter of the barrel
(D₀/D)  Reduction ratio
D'  Apparent shear rate
E  Exponential. Used to denote exponentials on plots
    where no facility for superscript is available e.g.
    "mE2" means "m²" and "10E3" means "10³"
Fₐ  Applied force
Fᵥ  Retardive force
φ  Angle of convergence
K  Power law viscosity constant
L  Length
m  Average particle size
M  Water content of a formulation expressed as % dry weight
n  Coefficient of viscosity
n*  Non-Newtonian viscosity coefficient
\( n_b \)  
Bagley entrance correction

\( n' \)  
Degree of non-Newtonian flow

\( r \)  
Radial distance

\( R \)  
Radius

\( \Delta P \)  
Pressure difference between two ends of a cylinder

\( P_e \)  
Exit pressure correction

\( P_0 \)  
Upstream pressure loss

\( P_0(\text{vel}_0) \)  
Upstream pressure loss at zero extrudate velocity

\( P_0(\text{vel}_V) \)  
Upstream pressure loss at extrudate velocity = \( V \)

\( P_T \)  
Total pressure drop on extrusion

\( P_T(\text{vel}_0) \)  
Total extrusion pressure at zero extrudate velocity

\( P_T(\text{vel}_V) \)  
Total extrusion pressure at extrudate velocity = \( V \)

\( q \)  
Constant

\( Q \)  
Volumetric flow rate

\( \sigma_y \)  
Material yield value

\( \sigma_{yo} \)  
Initial die entry yield stress

\( S \)  
Piston speed

\( t \)  
Shear stress

\( t_o \)  
Initial die wall shear stress

\( t_w \)  
Die wall shear stress

\( t_y \)  
Yield stress

\( U \)  
Plastic viscosity

\( v \)  
Velocity

\((-dv/dr)\)  
Shear rate

\((-dv/dr)_w\)  
Die wall shear rate

\( V \)  
Extrudate velocity

\( x \)  
Thickness of the die wall lubricating layer
PART ONE

INTRODUCTION AND THEORY
CHAPTER ONE

INTRODUCTION
The oral route is preferred for the administration of controlled release dosage forms because of the flexibility it allows in terms of dosage form design and administration. Solid dosage forms such as tablets and capsules predominate among oral controlled release products because of the inherent difficulty in the formulation of a controlled release liquid preparation. Oral controlled release dosage forms deliver their drug to the gastro-intestinal tract at a rate which is controlled by the dosage form design and not by the physiological processes of the alimentary canal (Sjogren, 1985). They may be designed to give positional release, intended to deliver the drug to a target area of the alimentary canal irrespective of transit time (e.g. the use of enteric coating to deliver drug to the small intestine), or to give temporal release, delivering drug either continuously over a certain period of time ("sustained", "extended", "slow", "retarded" release) or after a lag time ("delayed" release).

The controlled release of drugs offers several advantages. Therapeutically, controlled release products provide a more uniform blood concentration/response, they minimise the occurrence of unwanted adverse effects and result in improved patient compliance. Economically, they provide a less expensive daily treatment, improved drug utilisation, improved therapy and a decreased cost in nursing time (de Haan and Lerk, 1984).

Oral solid controlled release dosage forms may consist of a single unit (e.g. a tablet) or of several units (the so-called "multiple unit dosage form" or MUDF, e.g. a hard gelatin capsule containing many coated beads). The various categories of solid oral controlled release products are listed in Table 1.1.
### Table 1.1 Solid Oral Controlled Release Technologies

#### Single Unit Dosage Forms
- Reduced drug solubility (salts, complexes)
- Ion exchange resin complexes
- Slowly eroding matrix tablets
- Porous inert matrix tablets
- Strongly swelling hydrophilic gel tablets/capsules
- Tablets coated with diffusion controlling membranes

#### Multiple Unit Dosage Forms
- Tablets or capsules containing:
  - Coated granules disintegrating at a controlled rate
  - Granules coated with diffusion controlling membranes

Several advantages have been claimed for multiple unit dosage forms over single unit dosage products (Eskilson, 1985):

1. They exhibit highly reproducible transport through the gastro-intestinal tract
2. They are well-distributed over a large surface area of the gastro-intestinal tract, thereby minimizing the risks of local damage to the intestinal mucosa
3. They have a pattern of gradual gastric emptying which assists the attainment of controlled release
4. They give high accuracy in reproducibility dose to dose.
In addition, the MUDF products provide many other advantages:

(i) they are versatile in terms of dosing (a capsule containing many discrete granules, for example, may be opened to allow the dose of granules administered to be matched exactly with the patient's requirements), (ii) granules containing active drug may be mixed with one another to allow the production of combination products, or with placebo granules to allow the production of several dosage levels from a single-granule formulation, (iii) the use of granules minimises the dust hazard in the production area, (iv) the ease of flow and uniformity of spherical granules gives excellent control of fill-weight into capsules between narrow limits, (v) the low surface area to volume ratio of spherical granules facilitates the slowing of the drug dissolution rate.

Granules for use in multiple dosage forms should have good stability and provide the required drug loading. In addition, they should be able to withstand mechanical attrition during further processing and should allow the application of a smooth and integral coating for a uniform and reproducible rate of drug release. With these requirements in mind, the granules should (Eskilson, 1985; Jalal et al., 1972):

(i) be of sufficient mechanical strength and density, without brittleness
(ii) be of suitable size and shape and have a narrow size distribution
(iii) be compact and smooth-surfaced
(iv) have good flow properties

The most advantageous shape for a controlled release granule, in respect of the above criteria, is the sphere.
1.2 THE MANUFACTURE OF SPHERICAL GRANULES

Spherical granules for controlled release preparations have been manufactured by various techniques.

1.2.1 Pan/Drum/Plate Granulation

In this process, powders or seed particles, tumbling in a drum or pan or on a plate, are agglomerated by the addition of a granulating liquid. The growth of the granules is controlled by certain critical factors, such as the liquid phase separation, the particle size and size distribution of the powders, the degree of agitation and the use of binding agents such as polyvinylpyrrolidone.

This technique is capable of achieving a high drug loading of up to 50%. However, it often results in poor homogeneity in terms of granule size, shape and surface properties, and it requires considerable operator skills to control the variables.

1.2.2 Fluid Bed Granulation

This method involves the spraying of a solution or suspension of drug onto non-pareil seeds which are fluidized by means of a heated air current. A coat of drug of up to 50% loading can be built up around the seed in this way, but careful control of the process variables is required. The input air temperature must be controlled to avoid spray drying of the drug solution/suspension, the spray rate must not be such that the seeds become over-wet, and the design and position of the spray gun, and the atomizing pressure used to operate it, must be such that an even spray pattern and narrow droplet size distribution is achieved.
1.2.3 Rotary Granulation

In rotary granulation, powdered drug and binder solution are fed separately onto seed material which is fluidized around the periphery of a rotating plate inside a modified fluid bed dryer. The pellets so produced are dried by a warm air current from below the rotor, and then sprayed with a coating solution. This method has the advantage that only pellets of a certain size come off the rotating plate, resulting in a product with a narrower size distribution. However, the spray rate, the plate rotation speed and particularly the rate of addition of powder must be controlled with respect to the pellet yield, density, size, shape and quality (Gajdos, 1984).

1.2.4 Extrusion and Spheronization

The processes of extrusion and spheronization for the production of spherical granules have been described by Reynolds (1970) and by Conine and Hadley (1970). Extrusion involves the forcing of a wet powder mass, typically containing drug plus excipients with water as the granulation fluid, through small cylindrical holes (dies), usually of 0.5 to 2.0 mm in diameter. The resulting cylindrical strands of extrudate are then fed onto a spheronizer - a horizontally-rotating serrated plate at the base of a stationary smooth-walled drum - where they break into short lengths and gradually round off to form spheroids (Conine and Hadley, 1970). The spheroids are dried by direct fluid bed drying to avoid agglomeration; this drying process also has the advantage of yielding a product with a greater bulk density than those produced by air or oven drying (Conine and Hadley, 1970). The stages of production from powder to spheres are illustrated in figure 1.1.
Figure 1.1 The Stages of Production from Powder to Spheres by Extrusion and Spheronization (per Eskilson, 1975)

Powder(s)

Wet Mixing

Granulation Liquid Extrusion

Spheronization

Drying
The main advantages of this technique are that (Conine and Hadley, 1970; Chapman, 1985; Rowe, 1985):

(i) it allows very high drug loading of up to 90%.
(ii) provided that careful control is made of the process variables (such as formulation, plate speed and geometry, batch load and residence time) spheronization can be completed in five to ten minutes.
(iii) the granules produced are very nearly spherical ("spheroidal").
(iv) the spheroids can be produced within a narrow size distribution.
(v) the spheroids have uniform density and surface characteristics.
(vi) the spheroids have very low friability when dry.

Extrusion/spheronization has recently gained wider use in the pharmaceutical industry for the production of spherical granules, and will now be considered in more detail.

1.3 COMMERCIAL EXTRUSION AND SPHERONIZATION

1.3.1 Commercial Extrusion

Extrusion has a great many industrial applications, from traditional brick and tile manufacture to the modern extrusion of ceramic engine components and metals, the manufacture of foodstuffs and, more recently, the manufacture of pharmaceuticals by extrusion/spheronization (Benbow and Bridgwater, 1987(i)).

Extrusion may be defined as the forcing of a material from a large reservoir through a small hole (or "die"). Different materials have different extrusion requirements. For example, metals and polymers are often extruded at elevated temperatures to facilitate flow,
whereas high temperatures are not required for the extrusion of many food and/or pharmaceutical systems, which are usually easily deformable. (Indeed, the generation of high temperatures in the extrusion of these systems is undesirable, since it could cause decomposition.) Other extrusion parameters which may also be varied according to the requirements of the system include die shape, die dimensions and velocity of throughput of material.

Design of dies for extrusion may be simple or relatively complex, so that it is possible to produce extrudate with a cross-sectional shape specific to the requirements of the system being produced. A good example of this is the manufacture of "honeycomb"-shaped catalyst support structures by extrusion through matrix dies, (Benbow, 1984), thereby enabling the product to meet the requirement that catalyst systems should have a relatively high reactive surface area. In the pharmaceutical industry, the ability of the extrusion process to confer a specific shape on a system is used as a preforming technique to produce a cylindrical extrudate which is then processed further by spheronization to produce spherical granules. Commercial extruders for pharmaceuticals are similar in most respects to those used for other systems. They are capable of providing uniform pressure to a sufficiently large or continuous quantity of material so that extrudate is produced in more or less continuous lengths. This high output of extrudate is advantageous since it means that the spheronizer plate may be loaded with the required quantity of extrudate in the minimum time. There are various types of commercial extruder in current use, mostly using either screw-feed or gravity-feed mechanisms to transport the material to the die vicinity.
1.3.1(1) Screw-feed Extruders

Screw-feed extruders consist of one or more helical screws rotating inside a cylinder. The material is fed via a gravity-feed hopper into a channel between the flights of the screws, which then shear the material and force it into contact with the extruder wall. This action results in a pressure build up (Lovegrove and Williams, 1973) which is sufficient to cause extrusion either radially, through a die screen arranged cylindrically around the screw (figure 1.2) or axially, through an end-plate die (figure 1.3).

The use of a radial die screen requires alteration to be made in the design of the helical screw in the vicinity of the screen in order to ensure a constant pressure and flow rate. However, for extrusion of pharmaceuticals and other thermolabile or aqueous systems, the use of a radial die screen does confer several advantages over the end-plate arrangement. Firstly, a higher volumetric throughput is obtained because a radial screen usually has more holes in it than an end-plate die. More importantly, the use of a radial screen results in a lower temperature build up on extrusion because the frictional effects between the material and the cylinder wall are reduced for a given length of screw (Reynolds, 1970). In addition to the choice of a radial screen, frictional effects can be reduced by the use of a shortened helical screw, with deeper and wider helical channels. Of course, reduction of frictional effects also results in a decrease in the pressure build up required for extrusion. A means of reducing frictional effects (and thus extrusion temperature) while still maintaining extrusion pressure is to jacket the barrel, but this measure alone is not always sufficient. When the screw extruder design cannot be adequately modified to prevent an unacceptable
Figure 1.2 Radial Screw—Feed Extrusion

Figure 1.3 Axial Screw—Feed Extrusion
temperature rise, then the use of a gravity-feed extruder is preferable, since the build up of extrusion pressure will not be associated with frictional effects.

1.3.1(ii) Gravity-feed extruders

Gravity-feed extruders are generally of the "cylinder" or "gear" type.

Cylinder extruders (figure 1.4) consist of two contra-rotating cylinders, one of which is knurled and the other drilled along its length with equally spaced dies of identical diameter. Extrudate is produced when material is fed from a gravity-feed hopper into the nip between the cylinders, where the knurled cylinder forces the material through the dies of the drilled cylinder. The extrudate is collected from the inside of the drilled cylinder; its length can be controlled by means of a blade attachment.

Gear extruders (figure 1.5) operate on much the same basis as cylinder-type extruders. They consist of two contra-rotating gears such that extrudate is produced when the gear-teeth force the material through the dies positioned in the opposing roots. Output can be higher than that from cylinder extrusion, since extrudate is produced from inside both gears.

In both cylinder- and gear-type extrusion, the pressure build up and consequent volumetric output is determined by the length, diameter and separation of the drilled dies, the gap between the cylinders or between tooth and root of opposing gears, and the rotation rate. The disadvantages of gravity-feed systems are the possibility of improper feeding of material due to bridging and of material loss from the open system.
Figure 1.4 Cylinder-type Gravity-Feed Extrusion

Figure 1.5 Gear-type Gravity-Feed Extrusion
1.3.1(iii) Batch Extruders

Various types of pre-filled extrusion system are available (Fisher, 1976). In each case the material is first packed into a barrel to which a die has been attached, and then extruded through the die under applied pressure. The simplest type of pre-filled extruder is the ram extruder of Ovensten and Benbow (1968) (figure 1.6). This type of batch processing is generally not appropriate for commercial use, but remains a useful alternative for unstable materials which are sensitive to frictional forces, such as cellulose acetate (Adamson, 1955).

1.3.2 Commercial Spheronization

Spheronization is a technique originally invented in Japan in 1964 by Nakahara, and the design of the equipment has altered little since then (figure 1.7). It consists of a stationary smooth-walled vertical cylinder of diameter 20 to 100 cm. Within the base of this cylinder rotates a grooved plate with its periphery 0.25 mm from the internal surface of the cylinder. The plate rotation speed may be varied from 400 to 1600 rpm, and the plate grooves may be of the "cross-hatched" or "radial" type (see figures 1.8 and 1.9). The vertical cylinder is fitted with a door to allow the discharge of the spheroids.

Extrudate is fed onto the rotating spheronizer plate, where centrifugal forces dispose it against the walls of the cylinder in an annular or "doughnut-like" shape with a quadrant cross-section (figure 1.10 (i) (ii) (iii)). This doughnut-shaped mass has a torroidal (or "twisting rope") motion, because the residual momentum of the pellets causes them to move up the walls of the stationary cylinder, and they then fall over or within the mass of pellets as their momentum is dissipated (Reynolds, 1970).
Figure 1.6 The Ram Extruder

Figure 1.7 The Sphonizer

Figure 1.8 The Cross-Hatched Plate

Figure 1.9 The Radial Plate
The extrudate is initially broken down by this motion into short cylinders of approximately equal length. The frictional forces of the grooved plate and the interparticulate friction of the moving pellets result in the gradual densification and spheronization of these short lengths of extrudate in stages identified by Chapman (1985). Figure 1.11 shows the graph used by Chapman to represent the change in shape of the extrudate, as measured by the one plane critical stability (OPCS) (the lower this value the more spherical the product) with respect to residence time in the spheronizer. In addition to residence time, he found that spheronization was also affected by:

(i) the plate rotation speed, which should be high enough to result in densification but not so high that densification goes out of control and leads to agglomeration — the optimum speed was found to be dependent on the formulation, the load, the groove geometry and, of course, the plate diameter.

(ii) the groove geometry — the radially cut plate was found to be slightly more efficient in terms of the rate of densification and spheronization. (The cross-hatched plate has the advantage, however, that it is easier to manufacture and to clean.)

1.4 FORMULATING FOR EXTRUSION AND SPHERONIZATION

The basic technique for formulation in extrusion/spheronization is similar to that used in wet granulation. The drug and excipients are dry-blended in a conventional planetary mixer, and then the granulating fluid (which is usually water but may be a water-alcohol mixture or a binder solution) is added for a further period of mixing. Formulation is one of the main controlling factors in successful extrusion/spheronization; the liquid content and its distribution are highly critical to the success of the processes, with wet mixes
Figure 1.10 The Movement of Extrudate on the Spheronizer Plate

(i) Cross-Section of the Spheroniser  
(ii) Movement of Individual Granule on the Plate  
(iii) Torroidal Movement of the Granule Mass

(per Chapman, 1985)

Figure 1.11 The Change in Extrudate Shape on Spheronization:
(as shown by the One Plane Critical Stability with respect to residence time on the spheronizer plate. After Chapman, 1985)

<table>
<thead>
<tr>
<th>SHAPE</th>
<th>OPCS (Degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cylinders</td>
<td>70</td>
</tr>
<tr>
<td>Cylinders with Rounded Ends</td>
<td></td>
</tr>
<tr>
<td>Dumb-bells</td>
<td></td>
</tr>
<tr>
<td>Ellipsoids</td>
<td></td>
</tr>
<tr>
<td>Spheroids</td>
<td></td>
</tr>
</tbody>
</table>

Residence Time (Minutes)
generally requiring a much higher moisture content (about 35%) than conventional wet granulations for tableting. The aim is to produce as dense a material as possible for extrusion. Under-wetted material is found to feed poorly into the extruder and results in excessive pressure build up and friction on extrusion. It also results in the production of large quantities of fines in the spheronizer, and spheronization is often incomplete (Fielden, 1987). Material which is over-wet, on the other hand, results in extrudate which is sticky and so tends to adhere to itself on collection and to agglomerate on spheronization.

Unfortunately, the formulae with good extrusion characteristics do not necessarily produce the best spheroids. The desirable characteristics required for extrusion and for spheronization and the excipients which meet those requirements are outlined below:

1.4.1 Formulating for Extrusion
For successful extrusion, the wet mass must not adhere to the extruder screws nor screens yet it must constitute a cohesive plastic mass that can provide adequate lubrication during the extrusion from the feed chamber through the dies. The mass must remain homogenous throughout the extrusion process and thermal and/or pressure changes must be minimised by the inclusion of an easily-extrudable excipient.

It has been shown (Rumpf, 1958) that several factors influence the intraparticulate cohesion during granulation. These include powder particle size, the wetting and solution properties of the powders, and the surface tension and viscosity of the liquid component. Most formulations require binders, which may be either adhesive in nature (e.g. cellulose gums, natural gums, gelatin, synthetic polymers) or
capillary binders whose inert attraction of the liquid phase imparts strong cohesive properties to the granule (e.g. kaolin, bentonite, talc, microcrystalline cellulose) (Reynolds, 1970).

1.4.2 Formulating for Spheronization

For successful spheronization, the wet extrudate must possess a certain inherent strength: it must be brittle enough to enable it to be broken down into short lengths on spheronization, but not so brittle that it disintegrates completely. The extrudate must be plastic enough to be rolled into spheres by the action of the spheronizer plate, and yet not be so adhesive to itself that it agglomerates.

Excess extrudate friability can be avoided by using a higher proportion of liquid or binder in the mix, or by adding a liquid or finely powdered binding agent during spheronization (Reynolds, 1970). The use of a higher proportion of liquid in the mix can also be used to confer a greater plasticity to the extrudate, so that it is able to round off into spheroids. Adhesion between pellets during spheronization can usually be overcome by reducing the liquid content of the mix or by adding a proportion of the finely divided powdered formula during spheronization, to absorb onto the sticky surfaces and prevent agglomeration.

1.4.3 Excipients for Use in Extrusion and Spheronization

Miyake et al. (1973) reported that microcrystalline cellulose exhibited the required elasticity for extrusion and spheronization, whereas corn starch and lactose could not be extruded when mixed with various quantities of water. Other workers have also indicated that microcrystalline cellulose is an essential ingredient in the
production of wet powder masses for extrusion and spheronization (Reynolds, 1970; Conine and Hadley, 1970; Harrison, 1982; Rowe, 1985) and that the amount of water added to the formulation must also be strictly controlled (Miyake et al., 1973; Malinowski and Smith, 1975).

The precise nature of microcrystalline cellulose which is responsible for its suitability for the extrusion and spheronization processes is still unclear, although Harrison et al. (1987) suggested that the very narrow range of suitable materials indicates that there is a specific rheological requirement for the process.

Some insight into the essential properties of microcrystalline cellulose can be gained by briefly reviewing the literature concerning its use. The studies of microcrystalline cellulose in the tableting process, in particular those of Coffin-Beach et al. (1983), who used a calorimetric technique to show the superior compression bonding characteristics of microcrystalline cellulose, appear to indicate that compaction during extrusion is likely to involve the formation of hydrogen bonds between the microcrystalline cellulose crystals and water. Additionally, Harrison (1982) found that the amount of water added in granulation affected the extrusion performance of microcrystalline cellulose mixtures. Using lactose as a model drug, he found that the most suitable formulation for extrusion was a mixture of microcrystalline cellulose, lactose and water in the ratio 5:5:6. The conclusion that an optimum water content is required for successful extrusion, and that microcrystalline cellulose interacts with the water in a way which facilitates extrusion, has been drawn by several workers (Harrison, 1982; Chapman, 1985; Fielden, 1987). By the use of thermal analysis techniques and of pressure membrane apparatus for the study of the flow of liquids through powder beds,
Fielden (1987) showed that almost 70 ml of water per 100 g microcrystalline cellulose is held in hydraulic isolation (Morrow, 1970) and that a further 15 ml per 100 g is held at absorption sites and as free water. The majority (70 to 80%) of the non-hydraulically isolated water was found by Fielden (1987) to be in its "free" state, and it was concluded that microcrystalline cellulose is able to trap and retain a large volume of liquid within its structure as a kind of "molecular sponge". It may be that this ability of microcrystalline cellulose to retain large quantities of water is the property responsible for its inherent "extrudability".

1.4.4 Microcrystalline Cellulose Available Commercially

Microcrystalline cellulose is produced by various manufacturers, and in two basic types.

Firstly, there are the so-called "powdered" grades of microcrystalline cellulose, of which the best-established manufacturer is the FMC Corporation (Philadelphia PA 19103). FMC first introduced microcrystalline cellulose in 1960 after a serendipitous discovery during basic research on alpha-cellulose. The first commercial quantities were produced by FMC in 1962, and in recent years two other producers of powdered microcrystalline cellulose have emerged into the market, namely Unitika Rayon Ltd. (Osaka, Japan) and Finnsugar Group (Helsinki, Finland).

Secondly, there are the so-called "colloidal" grades of microcrystalline cellulose, which consist of microcrystalline cellulose and sodium carboxymethylcellulose in a co-formulation, of which the only producer is FMC Corporation.
1.4.4 (i) "Powdered" Microcrystalline Cellulose Grades

Powdered grades of microcrystalline cellulose are 100% microcrystalline cellulose supplied as a spray-dried powder. They are available as various grades with specific particle sizes and moisture contents.

The starting material for powdered microcrystalline cellulose is alpha-cellulose (figure 1.12), which is derived from fibrous plants. Alpha-cellulose is composed of millions of "micro-fibrils" and each microfibril is composed of two regions: the paracrystalline region, which is an amorphous and flexible mass of cellulose chains, and the crystalline region, which is composed of tight bundles of cellulose chains arranged linearly (figure 1.13). The production of microcrystalline cellulose is undertaken in three stages (figure 1.13). Firstly, the alpha-cellulose undergoes hydrolytic depolymerization with dilute mineral acid. This selectively weakens the paracrystalline regions, thereby unhinging the 1.4-β-glycosidic bonds in the cellulose molecule which originally connected the regions of high crystallinity. Secondly, the depolymerized cellulose undergoes attrition to release the cellulose aggregates, which constitute the basic raw material. By controlling the conditions of hydrolysis, it is possible to obtain the cellulose as microcrystals, which may subsequently be spray-dried. Spray-drying causes the microcrystals to re-hydrogen bond together in a spongy, porous, random pattern (Battista and Smith, 1962), in which they are arranged like a pile of matchsticks (Battista, 1965). The resultant powder particles, then, each consist of aggregates of cellulose microcrystals, and by varying the hydrolytic, degradative and spray-drying conditions, powdered microcrystalline cellulose may be produced in various grades. The grades used in this study, which include the well-established "Avicel
Figure 1.12 The Structure of Cellulose

![Cellulose Structure Diagram]
ALPHA-CELLULOSE PULP

consists of

MICROFIBRILS

which have two regions

PARACRYSTALLINE REGION
Amorphous, flexible mass of cellulose chains (A)

CRystalline REGION
Bundles of cellulose chains in a rigid linear arrangement

1. HYDROLYSIS WEAKENS PART (A)

2. SHEAR RELEASES PART (B)

3. SPRAY DRYING RESULTS IN POROUS PARTICLES

WHICH ARE AGGREGATES OF MICROCRYSTALS

POWDERED MICROCRYSTALLINE CELLULOSE

- 55 -
PH" (FMC Corp) grades as well as the newer "Unimac" (Unitika Rayon) and "Emcocel" (Finnsugar) grades, are shown in Table 1.2.

Table 1.2 shows the average particle sizes of the various powdered grades of microcrystalline cellulose, but it should also be noted that Avicel PH105 has a smaller particle size distribution than Avicel PH101 (Sixsmith, 1975). It is also worth noting that although the values of median Stokes diameter (Marshall et al., 1972) agree generally with the published values in the manufacturers' literature, the corresponding surface area values obtained by the same authors demonstrate certain anomalies: Avicel PH102 has a larger average particle size than Avicel PH101 and yet the former appears to have the larger surface area. (Although the actual numerical values calculated by Marshall et al. (1972) have recently been disputed due to a possible calculation error (Zografi et al., 1984), this anomalous trend of particle size with surface area is not in question.)

1.4.4 (ii) "Colloidal" Microcrystalline Cellulose Grades

Colloidal grades of microcrystalline cellulose were first produced commercially by FMC Corporation in 1968 (Thomas, 1979). The rationale behind their development was to enable attrited microcrystalline cellulose to be stored in its dried form and yet be rehydrated, without the necessity for an additional attrition step, to form the semi—colloidal suspensions required for use in food preparations (Durand et al., 1971).

The production of colloidal microcrystalline cellulose begins in a similar way to that of the powdered grades, with acid hydrolysis of alpha—cellulose followed by attrition to release the cellulose microcrystals (figure 1.13). However, in order to prevent the microcrystals reaggregating during the drying process, they are first
co-processed with the hydrophilic dispersant sodium carboxymethyl-cellulose (NaCMC), which will aid subsequent dispersion and also serve as a protective colloid against hornification of the cellulose due to hydrogen bonding. The co-processed material can then be either bulk or spray-dried to produce the final product. The grades are termed "colloidal" because, when properly dispersed, they form an insoluble network of aqueous hydrocolloid with many particles (often 60 to 70%, Avicel Technical Bulletin G-34, FMC Corp) less than 0.2µ in size.

The colloidal grades of microcrystalline cellulose used in this study (Avicel RC and CL grades, FMC Corp) are shown in Table 1.3. They vary in terms of the amount of sodium carboxymethylcellulose added during their manufacture and its viscosity. They also vary with regard to the method used to dry the finished product and the extent to which a fully-homogenized dispersion is "colloidal".

The sodium carboxymethylcellulose used in the production of colloidal microcrystalline cellulose is produced by the chemical derivation of alpha-cellulose, in which carboxymethyl groups are substituted for some of the hydrogens of the cellulose hydroxyl groups (figure 1.14). The factors which determine the viscosity of the NaCMC in solution are the degree of substitution (DS) of carboxymethyl groups onto the cellulose molecule, and the average chain length of the molecule. Cellulose has three hydroxyl groups available for substitution, and so the maximum theoretical DS is 3.0. However, a DS of about 0.7 results in grades of NaCMC which meet most viscosity requirements (Blanose Technical Bulletin 6/87.502-E3, Aqualon, Delaware 19894, US). It should be noted that the viscosity of NaCMC solutions is non-Newtonian.
### Table 1.2 Grades of Powdered Microcrystalline Cellulose

<table>
<thead>
<tr>
<th>Average Particle</th>
<th>Median Stokes</th>
<th>Moisture Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (µ)</td>
<td>Diameter (µ)</td>
<td>(%)</td>
</tr>
<tr>
<td>(ca.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*</td>
<td>**</td>
<td>*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Powdered Cellulose</th>
<th>Average Particle Size (µ)</th>
<th>Median Stokes Diameter (µ)</th>
<th>Moisture Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avicel PH101</td>
<td>50</td>
<td>37</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Avicel PH102</td>
<td>100</td>
<td>62</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Avicel PH103</td>
<td>50</td>
<td>36</td>
<td>&lt; 3</td>
</tr>
<tr>
<td>Avicel PH105</td>
<td>20</td>
<td>25</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Emcocel</td>
<td>56</td>
<td></td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Unimac MG100</td>
<td>38</td>
<td></td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Unimac MG200</td>
<td>105</td>
<td></td>
<td>&lt; 5</td>
</tr>
</tbody>
</table>

### Table 1.3 Grades of Colloidal Microcrystalline Cellulose

<table>
<thead>
<tr>
<th>NaCMC (%)</th>
<th>Relative n of NaCMC</th>
<th>Method of Drying</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ca.)</td>
<td>(%)</td>
<td></td>
</tr>
<tr>
<td>*</td>
<td>**</td>
<td>**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Colloidal Cellulose</th>
<th>NaCMC (%)</th>
<th>Relative n of NaCMC</th>
<th>Method of Drying</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avicel RC501</td>
<td>8.5</td>
<td>Medium</td>
<td>30</td>
</tr>
<tr>
<td>Avicel RC581</td>
<td>11.0</td>
<td>Medium</td>
<td>70</td>
</tr>
<tr>
<td>Avicel RC591</td>
<td>11.0</td>
<td>Medium</td>
<td>70</td>
</tr>
<tr>
<td>Avicel CL611</td>
<td>15.0</td>
<td>Low</td>
<td>70</td>
</tr>
</tbody>
</table>

* Manufacturers' literature ** Marshall et al. (1972)
The grades of sodium carboxymethylcellulose used by FMC Corp in the production of Avicel RC and CL grades of microcrystalline cellulose are shown in Table 1.4

1.4.5 Objectives
The various grades of microcrystalline cellulose available were originally produced for use in the food industry and for pharmaceutical tableting. However, the more recent interest in pharmaceutical extrusion and spheronization using microcrystalline cellulose has led the manufacturers to investigate its use in this field.

Several heuristic rules appear to have been formulated, not least those of Shwartz (FMC Corp. Publication, undated), who concludes, for example, that the colloidal grades of microcrystalline cellulose produce more acceptable spheres at low drug content than the powdered grades. Research in this area has been largely empirically—based: the aim of the present work is to specifically determine the effect that the grade of microcrystalline cellulose used in formulation has on extrusion of the wet powder mass.

The technique of ram extrusion (Harrison, 1982) will be used to characterize the rheological properties of wet powder masses containing different grades of microcrystalline cellulose at various moisture contents. In addition, the work will also aim to assess the bulk and surface quality of extrudate produced from each formulation. The results will be used in an attempt to compare the potential of the various grades of microcrystalline cellulose as successful aids to formulation in extrusion and spheronization.
Table 1.4  THE GRADES OF SODIUM CARBOXYMETHYLCELLULOSE USED BY FMC CORP IN MANUFACTURE OF AVICEL RC/CL GRADES

<table>
<thead>
<tr>
<th>Substitution</th>
<th>Viscosity of 2% Sol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range (DS)</td>
</tr>
<tr>
<td>Blanose 7MF</td>
<td>0.65 - 0.90</td>
</tr>
<tr>
<td>(used in Avicel RC grades)</td>
<td></td>
</tr>
<tr>
<td>Blanose 7LF</td>
<td>0.65 - 0.90</td>
</tr>
<tr>
<td>(used in Avicel CL grades)</td>
<td></td>
</tr>
</tbody>
</table>

* Brookfield Viscometer (Bull. 6/87.502–E3, Aqualon, US)
CHAPTER TWO

THEORY
Capillary rheometry has been a classical method for measuring the viscosity of liquids. Its use has been extended to the rheological characterization of polymers because it allows the study of flow at the high shear rates often used in polymer processing (Fenner, 1979). The shear stress at the capillary wall \( t_w \) is calculated at various apparent shear rates \( \dot{\gamma} \) by altering both the dimensions of the capillary and the volumetric flow rate of the material through the capillary. The long capillaries used for polymers are unsuitable for use with multiphase systems because moisture gradients are set up along their length. The short capillaries ("dies") required for multiphase systems (Benbow, 1971) are utilized in the ram extruder described in the Introduction (Section 1.3.1(iii)).

2.1 THE DETERMINATION OF THE SHEAR STRESS AT THE DIE WALL

The general expression for the flow of liquids can be arrived at by imagining the motion of a fluid between two parallel plates, one of which is stationary and one moving at constant velocity. The fluid adheres to both plates, such that the fluid velocity at the stationary plate is zero and at the moving plate is equal to the upper plate velocity. There is a linear velocity gradient between the plates, so that the fluid velocity is proportional to the distance from the lower plate, as in figure 2.1. For a Newtonian fluid in laminar flow, the shearing stress \( t \) within the fluid at any point is proportional to the velocity gradient \( (-dv/dr) \) i.e.

\[
t = n (-dv/dr) \quad \text{eq. 2.1}
\]

where \( n \) is the coefficient of viscosity. This expression can be used to describe fluid flow in a straight cylinder.
2.1.1 Ideal Fluid Flow through a Cylinder

Imagine a fluid flowing in a straight cylinder of radius \( R \) and length \( L \), with a pressure difference between the two ends of the cylinder \( \Delta P \). If it is assumed that a column of fluid of radius \( R \) is in laminar flow, it can be said that the applied force tending to move the liquid \( (F_A) \) results from the pressure difference between the two ends of the cylinder acting over the whole cross-sectional area of the column i.e.

\[
F_A = \Delta P \left( \pi r^2 \right) \quad \text{eq. 2.2}
\]

This force will be balanced by the viscous force tending to retard the fluid movement \( (F_V) \) which is due to the shear stress \( (\tau) \) acting over the surface area of the column i.e.

\[
F_V = \tau \left( 2\pi r L \right) \quad \text{eq. 2.3}
\]

Combining these equations gives the basic equation of capillary rheometry, which states that the shear stress is directly proportional to the distance from the centre of the capillary \( (r) \) and to the pressure gradient along the capillary \( (\Delta P/L) \) i.e.

\[
\tau = \frac{\Delta P r}{2L} \quad \text{eq. 2.4}
\]

The shear rate \( (\dot{\gamma}) \), at which the shear stress is measured, also varies with the distance from the centre of the capillary and so both values must be determined at the same point within the capillary. The
most convenient location is at the wall of the capillary, so that the
die wall shear stress, \( t_w \), is given by:

\[
t_w = \frac{\Delta P R}{2L} \quad \text{eq. 2.5}
\]

2.1.2 End Effects

The above equation 2.5 assumes an ideal pressure gradient within the
capillary, as illustrated in figure 2.2. In other words it assumes
that (Han, 1973; Chalifoux et al., 1980):

(i) The pressure within the capillary is independent of the position
of the piston within the barrel.

(ii) The pressure gradient is constant over the whole length of the
capillary.

(iii) The pressure falls to atmospheric at the exit of the capillary.

In fact, the pressure gradient consists of three separate regions, as
shown in figure 2.3:

(A) The Capillary Entry Region
Pressure is lost as material is forced from the large reservoir into
the small capillary, due to viscous dissipation of energy. The energy
dissipation results from two sources (Bagley, 1957): firstly the
convergence of flow into a vortex prior to the capillary entrance, and
secondly the development of a laminar flow profile within the
capillary.

(B) The Laminar Flow Region
The entrance effects in the Capillary Entry Region will cause a dis­
turbance in the flow pattern which will extend along a certain tube
length before laminar flow can be established. In the Laminar Flow
Region a characteristic velocity profile is maintained with a constant
pressure gradient. The length of the capillary along which laminar
flow occurs is known as the viscometric region (see figure 2.3).
Figure 2.1 The Linear Velocity Gradient of a Fluid Flowing Between Two Parallel Plates

Figure 2.2 The Ideal Pressure Gradient in a Capillary

Figure 2.3 The Regions of Pressure in a Capillary
The flow in the exit region is non-laminar due to an abrupt change in the boundary conditions causing a change in the velocity profile; thus the pressure does not fall to atmospheric at the capillary exit. This exit pressure was surmised by Han and Charles (1971) as the "recoverable pressure" carried with the material as it leaves the tube.

2.1.3 End Corrections

Capillary entrance and exit effects assume a greater significance when the capillary is a short die of the type used in ram extrusion. Failure to correct for these effects will result in erroneous values for the calculated die wall shear stress.

2.1.3(i) Entrance Corrections

Walters (1975) states that a large proportion of the pressure lost in end effects is lost in the entrance region, and Jastrzebski (1967) found that entrance losses presented a considerable source of error for highly concentrated suspensions in particular.

Harrison (1982) presented several data for the extrusion of pharmaceutical wet powder masses containing microcrystalline cellulose, lactose and water. By the use of coloured tracer markers in the material, he demonstrated the presence of static regions above the die entry, surmounted by a convergent flow vortex (figure 2.4). These findings are similar to those found in polymer systems (e.g. Tordella, 1969; Ballinger and White, 1949). The vortex appears to form at a natural "angle of convergence", \( \phi \) (figure 2.4), which is dependent on both material and process conditions. Large angles of convergence effectively increase the length of the capillary, thereby causing large entrance pressure losses. Bagley (1957) used a correction factor to account for this effect in molten polymers. The effective
increase in capillary length was expressed in terms of multiples of
the capillary radius, i.e. the effective capillary length = L + n_bR so
that equation 2.5 becomes:

\[ t_w = \frac{\Delta P}{2(L/R + n_b)} \quad \text{eq. 2.6} \]

so that:

\[ \Delta P = 2 t_w (L/R + n_b) \quad \text{eq. 2.7} \]

where \( n_b \) = the Bagley entrance correction. The value of \( n_b \) is found
by measuring the pressure drop along two or more capillaries of
different length but constant diameter, at constant extrusion speed.
The pressure drop for each capillary length, when plotted against the
length to radius ratio of the capillary (L/R), should lie on a
straight line (the so-called "Bagley plot"), figure 2.5. Extrapola-
tion to zero pressure allows the determination of \( n_b \) as an inter-
cept on the (L/R) axis.

2.1.3(ii) Exit Corrections

The equation corrected for the Bagley Entrance Effect (equation 2.6)
still makes the assumption that the pressure at the capillary or die
exit is atmospheric, or that any exit pressure losses are negligibly
small compared to entrance effects. Using capillaries instrumented
with pressure transducers along their length, Han and Charles (1971)
measured the pressure distribution along a capillary and showed for
polyethylene and polypropylene melts that the exit pressure is
actually above atmospheric and depends on the shear rate. They
proposed a modification of equation 2.6 to correct for exit pressure
losses:

\[ t_w = \frac{(\Delta P - P_e)}{2(L/R + n_b)} \quad \text{eq. 2.8} \]
Figure 2.4 The Movement of Coloured Marker Layers within the Reservoir during Extrusion (Harrison, 1982)

Figure 2.5 The Bagley Plot, showing the Bagley Entrance Correction ($n_b$) & the Upstream Pressure Loss ($P_o$)
where $P_e$ = the exit pressure. The use of this correction factor for exit effects resulted in curvature of the Bagley plots at low capillary length to radius ratios (i.e. near the entrance of the capillary), the curvature becoming more pronounced as the shear rate increases. Indeed, a Bagley plot, when properly corrected for entrance and exit pressure losses, is no more than the axial pressure profile within the capillary (Han, 1973).

2.1.3(iii) The Upstream Pressure Loss

Harrison (1982) used the alternative approach of Jastrzebski (1967) to account for entrance and exit effects. He used the intercept on the pressure axis of the Bagley plot at zero die length to radius ratio ($L/R$), the "Upstream Pressure Loss" ($P_0$), to represent the finite pressure loss associated with end effects (figure 2.5). Thus $\Delta P = P_T - P_0$ where $P_T$ = the total pressure drop on extrusion and $P_0$ = the Upstream Pressure Loss. Equation 2.5 therefore becomes:

$$t_w = (P_T - P_0) R/2L \quad \text{eq. 2.9}$$

so that:

$$P_T = P_0 + 2t_w (L/R) \quad \text{eq. 2.10}$$

The Upstream Pressure Loss includes additional pressure losses which are minor in comparison to the end effects:

(A) Kinetic Energy Losses

Some of the applied pressure is not used in shearing the sample but imparts kinetic energy to the sample as it enters the capillary.

(B) Head Effects

Head effects are pressure losses within the reservoir such as piston sticking or energy dissipated in the flow of the material within the cylinder. These effects are small provided that the diameter of the reservoir is much larger than the capillary diameter.
(C) Elastic Energy Losses

These losses are due to any non-recoverable elastic deformation of the material during capillary flow.

(D) Turbulence

Some pressure may be lost as a result of non-laminar flow.

By combining equations 2.7 and 2.10, the relationship of the Upstream Pressure Loss \( (P_0) \) to the Bagley Entrance Correction Factor \( (n_b) \) is given:

\[
    n_b = \frac{P_0}{2t_w} \quad \text{eq. 2.11}
\]

Harrison (1982) found that the Upstream Pressure Loss increased with increasing shear rate for pharmaceutical wet powder masses. This effect, however, must be mainly due to an increase in the die wall shear stress with increasing shear rate, since the application of equation 2.11 to Harrison's results shows that \( n_b \) decreases with shear rate, implying that entrance pressure losses are lower at higher rates of throughput. This result is in opposition to that of Bagley (1957) who found that the entrance correction factor increased with the logarithm of the shear rate for the extrusion of polyethylenes.

It can be seen from equation 2.10 that a Bagley plot of extrusion pressure vs. die length to radius ratio will have a gradient = 2 \( \times \) the die wall shear stress \( (t_w) \) and a y-intercept = the upstream pressure loss \( (P_0) \). The value of the die wall shear stress obtained for each formulation will depend on the shear rate within the die.
Recalling equation 2.1, it can be seen that a Newtonian fluid in laminar flow has shear stress proportional to the velocity gradient i.e. \( \tau = n (-\frac{dv}{dr}) \). Substituting this equation into equation 2.4 gives:

\[
-\frac{dv}{dr} = \frac{\Delta P r}{2nL}
\quad \text{eq. 2.12}
\]

Integration of equation 2.12 will give the velocity distribution within the capillary, so that the velocity at any distance, \( r \), from the centre of the capillary is given by:

\[
-\frac{dv}{dr} = \int \frac{\Delta P r}{(2nL)} \, dr
\]

\[
v(r) = \frac{\Delta P r^2}{4nL} + C
\quad \text{eq. 2.13}
\]

If it is assumed that the velocity at the capillary wall is zero, i.e. \( v=0 \) when \( r=R \), then \( C = -\frac{\Delta P R^2}{4nL} \). Substituting this value for \( C \) into equation 2.13 gives:

\[
v(r) = \frac{\Delta P (r^2 - R^2)}{4nL}
\quad \text{eq. 2.14}
\]

The volumetric flow rate through the capillary is equal to the integral of the velocity distribution, with respect to \( r \), from \( r=0 \) to \( r=R \), over the whole capillary circumference, i.e.:

\[
Q = R \int_0^R v(r) \, 2\pi r \, dr
\]

Therefore:

\[
Q = R \int_0^R \frac{\Delta P (r^2 - R^2)}{4nL} \, 2\pi r \, dr
\]
This equation 2.15 is known as the Hagan–Poiseuille law for laminar flow in tubes. (The average velocity can be obtained by dividing the volumetric flow rate, Q, by the cross-sectional area of the capillary, \( \pi r^2 \), to give \( V(\text{average}) = \frac{\Delta P r^2}{8nL} \)).

From equation 2.12 we can see that the shear rate at a die wall, \( (-\frac{dv}{dr})_w \), is given by:

\[
(-\frac{dv}{dr})_w = \frac{\Delta P r}{2nL} \quad \text{eq. 2.16}
\]

By substituting the Hagan–Poiseuille law into the above equation, we obtain the following expression for the die wall shear rate:

\[
(-\frac{dv}{dr})_w = \frac{4Q}{\pi R^3} \quad \text{eq. 2.17}
\]

The above derivation assumes that the material flow is Newtonian (cf. equation 2.1). Jastrzebski (1967) used the Mooney–Rabinowitsch equation (Mooney, 1931; Rabinowitsch, 1929) to correct the shear rate for non–Newtonian flow:

\[
(-\frac{dv}{dr})_w = \left(\frac{3n' + 1}{n'}\right)\left(\frac{Q}{\pi R^3}\right) \quad \text{eq. 2.18}
\]

where \( n' \) is called the "Degree of non–Newtonian Flow" and is determined from the gradient of a log–log plot of shear stress vs. apparent shear rate (as will be seen from equation 2.21). However, both equations 2.17 and 2.18 also make several other assumptions (Wilkinson, 1960):
(i) that flow is laminar, each particle moving with constant velocity in a straight line parallel to the die axis,
(ii) that there is no slip at the die wall (i.e. that the boundary conditions that $v=0$ when $r=R$ are met),
(iii) that the rate of shear ($-\frac{dv}{dr}$) depends only on the shear stress ($\tau$) at its point of measurement and is independent of time.

If these assumptions are valid, the shear rate at a given shear stress should be independent of capillary radius and so a flow curve of the observed die wall shear stress vs. shear rate for different die radii should lie on a single curve (Oldroyd, 1956). Using this approach, Harrison (1982) found that the ram extrusion of pharmaceutical wet powder masses containing microcrystalline cellulose, lactose and water resulted in different flow curves when dies of different diameter were used. The material was assumed to be time-independent and flow was shown to be laminar by the use of tracer dies in the material. Harrison therefore concluded that there was an effective velocity of slip at the wall of the die. Anomalous flow effects such as these had previously been reported in capillary flow of polymer systems (Kozicki et al., 1970) and concentrated suspensions (Jastrzebski, 1967). Like Jastrzebski (1967), Harrison (1982) found that the slip velocity depended on the die wall shear stress and on the die radius, the slip velocity being greater at low die diameters.

2.3 FLOW CURVE MODELS

An extrusion flow curve of die wall shear stress ($\tau_w$) vs. apparent shear rate ($D'$) will be characteristic for a given formulation, and will assist in its rheological characterization (allowing for the assumptions made in the calculation of the shear rate, Section 2.2).
It is common practice, whenever possible, to fit a mathematical model to a flow curve, either in an attempt to represent some theoretical concept with regard to the molecular or particulate structure of the system, and/or to express the flow curve relationship in terms of a small number of parameters which may then be studied in relation to formulation and other variables. Various flow models have been used previously: the model which reveals the most significant trends in flow parameters due to experimental changes is usually the model of choice.

2.3.1 The Newtonian Flow Model

The Newtonian Flow model is the simplest mathematical model. It directly relates the die wall shear stress \( t_w \) to the apparent shear rate \( D' \) by a single parameter termed the "apparent viscosity" \( n \) i.e.:

\[
t_w = D'n
\]

eq. 2.19

The Newtonian model is illustrated by line (a) in figure 2.6. Unfortunately this model is not generally applicable to the flow of complex systems. To facilitate description of the flow curve, additional parameters are commonly used, such as the "Yield Stress" \( t_y \), which is the stress required to initiate flow, and the "Degree of non-Newtonian Flow" \( n' \), which is a power law term describing the degree of deviation from Newtonian behaviour.

2.3.2 The Bingham Body Model

The Bingham Body model is used to describe plastic flow, i.e. where a yield stress \( t_y \) precedes Newtonian flow, line (b) in figure 2.6. It is expressed mathematically as:
Figure 2.6 Mathematical Models for Flow Curves

(a) Newtonian flow
(b) Bingham Body flow
(c) Power Law flow
   (i) Shear-thinning
   (ii) Shear-thickening
(d) Herschel-Bulkley flow
where $U$ = the plastic viscosity. The model reduces to the Newtonian flow model if there is no material yield prior to flow. Bingham type flow was found to occur for pastes of kaolin at high shear rates (Farooqi and Richardson, 1980). At low shear rates, however, Farooqi and Richardson found kaolin pastes to exhibit pseudoplastic (or "shear thinning") flow behaviour, which is best described by the Power Law model.

2.3.3 The Power Law Model

The Power Law model describes a flow curve such as that illustrated by lines (c:i,ii) of figure 2.6. This type of flow curve becomes linear when plotted logarithmically, and is represented mathematically as:

$$t_w = K D' U$$  \hspace{1cm} \text{eq. 2.20}

$$t_w = K D' n'$$  \hspace{1cm} \text{eq. 2.21}

where $K$ = the power law viscosity constant and $n'$ = the degree of non-Newtonian flow. (A "shear thinning" material is characterised by a value of $n'$ which is greater than unity and a "shear thickening" material by a value for $n'$ which is less than unity. When $n'$ is equal to unity the equation reduces to the Newtonian Flow model.)

2.3.4 The Herschel-Bulkley Model

The Herschel-Bulkley model is used to describe a material which has a Bingham type Yield Value followed by non-Newtonian flow of the Power Law type. It is illustrated by curve (d) in figure 2.6 and is expressed in the following equation (Herschel and Bulkley, 1926):

$$t_w = t_y + K D' n'$$  \hspace{1cm} \text{eq. 2.22}
The model reduces to a Bingham Body model if the flow subsequent to material yield is Newtonian, and to a Power Law Model if there is no Yield Value.

Harrison (1982) found that pharmaceutical wet powder masses exhibited non-Newtonian die flow subsequent to a small Yield Stress (obtained from the flow curve as the stress-intercept at zero shear rate). When the results were plotted logarithmically, the resultant curves were non-linear and so a Herschel-Bulkley model could not be accurately fitted. Harrison (1982) attributed the deviation from linearity at low shear rates to deviations in the material Yield Stress, and at high shear rates to changes in the degree of slip at the die wall. Any mathematical solution could therefore be only descriptive, rather than absolute, and would describe the flow curve under changing slip conditions. By broadly describing his flow curves using the Herschel-Bulkley model, Harrison (1982) was able to calculate the degree of non-Newtonian flow ($n'$) from equation 2.22. The value of $n'$ could then be used to determine the die wall shear rate corrected for non-Newtonian flow, according to Jastrzebski (1967), from equation 2.18. Since $n'$ was constant, the correction factor to obtain the Jastrzebski shear rate ($[3n' + 1]/n'$) would be constant and so could be neglected for the sake of ease of calculation.

When Harrison (1982) solved the Herschel-Bulkley model for his systems he found that the calculated value of yield stress was smaller than expected, indicating a plug flow of relatively small diameter - this result was not borne out by flow visualization studies using coloured marker materials, which showed that the central core undergoing plug flow was of large diameter. This experimental evidence for broad plug flow was supported by the fact that the calculated values for the
Upstream Pressure Loss ($P_0$) were large in comparison to the values for die wall shear stress ($t_w$) - if we assume that a major component of the Upstream Pressure Loss is the stress required to induce flow in the material, these high values of $P_0$ would indicate high values of material yield stress and thus broad plug flow. These findings led Harrison (1982) to conclude that the rheological parameters evaluated from the mathematical modelling of the flow curve do not adequately describe the flow properties of the material, and thus the assumption of zero slip at the die wall is invalid. He suggested that the anomalous flow behaviour close to the wall occurs in a lubricating film, consisting of liquid alone or of some mixture of liquid and solid components of the mix, whose rheological properties differ from that of the bulk. Thus the measured wall shear stress would describe the rheological nature of the lubricating layer, rather than that of the bulk material. It will be shown that the apparent thickness of this lubricating film can be estimated for formulations extruded at a given shear rate using the Benbow-Bridgwater approach (Section 2.4).

2.4 THE BENBOW-BRIDG water APPROACH

2.4.1 The Die Wall Shear Stress in Relation to the Extrudate Velocity

Ovensten and Benbow (1968) and Benbow (1971) found that in a die of uniform cross-section, the yield stress ($t_0$) of catalyst pastes is not exceeded in the bulk of the material. They therefore proposed that there is a broad plug flow with shearing occurring in a thin layer of liquid near the die wall. They assumed that this wall layer behaves as a Newtonian liquid of thickness ($x$) and viscosity ($\eta$), so that if the initial wall shear stress required to initiate flow through the die is $t_0$, then the total die wall shear stress at a given extrudate velocity ($V$) is given by:
\[ t_w = t_0 + (n/x)V \]  \hspace{1cm} \text{eq. 2.23}

Since \( n \) and \( x \) are not generally known, it is more convenient to write:

\[ t_w = t_0 + \beta V \]  \hspace{1cm} \text{eq. 2.24}

where \( \beta \) is called the "die land velocity factor" and is given by:

\[ \beta = n/x \]  \hspace{1cm} \text{eq. 2.25}

Combining equations 2.24 and 2.10 results in an expression for the total pressure drop on extrusion which relates the die wall shear stress to the extrudate velocity:

\[ P_T = P_0 + 2(L/R) (t_0 + \beta V) \]  \hspace{1cm} \text{eq. 2.26}

The initial die wall shear stress (\( t_0 \)) can be thought of as the theoretical die wall shear stress at zero extrudate velocity, and the expression (\( \beta V \)) as the component which accounts for the increase in die wall shear stress with increasing extrudate velocity.

The value of the initial die wall shear stress (\( t_0 \)) is determined by plotting graphs of total extrusion pressure vs. extrudate velocity (\( V \)) for extrusion through several dies of various length to radius ratio (\( L/R \)). The extrapolated values of extrusion pressure at \( V=0 \) can be used to derive a theoretical Bagley plot at zero extrudate velocity. Since \( \beta V \) will be zero when \( V=0 \), equation 2.26 becomes:

\[ P_T(\text{vel}_0) = P_0(\text{vel}_0) + 2(L/R) t_0 \]  \hspace{1cm} \text{eq. 2.27}
where $P_T(vel_o)$ is the total extrusion pressure at zero extrudate velocity and $P_o(vel_o)$ is the Upstream Pressure Loss at zero extrudate velocity. So from equation 2.27 we see that the initial die wall shear stress ($t_o$) is equal to half the gradient of a zero velocity Bagley Plot.

The value of the die-land velocity factor ($\beta$) is determined by comparing values of die wall shear stress ($t_w$) at various extrudate velocities with the value for initial die wall shear stress ($t_o$). It is given by rearranging equation 2.26:

$$\beta = \frac{(P_T - P_o)}{2(L/R)V} - \frac{t_o}{V}$$

and then substituting for $t_o$ from equation 2.27:

$$\beta = \frac{[P_T(vel_v) - P_o(vel_v)] - [P_T(vel_o) - P_o(vel_o)]}{2[L/R]V} \quad \text{eq. 2.28}$$

where $P_T(vel_v)$ is the total extrusion pressure at extrudate velocity = $V$, and $P_o(vel_v)$ is the Upstream Pressure Loss at extrudate velocity = $V$.

### 2.4.2 The Paste Yield Value

Benbow (1971, 1984) used the expression of Berghaus (1957) who had previously found that the pressure drop at the die entry could be accounted for by the theory used in metal wire drawing, involving only the material yield value ($\sigma_y$) and the change in cross-sectional area on extrusion ($A_o/A$) i.e.

$$P_o = \sigma_y \ln(A_o/A) = 2\sigma_y \ln(D_o/D) \quad \text{eq. 2.29}$$
where \( D_o \) = the barrel diameter, \( D \) = the die diameter and \( (D_o/D) \) is known as the reduction ratio. The equation assumes that the deformation at the die entry is plastic and time-independent. Equation 2.29 shows that the value of \( \sigma_y \) can be calculated from the pressure-intercept of a Bagley plot divided by twice the logarithm of the reduction ratio.

2.4.3 Flow Into and Through a Die

Benbow and Bridgwater (1987:i;ii) and Benbow et al. (1987) combined equations 2.26 and 2.29 to give an expression for the total pressure drop \( (P_T) \) on extrusion into and through a parallel die:

\[
P_T = 2\sigma_y \ln(D_o/D) + 2(L/R) (t_o + \beta V) \text{ eq. 2.30}
\]

The first term on the right hand side of equation 2.30 relates to flow into the die from the barrel. The second term describes flow through the die and divides the die wall shear stress into the two components: the "initial die wall shear stress" \( (t_o) \), and the component which accounts for the increase in die wall shear stress with increasing extrudate speed \( (\beta V) \).

The expression assumes that all the parameters are independent of extrudate velocity and that the liquid layer is Newtonian. This in turn implies that the viscosity \( (n) \) and the thickness \( (x) \) of the liquid layer near the wall are both constant with extrudate velocity (or that the ratio \( n/x \) is constant while \( n \) and \( x \) vary). If the die-land velocity factor \( (\beta) \) is found to vary with extrudate velocity, then it must either be calculated and presented separately for each extrusion velocity or, where possible, described using a power law: for non-Newtonian flow the viscosity of the fluid is dependent on the
shear rate, (i.e. \( n = n^k (-dv/dr)^{-n'} \)), and so, assuming that the same type of deformation is occurring (i.e. plug flow in the die), then equation 2.30 becomes:

\[
P_T = 2\sigma_y \ln(D_0/D) + 2(L/R) (t_o + \beta^* y^{1-n'}) \quad \text{eq. 2.31}
\]

where \( \beta^* \) is a modified power law constant (cf. the Herschel-Bulkley equation 2.21) and \( n' \) is the degree of non-Newtonian flow.

2.4.4 The Extrudate Velocity Dependent Yield Value

Equation 2.30 was shown by Benbow (1971) to be satisfactory for describing the extrusion of some \( \gamma \)-alumina pastes, but in 1987, Benbow et al. and Benbow and Bridgwater, using barrels and dies of various diameter, found that the pressure gradient for flow not only through the die but also for flow into the die was dependent on extrudate velocity for \( \alpha \)-alumina pastes. To describe the effect, the yield value (\( \sigma_y \)) was replaced empirically by two parameters, the "initial die entry yield stress" (\( \sigma_{yo} \)) and the "die entry yield stress velocity factor" (\( \alpha \)) so that equation 2.29 becomes:

\[
P_o = 2 (\sigma_{yo} + \alpha V) \ln(D_0/D) \quad \text{eq. 2.32}
\]

and equation 2.30 becomes:

\[
P_T = 2(\sigma_{yo} + \alpha V)\ln(D_0/D) + 2(L/R)(t_o + \beta V) \quad \text{eq. 2.33}
\]

The value of the initial die entry yield stress (\( \sigma_{yo} \)) is found by deriving a theoretical Bagley Plot at zero extrudate velocity as described in Section 2.41. Since \( \alpha V \) will equal zero when \( V=0 \), equation 2.32 becomes:

\[
P_o = 2\sigma_{yo} \ln(D_0/D) \quad \text{eq. 2.32}
\]
\[ P_0(vel_0) = 2 \sigma_{yo} \ln(D_0/D) \quad \text{eq. 2.34} \]

and so \( \sigma_{yo} \) can be found from the pressure-intercept of the zero velocity Bagley Plot.

The value of the die entry yield stress velocity factor \( (\alpha) \) is determined by comparing values of yield stress \( (\sigma_y) \) at various extrudate velocities with the value for initial die entry yield stress \( (\sigma_{yo}) \). It is given by rearranging equation 2.32 to give:

\[
\alpha = \frac{P_0 / 2 \ln(D_0/D)V - \sigma_{yo} / V}{\ln(D_0/D)V}
\]

and substituting for \( \sigma_{yo} \) from equation 2.34 to give:

\[
\alpha = \frac{P_0(vel_v) - P_0(vel_o)}{2 \ln(D_0/D)V} \quad \text{eq. 2.35}
\]

Benbow et al. (1987) found that the dependence of the two parameters, \( \alpha \) and \( \beta \), on paste formulation was linked to paste rheology, liquid viscosity and the excess of liquid above the inter-particle volume.

2.4.5 The Thickness of the Die Wall Lubricating Layer

According to Benbow et al. (1987), the geometrical structure of the liquid layer in contact with the die wall in the extrusion of \( \alpha \)-alumina pastes is complex and is affected by the particle size, size distribution and shape. However, if the wall layer for a certain formulation extruded at a given extrudate velocity is assumed to have a uniform thickness, it will be possible to calculate this thickness from the ratio of the liquid phase plastic viscosity \( (n) \) and the die land velocity factor \( (\beta) \) from equation 2.25.
PART TWO

EXPERIMENTAL
CHAPTER THREE

MATERIALS AND METHODS
3.1 MATERIALS

3.1.1 Microcrystalline Cellulose
The various grades of microcrystalline cellulose available commercially have been described in Section 1.4.4. Each of the grades described was used in this work: their batch numbers are listed in Table 3.1.

3.1.2 Lactose
Lactose has previously been used as a model drug in formulations for extrusion and spheronization (Harrison, 1982; Chapman, 1985; Fielden, 1987). It is a naturally occurring sugar derived from cheese whey and is produced in various grades of specific particle size. The work of Fielden (1987) has shown that the particle size of the lactose used affects the extrusion properties of a formulation. It was found that the use of "fine", as opposed to "coarse", grade lactose (Dairy Crest, Surrey, England) results in formulations with improved extrusion flow characteristics. The present study, therefore, uses Dairy Crest Fine Grade 300 mesh Lactose (average particle size , 117μ by sieve analysis) (Batch number B170).

3.1.3 Water
Throughout this work, the water referred to is double distilled.

3.1.4 Sodium Carboxymethylcellulose
Section 1.4.4(ii) describes the way that sodium carboxymethylcellulose (NaCMC) is co-processed with microcrystalline cellulose to produce "colloidal" grades of microcrystalline cellulose with improved dispersion characteristics (Avicel RC/CL grades, FMC Corp). Part of this thesis aims to examine the effect that this NaCMC has on the
extrusion performance of "colloidal" microcrystalline cellulose formulations. For this purpose, the grade of NaCMC used in experimental work corresponded to that used by FMC Corp in the manufacture of the Avicel RC grades of microcrystalline cellulose (Table 1.4). The grade used throughout this work is Blanose 7MF (Batch number 41411) (Aqualon).

3.2 METHODS

The methods used in commercial extrusion of pharmaceutical formulations have been outlined in Section 1.3. They include screw- and gravity-feed systems and, occasionally, batch extruders. Unfortunately, the two parameters required to characterize the flow of material through a die according to capillary rheometry (i.e. the extrusion force and the velocity of throughput) cannot be measured directly on commercial screw/gravity-feed extruders. In this work, therefore, a simple ram extrusion system (Ovensten and Benbow, 1968) is used for the characterization of the various microcrystalline cellulose formulations.

3.2.1 The Preparation of the Material

3.2.1(i) The Formulations Studied

Most of the formulations studied were based on the standard mix of microcrystalline cellulose, lactose and water in the ratio of 5:5:6. However, it should be noted that preliminary investigations indicated that the colloidal grades of microcrystalline cellulose could not be formulated effectively in the standard 5:5:6 ratio. The addition of six parts of water was found to result in overwetting of the granular mass, resulting in excessive stickiness, and "gumming" in the mixer bowl. (This was particularly true for formulations based on Avicel
CL611, the colloidal grade with the most (15%) NaCMC included, and was probably due to hydration of the NaCMC.) It was found that colloidal grades could be formulated successfully by ensuring that the amount of water added during mixing was equal to six parts with respect to the actual microcrystalline cellulose content of the colloidal grade. Thus the standard 5:5:6 formulation was modified to consist of 5 parts microcrystalline cellulose grade, 5 parts lactose, and 6 parts water with respect to actual microcrystalline cellulose, and is hereafter referred to as "5:5:6\textsubscript{MNC}". As a result of this modification, colloidal microcrystalline cellulose formulations were mixed with quantities of water which were different to one another, and to those used in the formulation of powdered grades. The amounts of water used in the 5:5:6\textsubscript{MNC} formulations are listed in Table 3.2.

Some of the experimental work required the use of non-standard formulations, and so in some cases the amount or composition of the aqueous phase was altered. A broad indication of the formulations used for various investigations is given in Table 3.3.

3.2.1(ii) The Method of Formulation

All measurements of powder and liquids were made by weight (Mettler balance PC1616). The dry powders were mixed in a planetary mixer (Hobart Model A200 for quantities more than 1kg and Kenwood Chef for quantities less than 1kg) set at its lowest speed for 5 minutes. The selected amount of water or sodium carboxymethylcellulose gel (which had been formulated previously by allowing the required quantity of NaCMC to dissolve in an appropriate amount of water) was added, and mixing was continued for a further 10 minutes. It was necessary, at intervals, to detach material adhering to the blade and the sides of the bowl in order to ensure that a homogenous wet powder mass was
Table 3.1  GRADES OF MICROCRYSTALLINE CELLULOSE USED

<table>
<thead>
<tr>
<th>Powdered Grades'</th>
<th>Colloidal Grades'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch Numbers</td>
<td>Batch Numbers</td>
</tr>
<tr>
<td>Avicel PH101 6511</td>
<td>Avicel RC501 A3241</td>
</tr>
<tr>
<td>Avicel PH102 7534</td>
<td>Avicel RC581 B5161</td>
</tr>
<tr>
<td>Avicel PH103 3505</td>
<td>Avicel RC591 D5081</td>
</tr>
<tr>
<td>Avicel PH105 5407</td>
<td>Avicel CL611 E3221</td>
</tr>
<tr>
<td>Emcocel 5114</td>
<td></td>
</tr>
<tr>
<td>Unimac MG100 5175</td>
<td></td>
</tr>
<tr>
<td>Unimac MG200 5125</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.2  THE WATER CONTENT USED IN 5:5:6\text{MCC} FORMULATION

<table>
<thead>
<tr>
<th>5:5:6\text{MMC FORMULATION OF}</th>
<th>AMOUNT OF WATER USED</th>
</tr>
</thead>
<tbody>
<tr>
<td>POWDERED GRADES (100% MCC)</td>
<td>= 6.00 parts</td>
</tr>
<tr>
<td>AVICEL RC501 (91.5% MCC)</td>
<td>(91.5/100)x6 = 5.49 parts</td>
</tr>
<tr>
<td>AVICEL RC581 (89.0% MCC)</td>
<td>(89.0/100)x6 = 5.34 parts</td>
</tr>
<tr>
<td>AVICEL RC591 (89.0% MCC)</td>
<td>(89.0/100)x6 = 5.34 parts</td>
</tr>
<tr>
<td>AVICEL CL611 (85.0% MCC)</td>
<td>(85.0/100)x6 = 5.10 parts</td>
</tr>
</tbody>
</table>
Table 3.3 THE FORMULATIONS USED IN EXPERIMENTAL WORK

To Study the Effect of the Grade of Microcrystalline Cellulose used in the Formulation

Formulations based on each grade of microcrystalline cellulose (Section 3.11) with lactose and water in the standard ratio, 5:5:6\textsubscript{MCC}

To Study the Effect of Water Content

Formulations based on various grades of micro-crystalline cellulose (Avicel PH101, Avicel PH102, Unimac MG100, Unimac MG200, Emcocel) with lactose and water in various ratios, (5:5:4\textsubscript{MCC}, 5:5:5\textsubscript{MCC}, 10:10:11\textsubscript{MCC}, 5:5:6\textsubscript{MCC}, 10:10:13\textsubscript{MCC}, 5:5:7\textsubscript{MCC}, 5:5:8\textsubscript{MCC})

To Study the Effect of Sodium Carboxymethylcellulose (NaCMC) Solution as the Binder in the Formulation

Formulations based on Avicel PH101 microcrystalline cellulose with lactose and NaCMC gel (8% or 16%) in the standard ratio, 5:5:6\textsubscript{MCC}
produced. The wet mixes were transferred into polythene bags, sealed and stored until ready for use.

3.2.2 Extrusion of the Wet Mass

Ram extrusion was used to assess the extrusion performance of the various formulations.

3.2.2(i) The Design of the Ram Extruder

The ram extruder used in this work is based on the design of Ovensten and Benbow (1968) and is illustrated in Figure 3.1. It consists of a stainless or hardened steel barrel of 2.54cm in diameter and approximately 20cm in length. The lower end of this barrel terminates in a 1.5cm flange, to which one of a set of interchangeable dies can be fitted using three cap-headed socket screws. An elastomer seal ("O"-ring) is inserted between the barrel and the die to ensure a watertight connection. Each die is comprised of a stainless steel or hardened steel flat plate with a single hole of diameter 1.5mm and of specified length (1.5, 3, 6, 9 or 12mm). The piston consists of a stainless or hardened steel rod with diameter of 2.3cm along most of its length, but increasing to 99.5% of the internal barrel diameter at its lowest end, where a fluon ring provides a low friction seal to prevent material escaping upwards beyond the piston face during extrusion.

3.2.2(ii) Experimental Extrusion

Prior to extrusion, approximately 50g of wet powder mass is packed into the barrel and die assembly by hand pressure on the piston. The whole assembly is then mounted onto a thick-walled "C-piece" - a hollow cylinder which has part of its wall removed to allow access to, and collection of, the extrudate. The C-piece rests on the load cell of a mechanical press (Instron Universal Testing Instrument Model TT-CM, Instron Ltd., High Wycombe, Bucks). (The load cell is cali-
Figure 3.1 The Ram Extruder, showing Barrel, Piston and Die Assembly

- Piston
- Barrel
- PTFE Ring

Elevation of Underside of Die

Elevation of Barrel flange

Elevation of Topside of Die

INSERT cap-headed socket screws (countersunk)
brated previously and adjusted for the weight of the ram extruder.) The cross-head of the press is used to drive the piston down within the barrel at a constant pre-selected speed (2, 5, 10, 20 or 40 cm per minute). As the piston moves down the barrel, the force it exerts on the material is measured by the load cell, and the displacement of the piston is monitored by a linear variable displacement transducer (Sangamo Transducers, W. Sussex). The force acting on the material is plotted as a function of the piston displacement by an X-Y chart recorder (Gould Series 6000) to produce a force/displacement profile.

A typical force/displacement profile is shown in Figure 3.2. Such a profile has been described previously as having three distinct regions (Harrison, 1982). The Compression Stage occurs before extrusion begins and continues until the wet mass is compacted to a density almost equal to that of the material itself. When compaction is complete, the material in the barrel yields and begins to extrude. During the Steady State Region, convergent flow patterns are set up from the barrel into the die (Harrison, 1982), and the force required to maintain extrusion remains constant - the "Steady State Extrusion Force". However, once the piston reaches a certain critical point above the die, the Steady State Flow patterns within the barrel can no longer be maintained and a region of Forced Flow ensues. In this region, the extrusion force increases with increasing piston displacement. Extrudate collected under Forced Flow conditions has a non-uniform moisture content because the increased forces cause a moisture gradient to be set up between the material in the barrel and the extrudate (Harrison, 1982). For these reasons, extrudate is collected only during Steady State flow, and the extrusion force is determined as the Steady State Extrusion Force, read from the force/displacement profiles as shown in Figure 3.2. The Steady State Extrusion Force
Figure 3.2 The Force/Displacement Profile

Characteristics of a particular material extruded at a certain speed through a die of known length to radius ratio (L/R).
will be characteristic of a particular material mix extruded at a
given speed through a die of a certain length to radius ratio (L/R).

3.2.2(iii) Treatment of the Ram Extrusion Results

The Steady State Extrusion Force was obtained from the force/displacement profiles for every formulation extruded at each speed and through each die. The piston pressure values (calculated from the steady state force divided by the surface area of the piston face) were plotted against die length to radius ratio to construct Bagley Plots (see Section 2.1.3 and Figure 2.5). The highest value of die length to radius ratio used was 16, since it has been shown previously that when the ratio exceeds 16 the Bagley Plots exhibit deviation from linearity, possibly due to the creation of a moisture gradient within the die during extrusion (Harrison, 1982). The die wall shear stress and upstream pressure loss were derived from the plots (Equation 2.10) for each formulation at each extrusion speed. The apparent die wall shear stress was then plotted against the apparent die wall shear rate (calculated from Equation 2.17) to give a characteristic "flow curve" for each formulation. The ram extrusion data were also analysed according to the equation of Benbow and Bridgwater (1987 i and ii) (Section 2.4, Equation 2.33) to calculate the theoretical material yield stress, the theoretical initial die wall shear stress, and the yield stress and die land velocity factors for each formulation. The flow curves and the Benbow-Bridgwater parameters were used to characterize and compare the various formulations under investigation.

It should be noted that the Benbow-Bridgwater equations include the parameter, V, "extrudate velocity". The extrudate velocity in each case was calculated by multiplying the piston speed (S) by a factor to account for the reduction in volume from the barrel to the die as follows:
\[ V = \pi \left( \frac{D_0}{2} \right)^2 S \]
\[ \pi \left( \frac{D}{2} \right)^2 \]
\[ V = \left( \frac{D_0}{D} \right)^2 S \quad \text{eq. 3.1} \]

where \( D_0 \) = diameter of the barrel (2.54cm) and \( D \) = diameter of the die (1.5mm).

3.2.3 The Assessment of the Extrudate Quality

For each formulation, extrudate produced under Steady State conditions through each die and at each extrusion speed was assessed in terms of its quality. Any correlation between the extrudate quality results and any of the calculated parameters was noted.

3.2.3(i) Extrudate Surface Quality Assessment

The surface of each piece of extrudate was examined for impairment and placed into one of three categories: smooth, rough or sharkskinned. The three categories are shown diagramatically in Figure 3.3.

3.2.3(ii) Extrudate Bulk Quality Assessment

Each extrudate was examined for bulk qualities during Steady State extrusion. In particular, any continuous production of extrudate (as opposed to the commonly observed production of extrudate in short lengths of about 2 to 5cm) and any coiling of extrudate were noted.

3.2.3(iii) High Speed Video Recording

A high speed video recorder (Kodak Ektapro 1000 Imager, Serial number 6278) was used to compare the production of smooth-surfaced extrudate with that of badly sharkskinned extrudate. Recordings were made of the extrusion "runs" given in Table 3.4. All extrusions were made
Figure 3.3 The Surface Characteristics of the Extrudate

Table 3.4 THE EXTRUSION RUNS RECORDED ON HIGH SPEED VIDEO

<table>
<thead>
<tr>
<th>Run</th>
<th>Formulation</th>
<th>Extrusion Piston</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Speed</td>
</tr>
<tr>
<td>1</td>
<td>Avicel PH101 (5:5:6&lt;sub&gt;H&lt;/sub&gt;&lt;sub&gt;ccc&lt;/sub&gt;)</td>
<td>10 cm/min</td>
</tr>
<tr>
<td>2</td>
<td>Avicel PH101 (5:5:6&lt;sub&gt;Mc&lt;/sub&gt;&lt;sup&gt;C&lt;/sup&gt;)</td>
<td>20 cm/min</td>
</tr>
<tr>
<td>3</td>
<td>Avicel PH101 (5:5:6&lt;sub&gt;H&lt;/sub&gt;&lt;sub&gt;ccc&lt;/sub&gt;)</td>
<td>50 cm/min</td>
</tr>
<tr>
<td>4</td>
<td>Unimac MG100 (5:5:6&lt;sub&gt;H&lt;/sub&gt;&lt;sub&gt;ccc&lt;/sub&gt;)</td>
<td>10 cm/min</td>
</tr>
<tr>
<td>5</td>
<td>Unimac MG100 (5:5:6&lt;sub&gt;H&lt;/sub&gt;&lt;sub&gt;ccc&lt;/sub&gt;)</td>
<td>20 cm/min</td>
</tr>
<tr>
<td>6</td>
<td>Unimac MG100 (5:5:6&lt;sub&gt;H&lt;/sub&gt;&lt;sub&gt;ccc&lt;/sub&gt;)</td>
<td>50 cm/min</td>
</tr>
</tbody>
</table>
through a die of 1.5mm diameter and length to radius ratio = 16. In order to make the recordings, the two arms of a non-heat-producing light source (Olympus Type FLQ 85E, Olympus Optical Co., Hamburg, W.Germany) were positioned through holes which had previously been drilled through the collecting C-piece at an angle such that the extrudate was illuminated as it emerged from the die. (Both the C-piece and the underside of the die had been painted with non-reflective black paint to minimise reflections.) The imager was focussed onto the extrudate using a Fuginon Zoom lens (H6 x 12.5R 1;12/12.5 - 75, no. 958630) with a Paillard-Bolex 10mm extension ring. The whole assembly was mounted on a Manfrotto Professional Tripod (Model #058). The appropriately positioned and focussed imager was switched on and allowed to record at 1000 frames per second for thirty seconds. (Thirty seconds is the maximum time for which the equipment is able to record in one unbroken run, and is easily adequate for the investigations undertaken here.) The imager was connected to a Kodak Ektapro 1000 Processor (Serial no. 3243) which recorded the image on Kodak Ektapro 1000 Cassette Tape. The recorded images were displayed on a Pansonic Video Monitor (Model W5-5410/B, Serial no. 6104574) and thermally printed "stills" could be obtained at appropriate time intervals using a Mitsubishi Video Copy Processor (Model P60B). Each recording was transferred onto Kodak Eastman Professional E-120 HG Video Tape using a Panasonic Video Recorder (Model AG-6200-B, Serial no. H6TA00242) which records at 30 frames per second. Thus, the resulting video tape shows the extrusion process at one thirtieth of the actual speed of extrusion. The "stills", on Mitsubishi thermal paper SCT-K60S/K60S, are presented as part of Chapter Nine, along with an edited version of the final video tape.
3.2.4 Electron Microscopy

Two electron microscopy techniques were used to examine extrudate samples as well as individual microcrystalline cellulose powders. All the electron microscopy work reported in this thesis was performed at FMC Corp., Chemical Products Group, to whom I remain indebted.

3.2.4(i) Cryogenic Scanning Electron Microscopy of Extrudate Samples

A cryogenic scanning electron microscopy technique was used to compare extrudate samples produced from formulations based on different grades of microcrystalline cellulose. The cryogenic technique was chosen because it allows an image to be achieved which reflects the structure of the extrudate in its "wet" (flash frozen) state, whereas conventional electron microscopy requires that the extrudate be dried.

All samples were prepared following the same procedure. First, the extrudate sample was placed in the hole of a specimen stub, allowing for the sample to stand vertically upright. The extrudate was then frozen in a nitrogen slush, using the nitrogen slushing chamber of a Hexland Cryotrans System CT1000. The sample was vacuum transferred to a Scanning Electron Microscope (SEM) pre-chamber, where it was fractured along its longitudinal axis. It was then moved to the SEM chamber of an Amray 1000B SEM, sublimed by heating from -160°C to -75°C, and then removed to the pre-chamber where it was cooled to -160°C again. While in the pre-chamber, the sample was gold-coated for six seconds. It was then returned to the SEM chamber for viewing at magnifications of 250x, 500x, 1000x, 1500x, 2000x and 2500x. Photographic prints were obtained at each of these magnifications for extrudate samples based on standard formulations of the following
grades of microcrystalline cellulose: Avicel PH101, Unimac MG100, Emcocel, Avicel RC581.

3.2.4(ii) Scanning Electron Microscopy of Microcrystalline Cellulose Powders

In order to assist in the interpretation of the cryogenic SEMs of extrudate samples, individual grades of microcrystalline cellulose were also examined by scanning electron microscopy. A sample of each powder was sprinkled onto conductive copper tape and then gold-coated using three cycles. They were viewed at 150x and 600x and photomicrographs were obtained at each of these magnifications for the following grades: Avicel PH101, Avicel PH102, Unimac MG100, Unimac MG200, Emcocel.
PART THREE

RESULTS AND DISCUSSION
Preliminary investigations were undertaken to enable the experimental procedures used throughout this work to be more closely defined. They included an assessment of the effect on the steady state extrusion force of (a) the equilibration time allowed between the mixing of the wet powder mass and its subsequent extrusion and (b) the materials from which the barrel and die were manufactured.

4.1 THE EFFECT OF EQUILIBRATION TIME

Wet mixes based on six different grades of microcrystalline cellulose were mixed in the standard formulation of 5:5:6\(_{\text{MCC}}\). Immediately after mixing, the formulations were extruded at a constant piston speed of 20cm/min through dies of various length to radius ratio. The extrusions were repeated after the mixes had been allowed to equilibrate in sealed polythene bags for various lengths of time, and for each extrusion a force/displacement profile was obtained.

The steady state extrusion forces were read from the force/displacement profiles and the results for each formulation are shown graphically in Figures 4.1 (i) to (vi), in terms of the steady state extrusion force with respect to equilibration time of the wet mix, with die length to radius ratio as a variable.

It can be seen from Figures 4.1 (i) to (vi) that each formulation exhibits a "cut off" equilibration time, before which the forces required for steady state extrusion are not reproducible. For some formulations, e.g. Avicel PH101 (5:5:6\(_{\text{MCC}}\)), this cut off time is about four hours, whereas for others, e.g. Avicel RC581 (5:5:6\(_{\text{MCC}}\)), it is longer. In practice, it was concluded that the most satisfactory procedure for obtaining reproducible results in terms of the forces
Fig 4.1(i) Effect of Equilibration Time

Avicel PH101 (5:5:6mcc)

Steady State Extrusion Force (kg)

Fig 4.1(ii) Effect of Equilibration Time

Avicel PH103 (5:5:6mcc)

Steady State Extrusion Force (kg)

Equilibration Time (Hours)
Fig 4.1 (v) Effect of Equilibration Time

Avicel RC581 (5:5:6mcc)

Steady State Extrusion Force (kg)

Equilibration Time (Hours)

Die L/R: 2 8 20

Avicel RC591 (5:5:6mcc)

Steady State Extrusion Force (kg)

Equilibration Time (Hours)

Die L/R: 2 8 16
required for steady state extrusion, was to mix the wet masses and then allow them to equilibrate overnight (thus giving an equilibration time exceeding twelve hours), in sealed polythene bags, prior to extrusion. This procedure was adopted and applies to the remainder of the results in this thesis.

4.2 THE EFFECT OF THE BARREL AND DIE MATERIALS

A single batch of Avicel PH101 \(5:5:6_{\text{HCC}}\) formulation was mixed and allowed to equilibrate in the usual way. It was then extruded at a piston speed of 40cm/min through a 1.5mm diameter die of length to radius ratio = 16, but using different combinations of barrel and die as follows:

(a) Hardened steel barrel plus hardened steel die  
(b) Hardened steel barrel plus stainless steel die  
(c) Stainless steel barrel plus stainless steel die  
(d) Mild steel barrel plus stainless steel die

For each extrusion a force/displacement profile was obtained, from which the steady state extrusion force was extrapolated. The forces required for steady state extrusion of the Avicel PH101 \(5:5:6_{\text{HCC}}\) formulation using each barrel and die assembly are presented in Table 4.2.

The results indicate that the material from which the die is manufactured affects the force required for steady state extrusion, whereas the material from which the barrel is made has little or no effect on this force. This may be due to differences in the frictional effects between the various die materials and the formulation when the latter is forced through the die.
Table 4.2  THE EFFECT OF BARREL AND DIE MATERIALS ON THE FORCE REQUIRED FOR THE STEADY STATE EXTRUSION OF AN AVICEL PH101 (5:5:6w/w) FORMULATION

Piston Speed = 40cm/min, Die L/R = 16

<table>
<thead>
<tr>
<th>BARREL MATERIAL</th>
<th>DIE MATERIAL</th>
<th>STEADY STATE EXTRUSION FORCE (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardened steel</td>
<td>Hardened steel</td>
<td>1035</td>
</tr>
<tr>
<td>Hardened steel</td>
<td>Stainless steel</td>
<td>530</td>
</tr>
<tr>
<td>Stainless steel</td>
<td>Stainless steel</td>
<td>560</td>
</tr>
<tr>
<td>Mild steel</td>
<td>Stainless steel</td>
<td>550</td>
</tr>
</tbody>
</table>


It was concluded that, in order to obtain results which were reproducible in terms of the steady state extrusion force, a single type of barrel and die should be used throughout the work. Accordingly, a single stainless steel barrel and a single set of stainless steel dies were used for all subsequent extrusions recorded in this thesis.
CHAPTER FIVE

THE FORCE/DISPLACEMENT PROFILE RESULTS
During the experimental extrusion process, the force applied by the piston on the material in the barrel is monitored, in terms of the piston displacement, in the form of a force/displacement profile, as described in Section 3.2.2(ii).

Force/displacement profiles were obtained for the extrusion of formulations based on each grade of microcrystalline cellulose through dies of various length to radius ratio and at various extrusion speeds. The profiles could be divided into three stages; the compression stage, the steady state flow stage and the forced flow stage, (Section 3.2.2(ii)). The ideal force/displacement profile should exhibit a short compression stage, a long steady state flow stage with a low and even steady state extrusion force, and little or no forced flow. The profiles obtained are shown in Figures 5.1 to 5.4.

The first result to be noted is the effect that the amount of water used in the formulation has on the force/displacement profiles. (This effect could be seen only for formulations based on powdered grades of microcrystalline cellulose, since formulations based on colloidal grades are too moisture sensitive to allow a wide range of water contents to be studied - cf the strict requirement for the addition of water to colloidal grade formulations during wet massing, Section 4.1.) Secondly, the effect of the grade of microcrystalline cellulose used in the formulation on the profiles may be examined, in particular with respect to the die length to radius ratio and the extrusion speed. Finally, the use of sodium carboxymethylcellulose solution as the binder in otherwise standard powdered grade formulations, in an attempt to mimic the behaviour of the colloidal grade formulations (which include sodium carboxymethylcellulose as a co-constituent of
the proprietary grade of microcrystalline cellulose; Avicel RC/CL grades), may be investigated.

5.1 THE EFFECT OF THE WATER CONTENT OF THE FORMULATION

The effect of the water content of the formulation on the force/displacement profiles is shown typically by Figure 5.1. This figure illustrates the profiles obtained for the extrusion (through a 1.5mm diameter die of length to radius ratio = 4, at a piston speed of 40cm/min) of formulations based on Unimac MG200 microcrystalline cellulose and lactose, with water in various quantities. It can be seen from Figure 5.1 that the quantity of water used in the formulation affects all three stages of the force/displacement profile: compression, steady state flow and forced flow. It was found that formulations based on all powdered grades of microcrystalline cellulose resulted in force/displacement profiles which were affected by the water content of the formulation in a similar manner to that shown in Figure 5.1. Thus Figure 5.1 may be taken as representative of the effect of the amount of water in the formulation on the force/displacement profiles of microcrystalline cellulose powdered grade formulations.

5.1.1 The Effect of the Water Content of the Formulation on the Compression Stage

During the compression stage, the material in the barrel is reduced in volume by particle rearrangement, and this results in a densification of the wet powder mass. The compression stage has been shown (by Sheppard and Clare (1972) for aluminium powders, and by Harrison et al. (1987) for pharmaceutical wet masses) to continue until densification is complete, i.e. until the apparent density of the material in
FIG. 5.1 THE EFFECT OF WATER CONTENT ON THE FORCE/DISPLACEMENT PROFILE

Unimac MG200 + Lactose & Water
Extruded at piston speed 20 cm/min through L/R die = 4
the barrel is approximately equal to the apparent density of the mass itself. Figure 5.1 shows that the amount of water in the formulation affects the compression stage in two ways, as follows.

5.1.1(i) The Length of the Compression Stage

It may be seen from Figure 5.1 that a reduction in the amount of water used in the formulation results in an increase in the length of the compression stage. This indicates that dry material requires a greater degree of volume reduction in order to achieve zero interparticulate voidage prior to flow than correspondingly wet material. This result may be explained as follows. Prior to compression, the material in the barrel is initially composed of powder particles, water and air. The material is known, however, to pack to zero porosity on compression - this means that immediately prior to extrusion any water in the formulation must be in the "capillary" state, i.e. with the powder particle interstices occupied only by water. The compression stage can therefore be surmised as the removal of air from the system. Formulations containing a lower proportion of water (and thus a correspondingly higher proportion of air) will therefore require a greater degree of compaction in order to achieve this zero porosity capillary state, and so the volume to which they are compressed prior to extrusion will be smaller. (This explanation is supported by the work of Benbow et al. (1987) who state that a slow build up of force without paste extrusion indicates the presence of large air bubbles.)

5.1.1(ii) The Build Up of Force Prior to Extrusion

Figure 5.1 also indicates that the rate of change of applied force with displacement during the compression stage (i.e. the build up of force prior to extrusion) is lower for formulations containing a higher proportion of water. This implies that the force required to rearrange the powder mass to its minimum volume (i.e. the force
required to overcome interparticulate friction and friction between the material and the barrel wall) is lower at higher water contents. This may be explained in part by the fact that wetter material does not require such a high degree of volume reduction in order to achieve zero porosity as dry material, as outlined in 5.1.1(i) above. Additionally, the superior lubricating and flow properties of water in comparison to the powder particles used, mean that when a greater amount of water is contained within a formulation, less force is required to cause the constituents of that formulation to rearrange.

5.1.2 The Effect of the Water Content of the Formulation on the Steady State Flow Stage

During steady state flow, the force required for continuing extrusion does not change with piston displacement. This has been attributed to the existence of characteristic convergent flow patterns within the material as it moves from the barrel into the die (Harrison et al., 1984) (see Section 3.2.2(ii)). Figure 5.1 indicates that the amount of water in the formulation affects various aspects of the steady state extrusion stage as outline below.

5.1.2(1) The Magnitude of the Force Required for Steady State Extrusion

It may be seen from Figure 5.1 that formulations containing a lower proportion of water require a higher applied force in order to develop steady state extrusion than those containing a higher proportion of water. In addition, it may be noted that the steady state extrusion forces of the drier formulations are more uneven. These results indicate that the wetter formulations pass through the die more easily and with better homogeneity than the drier formulations, possibly due to an increased "self-lubrication" of the formulations at the die wall with increasing water content.
5.1.2(11) The Contribution of the Barrel Wall Stresses to the Steady State Extrusion Force

Figure 5.1 shows that the supposed "plateau" steady state extrusion force actually decreases gradually with piston displacement for the two wettest formulations. This phenomenon has been found to occur in the extrusion of some α-alumina pastes (Benbow et al., 1987) and indicates that the stresses at the barrel wall play a significant part in the total extrusion force. As the piston descends, the length of the material in the barrel decreases, and so there is a corresponding drop in the resistance to flow offered by the barrel wall. This resistance will be proportional to the column length and inversely dependent on barrel diameter. The contribution made by the barrel to the total pressure drop is usually insignificant in pharmaceutical systems, because the barrel diameter is so much larger than that of the die. However, in the case of the two wettest formulations, the contribution of the barrel resistance is detectable in the gradually decreasing steady state extrusion forces seen for those formulations in Figure 5.1.

5.1.2(11) The "Pressure Overshoot" Phenomenon

An additional point of interest in Figure 5.1 is that the formulation containing just 28.6% water exhibits an initial peak force immediately prior to the development of steady state flow. This phenomenon has been found to occur previously in pharmaceutical systems (Jehl, 1977; Fielden, 1987) but has remained without explanation. It is sometimes seen to occur in the extrusion of polymer melts, and has been described as "pressure overshoot". For example, Akay (1982) has found pressure overshoot to occur in the capillary flow of filled and unfilled poly-propylene melts, and attributes it to capillary resistance. This explanation may also be applied to these pharmaceutical systems; it is clear that drier formulations, which require
correspondingly greater forces to be extruded than wetter formulations (Section 5.1.2(i)), will be less able to overcome capillary resistance and will therefore be more likely to exhibit pressure overshoot. A convenient way of surmising this effect is to imagine that the compression and steady state flow stages overlap so that the material in the barrel continues to undergo compression for some time after steady state flow has been established. The extent of the overlap will be inversely dependent on the ability of the material to overcome capillary resistance. Thus, the drier the formulation, the greater the overlap of the compression stage into the steady state flow stage, and therefore the more significant the pressure overshoot.

It can be concluded that wetter material requires a lower force to maintain steady state flow than drier formulations. However, for the wet formulations, the measured force includes a component relating to barrel resistance which is not seen in drier formulations. For the driest formulations, the steady state flow stage is preceded by a region of pressure overshoot. Formulations with an intermediate water content of about 32 to 38% do not display either of these disadvantageous characteristics in the steady state flow stage.

5.1.3 The Effect of the Water Content of the Formulation on the Forced Flow Stage

During the forced flow stage, the force required for continuing extrusion increases with piston displacement. This has been attributed to the inability of the material to maintain its natural convergent flow patterns either because the piston has reached the vicinity of the die (Harrison et al., 1984) (see Section 3.2.2(ii)) or because water has been pushed out in the early stages of extrusion (Fielden, 1987). Once the piston has entered the annular "static zone" beneath
the convergent flow vortex, the flow patterns break down and forced flow ensues (Benbow et al, 1987). The forced flow stage is affected by the water content of the formulation as follows.

5.1.3(i) The Onset of Forced Flow

Figure 5.1 shows that the formulations containing a lower proportion of water have shorter steady state flow stages than the wetter formulations. This may be explained in part by the fact that the drier formulations exhibit longer compression stages. However, it should also be noted that the wetter formulations are able to maintain steady state flow even when the piston begins to approach the vicinity of the die - a situation in which the convergent flow patterns of the drier formulations break down, resulting in forced flow. (This finding is in agreement with those of Fielden (1987), who showed that forced flow may ensue when water is lost in the early stages of extrusion.) This implies that any static zone present in the wetter materials is very small compared to those which occur in the drier formulations.

5.2 THE EFFECT OF THE MICROCRYSTALLINE CELLULOSE GRADE USED IN THE FORMULATION

The effect of the grade of the microcrystalline cellulose used in the formulation on the force/displacement profiles is illustrated by Figures 5.2 (i) to (xi) and 5.3 (i) to (xi):

Figures 5.2 show the effect of the grade used with respect to the length to radius ratio of the die. They show the profiles obtained for the extrusion (at a piston speed of 20cm/min) of formulations based on each grade of microcrystalline cellulose through dies of 1.5mm diameter and various length to radius ratio.
Figures 5.3 show the effect of the grade used with respect to the piston speed. They show the profiles obtained for the extrusion (through a die of 1.5mm diameter and length to radius ratio = 4) of formulations based on each grade of microcrystalline cellulose at various piston speeds.

5.2.1 The Effect of the Microcrystalline Cellulose Grade Used, with Respect to the Length to Radius Ratio of the Die

It can be seen from Figures 5.2 (i) to (xi) that the die length to radius ratio does not appreciably affect the length of the compression stage, nor the build up of force prior to extrusion, for any of the formulations studied. Neither does it affect the length of the steady state flow stage before the onset of forced flow. However, an increase in the die length to radius ratio does result in an increase in the applied force necessary to maintain steady state flow, and in an increase in the magnitude of the forces exhibited during the forced flow stage. This is the case for formulations based on all grades of microcrystalline cellulose studied. These results are in agreement with Harrison et al. (1987), who found that the extrusion force depended on die length to radius ratio for pharmaceutical wet masses based on microcrystalline cellulose, but are at variance with the results of Sheppard and Clare (1972), who found that extrusion force was independent of length to radius ratio for aluminium powders. The difference between these results may be explained by the fact that Sheppard and Clare used systems in which the dies were intentionally lubricated at the wall by a liquid film, which minimised the die wall shear stress, thereby rendering the systems less sensitive to differences in shear stress caused by increasing the die length. The unlubricated extrusion of pharmaceutical wet powder masses, however, is clearly more susceptible to increased die length, exhibiting larger
shear stresses through dies with longer walls. The extent to which an increased die length to radius ratio affects the steady state extrusion force of pharmaceutical wet masses will thus depend on the specific rheological characteristics of each formulation, and in particular the extent to which each has the ability for "self-lubrication" at the die wall. It is therefore worthwhile to examine the effect of the formulation on the force/displacement profiles, with respect to the die length to radius ratio, in more detail.

5.2.1(i) The Powdered Grade Formulations

Figures 5.2 (i) to (iv) show the force/displacement profiles with respect to the die length to radius ratio for formulations based on the "Avicel PH" grades of microcrystalline cellulose. Figures 5.2 (v) to (vii) show the profiles for formulations based on "Emcocel" and "Unimac" powdered grades. The Avicel-based formulations are seen to exhibit comparatively even forces throughout steady state extrusion (and even during the forced flow stage the increase in force is fairly uniform). However, the Emcocel- and particularly the Unimac-based formulations exhibit more variable forces during both stages of extrusion. This result implies that the rheology of the formulations based on Emcocel and especially Unimac grades of micro-crystalline cellulose, is subject to a greater degree of local variation than that of the Avicel-based formulations. It may be that those grades' formulations mix or equilibrate or compress slightly differently from Avicel-based formulations, so that they are then less homogeneous in terms of the force required for their steady state extrusion.

Figures 5.2 (i) to (vii) also show that the effects of increasing the die length to radius ratio (i.e. an increase in steady state extrusion force and a more prominent forced flow stage, as discussed in Section 5.1.2) are more pronounced for formulations based on Emcocel and
FIG. 5.2 EFFECT OF DIE L/R RATIO ON THE FORCE/DISPL. PROFILE
at Piston Speed 20 cm/min
FIG 5.2 EFFECT OF DIE L/R RATIO ON THE FORCE/DISPL. PROFILE
at Piston Speed 20 cm/min.
Unimac grades than for Avicel-based formulations. For example, an increase in die length to radius ratio from 4 to 16 causes the steady state extrusion force of the Avicel PH101 formulation to increase from about 270 to about 520 kg, whereas this same increase in die length to radius ratio causes the steady state extrusion force of the Unimac MG100 formulation to increase from about 280 to about 770 kg. As stated previously, these differences in response to die length to radius ratio arise due to the different rheological characteristics of each formulation, which result in each having a characteristic type and/or extent of interaction with the die wall. The differences can best be represented as differences in the calculated die wall shear stresses for each formulation (see Section 2.1.3(iii), equation 2.10) and these will be discussed later in Chapter Six ("The Bagley Plot Results").

5.2.1(ii) The Colloidal Grade Formulations

Figures 5.2 (viii) to (xi) show the force/displacement profiles with respect to die length to radius ratio for formulations based on the "Avicel RC/CL" colloidal grades of microcrystalline cellulose. As for powdered grade formulations, an increase in the die length to radius ratio causes an increase in the steady state extrusion force, and this increase is more pronounced for some formulations than for others. However, unlike powdered grade formulations, colloidal grade formulations exhibit no forced flow on extrusion - even at the highest value of die length to radius ratio. Forced flow has been attributed to the penetration by the piston of the static zone beneath the convergent flow vortex (as mentioned in Section 5.1.3) and so the absence of forced flow in the extrusion of colloidal grade formulations implies that their convergent flow vortices are very shallow compared to those which form within powdered grade formulations (or that they are less sensitive to interruption by the piston). In this respect, the
colloidal grade formulations are similar to the wettest powdered grade formulations (Section 5.1.2(ii)) which also appear to form very shallow flow vortices.

Figures 5.2 (viii) to (xi) also indicate a similarity between the colloidal grade formulations and the driest powdered grade formula­tion, in that both are seen to exhibit a peak force, or "pressure overshoot", at the onset of steady state flow (see Section 5.1.2(iv)). The pressure overshoot phenomenon, in which the compression of the material continues for some time after the development of steady state flow, is shown by the figures to become more significant at higher die length to radius ratios. Akay (1982), in the extrusion of filled and unfilled polypropylene melts, also found that pressure overshoot was more significant when the die length to radius ratio was large, and attributed it to the increased capillary resistance of longer dies. These results for pharmaceutical formulations are further evidence that long, narrow dies offer a greater degree of capillary resistance to the material in the barrel, and that this results in a greater degree of pressure overshoot.

The degree to which each formulation exhibits pressure overshoot is a measure of its difficulty in overcoming capillary resistance. Capillary resistance may be thought of as an entrance pressure loss, and as such will be included in the value for the upstream pressure loss ($P_0$) when it is calculated for each formulation from equation 2.10 (Section 2.1.3(iii)). Thus, those formulations which exhibit a high degree of pressure overshoot would be expected to have a high value for the upstream pressure loss. This prediction is confirmed by the results in Chapter Six ("The Bagley Plot Results").
5.2.2 The Effect of the Microcrystalline Cellulose Grade Used, with respect to the Piston Speed

It can be seen from Figures 5.3 (i) to (xi) that the piston speed does not appreciably affect the length of the compression stage, nor the build up of force prior to extrusion for any of the formulations studied. However, an increase in the piston speed does cause an increase in the applied force required to maintain steady state extrusion, and also results in a lengthening of the steady state flow stage before the onset of forced flow. These results are supported by those of Harrison et al. (1984) who found similar effects for pharmaceutical wet powder masses. It is worthwhile to examine the effect of the formulation on the force/displacement profiles, with respect to piston speed, in more detail.

5.2.2(i) The Powdered Grade Formulations

Figures 5.3 (i) to (vii) show the force/displacement profiles with respect to extrusion speed for formulations based on powdered grades of microcrystalline cellulose. The figures illustrate the dependence of the steady state extrusion force and the length of the steady state plateau on extrusion speed. Harrison et al. (1984) attributed the early onset of forced flow at slow extrusion speeds to the existence of a moisture gradient between the material in the barrel and the extrudate. They postulated that this moisture gradient occurs more readily at low piston speeds, with the consequence that the convergent flow patterns break down, resulting in forced flow. Simple observation of the extrusion of powdered grade formulations throughout this present work has shown that a small amount of water is "pushed out" of the material mix immediately prior to the onset of extrusion flow (see the high speed video recording presented as part of Chapter Nine). However, the amount of water lost from the formulations in this way does not appear to be affected by ram speed. An alternative
FIG. 5.3 THE EFFECT OF EXTRUSION SPEED ON THE FORCE/DISPL. PROFILE through die $L/R = 4$
FIG 5.3 THE EFFECT OF EXTRUSION SPEED ON THE FORCE/DISPL. PROFILE through die $L/R = 4$
explanation for the fact that steady state prevails for longer at high extrusion speeds could be that while increased speed will clearly be resisted in terms of flow through the die, it may actually be a facilitating force in terms of flow into the die. In other words, increased speed may assist the formulation in rearranging into a shallower convergent vortex than would be expected. Although this hypothesis is very different from that of Harrison et al. (1984), support for it arises from two sources: (a) the flow curves for powdered grade formulations (Chapter Seven) show clearly that their internal structures are rearranged at high shear rates and (b) the Benbow-Bridgwater results for powdered grade formulations (Chapter Eight, Table 8.2) indicate that, while the die wall shear stress increases fairly steadily with extrusion speed, the yield value of the materials increases significantly less as shear rate increases, implying that the fundamental change in structure affects flow into, rather than through, the die.

The effects of increasing the piston speed (i.e. higher steady state extrusion forces and longer steady state plateaux) were more pronounced for formulations based on Unimac or Emcocel grades of microcrystalline cellulose than for those based on Avicel powdered grades. The differences between formulations, in terms of the response of their steady state extrusion forces to piston speed, are best represented as differences in the calculated values of their die land velocity factors and die entry yield stress velocity factors (see Section 2.4.1, equation 2.28 and Section 2.4.4, equation 2.35, respectively). These values will be discussed in Chapter Eight ("The Benbow-Bridgwater Results").
5.2.2(ii) The Colloidal Grade Formulations

Figures 5.3 (viii) to (xi) show the force/displacement profiles with respect to extrusion speed for formulations based on colloidal grades of microcrystalline cellulose. As for powdered grade formulations, the steady state extrusion force and the length of the steady state plateau are dependent on piston speed. However, colloidal grade formulations exhibit no forced flow even at the lowest extrusion speeds. Visual observation of the extrusion process indicates that the colloidal grade formulations do lose water prior to extrusion – further evidence that the theory of Harrison et al. (1984), that forced flow at low extrusion speeds is linked to the presence of a moisture gradient between the material in the barrel and the extrudate, is not an adequate explanation of the phenomenon (see Section 5.2.2(i).

The colloidal grade formulations all exhibit pressure overshoot at the onset of steady state flow (see Section 5.1.2(iv)). The pressure overshoot (the overlap between the compression and steady state flow stages) is shown by the figures to become more significant at higher piston speeds. This result is supported by the work of Akay (1982), who also found that pressure overshoot increased with the flow rate of 40% calcium carbonate-filled polypropylene melts, and so implies that it is harder to overcome capillary resistance at high extrusion speeds. (In 1983, Akay found that the apparent "pressure overshoot" exhibited by short glass fibre reinforced polypropylene melts did not grow with increasing flow rate, but disappeared once the flow rate had increased to a critical level. This peak was described by him as the single isolated peak of a pressure oscillation cycle, occurring when the flow rate of the system was very nearly equal to the flow rate above which unstable flow was eliminated. This different type of
FIG. 5.3 THE EFFECT OF EXTRUSION SPEED ON THE FORCE/DISPL.PROFILE through die $L/R = 4$
"pressure overshoot" may thus be attributed to unstable flow, and is not implicated for the colloidal grade formulations discussed in this section.) As mentioned in Section 5.2.1(ii), the prediction that formulations exhibiting a high degree of pressure overshoot will also have a high value for upstream pressure loss is confirmed by the results presented in Chapter Six.

5.3 THE USE OF SODIUM CARBOXYMETHYLCELLULOSE SOLUTION AS THE BINDER IN THE FORMULATION

Figures 5.4 (i) to (iv) show that the attempt to mimic colloidal grade formulations by the use of sodium carboxymethylcellulose as the binder in an otherwise standard Avicel PH101 formulation results in force/displacement profiles which are similar in some respects to those of the wettest powdered grade formulations and in other respects to those of the colloidal grade formulations.

They exhibit very short compression stages, steady state plateaux which decrease slightly with piston displacement and no forced flow. It may also be noted that the forces required to maintain steady state extrusion are very low for extrusion through dies of all length to radius ratios and at all piston speeds. These results imply that the use of sodium carboxymethylcellulose in the water used for wet massing confers properties on powdered grade formulations which are usually associated with those which have been overwetted, i.e. (a) a low degree of volume reduction is required to achieve the zero-porosity compact state prior to the commencement of flow (b) a degree of interaction exists between the formulation and the barrel wall (c) the formulations have a convergent flow vortex which is negligible in size
FIG 5.4 EFFECT OF DIE \( L/R \) RATIO ON THE FORCE/DISPL. PROFILE

at Piston Speed 20 cm/min
FIG 5.4  THE EFFECT OF EXTRUSION SPEED ON THE FORCE/DISP. PROFILE
through die $L/R = 4$

(iii) AVICEL PH101 (5:5:6 with 8% NaCMC Solution as Binder)

(iv) AVICEL PH101 (5:5:6 with 16% NaCMC Solution as Binder)
(or else affected negligibly by the proximity of the piston to the die entry region).

Figures 5.4 (i) to (iv) also indicate that powdered grade formulations wet massed with sodium carboxymethylcellulose solution exhibit a degree of pressure overshoot at the onset of steady state flow. In other words, like the colloidal grade formulations (which include sodium carboxymethylcellulose as a co-constituent of the proprietary grade of microcrystalline cellulose), these formulations show some inability to overcome capillary resistance, with the result that the compression and steady state flow stages overlap.

The amount of sodium carboxymethylcellulose used in the binder of the Avicel PH101 formulation appears to affect the force/displacement profile. The formulation bound with 8% NaCMC solution has a superior profile (lower steady state extrusion forces, less pressure overshoot) to that bound with 16% NaCMC solution. It may be that there is an optimum level of lubrication enhancement provided at a certain concentration of NaCMC, and this possibility will be discussed more fully in later Chapters.
CHAPTER SIX

THE BAGLEY PLOT RESULTS
The force/displacement profiles discussed in Chapter Five were used to determine the force required for the steady state extrusion of each formulation at different extrusion speeds through dies of various length to radius ratio. The values of steady state extrusion force were converted to steady state extrusion pressure, by dividing by the surface area of the piston face, 5.067 cm$^2$ (the area over which the force was applied). The results are presented in Tables 6.1 to 6.4; each value is a mean of five results and is presented with its associated standard deviation.

For each of the formulations, extruded at each speed, the steady state extrusion pressure was plotted as a function of the die length to radius ratio to create a "Bagley Plot" (see Section 2.1). The Bagley plots are presented in Figures 6.1 to 6.16. (In each case, the highest value of die length to radius ratio used was 16, because previous workers (such as Harrison, 1982) have found that Bagley plots may deviate from linearity when the length to radius ratio exceeds this value, probably due to the formation of a moisture gradient within the die.)

From Figures 6.1 to 6.16, and from the values of the correlation coefficients presented in Tables 6.1 to 6.4, it may be seen that linearity of the Bagley plots was maintained for all formulations over the range of die length to radius ratios used (although the plots of some of the drier formulations were non linear at the lowest extrusion speeds). This linearity enabled the values of the upstream pressure loss ($P_0$) to be obtained as the y-intercepts of the Bagley plots, and the die wall shear stresses ($t_w$) as half the gradients (equation 2.10). The values of die wall shear stress and upstream pressure loss for the various formulations at different extrusion speeds are
presented in Tables 6.5 to 6.8. The die wall shear stress may be seen to be extrusion rate dependent, and this is probably due to increased friction at the die wall as the extrusion rate is increased. The upstream pressure loss also increases with the extrusion rate, presumably due to an increase in the frictional losses created by the shear of the material upstream of the die entrance.

6.1 THE EFFECT OF THE WATER CONTENT OF THE FORMULATION ON THE BAGLEY PLOT RESULTS

The effect of the water content of the formulation on the Bagley plots may be seen from the results for the Avicel PH101 formulation illustrated in Figures 6.1 to 6.4 and shown in Table 6.1. Formulations containing non-standard amounts of water were found to exhibit values of steady state extrusion pressure which did not correlate well with die length to radius ratio at low extrusion speeds; the table thus shows values only for higher extrusion speeds.

Table 6.1 gives results at three different water contents, but they are representative of the trends which are shown when the water content is varied over seven different levels, illustrated for the Avicel PH101 formulation extruded at 40cm/min through a die length to radius ratio = 16 by Figure 6.17. Similar results were found for all powdered grade formulations. It may be seen from Figure 6.17 that an increase in water content results in a general decrease in the pressure required to maintain steady state extrusion. The decrease may be seen to negatively deviate from the general trend when the water content of the formulation is about 37.5%, i.e. a standard 5:5:6 formulation. This result implies that the 5:5:6 formulation contains water at some kind of optimum level for extrusion, which results in
Table 6.1 The Effect of the Water Content of the Formulation on the Bagley Plot Results

<table>
<thead>
<tr>
<th>Piston Speed (cm/min)</th>
<th>Av. Steady State Extrusion Pressure (kN/m², x10³) through various dies of L/R=</th>
<th>Gradient (kN/m²)</th>
<th>Y-Intercept (kN/m²)</th>
<th>Correln Coeff.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>16.3 ± 0.97 19.9 ± 1.47 22.1 ± 1.88 25.6 ± 1.98</td>
<td>752</td>
<td>13450</td>
<td>0.996</td>
</tr>
<tr>
<td>20</td>
<td>13.0 ± 1.05 17.2 ± 1.59 19.2 ± 1.75 22.1 ± 2.30</td>
<td>731</td>
<td>10550</td>
<td>0.989</td>
</tr>
<tr>
<td>40</td>
<td>21.8 ± 1.99 30.5 ± 2.75 35.2 ± 3.56 39.5 ± 3.81</td>
<td>442</td>
<td>17340</td>
<td>0.983</td>
</tr>
<tr>
<td>Avicel PH101 (5:5:4) Formulation (28.5% Water)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>8.9 ± 0.79 11.1 ± 1.20 12.8 ± 1.49 14.9 ± 1.28</td>
<td>491</td>
<td>6990</td>
<td>0.998</td>
</tr>
<tr>
<td>20</td>
<td>6.0 ± 0.62  7.7 ± 0.69  9.0 ± 0.87  9.8 ± 0.99</td>
<td>315</td>
<td>4980</td>
<td>0.986</td>
</tr>
<tr>
<td>40</td>
<td>12.3 ± 1.49 17.0 ± 1.27 19.2 ± 1.67 22.4 ± 2.24</td>
<td>816</td>
<td>9570</td>
<td>0.990</td>
</tr>
<tr>
<td>Avicel PH101 (5:5:5) Formulation (33.3% Water)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.2 ± 0.24  1.7 ± 0.19  1.8 ± 0.19  2.5 ± 0.21</td>
<td>104</td>
<td>770</td>
<td>0.968</td>
</tr>
<tr>
<td>10</td>
<td>1.7 ± 0.17  2.4 ± 0.29  3.0 ± 0.22  3.8 ± 0.36</td>
<td>175</td>
<td>970</td>
<td>0.999</td>
</tr>
<tr>
<td>20</td>
<td>1.7 ± 0.09  2.1 ± 0.25  2.9 ± 0.26  3.5 ± 0.33</td>
<td>157</td>
<td>980</td>
<td>0.996</td>
</tr>
<tr>
<td>40</td>
<td>2.7 ± 0.27  3.6 ± 0.31  4.5 ± 0.53  5.6 ± 0.61</td>
<td>246</td>
<td>1650</td>
<td>0.998</td>
</tr>
<tr>
<td>Avicel PH101 (5:5:8) Formulation (44.4% Water)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Figure 6.1** The Bagley Plot for the Avicel PH101 (5:5:4) Formulation

- **Extrusion Pressure (kN/m² x 10E3)**
- **Piston Speed (cm/min)**
  - X 10
  - X 20
  - X 40
- **Die Length To Radius Ratio**

**Figure 6.2** The Bagley Plot for the Avicel PH101 (5:5:5) Formulation

- **Extrusion Pressure (kN/m² x 10E3)**
- **Piston Speed (cm/min)**
  - X 10
  - X 20
  - X 40
- **Die Length to Radius Ratio**
Figure 6.3 The Bagley Plot For the Avicel PH101 (5:5:8) Formulation

Figure 6.4 The Bagley Plot for the Avicel PH101 (5:5:6) Formulation

Extrusion Pressure (kN/m², x10E3)

Piston Speed (cm/min)

5  X  20
10  X  40

Die Length to Radius Ratio

Extrusion Pressure (kN/m², x10E3)

Piston Speed (cm/min)

2  X  20
5  X  40
10

Die Length to Radius Ratio
the value of steady state extrusion pressure being lower than expected. Further information about the effect of the water content on extrusion may be obtained by examining its effect on the values of die wall shear stress and upstream pressure loss derived from the Bagley plots.

Table 6.5 shows that an increase in water content tends to result in a decrease in the die wall shear stress at any particular extrusion speed. This result is to be expected since the formulations containing a higher proportion of water are likely to have superior self-lubricating properties as they flow through the die, resulting in reduced friction at the die wall. However, the graph in Figure 6.18 shows that the die wall shear stress decreases even more than expected when the water content of the formulation is about 37.5%, implying that this level of water provides very efficient die lubrication.

The value of the upstream pressure loss also decreases with increasing water content, indicating that less pressure is lost upstream of the die when the formulation is very wet. According to Bagley (1957), this result implies that a high proportion of water in the formulation facilitates the formation of a convergent flow vortex at the die entrance, and aids the development of a laminar flow profile within the die (and/or reduces other minor pressure losses, such as kinetic energy losses; see Section 2.1.3(iii)). These conclusions appear reasonable, since a high proportion of water within the formulation should facilitate the ease of flow of the particles over one another as they converge at the die entrance. The graph in Figure 6.19 indicates that a water content of about 37.5% is particularly efficient in respect of the lowering of the upstream pressure loss.
6.2 THE EFFECT OF THE MICROCRYSTALLINE CELLULOSE GRADE USED IN THE
FORMULATION ON THE BAGLEY PLOT RESULTS: POWDERED GRADES

The effect on the Bagley plots of changing the grade of powdered microcrystalline cellulose used in the formulation is illustrated by Figures 6.4 to 6.10 and shown in Table 6.2.

All the powdered grade formulations exhibit Bagley plots with values for die wall shear stress ($\tau_w$) and upstream pressure loss ($P_0$) which are similar in magnitude (Table 6.6), but some trends may nonetheless be seen.

6.2.1 The Effect of the Microcrystalline Cellulose Particle Size

The effect of the particle size of the powdered microcrystalline cellulose used in the formulation on the Bagley plot results may be seen by comparing standard (5:5:6) formulations based on Avicel PH101 (average particle size, $m = 50\mu$), Avicel PH102 ($m = 100\mu$) and Avicel PH105 ($m = 20\mu$), and by comparing formulations based on Unimac MG100 ($m = 50\mu$) and Unimac MG200 ($m = 100\mu$).

For both series (Avicel and Unimac), the formulations based on the powder with the largest particle size generally exhibit a larger die wall shear stress but a smaller upstream pressure loss than the formulations based on the powder with the next largest particle size, i.e.

Die Wall Shear Stress:
- Avicel PH102 formulation > Avicel PH101 formulation
- Unimac MG200 formulation > Unimac MG100 formulation

Upstream Pressure Loss:
- Avicel PH101 formulation > Avicel PH102 formulation
- Unimac MG100 formulation > Unimac MG200 formulation
<table>
<thead>
<tr>
<th>Piston Speed (cm/min)</th>
<th>Av. Steady State Extrusion Pressure (kN/m², x10³) through various dies of L/R=</th>
<th>Gradient (kN/m²)</th>
<th>Y-Intercept (kN/m²)</th>
<th>Correln Coeff.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avicel PH101 (5:5:6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.1 ± .23 2.3 ± .17 2.8 ± .33 3.0 ± .21 3.4 ± .19</td>
<td>88</td>
<td>1990</td>
<td>0.993</td>
</tr>
<tr>
<td>5</td>
<td>3.5 ± .21 3.8 ± .35 5.1 ± .62 5.7 ± .21 6.6 ± .68</td>
<td>221</td>
<td>3094</td>
<td>0.993</td>
</tr>
<tr>
<td>10</td>
<td>4.4 ± .47 4.8 ± .43 6.5 ± .54 7.6 ± .50 8.7 ± .60</td>
<td>316</td>
<td>3762</td>
<td>0.995</td>
</tr>
<tr>
<td>20</td>
<td>4.6 ± .43 5.2 ± .58 7.2 ± .93 8.3 ± .81 10.0 ± .97</td>
<td>388</td>
<td>3828</td>
<td>0.996</td>
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<tr>
<td>40</td>
<td>5.2 ± .60 5.8 ± .74 7.6 ± 1.3 8.8 ± 1.3 10.6 ± 1.4</td>
<td>389</td>
<td>4327</td>
<td>0.999</td>
</tr>
<tr>
<td>Avicel PH102 (5:5:6)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.5 ± .45 2.6 ± .31 3.4 ± .52 3.8 ± .58 4.1 ± .60</td>
<td>125</td>
<td>2215</td>
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<tr>
<td>5</td>
<td>3.3 ± .33 3.9 ± .33 5.3 ± .56 6.0 ± .54 7.1 ± .60</td>
<td>270</td>
<td>2838</td>
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<tr>
<td>10</td>
<td>4.0 ± .50 4.6 ± .37 6.6 ± .68 7.7 ± .64 8.9 ± .76</td>
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<td>3373</td>
<td>0.994</td>
</tr>
<tr>
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<td>400</td>
<td>3783</td>
<td>0.996</td>
</tr>
<tr>
<td>40</td>
<td>5.1 ± .77 5.5 ± .76 7.4 ± .91 9.1 ± 1.2 11.0 ± 1.5</td>
<td>432</td>
<td>3975</td>
<td>0.998</td>
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</table>
Table 6.2 cont. The Effect of the Grade of Microcrystalline Cellulose used in the Formulation on
the Bagley Plot Results: Powdered Grades (continued overleaf)

<table>
<thead>
<tr>
<th>Piston Speed (cm/min)</th>
<th>Av. Steady State Extrusion Pressure (kN/m², x10³) through various dies of L/R=</th>
<th>Gradient (kN/m²)</th>
<th>Y-Intercept (kN/m²)</th>
<th>Correln Coeff.</th>
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<td></td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>12</td>
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<tr>
<td><strong>Avicel PH103 (5:5:6) Formulation</strong></td>
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<td></td>
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<tr>
<td>2</td>
<td>2.7 ± .19</td>
<td>3.0 ± .41</td>
<td>3.7 ± .17</td>
<td>4.3 ± .21</td>
</tr>
<tr>
<td>5</td>
<td>3.8 ± .15</td>
<td>4.4 ± .21</td>
<td>5.9 ± .41</td>
<td>6.8 ± .43</td>
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<tr>
<td>10</td>
<td>4.4 ± .37</td>
<td>5.1 ± .64</td>
<td>6.9 ± 1.2</td>
<td>8.3 ± 1.3</td>
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<tr>
<td>20</td>
<td>5.0 ± .39</td>
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<td>7.8 ± .62</td>
<td>9.6 ± .68</td>
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<tr>
<td>40</td>
<td>5.6 ± .58</td>
<td>6.2 ± .50</td>
<td>8.1 ± .56</td>
<td>10.0 ± .91</td>
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<tr>
<td><strong>Avicel PH105 (5:5:6) Formulation</strong></td>
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<td>2</td>
<td>2.3 ± .14</td>
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<td>3.0 ± .25</td>
<td>3.3 ± .23</td>
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<tr>
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<td>5.1 ± .56</td>
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</tr>
<tr>
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<td>8.8 ± 1.2</td>
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<td>4.8 ± .91</td>
<td>5.5 ± .93</td>
<td>7.3 ± 1.1</td>
<td>9.0 ± 1.3</td>
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</table>
### Table 6.2 cont.

The Effect of the Grade of Microcrystalline Cellulose Used in the Formulation on the Bagley Plot Results: Powdered Grades (continued overleaf)

<table>
<thead>
<tr>
<th>Piston Speed (cm/min)</th>
<th>Av. Steady State Extrusion Pressure (kN/m², x10³) through various dies of L/R=</th>
<th>Gradient (kN/m²)</th>
<th>Y-Intercept (kN/m²)</th>
<th>Correln Coeff.</th>
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<tr>
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<td>4</td>
<td>8</td>
<td>12</td>
<td>16</td>
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<tr>
<td><strong>Emcocel (5:5:6) Formulation</strong></td>
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<td>2</td>
<td>2.8 ± 0.74</td>
<td>3.0 ± 0.74</td>
<td>3.3 ± 0.76</td>
<td>3.6 ± 0.76</td>
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<td>4.4 ± 0.70</td>
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<td>5.8 ± 0.62</td>
<td>6.6 ± 0.77</td>
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<td>10</td>
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<td>7.6 ± 0.56</td>
<td>9.0 ± 0.64</td>
<td>10.5 ± 0.48</td>
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<td>11.2 ± 0.64</td>
<td>13.9 ± 1.12</td>
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<tr>
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<td>11.7 ± 1.07</td>
<td>14.4 ± 1.74</td>
</tr>
<tr>
<td><strong>Unimac MG100 (5:5:6) Formulation</strong></td>
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<tr>
<td>2</td>
<td>2.1 ± 0.25</td>
<td>2.5 ± 0.35</td>
<td>2.7 ± 0.21</td>
<td>2.9 ± 0.27</td>
</tr>
<tr>
<td>5</td>
<td>3.6 ± 0.27</td>
<td>4.6 ± 0.27</td>
<td>5.3 ± 0.21</td>
<td>6.1 ± 0.52</td>
</tr>
<tr>
<td>10</td>
<td>4.8 ± 0.17</td>
<td>6.6 ± 0.27</td>
<td>8.4 ± 0.43</td>
<td>10.3 ± 0.41</td>
</tr>
<tr>
<td>20</td>
<td>5.6 ± 0.27</td>
<td>8.5 ± 0.48</td>
<td>10.9 ± 0.23</td>
<td>14.2 ± 0.58</td>
</tr>
<tr>
<td>40</td>
<td>6.2 ± 0.14</td>
<td>9.6 ± 0.35</td>
<td>12.9 ± 0.56</td>
<td>16.7 ± 0.70</td>
</tr>
</tbody>
</table>
Table 6.2 cont. The Effect of the Grade of Microcrystalline Cellulose Used in the Formulation on the Bagley Plot Results: Powdered Grades

<table>
<thead>
<tr>
<th>Piston Speed (cm/min)</th>
<th>Av. Steady State Extrusion Pressure (kN/m², x10³)</th>
<th>Gradient (kN/m²)</th>
<th>Y-Intercept (kN/m²)</th>
<th>Correln Coeff.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>through various dies of L/R=</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2.4 ± 0.25</td>
<td>79</td>
<td>2159</td>
<td>0.988</td>
</tr>
<tr>
<td>8</td>
<td>2.8 ± 0.29</td>
<td>3.4 ± 0.35</td>
<td>2159</td>
<td>0.988</td>
</tr>
<tr>
<td>12</td>
<td>3.2 ± 0.35</td>
<td>79</td>
<td>2159</td>
<td>0.988</td>
</tr>
<tr>
<td>16</td>
<td>3.4 ± 0.35</td>
<td>79</td>
<td>2159</td>
<td>0.988</td>
</tr>
<tr>
<td>40</td>
<td>6.0 ± 0.21</td>
<td>820</td>
<td>2681</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>9.2 ± 0.16</td>
<td>12.5 ± 0.29</td>
<td>2681</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>15.8 ± 0.47</td>
<td>820</td>
<td>2681</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Unimac MG200 (5:5:6) Formulation
Figure 6.6 The Bagley Plot for the Avicel PH103 (5:5:6) Formulation

Figure 6.7 The Bagley Plot for the Avicel PH102 (5:5:6) Formulation
Figure 6.7 The Bagley Plot for the Avicel PH105 (5:5:6) Formulation

Extrusion Pressure (kN/m², x10E3)

Die Length to Radius Ratio

Piston Speed (cm/min)
- 2 X 20
- 5 X 40
- 10

Figure 6.8 The Bagley Plot for the Emcocel (5:5:6) Formulation

Extrusion Pressure (kN/m², x10E3)

Die Length to Radius Ratio

Piston Speed (cm/min)
- 2 X 20
- 5 X 40
- 10
The Avicel PH105 formulation does not fit into the trend for the die wall shear stress and upstream pressure loss (it would have been expected to exhibit the smallest die wall shear stress and the largest upstream pressure loss). This incident of anomalous behaviour by Avicel PH105 microcrystalline cellulose is not isolated. Marshall and Sixsmith (1974) and Sixsmith (1982) suggest that differences in the tableting properties of Avicel PH105 are due to differences not only in particle size between PH105 and the other Avicel grades, but also in particle shape. Most probably, the anomaly may be attributed to the fact that Avicel PH105 has a wider particle size distribution than the other Avicel grades (Sixsmith, 1975), and is therefore likely to granulate and pack differently. Benbow and Bridgwater (1987; i) found that the amount of water required to saturate powders with a wide particle size distribution was less than the amount required for those with a narrow distribution (for starch/clay/water mixtures). Thus it may be that the wide particle size distribution of Avicel PH105 results in the over-wetting of formulations based on this grade of microcrystalline cellulose when mixed in the standard (5:5:6) ratio. Unfortunately, such "over-wetting" does not help to explain the increase in the expected value of the die wall shear stress.

Accepting the above explanation for the Avicel PH105 anomaly, a reason for the observed trends of upstream pressure loss and die wall shear stress with the particle size of the microcrystalline cellulose may be suggested as follows. Smaller size particles have a higher contact area and therefore a higher degree of cohesivity between them than larger ones, and this results in an impediment to their flow. Formulations based on smaller particles will therefore be less able to form a convergent flow vortex at the die entrance and less able to develop laminar flow - thus they will exhibit higher values of upstream
pressure loss than those based on larger particles. On the other hand, smaller particles are able to pack more closely than larger particles, so that a formulation based on smaller particles will present a more integral surface to the die wall on extrusion. The consequence of this will be that formulations based on smaller particles will experience a lower degree of friction at the die wall (in much the same way that fine sand paper provides less friction than coarse sand paper) and will thus exhibit a lower value of die wall shear stress.

6.2.2 The Effect of the Microcrystalline Cellulose Moisture Content

By comparing the formulations based on Avicel PH101 (≤ 5% moisture) and Avicel PH103 (≤ 3% moisture) it is possible to determine the effect on the Bagley plot results of the original moisture content of the actual microcrystalline cellulose powder (as opposed to the water content of the formulation).

Table 6.6 shows that Avicel PH101-based formulations exhibit consistently lower values of die wall shear stress and upstream pressure loss than those based on Avicel PH103. This is an unexpected result - Avicel PH103 is simply the Avicel PH101 grade dried down to 3% moisture (Gilmour, Honeywill and Stein, 1987, private communication; Brine C.J., FMC Corp., 1988, private communication) and it would have been predicted that the comparatively large amount of water added during the wet massing of the formulations would swamp any effects due to the difference in initial moisture content of the powders. The result suggests that the interaction between microcrystalline cellulose and water, which is thought to be fundamental to the success of microcrystalline cellulose in the extrusion process, is different for the Avicel PH101 grade than for the PH103 grade. It should also
be noted that this apparently anomalous behaviour of the Avicel PH103 grade has been confirmed by torque rheometry (Rowe and Sadeghnejad, 1987). It may be that crucial differences in the microcrystalline cellulose-water interaction are caused by surface and/or pore changes, resulting from the manufacturing process by which the microcrystalline cellulose is dried down from 5 to 3% moisture, which are not reversible on wet massing. However, it should be noted that when Avicel PH103 grade was allowed to equilibrate over a period of several weeks, until its moisture content was the same as that of Avicel PH101, their formulations then exhibited similar values of $P_0$ and $t_w$ on extrusion. This result indicates that while the differences between Avicel PH103 and Avicel PH101 are not immediately reversible on wet massing, they are reconcilable over a longer equilibration period, suggesting that microcrystalline cellulose-water interactions are time-dependent.

6.2.3 The Effect of the Microcrystalline Cellulose Source

By comparing the results for formulations based on grades of microcrystalline cellulose which are nominally equivalent (e.g. those based on Avicel PH101, Unimac MG100 and Emcocel, and those based on Avicel PH102 and Unimac MG200) (Table 6.6) it may be seen that formulations based on microcrystalline celluloses from different sources exhibit different Bagley plot results. For example, formulations based on Unimac grades have very high die wall shear stresses in comparison to those based on the other grades, but have low upstream pressure losses. Formulations based on Emcocel, on the other hand, have fairly high die wall shear stresses and the highest upstream pressure losses.

Companies who manufacture the grades of microcrystalline cellulose used in this work (FMC Corp., Unitika Rayon, Finnsugar) each use
different trees from which to derive cellulose pulp as their starting material, and each use a slightly different manufacturing process. The precise details of the type of pulp and manufacturing process used by each company are, of course, of a commercially sensitive nature. However, it is widely acknowledged that while one company might use, for example, Canadian Fir as pulp source, another might use European Spruce, and that the manufacturing processes differ from one company to another, particularly in respect of the spray drying conditions used. Nuclear Magnetic Resonance (NMR) studies have shown that different native cellulosics are composites of two or more crystalline forms in different proportions (Atalla and Vanderhart, 1986; Cael et al., 1985), which suggests that microcrystalline cellulose powders derived from different pulp sources will have some differences in their crystallinity or crystallographic form. Moreover, manufacturing history is known to be a likely factor in determining a particular crystal morphology (Wegner, 1979; Sadeghnejad et al., 1985): It has been shown, for example, that the rate of hydrolysis of cellulosics affects their crystallization chain length (Battista, 1950).

An examination of the nominally/supposedly equivalent grades from the various sources (Avicel PH101, Unimac MG100, and Emcocel; Avicel PH102 and Unimac MG200) by scanning electron microscopy shows that there are, indeed, differences in their microscopic structure (Figures 6.20 to 6.23). These figures show SEMs for Avicel PH101, Unimac MG100, Emcocel (150x, 600x) and for Avicel PH102 and Unimac MG200 (150x, 600x). While all the grades may be seen to be composed of fibres and fibre aggregates, the integrity of the sample surfaces differs between grades. The surfaces of Avicel grades appear convoluted, whereas Emcocel appears less tortuous, and Unimac grades appear quite smooth in comparison. These variations result in differences in the amount
of surface area presented by each grade - the rank order of grades in terms of surface area is Avicel PH101>Emcocel>Unimac MG100 and Avicel PH102>Unimac MG200.

These differences in surface structure and surface area may help to account for the differences in the extrusion of the formulations based on the various grades of microcrystalline cellulose. It is certainly true that the internal morphologies of the extrudates produced by the formulations based on microcrystalline celluloses from different sources are different, as evidenced by the cryogenic scanning electron micrographs presented as Figures 6.24 to 6.29. These figures show cryogenic SEMs for standard extrudates based on Avicel PH101, Unimac MG100 and Emcocel at magnifications of 250x, 500x, 1000x, 1500x, 2000x and 2500x. Comparison of the micrographs shows that the formulation based on Unimac MG100 is the most different. Its particles are less discrete than those of extrudate based on Emcocel or Avicel PH101. In terms of surface area and void space available, the rank order for the extrudates would be extrudate based on Avicel PH101>Emcocel>Unimac MG100.

Accepting that differences in pulp source and manufacturing processes result in microcrystalline cellulose powders with slight differences in their crystallinity or crystal morphology, then it may be surmised that grades produced by different manufacturers will have a different type and/or extent of interaction with water. This may help to account for the variation in extrusion results between formulations based on grades from different sources.
6.3 THE EFFECT OF THE MICROCRYSTALLINE CELLULOSE GRADE USED IN THE FORMULATION ON THE BAGLEY PLOT RESULTS: COLLOIDAL GRADES

The effect on the Bagley plots of changing the colloidal grade of microcrystalline cellulose on which the formulation is based is illustrated by Figures 6.11 to 6.14 and shown in Table 6.3. (For the benefit of comparison with the powdered grades, Figure 6.30 shows cryogenic scanning electron micrographs of an Avicel RC581 formulation extrudate, at magnitudes of 250x, 500x, 1000x and 1500x.) The colloidal grade formulations exhibit Bagley plots with values for die wall shear stress which are considerably higher than those of powdered grade formulations, but their values for upstream pressure loss are only slightly higher (Table 6.7). This implies that although colloidal grade formulations form convergent flow patterns and develop laminar flow as easily as powdered grade formulations, they experience a greater frictional resistance when flowing through the die.

6.3.1 The Effect of the Amount of Sodium Carboxymethylcellulose in the Colloidal Grade

The effect of the amount of sodium carboxymethylcellulose (NaCMC) co-processed with the microcrystalline cellulose may be determined by comparing the results for formulations based on Avicel PH101 (0% NaCMC) (Table 6.6) with those based on Avicel RC501 (8.5% NaCMC) and Avicel RC581 and RC591 (11.0% NaCMC) (Table 6.7).

It is clear that the grades with the most sodium carboxymethylcellulose incorporated result in formulations which exhibit the highest shear stresses at the die wall. A possible explanation is that the sodium carboxymethylcellulose gels with the water to a certain extent, thereby altering the manner in which the water is held within the
Table 6.3  The Effect of the Grade of Microcrystalline Cellulose Used in the Formulation on the Bagley Plot Results: Colloidal Grades (continued overleaf)

<table>
<thead>
<tr>
<th>Piston Speed (cm/min)</th>
<th>Av. Steady State Extrusion Pressure (kN/m², x10³) through various dies of L/R=</th>
<th>Gradient (kN/m²)</th>
<th>Y-Intercept (kN/m²)</th>
<th>Correln Coeff.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>3.9 ± .38 4.3 ± .58 5.8 ± .12 7.4 ± 0.0 9.0 ± .97</td>
<td>375</td>
<td>2929</td>
<td>0.998</td>
</tr>
<tr>
<td>5</td>
<td>3.9 ± .12 4.4 ± .16 5.9 ± .33 7.6 ± .23 9.4 ± .27</td>
<td>399</td>
<td>2869</td>
<td>0.997</td>
</tr>
<tr>
<td>10</td>
<td>4.3 ± .77 4.8 ± .39 6.5 ± .14 8.2 ± .17 10.1 ± .25</td>
<td>422</td>
<td>3204</td>
<td>0.998</td>
</tr>
<tr>
<td>20</td>
<td>4.7 ± .12 5.4 ± .77 7.1 ± .43 9.0 ± .16 11.1 ± .97</td>
<td>455</td>
<td>3644</td>
<td>0.998</td>
</tr>
<tr>
<td>40</td>
<td>5.5 ± .27 6.2 ± .23 8.2 ± .25 10.1 ± .97 12.3 ± .45</td>
<td>488</td>
<td>4248</td>
<td>0.999</td>
</tr>
</tbody>
</table>

Avicel RC501 (5:5:6 w/w) Formulation

Avicel RC581 (5:5:6 w/w) Formulation
Table 6.3 cont.  The Effect of the Grade of Microcrystalline Cellulose Used in the Formulation on the Bagley Plot Results: Colloidal Grades

<table>
<thead>
<tr>
<th>Piston Speed (cm/min)</th>
<th>Av. Steady State Extrusion Pressure (kN/m², x10³) through various dies of L/R=2</th>
<th>Gradient (kN/m²)</th>
<th>Y-Intercept (kN/m²)</th>
<th>Correlation Coeff.</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Avicel RC951 (5:5:6wο) Formulation</td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td>4.6 ± .25</td>
<td>5.4 ± .25</td>
<td>8.2 ± .23</td>
<td>11.0 ± .37</td>
</tr>
<tr>
<td>5</td>
<td>5.4 ± .25</td>
<td>6.5 ± .23</td>
<td>10.3 ± .43</td>
<td>13.6 ± .50</td>
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<tr>
<td>10</td>
<td>5.9 ± .43</td>
<td>7.2 ± .41</td>
<td>11.6 ± .39</td>
<td>15.3 ± .50</td>
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<td>20</td>
<td>7.2 ± .99</td>
<td>8.6 ± 1.1</td>
<td>13.5 ± 1.1</td>
<td>17.6 ± 1.2</td>
</tr>
<tr>
<td>40</td>
<td>8.2 ± .87</td>
<td>9.9 ± .77</td>
<td>15.2 ± .89</td>
<td>19.7 ± .77</td>
</tr>
<tr>
<td>Avicel CL611 (5:5:6wο) Formulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.8 ± .27</td>
<td>3.3 ± .33</td>
<td>5.0 ± .43</td>
<td>6.5 ± .45</td>
</tr>
<tr>
<td>5</td>
<td>3.3 ± .25</td>
<td>3.9 ± .33</td>
<td>6.0 ± .39</td>
<td>7.8 ± .43</td>
</tr>
<tr>
<td>10</td>
<td>3.8 ± .19</td>
<td>4.5 ± .35</td>
<td>6.8 ± .37</td>
<td>9.1 ± .58</td>
</tr>
<tr>
<td>20</td>
<td>4.3 ± .25</td>
<td>5.2 ± .37</td>
<td>8.1 ± .60</td>
<td>10.5 ± .89</td>
</tr>
<tr>
<td>40</td>
<td>5.1 ± .33</td>
<td>6.2 ± .47</td>
<td>9.7 ± .58</td>
<td>12.5 ± .93</td>
</tr>
</tbody>
</table>
system. This could result in a decrease in the formulations' potential for "self-lubrication" at the die wall. It will be made clear later, however, that the viscosity (cf Section 6.3.2) and the position (cf Section 6.4) of the sodium carboxymethylcellulose within the system, as well as its quantity, are important factors in the die wall shear stress exhibited by a formulation.

6.3.2 The Effect of the Viscosity Grade of Sodium Carboxymethylcellulose in the Colloidal Grade

The grades of sodium carboxymethylcellulose used in the production of the Avicel RC/CL grades are of two viscosity types (see Section 1.4.4(ii) and Table 1.3). The Avicel RC grades of microcrystalline cellulose are co-processed with a medium viscosity grade NaCMC (Blanose 7MF, Hercules), whereas Avicel CL611 is co-processed with a low viscosity grade (Blanose 7LF, Hercules) (Lyons, Honeywill and Stein, private communication, 1986). The effect of the viscosity grade of the NaCMC used may be determined by comparing the results for formulations based on Avicel PH101 (0% NaCMC) (Table 6.6) with those based on Avicel CL611 (15.0% low viscosity NaCMC), Avicels RC581 and RC591 (11.0% medium viscosity NaCMC) and Avicel RC501 (8.5% medium viscosity NaCMC) (Table 6.7).

The rank order for the die wall shear stress results, under most shear rate conditions, is as follows:

Avicel RC581/591 > CL611 > RC501 > PH101 formulations

This rank order illustrates that although Avicel CL611 has the greatest quantity of NaCMC co-processed with it (15.0%), its formulation exhibits a lower die wall shear stress than formulations based on Avicel RC581 and Avicel RC591, which contain a lower quantity of NaCMC (11.0%) but of a higher viscosity grade. This result is not entirely
unexpected, and implies that 11.0% medium viscosity grade NaCMC confers a higher overall viscosity to the system than 15.0% low viscosity grade NaCMC. By definition, a system with a higher overall viscosity will be less inclined to flow than one with a lower viscosity, and so the resistance to flow through the die will be greater, resulting in the higher values for die wall shear stress observed in this work.

The rank order for die wall shear stress also illustrates that the Avicel CL611-based formulation exhibits a higher die wall shear stress than that based on Avicel RC501, implying that 15.0% low viscosity NaCMC confers a higher overall viscosity on the system than 8.5% medium viscosity NaCMC. The Avicel PH101 formulation, of course, would be expected to have the lowest overall viscosity (0% NaCMC) and this corresponds with the fact that it exhibits the lowest value of die wall shear stress. These results show, therefore, that the viscosity of the NaCMC, as well as its quantity, is an important factor in the determination of the die wall shear stress value exhibited by the formulation.

6.3.3 The Effect of the Method of Drying of the Colloidal Grade

The Avicel RC581 and RC591 grades of microcrystalline cellulose are identical in every respect (e.g. the amount and viscosity of NaCMC included, the particle size distribution) except for the method of drying used in the final stages of their production. Avicel RC581 is bulk dried, whereas Avicel RC591 is spray dried. The values of die wall shear stress and upstream pressure loss exhibited by formulations based on these two grades are more or less identical (Table 6.7), implying that the choice of bulk or spray drying in the manufacture of the colloidal microcrystalline cellulose grades does not affect their
interaction with water to any extent which would alter the extrusion parameters exhibited by their formulations.

6.4 THE EFFECT OF THE USE OF SODIUM CARBOXYMETHYLCELLULOSE SOLUTION AS THE BINDER IN THE FORMULATION

The effect of the use of sodium carboxymethylcellulose (NaCMC) (Blanose 7MF, Hercules) solution as the binder in a standard powdered grade (Avicel PH101) formulation (in an attempt to mimic a colloidal grade formulation) is illustrated by Figures 6.15 and 6.16 and shown in Table 6.4.

The results indicate that the introduction of sodium carboxymethylcellulose in solution form into the formulation causes a reduction in both the die wall shear stress and the upstream pressure loss. It may be recalled that the effect of sodium carboxymethylcellulose when it is co-processed with the microcrystalline cellulose (the "colloidal" grades) is to increase the die wall shear stress significantly and to slightly increase the upstream pressure loss (Section 6.3). It may thus be concluded that the form in which the sodium carboxymethylcellulose is present within a formulation is a factor in determining the effect it has on extrusion. A possible explanation may be as follows. In colloidal grade formulations, the NaCMC is closely associated with the microcrystalline cellulose, having been co-processed with it during the production process. During wet massing for extrusion, the exposed surfaces of the NaCMC may partly hydrate, with the result that the microcrystalline cellulose particles would be coated with a sticky gel. It is supposed that this gel would act as a glue-like substance, impeding the flow of particles over one another and adversely affecting the movement of water through the system,
Table 6.4 The Effect of the Use of Sodium Carboxymethylcellulose Solution as the Binder in the Formulation on the Bagley Plot Results

<table>
<thead>
<tr>
<th>Piston Speed (cm/min)</th>
<th>Av. Steady State Extrusion Pressure (kN/m², x10³) through various dies of L/R=</th>
<th>Gradient (kN/m²)</th>
<th>Y-Intercept (kN/m²)</th>
<th>Correln Coeff.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>8</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Avicel PH101 (5:5:6) Formulation, with NaCMC Soln 8% as Binder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.4 ± 0.12</td>
<td>1.8 ± 0.15</td>
<td>2.0 ± 0.15</td>
<td>2.2 ± 0.19</td>
</tr>
<tr>
<td>5</td>
<td>1.6 ± 0.14</td>
<td>1.9 ± 0.20</td>
<td>2.1 ± 0.19</td>
<td>2.4 ± 0.22</td>
</tr>
<tr>
<td>10</td>
<td>1.7 ± 0.13</td>
<td>2.1 ± 0.19</td>
<td>2.4 ± 0.21</td>
<td>2.6 ± 0.24</td>
</tr>
<tr>
<td>20</td>
<td>2.0 ± 0.14</td>
<td>2.3 ± 0.21</td>
<td>2.6 ± 0.16</td>
<td>2.9 ± 0.25</td>
</tr>
<tr>
<td>40</td>
<td>2.3 ± 0.21</td>
<td>2.6 ± 0.21</td>
<td>3.0 ± 0.29</td>
<td>3.6 ± 0.35</td>
</tr>
<tr>
<td>Avicel PH101 (5:5:6) Formulation, with NaCMC Soln 16% as Binder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.2 ± 0.18</td>
<td>2.7 ± 0.23</td>
<td>2.9 ± 0.25</td>
<td>3.2 ± 0.31</td>
</tr>
<tr>
<td>5</td>
<td>2.4 ± 0.21</td>
<td>3.0 ± 0.28</td>
<td>3.2 ± 0.29</td>
<td>3.5 ± 0.34</td>
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<tr>
<td>10</td>
<td>2.7 ± 0.27</td>
<td>3.3 ± 0.32</td>
<td>3.7 ± 0.34</td>
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<tr>
<td>20</td>
<td>3.2 ± 0.31</td>
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<td>4.1 ± 0.41</td>
<td>4.5 ± 0.47</td>
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<tr>
<td>40</td>
<td>3.8 ± 0.35</td>
<td>4.3 ± 0.44</td>
<td>4.7 ± 0.28</td>
<td>5.2 ± 0.39</td>
</tr>
</tbody>
</table>
Fig 6.15 The Bagley Plot for the Avicel PH101 (5:5:6mcc) Formulation Wet Massed with NaCMC Solution 8%  

Extrusion Pressure (kN/m², x10E3)  

Piston Speed (cm/min)  
• X 2 20  
• X 5 40  
• X 10

Die Length to Radius Ratio

Fig 6.16 The Bagley Plot for the Avicel PH101 (5:5:6) Formulation Wet Massed with NaCMC Solution 16%  

Extrusion Pressure (kN/m², x10E3)  

Piston Speed (cm/min)  
• X 2 20  
• X 5 40  
• X 10
Fig 6.17 The Effect of the Water Content of the Formulation on the Steady State Extrusion Pressure: Avicel PH101 Formulations

Piston Speed 40cm/min

Die L/R = 16

The green curve shows how the pressure deviates at around 37.5% water content.
Figure 6.18 The Effect of the Water Content of the Formulation on the Die Wall Shear Stress of the Avicel PH101 Formulation

Piston Speed 40cm/min

The red curve shows how the die wall shear stress deviates at around 37.5% water content.
Figure 6.19 The Effect of the Water Content of the Formulation on the Upstream Pressure Loss of the Avicel PH101 Formulation

Piston Speed 40cm/min

The orange curve shows how the upstream pressure loss deviates at around 37.5% water content.
Table 6.5 The Effect of the Water Content of the Formulation on the Die Wall Shear Stress ($\tau_w$) and the Upstream Pressure Loss ($P_o$)

This table shows results for an Avicel PH101-based formulation; other powdered grade formulations show similar trends with water content.

<table>
<thead>
<tr>
<th>Water Content (%)</th>
<th>Die Wall Shear Stress ($\tau_w$) (kN/m²) at various piston speeds (cm/min)=</th>
<th>Upstream Pressure Loss ($P_o$) (kN/m²) at various piston speeds (cm/min)=</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>28.5</td>
<td>376</td>
<td>366</td>
</tr>
<tr>
<td>33.3</td>
<td>246</td>
<td>158</td>
</tr>
<tr>
<td>37.5</td>
<td>111</td>
<td>158</td>
</tr>
<tr>
<td>44.4</td>
<td>52</td>
<td>88</td>
</tr>
</tbody>
</table>
Table 6.6  The Effect of the Grade of Microcrystalline Cellulose (MCC) Used in the Formulation on the Die Wall Shear Stress ($t_w$) and the Upstream Pressure Loss ($P_o$) for Powdered Grades

All formulations were the standard (5:5:6) mix.

<table>
<thead>
<tr>
<th>Grade of MCC Used</th>
<th>Die Wall Shear Stress ($t_w$) (kN/m²) at various piston speeds (cm/min)=</th>
<th>Upstream Pressure Loss ($P_o$) (kN/m²) at various piston speeds (cm/min)=</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2  5  10  20  40</td>
<td>2  5  10  20  40</td>
</tr>
<tr>
<td>Avicel PH101</td>
<td>44  111  158  194  195</td>
<td>1990 3094 3762 3828 4327</td>
</tr>
<tr>
<td>Avicel PH102</td>
<td>63  135  179  200  216</td>
<td>2215 2838 3373 3783 3975</td>
</tr>
<tr>
<td>Avicel PH103</td>
<td>70  142  210  239  235</td>
<td>2470 3345 3479 3944 4459</td>
</tr>
<tr>
<td>Avicel PH105</td>
<td>48  123  179  216  204</td>
<td>2145 2938 3746 3657 3996</td>
</tr>
<tr>
<td>Emcocel</td>
<td>34  82  207  301  319</td>
<td>2497 3998 4008 4182 4172</td>
</tr>
<tr>
<td>Unimac MG100</td>
<td>33  103  229  356  432</td>
<td>1897 2856 2962 2720 2710</td>
</tr>
<tr>
<td>Unimac MG200</td>
<td>40  151  249  348  410</td>
<td>2159 2681 2875 2527 2681</td>
</tr>
</tbody>
</table>
Table 6.7  The Effect of the Grade of Microcrystalline Cellulose (MCC) Used in the Formulation on the Die Wall Shear Stress ($t_w$) & the Upstream Pressure Loss ($P_0$) for Colloidal Grades

All formulations were the standard (5:5:6_{MCC}) mix.

<table>
<thead>
<tr>
<th>Grade of MCC Used</th>
<th>Die Wall Shear Stress ($t_w$) (kN/m²) at various piston speeds (cm/min)=</th>
<th>Upstream Pressure Loss ($P_0$) (kN/m²) at various piston speeds (cm/min)=</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Avicel RC501</td>
<td>188</td>
<td>200</td>
</tr>
<tr>
<td>Avicel RC581</td>
<td>344</td>
<td>426</td>
</tr>
<tr>
<td>Avicel RC591</td>
<td>348</td>
<td>427</td>
</tr>
<tr>
<td>Avicel CL611</td>
<td>196</td>
<td>240</td>
</tr>
</tbody>
</table>
Figure 6.20 Scanning Electron Micrographs

(i) Avicel PH101 powder x 150

(ii) Unimac MG100 powder x 150

(iii) Emcocel powder x 150
Figure 6.21 Scanning Electron Micrographs

(i) Avicel PH101 powder x 600

(ii) Unimac MG100 powder x 600

(iii) Emcocel powder x 600
Figure 6.22
Scanning Electron Micrographs

(i) Avicel PH102 powder x 150

(ii) Unimac MG200 powder x 150

Figure 6.23
Scanning Electron Micrographs

(i) Avicel PH102 powder x 600

(ii) Unimac MG200 powder x 600
Figure 6.24 Cryogenic Scanning Electron Micrographs

(i) Avicel PH101 Formulation Extrudate x 250

(ii) Unimac MG100 Formulation Extrudate x 250

(iii) Emscel Formulation Extrudate x 250
Figure 6.25 Cryogenic Scanning Electron Micrographs

(i) Avicel PH101 Formulation Extrudate x 500

(ii) Unimac MG100 Formulation Extrudate x 500

(iii) Emcocel Formulation Extrudate x 500
Figure 6.26  Cryogenic Scanning Electron Micrographs

(i) Avicel PH101 Formulation Extrudate x 1000

(ii) Unimac MG100 Formulation Extrudate x 1000

(iii) Emcocel Formulation Extrudate x 1000
Figure 6.27 Cryogenic Scanning Electron Micrographs

(i) Avicel PH101 Formulation Extrudate x 1500

(ii) Unimac MG100 Formulation Extrudate x 1500

(iii) Emcocel Formulation Extrudate x 1500
Figure 6.28  Cryogenic Scanning Electron Micrographs

(i) Avicel PH101 Formulation Extrudate x 2000

(ii) Unimac MG100 Formulation Extrudate x 2000

(iii) Emcocel Formulation Extrudate x 2000
Figure 6.29 Cryogenic Scanning Electron Micrographs

(i) Avicel PH101 Formulation Extrudate x 2500

(ii) Unimac MG100 Formulation Extrudate x 2500

(iii) Emcocel Formulation Extrudate x 2500
Figure 6.30 Cryogenic Scanning Electron Microscopy of Avicel RC581 Formulation Extrudate

(i) x 250

(ii) x 500

(iii) x 1000

(iv) x 1500
thereby causing an increase in the die wall shear stress and upstream pressure loss on extrusion. In powdered grade formulations wet massed with sodium carboxymethylcellulose solution, however, the NaCMC is not in such close association with the microcrystalline cellulose — indeed, it is completely gelled in water before being added to the formulation. In this case, this "free" gel may act as a lubricating aid, thus reducing the values of die wall shear stress and upstream pressure loss on extrusion.

If the above explanation is accepted, it would be expected that formulations wet massed with the more concentrated NaCMC solution would exhibit the lowest values of die wall shear stress and upstream pressure loss. However, the results in Table 6.8 indicate that formulations wet massed with 8% NaCMC solution exhibit lower die wall shear stresses and upstream pressure losses than those wet massed with 16% gel. The reason for this apparent anomaly may be that there is a balance of the postulated "adhesive" and "lubricating" properties of NaCMC gel, determined both by the position of the gel and its quantity. It may be that 8% NaCMC gel has superior lubricating properties, whereas at a level of 16% the adhesive properties of the NaCMC may become slightly more influential.
Table 6.8  The Effect of the Use of Sodium Carboxymethylcellulose (NaCMC) Solution as the Binder in the Formulation on the Die Wall Shear Stress ($\tau_w$) & the Upstream Pressure Loss ($P_0$)

All formulations were the standard (5:5:6) mix.

<table>
<thead>
<tr>
<th>Conc. of NaCMC Soln Used (%)</th>
<th>Die Wall Shear Stress ($\tau_w$) (kN/m²) at various piston speeds (cm/min)=</th>
<th>Upstream Pressure Loss ($P_0$) (kN/m²) at various piston speeds (cm/min)=</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>0.0</td>
<td>44</td>
<td>111</td>
</tr>
<tr>
<td>8.0</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>16.0</td>
<td>40</td>
<td>45</td>
</tr>
</tbody>
</table>
CHAPTER SEVEN

THE FLOW CURVES
Representation of the extrusion process using Bagley's Equation has been discussed in Chapter Six. The Bagley results were used to derive the die wall shear stress \( (t_w) \) values for the extrusion of each formulation at various apparent die wall shear rates (\( D' \)). The values for apparent die wall shear rate were calculated from the extrusion speed (equation 2.17) and are given in Table 7.1. Graphs of die wall shear stress versus die wall shear rate were constructed to produce an extrusion flow curve for each formulation. The results are given in Tables 7.2 to 7.14 and the flow curves are presented in Figures 7.1 to 7.4.

The flow curves all show an increase in die wall shear stress with die wall shear rate, probably due to the increased friction at the die wall as the extrusion rate is increased. The curves did not, unfortunately, fit any of the mathematical models outlined in Section 2.3. However, critical examination of the flow curve characteristics does help to provide a qualitative description of the rheological behaviour of each formulation on extrusion.

7.1 THE EFFECT OF THE MICROCRYSTALLINE CELLULOSE GRADE USED IN THE FORMULATION ON THE FLOW CURVE RESULTS: POWDERED GRADES

The flow curve results for formulations based on powdered grades of microcrystalline cellulose are given in Tables 7.2 to 7.8, and the curves are presented in Figures 7.1 and 7.2. It may be seen that the magnitude of the die wall shear stress exhibited at a given shear rate clearly depends on the particle size (Figure 7.1), the moisture content (Figure 7.1) and the source (Figure 7.2) of the original microcrystalline cellulose powdered grade on which the formulation is based. The reasons for these differences have been discussed previously in Sections 6.2.1 to 6.2.3.
Table 7.1  Values of Extrusion Speed and Equivalent Die Wall Shear Rate

<table>
<thead>
<tr>
<th>Extrusion Speed (cm/min)</th>
<th>Shear Rate, D' (s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>510</td>
</tr>
<tr>
<td>5</td>
<td>1274</td>
</tr>
<tr>
<td>10</td>
<td>2549</td>
</tr>
<tr>
<td>20</td>
<td>5098</td>
</tr>
<tr>
<td>40</td>
<td>10195</td>
</tr>
</tbody>
</table>

Table 7.2  Flow Curve Results for the Avicel PH101 Formulation (5:5:6 MCC)

<table>
<thead>
<tr>
<th>Shear Rate (s⁻¹)</th>
<th>Die Wall Shear Stress (KN/m²)</th>
<th>Standard Deviation (KN/m²)</th>
<th>Die Wall Shear Stress Range (KN/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>510</td>
<td>44.24</td>
<td>10.17</td>
<td>34.07 - 54.41</td>
</tr>
<tr>
<td>1274</td>
<td>110.44</td>
<td>12.71</td>
<td>97.73 - 123.15</td>
</tr>
<tr>
<td>2549</td>
<td>157.98</td>
<td>5.45</td>
<td>152.53 - 163.43</td>
</tr>
<tr>
<td>5098</td>
<td>193.95</td>
<td>18.97</td>
<td>174.98 - 212.92</td>
</tr>
<tr>
<td>10195</td>
<td>194.45</td>
<td>28.19</td>
<td>166.26 - 222.64</td>
</tr>
</tbody>
</table>
### Table 7.3 Flow Curve Results for the Avicel PH102 Formulation (5:5:6 MCC)

<table>
<thead>
<tr>
<th>Shear Rate (s⁻¹)</th>
<th>Die Wall Shear Stress (KN/m²)</th>
<th>Standard Deviation (KN/m²)</th>
<th>Die Wall Shear Stress Range (KN/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>510</td>
<td>60.90</td>
<td>11.26</td>
<td>49.60 - 72.20</td>
</tr>
<tr>
<td>1274</td>
<td>135.00</td>
<td>11.63</td>
<td>123.40 - 146.60</td>
</tr>
<tr>
<td>2549</td>
<td>179.05</td>
<td>12.89</td>
<td>166.20 - 191.90</td>
</tr>
<tr>
<td>5098</td>
<td>202.48</td>
<td>31.43</td>
<td>171.10 - 233.90</td>
</tr>
<tr>
<td>10195</td>
<td>217.11</td>
<td>29.48</td>
<td>187.60 - 246.60</td>
</tr>
</tbody>
</table>

### Table 7.4 Flow Curve Results for the Avicel PH103 Formulation (5:5:6 MCC)

<table>
<thead>
<tr>
<th>Shear Rate (s⁻¹)</th>
<th>Die Wall Shear Stress (KN/m²)</th>
<th>Standard Deviation (KN/m²)</th>
<th>Die Wall Shear Stress Range (KN/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>510</td>
<td>69.35</td>
<td>8.61</td>
<td>66.74 - 77.96</td>
</tr>
<tr>
<td>1274</td>
<td>142.22</td>
<td>13.73</td>
<td>128.49 - 155.95</td>
</tr>
<tr>
<td>2549</td>
<td>208.62</td>
<td>14.70</td>
<td>193.92 - 223.32</td>
</tr>
<tr>
<td>5098</td>
<td>239.17</td>
<td>20.07</td>
<td>219.17 - 259.24</td>
</tr>
<tr>
<td>10195</td>
<td>234.24</td>
<td>27.12</td>
<td>207.12 - 261.36</td>
</tr>
</tbody>
</table>
Table 7.5  Flow Curve Results for the Avicel PH105 Formulation (5:5:6mcc)

<table>
<thead>
<tr>
<th>Shear Rate (s⁻¹)</th>
<th>Die Wall Shear Stress (KN/m²)</th>
<th>Standard Deviation (KN/m²)</th>
<th>Die Wall Shear Stress Range (KN/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>510</td>
<td>48.16</td>
<td>9.49</td>
<td>38.68 - 57.65</td>
</tr>
<tr>
<td>1274</td>
<td>123.13</td>
<td>10.86</td>
<td>112.27 - 133.99</td>
</tr>
<tr>
<td>2549</td>
<td>191.42</td>
<td>21.17</td>
<td>170.24 - 212.58</td>
</tr>
<tr>
<td>5098</td>
<td>215.86</td>
<td>20.50</td>
<td>195.35 - 236.36</td>
</tr>
<tr>
<td>10195</td>
<td>203.76</td>
<td>10.18</td>
<td>193.59 - 213.93</td>
</tr>
</tbody>
</table>

Table 7.6  Flow Curve Results for the Emcocel Formulation (5:5:6mcc)

<table>
<thead>
<tr>
<th>Shear Rate (s⁻¹)</th>
<th>Die Wall Shear Stress (KN/m²)</th>
<th>Standard Deviation (KN/m²)</th>
<th>Die Wall Shear Stress Range (KN/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>510</td>
<td>34.57</td>
<td>9.29</td>
<td>25.27 - 43.85</td>
</tr>
<tr>
<td>1274</td>
<td>83.93</td>
<td>10.85</td>
<td>73.08 - 94.77</td>
</tr>
<tr>
<td>2549</td>
<td>205.32</td>
<td>6.68</td>
<td>198.63 - 211.99</td>
</tr>
<tr>
<td>5098</td>
<td>300.56</td>
<td>16.36</td>
<td>284.20 - 316.92</td>
</tr>
<tr>
<td>10195</td>
<td>320.90</td>
<td>42.02</td>
<td>278.88 - 362.91</td>
</tr>
</tbody>
</table>
Table 7.7  Flow Curve Results for the Unimac MG100
Formulation (5:5:6 Mw/PP)

<table>
<thead>
<tr>
<th>Shear Rate (s(^{-1}))</th>
<th>Die Wall Shear Stress (KN/m(^2))</th>
<th>Standard Deviation (KN/m(^2))</th>
<th>Die Wall Shear Stress Range (KN/m(^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>510</td>
<td>39.49</td>
<td>17.81</td>
<td>21.68 - 57.30</td>
</tr>
<tr>
<td>1274</td>
<td>107.74</td>
<td>17.82</td>
<td>89.92 - 125.55</td>
</tr>
<tr>
<td>2549</td>
<td>228.74</td>
<td>16.94</td>
<td>211.80 - 245.68</td>
</tr>
<tr>
<td>5098</td>
<td>355.26</td>
<td>19.27</td>
<td>335.99 - 374.52</td>
</tr>
<tr>
<td>10195</td>
<td>431.53</td>
<td>26.82</td>
<td>404.72 - 458.35</td>
</tr>
</tbody>
</table>

Table 7.8  Flow Curve Results for the Unimac MG200
Formulation (5:5:6 Mw/PP)

<table>
<thead>
<tr>
<th>Shear Rate (s(^{-1}))</th>
<th>Die Wall Shear Stress (KN/m(^2))</th>
<th>Standard Deviation (KN/m(^2))</th>
<th>Die Wall Shear Stress Range (KN/m(^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>510</td>
<td>40.64</td>
<td>15.68</td>
<td>24.96 - 56.32</td>
</tr>
<tr>
<td>1274</td>
<td>151.55</td>
<td>29.33</td>
<td>122.22 - 180.88</td>
</tr>
<tr>
<td>2549</td>
<td>257.98</td>
<td>25.37</td>
<td>232.62 - 283.35</td>
</tr>
<tr>
<td>5098</td>
<td>332.90</td>
<td>31.85</td>
<td>301.05 - 364.74</td>
</tr>
<tr>
<td>10195</td>
<td>410.89</td>
<td>19.36</td>
<td>391.54 - 430.26</td>
</tr>
</tbody>
</table>
Fig 7.1 Flow Curves: Avicel Powdered Grade Formulations (5:5:6)

Die Wall Shear Stress (KN/m^2)

Apparent Shear Rate (s^-1)

Avicel PH101 formulation
Avicel PH102 formulation
Avicel PH103 formulation
Avicel PH105 formulation
Fig 7.2 Flow Curves: Comparison of Avicel, Unimac & Emcocel Formulations

Die Wall Shear Stress (kN/m²)

Apparent Shear Rate (sE⁻¹)

- Avicel PH101 formulation
- Avicel PH102 formulation
- Emcocel formulation
- Unimac MG100 formulation
- Unimac MG200 formulation
In terms of the rheological characterization of the powdered grade formulations, it should be noted that the die wall shear stress increases, to a limit, with die wall shear rate, and then "plateaus out" (i.e. lower die wall shear stresses are exhibited at high shear rates than would be expected if flow were Newtonian, see Section 2.3.3).

This type of flow curve represents pseudoplastic, or "shear thinning", flow, and indicates that the internal structure of these systems may realign or reorientate themselves, perhaps by some kind of water movement, upon the application of stress. Jastrzebski (1967) postulated that concentrated aqueous kaolinite suspensions undergo structural breakdown on extrusion, resulting in the release of water. It may be that water released in such a manner forms a lubricating boundary layer between the material and the die, so reducing frictional resistance to extrusion. Reorientation of the systems presented in Figures 7.1 and 7.2 is progressive with increased shearing, until at high shear rates a state of maximum fluidity is achieved, characterized by a minimum apparent viscosity.

By comparing the rheological behaviour of the various powdered grade formulations, it can be seen that formulations based on the Unimac grades of microcrystalline cellulose appear to be slightly less shear thinning (their curves do not plateau out quite so early) than the others. This discrepancy is likely to be due to differences in the microcrystalline cellulose-water interaction caused by differences in the wood pulp used as raw material for the microcrystalline cellulose powders, and in the manufacturing processes used in their production (as discussed in Section 6.2.3). The possibility of formulations based on powdered grades from different sources being made equivalent...
(in terms of extrusion rheology) by the alteration of the amount of water used in the formulation has been investigated, and will be discussed in Section 7.4.

7.2 THE EFFECT OF THE MICROCRYSTALLINE CELLULOSE GRADE USED IN THE FORMULATION ON THE FLOW CURVE RESULTS: COLLOIDAL GRADES AND THE USE OF NaCMC AS A BINDER

The flow curve results of the formulations based on colloidal grades of microcrystalline cellulose are given in Tables 7.9 to 7.12 and presented in Figure 7.3. The results for a standard powdered grade formulation based on Avicel PH101 but wet-massed with sodium carboxymethylcellulose solution are given in Tables 7.13 and 7.14 and presented in Figure 7.4.

It can be seen that the magnitude of the die wall shear stress exhibited at a given shear rate clearly depends on the amount (Figure 7.3), the viscosity (Figure 7.3) and the position (Figure 7.4) of the sodium carboxymethylcellulose incorporated in the formulation. The reasons for these differences have been discussed previously (Sections 6.3.1, 6.3.2 and 6.3.4. A comparison may be made between the extrusion rheology of colloidal grade formulations and that of formulations based only on powdered grades of microcrystalline cellulose. Figure 7.3 indicates that the inclusion of sodium carboxymethylcellulose within the microcrystalline cellulose results in a formulation whose flow is generally rather more plastic than the pseudoplastic flow of powdered grade formulations. The material fails to flow until a certain shearing force is applied but, once flow is initiated, at higher shear rates it is Newtonian. This type of flow curve suggests that the internal structures of these systems do not
Table 7.9  Flow Curve Results for the Avicel RC501  
Formulation (5:5:6MCC)  

<table>
<thead>
<tr>
<th>Shear Rate (s⁻¹)</th>
<th>Die Wall Shear Stress (KN/m²)</th>
<th>Standard Deviation (KN/m²)</th>
<th>Die Wall Shear Stress Range (KN/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>510</td>
<td>187.28</td>
<td>2.99</td>
<td>184.29 - 190.27</td>
</tr>
<tr>
<td>1274</td>
<td>199.59</td>
<td>5.14</td>
<td>194.45 - 204.73</td>
</tr>
<tr>
<td>2549</td>
<td>211.19</td>
<td>8.44</td>
<td>202.75 - 219.63</td>
</tr>
<tr>
<td>5098</td>
<td>227.72</td>
<td>5.44</td>
<td>222.28 - 233.15</td>
</tr>
<tr>
<td>10195</td>
<td>243.89</td>
<td>5.35</td>
<td>238.54 - 249.24</td>
</tr>
</tbody>
</table>

Table 7.10  Flow Curve Results for the Avicel RC581  
Formulation (5:5:6MCC)  

<table>
<thead>
<tr>
<th>Shear Rate (s⁻¹)</th>
<th>Die Wall Shear Stress (KN/m²)</th>
<th>Standard Deviation (KN/m²)</th>
<th>Die Wall Shear Stress Range (KN/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>510</td>
<td>344.10</td>
<td>36.80</td>
<td>307.30 - 380.90</td>
</tr>
<tr>
<td>1274</td>
<td>425.32</td>
<td>32.40</td>
<td>392.90 - 457.70</td>
</tr>
<tr>
<td>2549</td>
<td>486.04</td>
<td>27.31</td>
<td>458.70 - 513.30</td>
</tr>
<tr>
<td>5098</td>
<td>539.73</td>
<td>39.54</td>
<td>500.20 - 579.30</td>
</tr>
<tr>
<td>10195</td>
<td>601.13</td>
<td>53.05</td>
<td>540.10 - 654.20</td>
</tr>
</tbody>
</table>
Table 7.11  Flow Curve Results for the Avicel RC591 Formulation (5:5:6×6×6)

<table>
<thead>
<tr>
<th>Shear Rate (s⁻¹)</th>
<th>Die Wall Shear Stress (KN/m²)</th>
<th>Standard Deviation (KN/m²)</th>
<th>Die Wall Shear Stress Range (KN/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>510</td>
<td>347.42</td>
<td>5.04</td>
<td>342.38 - 352.45</td>
</tr>
<tr>
<td>1274</td>
<td>426.89</td>
<td>14.04</td>
<td>412.86 - 440.94</td>
</tr>
<tr>
<td>2549</td>
<td>494.84</td>
<td>26.91</td>
<td>467.93 - 521.75</td>
</tr>
<tr>
<td>5098</td>
<td>537.63</td>
<td>17.52</td>
<td>520.11 - 555.15</td>
</tr>
<tr>
<td>10195</td>
<td>604.23</td>
<td>32.24</td>
<td>571.99 - 636.46</td>
</tr>
</tbody>
</table>

Table 7.12  Flow Curve Results for the Avicel CL611 Formulation (5:5:6×6×6)

<table>
<thead>
<tr>
<th>Shear Rate (s⁻¹)</th>
<th>Die Wall Shear Stress (KN/m²)</th>
<th>Standard Deviation (KN/m²)</th>
<th>Die Wall Shear Stress Range (KN/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>510</td>
<td>196.13</td>
<td>11.93</td>
<td>184.20 - 208.06</td>
</tr>
<tr>
<td>1274</td>
<td>239.51</td>
<td>15.16</td>
<td>224.35 - 254.67</td>
</tr>
<tr>
<td>2549</td>
<td>283.63</td>
<td>21.88</td>
<td>261.76 - 305.51</td>
</tr>
<tr>
<td>5098</td>
<td>318.81</td>
<td>21.82</td>
<td>296.93 - 340.56</td>
</tr>
<tr>
<td>10195</td>
<td>372.87</td>
<td>38.41</td>
<td>334.47 - 411.28</td>
</tr>
</tbody>
</table>
Fig 7.3 Flow Curves: Avicel Colloidal Grade Formulations (5:5:6mcc)

Die Wall Shear Stress (kN/m²)

Apparent Shear Rate (s⁻¹)

- Avicel RC501 formulation
- Avicel RC581 formulation
- Avicel RC591 formulation
- Avicel CL611 formulation
### Table 7.13 Flow Curve Results for the Avicel PH101
Formulation Wet Massed with NaCMC Gel 8% (5:5:6MCC)

<table>
<thead>
<tr>
<th>Shear Rate (s⁻¹)</th>
<th>Die Wall Shear Stress (KN/m²)</th>
<th>Standard Deviation (KN/m²)</th>
<th>Die Wall Shear Stress Range (KN/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>510</td>
<td>32.90</td>
<td>0.29</td>
<td>32.61 - 33.19</td>
</tr>
<tr>
<td>1274</td>
<td>33.20</td>
<td>0.36</td>
<td>32.84 - 33.56</td>
</tr>
<tr>
<td>2549</td>
<td>36.19</td>
<td>0.34</td>
<td>35.76 - 36.44</td>
</tr>
<tr>
<td>5098</td>
<td>37.80</td>
<td>0.36</td>
<td>37.44 - 38.16</td>
</tr>
<tr>
<td>10195</td>
<td>51.60</td>
<td>0.41</td>
<td>51.19 - 52.01</td>
</tr>
</tbody>
</table>

### Table 7.14 Flow Curve Results for the Avicel PH101
Formulation Wet Massed with NaCMC Gel 16% (5:5:6MCC)

<table>
<thead>
<tr>
<th>Shear Rate (s⁻¹)</th>
<th>Die Wall Shear Stress (KN/m²)</th>
<th>Standard Deviation (KN/m²)</th>
<th>Die Wall Shear Stress Range (KN/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>510</td>
<td>40.20</td>
<td>0.21</td>
<td>39.99 - 40.41</td>
</tr>
<tr>
<td>1274</td>
<td>44.60</td>
<td>0.21</td>
<td>44.39 - 44.81</td>
</tr>
<tr>
<td>2549</td>
<td>52.60</td>
<td>0.29</td>
<td>52.31 - 52.89</td>
</tr>
<tr>
<td>5098</td>
<td>57.90</td>
<td>0.31</td>
<td>57.59 - 58.21</td>
</tr>
<tr>
<td>10195</td>
<td>59.40</td>
<td>0.37</td>
<td>59.03 - 59.77</td>
</tr>
</tbody>
</table>
Fig 7.4 Flow Curves: Avicel PH101 Formulations (5:5:6) Wet Massed with Sodium Carboxymethylcellulose (NaCMC) Solutions

Die Wall Shear Stress (kN/mE2)

Apparent Shear Rate (sE-1)

- 0% NaCMC Solution
- 8% NaCMC Solution
- 16% NaCMC Solution
realign or reorientate themselves to any great extent after the commencement of flow. This suggestion appears appropriate, since it is likely that the sodium carboxymethylcellulose, on the surface of the microcrystalline cellulose, will hydrate/dissolve to a certain extent in the water on wet-massing. This gel-like coating on the surface of the particles will then hinder the reorientation of the disperse phase on the application of stress, and so the system will exhibit flow tending more towards plasticity. When the sodium carboxymethylcellulose is introduced into the formulation via the water, however (Figure 7.4), it appears to improve the pseudoplasticity of the formulation, suggesting that it confers superior lubricating properties than those of water alone.

7.3 THE EFFECT OF THE WATER CONTENT OF THE FORMULATION ON THE FLOW CURVE RESULTS

The effect of the water content of powdered grade formulations on their die wall shear stress results has been discussed in Section 6.1. An increased level of water in the formulation lowers the value of die wall shear stress exhibited, with a water level of around 37.5% appearing to be particularly efficient in this respect. By comparing this effect for formulations based on powdered grades of microcrystalline cellulose from different sources, an attempt has been made to determine the level of water required in each formulation in order to result in their flow curves being equivalent.

Figures 7.5 (a) and (b) show the effect of the water content on the die wall shear stress for formulations based on various powdered grades of microcrystalline cellulose extruded at 40cm/min piston speed. It may be seen that the trend of decreasing die wall shear
stress with increasing water content occurs at different rates for each formulation. By superimposing a horizontal line onto these graphs, it is possible to determine the amount of water required to cause each formulation to be equivalent, in terms of die wall shear stress at 40cm/min piston speed, to the standard Avicel PH101 5:5:6 formulation. For example, formulations based on Emcocel and on Unimac MG100 may be made equivalent to the Avicel PH101 (5:5:6) formulation by formulating with the amounts of water derived from the graphs and shown in Table 7.15.

These results support the theory that microcrystalline celluloses from different sources interact with water in different ways or to different extents, thereby producing systems with different extrusion rheology. However, further work has shown that formulations which are equivalent at 40cm/min extrusion speed, are not equivalent at other extrusion speeds. For example, Figure 7.6 shows the effect of the water content of the formulation on the die wall shear stress at an extrusion speed of 10cm/min for formulations based on Avicel PH101, Emcocel and Unimac MG100. Equivalent formulations may be derived from this graph in the same way as before, and the results are presented in Table 7.16.

These results show that the cellulose source of the microcrystalline cellulose, and its manufacturing process, have a complicated effect on the extrusion performance of formulations, which cannot be negated across the whole flow curve range simply by altering the water content of the mix.
Fig 7.6 The Effect of the Water Content of the Formulation on the Die Wall Shear Stress at Piston Speed 10 cm/min

Formulations
- Avicel PH101
- Emcocel
- Unimac MG100
### Table 7.15 Equivalent Formulations at an Extrusion Speed of 40cm/min

<table>
<thead>
<tr>
<th>Grade of Microcrystalline Cellulose</th>
<th>Amount of Water Required for Corresponding Formulation at 40cm/min (MCC:Lactose:Water)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Avicel PH101</td>
<td>37.5%</td>
<td>5:5:6</td>
</tr>
<tr>
<td>Emcocel</td>
<td>41.0%</td>
<td>5:5:6.96</td>
</tr>
<tr>
<td>Unimac MG100</td>
<td>39.9%</td>
<td>5:5:6.64</td>
</tr>
</tbody>
</table>

### Table 7.16 Equivalent Formulations at an Extrusion Speed of 10cm/min

<table>
<thead>
<tr>
<th>Grade of Microcrystalline Cellulose</th>
<th>Amount of Water Required for Corresponding Formulation at 10cm/min (MCC:Lactose:Water)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Avicel PH101</td>
<td>37.5%</td>
<td>5:5:6</td>
</tr>
<tr>
<td>Emcocel</td>
<td>39.4%</td>
<td>5:5:6.5</td>
</tr>
<tr>
<td>Unimac MG100</td>
<td>38.9%</td>
<td>5:5:6.37</td>
</tr>
</tbody>
</table>
CHAPTER EIGHT

THE BENBOW-BRIDGWATER RESULTS
Chapters Six and Seven have shown how simple ram extrusion can provide the data necessary for the rheological characterization of pharmaceutical formulations in terms of extrusion flow curves. Qualitative assessment of the type of flow exhibited was made by comparing the manner in which the die wall shear stress \((t_w)\) is dependent on the extrusion rate. The magnitude of the values of die wall shear stress \((t_w)\) and upstream pressure loss \((P_0)\) allowed quantitative comparisons to be made between formulations. The flow curves did not, however, fit any of the established mathematical flow models outlined in Section 2.3. Thus no material-specific rheological parameters could be obtained independently of shear rate by this method.

This chapter presents the results obtained by using the approach of Benbow et al. (1968, 1971, 1984, 1987 (i) (ii)), which has been described in Section 2.4. The approach was originally developed for the analysis of clay-like materials and catalyst pastes, but is shown here to be equally useful in the assessment of pharmaceutical formulations. The Benbow-Bridgwater equation (eq. 2.33) may be discussed most readily by considering it in parallel with the Bagley equation:

\[
\text{The Bagley Equation - } \\
P_T = [P_0] + [2L/R (t_w)]
\]

\[
\text{The Benbow-Bridgwater Equation - } \\
P_T = [2(dy_o + \alpha V)lnDo/D] + [2L/R (t_o + \beta V)]
\]

The first term on the right hand side of the Benbow-Bridgwater equation is equivalent to the Bagley Upstream Pressure Loss \((P_0)\) separated out into various components:

(i) \(2(\ln Do/D)\) allows for the reduction ratio from the barrel into the die.
(ii) $\delta y_0$, the "initial die entry yield stress", is a theoretical value of material yield stress at zero extrudate velocity. It provides a measure of the resistance to yield of a material upstream of the die.

(iii) $\alpha$, the "die entry yield stress velocity factor", describes the way in which $\delta y_0$ changes with extrudate velocity, $V$.

The second term on the right hand side of the Benbow-Bridgwater equation is equivalent to the second term on the right hand side of the Bagley equation, but with the Bagley die wall shear stress ($t_w$) separated into the following constituents:

(i) $t_0$, the "initial die wall shear stress", is a theoretical material die wall shear stress at zero extrudate velocity. It provides a measure of the resistance to flow of a material through the die.

(ii) $\beta$, the "die-land velocity factor", describes the way in which $t_0$ changes with extrudate velocity, $V$.

The Benbow-Bridgwater parameters have been determined for each of the formulations studied using equations 2.27, 2.28, 2.34 and 2.35. (These equations require the input of values for extrudate velocity. Extrudate velocities corresponding to the extrusion piston speeds were calculated using equation 3.1 and are presented in Table 8.1.) Briefly, the Benbow-Bridgwater calculations were made using data from the Bagley Plots (presented in Chapter Six) and from graphs of steady state extrusion pressure versus extrudate velocity (hereafter referred to as "Benbow plots" and presented in Figures 8.1 to 8.17). The Benbow plots are plotted for extrusions through dies of various length to radius ratio, and are extrapolated to their $y$-intercepts in order to derive values with which to construct theoretical Bagley plots at
zero extrudate velocity. These theoretical zero-velocity Bagley plots are presented in Figures 8.18 to 8.34. A mathematical explanation of the methods of calculation is given in Section 2.4.

The thickness of the die wall lubricating layer has also been determined for each formulation at each extrusion speed from equation 2.25 (as outlined in Section 2.4.5). The calculation requires a value for the liquid phase viscosity, \( n \). This work assumes that the liquid phase of a standard (5:5:6\text{MCC}) formulation is a saturated lactose solution, whose viscosity has been determined as 1.5cps and Newtonian (Benbow, 1987, private communication).

8.1 THE EFFECT OF THE MICROCRYSTALLINE CELLULOSE GRADE USED IN THE FORMULATION ON THE BENBOW-BRIDGWATER RESULTS: POWDERED GRADES

The Bagley Plots for formulations based on powdered grades of microcrystalline cellulose are given as Figures 6.4 to 6.10, and have been discussed previously in Section 6.2. The Benbow Plots are shown as Figures 8.1 to 8.7. The theoretical Bagley Plots at zero extrudate velocity are shown as Figures 8.18 to 8.24.

For all powdered grade formulations, the Benbow Plots of steady state extrusion pressure versus extrudate velocity are non-linear. This indicates that the changes, with extrudate velocity, in the values of initial die entry yield stress (\( \delta y_o \)) and/or initial die wall shear stress (\( t_o \)), are not constant with extrudate velocity, i.e. that the values of die entry yield stress velocity factor (\( \alpha \)) and/or die-land velocity factor (\( \beta \)) are not constant with changing extrudate velocity. This non-linearity of the Benbow plots results in difficulty in extrapolation to their y-intercepts. The curves have been, however, extra-
Fig. 8.1 Benbow Plot for the Avicel PH101 Formulation (5:5:6)

Steady State Extrusion Pressure (kN/mE2)

Apparent Shear Rate (sE-1)
Fig. 8.2 Benbow Plot for the Avicel PH102 Formulation (5:5:6)

Steady State Extrusion Pressure (kN/m²)

Apparent Shear Rate (s⁻¹)

Die L/R
- 2
- 4
- 8
- 12
- 16
Fig 8.3 Benbow Plot for Avicel PH103 Formulation (5:5:6)
Fig 8.4 Benbow Plot for the Avicel PH105 Formulation (5:5:6)
Fig 8.5 Benbow Plot for the Emcocel Formulation (5:5:6)
Fig. 8.6 Benbow Plot for the Unimac MG100 Formulation

Steady State Extrusion Pressure (kN/mE2)

Apparent Shear Rate (sE-1)

Die L/R

- 4  - 12
- 8  - 16
Fig. 8.7 Benbow Plot for the Unimac MG200 Formulation (5:5:6)
Table 8.1 Extrudate Velocities Corresponding to Piston Speeds

<table>
<thead>
<tr>
<th>Piston Speed (cm/min)</th>
<th>Apparent Shear Rate (s⁻¹)</th>
<th>Extrudate Velocity (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>510</td>
<td>0.096</td>
</tr>
<tr>
<td>5</td>
<td>1274</td>
<td>0.24</td>
</tr>
<tr>
<td>10</td>
<td>2549</td>
<td>0.48</td>
</tr>
<tr>
<td>20</td>
<td>5098</td>
<td>0.96</td>
</tr>
<tr>
<td>40</td>
<td>10195</td>
<td>1.92</td>
</tr>
</tbody>
</table>

Polated by estimation, in order to provide the data necessary for the construction of the theoretical zero-velocity Bagley plots. These theoretical plots are linear for all powdered grade formulations, thereby correlating with the results found for experimental Bagley plots (Chapter Six), and thus confirming that estimated extrapolations of the Benbow plots are appropriate.

The Benbow-Bridgwater parameters were calculated from values derived from the plots as outlined in Section 2.4. The parameters are given in Table 8.2. Graphs of die entry yield stress velocity factor \((\alpha)\) and die-land velocity factor \((\beta)\) versus extrudate velocity \((V)\) were plotted and are shown in Figures 8.35 to 8.41. Although the relationships are clearly of the power law type, attempts to represent the velocity-dependence of the terms \(\alpha\) and \(\beta\) in mathematical terms were not successful. However, for all powdered grade formulations, the values of \(\alpha\) and \(\beta\) may be seen to decrease, to a limit, with
extrudate velocity (although the value of $\beta$ increases slightly before decreasing). The implication of the limit to the decrease of $\alpha$ and $\beta$ with $V$, is that, at very high extrusion speeds, the Benbow plots would become linear. The changing values of $\beta$ are also reflected in the results for lubricating layer thickness. If it is assumed that the extrudate flows as a uniform plug through the die, and that a uniform layer of liquid is formed between the outer particles and the inner die wall, the thickness of the lubricating layer may then be calculated from the simple ratio of the viscosity of the continuous phase to the die land velocity factor (equation 2.25). The lubricating layer results are shown in Table 8.3; the values are comparable to those found by Benbow et al. (1987) for alumina pastes.

8.1.1 The Effect of the Microcrystalline Cellulose Particle Size

The effect of the particle size of the microcrystalline cellulose used in the formulation may be determined by comparing the Benbow-Bridgwater parameters (Table 8.2) for formulations based on Avicel PH101 ($m = 50\mu$), Avicel PH102 ($m = 100\mu$) and Avicel PH105 ($m = 20\mu$) and for formulations based on Unimac MG100 ($m = 50\mu$) and Unimac MG200 ($m = 100\mu$). It may be seen that formulations based on grades with a larger particle size exhibit higher values of initial die wall shear stress ($t_0$). This correlates with the results of Chapter Seven, in which formulations based on grades of microcrystalline cellulose with a larger particle size exhibited higher values of die wall shear stress. They also exhibit higher values of die entry yield stress, although values of $[\delta y_0 + \alpha V]$ are higher for formulations based on grades with a smaller particle size. This latter fact also correlates with the results of Chapter Seven, in which the same formulations were seen to exhibit higher values of Upstream Pressure Loss. The exception to this trend is the formulation based on Avicel PH105.
<table>
<thead>
<tr>
<th>GRADE MCC</th>
<th>( \sigma_y )</th>
<th>( t_o )</th>
<th>( \alpha ) at various values of ( V ) (m/s)</th>
<th>( \beta ) at various values of ( V ) (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KN/m²</td>
<td>KN/m²</td>
<td>KNs/m³</td>
<td>KNs/m³</td>
</tr>
<tr>
<td>Avicel PH101</td>
<td>172</td>
<td>12.7</td>
<td>0.096 0.24 0.48 0.96 1.92</td>
<td>0.096 0.24 0.48 0.96 1.92</td>
</tr>
<tr>
<td>Avicel PH102</td>
<td>287</td>
<td>30.5</td>
<td>1874 1562 1027 526 309</td>
<td>329 407 303 189 95</td>
</tr>
<tr>
<td>Avicel PH103</td>
<td>312</td>
<td>25.8</td>
<td>1082 892 643 397 216</td>
<td>332 436 310 176 97</td>
</tr>
<tr>
<td>Avicel PH105</td>
<td>225</td>
<td>13.4</td>
<td>1294 1162 630 401 248</td>
<td>453 485 383 222 109</td>
</tr>
<tr>
<td>Emcocel</td>
<td>198</td>
<td>17.6</td>
<td>1607 1226 911 439 251</td>
<td>362 457 345 211 99</td>
</tr>
<tr>
<td>Unimac MG100</td>
<td>50</td>
<td>17.4</td>
<td>2533 2118 1062 563 281</td>
<td>165 267 395 295 157</td>
</tr>
<tr>
<td>Unimac MG200</td>
<td>89</td>
<td>20.7</td>
<td>2972 1894 986 449 223</td>
<td>159 356 440 352 216</td>
</tr>
</tbody>
</table>

\( \sigma_y \) = Initial die entry yield stress

\( t_o \) = Initial die wall shear stress

\( \alpha \) = Die entry yield stress velocity factor

\( \beta \) = Die land velocity factor

\( V \) = Extrudate velocity
<table>
<thead>
<tr>
<th>GRADE MCC</th>
<th>β at various values of V(m/s)</th>
<th>x^ at various values of V (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.096</td>
<td>0.24</td>
</tr>
<tr>
<td>Avicel PH101</td>
<td>329</td>
<td>407</td>
</tr>
<tr>
<td>Avicel PH102</td>
<td>332</td>
<td>436</td>
</tr>
<tr>
<td>Avicel PH103</td>
<td>453</td>
<td>485</td>
</tr>
<tr>
<td>Avicel PH105</td>
<td>362</td>
<td>457</td>
</tr>
<tr>
<td>Emcocel</td>
<td>165</td>
<td>267</td>
</tr>
<tr>
<td>Unimac MG100</td>
<td>159</td>
<td>356</td>
</tr>
<tr>
<td>Unimac MG200</td>
<td>198</td>
<td>540</td>
</tr>
</tbody>
</table>

β = Die land velocity factor

x = Lubricating layer thickness

V = Extrudate velocity

* assumes that the viscosity of a standard lactose solution is 1.5cps.
This may be explained by the fact that this particular grade of microcrystalline cellulose has a wider particle size distribution than the other Avicel grades (Sixsmith, 1975) and will therefore pack differently. The results may be explained by simple qualitative packing considerations (e.g. Furnas, 1931), which indicate that larger particles will pack with a more open structure and will therefore require a correspondingly larger volume of liquid phase to produce an extrudate paste. Thus, formulations which can be expected to pack with a relatively open structure will yield more easily upstream of the die, due to lower cohesivity, but will flow less easily through it, due to insufficient lubrication. These results are supported by those of Benbow (1984) with catalyst pastes and by those of Benbow et al. (1987) with α-alumina pastes, for which it was found that powders which packed more closely had lower values of initial die wall shear stress.

8.1.2 The Effect of the Microcrystalline Cellulose Moisture Content

The effect of the moisture content of the microcrystalline cellulose used in the formulation may be determined by comparing the Benbow-Bridgwater parameters (Table 8.2) for formulations based on Avicel PH101 (< 5% initial moisture) and Avicel PH103 (< 3% initial moisture content). It may be seen that the formulation based on Avicel PH103 exhibits higher values of initial die entry yield stress and initial die wall shear stress. These results support those found previously in Chapter Seven, that Avicel PH103 formulations exhibit consistently higher values of die wall shear stress and upstream pressure loss than those based on Avicel PH101. These unexpected results have been discussed previously in Section 6.2.2, and indicate that crucial differences exist in the way that the microcrystalline celluloses interact with water, which are not immediately reversible on wet massing.
8.1.3 The Effect of the Microcrystalline Cellulose Source

The effect of the source of the microcrystalline cellulose used in the formulation may be determined by comparing the Benbow-Bridgwater parameters (Table 8.2) for formulations based on Avicel PH101, Unimac MG100 and Emcocel (all nominally equivalent to one another) and those based on Avicel PH102 and Unimac MG200 (nominally equivalent to each other). It may be seen that, while the Avicel PH formulations and the Emcocel formulation exhibit values of initial die entry yield stress and initial die wall shear stress which are broadly similar, the values of initial die entry yield stress exhibited by the Unimac grade formulations are considerably lower. This difference will be shown to be of particular relevance when viewed in the light of the results for extrudate surface quality (Chapter Nine). The differences between grades of microcrystalline cellulose from different manufacturing sources have been discussed previously (Section 6.2.3). Broadly, the varying extrusion performances of formulations based on these grades may be explained in terms of the differing crystallinity/crystal morphology of the grades, due to differences in the cellulose pulp used as their raw material, and differences in their manufacturing processes.

8.2 THE EFFECT OF THE AMOUNT OF WATER USED IN THE POWDERED GRADE FORMULATIONS ON THE BENBOW-BRIDGWATER RESULTS

The Bagley plots for formulations based on Avicel PH101 but mixed with water in varying ratios (5:5:4, 5:5:5, 5:5:8, 5:5:6) are given in Figures 6.1 to 6.4 and have been discussed previously in Section 6.1. It may be recalled that formulations containing smaller amounts of water (5:5:4, 5:5:5 formulations) exhibited values of steady state extrusion pressure which did not correlate well with die length to radius ratio at low shear rates. As a result, the Benbow plots
(Figures 8.8 to 8.11) have been plotted using the values of steady state extrusion pressure at shear rates of 2549 and 10195 s\(^{-1}\) only (equivalent extrudate speeds; 0.48, 1.92 m/s). The theoretical Bagley plots at zero velocity were then derived, Figures 8.25 to 8.28. This method is limited by the fact that it assumes that steady state extrusion pressure increases linearly with extrudate speed (whereas it has been shown, Figures 8.1 to 8.7, that it does not). However, a rank comparison of the relative values of initial die entry yield stress \((\delta y_0)\) and initial die wall shear stress \((t_0)\) for the different mixes may be made. The values of die entry yield stress velocity factor \((\alpha)\) and die-land velocity factor \((\beta)\) may be calculated and quoted with reference to the average extrudate speed, i.e. \((1.92 + 0.48)/2 = 1.2\) m/s. The effect of the water content of the formulations may thus be determined by comparing the Benbow-Bridgwater parameters (Table 8.4) for mixes formulated with varying amounts of water. These results are presented in Figures 8.42 to 8.45. When interpreting these results, it should be borne in mind that altering the water content of the formulation is unlikely, in these systems, to result in a change in the rheological properties of the liquid phase, since the liquid phase may be assumed in each case to be a saturated solution of lactose.

It can be seen from the figures that initial die entry yield stress \((\delta y_0)\) and initial die wall shear stress \((t_0)\) decrease with increasing water content. This result is not unexpected - certainly it would be predicted that wetter formulations would yield more readily and flow through the die more easily due to their increased lubrication. These results are supported by those discussed in Section 8.1.1, which indicate that formulations based on small particles exhibit lower values of initial die entry yield stress and initial die wall shear...
Fig. 8.8 Benbow Plot for the Avicel PH101 Formulation (5:5:4)

Fig. 8.9 Benbow Plot for the Avicel PH101 Formulation (5:5:5)

Steady State Extrusion Pressure (kW/m²)

Apparent Shear Rate (s⁻¹)

Die L/R
- 4
- 8
- 12
- 16
Fig. 8.10 Benbow Plot for the Avicel PH101

Formulation (5:5:6)

Steady State Extrusion Pressure (kN/m^2)

Apparent Shear Rate (s^-1)

Fig. 8.11 Benbow Plot for the Avicel PH101

Formulation (5:5:8)

Steady State Extrusion Pressure (kN/m^2)

Apparent Shear Rate (s^-1)
stress. Both sets of results (the decrease in extrusion parameters with increasing proportion of liquid and with decreasing particle size) support the view that the mechanical properties of the formulations are determined to some extent by the degree to which the liquid exceeds that required to fill the spaces between a bed of dry particles. These results are also supported by those of Benbow et al. (1987), who found that initial die entry yield stress ($\sigma y_0$) and initial die wall shear stress ($t_0$) decreased with increasing water content for $\alpha$-alumina pastes, and who comment that similar results are found for the dependence of soil triaxial strength on water content. These authors also report that, according to Hodgkinson and Goodson (1959), the pressure required to initiate extrusion of many clays is of the form $A'e^{q-M}$, where $A'$ and $q$ are constants and $M$ is the water content expressed in percent of the weight of dry clay. A graph of $\ln\sigma y_0$ versus water content (as percent dry weight) for the Avicel PH101 formulation is shown in Figure 8.46. The graph is linear and is of the form $\ln\sigma y_0 = cM + \text{constant}$, where $c = \text{the gradient of the graph}$. It may thus be concluded that the pressure required to initiate the extrusion of Avicel PH101 formulations is of the form $A'e^{q-cM}$, i.e. it is dependent on water content in a manner similar to a Hodgkinson-Goodson clay.

Figures 8.44 and 8.45 show that the values of die entry yield stress velocity factor ($\alpha$) and die-land velocity factor ($\beta$) decrease, to a limit, with increasing water content. This result correlates with that of Harrison (1982), who found that increasing the water content of a formulation resulted in a reduction in the dependency of the upstream pressure loss ($P_o$) on extrudate velocity. The limit to the decrease of $\alpha$ and $\beta$ is reached at a water content of about 37.5%, implying that the 5:5:6 formulation contains a "saturation" quantity.
of water above which no further decrease in the velocity dependence of initial die entry yield stress \((\sigma_{y_0})\) and initial die wall shear stress \((t_0)\) may be made.

The changing values of die-land velocity factor \((\beta)\) are reflected in the results for lubricating layer thickness given in Table 8.5. These values reflect the "saturation" phenomenon, and appear to imply that there is a limit to the extent to which an increase in water content will cause an increase in the thickness of the die wall lubricating layer, at a given extrusion speed. At first sight, this result seems difficult to explain: clearly, lubricating layer thickness will be zero when there is only enough liquid present to fill the void spaces between the unwetted particles, and if the proportion of liquid is increased, it would be expected that the thickness of the lubricating layer would increase accordingly. The result may be explained by postulating that lubricating layer thickness increases with water content to a limit beyond which plug flow cannot be maintained. Any extra water above this limit would remain within the mass resulting in flow of a more liquid, rather than semi-solid, nature.

Theoretically, the values of wall layer thickness \((x)\) and water content could be used to plot a graph whose x-intercept would represent the water content which is just sufficient to fill the interparticulate voids within the unwetted powder. However, for these pharmaceutical systems, die-land velocity factor \((\beta)\), and hence lubricating layer thickness \((x)\), has been shown to depend on extrudate velocity (Section 8.1) and so such a plot at any one velocity value would be meaningless. If the plots were constructed for various values, it might or might not be found that they shared a common x-intercept which could be interpreted as the voidage water - this
Table 8.4  The Effect of the Water Content of the Avicel PH101 Formulation on the Benbow-Bridgwater Parameters

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Water Content (%)</th>
<th>(\phi y_0) (KN/m²)</th>
<th>(t_0) (KN/m²)</th>
<th>(\alpha) at (V = 1.2\text{m/s}) (KNs/m³)</th>
<th>(\beta) at (V = 1.2\text{m/s}) (KNs/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5:5:4</td>
<td>28.6</td>
<td>2129</td>
<td>263</td>
<td>490</td>
<td>222</td>
</tr>
<tr>
<td>5:5:5</td>
<td>33.3</td>
<td>1084</td>
<td>192</td>
<td>321</td>
<td>109</td>
</tr>
<tr>
<td>5:5:6</td>
<td>37.5</td>
<td>629</td>
<td>146</td>
<td>71</td>
<td>26</td>
</tr>
<tr>
<td>5:5:8</td>
<td>44.4</td>
<td>120</td>
<td>80</td>
<td>89</td>
<td>24</td>
</tr>
</tbody>
</table>

Table 8.5  The Effect of the Water Content of the Avicel PH101 Formulation on the Thickness of the Die Wall Lubricating Layer (\(x\))

<table>
<thead>
<tr>
<th>Water Content (%)</th>
<th>Comparative Value of (\beta) at (V = 1.2\text{m/s}) (KNs/m³)</th>
<th>Comparative Value of (x) at (V = 1.2\text{m/s}) ((\mu))</th>
</tr>
</thead>
<tbody>
<tr>
<td>28.6</td>
<td>222</td>
<td>0.68</td>
</tr>
<tr>
<td>33.3</td>
<td>109</td>
<td>1.38</td>
</tr>
<tr>
<td>37.5</td>
<td>26</td>
<td>5.77</td>
</tr>
<tr>
<td>44.4</td>
<td>24</td>
<td>6.25</td>
</tr>
</tbody>
</table>

\(\phi y_0\) = Initial die entry yield stress  
\(t_0\) = Initial die wall yield stress  
\(\alpha\) = Die entry yield stress velocity factor  
\(\beta\) = Die land velocity factor  
\(V\) = Extrudate velocity  
\(x\) = Lubricating layer thickness
approach is not presented here because the appropriate data are available for only one extrusion speed (as explained earlier in this section). However, a plot at this single velocity value (1.2m/s) has been made (Figure 8.47). The stages of the graph appear to indicate that levels of water below about 33% are involved mainly with filling the interparticulate voids of the Avicel PH101 system. Quantities of water between about 33 and 38% are in excess of that required to fill the voids and can thus increasingly lubricate the system as a surface layer. Levels of water above about 38% provide no increase in the contribution to the lubricating layer, possibly due to the breakdown of semi-solid plug flow. Clearly, more data would be required before these statements can be made with any accuracy, and this would be an area for further work. In the meantime, Figure 8.47 does seem to provide a clue as to the reasons why a level of 37% water should prove so effective for extrusion of an Avicel PH101 Formulation.

8.3 THE EFFECT OF THE MICROCRYSTALLINE CELLULOSE GRADE USED IN THE FORMULATION ON THE BENBOW-BRIDGWATER RESULTS: COLLOIDAL GRADATES

The Bagley plots for formulations based on colloidal grades of microcrystalline cellulose are given as Figures 6.11 to 6.16, and have been discussed previously in Section 6.3. The Benbow plots are shown as Figures 8.12 to 8.17. The theoretical Bagley plots at zero extrudate velocity are shown as Figures 8.29 to 8.34.

For all colloidal grade formulations, except for that based on Avicel RC501, the Benbow plots of steady state extrusion pressure versus extrudate velocity are non-linear. In other words, like powdered grade formulations, the formulations exhibit values of die entry yield
Fig 8.12 Benbow Plot for the Avicel RC581 Formulation (5:5:6mcc)

Die L/R: 2 4 8

Apparent Shear Rate (sE-1)

Steady State Extrusion Pressure (KN/m²)

- 228 -
Fig 8.13 Benbow Plot for the Avicel RC591 Formulation (5:5:6mcc)

Steady State Extrusion Pressure (kN/m²)

Apparent Shear Rate (s⁻¹)

Die L/R
- 2
- 12
- 4
- 16
- 8
Fig 8.14 Benbow Plot for the Avicel RC501 Formulation (5:5:6mcc)
Fig. 8.15 Benbow Plot for the Avicel CL611 Formulation (5:5:6mcc)
Fig. 8.16 Benbow Plot for the Avicel PH101 Formulation
Wet Massed with Sodium CMC Gel 8% (5:5:6)

Steady State Extrusion Force (kN/m²E)

Apparent Shear Rate (s²E⁻¹)
Fig 8.17 Benbow Plot for the Avicel PH101 Formulation
Wet Massed with Sodium CMC Gel 16% (5:5:6)
Figures 8.18 to 8.21: Zero-Velocity Bagley Plots for the Avicel PH Grade Formulations

- Fig. 8.18: PH101
- Fig. 8.19: PH102
- Fig. 8.20: PH103
- Fig. 8.21: PH105

Zero-velocity Extrusion Pressure (kN/mE2)

Die L/R
Figures 8.22 to 8.24: Zero-Velocity Bagley Plots for the Emcocel & Unimac Grade Formulations

Zero-velocity Extrusion Pressure (kN/mE2)

Die L/R

- Fig. 8.22: Emcocel
- Fig. 8.23: Unimac MG100
- Fig. 8.24: Unimac MG200
Figures 8.25 to 8.28: Zero-Velocity Bagley Plots for the Avicel PH101 Formulations at Different Water Contents
stress ($\sigma_0$) and/or initial die wall shear stress ($t_0$) whose dependence on extrudate velocity varies non-linearly with extrudate velocity, i.e. their values of die entry yield stress velocity factor ($\alpha$) and/or die-land velocity factor ($\beta$) are not constant with changing extrudate velocity. The Avicel RC501 formulation was the exception to this observation - exhibiting values of die entry yield stress ($\sigma_0$) and/or initial die wall shear stress ($t_0$) whose change with extrudate velocity was linear, i.e. values of die entry yield stress velocity factor ($\alpha$) and/or die-land velocity factor ($\beta$) which were constant across the range of extrudate velocities used experimentally. The reason why the Avicel RC501 formulation should exhibit a linear Benbow plot is uncertain. It may be related to the position or quantity or availability of the sodium carboxymethylcellulose in the continuous phase of the extruded system. Certainly it is true that the formulations based on Avicel PH101 but wet-massed with 8% or 16% sodium carboxymethylcellulose gel exhibit Benbow plots which approach linearity (Figures 8.16 and 8.17) and Benbow et al. (1987) have stated that the shape of a Benbow plot depends on the rheology of the liquid phase. This similarity between the Avicel RC501 formulation and the Avicel PH101 - sodium carboxymethylcellulose gel formulations will be discussed later in this section.

The Benbow plots were extrapolated to zero velocity in order to provide the data necessary for the construction of the theoretical zero-velocity Bagley plots. These theoretical plots were linear for all colloidal grade formulations, thereby correlating with the results found for experimental Bagley plots (Chapter Six).

The Benbow-Bridgwater parameters were calculated from values derived from the plots as outlined in Section 2.4. The parameters are given
Figures 8.29 to 8.32: Zero-Velocity Bagley Plots for the Avicel 'Colloidal' Grade Formulations

- Fig. 8.29: RC581
- Fig. 8.30: RC591
- Fig. 8.31: RC501
- Fig. 8.32: CL611
Figures 8.33 and 8.34: Zero-Velocity Bagley Plots for the Avicel PH101 Formulations Wet Massed with Sodium CMC Gel

- Fig. 8.33: Sodium CMC 8%
- Fig. 8.34: Sodium CMC 16%
in Table 8.6. Graphs of die entry yield stress velocity factor (α) and die-land velocity factor (β) versus extrudate velocity (V) were plotted and are given in Figures 8.48 to 8.53. The relationship of α and β to extrudate velocity is of the power law type for all colloidal grade formulations (except that based on Avicel RC501 as mentioned previously), although a mathematical model to describe the curves could not be fitted easily. It may be seen that the values of α and β decrease, to a limit, with extrudate velocity. The plots imply that, at high extrudate speeds (greater than 2m/s at least), α and β would become constant and that consequently the Benbow plots would become linear. Clearly, the Avicel RC501 formulation exhibits such linearity at extrusion speeds well below the limit which applies to other formulations.

The values for die-land velocity factor (β) are reflected in the results for lubricating layer thickness (x), calculated from equation 2.25. The lubricating layer thickness results are shown in Table 8.7. The values for all colloidal grade formulations are comparable to those found by Benbow et al. (1987) for alumina pastes and to those found for powdered grade formulations (Table 8.3). The exceptions are the Avicel RC501 formulation and the Avicel PH101 formulations wet-massed with sodium carboxymethylcellulose gel, which both exhibit much larger values. If it is assumed that the "colloidal" grade formulations have a lubricating layer composed solely of a saturated lactose solution, and that the viscosity of a saturated lactose solution is about 1.5cps, then the Avicel RC501 formulation has a lubricating layer which is 10 to 20 times thicker than those of powdered formulations. In fact, the lubricating layers of the "colloidal" formulations most probably contain some hydrated sodium carboxymethylcellulose, whose viscosity will be greater than 1.5cps. Thus, the
### Table 8.6  
**BENBOW-BRIDGWATER PARAMETERS FOR COLLOIDAL GRADE FORMULATIONS**

<table>
<thead>
<tr>
<th>GRADE MCC</th>
<th>$\delta y_{o}$</th>
<th>$t_{o}$</th>
<th>$\alpha$ at various values of $V$(m/s)</th>
<th>$\beta$ at various values of $V$ (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KN/m²</td>
<td>KN/m²</td>
<td>KNs/m³</td>
<td>KNs/m³</td>
</tr>
<tr>
<td>Avicel RC501</td>
<td>490</td>
<td>193</td>
<td>0.096 0.24 0.48 0.96 1.92</td>
<td>0.096 0.24 0.48 0.96 1.92</td>
</tr>
<tr>
<td>Avicel RC581</td>
<td>480</td>
<td>284</td>
<td>0.096 0.24 0.48 0.96 1.92</td>
<td>0.096 0.24 0.48 0.96 1.92</td>
</tr>
<tr>
<td>Avicel RC591</td>
<td>461</td>
<td>256</td>
<td>0.096 0.24 0.48 0.96 1.92</td>
<td>0.096 0.24 0.48 0.96 1.92</td>
</tr>
<tr>
<td>Avicel CL611</td>
<td>275</td>
<td>144</td>
<td>0.096 0.24 0.48 0.96 1.92</td>
<td>0.096 0.24 0.48 0.96 1.92</td>
</tr>
<tr>
<td>Avicel PH101 with:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8% NaCMC</td>
<td>187</td>
<td>31.2</td>
<td>0.096 0.24 0.48 0.96 1.92</td>
<td>0.096 0.24 0.48 0.96 1.92</td>
</tr>
<tr>
<td>16% NaCMC</td>
<td>315</td>
<td>36.3</td>
<td>0.096 0.24 0.48 0.96 1.92</td>
<td>0.096 0.24 0.48 0.96 1.92</td>
</tr>
</tbody>
</table>

- $\delta y_{o}$ = Initial die entry yield stress
- $t_{o}$ = Initial die wall shear stress
- $\alpha$ = Die entry yield stress velocity factor
- $\beta$ = Die land velocity factor
- $V$ = Extrudate velocity

- Extrudate velocity
Table 8.7
VALUES OF LUBRICATING LAYER THICKNESS (x) FOR COLLOIDAL GRADE FORMULATIONS

<table>
<thead>
<tr>
<th>GRADE MCC</th>
<th>0.096</th>
<th>0.24</th>
<th>0.48</th>
<th>0.96</th>
<th>1.92</th>
<th>0.096</th>
<th>0.24</th>
<th>0.48</th>
<th>0.96</th>
<th>1.92</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avicel RC501</td>
<td>27</td>
<td>27</td>
<td>27</td>
<td>27</td>
<td>27</td>
<td>55.6</td>
<td>55.6</td>
<td>55.6</td>
<td>55.6</td>
<td>55.6</td>
</tr>
<tr>
<td>Avicel RC581</td>
<td>630</td>
<td>590</td>
<td>422</td>
<td>268</td>
<td>165</td>
<td>2.4</td>
<td>2.5</td>
<td>3.6</td>
<td>5.6</td>
<td>9.1</td>
</tr>
<tr>
<td>Avicel RC591</td>
<td>955</td>
<td>713</td>
<td>498</td>
<td>294</td>
<td>182</td>
<td>1.6</td>
<td>2.1</td>
<td>3.0</td>
<td>5.1</td>
<td>8.2</td>
</tr>
<tr>
<td>Avicel CL611</td>
<td>546</td>
<td>399</td>
<td>291</td>
<td>182</td>
<td>119</td>
<td>2.7</td>
<td>3.8</td>
<td>5.2</td>
<td>8.2</td>
<td>12.6</td>
</tr>
</tbody>
</table>

Avicel PH101 with:

<table>
<thead>
<tr>
<th>8% NaCMC</th>
<th>18</th>
<th>8</th>
<th>10</th>
<th>7</th>
<th>11</th>
<th>6x10^5</th>
<th>13x10^5</th>
<th>10x10^5</th>
<th>14x10^5</th>
<th>9x10^5</th>
</tr>
</thead>
<tbody>
<tr>
<td>16% NaCMC</td>
<td>198</td>
<td>540</td>
<td>476</td>
<td>340</td>
<td>203</td>
<td>3x10^5</td>
<td>3x10^5</td>
<td>3x10^5</td>
<td>4x10^5</td>
<td>8x10^5</td>
</tr>
</tbody>
</table>

\( \beta \) = Die land velocity factor

\( x \) = Lubricating layer thickness

\( V \) = Extrudate velocity

* assumes that the continuous phase of a colloidal grade formulation consists solely of a saturated lactose solution whose viscosity = 1.5cps, and that the viscosity of 8% and 16% sodium carboxymethylcellulose gel > 10,000 cps (Bionose technical literature, Aqualon (UK) Ltd, Cheshire).
Fig. 8.35 Velocity Factors vs. Extrudate Speed for Avicel PH101 Formulation

Die Entry Yield Stress Velocity Factor

Die Land Velocity Factor

Fig. 8.36 Velocity Factors vs. Extrudate Speed for Avicel PH102 Formulation

Die Entry Yield Stress Velocity Factor

Die Land Velocity Factor
Fig. 8.4 Velocity Factors vs. Extrudate

Speed for Unimac MG200 Formulation

Die Entry Yield Stress
Velocity Factor

Die Land Velocity
Factor

Velocity Factor (kN/m²)

Speed of Extrudate (m/s)
Fig. 8.42 Initial Die Entry Yield Stress vs. Water Content of the Formulation

Fig. 8.43 Initial Die Wall Shear Stress vs. Water Content of the Formulation
Fig. 8.44 Initial Die Entry Yield Stress
Velocity Factor vs. Water Content of the Formulation

Fig. 8.45 Initial Die Wall Shear Stress
Velocity Factor vs. Water Content of the Formulation
Fig. 8.50 Velocity Factors vs. Extrudate Speed for Avicel RC591 Formulation

- Die Entry Yield Stress Velocity Factor
- Die Land Velocity Factor

Fig. 8.51 Velocity Factors vs. Extrudate Speed for Avicel CL611 Formulation

- Die Entry Yield Stress Velocity Factor
- Die Land Velocity Factor
calculated values of \( x \) for the "colloidal" grade formulations are likely to be considerable underestimates. For the Avicel PH101 formulations wet-massed with 8% and 16% sodium carboxymethylcellulose gel, it must be assumed that the lubricating layers are composed solely of the gels and that the gels' viscosities are somewhat greater than 10,000 cps (since this is the viscosity attributed to a 4% sodium carboxymethylcellulose gel in Blanose technical literature, Aqualon (UK) Ltd.). This assumption results in calculated values for lubricating layer thickness for the Avicel PH101-sodium carboxymethylcellulose gel formulations which are so large as to be totally meaningless given the dimensions of the die (indicating, probably that the model of plug flow with a lubricating layer is not applicable to these systems). It may be said, then, that the Avicel RC501 formulation and the Avicel PH101-sodium carboxymethylcellulose gel formulations, while being the only formulations to produce smooth-surfaced extrudate under all extrusion conditions, were also the only formulations to exhibit systems other than the kind of plug flow systems with very thin lubricating layers exhibited by all the other formulations. This supports the findings of Benbow (1984), who states that the liquid phase rheology affects both the extrudate shape retention (i.e. smoothness) and extrusion parameters. These results will be discussed further in Chapter Nine (Extrudate Quality Assessment).

8.3.1 The Effect of the Amount and Viscosity of Sodium Carboxymethylcellulose in the Colloidal Grade
The effect of the amount and viscosity of the sodium carboxymethylcellulose co-processed into a "colloidal" grade of microcrystalline cellulose may be determined by comparing the Benbow-Bridgwater parameters for formulations based on Avicel RC501, Avicel RC581/RC591 and Avicel CL611. Trends dependent on amount or viscosity of sodium
carboxymethylcellulose cannot be seen by examining the $\delta y_0$ and $t_o$ parameters in isolation from the effects of shear rate. It is true, however, that "colloidal" grade formulations in general do exhibit higher values of initial die entry yield stress and initial die wall shear stress than powdered grade formulations, indicating that their increased resistance to flow occurs for flow both into and through the die. It may also be seen that the values of die entry yield stress velocity factor ($\alpha$) and die-land velocity factor ($\beta$) are more constant over the range of extrusion velocities studied for colloidal grade formulations than they are for powdered grade formulations. This implies that colloidal grade formulations are less able to restructure themselves on the application of stress than the powdered grade formulations, as discussed in Section 7.2.

8.3.2 The Effect of the Method of Drying of the Colloidal Grade

Avicel RC581 and RC591 are identical except for the fact that they are dried by different methods (bulk and spray drying, respectively). As reported in Chapter Six, for the Bagley Plot results, and Chapter Seven, for the Flow Curve results, the method of drying does not appear to have any effect on the extrusion parameters exhibited by the formulations based on these grades.

8.3.3 The Effect of the Use of Sodium Carboxymethylcellulose as the Binder in a Powdered Grade Formulation

When sodium carboxymethylcellulose is used as the binder in an otherwise conventional Avicel PH101 formulation (in an attempt to mimic a colloidal grade formulation) the values exhibited for initial die entry yield stress and initial die wall shear stress are very similar to those exhibited by powdered grade formulations themselves (compare values in Table 8.6 with those in Table 8.2). This result at first
appears anomalous, since it has been established in Chapters Six and Seven that the use of sodium carboxymethylcellulose gel as the binder within the formulation affects the extrusion results obtained. However, it may be seen, by extrapolating the relevant flow curves (Figure 7.4) to the y-intercept, that a powdered grade formulation wet massed with water will indeed exhibit a theoretical die wall shear stress at zero extrudate velocity which is similar in value to that exhibited by one which has been wet massed with sodium carboxymethylcellulose gel. It should be noted that the effect of including sodium carboxymethylcellulose as a binder is much more evident at extrusion speeds above zero, as evidenced both by the flow curves (Figure 7.4) and by the values of die entry yield stress velocity factor, $\alpha$, and die-land velocity factor, $\beta$, (which are much lower for formulations bound with sodium carboxymethylcellulose; Tables 8.2 and 8.6). It would thus appear, and this seems logical, that the lubricant action of the sodium carboxymethylcellulose discussed in Section 6.4 is only significant on the application of stress.
"..... the usual doleful remark - that the reasons for this particular extrudate defect are not understood - must be made".
Bagley and Schreiber, 1969
Chapters Five, Six, Seven and Eight have dealt with various aspects of the quantitative analysis of extrusion. This chapter is concerned with the quality of the extrudate produced by a given formulation. The analysis of extrudate quality is important, whether or not the extrudate is to be processed further. If, for example, the extrudate is to be used without further processing (e.g. as a weed control pellet) then it should be of a suitable bulk quality to withstand handling and should ideally be of a quality which is pleasing to the eye. If the extrudate is to be processed into spheroids, then it must possess a combination of qualities: (a) it must be brittle enough to break up on the spheronizer plate and (b) it must be plastic enough to undergo the shape change into spheroids. Thus, an extrudate which is produced continuously from the die, without breaking, is unlikely to be suitable for spheronization - it would probably agglomerate uncontrollably on the spheronizer plate. An extrudate whose surface imperfections are so severe that it breaks into very short, irregularly-shaped pieces, on the other hand, is likely to produce a lot of fines on spheronization. It is unlikely to undergo the appropriate shape changes to produce spheroids. (For a description of the shape changes which take place on a spheronizer plate, see Chapman, 1985.) It was therefore considered important to record both the bulk and surface characteristics for extrudate produced by each microcry-stalline cellulose formulation under the various experimental conditions used.

For the formulations studied in this work, extrudate bulk characteristics such as continuity of production and coiling/spiralling at the die exit were noted subjectively, and surface characteristics were recorded as belonging to one of three categories: smooth, rough or sharkskinned (Figure 3.3). A smooth extrudate is characterized by a
uniformly smooth, integral surface; a rough extrudate has random irregularities along all of its length; a sharkskinned extrudate has regular, circumferential ridges at intervals along its length. A convenient method of recording this extrudate quality information is to superimpose it onto a Bagley plot, thereby providing an immediate visual indication of the range of extrusion conditions over which good quality extrudate may be produced. An example of such a representation is given in Figure 9.1.

9.1 THE ANALYSIS OF EXTRUDATE IMPAIRMENT

The existence of surface impairment in wet powder mass extrusion was first noted by Harrison (1982), although Cheng (1970) had reported shape impairment and the study of extrudate defects in polymer extrusion was common. In 1957, Tordella had noted that a spiralling surface impairment of polyethylene extrudate occurred above a certain value of shear rate: the so-called "critical shear rate". Visual observation indicated that a macroscopic, spiralling flow disturbance occurred in the die entry region at a shear rate corresponding to the critical value. Tordella termed this disturbance "melt fracture" (others have called it "elastic turbulence"), and would later (1969) attribute it to a large critical elastic strain. The work of Bagley (1957, 1963) was in agreement with that of Tordella, and, further, showed that the value for critical shear rate was independent of the die length to radius ratio. Bagley also found that, at the value for critical shear rate, discontinuities occurred in the slopes of plots of log output versus log pressure and of Bagley End Correction ($n_b$) versus log shear rate. His results support the theory of Tordella that the defects observed in polyethylene originated at the die entry, and the explanation suggested by Bagley is as follows: Firstly, as a
Figure 9.1  A Typical Bagley Plot for the Avicel PH101 (5.5.6) Formulation, showing Extrudate Surface Characteristics
polymer flows into a capillary, the natural flow lines above the die cause viscous resistance (the origin of the end correction, as outlined in Section 2.1.3). Secondly, as the shear rate increases, so the end correction increases (so that the resistance provided by the die becomes smaller relative to that at the die entrance) until a kind of relief mechanism appears to set in, the so-called "melt fracture". In 1958, Bagley et al. found for the extrusion of linear polyethylene that there was a pressure region in which the output was double-valued, with extrudate which was smooth or impaired depending on the output value. This region is therefore one of oscillating flow conditions, and this so-called 'fluctuating flow' during extrudate impairment was confirmed by Tordella in 1969.

9.2 THE EXTRUDATE QUALITY RESULTS FOR MICROCRYSTALLINE CELLULOSE FORMULATIONS

The results for extrudate quality for the formulations used in this work are presented in Tables 9.1 to 9.13. Clearly, the range of conditions over which smooth-surfaced extrudate may be produced varies greatly depending upon the grade of microcrystalline cellulose upon which the formulation is based. However, for all the formulations, it may be seen that the results are quite different to those of Tordella (1957, 1969) and of Bagley (1957, 1963). Firstly, the onset of surface impairment does not appear to be dependent on the attainment of a given shear rate (cf. Tordella, 1957; Bagley, 1957) but rather it occurs at intermediate values of shear rate/stress. Secondly, the formulations have low die swell, exhibiting minimum elastic recovery (Harrison et al., 1985) (cf. Tordella, 1969). Thirdly, graphs of log output versus log pressure do not exhibit a discontinuity (example Figure 9.2) (cf. Bagley, 1957). Fourthly, End Correction does not
### Table 9.1 Extrudate Quality: Avicel PH101 (5:5:6)

<table>
<thead>
<tr>
<th>Shear Rate ($s^{-1}$)</th>
<th>Die Length to Radius Ratio (L/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 4 8 12 16</td>
</tr>
<tr>
<td>510</td>
<td>R R Sm Sm Sm</td>
</tr>
<tr>
<td>1274</td>
<td>Sh Sh Sm Sm Sm</td>
</tr>
<tr>
<td>2549</td>
<td>Sh R Sm Sm Sm</td>
</tr>
<tr>
<td>5098</td>
<td>R R Sm Sm Sm</td>
</tr>
<tr>
<td>10195</td>
<td>R Sm Sm Sm Sm</td>
</tr>
</tbody>
</table>

Extrudate was produced more continuously at slower speeds.

### Table 9.2 Extrudate Quality: Avicel PH102 (5:5:6)

<table>
<thead>
<tr>
<th>Shear Rate ($s^{-1}$)</th>
<th>Die Length to Radius Ratio (L/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 4 8 12 16</td>
</tr>
<tr>
<td>510</td>
<td>Sh R Sm Sm Sm</td>
</tr>
<tr>
<td>1274</td>
<td>Sh Sh Sm Sm Sm</td>
</tr>
<tr>
<td>2549</td>
<td>Sh Sh Sm Sm Sm</td>
</tr>
<tr>
<td>5098</td>
<td>Sh Sh Sm Sm Sm</td>
</tr>
<tr>
<td>10195</td>
<td>Sh Sm Sm Sm Sm</td>
</tr>
</tbody>
</table>

Extrudate was produced more continuously at slower speeds.

**Key:**
- **Sh**: Sharkskinned surface
- **R**: Rough surface
- **Sm**: Smooth surface
Table 9.3 Extrudate Quality: Avicel PH103 (5:5:6)

<table>
<thead>
<tr>
<th>Shear Rate (s⁻¹)</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>510</td>
<td>Sh</td>
<td>R</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
</tr>
<tr>
<td>1274</td>
<td>Sh</td>
<td>Sh</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
</tr>
<tr>
<td>2549</td>
<td>Sh</td>
<td>Sh</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
</tr>
<tr>
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<td>Sh</td>
<td>Sh</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
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<td>10195</td>
<td>R</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
</tr>
</tbody>
</table>

Extrudate was produced more continuously at slower speeds.

Table 9.4 Extrudate Quality: Avicel PH105 (5:5:6)

<table>
<thead>
<tr>
<th>Shear Rate (s⁻¹)</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>510</td>
<td>Sh</td>
<td>R</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
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<tr>
<td>1274</td>
<td>Sh</td>
<td>Sh</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
</tr>
<tr>
<td>2549</td>
<td>Sh</td>
<td>Sh</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
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<tr>
<td>5098</td>
<td>Sh</td>
<td>Sh</td>
<td>Sm</td>
<td>Sm</td>
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<tr>
<td>10195</td>
<td>R</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
</tr>
</tbody>
</table>

Extrudate was produced more continuously at slower speeds.

Key: Sh; Sharkskinned surface
R; Rough surface
Sm; Smooth surface
Table 9.5 Extrudate Quality : Emcocel (5:5:6)

<table>
<thead>
<tr>
<th>Shear Rate</th>
<th>Die Length to Radius Ratio (L/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(s⁻¹)</td>
<td>4</td>
</tr>
<tr>
<td>510</td>
<td>R</td>
</tr>
<tr>
<td>1274</td>
<td>Sev</td>
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<tr>
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<td>Sev</td>
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<tr>
<td>5098</td>
<td>Sev</td>
</tr>
<tr>
<td>10195</td>
<td>Sev</td>
</tr>
</tbody>
</table>

Extrudate was produced more continuously at slower speeds.

Table 9.6 Extrudate Quality : Unimac MG100 (5:5:6)

<table>
<thead>
<tr>
<th>Shear Rate</th>
<th>Die Length to Radius Ratio (L/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(s⁻¹)</td>
<td>4</td>
</tr>
<tr>
<td>510</td>
<td>R</td>
</tr>
<tr>
<td>1274</td>
<td>Sev</td>
</tr>
<tr>
<td>2549</td>
<td>Sev</td>
</tr>
<tr>
<td>5098</td>
<td>Sev</td>
</tr>
<tr>
<td>10195</td>
<td>Sev</td>
</tr>
</tbody>
</table>

Extrudate was produced more continuously at slower speeds.

Key: Sev; Sharkskinning so severe that the extrudate broke into individual "sharkskins" at the die exit.

Sh ; Sharkskinned surface
R ; Rough surface
Sm ; Smooth surface

- 263 -
### Table 9.7 Extrudate Quality: Unimac MG200 (5:5:6)

<table>
<thead>
<tr>
<th>Shear Rate $(s^{-1})$</th>
<th>Die Length to Radius Ratio (L/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 8 12 16</td>
</tr>
<tr>
<td>510</td>
<td>Sh Sm Sm Sm</td>
</tr>
<tr>
<td>1274</td>
<td>Sev Sh R R</td>
</tr>
<tr>
<td>2549</td>
<td>Sev Sev Sev Sev</td>
</tr>
<tr>
<td>5098</td>
<td>Sev Sev Sev Sev</td>
</tr>
<tr>
<td>10195</td>
<td>Sh Sh Sh Sh</td>
</tr>
</tbody>
</table>

Extrudate was produced more continuously at slower speeds.

### Table 9.8 Extrudate Quality: Avicel RC501 (5:5:6 MCC)

<table>
<thead>
<tr>
<th>Shear Rate $(s^{-1})$</th>
<th>Die Length to Radius Ratio (L/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 4 8 12 16</td>
</tr>
<tr>
<td>510</td>
<td>Sm Sm Sm Sm Sm</td>
</tr>
<tr>
<td>1274</td>
<td>Sm Sm Sm Sm Sm</td>
</tr>
<tr>
<td>2549</td>
<td>Sm Sm Sm Sm Sm</td>
</tr>
<tr>
<td>5098</td>
<td>Sm Sm Sm Sm Sm</td>
</tr>
<tr>
<td>10195</td>
<td>Sm Sm Sm Sm Sm</td>
</tr>
</tbody>
</table>

Extrudate was produced continuously at all extrusion speeds. Extrudate was highly deformable without breaking, and capable of coiling into a tight "rope" when die exit space was confined.

Key: Sev; Sharkskinning so severe that the extrudate broke into individual "sharkskins" at the die exit.

Sh; Sharkskinned surface

R; Rough surface

Sm; Smooth surface
Table 9.9  Extrudate Quality : Avicel RC581 (5:5:6 MCC)

<table>
<thead>
<tr>
<th>Shear Rate (s⁻¹)</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>510</td>
<td>R</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
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<tr>
<td>1274</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>Sm</td>
</tr>
<tr>
<td>2549</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
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<tr>
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<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>Sm</td>
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<tr>
<td>10195</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>Sm</td>
<td>Sm</td>
</tr>
</tbody>
</table>

The roughness observed was slight and extrudate was produced continuously. It was highly deformable without breaking, and capable of coiling into a tight "rope" when die exit space was confined.

Table 9.10  Extrudate Quality : Avicel RC591 (5:5:6 MCC)

<table>
<thead>
<tr>
<th>Shear Rate (s⁻¹)</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>510</td>
<td>R</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
</tr>
<tr>
<td>1274</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>Sm</td>
</tr>
<tr>
<td>2549</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>5098</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>10195</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>Sm</td>
</tr>
</tbody>
</table>

The roughness observed was slight and extrudate was produced continuously. It was highly deformable without breaking, and capable of coiling into a tight "rope" when die exit space was confined.

Key: R ; Rough surface
Sm ; Smooth surface
The roughness observed was very slight and extrudate was produced continuously. Extrudate was highly deformable without breaking, and capable of coiling into a tight "rope" when die exit space was confined.

Extrudate was produced continuously and was highly deformable without breaking.

**Key:**
- R ; Rough surface
- Sm ; Smooth surface
### Table 9.13 Extrudate Quality : Avicel PH101 (5:5:6, NaCMC Gel 16%)

<table>
<thead>
<tr>
<th>Shear Rate (s⁻¹)</th>
<th>Die Length to Radius Ratio (L/R)</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>510</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
</tr>
<tr>
<td>1274</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
</tr>
<tr>
<td>2549</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
</tr>
<tr>
<td>5098</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
</tr>
<tr>
<td>10195</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
<td>Sm</td>
</tr>
</tbody>
</table>

Extrudate was produced continuously and was highly deformable without breaking.

**Key:** Sm ; Smooth surface
increase with shear rate and graphs of End Correction versus Log Shear Rate do not show a discontinuity (example Figure 9.3) (cf. Bagley, 1957). Indeed, calculated values of Bagley's End Correction cannot be related in any way to the appearance of imperfections in the extrudate, implying that the extrudate impairment seen in all of these systems originates at a location downstream of the die entry.

Despite the differences between these results and those for polymer systems, it should be noted that some kind of flow fluctuation is certainly occurring, even if its origin is not the same as the "fluctuating flow" of Tordella (1969). This may be seen by relating the force/displacement profiles presented in Chapter Five to the corresponding result for extrudate quality. For example, the Avicel PH101 formulation (Figure 5.2(i)) which produces smooth extrudate over a comparatively wide range of extrusion conditions, exhibits a fairly even steady state flow stage. The Unimac MG100 formulation, on the other hand (Figure 5.2(vi)) produces sharkskinned extrudate under all experimental extrusion conditions and exhibits a more fluctuating steady state flow stage.

The above results indicate that an alternative explanation is required for extrudate impairment in microcrystalline cellulose systems, other than that proposed by previous workers. In 1960, Benbow et al. postulated that rough and sharkskinned extrudate was produced by a different phenomenon to Tordella's melt fracture (which had produced spiralling extrudate). By using cine film to record the extrusion process, they proposed that roughness and sharkskinning originated at the die exit. Their explanation was as follows. As the extrudate leaves the die its diameter expands; concurrently the body of the extrudate moves away from the die with a velocity which is constant
Fig. 9.2 Graph of Log Output vs. Log Pressure for Avicel PH101 Formulation

Fig. 9.3 Bagley End Correction vs. Log Apparent Shear Rate for Avicel PH101 (5:5:6) Formulation

Values of Entrance Correction have been calculated from the Bagley Plot equations (plots presented in Chapter Six)
across its diameter. However, when the extrudate is still within the die, the velocity profile is not constant across the diameter and its maximum is at the centre. So, when the extrudate leaves the die, it attains an average velocity which is less than it was along its central axis, but greater than it was along the die wall. Thus the outer surface of the extrudate is subject to tension immediately it leaves the die. If the tension exceeds the forces required to maintain the smooth surface and cylindrical shape of the extrudate, it will fracture, with the central core proceeding as the main filament, while the outer part remains near the die exit, resulting in a surface impairment. The material in the die then pushes the impaired extrudate away from the die exit at the same velocity as the main body of the extrudate, until the flow returns to the state when tension is again built up on the surface and the cycle restarts. Benbow et al. (1960) attribute this phenomenon to a kind of "slip-stick" process within the die. This hypothesis was supported by Harrison et al. (1985), who found that surface defects in wet powder mass extrusion were more prevalent when using short dies, in which steady state lubricated flow conditions were less likely to be achieved. The "stick-slip" conditions arising from the non-uniform thickness of the lubricating layers resulted in severe surface impairment. Their findings are supported by the results of this work, which also show that surface impairment is more severe when using dies of low length to radius ratio (Tables 9.1 to 9.13).

9.3 SURFACE QUALITY RESULTS IN RELATION TO THE BENBOW-BRIDGWARNER PARAMETERS

The significance of the non-attainment of steady state lubricated flow conditions within the die to the surface quality of the extrudate
produced is revealed more fully by an examination of the Benbow-Bridgwater results in Chapter Eight. The values for lubricating layer thickness, calculated from the Benbow-Bridgwater parameters, are given in Tables 8.3 and 8.7 for the various formulations studied. (It is worth noting that when comparing values of lubricating layer thickness, it is most meaningful to compare them at the highest shear rate used since, according to Harrison (1982), flow curves for extrusion through dies of different diameter merge at high shear rates. This implies that at high shear rates the thickness of the lubricating layer becomes constant with respect to die diameter - or, possibly, that the viscosity of the layer alters with its thickness, so that consistency is maintained constant.)

When the values of lubricating layer thickness at a shear rate of 10195 s⁻¹ are related to the results for extrudate quality (Table 9.14) it can be seen that the formulation with the thickest lubricating layer (that based on Avicel RC501) produces a smooth-surfaced extrudate at all combinations of extrusion speed and die length to radius ratio. Formulations with comparatively thinner lubricating layers produce extrudate with relatively more severe surface impairment and formulations exhibiting the thinnest lubricating layers (those based on Unimac MG100 and Unimac MG200) produce extrudate with catastrophic surface impairment under all extrusion conditions. Clearly the existence of a thick lubricating layer assists in the prevention of the "stick-slip" condition which leads to surface impairment.

It is worth noting the trends which may be seen by relating the value of other Benbow-Bridgwater parameters (Table 9.14) to extrudate quality. For example, it appears that a formulation which exhibits
Table 9.14  
Relation of Benbow-Bridgwater Parameters to Extrudate Surface Impairment

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Lubricating Layer Thickness (x) at 10195 s⁻¹</th>
<th>Initial Die Entry Yield Stress (σγ₀) (KN/m²)</th>
<th>Initial Die Wall Shear Stress (τ₀) (KN/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avicel RC501</td>
<td>56 *</td>
<td>490</td>
<td>193</td>
</tr>
<tr>
<td>Avicel RC581</td>
<td>9 *</td>
<td>480</td>
<td>284</td>
</tr>
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<td>Avicel RC591</td>
<td>8 *</td>
<td>461</td>
<td>256</td>
</tr>
<tr>
<td>Avicel CL611</td>
<td>13 *</td>
<td>275</td>
<td>144</td>
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<td>18</td>
</tr>
<tr>
<td>Unimac MG200</td>
<td>7</td>
<td>89</td>
<td>21</td>
</tr>
<tr>
<td>Unimac MG100</td>
<td>7</td>
<td>50</td>
<td>17</td>
</tr>
</tbody>
</table>

x = thickness of lubricating layer  
σγ₀ = initial die entry yield stress  
τ₀ = initial die wall shear stress

* values thus marked are recognised as significant underestimates of the true layer thickness (this is because the calculation has been made assuming that the layer consists solely of a saturated lactose solution. In fact, the layer is considerably more viscous than a saturated lactose solution - see Section 8.3).
low values of initial die entry yield stress and initial die wall shear stress is more likely to produce an extrudate with surface defects and which breaks up readily at the die exit. On the other hand, a formulation exhibiting high values of initial die entry yield stress and initial die wall shear stress is more likely to produce a smooth extrudate which is produced continuously from the die without breaking. These results seem logical since low values of initial yield and shear stresses indicate that a material would yield more easily both into and through the die, and therefore that it would be more susceptible to imperfections and breakage. It may thus be concluded that these parameters do offer an appropriate measure of material yield from the barrel and through the die for these pharmaceutical systems.

9.4 HIGH SPEED VIDEO RECORDING OF THE EXTRUSION PROCESS

High speed video recordings of the extrusion of microcrystalline cellulose formulations have been made in an attempt to compare the production of smooth-surfaced extrudate with that of badly shark-skinned extrudate, and to provide some evidence for or against the proposed mechanisms underlying extrusion defects. The methods and conditions used in the preparation of the video presentations are outlined in Section 3.2.3 (iii). Excerpts from six different extrusion runs are presented on the videotape submitted as Appendix I to this thesis. The extrusion runs examine the extrusion of formulations based on Avicel PH101 and Unimac MG100, each at three different extrusion speeds (10, 20 and 50 cm/min piston speed) through a die of length to radius ratio = 16. (It is appropriate to note that, by the use of a relatively long die, L/R = 16, the formulations were given an optimum chance of producing smooth-surfaced extrudate.) When viewing
the videotape, it should be noted that careful use of lighting has ensured that all but the extrudate is in darkness. Thus the only image revealed on tape is that of the extrudate as it exits the die.

It may be seen immediately from the video presentations that the surface quality of the Unimac MG100 formulation is vastly inferior at all three extrusion speeds to that of the Avicel PH101 formulation. The former formulation produced extrudate which was catastrophically sharkskinned, particularly at the highest extrusion speed. This finding is in direct contradiction to the advertising literature for Unimac grades, which states that they are capable of producing smooth-surfaced products.

9.4.1 The Unimac MG100 Formulation

A close examination of the behaviour of the Unimac MG100 formulation presented on the videotape reveals quite clearly that the outer layers of extrudate appear to split and "peel away" from the main body, thereby causing the sharkskinning. This visual evidence lends credence to the "stick-slip" explanation of Benbow et al. (1960), which says that sharkskinning is caused when discontinuities in the lubricating layer result in differences in the velocity gradients across the die which, upon resolution at the die exit, cause regions of tension on the extrudate surface (Section 9.1). At the highest piston speed of 50cm/min, the videotape records that the Unimac MG100 formulation produces extrudate which splits right to the central axis. This implies that, at higher extrusion speeds, the differences in velocity gradient along the die extend deeper in towards the centre of the extrudate.
9.4.2 The Avicel PH101 Formulation

A close examination of the behaviour of the Avicel PH101 formulation, particularly at a piston speed of 50cm/min, reveals a phenomenon which has previously remained unnoticed by the naked eye. A mechanism which appears to cause breakage of the extrudate by a relative "contraction" back into the die may be seen, and this may be considered more closely by examining the stills presented in Figure 9.4. Since the piston speed is known to be 50cm/min, the velocity with which the extrudate leaves the die (calculated by accounting for the reduction ratio from the barrel to the die) is expected to be 2.40m/s. The first frame, Figure 9.4(i), shows a strand of extrudate, intact, exiting the die. The second frame, (ii), one thousandth of a second later, shows the start of a break in the extrudate. In subsequent frames, (iii) to (viii), over the next 18 milliseconds, the piece of extrudate below the break falls away from the die. However, the extrudate above the break appears to remain almost stationary at the die exit, instead of travelling at the expected velocity of 2.40m/s. At the 19th millisecond from the start of the breaking process (frame ix), the extrudate above the break resumes travel at high speed as expected, until the breaking cycle begins again. Thus it may be seen that for ca. 18 milliseconds after the break first occurs, the extrudate appears to be stationary. In other words, the extrudate is travelling at - 2.40m/s relative to its expected velocity. This phenomenon leads to the supposition that the breaking process is caused by a relative contraction of the material back into the die, which happens over such a short timespan that it normally remains unnoticed.

9.4.3 The Movement of Water within the Formulation

At various points throughout this thesis, the roles of water and water-microcrystalline cellulose interactions have been suggested as a
Extruded at a Piston Speed of 50 cm/min.

(i) Relative Time = 0.000 seconds

(ii) Relative Time = 0.001 seconds

(iii) Relative Time = 0.002 seconds
Extruded at a Piston Speed of 50 cm/min.

(iv) Relative Time = 0.003 seconds

(v) Relative Time = 0.005 seconds

(vi) Relative Time = 0.006 seconds
Extruded at a Piston Speed of 50cm/min.

(vii) Relative Time = 0.007 seconds

(viii) Relative Time = 0.018 seconds

(ix) Relative Time = 0.019 seconds
basis for the ability of microcrystalline cellulose formulations to be extruded. The use of the high speed video has provided further evidence that the movement of water through the formulation has a role in extrusion. During the initial stages of extrusion of both Avicel PH101 and Unimac MG100 formulations, high speed video photography has revealed that water, in minute quantities normally unnoticed, is squeezed out of the die prior to extrusion. This phenomenon has been edited from the videotape sequences for the sake of conciseness, but may be seen by examining the video stills presented in Figure 9.5 (i-vi). Figure 9.5 shows the initial stages of the extrusion of an Avicel PH101 formulation at a piston speed of 10cm/min, and clearly illustrates the preferential 'extrusion' of water, which does not completely remit until more than 1 second into the extrusion. It is conceivable that the 'Compression Stage' of the Force/Displacement profile, is actually a period in which the compression upon the wet mass results in the movement of water through the formulation, dependent in part on the affinity between the microcrystalline cellulose bonding sites and the water. This would confirm the work of Fielden (1987), who identified that microcrystalline cellulose is able to act as a "molecular sponge" for water, holding considerable quantities in hydraulic isolation.
Extruded at a Piston Speed of 10cm/min - Initial Stages.

(i) Real Time = 0.030 seconds

(ii) Real Time = 0.130 seconds

(iii) Real Time = 0.340 seconds
Extruded at a piston speed of 10cm/min: Initial Stages:

(iv) Real Time = 0.394 seconds

(v) Real Time = 0.762 seconds

(vi) Real Time = 0.815 seconds
PART FOUR

CONCLUDING REMARKS
The process of extrusion is fundamental to many of the dosage forms produced by modern pharmaceutical industry. Often, the excipient of first choice in pharmaceutical extrusion is microcrystalline cellulose. The work outlined in this thesis indicates that the extrusion behaviour of formulations based on microcrystalline cellulose can be studied and compared effectively using various techniques to assess the relationship between force and displacement during ram extrusion through a single-holed die. The results show that the grade of microcrystalline cellulose used in the formulation affects markedly the behaviour of that formulation in the ram extruder.

This Chapter addresses the task of assimilating the many results discussed in Part Three of this thesis, and of drawing conclusions from them.

10.1 CONCLUSIONS FROM THE RESULTS

10.1.1 The Compression Stage is One of Compaction to Maximum Material Density

The suggestion that the Compression Stage is one of densification to maximum material density (Sheppard and Clare, 1972; Harrison et al., 1987) is supported by the findings of this work, in which the presence of large quantities of water within a formulation reduces the amount of volume reduction required prior to the commencement of flow. This result also supports those of Benbow et al. (1987), who attribute a slow build up of force during the Compression Stage to the presence of air within a paste.
10.1.2 Poor Quality Extrudate is Linked to Unstable Flow

An uneven, or "fluctuating", Steady State Flow Stage is, according to Tordella (1969), indicative of unstable flow. Although true "fluctuating flow" is not observed in these systems, the formulations based on Unimac grades of microcrystalline cellulose do exhibit very uneven Steady State Flow Stages, implying that their flow is subject to local variations within the mixes. Further evidence for the unstable flow of Unimac grade formulations is provided by the corresponding poor surface quality of their extrudates. The reasons for the unstable flow of the Unimac grade formulations probably lie in the source of the original cellulose and in its subsequent processing, resulting in structural differences between this grade of microcrystalline cellulose and the Avicel powdered grades.

10.1.3 Declining Steady State Flow is Indicative of Interaction with the Barrel Wall

Benbow et al. (1987) have said that when the expected "plateau" of the Steady State region is, in reality, exhibited as a gradually decreasing value as piston displacement progresses, the implication is that stresses at the barrel wall are playing a significant part in the total extrusion force. Their theory is supported by the results of this work, in which only the wettest formulations exhibit a gradually decreasing Steady State Force. Wet formulations obviously come into more intimate contact with the barrel wall than their drier counterparts, and thus material-barrel wall interactions will be increased.
10.1.4 Pressure Overshoot is an Indication of Difficulty in Overcoming Capillary Resistance

According to Akay (1982), the phenomenon of "Pressure Overshoot", prior to the establishment proper of Steady State Flow, suggests difficulty in overcoming capillary resistance. In this work, pressure overshoot is exhibited only by the driest powdered grade formulations and by colloidal grade formulations (Sections 5.1.2 (iii) and 5.2.2 (ii)). The fact that it is exhibited particularly at high values of die length to radius ratio supports Akay's theory. Further confirmation is supplied by the fact that the formulations which exhibit pressure overshoot also exhibit the highest values for Upstream Pressure Loss (of which capillary resistance is a component).

10.1.5 Pressure Overshoot is not Necessarily Related to Difficulty of Flow once Extrusion has Commenced

Forced Flow is claimed to occur when convergent flow patterns from the barrel into the die break down (Harrison, 1982). It follows that a high degree of forced flow is associated with a steep convergent flow vortex. The fact that colloidal grade formulations exhibit no forced flow would therefore appear to indicate that the convergent flow vortices of these systems are very shallow indeed. However, this is contradictory to the observation that these same systems exhibit pressure overshoot (indicative of difficulty in overcoming capillary resistance) and also exhibit high values of Upstream Pressure Loss (said by Bagley, 1957, to indicate poor convergent flow). It would appear that these systems have some considerable resistance to the initiation of flow (hence the "pressure overshoot") but are capable of good convergent flow once extrusion is established (hence the lack of Forced Flow). This conclusion is supported by the Benbow-Bridgwater results (Table 8.6), which show that colloidal grade formulations
exhibit higher values of initial die entry yield stress and initial
die wall shear stress, but lower values of the velocity factors $\alpha$ and
$\beta$, than powdered grade formulations.

10.1.6 Forced Flow Arises at the Die Entry

The increase in Forced Flow observed at slow extrusion speeds for
powdered grade formulations (colloidal grade formulations do not
exhibit forced flow) has previously been attributed, for an Avicel
PH101 formulation, to moisture gradients within the material (Harrison
et al., 1984). This assertion was based on measurements of moisture
content which, at slow extrusion speeds, show differences between the
level of moisture in the material in the barrel and that in the
extrudate. It is based also on the observation that water is
"extruded" from the die prior to the commencement of material flow,
and that the quantity of water so extruded is greater at low extrusion
speeds. This theory of Harrison et al. (1984) is not contradicted by
this work, although the results of high speed video photography
certainly dispute that there is a difference between the quantity of
water "extruded" at low and high speeds. However, the combined
results of this work do provide additional information about the
mechanism underlying reduced forced flow at high extrusion speeds.

The pseudoplastic flow curves for the powdered grade formulations
indicate that, at high extrusion speeds, the internal structure of the
systems is able to rearrange to facilitate flow. It may be that this
results in a change in the water distribution within the system, thus
causing the moisture gradient cited by Harrison et al. (1984), but the
question arises regarding how this results in a decrease in Forced
Flow. Certainly, it is possible that this particle and/or water
rearrangement at high speeds results in a more shallow convergent flow
vortex. However, until now, the assertion that there is an association between a shallow vortex and lack of Forced Flow has been substantiated only qualitatively, by the use of layers of coloured material within the barrel (Harrison, 1982). The results of the work presented here, though, provide numerical proof for this theory, based on the Benbow-Bridgwater results.

Benbow-Bridgwater analysis of the results indicates that the rate of increase with speed ($\alpha$) of the initial die entry yield stress ($\sigma_{y_0}$) decreases by at least an order of magnitude as piston speed increases from 2 to 40 cm/min. On the other hand, the rate of increase with speed ($\beta$) of the initial die wall shear stress ($t_w$) decreases only marginally as speed increases. This implies that the rearrangement of structure within the material at high speed (whether by water movement or by some other mechanism, and this is the subject of conclusions in Section 10.1.8) acts to facilitate flow into (rather than through) the die. Clearly then, reduced Forced Flow is associated predominantly with ease of flow at the die entry and it may be concluded that Forced Flow is a die entry phenomenon.

10.1.7 Extrudate Impairment Originates Downstream of the Die Entry Region

The conclusions in Section 10.1.6 indicate that Forced Flow is a die entry phenomenon. The initial temptation, then, is to conclude that extrudate impairment also arises at the die entry, particularly as this has been said to be the case for extrusion of some polymers (Tordella, 1957, 1969; Bagley, 1957, 1963). From the results of Chapter Nine, though, it may be concluded that imperfections arise from phenomena downstream of the die entry, such as "stick-slip". This conclusion is based on the fact that the formulations with the
thickest lubricating layers (and thus with the least likelihood of experiencing "stick-slip") suffer the least extrudate impairment. It is supported by the high speed video recordings, which provide a visual indication that imperfections occur at the die exit. The high speed video results also lead to the suggestion that extrudate breakage at the die exit is due to a relative contraction of material back into the die (possibly due to a momentary, but intense, condition of stick).

10.1.8 The Formation of the Lubricating Layer is Fundamental to Flow

The evidence presented in Section 10.1.6 suggests that the movement of water within microcrystalline cellulose systems may be the basis for their pseudoplasticity, suggesting that there is a critical role within the formulation for bulk water. Pseudoplasticity is indicative of flow becoming easier as shear rate increases, due to structure realignment. If it is true that the pseudoplasticity of microcrystalline cellulose systems is based upon the movement of water to form a lubricating layer at the die wall, then it would be expected that the degree of pseudoplasticity exhibited by a formulation would correlate with the thickness of its lubricating layer. By drawing together the results discussed in Chapters Seven and Eight, it may be seen that those formulations which exhibit a high degree of pseudoplasticity (as measured subjectively by a low magnitude of die wall shear stress and of apparent shear rate at the point where the flow curve reaches its plateau) also have the thickest lubricating layers (Tables 8.3 and 8.7). These results provide a quantitative basis for the conclusion that the movement of water to form a lubricating layer at the die wall is fundamental to the facilitation of flow of these systems.
Additional support for the conclusion that the movement of bulk water facilitates flow is given by the fact that extrusion parameters \( t_w, P_o, dy_o, t_o \) generally decrease with an increasing proportion of liquid in the formulation (Table 8.4) and also with decreasing particle size of microcrystalline cellulose (Table 8.2). This implies that the flow of formulations is determined to some extent by the degree to which the liquid exceeds that required to fill the spaces within a bed of dry particles. Indeed, it may be concluded from the results presented in Chapter Eight that, for an Avicel PH101 formulation, a level of at least 33% water is required to exceed significantly the interparticulate voidage and contribute towards a lubricating layer. The contribution of the lubricating layer increases as the water content is increased, but reaches a limit at about 38%, above which plug flow appears to break down.

10.1.9 The Role of the Continuous Phase is also Effected at the Molecular Level

The results for extrusion of formulations containing sodium carboxymethylcellulose in the water used for wet massing also lead to the conclusion that the bulk rheology of the continuous phase affects extrusion flow. They exhibit the lowest die wall shear stresses of all the formulations studied, implying that sodium carboxymethylcellulose gel acts as a superior lubricant to water. However, when the sodium carboxymethylcellulose is in a more intimate physical position with respect to the microcrystalline cellulose surface (i.e. colloidal grade formulations), it has an adverse effect on flow both into and through the die. This implies that, in addition to the effect of the bulk rheology of the continuous phase, the more fundamental properties of the microcrystalline cellulose surface and the way it interacts with the continuous phase at a microscopic level
appear to affect flow behaviour. Further support for a critical role for water at a molecular level is given by the fact that extrusion rheology varies for formulations based on different manufacturers' grades of powdered microcrystalline cellulose. The differences between the grades can arise only from differences in the source of cellulose pulp and in the manufacturing process used for the production of the microcrystals. These differences result in variations in crystallinity and/or microscopic structure and therefore in differences in the extent or type of interaction between the microcrystalline cellulose and the water.

There is further evidence on which to base the conclusion that the physico-chemical behaviour of water at the microcrystalline cellulose surface is also of importance. Avicel PH103 consists simply of Avicel PH101 particles dried down from 5% to 3% moisture, but its formulation exhibits higher values for extrusion parameters ($t_w$, $P_o$, $t_o$, $\delta y_o$) (Tables 6.6 and 8.2). This suggests that the amount of moisture in the microcrystalline cellulose powder itself affects extrusion, despite the fact that this small quantity of water is swamped by comparatively huge quantities during wet massing. It may be that there are surface and/or pore changes which occur during the drying process, which affect the interaction between the microcrystalline cellulose and water, and which are not immediately reversible on wet massing. It must be concluded, however, that any such changes are reversible over a period of several weeks, since when Avicel PH103 was allowed to equilibrate for that time period, it became equivalent to Avicel PH101 in terms of its extrusion formulation.
10.1.10 The Physical Characteristics of the Formulation Excipients

Affect Flow

Formulations based on grades of microcrystalline cellulose of different particle size exhibit some differences in the magnitude of their flow curves (Figures 7.1 and 7.2) and Benbow-Bridgwater parameters (Table 8.2). Of course, the particle size of the microcrystalline cellulose will affect its interaction with water at both the bulk physical and surface chemical levels. The importance of this interaction to the extrusion process has already been noted (Section 10.1.7). However, it may be concluded that the purely physical differences in particle size (and in particle size distribution) will have an effect in their own right. For example, the fact that formulations based on small particles exhibit high values of Upstream Pressure Loss may be attributed to their relatively cohesive, closed structure. The fact that the same formulations exhibit low values of Die Wall Shear Stress may be attributed to the facts that (i) they are more readily lubricated at the die wall and that (ii) improved packing will mean that a smoother, more integral surface will be presented to the die wall, causing less die wall friction.

10.1.11 It is the Response of Water to a Particular Shear Rate which Defines Flow Behaviour

A collection of the results for all powdered grade formulations at a single extrusion speed appears to suggest that the formulations can be made equivalent in terms of flow simply by altering the amount of water used in the formulation (Figure 7.5). However, formulations which have been made equivalent at one extrusion speed, are not equivalent at another (Figure 7.6). It may thus be concluded that it is the response of water and other factors within the individual formulation to a particular shear rate which defines flow behaviour.
10.2 SUMMARY

It has been shown that the grade of microcrystalline cellulose upon which a formulation is based affects its extrusion in terms of the rheological parameters measured and the quality of the extrudate produced. The differences appear to be due to physical differences in the powders themselves (e.g. particle size) and to physico-chemical differences in the interaction of the microcrystalline cellulose with the continuous phase.

The precise nature of the microcrystalline cellulose-water interaction remains unclear. However, it has been demonstrated that the "molecular sponge" properties of microcrystalline cellulose enable the formulation to respond to shear by the formation of a lubricating layer at the die wall, which facilitates stable flow and yields a better quality product. There is an optimum quantity of water required to lubricate flow.

The origin of imperfections in the flow of these systems has been identified. Declining or uneven Steady State Flow Stages are indicative of barrel wall interaction and unstable flow respectively. Pressure overshoot is indicative of difficulty in overcoming capillary resistance at the yield stage, but is not necessarily related to ease of flow after yield has occurred. Forced Flow arises at the entrance to the die, and may result in a moisture gradient within the extruded material. Extrudate surface impairments arise at some point downstream of the die-entry, and are probably due to stick-slip at the die wall.
CHAPTER ELEVEN

FURTHER WORK
There is no doubt that the results discussed in this thesis, and the conclusions drawn from them, could be further substantiated by additional research. In particular, the nature of the microcrystalline cellulose-water interaction requires further investigation. Also, a description of the rheological characteristics of the extrudate itself would assist in assessing its suitability for subsequent processing such as spherization.

11.1 THE NATURE OF THE MICROCRYSTALLINE CELLULOSE-WATER INTERACTION

Several methods may be suggested as a means of establishing information about the nature of the interaction between microcrystalline cellulose and water. Thermogravimetric analysis, differential thermal analysis, immersional calorimetry and differential scanning calorimetry would all facilitate a comparison of the interactions set up by the various grades of microcrystalline cellulose with water. An initial attempt was made during this research to characterize the interaction by differential thermal analysis of the various extrudate samples. The attempt was largely unsuccessful, because time did not permit the large numbers of repeat experiments necessary to overcome the relatively large error inherent in the technique and produce statistically meaningful results. Certainly, it would be particularly interesting to examine extrudates with different water contents using this technique, in the hope that the results would confirm or deny the conclusion that an optimum quantity of water is required for lubricated plug flow.

The effect of the bulk rheology of the continuous phase (as opposed to its effect at a molecular level) is also of interest. The effect of
bulk rheology could be examined by modifying the viscosity of the continuous phase to produce a series of formulations and measuring the resultant differences in extrusion parameters.

11.2 THE RHEOLOGICAL NATURE OF THE EXTRUDATE ITSELF

The methods outlined in this thesis provide for a rheological assessment of the wet powder mass on extrusion. It would be interesting, however, to be able to characterize the rheological nature of the extrudate itself. Such a characterization has been made qualitatively in this work. For example, an Avicel PH101 formulation produces extrudate which breaks into short lengths of about 1cm on exiting the die, whereas an Avicel RC501 formulation produces extrudate continuously from the die, which is highly deformable without breaking.

The difficulty in making a quantitative assessment of extrudate rheology is that the wet extrudate is very delicate and difficult to handle. (The assessment of dried extrudate would be far easier, but inappropriate because extrudate is always used in the wet state when it is to be processed further.) Several ideas have emerged as possibilities, and in the main are adaptations of bending tests. One such idea is to allow extrudate to fall around cylindrical rods of decreasing diameter, to give a measure of how bendable they are without breaking. Another idea is to modify an indentation test to establish the "hardness" of the extrudate.

A possibility which has been the subject of preliminary investigation during this research, is to utilize the plug of wet mass remaining in the barrel at the end of extrusion. This plug will have been
compacted to maximum density during the extrusion process, and may therefore be regarded as extrudate with large diameter. The plug may be removed from the barrel and then examined by various rheological techniques, such as indentation testing, diametral compression testing, and parallel plate rheometry. The only extra requirement would be that the testing environment should be controlled so that the water content of the plug could be maintained.
Adamson P.S., Cellulose Plastics (1955): Part II, Plastics Monograph
C.7, Plastics Institute, London.


Avicel Technical Bulletin, G-34, FMC Corp, PA 19103, USA.


Ballenger T.F. and White J.L., J. Appl. Polym. Sci. (1949) 8, 1129-
1138.


753-66.

915-19.

Benbow J.J., Brown R.N. and Howells E.R., Coll. Inter. Rheologie,
Paris (1960), 65-82.

(9), 2151-162.


Blanose Technical Bulletin, 6/87.502-E3, Aqualon, Delaware 19894, USA.

Cael J.J., Kwoh D.L.W., Bhattacharjee S.S. and Patt S.L., Macromol.

205-10.


Coffin-Beach D.P. and Hollenbeck R.G., Int. J. Pharm. (1983) 17,
313-24.


Gajdos B., Drugs Made in Germany (1984) 27, 30-36.


Rabinowitsch B., Z. Phys. Chem. (1929) 1, 145A.


Rowe R.C., Pharm. Int. (1985) 6, 119-23.


Schwartz J.B., Spheronization Technology; Processing and Product Performance (undated), Pshd. FMC Corp, PA 19103, USA.


