Rheological Evaluation of Mixtures of Lactose, Microcrystalline Cellulose and Water Suitable for the Preparation of Spherical Granules.

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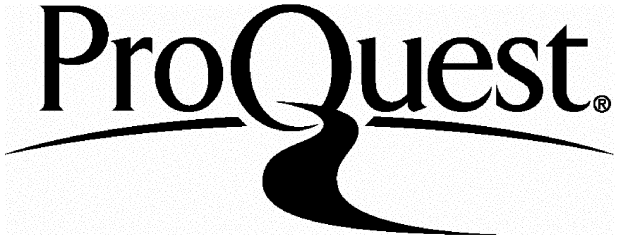

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Abstract

Extrusion/spheronisation is a method used widely in the pharmaceutical industry to produce small spheres (approximately 1mm in size) of formulated drug. These spheres are the ideal shape for coating and the technique is often used to produce spheres with a sustained-release action. The technique does not always produce spheroids because of its high sensitivity to both the drug formulation and to process parameters. Previous studies undertaken have identified the relative importance of process parameters and drug formulation on the extrusion/spheronisation technique and have established that the rheological nature of the formulation is of primary importance.

In this work the rheology of formulations suitable for extrusion and spheronisation has been assessed using the established technique of capillary rheometry and compared to that of controlled-stress rheometry. Capillary rheometry requires several days work to analyse a formulation and consequently the technique is unsuitable for quality control purposes and time-consuming for formulation development. Controlled-stress rheometry has the advantage of being far quicker to perform than capillary rheometry. In addition it provides information on the relative elasticity and viscosity of the material that cannot be obtained from capillary rheometry. Formulations investigated contained lactose as a model water-soluble drug and microcrystalline cellulose as the excipient that allows the formation of good quality extrudate. Spheres were successfully produced with a lactose content of greater than 70% dry weight.

Results indicate that controlled-stress rheometry is an accurate and sensitive alternative to capillary rheometry in establishing the rheological parameters of a drug formulation. With variation in the moisture content of the formulation the elastic component of the material is affected more than the viscous component and these changes can be used to explain why a formulation will not spheronise. Consequently the technique can be used to predict the behaviour of materials before they undergo extrusion/spheronisation and therefore is a useful tool in the development of spherical granules.

For Helen

Acknowledgments

I'd like to thank most of all Prof. Mike Newton and Dr Ray Rowe of Zeneca Pharmaceuticals for all their work and comments in helping me complete this thesis. Their knowledge and experience were invaluable in designing the experiments and evaluating the results.

I'd also like to thank all the technical staff and my student colleagues, particularly those in the basement lab., for making all the time fly past. Thanks to Gary Parsons for the loan of his printer and of course to Helen, my wife, for all her help in writing the contents pages and proof-reading my work.

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Chapter 1

INTRODUCTION

1. INTRODUCTION

In the past 10-15 years, the use of spherical pellets within the pharmaceutical industry has become widespread due to the inherent advantages spherical granules possess over other solid dosage forms (O'Connor and Schwartz, 1989). These advantages include accurate control of dosage, speed of production and choice of batch or continuous flow production (Woodruff and Nuessle, 1972). Interest continues to grow as many chemical compounds reach the end of their patent lifes and companies develop new formulations to give their products a marketable advantage against new competitors.

1.1 THE PROCESS OF PELLETISATION

Granules manufactured for pharmaceutical dosage forms have traditionally been formulated to facilitate the manufacturing of the final dosage form e.g a tablet. However the therapeutic advantages offered to patients by controlling the release of pharmaceuticals has resulted in the granule itself becoming the end product of dosage form design.

The process of pelletisation has been described as 'an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free-flowing, spherical or semi-spherical units, referred to as pellets' (Ghebre-Sellassie, 1989). The process is well established both in the food and pharmaceutical industries.

1.1.1 Advantages of Pelletisation

Increasing interest in the controlled-release of pharmaceuticals has led to an increase in the use of pelletisation technology to manufacture drug containing spheres. This is due to the many advantages that can be conferred on a product using the pelletisation technique (Ghebre-Sellassie, 1989).

Generally, pelletisation offers an improvement in the safety and efficacy of pharmaceutical compounds. It is preferred in particular to single-unit dosage forms for controlled-release because pellets disperse freely in the gastro-intestinal tract and are less susceptible to dose dumping (Ghebre-Sellassie, 1985). This minimises the potential incidence of side-effects due to the reduction of peak plasma drug levels and fluctuations, although drug bioavailability is not lowered (Beechgaard and Neilson, 1978). Pellets also reduce the variations in gastric emptying rates and transit times and avoid the high localised concentrations of drug that can occur with single-unit dosages and their consequent local side-effects (Eskilson, 1985). Pellets themselves can be

adapted to increase the therapeutic response of an agent at a specific gastro-intestinal site (e.g. the colon) or to alter the rate of action of the active material (e.g. varying the density of pellets influences the rate of gastric emptying [Devereux *et al.*, 1990]).

Pellets flow freely and pack uniformly and can alleviate potential dust problems during the manufacturing of the final product (Reynolds, 1970). They have a minimum surface area-to-volume ratio and provide the ideal shape for the application of film coatings producing savings in coating material and also of time and money. Coatings can be applied either for aesthetics or controlled release of the active drug.

Batches of pellets can be blended or formulated to provide combinations of two or more chemically incompatible drug materials within the same capsule or combinations of pellets containing the same drug but with different release rates. This is be useful for increasing patient compliance by reducing the number of dosage units that need to be administered.

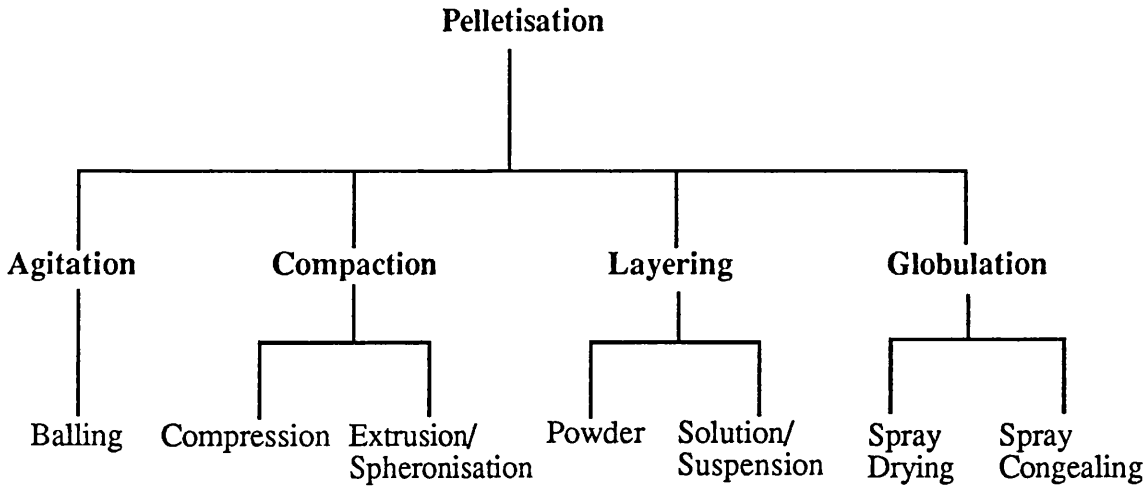
Despite the obvious advantages that a pelletised product can confer on a particular drug substance, pelletisation has not superceded in importance the traditional established methods of solid dosage form preparation, namely tabletting and encapsulation. This is probably due to the fact that pelletisation equipment is usually specialised for one particular purpose and that the manufacturing process is generally more labour intensive and less amenable to automatic control than e.g. tabletting from a wet granulation. However as more manufacturers become familiar with pelletisation techniques then demand for the process will continue to rise.

1.2 METHODS OF MANUFACTURING SPHERICAL GRANULES

Over the years many industries have sought to develop their own particular processes for the manufacture of spherical granules or pellets and subsequently many different processes exist. Sherrington and Oliver (1981) have summarised the various methods of manufacturing into four categories, depending on the main physical method employed in the formation of the granule (Figure 1.1).

In the Pharmaceutical industry the most widely used processes for manufacturing spherical granules are extrusion/spheronisation, solution/suspension and powder layering. The techniques of balling, globulation and compression are of only limited application in the development of pharmaceutical pelletised products, although they are used for a variety of other purposes (Ghebre-Sellassie, 1989).

Figure 1.1 Categorisation Of Pellet Manufacturing



1.2.1 Layering Techniques

Pan Granulation

Pan granulation and the related processes of plate or drum granulation form spherical granules by the addition of a granulating fluid to fine powders or sugar seeds (also known as non-pareils) that are constantly rotating. The process is controlled by such factors as the rate of addition of the drug solution/suspension, the particle size and size distribution of the powders, presence/absence of binders and the degree of agitation of the powders. The main disadvantage of this technique is that complete granulation takes a long time to occur (up to several days) since each coat must be dried thoroughly before the next granulating coat can be applied.

Pan granulation was used for the development of pharmaceutical pellets in the 1940s by workers from Smith Kline and French (Ghebre-Sellassie, 1989). It is still used extensively in fertiliser production.

Fluid Bed Granulation

Fluid bed granulators have been developed from the original concept of fluid bed drying. With the introduction of an expansion space between the product container and the filter chamber and the inclusion of a liquid-spray nozzle, either at the top or bottom of the chamber, the dryers have been modified into granulating and coating machines. The method involves applying a solution or suspension of drug material through the spray nozzle, situated in the expansion chamber, onto a powder bed that is fluidized by means of a current of hot air. The method benefits from being entirely contained within one piece of equipment, thereby preventing contamination and dust

problems. However process variables do requires careful monitoring. Variables that affect the granulation include the air pressure acting on the fluid bed, the air inlet temperature, the position of the spray gun, the nozzle design and the atomising pressure of the spray. These require judicious experiment to provide the optimum conditions for manufacturing spherical granules.

Rotary Granulation

The process of rotary granulation (or rotorgranulation) is based on an apparatus consisting of a rotating disc mounted inside the drying chamber of a fluidised bed dryer. Spherical granules are manufactured by spraying granulating fluid onto a powder mass that is fluidised in a rapid annular motion. The toroidal motion of the powder/granules is achieved by centifugal and gravitational forces and the upthrust force provided by the fluidising air. Rotorgranulation provides dense robust spheres with a smooth surface and a narrow size distribution (Niskanen *et al.*, 1990). Since product motion can be maintained independently of fluidising air rates, rotary granulation has advantages over other layering techniques because it can provide higher spray rates and higher product moisture levels, both of which facilitate pellet formation. Formulation variables include spray rate, the rate of addition of powder and the rotation speed of the disc employed (Gajdos, 1984). The effects of product load, granulating fluid volume and granulation fluid addition rate have been investigated (Hodges *et al.*, 1990) as well as the effects of binder solution concentration and powder particle size (Niskanen *et al.*, 1990).

Other Techniques

High Shear Mixer Granulators

High shear mixer granulators are widely employed in the pharmaceutical industry to produce granules. The most common type of granulator used is a horizontal granulator which consists of a mixing bowl that has slightly conical sides to improve mixing e.g. Diosna^{TM}. The bowl contains a three-bladed rotor at its base and a two-bladed chopper that is situated on its side. Granulating fluid is added by a pressurised spray from the top of the bowl to the dry blended powder already charged. The combination of fluid and the blade motion facilitates wet granulation of the powder bed. Mixing times are dependent on the batch size and are generally of the order of 5-10 minutes. Depending on the formulation of the material being used the granules prepared by this method may be sufficiently spherical to allow for their use as an end product without further processing being required.

Further methods of manufacturing spheres are still being developed e.g. Continuous Multi-Purpose Melt Technology, 'CMT' - a technique that employs both layering and globulation technology. This technique involves.the atomisation of a fluid into a fine mist that then envelopes individual solid particles as they are simultaneously introduced into a turbine chamber via a separate inlet. The initial fluid is a solid or viscous material that has been heated to ensure an acceptable viscosity. The process is designed to provide a continuous operation and to handle heat-labile materials. (Appelgren and Eskilson, 1990).

A review of the technologies available to manufacture pellets has been published in the book Pharmaceutical Pelletisation Technology (edited by Ghebre-Sellassie, 1989) and further information into each method described above has been documented.

1.3 EXTRUSION-SPHERONISATION

Extrusion of pharmaceutical materials involves the compression of wet powder into short, cylindrical strands of extrudate with a uniform diameter. The extrudate is then spheronised, whilst still wet, in a drum with a rotating base (the spheroniser) utilising frictional and surface forces. The size of sphere produced is generally related to the initial extrudate diameter. The spherical or near-spherical granules (also known as spheroids) are then dried in a fluid-bed drier before further processing e.g. coating. Spheronisation was invented by Nakahara in Japan in 1964 but Rowe (1985) states that it only came to prominence in the United Kingdom due to the review of Reynolds (1970) and in the United States to the review of Conine and Hadley (1970). Subsequent work has demonstrated the viability of extrusion/spheronisation as a method of producing spherical granules [Woodruff and Nuessle (1972), Miyake *et al.* (1973), Malinowski and Smith (1975)].

In the United Kingdom several pharmaceutical products are available that have been prepared by extrusion/spheronisation. These include Inderal LA™ (sustained-release propranolol, ICI Pharmaceuticals), Froben SR™ (sustained-release flurbiprofen, Boots PLC), Indocid R™ (sustained-release indomethacin, Merck, Sharpe and Dohme Ltd) and Erymax™ (sustained-release erythromycin, Parke-Davis and Co.).

Advantages of Extrusion-Spheronisation

Of the methods available to produce pellets, extrusion-spheronisation offers the following advantages (Russell Marumerizer™ literature) :-

(i) consistently uniform granules in any one of a whole range of shapes from rods to spheres.

(ii) wide granule size range from 0.5 to 15mm in diameter.

(iii) wide range of applications e.g. pharmaceuticals, agricultural products, foods, rubber chemicals and catalysts.

(iv) dense granules, with excellent flowability and low dusting characteristics.

(v) stable, controllable and reproducible operation in batch and continuous system design.

(vi) improved end-use properties - including quicker dissolution and better controlled release than with any other granulation technology.

However extrusion/spheronisation alone can cause reduced drug dissolution e.g. O'Connor and Schwartz (1985) have reported that uncoated 10% theophylline spheres produced by extrusion/spheronisation have reduced dissolution rates when compared to conventional dosage forms depending on the type of micro-crystalline cellulose employed. (The micro-crystalline cellulose is used as an excipient to enhance the extrusion characteristics of the formulation.). Similarly Zhang *et al.* (1990) has stated that beads made via extrusion/spheronisation behave as 'an inert matrix system' when compared on disintegration to beads made from a traditional pan method.

1.4 EXTRUSION AND SPHERONISATION EQUIPMENT

The equipment able to perform extrusion and spheronisation has been documented by Hicks and Freese (1989).

1.4.1 Extruders

Since extrusion involves the compression of wet powder into variably lengthed cylindrical strands of extrudate, a method of applying sufficient pressure to the powder must be obtained. The pressure required to produce extrudate varies with the type of extruder, the nature of the wet powder under investigation and the width and length of the capillary that the powder must be forced through. Although the capillary determines the cross-sectional geometry of the extrudate many other factors become important in determining the extrudate length.

The various types of extruder available can be briefly categorised into four types - screw, sieve, roll and ram. These categories can be distinguished by the magnitude of the compaction forces developed during extrusion (Sherrington and Oliver, 1981).

Screw Extruders

Screw extruders, either with one or two screws, use a screw-feed mechanism to compact and transport a wet powder mass at high pressure through one or more orifices. These orifices can either be arranged as a plate at the end of the screw perpendicular to the screw axis (an axial extruder, Figure 1.2a) or as a screen fitted cylindrically around the screw (a radial extruder, Figure 1.2b). A twin-screw extruder generally produces a higher throughput than a single-screw but the resulting extrudate is of a lower density. Similarly a screw extruder with a radial screen produces more extrudate than an axial extruder but again with a lower density. Reynolds (1970) has suggested that an axial extruder may be of use in producing large pellets with diameters ranging from 2mm to 15mm, whereas a radial extruder may be used to produce extrudate of 0.5 to 3mm diameter.

Screw extruders are the only truly continuous extruders since extrudate is produced in a continuous stream. Other types of extruder produce extrudate in surges, depending on the motion of the mechanism forcing the wet powder through the die.

Figure 1.2a An Axial Screw Extruder (Side View)

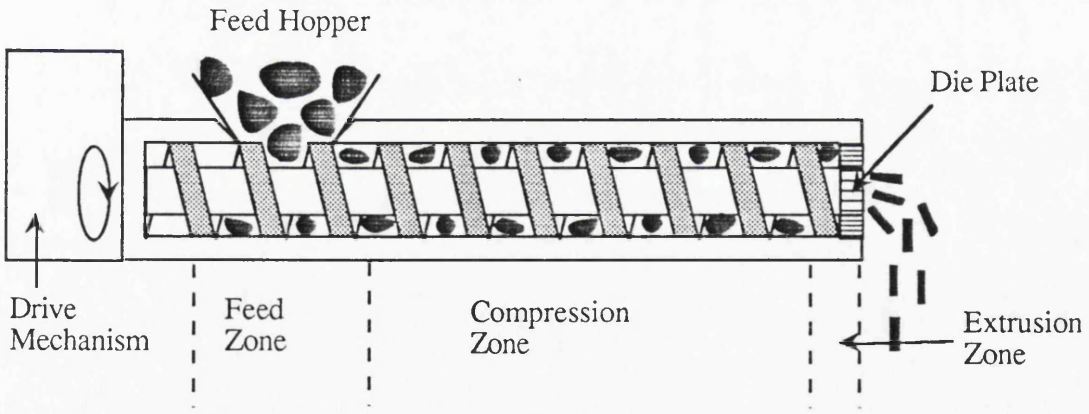
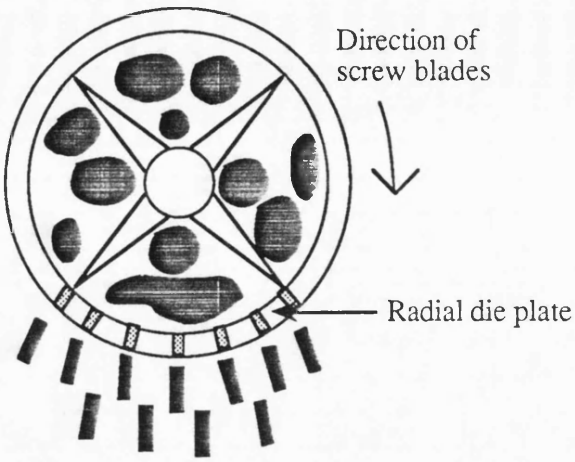


Figure 1.2b A Radial Screw Extruder (End View)



Generally a screw extruder has three zones - a feed zone, a transport and compression zone and an extrusion zone (Figure 1.2a). The feed zone either introduces the wet powder mass directly into the screw mechanism or it can facilitate the addition of individual components of the mix, e.g. two powders and a granulating fluid, into the screw, with these components then mixed *in situ*. The transport zone compresses the powder as it moves along the screw prior to extrusion. In this zone air vents or a temperature control jacket may be introduced to improve extrudate quality. The extrusion zone is where the powder mass is forced through the die holes to produce extrudate - the die holes generally have a diameter between 0.5 and 1mm and a thickness of between 0.5 and 2.0mm (Hicks and Freese, 1989). Within any of these zones further modifications may be employed, such as a variable screw design to produce higher or lower extrusion forces, an extruder blade at the end of an axial extruder to chop the extrudate formed, or varying die designs on the screen or plate to change the extrudate quality.

Screw extruders are successfully used in a variety of industries and can be used to manufacture extrudate for subsequent spheronisation. However due to the high pressures involved in the extrusion process, they may be of less importance in pharmaceutical spheronisation than other types of extruder (Goodhart *et al.*, 1973). The high pressures result in the generation of heat which may either adversely affect any heat labile substances present in the formulation or alter the initial moisture content of the wet mass charged into the extruder (Gamlen and Eardley, 1987).

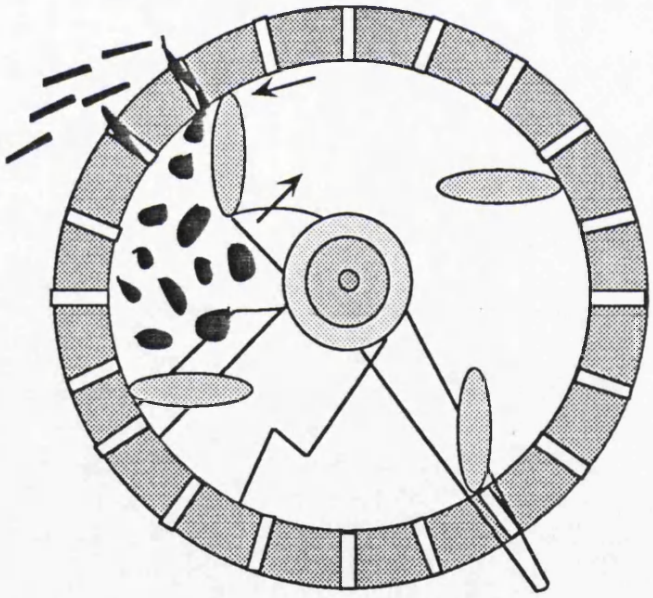
Sieve Extruders

Sieve extruders manufacture extrudate by forcing a wet powder mass through a mesh screen or perforated plate with a rotating or oscillating arm.The moist feed material is nipped in the angle between the arm and the sieve plate and is forced through the sieve. Sieves with meshes of 2mm or smaller are used to produce extrudate.

Sieve extruders produce relatively low pressures and therefore the extrudate formed may be of a low density and suffer from surface defects and consequently not be of an appropriate quality for spheronisation. However this low power consumption prevents a large increase in the amount of heat produced by extrusion and may eliminate the risk of any potential moisture gradients. Sieve extruders may be employed to manufacture granules suitable for tabletting where the material being sieved has been dried before processing.

One of the most widely used sieve extruders is part of the Nica^{TM} system and a schematic representation of its extruding action is shown in Figure 1.3.

Figure 1.3 Schematic View of a Nica^{TM} Extruder



Since sieve extruders have a large numbers of die holes per unit area compared with other extruder types the rate of throughput of material is very high. To prevent excess pressure generation screens are not usually greater than 0.5mm in thickness. This can result in poor surface quality in the resulting extrudate.

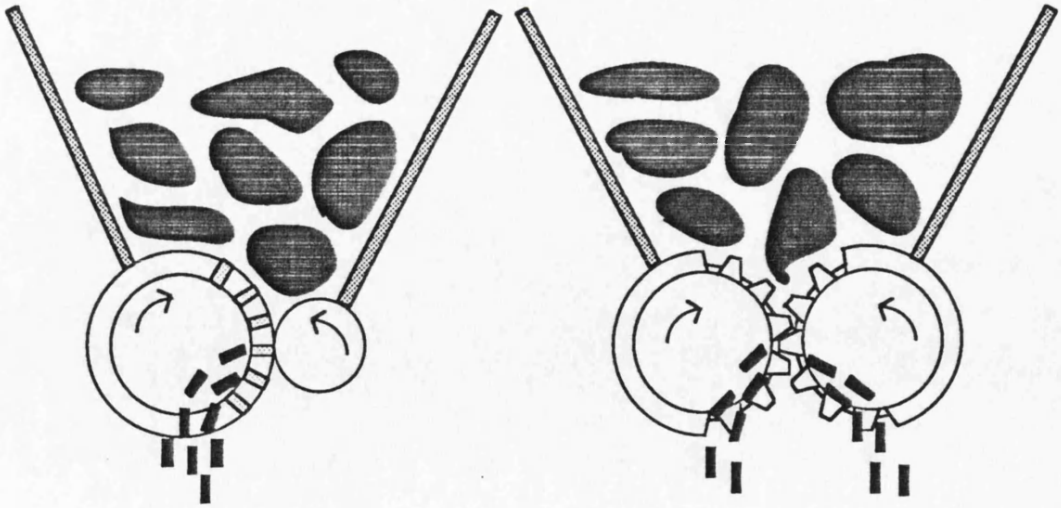
Roll Extruders

Roll extruders use the compaction force between two contra-rotating rollers to force a wet powder mass through holes in one of the rollers (Figure 1.4a).This type of roll extruder is sometimes known as a Cylinder-type extruder. The pressure induced by roll extrusion is generally less than that produced by screw extrusion because there is no feed compression force involved in introducing the powder to the capillary in a roll extruder (the powder enters by gravity).Therefore there is no shear applied to the wet powder mass before it reaches the site of extrusion. In extruders of comparable size the shear forces involved in roll extrusion are generally lower than screw extrusion because forces in roll extrusion are generally exerted in a normal direction rather than by a diagonal drag-flow force (Hicks and Freese, 1989).

Roll extruders may take further forms including varieties in which :-

a. the two rollers have teeth, in whose roots there are dies in the form of drilled plates. The extrudate is formed as the two rollers come together and the wet powder mass is forced into the dies and then discharged via gravity as the rollers come apart (Figure1.4b). This type of extruder is sometimes known as a Gear-type extruder (Rowe, 1985).

Figure 1.4 Schematic Diagrams of Two Types of Roll Extruder



a. Cylinder-type **b. Gear-type**

b. one or more rollers are rotated in a planetary fashion and force extrudate through perforations found around the drum. The wet powder is fed in above the extrusion zone and forced out the pellet mill by the rollers. Modifications may include the use of cutters to regulate the length of extrudate formed by the mill.

Roll extruders are commonly utilised for pharmaceutical extrusion with the product then subsequently spheronised because of the high extrusion pressures but low frictional pressures that they exert. This allows good quality extrudate to be formed without an excess heat generation. They also have the added advantage of a high throughput rate (the rate being varied by altering the speed of the rollers) which makes them more cost-effective.

Recent work has been made to instrument a gravity feed extruder and thus measure the influence of particle size of insoluble material and of product solubility on the extrusion forces (Baert *et al.*, 1991). Results have indicated that variations in lactose and microcrystalline cellulose particle size did not affect the extrusion force produced by the gravity feed extruder. However variation in water content and initial differences in solubility between various grades of lactose markedly influenced the extrusion force produced.

Ram Extruders

Ram extruders can be used to produce either continuous (by a piston-type mechanism) or batch flow of extrudate. They produce extrudate of a high density but they generally have a low output.

Ram extruders are used in laboratory experimentation since the energy exerted on the wet powder mass to force it through a capillary can be accurately measured. This measurement can then be used to examine the rheological behaviour of wet powder masses undergoing extrusion (*cf.* Section 2.1).

1.4.2 Spheronisers

Spheronisers provide a compact means of quickly converting cylindrical shaped extrusions into spherical granules of accurately controlled size and density (Gebbett, 1973). All spheronisers (or *Marumerizers*™, as they are sometimes known) are of the same basic construction. They consist of a stationary vertical cylinder, with an opening at the top for filling, and a base plate (friction plate) that rotates at high speeds. The speed of rotation can be varied for each formulation processed or for the degree of rounding required. The cylinder has smooth internal walls but the base plate may be

grooved in various shapes to increase the efficiency of the spheroniser in cutting and rounding the initial extrudate. There is usually a door on the side of the vertical cylinder to allow discharge of the final product. Any fine powder that is produced either due to surface defects on the extrudate or to an extrudate that is over-brittle is removed from the spheronising chamber by falling down the gap that exists between the stationary vertical walls of the spheroniser and the rotating base plate.

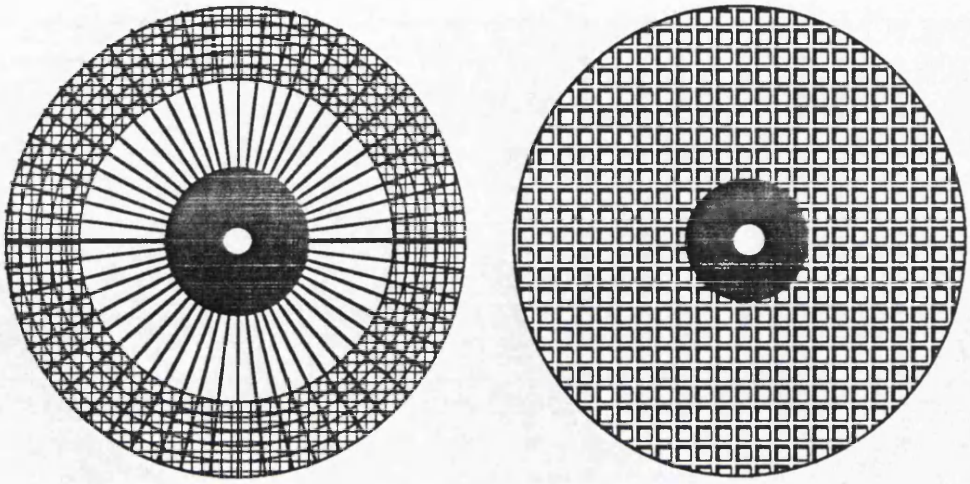
Due to the design of the equipment, spheronisation is inherently a batch process. Given an approximate spheronisation time of 15 minutes an industrial-scale spheroniser can produce upwards of 200kg per hour although the exact rate of spheronisation depends on the formulation of the extrudate and the size of the spheroniser. Although the time to spheronise extrudate is usually between 15 seconds and 5 minutes, with an average time being of 1 to 2 minutes (Reynolds, 1970), the process rarely exceeds 30 minutes. Since spheronisation of material is undertaken whilst it is still wet after extrusion, then if the extrudate has not fully rounded or agglomerated after 30 minutes it will begin to dry in the spheroniser and no further rounding will occur.

During the spheronisation process moisture may accumulate on the walls and ceiling of the spheroniser due to the heat generated by the process and moisture being forced to the surface of the spheroids by the centrifugal forces. This may result in individual spheroids adhering to the walls of the spheroniser, prompting other spheres to adhere and producing agglomeration. To prevent any agglomeration from occuring an air extraction device can be fitted to the roof of the spheroniser to control the humidity. Alternatively a temperature controlling jacket can be placed around the spheronising bowl to prevent moisture accumulation. Additionally a fine dusting of powder, such as microcrystalline cellulose, can be introduced into the spheronising chamber to reduce any moisture build-up either on the spheroniser walls or on the individual spheres. Spheres may become wetter on their surface as the solvent migrates under the influence of the applied stresses. This process causes a densification of the spheres and produces spherical granules with good hardness and very low friability.

The design of the friction plate on which the extrudate is spun has been found to influence the quality of the resultant spheroids (Chapman, 1985). Plates are most commonly made from a cross-hatched grid pattern where the grooves intersect each other at 90^{o} angles (Figure 1.5b). These grooves promote some of the initial cutting of extrudate. However a radial design, where grooves emanate out from the centre of the plate like a bicycle wheel, is believed to be more efficient (Hicks and Freese, 1989)[Figure 1.5a]. This efficiency stems from the fact that more of the cutting edge is

perpendicular to the direction of rotation than with a cross-hatched design, therefore more energy is transferred into the cutting process.

Figure 1.5 Friction Plate Design of a Radial Plate and Cross-Hatched Plate.



a. The Radial Plate **b. The Cross-Hatched Plate**

With the radial plate the distance between each cutting surface increases as the grooves move out from the centre, reducing the effectiveness of the plate. The size of grid pattern to be designed for each plate is determined by the size of the spheroids that are desired. The size of groove required is generally 50-100% larger than the diameter of the spheroid (Hicks and Freese, 1989). This increased width of groove (generally V-shaped) allows the extrudate to fall into the opening and promotes the fracture of the extrudate into uniform lengths as other strands of extrudate roll over the top of it.

The efficiency of any friction plate design can often be compromised by the formulation of the material undergoing spheronisation. If the material is slightly too wet or adhesive then the grooves of the friction plate quickly become clogged with wet powder. This then prevents further chopping of the extrudate into uniform lengths and can lead to a large size and shape distribution in the final product. This is slightly overcome with friction plates that have a teflon edging. This edging reduces the amount of wet powder that adheres to the spheroniser wall adjacent to the friction plate and increases the upward motion of particles after they have collided with the spheroniser wall.

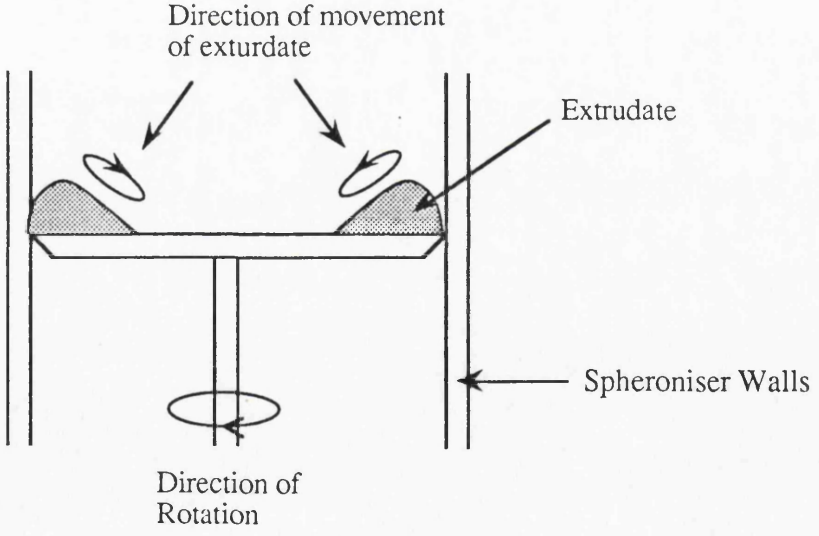
Spheronisers may possess other components to increase their efficiency. These include powder feeders that add powder to the spheroniser if the extrudate is slightly

too wet and may agglomerate and brushes that can be used to clean the spheroniser plate whilst spheronisation is still in process. Baffles may be used to increase the degree of agitation within the spheronising chamber, promoting a more vigorous cutting process and consequently a faster spheronisation time. Apart from baffles, dry air can be blown up from underneath the friction plate to increase agitation. The air can also reduce the amount of moisture within the spheronising chamber and prevent agglomeration of overwet extrudate.

1.5 SPHERONISATION

The spheronisation process begins when centrifugal forces throw the various lengths of extrudate against the walls of the spheroniser. The extrudate is then broken down into short strands of material which are of approximately equal length. As the spheroniser spins, the centrifugal forces push the extrudate up the spheroniser walls until the kinetic energy is dissipated and the material falls back onto the base plate. This behaviour makes the extrudate appear to be acting with a rope-like toroidal movement (Figure 1.6).

Figure 1.6 Schematic Cross-Section of a Spheroniser and The Direction of Movement of the Spheroniser Plate and Extrudate.



As the material moves over itself a combination of frictional and centrifugal forces causes moisture to move from the pellet interior to the outside and imparts plasticity to the pellet surface (Ghebre-Sellassie, 1989). The surface plasticity and the tumbling nature of the particles in the spheroniser allows for spheroid formation. As

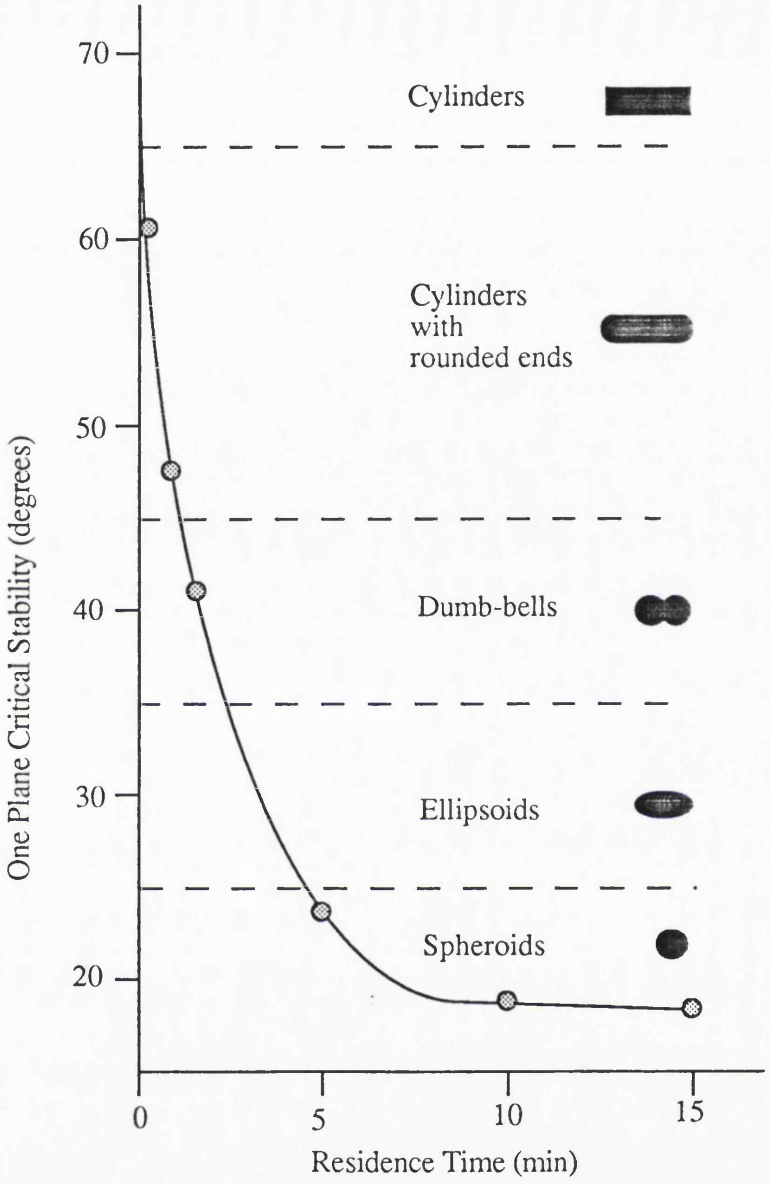
moisture is lost from the pellet surface any dissolved substances within the pellet begin to crystallise out and form solid bridges. These bridges confer a high degree of mechanical strength on spheroids. Low levels of moisture that are retained within the pellet may also contribute to the mechanical strength of the pellet. On drying some of this residual moisture may be lost and, depending on the formulation of the spheroid, the resultant dried sphere may possess less mechanical strength because of its slight porous nature (Ghebre-Sellassie, 1989).

The change in shape of extrudate under spheronisation has been investigated by Chapman (1985). Initially extrudate is charged into the spheroniser as variably lengthed cylinders. The shape of these cylinders can be assessed by a technique known as the One Plane Critical Stability measurement (*cf.* Section 2.3.1). As the spheroniser begins to exert an effect the shape of particles within the chamber changes. These changes are summarised in Figure 1.7 (Rowe, 1985).

During spheronisation extrudate typically follows the pattern in Figure 1.7 where cylinders first have their ends rounded then dumb-bells are created. These then form rugby-ball shaped ellipsoids which eventually round to form spheroids. The whole process may cease at any particular stage, depending on the processing parameters and the formulation under investigation.

For a formulation to be successfully spheronised it must first have been successfully extruded. However not all formulae that extrude well will necessarily spheronise. Formulations generally tend to be wetter than those used in wet granulation for tabletting and need not contain a conventional binder. In fact the ideal excipients for extrusion and spheronisation appear to be substances that attract the liquid phase (usually water) by a capillary attraction to give the granule strong, cohesive properties. Excipients that exhibit these properties include microcrystalline cellulose, bentonite, kaolin and talc. During the extrusion process the liquid binder is forced under pressure to the surface of the wet mass where it acts as the lubricating layer as the material is squeezed through the capillary. For successful spheronisation the liquid that has migrated to the surface of the extrudate must be able to be migrate back into the body of the extrudate, otherwise the surface moisture acts as a binder to agglomerate the extrudate in the spheroniser. Kaolin and talc appear to be more difficult to formulate for spheres than bentonite and microcrystalline cellulose because they allow less reabsorption of the water into the extrudate prior to spheronisation.

Figure 1.7 The Influence of Spheronisation Time on the Shape of Extrudate as Measured by the One Plane Critical Stability.



When the extrudate is charged onto the rotating plate it is broken down into shorter strands by contact with the friction plate, with contact with the spheroniser walls and by collisions with other strands of extrudate. The extrudate must be sufficiently brittle for these processes to break it down into short vermicelli-like strands or the material will not spheronise. However it must also be bound sufficiently so that it does not shatter under the applied stresses and produce a lot of powder (or fines). The extrudate must also be sufficiently plastic so that it can be moulded in spheres and non-sticky so that it does not cause agglomeration. These demands mean that the formulation of the powder mass under investigation is the most crucial determinant of

successful extrusion and spheronisation. Other process variables that can be altered to improve outcome include varying the spheronisation time, the load of extrudate in the spheroniser, the speed of rotation of the plate, the geometry of the grooves on the plate and the size of the spheroniser employed.

Aims of the Present Work

Several authors (O'Connor and Schwartz, 1989; Noché *et al.*, 1991; Bianchini *et al.*, 1991 and Eerikäinenn, 1991) have investigated the factors that influence successful extrusion and spheronisation. This work has tended to centre around preparing specific drug substances for extrusion and spheronisation with reporting into the physical qualities of the pelletised product as a measure of experimental outcome. Other research has been undertaken to assess the influence of formulation on the rheological parameters measured during extrusion (Harrison *et al.*, 1987; Raines *et al.*, 1990; Andersen and Newton, 1990).

Work has been previously been undertaken with formulations containing high drug loading. Conine and Hadley (1970) reported that spheres with up to 90-95% of active ingredient could be manufactured using extrusion/spheronisation providing that any insoluble or soluble materials maintained their crystallinity in the presence of solvent used. They reported that mixtures constituting sucrose powder (80%) and microcrystalline cellulose (20%) and lactose (70%) and microcrystalline cellulose (30%) could be successfully spheronised. However no details were published on processing conditions. More recent attempts to manufacture spheres with high drug loading have utilised modified grades of microcrystalline cellulose that contain sodium carboxymethylcellulose as an additive (O'Connor and Schwartz, 1985).

The aim of the present work has been to increase the amount of rheological information that can be obtained for a representative group of mixtures. To that end controlled-stress rheometry has been applied and assessed as a method of increasing the amount of rheological data obtained. The differences in the behaviour of the sample mixtures when subjected to the processes of extrusion and spheronisation can then be explained by their differences in rheological behaviour. If rheological differences allow then predictions into the possible behaviour during extrusion/spheronisation of untested materials may then be feasible.

The work undertaken in this thesis examines the effect of moisture and die diameter on binary mixtures containing lactose (70-80%) and microcrystalline cellulose (20-30%). Spheronisation has been attempted on formulations extruded through 1mm diameter dies. The specific rheological properties of each formulation have been

identified by using capillary rheometry and controlled-stress rheometry. This has been undertaken in order to assess whether the rheology of each formulation can give any clues as to whether the material will successfully extrude and spheronise.

Chapter 2

THEORY

2. THEORY

2.1 THE BEHAVIOUR OF A WET POWDER MASS DURING EXTRUSION THROUGH A DIE

For successful preparation of spheres from pharmaceutical powders using the process of extrusion /spheronisation there is only a narrow range of materials which appear to be suitable. This suggests that there is a specific rheological requirement involved in the process (Harrison *et al.*, 1987). Successful spheronisation further requires the initial production of good quality extrudate. It is therefore important to characterise the behaviour of pharmaceutical formulations in an attempt to relate extrusion rheology to the quality of extrudate produced (Raines *et al.*, 1990).

Previous studies have demonstrated that the application of capillary rheometry to the extrusion of wet powder masses can yield useful information as to the behaviour of these masses during the extrusion process (Harrison *et al.*, 1987; Fielden *et al.*, 1989).

CAPILLARY RHEOMETRY

Two parameters are required to characterise the flow of a material through a die:-

1. The force required to push the material through the die.

2. The velocity of throughput of material through the die.

Capillary rheometry is a well-established method of determining the behaviour of materials as they are extruded from an area of high pressure to low pressure (Benbow *et al.*, 1989). Capillary rheometry uses the two parameters above to characterise the mechanism behind the extrusion of a wet powder mix. Hopefully it may also give information as to whether a specific mix will extrude and spheronise successfully, independent of the extruder employed.

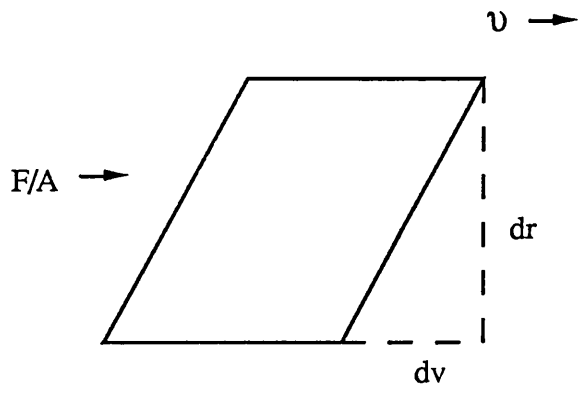
Commercial extruders e.g. the screen, radial or gear extruders, have complex movements and therefore there are many interacting forces, including a large frictional component, which will distort any force measurements recorded. Since the method requires accurate measurement of both the force and velocity of extrusion, a simple ram extruder is usually employed for experimentation.

The theory underlying capillary rheometry is given below.

2.1.1 Newton's Model for the Movement of Liquids under Shear

The application of a shear stress (τ) to a Newtonian fluid under laminar flow produces a shear strain that can be described by 'pack of cards' flow (Figure 2.1). This shear stress produces a linear velocity gradient from the upper plate moving at velocity υ to the lower plate that is stationary.

Figure 2.1 The Application of a Shear Stress (F/A) to a Body of Fluid



The velocity gradient (dv/dr) can be defined as the shear rate (α) and is related to the shear stress applied to the sample (equation 2.1):-

$$\tau = \eta \, (dv/dr) \qquad 2.1$$

where η is the coefficient of absolute or dynamic viscosity. This model can be used to determine the flow of a fluid through a cylinder.

2.1.2 The Flow of a Fluid Through a Capillary

A fluid passing through a straight capillary is affected by two forces; the applied force (F_A) which causes the fluid to move and the viscous force (F_V) which acts to retard the flow. Assuming the capillary has a radius R and a length L and there is a pressure difference between the two ends of the capillary, ΔP, then the applied force (F_A) will act over the whole cross-sectional area of the body of fluid i.e.

$$F_A = \Delta P \, (\pi R^2) \qquad 2.2$$

where R is also the radius of the column of fluid. The viscous force (F_V) resulting from the shear stress acts over the surface area of the column of fluid i.e.

$$F_V = \tau (2\pi RL) \qquad 2.3$$

Equations 2.2 and 2.3 can be combined to provide an expression that relates the shear stress to its distance from the centre of the capillary (r) and to the pressure gradient along the capillary ($\Delta P/L$) :-

$$\tau = \Delta Pr/2L \qquad 2.4$$

The die wall shear stress, τ_W, can be calculated using equation 2.4 but the distance from the centre of the capillary has now become the radius of the capillary, R. Hence:-

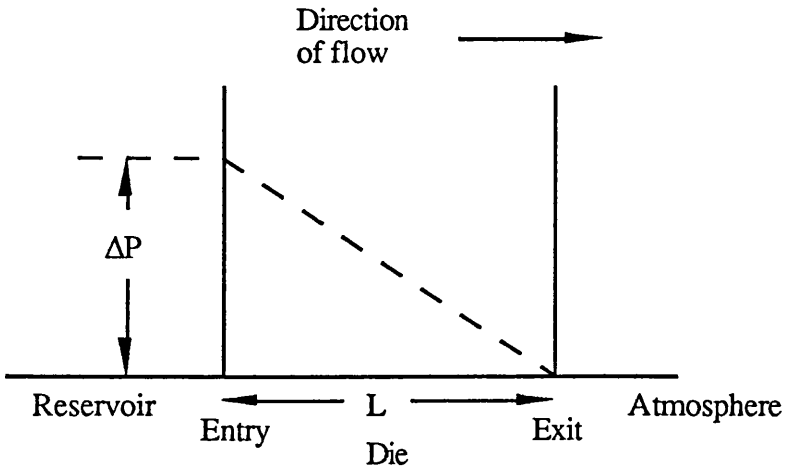
$$\tau_W = \Delta PR/2L \qquad 2.5$$

This also allows the shear rate (α) to be calculated simply from the velocity gradient (dv/dt) as described above.

2.1.3 End Effects of a Non-Ideal Pressure Gradient

Raines (1990) has summarised the assumptions made on the pressure gradient for an ideal system (Figure 2.2):-

Figure 2.2 The Ideal Pressure Gradient in a Capillary



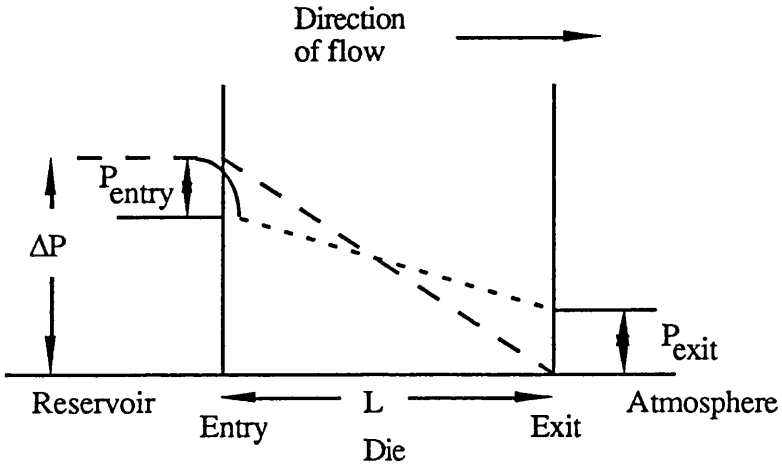
i. The pressure within the capillary is independent of the position of the applied stress within the reservoir.

ii. The pressure is consistent over the whole length of the capillary.

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

These three assumptions do not hold in practice and there is generally a lower die-entry pressure than the ideal, non-laminar flow within the die and a pressure greater than atmospheric at the die exit (Figure 2.3).

Figure 2.3 The Pressure Gradient in a Real Capillary



Loss of pressure as the material moves from a large reservoir to a small capillary results from loss of energy due to both vortex flow as the material converges into the capillary and to laminar flow of the material once in the capillary. Retention of pressure in the capillary may be due to entrance effects which can cause disturbance of the laminar flow of material. Therefore a certain distance may have to be travelled by the material before laminar flow is established. Once laminar flow has been established then the equations above relating velocity with pressure are applicable. The length of capillary along which laminar flow occurs is known as the viscometric region (Raines, 1990). Finally the pressure of the material on exit from the capillary does not return to atmospheric, at least initially, due to the abrupt change in boundary conditions upsetting the velocity gradient.

Variations in the entry and exit pressures of the die and the die length may contribute to the surface defects that occur with different formulations, particularly when the shear rate is high or the die has a very short or long length. However since the value of ΔP is the same whether the assumptions hold true or not then pressure values can still be used to obtain a measurement of the die wall shear stress.

2.1.4 End Corrections

The application of an end correction factor to compensate for pressure loss upstream of the die entry has been described by Bagley (1957). The entrance correction has been described by equation 2.6 where the effective capillary length has been extended to take into account the lower than expected entrance pressure:-

$$\tau_w = \Delta P / 2 (L/R + n_b) \qquad 2.6$$

with n_b being the Bagley entrance correction factor. The value of n_b can be determined by extrapolation of the line produced by the Bagley plot (Figure 2.4) through the Y-axis to intercept the X-axis. Depending on the velocity of the material entering the die the value of n_b will vary. The above correction factor has been found to be applicable to the model system under investigation since previous flow visualisation studies using lactose, microcrystalline cellulose and water demonstrate the presence of convergent flow vortices (Harrison *et al.*, 1983).

A further correction can be included to take into account the effect of a pressure greater than atmospheric at the exit point of the capillary. The exit pressure, P_e is deducted from the overall pressure drop, ΔP (equation 2.7):-

$$\tau_w = \frac{(\Delta P - P_e)}{2(L/R + n_b)} \qquad 2.7$$

2.1.5 The Upstream Pressure Loss

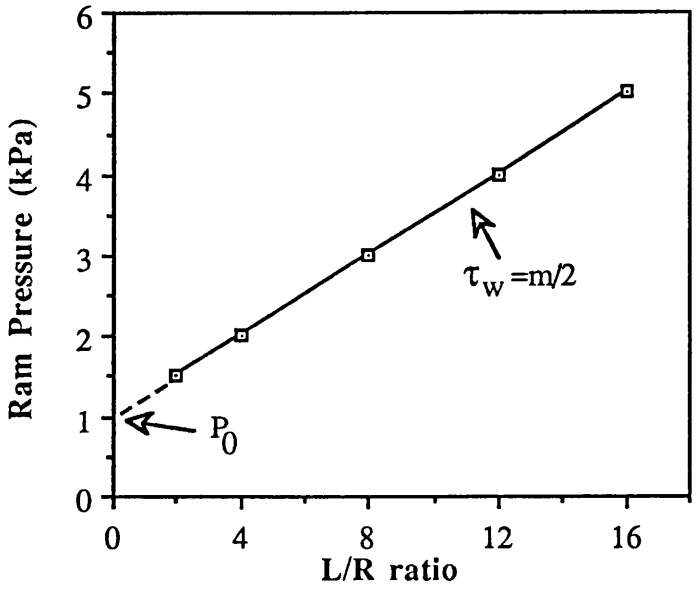
An alternative approach to quantify the effect of entrance and exit pressure variables is to calculate the upstream pressure loss, P_o, which represents the finite pressure loss associated with end effects (Harrison, 1982). The die wall shear stress, τ_w, can be expressed as follows:-

$$\tau_w = \frac{(P_T - P_o) R}{2L} \qquad 2.8$$

where P_T is the total pressure on the piston, P_o is the upstream pressure loss (i.e. pressure drop along the barrel), R is the radius of the die hole and L is the length of the die hole. A plot of ram pressure exerted on the material against the L/R ratio of various dies will yield τ_w as half the slope of the line and P_o as the y-intercept (Figure 2.4). This graph is also known as a Bagley Plot.

Raines (1990) has described the additional pressure losses that are incorporated into P_O that are not end effects. These include kinetic energy losses, elastic energy losses, turbulence and head effects, which are pressure losses incurred by friction of the various parts involved in the extrusion process.

Figure 2.4 A Bagley Plot of Ram Pressure vs L/R Ratio of Different Dies



The relationship between the upstream pressure loss, P_O, and the Bagley entrance correction factor, n_b, can be deduced by combining equations 2.6 and 2.8 to yield:-

$$n_b = \frac{P_O}{2\tau_w} \qquad 2.9$$

Depending on the relative effects on the upstream pressure loss and shear stress, increasing the shear rate may increase or decrease the entrance correction factor (Harrison, 1982; Bagley, 1957). Increasing the extrusion rate increases the ram pressure obtained for any given L/R ratio of die. A linear relationship remains however so further values of τ_w can be calculated. Using L/R ratios of dies above a value of 16 can introduce a deviation from the proportionality as expressed above, depending on the formulation employed. This deviation has been attributed to a moisture gradient occurring within the die during extrusion (Harrison *et al.*, 1984).

2.1.6 Die Wall Shear Rate, σ

One of the earliest attempts to describe the viscosity of a fluid flowing through a capillary resulted in Poiseuille's Law (equation 2.10) [for a full derivation - Gitlus, 1975]:-

$$\eta = \frac{\pi r^4 \Delta P}{8LQ} \qquad 2.10$$

where η is the viscosity, r is the radius, ΔP is the difference in pressure between the top of the capillary and the bottom, L is the length of the tube and Q is the volume flowing through the tube per second.

Substituting the equation relating the shear stress to velocity gradient (equation 2.1) into that relating the die wall shear stress to the dimensions of the capillary (equation 2.5) yields the equation for the die wall shear rate:-

$$\frac{dv}{dr} = \frac{\Delta PR}{2\eta L} \qquad 2.11$$

Equation 2.11 can be used by substitution into Poiseuille's Law to yield another derivation for the die wall shear rate. In this case the die wall shear rate, α_w, can be expressed as:-

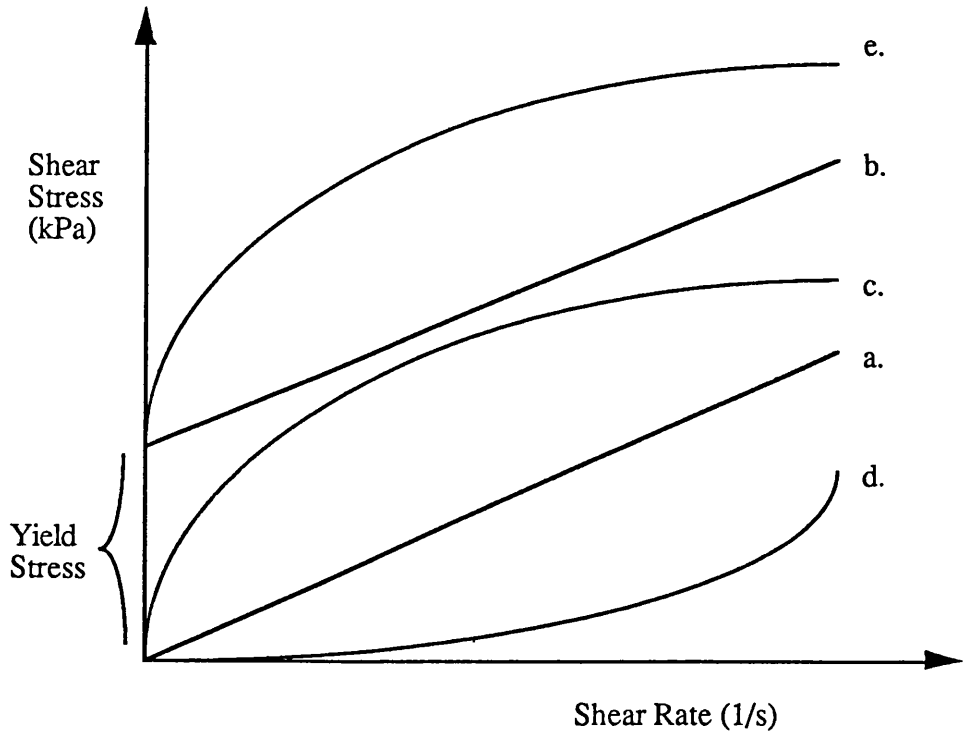
$$\alpha_w = \frac{4Q}{\pi R^3} \qquad 2.12$$

where Q is the volumetric throughput. Equation 2.12 assumes that the flow of material is Newtonian. However Berghaus (1951) developed a method for determining the flow behaviour in concentrated suspensions which he suggested flowed through a die with a boundary layer of solvent against the die wall. This involved calculations to determine values for slip velocity since the amount of slip present would be determined by the shear stress at the die wall. Further modifications were performed by Jastzrebreski (1967) who stated that for concentrated pastes the effective slip coefficient was dependent on both the wall shear stress and the die diameter. Experiments undertaken by Harrison *et al.* (1987) indicated that ram extrusion of wet powder masses containing lactose, microcrystalline cellulose and water followed the general behaviour of

concentrated suspensions as observed by Jastzrebreski (1967) but these did not fit any previous mathematical model proposed.

Having calculated the die wall shear stress and the shear rate it is now possible to plot a flow diagram to characterise the behaviour of the materials under investigation during extrusion. Various mathematical models can then be applied to help interpret the flow behaviour of the material as the shear rate varies. Materials undergoing an applied stress typically behave as one of the bodies described in Figure 2.5.

Figure 2.5 Mathematical Models for Various Rheological Flow Curves



a. Newtonian Model.
b. Bingham Body Model.
c. Power Law Model - Shear Thinning.
d. Power Law Model - Shear Thickening.
e. Herschel-Bulkley Model.

Previous experiments on wet powder masses of the type under investigation have shown that, of the five models above, mixtures most closely followed the Herschel-Bulkley model of material flow (equation 2.13):-

$$\tau = \tau_y + k\alpha^n \qquad 2.13$$

where τ is the shear stress, τ_y = yield stress, k is the power law viscosity constant, α is the shear rate and n is the degree of non-Newtonian flow. Harrison (1982), Fielden (1987) and Raines (1990) have demonstrated that rheological flow models of various lactose, microcrystalline cellulose and water mixtures have all resulted in flow curves that possess both a yield stress value and shear thin as the shear rate increases.

The slope of a line on a logarithmic graph of τ_w (wall shear stress) *versus* α_w (wall shear rate) will express the degree of non-Newtonian flow exhibited by the powder mass in the die. This can provide useful information if it is used in tandem with the yield value, τ_y, from the shear stress/shear rate model. However Harrison (1987) found that results from the lactose, microcrystalline cellulose and water mixtures under investigation yielded non-linear slopes. The deviations from linearity were attributed to the significance of the yield stress when materials were subjected to low wall shear stresses and to slip at the die wall when a high shear rate was applied. Any values calculated from the Herschel-Bulkley mathematical model were consequently only descriptive rather than definitive. The occurrence of slip at the die wall led Harrison (1987) to believe that calculated values for die wall shear stress were those of a lubricating layer of material that varied in its consistency from the bulk of material moving through the capillary.

Further experiments have been undertaken by Raines (1990) using the approach developed by Benbow *et al.* (1987) to estimate the apparent thickness of the lubricating layer for various formulations extruded at a particular shear rate.

2.1.7 Benbow-Bridgwater Theory

Ovenston and Benbow (1968) in calculations to solve the problem of wall slip proposed that the die wall shear stress could be composed of two components, τ_o, the initial die wall shear stress and an expression βV, which is a component that accounts for the increase in the die wall shear stress with increasing extrudate velocity.

$$\tau_w = \tau_o + \beta V \qquad 2.14$$

The initial die wall shear stress, τ_o, relates to a theoretical die wall shear stress value that occurs at an extrudate velocity of zero, β is the die-land velocity factor and V

is the extrudate velocity. The die-land velocity factor is a measure of the relative viscosity to thickness of the model Newtonian fluid that acts as a die-wall lubricant.

The static component, τ_o, can be determined from a plot of total extrusion pressure *versus* extrudate velocity when extrusion occurs through various length to radius ratio dies. By extrapolation of the extrusion pressures to zero velocity a theoretical Bagley plot can be derived at a zero extrudate velocity. When V=0 then the expression βV becomes zero and the previously derived Bagley equation (equation 2.8) can be used to determine the value of τ_o.

By rearrangement of previous equations the term β can be expressed as:-

$$\beta = \frac{[P_T(vel_V) - P_o(vel_V)] - [P_T(vel_o) - P_o(vel_o)]}{2(L/R).V} \qquad 2.15$$

where P_T (vel_V) is the total extrusion pressure at velocity V and P_o (vel_V) is the upstream pressure loss at extrudate velocity V.

In an attempt to calculate the effects of die wall slip on the extrusion of clay pastes Ovenston and Benbow (1968) proposed a relationship between the pressure applied in the extruder barrel, P_T, and the extrudate velocity, V, during flow from a cylindrical barrel of diameter D_o into a die-land of diameter D and length L:-

$$P_T = 2\sigma_y \ln (D_o/D) + 4 (L/D) (\tau_o + \beta V) \qquad 2.16$$

where σ_y is the paste yield value. The yield value can be calculated by dividing the upstream pressure loss, P_o, by twice the logarithm of the reduction ratio of the barrel to die diameter (Raines 1990). Equation 2.16 relates the total pressure acting on the extruder barrel to two terms that relate to the flow of material into the die from the barrel and to the flow of material through the die.

Benbow *et al.* (1987) have stated that the equation above (equation 2.16) assumes that all parameters are independent of extrudate velocity and that the liquid layer is Newtonian. If graphs of extrudate velocity *versus* total pressure are non-linear then the die land velocity factor, β, will vary with extrudate velocity. Consequently the lubricating layer against the die wall will be non-Newtonian in behaviour and a modified power law, based on the Herschel-Bulkley model, will be required to replace the βV expression. A modified equation to describe the flow of a paste made with a polymer solution has, for example, taken the following form (Benbow *et al.*, 1989):-

$$P_T = 2[\ln (D_O/D)].(\sigma_{yo} + \alpha_x V^n) + 4 (L/D)(\tau_o + \beta_x V^m) \qquad 2.17$$

where σ_y, the paste yield value, has been replaced by an expression containing two parameters, σ_{yo}, the initial die entry yield stress, and α, the die entry yield stress velocity factor. As with the calculation of a value for the initial die wall shear stress, τ_o, σ_{yo} can be calculated by extrapolation of a line derived from a theoretical Bagley plot of pressure versus zero extrudate velocity to the y-intercept. Since the expression αV will $= 0$ the σ_o value can be expressed as:-

$$P_O (vel_O) = 2 \sigma_{yo} \ln (D_O/D) \qquad 2.18$$

Similarly a value of α can be calculated by solving previous equations for σ_{yo}, yielding:-

$$\alpha = \frac{P_O (vel_V) - Po (vel_O)}{2 \ln (D_O/D) V} \qquad 2\ 19$$

Three extrusion parameters now exist to describe flow in the die entry and three to describe flow through the die-land. Work undertaken by Benbow *et al.* (1987) found that the influence of the paste formulation of α-alumina pastes on extrusion parameters, particularly α and β, was linked to paste rheology, liquid viscosity and the excess of liquid above the inter-particulate volume (Raines, 1990).

2.2 CONTROLLED-STRESS RHEOMETRY

Using capillary rheometry to determine the rheological characteristics of wet powder masses during extrusion does allow for the application of an experimental rheological system that is similar in many ways to the actual process of extrusion and spheronisation. However precise rheological data cannot be obtained from this approach due to the effects of die wall slip and of the convergence of material into the die which may introduce complex changes in the structure of the wet mass (Harrison *et al.*, 1987).

An indication as to the elastic nature of the materials under investigation may be useful in determining the amount of surface defects that might be seen during extrusion/spheronisation. Bagley and Schreiber (1969) have used swelling ratios to determine the amount of deformation imposed on a material as it enters the die that can be recovered by the swelling of the product as it leaves the die i.e. its elastic recovery. Harrison (1984) has questioned whether this rationale can adequately describe the incidence of surface defects and has suggested a 'stick-slip' phenomenon may be more useful in analysis. Nevertheless an elastic component may give useful information into the occurrence of flow defects. The relative elasticity to viscosity of the material being extruded may also be pivotal in determining whether a material will successfully spheronise.

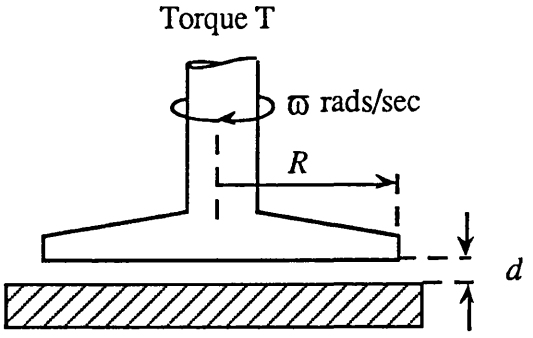
Controlled-stress rheometry can be used to examine the rheology of a wide range of materials. The device for experimentation can utilise any type of measuring system, e.g. cone and plate, concentric cylinder etc, and can undertake creep and oscillation experiments as well as providing conventional flow curves. To investigate samples of high viscosity (approximately 10^8 Pa.s) a parallel plate system is required and only creep and oscillation experiments can be performed.

2.2.1 The Parallel Plate System

The parallel plate system of rheological measurement can be used to induce high shear rates in the sample under investigation - smaller plates and larger gaps (between the plates) allowing an even greater shear rate. Theoretically the system only requires small samples, can be easily cleaned and can tolerate large particle sizes, providing the minimum gap is at least ten times the diameter of the largest particle (Figure 2.6). In addition, a textured surface can be used on each plate to prevent slip due to a surface film of liquid, although this will sacrifice absolute accuracy for an improvement in

reproducibility. An increase in the shear gap (d) provides an increase in sensitivity of the instrument when used in the creep mode (Carrimed manual).

Figure 2.6 The Parallel Plate System



$$\text{Compliance (J) at the rim} = \frac{\pi R^4 \gamma}{2 d T} \qquad 2.20$$

where R is the radius of the top plate, d is the shear gap, T is the torque and γ is the angle of deformation (strain).
A continuous shear may be calculated by the following formula which refers to conditions at the rim (ϖ is the angular velocity):-

$$\text{Shear rate } (\gamma') = \frac{R \varpi}{d} \qquad 2.21$$

$$\text{and Newtonian shear stress, } \tau_r = \frac{2T}{\pi R^3} \qquad 2.22$$

The above equation must take into consideration system factors and moments of inertia before true values can be calculated.

2.2.2 Creep Theory

Creep is a rheological technique that can provide information on stress-controlled effects on a wide variety of materials. It is commonly used to examine phenomena such as the settling of suspensions, the levelling of coatings due to surface tension or sagging of coatings due to gravity. It can also characterise the viscoelastic structure of a material without changing that structure (Carrimed manual). Using a creep experiment to determine the rheological characteristics of a material has the

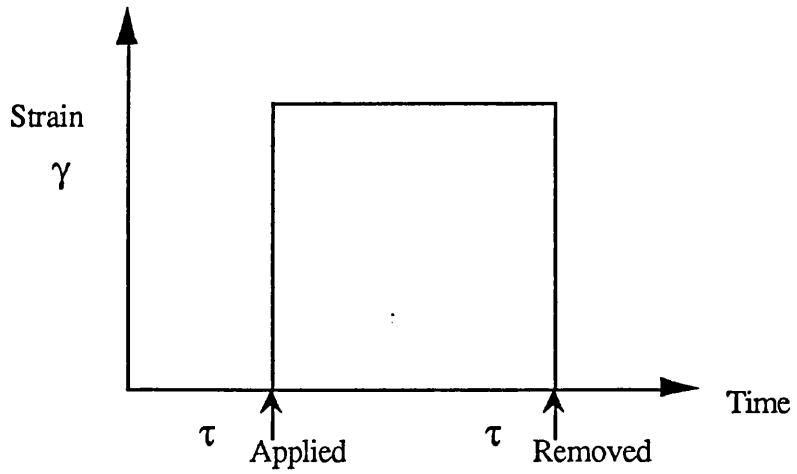
advantage of not requiring very high shear rates and stresses which destroy the structure of the material under investigation. Such shear rates and stresses may be required to produce a flow curve from a conventional rotational viscometer if the material does have such a very strong structure.

A creep experiment is undertaken by applying a shear stress of a constant magnitude to a sample for a constant period of time. This means the material is treated as if it were an elastic solid, the elasticity being determined by Hooke's Law.

Hooke's Law

If a constant force (or stress, τ) is applied to a purely elastic material then there will be an immediate deformation in the material so that it moves a certain distance (or strain, γ). The deformation remains constant as long as the stress is applied. On removing the stress there will be complete recovery of structure and the material will return to its original state (Figure 2.7).

Figure 2.7 The Application of a Stress to a Purely Elastic Material



This behaviour is described by Hooke's Law for an elastic response :-

$$\tau = G.\gamma \qquad 2.23$$

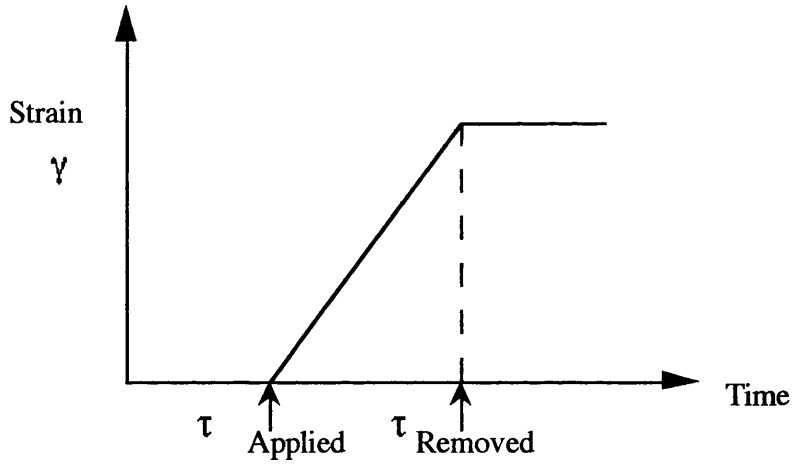
where τ is the stress, γ is the strain and G is the Shear Modulus. The value of the shear modulus varies depending on the material, the higher the shear modulus the greater the stiffness of the material and the greater its resistance to movement. A spring can be thought of as a model for Hookean elastic response (Figure 2.9a).

If the sample under investigation is not a purely elastic body but instead is a fluid then the constant stress applied behaves as a shear stress rather than an elongational stress. If the fluid is Newtonian then the effect of a constant stress will be to produce a constant shear rate, the rate being determined by the magnitude of the applied stress and the inherent viscosity of the sample as defined by Newton's Law.

Newton's Law

If a constant stress is applied to a purely viscous material then there will be flow of that material at a certain rate as long as the stress is applied. The rate is proportional to the stress applied and governed by the inherent viscosity of the material. When the stress is removed on this occasion, the material will remain permanently strained (Figure 2.8).

Figure 2.8 The Application of a Stress to a Purely Viscous Material



This behaviour is described by Newton's Law for a viscous response :-

$$\tau = \eta \dot{\gamma} \qquad 2.24$$

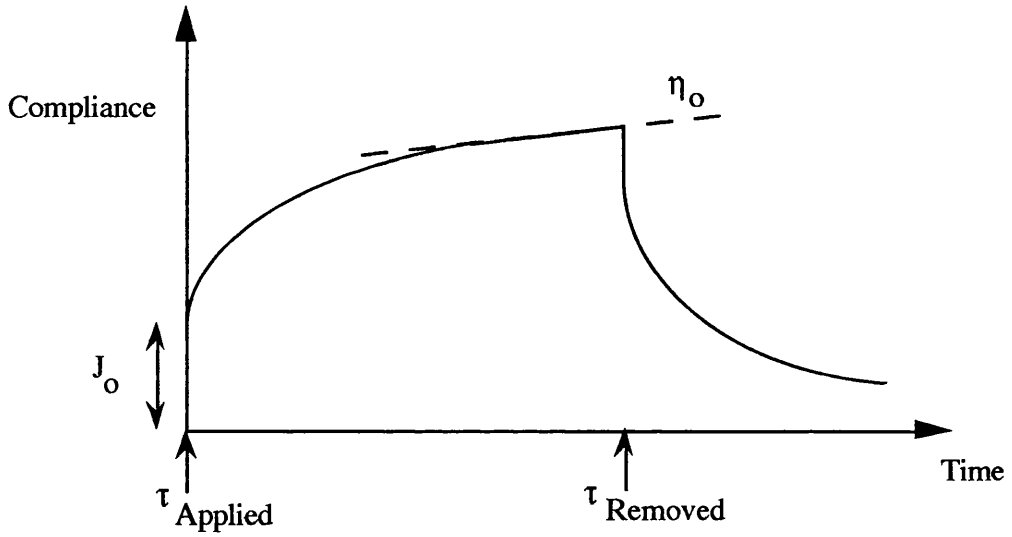
where τ is the stress, $\dot{\gamma}$ is the strain rate and η is the Newtonian viscosity. Both glycerin and water are liquids that can be regarded as obeying Newton's Law. A dashpot is used as a model for Newtonian viscous flow, typically represented by a piston moving in a cylinder of liquid (assuming no end- or wall-effects) (Figure 2.9b).

Figure 2.9 Diagrammatic Representations of Elastic and Viscous Elements.

a. The Hookean Spring b. The Newtonian Dashpot

If the sample under consideration does not behave as a simple Newtonian fluid but instead possesses some structure, then this structure can be defined from the curve of movement towards the applied stress that such a viscoelastic material would exhibit. A typical creep curve for a viscoelastic material is represented in Figure 2.10 :-

Figure 2.10 The Application of a Stress to a Viscoelastic Material.



When the stress is initially applied there is an immediate deformation of the sample due to the undamped elastic behaviour of the sample. This is the instantaneous compliance, J_O (Figure 2.10). The curved section of the response (Figure 2.10) can be described by employing a mechanical model that fragments the curve into individual visco-elastic components called Voigt units. Each Voigt unit has two elements, the Hookean spring and the Newtonian dashpot, which are in parallel (Figure 2.11). The rate at which an individual Voigt unit moves depends on the relative strengths of the

spring and the damping dashpot. The ratio of these strengths is called the Retardation Time. Under the effect of constant stress, the Voigt unit with the shortest retardation time reaches equilibrium most quickly and then ceases to move. If the stress is great enough then each Voigt unit will in turn equilibrate until there is some structure breakdown and the material begins to flow. This final steady shear viscosity is the Newtonian viscosity, η_o.

In principle the structural information obtained from a creep experiment can be directly related to the bonds and mechanisms that operate in the sample fluid.

The Kelvin Model

One of the simplest models of viscoelasticity is the Kelvin or Voigt model. This represents the viscoelastic response of a material (e.g. a lactose : microcrystalline cellulose : water sample) to a constant stress as the sum of both the elastic and viscous components, i.e.

$$\tau = G.\gamma + \eta.\dot{\gamma} \qquad 2.25$$

Given that Compliance, $J = \gamma/\tau = 1/G$

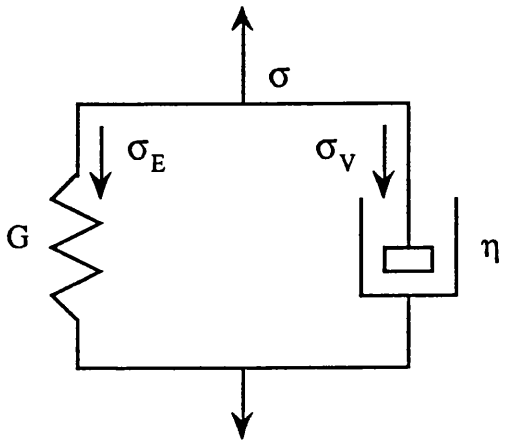
and the Retardation or Relaxation Time, $RT = \eta/G$

the degree and the rate of deformation at any time can be described. The Kelvin model results from a parallel combination of a spring and dashpot where the strain acting on each element is equal at all times (Figure 2.6). Hence, for the Kelvin model the total stress σ is equal to the sum of the stresses in each element, i.e.

$$\sigma = \sigma_E + \sigma_V \qquad 2.26$$

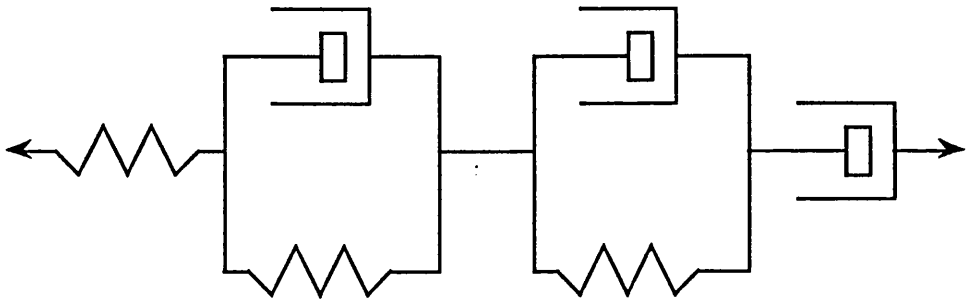
where σ_E is the stress acting on the spring and σ_V is the stress acting on the dashpot.

Figure 2.11 Diagrammatic Representation of the Kelvin Model (or Voigt unit)



A fuller analogue to model the observed behaviour of a viscoelastic sample (as in Figure 2.9) combines the Kelvin model with a spring and dashpot to produce the Burgers model. The spring and dashpot represent J_O and η_O respectively and further Voigt units can be added in series to exactly demonstrate viscoelastic flow (Figure 2.12).

Figure 2.12 Viscoelastic Model with 2 Voigt Units



Two Voigt units may be required to describe rheological behaviour where different types of bonds are breaking and reforming at various rates. Further units may be required to describe more complex rheological behaviour but in practice a maximum of three Voigt units will usually suffice.

Creep therefore can quantify how a material will deform with time, allowing predictions of deformation under stress to be made. Over long time scales the material's fluid-like behaviour, described by η_O, plays the dominant role. At shorter time scales of the order of retardation times, the elasticity of the material, as described by J_O and the

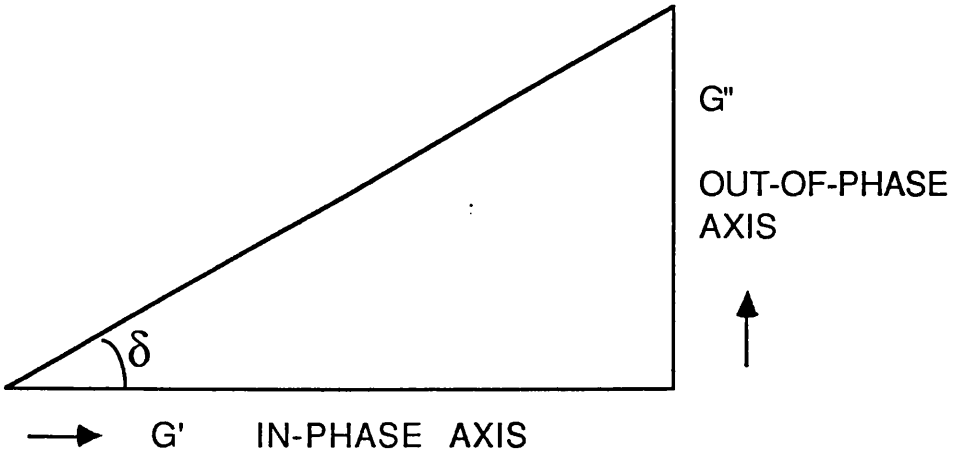
compliance values for each Voigt unit (J_1, J_2 etc), exerts the dominant effect on the rheological behaviour of the sample.

2.2.3 Controlled Stress Oscillation

Oscillation can be used to examine the effects of stresses that are applied to materials over relatively short periods of time e.g. a few seconds. During an oscillation experiment a small amplitude stress is sinusoidally oscillated and the resultant material strain measured. If the material is purely elastic then its Hookean response implies that it will exhibit a certain strain proportional to the applied stress. This strain will be immediate and completely in phase (phase angle difference, $\delta = 0^o$) (Figure 2.13). Conversely a purely viscous response has a phase angle difference of 90^o (i.e. completely out of phase) since the strain rate is proportional to the applied stress (Figure 2.13). For a visco-elastic material the phase angle difference is between 0^o and 90^o.

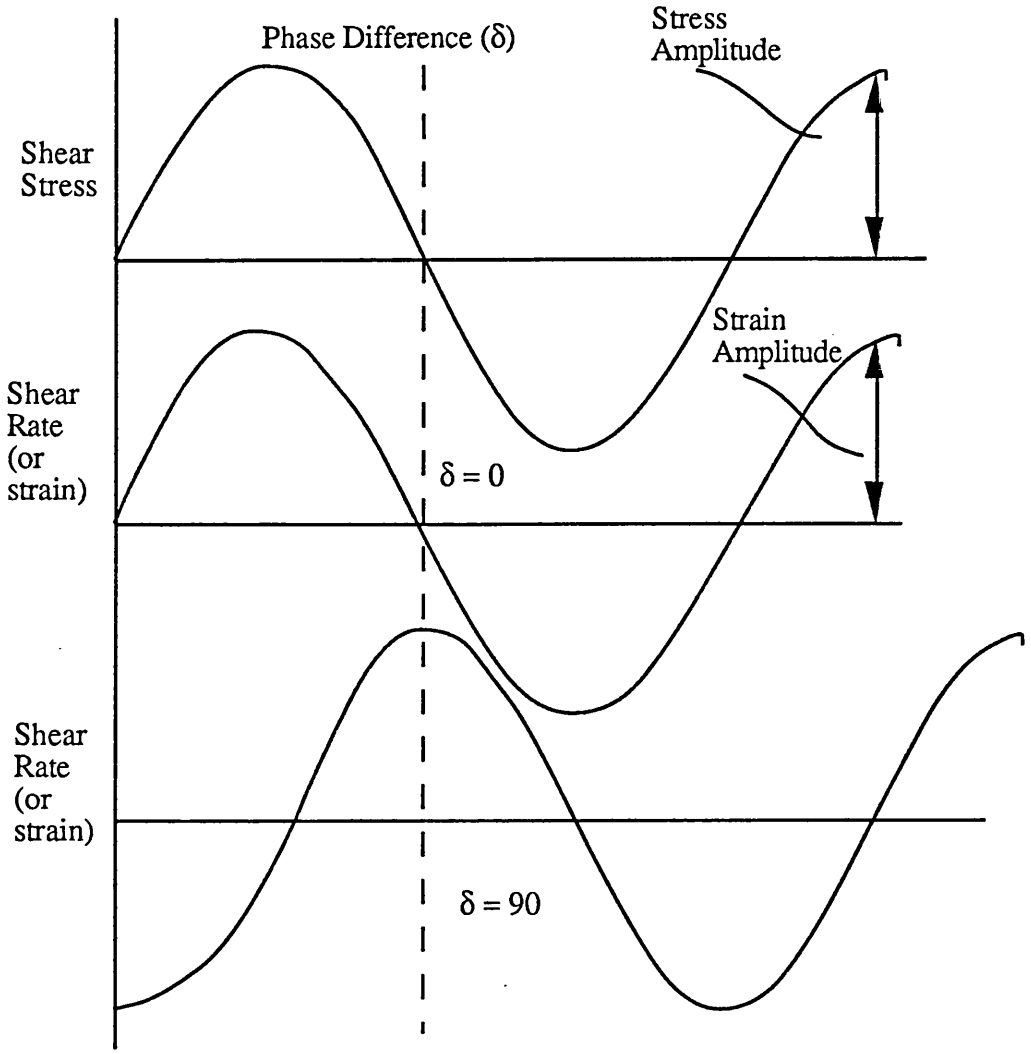
The phase angle difference and the strain amplitude can be resolved into two components - an in-phase and an out-of-phase (Figure 2.14).

Figure 2.14 Resolution of Phase Difference into In-Phase and Out-of-Phase Components.



G', the in-phase component, is the Storage Modulus (also known as the elastic component or the dynamic rigidity) and G", the out-of-phase component, is the Loss Modulus (also known as the viscous component).

Figure 2.13 A Phase Diagram of the Response of Purely Elastic and Viscous Bodies to the Application of a Shear Stress During an Oscillation Test.



Purely elastic behaviour	$\delta = 0^o$
Purely viscous behaviour	$\delta = 90^o$
=> Visco-elastic behaviour	$0^o < \delta < 90^o$

G" can also be expressed as a viscosity value :-

$$\eta' = \frac{G''}{\omega} \qquad 2\,27$$

where η' is the dynamic viscosity and ω is the frequency of oscillation in $rad.s^{-1}$ ($2\pi rad$ = 1 cycle).

G' and G" give an indication as to the elasticity and viscosity of the material under investigation. In general terms G' is time independent whilst G" is time dependent. Therefore during oscillation experiments with a high frequency of oscillation (e.g. 10Hz), the elastic nature of the material will dominate its overall behaviour because elasticity is an immediate phenomenon. At low oscillatory frequencies (e.g. 0.01Hz) the viscous nature of the material will dominate as it is given more time to flow.

The phase angle, δ (more often denoted as a tan δ value), describes the relative viscoelasticity of the sample. If the sample has a low phase angle (i.e. approaching zero) then the sample behaves predominantly as a elastic solid (tan δ also approaching zero). However if the phase angle is large (approaching 90^{o}) then the sample is behaving predominantly as a purely viscous fluid (tan δ approaching infinity). This means that a sample can be both highly elastic and viscous but behave more like a solid or a fluid depending on the phase angle measurement.

2.3 THE ASSESSMENT OF THE SPHERICITY OF GRANULES

The extrusion/spheronisation process of manufacturing spherical granules does not always yield perfectly round spheres. Any granules produced from the process that are not round are generally referred to as spheroids. Various methods have been used to determine the quality of spheres produced by a particular formulation under set process conditions as defined by their relative sphericity.

Chapman *et al.* (1988) assessed several methods of determining the sphericity of granules to establish whether such methods were precise enough to qualitate different batches of spheroids. These included a shape factor as determined by a $(\text{perimeter})^2/\text{area}$ measurement and measures of ellipticity and circularity as defined by Profitt (1982). Simple changes in tap density with increasing spheronisation time were also assessed to see if this alone would give an indication of sphere quality. Results demonstrated that all methods, whilst recording a difference in value between particles shaped as cylinders, dumb-bells and spheres, were too insensitive to highlight differences between various batches of near-round spheroids.

Another recent attempt to characterise the sphericity of pellets produced by extrusion/spheronisation was performed by Lovgren and Lundberg (1989). By measuring the maximum length and width of a spheroid using a video image they then calculated a value for overall sphericity :-

$$\text{Overall Sphericity (\%)} = \frac{1}{\sum(b.rf)} \cdot 100 \qquad 2.28$$

where b is the lower class limit and rf the relative frequency of the length to width ratio of the pellets as classified in a sample histogram.

To increase the numerical difference between samples with different roundness a modified equation for sphericity (S) was introduced :-

$$S\,(\%) = \frac{1}{\Sigma\,(b^2 \,.\, rf)} \,.\, 100 \qquad 2.29$$

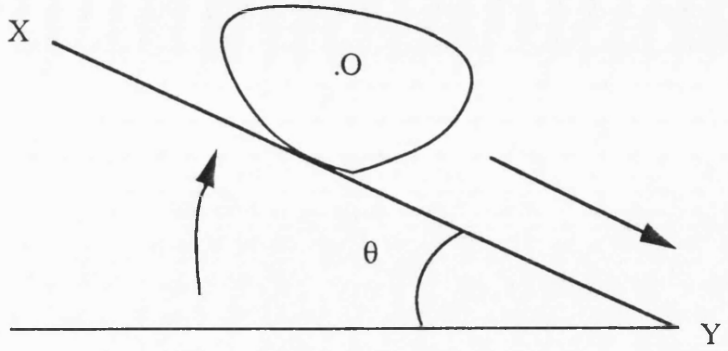
2.3.1 One Plane Critical Stability Measurement

A novel method of characterising the roundness of spherical granules produced by extrusion/spheronisation was developed by Chapman *et al.* (1988). The method assesses the roundness of spheroids by determining the theoretical angle of tilt of a plane that is required to make the spheroid roll.

The method relies on the determination of the centre of gravity of the particle that is produced from a two-dimensional drawing of the spheroid. This drawing is obtained digitally by using a light pen to draw around the image of each individual spheroid that is selected under a light microscope. Using 32 points to represent the outline of the sphere, the angle necessary to incline a plane such that the centre of gravity of the sphere moves outside the boundary of the particle is calculated using a computer. This angle is defined to be the 'one plane critical stability' (OPCS) angle and can be calculated as detailed below (Chapman *et al.*, 1988).

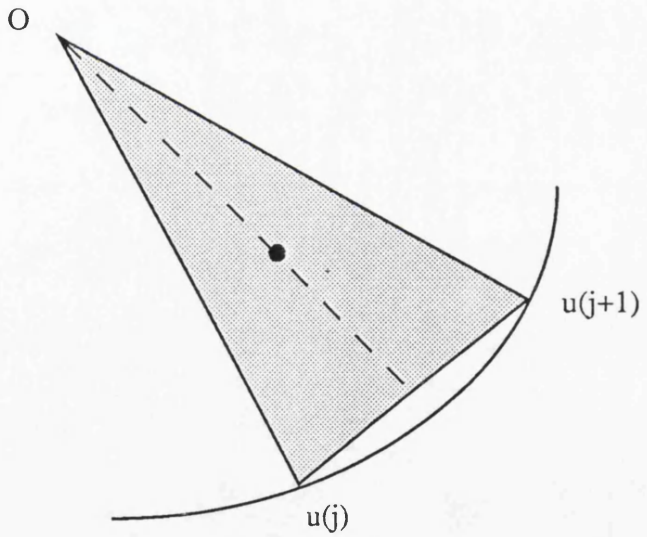
If an object is resting on a plane then the angle required to make the object move is the angle at which the centre of gravity of the particle profile moves outside the particle. The angle through which the plane has to be raised (θ) is defined as the one plane critical stability (Figure 2.15).

Figure 2.15 A Two-dimensional Image of an Object Rolling on a Plane at an Angle θ.



As plane XY is raised through angle Q then the object with a centre of gravity, O, will begin to roll. The two dimensional image has a total area, A, with a number of points on its perimeter, N, that divide the image into equal segments. Each segment is connected in a triangular fashion to the centre of gravity, O (Figure 2.16).

Figure 2.16 Diagram of Area Segment of Particle Profile.



Each segment of triangle is edged by the centre of gravity, O, and two points u(j) and u(j+1) which are assumed to be on a straight line. The point u(j) can be denoted as a point on the complex plane where :-

$$u(j) = x(j) + iy(j) \qquad 2.30$$

If all the points on the boundary, N, are considered then they have a mean of zero. Therefore

$$\sum_{J=0}^{N-1} x(j) = 0 \qquad 2.31$$

and

$$\sum_{J=0}^{N-1} y(j) = 0 \qquad 2.32$$

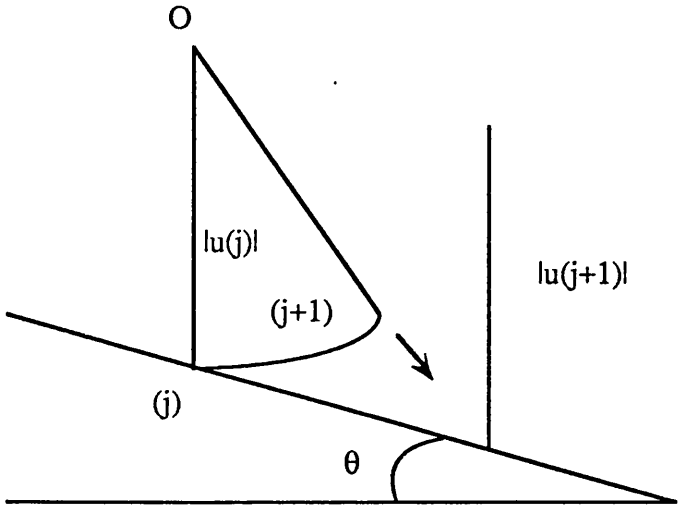
and since each triangle has an equal area then the centre of area for the sphere is at the origin.

Chapman *et al.* (1988) showed that for a granule rolling down a plane that is inclined at angle θ, then the critical angle can be given by:-

$$\theta = \text{arc sin max} \left(\left| \frac{u(j+1)| - |u(j)}{u(j) - u(j+1)} \right| \right) \qquad 2.33$$

where |u(j)| and |u(j+1)| can be thought of as the maximum heights that the granule will roll through whilst inclined at angle θ (Figure 2.17).

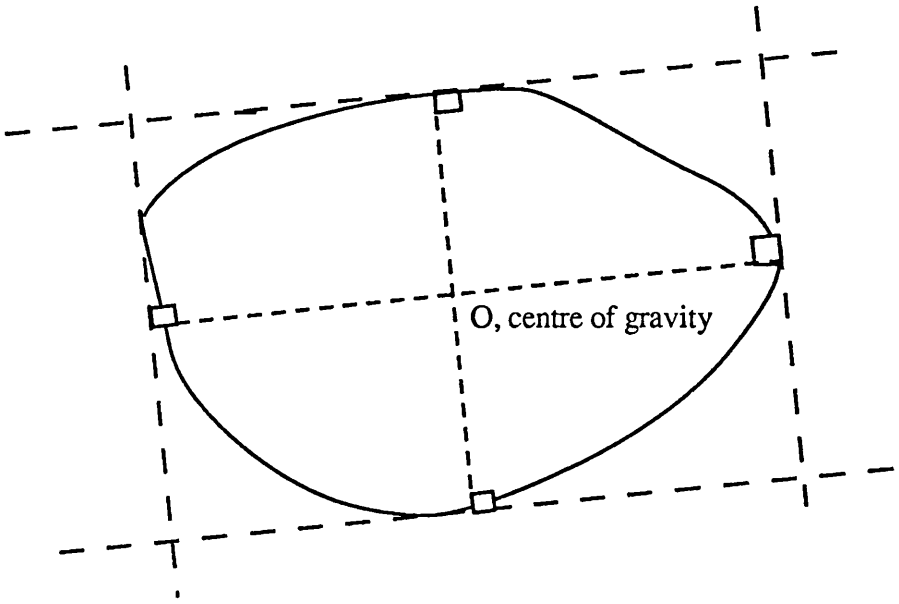
Figure 2.17 The Movement of the Centre of Gravity, O, of a Granule under an Inclined Plane θ.



In practice, the centre of gravity is initially calculated by drawing two parallel lines perpendicular to the two points furthest away from each other on the horizontal axis and two parallel lines perpendicular to the two points furthest away on the vertical

axis of the granule. The centre of the square so formed is then deemed to be the centre of gravity (Figure 2.18).

Figure 2.18 Determination of the Centre of Gravity of a Granule



For each image of granule stored on the computer a 32 point picture is recorded to determine how difficult it will be for the granule to roll. The greater the theoretical difficulty that the spheroid has of rolling, the greater the angle of inclination,θ, required to make the spheroid roll.

Given the various methods described above, OPCS values were used to determine the relative sphericity of granules prepared from various formulations that have been extruded and spheronised in the work subsequently undertaken (*cf.* Section 4.2).

Chapter 3

MATERIALS AND METHODS

3. MATERIALS AND METHODS

3.1 MATERIALS

Lactose

Lactose has been used as a water-soluble model drug in previous work undertaken to examine the rheology of wet powder masses undergoing extrusion and spheronisation (Harrison, 1982; Chapman, 1985). The particle size of lactose has been found not only to have an effect on the rheology of the wet powder mass but also on its ability to form good quality extrudate and spheres (Fielden *et al.*, 1989). Other workers have also found that the drug raw material source does affect the outcome of extrusion/spheronisation experiments (Timmins and Delargy, 1992). The work undertaken by Fielden *et al.* (1989) was found that a fine grade lactose (mean particle size 18.0μm) produced better quality extrudate and spheres than a coarse grade lactose (mean particle size 117.0μm) and that these differences could be quantified using the apparent shear stress *vs* shear rate relationship. To prevent any differences that may have been due to lactose particle size, a fine-grade lactose was used throughout the work (*Pharmatose*, alpha lactose monohydrate, 450 mesh, De Melkenindustrie Veghel bv [Batch Nos. 18109 + 19100]).The lactose had a number median particle size of 31μm as determined by using an equivalent spherical diameter method of analysis (Quantimet Image Analyser).

Microcrystalline Cellulose

Microcrystalline cellulose appears to be the best excipient available for allowing model drugs to successfully extrude and spheronise. This is due to both its plasticity and ability to act as a 'molecular sponge' when combined in specific amounts with water. Avicel PH101 (FMC Corporation [Batch numbers 6813 and 6002]) was employed as the standard microcrystalline cellulose since work has shown that it provides the best quality extrudate from a collection of commercially-available microcrystalline cellulose excipients (Raines, 1990). Avicel PH101 has an average particle size of 50μm (median weight diameter) and a moisture content of less than 5% (manufacturer's literature).

Water

Water acts as both a granulating agent and as a lubricant in the extrusion process. Conventional binders such as gelatin or starch are not usually necessary in the formulation of pellets manufactured via extrusion and spheronisation although they may be of use in other pelletisation methods (Harris and Ghebre-Sellassie, 1989). De-ionised water has been used throughout this work.

Water contents of mixtures have been expressed as either an amount in parts of the mixture or as a percentage of the total weight.

3.2 METHODS

3.2.1 Mixing

Prior to mixing all powders and liquids were measured by weight (Mettler PC1616 balance). For mixtures to be used in extrusion (1kg of dry powder + granulating fluid) a planetary mixer (Hobart A200) was employed. For mixtures to be used to prepare plugs of material for controlled-stress rheology (200g of dry powder + granulating fluid) a different planetary mixer (Kenwood Major) was employed. All powders were dry-mixed for 5 minutes at the lowest speed setting on the appropriate mixer. The selected amount of water was added and wet-mixed for 10 minutes, again at the lowest speed setting of the mixer employed. Occasional scrape-downs of mixer-bowl contents were required to ensure good water distribution and to provide homogeneous wet powder mixtures for extrusion and spheronisation. In addition, mixtures were double-sealed in polythene bags to allow for further water equilibration.

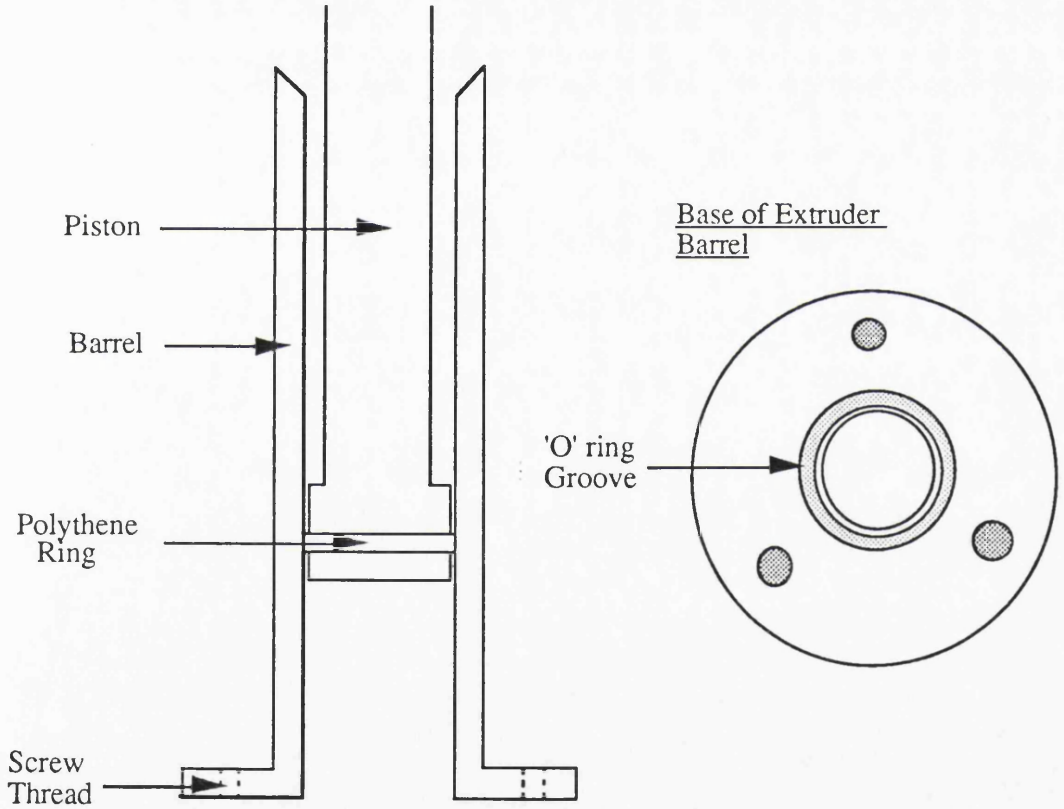
Work undertaken by Fielden (1987) and Raines (1989) has shown that for 5 : 5 : 6 lactose : microcrystalline cellulose : water mixtures, the force required for steady-state extrusion, in the first few hours since the mix was manufactured, is variable. Each formulation exhibited a "cut-off" equilibration time, after which the wet powder mix produced a constant steady-state force during extrusion. For Avicel PH101 the "cut-off" equilibration time was approximately 4 hours. To ensure complete water equilibration, mixes were stored for at least 12 hours (*i.e.* overnight) before extrusion or plug formation.

3.2.2 Extrusion of Wet Powder Masses

Design of the Ram Extruder

Figure 3.1 illustrates the hardened steel barrel and dies employed in this work. These are based on the designs of Ovensten and Benbow (1968). The barrel has an internal diameter of 25.4mm and a length of approximately 180mm, allowing for a 168mm displacement of a piston. The bottom end of the barrel is connected to a flange which allows the connection of interchangeable dies using three cap-headed socket screws. A rubber 'O'-ring seal is fitted between grooves on both the barrel and dies to ensure no water seepage.

Figure 3.1 The Extruder Barrel and Piston



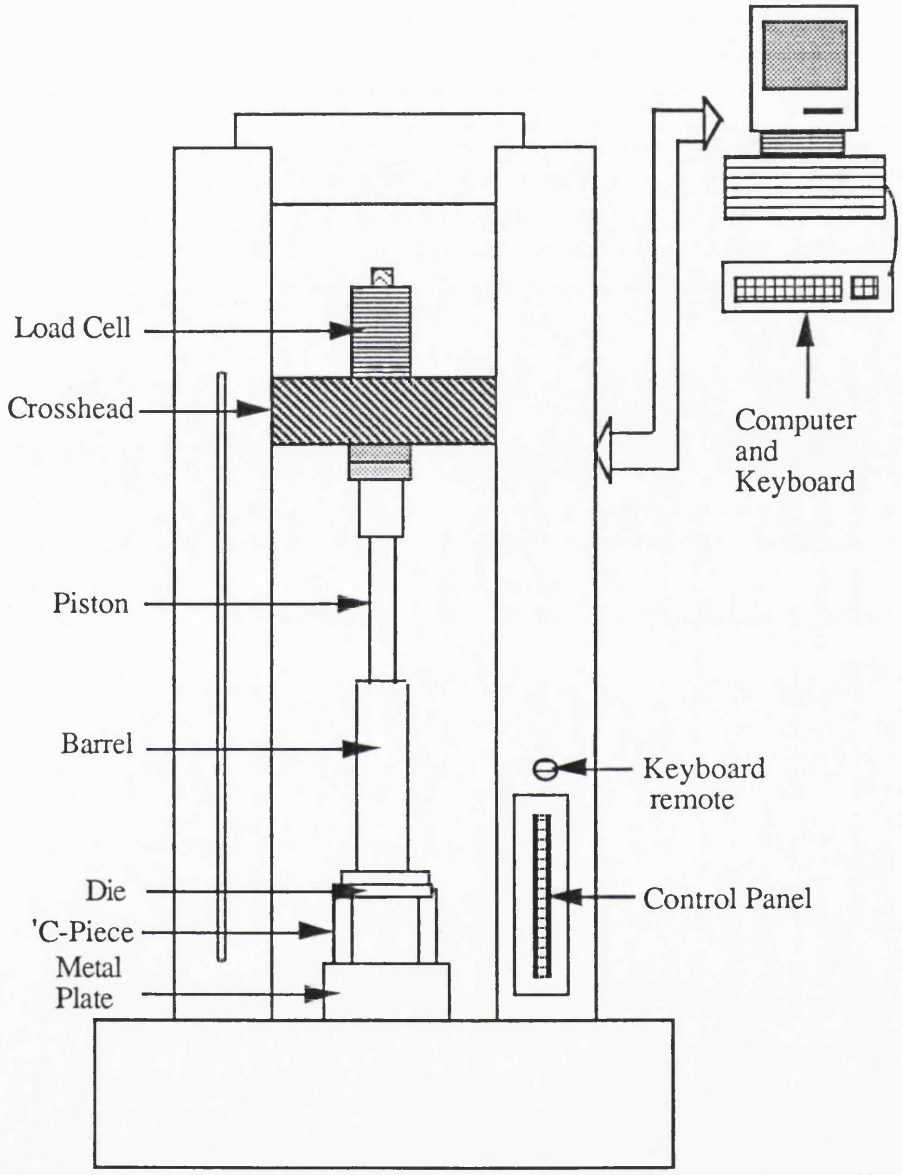
Hardened steel dies were manufactured to provide die diameters of 1, 1.5 and 2mm and die lengths of between 2mm and 16mm. These dies thus provided groups of dies that possessed length-to-radius ratios of 4, 8, 12 and 16 for each die diameter. In addition a die was manufactured with a blank end for the formation of wet powder plugs. The stainless steel piston allowed for a 1mm gap around the barrel and contained a polythene ring to provide a low friction seal to prevent powder and water from regressing back up the barrel during extrusion.

Raines (1990) has indicated that the fabric of the material used in the barrel and dies may alter the forces produced during extrusion. In particular, hardened steel dies appear to significantly increase forces produced in extrusion. This may be due to the surface texture of the material used in the barrel construction. However since the mixtures under investigation in this work contain proportionally less water than previously, hardened steel dies are the only ones which are capable of dealing with increased extrusion pressures due to formulation. Hence, in all the work undertaken, a hardened barrel and hardened dies were employed to reduce the risk of metal wear.

Experimental Method of Extrusion

To produce an extrudate, approximately 60g of the wet powder mass under investigation was packed into the barrel with a die attached by tapping the assembly against the bench. It was found that the application of hand-pressure on the contents of the barrel caused the displacement of water. During the course of an extrusion experiment, any amount of wet powder mass added to the barrel after the use of hand-pressure was not extruded but acted instead as an extension to the piston, since an area of forced flow had already been established 'downstream' of the packing region. The barrel and die set was placed on a hardened-steel 'C-piece' - an open cylinder shaped in a C shape which allowed the collection of extrudate, which in turn was placed on a hardened steel plate on the base of the extruder. The bottom of the piston was fitted to the top of the barrel and the top of the piston was placed inside a cup cylinder.This was in turn connected to the 50kN load cell of a materials testing machine (Lloyd MX50/1000) (Figure 3.2).This computer-controlled machine provided a variety of ram velocities (50, 100, 200, 400 and 800mm/min) and measured the extrusion force either against displacement or time.The results were then stored on standard $5^1/_4$inch floppy disks.

Figure 3.2 Schematic Representation of Lloyd MX50/1000 Ram Extruder with Barrel Assembly *in situ*



Force/displacement profiles obtained by extrusion are found to contain three regions - typically of the type shown in Figure 3.3.

a. The Compression Stage

The Compression Stage occurs whilst there is consolidation of the wet powder mass with only a small amount of applied pressure. This consolidation continues until the mass contains no more interstitial air, i.e. the apparent density value of the material

in the barrel has been reached. This density can be calculated by determining the weight and volume of material in the barrel and then comparing it to the apparent density values for each individual particle component in the material mix (Harrison, 1982). However extrusion can still occur even if all the air pockets within the mix have not been eliminated. Once the compression stage is complete, there is a rapid increase in the pressure exerted on the wet mass which as a result begins to flow.

The length of the Compression Stage is generally dependent on the amount of material added to the barrel. The moisture content of mix may vary the length of the compression stage, i.e. the greater the water content then the shorter the compression stage - since water is not compressible.

b. The Steady State Stage.

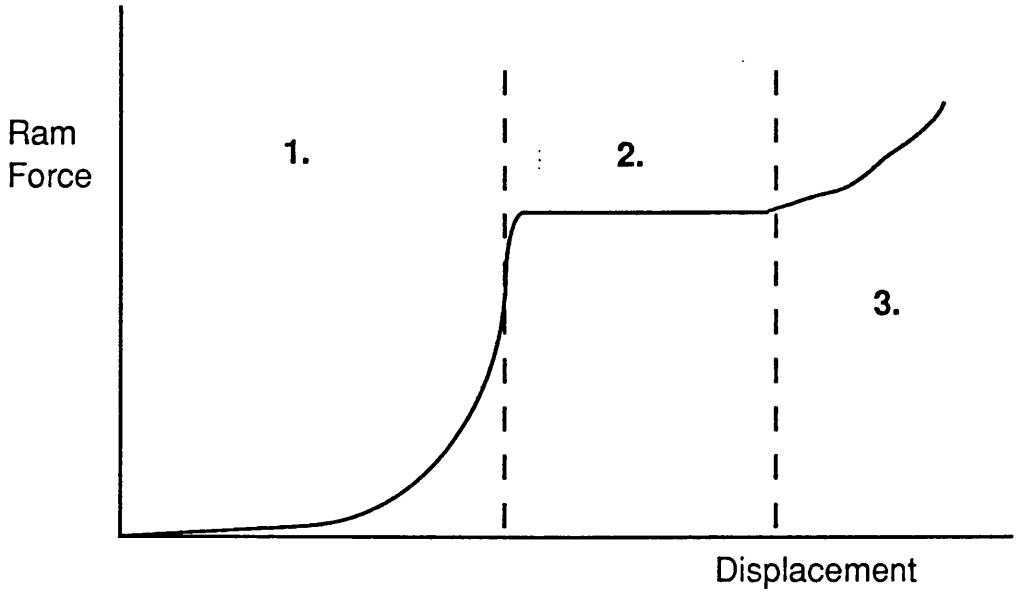
The Steady State Stage occurs after compression when the applied pressure required to maintain the flow of extrudate from the barrel remains constant provided that the flow patterns within both the barrel and die remain constant (Harrison, 1984). At the entry to the die, plastic deformation occurs throughout the whole cross section of the material. However once in the die-land, where no change in cross section is required, shearing of the sample is confined to a thin layer of the liquid phase near the die walls (Benbow, 1989). The actual pressure required to produce steady-state flow within the barrel is dependent on the size of the barrel itself, the formulation of the wet mass, the die length, die diameter, die design and the velocity of the piston (see Section 2.1). The extrusion force increases with increasing die length and extrusion rate and decreases with an increase in die diameter. Harrison (1984) has stated that the dependency of extrusion force on die length for wet powder mixes under investigation implies that the wall shear stress is dependent on the rheological properties of the wet powder mass and the experimental conditions selected.

The length of the Steady State Stage is dependent on a number of variables. A longer steady-state can generally be achieved by increasing the extrusion rate. Similarly an increase in the water content of the formulation can often increase the length of steady-state flow (if steady-state flow occurs.) If the extrusion profile exhibits a very long steady-state flow produced from a low extrusion pressure then this may suggest (at high lactose contents anyway) that the extrudate is too wet for spheronisation.

c. The Forced Flow Stage

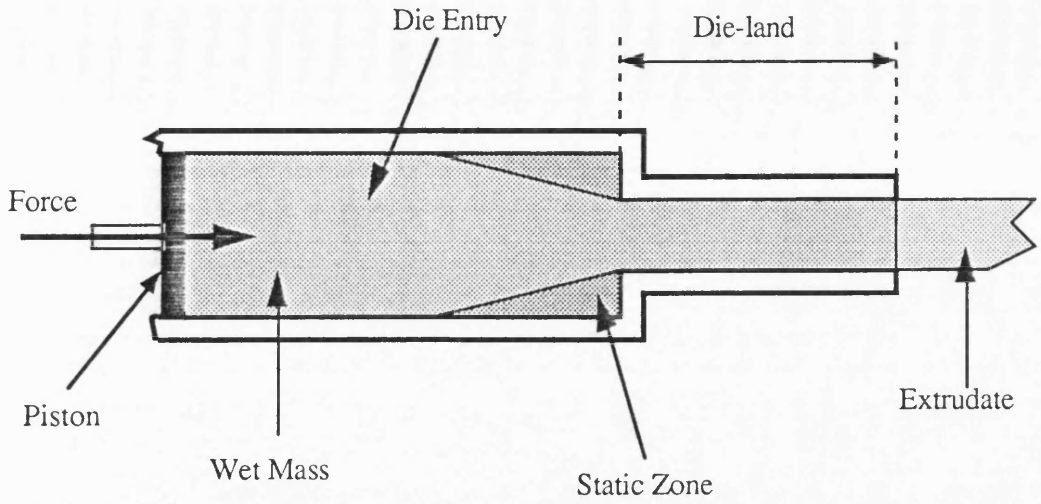
When the piston approaches the annular "static zone" of unextruded but compacted paste surrounding the entry of the die the pressure required to maintain flow through the die increases (Figure 3.4). This is the Forced Flow Stage which occurs when the flow pattern within the barrel changes from being axial to radial (Benbow, 1987). Further evidence of changes in material flow during the forced flow stage has been demonstrated by Harrison (1984) who showed that the angle of convergence, as indicated by the angle of entry of powder to the die, is affected during the forced flow stage. The extrudate obtained from this stage of the extrusion profile is of variable quality due to its non-uniform water content. This is due to the moisture gradient that is set up between the material in the barrel and the extrudate as the more mobile aqueous phase is pushed through the die by the increased pressure ahead of the particulate matter (Harrison, 1982). Hence any extrudate produced during the Forced Flow stage will always be wetter than the powder remaining in the barrel. Since the quality of extrudate is variable during the Forced Flow Stage, material for spheronisation is collected only during the Steady State Stage.

Figure 3.3 A Schematic Force/Displacement Profile



a. Compression Stage.
b. Steady State Stage.
c. Forced Flow Stage.

Figure 3.4 Diagram of a square-entry die with static zones

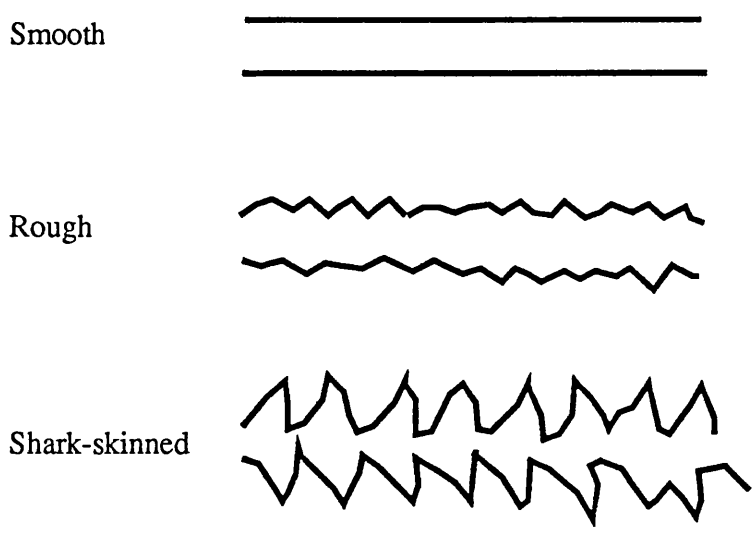


Pressure values recorded have been shown by previous workers to be very reproducible (Fielden, 1987; Raines, 1990). Results obtained from extrusion were used to construct graphs of apparent die wall shear stress *vs* apparent die wall shear rate for each formulation (*cf.* Section 4.1.2). These results demonstrate a 'flow curve' characteristic for each formulation extruded through each set of dies of a particular diameter. Results were also used to calculate the theoretical material yield stress, initial die wall shear stress and the die-land velocity factor for each formulation using the equations derived by Benbow *et al.* (1987).

The Quality of Extrudate

The extrudate produced from various formulations under different processing conditions is of variable quality. Apart from good, smooth extrudate, flow defects can occur to give the extrudate a rough or shark-skinned appearance (Figure 3.5). In general, these defects are found in wet powder masses extruded through short length-to-radius dies (the length being less or equal to the diameter of the die) or at high speeds of extrusion (Harrison, 1985). Surface defects may alter the ability of extrudate to form good quality spheroids and tend to increase the variation in particle size of the resulting spheres.

Figure 3.5 The Surface Quality of Extrudate



3.2.3 Manufacturing of Spheres

Preparation of Extrudate

The extrudate used for spheronisation was prepared using dies with a length-to-radius ratio of 8 (e.g. a 1mm diameter by 4mm length die) and a standardised ram speed of 100mm/min. Approximately 4 barrelfuls of wet powder mass were required to collect 200g of extrudate which was collected in polythene bags attached to the 'C-piece' and sealed until required. Extrudate was only kept until a sufficient quantity had been generated to begin immediate spheronisation.

Method of Spheronisation

The spheroniser used throughout the work was an 22.5cm diameter spheroniser (G.B. Caleva) with a radially cut spheroniser plate (Figure 1.5) The speed of spheronisation was kept constant at 1000rpm and was checked occasionally using an optical tachometer. The load was kept constant at 200g, which is low for the size of spheroniser employed. These parameters have all been assessed previously to be near the optimum for the spheroniser employed (Chapman, 1985).

The residence time of extrudate in the spheroniser was varied and set at time intervals of 20 seconds, 1, 2, 5 and 10 minutes. A residence time of 20 minutes was used occasionally if it was felt the extrudate was slightly dry and required a longer residence time to produce spheroids.

Drying of Spheres

Spheres collected from the spheroniser were dried for 30 minutes at a temperature of 60°C in a laboratory fluid-bed dryer (PRL Model FBD/L70) to ensure a constant moisture content. The spheres were then sealed and labelled in polythene bags for storage.

3.2.4 Methods of Analysis of Spheres

Sieve Analysis

A nest of sieves was selected to give the maximum separation of spheres into different particles sizes. Sieving was performed for 10 minutes using British Standard sieves (B.S.410, 1976) on an Endecote sieve shaker. Those sieves chosen were based on the approximate size of spheres produced by spheronisation and were not restricted to those following a $\sqrt{2}$ progression. The results from sieve analysis were used to determine the median weight diameter size of the spheres.

One Plane Critical Stability Analysis

Using the method developed by Chapman *et al.* (1988) the sphericity of particles produced by spheronisation was investigated (see Section 2.3.1). A standard sample of spheres from each batch under inspection was attached to a glass slide using adhesive tape and observed under a light microscope (Vickers M75 laboratory microscope). The image of each individual spheroid was super-imposed using a camera-lucida drawing tube (Vickers M173480) onto a graphics tablet which allowed a magnetic pen to be used to draw around it. This digitalised image was analysed by an Apple IIe Computer, which assessed the length and width of each sphere as well as calculating a perimeter value (P^2/A) and a roll value - the One Plane Critical Stability (OPCS). For each batch under investigation, 46 spheres were examined under the microscope and analysed to give a mean and standard deviation. This number of spheres was chosen to ensure that a representative sample for each batch had been selected and that the reproducibility of results was maintained (Chapman, 1985).

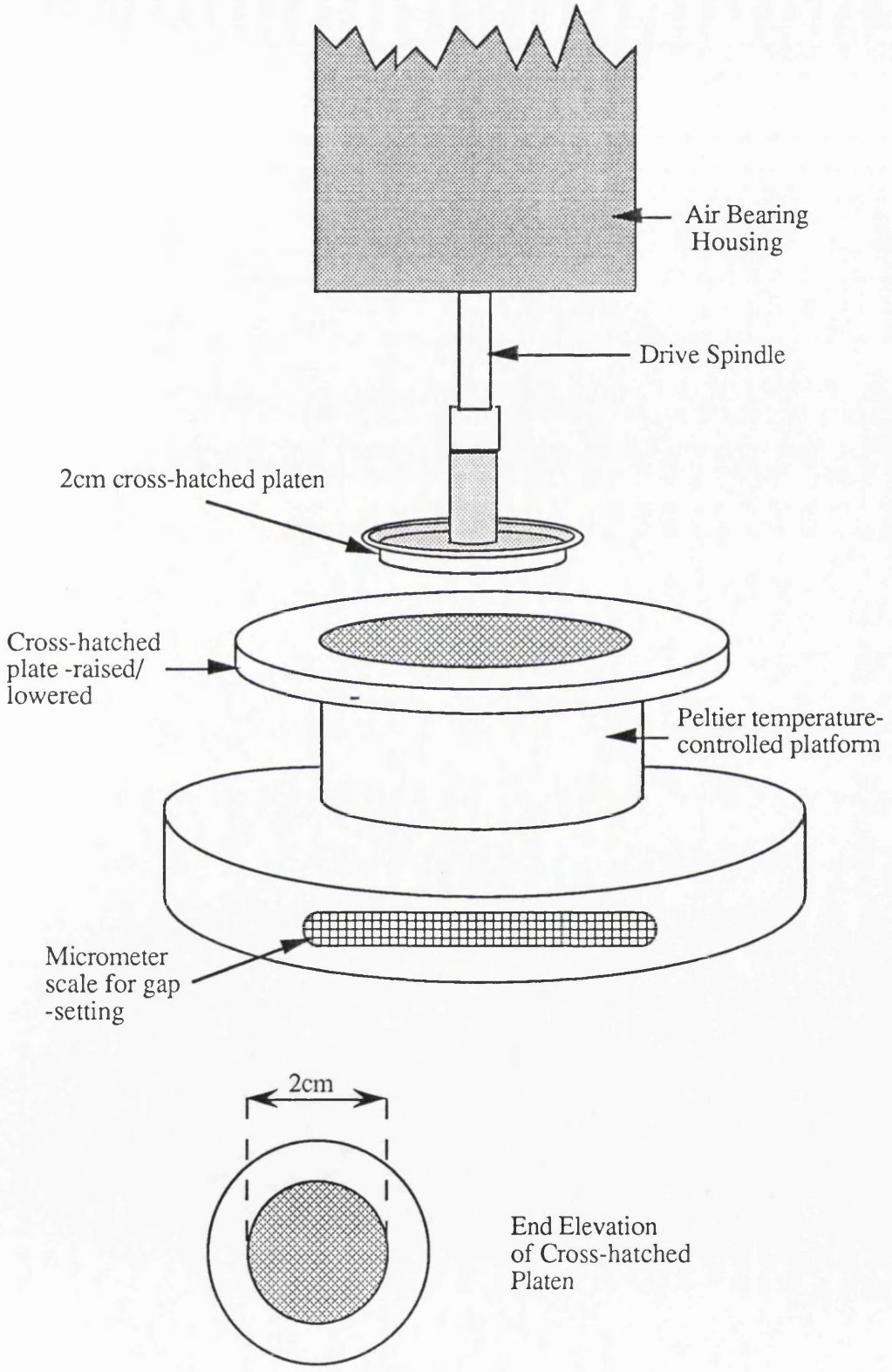
3.2.5 Controlled-Stress Rheometry

Although capillary rheometry has the advantage of exposing the wet powder mass to shear rates similar to those produced by commercial types of equipment, the method does have its disadvantages. As the amount of water in the mass has been reduced, the pressures involved with extrusion may, as a consequence, be higher than those encountered with 5 : 5 : 6 lactose : microcrystalline cellulose : water mixes - high enough to cause deformation to short length-to-radius ratio stainless-steel 1mm diameter dies. Shear stress *versus* shear rate profiles produced by capillary extrusion also take several days to construct so the technique is unsuitable for quality control purposes and time-consuming for formulation development. Consequently a quicker method of investigating the rheology of the wet mix has been developed and compared against the more established method of capillary rheometry. This involves the application of a controlled stress to the wet powder mass and examination of its response. The relative rates of shear applied to the samples are much lower than those applied by capillary extrusion ($< 1 \times 10^{-3}$ s^{-1} compared with $>600s^{-1}$). However the tests can be completed in a few hours and provide information on the visco-elasticities of the formulations under investigation.

Samples of wet powder mass for controlled-stress rheology were prepared using the extrusion equipment as described previously (Section 3.2.2). Samples of material (8.0g) were compressed against a blank die at a velocity of 50mm/min and a final compression force of 2kN. The resultant wet powder plugs, of approximately 11mm in height, were subjected to oscillatory and creep tests (Sections 5.1 and 5.2) using a controlled-stress rheometer (Carrimed CSL 500) (Figure 3.6).

The plugs were compressed between a 2cm platen and plate (stainless steel) both of which had a cross-hatched roughened end to ensure that the sample would be properly gripped. The depth of compression was kept at 0.90mm. The temperature was maintained at a constant 20°C using the Peltier temperature control system housed in the rheometer. A variety of torques were applied (up to a maximum of 50mNm) and oscillations used (0.01-10Hz) to investigate the samples. An optical displacement encoder located within the air bearing housing (which provides an air cushion for the upper platen) was used to accurately determine the amount of movement induced within each sample.

Figure 3.6 Diagram of the Carrimed CSL500 Rheometer and Platen (similar scales).



It was found that conventional shear stress *versus* shear rate profiles could not be produced by the rheometer due to the high viscosities of sample under examination. Therefore tests were limited to creep and oscillation.

Creep tests were performed to provide values of Compliance (J_O) for various formulations under different stresses (*cf.* Section 2.2). Oscillation tests provided information into the Storage, Loss and Complex Moduli (G' G" and G* respectively) of each formulation and to what extent the behaviour of the materials was either viscous or elastic (as determined from tan δ values) in nature (*cf.* Section 2.2).

3.3 PRELIMINARY CONTROLLED-STRESS RHEOMETRY RESULTS

Preliminary experiments were undertaken to assess the effects of various parameters on the reproducibility of results obtained from the wet powder samples during controlled-stress rheometry. Each sample was used only once and then discarded.

All plugs under investigation were kept at a constant temperature (20°C) using the Peltier temperature-control device of the rheometer. This was to prevent any physico-chemical effects on the plug of material from a rise in temperature and to prevent a reduction in the gap between the two parallel plates, estimated to be 0.5µm per degree Celsius (Carrimed manual, 1989).

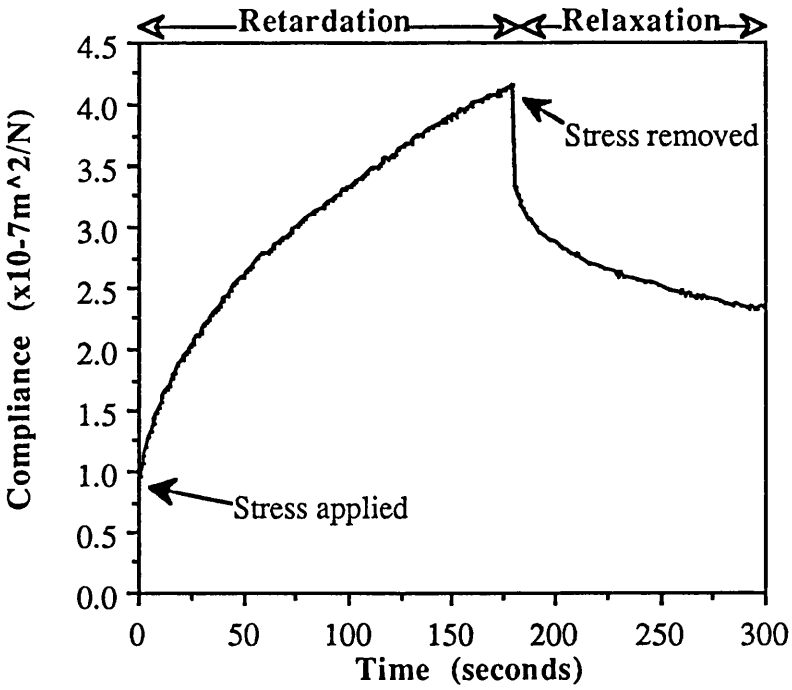
3.3.1 Preparation Of Plugs

The size of plugs prepared for the controlled-stress rheometer was limited by both the material itself and by the constraints of the measuring instrument. It was found to be very difficult to produce plugs of a mass less than 8.0g (approximately 11mm in height) due to breakage of the plugs as they were removed from the extruder barrel mechanism used to compact them (Section 3.2.2). Conversely plugs of a height greater than 19.0mm (approximately 13g of wet powder) could not be placed between the roughened parallel plates of the rheometer.

3.3.2 Creep Experiments - Interpretation of Results

The materials under investigation exhibit visco-elastic properties typified by the behaviour of a sample plug containing lactose (7) microcrystalline cellulose (3) and 4.0 parts water (28.6%) under an applied stress of 6366Nm^{-2} (equivalent to a torque of 10mNm) (Figure 3.7). The stress was applied for 3 minutes and the material was allowed to relax for 2 minutes.

Figure 3.7 The Influence of Time on the Compliance Value Obtained from a Mixture containing Lactose (7) and Microcrystalline cellulose (3) with 4.0 Parts Water (28.6%) under an Applied Stress of 6366Nm^{-2}.



Using mathematical modelling the computer attached to the rheometer can calculate values for instantaneous compliance, the purely elastic component, and for Newtonian viscosity, the purely viscous component, for both the retardation and relaxation curves. For measuring the instantaneous compliance the principle is to set the marker at the point where the curve intercepts the Y-axis. This modelling is required due to inertia in the platen and plate, which means that in reality the sample cannot move the instant the torque is applied, and to the delay in transmitting the signal across the test sample, which is determined by the speed of sound (Barnes *et al.*, 1989). The value calculated for Newtonian viscosity is dependent on the number of points used to determine the gradient of the slope. This means that the shear rate for each individual run is arbitrarily set and needs to be recalculated if separate runs are to be compared. The curved portion of the graph can be further analysed and, depending on its shape, fitted with elastic and viscous components. One set of elastic and viscous components in parallel is known as a Voigt Unit (*cf.* Section 2.2).

The graph in Figure 3.7 shows that the sample under stress during retardation quickly deforms to produce a steady, relatively low, shear rate. The maximum

compliance of the plug after 3 minutes is approximately 4 x $10^{-7}m^2N^{-1}$, which is very low. Other values of compliance generated by mathematical analysis (Table 3.1) confirm that the sample is very stiff.

Table 3.1 Automatic Retardation Results for a 7 : 3 : 4.0 Lactose : Microcrystalline cellulose : Water under an Applied Stress of 6366Nm^{-2}.

J_O - Instantaneous Compliance = 8.595 x $10^8m^2N^{-1}$

η_O - Newtonian Viscosity = 9.441 x 10^8Pa.s at a shear rate of 6.743 x $10^{-6}s^{-1}$.

Voigt Unit	Compliance (m^2N^{-1})	Retardation Time (sec)	Viscosity (Pa.s)
1	1.079 x 10^{-7}	32.62	3.024 x 10^8
2	3.655 x 10^{-8}	3.133	8.571 x 10^7

The maximum number of Voigt units that can be fitted to the retardation curve is 4. With some samples it is possible to extend the number of points for analysis almost indefinitely and still obtain an improving fit. If this is the case then the test material has a simple visco-elastic behaviour which can be described by a single Voigt unit. Alternatively, if it is found that there is no well defined optimum number of points and the results show the maximum number of Voigt units then the material has a complex structure and the computer is attempting to fit a line relaxation spectrum to what should really be regarded as a continuum. The automatic analysis of the creep curve gives a result which is to a certain extent arbitrary, that is it may well not be the exact optimum analysis, but it is an analysis which is repeatable for any given creep curve without operator intervention (Carrimed manual 1989).

For the materials under investigation, both automatic and manual analysis of retardation and relaxation curves consistently produced results which suggested that the plugs contained two Voigt units.

Voigt unit analysis is not only of use in determining compliance values but also the retardation times for each unit.The retardation time is the time taken for the strain in a material that obeys the Kelvin model to reduce to 1/e of its original equilibrium value after the removal of the stress (Barnes *et al.*, 1989). These retardation times give some measure of the total time it takes for the elastic components of a sample to relax under a given stress. Creep experiments are undertaken to ensure that the retardation times of all

Voigt units likely to be encountered have been reached. Hence creep experiments were performed with a retardation time of 3 minutes.

The same process is repeated for the sample during relaxation where there is some recovery of structure after the stress has been removed from the sample. The relaxation time has been described as the time taken for the shear stress of a fluid that obeys the Maxwell model to reduce to 1/e of its original equilibrium value on the cessation of steady shear flow (Barnes *et al.*, 1989). The creep experiments undertaken provided information on relaxation times for 2 minutes.

The Newtonian component of the sample material, η_0, has a high viscosity of approximately 1 x 10^9Pa.s. This gives the wet powder plug a viscosity similar to a material such as bitumen (Barnes *et al.*, 1989). The retardation times for both Voigt units (Table 3.1) are relatively short and there is a large elastic recovery in the sample as the stress is removed (Figure 3.7). Hence the wet powder plug behaves mostly as an elastic, solid-like material which will be difficult to deform and will not appear to flow, unless under very long time conditions. This is important since it suggests that wet extrudate or spheres produced from this sample mix will not deform under the combined stress of gravity and general process handling.

From the above results it would appear that if a shear stress is applied to lactose : microcrystalline cellulose plugs with varying water contents during a standard creep test, then it should be possible to measure the effect of the water on the elastic and viscous components of each sample, as defined by J_0 and η_0. This type of experiment has been undertaken in Section 5.1.

3.3.3 The Effect of Sample size on Rheological Parameters Determined by Creep Experiments

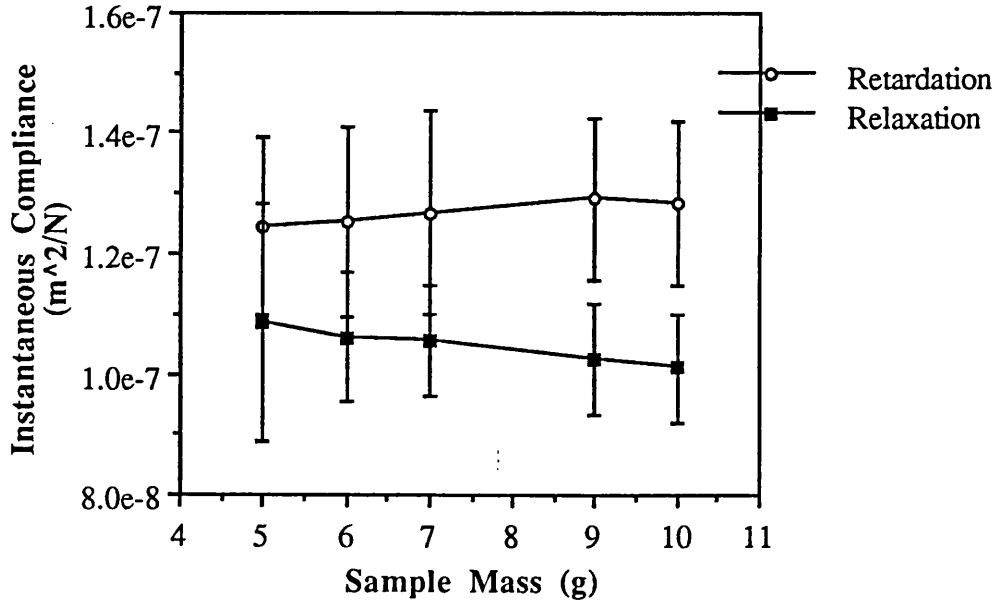
The effects of sample plug mass on the rheological parameters measured during a creep experiment were examined. As the creep test applies a stress across the entire plug then variation in the size of the plug may result in variation of the parameters recorded.

The Effect of Sample Size on Instantaneous Compliance

The instantaneous compliance is a measure of the elasticity of the experimental sample determined by its instant response to an applied stress (a strain over stress measurement). Variation in the size of the stress will vary the amount of compliance recorded. The effect of varying the sample size was examined to see if this affected the value of the instantaneous compliance recorded.

A formulation of lactose (7) microcrystalline cellulose (3) and 4.4 parts water (30.5%) was used to determine the effect of variation in the plug size on the value of instantaneous compliance (Figure 3.8). A stress of 6366Nm^{-2} was applied. The results contained in Figure 3.8 highlight that increasing the sample weight slightly increases the instantaneous compliance recorded during retardation. With an increase in sample size the amount of flow that occurs during the linear part of the creep test increases. Consequently during relaxation the magnitude of the instantaneous compliance decreases with increasing sample size.

Figure 3.8 The Effect of The Mass of a Sample Containing Lactose (7), Microcrystalline Cellulose (3) and 4.4 Parts Moisture (30.5%) on the Instantaneous Compliance Measured During A Standard Creep Test.



The Effect of Sample Size on Newtonian Viscosity

Newtonian viscosity is measured by the rheometer during a creep test when the response to the applied stress becomes linear with an increasing time during either retardation or relaxation. Variation in the applied stress will result in variation of the Newtonian viscosity (a stress over strain measurement). The effect of varying the sample size on Newtonian viscosity has been examined below.

The point at which the rheometer calculates the Newtonian viscosity varies with individual runs and therefore the shear rate at which the viscosity is calculated varies between individual runs. Consequently to be able to compare different runs of the same

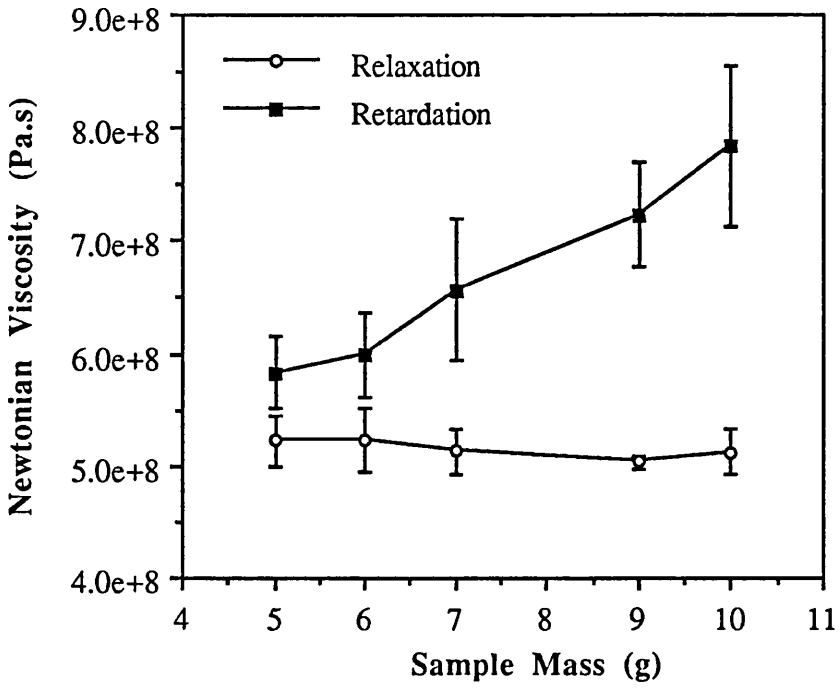
formulation at the same applied stress or to compare different formulations at the same applied stress a representative shear rate must be assigned to all runs. Once this shear rate has been assigned the viscosities of individual runs can be extrapolated from that recorded by the individual run to the value calculated at the standard shear rate. This should be possible because variations in shear rate are relatively small and there is a linear relationship between shear rate and Newtonian viscosity.

A formulation of lactose (7) microcrystalline cellulose (3) and 4.4 parts water (30.5%) was used to determine the effect of variation in the plug size on the derived value of Newtonian viscosity (Figure 3.9). The results contained in Figure 3.9 demonstrate that during retardation of the samples using a standard applied stress ($6366 Nm^{-2}$) an increase in the mass of the sample plug increases the Newtonian viscosity measured. However during the relaxation of the sample Newtonian viscosities are approximately linear, despite variations in the amount of 'flow' that each sized plug sample has undergone.

Similar effects can be demonstrated when various sized samples of other formulations are subjected to the same standard creep test as used above (Figures 3.8 and 3.9). The effects of varying sample mass on the instantaneous compliance, J_O, and Newtonian viscosity, η_O, were determined for a formulation containing lactose (7), microcrystalline cellulose (3) and 4.8 parts water (32.4%) [Figures 3.10 and 3.11 respectively].

Investigation into variously sized samples containing lactose (8), microcrystalline cellulose (2) and 3.0 parts water (23.1%) were also conducted using the standard creep experiment described previously (Figures 3.12 and 3.13).

Figure 3.9 The Effect of The Mass of a Sample Containing Lactose (7), Microcrystalline Cellulose (3) and 4.4 Parts Moisture (30.5%) on the Newtonian Viscosity Measured During A Standard Creep Test.



The Newtonian viscosity in Figure 3.9 was calculated during Retardation at a standard shear rate of $1.121 \times 10^{-5} s^{-1}$ and during Relaxation at a standard shear rate of $1.276 \times 10^{-5} s^{-1}$. These values of shear rate are approximately in the middle of shear rate values encountered during the experiment. However as the moisture content increases the shear rate values become lower as the formulations become less viscous and flow more easily. Consequently the Newtonian viscosity recorded for Figure 3.11 was calculated at a standard shear rate of $8.614 \times 10^{-6} s^{-1}$ during Retardation and at a standard shear rate $1.563 \times 10^{-6} s^{-1}$ during Relaxation.

With a change in the solid components in the formulation studied (Figure 3.13) a change in the shear rate recorded will again vary.

Figure 3.10 The Effect of The Mass of a Sample Containing Lactose (7), Microcrystalline Cellulose (3) and 4.8 Parts Moisture (32.4%) on the Instantaneous Compliance Measured During A Standard Creep Test.

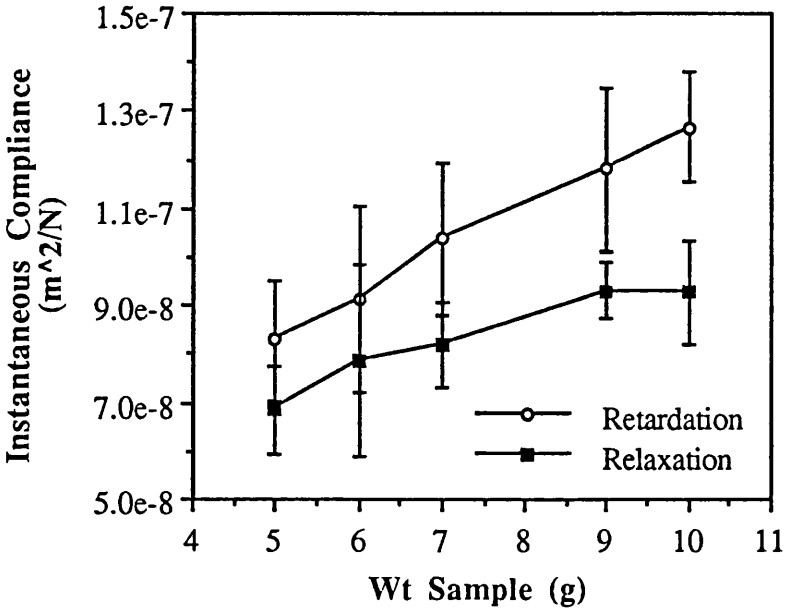


Figure 3.11 The Effect of The Mass of a Sample Containing Lactose (7), Microcrystalline Cellulose (3) and 4.8 Parts Moisture (32.4%) on the Newtonian Viscosity Measured During A Standard Creep Test.

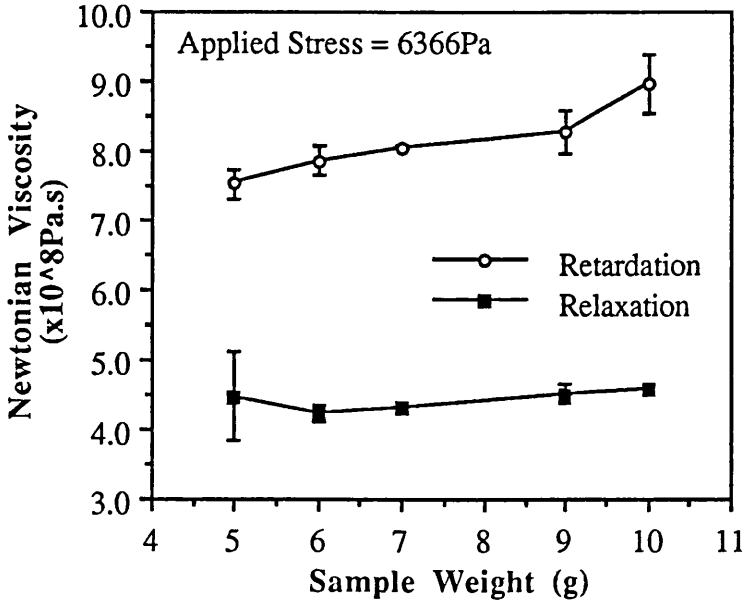


Figure 3.12 The Effect of The Mass of a Sample Containing Lactose (8), Microcrystalline Cellulose (2) and 3.0 Parts Moisture (23.1%) on the Instantaneous Compliance Measured During A Standard Creep Test.

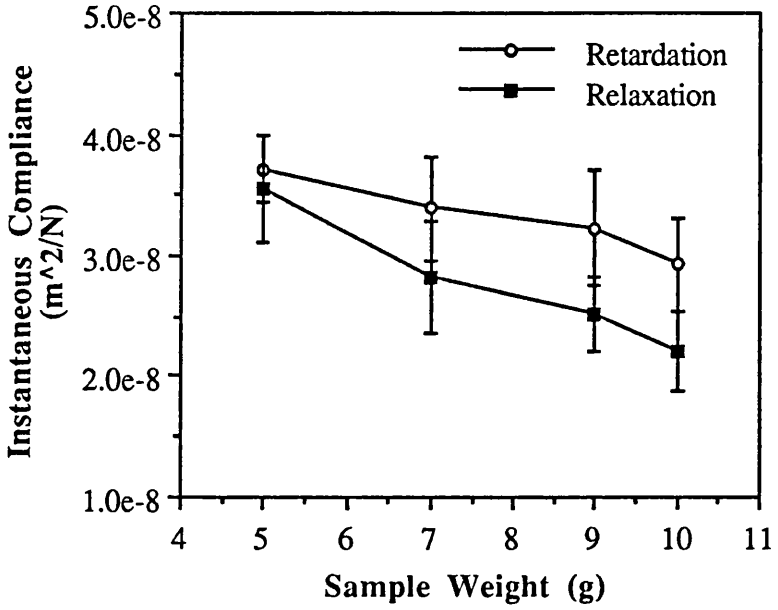
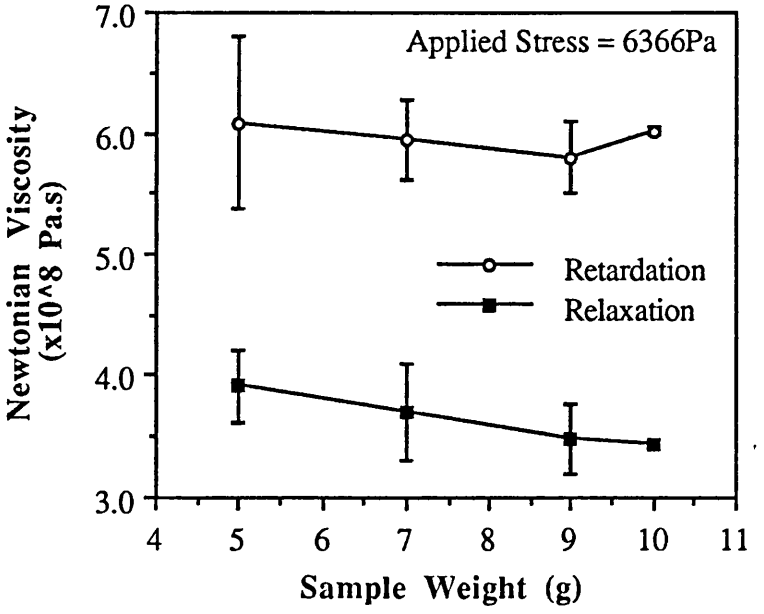


Figure 3.13 The Effect of The Mass of a Sample Containing Lactose (8), Microcrystalline Cellulose (2) and 3.0 Parts Moisture (23.1%) on the Newtonian Viscosity Measured During A Standard Creep Test.



The Newtonian viscosity in Figure 3.13 was calculated at a shear rate of 1.137 x $10^{-6}s^{-1}$ during Retardation and at a shear rate of 1.926 x $10^{-6}s^{-1}$ during Relaxation. Results from the application of a stress to various samples of plugs containing lactose : microcrystalline cellulose and water demonstrate that sample size alters the response of the plug to the applied stress. There does not appear to be any correlation between the mass of the sample and the rheological parameters examined that is upheld for all formulations studied. In order therefore to compare samples of different formulations it is necessary to standardise the sample size and to subject samples to the same applied stress. For subsequent experiments a sample size of 8.0g was used as standard.

3.3.4 Oscillation Experiments - Interpretation of Results

Experiments using oscillatory stresses to examine the behaviour of materials can be used to compare samples where creep experiments would be inappropriate.

Effect of Torque

In oscillation experiments, a standard sweep of torque forces (1-20mNm) was applied to each plug of wet powder mass under investigation at a variety of oscillatory frequencies (0.01, 0.1, 1 and 10Hz). After each oscillation the plug was discarded and replaced with a new one.

A wet powder plug containing lactose (7) microcrystalline cellulose (3) and 4.2 parts water (29.5%) oscillated at 0.01Hz exhibits the properties displayed in Figures 3.14a and 3.14b. The sample possesses both high G' (the storage modulus) and G" (the loss modulus) values which means that it is both highly elastic and viscous, although G' values are higher. It also has a relatively low tan δ value (the ratio of G' to G") which implies that it acts predominantly as an elastic body. At low torque values G' and G" begin to rise as the optical encoder on the rheometer begins to resolve some movement in the sample. As the applied torque is increased the sample passes through a short linear region of visco-elastic response (between approximately 5 and 7mNm). Above this region G' and G" both begin to fall as there is some structure breakdown due to the plug becoming more fluid-like and beginning to flow. In this area G' is affected more than the G" and hence the tan δ value increases (Figure 3.14b). This implies that although the plug is still predominantly elastic in structure, it has increasing viscous behaviour. G*, the complex modulus, is a measure of the ratio of stress amplitude to strain.

Figure 3.14a The Effect on the Storage Modulus (G') and Loss Modulus (G") of a 1-20mNm Torque Sweep Applied to a Lactose (7) and Microcrystalline Cellulose (3) Mixture Containing 4.2 Parts Water (29.5%) under an Oscillatory Frequency of 0.01Hz.

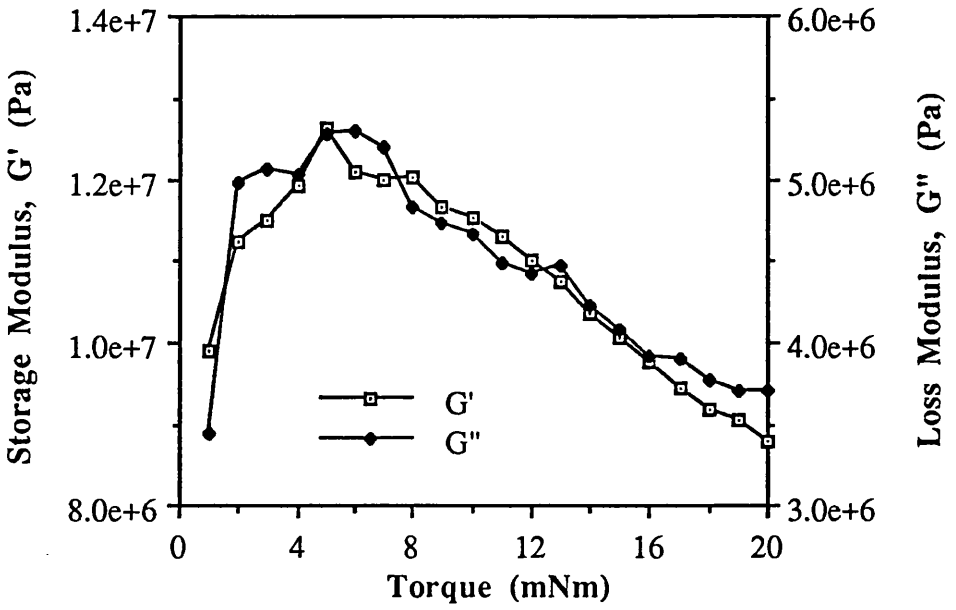
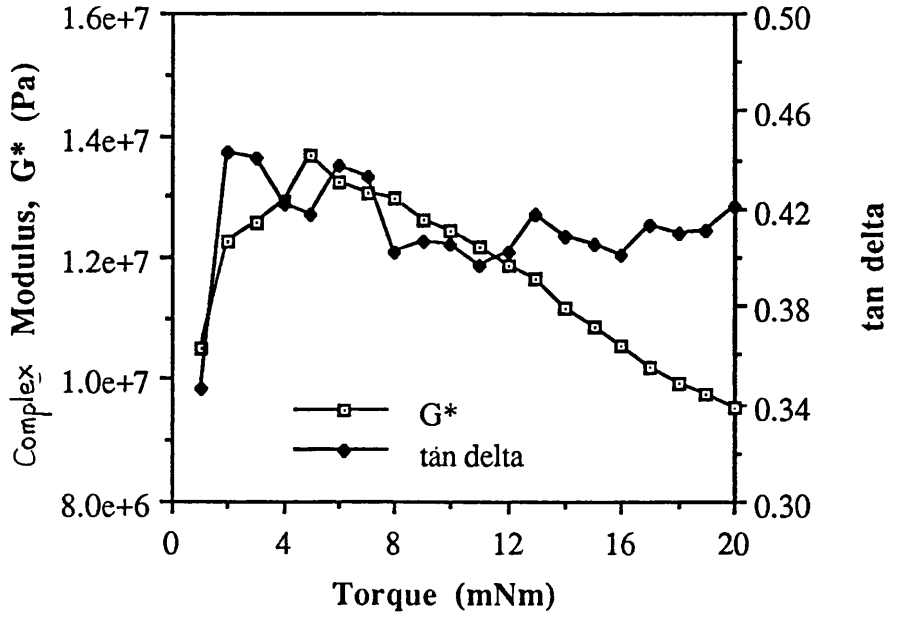


Figure 3.14b The Effect on Complex Modulus (G*) and Tan Delta value of a 1-20mNm Torque Sweep Applied to a Lactose (7) and Microcrystalline Cellulose (3) Mixture Containing 4.2 Parts Water (29.5%) under an Oscillatory Frequency of 0.01Hz.



As the applied stress increases the amount of strain produced in the sample greatly increases as the structure within the sample begins to break down. Hence there is a sharp fall in the value of G* with increasing torque.

Effect of Oscillatory Frequency

The general properties exhibited by the plug above under a torque sweep at 0.01Hz oscillatory frequency are repeated for all lactose : microcrystalline cellulose : water mixtures under investigation. The properties also hold true when a torque sweep is exerted over different oscillatory frequencies of 0.1, 1 and 10Hz.

As the frequency of oscillation increases the effects of the applied torque on the sample plug are diminished and both G' and G" values are affected. Figures 3.15a and 3.15b demonstrate the effect of varying the oscillatory frequency of a constant applied torque on a sample of a 7 : 3 : 4.6 lactose : microcrystalline cellulose : water formulation.

Figure 3.15a The Effect on G' and G" of a 10-0.01Hz Logarithmic Frequency Sweep on a Lactose (7) and Microcrystalline Cellulose (3) Mixture Containing 4.6 Parts Water (31.5%) under an Applied Torque of 4mNm.

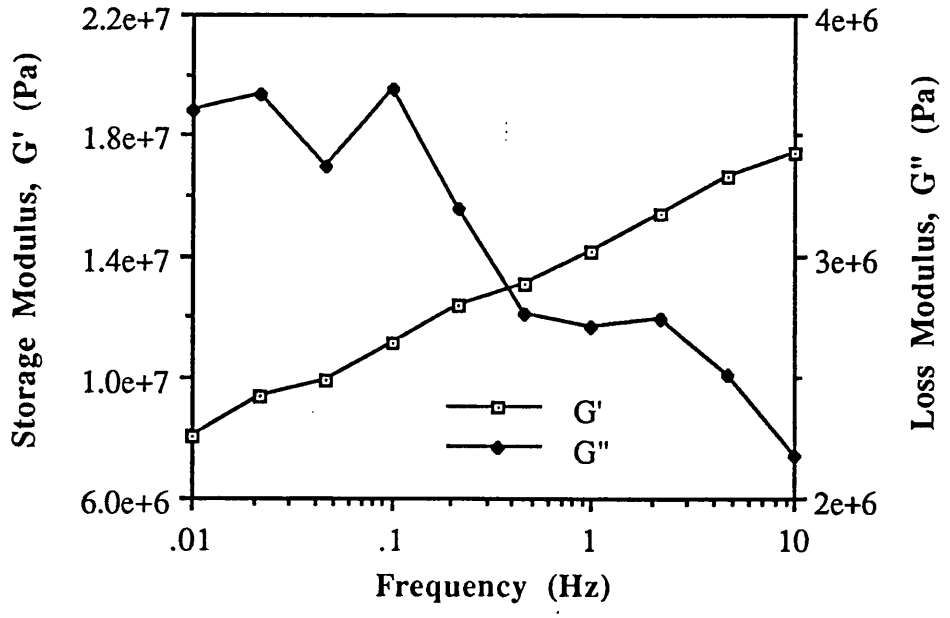
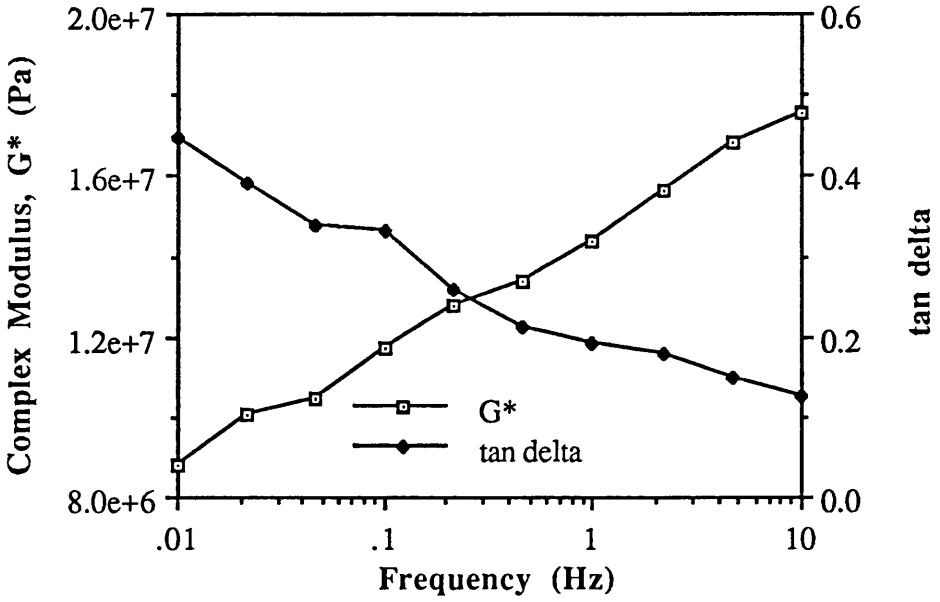


Figure 3.15b The Effect on G* and Tan Delta of a 10-0.01Hz Logarithmic Frequency Sweep on a Lactose (7) and Microcrystalline Cellulose (3) Mixture Containing 4.6 Parts Water (31.5%) under an Applied Torque of 4mNm.



Since the in-phase component, G', acts immediately, its value increases uniformly with a logarithmic increase in oscillation frequency, i.e. an increasing frequency of oscillation makes the sample appear more elastic in nature. Conversely G", the out-of-phase component, is time dependent and falls uniformly with a logarithmic increase in oscillatory frequency, i.e. the sample appears to be less viscous in nature. The net effect of these actions is a reduction in the tan δ value. Therefore as the oscillatory frequency increases, the behaviour of the wet powder plugs becomes even more solid-like with elastic behaviour dominating. This is reflected also in the value of the complex modulus, G*, which increases as the frequency increases, i.e. the applied stress produces far less strain at high oscillatory frequencies as compared to low frequencies.

The region of linear visco-elastic response is not constant over varying oscillatory frequencies or water contents. With an increasing frequency the linear region occurs at lower torques than the linear region obtained from the sample shown in Figure 3.14. Similarly an increasing water content produces linear visco-elastic regions at lower torques than drier formulations. For many samples the linear region is not represented in torque sweeps of 1-20mNm. At torques near or below 1mNm, due to the extremely viscous nature of the samples under investigation, the resolution of the rheometer becomes questionable and the reproducibility of the responses is impaired.

The movement of the linear visco-elastic region makes direct comparisons between samples of different water contents more difficult, particularly when subjected to varying frequencies under constant torque. Hence only simple torque sweeps have been performed at constant frequencies for comparator studies.

3.3.5 The Depth of Contact Between the Rheometer Plates

Initial experiments were undertaken to establish the effect of varying the depth of contact to which the cross-hatched platen and plate were immersed to ensure a good firm contact with the sample.

Figures 3.16a and 3.16b show graphs of the effect on G' and G" for a 8 : 2 : 3.6 lactose : microcrystalline cellulose : water mixture immersed at different heights between the platen and plate of the rheometer. The experiments were undertaken at an oscillatory frequency of 1Hz. It can be seen from Figure 3.16a that as the sample becomes less embedded between the platen and plate of the rheometer the value the G' value recorded becomes reduced. However for depths of immersion of 0.70mm or greater there is little effect on G' values around the region of linear visco-elasticity (at about 2-4mNm). G" values in Figure 3.16b follow a similar pattern where differences between the depths of immersions become apparent as the torque applied moves out of the linear visco-elastic region at about 2-4mNm and as the depth of immersion falls below 0.70mm.

Figure 3.16a The Effect of Depth of Contact on the Storage Modulus (G') Value for a Lactose (8) and Microcrystalline Cellulose (2) Mixture Containing 3.6 Parts Water (26.5%) recorded during the Application of Various Torques.

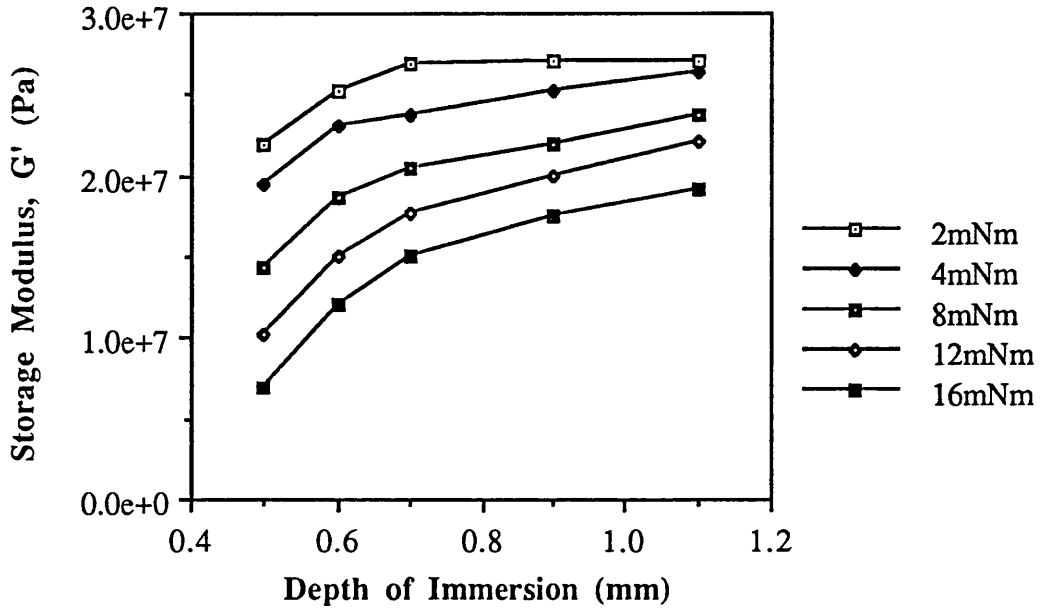
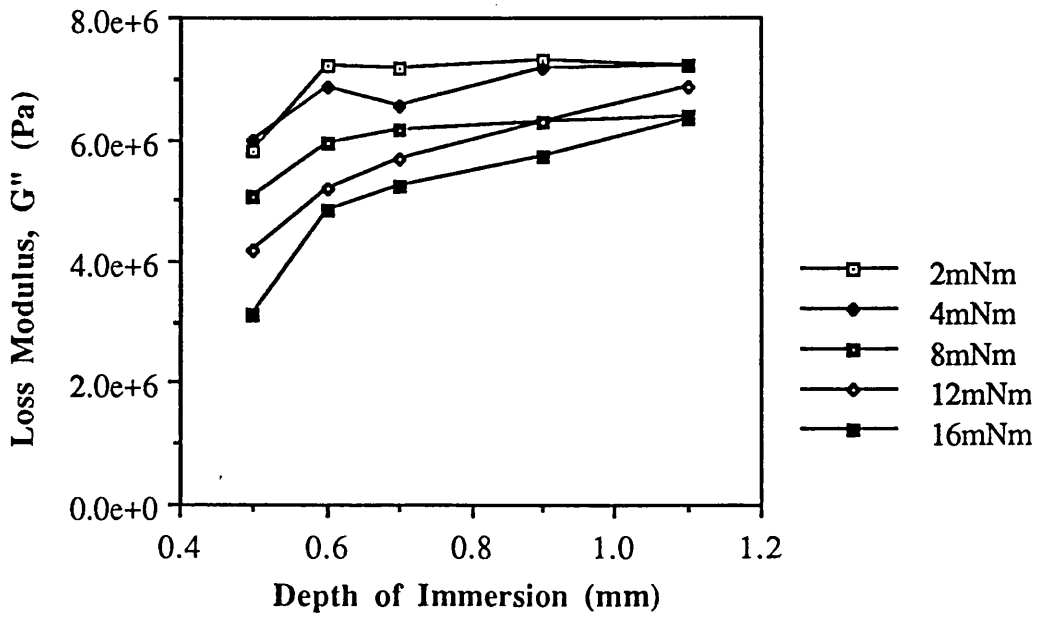
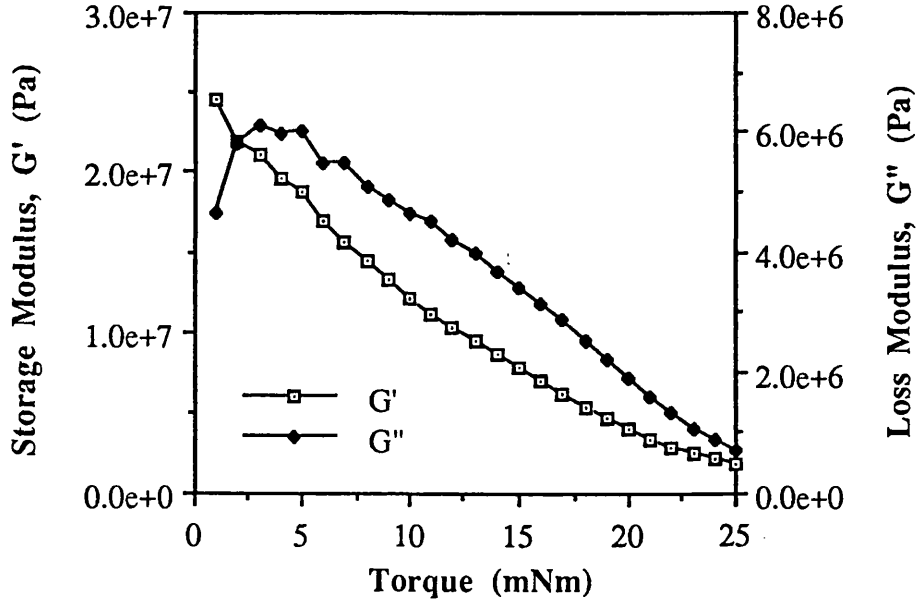


Figure 3.16b The Effect of Depth of Contact on the Loss Modulus (G") Value for a Lactose (8) and Microcrystalline Cellulose (2) Mixture Containing 3.6 Parts Water (26.5%) recorded during the Application of Various Torques.



The reason for the sudden fall-off in both G' and G" values when the depth of immersion is reduced below 0.70mm can be deduced if a complete torque sweep from 1-25mNm is analysed (Figure 3.17). This sweep shows a catastrophic fall in G' and G" as the torque is increased suggesting that there is shear breakdown in the area of the sample that is in direct contact with the upper platen. Further evidence of this shear breakdown is provided by the rheometer. When the applied sine wave of oscillatory torque produces a square or otherwise deformed (e.g. low amplitude) wave of response from the sample then there is a likely to have been shear breakdown within the sample. This is a useful indicator as to whether a particular torque sweep has been successfully applied.

Figure 3.17 The Effect On Storage Modulus (G') and Loss Modulus (G") of a 1-25mNm Torque Sweep Applied at an Oscillatory Frequency of 1Hz on a Lactose (8) and Microcrystalline Cellulose (2) Mixture Containing 3.6 Parts Water (26.5%) Immersed to a Contact Depth of 0.50mm.



Conclusions

From the results above both the amount of torque applied and depth of immersion of a sample between the rheometer platen and plate affect the response of that sample to an oscillatory torque sweep. To minimise the differences between samples, G' and G" values can only be compared when expressed as values obtained from the region of linear visco-elastic response. If this is not possible (because varying

the formulation alters the linear region) then samples should be compared at the lowest possible torque values available, i.e. below 10mNm. Similarly samples should be immersed between the platen and plate of the rheometer at least 0.70mm to ensure that there is firm contact between the rheometer and the sample.

In practice a gap of 0.90mm was established to ensure firm contact between the rheometer and the experimental sample.

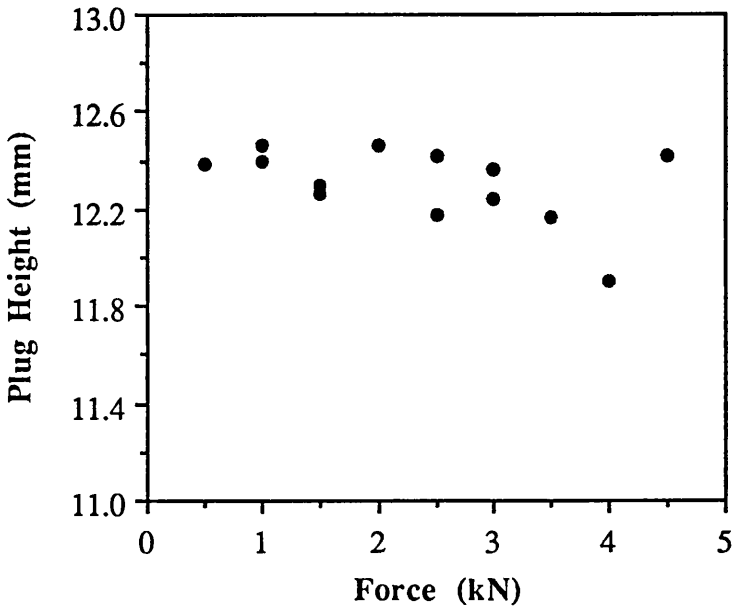
3.3.6 The Effect of Compression Force on the Visco-elasticity of Experimental Samples.

To prepare plugs of the various lactose : microcrystalline cellulose : water formulations of standard consistency for controlled-stress rheometry experiments, the formulations were first compressed into reproducibly sized samples to eliminate any trapped air within the wet mass. This compression was performed in a hardened steel barrel under pressure from a ram extruder. The effect of compression force on the visco-elasticity of the sample as measured by controlled-stress oscillatory rheometry was examined to determine whether compression force affected visco-elasticity.

The compression force was varied between values of 0.5kN and 4.5kN. A force of 0.5kN was the minimum required to provide an intact sample that did not possess visible air pockets. A force of 4.5kN was the maximum applied to the sample to prevent fatigue in the extruder barrel and die from higher forces and also to prevent any possible loss of moisture from the sample due to the high compression force applied.

The effect of compression force on the height of the plug of material obtained after compression was examined. 8.0g samples of a 7 : 3 lactose : microcrystalline cellulose mixture containing 4.4 parts moisture (30.5%) were used to determine whether applying a greater force to the material in the extruder barrel resulted in a more compressed, i.e. smaller, plug (Figure 3.18).

Figure 3.18 The Effect of Varying the Compression Force on the Plug Height Obtained from a Mixture of Lactose (7) and Microcrystalline Cellulose (3) Containing 4.2 Parts Moisture (30.5%).



The results contained in Figure 3.18 demonstrate that plug height is not affected by the force of compression applied to the material in the extruder barrel. Therefore the force of compression is not only sufficient enough to expunge the trapped air within the plug but also to cause an elastic rebound within the sample as the force is removed. At the compression forces studied this elastic response did not result in the loss of moisture from the plug of material during compression. Such moisture loss could have occurred through leaks in the teflon seal on the extruder piston or through the gap between the extruder barrel and the attached die (*cf.* Section 3.2.2).

The effect of varying the compression force on the visco-elastic parameters of a 7 : 3 lactose : microcrystalline cellulose mixture with a 4.4 parts water content (30.5%) was examined to determine whether a variation in the force of sample preparation resulted in a variation in visco-elastic response. The results contained in Figures 3.19 - 3.22 demonstrate that there is no relationship between the compression force required to produce a sample and the values of G', G", G* and tan δ recorded for that sample.

Figure 3.19 The Effect of Varying the Compression Force on the Storage Modulus (G') Value Obtained from a Mixture of Lactose (7) and Microcrystalline Cellulose (3) Containing 4.2 Parts Moisture (30.5%).

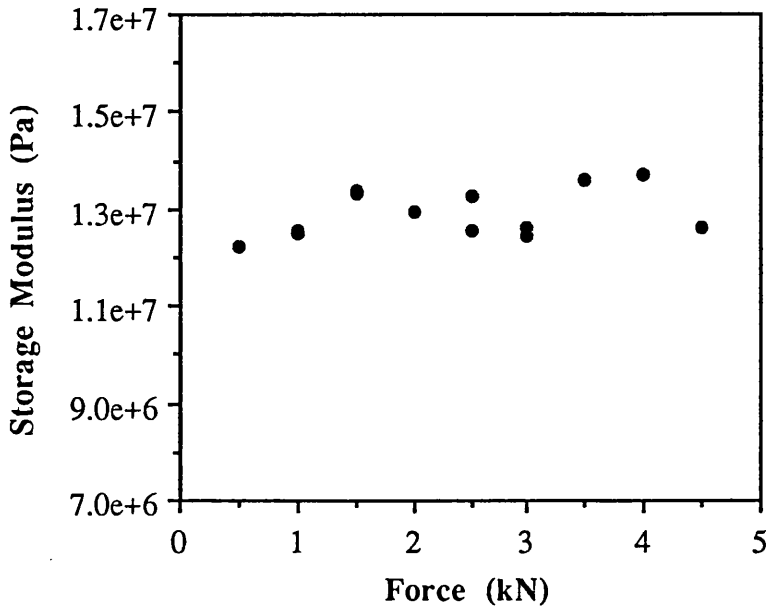


Figure 3.20 The Effect of Varying the Compression Force on the Loss Modulus (G") Value Obtained from a Mixture of Lactose (7) and Microcrystalline Cellulose (3) Containing 4.2 Parts Moisture (30.5%).

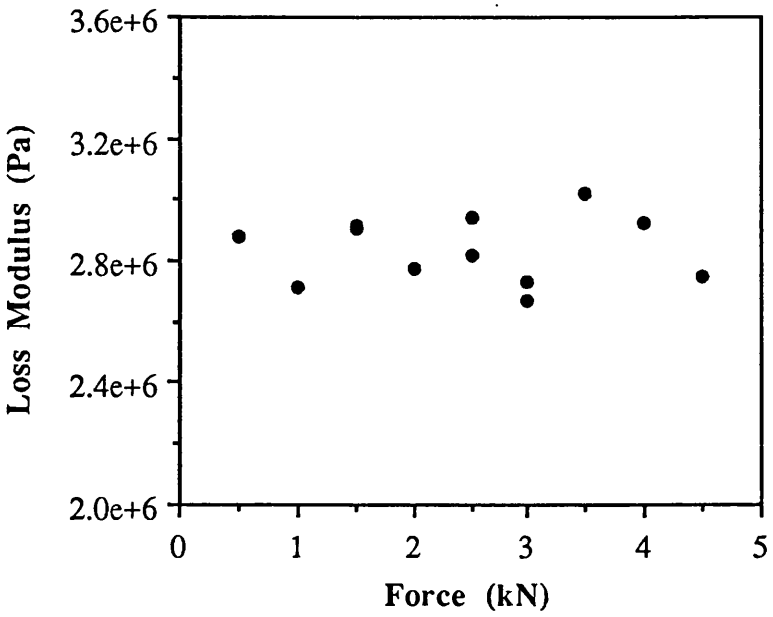


Figure 3.21 The Effect of Varying the Compression Force on the Complex Modulus (G*) Value Obtained from a Mixture of Lactose (7) and Microcrystalline Cellulose (3) Containing 4.2 Parts Moisture (30.5%).

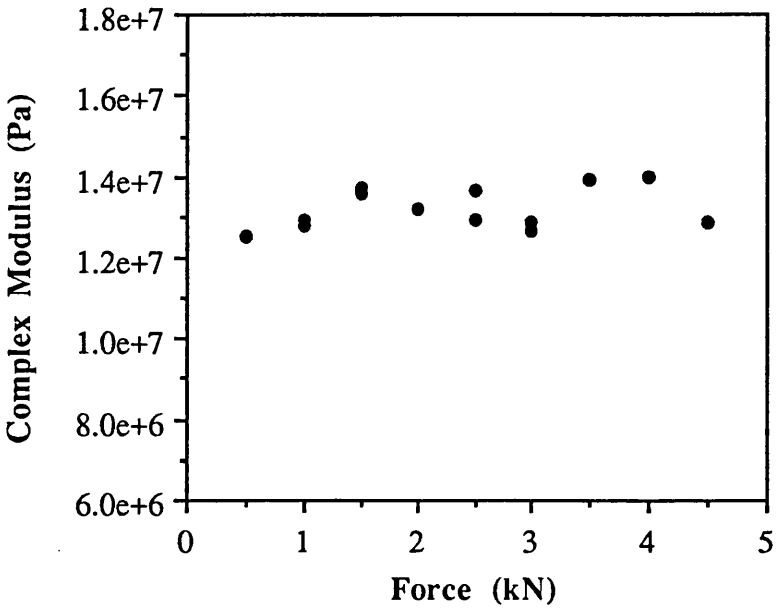
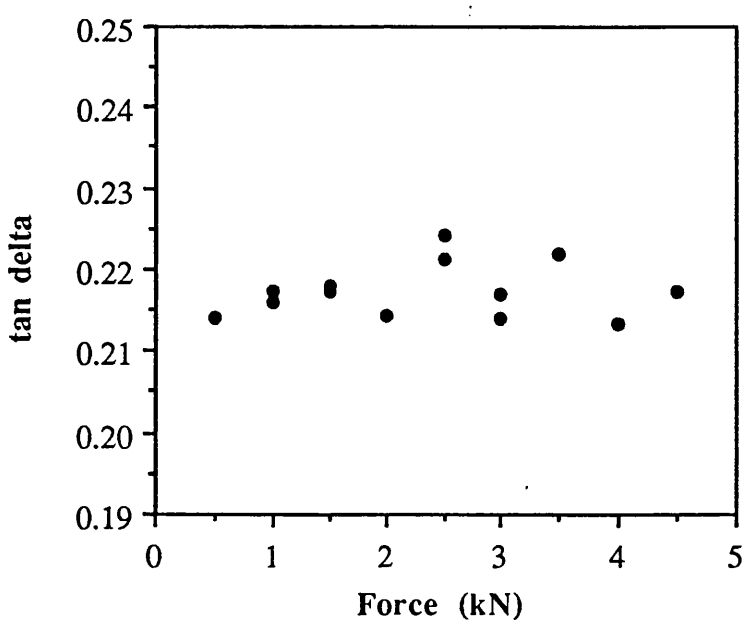


Figure 3.22 The Effect of Varying the Compression Force on the Tan Delta Value Obtained from a Mixture of Lactose (7) and Microcrystalline Cellulose (3) Containing 4.2 Parts Moisture (30.5%).



Conclusions

The results contained in Figures 3.19 - 3.22 confirm that over the range studied there is no relationship between the force of compression employed to produce the sample plug and the final height of the plug produced. Similarly there is no relationship between the compression force and the visco-elastic properties of the resultant plug nor is there a relationship between the height of plug produced and the visco-elastic properties of that plug. Therefore the actual height of plug produced does not influence the rheological properties of the sample when examined using controlled-stress oscillatory rheometry.

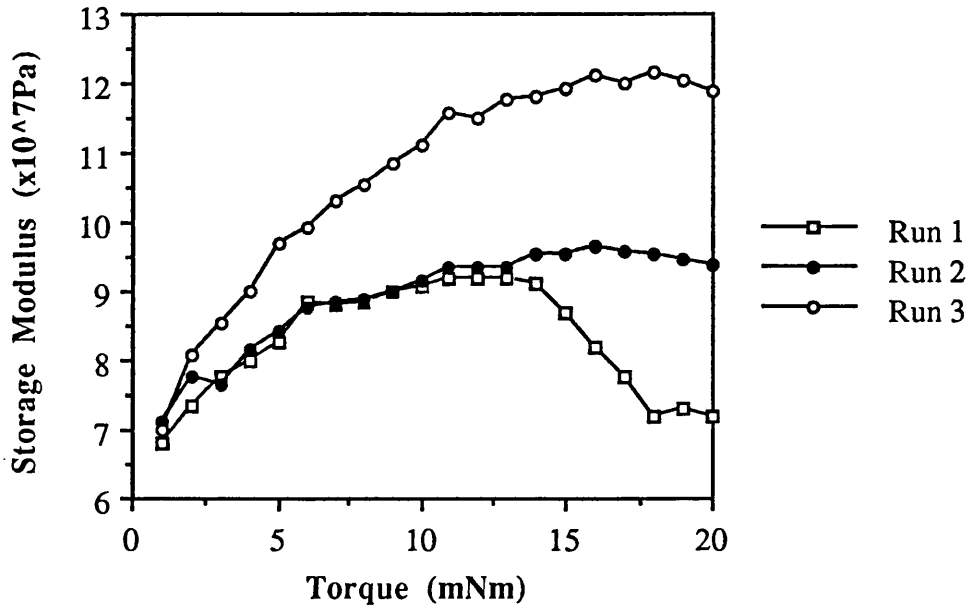
In practice a compression force of 2kN was used to prepare plugs of material for controlled-stress rheometry measurements.

3.3.7 The Effect of Repeated Experiments on a Sample Preparation

When a plug sample of a formulation was subjected to repeated experiments under the same conditions as the first experiment, it was found that the rheological values obtained on subsequent experimentation varied from the initial response to the controlled-stress oscillatory experiment.

Figures 3.23 - 3.25 examine the relationship between repeated experiments and values obtained for G', G" and tan δ respectively for an 8.0g sample of a formulation containing lactose (7), microcrystalline cellulose (3) and 4.6 parts water (31.5%). The sample plug was subjected to a 1-20mNm torque sweep at an oscillatory frequency of 0.01Hz.

Figure 3.23 The Effect of Repeated Experiments on the Storage Modulus (G') Value Obtained for a Formulation Containing Lactose (7) and Microcrystalline Cellulose (3) with 4.6 Parts Moisture (31.5%) under a 1-20mNm Torque Sweep applied at a Oscillatory Frequency of 0.01Hz.



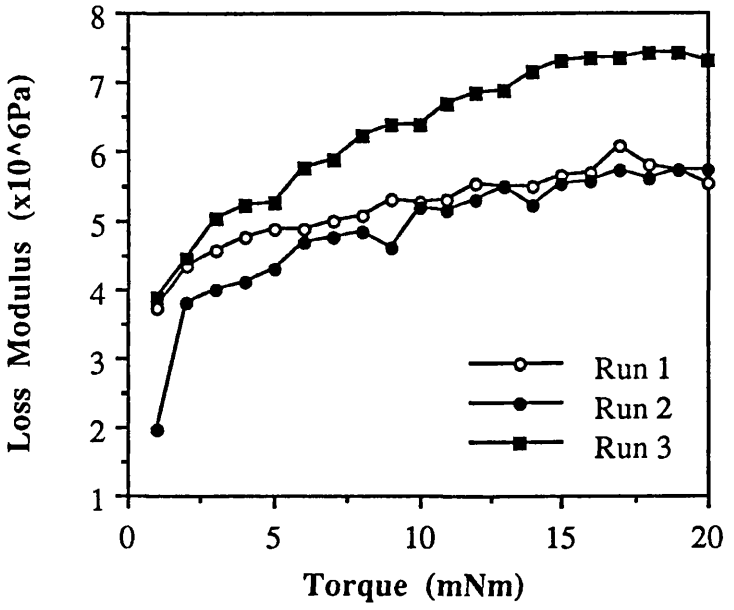
The results contained in Figure 3.23 demonstrate that on the initial experimental run (Run 1) the value of G' rises to about 9 x 10^7Pa under an applied torque of 6mNm. The value remains approximately constant until a torque of 14mNm whereafter it falls rapidly. On the subsequent experiment (Run 2) a similar constant value of G' is obtained at the same applied torque. However the sharp drop that occurred in the first experiment as the torque was increased beyond 14mNm is this time absent from the experimental run. With a third sweep applied to the same sample (Run 3), G' values increase dramatically up as far as 12 x 10^7Pa obtained at an applied torque of 13mNm. Values then remain at a plateau with further increases in applied torque.

The results contained in Figure 3.23 indicate that with repeat experimentation G' values increase with repeated applied torques to values greater than those obtained with an initial torque sweep.

The results contained in Figure 3.24 show the effect on the loss modulus values recorded for a sample with repeated torque sweep runs. The initial run (Run 1) demonstrates that increasing torque increases the G" value recorded as far as an applied torque of about 13mNm where G" values then level out at a value of about 5.5 x 10^6Pa. A repeated run (Run 2) follows almost the exact same course as the initial run.

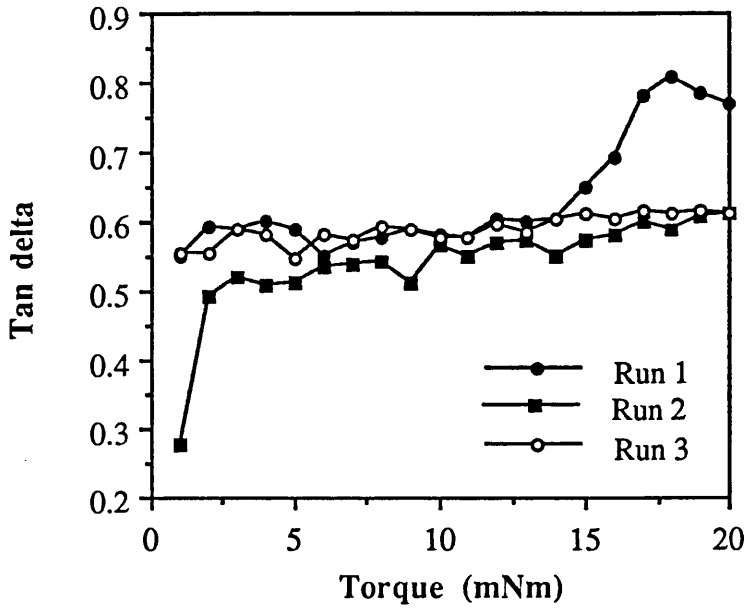
However the second repeat run (Run 3) shows a much higher G" value at lower torques which then increase to plateau at an applied torque of 14mNm with a G' value of approximately 7 x 10^7Pa.

Figure 3.24 The Effect of Repeated Experiments on the Loss Modulus (G") Value Obtained for a Formulation Containing Lactose (7) and Microcrystalline Cellulose (3) with 4.6 Parts Moisture (31.5%) under a 1-20mNm Torque Sweep applied at a Oscillatory Frequency of 0.01Hz.



The results in Figure 3.25 demonstrate the combined effects of repeated torque sweeps on the G' and G" values by examining tan δ values. On the initial torque sweep (Run 1) the effect of an increase in applied torque is reflected in an increase in tan δ value as the material becomes more viscous-like in its behaviour. A repeat of the torque sweep (Run 2) produces values of tan δ that are lower than those produced from the initial run (Run 1). Lower values of tan d suggest that the material is becoming more solid-like in its behaviour and implies that the sample is beginning to harden due either to the exertion of repeated applied stresses on the sample or to the loss of moisture from the sample into the atmosphere. A second repeat run (Run 3) demonstrates no differences in tan δ values from the beginning to the end of the torque sweep. This plateau results from the loss of moisture from the sample which raises G' and G" equally - resulting in stasis of the tan δ value. Therefore the sample retains its tendency towards predominantly elastic behaviour as both the storage and loss modulus values rise.

Figure 3.25 The Effect of Repeated Experiments on the Tan Delta Value Obtained for a Formulation Containing Lactose (7) and Microcrystalline Cellulose (3) with 4.6 Parts Moisture (31.5%) under a 1-20mNm Torque Sweep applied at a Oscillatory Frequency of 0.01Hz.



Conclusions

From the studies conducted above, rheological values are affected by repeated application of the same applied torques and by a loss of moisture from the sample. Torque sweep experiments undertaken at an oscillatory frequency of 0.01Hz take approximately 60 minutes to perform. Repeated runs were undertaken immediately after the cessation of the preceding run, therefore there was no opportunity for the sample to relax and recover some of its original structure. Three 60 minute runs also afforded the opportunity of loss of moisture from the sample to the atmosphere.

In practice no repeat runs were undertaken on the same sample plug. In order to avoid loss of moisture from the sample during the course of long experiments a water saturated environment was created around the sample to minimise potential moisture losses by the use of the upper platen solvent trap and a plastic housing surrounding the sample.

Chapter 4

EXTRUSION AND SPHERONISATION RESULTS

4. EXTRUSION AND SPHERONISATION RESULTS

4.1 EXTRUSION

4.1.1 The Qualitative Study of Extrudate and Bagley Plot Derivation

The derivation of the die wall shear stress for a formulation that has been extruded at a particular shear rate requires the contribution of a graph of length-to-radius ratio of the die used *versus* the total pressure of extrusion.This is known as a Bagley plot (Barnes *et al.*, 1989). The plot produces a line that demonstrates that the l/r ratio of the die is directly proportional to the total pressure of extrusion. The gradient of the line can be shown to be twice the die wall shear stress and that the upstream pressure loss, i.e. the amount of pressure required to overcome frictional forces, can be calculated by extrapolating the line to the y-intercept, i.e. where the l/r ratio is zero (*cf.* Section 2.1.6).

Bagley plots have been produced for lactose : microcrystalline cellulose 7 : 3 mixes with varying water contents. Work previously undertaken by Harrison *et al.* (1987) demonstrated that the rheological behaviour of 5 : 5 : 6 lactose : microcrystalline cellulose : water mixtures varied with the diameter of the extruding die. Consequently the present mixtures were extruded through dies of diameter 1mm, 1.5mm and 2mm.

As well as providing information on the rheology of formulations during extrusion, the Bagley plot has been used to demonstrate the quality of extrudate produced under the various experimental conditions. Previous studies have shown that varying the water content of the wet powder mass affects the surface quality of the extrudate (Harrison *et al.*, 1984). Extrudate quality is important since it will affect the outcome of any subsequent spheronisation, e.g.by altering of sphere size, shape or size distribution. It has been suggested that the water in the formulation forms a lubricating layer during extrusion to allow the flow of the solid material. This lubricating layer allows for the production of good, smooth extrudate. With very high extrusion rates or very short l/r die ratios the lubricating layer, if present, is less liable to have an influence on the quality of extrudate produced. Consequently extrudate quality may suffer and surface defects can occur. For each formulation examined the quality of extrudate was recorded. Quality was classified as being either smooth, rough or shark-skinned (*cf.* Section 3.2.2).

The quantity of water required to bind and lubricate extrudate produced by 5 : 5 lactose : microcrystalline cellulose has been studied extensively (Fielden, 1987; Raines, 1990). However, since the present work has been employing greater relative quantities of lactose in the mixtures under investigation, the relative solubility of the solids in the

mix may have altered and therefore the effect of the lubricating layer on extrusion may also have been altered. Similarly the amount of water required for optimal extrusion and spheronisation (as a percentage) is likely to be have been altered and mixtures may require longer periods of equilibration prior to extrusion.

The presence of lactose in the formulation reduces the deformability of the microcrystalline cellulose and thus may increase the strength of the surface of the extrudate and consequently improve the quality of extrudate (Harrison *et al.*, 1984). Further increases in lactose content above those previously studied may continue to strengthen the extrudate surface or allow the surface to become more brittle and therefore increase the frequency of surface defects.

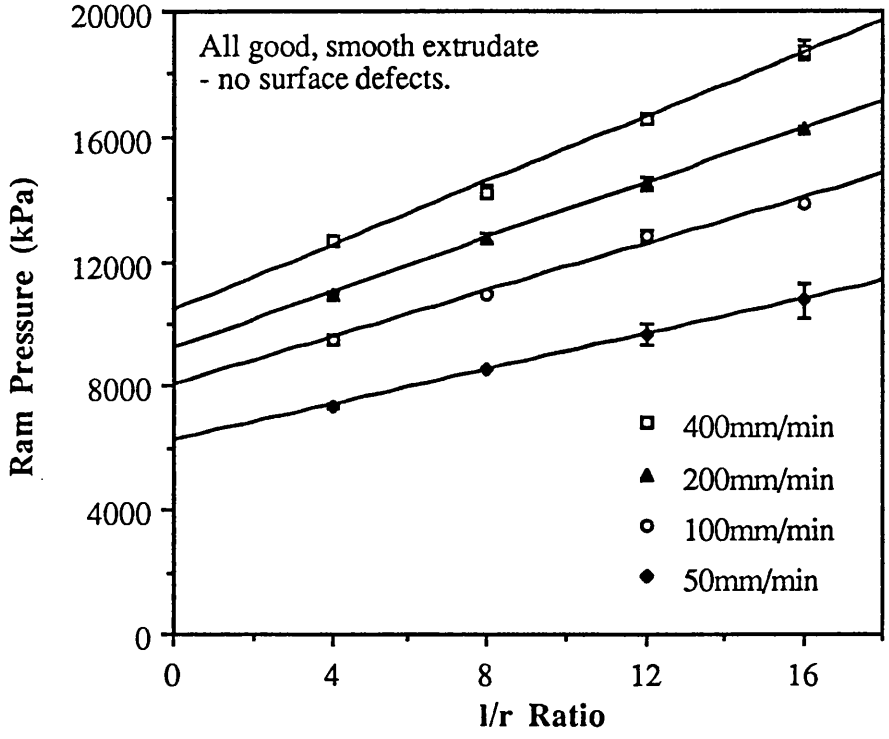
7 : 3 Lactose : Microcrystalline Cellulose Formulations

Five formulations of lactose (7 parts) and microcrystalline cellulose (3 parts) were extruded through 1, 1.5 and 2mm diameter dies. These consisted of 4.0 parts (28.6%), 4.2 parts (29.5%), 4.4 parts (30.5%), 4.6 parts (31.5%) and 4.8 parts (32.4%) moisture. The effects of varying the moisture content on extrudate quality and the pressures recorded have been recorded.

1mm Diameter Dies

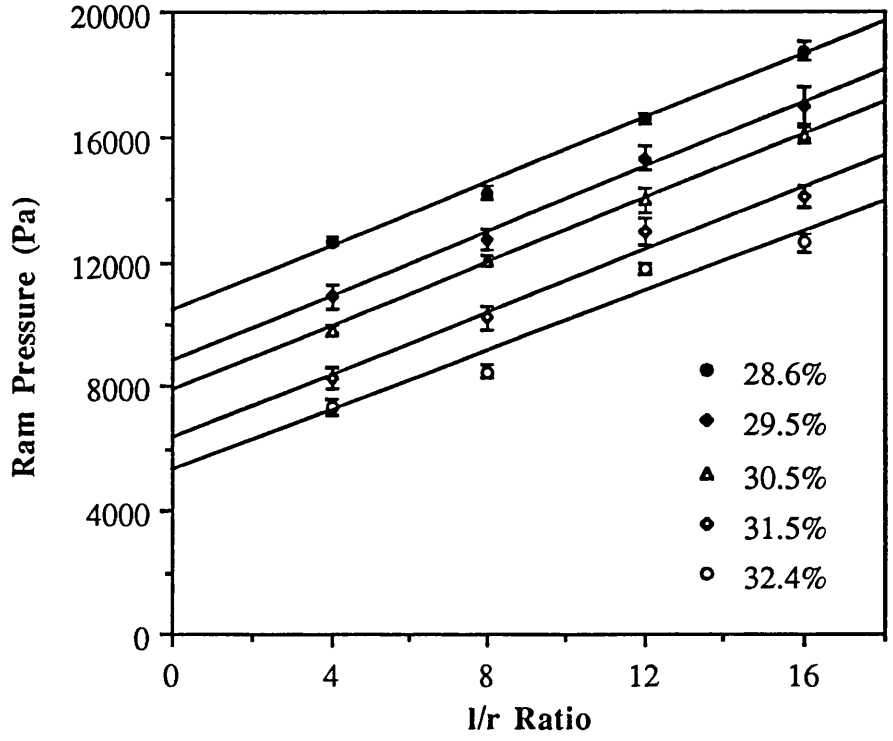
The Bagley plot of a lactose (7 parts) and microcrystalline cellulose (3 parts) mixture containing 4.0 parts (28.6%) water extruded through 1mm diameter dies (Figure 4.1) demonstrates that as the length-to-radius ratio of the die increases at a constant ram speed, the ram pressure (i.e. the pressure acting on the die) also increases. Similarly as the ram speed increases at a constant l/r die ratio, the ram pressure increases. Despite the various speeds and die ratios that were employed to construct the Bagley plot no surface defects could be found on the extrudate produced. This suggests that the formulation may be of potential use for spheronisation.

Figure 4.1 The Influence of Die Length-to-radius Ratio on the Ram Pressure Produced for a Mixture of Lactose (7 Parts), Microcrystalline Cellulose (3 Parts) and 4.0 Parts (28.6%) Water Extruded at Various Speeds using 1mm Diameter Dies.



By altering the moisture content of the formulation the pressure recorded for each individual l/r ratio at a particular extrusion velocity is varied. The effect of increasing the moisture content of the 7 : 3 lactose : microcrystalline cellulose mixture when extruded at 400mm/min is demonstrated in Figure 4.2. The results contained in this graph highlight that with an increase in moisture content there is a decrease in the ram pressure recorded at a similar l/r ratio and extrusion velocity. In the case of 1mm diameter dies all extrudate produced by all formulations at all length-to-radius die ratio and extrusion velocities appears smooth with no surface defects. Consequently all 1mm diameter die extrudate is of potential use for subsequent spheronisation.

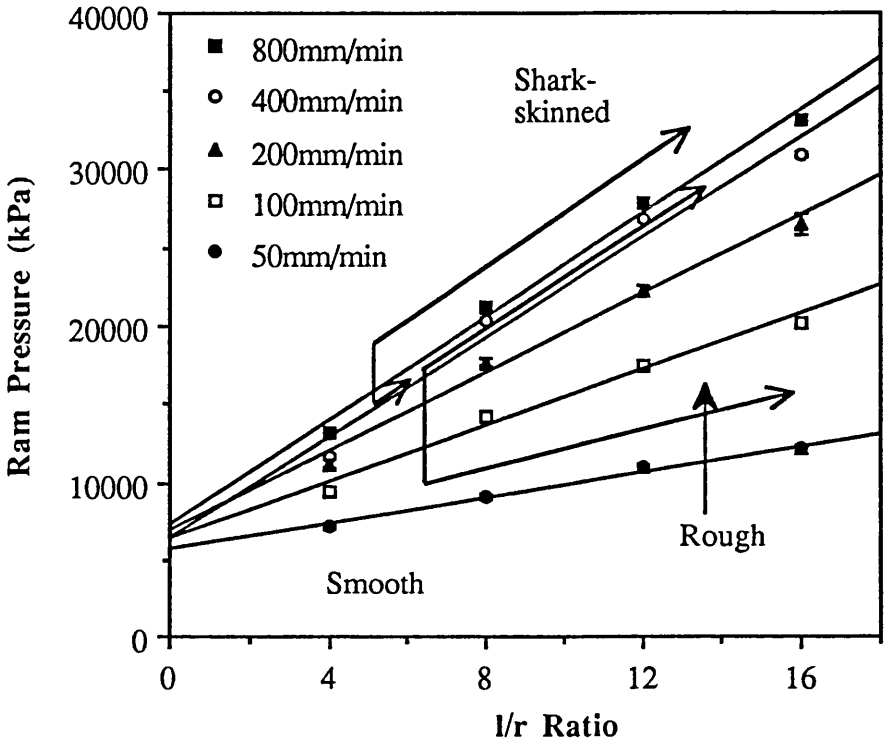
Figure 4.2 The Influence of l/r Die Ratio on the Ram Pressure Produced for Mixtures Containing Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) with Various Water Contents Extruded at 400mm/min using 1mm Diameter Dies.



1.5mm Diameter Dies

Extrusion of a lactose (7 parts) and microcrystalline cellulose (3 parts) mixture containing 4.0 parts water (28.6%) through 1.5mm diameter dies (Figure 4.3) exhibits similar characteristics to those produced during extrusion through 1mm diameter dies (Figure 4.1) but as the extrusion rate increases the pressures required to extrude the material through 1.5mm diameter dies become greater than those required to extrude 1mm diameter dies at similar l/r ratios.

Figure 4.3 The Influence of Die Length-to-radius Ratio on the Ram Pressure Produced for a Mixture of Lactose (7 Parts), Microcrystalline Cellulose (3 Parts) and 4.0 Parts (28.6%) Water Extruded at Various Speeds using 1.5mm Diameter Dies.



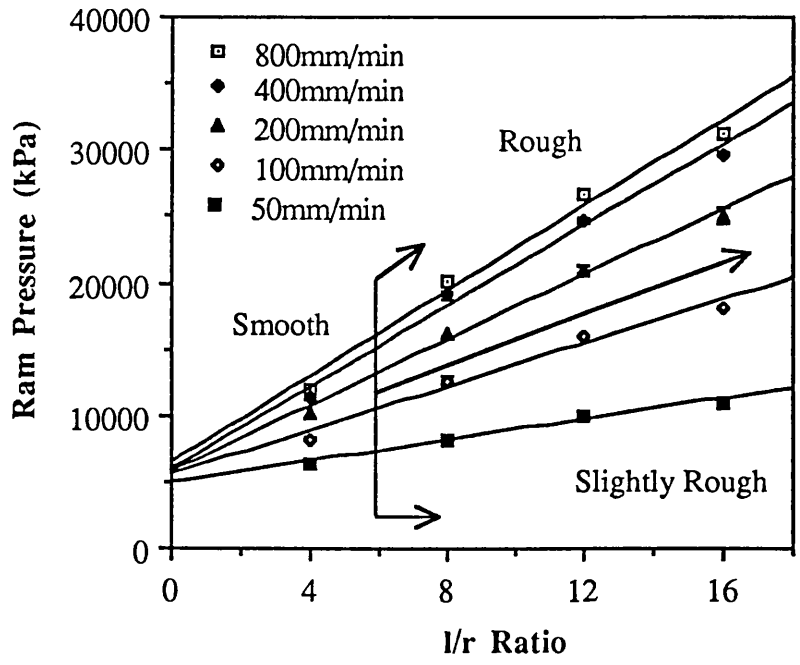
Extrusion through 1.5mm diameter dies has introduced the problem of surface defects although for this formulation these are slight and do not include sharkskinning. They begin to occur at the high pressures required to extrude the formulation through high l/r ratios and high extrusion rates. The defects are produced because the lubricating layer of fluid that enables the movement of solid material through the die-land is inadequate to maintain a smooth flow of material. If the ram speed is too fast a lubricating layer does not have enough time to form whereas if the length-to-radius ratio of the die has been overextended then there may be insufficient moisture available to keep the surface of the extrudate lubricated. For this mixture l/r ratios of greater than 8 combined with ram speeds of greater than 50mm/min produce extrudates with surface defects.

Comparing all the formulations extruded through 1.5mm diameter dies together (Figures 4.3 - 4.7) it becomes apparent that changes in moisture content introduce complex changes to the amount of surface defects recorded for each formulation. A wetter formulation increases the number of surface defects that occur during extrusion. These defects occur even although the amount of pressure recorded for each l/r die ratio

at each extrusion velocity decrease with an increase in moisture content. With an increase in the water content the production of good quality extrudate becomes more difficult with only material extruded through dies of a length-to-radius ratio of 4 being smooth. Higher l/r ratios, at all extrusion rates studied, produce rough or slightly rough extrudate.

The effect of an increase in moisture content is again to reduce the ram pressure recorded for each particular l/r die ratio and ram velocity. However differences in the surface defects between formulations are not pressure dependent.

Figure 4.4 The Influence of Die Length-to-radius Ratio on the Ram Pressure Produced for a Mixture of Lactose (7 Parts), Microcrystalline Cellulose (3 Parts) and 4.2 Parts (29.5%) Water Extruded at Various Speeds using 1.5mm Diameter Dies.



Although surface defects can occur due to an insufficient lubricating layer being present to maintain smooth flow of material through the die-land, an increase in the water content of the formulation does not necessarily increase the quality of the extrudate produced. An increase in the water content of the formulation may increase the amount of swelling of the material as it exits from the die therefore compromising extrudate quality (Harrison *et al.*, 1984). Similarly as the shear rate increases (due to an increase in l/r ratio of the die or an increase in ram speed) any increase in water content may promote a greater amount of roughness/sharkskinning as the forces acting on the

extrudate during extrusion are greater than the surface forces holding the material together. This effect is seen to occur when a formulation containing 4.4 parts water (30.5%) is extruded through 1.5mm diameter dies (Figure 4.5). It produces extrudate that is only smooth at the lowest l/r ratio studied (l/r = 4). At higher extrusion rates and l/r ratios roughness occurs which eventually leads to shark-skinning at the highest ram speed/length-to-radius ratios studied. Shark-skinning was absent in the two lower moisture content formulations extruded through 1.5mm diameter dies (Figures 4.3 and 4.4) therefore increasing the water content of the mixture has promoted surface defects during the extrusion process.

Extrusion of a 7 : 3 lactose : microcrystalline cellulose mixture containing 31.5% and 32.4% water through 1.5mm diameter dies (Figures 4.6 and 4.7 respectively) demonstrates that shark-skinning of extrudate remains a problem only at the highest ram velocities and l/r ratios investigated.

Figure 4.5 The Influence of Die Length-to-radius Ratio on the Ram Pressure Produced for a Mixture of Lactose (7 Parts), Microcrystalline Cellulose (3 Parts) and 4.4 Parts (30.5%) Water Extruded at Various Speeds using 1.5mm Diameter Dies.

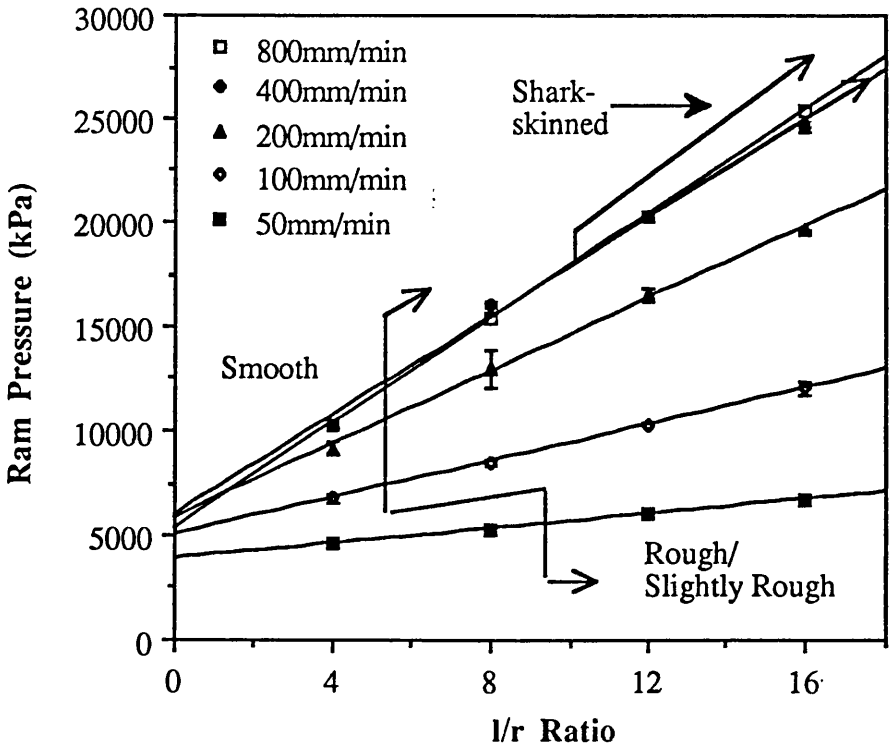
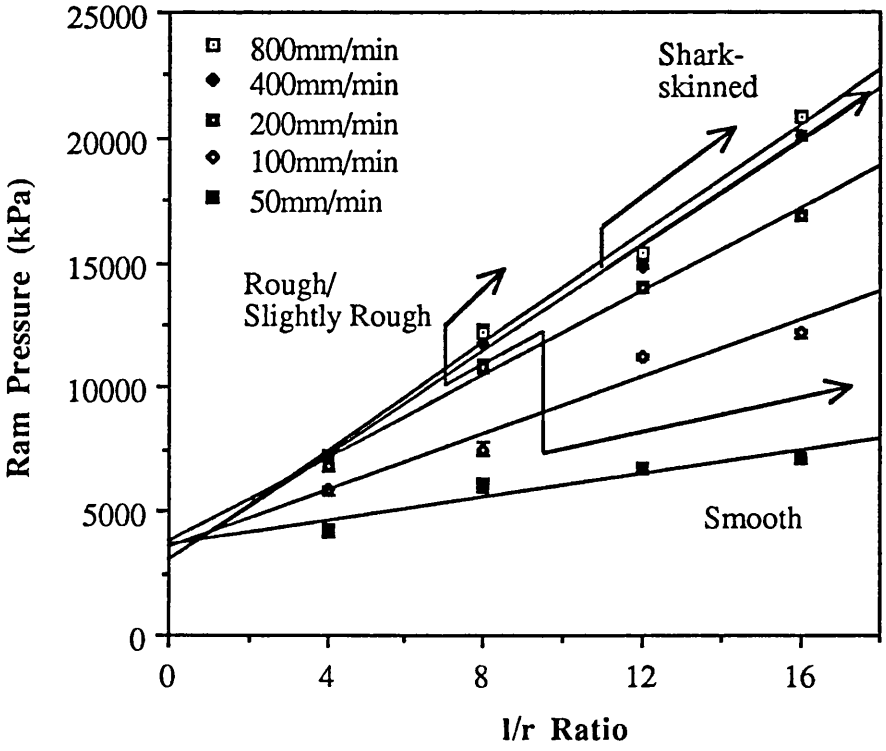
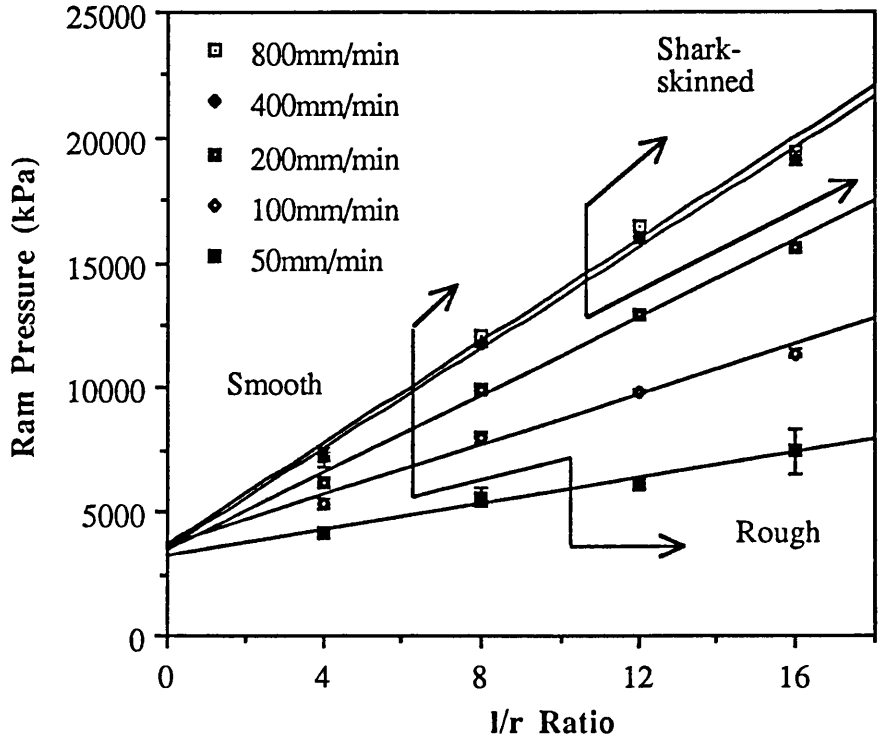


Figure 4.6 The Influence of Die Length-to-radius Ratio on the Ram Pressure Produced for a Mixture of Lactose (7 Parts), Microcrystalline Cellulose (3 Parts) and 4.6 Parts (31.5%) Water Extruded at Various Speeds using 1.5mm Diameter Dies.



The ram pressure values recorded at the 2 highest extrusion velocities undertaken in the experiments (400mm/min and 800mm/min) are similar in magnitude. Although individual pressure values for each l/r ratio recorded at 400mm/min are lower than those recorded at 800mm/min there is crossover in the gradients produced by the 2 ram velocities due to their close proximity.

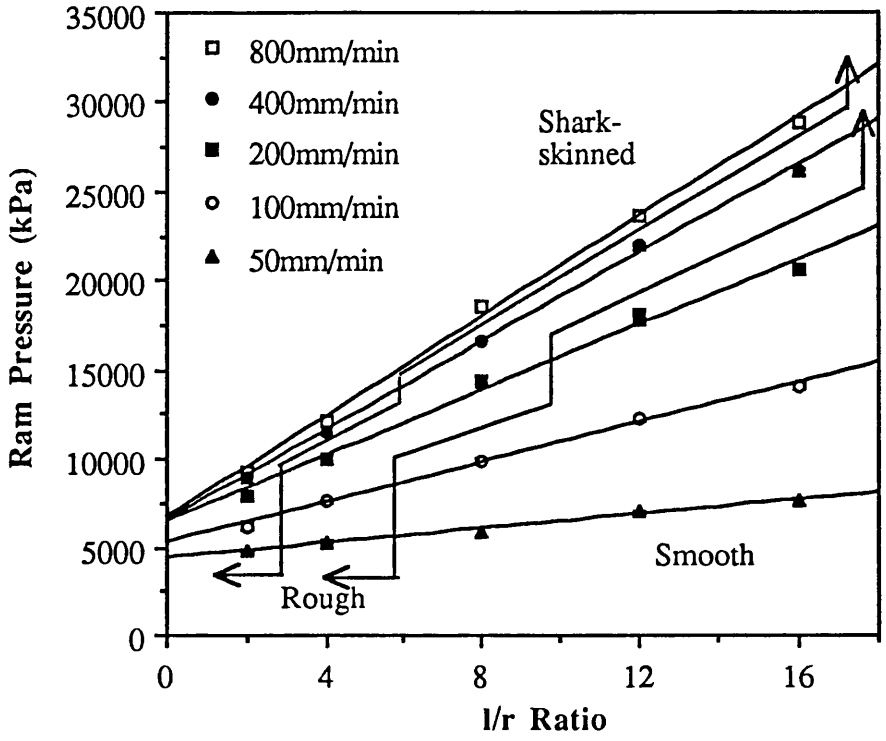
Figure 4.7 The Influence of Die Length-to-radius Ratio on the Ram Pressure Produced for a Mixture of Lactose (7 Parts), Microcrystalline Cellulose (3 Parts) and 4.8 Parts (32.4%) Water Extruded at Various Speeds using 1.5mm Diameter Dies.



2mm Diameter Dies

A Bagley plot of a lactose (7 parts) and microcrystalline cellulose (3 parts) mixture containing 4.0 parts water (28.6%) extruded through 2mm diameter dies (Figure 4.8) demonstrates that the ram pressures recorded are similar to those required to extrude the formulation through 1.5mm diameter dies at equivalent l/r die ratios and ram speeds (Figure 4.3). With 2mm diameter dies (Figure 4.8) there are problems with surface defects, particularly at low l/r ratios and high extrusion speeds. Smooth extrudate can only be manufactured at long l/r ratios with low extrusion speeds where a lubricating layer has been allowed to form between the wet mass and the die wall. Otherwise rough extrudate is produced or more severely, at low l/r ratios and high extrusion rates, sharkskinned extrudate is formed.

Figure 4.8 The Influence of Die Length-to-radius Ratio on the Ram Pressure Produced for a Mixture of Lactose (7 Parts), Microcrystalline Cellulose (3 Parts) and 4.0 Parts (28.6%) Water Extruded at Various Speeds using 2mm Diameter Dies.

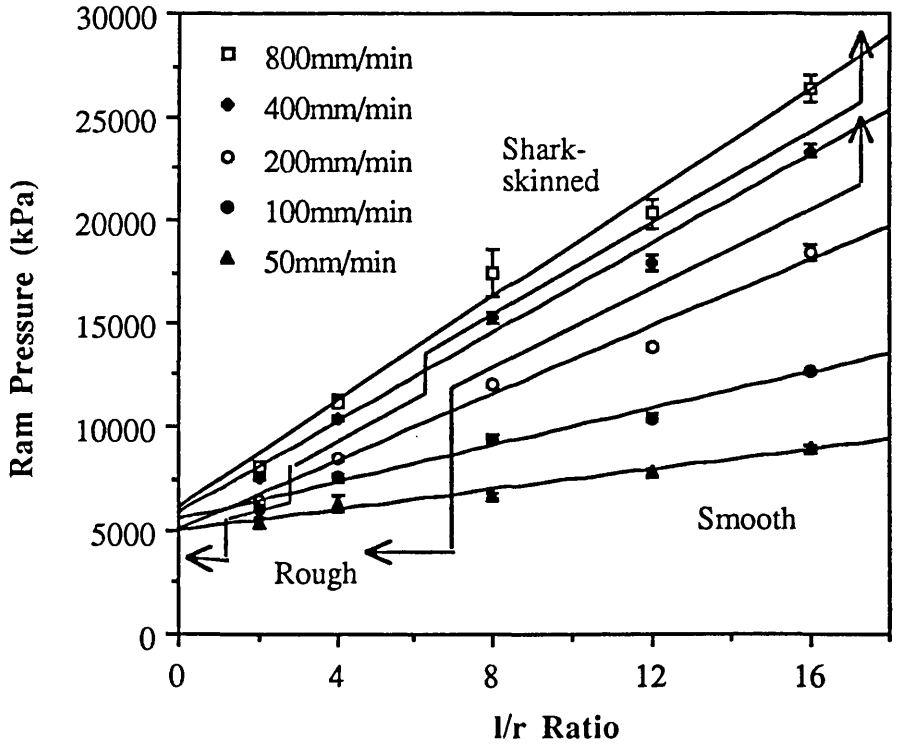


Nickell *et al.* (1974) have suggested that a 'stick-slip' phenomenon occurs when a material is extruded which causes a compression of layers of material in the centre of the die during extrusion. The outer layers of material in contact with the die wall exhibit tension due to the variance in velocities between the centre of the material and its perimeter. If the tension exceeds the forces acting to maintain a smooth surface and cylindrical shape of extrudate then splitting in the wall of the extrudate will occur. With short l/r die ratios this phenomenon may become marked since there is a less time for the material to create a lubricating layer to facilitate extrusion. There may also be even greater disparities between the velocities of the centre and perimeter of the material. Indeed if the velocity at the perimeter is zero, due to sticking at the die wall, shark-skinning will occur. Harrison (1984) has stated that sharkskinning can be avoided by reducing the wall shear stress within the die by decreasing the ram speed or by increasing the number of holes in the die. Reducing the deformability of the extrudate by decreasing the moisture content or changing the formulation in terms of the solid components have also been suggested as reducing sharkskinning. For the formulation under investigation sharkskinning occurs at all rams speeds tested for the

shortest l/r ratio die and lower ram speeds would produce extrudate that was too wet for spheronisation. Multi-holed dies may therefore be the most appropriate way of reducing the incidence of sharkskinning.

Varying the moisture content of the mixture extruded through 2mm diameter dies (Figures 4.9 - 4.12) introduces complex changes in surfaces defects that are different from those produced from 1.5mm diameter dies (Figures 4.3 - 4.7). The effect of varying the moisture content is recorded below. At high extrusion rates and/or low l/r ratios either roughness or shark-skinning becomes prevalent.

Figure 4.9 The Influence of Die Length-to-radius Ratio on the Ram Pressure Produced for a Mixture of Lactose (7 Parts), Microcrystalline Cellulose (3 Parts) and 4.2 Parts (29.5%) Water Extruded at Various Speeds using 2mm Diameter Dies.



When a lactose (7 parts) and microcrystalline cellulose (3 parts) mixture containing 4.2 parts water (29.5%) is extruded through 2mm diameter dies (Figure 4.9) the number of individual die/ram speed combinations that experience surface defects has decreased when compared to a mix containing 4.0 parts (28.6%) water (Figure 4.8). Therefore with 2mm diameter dies, increasing the water content of the mixture has reduced the tendency of 7 : 3 lactose : microcrystalline cellulose formulations to

exhibit surface defects during extrusion. This is not the case with 1.5mm diameter dies where an increase in water content increased the tendency of the formulation to exhibit surface defects upon extrusion.

The trend towards fewer surface defects is repeated with a further increase in the moisture content to 4.4 parts (30.5%) [Figure 4.10]. Defects now occur only at the shortest l/r ratios studied (l/r = 2 or 4) or at the very highest l/r ratio/ram speed studied (l/r = 16, ram speed = 800mm/min). The increase in the moisture content of the formulation may reduce the amount of surface defects by promoting the formation of a good lubricating layer of fluid in the material as it is extruded through the die. This prevents defects on the surface of the extrudate as the surface tension of the extrudate becomes great enough to withstand the pressures exerted on it by the die wall. This means that the 'stick-slip' effect is reduced (Harrison *et al.*, 1985).

However further increases in moisture content increase the amount of defects recorded (Figures 4.11 and 4.12).

Figure 4.10 The Influence of Die Length-to-radius Ratio on the Ram Pressure Produced for a Mixture of Lactose (7 Parts), Microcrystalline Cellulose (3 Parts) and 4.4 Parts (30.5%) Water Extruded at Various Speeds using 2mm Diameter Dies.

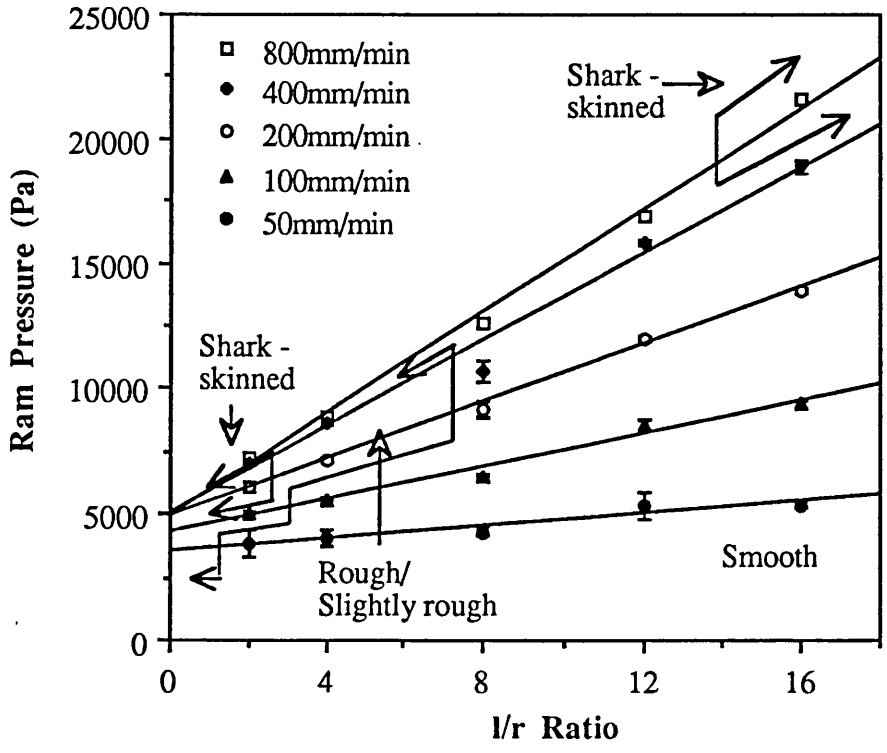
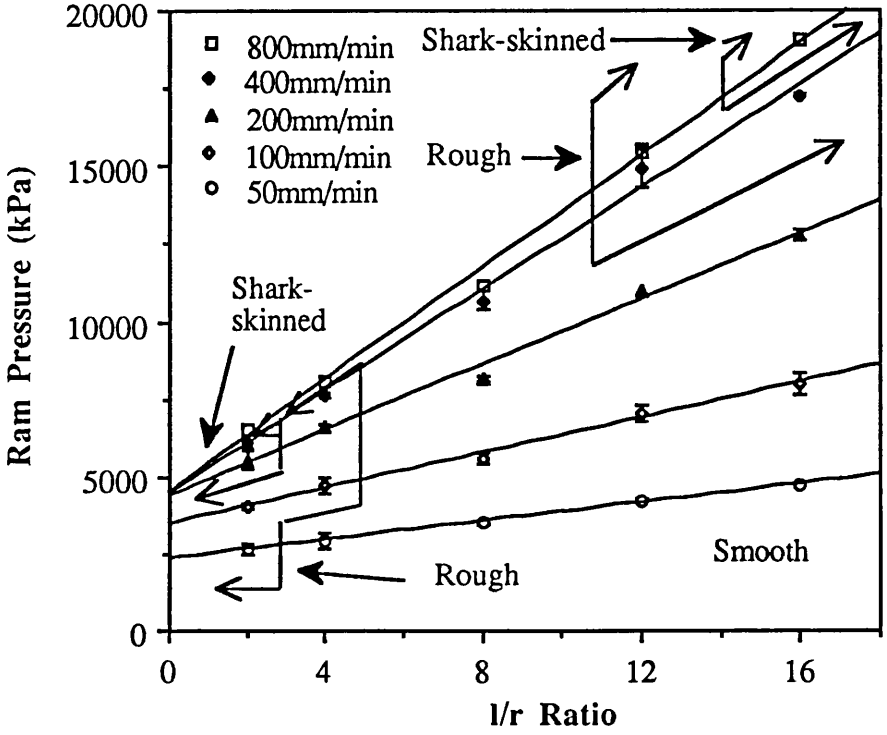
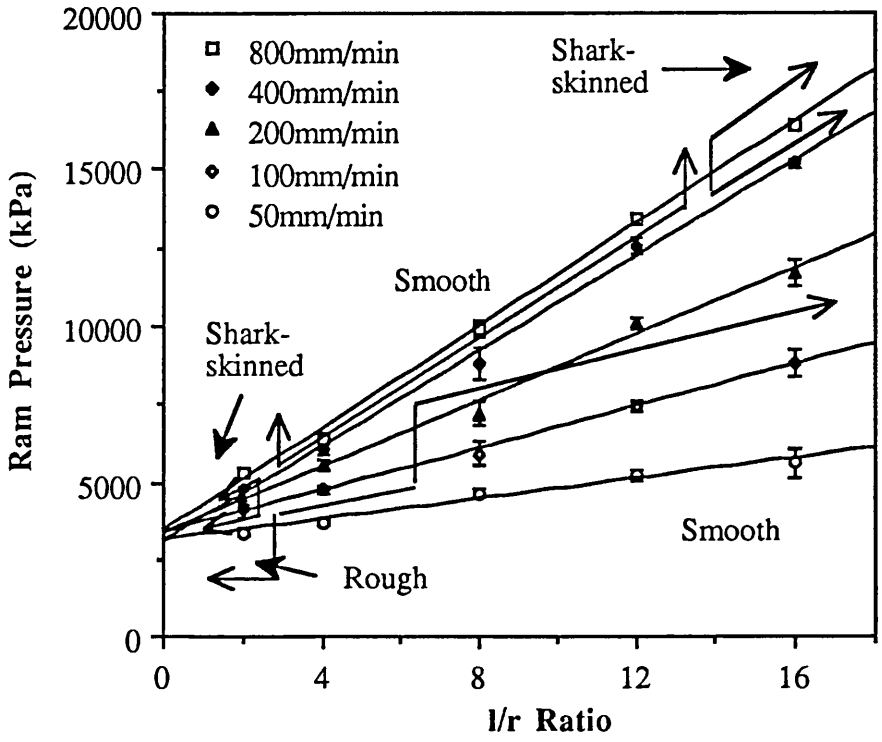


Figure 4.11 The Influence of Die Length-to-radius Ratio on the Ram Pressure Produced for a Mixture of Lactose (7 Parts), Microcrystalline Cellulose (3 Parts) and 4.6 Parts (31.5%) Water Extruded at Various Speeds using 2mm Diameter Dies.



The variation in the quality of extrudate produced by 2mm diameter dies at individual l/r ratios and extrusion velocities (Figures 4.10 - 4.12) with only small changes in the moisture content highlights the difficulty in predicting which formulation will successfully extrude and spheronise when extruded through 2 diameter dies. These results also suggest that a factorial experimental design may not be the best way of predicting the effect of formulation and process variables on extrusion and spheronisation.

Figure 4.12 The Influence of Die Length-to-radius Ratio on the Ram Pressure Produced for a Mixture of Lactose (7 Parts), Microcrystalline Cellulose (3 Parts) and 4.8 Parts (32.4%) Water Extruded at Various Speeds using 2mm Diameter Dies.



Conclusions

All formulations when extruded through 1mm diameter dies produce smooth extrudate at all the length-to-radius ratio of dies and extrusion rates studied. Extrudate from 1mm diameter dies may therefore be of use in the subsequent manufacture of spheroids from spheronisation.

From the results of investigations using 1.5mm diameter dies to perform extrusion, it is difficult to predict the incidence of surface defects that occurs with each formulation. Short l/r ratios and low extrusion rates yield extrudate with the least number of surface defects. As the ram velocity and the l/r ratio of the dies increase roughness and then shark-skinning of extrudate become prevalent.

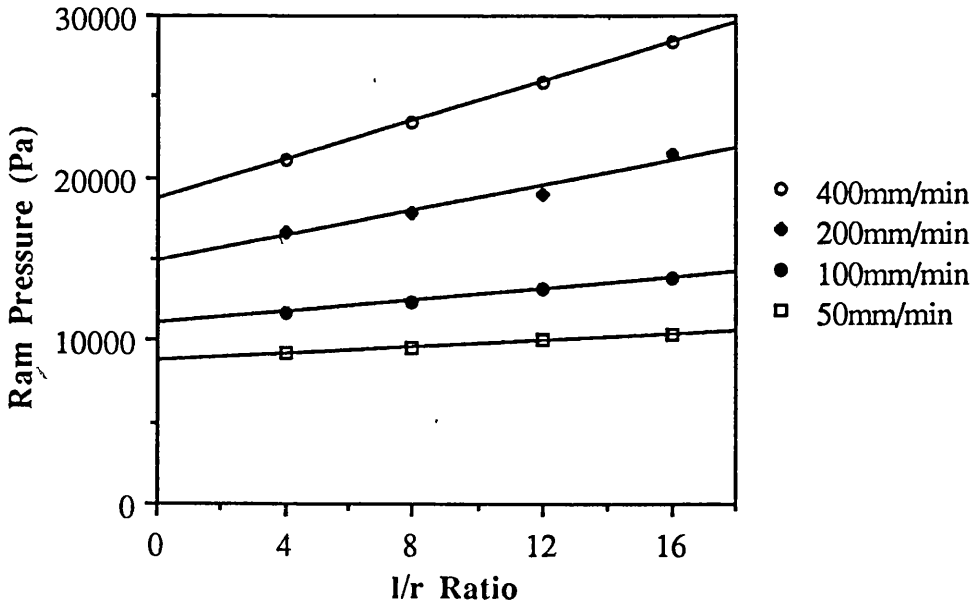
Increasing the moisture content of the formulation studied produces first a reduction and then an increase in the number of surface defects observed when the material is extruded through 2mm diameter dies. Predicting the quality of extrudate produced from 2mm diameter dies is extremely difficult. To produce consistently

smooth extrudate high l/r die ratios should be used in combination with low ram speeds.

8 : 2 Lactose : Microcrystalline Cellulose Formulations

Extruding lactose (8 parts) and microcrystalline cellulose (2 parts) mixtures through 1.5 and 2mm diameter dies was difficult to accomplish for all the length-to-radius die ratios and ram velocities that were studied for 7 : 3 mixtures. This was due to a reduction in moisture required for 8 : 2 formulations that was appropriate for spheronisation, approximately 23 - 26% moisture for 8 : 2 mixtures as opposed to 28 - 33% moisture for 7 : 3 mixtures. This makes the pressures required to extrude these materials greater than previously recorded. Consequently only 1mm diameter dies were used to examine the rheological behaviour of 8 : 2 lactose : microcrystalline cellulose mixtures. Figure 4.13 demonstrates the influence of l/r die ratio and ram velocity on the ram pressure recorded for a formulation containing lactose (8 parts), microcrystalline cellulose (2 parts) and 3.0 parts (23.1%) water. Comparing the pressures recorded in Figure 4.13 with the driest 7 : 3 formulation studied (containing 28.6% moisture - Figure 4.1) highlights the increase in ram pressure that is recorded with a reduction in the moisture content.

Figure 4.13 The Influence of Die Length-to-radius Ratio on the Ram Pressure Produced for a Mixture of Lactose (8 Parts), Microcrystalline Cellulose (2 Parts) and 3.0 Parts (23.1%) Water Extruded at Various Speeds using 1mm Diameter Dies.



Like all the 7 : 3 formulations extruded through 1mm diameter dies all the 8 : 2 formulations extruded through 1mm diameter dies produced extrudate that was smooth. Therefore all the extrudate produced by 8 : 2 mixtures is of potential use in subsequent spheronisation. Increasing the moisture content of 8 : 2 mixtures again reduces the pressure recorded for each l/r die ratio and ram velocity studied.

4.1.2 Shear Stress-Shear Rate Flow Curves

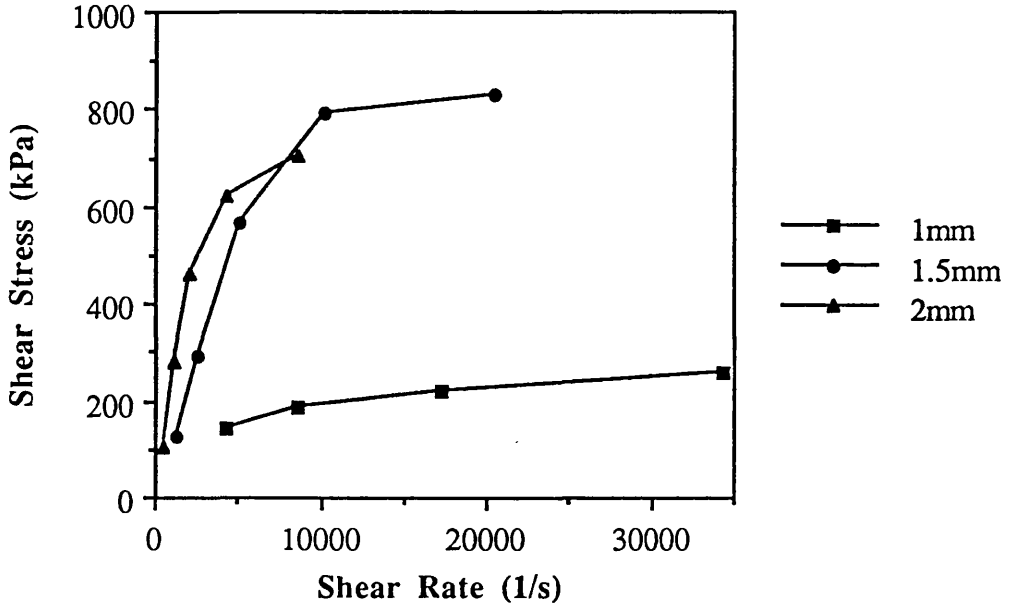
Rheological flow curves constructed from die wall shear stress *versus* shear rate figures have previously been used to describe the behaviour of formulations that contain two different particle sizes of lactose (Fielden *et al.*, 1989). Results concluded that a coarse grade of lactose produced a far lower yield stress (extrapolating to zero stress at zero shear rate) than a fine grade of lactose. At low shear rates the stress at the die wall for the coarse grade of lactose was reduced when compared to that containing fine lactose. The flow curves produced by the two grades of lactose emphasised the differences in the rheological properties of the two formulations studied. These differences are of potential use in determining the quality of pellets produced when the two formulations are spheronised (Fielden *et al.*,1992). This work was undertaken using 5 : 5 : 6 lactose : microcrystalline cellulose : water formulations. The flow curves described below may also be of use in determining the quality of spheroids produced by spheronisation. The formulations under investigation consisted of lactose (7 parts) and microcrystalline cellulose (3 parts) with varying amounts of water.

Using the data produced from graphs in Section 4.1.1 it is possible to construct shear stress *versus* shear rate profiles for the various formulations studied as they are extruded through different diameter dies.

The Effect of Die Diameter on Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) Formulations Containing Varying Amounts of Moisture.

Extrusion of a lactose (7 parts) and microcrystalline cellulose (3 parts) mixture containing 4.0 parts water through 1mm, 1.5mm and 2mm diameter dies at various extrusion rates produced the flow curves illustrated in Figure 4.14.

Figure 4.14 Shear Stress *vs* Shear Rate Profiles for a Mixture Containing Lactose (7 Parts), Microcrystalline Cellulose (3 Parts) and 4.0 Parts (28.6%) Water Extruded through Various Diameter Dies



Extrusion of the formulation through 1mm diameter dies produces shear rates much greater than those produced for 1.5mm and 2mm diameter dies at similar extrusion velocities. This is due to the shear rate being inversely proportional to the cube of the radius of the die.

The relationship between the shear stress and shear rate for the formulation extruded through 1mm diameter dies is almost linear. The value of die wall shear stress that results as the shear rate increases levels out at a value below that resulting from extrusion through 1.5mm and 2mm diameter dies at lower shear rates. Harrison *et al.* (1987) suggested that similar behaviour demonstrated by a formulation containing 5 : 5 : 6 lactose : microcrystalline cellulose : water when extruded through 1mm diameter dies may have resulted from either non-laminar flow in the die-land, non-uniform consistency of the material as it passed through the die or to the velocity of throughput at the die wall not being equal to zero. Experiments revealed that laminar flow occurred as the material moved through the die and that uniform consistency in the formulation was maintained in the die-land when the formulation exhibited a minimum value of apparent fluidity (Harrison, 1983). However, if the material had a velocity of throughput below the minimum value of fluidity then the rheological nature of the material changed in the die to maintain the flow of material at a particular wall shear rate. Consequently the dependence of shear stress/shear rate curves on die diameter was

attributed to the existence of slip at the die wall, which reduces the value of shear stress at a particular shear rate. The amount of slip calculated to occur at the two largest die diameters, 1.5mm and 2mm, was found to be negligible but despite this, the application of a modified power-law mathematical model to a 2mm diameter die flow curve still did not provide a model to which the curve would fit.

Although a modified power-law has not been applied to the flow curves produced by the formulation under investigation the similarities in shape and stress values obtained from the sample and those resulting from the work of Harrison *et al.* (1983) suggests that similar problems in applying a mathematical model would occur. The behaviour is best described by the Herschel-Bulkley model of rheological behaviour with a maximum shear stress of approximately 250kPa obtained from a shear rate of $30{,}000s^{-1}$. This model also predicts a yield stress value occurs at zero shear rate. This is in agreement with the results of Harrison *et al.* (1987) who found that a 5 : 5 : 6 lactose : microcrystalline cellulose : water mixture exhibited shear thinning when extruded through various diameter dies and that the shear stress recorded for the formulation extruded through 1mm diameter dies was approximately 300kPa at a shear rate of $30{,}000s^{-1}$.

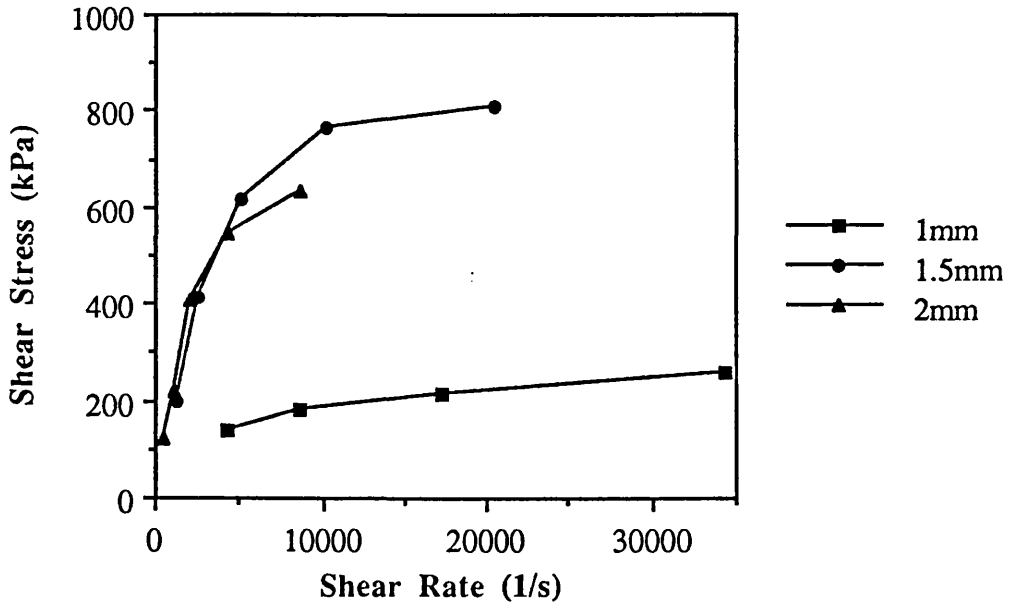
A die diameter of 1.5mm produces a lower shear rate at similar extrusion velocities when compared with 1mm diameter dies (Figure 4.14). However the shear stress values resulting from extrusion through 1.5mm diameter dies are much greater than those produced when the formulation is extruded at a similar shear rate through 1mm diameter dies. This is due to a reduction in the slip at the die wall which decreases as the diameter of the die increases, allowing for the formation of a consistent lubricating layer in the die-land. With an increase in shear rate the shear stress produced increases but stress values plateau (at about 800kPa) as the material begins to shear thin. Although the plateau occurs at a higher shear stress than that produced by 1mm diameter dies it occurs at a much lower shear rate (at $10{,}000s^{-1}$ rather than $33{,}000s^{-1}$). The flow curve when extrapolated to the Y-axis reveals a yield stress approximating to zero implying that the formulation when extruded through 1.5mm diameter dies follows the Shear Thinning model of rheological behaviour (*cf.* Section 2.1).

Extrusion of a 7 : 3 : 4.0 lactose : microcrystalline cellulose : water mixture through 2mm diameter dies produces a large shear stress at low shear rates (Figure 4.14). The steep rate of increase in shear stress with only a slight increase in shear rate can produce extrudate that is susceptible to variation in surface defects with only a slight change in extrusion rate. The shear stress is greater at a lower shear rate than the same formulation extruded through 1.5mm diameter dies but the stress on the material begins to plateau at a lower shear rate when extruded through 2mm diameter when compared to 1.5mm diameter dies. Consequently it can be assumed that a certain degree of slip at the die wall, which reduces the total force required to force the central mass of

material through the die, still occurs when the material is extruded through 1.5mm diameter dies. Extrapolation of the flow curve produced by 2mm diameter dies to the Y-axis again produces a yield stress approximating to zero. Therefore extrusion of a lactose (7 parts), microcrystalline cellulose (3 parts) and water (4.0 parts) mixture through 2mm diameter dies again follows the shear thinning model of rheological behaviour.

The flow curves produced from a lactose (7 parts), microcrystalline cellulose (3 parts) and 4.2 parts water (29.5%) mixture are represented in Figure 4.15. The curves are similar in size and magnitude to those produced from extrusion of a 7 : 3 : 4.0 lactose : microcrystalline cellulose : water mixture through 1, 1.5 and 2mm diameter dies (Figure 4.14).

Figure 4.15 Shear Stress *vs* Shear Rate Profiles for a Mixture Containing Lactose (7 Parts), Microcrystalline Cellulose (3 Parts) and 4.2 Parts (29.5%) Water Extruded through Various Diameter Dies



Extrusion of the formulation through 1mm diameter dies produces a flow curve that is approximately linear until high shear rates where there is a plateau in shear stress value with increasing shear rate. The low stress value obtained from the high shear rate again demonstrates the existence of slip at the die wall. If the material follows the Herschel-Bulkley model of behaviour then a yield stress value occurs at zero shear rate.

However extrapolation of the flow curve produced from 1mm diameter dies to the Y-axis is difficult with the few points calculated and it could produce no yield stress.

Both 1.5mm and 2mm diameter dies produce flow curves that do not possess a yield stress and shear thin at shear rates of approximately 10,000s^{-1} (Figure 4.15). The difference in shear stress values between 1.5mm and 2mm diameter dies are very small which may reflect that slip at the die wall does not occur for formulations extruded through 1.5mm diameter dies. The shear stress produced when shear thinning occurs with 1.5mm diameter dies is similar to that produced from a 7 : 3 : 4.0 lactose : microcrystalline cellulose : water mixture when it shear thins during extrusion through 1.5mm diameter dies (Figure 4.14). However extrusion of the formulation containing 29.5% moisture through 2mm diameter dies produces shear stress values and a plateau stress value lower than a formulation containing 28.6% moisture (Figure 4.15).

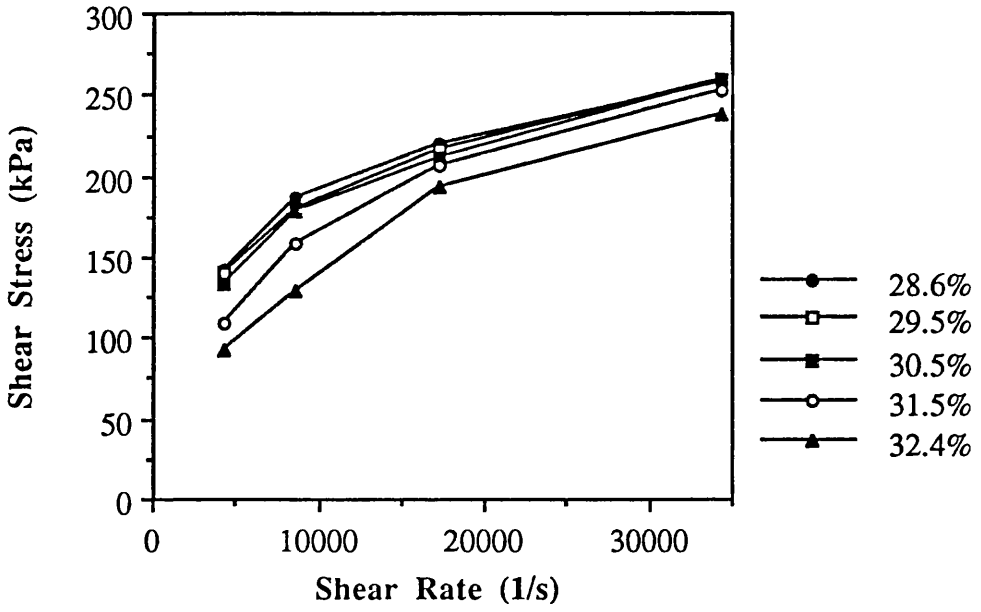
Further increases in the moisture content produces shear stress *vs* shear rate profiles similar in shape to those produced by formulations containing 4.0 parts and 4.2 parts moisture. Differences in the profiles obtained with a change in die diameter also remained similar with a change in moisture content.

Comparison of Shear Stress vs Shear Rate Profiles for Mixtures Containing Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) with Various Quantities of Water Extruded Through Similar Sized Dies.

1. 1mm Diameter Dies

7 : 3 lactose : microcrystalline cellulose formulations with various water contents have been compared when extruded through 1mm diameter dies (Figure 4.16). As the water content increases the shear stress recorded for each formulation at a particular extrusion rate decreases.

Figure 4.16 Shear Stress *vs* Shear Rate Profiles for Mixtures Containing Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) with Various Water Concentrations Extruded through 1mm Diameter Dies



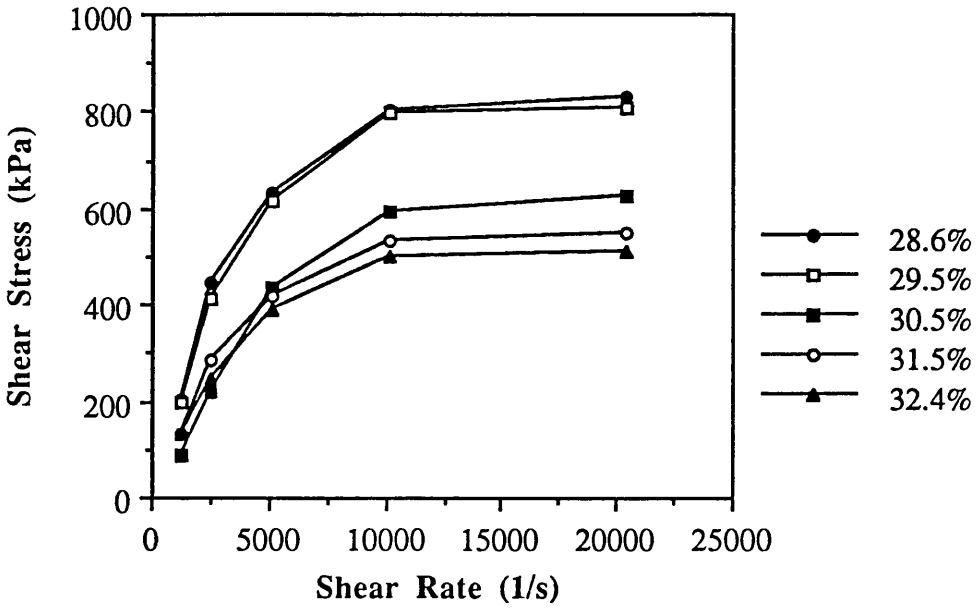
Although the differences in shear stress values between each formulation are small, the shape of flow curve produced by each formulation changes as the water content is varied. Increasing the water content lowers the shear stress recorded for each formulation at the same shear rate value. The difference in stress value between formulations is greatest when the shear rate is low. Fielden *et al.* (1989) has proposed that the greatest variation in the spheronised product of two formulations will occur when the materials are extruded at shear rates that maximise the differences in the resultant shear stresses. The shape of the flow curves are becoming increasingly Newtonian in behaviour with increasing water content.

2. 1.5mm Diameter Dies

The same lactose (7 parts) and microcrystalline cellulose (3 parts) formulations when extruded through 1.5mm diameter dies all produce shear thinning flow curves that begin to plateau between shear rates of 10,000 and 20,000s^{-1} (Figure 4.17). The differences in shear stress values recorded for each formulation at the same shear rate are greater than differences produced by extrusion through 1mm diameter dies (Figure 4.16). In particular there is a large difference in shear stress values produced by formulations containing 28.6% (4.0 parts) and 29.5% (4.2 parts) water and those

containing 30.5% (4.4 parts), 31.5% (4.6 parts) and 32.4% (4.8 parts) water. All formulations extruded through 1.5mm diameter dies produce flow curves that extrapolate to zero, i.e. they do not possess a yield stress value.

Figure 4.17 Shear Stress *vs* Shear Rate Profiles for Mixtures Containing Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) with Various Water Concentrations Extruded through 1.5mm Diameter Dies



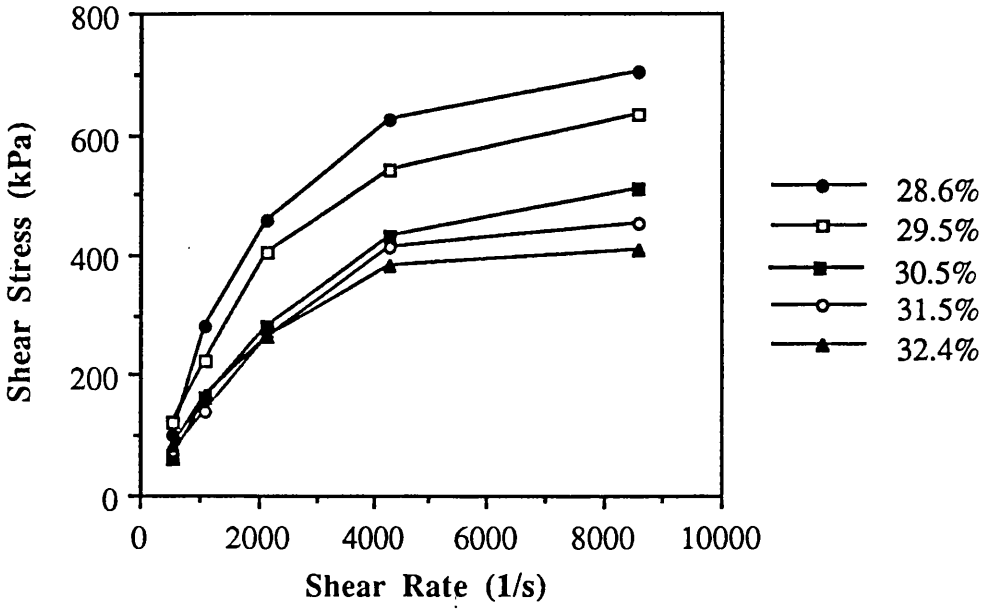
The flow curves produced using 1.5mm diameter dies do not appear to possess yield values whereas the shape of flow curves produced by 1mm diameter dies indicate yield values are present. Unlike the flow curves produced from 1mm diameter dies (Figure 4.16) differences in the shear stress values between formulations extruded through 1.5mm diameter dies increase with increasing shear rate. Hence variations in the quality of extrudate and spheroids between formulations are likely to arise when the rate of extrusion is increased.

3. 2mm Diameter Dies

Extrusion of the various formulations through 2mm diameter dies again produces flow curves that extrapolate to provide a zero yield stress for each mixture (Figure 4.18). There is a greater difference in shear stress values between each mix as the shear rate is increased as compared to differences produced by 1mm or 1.5mm diameter dies (Figures 4.16 and 4.17 respectively). The degree of stress produced as

the material is extruded appears to drop markedly between formulations containing 29.5% (4.2 parts) and 30.5% (4.4 parts) water. Similarly the shape of the flow curve begins to flatten as the moisture content is increased above 29.5% indicating that shear thinning is beginning to occur at a lower shear rate as the moisture content is increasing.

Figure 4.18 Shear Stress *vs* Shear Rate Profiles for Mixtures Containing Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) with Various Water Concentrations Extruded through 2mm Diameter Dies

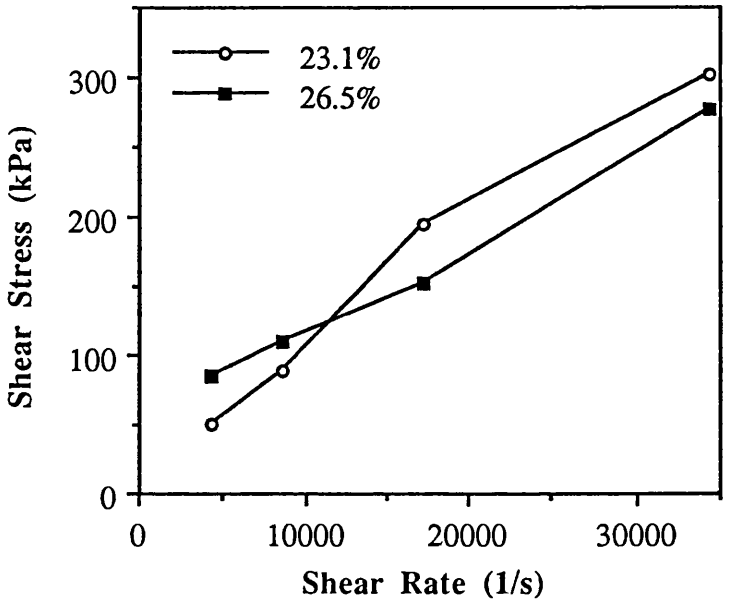


As with formulations extruded through 1.5mm diameter dies (Figure 4.17) the differences in the shear stress values recorded for each mixture when extruded through 2mm diameter dies increase with increasing shear rate. Therefore potential differences in the quality of extrudate and spheres are likely to occur at higher extrusion rates.

Comparison of Shear Stress *vs* Shear Rate Profiles for Mixtures Containing Lactose (8 Parts) and Microcrystalline Cellulose (2 Parts) with Two Quantities of Water Extruded Through 1mm Diameter Dies.

Extrusion of 8 : 2 lactose : microcrystalline cellulose mixtures through 1mm diameter dies produces flow profiles that appear similar in magnitude and shape (Figure 4.19).

Figure 4.19 Shear Stress *vs* Shear Rate Profiles for Mixtures Containing Lactose (8 Parts) and Microcrystalline Cellulose (2 Parts) with Two Water Concentrations Extruded through 1mm Diameter Dies



The two flow curves produced from 8 : 2 mixtures are approximately Newtonian in shape, particularly when compared to 7 : 3 mixtures extruded through 1mm diameter dies (Figure 4.16). The shear stress values recorded at low shear rates are lower than those produced by 7 : 3 mixes but become greater as the shear rate increases. The flow curve produced by the mixture containing 23.1% does not demonstrate a yield stress on extrapolation to the Y-axis unlike that produced by a mixture containing 26.5% moisture which would appear to have a yield stress value. This apparent anomaly may be due to the high degree of moisture movement that occurs with extrudate produced by a formulation containing 23.1% water. The steady-state stage of extrusion is very short and, although the pressure recorded for the mix at each l/r die ratio is greater than that for the higher moisture content mix, the pressure differences between l/r ratios at low ram velocities are less than the higher moisture content formulation (*cf.* Figure 4.19).

4.2 SPHERONISATION

Spheronisation was performed on 7 : 3 and 8 : 2 lactose : microcrystalline cellulose mixtures with varying water contents that had been extruded under standard conditions (*cf.* Section 3.2.3). Only extrudate that had been produced during steady-state flow extrusion was used for spheronisation (*cf.* Section 3.2.2). Each formulation was spheronised for 20 seconds, 1 minute, 2, 5, 10 and 20 minutes in the case of 7 : 3 mixtures and for 20 seconds, 1 minute, 2, 5 and 10 minutes in the case of 8 : 2 blends in order to assess the effect of processing time on the final size and shape of the product. A new batch of extrudate of each formulation was prepared for each individual spheronisation time. Other spheronisation variables were kept constant (*cf.* Section 3.2.3).

Size and shape analysis were performed on spheres produced to establish the effect of formulation on sphere quality and to identify the optimum conditions for producing 7 : 3 and 8 : 2 lactose : microcrystalline spheres.

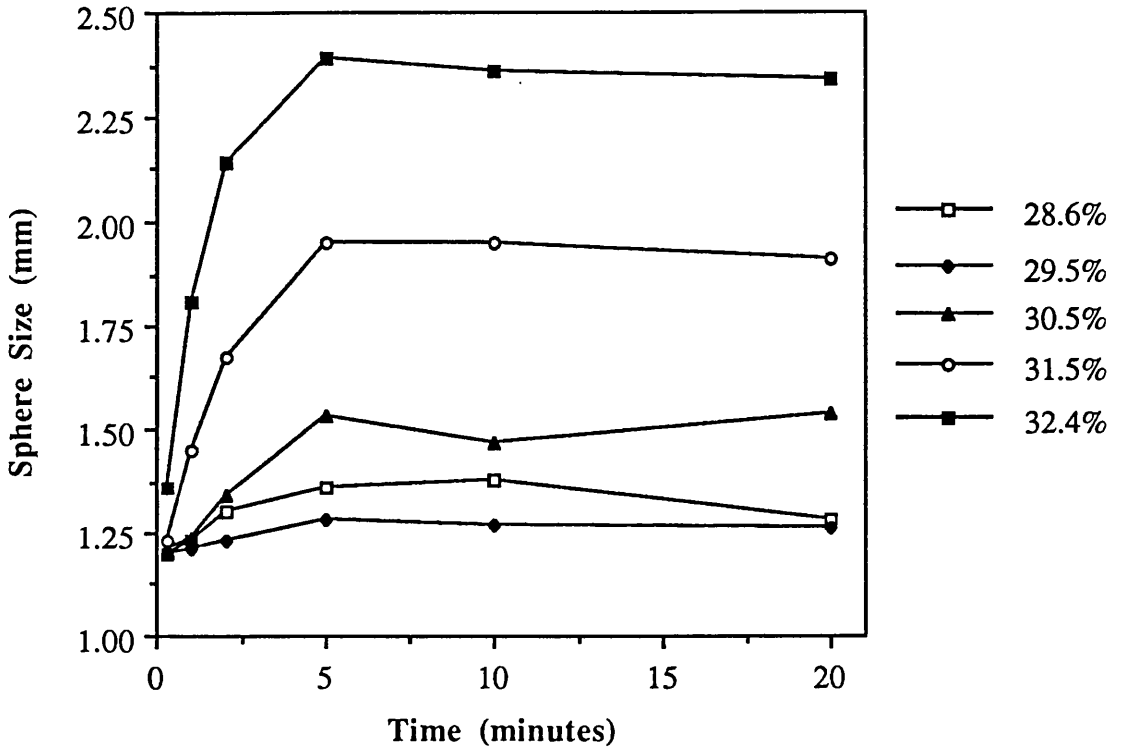
4.2.1 7 : 3 Lactose : Microcrystalline Cellulose Formulations

Five formulations of 7 : 3 lactose : microcrystalline cellulose mixtures were investigated to assess the effect of moisture on sphere quality. Formulations based on 4.0 parts water (28.6%), 4.2 parts (29.5%), 4.4 parts (30.5%), 4.6 parts (31.5%) and 4.8 parts (32.4%) were studied.

The Effect of Spheronisation Time on Sphere Size

A graph demonstrating the influence of spheronisation time on the median weight diameter of all spheres produced from 7 : 3 lactose : microcrystalline cellulose formulations with varying water contents was constructed (Figure 4.20). The graph demonstrates that with an increase in water content there is an increase in sphere size. Sphere growth is completed within a spheronisation time of 5 minutes for all formulations, with only minor changes in sphere size occurring with longer spheronisation times.

Figure 4.20 The Influence of Spheronisation Time on the Sphere Size (Median Weight Diameter) For Mixtures of Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) with Various Water Contents.



A 7 : 3 : 4.0 Lactose : Microcrystalline Cellulose : Water Formulation

From the results contained in Figure 4.20 extrudate with a moisture content of 28.6% and a nominal 1mm diameter after extrusion, does not form spheroids with a diameter of 1mm. Previous studies (Chapman, 1985) have determined that spheres manufactured by extrusion/spheronisation are approximately 1.2x the diameter of the initial extrudate. The extrudate under investigation quickly produces spheroids of a diameter even greater than 1.2mm. With an increasing spheronisation time of up to 10 minutes the spheroids continue to grow to a maximum size of just over 1.35mm. However spheroids that have been processed for 20 minutes have become smaller in size than those produced after 10 minutes. This is due to the continual effects of attrition that occur between individual spheroids and between spheroids and the walls of the spheroniser after the initial rounding stage has been completed. An increase in spheronisation time can also lead to further size reduction as the material is compressed and densifies, with the possible loss of some moisture, under the continuing influence of spheronising forces.

The growth of spheroids is due to excess moisture in the initial extrudate which is forced to the surface during spheronisation. The surface moisture allows other spheroids or strands of extrudate to adhere to each other as the spheronisation continues. The degree to which spheroid growth occurs is dependant on how much excess moisture is present.

A 7 : 3 : 4.2 Lactose : Microcrystalline Cellulose : Water Formulation

Spheronisation of extrudate with a moisture content of 29.5% water demonstrates that with an increasing spheronisation time of up to 5 minutes the size of spheres produced increases (Figure 4.20). Samples of spheres taken after 10 and 20 minutes of spheronisation have not grown any further and have actually reduced in size from those produced after 5 minutes spheronisation. This phenomenon can again be attributed to the continual erosion of spheres and compression effects that occur in the spheronising chamber after the initial rounding phase has been completed.The initial rounding period during spheronisation is shorter for extrudate with a 29.5% water content than for extrudate with a 28.6% water content. Similarly at all equivalent spheronisation times, the extrudate containing 29.5% water produces spheres that have a smaller median weight diameter that those produced by the extrudate containing 28.6% water. This implies that the extrudate of 28.6% water content is slightly too dry to produce optimal quality spheres in comparison to spheres produced by extrudate with a 29.5% moisture content.

A 7 : 3 : 4.4 Lactose : Microcrystalline Cellulose : Water Formulation

Extrudate with a 30.5% water content continues the pattern established by extrudate with 28.6% and 29.5% water contents (Figure 4.20). With an increasing spheronisation time of up to 5 minutes the size of spheres produced increases. After 10 minutes spheronisation the spheres have rounded and become slightly smaller due to frictional forces. However after 20 minutes spheronisation the frictional forces have been overcome by residual moisture that has collected in the spheronising chamber. This moisture is produced as the spheres begin to dry in the chamber and water is driven out of them by the spheronising forces. The moisture acts as a binder and promotes agglomeration of spheres to produce particles that are slightly larger than those produced after 10 minutes spheronisation.

Spheres produced by a formulation with 30.5% moisture are larger than those produced by a mixture with a moisture content of 29.5%. Further increases in the water content of extrudate will increase the size of spheres produced from spheronisation.

A 7 : 3 : 4.6 Lactose : Microcrystalline Cellulose : Water Formulation

The spheres produced from extrudate with a 31.5% water content demonstrate agglomeration as the spheronisation time increases. After only 1 minute three distinct types of spheroid have begun to form, hence the wide size variations that are observed between 1, 2 and 5 minute spheronisation samples (Figure 4.20). The first type of spheroid has very quickly undergone the cutting and rounding process that is described previously (*cf.* Section 1.5), producing relatively small, rounded spheres. The second type of spheroid has been formed by a moulding process where the extrudate has been moulded into crescent-shaped particles whose open ends fuse to produce one large spheroid. This process occurs because the initial extrudate is too wet and plastic and therefore not brittle enough to allow cutting of the extrudate into short strands prior to rounding. The third type of spheroid observed is an amalgam of two of the crescent-shaped strands of extrudate that produces one very large diameter spheroid.

Due to the high moisture content of the spheroids many of them impact against each other and fuse as the spheronisation process continues. After 5 minutes spheronisation the spheroids have grown in size to almost double the diameter of the initial extrudate but due to the elimination of small spheroids through adhesion, the size distribution has diminished. With 10 and 20 minute spheronisation times there is no further increase in particle size. Instead there is a slight size reduction as the counteracting forces of moisture accumulation in the spheronising chamber and inter-particulate frictional forces balance each other. There is also a slight reduction in particle size distribution with increasing spheronisation time as sphere size becomes more uniform.

A 7 : 3 : 4.8 Lactose : Microcrystalline Cellulose : Water Formulation

The wettest extrudate that spheronisation was attempted on (32.4% water content) produced spheres larger than those produced by extrudate with a moisture content of 31.5%. This time the small number of spheres that were produced by the classic spheronisation procedure with extrudate of 31.5% moisture content are absent. Instead after only 20 seconds there is considerable agglomeration which continues up to a spheronisation time of 5 minutes (Figure 4.20). Spheres produced by this formulation are even larger than those formed previously due to an agglomeration process that fuses three or more spheres together to form one large spheroid. As with the previous extrudate containing a moisture content of 31.5%, extrudate containing 32.4% water when spheronised for 10 and 20 minutes does not possess significantly altered particle sizes of spheroids but longer spheronisation times do act to narrow the size distribution of spheroids produced. This is due to the dual influences of accumulated moisture

promoting further agglomeration of small spheres and the continuing effect of spheronising forces causing sphere compression.

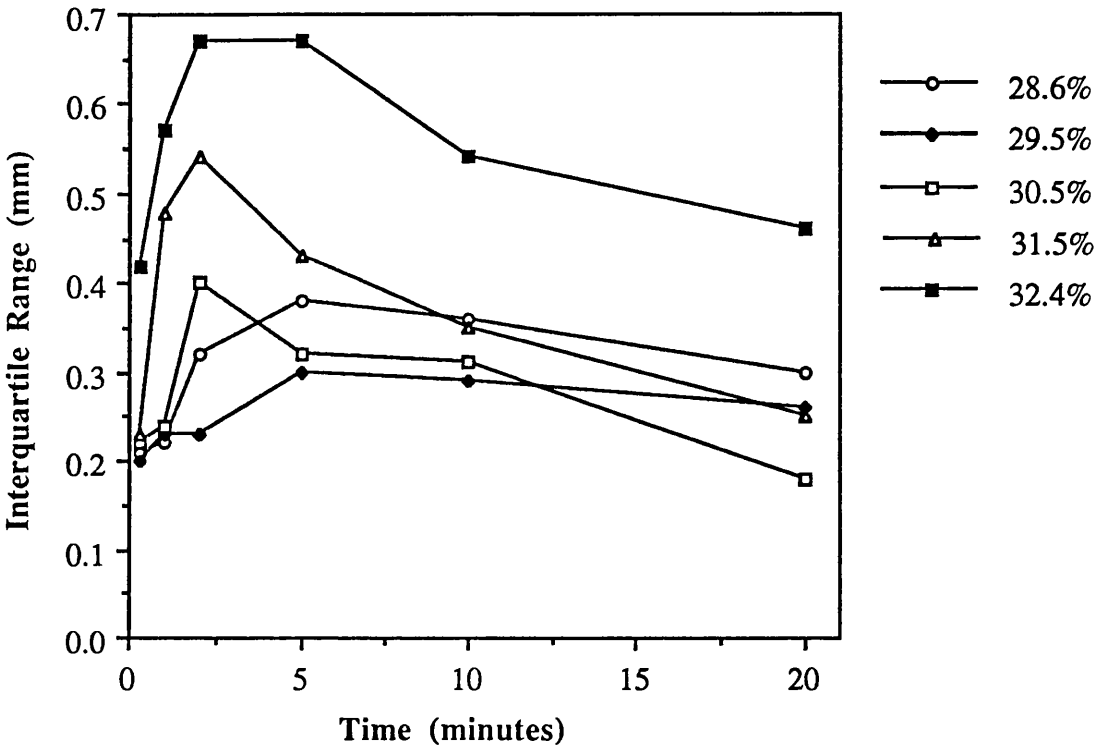
Given a nominal extrudate diameter of 1mm produced from a 1mm diameter die, a formulation of 7 : 3 lactose : microcrystalline cellulose containing 29.5% water is the optimum formulation examined as it comes closest to producing spheres of a size of 1mm. Results with this formulation confirm the observations of Chapman (1985) that ideal extrudate should produce spheres approximately 1.2 times the diameter of the initial extrudate.

Formulations with overall water contents plus or minus 1% of the optimum (i.e. 28.6% and 30.5% contents) appear to be the next best at producing relatively small-sized spheres. The extrudate produced by the wetter formulation (30.5%) has become slightly too wet and caused some agglomeration of spheres. Spheronisation of the drier formulation (28.6%) has also resulted in some agglomeration because the extrudate produced is wetter than the original water content of the mass prior to extrusion. This is due to the short period of steady-state flow that exists before the onset of forced flow during extrusion. A short period of steady-state flow results in lower extrudate yields than those produced for wetter formulations and increases the possibility of wetter, forced-flow extrudate contaminating the spheronisation chamber. The steady-state extrudate itself may also be wetter than the original formulation indicated due to the migration of water towards the end of the barrel during extrusion.

Formulations with water contents greater than 40.5% produce agglomerated spheroids far larger than the diameter of the initial extrudate. These formulations are of little use since the rate and degree of agglomeration are impossible to control accurately to manufacture a uniform product.

The spread of sphere sizes produced by each formulation at each spheronisation time can be assessed by examination of the interquartile range for each set of spheres. Figure 4.21 illustrates the effect of increasing spheronisation time on the five 7 : 3 lactose : microcrystalline cellulose mixtures considered.

Figure 4.21 The Effect of Spheronisation Time on The Interquartile Range of Spheres For Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) Mixtures With Varying Moisture Contents.

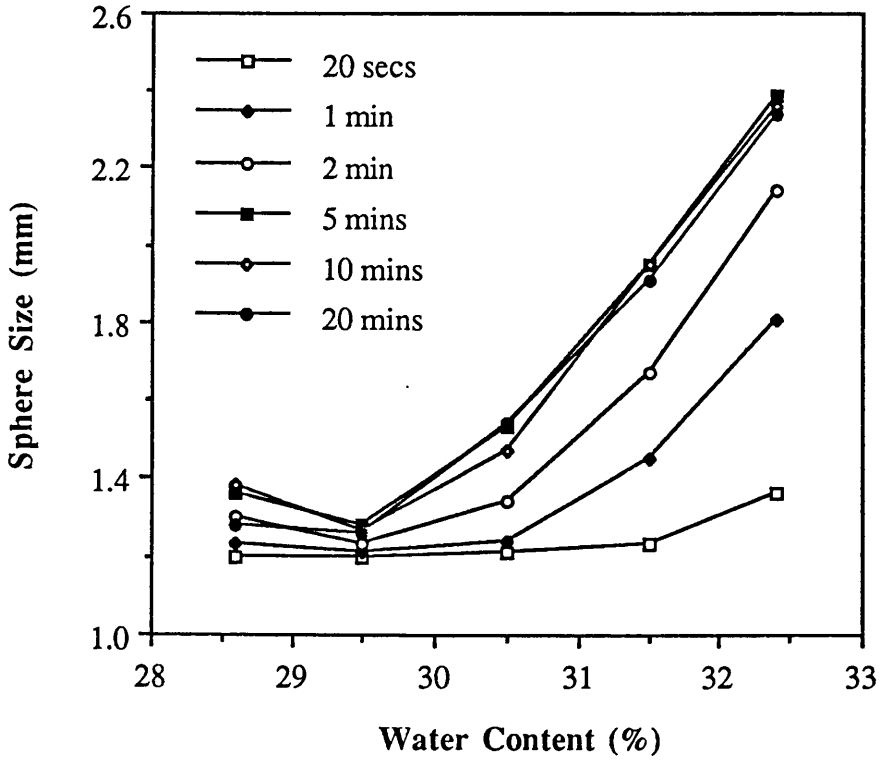


Results for formulations containing 28.6% and 29.5% moisture do not have large interquartile ranges and do not appear to vary widely with changes in spheronisation time. This suggests that the extrudate from these two formulations behaves in a uniform fashion during spheronisation. As the moisture content of the formulation increases there is an increase in the changes in interquartile range with spheronisation time. This demonstrates the variable nature of spheroid size that occurs as the moisture content is increased.

To produce spheres from 7 : 3 lactose : microcrystalline cellulose requires very specific quantities of water. These quantities are subject to only a minimal variation (+/- 3% of the optimal moisture content) before sphere size is compromised. Figure 4.22 demonstrates the effect of increasing moisture content on the size of spheres produced with an increase in spheronisation time. This sensitivity is not as apparent in formulations of 5 : 5 lactose : microcrystalline cellulose where larger changes in

moisture content (+/- 7% of optimum water content) still allow the production of good quality spheres (Chapman, 1985). The results are in agreement with the observations of Bains *et al.* (1991) who stated that decreasing the microcrystalline cellulose content of the formulation increased the sensitivity of moisture in determining final sphere quality. Consequently formulations of 8 : 2 lactose : microcrystalline cellulose may be expected to be even more susceptible to agglomeration during spheronisation with only slight modifications in moisture content than 7 : 3 lactose : microcrystalline cellulose mixtures.

Figure 4.22 The Influence of Moisture Content on the Sphere Size (Median Weight Diameter) for a Mixture containing Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) at Various Spheronisation Times.



The Effect of Spheronisation Time on Sphere Shape

Sphere shaping studies were undertaken using the OPCS method of analysis (*cf.* Section 2.3.1) to determine the sphericity of granules formed after extrusion/spheronisation of 7 : 3 lactose : microcrystalline cellulose formulations with varying water contents and spheronisation times. Studies were undertaken on the largest sieve fraction of spheres recorded for each spheronisation time.

The results contained in Figures 4.23 - 4.27 demonstrate that an increasing spheronisation time increases the roundness of spheroids produced by all the extrudates under investigation. Similarly, with an increasing spheronisation time, the variation in shape of individual batches of spheroids, as measured by the standard deviation, is reduced. In general the spread of shapes produced from each formulation (as determined by the standard deviation) increases with increasing water content.

Figure 4.23 The Influence of Spheronisation Time on the Shape of Particles Produced from a Mixture of Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) Containing 4.0 Parts Water (28.6%).

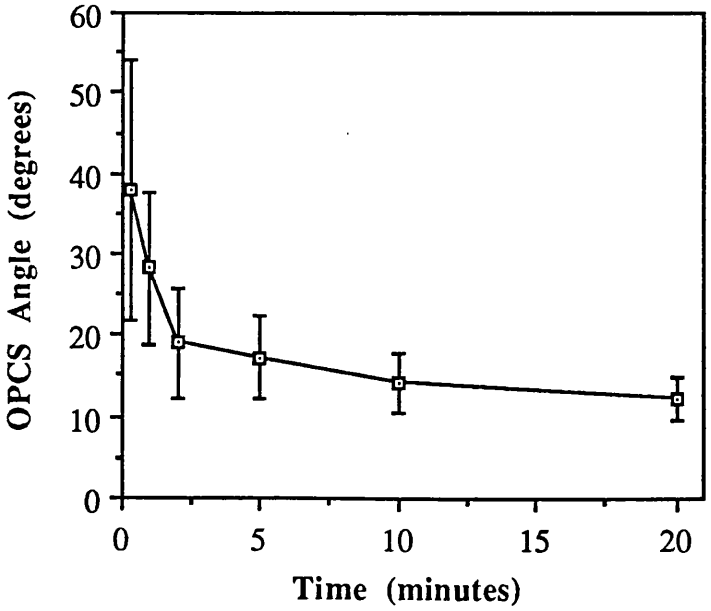


Figure 4.24 The Influence of Spheronisation Time on the Shape of Particles Produced from a Mixture of Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) Containing 4.2 Parts Water (29.5%).

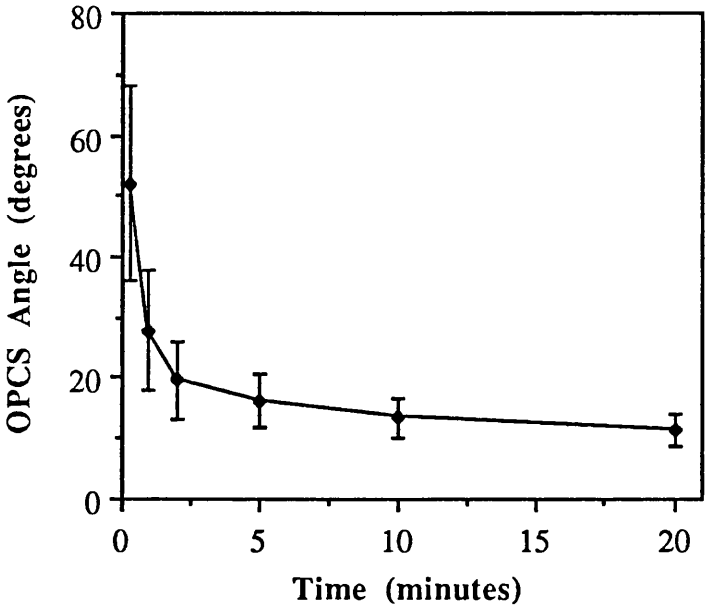


Figure 4.25 The Influence of Spheronisation Time on the Shape of Particles Produced from a Mixture of Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) Containing 4.4 Parts Water (30.5%).

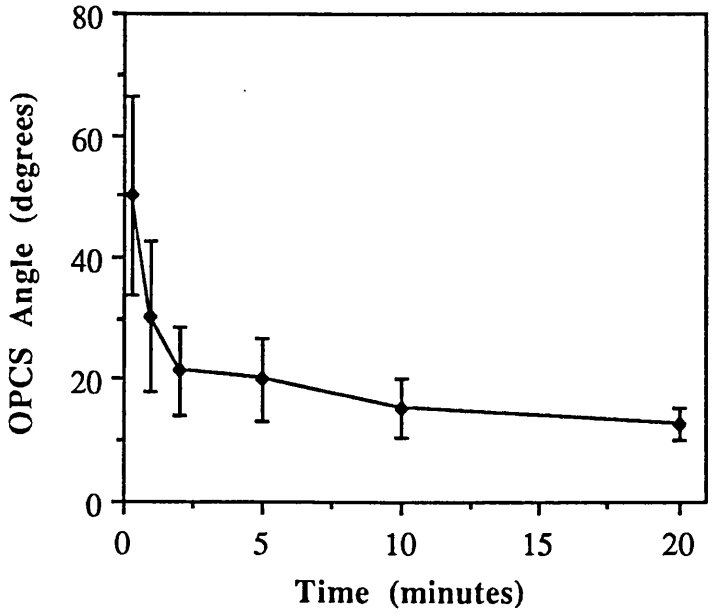


Figure 4.26 The Influence of Spheronisation Time on the Shape of Particles Produced from a Mixture of Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) Containing 4.6 Parts Water (31.5%).

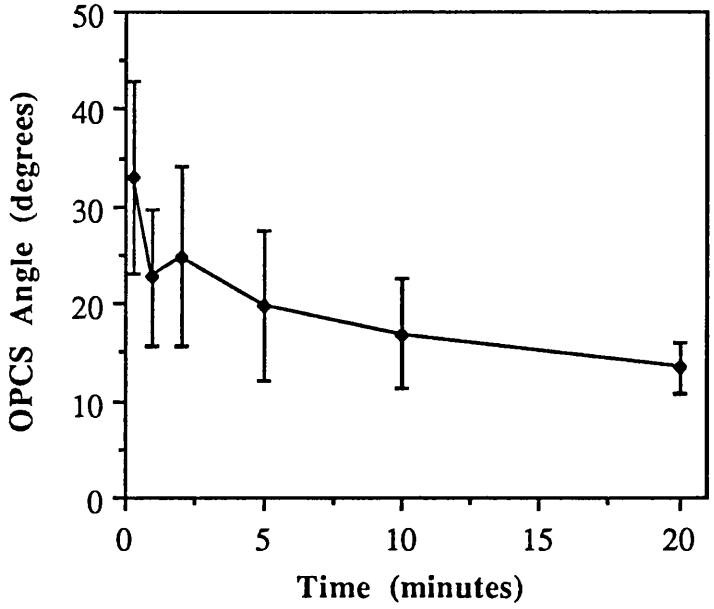
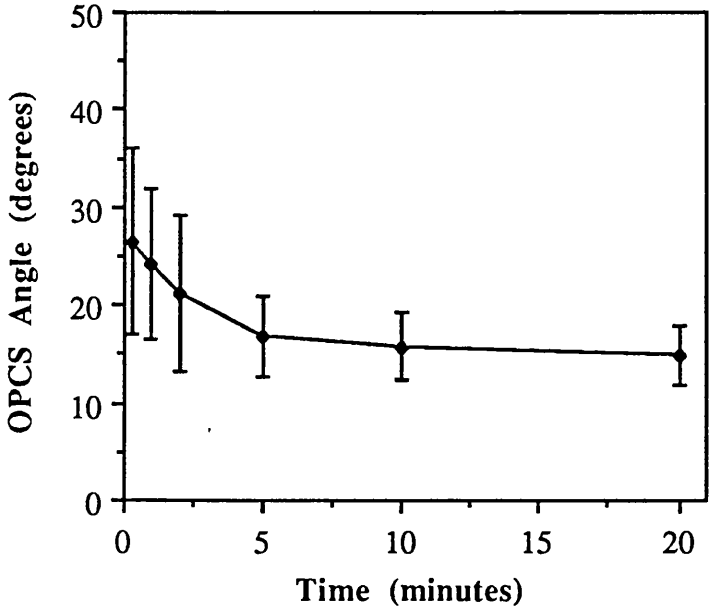


Figure 4.27 The Influence of Spheronisation Time on the Shape of Particles Produced from a Mixture of Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) Containing 4.8 Parts Water (32.4%).



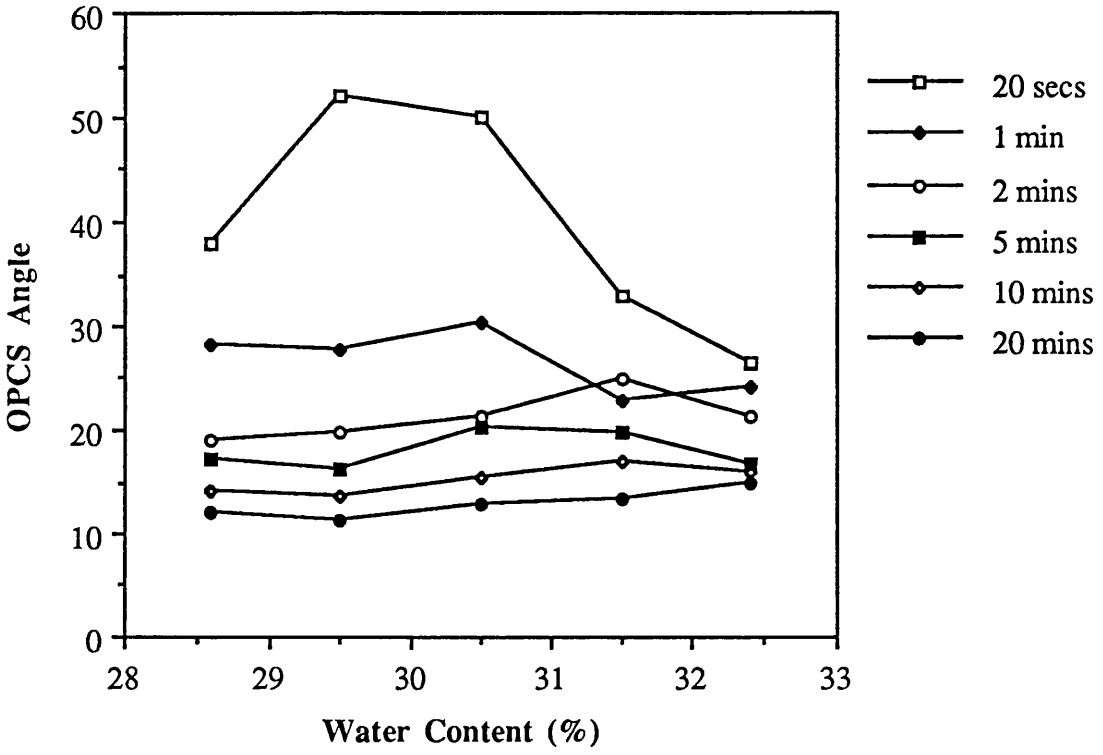
From the results in contained in Figures 4.23 - 4.27 the standard deviation of OPCS angle values for spheres indicate that there is greater shape variation with drier formulations than with wetter formulations at short spheronisation times. Similarly drier extrudates retain a rod-like structure for longer spheronisation times (mean OPCS angles > 40^{o}) since it takes longer for dry material to be fully chopped into short strands and rounded (Figure 4.28).

The spheronisation process described by Rowe (1985) highlights five distinct stages as extrudate move from a cylindrical state to spheroids [*cf.* Section 1.5]. For the formulations under consideration only extrudate with a moisture content of 29.5% exhibits all the stages (Figure 4.24). As the extrudate becomes wetter (Figures 4.25 - 4.27) the initial phases of spheronisation, the cutting and rounding of the cylindrical extrudate, are lost. This is due to the excess moisture causing the spheronising forces to agglomerate and mould the extrudate rather than allowing them to reduce the overall length of each strand of extrudate.

OPCS measurements do not take into account the actual dimensions of the spheroids investigated so direct information about agglomeration cannot be obtained. However with an increase in water content there is an increase in likelihood of agglomeration occurring and strands of extrudate that agglomerate form irregular-shaped spheroids that may possess high OPCS angle values. Therefore with an increase in spheronisation time there is less of a reduction in the spread of sphere shapes with wetter formulations than with drier formulations. In effect, wetter formulations re-round with increasing spheronisation times as previously rounded spheroids agglomerate into non-spherical aggregates.

From the results contained in Figure 4.28 it appears that with an increasing water content there is a decrease in the mean OPCS angle value obtained from spheres produced after 20 seconds of spheronisation. Extrudate with an increasing water content becomes much more deformable than extrudate with a low water content. Consequently there is a rapid decrease in mean OPCS angle values (angles < 40^{o}) after short spheronisation times with formulations of high water content. The exception to this pattern is the formulation containing 28.6% moisture which at 20 seconds spheronisation time has spheroids with a lower OPCS mean value than a mixture containing 29.5% moisture. This is due to the extrudate produced having a higher than expected moisture content due to a shorter steady-state flow region.

Figure 4.28 The Influence of Water Content on the Shape of Spheroids (determined by OPCS Angle) Produced by a Mixture of Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts).



The reduction in the OPCS angle measurements for each formulation with increasing spheronisation time means that each formulation forms spheroids after no more than 5 minutes spheronisation (OPCS angle < 25°). The most rounded spheroids with the lowest standard deviation in OPCS angles occur with a formulation containing 29.5% moisture (Figure 4.28). Therefore the 7 : 3 lactose : microcrystalline cellulose formulation that forms the 'best' spheroids in terms of shape and shape distribution contains 29.5% water.

Conclusions

It is possible to manufacture spherical granules from formulations of 7 : 3 lactose : microcrystalline cellulose containing various moisture contents. These observations support results from previous studies (Reynolds, 1970; Woodruff and Nuessle, 1972).

For the formulations studied spheronisation times of 5 minutes are sufficient for sphere formation to be completed. However rounding continues for as long as the

extrudate remains in the spheronising chamber. This rounding and the continuing effects of spheroniser forces on the spheroids affect final sphere size and hence there is a general decrease in sphere size after 5 minutes.

A formulation of 7 : 3 lactose : microcrystalline cellulose containing 29.5% water produces spheres of the optimum size, size distribution, shape and shape distribution. For this formulation the ratio of microcrystalline cellulose content to water content is 1 : 1.4. This is an increase in ratio compared to 5 : 5 lactose : microcrystalline cellulose mixtures where optimum sphere size and shape is produced with a microcrystalline cellulose : water ratio of 1 : 1.2 (Chapman, 1985). Therefore with 7 : 3 lactose : microcrystalline cellulose formulations there has been an increase in the relative amount of water required to allow for the production of good quality extrudate and subsequently good quality spheres, although the actual amount of water required to extrude the material has been reduced (29.5% moisture for a 7 : 3 mixture compared to 37.5% moisture for a 5 : 5 blend).

4.2.2 8 : 2 Lactose : Microcrystalline Cellulose Formulations

Four formulations of lactose (8 parts) and microcrystalline cellulose (2 parts) were studied to determine the effects of water content on the size and shape of spheroids produced by extrusion/spheronisation. These formulations contained 3.0 parts water (23.1%), 3.2 parts (24.2%), 3.4 parts (25.4%) and 3.6 parts water (26.5%). An increase in the amount of soluble 'drug' component, e.g. lactose, and consequently the reduction in microcrystalline cellulose reduces the amount of water required for successful extrusion. However it may make subsequent spheronisation of extrudate more sensitive to moisture content when determining optimal size and shape.

All materials were extruded through the same 1mm diameter die at the same extrusion rate as spheroids prepared with 7 : 3 lactose : microcrystalline cellulose mixtures. Only extrudate produced during the steady-state stage of extrusion was used for each spheronisation.

Direct Comparison of Median Weight Diameters of Spheres Produced by 8 : 2 Lactose : Microcrystalline Cellulose Blends with Various Water Contents

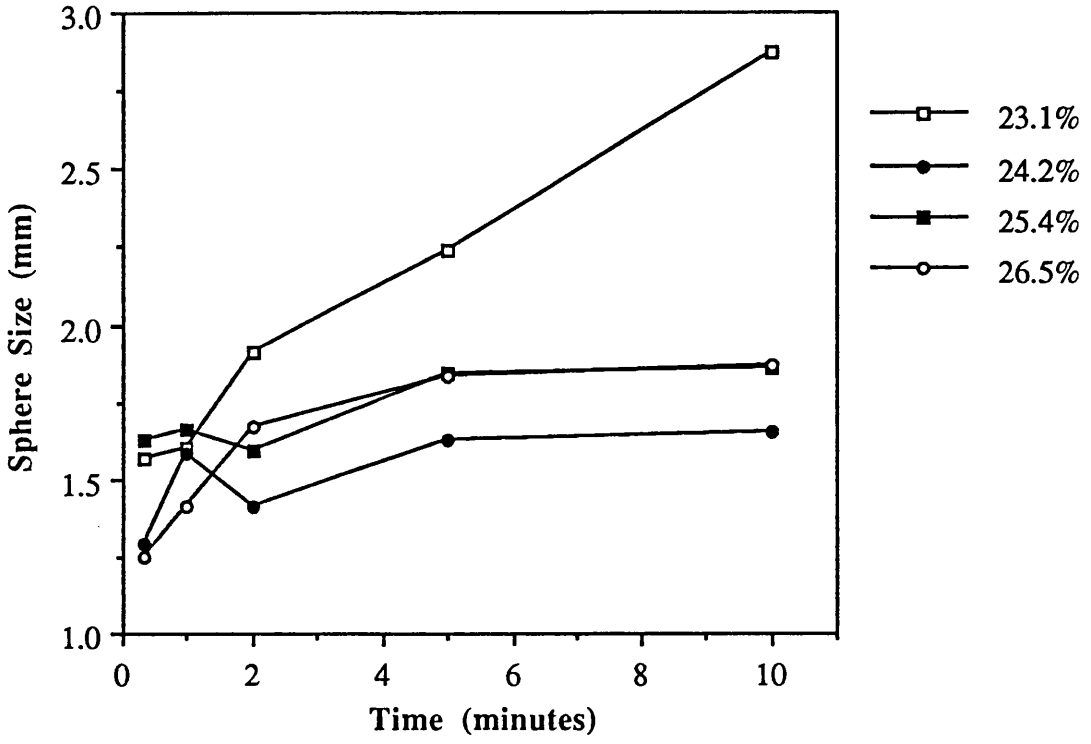
The influence of spheronisation time on the median weight diameter of all spheres produced from 8 : 2 lactose : microcrystalline cellulose formulations with varying water contents was constructed (Figure 4.29). The change in the interquartile range of sphere sizes with an increase in spheronisation time for all the formulations examined was also plotted (Figure 4.31). As with 7 : 3 lactose : microcrystalline cellulose formulations (Figure 4.16) sphere growth is completed within a spheronisation time of 5 minutes for all formulations except for a mixture containing 23.1% moisture which continues to grow after 10 minutes spheronisation time.

An 8 : 2 : 3.0 Lactose : Microcrystalline Cellulose : Water Formulation

A lactose (8 parts) and microcrystalline cellulose (2 parts) formulation containing 23.1% water (3.0 parts) was the driest mixture extruded and then spheronised. Results from spheronisation (Figure 4.29) suggest that the extrudate immediately begins to agglomerate when it is placed in the spheronising chamber. This agglomeration continues until the spheroniser was stopped after 10 minutes with the resultant spheroids becoming unmanageable in size (median weight diameter of approximately 3mm).

Although the initial moisture content of the mixture was 23.1%, the extrudate produced contains a far greater water content due the large amount of forced flow that occurs during extrusion. Extrudate that is collected only during the steady-state stage of extrusion still has a greater water content than 23.1%. Consequently there is large amount of agglomeration during spheronisation. An increase in the initial water content of the formulation may reduce the tendency for forced flow during extrusion and prevent agglomeration of extrudate during spheronisation.

Figure 4.29 The Influence of Spheronisation Time on the Sphere Size (Median Weight Diameter) For Mixtures of Lactose (8 Parts) and Microcrystalline Cellulose (2 Parts) with Various Water Contents.



An 8 : 2 : 3.2 Lactose : Microcrystalline Cellulose : Water Formulation

Increasing the moisture content of the 8 : 2 lactose : microcrystalline cellulose formulation from 23.1% to 24.2% (3.2 parts) reduces the amount of agglomeration produced by extrudate after spheronisation (Figure 4.29).

Extrudate with an initial formulation moisture content of 24.2% (3.2 parts water) produces spheroids that are greater in diameter than the 1mm die diameter. In the first two minutes of spheronisation extrudate is first cut to provide short stranded rods of material before accumulation of moisture promotes some agglomeration. The spheronising forces prevent further agglomeration after five minutes spheronisation and the spheroids continue to round in the intervening period. The agglomeration of spheroids is limited compared with the formulation containing 23.1% moisture (Figure 4.29) as there is less forced flow in the original extrusion of the material.

An 8 : 2 : 3.4 Lactose : Microcrystalline Cellulose : Water Formulation

As the moisture content of the blend continues to rise extrudate becomes again progressively wetter, although the incidence of forced flow during extrusion is reduced. Increasing the moisture content to 25.4% (3.4 parts) produces extrudate that does not have a chance round before some agglomeration occurs (Figure 4.29). This prevents any size reduction from the initial rod-like strands produced during the cutting stage of spheronisation.

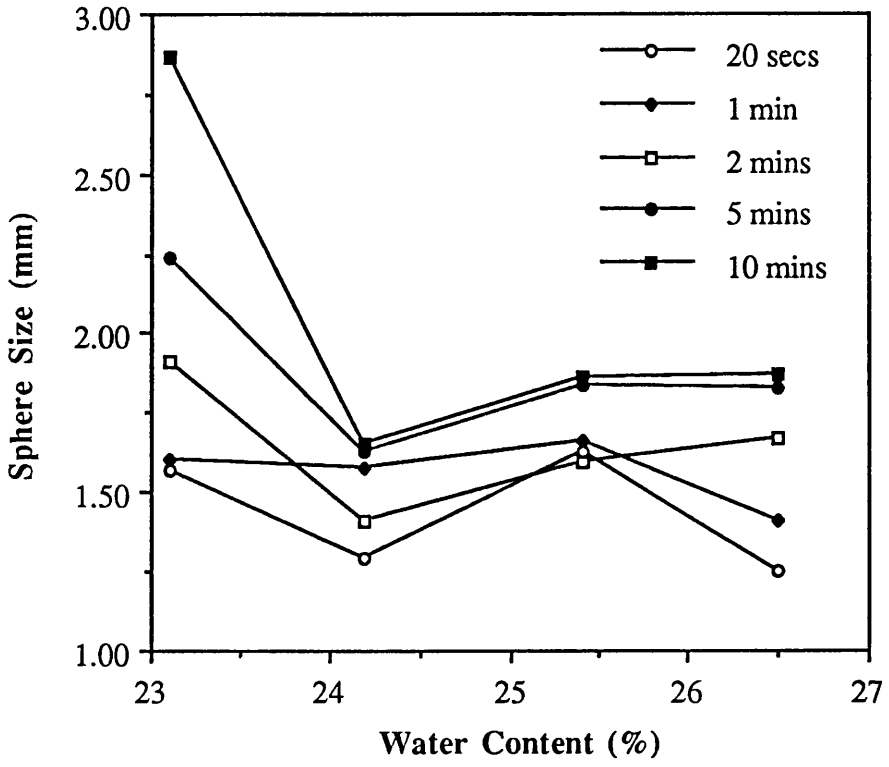
However the moisture content remains low enough that a plateau in the spheroid size occurs after 5 minutes spheronisation. Therefore a formulation containing 25.4% moisture produces spheres that are smaller in size than those produced by a formulation containing 23.1% moisture (Figure 4.29).

An 8 : 2 : 3.6 Lactose : Microcrystalline Cellulose : Water Formulation

Extrudate with a moisture content of 26.5% produces spheroids that increase in diameter as the spheronisation time increases (Figure 4.29). However further growth of the spheroids is very limited after 5 minutes spheronisation.

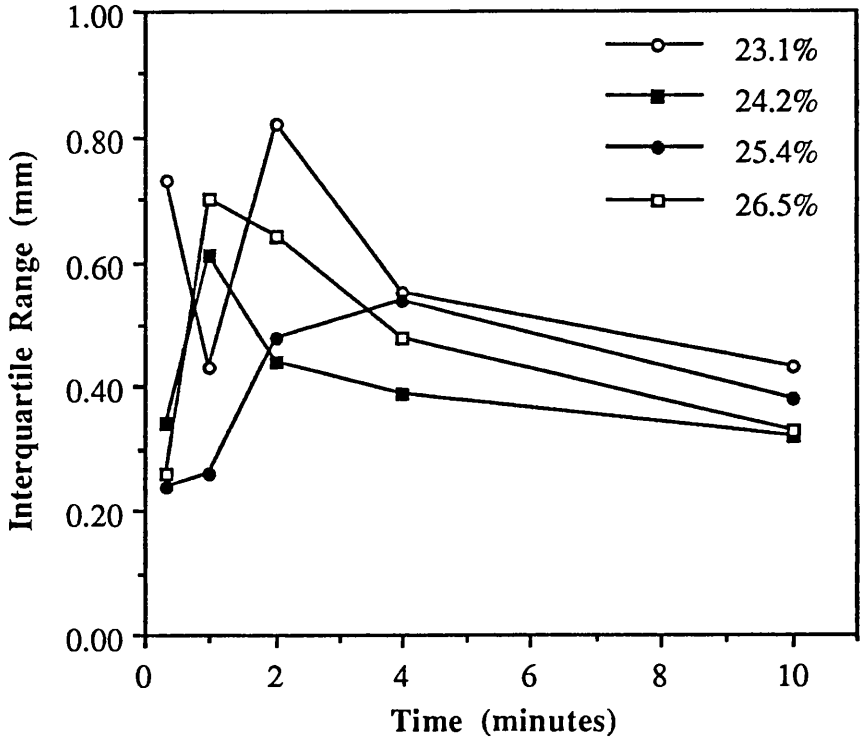
From those 8 : 2 lactose : microcrystalline cellulose formulations examined the closest to producing optimum-sized spheres of diameters between 1 - 1.2mm contains a moisture content of 24.2% (Figure 4.30). This mixture produces the smallest sized spheres of approximately 1.6mm diameter. Formulations with greater amounts of water than 24.2% are capable of producing spheres but these are markedly larger in size than drier formulations and their growth is difficult to predict (approximately 1.8mm in diameter for blends containing 25.4 and 26.5% moisture). Formulations with less water than 24.2% are likely to produce forced-flow extrudates with widely variable moisture contents. Even although extrudate was collected during the steady-state stage of extrusion only this period is very short and contains more moisture than the initial formulation. These extrudates promote the agglomeration of granules during the spheronisation process and consequently are unsuitable materials for spheronisation (Figure 4.30).

Figure 4.30 The Influence of Moisture Content on the Sphere Size (Median Weight Diameter) for a Mixture Containing Lactose (8 Parts) and Microcrystalline Cellulose (2 Parts) at Various Spheronisation Times.



Further evidence of the optimal formulation for spheroids is produced by plotting the interquartile range for each formulation with an increase in spheronisation time (Figure 4.31). This graph indicates the size variation in each set of spheres produced. With an increase in spheronisation time the spread of sizes of spheres decreases for all formulations studied. However the smallest spread of sizes is produced by the formulation containing 24.2% moisture.

Figure 4.31 The Effect of Spheronisation Time on The Interquartile Range of Spheres For Lactose (8 Parts) and Microcrystalline Cellulose (2 Parts) Mixtures With Varying Moisture Contents.



The effect of moisture on the size of spheres produced by 8 : 2 blends of lactose and microcrystalline cellulose is more marked than the effect of moisture on 7 : 3 blends. The increase in the amount of soluble 'drug' material and the subsequent reduction in the amount of the 'sponge-like' microcrystalline cellulose results in less room for error in the correct amount of water that will allow for successful extrusion and spheronisation. In terms of producing spheroids of a diameter of approximately 1.2mm no formulation containing 8 parts lactose and 2 parts microcrystalline cellulose appears to be capable of performing the task, without resort to manipulation of the conditions under which spheronisation takes place e.g variation in the spheronising load, spheroniser plate geometry, spheroniser size or speed.

The Effect of Spheronisation Time on Sphere Shape

The results contained in Figures 4.32 - 4.35 indicate that all 8 : 2 formulations studied provide spheroids after 10 minutes spheronisation since the OPCS for each sample after 10 minutes is below 20°. With an increasing spheronisation time the OPCS angle falls as the extrudate rounds off and the standard deviation of samples falls producing more homogenous shape distributions.

The OPCS angles for 20 second samples for all 8 : 2 mixtures (Figure 4.36) are lower than those produced for 7 : 3 formulations (Figure 4.28). This suggests that the 8 : 2 mixtures have not undergone the established method of spheronisation that recognises five distinct stages of the process (*cf.* Section 1.5). OPCS values for 20 seconds spheronisation times of about 35° for each formulation indicate that samples have either been cut and begun to round very quickly or that the initial rod-like structures have been been moulded without cutting. As moisture contents are critical and sieve sizing results indicate an immediate 'growth' of spheroids beyond predicted 1.2mm diameters, the latter mechanism can be concluded to have occurred. Extrudate that has a low moisture content is also likely to be more brittle and consequently may break more easily and quickly under the influence of the spheronising forces (*cf.* Figure 4.30).

Direct comparison of spheroids produced by 8 : 2 formulations with various water contents demonstrates that there is little difference in the shape of spheres after 10 minutes spheronisation and that no one particular formulation produces rounder spheroids than another (Figure 4.36). However the size analysis of spheres illustrates that a formulation containing 24.2% moisture provides the optimum sized spheres. Consequently a formulation containing 24.2% moisture yields the best spheres in terms of size and shape from those 8 : 2 lactose : microcrystalline cellulose mixture studied.

Figure 4.32 The Influence of Spheronisation Time on the Shape of Particles Produced from a Mixture of Lactose (8 Parts) and Microcrystalline Cellulose (2 Parts) Containing 3.0 Parts Water (23.1%).

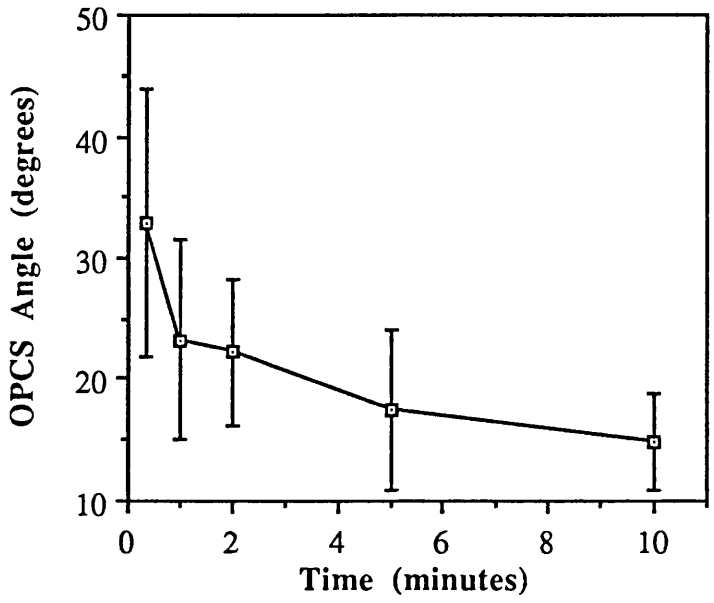


Figure 4.33 The Influence of Spheronisation Time on the Shape of Particles Produced from a Mixture of Lactose (8 Parts) and Microcrystalline Cellulose (2 Parts) Containing 3.2 Parts Water (24.2%).

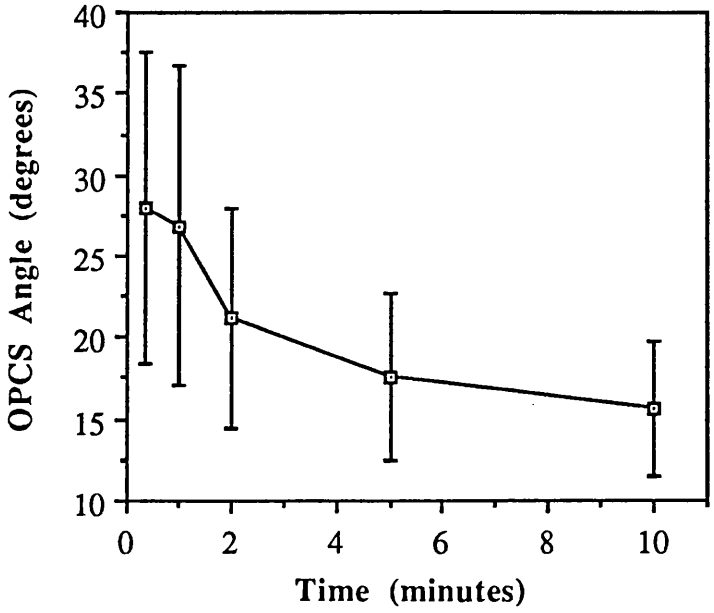


Figure 4.34 The Influence of Spheronisation Time on the Shape of Particles Produced from a Mixture of Lactose (8 Parts) and Microcrystalline Cellulose (2 Parts) Containing 3.4 Parts Water (25.4%).

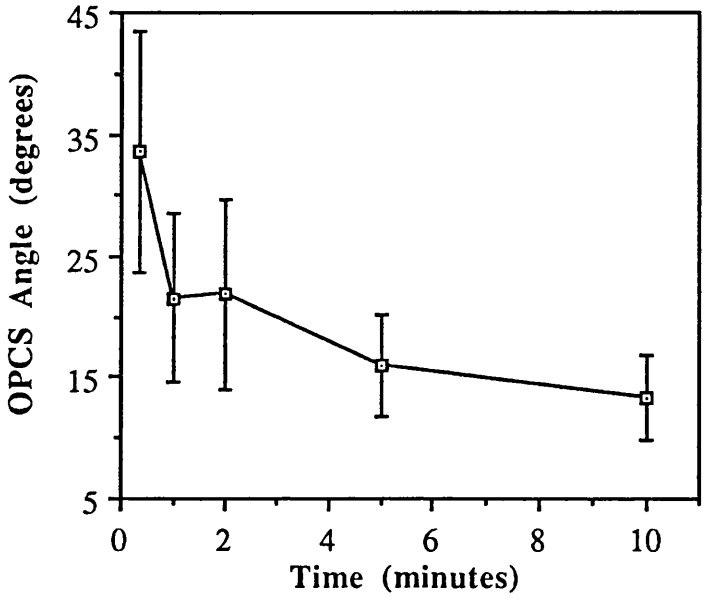


Figure 4.35 The Influence of Spheronisation Time on the Shape of Particles Produced from a Mixture of Lactose (8 Parts) and Microcrystalline Cellulose (2 Parts) Containing 3.6 Parts Water (26.5%).

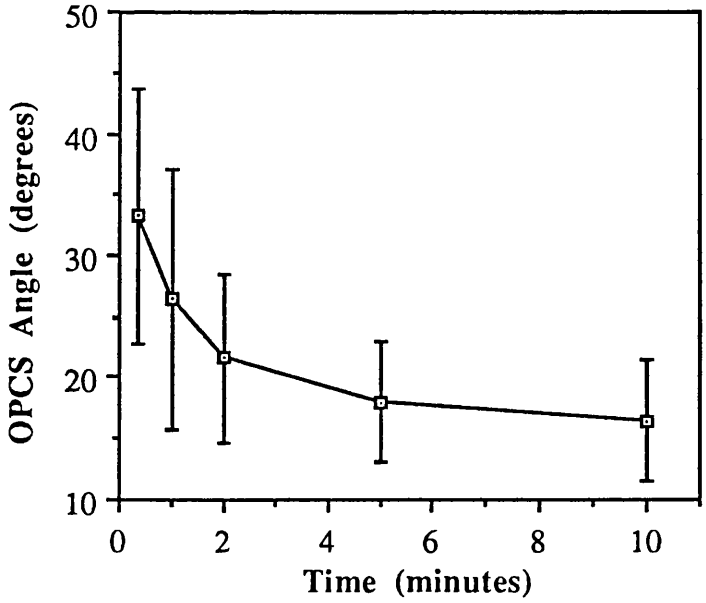
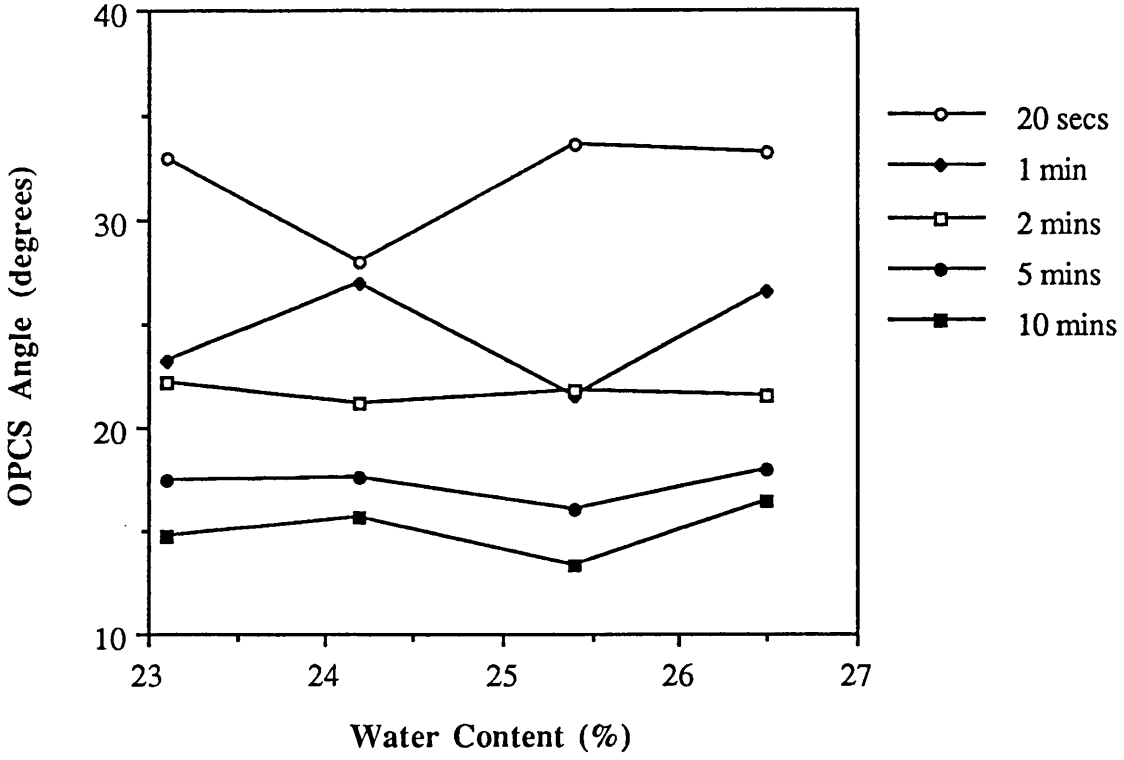


Figure 4.36 The Influence of Water Content on the Shape of Spheroids (determined by OPCS Angle) Produced by a Mixture Containing Lactose (8 Parts) and Microcrystalline Cellulose (2 Parts) at Various Spheronisation Times.



Conclusions

It is possible to manufacture spherical granules from formulations of 8 : 2 lactose : microcrystalline cellulose containing various moisture contents. However the quality of spheroids produced are not as good as those produced by 7 : 3 lactose : microcrystalline cellulose formulations in terms of both size and shape.

For the formulations studied spheronisation times of 5 minutes are sufficient for sphere growth to be completed, except with blends containing less than 23.1% moisture which continue to agglomerate with the duration of spheronisation. The rounding process continues, for all formulations, for as long as the extrudate remains in the spheronising chamber, although the approximate OPCS value for each sample is obtained after 5 minutes spheronisation.

A formulation of 8 : 2 lactose : microcrystalline cellulose containing 24.2% (3.2 parts) water produces spheres of the optimum size, size distribution, shape and shape distribution. Bataille *et al.* (1991) manufactured lactose (8) and microcrystalline cellulose (2) spheres containing 3.4 parts water through a 1.5mm diameter die but found these to possess both low hardness and high friability. In addition the pellet size distribution suggested a non-ideal formulation. There was no measurement of shape.

For the optimal formulation above containing 24.2% water the ratio of microcrystalline cellulose content to water content is 1 : 1.6. This is an increase in ratio as compared to 7 : 3 lactose : microcrystalline cellulose mixtures where optimum sphere size and shape is produced with a microcrystalline cellulose : water ratio of 1 : 1.4. The increase in solubility of the 8 : 2 lactose : microcrystalline cellulose formulation has increased the relative amount of water required to allow for the production of good quality extrudate and subsequent spheronisation, although the overall amount of moisture required to extrude the material has fallen (24.2% moisture required for a 8: 2 blend compared to 29.5% moisture for a 7 : 3 blend). A similar phenomenon was observed using a water insoluble model drug, barium sulphate, as a replacement for lactose during work undertaken by Bains *et al.* (1991).

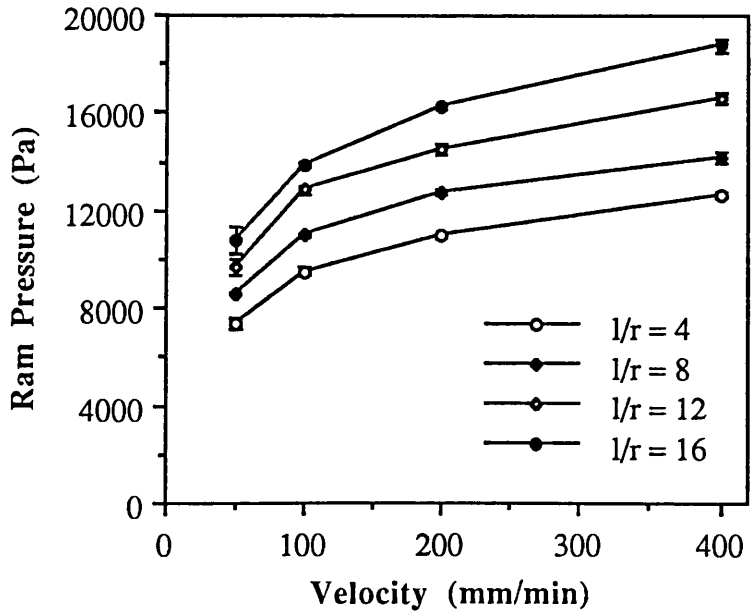
Both the results obtained from 7 : 3 and 8 : 2 lactose : microcrystalline cellulose mixtures illustrate the importance of water, water movement and the rheology of the mass in obtaining good quality extrudate and spheres.

4.3 BENBOW-BRIDGWATER CALCULATIONS

4.3.1 7 : 3 Lactose : Microcrystalline Cellulose Mixtures

Using the approach developed by Benbow and Bridgwater (1987) values for the die entry and die land components of the capillary rheometry process were calculated from graphs of ram pressure *versus* the extrusion velocity recorded for each die used (*cf.* Section 2.1.7). The results from the five formulations containing lactose (7) and microcrystalline cellulose (3) extruded through 1mm diameter dies are represented by the results contained in Figures 4.37. Unlike the α-alumina pastes used by Benbow and Bridgwater when developing their rheological mechanism, all the formulations under investigation exhibited a non-linear relationship between ram pressure and extrusion velocity. Similarly due to the non-linear nature of all the graphs, extrapolation of each curve to the Y-axis was difficult as the results did not follow any mathematical model. Hence when calculating $P_T(vel_O)$ [the pressure recorded for each length-to-radius die ratio at zero velocity] an extrapolation of the two lowest value points was employed i.e. extrapolation of pressure values recorded at 50mm/min and 100mm/min extrusion rates. For all the 1mm diameter die graphs analysed this method proved to be reliable at providing pressure values that could be used to calculate α, β, σ_{yo} and τ_o values.

Figure 4.37 The Influence of Extrusion Velocity on the Ram Pressure Produced for a Mixture of Lactose (7 Parts), Microcrystalline Cellulose (3 Parts) and 4.0 parts (28.6%) Water Extruded at Various Length-to-Radius Ratios using 1mm Diameter Dies.



With an increase in moisture content there is a decrease in the ram pressure recorded for each die ratio studied. The resulting curves also become more linear in appearance than those produced from drier formulations (e.g. Figure 4.37).

Tables 4.1 - 4.5 contain the values of both α, the die entry yield stress velocity factor, and of β, the die land velocity factor, calculated at each each ram velocity and length-to-radius die ratio for each 7 : 3 lactose : microcrystalline cellulose formulation analysed.

Table 4.1 **α and β Values Calculated for a Mixture Containing Lactose (7 Parts), Microcrystalline Cellulose (3 Parts) and 4.0 Parts Water (28.6%).**

β values	Ram Velocity			
l/r ratio	50mm/min	100mm/min	200mm/min	400mm/min
4	0.82	0.82	0.600	0.467
8	0.79	0.79	0.588	0.334
12	1.10	1.10	0.665	0.425
16	0.80	0.80	0.594	0.401
α	5.61	5.61	3.70	2.313

Table 4.2 **α and β Values Calculated for a Mixture Containing Lactose (7 Parts), Microcrystalline Cellulose (3 Parts) and 4.2 Parts Water (29.5%).**

β values	Ram Velocity			
l/r ratio	50mm/min	100mm/min	200mm/min	400mm/min
4	0.635	0.634	0.490	0.360
8	0.892	0.892	0.680	0.414
12	0.889	0.889	0.561	0.428
16	0.763	0.763	0.585	0.387
α	3.792	3.792	2.688	1.453

Table 4.3 **α and β Values Calculated for a Mixture Containing Lactose (7 Parts), Microcrystalline Cellulose (3 Parts) and 4.4 Parts Water (30.5%).**

β values	Ram Velocity			
l/r ratio	50mm/min	100mm/min	200mm/min	400mm/min
4	0.690	0.69	0.615	0.364
8	0.989	0.989	0.674	0.473
12	1.00	1.00	0.545	0.425
16	0.839	0.839	0.644	0.387
α	6.526	6.526	3.646	2.00

Table 4.4 **α and β Values Calculated for a Mixture Containing Lactose (7 Parts), Microcrystalline Cellulose (3 Parts) and 4.6 Parts Water (31.5%).**

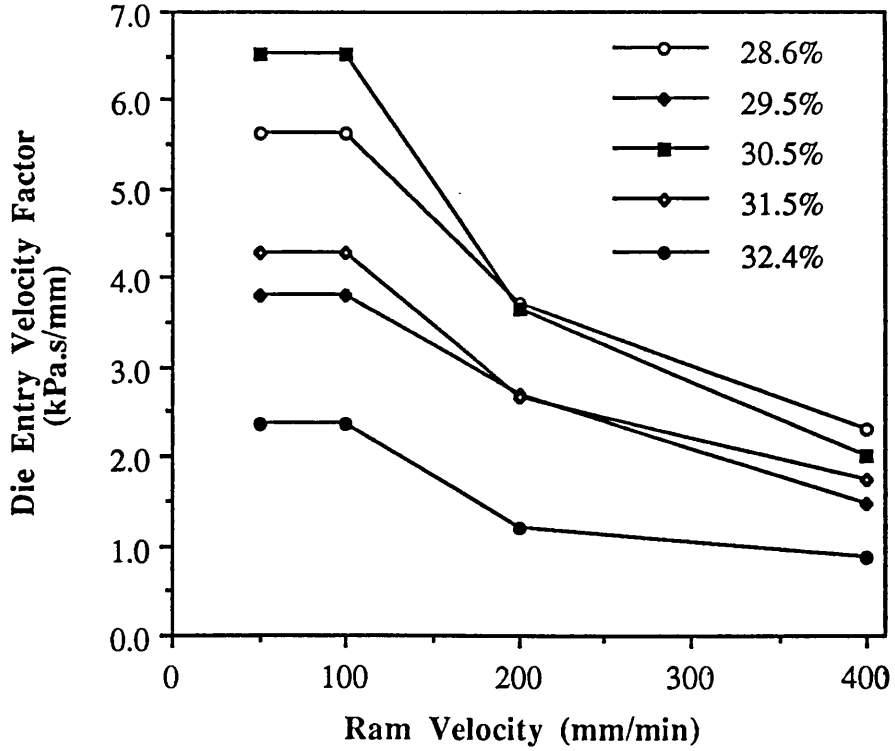
β values	Ram Velocity			
l/r ratio	50mm/min	100mm/min	200mm/min	400mm/min
4	1.42	1.42	0.887	0.523
8	0.472	0.472	0.555	0.382
12	1.229	1.229	0.805	0.567
16	0.943	0.943	0.721	0.453
α	4.289	4.289	2.655	1.74

Table 4.5 **α and β Values Calculated for a Mixture Containing Lactose (7 Parts), Microcrystalline Cellulose (3 Parts) and 4.8 Parts Water (32.4%).**

β values	Ram Velocity			
l/r ratio	50mm/min	100mm/min	200mm/min	400mm/min
4	0.441	0.441	0.527	0.426
8	0.662	0.662	0.741	0.378
12	1.095	1.095	0.776	0.587
16	0.551	0.551	0.634	0.402
α	2.364	2.364	1.197	0.868

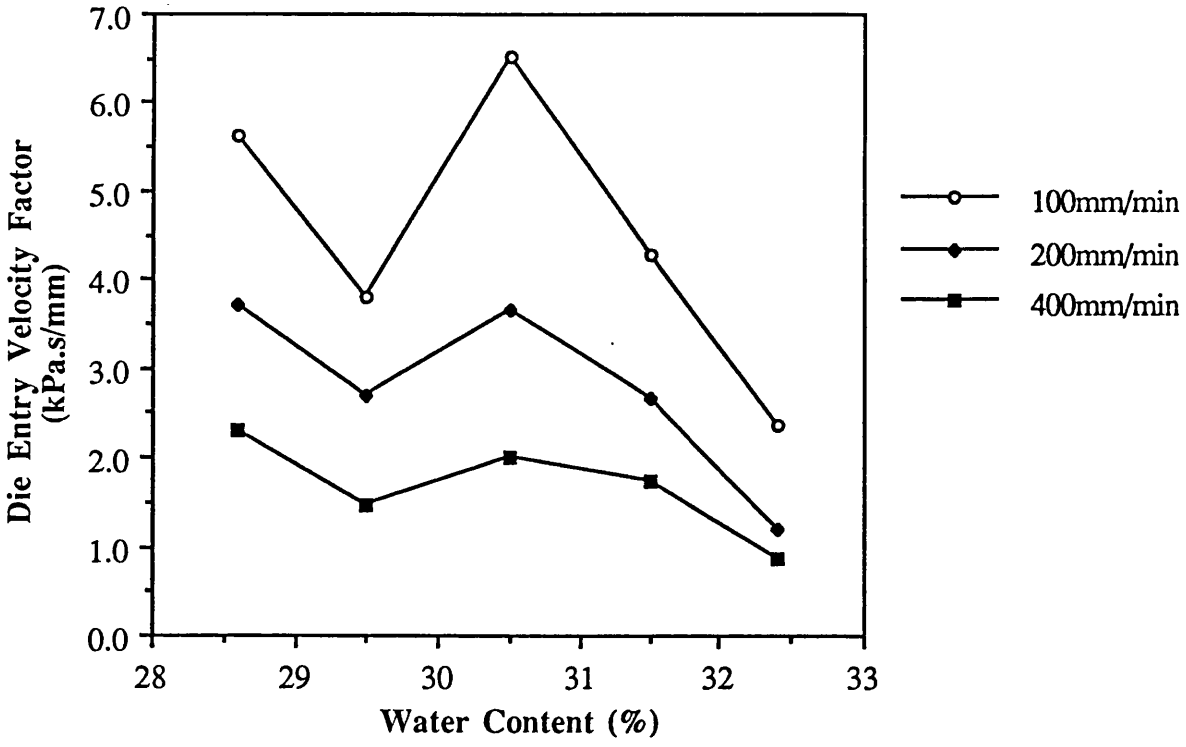
Estimation of the die entry yield stress velocity factor (or die entry velocity factor, α) relies on calculation involving both the upstream pressure loss recorded at zero velocity for each length-to-radius die ratio and the initial die entry yield stress, σ_{yo}. As both these values are obtained by linear extrapolation of a non-linear relationship (see above) then any calculation of α will be approximate. Figure 4.38 demonstrates that with an increase in ram velocity there is a reduction in the die entry yield stress velocity factor. This highlights that as the ram velocity increases the amount of die entry yield stress that is velocity dependent is reduced. Since calculation of α requires the use of values obtained from linear extrapolation of ram pressures recorded at 50mm/min and 100mm/min extrusion velocities these values appear in Figure 4.38 as being equivalent.

Figure 4.38 The Effect of Ram Velocity on The Die Entry Velocity Factor (α) for Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) Mixtures Containing Various Moisture Contents.



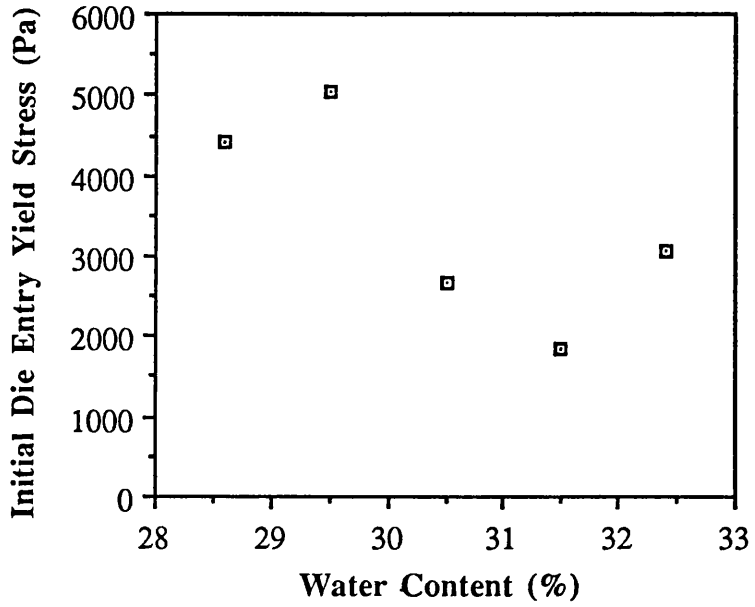
Previous workers (Benbow and Bridgwater, 1987; Raines, 1990; Andersen and Newton, 1990) have all demonstrated that α decreases with an increase in ram velocity and with an increase in the moisture content of the formulation being extruded. The effect of moisture content on the die entry velocity factor of the current formulations under investigation is plotted in Figure 4.39. Although there is some variation in the individual values the graph demonstrates that with an increase in moisture content there is a decrease in die entry velocity factor. Consequently an increase in moisture content would be expected to reduce the die entry yield stress as the formulation becomes less viscous and more deformable in behaviour.

Figure 4.39 The Effect of Moisture Content on The Die Entry Velocity Factor (α) of Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) Mixtures Recorded at Various Ram Velocities.



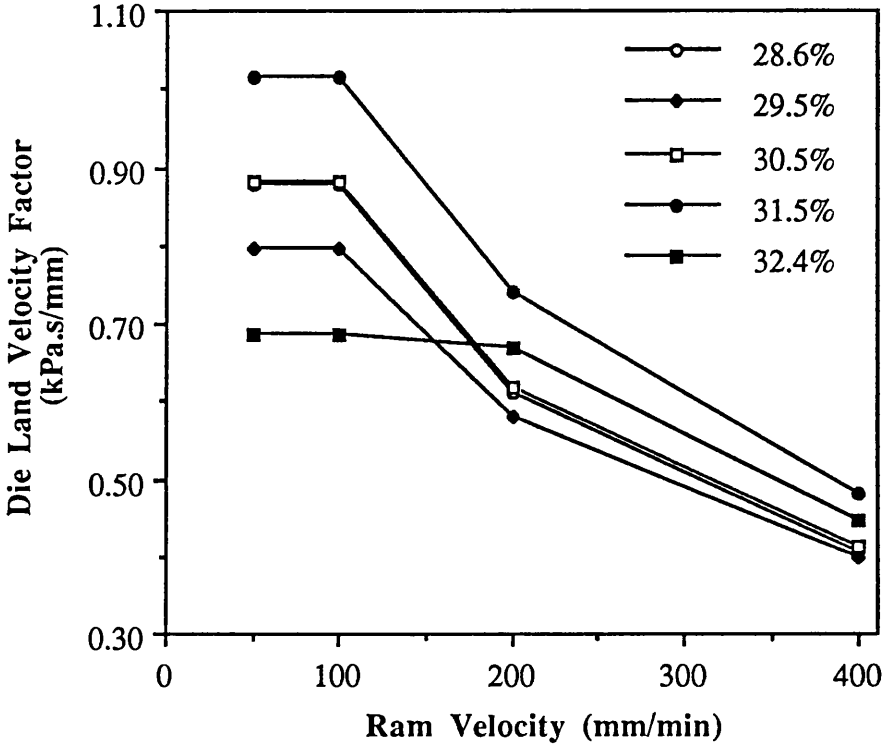
The effect of moisture on the initial die entry yield stress, σ_{yo}, recorded for each formulation under investigation is demonstrated in Figure 4.40. Although there is fluctuation in the results an increase in the moisture content appears to reduce the σ_{yo} value recorded for the formulation. This result is in line with the overall total decrease in ram pressure with an increase in moisture content.

Figure 4.40 The Effect of Moisture Content on the Initial Die Entry Yield Stress Value Recorded for Various Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) Mixtures.



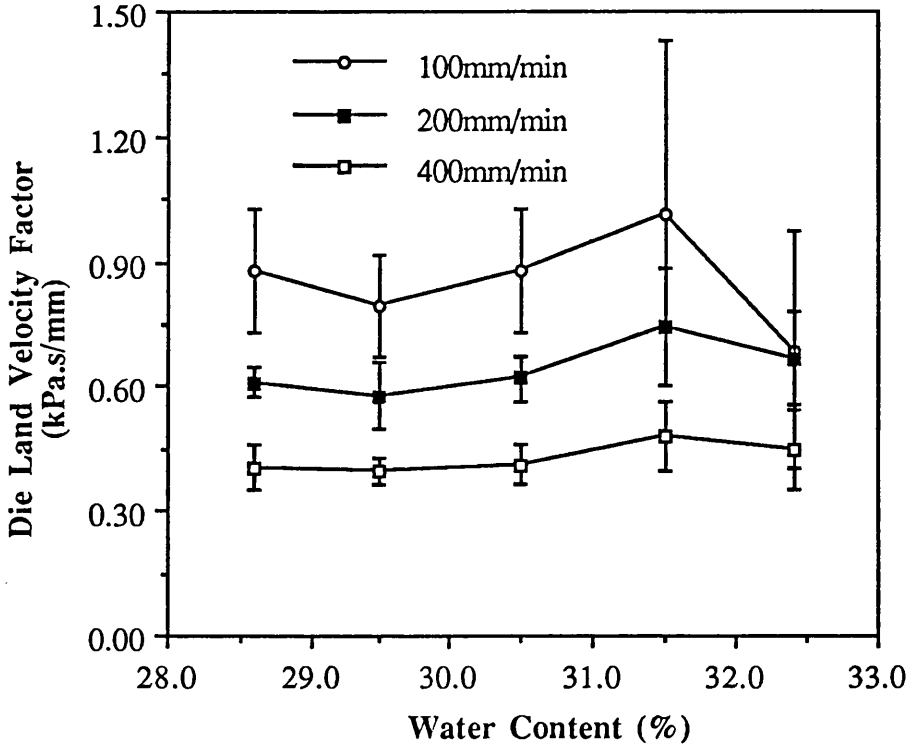
The influence of ram velocity on the mean die land velocity factor (β) recorded for each formulation has been plotted in Figure 4.41. The results contained in the graph demonstrate that β values decrease with an increase in ram velocity. The term β is a measure of the relative viscosity to thickness of the model Newtonian fluid that is acting as the die-wall lubricant during extrusion. Therefore if there is a decrease in the β value with increasing ram velocity then there is a reduction in the thickness of the lubricating layer in contact with the die-wall. This trend in the results is similar to that described by Raines (1990) and Andersen and Newton (1990) when assessing the rheological characteristics of various grades of barium sulphate in combination with microcrystalline cellulose and moisture. The equivalence in values recorded for ram velocities of 50mm/min and 100mm/min are again due to the use of these values in calculating the pressure at zero velocity for each set of die ratios employed (as above).

Figure 4.41 The Effect of Ram Velocity on the β Value (Die Land Velocity Factor) on Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) Mixtures Containing Various Moisture Contents.



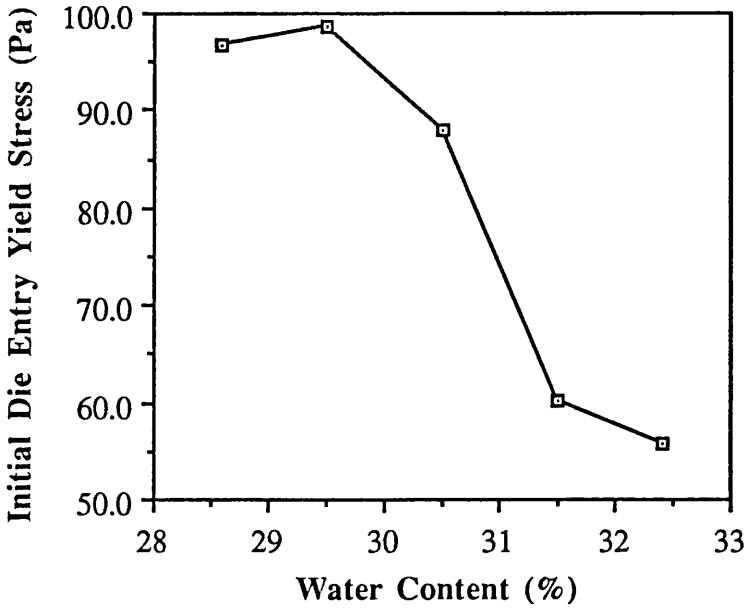
The effect of varying the moisture content of the formulation on the die land velocity factor was also plotted (Figure 4.42). Despite the large standard deviation in values it would appear that varying the moisture content of the lactose (7 parts) and microcrystalline cellulose (3 parts) mix does not alter the β value recorded at an equivalent ram velocity.

Figure 4.42 The Effect of Moisture Content on the β value (Die Land Velocity Factor) Recorded for Various Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) Mixtures.



Since the β value is a measure of the relative viscosity to thickness of the model Newtonian fluid that is acting as the die-wall lubricant during extrusion then the results contained in Figure 4.42 suggest that the thickness of the lubricating layer does not vary with a change in moisture content of the formulation. However a graph of the change in the initial die wall shear stress with variation in the moisture content (Figure 4.43) does demonstrate that the amount of stress produced during extrusion is reduced when there is an increase in moisture. Consequently increasing the moisture content does increase the deformability of the extrudate resulting in a reduction in the amount of stress applied on the die wall.

Figure 4.43 The Effect of Moisture Content on the Initial Die Wall Shear Stress (τ_o) Produced by Various Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) Mixtures .



Repeating the Benbow-Bridgwater calculations for the same formulations extruded through 1.5mm and 2mm diameter dies proved to be impossible to undertake with the data available. Figures 4.44 and 4.45 highlight the changes in ram pressure with an increase in extrusion velocity for a lactose (7 parts) and microcrystalline cellulose (3 parts) mixture containing parts 4.0 moisture (28.6%) extruded through 1.5mm and 2mm diameter dies respectively. For both sets of dies, all curves produced by different length-to-radius die ratios would appear to extrapolate to the Y-axis at zero pressure. Consequently any calculated values of α,β, τ_o and σ_{yo} would be unrealistic.

Figure 4.44 The Influence of Extrusion Velocity on the Ram Pressure Produced for a Mixture of Lactose (7 Parts), Microcrystalline Cellulose (3 Parts) and 4.0 parts (28.6%) Water Extruded at Various Length-to-Radius Ratios using 1.5mm Diameter Dies.

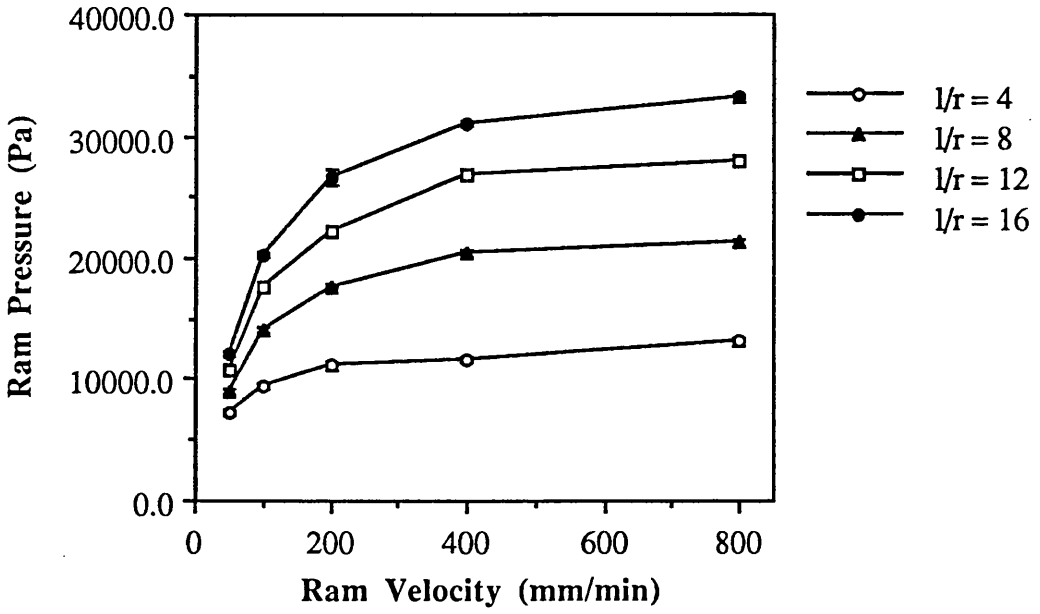
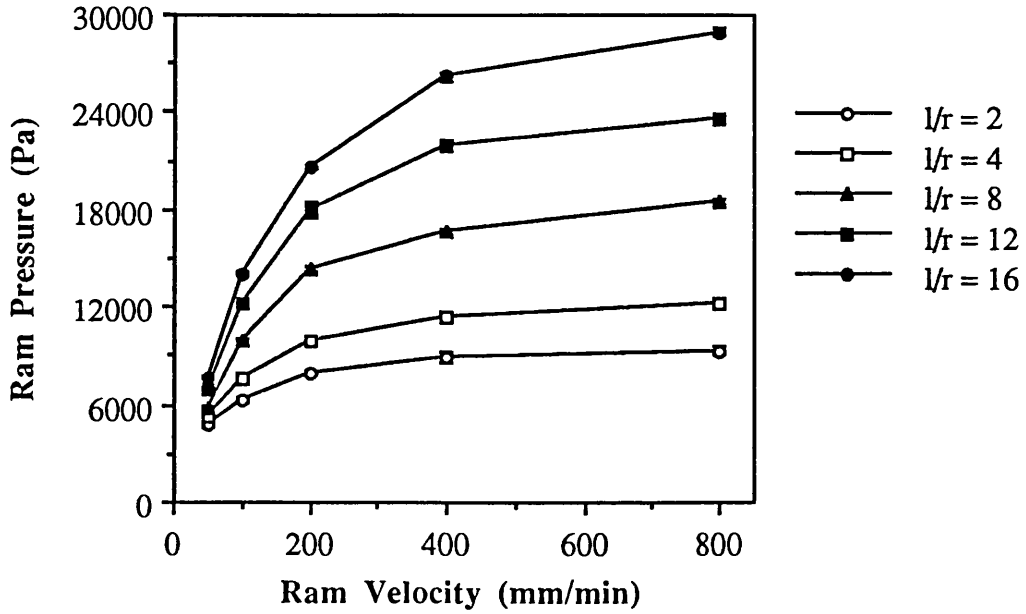


Figure 4.45 The Influence of Extrusion Velocity on the Ram Pressure Produced for a Mixture of Lactose (7 Parts), Microcrystalline Cellulose (3 Parts) and 4.0 parts (28.6%) Water Extruded at Various Length-to-Radius Ratios using 2mm Diameter Dies.

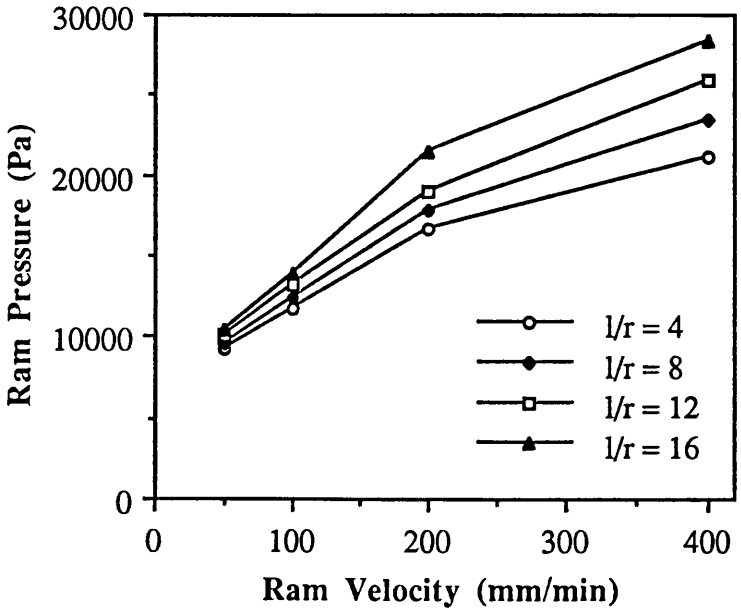


4.3.2 8 : 2 Lactose : Microcrystalline Cellulose Mixtures

Calculation of Benbow-Bridgwater results for the two 8 : 2 lactose : microcrystalline cellulose mixtures produces values that are of a similar magnitude to those produced by 7 : 3 lactose : microcrystalline cellulose mixture but show quite different trends.

The results obtained by plotting the rate of extrusion against the ram pressure produced by various l/r die ratios for an 8 : 2 mixture containing 3.0 parts (23.1%) are demonstrated in Figure 4.46. When the results are compared to those from a 7 : 3 mixture (Figure 4.37) it becomes apparent that 8 : 2 mixtures are more linear in response to an increase in ram velocity, even at the much reduced moisture contents of these mixtures.

Figure 4.46 The Influence of Extrusion Velocity on the Ram Pressure Produced for a Mixture of Lactose (8), Microcrystalline Cellulose (2) and 3.0 parts (23.1%) Water Extruded at Various Length-to-Radius Ratios using 1mm Diameter Dies.



Calculation of α and β values were again undertaken by extrapolation of a line drawn from the two points produced from ram velocities of 50 and 100mm/min. Using a third point (from a ram velocity of 200mm/min) resulted in line overlap for the drier formulation and loss of linearity in the wetter mixture. Tables 4.6 and 4.7 contain the α and β values obtained from the two formulations studied.

Table 4.6. α and β Values Calculated for a Mixture Containing Lactose (8 Parts), Microcrystalline Cellulose (2 Parts) and 3.0 Parts Water (23.1%).

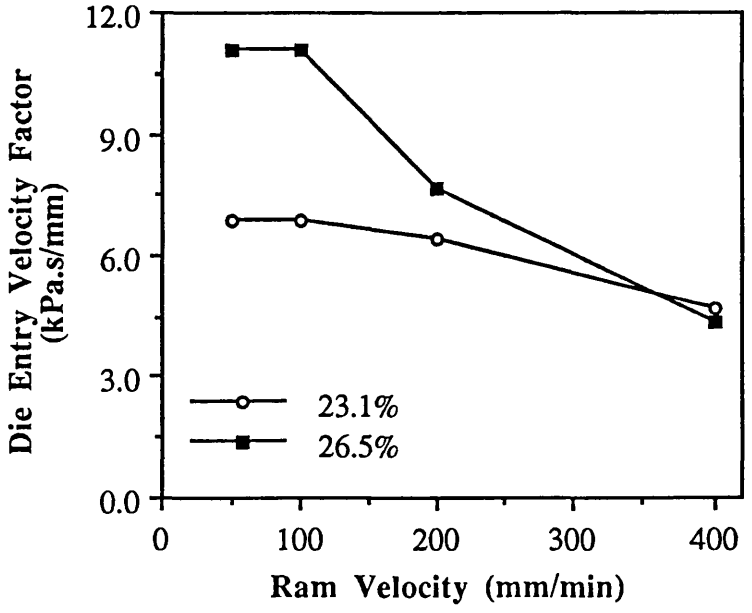
β values	Ram Velocity			
l/r ratio	50mm/min	100mm/min	200mm/min	400mm/min
4	0.837	0.837	1.104	0.737
8	0.666	0.666	0.836	0.714
12	0.773	0.773	0.816	0.775
16	0.752	0.752	0.970	0.725
α	5.61	5.61	3.70	2.313

Table 4.7 α and β Values Calculated for a Mixture Containing Lactose (8 Parts), Microcrystalline Cellulose (2 Parts) and 3.6 Parts Water (26.5%).

β values	Ram Velocity			
l/r ratio	50mm/min	100mm/min	200mm/min	400mm/min
4	1.176	1.176	0.786	0.671
8	0.022	0.022	0.240	0.387
12	0.445	0.445	0.435	0.619
16	0.599	0.599	0.513	0.529
α	11.10	11.10	7.65	4.34

Results for the die entry yield stress velocity factor (or die entry velocity factor, α) for 8 : 2 mixtures (Figure 4.47).demonstrates that with an increase in ram velocity there is a reduction in the α value. This highlights that as the ram velocity increases the amount of die entry yield stress that is velocity dependent is reduced. Since calculation of α requires the use of values obtained from linear extrapolation of ram pressures recorded at 50mm/min and 100mm/min extrusion velocities these values appear in Figure 4.47 as being equivalent. The values of α obtained from the 8 : 2 mixtures are greater than those obtained from 7 : 3 formulations (Figure 4.38) which is consistent with a decrease in moisture content and increase in rigidity in the material.

Figure 4.47 The Effect of Ram Velocity on The Die Entry Velocity Factor (α) for Lactose (8 Parts) and Microcrystalline Cellulose (2 Parts) Mixtures Containing Various Moisture Contents.



Values for the die entry yield stress, σ_{yo}, for the two experimental mixtures highlight that an increase in the moisture content dramatically reduces the stress value - from 6542Pa for the mixture containing 23.1% water down to 731Pa for a mixture containing 26.5% moisture. This change in values is much greater and over a smaller moisture variation than for 7 : 3 lactose : microcrystalline cellulose mixtures (Figure 4.40) suggesting that 8 : 2 formulations are much more sensitive to variations in moisture content.

The results for β values contained in Tables 4.6 and 4.7 show that an increase in ram velocity does reduce the die land velocity factor for 8 : 2 mixtures but to a much lesser extent than for 7 : 3 mixtures (Figure 4.41). This is in keeping with the results obtained by plotting the ram velocity against the pressure induced (Figure 4.46) which shows much less curvature with an increase in ram velocity than 7 : 3 formulations. However unlike 7 : 3 mixes (Figure 4.42), increasing the moisture content of the formulation may reduce the β value, perhaps due to the large amount of forced flow that occurs in a formulation with a low moisture content which will disrupt steady-state pressure values by altering the extrudate moisture content. Changes may also be due phase separation that occurs particularly at low extrusion velocities (*cf.* Section 5.1).

Chapter 5

CONTROLLED-STRESS RHEOMETRY RESULTS

5. CONTROLLED-STRESS RHEOMETRY RESULTS

5.1 CREEP EXPERIMENTS

The effect of applying a controlled stress to a sample for a defined period of time can be measured by the use of a creep experiment. Creep experiments give useful information on two rheological parameters - the instantaneous compliance, J_O, and a Newtonian viscosity value calculated at a particular shear rate (*cf.* Section 2.2.2). By varying the moisture content the rheological value measured for each sample examined will vary. The effect of these changes has been investigated.

5.1.1 The Effect of Moisture Content on the Rheological Values Obtained During a Creep Experiment for Various Lactose : Microcrystalline Cellulose Formulations.

By applying a stress of $6366Nm^{-2}$ (equivalent to an applied torque of 10mNm) to samples of 7 : 3 lactose : microcrystalline cellulose formulations the effect of varying the moisture content on J_O and the apparent viscosity has been examined during both retardation and relaxation of the sample. Retardation of the sample with the applied stress was performed for 3 minutes and the relaxation spectrum was recorded for 2 minutes.

Increasing the moisture content of the experimental material increases the amount of strain produced by each sample for the same applied stress. This implies that with an increasing moisture content the instantaneous compliance (strain over stress measurement) should increase. This effect is observed during retardation of samples in Figure 5.1. The increase in J_O value is approximately linear between moisture contents of 26.5% and 31.5% after which a further increase in moisture dramatically increases the J_O value recorded. A similar pattern in the instantaneous compliance values occurs when the applied stress is removed and the material is allowed to relax. As the moisture content of the sample increases the difference in J_O values between retardation and relaxation increases. The difference increases linearly with increasing water content from a formulation containing 26.5% moisture up to a formulation containing 31.5% after which the difference increases markedly (Figure 5.2). This effect is due to the partial loss of the elastic component during the period of time that the stress is applied to the sample. Increasing the water content increases the amount of elastic component lost. At a moisture content of 26.5% there is no loss of compliance value between retardation and relaxation.

Figure 5.1 The Effect of Moisture Content on the Instantaneous Compliance Recorded for Various Lactose (7) and Microcrystalline Cellulose (3) Mixtures Obtained During a Standard Creep Experiment.

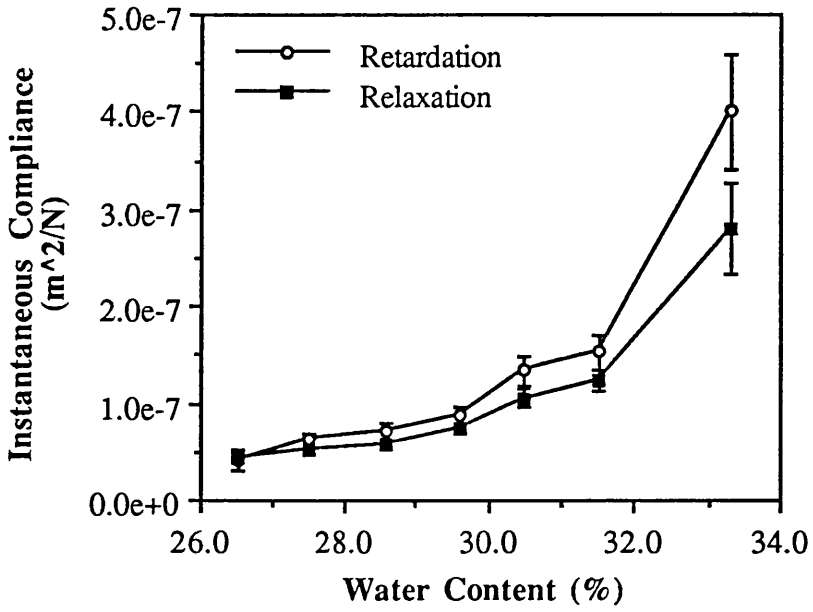
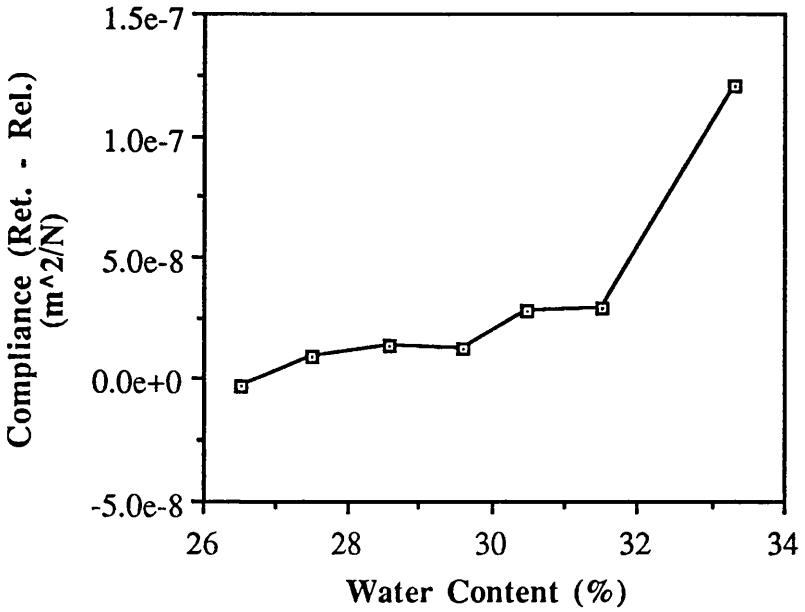


Figure 5.2 The Effect of Moisture Content on the Mean Difference Between the Instantaneous Compliance Values for Retardation and Relaxation Recorded for Various Lactose (7) and Microcrystalline Cellulose (3) Mixtures Obtained During a Standard Creep Experiment.



Variations in the amount of stress applied to the 7 : 3 lactose : microcrystalline cellulose mixtures results in the same pattern of graph occurring but at different values of compliance i.e. with an increase in applied stress there is an increase in the instantaneous compliance for each formulation but the shape of the graph remains the same. As the stress is increased the difference in compliance values (as demonstrated in Figure 5.2) increases and there is no longer zero difference at a moisture content of 26.5%. This is due to an increase in the amount of flow undergone by the material during stress retardation.

The 'Newtonian' viscosity measured during the creep experiment varies with each individual run of the rheometer. This is due to the mathematical modelling performed by the rheometer that occurs during the phase of linear viscoelasticity on both the retardation and relaxation responses to the application of an applied stress. The viscosity for a particular formulation can be calculated at one specific viscosity value as the spread of shear rates is generally low and approximately linear. Hence in Figures 5.3 and 5.4 mean and standard deviation results have been plotted to determine the effect of moisture content on shear rate and viscosity respectively.

Figure 5.3 demonstrates that increasing the moisture content of the formulation results in an increase in the shear rate recorded for the sample when subjected to an applied stress of $6366Nm^{-2}$ (equivalent to applied torque of 10mNm) during both the retardation and relaxation phases of a creep experiment. The increase in shear rate is linear for all moisture contents until the highest moisture content examined when the shear rate appears to increase rapidly. This implies that there could be the beginning of shear breakdown (i.e. flow) when the moisture content increases to as much as 33.3%. The shear rate recorded for the relaxation spectrum is greater than that recorded for the retardation curve suggesting that the stress has caused some structure breakdown during retardation.

As the moisture content increases there is a gradual decrease in the viscosity recorded (Figure 5.4). Hence an increase in moisture content results in a increase in shear rate and decrease in viscosity for 7 : 3 lactose : microcrystalline cellulose formulations. The viscosity value recorded during relaxation is lower than that recorded during retardation reflecting the loss of structure that has occurred with the application of a controlled stress.

Figure 5.3 The Effect of Varying Moisture Content on the Shear Rate Produced for Lactose (7) and Microcrystalline Cellulose (3) Mixtures when Subjected to a Constant Applied Stress.

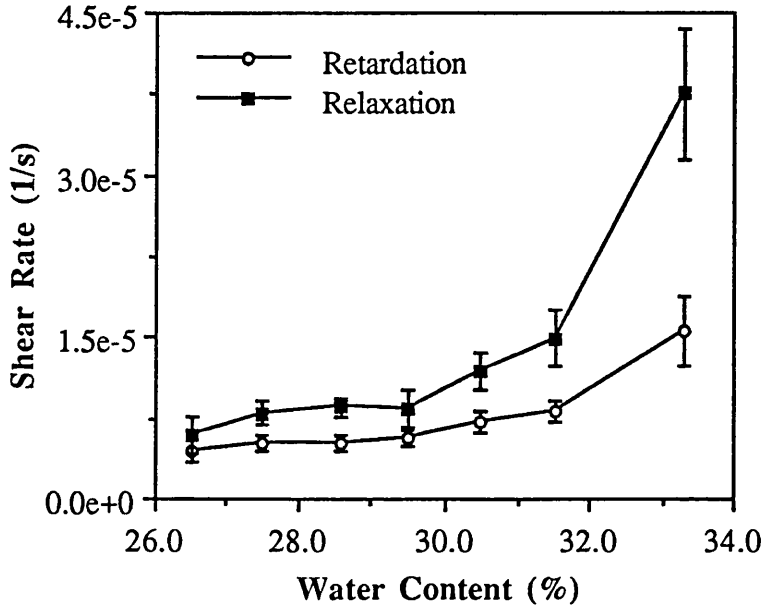
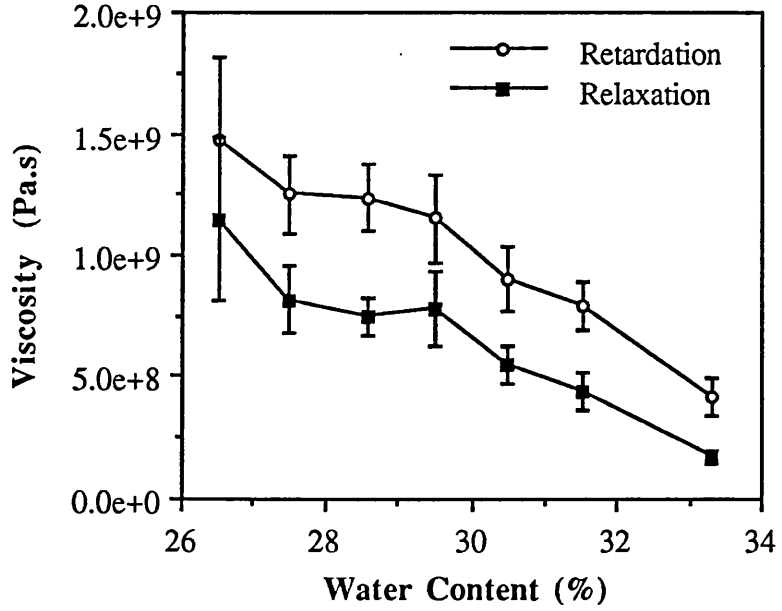


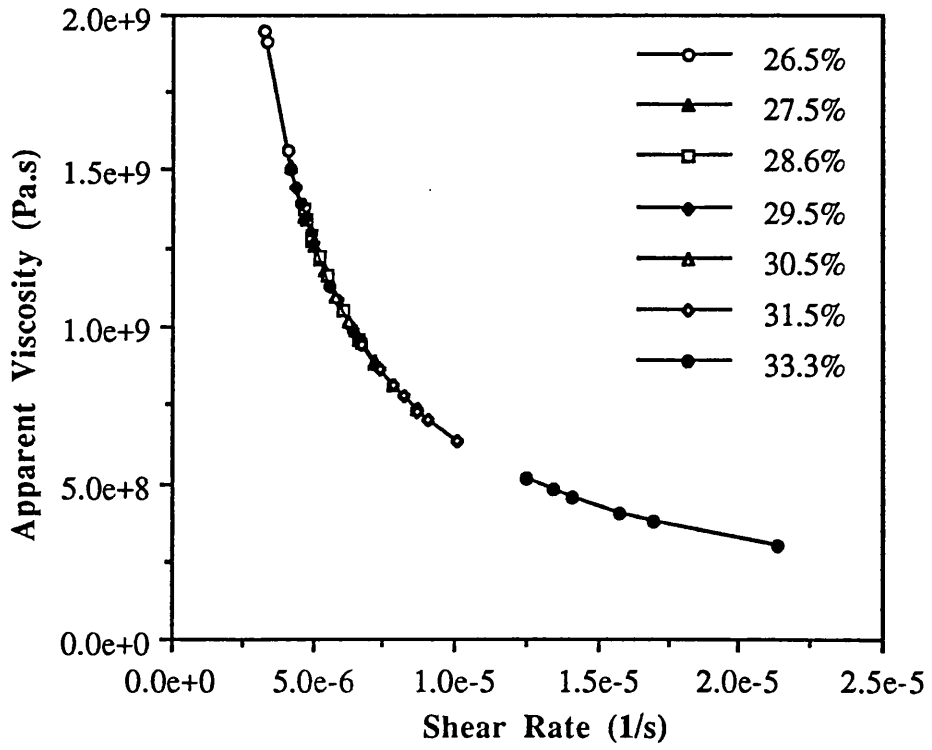
Figure 5.4 The Effect of Varying Moisture Content on the Apparent Viscosity Recorded for Lactose (7) and Microcrystalline Cellulose (3) Mixtures Obtained at Various Shear Rates.



As with values calculated for instantaneous compliance, variation in the amount of stress applied alters the shear rate and viscosity measured for each formulation. Increasing the applied stress increases the shear rate and reduces the viscosity However the large difference between shear rate values recorded at 31.5% and 33.3% (Figure 5.3) does not appear. Instead there is greater divergence between each individual moisture content.

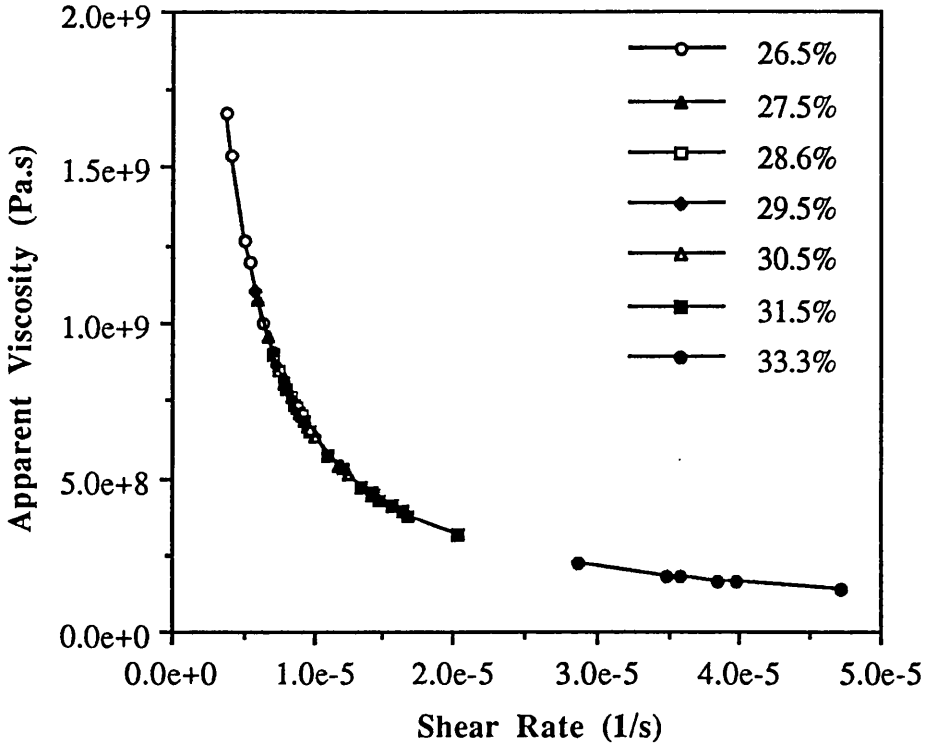
The net effects of the increase in shear rate and fall in apparent viscosity with an increase in moisture content have been represented in Figures 5.5 and 5.6. Each graph represents the individual shear rates and viscosities recorded for all experiments undertaken and highlights the non-linear relationship between shear rate and viscosity. The effect of shear rate on the apparent viscosity recorded during retardation of the sample with the applied stress has been plotted in Figure 5.5.

Figure 5.5 The Effect of Shear Rate on the Apparent Viscosity Recorded for Lactose (7) and Microcrystalline Cellulose (3) Mixtures Containing Various Moisture Contents Obtained During the Retardation Phase of a Creep Experiment.



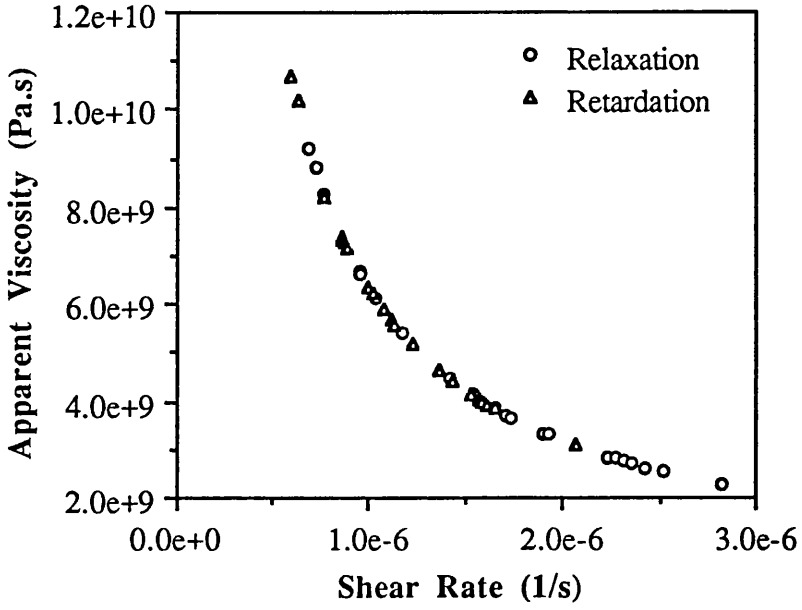
The same process occurs during relaxation after an applied stress has been removed (Figure 5.6). The increase in moisture content results in a higher shear rate being produced and this increase in shear rate produces a decrease in viscosity.

Figure 5.6 The Effect of Shear Rate on the Apparent Viscosity Recorded for Lactose (7) and Microcrystalline Cellulose (3) Mixtures Containing Various Moisture Contents Obtained During the Relaxation Phase of a Creep Experiment.



Varying the moisture content alters the shear rate and the apparent viscosity measured at a particular point. The same process is repeated for lactose (8) and microcrystalline cellulose (2) mixtures. In Figure 5.7 the effect of different shear rates on the viscosity produced from an 8 : 2 : 3.0 lactose : microcrystalline cellulose : water formulation have been plotted. The graph highlights the difficulty in establishing a representative viscosity for which comparisons can be made with other formulations.

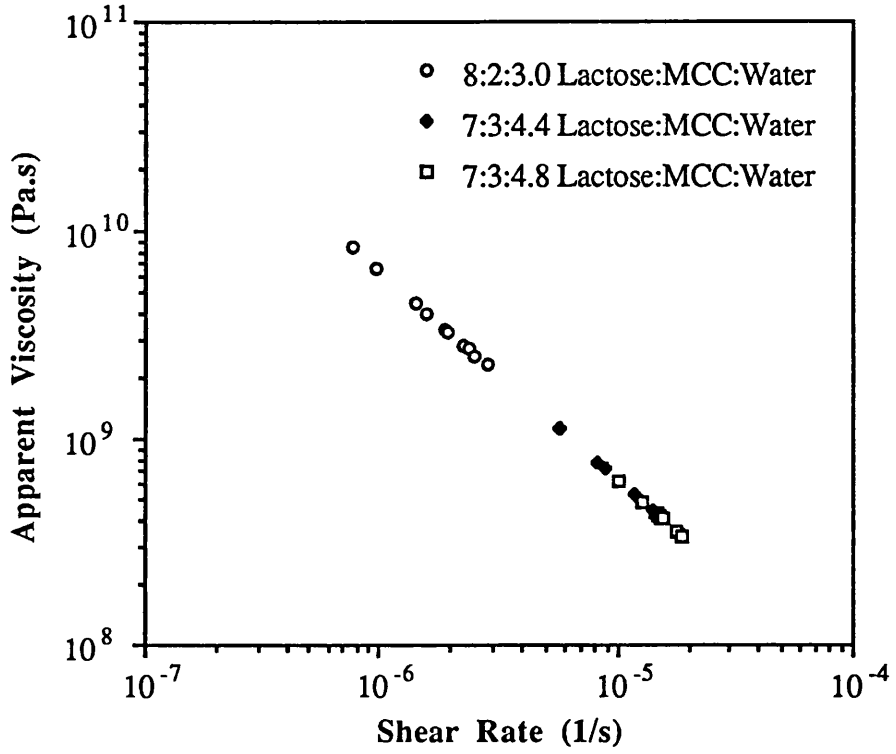
Figure 5.7 The Effect of Shear Rate on the Apparent Viscosity Recorded for a Lactose (8) and Microcrystalline Cellulose (2) Mixture Containing 3.0 Parts Water (23.1%) at an Applied Torque of 10mNm.



The relaxation curve in Figure 5.7 superimposes itself upon the retardation curve (as do the curves in Figures 5.5 and 5.6). This is in line with the superposition principle which states that the response (i.e. the strain) of the sample at any time is directly proportional to the value of the initiating signal (i.e. the stress).[Barnes *et al.*, 1989]. Only by altering the value of the applied stress will the values recorded for viscosity at a particular shear rate vary, e.g. doubling the stress will double the strain. Figure 5.8 demonstrates that 3 formulations undergoing a creep experiment at an applied torque of 10mNm ($6366Nm^{-2}$) all lie on the same plane on a log/log plot of shear rate *versus* viscosity.

Experiments conducted at other torque values indicate the exact same curve shape as produced in e.g. Figure 5.7 but instead the curve is shifted to the right as the applied stress is increased and shifted to the left as the applied stress is reduced. Figure 5.9 shows a scatter plot of various points obtained from performing creep experiments on a 8 : 2 : 3.0 lactose : microcrystalline cellulose : water formulation at 4 different applied torque values. As the torque is increased the apparent viscosity produced for the same shear rate is increased. Each series of points are linear and are separated by distances which reflect the change in applied torque.

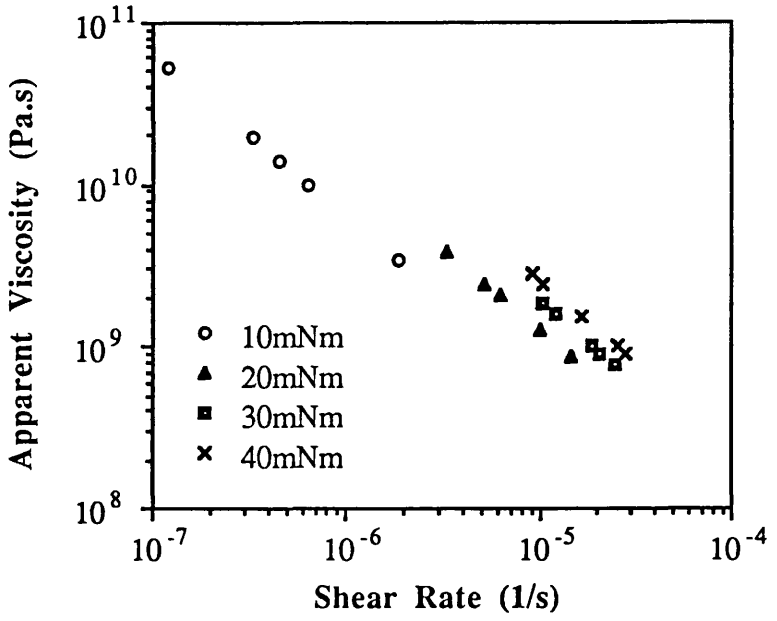
Figure 5.8 The Effect of Shear Rate on the Apparent Viscosity Recorded for Various Formulations at an Applied Torque of 10mNm During Both Retardation and Relaxation.



5.1.2 Conclusions

Creep experiments undertaken on lactose : microcrystalline cellulose : water mixtures demonstrate that with a change in moisture content, the compliance and viscosity values vary. Increasing the moisture content increases the instantaneous compliance recorded both during the retardation of the sample with the applied stress and during the relaxation of the sample from the applied stress. This increase in compliance is associated with a loss of elastic component in the sample as the material begins to flow slightly. Increasing the moisture content of the formulations also increases the shear rate induced in the sample and decreases the apparent viscosity recorded. This change appears to be only a function of moisture content and not to change in the solid components of the formulation.

Figure 5.9 The Effect of Shear Rate on the Apparent Viscosity for a Lactose (8) and Microcrystalline Cellulose (2) Mixture Containing 3.0 Parts Water (23.1%) Measured at Various Applied Torques.



Further changes in shear rate and apparent viscosity can be obtained by altering the applied stress acting on the sample. This will cause an increase in both the shear rate and apparent viscosity with an increase in applied stress.

The results indicate that for all formulations studied, at a particular shear rate, the viscosity is constant and therefore independent of the water content of the mixture. Very high moisture contents in such formulations would make the material slurry-like and would then change the nature of their behaviour under stress. However these moisture limits have not been reached with the mixtures under investigation. Consequently when the formulations undergo extrusion any differences between them will be due to variations in their deformability due to changes in the shear rate rather than to changes in the moisture content or in the relative quantities of the solid components. This is in line with results from Benbow-Bridgwater calculations (Section 4.3) which suggest that during extrusion there is no variation in the thickness of the lubricating layer that enables extrusion between formulations containing different moisture contents. Changes in the thickness of the layer are brought about only by a change in the extrusion velocity.

5.2 OSCILLATION

After the initial development work into establishing the optimum parameters for undertaking the rheological study of wet powder plugs containing lactose and microcrystalline cellulose, a standard procedure was used in their preparation (*cf.* Section 3.2.5).

Oscillatory analysis of the material gives details of the Storage Modulus (G' - also known as the Elastic Modulus) and the Loss Modulus (G" - also known as the Viscous Modulus) as well as the relative viscosity/elasticity of the sample as defined by the tan δ value. These values are obtained from the Complex (shear) Modulus which is the mathematical representation of a (shear) modulus as the sum of a real and imaginary part (Barnes *et al.*, 1989). The real part is the storage modulus and the imaginary part is the loss modulus. All these parameters are important because simple flow analysis cannot be accomplished with the samples under investigation as they are too viscous. In oscillation a standard sweep of torque forces was applied to the sample (1-20mNm) at a variety of oscillatory frequencies (0.01, 0.1, 1 and 10Hz). After each experiment the sample was discarded and replaced with a new one. Other experiments which varied the oscillatory frequency whilst maintaining a constant torque were also undertaken.

5.2.1 7:3 Lactose : Microcrystalline Cellulose Mixtures

The Effect of Moisture on Rheological Values

The effect of varying the moisture content of 7 : 3 lactose : microcrystalline cellulose formulations on the Storage and Loss Modulus values, the Complex Modulus and the tan δ value obtained for each sample at various torque values and oscillatory frequencies have been recorded.

Figures 5.10 and 5.11 highlight the effect of water content on the storage and loss modulus values recorded for 7 : 3 lactose : microcrystalline cellulose mixtures that were subjected to an applied torque value of 8mNm at a frequency of oscillation of 1Hz.

Figure 5.10 The Effect of Varying Moisture Content on the Storage Modulus Value Obtained for 7 : 3 Lactose : Microcrystalline Cellulose Samples at an Applied Torque of 8mNm at an Oscillatory Frequency of 1Hz.

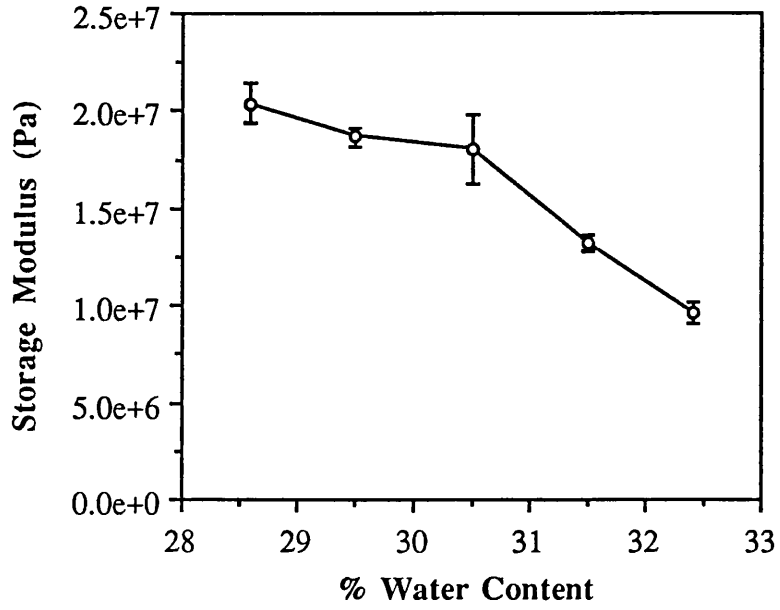
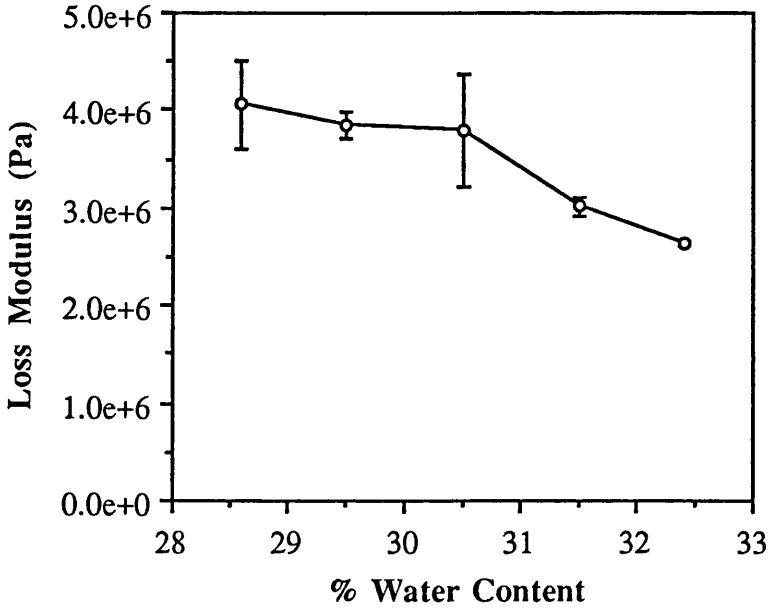
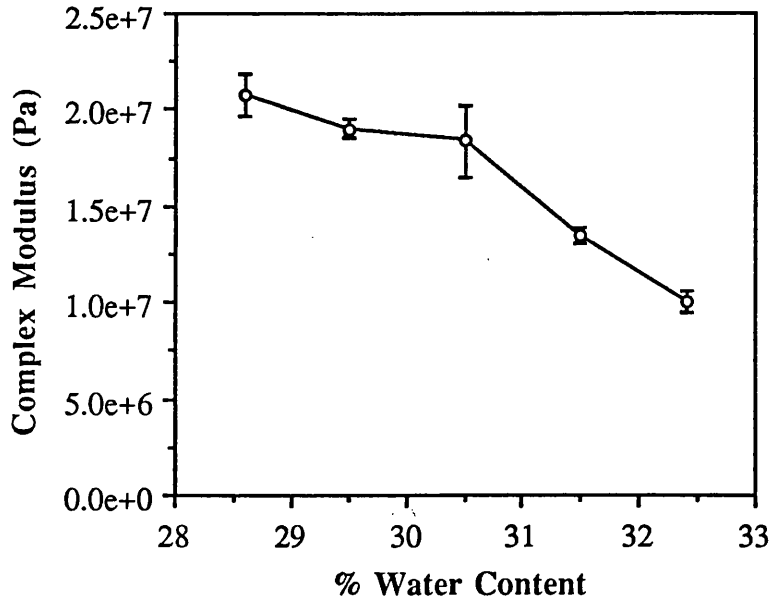


Figure 5.11 The Effect of Varying Moisture Content on the Loss Modulus Value Obtained for 7 : 3 Lactose : Microcrystalline Cellulose Samples at an Applied Torque of 8mNm at an Oscillatory Frequency of 1Hz.



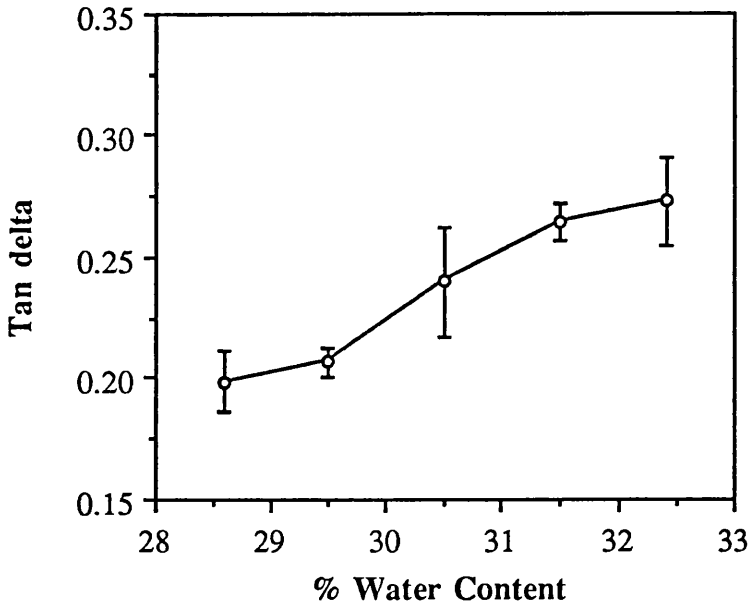
A comparison of formulations subjected to an applied torque of 8mNm (recorded during a torque sweep run) at a frequency of 1Hz demonstrates that the driest formulation examined provides the highest value of G' and G" (Figures 5.10 and 5.11). The driest formulation is then the most elastic and the most viscous material of those tested. The high G' and G" values are reflected in the high complex modulus values that are recorded for each formulation (Figure 5.12). G* reflects the overall response of the material to the applied stress.

Figure 5.12 The Effect of Varying Moisture Content on the Complex Modulus Value Obtained for 7 : 3 Lactose : Microcrystalline Cellulose Samples at an Applied Torque of 8mNm at an Oscillatory Frequency of 1Hz.



The storage modulus recorded for each formulation investigated has a higher value than that of the loss modulus. Therefore the rheological behaviour of the each formulation is likely to be predominantly elastic in nature. As the moisture content increases both the G' and G" values begin to fall, suggesting that the materials are becoming both less elastic and less viscous. G' values are affected by the increase in moisture more than G" and this changes the rheological response of the material to the applied stress. The extent to which each parameter is affected by an increase in water content can be assessed by the effect of moisture content on the tan δ value (Figure 5.13).

Figure 5.13 The Effect of Varying Moisture Content on the Tan Delta Value Obtained for 7 : 3 Lactose : Microcrystalline Cellulose Samples at an Applied Torque of 8mNm at an Oscillatory Frequency of 1Hz.



The tan δ value is a measure of the relative elasticity to viscosity of the material under investigation. As the tan δ decreases towards zero the material behaves predominantly as an elastic body. The higher the tan δ value (towards infinity) the more the material behaves as a viscous body. Tan δ measurements of the various formulations under investigation indicate that all the samples are predominantly elastic bodies as the tan δ values are low. However as the moisture content increases the storage modulus value is affected more than the loss modulus value so the tan δ value increases and the degree of viscous behaviour of the sample increases.

The trend of reduction in modulus values with increasing water content is repeated at other torque values recorded at an oscillatory frequency of 1Hz. Under an applied torque of 18mNm (recorded during a torque sweep from 1-20mNm) G', G" and G* are all affected by an increase in water content (Figures 5.14, 5.15 and 5.17 respectively). A sharp decrease in values of G', G" and G* occurs between water contents of 30.5% and 31.5% although there is no sudden increase in tan delta value. The rank order of the driest formulation having the highest G' and G" and lowest tan δ values and the wettest formulation having the lowest G' and G" and highest tan δ values remains.

Figure 5.14 The Effect of Varying Moisture Content on the Storage Modulus Value Obtained for 7 : 3 Lactose : Microcrystalline Cellulose Samples at an Applied Torque of 18mNm at an Oscillatory Frequency of 1Hz.

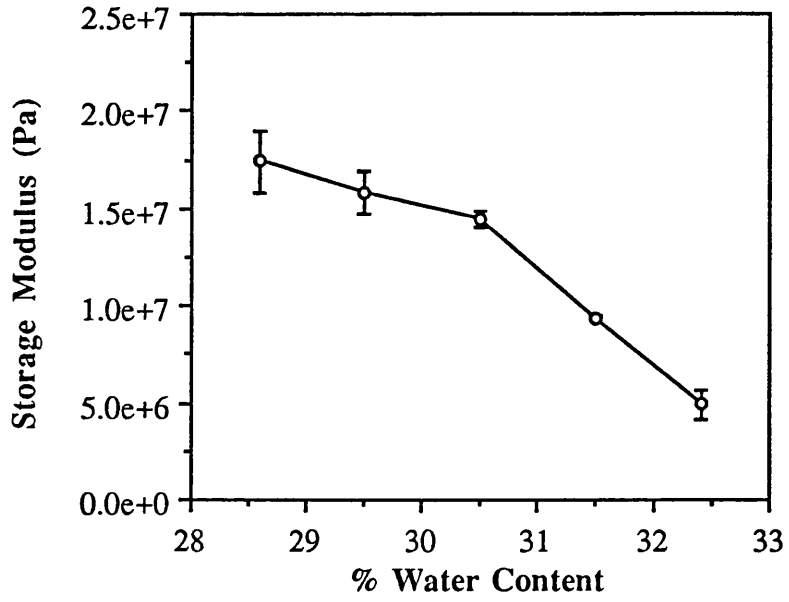


Figure 5.15 The Effect of Varying Moisture Content on the Loss Modulus Value Obtained for 7 : 3 Lactose : Microcrystalline Cellulose Samples at an Applied Torque of 18mNm at an Oscillatory Frequency of 1Hz.

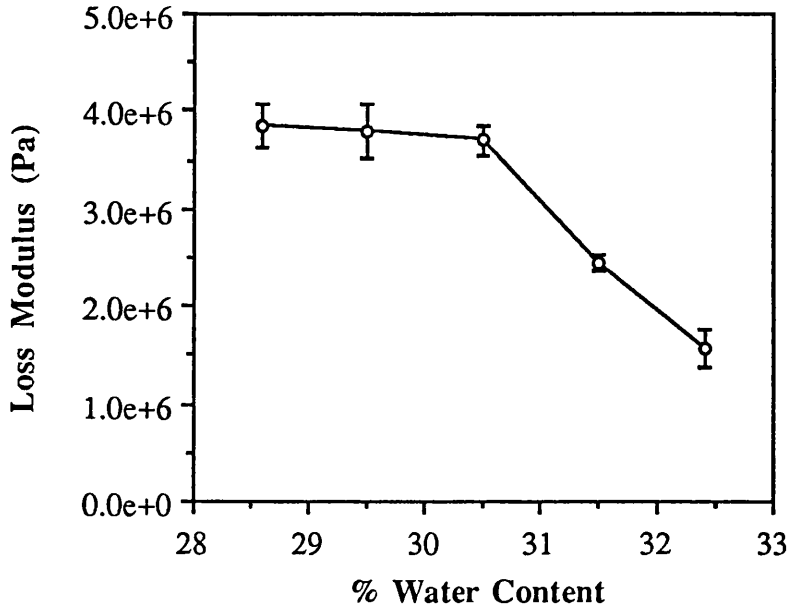
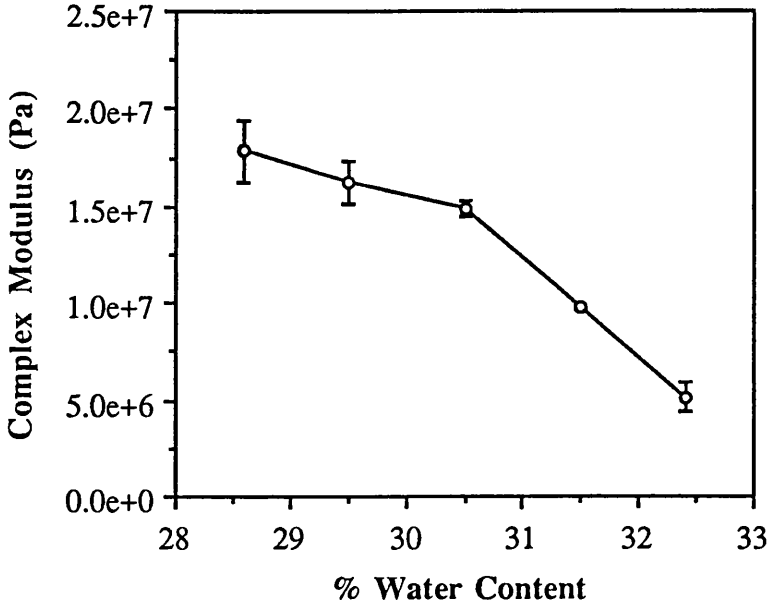


Figure 5.16 The Effect of Varying Moisture Content on the Complex Modulus Value Obtained for 7 : 3 Lactose : Microcrystalline Cellulose Samples at an Applied Torque of 18mNm at an Oscillatory Frequency of 1Hz.

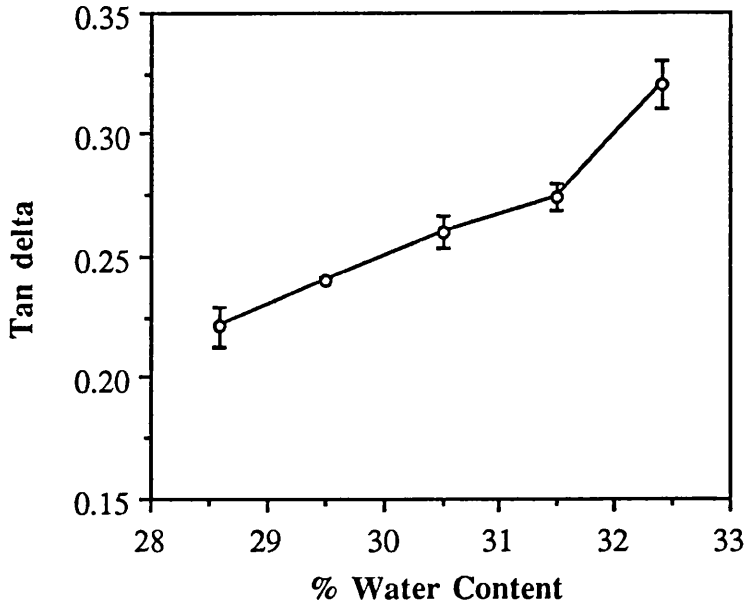


All the values recorded for the storage, loss and complex moduli resulting from an applied torque of 18mNm (Figures 5.14, 5.15 and 5.16 respectively) are lower than those recorded from an applied torque of 8mNm (Figures 5.10, 5.11 and 5.12 respectively). Hence an increase in the force applied to each formulation has resulted in a reduction in the elasticity and viscosity of that sample.

The difference between G', G" and G* values recorded for 7 : 3 lactose : microcrystalline cellulose mixtures containing 28.6%, 29.5% and 30.5% moisture are small when compared to the differences between values for the formulations containing 31.5% and 32.4% water. This indicates there is some change in visco-elastic behaviour of the material which may become apparent during extrusion and spheronisation of the samples under investigation.

Tan δ values are a measure of the relative elasticity to viscosity of the samples under investigation. 7 : 3 lactose : microcrystalline cellulose mixtures with various water contents exhibit a gradual increase with increasing moisture content (Figure 5.17).

Figure 5.17 The Effect of Varying Moisture Content on the Tan Delta Value Obtained for 7 : 3 Lactose : Microcrystalline Cellulose Samples at an Applied Torque of 18mNm at an Oscillatory Frequency of 1Hz.



An increase in the tan δ value recorded for 7 : 3 lactose : microcrystalline cellulose mixtures with an increase in water content implies that there is a change in behaviour of the material from a predominantly elastic body to one with an increasing viscous component. The gradual increase in tan δ also indicates that the sudden change in G', G" and G* values between water contents of 30.5% and 31.5% could be due to changes in the region of linear visco-elastic response for each formulation. The region of linear visco-elastic response shifts to a lower applied stress as the water content of the material increases and the oscillatory frequency of the applied stress is increased. For wet formulations under an oscillatory frequency of 1Hz the region of linear visco-elastic response may be lower than 8mNm - hence the large difference in modulus values seen in formulations containing 30.5% and 31.5% water even at an applied torque of 8mNm (Figures 5.10, 5.11 and 5.12).

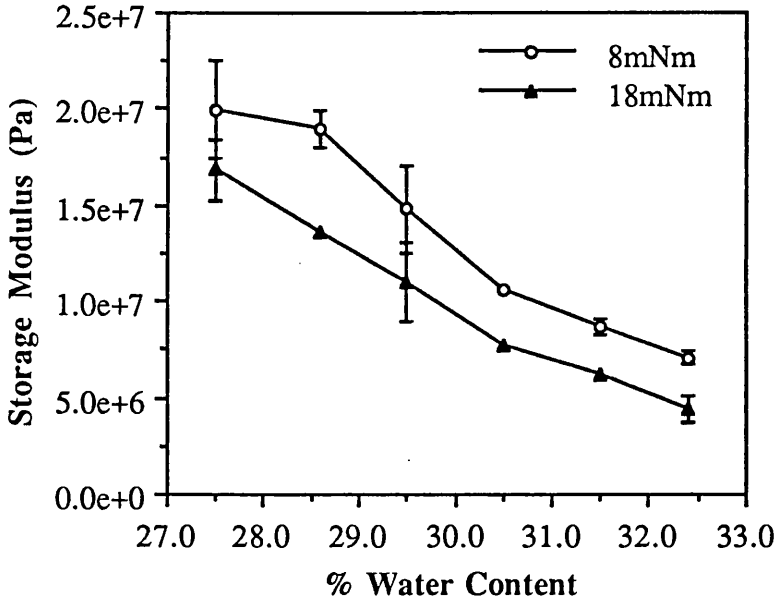
To assess whether variation in the region of linear visco-elastic response results in differences in the overall behaviour to applied stresses, controlled-stress oscillatory rheometry experiments were performed at various oscillatory frequencies.

The effect on the storage, loss and complex modulus values of 7 : 3 lactose : microcrystalline cellulose mixtures with varying water contents are detailed in Figures 5.18 - 5.21. These experiments were performed at applied torques of 8mNm and

18mNm (recorded during a torque sweep of 1-20mNm) at an oscillatory frequency of 0.1Hz.

A decrease in the oscillatory frequency of the torque sweep to 0.1Hz affects the storage and loss modulus values for the formulations when compared to values obtained from a torque sweep performed at an oscillatory frequency of 1Hz. The G' measurements obtained for the experimental formulations highlights that a decrease in the oscillatory frequency reduces the G' value recorded for each formulation (Figure 5.18) when compared to a frequency of 1Hz (Figures 5.10 and 5.14).

Figure 5.18 The Effect of Varying Moisture Content on the Storage Modulus Value Obtained for 7 : 3 Lactose : Microcrystalline Cellulose Samples at Applied Torques of 8mNm and 18mNm at an Oscillatory Frequency of 0.1Hz.

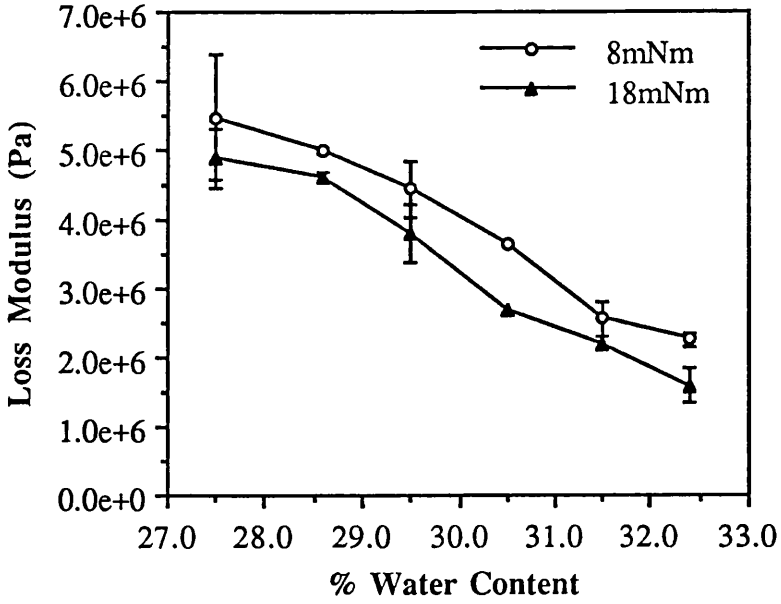


The rank order of the formulation with the lowest moisture content having the highest G' through to the highest moisture content mixture having the lowest G' value is maintained. Therefore the moisture content maintains its direct effect on storage modulus value despite a change in oscillatory frequency.

Decreasing the oscillatory frequency of the torque sweep increases the loss modulus figure obtained for the formulations containing 27.5% to 29.5% moisture (Figure 5.19) when compared with the values obtained during a 1Hz sweep at an applied torque of 8mNm (Figure 5.11). However the G" values obtained for wetter formulations are lower than those obtained during a 1Hz sweep. This implies that

running a controlled-stress oscillatory experiment at low oscillatory frequencies increases the diversity of G" values measured for the wet mixtures under investigation.

Figure 5.19 The Effect of Varying Moisture Content on the Loss Modulus Value Obtained for 7 : 3 Lactose : Microcrystalline Cellulose Samples at an Applied Torque of 8mNm at an Oscillatory Frequency of 0.1Hz.



The difference in G' and G" figures between each formulation appears to be approximately constant for the mixtures studied (Figure 5.18 and 5.19). When complex modulus values are considered these too demonstrate a constant decrease with increasing water content (Figure 5.20).

The decrease in G* with increasing moisture content reflects the influence of the storage modulus component on G*, as G' values are approximately double the G" values for the formulations studied. Since storage moduli are adversely affected by the decrease in oscillatory frequency, values of G* obtained for 0.1Hz torque sweeps (Figure 5.20) are lower than those obtained from 1Hz torque sweeps (Figure 5.12).

Figure 5.20 The Effect of Varying Moisture Content on the Complex Modulus Value Obtained for 7 : 3 Lactose : Microcrystalline Cellulose Samples at an Applied Torque of 8mNm at an Oscillatory Frequency of 0.1Hz.

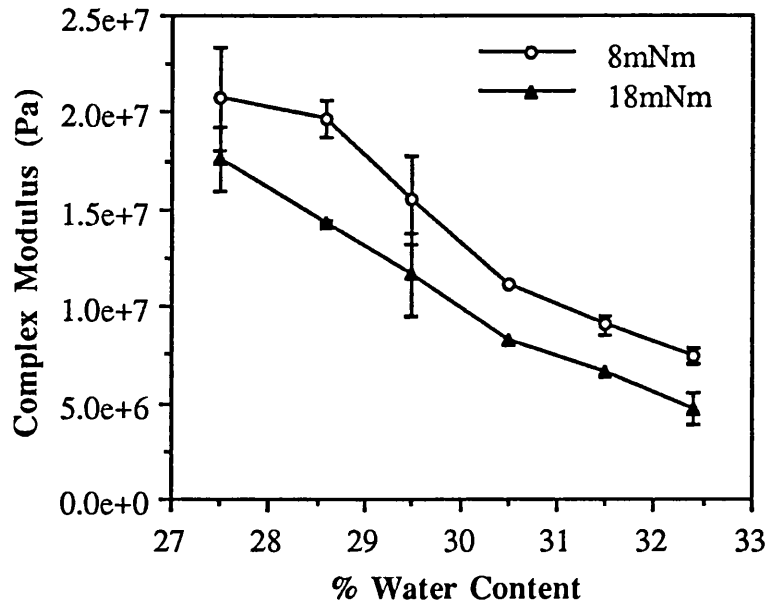
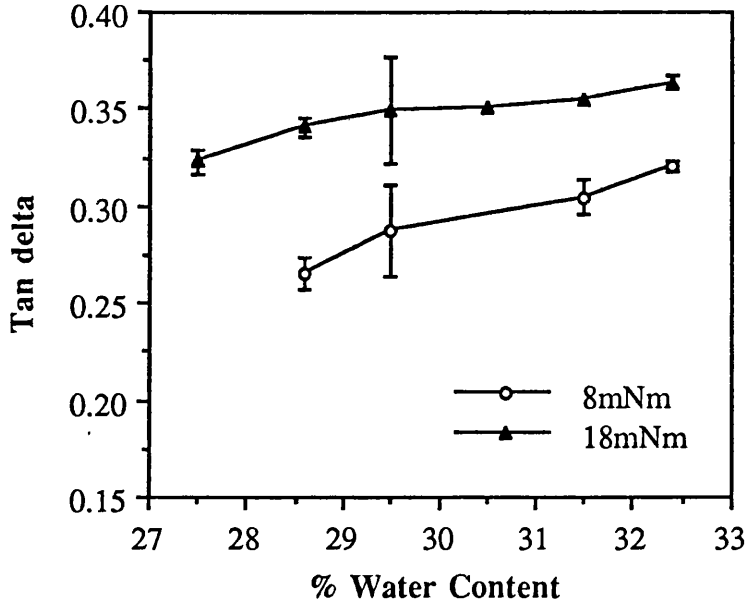


Figure 5.21 The Effect of Varying Moisture Content on the Tan Delta Value Obtained for 7 : 3 Lactose : Microcrystalline Cellulose Samples at an Applied Torque of 8mNm at an Oscillatory Frequency of 0.1Hz.



Tan δ values produced for the formulations under a 0.1Hz torque sweep highlight the increasing viscous behaviour of the mixtures as the moisture content rises and the oscillatory frequency falls (Figure 5.21).

Despite the increase in tan δ value for each formulation at an oscillatory of 0.1Hz when compared to a 1Hz oscillatory frequency (Figure 5.13) all values remain relatively low, implying that the formulations retain predominantly elastic behaviour when subjected to rheological examination.

Results from the experiments undertaken with a 8mNm torque applied at an oscillatory frequency of 0.1Hz suggest that the sharp falls in G', G" and G* values between a mixture with 30.5% moisture and 31.5% moisture obtained during a 1Hz oscillatory frequency experiment were an artifact of the experimental conditions. In effect a large difference in rheological values is probably due to measurement of some parameters within the area of linear visco-elastic response and others without this linear region. Increasing the water content of the formulation does affect the response of the material but no fundamental change in rheological behaviour is observed. This is verified from the observation that using an 18mNm applied torque at a 0.1Hz oscillatory frequency induces linear decreases in rheological parameters. The application of 8mNm and 18mNm torques to samples at oscillatory frequencies of 0.01Hz and 10Hz were also undertaken to examine their effects.

Results from applying torques of 8mNm and 18mNm at an oscillatory frequency of 0.01Hz to 7 : 3 lactose : microcrystalline cellulose mixtures with varying water contents are contained in Figures 5.22 - 5 25.

A gradual decrease in storage, loss and complex moduli with an increase in moisture content as described in all previous experiments is maintained with an oscillatory frequency of 0.01Hz (Figures 5.22, 5.23 and 5.24). However for the two driest formulations examined, containing 27.5% and 28.6% moisture, results demonstrate that an applied torque of 18mNm yields modulus values greater than those produced by an applied torque of 8mNm. This implies that the area of linear visco-elastic response for these samples has shifted from a low torque in the region of 8mNm to a higher torque in the region of 18mNm because of a decrease in oscillatory frequency.

Figure 5.22 The Effect of Varying Moisture Content on Storage Modulus Values Obtained for 7 : 3 Lactose : Microcrystalline Cellulose Samples at Applied Torques of 8mNm and 18mNm at an Oscillatory Frequency of 0.01Hz.

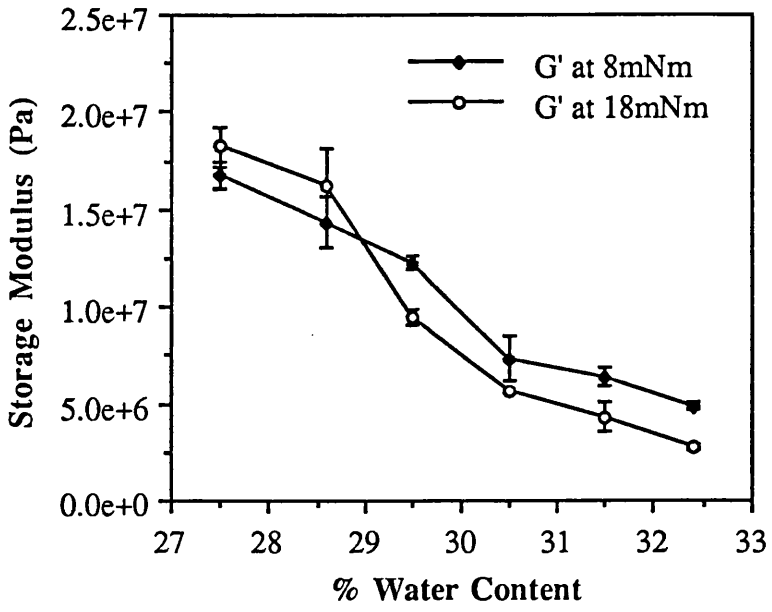


Figure 5.23 The Effect of Varying Moisture Content on Loss Modulus Values Obtained for 7 : 3 Lactose : Microcrystalline Cellulose Samples at Applied Torques of 8mNm and 18mNm at an Oscillatory Frequency of 0.01Hz.

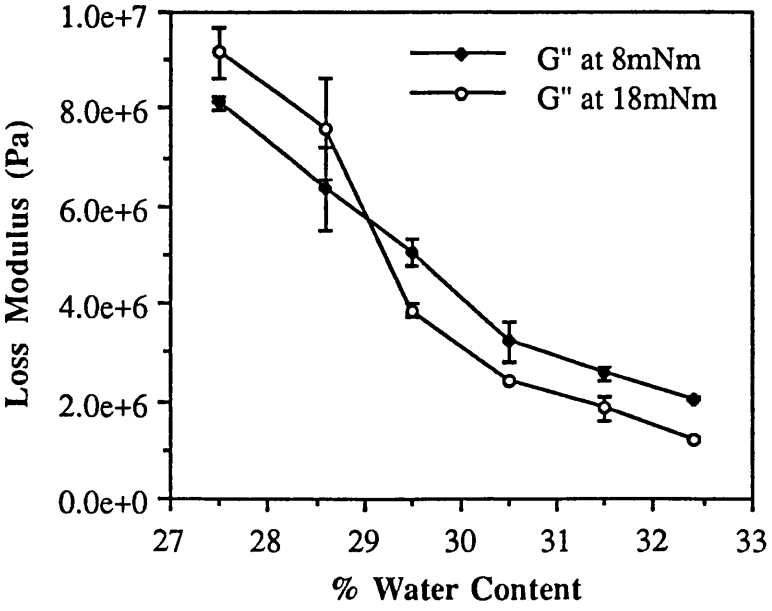


Figure 5.24 The Effect of Varying Moisture Content on Complex Modulus Values Obtained for 7 : 3 Lactose : Microcrystalline Cellulose Samples at Applied Torques of 8mNm and 18mNm at an Oscillatory Frequency of 0.01Hz.

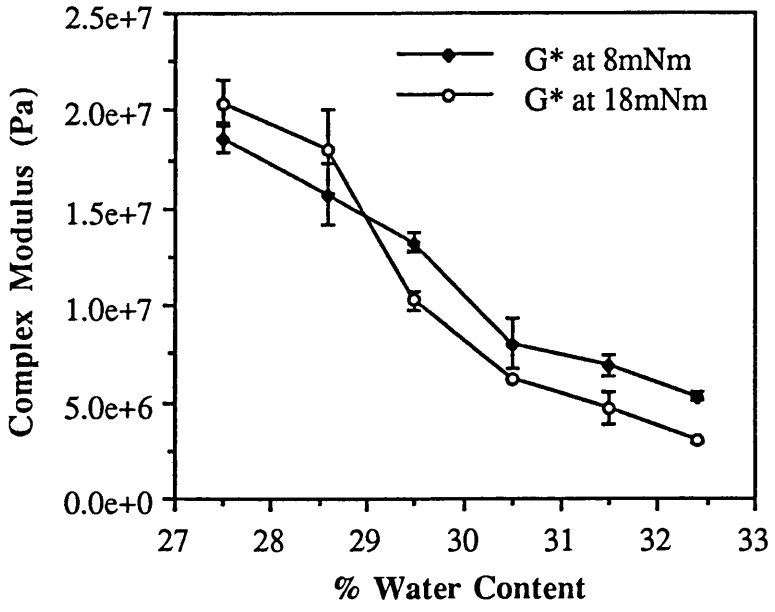
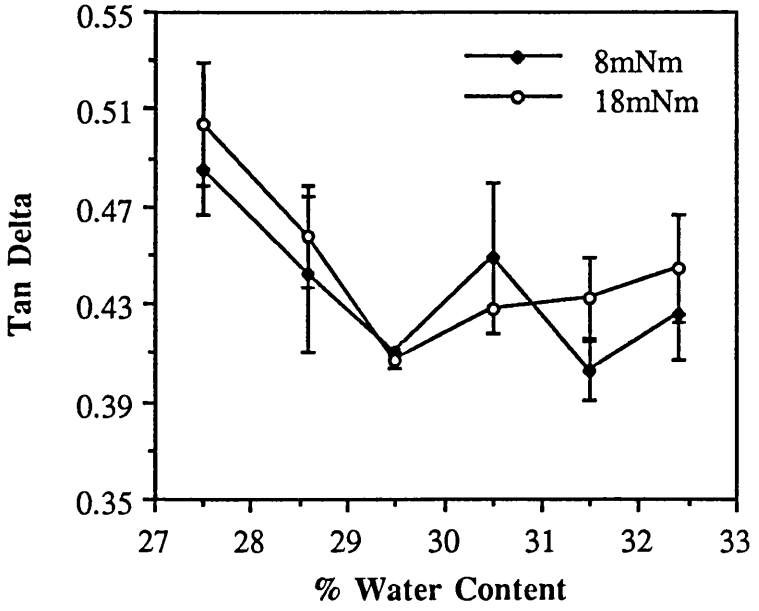


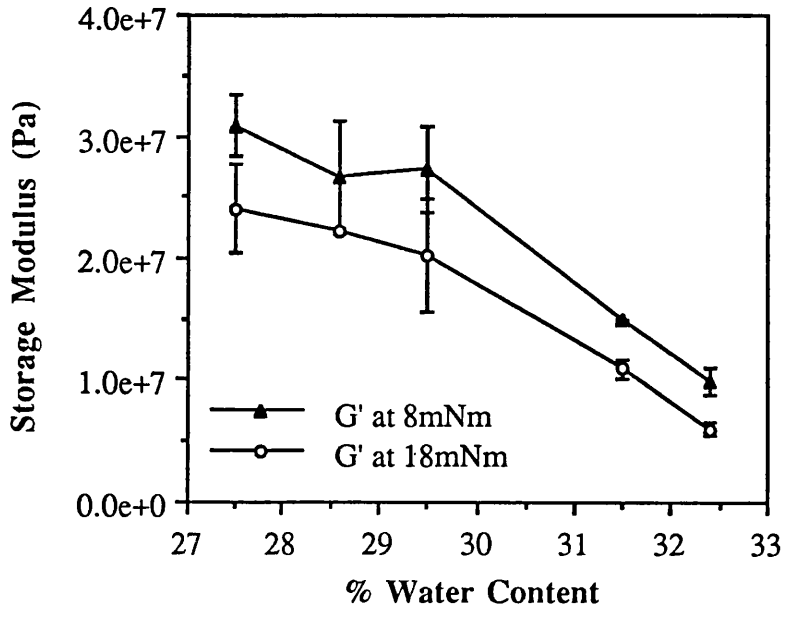
Figure 5.25 The Effect of Varying Moisture Content on Tan Delta Values Obtained for 7 : 3 Lactose : Microcrystalline Cellulose Samples at Applied Torques of 8mNm and 18mNm at an Oscillatory Frequency of 0.01Hz.



The changes in regions of linear visco-elastic response for samples due to the low oscillatory frequency also affects the tan delta values (Figure 5.25). Results indicate that at both torques of 8mNm and 18mNm tan delta falls with an increasing moisture content from 27.5% to 29.5% water. Then as the moisture content continues to rise an increase in tan delta value occurs indicating that the samples respond with increasing viscous behaviour to the applied stress. This change in direction of tan delta value is due to the movement of the linear visco-elastic region as the moisture content varies. No real information about the change in direction of the tan delta value can be assessed until further experimentation is performed on other formulations of lactose and microcrystalline cellulose.

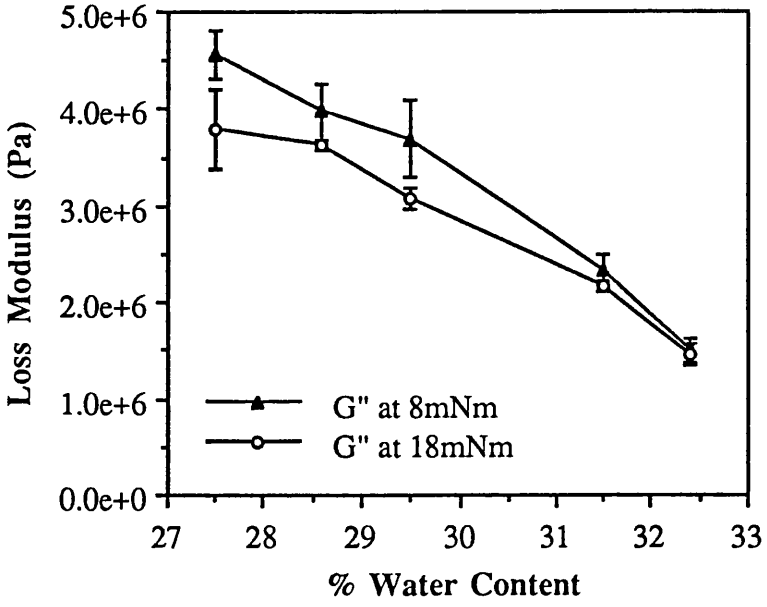
Using an oscillatory frequency of 10Hz results in the highest possible values of G' at applied torques of 8mNm and 18mNm (Figure 5.26). As the water content of the lactose (7) and microcrystalline cellulose (3) mixture increases the storage modulus decreases, with a large drop occurring between formulations containing 29.5% and 31.5% moisture. The difference between G' at torques of 8mNm and 18mNm is reduced as the moisture content is increased. This reflects the shift in the region of linear viscoelastic response which moves to the left (to applied torques of below 8mNm) and therefore minimises the difference in values recorded for the storage modulus.

Figure 5.26 The Effect of Varying Moisture Content on Storage Modulus Values Obtained for 7 : 3 Lactose : Microcrystalline Cellulose Samples at Applied Torques of 8mNm and 18mNm at an Oscillatory Frequency of 10Hz.



Loss modulus values decrease constantly with an increase in water content (Figure 5.27). As the moisture content has increased, the difference in values for G" between applied torques of 8mNm and 18mNm has reduced to almost zero.

Figure 5.27 The Effect of Varying Moisture Content on Loss Modulus Values Obtained for 7 : 3 Lactose : Microcrystalline Cellulose Samples at Applied Torques of 8mNm and 18mNm at an Oscillatory Frequency of 10Hz.



The effect on the complex modulus recorded for each formulation with an increase in moisture content (Figure 5.28) closely follows the pattern established by the storage modulus results (Figure 5.26). This is due to the storage modulus values being almost a factor of 10 greater than the loss modulus values recorded for the same formulation (Figure 5.27). Therefore the behaviour of all the samples is predominantly elastic even with an increase in moisture content.

The predominantly elastic behaviour of the samples investigated is confirmed with the low tan delta values recorded for each mixture (Figure 5.29). Nevertheless an increase in moisture content does alter the behaviour of the sample to incorporate more of a viscous response to a torque applied at an oscillatory frequency of 10Hz.

Figure 5.28 The Effect of Varying Moisture Content on Complex Values Obtained for 7 : 3 Lactose : Microcrystalline Cellulose Samples at Applied Torques of 8mNm and 18mNm at an Oscillatory Frequency of 10Hz.

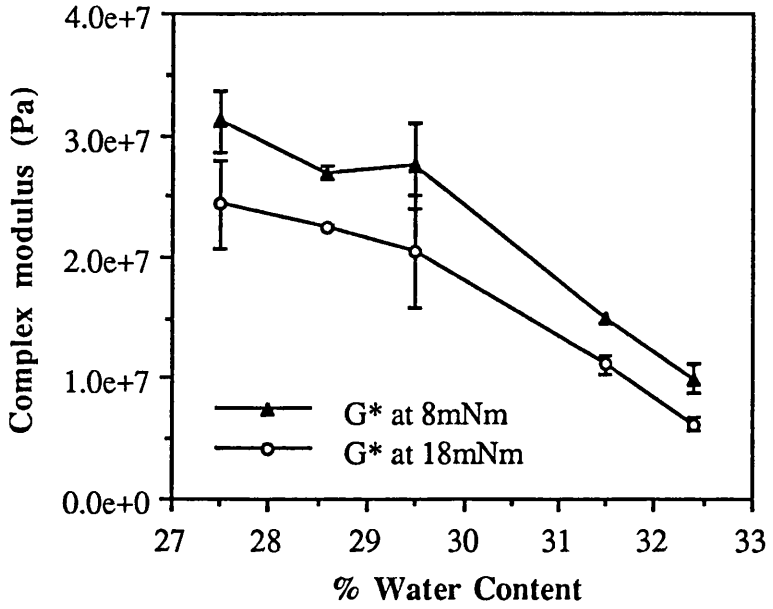
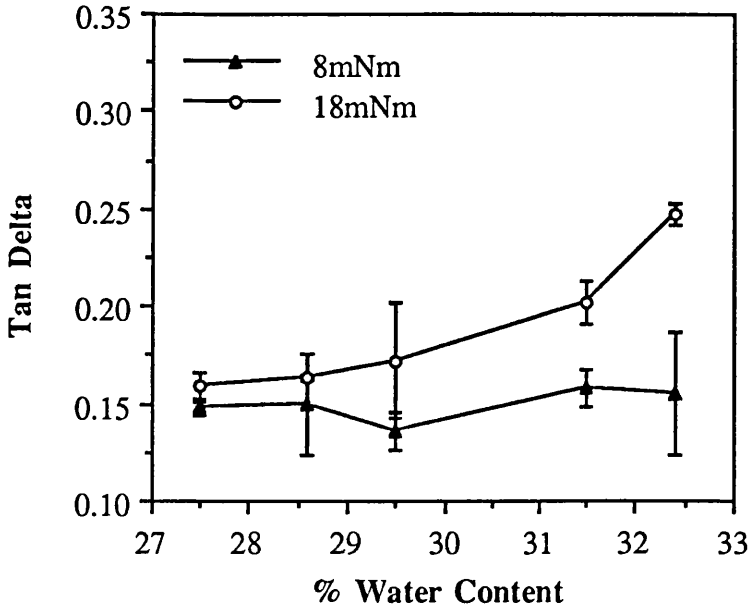


Figure 5.29 The Effect of Varying Moisture Content on Tan Delta Values Obtained for 7 : 3 Lactose : Microcrystalline Cellulose Samples at Applied Torques of 8mNm and 18mNm at an Oscillatory Frequency of 10Hz.

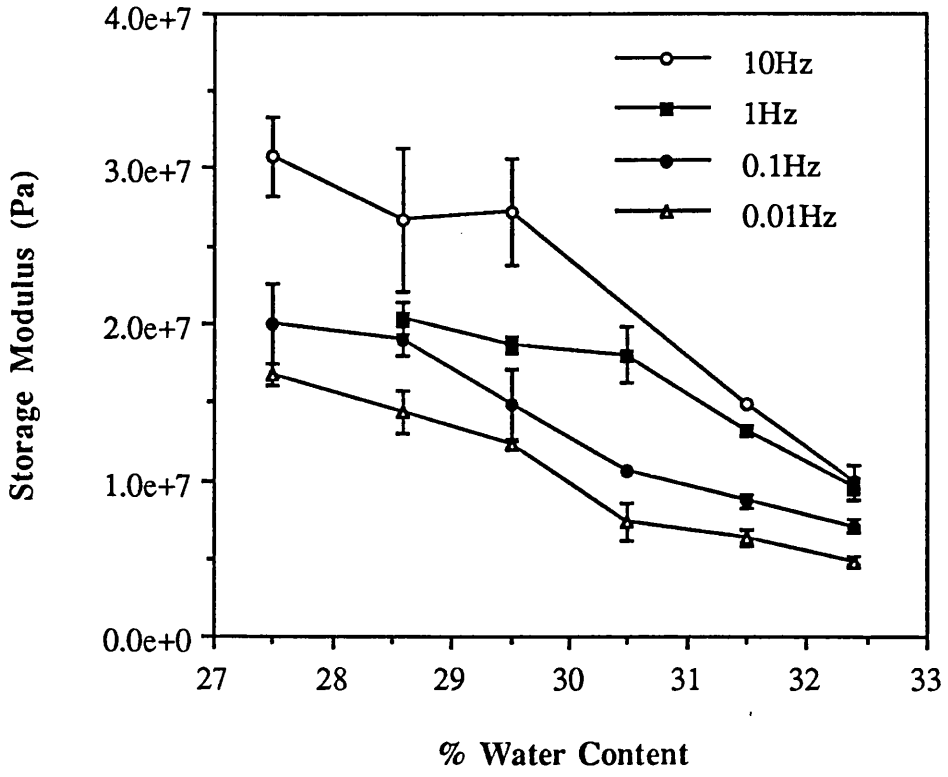


The Effect of Oscillatory Frequency on Rheological Values.

The effect of oscillatory frequency on each rheological parameter recorded for 7 : 3 lactose : microcrystalline cellulose mixtures with varying water contents was assessed at applied torques of 8mNm and 18mNm.

At 8mNm the storage modulus value for each formulation investigated for oscillatory frequencies of 0.01 to 10Hz was plotted (Figure 5.30). The results demonstrate that increasing the oscillatory frequency at which the controlled stress is applied increases the storage modulus value recorded for each formulation, regardless of water content. Comparison of differences in G' values with increasing moisture content demonstrates that larger differences in storage modulus values also occur with higher oscillatory frequencies.

Figure 5.30 The Effect of Oscillatory Frequency on the Storage Modulus Value Obtained from Lactose (7) and Microcrystalline Cellulose (3) Mixtures with Varying Moisture Contents under an Applied Torque of 8mNm.



At an oscillatory frequency of 10Hz the difference in G' values between formulations containing 29.5% and 31.5% moisture is greater than for lower oscillatory frequencies. This change in rheological behaviour is partly due to variation in the region of linear visco-elastic response which varies with moisture content.

For comparison with results obtained from capillary rheometry studies an oscillatory frequency that is compatible with the duration of experimental shear during extrusion is required. This can be calculated from the inverse of the oscillatory frequency which yields an approximate "experimental time". Since the extrusion process occurs in periods of time that range from 0.15 seconds to 19 seconds in duration then oscillatory frequencies of 0.1-10Hz are the closest for comparison of rheological effect (see Table 5.1).

Table 5.1 Comparison of Experimental Times Obtained from Capillary Rheometry and Controlled Stress Rheometry

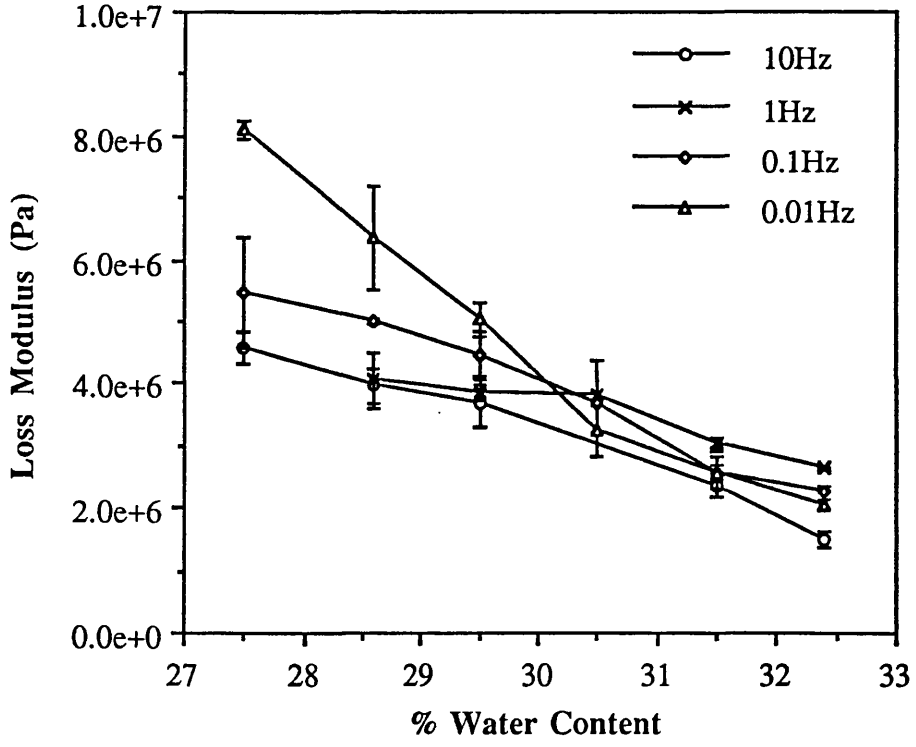
Oscillatory Frequency (Hz)	"Experimental" Time (seconds)	Die-length and Extrusion Rate	Time for Extrusion (seconds)
0.01	100	16mm at 50mm/min	19
0.1	10	8mm at 100mm/min	4.8
1	1	4mm at 200mm/min	1.2
10	0.1	2mm at 800mm/min	0.15

Using the values obtained in Figure 5.30 it would appear that at high extrusion rates (as demonstrated by an oscillatory frequency of 10Hz) there is a dramatic difference in the behaviour of materials with moisture contents below 29.6% moisture and those with 30.5% moisture and above. This correlates with rheological information obtained from capillary rheometry (Figures 4.17 and 4.18 - Section 4.1.2) that suggests that 7 : 3 formulations extruded through 1.5 and 2mm diameter dies demonstrate a marked decrease in the shear stress resulting from the same applied shear rate for formulations that contain 30.5% or more moisture. At lower extrusion velocities (as demonstrated by an oscillatory frequency of 0.1Hz) there is less

difference in the behaviour of these materials and this too is reflected in a convergence in values obtained from capillary rheometry (Figures 4.17 and 4.18 - Section 4.1.2).

Comparison of the loss modulus values recorded for each formulation when an applied torque of 8mNm is oscillated at various frequencies demonstrates that an increase in moisture content decreases G" (Figure 5.31). However a reduction in oscillatory frequency increases the loss modulus unlike the storage modulus (Figure 5.30).

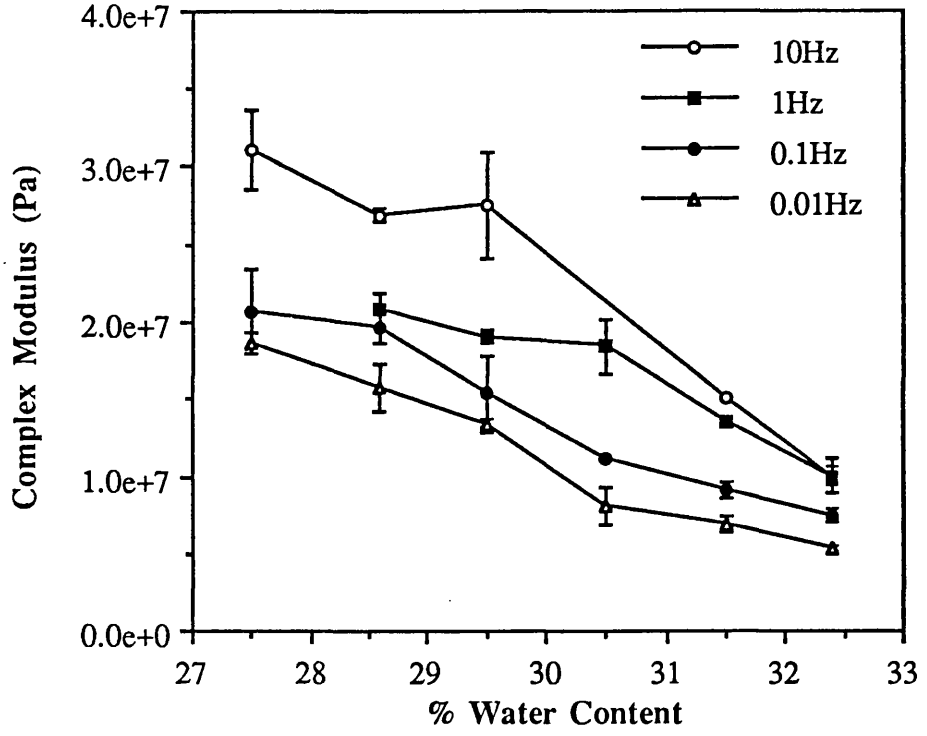
Figure 5.31 The Effect of Oscillatory Frequency on the Loss Modulus Value Obtained from Lactose (7) and Microcrystalline Cellulose (3) Mixtures with Varying Moisture Contents under an Applied Torque of 8mNm.



At all oscillatory frequencies there is a reduction in loss modulus with increasing water content of the formulation. Some cross-over of lines occurs due to changes in the region of linear visco-elastic response.

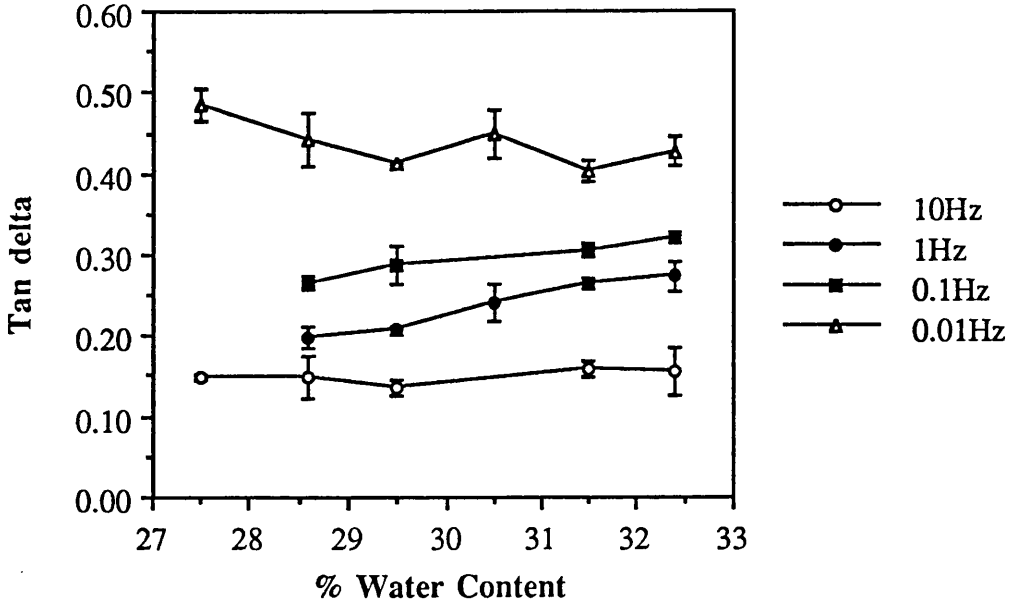
The values of the complex modulus (Figure 5.32) recorded for various formulations at 8mNm follow trends similar to those produced for G'. An increasing water content in the formulation reduces the complex modulus. Similarly an increase in oscillatory frequency increases the G* value recorded.

Figure 5.32 The Effect of Oscillatory Frequency on the Complex Modulus Value Obtained from Lactose (7) and Microcrystalline Cellulose (3) Mixtures with Varying Moisture Contents under an Applied Torque of 8mNm.



Tan delta reflects the degree of elasticity to viscosity of the sample formulations. As previously observed (*cf.* Figure 5.26) a high oscillatory frequency increases the elastic behaviour of the experimental samples. Therefore an oscillatory frequency of 10Hz produces the lowest tan delta values and an oscillatory frequency of 0.01Hz the highest (Figure 5.33).

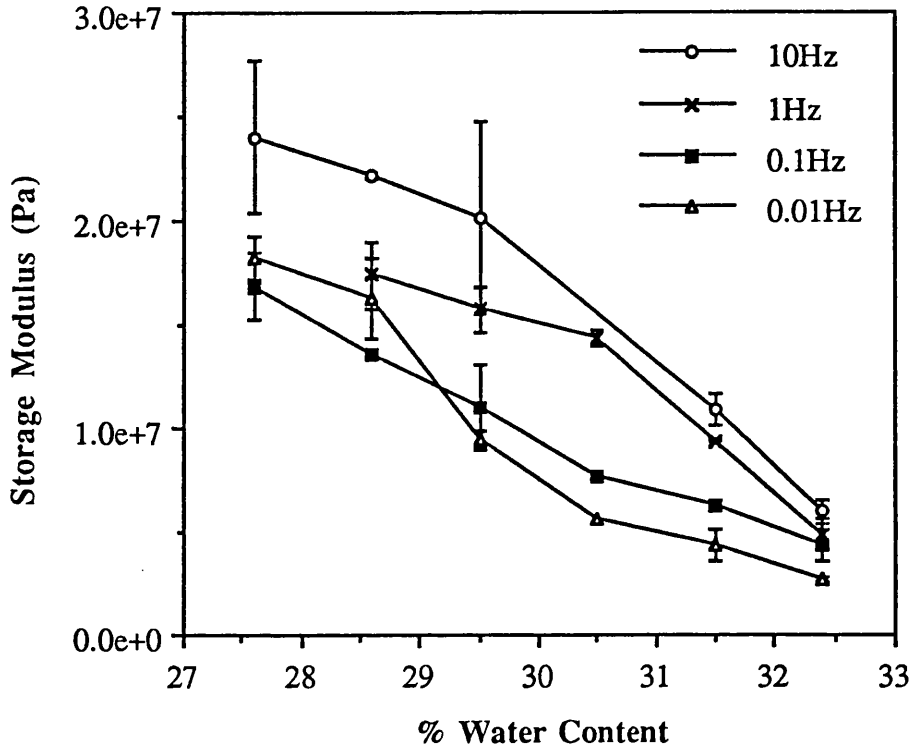
Figure 5.33 The Effect of Oscillatory Frequency on the Tan Delta Value Obtained from Lactose (7) and Microcrystalline Cellulose (3) Mixtures with Varying Moisture Contents under an Applied Torque of 8mNm.



Increasing the moisture content of the mix increases the viscous behaviour of the sample at oscillatory frequencies of 1 and 0.1Hz. At a frequency of 10Hz G* remains approximately constant with increasing moisture content. At a frequency of 0.01Hz G* falls initially with an increasing water content due to variation in the region of linear visco-elastic response.

Changing the oscillatory frequency when the applied torque is increased to 18mNm produces results similar to those produced at an applied torque of 8mNm. For example values recorded for the storage modulus demonstrate that G' decreases with a decreasing oscillatory frequency (Figure 5.34). The storage modulus value recorded at 0.01Hz initially appears greater than that recorded at 0.1Hz. This is due to the variation in the region of linear visco-elastic response with the change in oscillatory frequency. As the moisture content increases the linear region that occurs at 0.01Hz falls to a lower stress and G' falls below the value recorded for a 0.1Hz oscillation frequency.

Figure 5.34 The Effect of Oscillatory Frequency on the Storage Modulus Value Obtained from Lactose (7) and Microcrystalline Cellulose (3) Mixtures with Varying Moisture Contents under an Applied Torque of 18mNm.



As with the formulations oscillated at an applied torque of 8mNm there is a sharp decrease in G' values with an increase in the moisture content above 29.6% when the oscillatory frequency is high. This again is in agreement with results produced by capillary rheometry (Figures 4.17 and 4.18 - Section 4.1.2) that demonstrate a marked decrease in the shear stress as the shear rate increases when the moisture content rises to 30.5% or above. Other rheological parameters measured (*i.e.* G", G* and tan delta) follow the patterns established by the results obtained from controlled-stress oscillation at 8mNm (*cf.* Figures 5.31-5.33).

5.2.2 8:2 Lactose : Microcrystalline Cellulose Mixtures

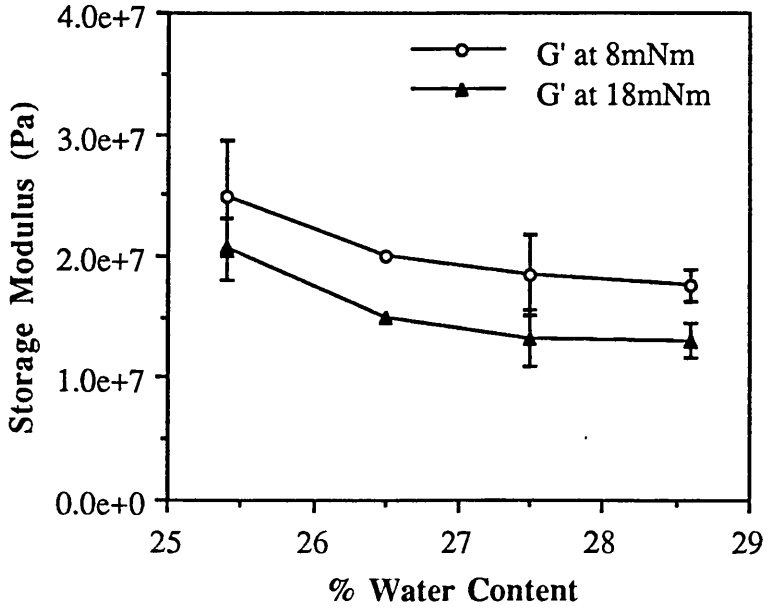
The Effect of Moisture on Rheological Values

The rheological parameters measured by oscillatory rheometry are affected by a change in the applied stress (or torque), the oscillatory frequency and the moisture content of the 8 : 2 lactose : microcrystalline cellulose formulation.

Since the moisture contents for formulations containing 8 parts lactose to 2 parts microcrystalline cellulose that are required for successful extrusion and spheronisation are lower than those moisture contents required for mixtures containing 7 parts lactose to 3 parts microcrystalline cellulose, the controlled-stress rheological parameters recorded for each set of mixes may be quite different.

Experiments were performed on blends at applied torques of 8mNm and 18mNm at oscillatory frequencies of 0.01, 0.1, 1 and 10Hz. When the oscillatory frequency of experiments performed on 8 : 2 blends is varied there are changes in the rheological parameters recorded for each individual mixture. With an increase in oscillatory frequency G' values increase whereas G" values fall. At 0.1Hz, as the moisture content of the formulation increases, the storage modulus recorded for each mixture decreases with both the applied torques (Figure 5.35).

Figure 5.35 The Effect of Varying Moisture Content on Storage Modulus Values Obtained for 8 : 2 Lactose : Microcrystalline Cellulose Samples at Applied Torques of 8mNm and 18mNm at an Oscillatory Frequency of 0.1Hz.

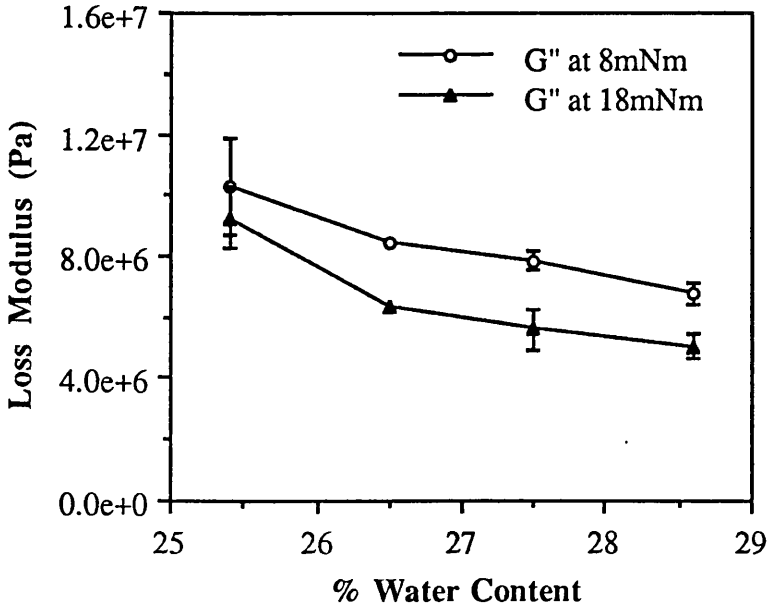


Storage modulus values recorded at applied torques of 8 and 18mNm at an oscillatory frequency of 0.1Hz exhibit constant decreases in value with an increase in moisture content. The value of G' has increased with an increase in oscillatory frequency from 0.01Hz. Values recorded at 8mNm are greater than those recorded at 18mNm implying that the region of linear visco-elastic response occurs towards the lower torque.

The values of G' for the 8 : 2 blends examined above (Figure 5.35) are much greater than those values recorded for 7 : 3 blends of lactose and microcrystalline cellulose examined previously (Figure 5.18) at similar applied stresses and oscillatory frequencies. The higher G' values for 8 : 2 mixtures are explained by their lower moisture contents which makes those mixtures much more rigid and elastic in nature.

A decrease in the loss modulus with an increase in moisture content is observed with samples tested at applied torques of 8mNm and 18mNm at an oscillatory frequency of 0.1Hz (Figure 5.36). Although the value of G" decreases with increasing moisture content, the difference in G" value between the driest and wettest formulation is much lower at a torque of 18mNm (approximately 2 x 10^6Pa difference) than at a torque of 8mNm (a difference of approximately 6 x 10^6Pa). The actual G" values recorded are lower than those produced at an oscillatory frequency of 0.01Hz.

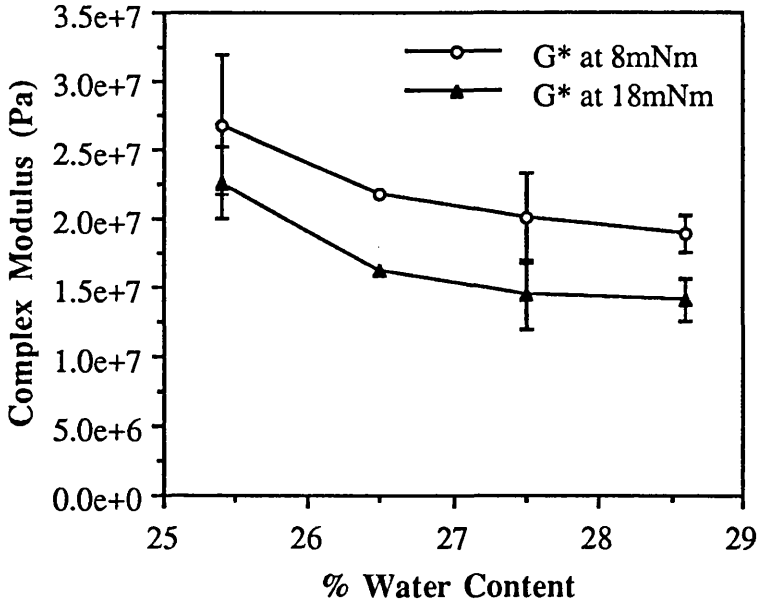
Figure 5.36 The Effect of Varying Moisture Content on Loss Modulus Values Obtained for 8 : 2 Lactose : Microcrystalline Cellulose Samples at Applied Torques of 8mNm and 18mNm at an Oscillatory Frequency of 0.1Hz.



Loss modulus values recorded for 8 : 2 lactose : microcrystalline cellulose blends (Figure 5.36) are greater than those recorded for 7 : 3 lactose : microcrystalline cellulose mixtures studied previously (Figure 5.27). This is due to the reduction in the moisture content of 8 : 2 mixtures when compared to those 7 : 3 mixtures examined. This makes 8 : 2 formulations not only more rigid and elastic but also more viscous in structure.

The change in complex modulus values with a change in moisture content reflects that the 8 : 2 lactose : microcrystalline cellulose formulations under investigation remain predominantly elastic in behaviour. This can be observed from the results contained in Figure 5.37 which highlights that the G* values decrease in a manner similar to reductions in the storage modulus with an increase in moisture content (Figure 5.35).

Figure 5.37 The Effect of Varying Moisture Content on Complex Modulus Values Obtained for 8 : 2 Lactose : Microcrystalline Cellulose Samples at Applied Torques of 8mNm and 18mNm at an Oscillatory Frequency of 0.1Hz.

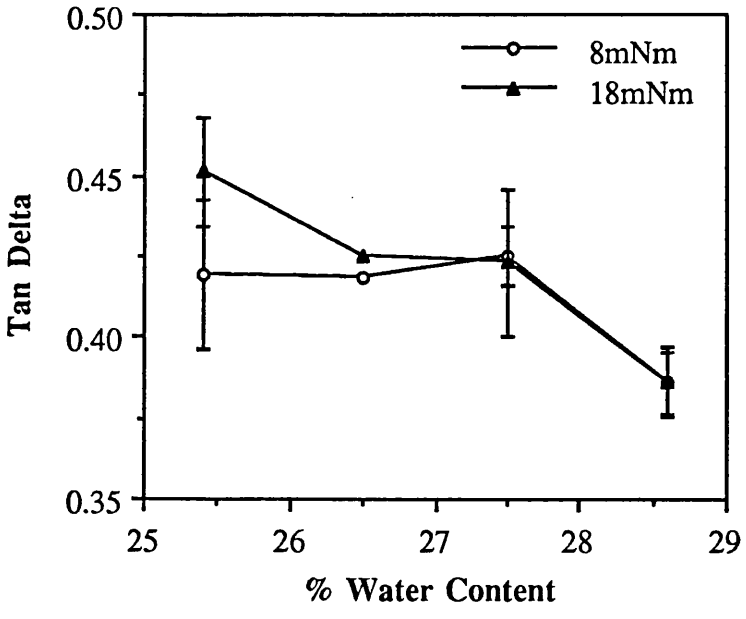


G* values recorded for the 8 : 2 lactose : microcrystalline cellulose formulations studied above (Figure 5.37) are much greater than those G* values recorded for 7 : 3 lactose : microcrystalline cellulose formulations studied at the same torques and oscillatory frequency (Figure 5.20). This is to be expected as the amount of moisture present in the 8 : 2 mixtures is lower than that present in the 7 : 3 mixtures and moisture

reduces the complex modulus value. Therefore the 8 : 2 lactose : microcrystalline cellulose mixtures investigated are both more viscous and more elastic than the 7 : 3 lactose : microcrystalline cellulose formulations studied.

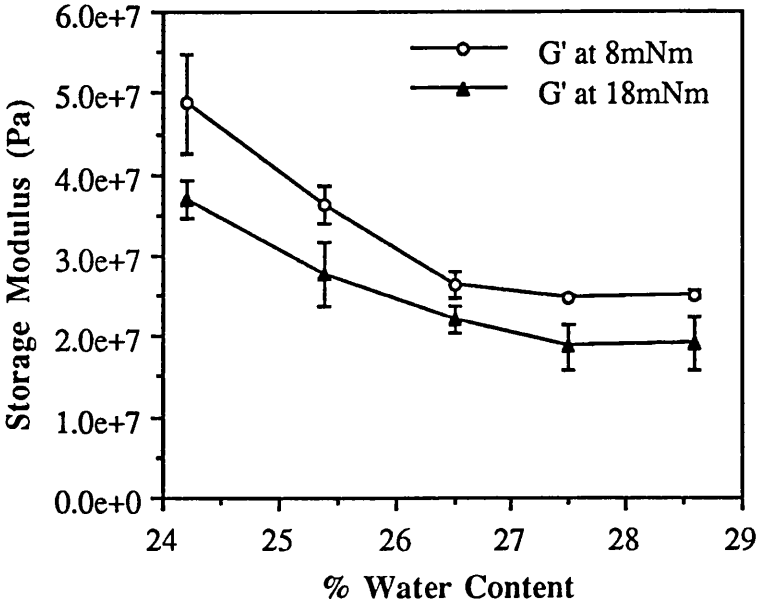
The high elasticities and viscosities of the 8 : 2 formulations mean that slight differences in tan delta values cause large deviations in measurements. However in general an increase in moisture content reduces the tan delta value of formulations investigated and suggests that materials are becoming more elastic in nature as moisture content increases. Results from G' and G" measurements (Figures 5.35 and 5.36 respectively) highlight a larger relative decrease in G" than G' with increasing moisture content which leads to an decrease in tan δ value (Figure 5.38).This effect is not repeated at other oscillatory frequencies and is probably the result of variations in the region of linear visco-elastic response which changes with oscillatory frequency and moisture content.

Figure 5.38 The Effect of Varying Moisture Content on Tan Delta Values Obtained for 8 : 2 Lactose : Microcrystalline Cellulose Samples at Applied Torques of 8mNm and 18mNm at an Oscillatory Frequency of 0.1Hz.



Applying torques at an oscillatory frequency of 1Hz produces a gradual decrease in G' which begins to level out as the moisture content increases (Figure 5.39). An increase in oscillatory frequency has again increased the magnitude of response for each formulation under investigation (*cf.* Figure 5.35).

Figure 5.39 The Effect of Varying Moisture Content on Storage Modulus Values Obtained for 8 : 2 Lactose : Microcrystalline Cellulose Samples at Applied Torques of 8mNm and 18mNm at an Oscillatory Frequency of 1Hz.



Values for the loss modulus produced from 8 : 2 mixtures oscillated at 1Hz indicate a decrease with an increasing moisture content up to 26.5% when a torque of 8mNm is applied (Figure 5.40). As the moisture content increases further differences in G" become much smaller. At an applied torque of 18mNm G" is initially low at a low moisture content and remains approximately constant with increasing moisture content. The consistency of G" at 18mNm torque reflects that although there is movement of the region of linear visco-elastic response around a torque value of 8mNm an increase in the applied stress at 1Hz does not alter the sample response as much as increases at other oscillatory frequencies (*cf.* Figure 5.36).

As the oscillatory frequency increases there is an increase in G' and a decrease in G" (Figure 40). Therefore G* measurements, which are predominantly contolled by the G' component, become even more of a reflection of the G' value. Figure 5.41 contains the results obtained from varying the moisture content of 8 : 2 lactose : microcrystalline cellulose mixtures at two torques applied at an oscillatory frequency of 1Hz. The results are very similar to those produced by the storage modulus as it is stressed under identical conditions (Figure 5.39).

Figure 5.40 The Effect of Varying Moisture Content on Loss Modulus Values Obtained for 8 : 2 Lactose : Microcrystalline Cellulose Samples at Applied Torques of 8mNm and 18mNm at an Oscillatory Frequency of 1Hz.

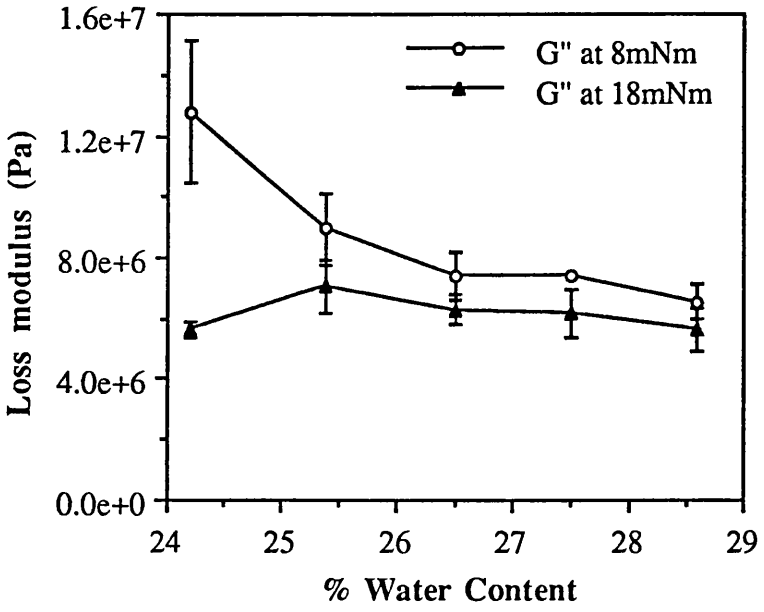
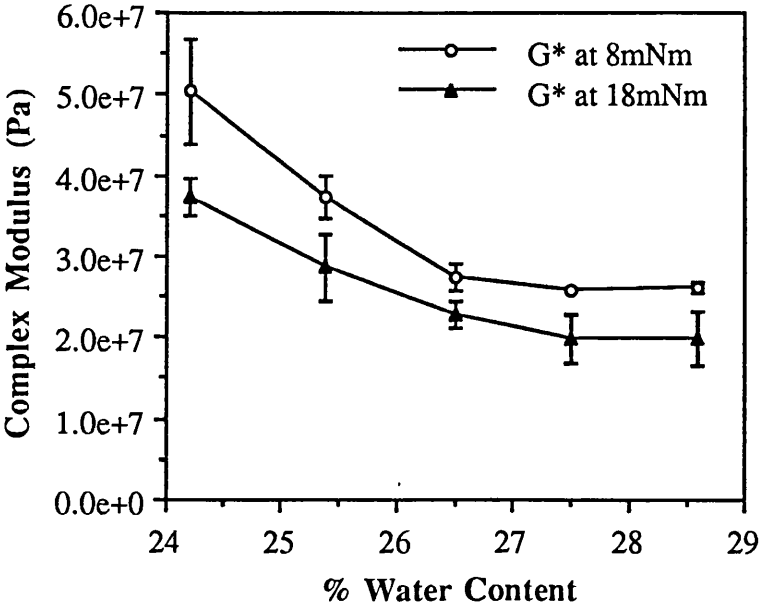
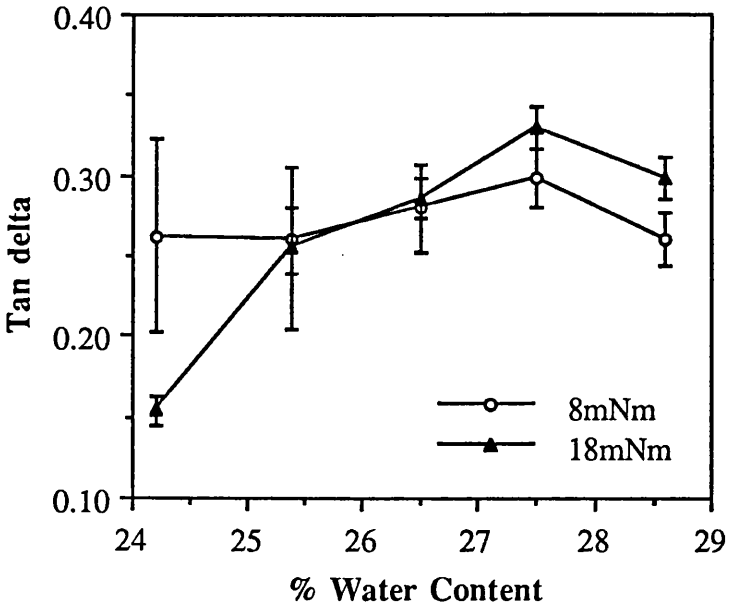


Figure 5.41 The Effect of Varying Moisture Content on Complex Modulus Values Obtained for 8 : 2 Lactose : Microcrystalline Cellulose Samples at Applied Torques of 8mNm and 18mNm at an Oscillatory Frequency of 1Hz.



Tan delta measurements for 8 : 2 blends stressed at a 1Hz oscillatory frequency demonstrate that at an applied torque of 8mNm there is little influence on tan delta as the moisture content is increased (Figure 5.42). At 18mNm an increase in moisture content increases the tan delta value, suggesting that the materials are becoming more viscous in behaviour with increasing moisture content. However these results are likely to be due to the effect of changes in the region of linear viscoelastic response which varies with moisture content. At low moisture contents the region occurs at high torque values (at approximately 18mNm) therefore tan delta values are low. As the moisture content increases the linear region moves below 18mNm and there is correlation between moisture content and tan delta. As the moisture content increases further the region of linear viscoelastic response moves to even lower torque values and tan delta values begin to fall.

Figure 5.42 The Effect of Varying Moisture Content on Tan Delta Values Obtained for 8 : 2 Lactose : Microcrystalline Cellulose Samples at Applied Torques of 8mNm and 18mNm at an Oscillatory Frequency of 1Hz.



Oscillatory rheometry undertaken at 10Hz on 8 : 2 lactose : microcrystalline cellulose mixtures produces the highest G' values measured (Figure 5.43). With an increasing moisture content G' decreases initially and then levels off with further increases in moisture content. Loss modulus values similarly decrease with an

increasing moisture content and then level off as the moisture content increases further (Figure 5.44). Despite a 10 fold increase in oscillatory frequency G" values for each formulation are similar in magnitude to values obtained through oscillation at 1Hz (Figure 5.40).

G* measurements again reflect the predominance of the storage modulus component (Figure 5.45) and results follow similar trends to those produced at an oscillatory frequency of 1Hz (Figure 5.41). Sharp drops in the values of complex modulus occur at both torques as the moisture content increases and then plateaus with further rises. Tan delta measurements indicate that at both applied torques an increase in moisture content increases the tan delta value i.e. with an increasing moisture content the behaviour of the sample plugs, whilst still predominantly elastic, becomes more viscous in nature (Figure 5.46).

Figure 5.43 The Effect of Varying Moisture Content on Storage Modulus Values Obtained for 8 : 2 Lactose : Microcrystalline Cellulose Samples at Applied Torques of 8mNm and 18mNm at an Oscillatory Frequency of 10Hz.

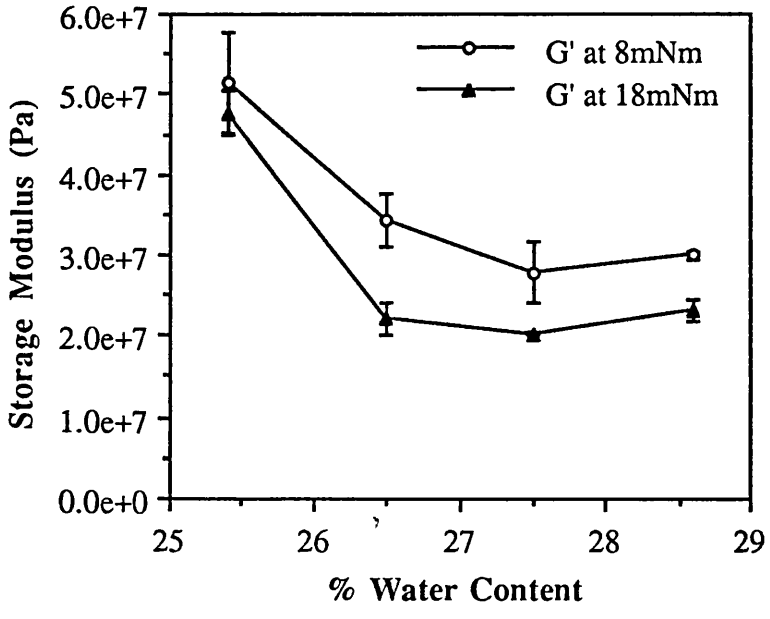


Figure 5.44 The Effect of Varying Moisture Content on Loss Modulus Values Obtained for 8 : 2 Lactose : Microcrystalline Cellulose Samples at Applied Torques of 8mNm and 18mNm at an Oscillatory Frequency of 10Hz.

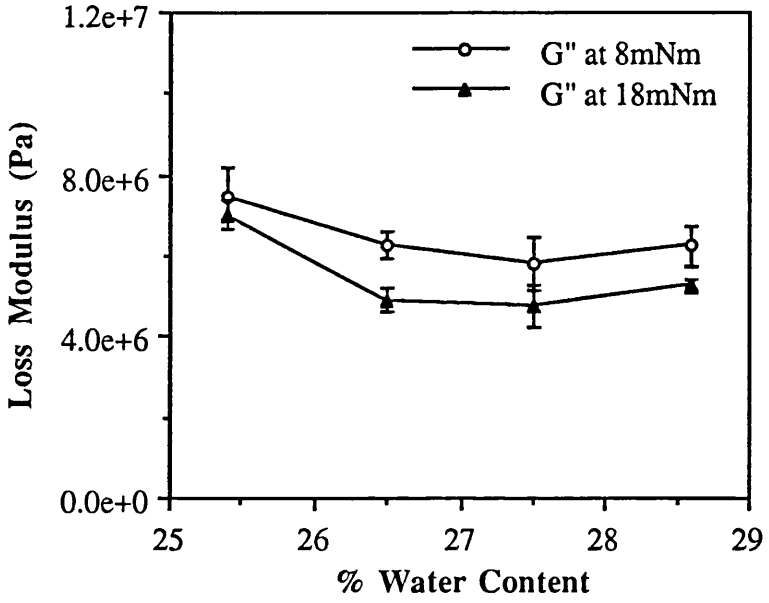


Figure 5.45 The Effect of Varying Moisture Content on Complex Modulus Values Obtained for 8 : 2 Lactose : Microcrystalline Cellulose Samples at Applied Torques of 8mNm and 18mNm at an Oscillatory Frequency of 10Hz.

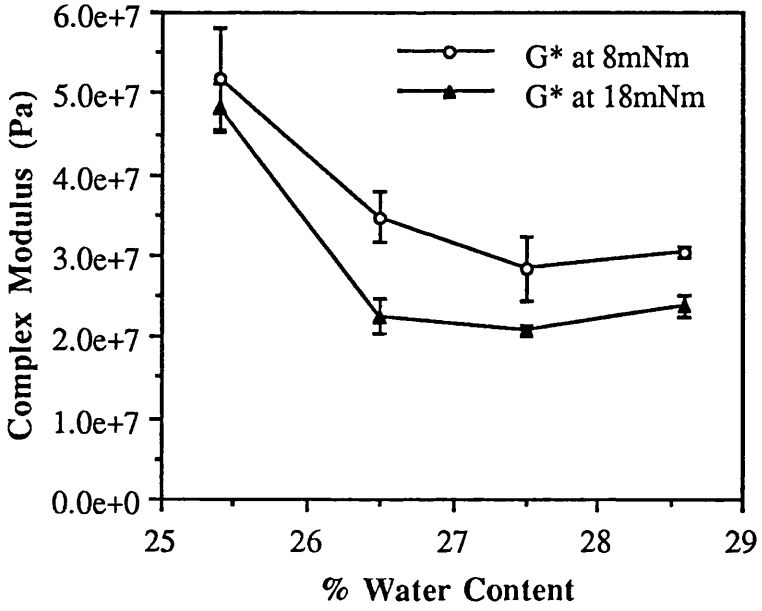
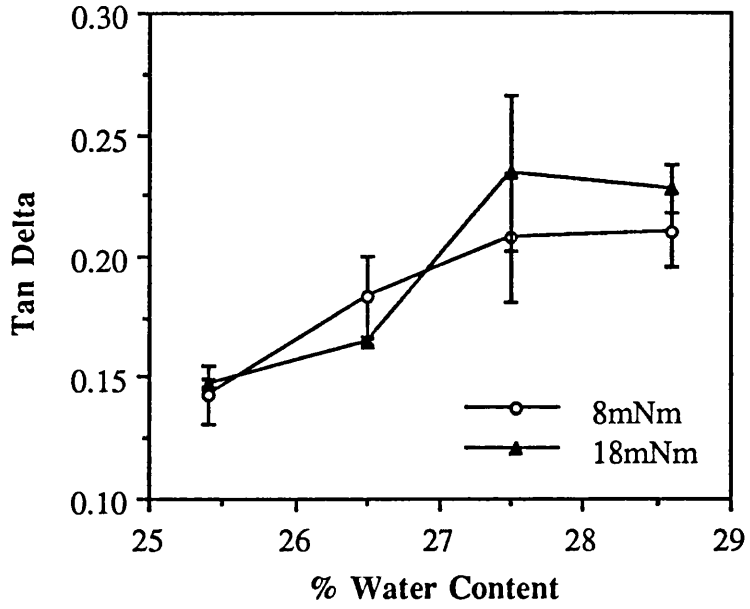


Figure 5.46 The Effect of Varying Moisture Content on Tan Delta Values Obtained for 8 : 2 Lactose : Microcrystalline Cellulose Samples at Applied Torques of 8mNm and 18mNm at an Oscillatory Frequency of 10Hz.

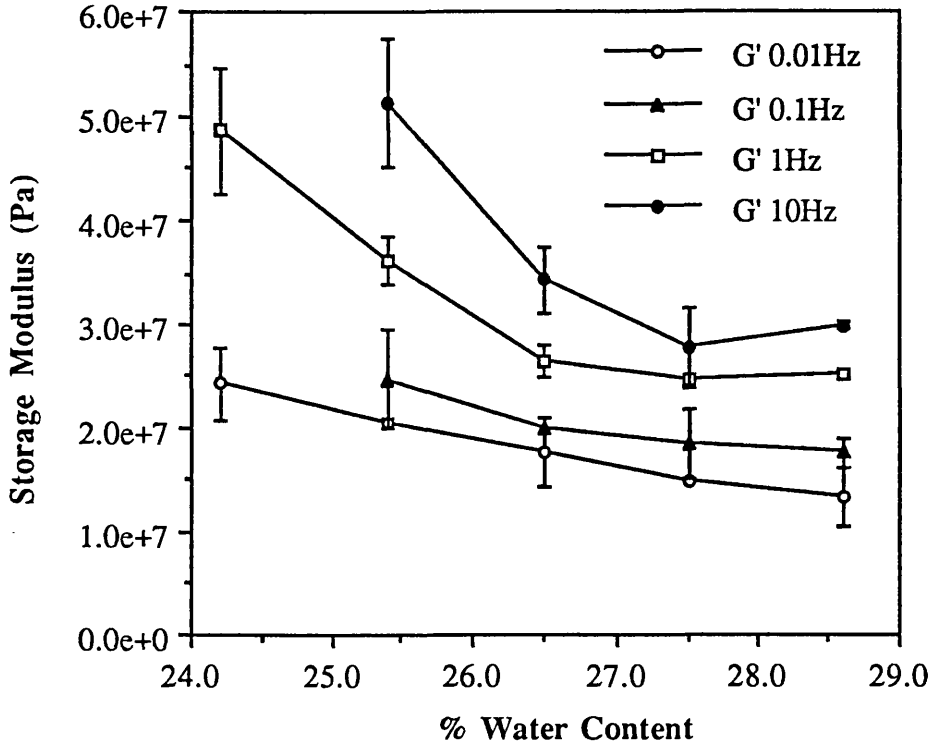


The Effect of Oscillatory Frequency on Rheological Values.

The effect of varying the oscillatory frequency at a constant shear stress (or torque) has been plotted for 8 : 2 lactose : microcrystalline cellulose mixtures stressed at 8mNm. As the rheological parameters measured by oscillation are related, values for the storage modulus have been used as an indicator of the behaviour of these mixtures.

Results for 8 : 2 formulations oscillated at various frequencies at an applied torque of 8mNm (Figure 5.47) demonstrate that there is an increase in all storage modulus values when compared to 7 : 3 formulations (Figure 5.30). The decrease in G' with increasing moisture content is most marked with mixtures oscillated at 1Hz and 10Hz. These frequencies are again those that equate to capillary rheometry experiment times. Consequently changes in G' may indicate that there is a change in the capillary rheometry behaviour of 8 : 2 formulations at a moisture content of approximately 26.5%.

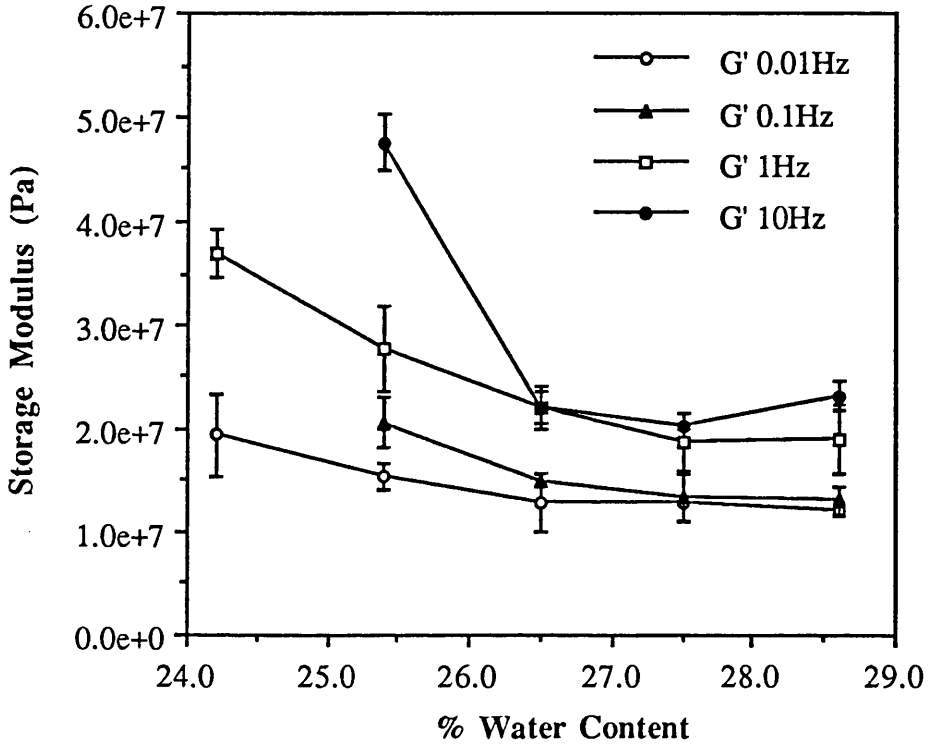
Figure 5.47 The Effect of Oscillatory Frequency on the Storage Modulus Value Obtained from Lactose (8) and Microcrystalline Cellulose (2) Mixtures with Varying Moisture Contents under an Applied Torque of 8mNm.



The results suggest that at very low extrusion rates (as represented by an oscillatory frequency of 0.01Hz) there would be very little difference in the rheological behaviour between each of the 8 : 2 mixtures undergoing capillary rheometry.

The reduction in G' values with an increasing moisture content and decreasing oscillatory frequency is repeated when materials are oscillated at an applied torque of 18mNm (Figure 5.48). Again changes in the value of G' at a moisture content of 26.5% at oscillatory frequencies of 1 and 10Hz demonstrate that there may be changes in the behaviour of these materials when examined with capillary rheometry. However comparison with the results from capillary rheometry performed on 8 : 2 lactose : microcrystalline cellulose mixtures is difficult to achieve because of the limited data available (*cf.* Section 4.1.2). The data available from capillary rheometry suggests there is little difference in rheological behaviour between mixtures. This finding is repeated with oscillatory rheometry performed at low oscillatory frequencies but high oscillatory frequencies highlight differences in rheological behaviour between formulations with different moisture contents.

Figure 5.48 The Effect of Oscillatory Frequency on the Storage Modulus Value Obtained from Lactose (8) and Microcrystalline Cellulose (2) Mixtures with Varying Moisture Contents under an Applied Torque of 18mNm.



5.2.3 Comparison of Oscillatory Rheometry Results Obtained from Mixtures Containing 7 : 3 and 8 : 2 Lactose : Microcrystalline Cellulose.

The results from the experiments conducted with an oscillatory controlled-stress rheometry highlight differences in the behaviour of materials when subjected to various torques and oscillatory frequencies. When the moisture content is increased for both lactose : microcrystalline cellulose ratios there is a decrease in the storage modulus value recorded. Comparison of the two different ratios together (Figure 5.49) demonstrates that the main effect of change in the storage modulus is the moisture content and not a change in the relative ratios of the solid components. This is in agreement with the results obtained from creep experiments conducted previously (*cf.* Section 5.1). Creep results also highlight that the important factor in changes in

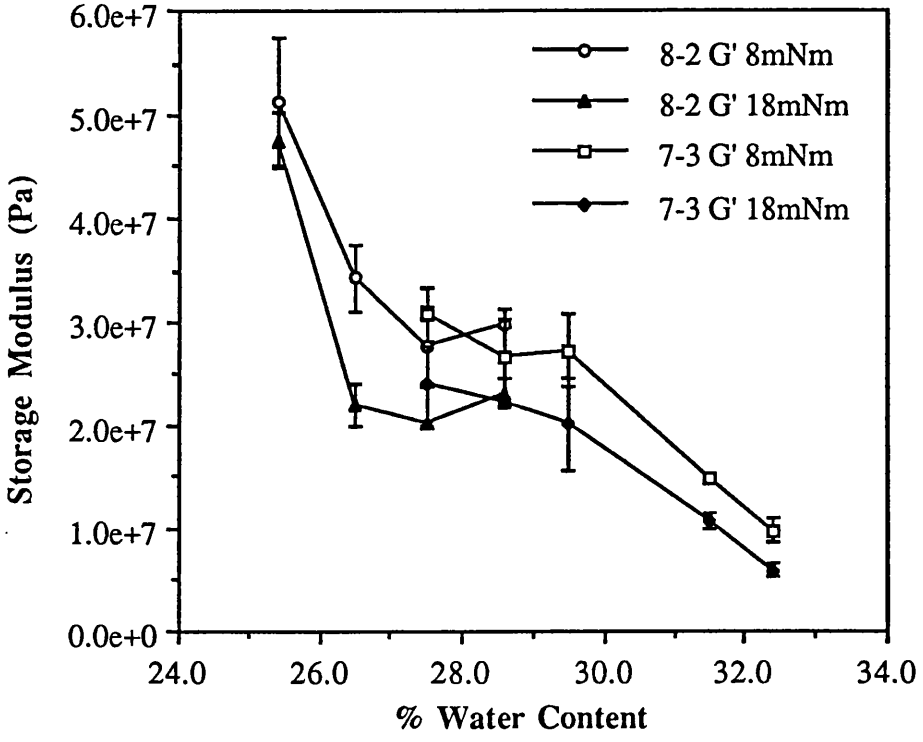
rheological measurement is variation in the moisture content which then results in a variation in the shear produced.

When moisture contents and oscillatory frequency are varied for each lactose : microcrystalline cellulose ratio examined, there is alteration in the region of linear visco-elastic response. This occurs at a lower applied torque and over a shorter range as the moisture content increases and the oscillatory frequency increases. Calculation of the difference between storage modulus values obtained at 8 and 18mNm at various frequencies may determine whether a change in lactose : microcrystalline cellulose ratio results in variation in the behaviour of mixtures to a sweep in torque values. Figures 5.50 and 5.51 demonstrate the effect of varying moisture content on the difference in mean values obtained at applied torques of 8 and 18mNm of G' and G" recorded for two lactose : microcrystalline cellulose ratios. G' values decrease with an increase in moisture content although the decrease is not linear. There does not appear to be a significant effect produced by a change in the solids ratio although an increase in the oscillatory frequency does exaggerate differences in G' values.

Values obtained from differences in the loss modulus (Figure 5.51) demonstrate that an increase in moisture content decreases the G" difference but that an increase in oscillatory frequency reduces the difference in G", unlike the storage modulus (Figure 5.50). There does appear to be an effect from changing the solid components ratio with 7 : 3 lactose : microcrystalline cellulose mixtures having much lower differences in G" values than 8 : 2 mixtures.

Results from comparison of 7 : 3 and 8 : 2 mixtures suggest that differences in rheological behaviour between the two sets of formulations are predominantly due to their differences in moisture content and that under similar test conditions each mixture would produce similar rheological values. This is in corroboration with results conducted using creep experiments (Section 5.1) and capillary rheometry which suggest that changes in the deformability of the material due to an increase in moisture content are responsible for the variations in the shear produced by each sample.

Figure 5.49 The Effect of Change in Moisture Content on the Storage Modulus Recorded for Two Lactose : Microcrystalline Cellulose Ratios Stressed at Applied Torques of 8 and 18mNm, at an Oscillatory Frequency of 10Hz.



[Key:-

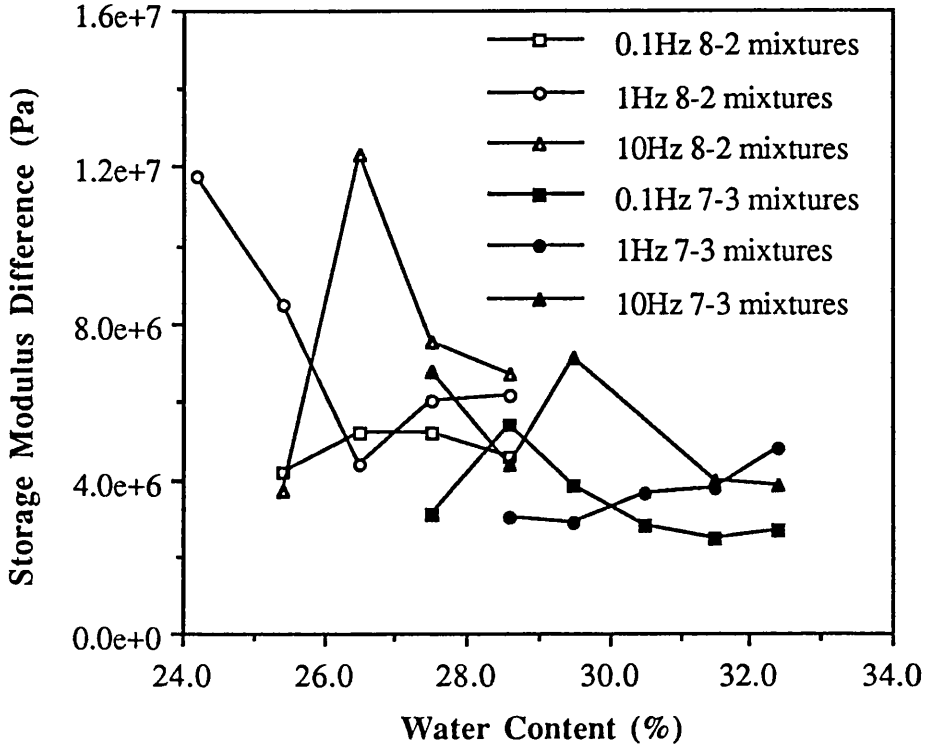
8-2 G' 8mNm - G' value for 8 : 2 lactose : microcrystalline cellulose mixtures obtained at an applied torque of 8mNm.

8-2 G' 18mNm - G' value for 8 : 2 lactose : microcrystalline cellulose mixtures obtained at an applied torque of 18mNm.

7-3 G' 8mNm - G' value for 7 : 3 lactose : microcrystalline cellulose mixtures obtained at an applied torque of 8mNm.

7-3 G' 18mNm - G' value for 7 : 3 lactose : microcrystalline cellulose mixtures obtained at an appiled torque of 18mNm.]

Figure 5.50 The Effect of Moisture Content on the Difference Between Storage Modulus Values Recorded at Applied Torques of 8 and 18mNm for 7 : 3 and 8 : 2 Lactose : Microcrystalline Cellulose Mixtures at Various Oscillatory Frequencies.



[Key:-

0.1Hz 8-2 mixtures - Difference in mean G' values for 8 : 2 lactose : microcrystalline cellulose mixtures undergoing oscillation at 0.1Hz.

1Hz 8-2 mixtures - Difference in mean G' values for 8 : 2 lactose : microcrystalline cellulose mixtures undergoing oscillation at 1Hz.

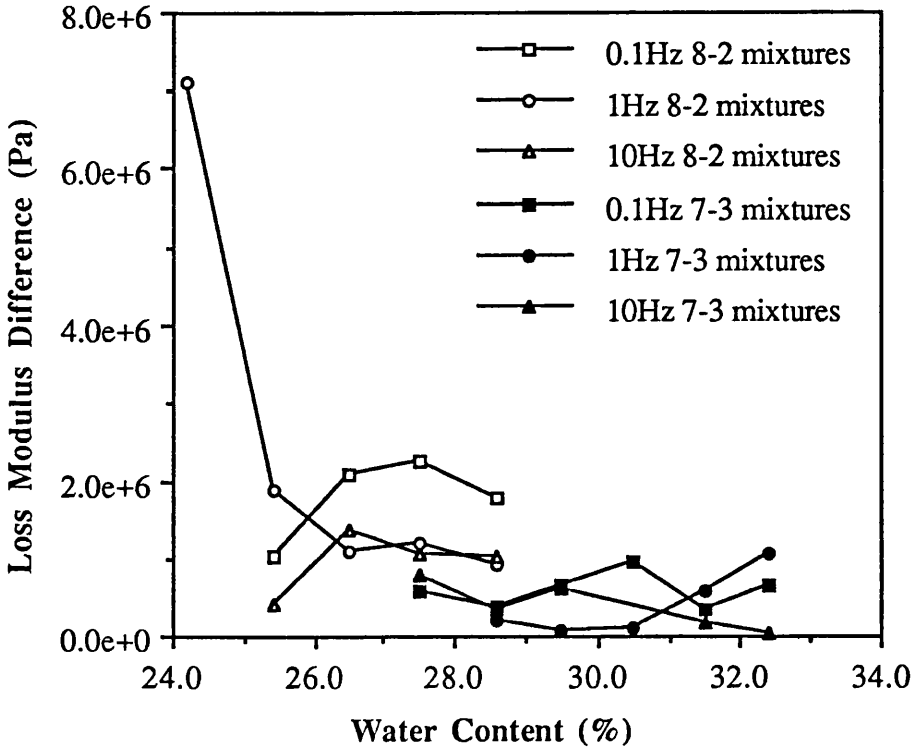
10Hz 8-2 mixtures - Difference in mean G' values for 8 : 2 lactose : microcrystalline cellulose mixtures undergoing oscillation at 10Hz.

0.1Hz 7-3 mixtures - Difference in mean G' values for 7 : 3 lactose : microcrystalline cellulose mixtures undergoing oscillation at 0.1Hz.

1Hz 7-3 mixtures - Difference in mean G' values for 7 : 3 lactose : microcrystalline cellulose mixtures undergoing oscillation at 1Hz.

10Hz 7-3 mixtures - Difference in mean G' values for 7 : 3 lactose : microcrystalline cellulose mixtures undergoing oscillation at 10Hz.]

Figure 5.51 The Effect of Moisture Content on the Difference Between Loss Modulus Values Recorded at Applied Torques of 8 and 18mNm for 7 : 3 and 8 : 2 Lactose : Microcrystalline Cellulose Mixtures.



5.3 Conclusions

Oscillatory rheometry provides useful and reproducible rheological information on the behaviour of various lactose : microcrystalline cellulose : water mixtures. Such behaviour is influenced by the size of the applied stress (or torque), the frequency of oscillation of the stress and the formulation of the material itself.

In general an increase in the amount of stress applied to a sample at a constant frequency decreases the storage, loss and complex moduli but increases the tan delta for the material. An increase in oscillatory frequency increases the storage and complex moduli but decreases the loss modulus and the tan delta recorded for each sample. An increase in moisture content decreases the storage, loss and complex moduli but increases the tan delta. This is due to the greater effect that extra moisture plays on reducing the elastic component as opposed to the viscous component.

All results from oscillatory rheometry are subject to the changes of the linear region of visco-elastic response which varies in magnitude and duration with changes in formulation, oscillatory frequency and applied stress. The linear region is generally located at lower applied stress (or torque) values and occur over shorter areas with an increase in the moisture content and with a decrease in oscillatory frequency. Consequently comparison of actual values obtained between formulations at the same oscillatory frequency and applied stress can only be indicative of trends. Nevertheless it would appear that these trends are supportive of evidence produced by capillary rheometry about the behaviour of these materials.

The implications of oscillatory rheometry on the performance of formulations undergoing extrusion and spheronisation are discussed in the Chapter 6.

Chapter 6

DISCUSSION

6. DISCUSSION

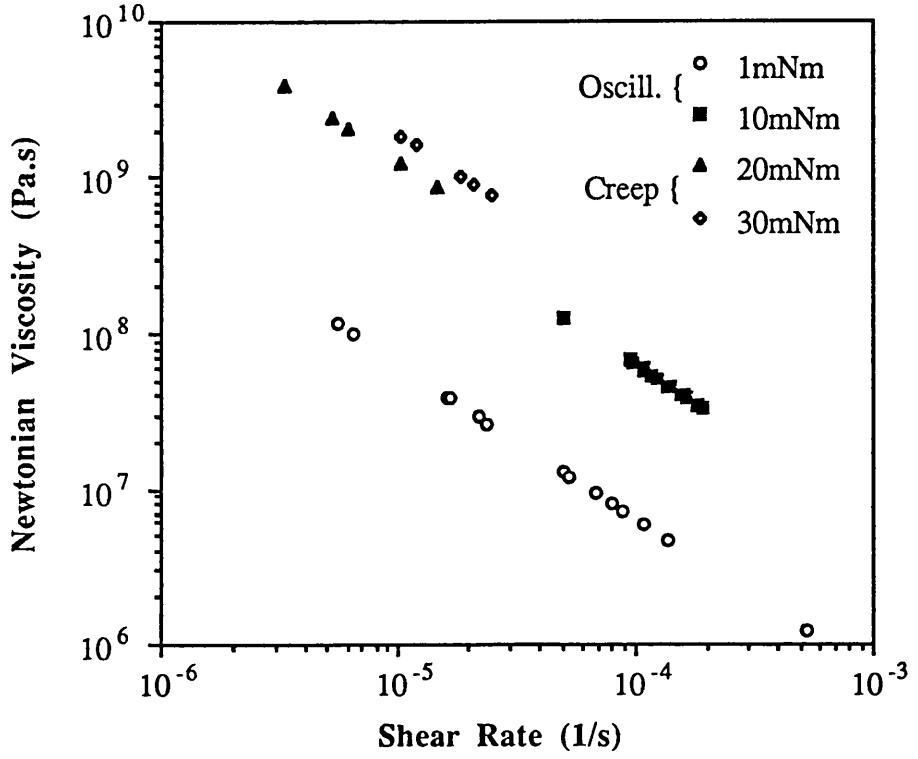
The results contained in Chapter 5 demonstrate the potential use of controlled-stress rheometry as a means of providing rheological information on samples that may undergo extrusion and spheronisation. The technique of controlled-stress rheometry is far quicker in constructing a shear profile for materials under investigation than the conventional method of capillary rheometry. Samples for controlled stress rheometry can be collected and analysed within a day whereas capillary rheometry, whilst allowing experimental examination of extrudate, takes at least two days to construct graphs with as few as four points on the profile. From initial experiments, further examination of controlled-stress rheometry may also remove the 12 hours that is required for water equilibration in the sample mixture before capillary rheometry can be undertaken.

Although the controlled-stress rheometry technique is a faster method of providing rheological information than the construction of shear stress *versus* shear rate profiles it does not provide direct rheological information that is useful in considering whether a mixture will successfully extrude and spheronise. An assessment of the technique as to its suitability as a possible predictor of extrusion and spheronisation behaviour would be worthwhile. To that end it would be appropriate to consider whether there are any similarities in rheological information that could unite both controlled-stress and capillary rheometry. This would then allow examination of the effects of formulation on the outcome of extrusion and spheronisation without the time-consuming empirical approach of trial and error.

6.1 Comparison of Creep and Oscillation Rheometry Results

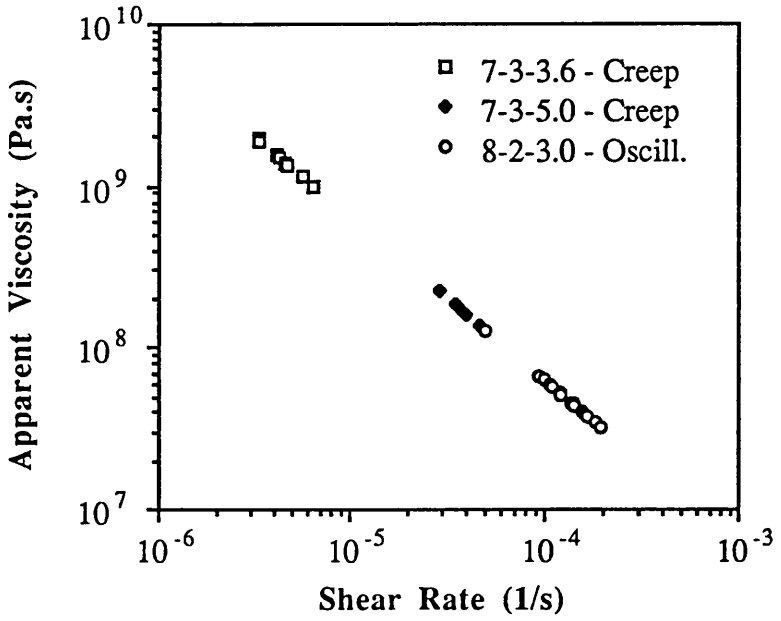
To examine whether the results of oscillatory and creep experiments are of similar shape and magnitude a graph of Newtonian viscosity *versus* shear rate was constructed for samples undergoing oscillatory rheometry. Values for strain can be assessed for each individual stress value obtained during a standard oscillatory torque sweep and hence a subsequent value of viscosity calculated. Figure 6.1 demonstrates the effect of various applied torques on an 8 : 2 : 3.0 lactose : microcrystalline cellulose : water mixture when subjected to both creep and oscillatory experiments. Creep experiments were undertaken at 20mNm and 30mNm whilst oscillation was performed at torques of 1mNm and 10mNm.

Figure 6.1 The Effect of Log. Shear Rate on the Log. Newtonian Viscosity Recorded for a Lactose (8 parts) and Microcrystalline Cellulose (2 parts) Mixture Containing 3.0 Parts (23.1%) Water Stressed under Various Applied Torques During Creep and Oscillation Experiments.



The results contained in Figure 6.1 highlight that increases in the shear rate decrease the Newtonian viscosity recorded for mixtures that have undergone both creep and oscillation experiments. The results are of a similar shape and magnitude to those produced by creep experiments when a constant torque is applied. Thus the graph highlights that there is a consistent response of shear strain to variations in the applied shear stress across both creep and oscillation experiments. The oscillatory frequency of the stressed sample varies from 0.01Hz to 10Hz. Consequently there is a large spread in calculated values of shear rate and Newtonian viscosity. Nevertheless a shift of shear rate values resulting from oscillation experiments to higher values than those that occur with creep experiments (Figure 6.1) indicates that an oscillatory experiment imparts more strain on a sample than a creep experiment performed at an identical applied stress (or torque). This can be demonstrated by comparing results at the same applied torque value (Figure 6.2).

Figure 6.2 The Effect of Log. Shear Rate on the Log. Newtonian Viscosity Recorded for Various Lactose : Microcrystalline Cellulose : Water Mixtures Stressed at an Applied Torque of 10mNm During Creep and Oscillation Experiments.



The results in Figure 6.2 were obtained from creep retardation values for the mixture containing lactose (7 parts), microcrystalline cellulose (3 parts) and 3.6 parts water (26.5%) and creep relaxation values for the mixture containing lactose (7 parts), microcrystalline cellulose (3 parts) and 5.0 parts moisture (33.3%). These represent extremes of shear induced by the creep experiment on samples under investigation. However the shear produced on the driest formulation investigated with oscillatory rheometry (lactose [8 parts], microcrystalline cellulose [2 parts] and 3.0 parts water [23.1%]) is greater than that produced by creep experiments.

The consistency in results obtained from creep and oscillation rheometry suggests that either set of results can be used to compare with the results obtained from capillary rheometry but that perhaps oscillatory results which occur at higher shear values may be of more merit.

6.2 Comparison of Capillary and Controlled-Stress Rheometry Results

Comparison of results from capillary rheometry and controlled-stress rheometry can be obtained if the flow profiles calculated with capillary rheometry are converted into apparent viscosity *versus* shear rate profiles. The flow profiles contained in Chapter 4 (Figures 4.16-4.19) can be used to calculate viscosity values. This process has been undertaken with 7 : 3 lactose : microcrystalline cellulose mixtures extruded through 1.5mm and 2mm diameter dies (Figures 6.3 and 6.4) and for 7 : 3 and 8 : 2 lactose : microcrystalline cellulose mixtures that have been extruded through 1mm diameter dies.

Figure 6.3 The Effect of Log. Shear Rate on the Log. Newtonian Viscosity Recorded for a Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) Mixture Containing Varying Amounts of Water Extruded Through a 1.5mm Diameter Die.

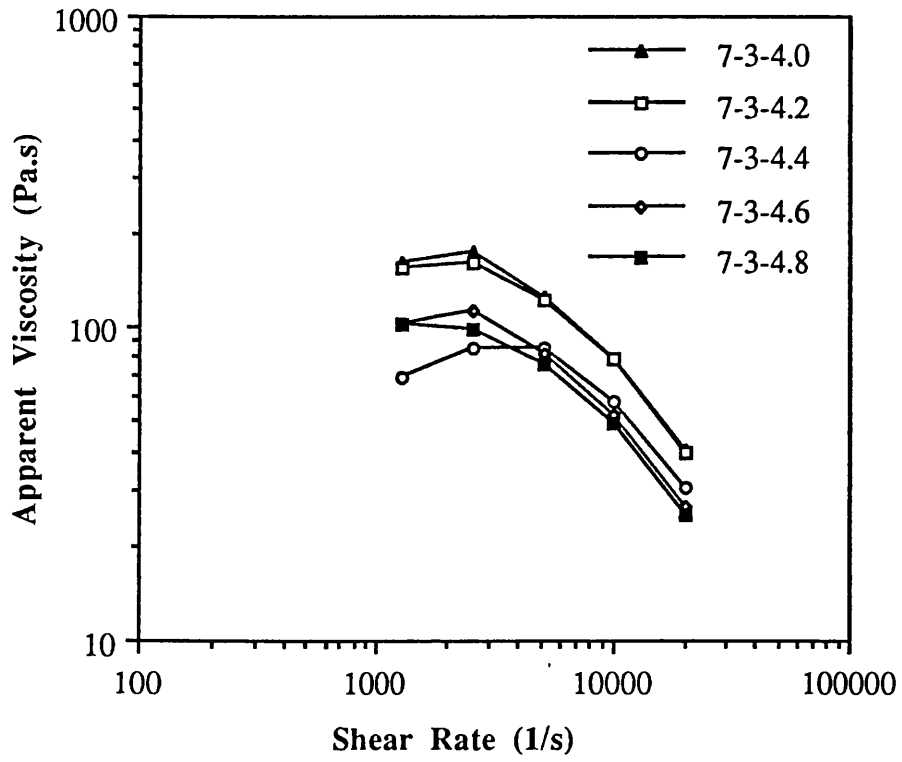
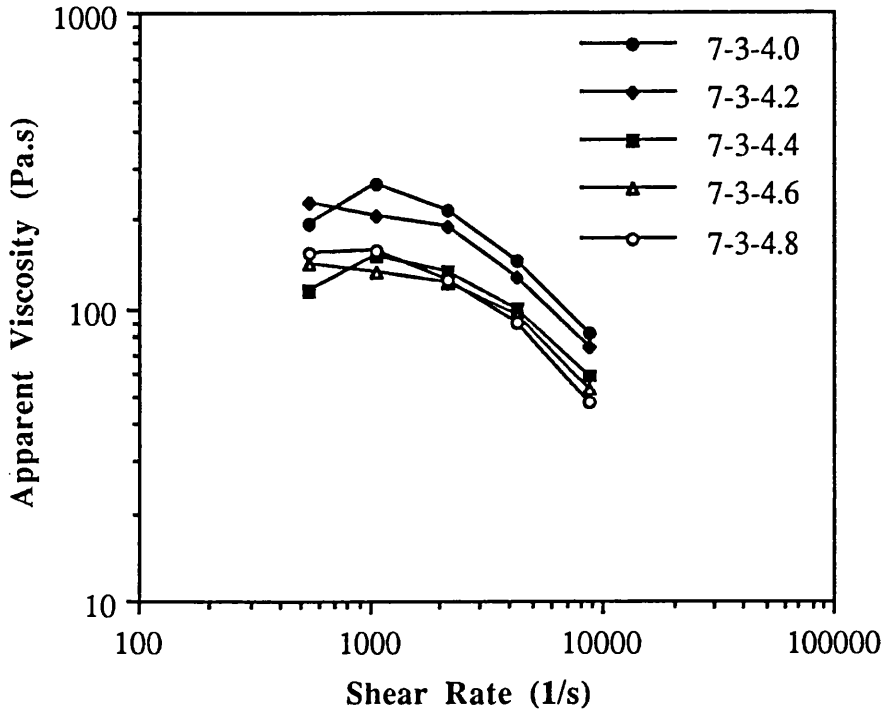


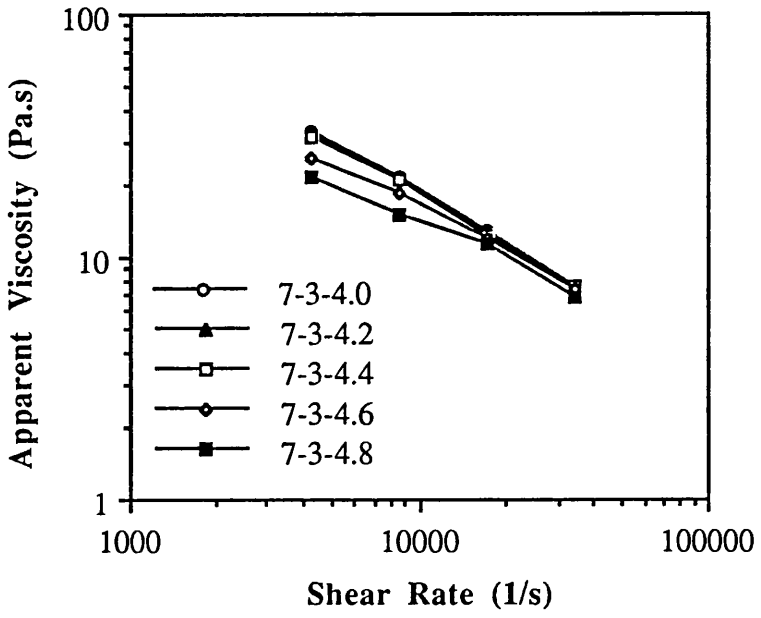
Figure 6.4 The Effect of Log. Shear Rate on the Log. Newtonian Viscosity Recorded for a Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) Mixture Containing Varying Amounts of Water Extruded Through a 2mm Diameter Die.



Figures 6.3 and 6.4 demonstrate that as the shear rate acting on the material decreases (*i.e.* there is a drop in the extruder velocity) then the viscosity value measured increases and then begins to level off or even decreases with further reductions in shear rate. This suggests that there is a fundamental change in the behaviour of the material as it is extruded at low shear rates that cannot be explained by variation in the moisture content alone. Consequently extrusion of any of the mixtures under investigation through 1.5mm and 2mm diameter dies should not occur at low extrusion velocities of approximately 100mm/min or under.

A plot of apparent viscosity *versus* shear rate for mixtures extruded through 1mm diameter dies (Figure 6.5) does not follow the profile obtained from extrusion through 1.5mm or 2mm diameter dies.

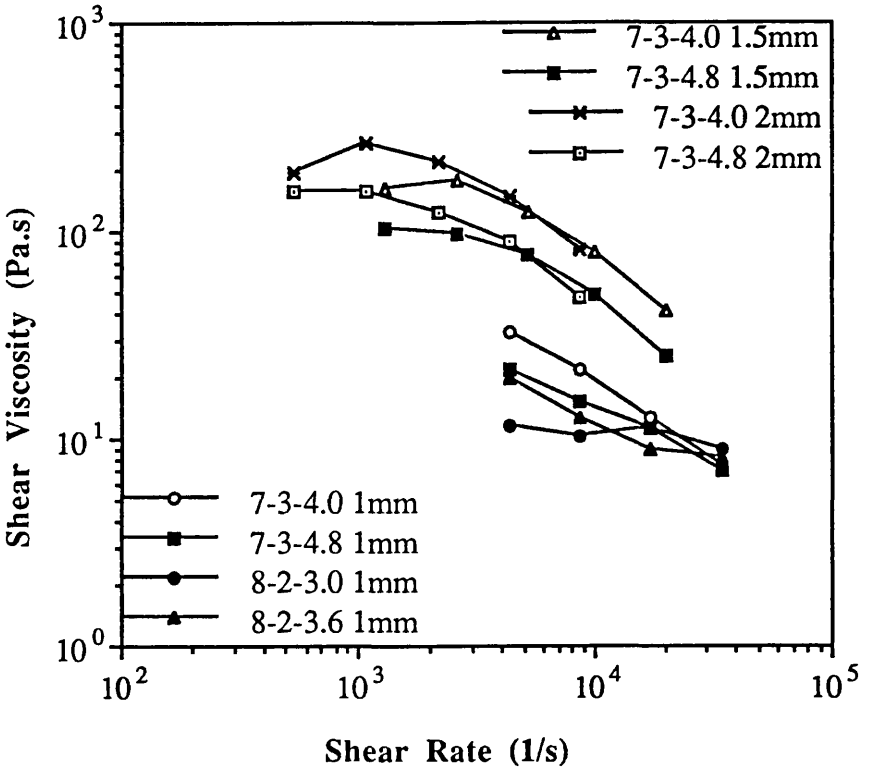
Figure 6.5 The Effect of Log. Shear Rate on the Log. Newtonian Viscosity Recorded for a Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) Mixture Containing Varying Amounts of Water Extruded Through a 1mm Diameter Die.



Extrusion through 1mm diameter dies at the shear rates studied indicate linear relationships between the apparent viscosity and the shear rate. Differences between the formulations begin to appear as the moisture content is increased. This results in wetter formulations demonstrating a lower gradient relationship between viscosity and shear rate. If shear rates were reduced far enough or the moisture content of formulations continued to increase then the effect seen with mixtures extruded through 1.5mm and 2mm diameter dies (Figures 6.3 and 6.4 respectively) may occur. For the 3 driest formulations (containing 4.0, 4.2 and 4.4 parts water) differences in viscosity values are so low that the lines are superimposed.

Figure 6.6 demonstrates that changes in the die diameter alters the positioning of the slope of shear viscosity *versus* rate but do not cause a variation in the gradient. This is similar in effect to changes in torque during controlled-stress rheometry (*cf.* Figure 6.1). The gradient appears to be replicated for 1.5mm and 2mm diameter dies but occurs at a lower viscosity for 1mm diameter dies. The slopes produced by the two lactose (8 parts) and microcrystalline cellulose (2 parts) mixtures (Figure 6.6) indicate that neither formulation is performing as expected if it was following typical flow behaviour. However the wetter mixture, containing 3.6 parts moisture (26.5%), shows less deviation from linearity and may be expected to produce better quality extrudate.

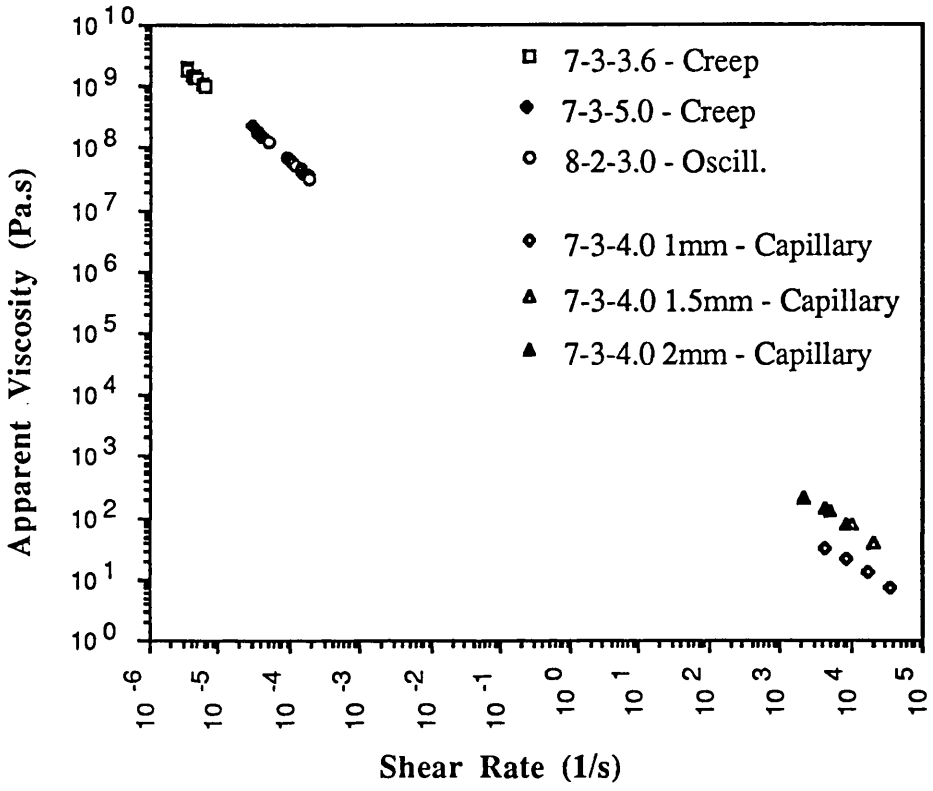
Figure 6.6 The Effect of Log. Shear Rate on the Log. Newtonian Viscosity Recorded for Various Lactose and Microcrystalline Cellulose Mixtures Containing Varying Amounts of Water Extruded Through a 1, 1.5 and 2mm Diameter Dies.



The linear relationship between viscosity and shear rate indicates that the materials behave as they would if they observed the power law model of rheological behaviour for non-Newtonian liquids (Barnes *et al.*, 1989). All the materials examined observe this model when subjected to creep and oscillatory experiments (Figure 6.7). It can therefore be concluded that if flow behaviour begins to deviate from this linearity then the actual mixture itself has been affected by the extruding conditions and consequently will not yield extrudate to the expected consistency. Figure 6.7 demonstrates that a formulation containing lactose (7 parts), microcrystalline cellulose (3 parts) and 4.0 parts moisture (28.6%) when extruded through 1,1.5 and 2mm diameter dies does exhibit a linear relationship at high shear rates but this begins to deviate at lower shear rates for 1.5mm and 2mm diameter dies (Figures 6.5 and 6.6 respectively). With deviation from linearity there is, in effect, a partial phase separation of the solid and liquid components which becomes more marked with wider diameter dies (*i.e.* 1.5mm and 2mm diameter dies) than it is with narrower dies. Nevertheless if

the shear rate was reduced still further then non-linearity would appear even for the 1mm diameter die.

Figure 6.7 The Effect of Log. Shear Rate on the Log. Newtonian Viscosity Recorded for Lactose and Microcrystalline Cellulose Mixtures Containing Varying Amounts of Water Obtained From Different Rheological Techniques.



(Applied Stress = 10mNm for Creep and Oscillation Experiments)

The results obtained from Figures 6.3 - 6.7 indicate that there is an important relationship between shear rate and the eventual quality of extrudate. This along with results obtained when constructing Bagley plots (Section 4.1.1) may provide accurate information about not only which extrudates are smooth on extrusion but also which of those smooth extrudates are liable to be of sufficient quality for subsequent spheronisation. However measurement of shear stress *versus* shear rate or viscosity *versus* shear rate does not give any indication as to which materials will successfully spheronise.

The results above also bring into question whether the mixtures follow the Herschel-Bulkley model of viscoelastic behaviour, *i.e.* do they possess a yield stress. There has been a long debate over whether a yield stress for materials exists or whether

the yield is merely an artifact of measurement technique (Barnes and Walters, 1985). A flow curve of a material that does not have a yield stress would classically show a sigmoidal profile of viscosity *versus* shear rate with viscosity measurements at very shear rates beginning to level off (Applied Rheology Newsletter, 1991). However materials that possess a yield stress would not plateau at low shear rates but continue to show an increase in viscosity with a slope of -1. Since the materials under investigation exhibit no levelling of viscosity at low shear levels they can be considered to possess a yield stress value.

6.3 Rheological Assessment of Formulations that Produce Quality Spheres.

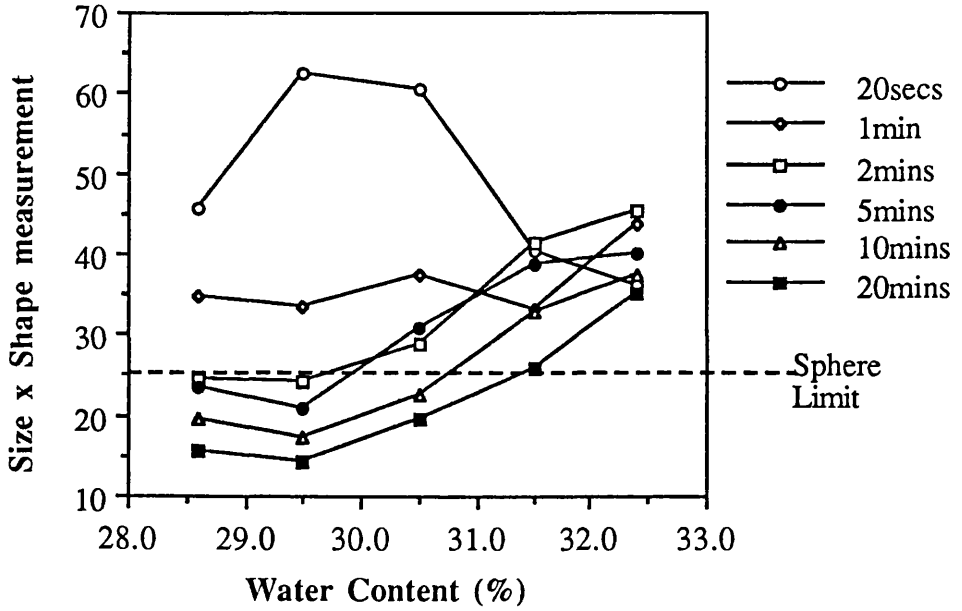
Attempts have been made to prioritise the importance of parameters that influence final spheroid size and shape, including factorial design experiments (Malinowski and Smith, 1975; Noché *et al.*, 1991). These attempts have found that the most important variants in the process of extrusion and spheronisation are the water content of the formulation and spheroniser speed. Other factors such as extrusion speed have been reported not to affect pellet roundness (Lövgren and Lundberg, 1989) and pH adjusters and insoluble polymers in the binding fluid do not prevent spheronisation (Bianchini *et al.*, 1991). Characterisation of the pellets produced by extrusion-spheronisation have often involved only simple measurements of sieved particle size, density and friability (O'Connor and Schwartz, 1985; Noché *et al.*, 1991). Further characterisation of spheroids by size and shape, using the OPCS method of analysis (*cf.* Section 2.3), has been used to assess the quality of pellets produced by different formulations and extruders (Fielden *et al.*, 1992; Newton *et al.*, 1992). The present work has used a combination of size and shape to identify good quality spheres. These criteria can then be used to analyse which formulations produce quality spheres given the manufacturing conditions employed (*cf.* Section 3.2.3). With this information a retrospective analysis of controlled-stress and capillary rheology results can be undertaken to identify which rheological conditions are conducive to producing quality spheres and, conversely, which rheological conditions do not allow for the formation of quality spheres.

Examination of the size and shape of spheroids produced by the formulations under investigation, when extruded through 1mm diameter dies, has already been undertaken (*cf.* Section 4.2). However a simple factor that could be used to assess which formulations produced adequate quality spheres would be useful. To that end the product of the sphere size (in millimetres) and shape (as defined by the OPCS angle) has been used to assess overall sphere quality. As this number decreases the quality of sphere increases, i.e. the rounder and smaller (towards 1mm diameter) the sphere

becomes. A limit of value of 25 for the size x shape product has been applied to establish which spheres are of quality. This limit must be reached within five minutes and not exceeded with further increases in spheronisation time. A limit of five minutes excludes formulations that begin to agglomerate with longer spheronisation times and is also an appropriate time to allow for a full spheronisation production time of 30 minutes (Chapman, 1985). Formulations that meet these criteria will inherently produce a narrow size and shape distribution so these data have not been represented.

The specifications set out above are more rigorous than those outlined in previous work (Chapman, 1985 and Newton *et al.*, 1992). They preclude the possibility of large spheres that are very round or very small, non-round spheroids being included within the limits. Using these parameters graphs of sphere quality versus moisture content have been constructed for 7 : 3 and 8 : 2 lactose : microcrystalline cellulose mixtures (Figures 6.8 and 6.9).

Figure 6.8 The Effect of Moisture Content on the Sphere Quality (Size x Shape Product) Of A Lactose (7 Parts) and Microcrystalline Cellulose (3 Parts) Mixture Obtained at Various Spheronisation Times.

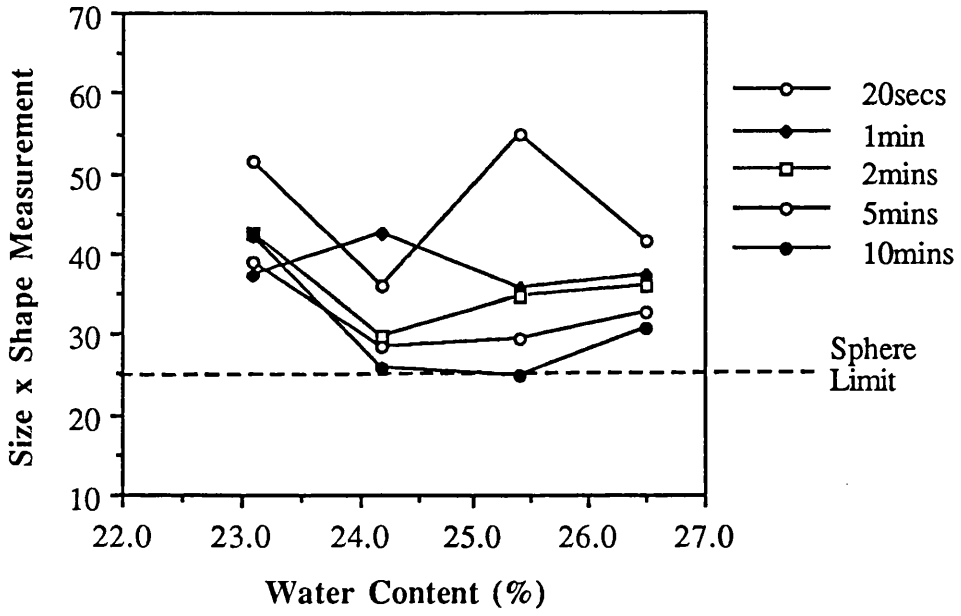


Examination of results contained in Figure 6.8 demonstrates that only 2 formulations from the five 7 : 3 lactose : microcrystalline cellulose mixtures investigated produce quality spheres. The 2 formulations contain 28.6% (4.0 parts) and 29.5% (4.2 parts) moisture. With increasing spheronisation times of up to 20 minutes formulations

with higher moisture contents do produce size x shape products of below 25 but these have been disregarded.

Results obtained from performing spheronisation on 8 : 2 lactose : microcrystalline cellulose formulations reveal that mixtures containing 24.2% and 25.4% almost produce quality spheroids but the process takes at least 10 minutes spheronisation (Figure 6.9). Therefore no 8 : 2 lactose : microcrystalline cellulose formulation investigated can be said to produce quality spheres.

Figure 6.9 The Effect of Moisture Content on the Sphere Quality (Size x Shape Product) Of A Lactose (8 Parts) and Microcrystalline Cellulose (2 Parts) Mixture Obtained at Various Spheronisation Times.



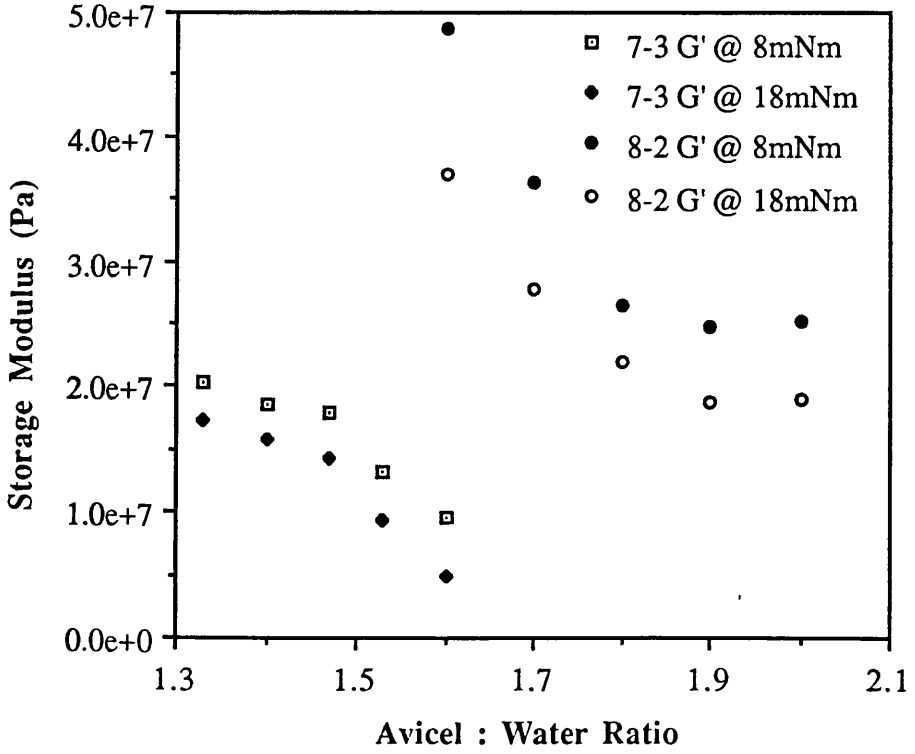
Comparison of the types of graph produced by 7 : 3 and 8 : 2 lactose : microcrystalline cellulose mixtures (Figures 6.8 and 6.9) highlight the changes in the way spheronisation occurs when the microcrystalline cellulose component is reduced. The reduction not only reduces the quality of spheres produced but also causes poor differentiation between spheroids produced by the various mixtures.

Given that only two of the 7 : 3 lactose : microcrystalline cellulose formulations produce quality spheres from all the mixtures studied differences in the rheological behaviour of each formulation may indicate why some materials spheronise more successfully than others. However from studies undertaken using capillary rheometry (Figures 6.3 - 6.5 and also Section 4.1.2) indicate that this technique is not sensitive enough to pick up differences between formulations that do spheronise and those that

do not. For comparison with results obtained from capillary rheometry studies an oscillatory frequency that is compatible with the duration of experimental shear during extrusion is required. This can be calculated from the inverse of the oscillatory frequency which yields an approximate "experimental time". Since the extrusion process occurs in periods of time under a second in duration then oscillatory frequencies of 1 or 10Hz are the closest for comparison of rheological effect.

Previous workers have highlighted the significance of the microcrystalline cellulose : moisture ratio in establishing which formulation produces the best extrudate (Chapman, 1985 and Raines, 1990). For 5 : 5 lactose : microcrystalline cellulose mixtures a microcrystalline cellulose : water ratio of 1 : 1.2 was identified as being the optimum. As the lactose content of the mixture increases and the microcrystalline cellulose content decreases the optimum microcrystalline cellulose : water ratio increases (*cf.* Section 4.2 and Bains *et al.*, 1990). The effect of microcrystalline cellulose : water ratio on controlled-stress rheometry parameters may be consequently be of use in comparing formulations.

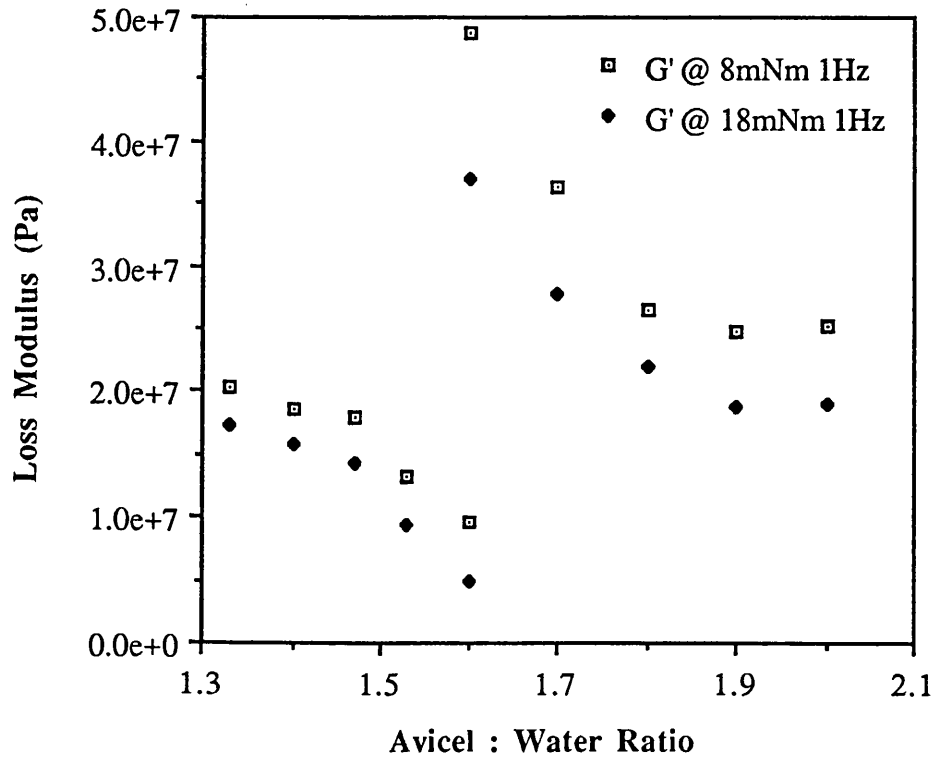
Figure 6.10 The Effect of Microcrystalline Cellulose : Water Ratio on the Storage Modulus Obtained from 7 : 3 and 8 : 2 Lactose : Microcrystalline Cellulose Mixtures Oscillated at 1Hz at Applied Torques of 8mNm and 18mNm.



Figures 6.10 and 6.11 examine the effect of the ratio on the storage modulus (G') and loss modulus (G") respectively when samples are oscillated at 1Hz at applied torques of 8 and 18mNm.

The results contained in Figures 6.10 and 6.11 indicate the difference in behaviour between materials that are of different lactose : microcrystalline cellulose ratios. The lower ratios are indicative of 7 : 3 lactose : microcrystalline cellulose mixtures and possess lower G' and G" values than mixtures containing 8 : 2 lactose : microcrystalline cellulose which have high microcrystalline cellulose : water ratios. However if these graphs are compared to overall moisture content (as a %) of the total mixture (as represented for G' in Figure 5.49) it can be seen that what affects the storage and loss moduli are the overall moisture contents rather than microcrystalline cellulose : water ratio.Therefore whilst a decrease in the proportion of microcrystalline cellulose present within the formulation causes a reduction in moisture content required for optimum sphere formation this does not affect the elastic and viscous components more than a straight reduction in moisture content would affect it.

Figure 6.11 The Effect of Microcrystalline Cellulose : Water Ratio on the Loss Modulus Obtained from 7 : 3 and 8 : 2 Lactose : Microcrystalline Cellulose Mixtures Oscillated at 1Hz at Applied Torques of 8mNm and 18mNm.



To produce spheres using the technique of extrusion and spheronisation the initial formulation must have sufficient viscosity to flow through the capillary at low enough forces to prevent any damage to the extruder. It then must have sufficient coherence and rigidity to remain in strands of extrudate on ejection from the die and during processing before spheronisation. During spheronisation the extrudate must exhibit sufficient brittleness to break into short strands but not to fracture into powder. It must also possess enough plasticity to mould under the influence of spheronising forces whilst not adhering to other spheroids. Whilst a lot of these processes are subject to the influence of water movement (Fielden, 1987) the main influence must be the viscosity and elasticity of the initial formulation.

The experiments contained in Section 5 were conducted to establish which parameters were important in defining a representative viscosity and elasticity for each formulation. Creep experiments (Section 5.1.2) suffer from being subject to the influence of the applied stress and there is no indication as to what an appropriate applied stress would be to imitate the conditions found in the capillary rheometry. However the almost linear relationship between results obtained from flow and creep and oscillation experiments (Figure 6.7) suggests low stress creep tests may be most appropriate.

Oscillation experiments can be used to examine the relationship between elasticity and viscosity (as measured by tan δ) and what effect a change in moisture content produces. Results contained in Section 5.2.1 (*e.g.* Figure 5.33 - The effect of oscillatory frequency on tan δ value obtained for lactose (7 parts) and microcrystalline cellulose (3 parts) with varying moisture contents) indicate that the value of tan δ is subject to large variations when the oscillatory frequency is altered but not when moisture content is changed. Hence the best indicators of elasticity and viscosity for each formulation and for the difference between them are the storage modulus (G') and the loss modulus (G").

Examination of oscillation results for 7 : 3 and 8 : 2 lactose : microcrystalline cellulose formulations highlight the importance of moisture content on rheological values recorded. The effect of formulation on G' and G" with respect to which formulations produce quality spheres have been plotted in Figures 6.12 and 6.13. These graphs have been constructed using an appropriate oscillatory frequency (1Hz) and an applied torque in the region of linear viscoelastic response (8mNm). These parameters are easily controlled by the controlled-stress rheometer and simple to reproduce.

Figure 6.12 The Effect of Moisture Content on The Storage Modulus (G') Obtained for 2 Different Lactose : Microcrystalline Cellulose Mixtures When Oscillated at 1Hz at an Applied Torque of 8mNm.

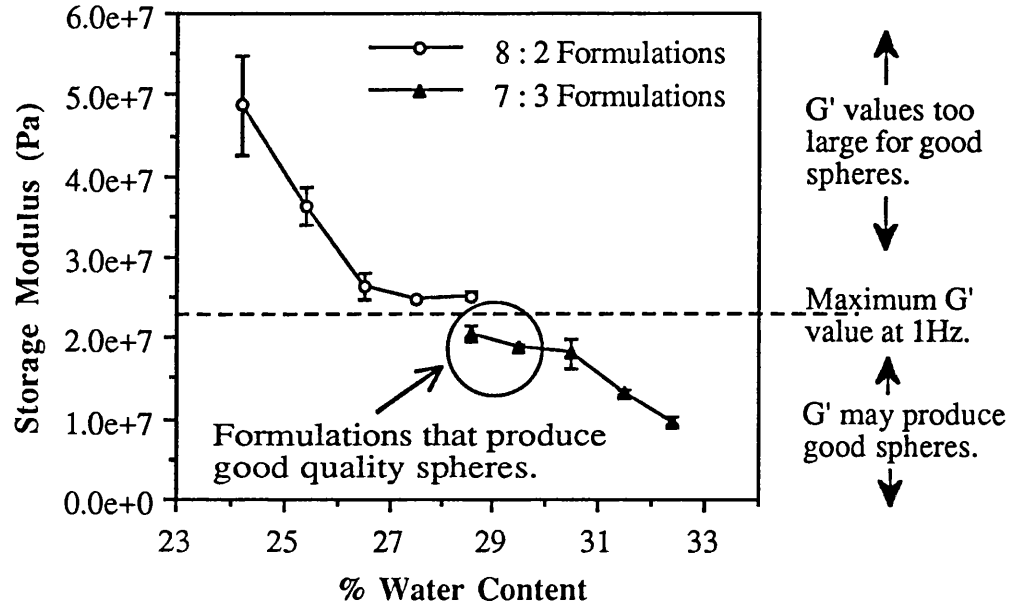
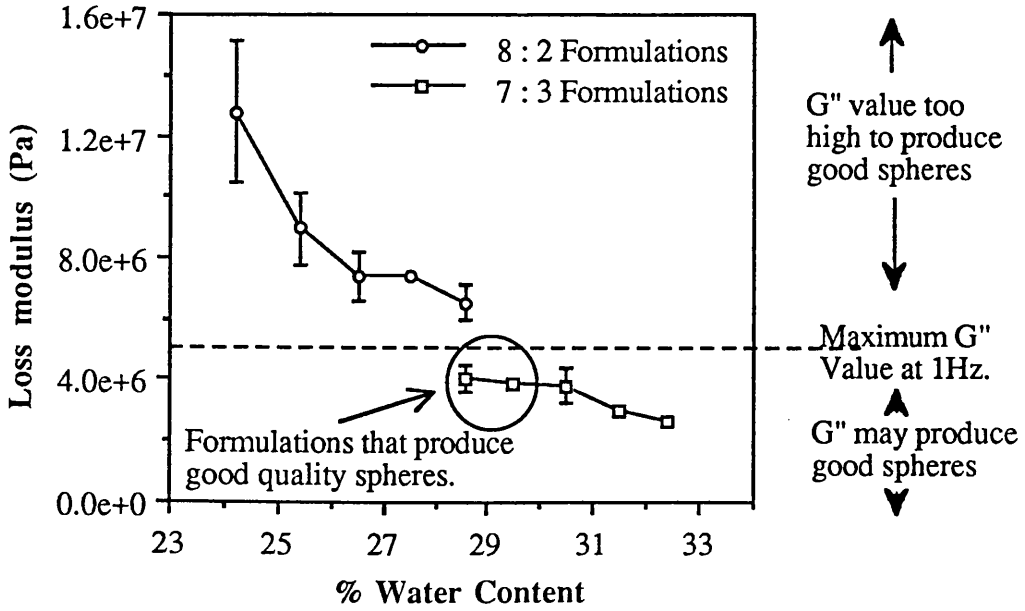


Figure 6.13 The Effect of Moisture Content on The Loss Modulus (G") Obtained for 2 Different Lactose : Microcrystalline Cellulose Mixtures When Oscillated at 1Hz at an Applied Torque of 8mNm.



The results contained in Figures 6.12 and 6.13 demonstrate that all the 8 : 2 lactose : microcrystalline cellulose mixes examined possess storage and loss modulus values that are greater than those obtained from the 2 formulations of 7 : 3 lactose : microcrystalline cellulose that produce quality spheres (28.6% and 29.5% moisture contents). Although the main influence on G' and G" values is the moisture content it can be seen that even an 8 : 2 mixture containing 28.6% moisture produces G' and G" values that exceed those of the 7 : 3 mixture with the same moisture content. The large drop in G' and G" values over a short moisture difference for 8 : 2 mixtures indicate that drier formulations are more sensitive to changes in moisture content. This is in agreement with results obtained from Benbow-Bridgwater calculations (Section 4.3) that highlight the sensitivity of 8 : 2 mixtures to changes in moisture content (Figure 4.46).

The relative values of G' and G" can be measured directly via tan δ. Given that the process of extrusion/spheronsation relies on both the elastic and viscous properties of the formulation under investigation tan δ should be a good rheological indicator of a mixture's performance during extrusion and spheronisation. However tan δ is too sensitive to changes in applied torque and frequency to be a reliable indicator of rheological behaviour. For materials examined in Chapter 5

From the results contained in Figures 6.12 and 6.13 the values that are suggested as maxima for G' and G" (2.2×10^7Pa for G' and 5.0×10^6Pa for G") are only relevant for other mixtures when they are oscillated at the same frequency (1Hz) and at the same applied torque (8mNm). A maximum value can be ascribed to both G' and G" as further rises in these values for a particular formulation will mean that it is too rigid to spheronise. However neither value can be taken in isolation as both the elastic and viscous components must be appropriate to allow spheronisation. New formulations that possess G' and G" values lower than these maximums will not necessarily spheronise as factors such as the extrusion rate and water movement then become prominent in determining the outcome of extrusion and spheronisation. The extrusion rate is of key importance when there are surface defects in the extrudate as these defects cannot be explained by the rheological parameters that are measured during capillary and controlled-stress rheometry. Capillary rheometry will identify problems in non-linear behaviour associated with changes in the mixture that has been extruded but cannot identify which extrusion rates with which die diameters will cause problems with surface defects. Similarly controlled-stress rheometry is only a modelling system and will not recognise which extrusion rate (via the oscillatory frequency) will promote extrudate defects. Consequently a degree of trial-and-error will always be required in developing formulations that are suitable for extrusion and spheronisation

Increases in the moisture content reduce the storage (elastic) modulus more than the loss (viscous) modulus and for the formulations studied makes extrusion and spheronisation difficult. Any formulation that has an initially low G' value compared to G" or has a G' value that is very sensitive to moisture content is therefore likely to cause difficulties in spheronisation. The loss modulus for all formulations studied is almost a order of magnitude lower than the storage modulus and falls more slowly than the storage modulus with increases in the moisture content. This suggests that a high elasticity (compared to viscosity) is the main determinant in establishing a sample formulation that will successfully undergo extrusion/spheronisation.

6.4 General Conclusions

- Extrusion and spheronisation can be performed on formulations containing 7 : 3 and 8 : 2 lactose : microcrystalline cellulose when extruded through 1mm diameter dies. However only 7 : 3 formulations produce spheres that can be considered to be of quality.

- The use of controlled-stress rheometry to investigate the properties of different formulations appropriate for extrusion-spheronisation is worthwhile as the technique provides information that cannot be obtained from capillary rheometry. It also proves to be both reliable and accurate. In addition it has the advantage of producing results much more quickly than traditional capillary rheometry.

- The various rheological parameters calculated for the test formulations highlight the importance of moisture content on the behaviour of the materials as they extrude. Capillary rheometry results and Benbow-Bridgwater calculations identify changes in the nature of the materials as they are extruded. Controlled-stress rheometry provides rheological information on the viscosity and elasticity of the materials in an unextruded form.

- The use of controlled-stress rheometry will speed up the identification of formulations that will successfully extrude and spheronise. Whilst it cannot replace capillary rheometry in establishing several useful parameters it will quickly allow for the elimination of inappropriate mixtures without the risk to any machinery or operator.

6.5 Further Work.

The usefulness of controlled-stress rheometry in predicting the behaviour of a material undergoing extrusion and spheronisation has been established for the formulations investigated but more work has to be undertaken to evaluate it further. This can occur with formulations that have previously been assessed for capillary rheometry, in particular 5 : 5 lactose : microcrystalline cellulose, and for formulations that contain an insoluble model drug, *e.g.* barium sulphate. Both these sets of formulations have been assessed for extrusion and spheronisation abilities (Harrison, 1982; Chapman 1985, Fielden, 1987 and Bains *et al.* 1991) and further investigation of their rheological properties using controlled-stress rheometry would extend the scope of the work. More investigation into the use of creep tests would be appropriate also given the approximately linear relationship that may exist between capillary flow and applied stresses of less than 10mNm (*cf.* Figure 6.7).

Extending the range of microcrystalline celluloses investigated would further highlight the benefits of controlled-stress rheometry. Various microcrystalline cellulose materials have been extruded (Raines, 1990) and spheronised (Newton *et al.*, 1992) but the fundamental differences in rheological behaviour between the celluloses have not been fully elucidated. Controlled-stress rheometry would allow accurate calculations of the relative viscosities and elasticities of each microcrystalline cellulose and could again allow predictions of their relative behaviours during extrusion and spheronisation. Moreover, with particularly low levels of microcrystalline cellulose in the target formulations, controlled-stress rheometry may predict which combination of celluloses could be most successful at producing quality extrudate and spheres.

The precise rheological reasons as to why materials do not spheronise have not been fully explained in the work that has been performed. This is probably due to the various process conditions, *e.g.* spheronisation time, size of spheroniser, extrusion rate *etc.*, that allow subtle differences to occur between materials that rheologically show very similar behaviour. Nevertheless further work with formulations that do not form quality extrudate or spheres *e.g.* 9 : 1 lactose : microcrystalline cellulose, may be useful in establishing what rheological conditions must be avoided to have any chance of success. Controlled-stress rheology would be beneficial with these formulations because the materials are liable to extrude at forces that are beyond the tolerance of either the capillary rheometer or of the hardened steel barrel and dies.

REFERENCES

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Andersen, A.H. and Newton, J.M. The Influence of moisture content and particle size of barium sulphate on the extrusion properties of mixtures with microcrystalline cellulose. *Rheology of Food, Pharmaceutical and Biological Materials with General Rheology*. (Ed. Carter, R.E.) Elsevier Science Publications Ltd, London. (1990) 258-267.

Appelgren, C. and Eskilson, C. A novel method for the granulation and coating of pharmacologically active substances. *Drug Dev. Ind. Pharm.* 16 (1990) 2345-2351.

Applied Rheology Newsletter, December 1991. An update on yield stress. Warren Spring Laboratory, Stevenage, Herts.

Baert, L.; Fanara, D.; de Baets, P. and Remon, J.P. Instrumentation of a gravity feed extruder and the influence of the composition of binary and ternary mixtures on the extrusion forces. *J. Pharm. Pharmacol.* 43 (1991) 745-749.

Bagley, E.B. End correction in the capillary flow of polyethylene. *J. Appl. Phys.* 28 (1957) 624-627.

Bagley, T.R. and Schreiber, H.P. Rheology Vol. 5 (ed. Eirich, F.R.) Academic Press, London. (1969) 93-125.

Bains, D; Boutell, S.L. and Newton, J.M. The influence of moisture content on the preparation of spherical granules of barium sulphate and microcrystalline cellulose. *Int. J. Pharmaceutics* 69 (1991) 233-237.

Barnes, H.A. and Walters, K. The yield stress myth? *Rheol. Acta.*, 24 (1985) 323-326.

Barnes, H.A.; Hutton, J.F. and Walters,K. *An Introduction to Rheology* Elsevier, Amsterdam, 1989.

Bataille, B; Rahman, L. and Jacob, M. Etude des parametres de formulation sur les caracteristiques physico-techniques de granules de theophylline obtenus par extrusion-spheronisation. *Pharm. Acta Helv.* 66 (1991) 233-236.

Beechgaard, H. and Neilson, G.H. Controlled release multiple units and single-unit doses. *Drug Dev. Ind. Pharm.*, 4 (1978) 53-67.

Benbow, J.J.; Oxley, E.W. and Bridgwater, J. The extrusion mechanics of pastes - the influence of paste formulation on extrusion parameters. Chem. Eng. Sci. 42 No.9 (1987) 2152-2162.

Benbow, J.J.; Lawson, T.A.; Oxley, E.W. and Bridgwater, J. Prediction of paste extrusion pressure. *Ceramic Bulletin* 68 No. 10 (1989) 1821-1824.

Berghaus, H.J. Flow of plastic materials through tubes and orifices. *Forsch Geb. Ing.* 23 (1951) 135-148.

Bianchini, R.; Bruni, G; Gazzaniga, A. and Vecchio, C. Influence of extrusion-spheronisation processing on the physical properties of d-indobufen pellets containing pH adjusters. 577-592 of Proceedings of The 10th Pharmaceutical Technology Conference, Bologna, Italy, 1991.

British Standards Institute - B.S. 410 : 1976 *Specification for Test Sieves.*

Chapman, S.R. *Influence of Process Variables on the Production of Spherical Granules.* Ph.D. Thesis, University of London (1985).

Chapman, S.R.; Rowe, R.C. and Newton, J.M. Characterisation of the sphericity of particles by the one plane critical stability. *J. Pharm. Pharmacol.* 40 (1988) 503-505.

Conine, J.W. and Hadley, H.R. Preparation of small solid pharmaceutical spheres. *Drug and Cosm. Ind.* 106 (1970) 38-41.

Devereux, J.E.; Newton, J.M. and Short, M.B. The influence of density on the gastro-intestinal transit of tablets. *J. Pharm. Pharmacol.* 42 (1990) 500-501.

Eerikäinenn, S. Effects of spheronisation on some properties of uncoated and coated granules containing different kinds of fillers. *Int. J. Pharmaceutics* 77 (1991) 89-106.

Eskilson, C. Controlled release by microencapsulation. Manufacturing Chemist. March (1985) 35-39 and April (1985) 49-53

Fielden, K.E. Extrusion and spheronisation of microcrystalline cellulose/lactose mixtures. Ph.D. Thesis, University of London (1987).

Fielden, K.E.; Newton. J.M. and Rowe, R.C. The effect of lactose particle size on the extrusion properties of microcrystalline cellulose-lactose mixtures. *J. Pharm. Pharmacol.* 41 (1989) 217-221.

Fielden, K.E.; Newton, J.M. and Rowe, R.C. A comparison of the extrusion and spheronisation behaviour of wet powder masses processed by a ram and a cylinder extruder. Int. J. Pharmaceutics 81 (1992) 225-232.

Gajdos, B. Rotary granulators: Evaluation of process technology for pellet production using a factorial experimental design. Drugs Made Ger. 27 (1984) 30-36.

Gamlen, M.J. and Eardley,C. Continuous extrusion using a Baker Perkins MP50 (multipurpose) extruder. *Pharmaceutical Technology - tabletting technology Vol.1* (ed. Rubinstein, M.H.) Ellis Horwood, Chichester 1987.

Gebbett, J. G. Granulation by extrusion and spheronisation. *Powder Technology* (1973) 1-5.

Ghebre-Sellassie, I. Pellets: A General Overview. Chapter 1 of *Pharmaceutical Pelletization Technology* (ed. Ghebre-Sellassie, I.) Marcel Dekker, New York (1989).

Ghebre-Sellassie, I.; Gordon, R.H., Nesbitt, R.U. and Fawsi, M.B. Evaluation of a high speed pelletisation process and epuipment. *Drug Dev. Ind. Pharm.* 11 (1985) 1523-1541.

Gitlus, J. *Creep, Viscoelasticity and Creep Fracture in Solids.* Applied Science Publishers, Englewood, NJ. (1975)

Goodhart, F.W.; Draper, J.R. and Ninger, F.C. Design and use of a laboratory extruder for pharmaceutical granulations. *J. Pharm. Sci.* 62 (1973) 133-136.

Harris, M.R. and Ghebre-Sellassie, I. Formulation Variables Chapter 10 of *Pharmaceutical Pelletization Technology* (ed. Ghebre-Sellassie, I.) Marcel Dekker, New York (1989).

Harrison, P.J. *Extrusion of Wet Powder Masses*, Ph.D. Thesis, University of London (1982).

Harrison, P.J.; Newton, J.M. and Rowe, R.C. Convergent flow analysis in the extrusion of wet powder masses. *J. Pharm. Pharmacol.* 36 (1984) 796-798.

Harrison, P.J.; Newton, J.M. and Rowe, R.C. Flow defects in wet powder mass extrusion. *J. Pharm. Pharmacol.* 37 (1985) 81-83.

Harrison, P.J.; Newton, J.M. and Rowe, R.C. The characterisation of wet powder masses suitable for extrusion/spheroinsation. *J. Pharm. Pharmacol.* 37 (1985) 686-691.

Harrison, P.J.; Newton, J.M. and Rowe, R.C. The application of capillary rheometry to the extrusion of wet powder masses. *Int.J. Pharm.* 35 (1987) 235-242.

Hicks, D.C. and Freese, H.L. Extrusion and Spheronizing Equipment. Chapter 4 of *Pharmaceutical Pelletization Technology* (ed. Ghebre-Sellassie, I.) Marcel Dekker, New York (1989).

Hodges. G.; Delargy, A. and Aulton, M. Studies on the process of rotorgranulation. Part 1: Effect of product load, granulating fluid volume and granulating fluid addition rate. 180-194 of Proceedings from The 9th Pharmceutical Technology Conference, Veldhoven, Holland 1990.

Jastzrebreski, Z.D. Entrance effects and wall effects in an extrusion rheometer during flow-concentrated suspensions. *I and E.C. Fund* 6 (1967) 445-454.

Lövgren, K. and Lundberg, P.J. Determination of the sphericity of pellets prepared by extrusion/spheronisation and the impact of some process parameters. *Drug Dev. Ind. Pharm.* 15 (1989) 2375-2392.

Malinowski, H.J. and Smith, W.E. Use of factorial design to evaluate granulations prepared by spheronisation. *J. Pharm. Sci.* 64 (1975) 1688-1692.

Miyake, Y.; Shinoda, A.; Furukawa, M.; Uesugi, K. and Nasu, T. Spheronising mechanism and properties of spherical granules. *Yakuzaigaku* 33 (1973) 161-166.

Newton, J.M.; Chow, A.K. and Jeewa, K.B. The effect of excipient source on spherical granules made by extrusion/spheronisation. *Pharm. Tech. Int.* 4 October (1992).

Nickell, R.E.; Tanner, R.I. and Caswell, B. *J. Fluid Mech.* 65 (1974) 189-206

Niskanen, M.; Yliruusi, J.K. and Niskanen, T. Pelletization in a centrifugal granulator *Pharm. Tech. Int.* November (1990).

Noché, C.; Huet de Barochez, B.; Brossard, C.; Horvath, S. and Cuiné, A. Optimization of the manufacturing process of coated pellets. 164-188 of Proceedings of The 10th Pharmaceutical Technology Conference, Bologna, Italy, 1991.

O'Connor, R.E. and Schwartz, J.B. Spheronisation II: Drug release from drug-diluent mixtures. *Drug Dev. Ind. Pharm.* 11 (1985) 1837-1857.

O'Connor, R.E. and Schwartz, J.B. Extrusion and Spheronisation Technology. Chapter 9 of *Pharmaceutical Pelletization Technology* (ed. Ghebre-Sellassie, I.) Marcel Dekker, New York (1989).

Ovenston, A. and Benbow, J.J. Effects of die geometry on extrusion of clay like materials. *Trans. Br. Ceram. Soc.* 67 (1968) 543-567.

Profitt, D. The measurement of circularity and ellipticity on a digital grid. *Pattern Recognition* 15 (1982) 383-387.

Raines, C.L. and Newton, J.M. The extrusion rheology of various grades of microcrystalline cellulose. *J. Pharm. Pharmacol.* 39 (1989) 90p.

Raines, C.L.; Newton, J.M. and Rowe, R.C. - Extrusion of microcrystalline cellulose formulations. *Rheology of Food, Pharmaceutical and Biological Materials with General Rheology*. (Ed. Carter, R.E.) Elsevier Science Publications Ltd, London. (1990) 248-257.

Raines, C.L. Rheological properties of different grades of microcrystalline celluloses. Ph.D. Thesis, University of London (1990).

Reynolds, A.D. A new technique for the production of spherical particles. *Manuf. Chem.*, 41 (1970) 40-44.

Rowe, R.C. Spheronization: A novel pill-making process? *Pharmacy International* May (1985) 119-123.

Russell Marumerizer™ literature, Russell Finex Ltd, London.

Sherrington, P.J. and Oliver, R. Compaction and Other Granulation Methods 141-144 of *Granulation.* Heyden and Son, London 1981.

Timmins, P. and Delargy, A.M. Influence of Drug raw material source on the processability of erythromycin beadlets. *Pharm Tech. Int.* April (1992) 36-44

Woodruff, C.W. and Nuessle, N.O. Effect of processing variables on particles obtained by extrusion-spheronisation processing. *J. Pharm. Sci.* 61, No.5 (1972) 787-790.

Zhang, G.; Schwartz, J.B. and Schnaare, R.L. Effect of spheronisation technique on drug release from uncoated beads. *Drug Dev. Ind .Pharm.* 16 (1990) 1171-1184.