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AN INVESTIGATION OF THE PRODUCTION OF NON-COATED SUSTAINED RELEASE BEADS BY EXTRUSION AND SPHERONIZATION

BY

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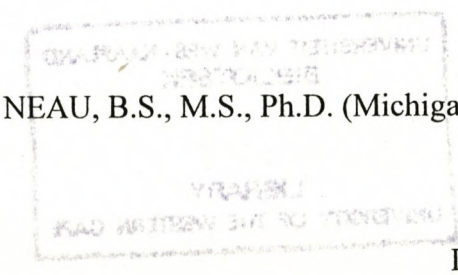

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CHAPTER 1: INTRODUCTION

This thesis describes attempts to produce non-coated sustained release dosage forms by the technique of extrusion and spheronization. In this introductory chapter, the reasons for this approach are argued against the background of the need for sustained release medication as well as a consideration of some of the types of sustained release solid oral dosage forms currently available.

1.1 THE POPULARITY OF SUSTAINED RELEASE MEDICATION

The advantages of sustained release medication have been recognised for many years. Some of these are patient convenience due to the smaller number of doses, increased compliance as a result thereof and, possibly, a lower total amount of drug administered. The chief advantage, from a clinical point of view, is the longer maintenance of drug blood levels within the therapeutic range in chronically ill patients. Ideally, the blood drug level-time profile should resemble that of a slow intravenous injection. In the case of theophylline, administered for the treatment of asthma, steady state plasma levels of 10 - 20 $\mu g/cm^3$ must be maintained. When "around-the-clock" treatment is provided in this way, side effects are reduced and a greater clinical improvement is seen (Hendeles et al., 1978). Conventional dosage forms produce a "see-saw" effect on the blood level-time profile. If the number of doses per day is increased, the fluctuations are reduced. However, for an appreciable advantage to be gained, a large number of doses would have to be given every day, which is impractical.

The recognition of the advantages of slow release medication has fuelled a research and development interest with the aim of improving the existing preparations and inventing new dosage forms. Extensive research activity, in recent years, has led to the fabrication of the highly sophisticated and effective preparations that are available on the market today. There are state-of-the-art formulations of many drugs for the alleviation of disease states, including Theophylline for asthma (Buckton et al., 1988) and Pentoxifylline for intermittent claudication and for cerebrovascular disease (Otsuka and Matsuda, 1994). There are also novel slow release dosage forms for problems of the modern age. These include hormonal implants for long-term contraception and transdermal therapeutic systems containing, for example, Estrogen for osteoporosis, Scopolamine for prolonged relief of travel sickness and Nicotine as an aid to giving up the smoking habit.

The difficulty and expense associated with the registration of new drug entities has also contributed to the profusion of sustained release products. Pharmaceutical companies have been tempted to expend their research efforts (and budgets) to an increasing extent on line extensions to existing products rather than on the development and testing of new chemical entities. Such line extensions frequently lead to the development of sustained release products.

1.2 COST CONSIDERATIONS

The popularity and increasing complexity of sustained release dosage forms has resulted in increased costs to the patient to an extent that these preparations are now out of the reach of many people, particularly in Third World countries. The need, therefore, is for effective, yet cheaper, sustained release medication.

The benefits of cost containment, even in affluent countries, are widely realised. The traditional pharmaceutical industry has recognised that it is important not only because health care is becoming increasingly expensive but also because of the "challenge of alternate medicine" (Anon., 1987). In the United States, one of the aims of the Clinton Health Reform Plan is the reduction in the cost of medicines. Such cost containment is absolutely essential in Third World countries, such as South Africa, if adequate treatment of patients is to be maintained. Simplification of the production process is one way to reduce the price of medicines. If there is a consequent reduction in the number of quality control tests required, it would be an added advantage.

1.3 MATRIX TABLETS

There are many types of sustained release preparations currently available and, of these, tablets offer the "lowest-cost approach" to the development of oral sustained release medication (Banker and Anderson, 1986). Often, however, even this dosage form does not offer a reasonably-priced solution to the development of sustained release medication, as exemplified by the Oros© system which has been described by Black (1983) and by Santus and Baker (1995). In this system, expensive laser technology is used to cut a tiny hole in the coating of a tablet which contains the drug and osmotically active substances.

In general, however, sustained release matrix tablets are cheap to produce. They consist of the drug embedded in a matrix or ground substance which retards the release of the drug. Matrix tablets have been used to sustain the release of numerous drugs, some examples of which are:

ChlorpheniramineMaleate (Lapidus and Lordi, 1966); Theophylline (Nakano et al., 1983; and Cameron and McGinity, 1987); and Potassium Chloride (Korsmeyer et al., 1983).

The rate of drug release from matrix tablets generally follows the square root of time law (Higuchi, 1963). In some instances, particularly where hydrophilic substances form the matrix, the release pattern closely resembles a zero order profile for a large part of the dissolution period (Nakano et al., 1983; and Huet de Barochez et al., 1989). Sustained drug release is due to slow diffusion of water into, and of drug solution out of, the tablet through a gel barrier formed upon hydration of the hydrophilic material. Upadrashta et al. (1993) combined the concepts of pore diffusion (as expressed by Higuchi), erosion of the matrix and relaxation of the matrix into one equation which describes release of the drug by any, or all, of these mechanisms. This equation was shown to accurately describe the rate of drug release from ethyl cellulose matrix tablets containing Theophylline (Pather et al., 1993).

When direct compression (which, in general, is a cheap way of producing tablets) is applied to the preparation of sustained release medication, the economic advantages are very attractive. However, the matrix type of tablets are single-unit dosage forms and, as a result, suffer from serious disadvantages *in vivo*, which are outlined in the next section.

1.4 MATRIX TABLETS VERSUS MULTIPARTICULATES

Matrix tablets have the potential to display bioavailability problems due to a combination of two factors:

(a) the vastly different environments to which a solid oral dosage form is exposed in different parts of the gastro-intestinal tract; and

(b) the uncertainty of the location of a matrix tablet within the gastro-intestinal tract at any particular time.

If drug release is pH dependent, the position of the matrix tablet within the gastro-intestinal tract affects the rate of drug release. The pH dependency may be due to the pH-solubility profile of the drug itself or to the effect of pH on the properties of the tablet excipients, in particular the retardant. The greater potential for variable drug release from matrix tablets, compared to multiparticulates, can be understood if one considers the transit of both types of solid oral dosage forms through the gastro-intestinal tract.

Gastro-intestinal motility can be divided into two phases: that occurring soon after a meal (the fed state) and that occurring between meals (the fasted state). Motility of the stomach during the fasted state consists of periods of strong contractions interspersed between periods of weak, or no, contractions and is thus very variable. Of greater importance is the motility pattern in the fed state which is uninterrupted and results in a continuous discharge of chyme from the stomach into the small intestine.

After a meal, food layers itself in the fundus and the body of the stomach. These parts of the stomach serve to store the food, while the antrum is responsible for grinding. During the second phase of antral activity (evacuation and retropulsion) chyme and particles less than 2 mm in diameter

pass through the pyloric sphincter, while larger particles are retropelled into the proximal antrum. This action causes grinding of the larger particles and also serves as a sieving mechanism for particles of different sizes (Rubinstein et al., 1988). When the particles are ground to a sufficiently small size, they pass through the pyloric sphincter. Thus, particles of various initial sizes are emptied from the stomach at different rates.

When a pelletized dosage form is administered, the passage of the pellets through the pyloric sphincter is not delayed, if the pellets are small enough (approximately 2mm, or less, in diameter). Hence, the effects of the highly acidic stomach contents on drug release are transient. On the other hand, a non-disintegrating matrix tablet cannot pass into the small intestine within a short time of administration. It is retained within the stomach until the "housekeeper" wave forces it into the duodenum. This wave occurs some hours after the consumption of a meal and its primary function is to clear the stomach of its residual contents. When the wave later passes over the small intestines, it clears this part of the gastro-intestinal tract as well. The passage of the housekeeper wave and, hence, the occurrence of complete gastric emptying are variable between individuals and also within the same individual. Therefore, the movement of a matrix tablet into the duodenum is also variable. The nature of the meal, its caloric content and the extent of the subject's physical activity are some of the factors that affect gastric emptying.

In addition to the prompt transfer of pellets from the stomach to the duodenum, the rate of transit of pellets through the small intestines is also highly reproducible both between and within subjects

(Bechgaard and Ladefoged, 1978). In contrast, single-unit dosage forms show a great variation in transit rates, both between and within subjects (Bechgaard and Ladefoged, 1981).

If, for any reason whatsoever, there is a failure of the drug releasing mechanism from a single unit dosage form, no drug will be liberated and, hence, no drug absorption will occur for that particular dose. With a multiparticulate system, failure of one, or a few, units still allows drug release from the remainder. This provides the opportunity for the absorption of the major part of the dose. Multiparticulates also spread out over a large portion of the gastro-intestinal tract, resulting in much greater mucosal contact at any instant compared to a tablet. This favours more consistent absorption of the drug. These factors provide a statistically better chance of an effective amount of the drug being absorbed from a multiparticulate system.

The entire small intestine is capable of drug absorption. Many drugs can also be absorbed through the colon. The small intestine, however, remains the most important region for drug absorption because of its large surface area. By contrast, the absorption of drugs from the stomach does not occur to a significant extent because of its small surface area, although some drugs can be absorbed. Hence, the fairly rapid removal of pellets from the stomach does not compromise drug absorption.

With a single-unit dosage form there is also a greater chance of dose dumping (Bechgaard and Hegermann Nielsen, 1978). This is the phenomenon whereby the entire drug content of a sustained release dosage form is released at once, instead of in a slow, continuous fashion. For the above reasons, a multiparticulate dosage form is preferred. It provides more consistent, predictable blood

levels (Bechgaard and Hegermann Nielsen, 1978; and Eskilson, 1985). The advantages of multiparticulates are summarized in Table 1.1.

TABLE 1.1: COMPARISON OF MATRIX TABLETS AND MULTIPARTICULATES

ATTRIBUTE	MATRIX TABS	MULTI-PARTICULATES
Passage through pyloric sphincter	Delayed until housekeeper wave	prompt
spreading out	-	yes
contact with intestines	limited	large area
intestinal transit rate	variable	reproducible
dose dumping	greater chance	less chance
result of failure of release mechanism	no drug released	minor portion of dose not released

1.5 TYPES OF MULTIPARTICULATE SYSTEMS

Multiparticulate dosage forms consist of a number of discrete sub-units or particles. The particles tend to disperse after administration and behave as individual dosing units. Some of the more popular types of multiparticulate dosage forms are pellets, microcapsules, nanoparticles and liposomes. Pellets are popular for oral medication because of the relative ease of producing them in large quantities and the confidence generated by the well documented evidence of previous successes. These include patented formulations of Minocycline (Valrose et al., 1989), Nicardipine hydrochloride (MacFarlane et al., 1990), Captopril (Joshi et al., 1989) and Ibuprofen (Heafiield et al., 1989).

The spherical shape of pellets also has several distinct advantages. A sphere has the lowest surface-to-volume ratio of any shape and, hence, pellets have a geometric advantage in sustained release products. This shape allows ease of coating and convenient physical characterization by means of only one dimension (the diameter). For smooth particles, the surface area exposed to the dissolution medium is calculated from the diameter and possible correlations between the surface area and the rate of dissolution are thus facilitated.

Pellets are small enough to allow passage through the pyloric sphincter without delay, if taken after food. However, pellets are not as small (and hence their surface area per unit mass is not as large) as the other multiparticulate systems. Hence, the problem of a rapid rate of drug release, due to the exposure of a very large surface area to the dissolution medium, is not inherent with pellets. Table 1.2 dramatically illustrates the effect of the size of particles (density = 1.3 g/cm^3) on their surface area (Mehta, 1989).

TABLE 1.2 : RELATIONSHIP BETWEEN PARTICLE SIZE AND SURFACE AREA

DIAMETER (mm)	NO. OF PARTICLES PER GRAM	SURFACE AREA PER GRAM (mm^2)
4.000	23	1 157
0.500	11 764	9 235
0.044	17 543 860	107 018

1.6 METHODS OF MANUFACTURING PELLETS

Pellets may be prepared by globulation; balling; compression; solution, suspension or powder layering; and by extrusion and spheronization. In the brief description of these methods that follows, some of the problems experienced during production will be highlighted.

Globulation may be performed by the processes of spray drying or spray congealing (Ghebre-Sellassie, 1989). In spray drying, a drug is dissolved or suspended in a suitable solvent and this liquid is sprayed into a hot air stream within a spray dryer. The intimate contact with the hot air causes the droplets to vaporise, leaving a sphere of solid material. Sometimes, due to too rapid drying, an outer shell of solid material forms while liquid still remains inside the spheres. In some of these instances, expansion of the crust allows the vapour to escape via pores. In other cases, however, all of the liquid cannot escape either because there is too much within the shell or because the shell is not able to expand rapidly enough. As a result, the vaporizing liquid causes the shell to burst. The final product, in this case, consists of intact spheres and portions of spheres. This technique is generally used to improve the dissolution rates and bioavailability of poorly soluble drugs by the incorporation of a strongly hydrophilic material, such as methyl cellulose. However, the method has, on occasion, been used for the preparation of sustained release pellets. Obviously, the non-uniform shape of the beads is a disadvantage.

Spray congealing is similar to spray drying but, in this case, the drug is dispersed in a melt of suitable materials which include gums, waxes and fatty acids. The dispersion is sprayed into the air chamber of the spray drying apparatus and meets cold incoming air which congeals the fatty or waxy

material. Unlike spray drying, there is no solvent to vaporize. Spray-congealed material that is produced under the correct conditions consists of spherical particles. The extent of the retardation of drug release depends on the nature, and the amount, of the fatty/waxy materials used. Globulation is an inherently slow process.

Pelletization by compression is the production of spherical, or almost spherical, tablets which are small enough to be filled into capsules. The shape is achieved by the use of deeply concave punches. Formulation and processing variables that must be taken into account are similar to those that are routinely considered in tablet production. This technique suffers from two major disadvantages. Firstly, the tablets are not perfectly spherical. The deeper the punches, the closer the shape of the tablet resembles a sphere. With very deep punches, however, there is a large difference in the pressure applied to the periphery of the tablet and at its centre. This leads to the tendency of the tablets to cap. The second disadvantage is that the rate of production of the final product (the bead-filled capsule) is relatively slow because the pellets are individually produced and a number of units have to be placed into one capsule. The production of sufficiently small tablets also requires very thin-stemmed punches which may bend under compaction forces.

In the balling process, the drug and other powders are mixed in a suitable apparatus such as a drum, or a rotating disc, mixer. The slow addition of an appropriate binder causes the powders to agglomerate and, eventually, to form spheres of approximately equal size. Of all the pelletization methods, balling results in pellets with the greatest degree of size variation.

In the solution layering technique, the drug is dissolved in a suitable binder solution which is applied to a bed of nonpareil seeds or starter pellets. The application of drying air, thereafter, removes the solvent, leaving the drug attached to the starter seeds. The addition of the drug/binder solution, with subsequent drying, is continued until the correct drug loading of the nonpareil seeds has been achieved. Suspension layering is similar but a suspension of the drug particles in a binder solution is used, instead of a solution of the drug. Powder layering is an analogous process but, in this case, the binder solution and the drug powder are added separately. The addition of the drug powder may follow the addition of the binder, adequate wetting of the seeds being first achieved before the addition of the powder; or they may be added simultaneously but separately. The process is continued, with intermittent drying, until the desired drug loading is obtained. Powder layering may achieve a higher level of drug loading than is possible with solution or suspension layering. The layering processes may be done in a conventional coating pan, in fluidized bed equipment or in specialized equipment, such as the centrifugal granulator. In addition, vented pans have been used to some extent but are not suitable for powder layering (Chambliss, 1989). The conventional coating pan remains the most common type of pan used for drug layering.

Several characteristics of the beads are critical to their performance and uniformity of the beads, especially in respect of these characteristics, is essential for a predictable biological response. However, layered beads may display batch variability since the techniques, although commonly practised in the industry, are still very much an art. For example, the extent of drug loading, and the size, of the pellets may vary because they are affected by several processing parameters which may not be easily controlled.

Variations in drug loading may be observed during powder layering, for instance, when some of the drug is lost to the atmosphere due to inappropriate technique in its addition; or the drug may adhere to the coating pan or other equipment. Consequently, there is a reduction in the amount of the drug reaching the pellets. In order to ensure content uniformity, assay of the pellets and the addition of more drug powder may have to be repeated several times during the production process.

For a sustained release effect, the pellets are usually coated. Pellet size affects the thickness of the film of coating material adhering to the pellets and, hence, the rate of drug release. The size of the pellets subjected to coating is influenced by the size of the starter nonpareil seeds. Variations in these could result in batch-to-batch variability. Inert powders are often added to adsorb moisture during the layering process. Variations in the amount added can cause between-batch variations in the size of the layered beads even though their drug contents are similar. The surface properties of the pellets are also important for adequate adhesion of the coating.

1.7 EXTRUSION AND SPHERONIZATION

A fairly recent innovation in pelletization technology is extrusion and spheronization. In this process, the drug substance is mixed with the other powdered excipients and a binder is added. The mixture is kneaded to form a wet mass, similar to that used to form granules for tabletting. The wet mass is transferred to an extruder which forces the material through small, round apertures, forming elongated strands of material which are circular in cross-section. The strands, commonly known as "spaghetti" or "vermicelli", are transferred to the spheronizer for further processing.

The spheronizer is a cylindrical vessel with a grooved, rotating base. The base is capable of rotation at speeds of up to 1000rpm. The rotation of the vermicelli on the rough base and their impacts with the sides of the vessel cause them to break up into segments of approximately equal length. Further treatment in the spheronizer causes the segments to "round-up" into almost equally-sized spheres. Compaction and, consequently, an increase in density occur to some extent during both the extrusion and the spheronization processes. The volume reduction is due to a decrease in the porosity of the material. Since liquid penetration is proportional to porosity (Washburn, 1921), a decrease in porosity leads to a slower rate of water uptake through the pores when the beads are subjected to dissolution testing. Ultimately, there is a slower rate of diffusion of the drug out of the pellets, assuming pore diffusion to be the release mechanism. Zang et al. (1990) found that uncoated Acetaminophen (Paracetamol) beads produced by the pan method disintegrated and released the drug faster than beads produced by extrusion and spheronization. The spheronized beads did not disintegrate but behaved as inert matrices. However, this effect caused only a small decrease in the rate of drug release and, therefore, additional retard measures are usually adopted.

1.8 COATING OF PELLETS

For a sustained release effect, pellets (irrespective of the method of production) are usually coated with a material that retards the release of the drug[1]. Examples of coating materials are ethylcellulose and the Eudragit© range of polymers. Coated pellets have been shown to control the release of the drug very well both *in vitro* and *in vivo* and are, therefore, excellent for oral sustained release

[1]One author claimed that they are "invariably coated" (Mehta, 1989).

products. They are, however, expensive to produce and imperfections in the coat can lead to an altered rate of drug release. The coating technique requires a great deal of operator skill and it has certain inherent problems and difficulties which are briefly referred to below.

During the coating process, all of the coating liquid does not reach the pellets: it is inevitable that some is lost to the atmosphere and to the walls of the coating apparatus. Gross differences in the amount of coating liquid deposited onto the beads changes the coating thickness which leads to batch-to-batch variation in the rate of drug release.

A drug retarding coat must be smooth and continuous and not reveal any flaws, such as pin-hole faults. Often, it is not easy to obtain an effective coat, the quality of which is largely dependent on the skill of the operator. Therefore, quality control tests must be performed routinely to ensure the adequacy of the coat. In addition, the extent to which drug release is sustained is dependent on the thickness of the coating which, in turn, is sensitive to the coating parameters used and to the properties of the base pellets. The particle size distribution and the surface roughness of the pellets can alter their surface area. Since a fixed amount of coating material is added to a fixed mass of pellets, batch-to-batch variation of the pellets in respect of these properties leads to different coating thicknesses and, hence, to variations in the rate of drug release. The following example illustrates how sensitive drug coating is to the mentioned parameters.

When two batches of coated pellets of a new, experimental drug showed vastly different dissolution rates, the surface characteristics of the coated pellets were examined and found to be smooth,

uniform and free from defects in both cases (Mehta, 1989). Electron microscopy of the uncoated pellets, however, revealed that the pellets of one batch had a much rougher surface. Hence, if the same amount of coating material was used in each case, the smooth pellets would have received a much thicker coating, the rough surface having a greater effective surface area. Electron micrographs of the sectioned pellets revealed that the smooth pellets did, in fact, have a much thicker coating.

1.9 AIMS AND OBJECTIVES

In the foregoing, it has been shown that matrix tablets are easy to prepare, that adequate sustained release effects have been obtained and that the release profiles have been fitted to mathematical expressions, demonstrating that the release mechanisms are understood. The great shortcoming of matrix tablets is the fact that their gastro-intestinal transit, and possibly also their drug release, may be variable both within a subject and between subjects. For this reason, multiparticulate dosage forms are preferred.

Of the various types of multiparticulate dosage forms available, pellets are preferred for oral use. They are relatively easy to prepare in large quantities and because their sizes are not very small, their release rates are not inherently very fast. Extrusion and spheronization produces drug-loaded pellets directly and rapidly, is an easier pelletization process than the drug layering techniques and also has less potential for variability of the beads. The shape and surface characteristics of the pellets are very good and a high degree of drug loading is possible. Hence for the production of drug loaded

pellets, extrusion and spheronization is simpler and has advantages over the other methods of bead production, such as the layering techniques.

Drug loaded beads are usually coated for a sustained release effect. However, if one could omit the coating step in the production of sustained release beads (by any process), it would avoid many problems. Elimination of the coating step would also save chemicals, labour and capital for the purchase of additional equipment. In addition, there may be a reduction in the number of quality control procedures required. The production of uncoated sustained release pellets by extrusion and spheronization, in particular, represents a significant advance in the simplification and cost reduction of pelletized dosage forms. It would also have the potential for a more consistent quality of the final product because of the elimination of several process variables associated with both the layering and coating techniques. While still expensive relative to matrix tablets, such a pelletized dosage form offers several therapeutic advantages over matrix tablets.

The primary aim of this project, therefore, is to investigate the preparation of uncoated, spheronized sustained release pellets. The development of such preparations represents a contribution towards the goal of cheaper and less variable sustained release medication. The term "lean production" which is used in manufacturing industries (such as the motor car industry) refers to the production of quality goods with the use of the least resources. These include time, equipment, materials and personnel. It is the candidate's opinion that the production of sustained release pellets by extrusion and spheronization without subsequent coating represents a form of "lean production" in the pharmaceutical industry.

A secondary aim of this project is to prepare beads that can be compressed into sustained release tablets. A tablet can accommodate a larger mass than can be incorporated into a bead-filled capsule. Also, the compaction forces employed during tabletting may assist the development of sustained release properties. If the tablets were to disintegrate into particles having approximately the same size as beads, the advantages of beads would be retained. If they do not, the preparation would resemble a conventional matrix tablet with its attendant shortcomings. However, such a product would nevertheless be useful since the beads from which it is compressed are easily produced in large quantities and are denser and more uniformly-sized than conventional granules. Most importantly, they would have excellent flowability due to their spherical shape. Insufficient flowability of granules leads to variations in mass, hardness, thickness and drug content of the tablets manufactured from them. The recognized advantages of spherical pellets or beads in the production of tablets has led to research efforts to produce pellets that can be tabletted. Some of these attempts are reviewed in the next chapter.

CHAPTER 2: LITERATURE REVIEW

Extrusion and spheronization is a relatively new process, the first patent in Western countries having appeared in 1964 (Nakahara, 1964). However, it was only in 1970 that interest in the technique was aroused after the publication of 2 papers in the scientific literature (Conine and Hadley, 1970; and Reynolds, 1970). Since then, a steadily increasing number of papers have appeared each year as the technique advanced from one which was approached with some curiosity, to an interesting scientific area for research, until the present time when the process is viewed as a serious option for the commercial production of sustained release medication.

In the previous chapter, the advantages of using beads for sustained release medication were described and, by way of introduction, the various methods of bead production, including extrusion and spheronization, were briefly sketched. The potential advantages of using uncoated beads were mentioned and reference was made to the fact that many reported attempts at such a formulation were not very successful. In this chapter, the process of extrusion and spheronization is discussed in more detail. A brief description of commonly-used equipment is followed by a discussion of the formulation of beads and of the processing variables encountered. Lastly, brief overviews are given of attempts (a) to produce uncoated sustained release beads and (b) to compress tablets from beads.

2.1 EQUIPMENT FOR EXTRUSION AND SPHERONIZATION

The bead manufacturing process of extrusion and spheronization consists of the following steps:

(i) dry mixing of the powders

(ii) wet massing of the powders

(iii) extrusion, and

(iv) spheronization

Dry mixing and wet massing of the powders can usually be done in the same apparatus. The most commonly used equipment for this purpose is a planetary mixer (O' Connor et al., 1984; Harrison et al., 1984, 1985a,b, 1987; and Fielden et al., 1988). It is important to obtain a homogeneous mix of the powders, before the addition of the granulating liquid, to ensure content uniformity of the finished beads. The planetary mixer is usually adequate for this purpose. Where a very small amount of active is present, geometric dilution of the powders must be used to ensure content uniformity.

The appearance of the wet massed material is usually coarse, while that of the extrudate is smoother. This difference is probably due to the high shear experienced within the extruder. Since shearing forces can affect the appearance of the material, it is conceivable that the type of mixer used to prepare the wet mass could also alter the properties of the extrudate made from it. This, in turn, may influence the properties of the final product. For this reason, there has been an interest in high shear mixers and some reports on their use have appeared in the literature (Baert et al. 1991). However, according to a recent review (Vervaet et al., 1995) no study has, thus far, been done to compare the effect of the type of mixer on the quality of the beads.

Extruders are of the following types: screw, sieve, basket, roll and ram. In the screw extruders, the wet mass is gravity-fed from a hopper to a chamber containing one or two (twin-screw)

Archimedes screws. The screws push the wet mass towards the screen which may be placed axially or radially to the screws. In the axial format, the screen is placed at the end of the screws, perpendicular to them. In the radial configuration, the screen surrounds the screws. The screw-type extruders are depicted diagrammatically in Figure 2.1.

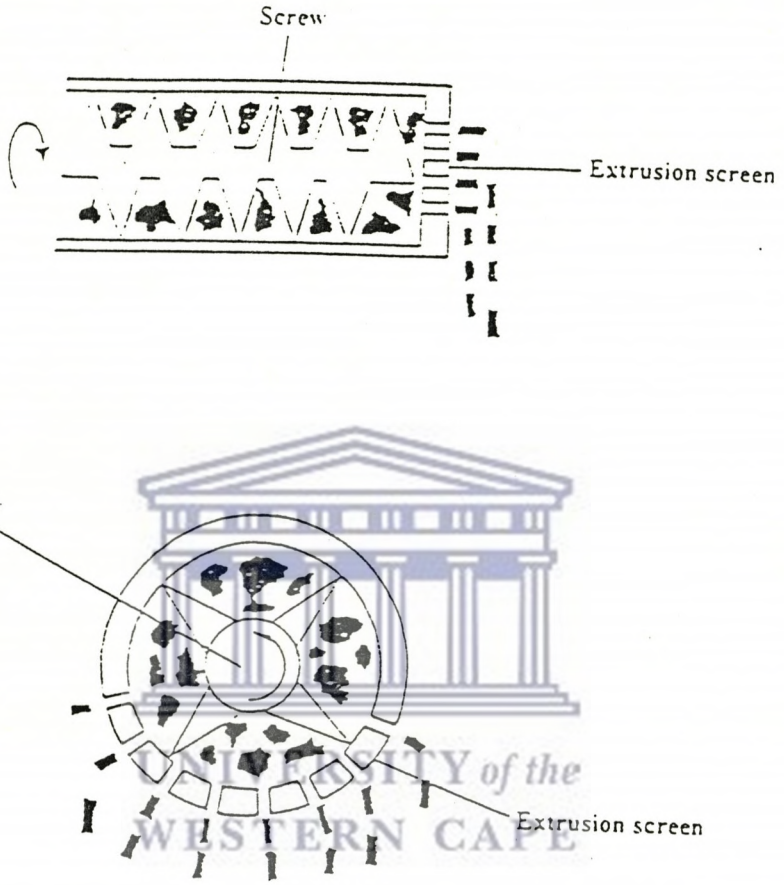


FIGURE 2.1: SCHEMATIC VIEW OF A SCREW EXTRUDER. (A) AXIAL TYPE AND (B) RADIAL TYPE (VERVAET ET AL., 1995).

In the sieve extruder, gravity causes the wet mass to fall from the hopper into the extrusion chamber from where it is propelled through the sieve below it by an impeller that spins or oscillates. The basket extruder is similar, except that the sieve forms the walls of the extrusion chamber and surrounds the impeller. The sieve and basket extruders (Hicks and Freese, 1989)

are analogous to the axial and radial screw extruders, the major difference between the two sets of extruders being the mechanism by which material is forced through the screen. This is done by an Archimedes screw in the latter and by an impeller in the former. The material may be drawn into the chamber of the sieve or basket extruder by a secondary feed screw, the rate of rotation of which can be set differently to that of the impeller. The sieve extruder and the basket extruder are depicted in Figure 2.2.

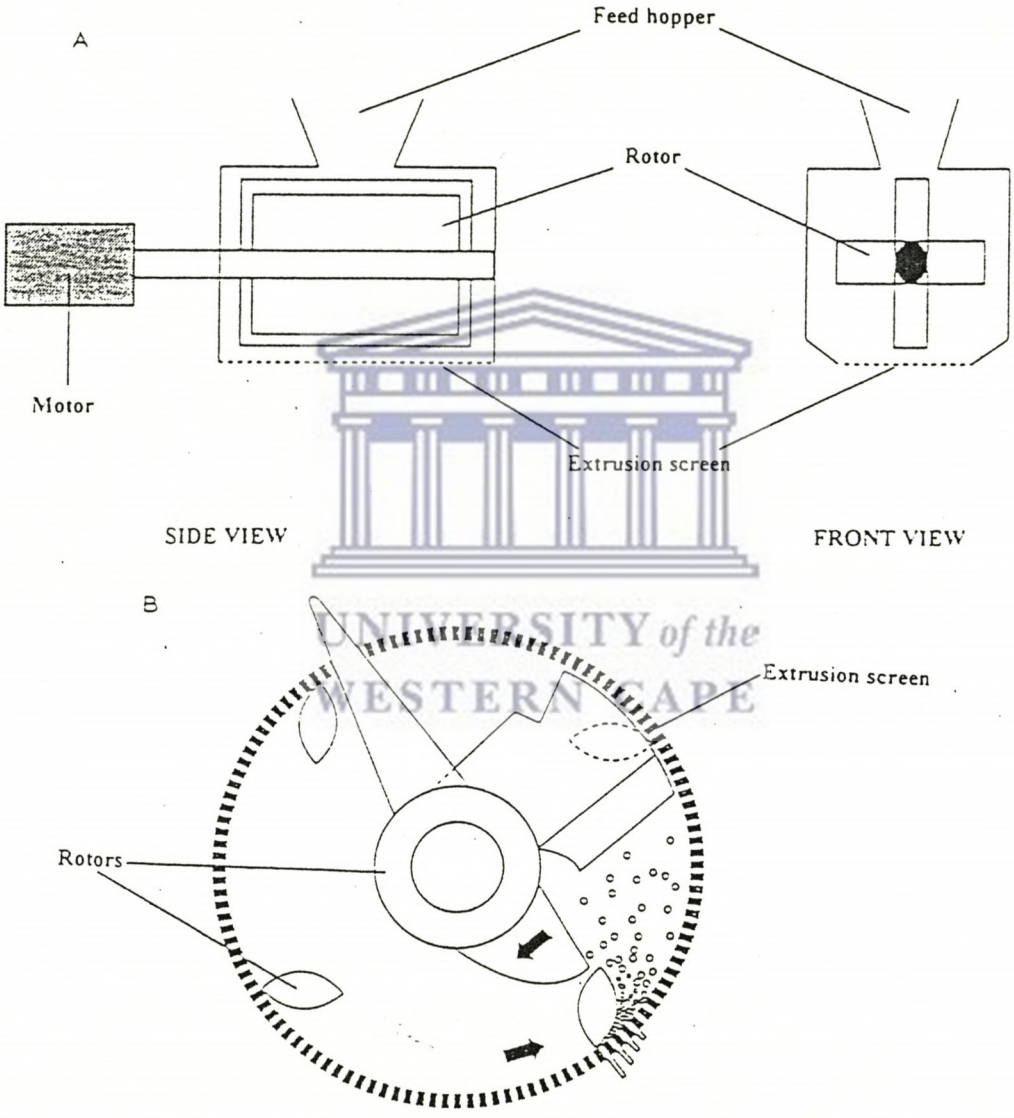


FIGURE 2.2: SCHEMATIC VIEW OF (A) A SIEVE EXTRUDER AND (B) A BASKET EXTRUDER (VERVAET ET AL., 1995).

Roll extruders (Hicks and Freese, 1989) are of two types. In the first type, the wet mass is gravity-fed from a hopper and is squeezed through the gap between two rollers situated below it, as the rollers rotate in opposite directions. This action is similar to a roller mill used, for example, for the milling of ointments. The difference between the roll extruder and a roller mill is the fact that one or both rollers of the extruder is perforated and the extrudate passes through the perforated roller. In the second type of roll extruder, a cylindrical screen rotates around one or more rollers and the extrudate passes through the screen to the outside. The two types of roll extruders are depicted diagrammatically in Figure 2.3.

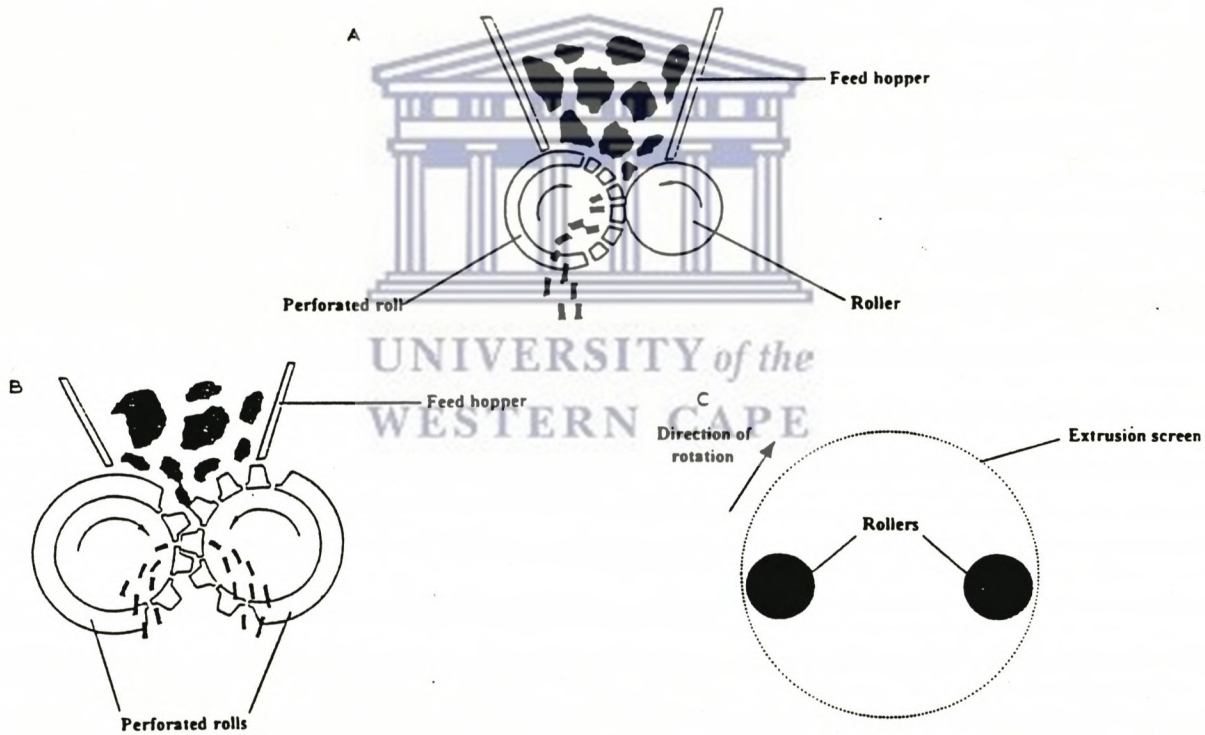


FIGURE 2.3: SCHEMATIC VIEW OF ROLL EXTRUDERS WITH (A) ONE PERFORATED ROLL (B) TWO PERFORATED ROLLS AND (C) EXTRUSION SCREEN ROTATING AROUND ROLLERS (VERVAET ET AL., 1995).

The ram extruder has a piston within a barrel and the reciprocating action of the piston draws the wet mass from the hopper into the barrel and forces it through a screen at the end of the barrel. The effects of several factors on the process of extrusion through the ram extruder have been studied by means of instrumentation (Fielden et al., 1989; and Harrison et al., 1985b, 1987).

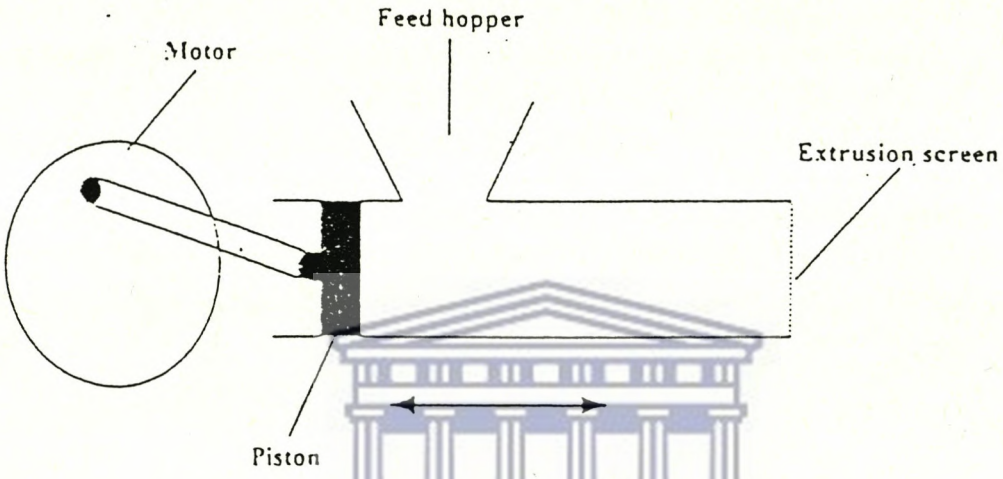


Fig. 5. Schematic view of a ram extruder.

FIGURE 2.4: SCHEMATIC VIEW OF A RAM EXTRUDER (VERVAET ET AL., 1995)

The product of the extruder (wet extrudate) is transferred to a spheronizer which can, very simply, be described as a cylindrical pot with a rough, rotating base. The rotating base or friction plate is motor driven and has a grooved surface to increase the frictional forces. Two types of geometry of the frictional plate are commonly used: cross-hatch (the grooves are at right angles on the surface of the plate) and radial geometry (the grooves run from the centre of the plate to the periphery) (Rowe, 1985; and Hicks and Freese, 1989).

The extrudate is broken soon after contact with the plate which usually rotates at rates up to 1000rpm, and sometimes at even higher rates. The mechanical energy that the plate imparts to the system is converted to kinetic energy which results in the particles forming a "mechanically fluidized bed" (Hicks and Freese, 1989). The proper motion of the particles, when all the variables have been correctly chosen, resembles a twisting rope rotating much more slowly than the friction plate, with the particles lifting off the surface of the plate and returning to it periodically. The friction between the material and the plate, as well as the collisions experienced by the particles, are responsible for the shaping of the beads. Collisions occur between the particles and the wall of the spheronizer and between the particles themselves. An increase in the spheronization time is translated into an increased number of collisions and, thus, a change in the shape of the particles (Hicks and Freese, 1989). A faster speed of rotation should have a similar effect. Hence, the speed of the spheronizer and the residence time are critical to the quality of the spheres and are discussed in section 2.2 as two of the significant processing variables.

2.2 FORMULATION AND PROCESSING VARIABLES THAT AFFECT THE QUALITY OF BEADS

Many formulation and processing variables have to be carefully monitored in order to obtain the desired product: spherical beads with a smooth surface. When the formula or the processing conditions are not correct, ellipses or dumbell-shaped particles may be formed; the beads may agglomerate; they may be excessively friable; or their surfaces may be rough and uneven. During subsequent coating, the latter condition results in a coat of uneven thickness and, as a

result, drug release may be erratic. Since coating is by far the most common method of achieving a sustained release of the drug, the surface properties of the beads are of tremendous importance.

The moisture content, cohesiveness, rigidity and plasticity of the wet mass appear to be of prime importance for beads of high quality and the formulation variables that affect these properties must be carefully controlled. In addition, many processing variables are also important. Amongst these are the extruder type and speed, and the spheronizer design, speed, and residence time. There is often an interaction between two, or more, formulation variables or between formulation factors and processing factors. For example, the optimal moisture content of the wet mass may be affected by the presence of a binder, its type and amount. The interaction of a formulation and a processing variable is exemplified by the influence of the type of mixer on the optimal moisture content of the wet mass. Baert et al. (1991) found that high shear mixers tended to cause water loss and the resultant drier material formed an inferior extrudate. Hence, the optimal moisture content, in this case, is higher than it is when a planetary mixer is used.

Formulation and processing variables cannot be studied in isolation because the interactions could be significant. Statistical designs may be used to study the compound effects (or "confounding") of such variables (Malinowski and Smith, 1975; Chariot et al., 1987; Ku et al., 1993; Hileman et al., 1993). Using a factorial design, Hasznos et al. (1992) studied the effect, on the size distribution of placebo pellets, of the moisture content of the wet mass, the extruder speed and the speed, time and load of the spheronizer. Such statistical designs assist the formulator in obtaining the optimal formulation as well as the ideal processing conditions.

2.2.1 Formulation Factors

The visco-elastic properties of the wet mass are of utmost importance in the extrusion and spheronization processes. The sequence of events leading to the formation of good beads will not occur if the material does not have the required properties. Microcrystalline cellulose has, almost invariably, been included in formulations for extrusion and spheronization[1]. The manufacturers of the most popular brand, Avicel©, claim that it imparts to the material the ideal properties for spheronization (FMC Corporation, 1985). The term, "spheronization enhancer", has been used in the literature to describe the action of this excipient (Harris and Ghebre-Sellassie, 1989). While it is not entirely clear which properties of microcrystalline cellulose enable it to function as the ideal spheronization enhancer, its behaviour may be partly explained by the ability of the elongated cellulose strands to reversibly bind water.

In order to give material for extrusion and spheronization the required plasticity, it is necessary that the powders absorb a large amount of water during the wet massing stage. A small amount of water is also necessary on the outside of the beads to serve as a lubricant during spheronization (Harris and Ghebre-Sellassie, 1989). On the other hand, a large amount of water on the surface will cause agglomeration during spheronization. Microcrystalline cellulose appears to behave like a "molecular sponge" (Fielden et al., 1988) in that it is capable of retaining a large amount of water, but the water is also readily released. In order to modulate the water content of the beads, microcrystalline cellulose is required in sufficient quantity.

[1]One exception is the reported use of powdered cellulose (Lindner and Kleinebudde, 1994). The pellets were shown to have a greater porosity and a faster dissolution rate than pellets made from microcrystalline cellulose.

Bains et al. (1991) found that good beads of Barium Sulphate, microcrystalline cellulose and water could be produced over a wide range of water content values if the beads contained from 20% to 60% Barium Sulphate; as the level of Barium Sulphate increased above 60%, the water content range became smaller. Above 80% Barium Sulphate, there was a critical moisture content for the formation of good beads. This phenomenon is due to the lower microcrystalline cellulose content of the beads with higher levels of Barium Sulphate.

Using thermogravimetric analysis, differential thermal analysis and immersional calorimetry, it was found that the bulk of the bound water in microcrystalline cellulose is present as free water and a small proportion as adsorbed, structured water (Fielden et al., 1988). As water evaporates from the surface of a bead during spheronization, water from its interior moves to the outside. Presumably, the replenishing water is that held by capillary forces between the particles of the bead. This water, in turn, is replenished by water from within the cellulose strands. Although many pharmaceutical powders can hold a large amount of water, they have not been shown to form good beads. A good spheronizing aid is able not only to hold a large amount of water but, also, to release it as required.

Blair et al. (1990) used a vacuum microbalance and a microcalorimeter to measure the sorption of water by microcrystalline cellulose exposed to air at different relative humidities. They proposed that water binds to anhydroglucose units within the amorphous regions of the solid. It was suggested that, initially, one molecule of water is bound between two anhydroglucose units, but that these bonds are then broken to form a 1:1 stoichiometry. Finally, there is the sorption of loosely bound water, if the material is exposed to sufficient moisture. Presumably,

it is this loosely bound water that can be gained and lost. This explains the ability of microcrystalline cellulose to hold varying amounts of water and, hence, to function as a spheronizing aid.

For tablet granulations, the study of the granulation endpoint is well developed and several methods are available for its determination. These include the measurement of amperage, power consumption, torque, conductivity, capacitance and motor slip of the mixing unit (Corvari et al., 1992). In the case of wet massing for extrusion and spheronization, on the other hand, such determinations on the mixer have, generally, not been made. One exception is the work of Elbers et al. (1992) who determined the power consumption of the mixer. Harrison et al. (1985a) attempted to determine when the correct amount of liquid had been added by observation of the quality of the extrudate, but this method is subjective.

In a few instances, the extruder has been instrumented and the readings were correlated with the quality of the extrudate and that of the final product. This, in turn, may be related to the amount of water added. Such correlations have been made using a ram extruder (Harrison et al., 1985b). Shah et al. (1994) instrumented the screen of a twin screw extruder and were able to relate screen pressure and screen temperature to the moisture content of the wet mass. Most often, however, the addition of the correct amount of water is determined subjectively by the operator feeling the material (O'Connor et al., 1984; O'Connor and Schwartz, 1985; Funck et al., 1991; and Millili and Schwartz, 1990) .

The determination of the amount of granulating liquid to add is complicated by the fact that the "correct" amount is influenced greatly by the ingredients of the formulation. A mixture of microcrystalline cellulose and coarse lactose was found to agglomerate at a lower water level than a similar mixture containing fine lactose particles (Fielden et al., 1993). It was thought that the smaller porosity of the beads containing the coarse lactose led to less water retention within the capillaries and, hence, more water was available on the surface. The excess surface moisture led to the agglomeration of the beads. The solubility of the drug also has a dramatic effect on the amount of granulation liquid required to obtain the correct plasticity without overwetting. A soluble drug will dissolve in the granulation liquid, increasing its volume. The powders may become overwet relative to a similar formulation containing an insoluble drug (Baert et al., 1991).

The effect, on the beads, of the amount of moisture in the wet mass has been the subject of many papers. Several authors have shown that there is a specific range of moisture content values for the production of beads of high quality (Gamlen, 1985; Bains et al., 1985; Fielden et al., 1993; and Kleinebudde, 1993). The higher water levels within the range used by Ku et al. (1993) produced a greater yield of the desired size of beads at low and moderate spheronizer speeds. Malinowski and Smith (1975) found that the amount of water added during wet massing affected all the parameters studied. For example, with an increase in water content there was an increase in bulk density and mean particle size, while the friability and the mean percent fines decreased. Reference has previously been made to the work of Bains et al. (1991) who found that beads could be successfully produced over a wide range of water content levels, if the formulation contained a large amount of microcrystalline cellulose. Elbers et al. (1992) also found the

optimal level of granulation fluid to be related to the level of microcrystalline cellulose. Increasing the level of granulation fluid in mixtures of Avicel© RC 581 and Theophylline increased the "plasticity" which then decreased with further increases in granulation fluid, before rising once more. The best spheres were formed with granulation fluid levels reflected by the rising part of the plasticity curve, after the dip.

The finding that the amount of water added to the wet mass could affect the rate of drug release from the beads (Baert and Remon, 1993) is, possibly, of greater significance. Mixtures of either 20% Theophylline, or 10% Sulphamethoxazole, and microcrystalline cellulose were wet massed with different amounts of water before extrusion and spheronization under identical conditions. The beads prepared with the higher amounts of water showed slower release of both drugs but the differences were more pronounced in the case of Sulphamethoxazole, the less soluble compound. These differences were attributed to the measured increases in hardness, and density, of the spheres as the water content of the starting material increased.

Ku et al. (1993) found that the temperature of the water used for wet massing was significant. Using water at room temperature or at 50° resulted in differences being observed during processing. For example, when the warmer water was used, the residence time in the spheronizer did not affect the quality of the beads, whereas it did when cold water was used.

In the vast majority of studies, water served as the granulating fluid. In a few cases, however, water/alcohol mixtures were used (Goodhart et al., 1973; Elbers et al., 1992; and Millili and Schwartz, 1990). In the production of pellets containing 0%, 10% or 50% Theophylline, little

difference was observed in the power consumption of the mixer, and of the extruder, or the plasticity of the wet masses granulated with either water or 40% ethanol (Elbers et al., 1992). Millili and Schwartz (1990) examined the effect of varying the concentration of ethanol in the solution used to granulate a mixture of 10% Theophylline and 90% microcrystalline cellulose. They found that beads could not be formed when pure ethanol served as the granulating fluid; with 95% ethanol, beads of poor quality were produced. The water-granulated beads did not disintegrate, whereas the beads granulated with 95% ethanol disintegrated rapidly. As the mole fraction of water in the granulating fluid increased, the pellets became larger, stronger and harder and the dissolution rate of the drug decreased.

There is an optimal amount of microcrystalline cellulose that must be used with each formulation; an excess often results in undesirable qualities, of the extrudate, or of the beads. Hence, when working with low dose drugs, a filler must be included. In addition to the property of inertness that is usually required of pharmaceutical excipients, the sensitivity of the extrusion and spheronization process to the physical quality of the wet mass places additional requirements on a potential filler. The particle size of the filler has been reported to be significant by Fielden et al. (1989). They examined the effects of two particle-size grades of lactose on the properties of the extrudate. The larger lactose particles produced a poor extrudate. Using force-displacement curves, they observed that the material containing the coarser lactose had poor flow properties whereas the mixture with the finer lactose displayed optimal extrusion. The flow of the material from the extruder die could be visualised by using charcoal to dye certain layers. This revealed that the fine lactose-formulation flowed symmetrically through a vortex while the formulation containing coarse lactose had a different flow pattern, with initial asymmetric flow.

A binder is not universally used although several authors have observed an improvement either in the process of bead production or in the final product, after the incorporation of a small amount of binder. Gamlen and Eardley (1986) found that the incorporation of 2% hydroxypropylmethylcellulose improved the extrudability, but not the quality, of the extrudate. Without the binder, the screen of the extruder often became blocked and the rate of extrusion varied unacceptably. With the binder, the extrudate was formed evenly at all water levels used but the extrudate remained rough or sharkskinned, a condition characterized by the presence of jagged edges on the surface of the extrudate. Funck et al. (1991) found that several binders, at the 2% level, improved the quality of beads containing 80% Theophylline.

2.2.2 Processing variables

In Section 2.1, several types of commercially-available extruders were described. In the formulation section (2.2.1), it was implied that the quality of the extrudate determined the quality of the beads and reference was made to publications in which extrudate quality was related to the extruder screen pressure, or its temperature, during extrusion. Since factors such as these are equipment related, it follows that the type of extruder could affect the nature of the extrudate, and hence, the quality of the final product. Several reports have appeared in which the influence of the extruder type was described (Reynolds, 1970; Rowe, 1985; Baert et al., 1992, 1993b; Fielden et al., 1992b). In general, the screw extruders are higher pressure extruders than the basket-type extruders and, consequently, the extrudate obtained from the former is denser than that from the latter. Rowe (1985) claimed that extrudate from an axial screw extruder was more dense than that from a radial screw extruder. The latter had a greater output but the temperature increase of the extrudate was also greater.

Baert et al. (1992) compared the extrusion forces that were developed in a ram extruder with those in a Caleva gravity feed extruder with two perforated rolls. In the ram extruder there was continuous pressure on the wet mass and a consequent movement of water. This resulted in a lower water requirement for good beads. Pressure, in the case of the roll extruder, was discontinuous and no water movement occurred. Hence, more water was needed to produce beads of good quality.

By means of instrumentation, this roll extruder was also compared with a twin screw extruder (Baert et al., 1993b). Because of technical difficulties, the two extruders could not be instrumented identically and changes in the extrusion forces, measured in the roll extruder, were regarded as equivalent to changes in the power consumption of the twin screw extruder. As the water content of damp microcrystalline cellulose increased, the extrusion forces of the roll extruder decreased and the power consumption of the twin screw extruder decreased as well. Ternary mixtures of microcrystalline cellulose, drug substitute and water were also examined. Lactose and dicalcium phosphate dihydrate served, respectively, as the substitutes for a soluble, and an insoluble, drug. Extrusion forces or power consumption were measured for increasing drug substitute concentrations. In the case of dicalcium phosphate dihydrate, similar profiles of extrusion force (or power consumption) versus the amount of drug substitute were obtained for the two extruders. With lactose, similar profiles were also obtained for the initial part of the curve in that extrusion force, or power consumption, decreased with increasing lactose concentration but the latter part of the curves differed. The power consumption of the twin screw extruder continued to decrease whereas extrusion forces increased in the case of the roll

extruder. These differences were attributed to the different length-to-radius ratios of the holes in the extruder screens and the fact that greater densification occurred with the roll extruder.

Ternary diagrams for the percentage of microcrystalline cellulose, dicalcium phosphate dihydrate and water were plotted. The zones for acceptable spheres were determined and were found to be in similar regions for the two extruders. However, the area of the acceptable region was much larger in the case of the roll extruder. Again, the authors attributed the observed differences to the different length-to-radius ratios of the screen holes. However, according to a recent review (Vervaet et al., 1995) it remains unclear whether this phenomenon is dependent on the type of extruder or on the thickness of the screen.

The mass of extrudate formed will always be less than the mass of the wet material fed into the extruder, since some material remains within its dead space. The amount lost varies with the type of extruder, the basket type being far more efficient than the twin screw extruder. For a particular extruder, the amount of lost material depends on the extrusion speed (Hellen et al., 1992). For economic reasons, therefore, it would appear that extrusion should be as fast as possible. However, several authors have stated that faster extrusion speeds adversely affect the quality of the extrudate (Goodhart et al., 1973; Harrison et al., 1985a,b, 1987; Bianchini et al., 1992).

Harrison et al. (1985a) found that the surface roughness and sharkskinning became more pronounced with increasing extrusion speed and that the irregular extrudate broke up unevenly during spheronization, leading to poor spheres. Other authors (Chariot et al., 1987; Hasznos et

al., 1992; and Hileman et al., 1993) found that extrusion speed did not influence the size of the pellets. Ku et al. (1993) found that a faster extrusion speed gave a larger yield of beads of the required size fraction at slow and medium spheronization rates. The effect of extruder speed is, therefore, not clear and may be formulation-dependent. In any event, the amount of material remaining in the extruder may only be significant when very few batches are manufactured on one day. On an industrial scale where the extruder is operational for many hours a day, the amount lost during cleaning at the end of the day is insignificant.

Mesiha and Valles (1993) examined the effects of a series of commonly-used pharmaceutical excipients on extrudate, and bead, quality. The excipients included tablet lubricants and glidants, surface active agents, humectants and a binder. Assessment of the effect of these additives on the ease of extrusion was done by observing the surface temperature of the extruder head and the reduction in energy consumption by the extrusion motor. Baseline values were obtained by extruding a wet mass containing no additives. As a group, the surface active agents were the most effective and, of these, sodium lauryl sulphate produced the best results. Less energy was used, the temperature of the extruder head was significantly lowered and the extrudate was smoother with fewer defects. The spheres were smooth and the surface active agent had no adverse effect on their hardness, strength or shape, but there was a large increase in bead size.

Rowe (1985) stated that the spheronization speed should be optimized to obtain the desired density increase. He claimed that slow speeds do not increase the density sufficiently to produce good spheres and that high speeds cause agglomeration of the pellets, implying a larger final pellet size. However, other authors have stated that lower speeds reduce attrition and abrasion

(Hicks and Freese, 1989; and Malinowski and Smith, 1975). Malinowski and Smith (1975) found that a faster spheronizer speed caused a decrease in mean particle size. There are, thus, conflicting views concerning the effect of higher spheronizer speed: (a) that it causes increased agglomeration and (b) that it causes more attrition. The latter view appears to be the more logical and is substantiated by the fact that higher speeds were observed to cause attrition of the beads in the present work.

Baert et al. (1993a) found that an increase in spheronizer speed resulted in a higher yield of spheres of the required size and that this effect became more important as the water content of the formula decreased. Ku et al. (1993) found that there was an optimum speed of spheronization (not the highest speed used) for a high yield of the desired size fraction and that the ideal speed varied with the water content of the beads. Spheronizer speed also affects the hardness of the beads (Bataille et al., 1993), the roundness (Woodruff and Nuessle, 1972; Bianchini et al., 1992; Hileman et al., 1993; and Baert et al., 1993a), porosity (Bianchini et. al., 1992), bulk and tapped densities (Chapman et al., 1986; and Hileman et al., 1993), friability (Malinowski and Smith, 1975) and surface structure (Bataille et al., 1993).

An increased length of spheronization, or residence time, causes the spheronizing particles to experience more friction and a greater number of collisions and, hence, the properties of the beads may be altered. Some of the reported effects are: an increase in diameter (O'Connor et al., 1984); a narrowing of the size distribution (Bianchini et al., 1992); an increase in the bulk and tapped densities (Malinowski and Smith, 1975); and an improvement in the roundness (Baert et al., 1993a). While both spheronizer speed and residence time increased the density of the beads,

a combination of high speed and long residence time produced a greater-than-expected increase (Malinowski and Smith, 1975).

2.3 UNCOATED SUSTAINED RELEASE BEADS

Both the extrusion, and the spheronization, processes increase the density of the processed material and, as previously mentioned, there is a synergistic effect between the speed, and the time, of spheronization. One of the expected effects of the densification of beads is a slower release of the drug. Other methods of bead production (with the exception of tabletting), do not provide this compaction and the uncoated beads are, therefore, expected to release the drug faster than uncoated, spheronized beads. Zang et al. (1990) quantified this difference and found that beads prepared by balling in a pan released the drug only slightly faster than beads produced by extrusion and spheronization. Hence, the extrusion and spheronization process, in itself, cannot be expected to produce a useful sustained release product and other drug-retarding mechanisms have to be introduced. A review of the literature reveals a few attempts to produce sustained release pellets by extrusion and spheronization without subsequent coating.

In one such attempt, different proportions of the drug (Chlorpheniramine Maleate, Theophylline, Quinidine Sulphate or Hydrochlorothiazide) were spheronized in a matrix of microcrystalline cellulose (Avicel© PH 101) or a commercial blend of microcrystalline cellulose and sodium carboxymethylcellulose (Avicel© RC 581 and Avicel© 611) (O'Connor and Schwartz, 1985). When dissolution tests were done by the basket method at 50rpm, it was found that the formulations containing Avicel© RC 581 and Avicel© 611 were able to extend the release of the drug to some extent. Avicel© 611 gave a slightly slower release than Avicel© 581. Extended

release was favoured by a low concentration (10%), and poor water solubility, of the drug. However, these authors reported that a "gelatinous plug" formed in the dissolution baskets. This plug, presumably, was formed from an aggregation of the pellets and this is to be expected when a hydrophilic matrix material (sodium carboxymethylcellulose) is a constituent of the formulation. The more successful formulations described in this work had a low drug concentration (10%) which is not practical, particularly with high-dose drugs such as theophylline. The significance of the formation of a gel plug is discussed later in this chapter.

Ghali et al. (1989b) also worked with 10% drug loading (Chlorpheniramine Maleate and Theophylline) in Avicel© PH 101 mixed in different proportions with Avicel© RC 581. The modification of the rate of drug release in distilled water was slight and followed the trend of increasing Avicel© RC 581 concentration. In acid medium, a gel did not form and drug release was rapid and followed a similar pattern for all matrix mixtures. The authors indicate that a gel will also not form in buffers (even if the pH is higher), since the ionic strength of the medium would prevent gel formation. As the retard effect is a consequence of gel formation, even the small effect observed will not occur in all dissolution media .

These workers also incorporated various waxes into microcrystalline cellulose matrix pellets in an attempt to slow down the rate of drug release (Ghali et al., 1989a). The addition of wax caused a slight increase in the rate of drug release because it appears to "interrupt matrix formation." While brief thermal treatment of the wax-containing pellets did decrease the rate of drug release in 4 of the 8 formulations, this effect was "not sufficient to produce a controlled release product."

With the basket method of dissolution testing of the above products, a gel plug formed due to the restricted space in which the beads could move and because they contained sodium carboxymethylcellulose, a sticky, gel-forming material. Observations made in the course of the present work indicate, on the other hand, that a plug is not formed when the paddle method is used. The beads are free to move about throughout the dissolution flask as separate, discrete entities and expose a much greater surface area to the dissolution fluid. Since one large, drug-retarding, gelatinous mass is not formed, the beads display little sustained release effect and, subsequently, slowly erode.

The fact that sustained release beads form a gel plug is of tremendous significance. In the first place, if the gel plug forms *in vivo*, it negates the previously-described advantages of multiparticulate systems. Secondly, the fact that it forms in the basket but not when the paddle method is used, means that the sustained release effect is an artifact of the basket method of dissolution testing. This deduction is applicable to all of the published work referred to, thus far, in this section. This contention is supported by the dissolution results obtained by Goskonda and Upadrashta (1993). They prepared beads of Acetaminophen and Theophylline in a matrix of Avicel© RC 591 and varying amounts of Chitosan. The mass of Avicel© RC 591 was adjusted to accommodate the varying levels of the retardant. Comparing the basket and paddle methods for each drug in acidic medium, they found that the paddle method resulted in much faster dissolution. Since Chitosan forms a gel in acidic media, the differences are probably due the formation of a gel plug within the basket.

Using the basket method, these authors also studied the influence of the medium (water or 0.1N HCl) on the dissolution of the beads. In acidic medium, it was found that the slowest release of Theophylline was from the preparation containing the highest concentration of Chitosan and the fastest was from the preparation containing no Chitosan. The order was reversed in water, the slowest release being from the preparation containing no Chitosan . Since Chitosan does not gel in water, sodium carboxymethylcellulose probably acted as the retardant in this medium and, hence, the slowest release was from the formulation containing the highest concentration of this polymer. A similar, though less clear, trend was observed for Acetaminophen. The loading was 20% for both drugs, which is unrealistically low for these high-dose drugs. With a higher drug loading, the sustained release effect would be less evident.

Tapia et al. (1993) also used Chitosan as a retardant in beads containing Avicel© PH 101 and Sodium Diclofenac. Dissolution tests were conducted in pH 7.5 phosphate buffer (using the paddle method) and release from a preparation containing a 1.25% drug loading was sustained over about six hours. Even this moderate sustained release effect was enhanced by the very low drug loading. Dissolution tests were not conducted in an acidic dissolution medium because of the very poor solubility of the drug in acid.

Using the paddle method at 50rpm in water or simulated intestinal fluid, Herman et al. (1988) found that Hydrochlorothiazide was released unexpectedly faster from beads containing a combination of microcrystalline cellulose and sodium carboxymethylcellulose (Avicel© RC 581) than it was from beads containing microcrystalline cellulose alone (Avicel© PH 101). In an acidic medium (simulated gastric fluid), the two preparations showed similar dissolution profiles.

They attributed the differences to the solubilizing effect of the sodium carboxymethylcellulose. The solubility of this polymer decreases dramatically below pH 2.5 and, in the undissolved state, it is unable to influence the solubility of the drug. Hence, similar dissolution profiles were observed for the two formulations in the acidic environment. In the less acidic media, the dissolved polymer caused faster dissolution of the drug. Even in the acidic medium, however, the sustained release effect was not large and in a bioavailability study, using 6 volunteers, "the plasma concentration-time profiles did not suggest slow release" in either formulation.

Bianchini et al. (1992) used a combination of pH adjusters and polymeric dispersions to retard the release of d-Indobufen, a carboxylic acid used as a platelet aggregation inhibitor. The pH adjusters (fumaric, tartaric and citric acids, as well as sodium citrate) were used to create, within the beads, an unfavourable microenvironment for the dissolution of the acidic drug. The dispersions were either a latex emulsion of ethylcellulose (Aquacoat©) or acrylic resin dispersions (Eudragit© RS 30D/Eudragit© RL 30D). This combination of retard mechanisms afforded a sustained release effect for 4 to 5 hours.

2.4 TABLETS FROM BEADS PRODUCED BY EXTRUSION AND SPHERONIZATION

The relative ease of producing spherical particles in large quantities by extrusion and spheronization and the obvious advantages of spheres, as compared to granules, in tablet production has led to an interest in the tabletting of spheres. The good flow properties inherent in the spherical shape and the reduction in dust formation, from a more cohesive unit than the

granule, make the use of spheres very attractive. However, the conversion of spheres to tablets is not as straightforward as it might appear.

The earliest reports on extrusion and spheronization made reference to the use of spheres for tabletting (Conine and Hadley, 1970; and Reynolds, 1970) but the use of spheres in tabletting is not widespread. An indication of the reason for the lack of popularity (in spite of the potential advantages), is gleaned from the statement by Conine and Hadley (1970) that less dense spheres are more efficiently compressed. In the spheronization process, the beads tend to become more dense the longer the spheronization process is continued and the density increase is, generally, seen as an advantage. For example, in the filling of hard gelatin capsules a greater fill weight is attainable, especially if a range of particle sizes is used (Conine and Hadley, 1970). The increased density contributes to the sustained release effect in preparations designed for this purpose. In the tabletting process, however, it is a disadvantage because it reduces compactibility.

Jalal et al. (1972) prepared an extrudate consisting of 20% Avicel© RC 581 and various actives which was spheronized for 60 seconds. The resulting beads were subsequently tabletted. In the context of tablet production, the authors claimed that beads dry faster, flow better and can be made with a higher drug loading than conventional granules. In addition, the spheronization process provides a convenient method for lubricant addition (to the swirling beads in the spheronizer). In the opinion of the present writer, the short spheronization time resulted in the production of soft beads which facilitated the formation of tablets.

Malinowski and Smith (1974) studied the effect of five extrusion and spheronization process variables on the hardness, and the dissolution rate, of the tablets compressed from the spheres. They found that a larger extruder screen size resulted in harder tablets, whereas an increased water content, spheronizer speed or residence time decreased tablet hardness. The water content of the wet mass was the only factor that affected the rate of dissolution of the tablets. As the water content was increased, the rate of dissolution decreased. While tablets compressed from beads made with 250ml water (1kg batch size) and 1 minute of spheronization had a hardness value of 6.5kg, those made from beads produced with 325ml water and 3 minutes of spheronization had a hardness value of 3kg. This is a dramatic drop in hardness, elicited by conditions that produce higher quality beads. The shorter spheronization time (1 minute) and lower amount of water (250ml) are not conducive to the production of good spheres, as noted in Section 2.2.2 and Section 2.2.1, respectively. Thus, it would appear that the beads that were more efficiently tabletted were not of good quality. As the authors provide neither photographs of the beads nor determinations of sphericity, however, this claim cannot be made with certainty.

Using a mixture of 10% Theophylline and 90% Avicel© PH 101 as the solids component, Millili and Schwartz (1990) studied the effect of the ethanol content of the granulating fluid on the properties of the prepared beads and of the tablets compacted from them. Beads could be formed when 95% ethanol served as the granulating fluid but not when absolute ethanol was used. With a series of ethanolic solutions, the beads were found to be stronger and harder as the mole fraction of water increased. When compacted at 3000 pounds force, the 95% ethanol-processed beads formed tablets with a breaking strength greater than 16kg, whereas the water-processed beads formed compacts which registered 0kg on the breaking strength apparatus. To obtain

compacts of equivalent hardness (5.5kg), 5000 pounds of force had to be applied to the water-processed beads, while for the 95% ethanol-processed beads 600 pounds sufficed. The dissolution rates of the tablets prepared from the 95% ethanol-granulated beads decreased with increasing compression force, whereas the tablets compressed from the water-processed beads, irrespective of compression force, released the drug at the same rate as the uncompacted beads.

These differences were explained in terms of the differing strengths of the various beads. The porosity of the water-processed beads was 14% while that of the 95% ethanol-processed beads was 54%. Water formed well-shaped, strong beads which did not shatter under compression forces. The alcohol-processed beads had a weaker internal structure with a greater porosity and fractured easily under compression, exposing a greater surface area for bonding with other particles. Hence, strong tablets were formed in the latter case. The ethanol-processed beads were more friable (up to 60% friability, for the beads processed with 95% ethanol) and had a poor shape.

The examples quoted indicate that extrusion and spheronization does not allow the easy preparation of compactible, high quality beads, with the desired spherical shape. The production of tablets from sustained release pellets manufactured by this technique is certainly not common. The ideal would be to compress non-coated sustained release beads into tablets which disintegrate into the constituent particles when immersed into aqueous liquids. Such a tablet would be able to accommodate a larger amount of the drug than is possible in the largest capsule that can comfortably be swallowed. By decreasing the surface area in contact with the dissolution fluids (until disintegration occurs), the tablet also decreases the potential for a burst

effect. Once the tablet disintegrates, the benefits of a multiparticulate system are provided. There do not appear to be any reports of this type of preparation in the literature. Vervaet et al., (1995) implied that Sandberg et al. (1988) prepared Metoprolol beads by extrusion and spheronization and compressed the coated beads into sustained release tablets. The original publication describes a bioavailability study of the drug from tablets prepared from coated beads and granules of other excipients, but it does not reveal whether or not the beads were produced by extrusion and spheronization.

As previously mentioned, the fact that spherical particles can easily be produced by extrusion and spheronization, in general, makes this technique attractive for the production of material for tablets but, as has been seen in the work described above, tablets are not easily formed from beads of high quality. The compaction of friable, poorly-shaped beads defeats the purpose of using beads for tabletting.

CHAPTER 3: SUSTAINED RELEASE BY THE USE OF BINDERS

3.1 INTRODUCTION

In pharmaceutical processing, binders are used to hold powders together to form a cohesive mass. During granulation, for example, binders provide the cohesiveness needed to form the granules. Material to be processed by extrusion and spheronization is required to be both cohesive, as well as plastic. The combination of these properties ensures that the wet mass forms narrow cylinders during extrusion, instead of breaking up or powdering. The wet extrudate must also be sufficiently plastic to round up into balls of almost spherical shape during spheronization. Microcrystalline cellulose and lactose usually provide the required plasticity. The binder also often contributes to the plasticity, in addition to providing cohesion.

Excessive use of binders may retard the release of drugs from prompt release solid dosage forms, in which case the effect is regarded as negative. Conversely, large amounts of strong binders may be used intentionally to achieve a sustained release effect. Solutions of shellac, waxes, fatty acids and alcohols, and various synthetic polymers have been used in sustained release tablets (Bandelin, 1989). Bianchini et al. (1992) were able to sustain the release of a low concentration (0.25%) of d-Indobufen, from uncoated sustained release beads, for 4 to 5 hours by using a combination of a pH modifier and a polymeric dispersion (Aquacoat© or Eudragit©).

The present work is directed towards obtaining a sustained release effect with amounts of drug that are more realistic. However, it is not just a matter of adding increasing amounts of binder to a formulation for extrusion and spheronization until a sufficiently slow release is obtained because the binder also alters the physical properties of the material. This may have a negative effect on the final product since the physical properties of the wet mass, especially its visco-elasticity, must fall within a narrow range for successful extrusion and spheronization.

While a plasticizer is necessary for successful processing, an excess can be detrimental to the formulation. The overplasticized material is characterised by the formation of extremely long strands upon extrusion whereas, for optimal processing, the strands must easily subdivide into shorter lengths, even as they fall from the extruder. These pieces subdivide further within the spheronizer, forming short rods which ultimately round up to form good spheres. In the case of the overplasticized material, very long strands are transferred to the spheronizer. Such strands can easily attain a length of 40 to 50cm and, since they divide into shorter lengths with difficulty, larger spheres will be formed initially. These wet spheres tend to agglomerate into increasingly larger spheres, the longer spheronization is continued. In extreme cases, one large ball is formed of the entire mass of material within the spheronizer. Hence, the binder must be carefully chosen and used in amounts that sustain the release of the drug, without greatly affecting the physical properties of the wet material.

In initial work, several commonly used binders were utilized. These included sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, Aquacoat© and Eudragit© NE30D. Aquacoat© appeared to increase the rate of drug release, while some degree

of retardation was achieved with a combination of Eudragit© RS powder and Eudragit© NE30D. Since the latter experiment formed part of a series of experiments with Eudragit© powders, it will be described in Chapter 5, in the context of matrix formulations. With the other binders mentioned, inclusion of a very small amount of binder improved the physical quality of the beads and the ease of spheronization. Amounts of the order of 1% of the dry mass of the beads were used in the form of aqueous solutions. Larger amounts, which may have been able to retard drug release, either caused the material to become so tacky that further processing was not possible, or resulted in agglomeration of the beads within the spheronizer.

For equivalent concentrations, ethanolic solutions of ethylcellulose are much less tacky, and display more potent retardant properties, than the other binders mentioned. As a result, much less of the solution is needed. Hence, ethylcellulose causes minimal disturbance of the very sensitive physical properties of material for extrusion and spheronization and, in this sense, displays exceptional behaviour.

3.2 FORMULATIONS USING ETHYLCELLULOSE AS BINDER

Ethylcellulose has been used as one component of a retardant mixture in matrix tablets. For example, Fassihi et al. (1986) melted together various retardants (including carnauba wax and ethylcellulose) and incorporated the drug, Theophylline, into the melt. The melt was then solidified and ground before tabletting. Ethylcellulose has also been successfully used in direct compression tabletting for sustained release (Pather et al., 1993 and Upadrashta et al., 1993). In addition, it has been extensively used for the sustained release coating of tablets (Seitz et al., 1986) and of beads (Lee and Robinson, 1978). In view of these successes, it was decided to use

an ethanolic solution of ethylcellulose as a binder/retardant, in beads, in the present work. Using Theophylline as a model drug at the usual adult dosage level of 300mg, the formulations described below were prepared.

3.2.1 Method

The basic formulation consisted of 250g of each of Theophylline (Sigma) and Avicel© PH 101 (FMC Corporation); variable amounts of ethylcellulose (10 cP viscosity grade) (Dow Chemical Company) added as an ethanolic solution; and polyvinylpyrrolidone (K30 viscosity grade) (Sigma). The beads were prepared according to the formulae given in Table 3.1.

TABLE 3.1: FORMULAE CONTAINING ETHYLCELLULOSE IN ETHANOL AS BINDER/RETARDANT

	3.1	3.2	3.2.2	3.3
Theophylline	250g	250g	250g	250g
Avicel© PH 101	250g	250g	250g	250g
Ethylcellulose in ethanol	200ml of 10% soln.	50ml of 10% soln.	50ml of 10% soln.	50ml of 15% soln.
Ethylcellulose equivalent*	20g	5g	5g	7.5g
Additional ethanol	-	-	150 ml	-
5% polyvinylpyrrolidone in water	50ml	50ml	50ml	75ml

*The amount of ethylcellulose in the ethanolic solution used.

The ethylcellulose solution was mixed with the Theophylline in a planetary mixer (Hobart) for 5 minutes. The wet mass was then transferred to an open container and left to stand, uncovered, for 20 minutes in order to allow partial evaporation of the ethanol. The material was mixed

occasionally with a spatula. Using the planetary mixer, the Avicel© was mixed with the polyvinylpyrrolidone solution and some water. The mixing bowl was then covered to reduce loss of moisture, while waiting for the Theophylline to partially dry. The damp Theophylline was gradually added to the wet Avicel©, in the planetary mixer, and mixed until homogeneous. More water was added, as required, until the mixture had the correct consistency for extrusion and spheronization.

The material was passed through an extruder (EXDS-60, LUWA Corporation), fitted with a screen with 1.5mm apertures and operated at 50 rpm. The damp extrudate was transferred to a spheronizer (Q400 Marumerizer, LUWA Corporation). At a speed of approximately 650 rpm, the material was spheronized for 2 minutes. The beads were allowed to air-dry for 1 hour and were then dried in an oven at 40° overnight before separation into different size fractions by sieving. The 1.4/0.710mm size fraction was used for further study. For each formulation, 6 size 0 elongated capsules were filled with an amount of beads equivalent to 300mg of Theophylline and a dissolution test was performed in deionised water using the paddle method at 50rpm or, in the case of Formula 3.1, the basket method at 100rpm. The dissolution samples were assayed by UV spectrophotometry at 272nm.

3.2.2 Results

The dissolution results are shown in Figure 3.1. Initially, the dissolution of Formula 3.1 beads was attempted using the same conditions as in the other dissolution tests (the paddle method at 50rpm). It was found that the beads floated in the dissolution flasks and that the initial drug release was very slow and variable. This was thought to be due to the method of dissolution testing and the experiment was, thus, discontinued. The test was repeated, using the basket

method in which, it was thought, there would be better contact between the beads and the dissolution medium. However, the beads were observed to rise to the upper part of each basket where they touched the solid metal disc of the shaft. Although contact with the dissolution medium was not very good, even with this method, it was judged to be better than it was with the paddle method. The hydrophobic nature of ethylcellulose causes it to resist contact with water. This is the reason for the floating, and the rising, of the beads during dissolution testing by the paddle method and the basket method, respectively.

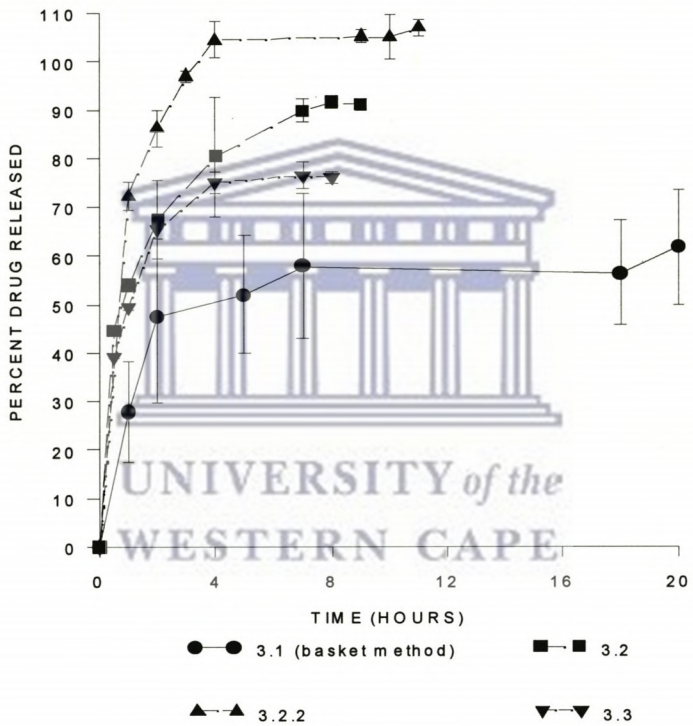


FIGURE 3.1: DISSOLUTION OF BEADS CONTAINING ETHYLCELLULOSE

The rate of drug release from Formula 3.1 beads was much slower than it was from Formula 3.2, reflecting the much larger amount of ethylcellulose in the first formulation (20g compared to 5g). Drug release from Formula 3.1 was also more erratic as shown by the larger standard deviation

values. The rate of dissolution from Formula 3.2 was only slightly faster than that from Formula 3.3 for the first 4 hours, in spite of the latter containing more ethylcellulose. Thereafter, Formula 3.2 continued to release the drug, whereas the amount of drug released from Formula 3.3 remained almost constant. The larger the amount of ethylcellulose in these formulations, the slower, and less complete, was the dissolution.

All formulations showed an initial burst effect and, with the exception of Formula 3.2.2, they also showed incomplete release. It is suggested that some of the crystals were largely exposed (not covered by ethylcellulose) and that these crystals released the drug very rapidly, resulting in the burst effect. On the other hand, some of the Theophylline particles were probably so deeply embedded in ethylcellulose that they could not be reached by the penetrating dissolution medium, resulting in incomplete release of the drug. These situations are depicted in Figure 3.2.

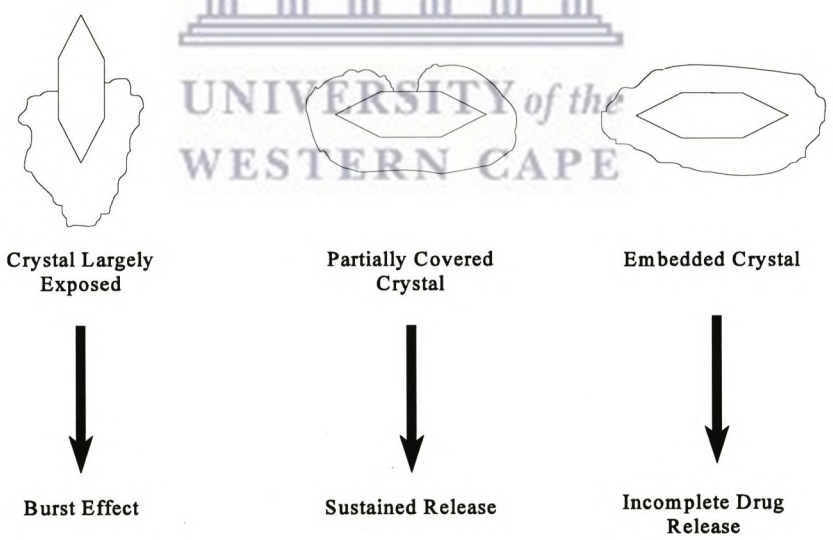


FIGURE 3.2: EFFECT OF DIFFERENT EXTENTS OF ETHYLCELLULOSE COVERAGE OF THEOPHYLLINE CRYSTALS

While it is recognised that the basket method should, strictly speaking, not be compared with the paddle method, the differences between the formulations were so large that it is possible to make observations regarding the general trend. Hanson (1982) found that for Theophylline tablets, the basket method at 100rpm was equivalent to the paddle method at 50rpm.

Formula 3.2.2 beads contained the same amount of ethylcellulose as Formula 3.2 beads. However, the release of the drug was much faster and more complete from the former preparation. This could be explained in terms of the volume of ethanol used. The larger volume resulted in the Theophylline powder containing far more ethanol at the end of the standard evaporation time of 20 minutes. Hence, when the wet Theophylline was added to the moist Avicel©, the ethylcellulose solution could spread, to a greater extent, over the Avicel© particles. Consequently, a thinner coat of ethylcellulose formed over the Theophylline crystals. The presence of ethylcellulose over the Avicel© particles increases its hydrophobicity and thus contributes to the sustained release effect. However, in those formulations which contain the smaller amount of ethanol, such as Formula 3.2, a thick coating of the polymer will be formed over the Theophylline crystals and it is the presence of this more substantial layer over the drug particles that has the major impact on the sustained release properties of the preparation.

In the case of the less wet Theophylline in the other formulations of this section, the following is postulated: when the Theophylline crystals (covered in a layer of ethanolic ethylcellulose solution) contact the moist Avicel© particles, the polymer precipitates because ethylcellulose is insoluble in water. The ethylcellulose solution, hence, does not spread much over the Avicel© particles, but precipitates around the Theophylline crystals instead. This suggested mechanism

is substantiated by the observation of the behaviour of a drop of ethanolic ethylcellulose solution placed on the surface of water in a beaker. The solutions do not mix, but the ethylcellulose forms a film on the surface of the water. In general terms, this mechanism is applicable also to Formula 3.2.2, but, in this case, the larger amount of ethanolic solution present on the Theophylline at the time of mixing with Avicel, allows it to spread to a greater extent before precipitation.

The ability of the larger amount of ethanol in this formulation to dissolve more Theophylline does not exert a major influence on the rate of drug release, since Theophylline is only soluble to the extent of 1 in 80 in ethanol (Reynolds, 1982). Calculations show that less than 1% of additional drug would have dissolved in the extra 150ml of ethanol used in this preparation.

3.3 EFFECT OF HEAT TREATMENT OF BEADS

In the previous section, it was proposed that poor coverage of the Theophylline crystals by ethylcellulose, within the beads, led to faster dissolution. An attempt was, therefore, made to improve the coverage of the Theophylline crystals by heating the beads to the melting point of ethylcellulose. It was thought that this would allow the ethylcellulose to spread over the Theophylline crystals to a greater extent.

3.3.1 Method

Approximately 5g of Formula 3.2 beads were spread as a thin layer on a disposable aluminium pan which was then heated for 4 hours at 130°. This temperature is marginally above the melting point of ethylcellulose (128°-129°) (Dow Chemical Company, 1993). After cooling, amounts of

beads equivalent to 300mg of Theophylline were filled into capsules which were subjected to dissolution tests in deionized water, using the paddle method at 50rpm.

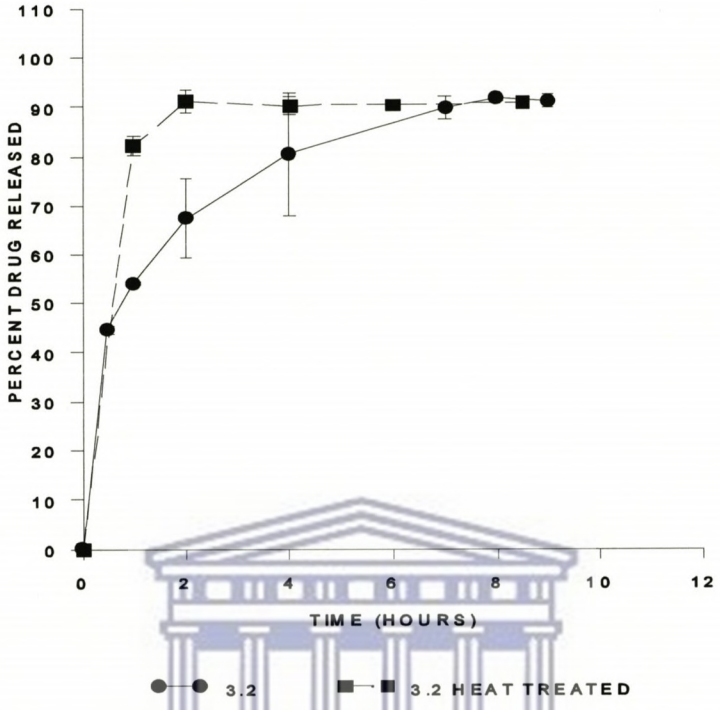
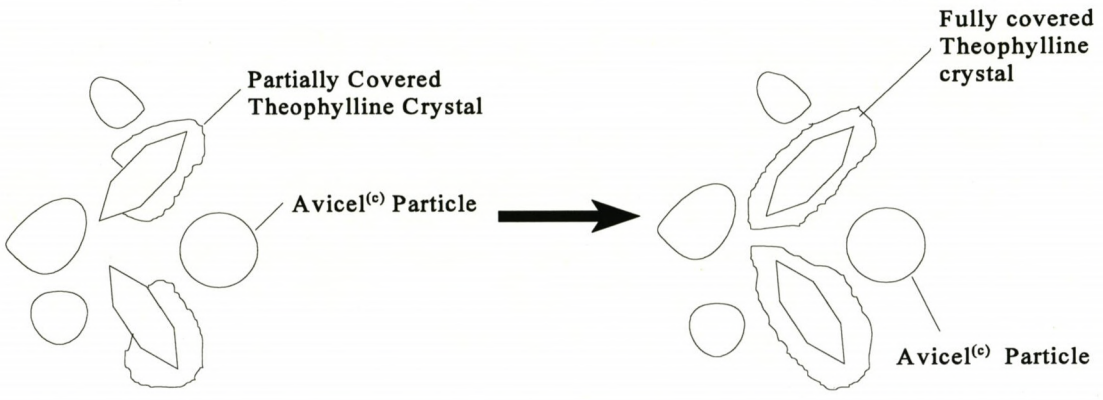


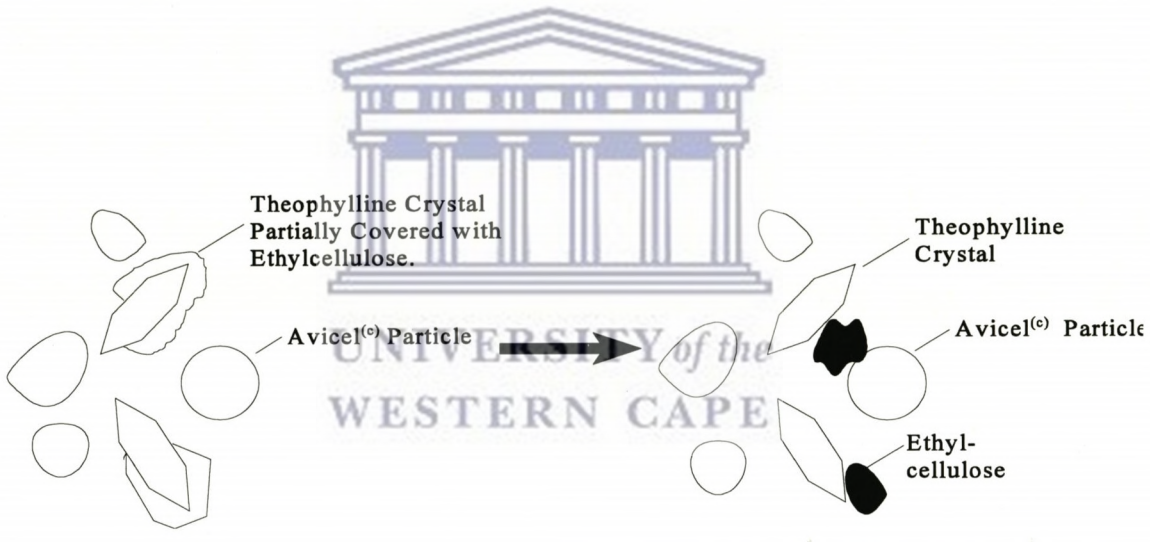
FIGURE 3.3: EFFECT OF HEAT TREATMENT ON DISSOLUTION RATE OF BEADS CONTAINING ETHYLCELLULOSE

3.3.2 Results and Discussion

The results of the dissolution test are shown in Figure 3.3 which also reflects the dissolution profile of untreated beads, for comparison. Contrary to what was expected, the heat-treated beads released the drug faster that the untreated beads. In an attempt to explain these results, it was postulated that the heat treatment caused melting of the ethylcellulose which settled largely in the interstices between particles, within the beads, instead of spreading over the Theophylline crystals as expected. This effect is illustrated diagrammatically in Figure 3.4(b), whereas Figure 3.4(a) shows the effect that was desired.



(a) Desired Effect



(b) Effect that Probably Occurred

FIGURE 3.4: DIAGRAMMATIC REPRESENTATION OF CHANGES IN ETHYLCELLULOSE DISPOSITION DUE TO HEAT TREATMENT

3.4 ETHYLCELLULOSE MODIFIED WITH A HYDROPHILIC AGENT

In view of the very slow, erratic and incomplete drug release obtained from beads containing higher amounts of ethylcellulose as binder, an attempt was made to modify this binder by the addition of a hydrophilic agent. In coating technology, ethylcellulose solutions are frequently modified in this way. In an aqueous environment, the hydrophilic material dissolves rapidly, creating pores for the entry of water through the impervious ethylcellulose coating (Lee and Robinson, 1978).

The concept of using a small amount of a hydrophilic material with a hydrophobic retardant has also been used in matrix tablet technology. In the fabrication of hydrophobic matrix tablets, a common problem is the incomplete release of the active ingredient due to it being so deeply embedded in the retardant, within the tablet, that the dissolution medium cannot reach it. To reduce this effect, a small amount of a hydrophilic channelling agent is included in the formulation. By rapidly dissolving and creating liquid-entry channels in the matrix, the channelling agent improves the penetration of the dissolution medium through the tablet. Dakkuri et al. (1978) used polyvinylpyrrolidone as the channelling agent in wax matrix tablets.

3.4.1 Method

The medium viscosity grade of hydroxypropylcellulose (Klucel MF, Aqualon) was used as the hydrophilic material. This polymer is soluble in ethanol, and ethylcellulose and hydroxypropylcellulose can, therefore, be dissolved in a common solvent. Triethylcitrate (Morflex Inc) served as the plasticizer. The beads were prepared according to the formulae given in Table 3.2.

TABLE 3.2: FORMULAE OF CONTROL BEADS AND BEADS PREPARED WITH MODIFIED ETHYLCELLULOSE SOLUTION

	FORMULA 3.23	FORMULA 3.24
Theophylline (g)	250	250
Avicel PH 101 (g)	235	235
Retardant solution (ml)	100	
15% Hydroxypropylcellulose solution (ml)		100

The retardant solution consisted of the following:

Ethylcellulose 10 cP	12.50g
Hydroxypropylcellulose (MF)	1.25g
Triethylcitrate	1.25g
Ethanol (95%)	to 100ml

In the control (Formula 3.24), the retardant solution was replaced with 15g of hydroxypropylcellulose in 100ml of ethanol. The formulations were otherwise the same and were prepared in a similar fashion. The Avicel© was mixed with 200ml of water and transferred to a container which was covered to reduce loss of moisture. The Theophylline was mixed with the retardant solution (or with the hydroxypropylcellulose solution, in the case of the control) in the tared vessel of the planetary mixer and mixing continued until the mass of the remaining alcohol was 60g. The moist Avicel© was then slowly added to the Theophylline/retardant mixture, with continued mixing. Further water was added until the mixture had the correct consistency for extrusion and spheronization, which was performed as described before. The beads were subjected to dissolution tests as previously described.

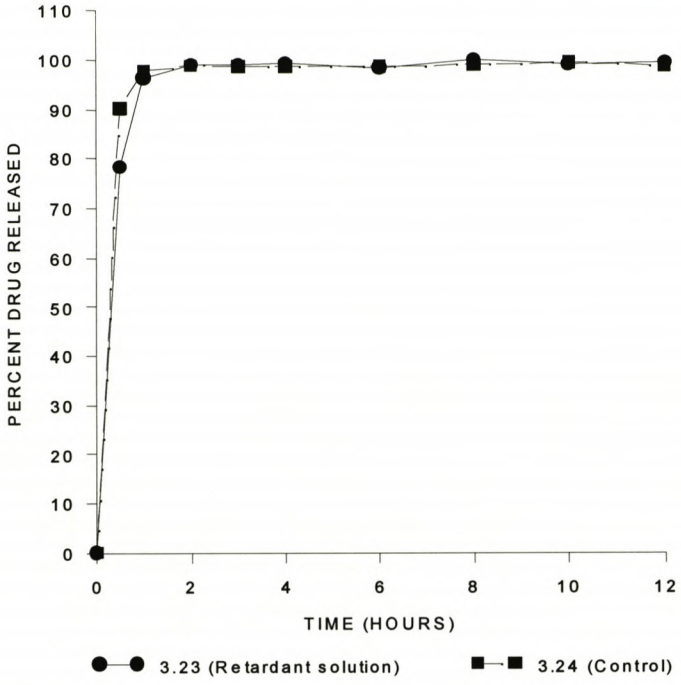


FIGURE 3.5: DISSOLUTION OF BEADS CONTAINING MODIFIED ETHYLCELLULOSE BINDER

3.4.2 Results and Discussion

The dissolution results are depicted in Figure 3.5. Dissolution from each of the formulations was rapid, with almost 100% of the drug being released after one hour. The test formulation and the control had almost identical dissolution patterns which reveals that the retardant mixture had practically no value in sustaining drug release. Triethylcitrate was included in the formulation in order to plasticize the wet mass, enabling it to be extruded more easily and uniformly and to allow efficient sphere formation. However, it is a soluble material and probably contributed to the rapid rate of dissolution. The amount of hydroxypropylcellulose included in the formulation constituted 10% of the mass of the ethylcellulose. In combination with the 10% of triethylcitrate, the coating formula contained soluble material to the extent of 20% of the mass of ethylcellulose. These materials probably dissolved rapidly when the beads were placed in the dissolution medium. The channels, thus created, allowed such rapid release of the drug that the

release profile was indistinguishable from that of the control. The presence of soluble material mixed with the ethylcellulose appears to hasten dissolution tremendously in this type of formulation.

3.5 CONCLUSIONS

It is possible to retard the release of Theophylline to some extent by the use of ethanolic solutions of ethylcellulose in bead formulations. In the case of Formula 3.2 beads, the release was sustained for approximately 4 hours, although there was a burst effect. From the perspective of sustained release technology, Theophylline is a fairly soluble drug (1 in 120) (Reynolds, 1982) and it is also required in a large dose (300mg for an adult). It is possible that the techniques described in this chapter will sustain the release of a less soluble drug to a greater extent, particularly if the drug has a smaller dose.

Increasing the amount of ethylcellulose in the formulation, did not improve the sustained release effect to a great extent: although drug release was slower, it also became less complete and more erratic, and the burst effect was still evident. Hence, there is a limit to the amount of ethylcellulose that may be added. Larger amounts of ethanol, added in the hope of obtaining more complete coverage, resulted in thinner coats of ethylcellulose over the Theophylline crystals. This increased the rate of drug release. Heat treatment of the beads, also attempted with the objective of getting more complete coating, led to a faster rate of drug release, possibly due to the removal of the ethylcellulose from its positions around the Theophylline crystals. The addition of a hydrophilic agent to the ethylcellulose solution resulted in a loss of the sustained

release properties. This effect may have been exacerbated by the use of too much of the soluble additive.

Small amounts of ethanol (of the order of 50ml), used with a 500g batch of material, do not adversely affect the physical quality of the beads. For instance, the shape does not deteriorate. With larger amounts of ethanol, the beads tend to have a poor shape. This effect is due to the lower surface tension of alcohol, as compared to water, and the consequent lack of strength of the beads. This effect has been comprehensively explained by Millili and Schwartz (1990) as well as by Sastry and Fuerstenau (1973).

CHAPTER 4: INDOMETHACIN FORMULATIONS

4.1 INTRODUCTION

Although ethanolic solutions of ethylcellulose retarded the release of Theophylline to some extent, the work described in Chapter 3 indicated that it was not easy to sustain the release of this drug by means of binders. Since Theophylline is soluble to the extent of 1 in 120 (Reynolds, 1982) and is required in a high dose (300mg), it is difficult to formulate beads from which the release of the drug is adequately sustained. Hence, it was considered appropriate to work with a poorly soluble drug that was not required in a large dose. The successful production of uncoated sustained release beads containing such a drug might indicate the way to formulate other drugs which do not lend themselves as readily to sustained release formulations. Also, other mechanisms to sustain the release of the drug, apart from the use of strong binders, should be considered. Since Indomethacin is practically insoluble (Reynolds, 1982) and sustained release formulations of this product contain only 75mg of the drug, it was considered ideal for the purpose indicated above.

4.2 THE INTERACTION OF INDOMETHACIN AND POLYVINYLPYRROLIDONE

Initial studies indicated the need for a binder/plasticizer in the beads. The function of such an ingredient was to hold the mass of powders together and to make it more plastic, thus enabling better formation of the spheres. The use of a binder/plasticizer in this context must be distinguished from the use of excess binder, described in the previous chapter. The excess binder's function was to serve as a sustained release mechanism whereas the binder/plasticizer described here simply confers

better physical characteristics on the wet mass, enabling easier and more efficient processing. It was decided to use polyvinylpyrrolidone for this purpose. While this polymer creates a good plastic mass, it also leads to greater tackiness of the wet material. In general, the relative potential of different grades of a particular polymer to create tackiness depends on the molecular masses of these grades (Millilli and Schwartz, 1990). These authors reported experimental evidence to support their postulate that it is the chains of polymer extending from one bead into the next that cause tackiness. For equal masses, the higher molecular mass grade has fewer individual chains of the polymer and, hence, fewer ends are available to extend from one bead into the next. Therefore, this grade causes less tackiness. Where a plasticizer was deemed necessary, polyvinylpyrrolidone K90 (Sigma), a high (360 000) molecular mass grade, was used.

4.2.1 Method

The formulae of the beads manufactured in this section are listed in Table 4.1. The only difference between the formulations, is the presence, or the absence, of polyvinylpyrrolidone. The Indomethacin (donated by Zenith Pharmaceuticals), lactose and Avicel© PH 101 were premixed in a planetary mixer for 3 minutes. The polyvinylpyrrolidone solution (when used) and sufficient water were added slowly with mixing. Mixing was continued for a further 7 minutes, giving a total mixing time of 10 minutes. The mixer was stopped occasionally and the damp material was scraped from the sides of the mixing bowl, using a spatula. Since the added polyvinylpyrrolidone solution contained 3g of solute, each formulation had a total mass of 500g of solids. The amount of water added was determined by subjective judgement of the consistency of the material.

TABLE 4.1: FORMULAE OF BEADS USED TO ILLUSTRATE THE EFFECT OF POLYVINYLPYRROLIDONE

	FORMULA 7.7	FORMULA 7.8
Indomethacin (g)	75	75
Lactose (g)	150	150
Avicel© PH 101 (g)	272	275
5% polyvinylpyrrolidone K90 solution (ml)	60	

The moist material was extruded and the extrudate spheronized at approximately 650rpm. Drying of the beads was followed by separation into different size fractions, as previously described. The 1.7/1.4mm size fraction was filled into size 0 (elongated) gelatin capsules which were subjected to dissolution testing according to the 3rd method described in the USP (23rd edition) for sustained release Indomethacin products. A medium having a pH of 6.2 and use of the baskets at 75rpm is prescribed. However, 900ml of dissolution medium was used instead of the 750ml mentioned in the USP. Since the drug is insoluble in acid, it is not necessary to perform a dissolution test in an acidic medium.

4.2.2 Results and Discussion

Formula 7.7 material extruded more easily and appeared to form beads that were more spherical. The dissolution results for both formulae are presented in Figure 4.1. The curves show that dissolution was very slow from both preparations. This was entirely unexpected since no sustained release mechanism was included and these formulations were, in fact, intended as standards for comparison with other sustained release formulations that were to be developed. While one of the

aims was to quantify the difference in dissolution rates between the two formulations, due to the presence of polyvinylpyrrolidone in Formula 7.7, this difference was expected to be negligible.

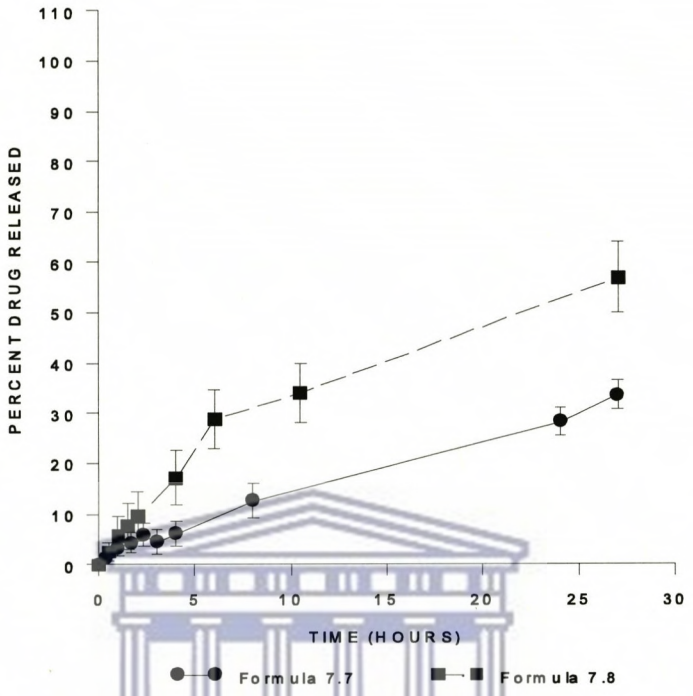


FIGURE 4.1: EFFECT OF POLYVINYLPYRROLIDONE ON THE DISSOLUTION OF INDOMETHACIN BEADS

The drug release after 27 hours from Formula 7.7 was 33.62% while that from Formula 7.8 was 56.96%. The former formulation released only approximately 60% of the amount of drug that the latter released over the same period. The observed effect is therefore large, considering that only 3g of polyvinylpyrrolidone was included in the formulation (0.6% of the dry mass).

In this section (4.2), attention will be focussed on the reasons for the large difference in dissolution rates between the preparations with, and without, polyvinylpyrrolidone and no explanation will be

offered for the slow release obtained from the beads which did not contain this polymer. The remainder of this chapter is devoted to (a) attempting to provide an explanation for the slow release of Indomethacin from beads which do not have an obvious sustained release mechanism, and (b) a description of attempts to develop an Indomethacin preparation having a 24 hour release profile suitable for use of the product as a once-a-day dosage form.

4.2.3 Possible Reasons for the Effect of Polyvinylpyrrolidone

Since polyvinylpyrrolidone unexpectedly decreased the rate of release of the drug to a large extent, the possible reasons for this effect were investigated. The pH of a 5% polyvinylpyrrolidone solution was determined and found to be 4.97. This could, possibly, have an influence on the dissolution rate of the drug as described below. The pH of the dissolution medium was 6.2 upon preparation and after a dissolution run it was found to be the same. Thus no component of the beads, including the polyvinylpyrrolidone, had altered the pH of the dissolution fluid measurably. This is in keeping with the very low polyvinylpyrrolidone content of the beads and, also, the fact that the dissolution medium possessed a buffer capacity. The pH of a suspension of Avicel© PH 101 is approximately 7 (Reynolds, 1982).

Although there was no appreciable change in the pH of the dissolution medium, the micro-environment within the beads could, nevertheless, have been altered. The matrix has narrow pores through which water enters, and by means of which drug solution leaves, the bead. The rate of movement of liquids through these pores is slow and if the bead contains soluble material, such material does not readily diffuse out of the bead to mix with the bulk dissolution medium. Hence,

a relatively small amount of the soluble species will have a greater influence than expected. This influence can be explained in terms of the effect that the substance has on the pH of the internal environment of the bead.

A possible interaction between Indomethacin and polyvinylpyrrolidone was considered as the major reason for the decrease in the dissolution rate of this drug and, therefore, examples of similar interactions were sought in the literature. In a study of the interaction of polyvinylpyrrolidone and aromatic compounds, it was found that complexation was possible (Plaizier-Vercammen and De Neve, 1981 and 1982). In a series of substituted benzoic acid and nicotinic acid derivatives, it was found that lipophilicity and hydrogen bonding played a predominant role (Plaizier-Vercammen and De Neve, 1981). A solid state interaction of Bromazepam and polyvinylpyrrolidone was observed by Fassihi and Persicaner (1987). Upon storage of the mixed powders, Bromazepam was deposited as surface grains on the polyvinylpyrrolidone particles. This resulted in incomplete dissolution. The binding, which followed the Freundlich isotherm, depended on the presence of moisture.

Polyvinylpyrrolidone was also found to inhibit the absorption of Acetaminophen in rats (Sekikawa et al., 1979). This was attributed to a chemical interaction between these compounds. Hilton and Summers (1986) found slower absorption of Indomethacin from polyvinylpyrrolidone-containing suspensions in rats. While they recognised the ability of Indomethacin and polyvinylpyrrolidone to complex, they did not attribute the slower absorption to a complexation reaction but to an increase in the viscosity of the diffusion layer around each Indomethacin particle. They found this

effect to be much greater *in vivo* than it was *in vitro* and attributed the difference to the lesser dilution of the polyvinylpyrrolidone in the smaller volume of liquid in the stomach of the rat.

This physical interaction could partly explain the retardation of drug release by polyvinylpyrrolidone in the present work. In the confined space within the bead, the polyvinylpyrrolidone could have decreased the dissolution rate by increasing the viscosity of the diffusion layer around the drug particles, as proposed by Hilton and Summers (1986). This effect is analogous to the modification of the microenvironment pH within a bead, or tablet, to alter the rate of drug release. If alteration of the pH (as suggested at the beginning of this section), and viscosity, of the microenvironment within the beads are proposed as the reasons for the retardation of drug release, the question of the length of time that this effect would last must be raised. Even slow penetration of water into and out of the bead must dissolve the polyvinylpyrrolidone, itself, within a reasonable time. Hence, on the basis of these reasons it is unlikely that the retard effect would persist for 27 hours. The prolonged retardation of drug release may be explained in terms of the influence of the fine, Indomethacin particles on the hydrophobicity of the interior of the bead. This effect would further retard the entry of water into the bead, decreasing the rate of diffusion of soluble material out of the bead and, hence, the effect of polyvinylpyrrolidone would be experienced for a prolonged time. It is suggested that polyvinylpyrrolidone and Indomethacin mutually influence the dissolution of each other.

In conclusion, it is probable that an alteration of both the pH and the viscosity of the microenvironment, due to the presence of polyvinylpyrrolidone, affected the rate of drug release and that the hydrophobicity of Indomethacin prolonged this effect. The contribution of the chemical

interaction, between Indomethacin and polyvinylpyrrolidone, to the extremely slow release of the drug cannot be ruled out. The effects of polyvinylpyrrolidone on the dissolution rate of Indomethacin from beads needs further investigation. This aspect could not be included here since the primary aim of this study is the investigation of a range of techniques to confer sustained release properties on uncoated beads prepared by extrusion and spheronization. Since the release of the drug was slower than required even without the polyvinylpyrrolidone, the latter was omitted from subsequent formulations in spite of the improvements in the processing, and in the quality, of the beads that it appeared to confer.

4.3 THE PRODUCTION OF ERODING BEADS

Since the dissolution profiles depicted in the previous section were too slow for once-a-day preparations, attempts were made to increase the dissolution rate. One approach is to include an agent that causes erosion of the bead surface. Erosion, or "surface erosion" as it is sometimes called, is the phenomenon whereby particles lose their bonding and slowly come off the surface of a solid dosage form when the dosage form is placed into an aqueous medium. Erosion is similar to disintegration but is distinguished from it by the fact that the former process occurs only from the surface of the dosage form. The slow removal of the surface layers exposes the underlying layers of the solid dosage form to the dissolution medium. Silicon dioxide is an agent causing erosion, when used in low concentrations, and the formulations that follow were prepared in an attempt to utilize this property to hasten the dissolution rate of Indomethacin beads.

4.3.1 Method

The formulae detailed in Table 4.2 were prepared. The formulations varied only by the amount of silicon dioxide (Cab-O-Sil M5, Cabot Corporation) that was included . The powders were premixed in a planetary mixer for 3 minutes. Water was then gradually added and mixing continued for a further 7 minutes. The wet mass was extruded and the extrudate transferred to the spheronizer where the material was processed for 15 minutes at 650rpm. The beads were dried and sieved as previously described and dissolution tests were performed as before.

TABLE 4.2: FORMULAE OF ERODIBLE BEADS

	7.12	7.13	7.14A
Indomethacin (g)	250	250	250
Avicel© PH 101 (g)	250	235	220
Silicon dioxide (g)		15	30

4.3.2 Results and Discussion

The inclusion of silicon dioxide in the formulae tended to make the wet mass less firm, as observed by squeezing a ball of the material between the fingers. Formula 7.13 material, which contained 3% silicon dioxide, was less firm that Formula 7.12 whereas the material from Formula 7.14A, which contained 6% silicon dioxide, was even softer. Upon spheronization, the extrudate from Formula 7.14A did not round into balls, but formed flat masses, which agglomerated with further spheronization. The formation of the flat masses and the tendency to agglomerate were the result, respectively, of the lack of strength, and of the increased tackiness, of the material. These qualities

are due to the presence of silicon dioxide. The material from Formula 7.14A, had to be discarded and the results that follow refer to the remaining formulations. The dissolution results are depicted in Figure 4.2. For comparison, the results obtained from a dissolution test of Indocin© capsules[1], the innovator's product, are included. The results show that there is a large difference in the dissolution rates of the two test formulations. Formulation 7.12 beads (which do not contain silicon dioxide) released 42% of the drug over 24 hours. The formulation containing silicon dioxide (Formulation 7.13) released 68% of the drug over the same period. Since these formulations are the same except for the presence of silicon dioxide in Formula 7.13, the difference in dissolution rates is attributable to silicon dioxide.

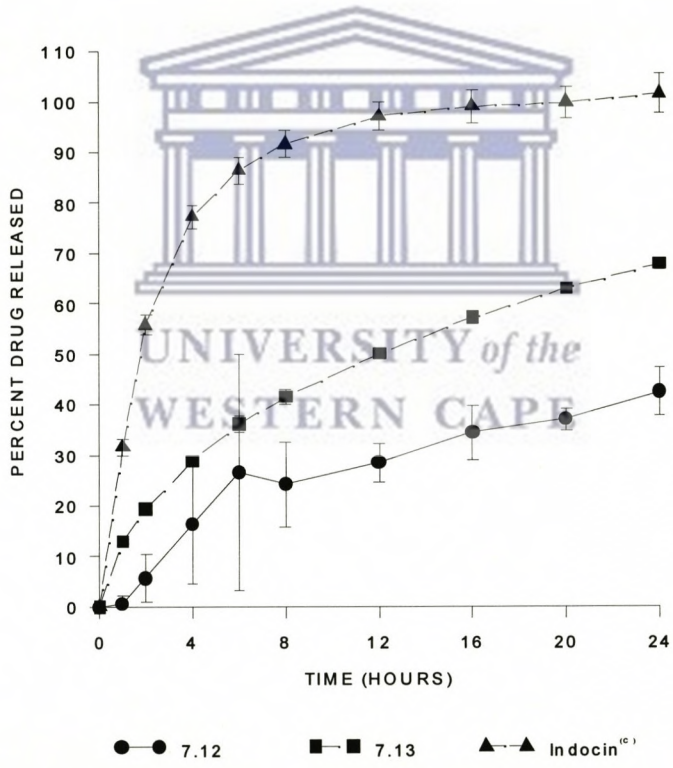


FIGURE 4.2: THE EFFECT OF EROSION ON THE DISSOLUTION OF INDOMETHACIN BEADS

[1] This product is known as "Indocid" in South Africa.

In general, drug release from matrices becomes progressively slower as the peripheral layers of the dosage form become depleted of drug and the dissolution medium has to penetrate into deeper layers to dissolve the remaining drug. This process gets progressively slower since liquid must travel through narrow, tortuous channels into, and out of, the dosage form. The outer most layers of the dosage form are removed when an agent causing erosion is used and the dissolution fluid has a shorter distance to travel before it reaches undissolved drug particles. Similarly, the drug solution has a shorter distance to diffuse out of the matrix and the overall effect is an increase in the rate of dissolution of the drug. The 3% silicon dioxide included in Formulation 7.13 increased the dissolution rate but this effect was not sufficient to release the drug at an adequate rate for use of the preparation as a once-a-day dosage form. The logical step was to add more of the silicon dioxide. With extrusion and spheronization, however, it is not a simple matter of adding more of the required ingredient. The physical properties of the wet mass are extremely sensitive to the effects of additional excipients and a slight change in the formulation may render it unsuitable for processing. Thus Formula 7.14A, which contained twice the amount of silicon dioxide, could not be processed.

When tested under the same conditions, the commercial product released 101% of the drug but the dissolution profile is not ideal. A large part of the dose (77%) is released in a short time (4 hours), with the remainder of the dose (23%) being released over 20 hours. This indicates the need for an improved sustained release product of Indomethacin.

4.4 THE PRODUCTION OF SWELLABLE BEADS

Since eroding beads did not produce sufficiently fast release and the rate of erosion could not be increased further by an increase in the level of silicon dioxide, it was decided to produce swellable beads in an attempt to hasten dissolution. Several authors, including Ghali et al. (1989b) and O'Connor and Schwartz (1985), have reported that the beads they produced swelled in the dissolution medium. A grade of Avicel© containing sodium carboxymethylcellulose was a common feature in these formulations. Sodium carboxymethylcellulose has a great capacity for water absorption, which causes it to swell. The swelling of the beads may be advantageous in the present work since it decreases the density of the beads and this is expected to be accompanied by an increase in the cross-sectional area of the pores. The latter would enhance the rate at which fluids moved through the beads and this, in turn, would increase the dissolution rate of the drug. For improving the rate of drug release from beads, this mechanism serves as an alternate approach to that of enhancing erosion.

4.4.1 Method

A series of formulations were developed, each containing 250g of Indomethacin and 250g of Avicel©. The Avicel© in each formulation contained varying amounts of the PH 101 grade and the RC 591 grade. The latter is a colloidal grade and contains sodium carboxymethylcellulose, whereas the former grade has particles approximately 50μm in diameter and does not contain the polymer. The varying amounts of Avicel© RC 591 would vary the content of sodium carboxymethylcellulose in the beads, and hence, the extent of swelling. The formulations listed in Table 4.3 were prepared

as before. Dissolution tests were conducted by the previously described methods but were performed in triplicate, as were the remaining dissolution tests in this chapter.

TABLE 4.3: FORMULAE OF SWELLABLE BEADS

	7.14	7.15	7.16
Indomethacin (g)	250	250	250
Avicel© PH 101 (g)	125	175	225
Avicel© RC 591 (g)	125	75	25
% RC 591 grade*	50	30	10

* expressed as a percentage of the total amount of Avicel© in the formulation

4.4.2 Results and Discussion

The dissolution profiles depicted in Figure 4.3 indicate that the rate of drug release was too slow for these preparations to be used as once-a-day dosage forms and that the inclusion of sodium carboxymethylcellulose is not effective in enhancing the rate of Indomethacin release from the beads. During the dissolution test the beads were observed to swell. This was particularly evident when the baskets were dismantled at the end of the dissolution run; the beads were soft and enlarged and were deformed upon handling. The lack of significant enhancement of the dissolution rate was, therefore, not due to a failure of the applied method to cause swelling of the beads but to a failure of the swelling mechanism to increase the dissolution rate.

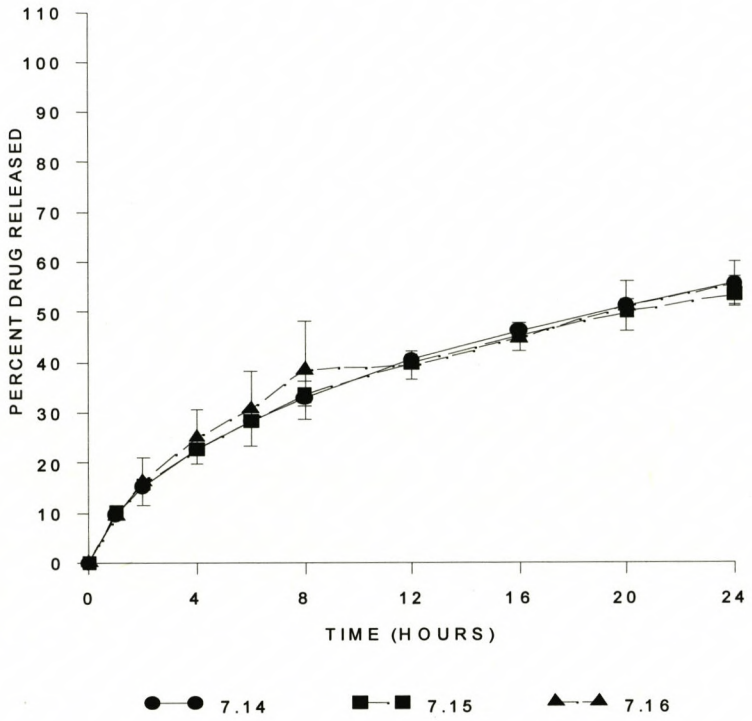


FIGURE 4.3: DISSOLUTION OF SWELLABLE BEADS

Allowing for experimental error, the three curves depicted in Figure 4.3 may be superimposed. Therefore, the amount of Avicel© RC 591 (and hence that of sodium carboxymethylcellulose) included in the formulation did not make a difference to the dissolution rate. This appears to indicate that the large amount of microcrystalline cellulose in the formulations (approximately 50%) controls the rate of drug release and that the level of sodium carboxymethylcellulose does not matter. The reason for the consistently higher standard deviation values displayed by Formula 7.16 could not be satisfactorily explained.

4.5 THE EFFECT OF VARYING THE AVICEL© CONCENTRATION

Since the work done in Section 4.4 appeared to indicate that the very slow rate of Indomethacin release could, possibly, have been due to the presence of a large amount of microcrystalline cellulose

in the formulations, it was decided to vary the amount of this spheronizing aid. The spheronzing aid would consist of equal parts of Avicel© PH 101 and Avicel© RC 591 (in order to maintain the ability of the beads to swell to some extent) but the total amount of Avicel© in the formulations would vary.

4.5.1 Method

The formulations described in Table 4.4 were prepared. Each formulation contained 50% Indomethacin and variable amounts of microcrystalline cellulose (in the form of equal parts of Avicel© PH 101 and Avicel©RC 591), the difference in mass being made up with lactose. The beads were prepared as previously described and dissolution tests were performed as before.

TABLE 4.4: FORMULAE OF BEADS CONTAINING VARIABLE AMOUNTS OF AVICEL©

	7.17	7.18	7.19	7.14
Indomethacin (g)	250	250	250	250
Avicel© PH 101 (g)	75	100	112.5	125
Avicel© RC 591 (g)	75	100	112.5	125
Proportion of Avicel© (%)	30	40	45	50
Lactose (g)	100	50	25	

4.5.2 Results and Discussion

The dissolution results, shown in Figure 4.4, indicate that none of the formulations released the drug at an adequate rate. The graphs also indicate that the variation in Avicel© concentration did not affect the rate of Indomethacin dissolution.

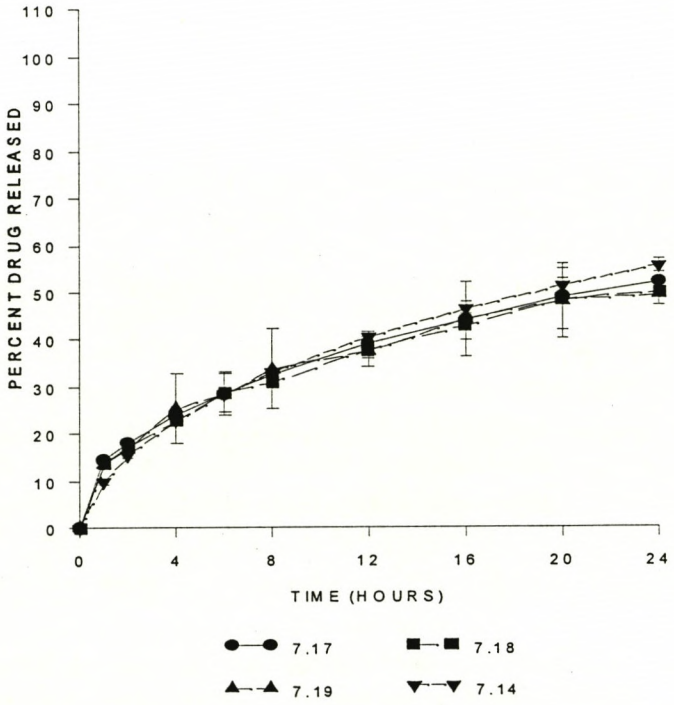


FIGURE 4.4: EFFECT OF AVICEL© CONCENTRATION ON INDOMETHACIN DISSOLUTION

In these formulations, the less the Avicel© concentration the greater is the concentration of lactose. Since lactose is very soluble, it was expected that the dissolution of this filler would create pores for the rapid entry of water, thus facilitating dissolution. However, an increase in the lactose concentration over the range 0% to 20% did not increase the dissolution rate. This could be due to one, or both, of the following reasons:

(a) the lactose did not dissolve to create the porosity that was expected; or

(b) that the porosity created after dissolution of lactose is not important in determining the rate of dissolution of the drug.

If the former were true, it means that the Indomethacin created such a hydrophobic environment within the beads that the lactose could not dissolve. The latter reason indicates the possibility of an interaction between Indomethacin and microcrystalline cellulose.

The rate of dissolution was also not affected by the variation in microcrystalline cellulose content, over the range 30% to 50%. If the proposed interaction did occur, Formula 7.17, which contained 30% Avicel©, probably had more microcrystalline cellulose than required for maximum interaction with the drug. Therefore, increases in the Avicel© level above this amount (as present in Formulae 7.18, 7.19, and 7.14) did not affect the retardant action. Using less than 30% Avicel©, while combining the 2 grades as done in this section, would probably have resulted in beads of poor quality. The dissolution rate, in general, is dependent to some extent on the quality of the beads: irregularly-shaped beads may have an increased surface area and a poor bead surface may have cracks or fissures which release the drug at a faster rate. While these factors would probably not have influenced the results if an interaction between microcrystalline cellulose and Indomethacin occurred, such variability had to be ruled out in properly planned experiments. It was, therefore, not considered reasonable to prepare beads with a lower concentration of the Avicel© mixture.

4.6 THE EFFECT OF DISINTEGRANTS

Since neither erosion of the beads, nor swelling, caused a large increase in the rate of drug release, the effects of disintegrants were examined. In general, if beads disintegrate completely, the greatly increased exposure to the dissolution medium would enhance the dissolution rate of the drug.

However, if an interaction occurred between Indomethacin and microcrystalline cellulose, the disintegration of the beads may only have a negligible effect on the rate of drug release.

Since Indomethacin is a hydrophobic substance, it is also possible that the drug created a hydrophobic interior to the bead which resisted the entry of water, i.e. the drug was its own retardant. Therefore, it was decided to use a low level of the drug with a high level of lactose, a very soluble ingredient. The inclusion of a large amount of lactose would be facilitated by the use of Avicel© RC 591, since this grade is required in lesser amounts than Avicel© PH 101. The former grade would also cause swelling of the beads. A soluble material and a swelling agent were included in these formulae (in spite of the results observed in the previous sections) because these ingredients may complement the action of the disintegrant.

4.6.1 Method

TABLE 4.5: FORMULAE OF BEADS CONTAINING DISINTEGRANTS

	7.25	7.26	7.27	7.31
Indomethacin (g)	150	150	150	150
Avicel© RC 591 (g)	110	110	110	110
Lactose (g)	215	215	235	240
Acdisol©	25			
Kaolin (g)		25		
Carbopol© 974P			5	

The disintegrants used were Acdisol© (FMC Corporation), Kaolin (Malinkrodt) and Carbopol 974P (B.F. Goodrich Inc). The formulae listed in Table 4.5 were manufactured as previously described and dissolution tests were performed as before. The formulations containing Acdisol© were stiff and additional water had to be added to reduce this effect to a small extent. Approximately 370ml of water was used in Formula 7.25 whereas approximately 225ml of water was used in each of the other formulations of this series. Acdisol© is known to absorb water strongly. The excess water gave the formulation the appearance of being slightly overwet but this did not affect the processing severely.

4.6.2 Results and Discussion

In this series of formulations, the concentration of Indomethacin in the beads was reduced because it appeared that higher concentrations caused a slower rate of dissolution. In Section 4.8, the influence of the concentration of Indomethacin on the dissolution rate is examined more carefully.

The present formulations differed only with respect to the disintegrant, while Formula 7.31 had no disintegrant and served as the control. Ideally, comparisons should have been made between formulations containing the same amount of the different disintegrants. This could not be done because the Carbopol© formulations became very tacky. Likewise, higher amounts of kaolin or Acdisol© could not have been included because of the difficulty of processing the material. The above formulae were derived after much preliminary investigation and contained the maximum amount of each disintegrant that allowed the beads to be successfully formed, as judged by their visual appearance and taking into account the feel of the wet mass prior to extrusion. This highlights, once more, the sensitivity of the extrusion and spheronization process since slight

changes in the formulation resulted in a wet mass that could not be successfully spheronized. The formulations, hence, do not compare the potency of the various disintegrants but make a comparison between 1% Carbopol© 974P, 5% kaolin and 5% Acdisol ©. These agents exert their disintegrant action by a swelling mechanism. While it has been mentioned that Carbopol© could not have been used in larger amounts because of the tackiness that it created, it improved the plasticity of the wet material and facilitated the production of the spheres, when used in small quantities.

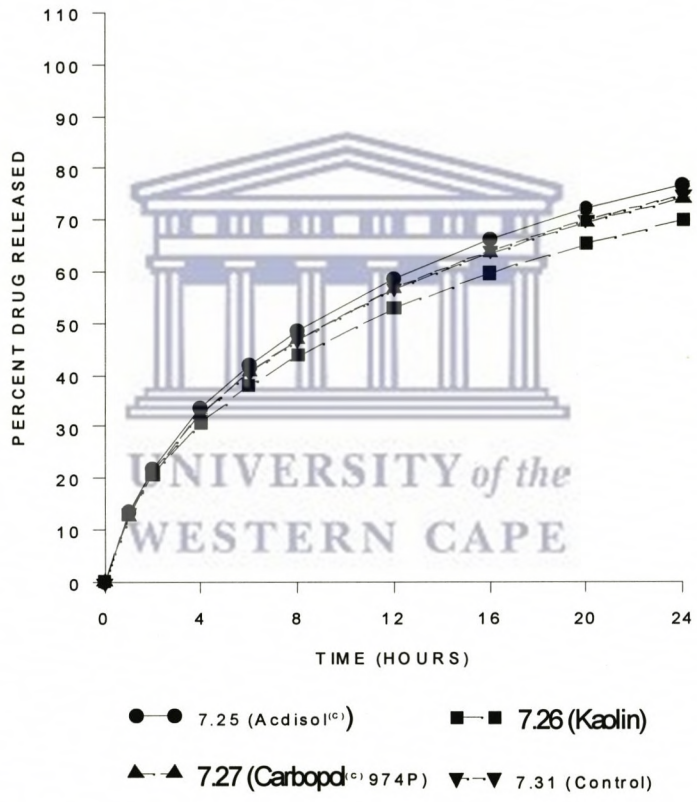


FIGURE 4.5: EFFECT OF DISINTEGRANTS ON DISSOLUTION RATE

The dissolution results are presented in Figure 4.5 which indicates that the dissolution of Indomethacin from this series of formulations was incomplete, once again. The control (7.31) was

practically indistinguisable from the Carbopol-containing formulation (7.27). The kaolin-containing formulation (7.26) displayed a slightly slower dissolution rate. Acdisol© increased the rate and extent of dissolution very slightly. However, there was very little difference between the four formulations and one may, therefore, conclude that the presence, and type, of disintegrant had very little influence on the dissolution of the drug. Even the potent disintegrant, Acdisol©, used in a relatively large concentration (5%) only improved the dissolution rate very slightly. This "super" disintegrant is capable of swelling 200% to 300% of its volume, whereas conventional starch only increases its volume by 10% to 25% in water (Peck et al., 1989). The degree of swelling of starch is mentioned for comparison; it is recognised that, in terms of modern theories, swelling is not regarded as the primary mechanism by means of which starch exerts its disintegrant action.

The improved extent of dissolution of these formulations over those described in the previous section is probably attributable to the lower concentration of Indomethacin (30% compared to 50%). It is unusual that a lower concentration of a drug should increase its release but this concept is in keeping with the previously-made proposal that the drug, because of its hydrophobic nature, served as its own retardant. Over 40% of lactose was used in these formulations. The fact that the beads were intact after 24 hours in the dissolution medium appears to indicate that not all of the lactose dissolved in this time; if it had, it is unlikely that the integrity of the bead structure would have been maintained. If this hypothesis is correct, then the Indomethacin retarded the release of the lactose, a very soluble substance. This is an indication that Indomethacin may act as a powerful retardant in bead formulations.

4.7 STAGE OF THE EXTRUSION AND SPHERONIZATION PROCESS CAUSING VERY SLOW DRUG RELEASE

It has been postulated that the hydrophobic nature of Indomethacin and an interaction between Indomethacin and microcrystalline cellulose are each partly responsible for the very slow release of this drug from beads. In this section of the work, one aspect of this possible interaction will be examined further. Since the extrusion and spheronization process consists of several steps, it is of interest to determine at which stage the postulated interaction occurs. This information might give an indication of the nature of the interaction.

4.7.1 Method

A batch of beads (7.35) was prepared using Formula 7.31 and a small amount of the material was removed at the following stages of production: after mixing the powders, after extrusion and after spheronization for 5 minutes and 10 minutes. In addition, some dried beads were finely ground, using a mortar and pestle. These materials, as well as the final product (which had been spheronized for 15 minutes), were filled into size 0 elongated capsules, after drying where appropriate. The various capsules were subjected to dissolution testing as previously described. Electron micrographs of the Indomethacin crystals, microcrystalline cellulose powder and the sectioned beads were also taken at 25kV.

4.7.2 Results and Discussion

Figure 4.6 reflects the dissolution pattern at various stages of processing. There was no significant difference between the dissolution profile of beads spheronized respectively for 5, 10 or 15 minutes.

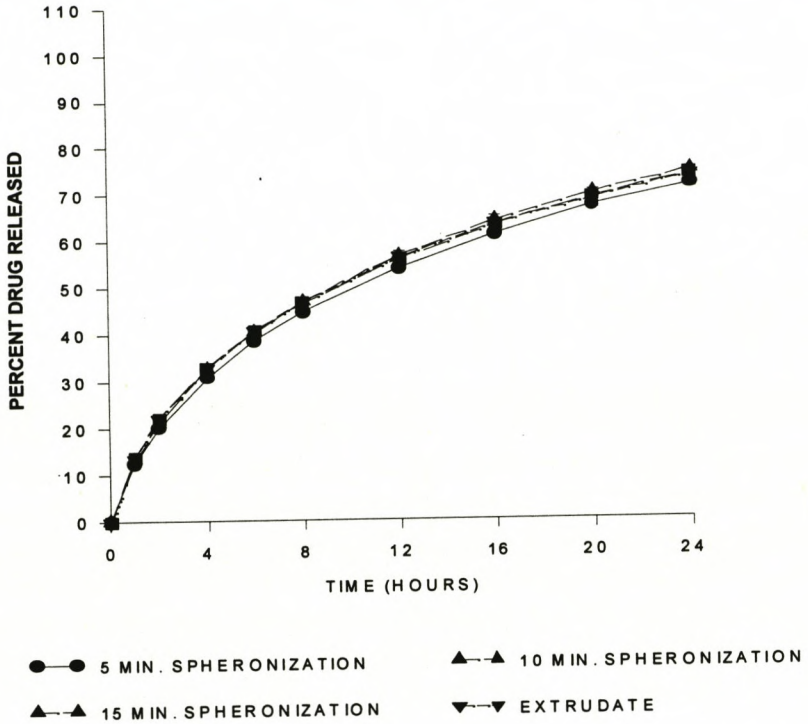


FIGURE 4.6: EFFECT OF DIFFERENT STAGES OF PROCESSING ON DISSOLUTION

There was also no difference between the beads and the extrudate with respect to the dissolution rate. Figure 4.7 compares the dissolution of Indomethacin powder; crushed beads; and a mixture of Avicel©, Indomethacin and lactose powders. The dissolution profile of the beads is included for comparison. Approximately 90% of the Indomethacin powder was dissolved in the first hour of the dissolution test. The mixed powders also showed a rapid initial dissolution rate but dissolution did not go to completion, the final extent of dissolution being less than 80%. This appears to signify that simply mixing the materials together (using the planetary mixer) causes a weak interaction that retards drug dissolution to some extent. Comparing the dissolution of the mixed powders and the crushed beads, the latter displayed a slower dissolution rate for the first four hours but thereafter dissolution was more extensive. This behaviour can be explained as follows:

(i) The interaction between Indomethacin and microcrystalline cellulose within the bead is stronger than the interaction between these constituents in the mixed powders.

(ii) the process of crushing the beads did not disrupt the strong interaction in all of the material (hence the slower initial release); and

(iii) the disruption of the interaction in other parts of the crushed bead material resulted in the greater extent of release, compared to the mixed powders in which the weak interaction persisted.

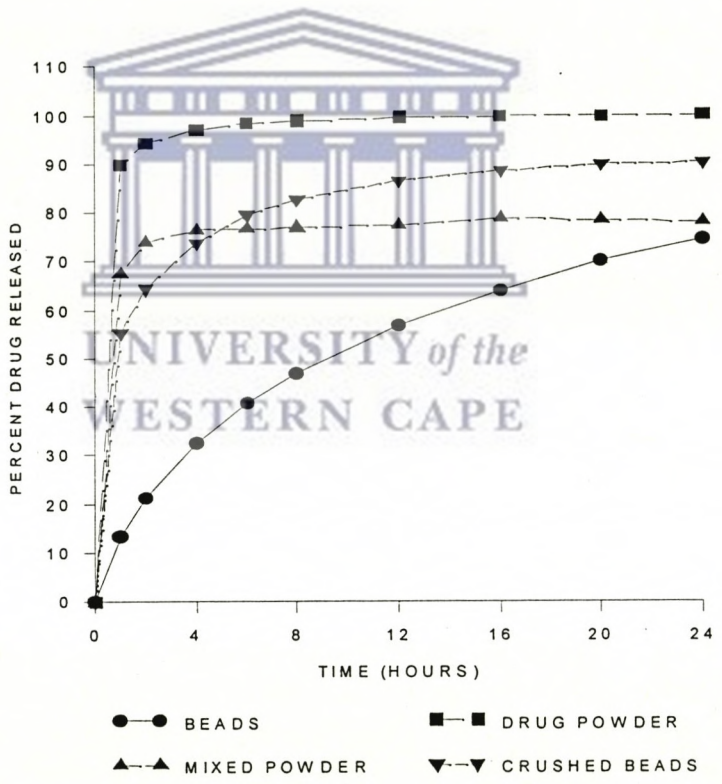


FIGURE 4.7: DISSOLUTION OF INDOMETHACIN PREPARATIONS IN POWDER FORM

These results indicate that the interaction between Indomethacin and microcrystalline cellulose occurred to some extent at the mixing stage and more fully at the extrusion stage. In this formulation, spheronization is not an absolute requirement for the development of sustained release properties but the extent of spheronization does affect the shape and physical quality of the beads. This is in contrast to the findings of Chien and Nuessle (1985) who observed that longer spheronization times decreased the release rate from beads. This was attributable to an increased density of the beads and, more importantly, to a case hardening of the beads, i.e. the formation of a thin layer of hard material on the periphery of the beads. In the present work, crushing the beads was also observed to partly destroy the sustained release effect.

While these results do not indicate the nature of the interaction between Indomethacin and microcrystalline cellulose, one may speculate that it is a physical one since it is disrupted, at least in part, by grinding. The following facts support this contention: microcrystallline cellulose is a porous substance and Indomethacin is a very fine powder, many of the particles of which have a diameter of less than 10μm, as seen in Figure 4.8(a). It is, therefore, feasible that the pressure exerted during extrusion either forces the Indomethacin particles into the hollows and irregularities on the surface of the microcrystalline cellulose particles and that they are held there by physical attraction; or the pressure brings them so closely together (possibly overcoming an energy barrier in the process) that some form of physical attraction between the substances is possible. From such positions, the drug is slowly dissolved by the dissolution fluids. Crushing the beads probably disrupts this association. If grinding had been done by a more efficient method than the mortar and pestle, the sustained release effect would probably have been lost more completely.

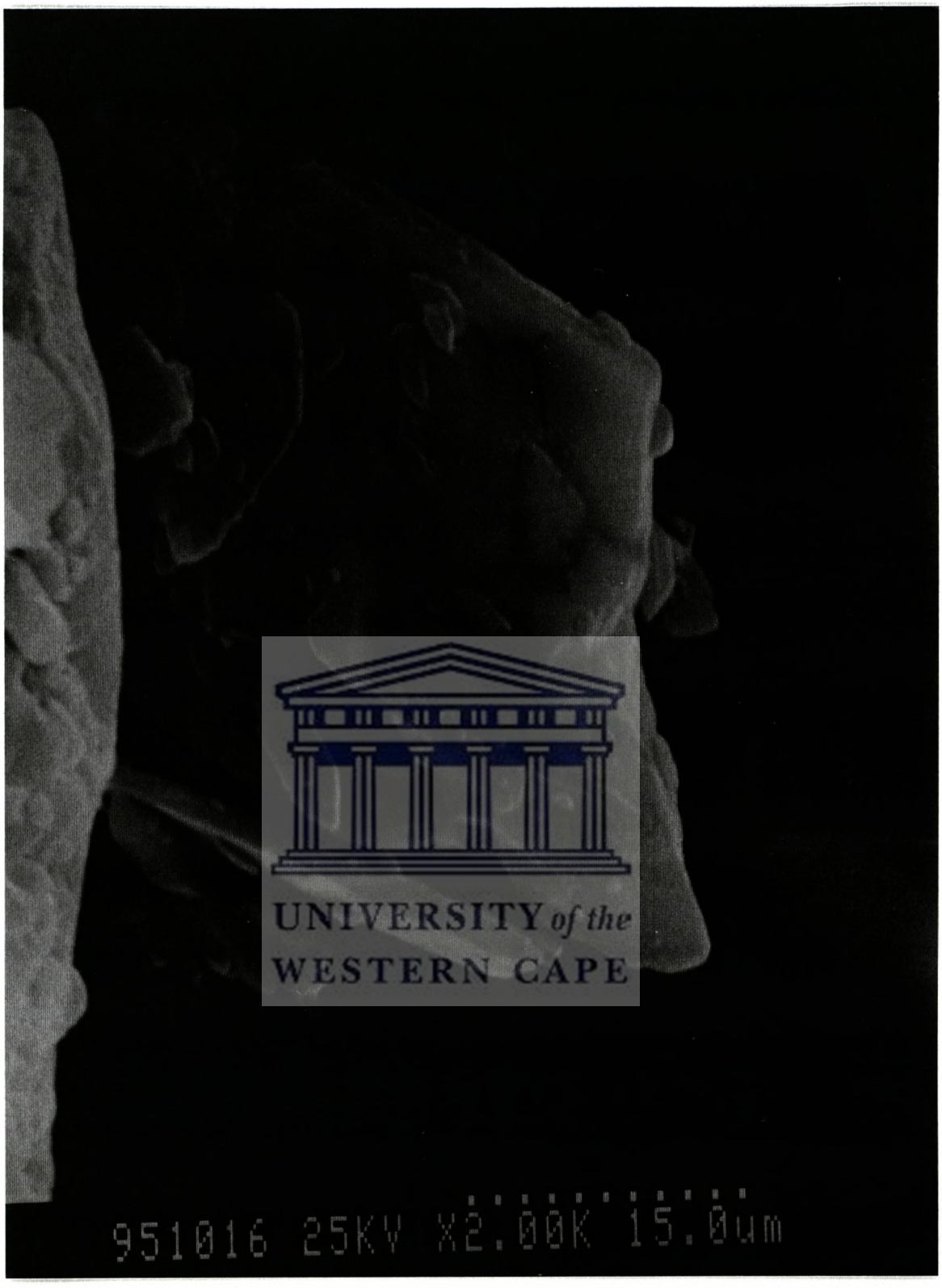


FIGURE 4.8(a): ELECTRON MICROGRAPH OF INDOMETHACIN CRYSTALS

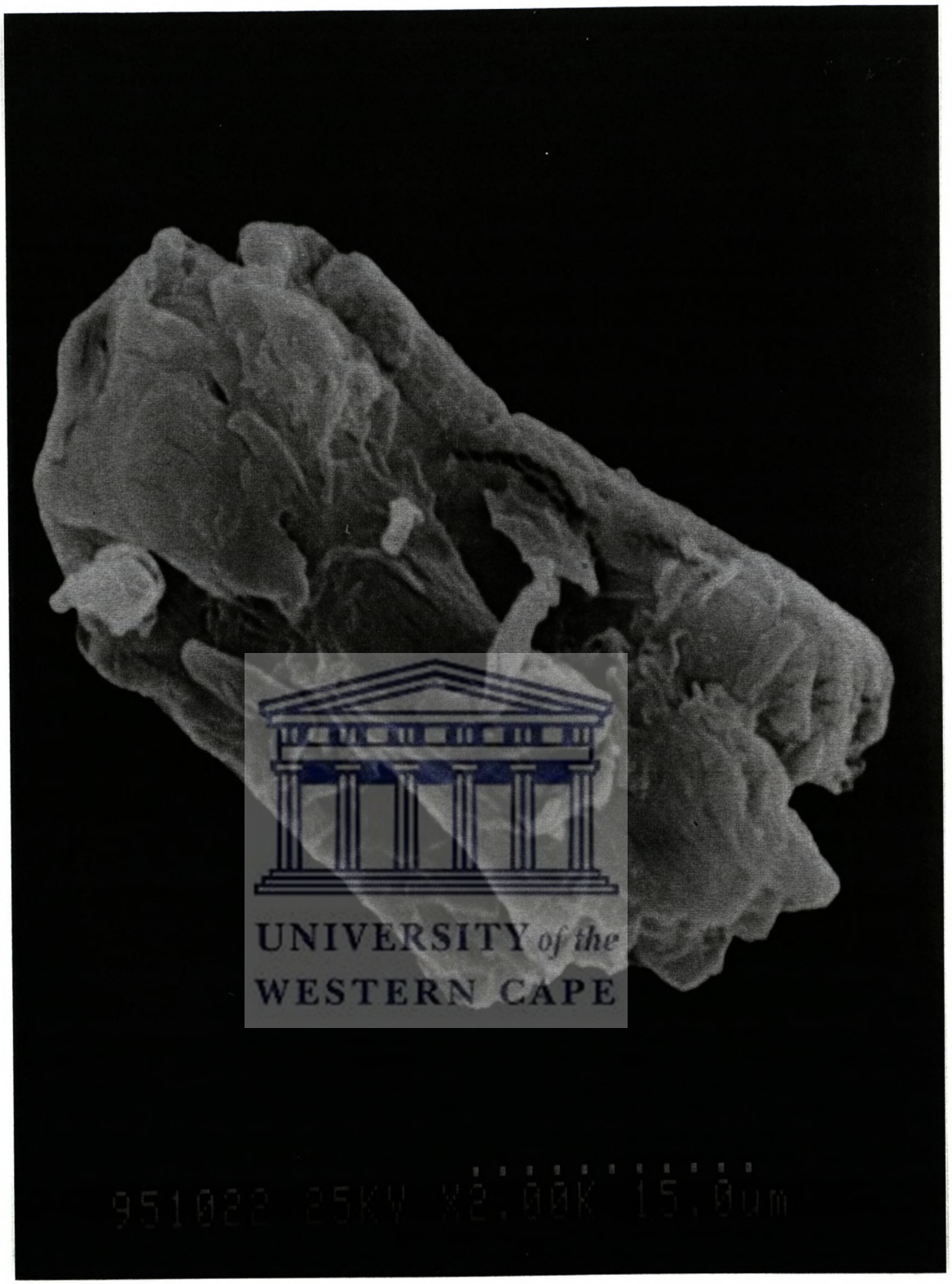


FIGURE 4.8(b): ELECTRON MICROGRAPH OF AVICEL PH 101 PARTICLES

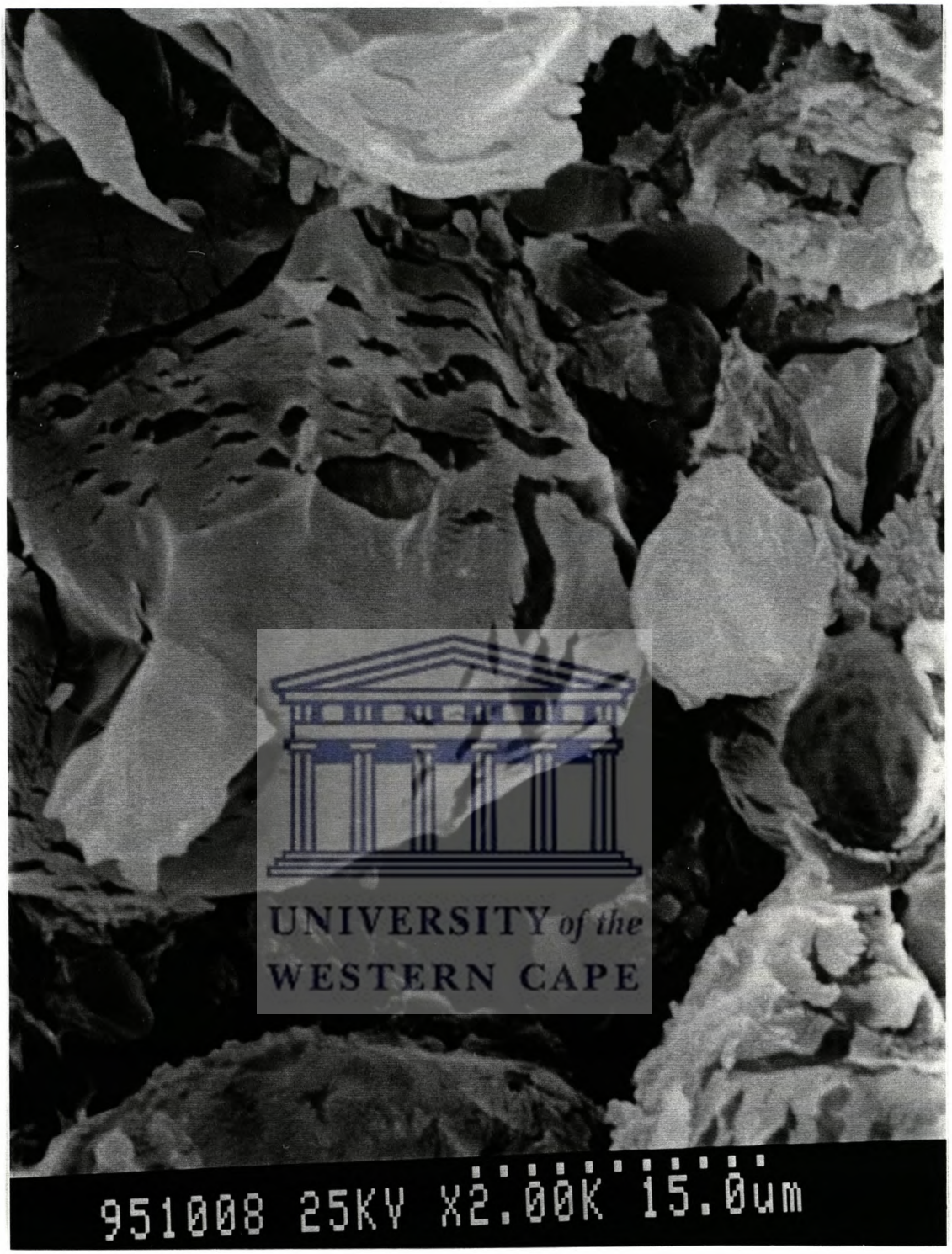


FIGURE 4.8(c): ELECTRON MICROGRAPH OF SECTIONED BEAD

The electron microscopic appearance of a sectioned bead as well as the bead constituents are shown in Figure 4.8. The appearance of the surface of the microcrystalline cellulose particles is rough with pits. The sectioned bead reveals the same type of hollows and crevices that could possibly accommodate fine crystals. What appears to be Indomethacin crystals, partially enclosed in cavities on the microcrystalline cellulose surface and partially jutting out, are observed in several places in Figure 4.8(c). The drug crystals appear lighter and are more reflective.

4.8 EFFECT OF THE CONCENTRATION OF INDOMETHACIN ON ITS DISSOLUTION FROM BEADS

In previous sections, it was postulated that greater concentrations of Indomethacin within the bead caused slower dissolution of the drug, at the same dosage level. In this section, an attempt is made to substantiate this hypothesis.

4.8.1 Method

A series of beads were prepared, each containing 22% of Avicel© RC 591 and concentrations of Indomethacin ranging from 15% to 45%. Lactose made up the remainder of the beads, the formulae of which are given in Table 4.6. The beads were prepared as previously described and dissolution tests were performed as before. The friability was determined by placing approximately 3g of beads (accurately weighed) into the drum of a friabilitator (Roche) and rotating for 4 minutes. Thereafter, the beads were weighed and the percentage loss in mass was determined. The hardness of the 2.36/1.7mm size fraction was determined using a mechnical hardness tester (Schleuniger).

TABLE 4.6: FORMULAE OF BEADS CONTAINING DIFFERENT CONCENTRATIONS OF INDOMETHACIN

	7.36	7.35	7.37
Avicel© RC 591 (g)	110	110	110
Lactose (g)	315	240	165
Indomethacin (g)	75	150	225
% Indomethacin	15	30	45

4.8.2 Results and Discussion

The results of the friability and hardness tests are shown in Table 4.7. The table reveals that hard beads with excellent friability scores were produced. Friability values of less than 1% are, generally, considered good.

TABLE 4.7: FRIABILITY AND HARDNESS OF INDOMETHACIN BEADS

FORMULA	FRIABILITY (%)	HARDNESS (± S.D.) (N)
7.35	0.15	31.4 (±1.5)
7.37	0.16	30.2 (± 1.9)
7.36	0.18	35.3 (± 2.6)

The results of the dissolution tests are shown in Figure 4.9. For similar formulations, the rate and extent of drug release followed the order of decreasing Indomethacin concentration. The lower the concentration of Indomethacin in the formulations, the higher is the concentration of lactose. Being more rapidly soluble, the lactose creates pores for the fast entry of water and, therefore, one possible

reason for the quicker dissolution rate is the higher content of lactose. However, it has been shown in Section 4.5 that the lactose concentration does not affect the rate of drug release. Hence, the only plausible explanation is that the Indomethacin acted as a hydrophobic agent limiting entry of water into the bead and causing retardation of its own release. The higher the concentration of Indomethacin present in the beads, the slower is the dissolution.

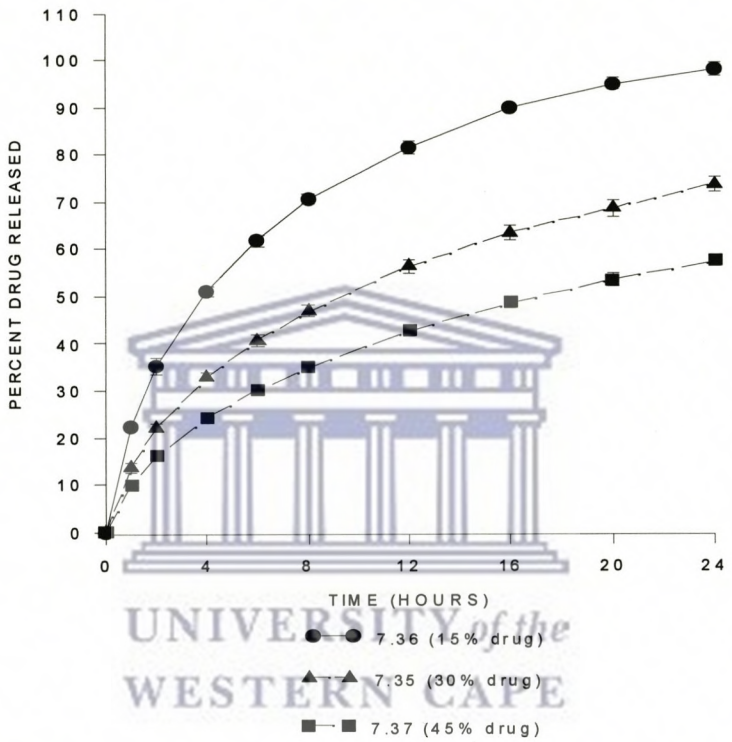


FIGURE 4.9: EFFECT OF INDOMETHACIN CONCENTRATION ON DISSOLUTION RATE

The concentration of the drug in the beads was plotted against the percentage of the dose released at 24 hours (final amount released) and a non-linear regression procedure was applied to the data using the computer program, Statistica©. The results are depicted in Figure 4.11 which also shows the equation of the fitted curve. While the correlation coefficient was determined to be 1.00, the

excellence of this result is probably due to the fact that there were only three points to the curve.

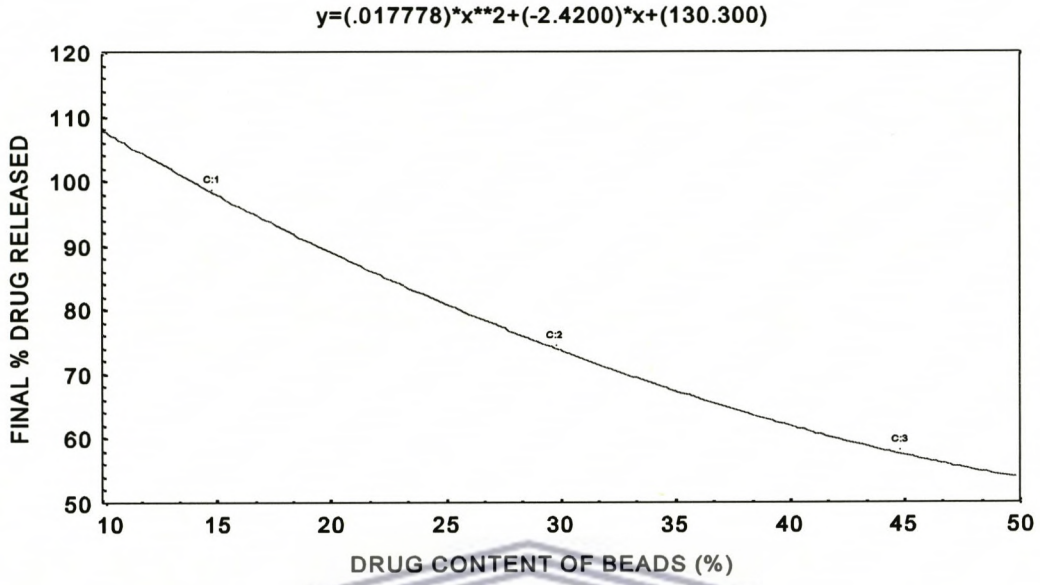


FIGURE 4.10: RELATIONSHIP BETWEEN INDOMETHACIN CONTENT AND EXTENT OF DRUG RELEASE

Formula 7.36, which contains 15% Indomethacin, released practically 100% of the drug over the 24 hour dissolution period. Although drug release is faster initially, this is not a disadvantage with Indomethacin. More of the drug must be absorbed soon after administration to a patient in order to bring about the initial anti-inflammatory response. The remainder of the drug is then slowly absorbed, after slow release from the dosage form, to maintain the pharmacological effect. The faster initial release may also be advantageous because of the possibility of an inherently less efficient absorption of Indomethacin from the distal portions of the gastrointestinal tract (Rogers et al., 1983).

Figure 4.11 compares the dissolution profiles of Formula 7.35 beads with that of the innovator's product. Both products display an initial fast release. Thereafter, the test formulation releases the drug at a more steady rate than the innovator's product. The test product represents a tremendous simplification of the manufacturing process. A batch of this product can be manufactured in less than one hour, which would have enormous advantages at an industrial level.

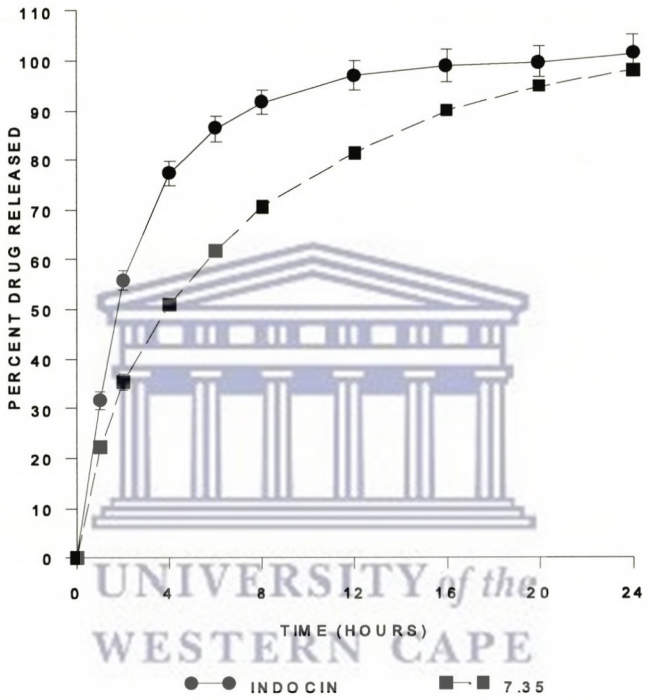


FIGURE 4.11: COMPARISON OF THE DISSOLUTION PROFILES OF INDOCIN© AND FORMULA 7.35

The release data with respect to both products were fitted to the square root of time equation (Higuchi, 1963), as well as to the diffusion, relaxation and erosion (DRE) equation (Upadrashta et al., 1993). The results of the mathematical modelling are summarized in Table 4.8 and show that

the DRE equation clearly fits the data better. The DRE equation reveals both better correlation coefficients and smaller errors in the fit between the data and the models.

TABLE 4.8: SUMMARY OF MATHEMATICAL MODELLING RESULTS

PRODUCT	HIGUCHI MODEL*		DRE MODEL**	
	S.S.R.	r^2	S.S.R.	r^2
Indocin	2892.2604	0.7283	67.8102	0.9936
Formula 7.35	328.1792	0.9667	4.2792	0.9996

$* \; y = at^{½}$ $** \; y = at^3 + bt^2 + ct + dt^{½}$

where y = percent drug released at time t,

t = time since start of dissolution test; and

a,b,c and d are constants.

The Higuchi equation considers only diffusion through pores in the matrix. The DRE equation, on the other hand, takes into account pore diffusion, relaxation of the matrix (expansion or swelling) and erosion. All mechanisms that could have an influence on the rate of drug release are taken into account and, hence, a better fit is obtained.

CHAPTER 5: MATRIX BEADS

5.1 INTRODUCTION

The idea of using matrices to retard the release of drugs, contained in beads, stems from the very successful use of this technique in the production of tabletted sustained release dosage forms. The ground substance or matrix is an inert material that retards the release of the drug, particles of which are within, or distributed between, the matrix particles. The latter situation is the more common. Various substances have been used as the matrix former in tablets, including Eudragits© (McGinity et al., 1983), mixtures of waxes (Fassihi et al., 1986) and hydroxypropylmethylcellulose (Christenson and Dale, 1962; and Baveja et al., 1988). While matrix tablets with excellent sustained release profiles have been achieved, it is much more difficult to obtain such a profile with beads because they have a vastly increased surface area, as described in Chapter 1. The tremendous potential advantage of such preparations, however, encourages an investigation of their formulation and development.

Work reported in the previous chapter indicated that there was a possible interaction between Indomethacin and microcrystalline cellulose. The unusual finding was made that the higher the concentration of the drug in the beads, the slower was the rate of drug release, for the same dose. This was thought to be the result of Indomethacin acting as its own retardant, due to its hydrophobic nature. Therefore, the inclusion of a hydrophobic substance was indicated in the development of sustained release matrix formulations of other drugs. Since Indomethacin is a very fine powder, it

was considered probable that the fineness of hydrophobic materials contributed to their retardant properties. Hence, several fine powders that are commonly used in pharmaceuticals were incorporated into beads containing either Acetaminophen (Ruger) or Theophylline as the model drugs.

5.2 ACETAMINOPHEN FORMULATIONS

5.2.1 Method

The matrix formers that were incorporated were magnesium trisilicate (Mallinckrodt), dicalcium phosphate dihydrate (Monsanto Company), magnesium stearate (Ruger) and talc (Ruger). The formulations listed in Table 5.1 were prepared as previously described and dissolution tests were performed as before.

TABLE 5.1: FORMULAE OF ACETAMINOPHEN BEADS

	6.1	6.2	6.3	6.4	6.5
Acetaminophen (g)	150	150	150	150	150
Avicel© PH 101 (g)	250	250	250	300	300
5% PVP K 90 (ml)	50	50	50	50	50
lactose (g)	100				
magnesium trisilicate (g)		100			
$Ca_2PO_4 \cdot 2H_20$ (g)			100		
magnesium stearate (g)				50	
talc (g)					50

5.2.2 Results and Discussion

When either magnesium stearate or talc served as the retardant (Formulae 6.4 and 6.5, respectively), only 10% was included because the hydrophobicity of these materials altered the physical nature of the wet mass adversely and only a limited amount could be used. When an attempt was made to incorporate 100g (20%) of these retardants, in keeping with the other formulae of the series, the wet mass had a somewhat "soapy" feel and was not very cohesive. Upon extrusion of the magnesium stearate-containing material, short, flat slivers were formed instead of long, cylindrical pieces of extrudate. Hence, these formulae were modified to contain half the amount of the retardant, the difference in mass being made up with Avicel© PH101. In the control (Formula 6.1), lactose was used in place of the retardant.

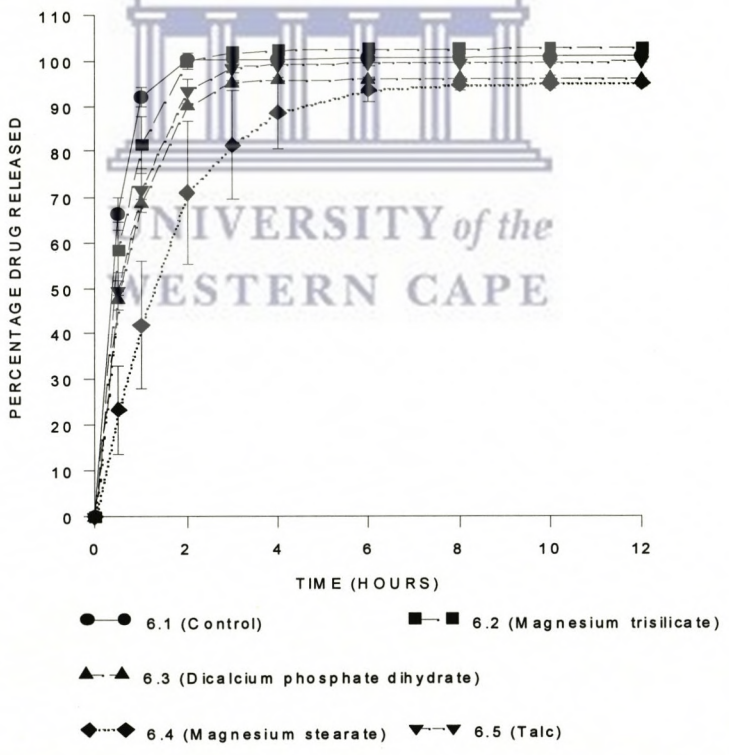


FIGURE 5.1: DISSOLUTION OF ACETAMINOPHEN MATRIX BEADS

The dissolution results appear in Figure 5.1. Magnesium trisilicate did not retard drug release by much; the release profile is similar to that of the beads with no retardant (Formula 6.1). Only magnesium stearate displayed a reasonable retardant effect, with slightly more than 90% of the drug being released over 6 hours. Dicalcium phosphate dihydrate and talc showed an intermediate effect with approximately 90% of the drug being released in 2 hours. There was significant variability in the amount of drug released by the individual capsules of the magnesium stearate-containing formulation. This was probably due to variability in the extent of coverage of the particles of the bead constituents by magnesium stearate. The magnesium stearate cover of the particles is responsible for creating the hydrophobic interior of the beads which decreases the entry of water and, consequently, retards the release of the drug. It is probable that extended mixing would have provided not only a more uniform release rate, but also a greater degree of retardation. Magnesium stearate has a laminar structure which sloughs off with prolonged mixing, affording an increased covering capacity (Bolhuis et al., 1975).

5.3 THEOPHYLLINE AND AVICEL© RC 591 FORMULATIONS

Since magnesium stearate sustained the release of Acetaminophen to some extent, the effect of this hydrophobic material on the release of Theophylline was examined. Avicel© RC 591 is supplied in very fine particle form and it also contains sodium carboxymethylcellulose. These attributes allow it to be used as a spheronizing aid in much smaller quantities than Avicel© PH 101. Considering that Theophylline is required in a dose of at least 300mg for an adult, the former grade was used since it can be used in smaller amounts. This gives the formulator flexibility, allowing increased amounts of retardant and other excipients without resorting to an unacceptably large capsule. The influence

of Aerosil© R972 (Degussa AG), a hydrophobic material, was also examined. Aerosil © is a brand of silicon dioxide and its very fine particle form contributes to the excellent covering capacity of the material when it is mixed with other powdered constituents. The grades (such as Aerosil© 200) that are usually used in the food and the pharmaceutical industries are hydrophilic. In Aerosil© R972, the silica chains have been modified to contain methyl end groups (Degussa AG, 1980), making the compound hydrophobic in nature. It is used in emulsion-type toothpastes to assist with the emulsification process. This compound was investigated in an effort to establish the principle that fine, hydrophobic material, included in matrix beads, would retard drug release from the beads.

5.3.1 Method

The formulations listed in Table 5.2 were prepared as previously described and dissolution tests were performed as before.

TABLE 5.2: FORMULAE OF THEOPHYLLINE AND AVICEL© RC 591 BEADS

	3.12	3.13	3.14	3.15	3.16
Theophylline (g)	240	240	240	240	240
Avicel© RC 591 (g)	100	100	100	100	100
Magnesium stearate (g)		60	40	20	
Lactose (g)	60		20	40	28
Aerosil© R972					32

5.3.2 Results and Discussion

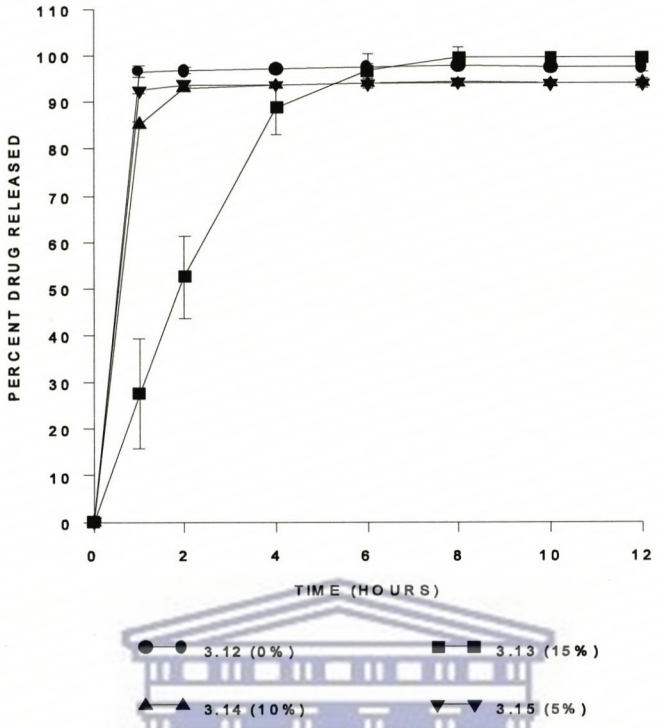


FIGURE 5.2: EFFECT OF MAGNESIUM STEARATE CONCENTRATION ON THEOPHYLLINE RELEASE

The formulations were identical except for the retardant, while Formula 3.12 served as the control. Formulae 3.13, 3.14 and 3.15 contained, respectively, 15%, 10% and 5% of magnesium stearate whereas the retardant in Formula 3.16 was Aerosil© R972. Where the formulation contained less than 15% retardant, the difference was made up with lactose. The dissolution results of the magnesium stearate-containing formulations are shown in Figure 5.2, whereas the profile for the Aerosil© R972 formulation is compared with the control in Figure 5.3. The control released almost all of the drug within 1 hour. The dissolution profiles for the products containing 5% and 10% magnesium stearate were not much different from each other and show that these concentrations of

retardant slowed down the dissolution of the drug only marginally. A concentration of 15% of magnesium stearate was required to sustain the release of the drug appreciably. In this case, the drug release was extended over a period of 8 hours.

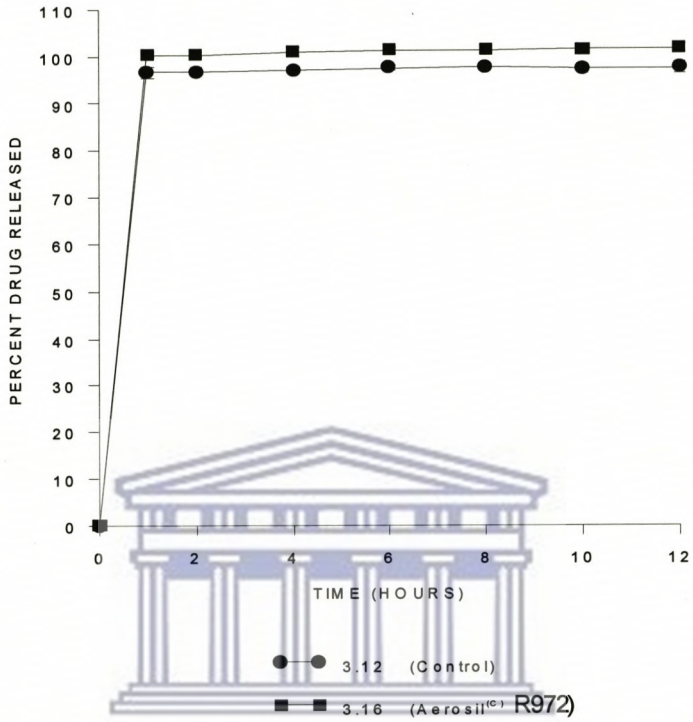


FIGURE 5.3: INFLUENCE OF AEROSIL© R972 ON THEOPHYLLINE RELEASE

Aerosil© R972, surprisingly, did not retard the release of the drug at all, though it is an hydrophobic material with a very small particle size. The lack of influence was probably due to the fact that silicon dioxide swells in water and that the dissolution-promoting swelling effect outweighed the retardant effect. This explanation is substantiated by the slightly more complete dissolution seen with Aerosil© R972, relative to the control.

Avicel© RC591 was chosen as a spheronizing aid because of its greater loading capacity but the sodium carboxymethylcellulose that it contains absorbs water rapidly which causes the beads to swell, thus enhancing dissolution. Hence, Avicel© RC591 had a negative effect on the sustained release properties of beads containing either magnesium stearate or Aerosil © R972.

5.4 EUDRAGIT© RSPO AND SULPHUR AS RETARDANTS

As previously mentioned, fine hydrophobic materials appeared to be indicated for use as retardants within beads. In keeping with this concept, the retardant properties of sulphur (Mallinckrodt) and Eudragit© RSPO (Rohm Tech Inc) were investigated. The latter is widely used to form matrix tablets displaying sustained release properties (Farhadieh et al., 1971a; and McGinity et al., 1983). Sulphur cannot be used as a retardant for oral sustained release preparations because of its toxicity. However, it is a hydrophobic material that is available in fairly fine particle form and, hence, could be used to evaluate the hypothesis that fine, hydrophobic materials can sustain the release of drugs from non-coated beads.

5.4.1 Method

The formulations reflected in Table 5.3 were prepared as previously described. Approximately 10g of each of the Eudragit©-containing formulations was subjected to heat treatment and to treatment by ethanol vapours. For the heat treatment, the beads were spread on a small aluminium pan and the pan was placed in a pre-heated laboratory oven. The oven was, thereafter, maintained at 140° for 30 minutes. The beads were removed from the oven and allowed to cool to room temperature before being packed into capsules for dissolution testing.

TABLE 5.3: FORMULAE OF BEADS CONTAINING EUDRAGIT© OR SULPHUR

	3.7	3.18	3.19	3.25
Theophylline (g)	250	250	250	250
Avicel© PH101 (g)	250	200	150	200
Eudragit© RSPO (g)		50	100	
Sulphur (precipitated) (g)				50

For the treatment with ethanol vapors, a laboratory vacuum oven (Precision Scientific) was first conditioned by placing into it approximately 150ml of ethanol, in an open jar, and heating until the temperature reached 50°. The beads were spread onto small (11cm diameter), fine-mesh sieves which were then placed into the oven. A vacuum was drawn (final pressure 20-25 inches Hg) and the beads were left in the oven for 60 minutes at 50°. After removal from the oven, the beads were allow to dry in a fume cupboard for 24 hours before packing into capsules for dissolution testing. Using the previously described method, dissolution tests were conducted on all the formulations as well as the heat-treated and ethanol-treated beads.

5.4.2 Results and Discussion

The dissolution results of the 3 retardant-containing formulations and the control are shown in Figure 5.4. There was little difference between the dissolution profiles of the two preparations containing Eudragit© RSPO which shows that the increase in concentration of this retardant from 10% to 20% had a negligible effect on the dissolution rate of the drug. For equal concentrations (10%), sulphur as slightly less effective than Eudragit© RSPO as a retardant. While sulphur is in fine powder form, magnesium stearate has a very large covering capacity (2.45 - 7.93m^2/g) (Boylan et al., 1986) and

this property may be partly responsible for the better retardant effect observed with magnesium stearate. As previously mentioned, the laminar structure of magnesium stearate also allows better coverage of the powders with which it is mixed.

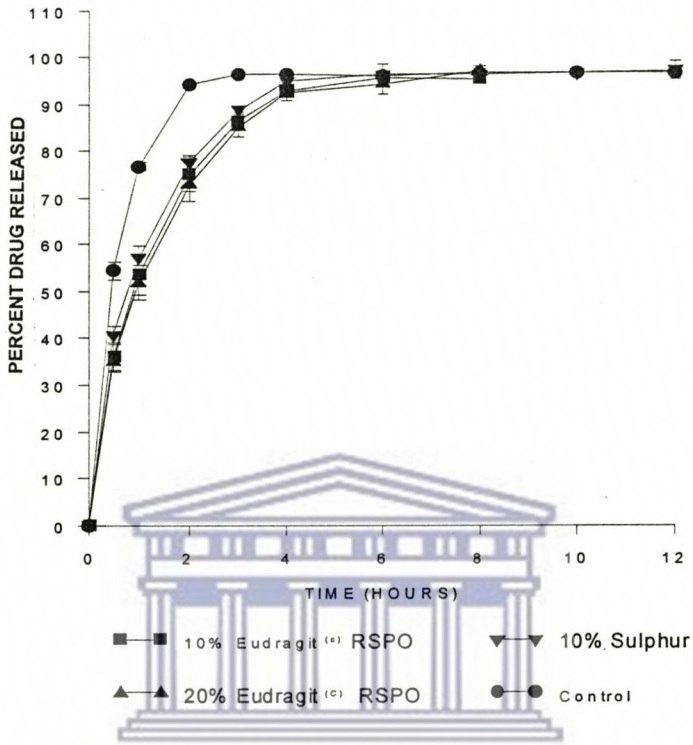


FIGURE 5.4: EFFECT OF EUDRAGIT© RSPO AND SULPHUR ON THE RELEASE OF THEOPHYLLINE

The effects of heat and ethanol treatment are shown in Figures 5.5 and 5.6. For both Eudragit-containing formulations, the effect of each treatment was to enhance the rate of dissolution. The treatments were undertaken to improve the sustained release effect of Eudragit© RSPO but they had the opposite effect. Eudragit RSPO melts over a very wide temperature range, but melting is complete at 140°. In the heat treatment procedure, the beads were heated to, and maintained at, this temperature for 30 minutes to provide the opportunity for the melted polymer to spread over the bead

constituents. It is assumed that the individual particles of Eudragit© RSPO have less sustained release effect than a continuous film or layer covering the particles. At the applied temperature, none of the other ingredients would melt.

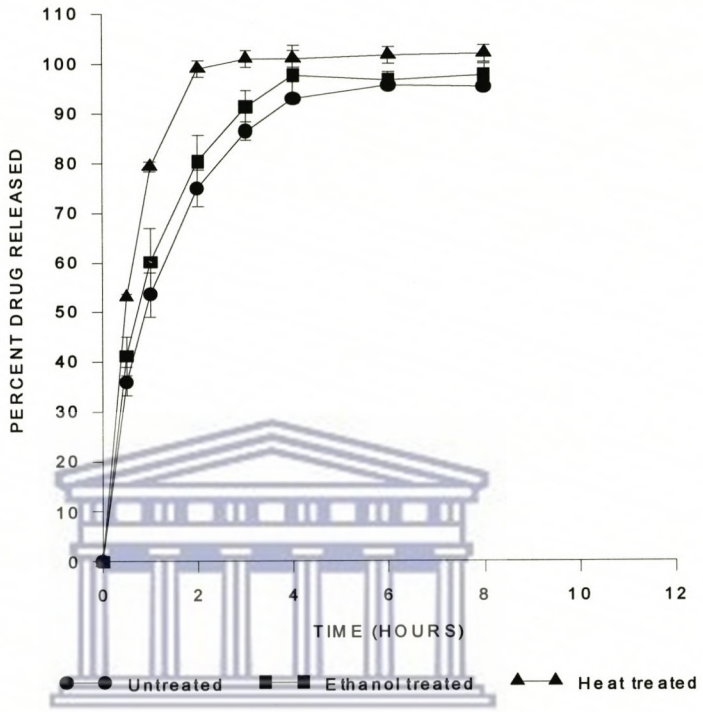


FIGURE 5.5: EFFECT OF HEAT AND ETHANOL TREATMENT ON FORMULA 3.18 BEADS

In the ethanol treatment, the beads were placed into an ethanol saturated atmosphere. The vacuum that is drawn removes the air from the chamber, which is replaced by ethanol vapours. Heating to 50° assists this process. It was expected that the ethanol vapours passing through the beads would dissolve the Eudragit© and that the solution so formed would spread more evenly over the constituents. Using acetone vapours to treat Eudragit©-containing matrix tablets, Farhadieh et al. (1971b) were able to improve the sustained release effect of these tablets.

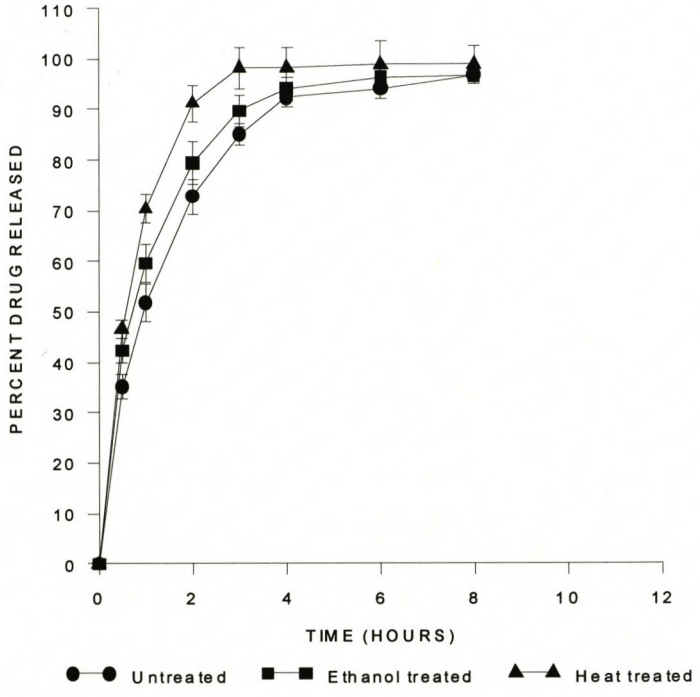


FIGURE 5.6: EFFECT OF HEAT AND ETHANOL TREATMENT ON FORMULA 3.19 BEADS

This technique failed in the present work probably because the dissolved polymer was deposited in the interstices between the particles of the beads, in a similar fashion to the diagrammatic depiction in Figure 3.4. This led to less covering of the powder particles by Eudragit© RSPO than in the pre-treated state. Farhadieh et al. (1971b) succeeded in improving the sustained release effect because there was far more Eudragit© within the tablets, in comparison with the beads described here. Since the tablets are also much more compressed than beads, there was little space for the Eudragit© to migrate. The primary effect of the solvent (acetone) in the quoted work was, therefore, to cause fusion of the Eudragit© particles. The authors were able to show that the tortuosity factor in the Higuchi equation (Higuchi, 1963) had increased. This is consistent with fusion of the particles.

5.5 EUDRAGIT© RSPO WITH ETHANOL, OR LATEX EMULSION, AS RETARDANT

In the previous section, it was shown that treating the formed beads with ethanol vapours unexpectedly increased the rate of dissolution. In the work described in the present section, therefore, an alternate attempt was made to obtain a better coverage of the bead constituents by Eudragit© RSPO. To achieve this, the Eudragit © RSPO powder was moistened with either ethanol or Eudragit© RS30D.

When ethanol is included in the formulation, the larger volume that contacts the retardant (compared to when vapours are used) has a better solvent effect and a better coverage of Eudragit© RSPO over the drug particles is expected. Eudragit© RS30D is a latex emulsion containing very fine particles of the polymer (product data sheet, Rohm Tech Inc.) When Eudragit© powder is mixed with the emulsion and allowed to dry, the fine particles from the drying latex form a link between the larger particles of the polymer powder. The emulsion constituents also soften the powder particles and this assists the bonding between the various Eudragit© particles. A continuous covering of the polymer forms over the other bead constituents which results in a sustained release effect.

5.5.1 Method

The formulae depicted in Table 5.4 were prepared. In the case of the formulation containing Eudragit© RS30D (Formulae 3.22), the dry ingredients were premixed and the stated amount of the emulsion was then added, with mixing. Triethylcitrate was included as a plasticizer and water was subsequently incorporated and mixed to give a wet mass having the correct consistency for extrusion and spheronization.

TABLE 5.4: FORMULATIONS OF BEADS CONTAINING EUDRAGIT© RSPO AND ETHANOL OR LATEX EMULSION

	3.7	3.20	3.21	3.22
Theophylline (g)	250	250	250	250
Avicel© PH101 (g)	250	200	150	200
Eudragit© RSPO (g)		50	100	27.5
Eudragit© RS30D (g)				22.5*
Triethylcitrate (g)				2.75

*solids content of 75ml of emulsion

In the case of Formulae 3.20 and 3.21, the Avicel© was mixed with 200ml of water and the wet mixture transferred to a plastic bag which was sealed to prevent loss of moisture. The Theophylline and Eudragit© RSPO were mixed for 3 minutes, using a planetary mixer, and 100ml of 95% ethanol was slowly incorporated into this premix. The wet Avicel© was then slowly added and more water was incorporated, as required, to obtain a mixture of the correct consistency. Formula 3.7 contained the premixed powders moistened with water. In each case, the wet mass was processed as previously described and dissolution tests were performed on the dried beads, as before.

5.5.2 Results and Discussion

In Formula 3.21 the Avicel© PH 101 content was decreased to 30% in order to accommodate the increased amount of Eudragit© RSPO. This low concentration of spheronizing aid is not consistent with good beads and the problem was compounded by the fact that ethanol was used as the

granulating agent. Ethanol does not form strong beads, as previously discussed. Although the material was fairly wet, the extrudate broke up in the spheronizer, resulting in smaller spheres which tended to form agglomerates. In an effort to obtain a reasonable product, the agglomerates were broken manually a few times during the spheronization process. However, the final product consisted of small spheres, some of which were in the form of loose agglomerates and this product (Formula 3.21) was, therefore, not considered suitable for further work. The dissolution profiles of the other formulations as well as that of the control are shown in Figure 5.7. The control beads do not contain any Eudragit© or alcohol, having been wet massed using water.

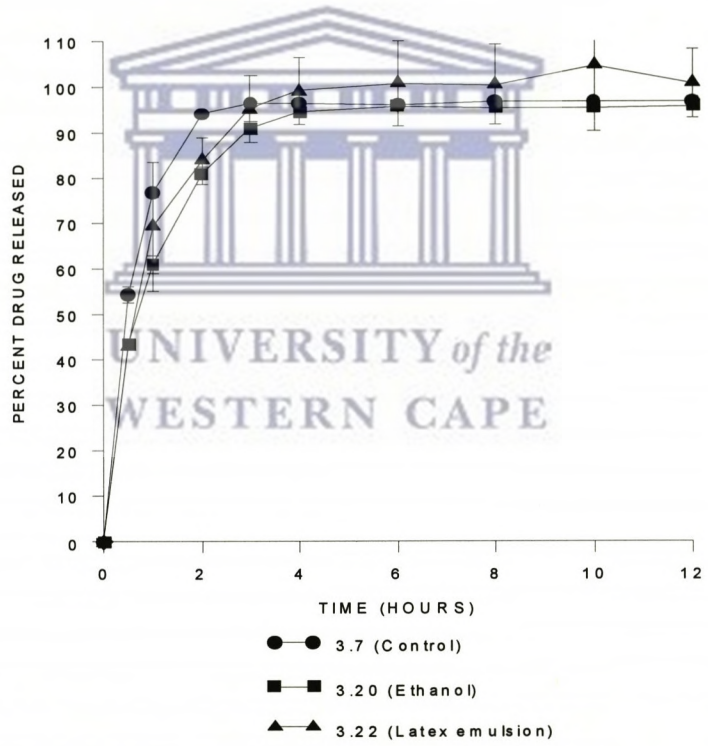


FIGURE 5.7: DISSOLUTION OF BEADS CONTAINING EUDRAGIT© RSPO

The release of the drug from the alcohol-containing beads was somewhat sustained relative to the control beads. The former released approximately 94% of the drug content in 4 hours, whereas the latter released this amount in 2 hours. While this is a notable difference, the drug's release was not sufficiently retarded to enable use of the product as a sustained release medication. The effect of the latex emulsion was less pronounced (approximately 95% was released in 3 hours).

The coverage of the bead constituents was probably incomplete even when liquid ethanol, as opposed to vapours, was used and this led to the dissolution profile being less than ideal. The coverage was probably also incomplete with the latex polymer which is partly due to the small amount of the emulsion that was used. Much larger amounts could not have been incorporated because the wet mass became tacky and over-plasticized. The chosen amounts gave a final concentration of Eudragit© equal to that of Formula 3.20 (10%) and hence these formulations can be compared. Triethylcitrate was included with the emulsion as a plasticizer as such an agent is commonly included in coating solutions. The primary use of Eudragit© RS30D is in coating. However, this plasticizer is water soluble and also swells in the presence of water and these effects may have had some influence on the small retardant action. The swelling probably caused the more complete drug release observed with this formulation and, possibly, also contributed to the much larger standard deviation values.

5.6 TABLETTING OF BEADS

As indicated in the introductory chapter, there is an interest amongst researchers to produce tablets from beads. The advantages of the tabletting of beads are the improved flowability of spheroids

compared to irregular granules, thus ensuring a greater uniformity of tablet mass; the greater loading of drug and retardants that is possible in a tablet, as compared to a capsule filled with beads; and the release retardation effect of the compaction process. In the present work, attempts were made to tablet several of the bead formulations described in this thesis. In most cases, tablets of poor quality were produced, with the tablets sometimes breaking as they came off the tablet press. Two formulations, which contained Eudragit© RSPO (3.18 and 3.19), tabletted well and the formulation and testing of these tablets are described below. In addition, Formula 3.27 was specially prepared for tabletting.

5.6.1 Method

Beads for tabletting were prepared according to the following formula (Formula 3.27):

Theophylline	300g
Eudragit© RSPO	100g
Avicel© RC 591	100g
Tributylcitrate	10g

The Avicel© was mixed with 175ml of water and transferred to a plastic bag which was sealed to decrease loss of moisture. The Theophylline and Eudragit© RSPO were premixed for 3 minutes and 100ml of 95% ethanol was added and mixed. The tributylcitrate (Morflex Inc) was added next and the wet Avicel© was then incorporated into this mixture. The resulting wet mass was extruded and spheronized as previously described. The dried beads were separated into different size groups and

the 1.18/0.991mm and 0.991/0.710mm size fractions were subjected to dissolution testing after filling into size O elongated capsules.

For the tabletting studies, 0.991/0.710mm beads of Formulae 3.18 and 3.19 were each compressed with equal parts, or half as much, non pareil seeds of average diameter 0.85mm (Ingredient Tech Inc). In addition, Formula 3.27 beads (0.991/0.710mm size fraction) were compressed at two hardness levels without the addition of any excipient. In all cases, a rotary tablet press (Stokes RB2) was used to form capsule-shaped tablets, each containing 300mg of Theophylline. The dies were filled by hand and lubrication was achieved by compressing a mixture of 9 parts of non pareil seeds to 1 part of magnesium stearate after every third drug-containing tablet. Hardness tests were performed on all batches of tablets (Schleuniger Hardness Tester) and the tablets were also subjected to dissolution testing as previously described.

5.6.2 Results and Discussion

The dissolution of the two size fractions of Formula 3.27 beads are shown in Figure 5.8. Smaller beads are expected to display a faster dissolution rate because of their greater surface area. Since the dissolution curves show this effect to be minimal and, taking into account the observation (from the present work) that smaller beads display improved compaction characteristics, the 0.991/0.710mm size fraction was used to produce tablets.

All the formulations referred to above produced good tablets probably because of their content of Eudragit© RSPO which is a directly compressible material. It appears that its inclusion in beads

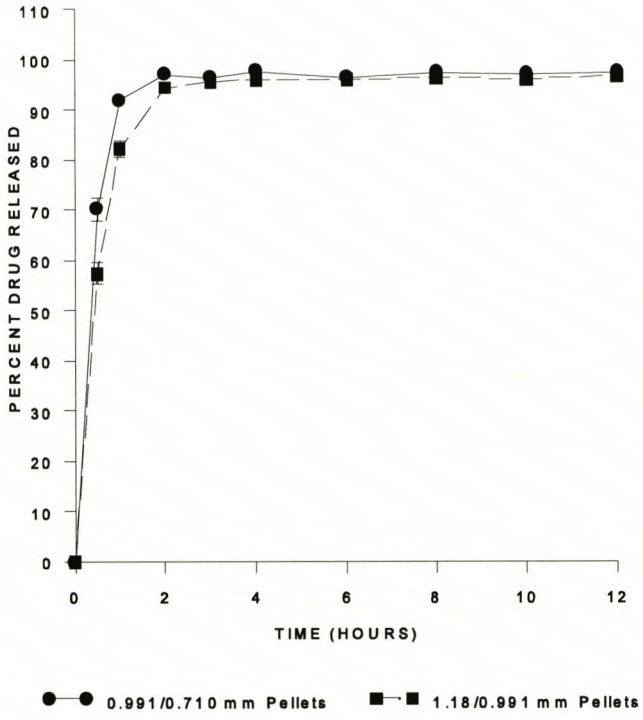


FIGURE 5.8: EFFECT OF SIZE ON DISSOLUTION OF FORMULA 3.27 PELLETS

assists their compression. Although beads produced by extrusion and spheronization do not compress well, in general, the hardness values given in Table 5.5 indicate that very hard tablets were produced. While microcrystalline cellulose (Avicel©) is a highly compressible substance, the beads no longer retain this quality. Two factors are likely to be responsible for the loss of compressibility: firstly, the wetting and subsequent drying of the material may change its physical characteristics adversely; and, secondly, the spheronization process hardens the materials. Chien and Nuessle (1985) referred to a case hardening (hardening of the surface layers) of the beads due to spheronization, and they found an increased hardness with longer spheronization times. The hard surface is not conducive to compaction of the material into tablets.

Milosovich (1963) reviewed the mechanisms by which materials consolidated into tablets. The chief of these are plastic deformation and brittle fracture. When plastic deformation occurs (under the

influence of compaction forces), particles in close packing within a tablet die are squeezed together and deform to fill the spaces between them. In the case of brittle fracture, the material fractures under the forces of compaction and the resultant smaller particles undergo a spatial rearrangement to fit more closely. In each mechanism, particles achieve a closer contact and this facilitates bonding between particles which occurs due to a further increase in pressure within the die. The formation of bonds between particles leads, ultimately, to the consolidation of the mass into a tablet.

TABLE 5.5: TABLET HARDNESS

	3.18	3.18	3.19	3.19	3.27 (SOFTER)	3.27 (HARDER)
Beads:NPS* ratio	1:0.5	1:1	1:0.5	1:1	1:0	1:0
Mean Hardness (N)	112.67	408.33	114.67	408.33	44.20	49.15
S.D. (N)	±18.23	±20.82	±19.22	±28.87	±5.23	±5.91

*NPS = non pareil seeds

In the described mechanisms, the ability to change shape, or to fracture, is an essential prerequisite to bonding and, hence, to the formation of a tablet. The hard, rigid spheres produced by extrusion and spheronization do not lend themselves to bonding by either mechanism and, thus, tablets of poor quality are usually produced. The spherical outlines of the beads can clearly be distinguished in such tablets. This illustrates the fact that the beads did not change shape much during compaction which lends credence to the theory that it is the rigidity of the beads that prevents the formation of good tablets. The inclusion of compressible components such as Eudragit© RSPO, on the other hand, facilitates the formation of tablets of good quality.

Microcrystalline cellulose has disintegrant properties and one of the reasons for its incorporation into tablets is to enhance disintegration. It is, therefore, interesting to note that beads containing Avicel© PH 101 do not disintegrate when placed into aqueous media. The effect of wetting and drying microcrystalline cellulose could decrease its disintegrant action (Bandelin, 1989). The case hardening of the beads may, also, have been responsible for the lack of disintegration.

Formula 3.27 beads were formulated with Avicel© RC 591 (in spite of this grade having displayed faster dissolution than Avicel© PH101 because the former grade allows a greater amount of drug and excipient loading. This formulation contains approximately 60% of the drug and 20% of the

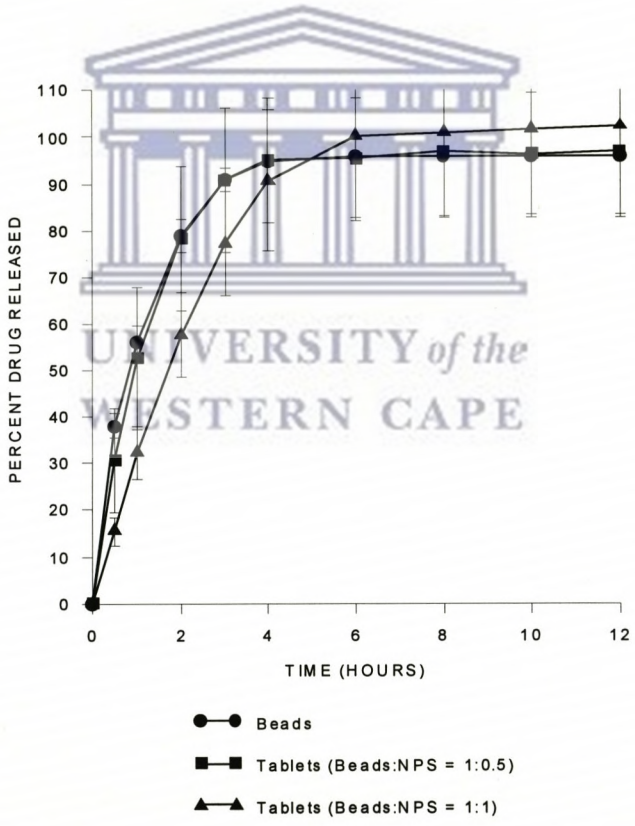


FIGURE 5.9: DISSOLUTION OF TABLETS COMPRESSED FROM FORMULA 3.18 BEADS

retardant. Such high concentrations would not have been possible with Avicel© PH 101. It was expected that the higher retardant loading would enable stronger tablets to be formed and would, also, more than offset the faster dissolution due to the presence of Avicel© RC 591. Tributylcitrate was included as a plasticizer. Because it is insoluble, it was not expected to enhance the rate of dissolution.

The dissolution profiles of tablets prepared from Formula 3.18, and Formula 3.19, beads and non pareil seeds (NPS) are shown, respectively, in Figure 5.9 and Figure 5.10. For comparison, the dissolution profiles of the beads are also shown. Each graph reveals a similar trend: dissolution is fastest from the beads and slowest from the tablets containing equal parts of beads and non-pareil

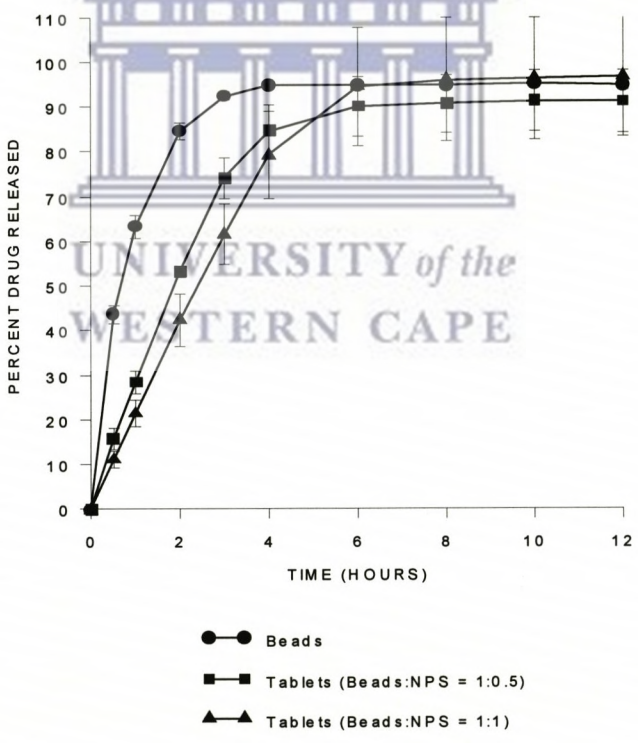


FIGURE 5.10: DISSOLUTION OF TABLETS COMPRESSED FROM FORMULA 3.19 BEADS

seeds, whereas the tablets containing half as much non-pareil seeds as beads had an intermediate release rate. The differences were more pronounced with Formula 3.19 which was compressed from the beads with the higher Eudragit© RSPO content (20% compared to 10% in Formula 3.18). The

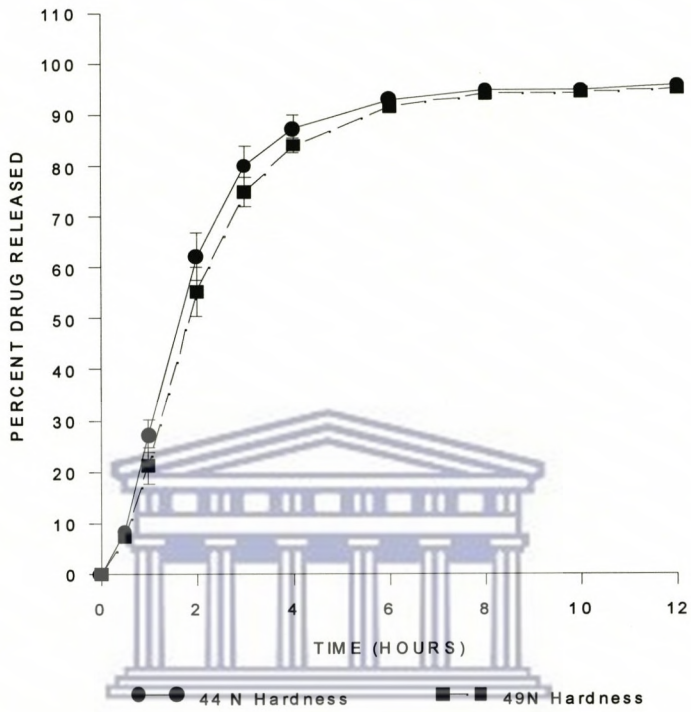


FIGURE 5.11: DISSOLUTION OF FORMULA 3.27 TABLETS

dissolution of the drug from tablets prepared from Formula 3.27 beads is shown in Figure 5.11. This graph shows that the harder tablets released the drug at a slightly slower rate; the small hardness difference between the two batches of tablets, however, did not make a large difference in the rate of dissolution.

Of the preparations containing non pareil seeds, tablets with equal parts of Formula 3.19 beads and non-pareil seeds gave the slowest release. Approximately 95% of the drug was released over 6

hours. The release from Formula 3.27 tablets (49N hardness) is approximately the same, with about 92% of the drug released after 6 hours. However, the latter release profile is not as flat as the former. These curves represent a reasonable retardation of drug release, though the sustained release effect is not adequate for administration of Theophylline to patients. However, these results indicate that the technique may have application with other drugs where a smaller retardation of drug release may be therapeutically acceptable; or where the drug has a smaller dose; or the drug is less soluble.

It is interesting to note that, within the dissolution flask, the tablets containing the lower proportion of non pareil seeds disintegrated completely in approximately one hour, whereas the beads with the higher proportion of non pareil seeds disintegrated in approximately half an hour. While the latter gave a slower dissolution rate, they also disintegrated faster. Thus, in this case, the advantages of beads with respect to stomach emptying rate are not lost by compressing the beads into tablets. Non pareil seeds contain a proportion of wax and it is likely that this wax is responsible for the increased retard effect observed. The disintegration in the case of Formula 3.27 beads took longer than 4 hours and was incomplete, in that a few large pieces of the tablet remained.

5.7 POSSIBLE REASONS FOR THE SMALL SUSTAINED RELEASE EFFECT OF MATRIX BEADS

Since none of the beads displayed a large sustained release effect, the possible reasons for this phenomenon were considered. Firstly, the low concentration of retardant probably contributed to this effect. When Avicel© PH 101 is used, a large amount is required to form beads of good shape. This spheronizing aid has the advantage of not causing the swelling and, therefore, the increased dissolution that occurs with carboxymethylcellulose-containing grades of microcrystalline cellulose.

When a high dose drug, such as theophylline, is used in combination with Avicel© PH 101, a large amount of the retardant cannot be accommodated in a reasonably-sized capsule. In the formulations described in the previous section, a maximum of 20% of the retardant was used. It is obvious that a larger amount of the retardant could have been accommodated if a lower concentration of drug was used and the beads filled into 2 capsules, but this was avoided in the present work. The lack of significant compaction pressure (relative to tablets) is a second reason for the inefficiency of the matrix formers used in this work. In matrix tablets, 20% Eudragit© RSPO can be expected to provide a significant retardation of drug release.

From the above considerations, the question of the distance between consecutive retardant particles within a matrix bead arose. Were the retardant particles within the bead sufficiently close to each other to form a matrix under the low compaction forces experienced by material undergoing extrusion and spheronization? To calculate the distance between consecutive matrix particles, an equation was developed. This necessitated the making of the following assumptions to simplify the derivation:

(i) that all the particles were spherical; and

(ii) that there was a perfect mix, i.e. the distribution of the various constituents within the powder was ideal.

The situation within a bead is depicted in Figure 5.12, where R = particles of retardant; A = Avicel© particles; D = drug particles. The R particles are not necessarily larger than the other particles, but are depicted as such for visual clarity. Two R particles are separated by A particles and D particles,

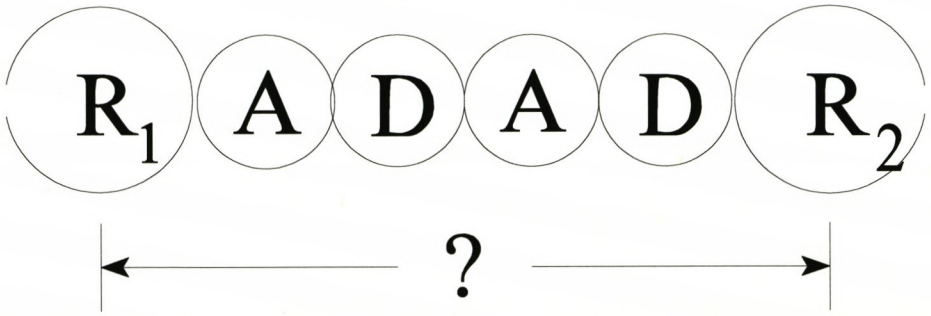


FIGURE 5.12: DIAGRAMMATIC REPRESENTATION OF ADJACENT POWDER PARTICLES

where the number of such particles is not known. The problem is reduced to calculating the distance between the consecutive R particles, in an ideal mixture of 3 spherical components. The distance between the two R particles is given by:

$$distance_{R_1-R_2} = (d_A \times n_A) + (d_D \times n_D) \quad \textbf{(1)}$$

where n_A = number of **A** particles between two **R** particles, and n_D = number of **D** particles between two **R** particles.

Now,

$$n_A = \frac{N_A}{N_R} \quad \text{and}$$

$$n_D = \frac{N_D}{N_R}$$

where N_A = total number of Avicel© particles in the batch,

N_D = total number of drug particles in the batch, and

N_R = total number of retardant particles in the batch.

Therefore, **(1)** can be written as:

$$distance_{R_1\text{-}R_2} = (d_A \times \frac{N_A}{N_R}) + (d_D \times \frac{N_D}{N_R}) \qquad \textbf{(2)}$$

Now,

$$N_A = \frac{M_A}{m_A}, \quad N_R = \frac{M_R}{m_R} \quad and \quad N_D = \frac{M_D}{m_D}$$

where N_A = total number of all **A** particles

M_A = total mass of all **A** particles, and

m_A = mass of one **A** particle, etc.

Equation (2) can therefore be written as:

$$distance_{R_1\text{-}R_2} = (\frac{d_A}{1} \times \frac{\frac{M_A}{m_A}}{\frac{M_R}{m_R}}) + (\frac{d_D}{1} \times \frac{\frac{M_D}{m_D}}{\frac{M_R}{m_R}})$$

$$= \frac{M_A m_R}{m_A M_R} d_A + \frac{M_D m_R}{m_D M_R} d_D \qquad \textbf{(3)}$$

Since $D = \frac{M}{V}$, where D = density and V = volume,

$$m_A = D_A V_A ;$$

$$m_D = D_D V_D ; \text{ and}$$

$$m_R = D_R V_R \qquad \textbf{(4)}$$

Substituting for m_A, m_D, and m_R into equation (3):

$$distance_{R_1\text{-}R_2} = \frac{M_A D_R V_R}{D_A V_A M_R} d_A + \frac{M_D D_R V_R}{D_D V_D M_R} d_D \qquad \textbf{(5)}$$

Assuming spherical particles:

$$V = \frac{4}{3}\pi r^3$$

or

$$V = \frac{4}{3}\pi\left(\frac{d}{2}\right)^3 \qquad \textbf{(6)}$$

Substituting equation (6) into equation (5):

$$distance_{R_1\text{-}R_2} = \frac{M_A D_R \left(\frac{4}{3}\pi\left(\frac{d_R}{2}\right)^3\right)}{D_A M_R \left(\frac{4}{3}\pi\left(\frac{d_A}{2}\right)^3\right)} d_A + \frac{M_D D_R \left(\frac{4}{3}\pi\left(\frac{d_R}{2}\right)^3\right)}{D_D M_R \left(\frac{4}{3}\pi\left(\frac{d_D}{2}\right)^3\right)} d_D$$

$$= \frac{M_A D_R (d_R)^3}{D_A M_R (d_A)^3} d_A + \frac{M_D D_R (d_R)^3}{D_D M_R (d_D)^3} d_D$$

$$distance_{R_1-R_2} = \frac{M_A D_R d_R^3}{D_A M_R d_A^2} + \frac{M_D D_R d_R^3}{D_D M_R d_D^2} \quad (7)$$

By substituting density, mass and particle size values for the components of the beads into equation (7), it is possible to determine the separation between matrix particles. Considering Formula 3.18 beads, as an example, the average distance between the Eudragit© RSPO particles was calculated to be 54.53μm. The data required for the calculation is contained in Table 5.6. The particle size of Avicel© PH101 and Theophylline were obtained from the manufacturers, while that of Eudragit© RSPO was determined by optical microscopy. The densities were determined using an air comparison pycnometer (Beckman) and are the average of 2 determinations.

TABLE 5.6: SUMMARY OF DATA FOR CALCULATION OF PARTICLE SEPARATION

	THEOPHYLLINE	EUDRAGIT© RSPO	AVICEL© PH101
Mass (g)	250	50	200
Density (g/ml)	1.44	1.23	1.53
Particle diameter (μm)	74	31	50

The large separation of the Eudragit© particles indicates that they are not likely to fuse within the bead to form a consolidated matrix. In a tablet formulation, the pressure of the punches results in the deformation, or the fracture, of the particles. Usually, the matrix forming material deforms more readily which causes it to wrap around the other constituents. With further pressure, the deformed or fractured constituents consolidate to form the matrix. The separation of the particles and the lack of significant pressure (relative to tabletting) in the extrusion and spheronization process means that the retardant remains largely as individual particles and, hence, matrix formation does not occur and drug release is not sustained to a great extent. This theory offers an explanation for the fact that the observed sustained release effect was not very large. In the described experiments, the individual retardant particles were hydrophobic and, hence, offered some resistance to the passage of fluids through the beads. This resulted in the observed retardation of drug release. If the retardant particles had consolidated into a matrix, a much larger retardation of drug release would have been observed.

CHAPTER 6: EXTERNAL MATRIX FORMATION

6.1 INTRODUCTION

In previous chapters, it was shown that it is not easy to obtain a sustained release effect by using binders (since excessive binder causes tackiness) nor was it a simple matter to sustain the release of a drug by utilizing a matrix (since the matrix former could not be incorporated into beads in sufficient quantity). It has also been shown mathematically, for the conditions described in Chapter 5, that the particles of the retardant within a spheronized bead will always be far apart. Such particles will not fuse to form a consolidated matrix and, hence, the development of an adequate sustained release system cannot be expected.

One of the major problems encountered in the extrusion and spheronization process is the estimation of the correct amount of water to add to the powders and the difficulty of spheronizing inadvertently overwet material. When a particular formulation is produced repeatedly, the appropriate amount of water would have been assessed in preliminary experiments and a precise volume, or mass, of water can be added. However, when preparing a particular formulation for the first time, it is extremely difficult to judge how much liquid is sufficient. This is usually done subjectively by feeling the wet mass. Once the material is in the spheronizer, however, the operator may be made aware that he has added too much liquid by the fact that the material agglomerates. In unpublished work undertaken by the present writer, it was found that agglomeration could be prevented by the addition of a powdered material onto the surface of the

rotating beads. The added material acted as an absorbent. Sodium carboxymethylcellulose was found to be particularly useful for this purpose, in spite of the material, itself, being tacky when wet. Addition of a small amount decreased the wetness of the beads that were forming and so avoided agglomeration during continued processing. Sodium carboxymethylcellulose was able to function in this way because of its high water-absorbing capacity.

Since, (1) it is not possible to add sufficient matrix former within the beads, and (2) it is feasible to add a powdered material to the outside of the beads while they are rotating in the spheronizer,

FIGURE 6.1: DIAGRAM OF AN EXTERNAL MATRIX

the concept of forming the matrix outside the beads was developed. This would be a "pure" matrix, containing no other material and no drug (Figure 6.1). The presence of a drug-free zone as a peripheral layer of the beads would decrease the rate of drug release and also has the potential to reduce the burst effect which occurs with many sustained release preparations. This phenomenon involves the rapid release of a large amount of the drug soon after contact with the

medium and may be due to the rapid dissolution of the drug particles situated at the periphery of the dosage form. The utility of the external matrix concept was tested using several potential matrix formers.

6.2 ACETAMINOPHEN FORMULATIONS

6.2.1 Method

Several batches of beads were produced, each consisting of the same basic bead core, but varying according to the nature of the external matrix added. The added external matrix materials were Avicel© PH 101 (Formula 6.7), sodium carboxymethylcellulose (FMC Corporation) (Formula 6.8), Eudragit© RSPO (Formula 6.9), ethylcellulose 10cP (Formula 6.10), magnesium stearate (Formula 6.11) and Cutina© HR (Henkel) (Formula 6.12). The ethylcellulose was finely ground and sieved and the 250/149μm fraction was used. The other matrix formers were used as received. The basic formulation for the beads was as follows:

Acetaminophen	300g
Avicel© PH 101	200g
5% Polyvinylpyrrolidone K90 solution	50ml

The mixing vessel of the planetary mixer was tared after the addition of the powders. Using a slow mixing speed (achieved by means of a rheostat attached to the mixer motor), the powders were pre-mixed for 3 minutes. The polyvinylpyrrolidone solution and the water were slowly added and the speed of mixing was gradually increased. Water was added until the total mass

of the added liquids was 289g. Wet mixing of the powders was continued over a period of seven minutes after the addition of liquids.

The wet mass was extruded through a screen with 1mm apertures and the extrudate was spheronized for 5 minutes at 650rpm. The spheres were removed from the spheronizer and were stored in a plastic bag which was sealed to reduce loss of moisture. A moisture content determination was done on approximately 5g of beads using a moisture balance (Ohaus). The results of the moisture content determinations were used to calculate the percentage of solids in each batch of beads. An amount of external matrix former, equivalent to 10% of the mass of the solids, was weighed out.

The beads were returned to the spheronizer and rotated at 350rpm for 5 minutes. The spheronizer was intermittently switched off during this time and a portion of the matrix former sprinkled over the beads. The spheronizer was then started again and, with the opening of the spheronizer covered, the powder was allowed to distribute over the beads. The speed of the machine was then increased to 650rpm, once more, and the beads rotated for a further 5 minutes. The beads were removed from the spheronizer and allowed to air dry for one hour. Thereafter, they were oven dried at a temperature of 40° overnight. The dried beads were classified into the following size groups: 1.4 to 0.991mm; 0.991 to 0.420mm; and less than 0.420mm. The 0.991/ 0.420mm size fraction was used for further study.

The equivalent of 150mg of Acetaminophen was filled into size 0 elongated capsules and a dissolution test was performed in deionized water, using the paddle method at 50rpm. The

dissolution samples were analysed by UV spectrophotometry at 244nm, the wavelength of maximum absorption of the drug.

6.2.2 Results and Discussion

In these formulations, control of the amount of liquid added was achieved by means of the difference in mass of the mixing bowl before, and after, the addition of liquid. This proved to be an excellent method, as the liquid that evaporated during the mixing operation could be accounted for.

After the addition of approximately one tenth of the weighed amount of sodium carboxymethylcellulose, the spheres became tacky and started to agglomerate. This matrix former was, therefore, considered unsuitable for use as envisaged. In the earlier work, referred to in the introductory section of this chapter, much less sodium carboxymethylcellulose had been used to remove excess moisture from the surface of the beads. This goal was achieved without the beads becoming tacky. However, the larger amounts envisaged as external matrix formers could not be accommodated without tackiness developing.

The sodium carboxymethylcellulose-containing beads (Formula 6.8) were discarded and the results and discussion that follow pertain to the remaining formulae. The dissolution profiles are depicted in Figure 6.2. With the exception of magnesium stearate, none of the external matrix formers retarded the release of the drug appreciably. It is surprising that Eudragit©, Cutina© HR and ethylcellulose retarded drug release to such a small extent. Eudragit© has been used extensively in matrix tablets, for example by McGinity et al. (1983). Pather et al. (1993) have

shown that ethylcellulose displays significant potential as a direct compression retardant. Similarly, Cutina© HR, which consists of hydrogenated castor oil, has been used as a matrix former in sustained release tablets.

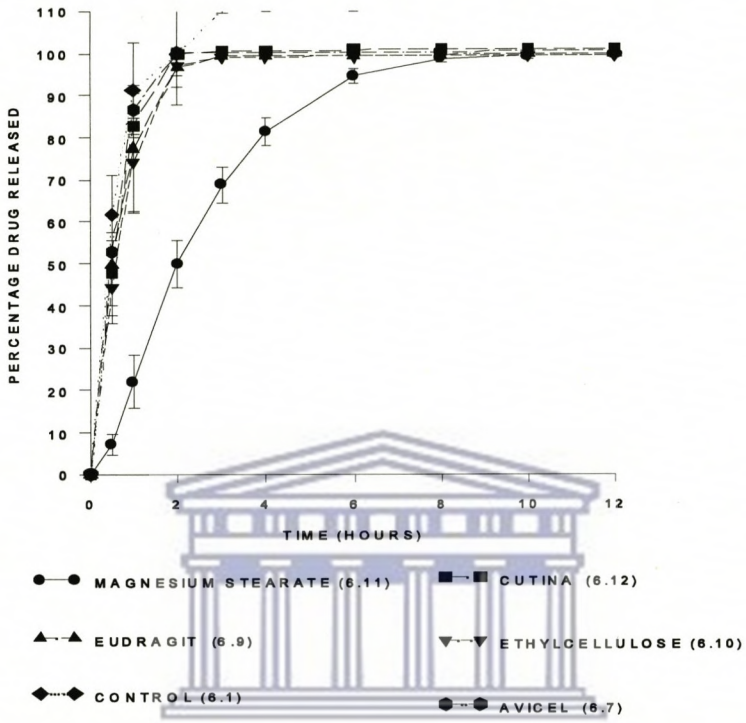


FIGURE 6.2: EFFECT OF EXTERNAL MATRIX FORMATION ON ACETAMINOPHEN DISSOLUTION

The lack of significant compaction during bead formation is probably the reason for the failure of these agents to afford significant retardation of drug release in the present work. The spheronization process and, particularly, the extrusion process exert some pressure on the wet material. It was hoped that these pressures would have provided sufficient compaction of the materials to form matrices. However, these pressures are very much less than the pressures involved in tabletting and probably resulted in little compaction of the external matrix. Hence, the retardation of drug release was small. While it was envisaged that a drug-free zone on the

periphery of the beads would have sustained the release of the drug, this effect was not apparent. If the particles of the external matrix did not consolidate adequately, large channels would have been available for the flow of water and, therefore, the effect of this layer was minimal.

Magnesium stearate, on the other hand, consists of very fine particles which are strongly hydrophobic and which have a great covering capacity for particles with which they are mixed. The beads acquire a hydrophobic surface layer after mixing with magnesium stearate. Only slow penetration of water through this external matrix is possible and this results in the sustained release effect observed. In this case, drug release was extended over 8 hours, making magnesium stearate a potentially useful external matrix former. In the dissolution test, each capsule contained only 150mg of the drug and Acetaminophen was used as a model drug in this series of formulations.

6.3 TABLETTING OF ACETAMINOPHEN FORMULATIONS

Attempts were made to compact tablets from the beads prepared in the previous section. Only the beads that contained Eudragit© RSPO and Cutina© HR formed good tablets. Of these, the tablets containing Cutina© HR had a better physical appearance and were chosen for further study.

6.3.1 Method

The beads containing Cutina© HR (Formula 6.12) were compressed on a rotary tablet press fitted with round, flat-faced punches having a diameter of 8.5mm. Amounts of beads equivalent to 150mg of the drug were individually weighed and filled by hand into the die cavities. Since

Cutina© HR can be compressed without a lubricant, none was added. Three batches of tablets were prepared, each batch differing in the force of compression used to prepare it. Hardness tests as well as dissolution tests were performed on each batch of tablets.

6.3.2 Results and Discussion

The results of the hardness tests appear in Table 6.1 and the dissolution results are shown in Figure 6.3. Compared to the beads, the tablets displayed a much slower rate of drug release. The effect of the compaction force was very great considering that the uncompressed Cutina© HR-containing beads released the drug at almost the same rate as the control (Figure 6.2). Comparing the different batches of tablets, it is observed that the greater the compaction force, the more complete was the dissolution. It is likely that there is a minimal compaction force

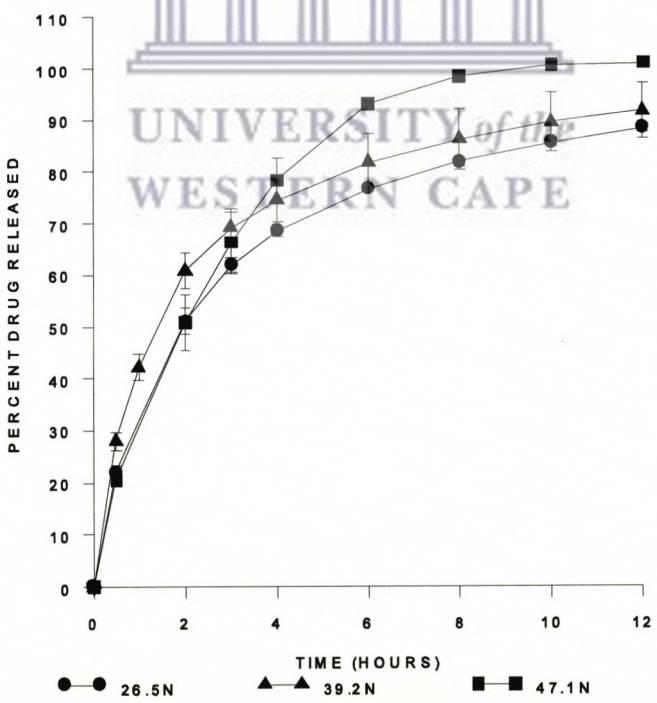


FIGURE 6.3: EFFECT OF COMPRESSION PRESSURE ON THE DISSOLUTION RATE OF ACETAMINOPHEN AND CUTINA© HR TABLETS

required to form the tablet and because consolidation of the matrix former occurs, the rate of drug release is greatly reduced. It is also possible that compaction pressures beyond this minimum create cracks or fissures in the external matrix while also compacting the matrix to a greater extent. The development of fissures in the external matrix is consistent with the presence of a hard, inflexible core. The process of compaction of the beads, therefore, has two effects: firstly consolidation of the matrix material, which slows down the rate of drug release; and, secondly, fissure formation in the matrix which increases the rate and extent of dissolution. The dissolution behaviour of the tablets can be understood in terms of the relative importance of each factor. If one compares the soft tablets with those of intermediate hardness, it appears that the development of fissures in the matrixes of the tablets of intermediate hardness, led to faster dissolution during the entire dissolution test. On the other hand, the increased consolidation of the matrix particles, in the hardest tablets, was more important initially and led to slower dissolution. Towards the latter part of the dissolution run, the influence of the fissures in the external matrix sheath was the predominant effect, which led to more complete dissolution.

TABLE 6.1: HARDNESS OF TABLETS CONTAINING CUTINA© HR

	MEAN HARDNESS (N) (N=3)	S.D. (N)
Batch 1	47.07	2.94
Batch 2	38.25	1.96
Batch 3	26.48	2.94

These tablets did not disintegrate rapidly and, therefore, the advantages of multiparticulates would be lost if such a preparation were to be administered to patients. However, considered as matrix tablets, these preparations have potential application. The beads from which they are

made can be rapidly prepared. These basic units for compaction are spherical and, therefore, free flowing. They need neither a glidant nor a lubricant and can be directly compressed to produce sustained release tablets. By manipulation of the Cutina© HR content and the compaction pressure, it is expected that the release profile can be altered to suit the needs of a particular drug or clinical situation.

6.4 THEOPHYLLINE FORMULATIONS

In view of the degree of success achieved with the beads containing Acetaminophen and magnesium stearate, it was decided to attempt a similar formulation using Theophylline. Theophylline is less soluble than Acetaminophen (1 in 120 compared to 1 in 70) (Reynolds, 1982) and sustained release preparations may, therefore, be easier to prepare. The larger dose, however, is a negative factor in the attempt to obtain a sustained release formulation.

6.4.1 Method

The control (Formula 3.5) was manufactured according to the following formula:

Theophylline	300g
Avicel© pH 101	200g
5% Polyvinylpyrrolidone K90 solution	50ml

The beads were prepared as previously described after fitting a screen with 1.5mm apertures to the extruder. A formula containing magnesium stearate as the external matrix (Formula 3.28) was also produced. The core beads were manufactured in an identical fashion to the control but

10% magnesium stearate was, thereafter, added according to the method described for Acetaminophen preparations. The dried beads were separated into several size fractions and dissolution tests were conducted in triplicate on each size. The paddle method at 50 rpm was used, with deionized water serving as the dissolution medium. Dissolution tests were also conducted in acidic dissolution medium (pH = 1.2), using the 1.4/1.18mm and the 0.991/0.710mm size fractions. Using a Roche Friabilator, the friability of accurately weighed samples of approximately 3g of 1.7/1.4mm beads was determined. The hardness of the beads was also assessed using the 2.36/1.7mm size fraction on a Schleuniger hardness tester.

6.4.2 Results and Discussion

The friability and hardness values are shown in Table 6.2 which indicates that the beads have excellent physical strength. The results of the dissolution tests in acidic medium are shown in

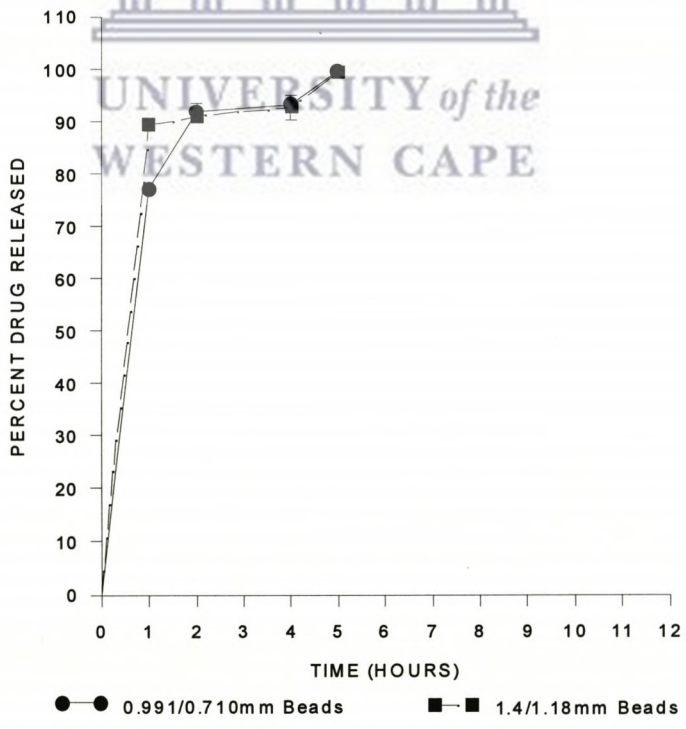


FIGURE 6.4: DISSOLUTION OF THEOPHYLLINE BEADS IN ACIDIC MEDIUM

Figure 6.4 which reveals that the beads released the drug rapidly in this medium. The smaller beads released the drug marginally slower than the larger beads, especially during the first hour. The results of the dissolution study in deionized water are shown in Figure 6.5.

TABLE 6.2: FRIABILITY AND HARDNESS OF THEOPHYLLINE BEADS

	3.5	3.28
Friability (%) (n=2)	0.05	0.07
Hardness (± S.D.) (N) (n=5)	44.6 (± 4.2)	42.4 (± 3.8)

The dissolution rate in deionized water is proportional to bead size, with the largest beads releasing the drug the fastest. In general, if size differences were found to be related to drug release rate, the opposite trend would have been expected. The smallest beads have the largest total surface area and, hence, would be expected to release the drug the fastest. The clear

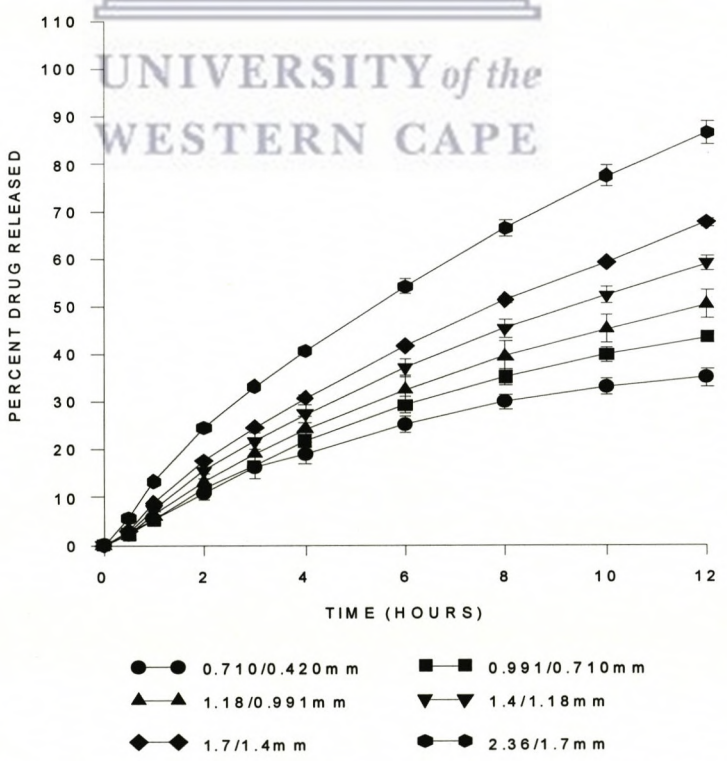


FIGURE 6.5: EFFECT OF SIZE ON DISSOLUTION OF BEADS WITH AN EXTERNAL MATRIX

opposite trend observed indicates that other factors are operational, apart from simply the surface area available to the dissolution medium. These size fractions were obtained from the same batch of beads and were not a series of batches, each made with a different aperture size extruder screen. Hence, within the spheronizer each bead competed for the added magnesium stearate. If small, and large, beads had an equal opportunity to pick up magnesium stearate, then the smaller beads can be expected to have a thicker layer of external matrix. This can also be visualised as the magnesium stearate being distributed equally amongst the various beads, with the smaller beads receiving as much as the larger beads. If this hypothesis is true, then the smaller beads will have a thicker layer of external matrix. They will, therefore, have a slower rate of drug release because of the greater distance that water molecules must travel through the hydrophobic layer to reach the drug particles in the core bead.

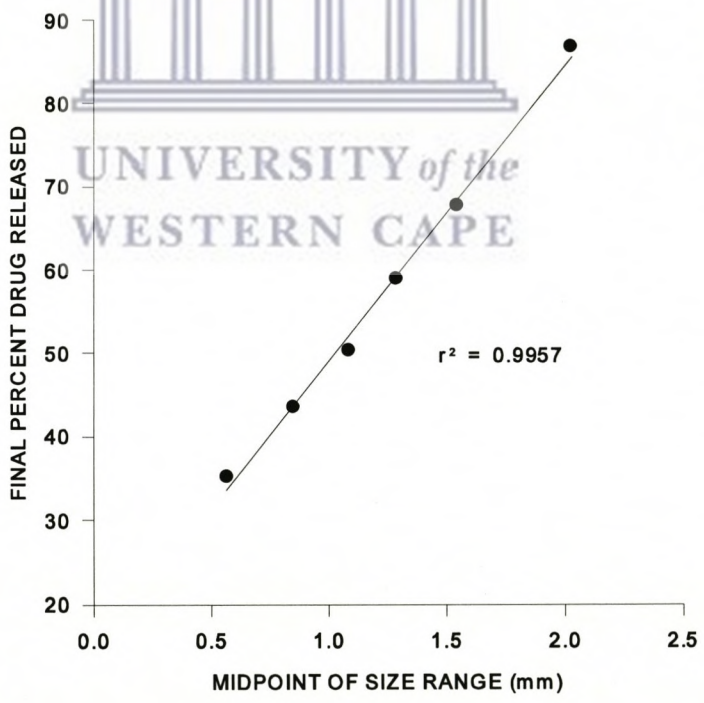


FIGURE 6.6: RELATIONSHIP BETWEEN FINAL AMOUNT OF DRUG RELEASED AND SIZE OF BEADS

The amount of drug released after 12 hours, for each size fraction, was plotted against the mean of the size range. This graph is shown in Figure 6.6 and reveals an excellent linear correlation between these variables.

6.5 CHLORPHENIRAMINE MALEATE FORMULATIONS

The use of magnesium stearate as an external matrix has been shown, above, to have sustained the release of drugs of intermediate solubility, although the release in acid medium was fast. The effect of this sustained release technique on the dissolution of a very soluble drug was determined as the next step in assessing the utility of the method.

Chlorpheniramine Maleate has a solubility of 160mg/ml (Eckhart and McCorkle, 1978) and it is, hence, difficult to prepare sustained release formulations of this drug, particularly if no coating is to be applied. The difficulty persists in spite of the small dosage (8 to 12mg every 12 hours for an adult). Since it is not easy to sustain its release, Chlorpheniramine Maleate was regarded as an extreme case and was, hence, chosen to study the usefulness of the technique of external matrix formation. Beads were produced in a manner similar to that for Acetaminophen and Theophylline. In anticipation of rapid dissolution of this soluble drug, a complementary retarding mechanism, involving the use of sodium bicarbonate, was utilized in additional formulations.

6.5.1 Method

Chlorpheniramine Maleate is the salt of the poorly soluble base, Chlorpheniramine. When Chlorpheniramine Maleate and sodium bicarbonate are dissolved in the same solution, they react

to form sodium maleate and the base, Chlorpheniramine. A relatively slow permeation of water can be expected through a bead containing magnesium stearate as the external matrix. If the bead contained Chlorpheniramine Maleate and sodium bicarbonate, the reaction of these substances within the bead would convert some of the Chlorpheniramine Maleate to Chlorpheniramine. Since the latter is poorly soluble, the release of the drug would be retarded.

The formulations detailed in Table 6.3 were prepared. These formulations contain lactose as the filler. The method of preparation was similar to that described before, the quantity of water added to each formulation being 200ml. The amount of sodium bicarbonate used is the equivalent of either 1.5 times, or 3 times, the molar ratio of the drug. The amount of magnesium stearate added was based on the solids content of the beads and this value was calculated after performing a moisture content determination, as previously described.

TABLE 6.3: FORMULAE OF BEADS CONTAINING A SOLUBLE FILLER

	8.1	8.2	8.3	8.4
Chlorpheniramine Maleate (g)	8	8	8	8
sodium bicarbonate (g)	-	-	2.587	5.166
Avicel© PH 101 (g)	200	200	200	200
lactose (g)	192	192	189.4	186.8
magnesium stearate (%)	-	10	5	10
5% polyvinylpyrrolidone K90 solution (ml)	40	40	40	40

A review of the literature shows that lactose is, by far, the most commonly used filler in extrusion and spheronization, probably due to the fact that it contributes to the plasticity of the

wet mass and, hence, assists in the formation of good beads. However, lactose is very soluble, having a solubility of 1 in 6 (Reynolds, 1982) and may thus contribute to the rapid release of the drug.

To examine the effect of an insoluble filler on the ease of preparation, and on the dissolution rate, of the beads, an alternate set of formulations was prepared using dicalcium phosphate dihydrate as the filler. The formulae for these beads are listed in Table 6.4. To each formulation, 225ml of water was added at the wet massing stage.

TABLE 6.4: FORMULAE OF BEADS CONTAINING AN INSOLUBLE FILLER

	8.5	8.6	8.7	8.8
Chlorpheniramine Maleate (g)	8	8	8	8
sodium bicarbonate (g)	-	-	5.166	5.166
Avicel© PH 101 (g)	200	200	200	200
dicalcium phosphate dihydrate (g)	192	192	189.4	186.8
magnesium stearate (%)	-	10	-	10
5% polyvinylpyrrolidone K90 solution (ml)	40	40	40	40

For dissolution testing, beads equivalent to 8mg of Chlorpheniramine Maleate were filled into size 0 elongated capsules. The dissolution samples were measured at 262nm, the wavelength of maximum absorption of Chlorpheniramine Maleate, after ensuring that the other ingredients did not absorb at this wavelength.

6.5.2 Results and Discussion

The formulations containing dicalcium phosphate dihydrate all produced wet masses that appeared drier and less cohesive than the lactose-containing formulations, when equal amounts of water were added. This filler consists of very fine particles which absorb more moisture than lactose. For this reason, additional water had to be added to this series of formulations, compared to the lactose formulations. In spite of this, the wet mass produced was less plastic, and more difficult to process, compared to the lactose-containing formulations.

The dissolution results in respect of the formulations containing lactose are shown in Table 6.5. The dissolution of the control beads (Formula 8.1) was fast, with practically all of the drug being released within 30 minutes. The release of the drug from Formula 8.2 beads, which contained 10% magnesium stearate as an external matrix, was slightly slower. Formula 8.3, which had 1.5 times the molar ratio of sodium bicarbonate to drug and 5% magnesium stearate, displayed an even slower rate of drug release. The release of the drug was slowest from Formula 8.4 which contained 3 times the molar ratio of sodium bicarbonate and 10% magnesium stearate.

TABLE 6.5: DISSOLUTION OF CHLORPHENIRAMINE MALEATE AND LACTOSE FORMULATIONS

	30 MIN (± S.D.) (%)	60 MIN (± S.D.) (%)
8.1	100.99 (±1.12)	101.78 (±2.34)
8.2	88.45 (±3.67)	97.15 (±4.58)
8.3	74.09 (±2.15)	86.28 (±2.69)
8.4	41.59 (±2.30)	64.70 (±3.69)

The effect of sodium bicarbonate can be assessed by comparing Formulae 8.2 and 8.4. These formulations are similar, except that the latter contains 3 times the molar ratio of sodium bicarbonate while the former contains none. This difference in the formulation altered the release at 30 minutes from 88.45% to 41.59% and at 60 minutes from 97.15% to 64.70%. This illustrates the principle that sodium bicarbonate retards the rate of release of the drug when used in combination with magnesium stearate. Even for this combination, however, release of the drug was much too fast for use of the product as a sustained release dosage form. Magnesium stearate on its own had little effect, as demonstrated by the very small difference in dissolution rates between Formulae 8.1 and 8.2.

Much higher concentrations of sodium bicarbonate have the potential to sustain the release of the drug to a greater extent but such formulations were not considered acceptable. Sodium bicarbonate, itself, leaches out of the bead due to its high solubility. Hence, higher concentrations would have appreciably altered the pH of the dissolution medium or that of the gastro-intestinal fluids, during *in vivo* testing. Thus, while it may have been possible to sustain the release of this soluble drug to a greater extent by replacing lactose in these formulations with sodium bicarbonate, such a formulation was not attempted since it would have altered a fundamental physiological variable (gastro-intestinal pH) when the product was administered to patients.

The dissolution of the beads containing dicalcium phosphate dihydrate is presented in Table 6.6. These formulations followed a similar trend to that of the lactose formulations, with the fastest drug release occurring from Formula 8.5 beads and the slowest from Formula 8.8 beads. The

lactose formulations and the dicalcium phosphate dihydrate formulations form an analogous series with the exception of Formula 8.3 in the lactose group (which contained sodium bicarbonate in 1.5 times the molar ratio and 5% magnesium stearate) and Formula 8.7 in the dicalcium phosphate dihydrate group (which contained 3 times the molar ratio of sodium bicarbonate and no magnesium stearate). The dicalcium phosphate dihydrate group did not show slower release than the lactose group, contrary to what had been expected. (The rate of drug release from the dicalcium phosphate dihydrate group was, actually, marginally higher.)

TABLE 6.6: DISSOLUTION OF CHLORPHENIRAMINE MALEATE AND DICALCIUM PHOSPHATE DIHYDRATE FORMULATIONS

	30 MIN (± S.D.) (%)	60 MIN (± S.D.) (%)
8.5	106.43 (± 1.12)	107.26 (± 3.2)
8.6	93.06 (± 4.56)	104.14 (± 3.21)
8.7	67.56 (± 3.76)	80.32 (± 2.95)
8.8	50.74 (± 1.19)	67.28 (± 0.67)

The effect of the diluent on the release rate of drugs, in general, may be significant. As a soluble diluent dissolves, it creates large channels for the entry of dissolution medium into the matrix and, hence, a faster rate of drug release is observed. The fact that the inclusion of lactose did not cause faster drug release, in the present work, can probably be attributed to the rate of solution of lactose. While lactose is very soluble, its rate of solution is slow (Reynolds, 1982). Hence, the Chlorpheniramine Maleate was probably released before a major portion of the lactose had dissolved and, therefore, the latter had little effect on the rate of release of the drug. A probable reason for the slightly faster release from beads containing dicalcium phosphate dihydrate is the

looser packing of the powder particles within the beads containing this diluent compared to lactose-containing beads.

6.6 APPEARANCE OF BEADS WITH AN EXTERNAL MATRIX

It was expected that the addition of an external matrix would improve the shape and surface texture of the beads. To test this hypothesis, some of the formulations with an external matrix were compared with similar formulations that did not have an external matrix. Scanning electron microscopy and image analysis were used to make the comparisons.

6.6.1 Method

For the electron microscopic studies, Formula 3.5 and Formula 3.28 beads were scanned at 25kV. The image analysis of the beads from these formulae, as well as those from Formula 8.7 and Formula 8.8, were performed on a Quantimet Image Analyser.

6.6.2 Results and Discussion

The image analysis data are given in Table 6.7. The roundness, a shape factor, was computed by the instrument from the perimeter and the area of the image of the bead, using the equation given below. The area is the total number of detected pixels within the image. The factor 1.064, in the equation, is used to correct the perimeter for the effect of the corners produced by the digitization of the image. A roundness score of unity indicates a perfect circle, whereas values up to 1.2 are acceptable for further pharmaceutical processing. For example, such beads have a shape that allows successful coating.

$$\text{Roundness} = \frac{P^2}{4 \times \pi \times A \times 1.064}$$

where P = perimeter of image,

A = area of image, and

1.064 = a correction factor

All the beads had excellent roundness values, approaching the theoretical limit. Hence, one cannot distinguish between the beads with, and without, an external matrix in terms of shape. It had been expected that the beads with the external matrix would have a better shape than those which did not have this layer, since the fine powder would have filled out the deviations from sphericity that may have been present. However, the shape could not have been improved by much since it was already excellent. The long spheronization time is considered the reason for the excellent shape of these beads.

TABLE 6.7: ROUNDNESS SCORES OF SELECTED BEAD FORMULATIONS

SAMPLE	NUMBER	ROUNDNESS (+ S.D.)
Formula 3.5 (1)	87	1.06 (± 0.02)
Formula 3.5 (2)	112	1.07 (± 0.03)
Formula 3.28 (1)	102	1.06 (± 0.03)
Formula 3.28 (2)	108	1.07 (± 0.05)
Formula 8.7 (1)	112	1.07 (± 0.02)
Formula 8.8 (1)	88	1.07 (± 0.03)
Formula 8.8 (2)	91	1.06 (± 0.02)

The scanning electron micrographs of the surface of Formula 3.5 and Formula 3.28 beads are shown in Figure 6.7. The surface of Formula 3.5 beads is rough and pitted. The deposition of the fine magnesium stearate powder onto the surface of Formula 3.28 beads has filled out the roughness, making the surface much smoother. It is expected that the relatively large pits on the surface of Formula 3.5 beads allow rapid entry of water and, hence, faster dissolution.

6.7 CONCLUSIONS

The technique of external matrix formation produces beads with an excellent appearance. The beads are very smooth and this represents a definite advantage over conventionally produced beads.

A very good sustained release profile was obtained in respect of the Theophylline beads, when water served as the dissolution medium. In an acidic medium, the release of the drug was much faster, which reduces the value of this technique. However, the true impact of the faster dissolution in acid can only be assessed from *in vivo* experiments. If stomach emptying is rapid, the faster dissolution in acid may be less disadvantageous. In general, beads empty from the stomach much faster than matrix tablets, as noted in Chapter 1. The release of Acetaminophen was sustained for 12 hours in water, while that of Theophylline was sustained for even longer. The dissolution of the extremely soluble drug, Chlorpheniramine Maleate, could not be prolonged for an extended period, even when an additional sustained release mechanism was incorporated.

FIGURE 6.7(a): SURFACE APPEARANCE OF FORMULA 3.5 BEADS (CONTROL)

FIGURE 6.7(b): SURFACE APPEARANCE OF FORMUAL 3.28 BEADS

The solubility of the drug plays a major role in the success of this technique, since the extent to which the release of the drug could be sustained followed a decreasing solubility trend: Chlorpheniramine Maleate (1 in 6.25), Acetaminophen (1 in 70) and Theophylline (1 in 120). In general terms, the technique of external matrix formation may prove to be more useful when using a less soluble drug or lower drug loading.

CHAPTER 7: OVERALL CONCLUSIONS

The concept of preparing sustained release beads without overcoating is an attractive one, particularly in an environment where cost containment is becoming increasingly important. Some of the advantages of such a preparation are:

(a) a saving in manufacturing time and labour, which translates into a cost reduction;

(b) less equipment to purchase which reduces capital expenses;

(c) avoidance of certain problems inherent in the coating technique (such as the loss of coating material during application) which may cause variability in coating thickness and drug release rate; and

(d) the elimination of a possible cycle of quality control tests, the addition of more coating solution, and further quality control tests, which increases costs.

Recognition of these advantages has prompted some research in this area, which has been reviewed in Chapter 2. Most of this research has not been very successful; or it has involved unrealistically low doses and, often, very poorly soluble drugs. Thus, it was appropriate and relevant to attempt to produce non-coated sustained release beads containing therapeutically useful amounts of drugs of various solubilities. This proved more difficult than originally anticipated although some successes were noted.

A range of techniques were employed to sustain the release of the drugs. In Chapter 3, methods involving the use of binders were described; in Chapter 5, matrix beads were

employed; and in Chapter 6, a unique system, termed an external matrix, was attempted. Chapter 4 describes work with Indomethacin in which it was discovered that no externally applied sustaining mechanism was necessary and, indeed, the release of the drug had to be hastened in order to obtain a profile that was sufficiently fast to be useful.

With respect to the use of binders, in particular, it was observed that the sensitivity of the extrusion and spheronization technique made formulation changes extremely difficult. Maintenance of sufficient plasticity and minimal tackiness were essential features for efficient processing. In contradiction to this, there was the need to add increased amounts of binder in order to achieve an adequate sustained release effect. A novel production method that was employed involved wetting the powders in two phases with subsequent mixing of the phases. The drug was mixed with an ethanolic solution of ethylcellulose, and water was used to moisten the Avicel© powder. When the two wet powders were mixed together an extrudable wet mass was obtained and, from this, beads of good physical appearance were produced. This technique obviated the problem of weak, fragile beads which are produced when ethanol forms a large part of the granulating liquid mixture. In addition, the ethanolic solution of ethylcellulose conferred little tackiness on the wet mass and, since ethylcellulose is a potent retardant, only a small amount was needed. When incorporated as described, the ethanolic solution of ethylcellulose was found to be far more useful as a retardant than other common binders. Using this technique, it was possible to sustain the release of Theophylline over approximately 8 hours (Formula 3.2). With some formulations of Theophylline that were prepared, drug release was incomplete, although a burst effect was also observed.

In the work described in Chapter 5, several materials were added to beads with the aim of forming sustained release matrixes. Only magnesium stearate was able to prolong the release of Acetaminophen and Theophylline for a reasonable time. In an attempt to explain why materials that were successfully used in sustained release matrix tablets were of very limited value in beads, the question of the distance between matrix particles, within a bead, arose. An equation was developed to calculate the approximate distance between the retardant particles. Calculations using this equation revealed that the retardant particles were too far apart to expect consolidation to occur. Similar concentrations of the retardant were able to display sustained release properties in tablets because of the large compaction pressure involved in tabletting. This pressure is responsible for deforming the retardant particles and for consolidating the material that is, thus, brought into closer contact.

While, in general, it is difficult to form tablets from beads prepared by extrusion and spheronization, Eudragit©-containing beads were successfully compressed into tablets both on their own and in combination with non pareil seeds. In each case, the sustained release effect was improved by compaction, which served to substantiate the theory that it was the lack of high pressure, during extrusion and spheronization, that was responsible for the small retard effect. In the case of the products manufactured with non pareil seeds, the tablets disintegrated rapidly, releasing the beads. This ensured that the advantages of multiparticulates were maintained.

It was concluded, in Chapter 5, that a consolidated matrix of retardant cannot be formed

within beads, if a high percentage of Avicel© PH 101 served as the spheronizing aid. There were two reasons for this: firstly, larger amounts of retardant cannot be accommodated with high dose drugs; and, secondly, there was a lack of appreciable compaction pressure. Arising partly from this realisation, the idea of forming the matrix outside the beads was developed. Several matrix formers were used in an attempt to sustain the release of the drug in this way. These substances were added to the rotating beads in the spheronizer. Eudragit© RSPO sustained the release of Theophylline for more than four hours. Only magnesium stearate was able to sustain the release of Acetaminophen and Theophylline appreciably. In the latter case, the dissolution, in water, of a standard adult dose of the drug was prolonged for more than 12 hours. However, the dissolution in an acidic medium was much faster. The dissolution of a highly water soluble drug, Chlorpheniramine Maleate, could not be sustained for long. Nevertheless, this technique represents an advance in extrusion and spheronization technology. Magnesium stearate functioned as a release retardant because of its hydrophobic nature. The other matrix formers were unsuccessful probably because the limited compaction that occurred during processing resulted in the formation of wide channels through which water could easily permeate the bead to dissolve the drug.

While the beads containing Cutina© HR did not show promise as sustained release units, they compacted to form tablets of good appearance and acceptable strength. Since they did not disintegrate completely during dissolution testing, they should be considered as matrix tablets that have a reasonable dissolution profile. The basic units from which these tablets were compressed can be prepared quickly and easily and, since they are

spherical, they flow well. While recognizing the disadvantages of all matrix tablets, particularly with regard to stomach emptying rate, the described tablets can be considered to be efficiently prepared because of the good flowability inherent in the spherical shape of the beads and because they can be compressed without the addition of a glidant or lubricant.

The production of sustained release Indomethacin beads with an excellent dissolution profile have been described in Chapter 4. These beads had a more steady release profile than the innovator's product. In a recent patent for a coated pellet formulation of Indomethacin (Mehta, 1990), the fact that Indocin© does not release the drug in an ideal fashion is also mentioned. The patented formulation consists of non pareil seeds onto which drug is loaded. These cores are subsequently coated with a solution containing, amongst other ingredients, ethylcellulose. In sharp contrast to the complexity of this formulation, the Indomethacin formulation described in Chapter 4 is simple to prepare and can be produced in less than one hour.

When effective non-coated sustained release beads are widely produced commercially by extrusion and spheronization, a significant advance in the technology of oral, sustained release medication would have been achieved. While much has yet to be done before this ideal can be achieved, the work described in this thesis represents progress towards this goal and may point the way to some future endeavours in this regard.

ABSTRACT

The popularity and increasing complexity of sustained release dosage forms has resulted in increased costs to the patient. One approach to achieve cheaper, yet effective, sustained release medication is through the simplification of production processes. Matrix tablets have been used to sustain the release of numerous drugs and are cheap to prepare. Since they are single-unit dosage forms, however, they display less predictable transit through the gastrointestinal tract. Hence, they provide less reliable blood levels of the drug in comparison with multiparticulate dosage forms.

Of the various types of multiparticulates available, pellets are popular for oral administration. A fairly recent innovation, in pelletization technology, is extrusion and spheronization. With this technique it is possible to produce pellets with a high degree of drug loading directly and rapidly. The drug loaded beads are usually coated for a sustained release effect. If one could omit the coating step, it would avoid many problems (thus reducing the number of quality control procedures required) and save chemicals, labour and capital for the purchase of additional equipment.

The primary aim of this project was to investigate the preparation of non-coated, spheronized sustained release pellets, while a secondary aim was to prepare beads that can be compressed into sustained release tablets. A tablet can accommodate a larger mass and the compaction forces involved may enhance the sustained release effect.

Several techniques were used in an attempt to sustain the release of drugs of different solubilities. In one series of formulations, a novel method was used to incorporate a binder consisting of ethylcellulose in ethanol. Using this technique, the release of Theophylline was sustained for approximately 8 hours.

In other formulations, several materials were added to beads with the aim of forming sustained release matrixes. Only magnesium stearate was able to prolong the release of Acetaminophen and Theophylline for a reasonable time. In an attempt to explain why materials that were successfully used in sustained release matrix tablets were of very limited value in beads, an equation was developed to calculate the approximate distance between the retardant particles. Calculations using this equation revealed that the retardant particles were too far apart, within each bead, to expect consolidation to occur. The discrete retardant particles do not retard drug release effectively. Eudragit©-containing beads, which sustained the release of the drug to a small extent, were successfully compressed into tablets, both on their own and in combination with non pareil seeds. In each case, the sustained release effect was improved by compaction. In the case of the products manufactured with non pareil seeds, the tablets disintegrated rapidly to release the beads, thus ensuring that the advantages of multiparticulates were maintained.

Because it was realised that a large amount of the matrix material could not be incorporated within the beads if a high dose drug was formulated with Avicel© PH 101, the idea of forming the matrix outside the beads was developed. Several materials were tried in an attempt to form a sustained release external matrix. Eudragit© RSPO prolonged the dissolution of Theophylline for more than

four hours. Magnesium stearate was able to sustain the release of Acetaminophen and Theophylline appreciably. In the latter case, the dissolution, in water, of a standard adult dose of the drug was prolonged for more than 12 hours. However, the dissolution in an acidic medium was much faster. The described technique represents an advance in extrusion and spheronization technology.

While beads containing Cutina© HR did not show promise as sustained release units, they compacted to form sustained release tablets of good appearance and acceptable strength. These tablets were considered to have been efficiently prepared because the constituent beads were easily manufactured and showed good flowability, and because a glidant and a lubricant were not required. The production of sustained release Indomethacin beads with a more steady release profile than the innovator's product has also been described in other experiments. The research described in this thesis represents progress towards the widespread commercial production of effective non-coated sustained release beads and may encourage further work towards this goal.

REFERENCES

Anonymous, Profitability in a changing market: the new realities of pharmaceutical manufacturing. Aerosol Age, 32 (9) (1987) 28-29.

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.

Baert, L., Remon, J.P., Knight, P. and Newton, J.M., A comparison between the extrusion forces and sphere quality of a gravity feed extruder and a ram extruder. Int. J. Pharm., 86 (1992) 187-192.

Baert, L., Vermeersch, H., Remon, J.P., Smeyers-Verbeke, J., and Massart, D.L., Study of parameters important in the spheronisation process. Int. J. Pharm., 96 (1993a) 225-229.

Baert, L., Remon, J.P., Elbers, J.A.C. and Van Bommel, E.M.G., Comparison between a gravity feed extruder and a twin screw extruder. Int. J. Pharm., 99 (1993b) 7-12.

Baert, L. and Remon, J.P., Influence of amount of granulation liquid on the drug release rate from pellets made by extrusion-spheronisation. Int. J. Pharm. 95 (1993) 135-141.

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. Pharm., 69 (1991) 233-237.

Bandelin, F.J., Compressed tablets by wet granulation. In: Lieberman, H.A., Lachman, L. and Schwartz, J.B. (eds.), Pharmaceutical Dosage Forms: Tablets (Vol. 1, 2nd edition). Marcel Dekker, Inc., New York and Basel; 1989.

Banker, G.S. and Anderson, N.R., Tablets. In: Lachman, L., Lieberman, H.A. and Kanig, J.L. (eds.), The Theory and Practice of Industrial Pharmacy (3rd edition). Lea and Febiger, Philadelphia; 1986.

Bataille, B., Ligarski, K., Jacob, M., Thomas, C., and Druru, C., Study of the influence of spheronization and drying conditions on the physico-mechanical properties of neutral spheroids containing Avicel PH 101 and lactose. Drug Dev. Ind. Pharm., 19 (1993) 653-671.

Baveja, S.K., Ranga Rao, K.V., Singh, A. and Gombar, V.K., Release characteristics of some bronchodilators from compressed hydrophilic polymeric matrices and their correlation with molecular geometry. Int. J. Pharm., 41 (1988) 55-62.

Bechgaard, H. and Hegermann Nielsen, G., Controlled-release multiple-units and single-unit doses. A literature review. Drug Dev. Ind. Pharm., 4 (1978) 53-67.

Bechgaard, H. and Ladefoged, K., Distribution of pellets in the gastrointestinal tract. The

influence on transit time exerted by the density or diameter of pellets. J. Pharm. Pharmacol., 30 (1978) 690-692.

Bechgaard, H. and Ladefoged, K., Gastrointestinal transit time of single-unit tablets. J. Pharm. Pharmacol., 33 (1981) 791-792.

Bianchini, R., Bruni, G., Gazzaniga, A. and Vecchio, C., Influence of extrusion-spheronization processing on the physical properties of d-Indobufen pellets containing pH adjusters. Drug Dev. Ind. Pharm., 18 (1992) 1485-1503.

Bolhuis, G.J., Lerk, C.F., Zijlstra, H.T. and de Boer, A.H., Film formation by magnesium stearate during mixing and its effect on tabletting. Pharm. Weekbl., 110 (1975) 317-325.

Boylan, J.C., Cooper, J., Chowhan, Z.T., Lund, W., Wade, A., Weir, R.F., and Yates, B.J., Handbook of Pharmaceutical Excipients. The American Pharmaceutical Association and The Pharmaceutical Society of Great Britain; 1986.

Black, C.D., Update: programmed drug delivery systems. US Pharm., 8 (11) (1983) 49-63.

Blair, T.C., Buckton, G., Beezer, A.E. and Bloomfield, S.F., The interaction of various types of microcrystalline cellulose and starch with water. Int. J. Pharm., 63 (1990) 251-257.

Buckton, G., Ganderton, D. and Shah, R., In vitro dissolution of some commercially available

sustained-release theophylline preparations. Int. J. Pharm., 42 (1988) 35-39.

Cameron, C.G. and McGinity, J.W., Controlled-release theophylline tablet formulations containing acrylic resins, III. Influence of filler excipient. Drug Dev. Ind. Pharm. 13 (1987) 303-318.

Chambliss, W.G., Conventional and specialized coating pans. In: Ghebre-Sellassie, I. (ed.), Pharmaceutical Pelletization Technology. Marcel Dekker, Inc., New York and Basel; 1989.

Chapman, S.R., Rowe, R.C., Harrison, P.J. and Newton, J.M., The influence of process variables on the density of granules produced by extrusion-spheronization. Proc. 4th Cong. Int. Tech. Pharm., III (1986) 9-14.

Chariot, M., Frances, J., Lewis, G.A., Mathieu, D., Luu, R.P.T. and Stevens, H.N.E., A factorial approach to process variables of extrusion-spheronization of wet powder masses. Drug Dev. Ind. Pharm., 13 (1987) 1639-1649.

Chien, T.Y. and Nuessle, N.O., Factors influencing migration during spheronization. Pharm. Tech., 9 (1985) 42-48.

Christenson, G.L. and Dale, L.B., U.S. Patent 3,065,143 (1962).

Conine, J.W. and Hadley, H.R., Preparation of small solid pharmaceutical spheres. Drug

Cosmet. Ind., 106 (1970) 38-41.

Corvari, V., Fry, W.C., Seibert, W.L. and Augsburger, L., Instrumentation of a high-shear mixer: evaluation of a new capacitive sensor, a watt meter, and a strain-gage torque sensor for wet granulation monitoring. Pharm. Res., 9 (1992) 1525-1533.

Dakkuri, A., Butler, L.D. and De Luca, P.P., Sustained release from inert wax matrices III: effect of povidone on tripelennamine hydrochloride release. J. Pharm. Sci., 67 (1978) 357-360.

Degussa AG, Technical Bulletin Pigments No. 55: Aerosil for toothpastes (1980).

Dow Chemical Company, Personal communication (1993).

Eckhart, C.G. and McCorkle, T., Chlorpheniramine Maleate. In: Florey, K. (ed.), Analytical Profiles of Drug Substances. Vol. 7. Academic Press, Inc., New York, San Francisco and London; 1978.

Elbers, J.A.C., Bakkenes, H.W. and Fokkens, J.G., Effect of amount and composition of granulation liquid on mixing, extrusion and spheronization. Drug Dev. Ind. Pharm., 18 (1992) 501-517.

Eskilson, C., Controlled release by microencapsulation. Manuf. Chem., 56 (1985) 33-39.

Farhadieh, B., Borodkin, S., and Buddenhagen, J.D., Drug release from methyl acrylate-methyl methacrylate copolymer matrix I: kinetics of release. J. Pharm., Sci., 60 (1971a) 209-212.

Farhadieh, B., Borodkin, S., and Buddenhagen, J.D., Drug release from methyl acrylate-methyl methacrylate copolymer matrix II: control of release rate by exposure to acetone vapour. J. Pharm., Sci., 60 (1971b) 212-215.

Fassihi, A.R., Continuous matrix formation for controlled drug release: compression of isotropic polymeric system. Int. J. Pharm., 34 (1986) 169-172.

Fassihi, A.R. and Persicaner, P.H.R., Solid state interaction of Bromazepam with polyvinylpyrrolidone in the presence of moisture. Int. J. Pharm., 37 (1987) 167-170.

Fielden, K.E., Newton, J.M., O'Brien, P. and Rowe, R.C., Thermal studies on the interaction of water and microcrystalline cellulose. J. Pharm. Pharmacol., 40 (1988) 674-678.

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., The influence of moisture content on spheronization of extrudate processed by a ram extruder. Int. J. Pharm., 97 (1993) 79-92.

FMC Corporation, Avicel Spheres. Philadelphia; 1985.

Funck, J.A.B., Schwartz, J.B., Reilly, W.J. and Ghali, E.S., Binder effectiveness for beads with high drug levels. Drug Dev. Ind. Pharm., 17 (1991) 1143-1156.

Gamlen, M.J., Pellet manufacture for controlled release. Manuf. Chem., 56 (1985) 55-59.

Gamlen, M.J. and Eardley, C., Continuous extrusion using a Baker Perkins MP50 (Multipurpose) extruder. Drug Dev. Ind. Pharm., 12 (1986) 1701-1713.

Ghali, E.S., Klinger, G.H. and Schwartz, J.B., Thermal treatment of beads with wax for controlled release. Drug Dev. Ind. Pharm., 15 (1989a) 1311-1328.

Ghali, E.S., Klinger, G.H. and Schwartz, J.B., Modified drug release from beads prepared with combinations of two grades of microcrystalline cellulose. Drug Dev. Ind. Pharm., 15 (1989b) 1455-1473.

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.

Goskonda, S.R. and Upadrashta, S.M., Avicel RC-591/Chitosan beads by extrusion-spheronization technology. Drug Dev. Ind. Pharm., 19 (1993) 915-927.

Hanson, W.A., Handbook of Dissolution Testing. Pharmaceutical Technology Publications, Springfield, Oregon; 1982.

Harris, M.R. and Ghebre-Sellassie, I., Formulation Variables. In: Ghebre-Sellassie, I. (ed.), Pharmaceutical Pellitization Technology. Marcel Dekker, Inc., New York and Basel; 1989.

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 (1985a) 81-83.

Harrison, P.J., Newton, J.M. and Rowe, R.C., The characterization of wet powder masses suitable for extrusion/spheronization. J. Pharm. Pharmacol., 37 (1985b) 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.

Hasznos, L., Langer, I. and Gyarmathy, M., Some factors influencing pellet characteristics made by extrusion-spheronization process. Part I: Effects on size characteristics and moisture content decrease of pellets. Drug Dev. Ind. Pharm., 18 (1992) 409-437.

Heafield, J., Leslie, S.T., Malkowska, S.T.A. and Neale, P.J., US Patent 4,867,985 (1989).

Hellen, L., Ritala, M., Yliruusi, J., Palmroos, P., and Kristoffersson, E., Process variables of the radial screen extruder: I. Production capacity of the extruder and properties of the extrudate. Pharm. Tech. Int. Biophys., 4 (1992) 50-60.

Herman, J., Remon, J.P., Lefebvre, R., Bogaert, M., Klinger, G.H. and Schwartz, J.B., The dissolution rate and bioavailability of Hydrochlorothiazide in pellet formulations. J. Pharm. Pharmacol., 40 (1988) 157-160.

Hendeles, L., Weinberger, M. and Johnson, G., Monitoring serum theophylline levels. Clin. Pharmacokinet., 3 (1978) 294-312.

Hicks, D.C. and Freese, H.L., Extrusion and spheronization equipment. In: Ghebre-Sellassie, I. (ed.), Pharmaceutical Pelletization Technology. Marcel Dekker Inc., New York and Basel; 1989.

Higuchi, T., Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci., 52 (1963) 1145-1149.

Hileman, G.A., Goskonda, S.R., Spalitto, A.J. and Upadrashta, S.M., A factorial approach to high dose product development by an extrusion-spheronization process. Drug Dev. Ind. Pharm., 19 (1993) 483-491.

Hilton, J.E. and Summers, M.P., The effect of polyvinylpyrrolidones on intestinal ulceration

caused by indomethacin. Int. J. Pharm., 32 (1986) 13-19.

Hirotani, Y., Arakawa, Y., Maeda, Y., Yamaji, A., Kamada, A. and Nishihata, T., Preparation of controlled-release granules of sodium diclofenac. Chem. Pharm. Bull., 35 (1987) 3049-3053.

Huet de Barochez, B., Julien, J.S., Lapeyre, F., Horvath., S. and Cuine, A., Influence of drug solubility in the formulation of hydrophilic matrices. Drug Dev. Ind. Pharm., 15 (1989) 2197-2212.

Jalal, I.M., Malinowski, H.J. and Smith, W.E., Tablet granulations composed of spherical-shaped particles. J. Pharm. Sci., 61 (1972) 1466-1468.

Joshi, Y.M., Bachman, W.R. and Jain, N.B., US Patent 4,808,413 (1989).

Kleinebudde, P., Application of low substituted hydroxypropylcellulose (L-HPC) in the production of pellets using extrusion-spheronization. Int. J. Pharm., 96 (1993) 119-128.

Kleinebudde, P. and Lindner, H., Experiments with an instrumented twin-screw extruder using a single-step granulation/extrusion process. Int. J. Pharm., 94 (1993) 49-58.

Korsmeyer, R.W., Gurny, R., Doelkar, E., Buri, P. and Peppas, N.A., Mechanisms of potassium chloride release from compressed, hydrophilic polymeric matrices: effect of entrapped air. J. Pharm. Sci., 72 (1983) 1189-1191.

Ku, C.C., Joshi, Y.M., Bergum, J.S. and Jain, N.B., Bead manufacture by extrusion/spheronization - a statistical design for process optimization. Drug Dev. Ind. Pharm., 19 (1993) 1505-1519.

Lapidus, H. and Lordi, N.G., Some factors affecting the release of a water-soluble drug from a compressed hydrophilic matrix. J. Pharm. Sci., 55 (1966) 840-843.

Lee, V. H-L. and Robinson, J.R., Methods to achieve sustained drug delivery. The physical approach: oral and parenteral dosage forms. In: Robinson, J.R. (ed.), Sustained and Controlled Release Drug Delivery Systems. Marcel Dekker, Inc., New York and Basel; 1978.

Malinowski, H.J. and Smith, W.E., Effects of spheronization process variables on selected tablet properties. J. Pharm. Sci., 63 (1974) 285-288.

Malinowski, H.J. and Smith, W.E., Use of factorial design to evaluate granulations prepared by spheronization. J. Pharm. Sci., 64 (1975) 1688-1692.

MacFarlane, C. B., Selkirk, A.B. and Dey, M.J., US Patent 4,940,556 (1990).

McGinity, J.W., Cameron, C.G. and Cuff, G.W., Controlled-release Theophylline tablet formulations containing acrylic resins. I. Dissolution properties of tablets. Drug Dev. Ind. Pharm., 9 (1983) 57-68.

Mehta, A.M., Evaluation and characterization of pellets. In: Ghebre-Sellassie, I. (ed.), Pharmaceutical Pelletization Technology. Marcel Dekker, Inc., New York and Basel; 1989.

Mehta, A. M., US Patent 4,938,968 (1990).

Mesiha, M.S. and Valles, J., A screening study of lubricants in wet powder masses suitable for extrusion-spheronization. Drug Dev. Ind. Pharm., 19 (1993) 943-959.

Millili, G.P. and Schwartz, J.B., The strength of microcrystalline cellulose pellets: The effect of granulating with water/ethanol mixtures. Drug Dev. Ind. Pharm., 16 (1990) 1411-1426.

Millili, G.P., Wigent, R.J. and Schwartz, J.B., Autohesion in pharmaceutical solids. Drug Dev. Ind. Pharm., 16 (1990) 2383-2407.

Milosovich, G., Direct compression of tablets. Drug Cosmet. Ind., 92 (1963) 557-669.

Nakahara, N., US Patent 3,277,520 (1964).

Nakano, M., Naoko, O., Ogata, A., Sugimoto K., Tobino, Y., Iwaoku, R. and Juni, K., Sustained release of theophylline from hydroxypropylcellulose tablets. J. Pharm. Sci., 72 (1983) 378-380.

O'Connor, R.E., Holinej, J. and Schwartz, J.B., Spheronization I. Processing and evaluation of spheres prepared from commercially available excipients. Am. J. Pharm., 156 (1984) 80-87.

O'Connor, R.E. and Schwartz, J.B., Spheronization 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 spheronization technology. In: Ghebre-Sellassie, I. (ed.), Pharmaceutical Pelletization Technology. Marcel Dekker, Inc., New York and Basel; 1989.

Otsuka, M. and Matsuda, Y., Controlled drug release of highly water-soluble Pentoxifylline from time-limit disintegration-type wax matrix tablets, Pharm. Res., 11 (1994) 351-354.

Pather, S.I., Russell, I., Syce, J.A. and Neau, S.H., The formulation and evaluation of slow release Theophylline tablets prepared by direct compression. Presented at the 8th Annual Meeting and Exposition of the American Association of Pharmaceutical Scientists, Lake Buena Vista, Florida, USA. November 14-18, 1993.

Peck, G.E., Baley, G.J., McCurdy, V.E. and Banker, G.S., Tablet formulation and design. In: Lieberman, H.A., Lachman, L. and Schwartz, J.B. (eds.), Pharmaceutical Dosage Forms: Tablets (Vol. 1, 2nd edition). Marcel Dekker, Inc., New York and Basel; 1989.

Plazzier-Vercammen, J.A. and De Neve, R.E., Interaction of povidone with aromatic compounds II: evaluation of ionic strength, buffer concentration, temperature, and pH by factorial analysis. J. Pharm. Sci., 70 (1981) 1252-1256.

Plazzier-Vercammen, J.A. and De Neve, R.E., Interaction of povidone with aromatic compounds III: Thermodynamics of the binding equilibria and interaction forces in buffer solutions at varying pH values and varying dielectric constant. J. Pharm. Sci., 71 (1982) 552-556.

Reynolds, A.D., A new technique for the production of spherical particles. Mfg. Chem. Aerosol News, 41 (1970) 40-43.

Reynolds, J.E.F., (ed.), Martindale, The Extra Pharmacopoeia (28th edition). The Pharmaceutical Press, London; 1982.

Rogers, J.D., Lee, R.B., Souder, P.R., Ferguson, R.K., Davies, R.O., Theeuwes, F. and Kwan, K.C., Pharmacokinetic evaluation of osmotically controlled indomethacin delivery systems in man. Int. J. Pharm., 16 (1983) 191-201.

Rowe, R.C., Spheronization: a novel pill-making process? Pharm. Int., 6 (1985) 119-123.

Rubinstein, A., Hon Kin Li, V., Gruber, P. and Robinson, J.R., Gastrointestinal - Physiological variables affecting the performance of oral sustained release dosage forms. In: Yacobi, A. and Halprin-Walega, E. (Eds.), Oral Sustained Release Formulation: Design and Evaluation. Pergamon Press, New York; 1988.

Sandberg, A., Ragnarsson, G., Jonsson, U.E. and Sjogren, J., Design of a new multiple-unit controlled-release formulation of metoprolol - Metoprolol CR. Eur. J. Clin. Pharmacol., 33

(1988) S3-S7.

Santus, G. and Baker R.W., Osmotic drug delivery: a review of the patent literature. J. Control. Release. 35 (1995) 23-34.

Sastry, K.V.S. and Fuerstenau, D.W., Mechanisms of agglomerate growth in green pelletization. Powder Technol., 7 (1973) 97-105.

Seitz, J. A., Mehta, S. P., Yeager, J.L., Tablet coating. In: Lachman, L., Lieberman, H.A., and Kanig, J.L. (eds.), The Theory and Practice of Industrial Pharmacy (3rd edition). Lea and Febiger, Philadelphia; 1986.

Sekikawa, H., Ito, K., Arita, T., Hori, R. and Nakano, M., Effects of macromolecular additives and urea on the intestinal absorption of acetaminophen in rats. Chem. Pharm. Bull., 27 (1979) 1106-1111.

Shah, R.D., Kabadi, M., Pope, D.G. and Augsburger, L.L., Physicomechanical characterization of the extrusion-spheronization process. I. Instrumentation of the extruder. Pharm. Res., 11 (1994) 355-360.

Tapia, C., Buckton, G. and Newton, J.M., Factors influencing the mechanism of release from sustained release matrix pellets, produced by extrusion-spheronization. Int. J. Pharm., 92 (1993) 211-218.

Upadrashta, S.M., Katikaneni, P.R., Hileman, G.A. and Keshary, P.R., Direct compression controlled release tablets using ethylcellulose matrices. Drug Dev. Ind. Pharm., 19 (1993) 449-460.

Valorose, J.J. Jr., Biehl, R.J., Sheth, N.V., Strathy, W.A. and Doelling, M.K., US Patent 4,837,030 (1989).

Vervaet, C., Baert, L. and Remon, J.P., Extrusion-spheronisation: a literature review. Int. J. Pharm., 116 (1995) 131-146.

Washburn, E.H., The dynamics of capillary flow. Phys. Rev., 17 (1921) 273-283.

Woodruff, C.W. and Nuessle, N.O., Effect of processing variables on particles obtained by extrusion-spheronization processing. J. Pharm. Sci., 61 (1972) 787-790.

Zhang, G., Schwartz, J.B. and Schnaare, R.L., Effect of spheronization technique on drug release from uncoated beads. Drug Dev. Ind. Pharm., 16 (1990) 1171-1184.