DEVELOPMENT OF ZERO-ORDER RELEASE TABLETS

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A thesis submitted to the Faculty of Health Sciences,
University of the Witwatersrand, in fulfilment of the
requirements for the degree

of

Doctor of Philosophy

Johannesburg, 1996

DECLARATION

I, Michael Paul Danckwerts declare that this thesis is my own work. It is being

submitted for the degree of Doctor of Philosophy in the Faculty of Health Sciences in

the University of the Witwatersrand, Johannesburg. It has not been submitted before

for any degree or examination at this or any other University.

....

This 30th Day of July 1996.

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS STUDY

Publications

Danckwerts, M.P., Development of a Zero-order Release Oral Compressed Tablet with the Potential for Commercial Tabletting Production, *INT. J. PHARM.*, **112**, (1994), 37-45.

Danckwerts, M.P. and van der Watt, J.G., The effect of processing variables on the compression properties of controlled - release core-in-cup compressed tablets from a new adjustable punch, *INT. J. PHARM.*, **123**, (1995), 85-94.

Danckwerts, M.P., van der Watt, J.G. and Moodley, I., The effect of processing variables on the release ibuprofen and caffeine from controlled release non-swellable core-in-cup compressed tablets, *DRUG DEV. IND. PHARM.*, **22**, (1996), 681-687.

Danckwerts, M.P. and van der Watt, J.G., Simultaneous *in vitro* release of levodopa and carbidopa from biocompatible core-in-cup implants, *DRUG DEV. IND. PHARM.*, **23**, (1997), 273-277.

Presentations

A poster, on the simultaneous *in vitro* release of levodopa and carbidopa from biocompatible core-in-cup implants was presented at the 1st World Conference on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology in Budapest on the 9th - 11th May 1995.

Future publications

A paper entitled "Zero-order release of theophylline from a novel core-in-cup tablet in simulated gastric and intestinal fluid" by M.P. Danckwerts, J.G. van der Watt and I. Moodley, is being written up and will be submitted to Drug Development and Industrial Pharmacy by the end of 1996.

A paper entitled "Pharmacokinetics of the *in vivo* release of theophylline from a novel core-in-cup controlled release tablet in Beagle dogs", by M.P. Danckwerts, J.G. van der Watt and I. Moodley, will be submitted to International Journal of Pharmaceutics by the end of 1996.

ABSTRACT

A new core-in-cup tablet manufactured from a novel adjustable punch, has been formulated and evaluated as to its ability to release various model drugs via a zero-order rate of release. The new punch, with an inner adjustable rod that can be adjusted to produce cup-shaped tablets of various thicknesses, was used to manufacture the core-in-cup tablets. These core-in-cup tablets were then evaluated as to their ability to be manufactured on a tabletting press, and to their ability to release model drugs both *in vitro* and *in vivo*. After evaluating the effect of various formulation factors on the compressibility and flow of various directly compressible powder combinations via factorial design, a directly compressible combination of $10\%^w/_w$ carnauba wax in ethylcellulose was found to produce the best cup tablets for the core-in-cup tablets. During the evaluation of the rate of release of the model drugs caffeine (soluble), ibuprofen (insoluble), and theophylline (intermediate solubility), it was found that polyethylene glycol 6000 was the most suitable polymer for the ibuprofen core tablet, and acacia gum was the most suitable polymer for the caffeine and theophylline core tablets. All model drugs were released *in vitro* from the core-in-cup tablets at a zero-order rate of release. To obtain a controlled release of ibuprofen over an 8 - 12 hour period, addition of $10\%^w/_w$ polyethylene glycol 6000 was most applicable. For the caffeine and theophylline, addition of $30\%^w/_w$ acacia gum was most applicable. On subsequent evaluation of the *in vivo* performance of the core-in-cup tablet, it was found that theophylline was released and absorbed in beagle dogs at a rate that was more strongly correlated with a zero-order rate model, as compared to the release and absorption of theophylline from core only tablets. The core-in-cup tablets produced is, therefore, a versatile zero-order release rate dosage form that is simple to produce.

Acknowledgements

Dedication

This thesis is dedicated to my daughter Paige Sarah Danckwerts. May it lead to a better future and create many opportunities in her life.

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1. INTRODUCTION.

1.1. BACKGROUND TO PROJECT.

One of the major objectives of pharmaceutical and pharmacological research is the discovery of new chemical entities with favourable therapeutic properties and relatively low risks of adverse effects. However, one of the major problems of the pharmaceutical industry today is the limited number of new chemical entities which have been approved on the worldwide market (Won Jun, 1995). Therefore, instead of the traditional approach for the discovery of new pharmacologically active agents, the strategy of many pharmaceutical companies and research institutes is to focus on the development of new drug formulations which achieve an optimal therapeutic effect not solely by the drug itself, but also by principles of release and absorption (Ranade, 1991; Squire and Lees, 1992; Chien, 1990). In the traditional dosage forms and the so-called sustained-release preparations, the drug input into the body is specified by the *amount* of the drug that could be sustained in the body. There are now delivery systems specified by the *rate* (a constant amount per time) at which they deliver the drug (Heller, 1993; Ritschel, 1992; Banerjee and Robinson, 1991; Steinijans, 1990). Therefore, rate-controlled drug delivery offers very promising perspectives to pharmacological and therapeutic applications, and industrial product development. Furthermore, the oral controlled-release drug delivery systems have the most appeal to patients since they improve compliance and therefore, are the most widely researched group of drug delivery systems.

Oral controlled-release drug delivery has many advantages (Read and Sugden, 1987). Controlled-release oral dosage forms are designed to increase drug efficacy by eluding sub-therapeutic concentrations and diminish the incidence of toxic side effects by smoothing out the peak blood levels. If different therapeutic effects are found at different drug levels, the stability of steady state plasma concentrations permits the prescriber to elect the desired effect/s (Urquhart, 1982; Goldman 1982). Drugs can be

used that otherwise might cause a high incidence of side effects. Thus, the use of controlled-release forms gives greater accuracy in therapy. Less frequent dosage should lead to greater patient compliance. Even in the most sophisticated clinical situations, the number of patients who take their medication as prescribed who have serum concentrations within the optimal therapeutic range is extraordinarily low (Porter, 1969; Ayd, 1974; Markus, 1976). If controlled-release forms allow patients to take drugs once or twice a day when they are at home instead of three or four times a day, the likelihood of skipped doses is likely to be smaller. Oral controlled-release systems also allow drugs with very short action or low therapeutic windows to be effectively used as oral systems. It is also believed that absorption rates are less dependant on luminal contents and can therefore be released *in vivo* according to a pharmacokinetically rational rate.

There are however, a few disadvantages to oral controlled-release drug delivery. The loss of therapeutic effect may well be greater if the patient were to miss a dose of a controlled-release formulation, than if they were to miss a dose of a conventional dosage form. The toxic effects of accidental release of the complete dose from a controlled-release formulation are also much greater than from a conventional form. This is because larger amounts of drug are frequently given in the controlled-release forms. Therefore, drugs with narrow therapeutic concentration ranges should preferably not be formulated in a controlled-release form. There are however, a number of exceptions where controlled-release systems have been produced from drugs that have narrow therapeutic ranges. Theophylline formulations are a notable exception. The most important limitation of oral controlled-release therapy is that it could lead to a greater fraction of the dose not being absorbed. This would then reduce the systemic availability of the drug in some patients. Controlled-release dosage forms should also be avoided for delivering drugs that have a long elimination half-life and run the risk of accumulation.

The benefit derived from the use of controlled-release systems, however, far outweigh the disadvantages and is why they are such popular dosage forms.

Controlled-release drug delivery systems are formulated in many different forms for a large range of uses. They range from simple compressed matrix type tablets (Melia, 1991) to highly sophisticated implantable bioresponsive pumps (Chien, 1990). Like the many different types of delivery systems available they also vary in their routes of controlled drug delivery. These range from the transdermal route (Danckwerts, 1991) through to implantable I.V. routes (Danckwerts and Fassihi, 1991). The many different types of controlled-release drug delivery systems, their routes of administration, and mechanisms of release have been widely reviewed in the literature in a wide variety of journals (Braybrook and Hall, 1990, Chien, 1985; Chien, 1989; Langer, 1980; Laurencin and Langer, 1987; Ranade, 1991; Szycher, 1986).

1.2. APPROACHES TO ZERO-ORDER RELEASE.

There are many oral drug delivery systems on the market currently that provide some type of sustained or prolonged release of an active drug. Most of the commercially available systems consist of simple compressed matrices incorporating active drug homogenously mixed together with a hydrophillic polymer or mixture of polymers (Ford et al., 1985; Korsmeyer et al., 1983; Gurny et al., 1982; Theeuwes, 1981). The polymers are mainly cellulose derivatives of which hydroxypropylmethyl cellulose (HPMC) is probably the most popular. These systems are usually simple to manufacture on a large scale and are mostly produced on a tabletting press. Because of the shape of the tablet (biconvex or disc) it is theoretically impossible for these tablets to release the active drug from it at a zero-order rate. This is because as the system erodes (which is the case with most polymers) the surface area exposed to the dissolution fluid continually decreases or the diffusion path that the dissolved drug has to travel before release into the dissolution medium also increases. Whether the matrix releases drug via swelling control or erosion (or both), it is almost impossible to achieve a zero-order release (Langer, 1980). Most of these matrix-type tablets release drug according to the Higuchi (Higuchi, 1963, 1962) square root of time kinetics (Rhine et al., 1980; Hsieh et al., 1983; Lapidus and Lordi, 1968; Ford et al., 1987).

This is because there is a higher rate of release of drug at the start of its release, which slowly decreases as time passes. A graph of the square root of time versus amount of drug released, should be linear.

Two possible means of altering the release kinetics from matrix systems have been used to obtain a zero-order rate of release of drugs. These are, (1) by means of altering the geometry of the erodible matrix systems, and (2) manipulating the rate of diffusion of drugs from the drug delivery systems together with the rate of erosion of the drug delivery system.

1.2.1 Manipulation of geometry

Zero-order rate release of drugs from matrix controlled release tablets can be achieved by means of creating a system in which the drug is released from a constant surface area of constant drug concentration to the dissolution fluid, i.e. release from one side of a flat tablet, slab, base of a cylinder, or inwardly releasing hemisphere. A few systems have been fabricated in which all sides except a single flat side, have been coated with a thin impermeable (to the active drug) polymer or other coating. Hsieh *et al.* (1983) produced inwardly releasing hemispheres of sodium salicylate in polyethylene, and bovine serum albumin in ethylene vinyl acetate matrices, which were coated with paraffin (fig. 1.1). The release of drug from this system was then conducted in saline solution. Zero-order release for 60 days at a rate of 0,5 mg/day was achieved from the polymer matrices containing bovine serum albumin.

CENTRAL HOLE

IMPERMEABLE
POLYMER
COATING

DRUG AND
POLYMER MATRIX
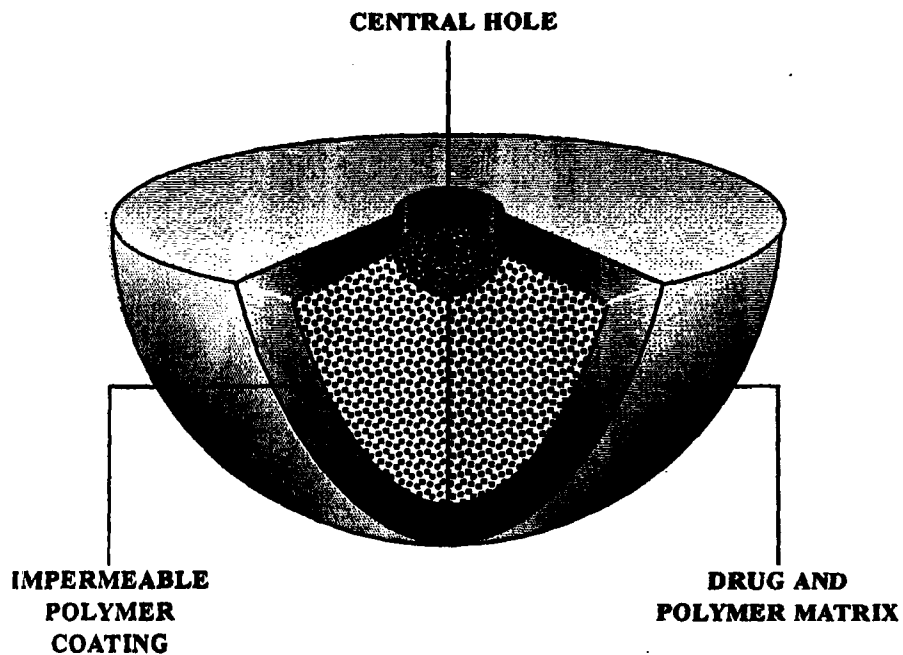
Fig. 1.1 Inwardly releasing hemisphere shown in section.

These systems however, are difficult to manufacture and consist of a number of intricate steps in their production. They first have to be moulded, and then dip coated, which is very difficult to automate and obtain effective quality control.

More recently, a perforated biconvex coated matrix tablet has been produced that exhibits an *in vitro* constant release rate of drug (Sangalli *et al.*, 1993). The tablet consists of a biconvex matrix tablet that is produced on a single punch tabletting press by means of special punches that have the ability to compress the tablet with a central 4 mm hole in it. The perforated matrix tablet is then coated with a drug impermeable polymer in a conventional coating pan (refer to figure 1.2 below). Ethylcellulose is used to coat the tablet as it exploits the relatively unfavourable exposure of the inner surface of the hole to the coating.

CENTRE DRILLED
HOLE

DRUG AND
POLYMER MATRIX

IMPERMEABLE
OUTER LAYER
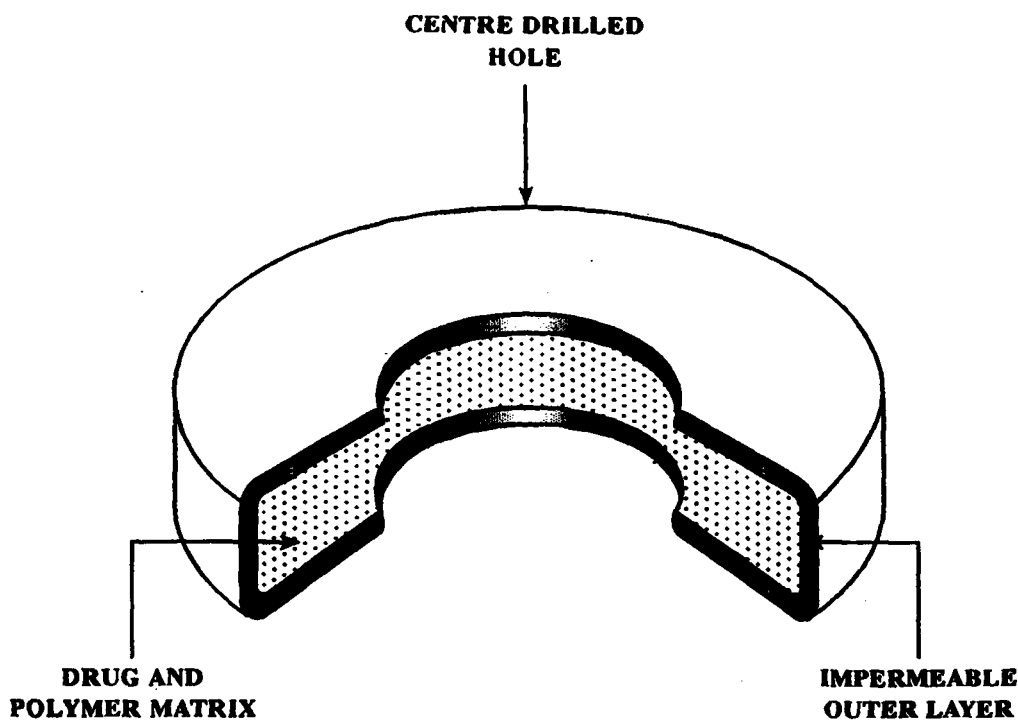
Fig. 1.2 Perforated coated matrix tablet shown in section

They found by means of visual inspection, that by gradually decreasing the plasticiser concentration, the production of a resistant, apparently continuous layer was limited to the more exposed core surface, while an irregular and weak membrane was obtained on the inner part of the hole. These coated perforated systems provided an approximate *in vitro* zero-order release of metoprolol tartrate for about 16 hours. From a theoretical point of view, drug release from perforated coated cores should occur only through the central hole, and the release kinetics depends on the increases in the releasing area and on the lengthening of the diffusional path. This of course, requires that there is an appropriate balance of the two processes in order to achieve linear drug release. To balance the two is very difficult and each system is probably only applicable to a specific drug. The system is also solely suitable to soluble drugs. For the release of the drug to be consistent from tablet to tablet, another method of only coating the exposed surfaces of the tablet will have to be obtained. An irregular

inner perforated hole will cause a variation in the release rate of the drug between tablets.

More recently, Kim (1995) has produced a similar perforated tablet matrix without coating. The theory of zero-order release is based on the fact that as the surface area of the outer surface of the 'donut'-shaped tablet is decreased due to erosion, the inner surface (hole) of the tablet is increased due to erosion. If the two rates are balanced, and the surface area decreases on the outside at the same rate, a zero-order rate of release is achieved. Again, the central hole must be drilled separately, and quite a lot of drug and adjuvants are wasted. The system is also not applicable to soluble drugs, which behave as if in a normal disc-shaped matrix tablet.

Another solid compressible tablet that claims to release drug at a near zero-order rate of release is the Geomatrix^R system which consists of a multilayer tablet in which one or two modulating barriers control the release of the drug from a deposit core containing the active ingredient (Conte *et al.*, 1993). Figure 1.3 below illustrates the Geomatrix^R system with its two possibilities.

SLOW RELEASE
DRUG MATRIX

IMPERMEABLE
BARRIER

GEOMATRIX® 1

QUICK RELEASE
COMPONENT
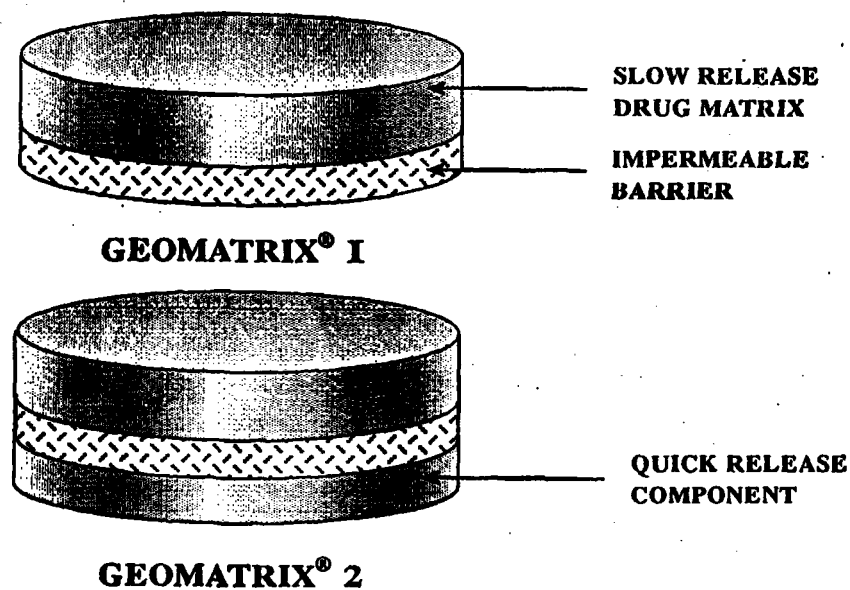
GEOMATRIX® 2

Fig. 1.3 Geomatrix^R system

The Geomatrix[R] is produced as a multi-layer tablet on a tabletting press and is very easy to automate its production. It cannot however, release drug at a zero-order rate of release since it consists of a polymer matrix, which it is. Depending on the mechanism of release, it will either constantly decrease its effective surface area of release by erosion or increase the solvent penetration path. Theoretically it cannot release drug at a zero-order rate of release.

Seta *et al.* (1988) prepared core-in-cup compressed tablets of disc-shaped bilayer core matrices of captopril and hydroxypropyl cellulose (HPC) surrounded on the bottom surface and circumference wall (the cup) with an inactive mixture of ethylcellulose and carnauba wax. The two layers of the core contained different concentrations of captopril. It was found that this type of system released captopril *in vitro* at a zero-order rate over a period of 3 to 6 hours. Shenouda *et al.* (1990) also prepared a similar core-in-cup type compressed tablet of dyphylline in HPMC as the core matrix and poly(ethyloxazoline) polymer as the inactive cup. Again, this type of system has the ability to release dyphylline *in vitro* at a zero-order rate of up to 7 to 8 hours. In both the above studies, the core-in-cup tablets were produced by means of first compressing out the active core on a single punch tabletting press using round flat face punches to form a disc. The disc was then placed by hand in the centre of a larger round flat - faced punch in the die cavity of the press, filled with the inert polymer mixtures, and then compression coated by hand at high pressure. To place the core in the centre of the round flat punch called for careful and tedious placement and judgement. The problem with this compression - coated method is that it cannot be automated and does not produce an even, elegant tablet. Both these properties are needed for commercial production of tablets.

1.2.1 Manipulation of diffusion of drug and erosion of polymer

If one can formulate a drug delivery system in which the rate that the drug diffuses from the drug delivery system, is balanced with the rate that the polymer used

in the drug delivery system erodes, then it can release drug at a zero-order rate. The zero-order rate release profile in these systems is postulated to arise from increased drug release (decreased drug diffusion path) from a decreasing thickness of polymer gel, thereby compensating for the decreasing surface area of the eroding dosage form. These systems have been extensively studied by Baveja, Rango Rao and others (Baveja *et al.*, 1988a, 1988b and 1987; Devi *et al.*, 1989). Using a series of soluble beta-blockers, they have shown that incorporating sodium carboxymethyl cellulose (NaCMC) into an HPMC matrix tablet reduced the initial "burst" of drug release and, by optimising the ratios of HPMC, NaCMC, and the active drug, the shape of the dissolution profile could be changed from a "square root of time" relationship to one where almost 100% drug was released via zero-order kinetics. It was also interesting that zero-order drug release was achieved throughout the entire 12 hour profile, notwithstanding a pH change from acid to neutral conditions after 3 hours. All tablets containing NaCMC, with or without HPMC, lacked an initial burst, and this effect may be a result of the suppression of swelling and dissolution of this anionic polysaccharide in the acid medium initially used. Zero-order release was accomplished with swelling and erosion control of the polymer matrix. The formulation involved mixing a soluble beta-blocker with a combination of HPMC and NaCMC, and then compressing it into a tablet. By optimising the ratio between the drug and the polymers, the rates of advancement of the swelling front into the glassy core and the attrition of the rubbery state polymer were made equal so that the diffusional path length for the drug remained constant.

These systems unfortunately, are only applicable to drugs that are readily water soluble, as they rely on solubilization and then diffusion out of the matrix. It also seems likely that different combinations of polymers would be applicable to different drugs to match the rate of the advancement of the swelling front into the glassy core and the rate of attrition of the swollen polymer.

1.3. STATEMENT OF PROBLEM.

Currently, traditional oral sustained-release drug delivery systems such as matrix tablets, microcapsules, hydrogel capsules and osmotic pumps do not lead to optimal drug therapeutic conditions, or are difficult and expensive to manufacture. Therefore, a need exists for sustained-release preparations that release constant levels of a wide variety of drugs for a period of approximately 12 hours at a zero-order rate. This drug delivery system must be relatively simple to produce on a commercial scale, and be reproducible in its release pattern.

1.4. DELINEATION OF PROBLEM.

For this study, a core-in-cup type tablet will be produced and evaluated. The core portion of the tablet will first be produced as a normal disc - shaped tablet. Then the cup portion of the tablet will be produced by means of a novel punch with an inner adjustable rod. Finally, the core will be compressed with the cup to produce a core-in-cup tablet (Refer to figure 1.6 for the schematic production process).

In formulating an effective core-in-cup zero-order (constant release with time) oral sustained-release drug delivery system, the problems that need to be solved are:

(1) The drug delivery system must release the active drug/s at a constant zero-order rate to the GIT for approximately 8 to 12 hours (GIT transit time). The core must release drug at a zero-order rate of release, and the cup portion of the tablet must maintain its shape for the period of release.

(2) Manufacturing the zero-order drug delivery system must be simple, reproducible, and relatively inexpensive.

(3) The drug delivery system must be applicable to a wide variety of drugs.

1.5. APPROACH TO PROBLEM.

This project will be approached from a pharmaceutical formulation point of view and will consider all factors that are responsible for the optimization of the drug delivery system. Whenever possible, the technique of factorial design will be used. This technique allows one to investigate many factors simultaneously, without having to investigate all possible combinations of factors. It also allows one to investigate interactions (different responses to one variable depending on the value of another variable) between variables. For example, if one considers the release rate of drug from a tablet that contains varying concentrations of polymer and that has been compressed to different hardnesses. From a theoretical point of view, one would expect the rate of release to decrease proportionally as the concentration of polymer in the formulation increased. Also, one would expect that the rate of release would decrease as the hardness of the tablet increased. Consequently, the tablet that contains the most polymer and that has been compressed to the highest hardness, to release drug at a rate that was proportionately lower than the rate of release from a tablet with the lowest concentration of polymer and lowest compression. There are however, times when this is not so. Sometimes there is an interaction between the two variables (concentration of polymer and hardness of compression) that could produce a tablet that does not behave according to predicted theory. Perhaps, the high compression force decreases the effectiveness of the polymer to hold back the drug and hence results in a quicker than expected rate of release. This type of interaction, then needs to be investigated further.

For this study, a standard tabletting top punch was adapted by the University of the Witwatersrand Engineering Department, so that it compresses a tablet into a cup-shape of 2 mm depth. This cup-shaped tablet is then compressed together with the active disc-shaped core tablet to give a core-in-cup tablet of perfect reproducible dimensions. Figure 1.4 illustrates this core-in-cup tablet. The adapted punch to produce the cup-shaped tablet is shown in Figure 1.5.

Active drug cores of various thicknesses (depending on the quantity of active drug required) are compressed into flat 7 mm diameter disc-shaped tablets. Then the inactive cups (outside cup diameter of 11 mm and inside cavity diameter of 7,5 mm) are compressed into cup-shaped tablets with the adapted punch.

Drug/polymer matrix core

Impermeable carnauba wax/ethylcellulose cup
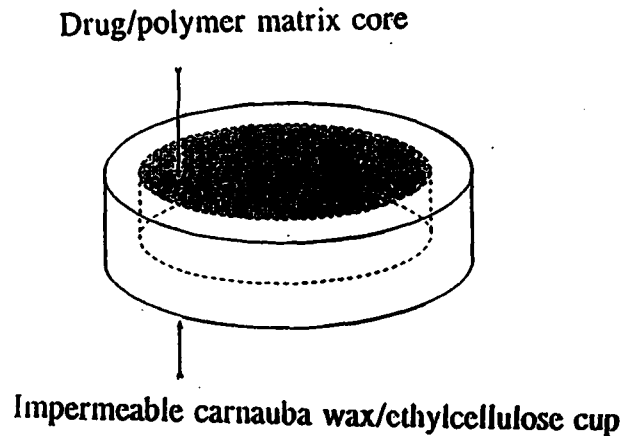
Fig. 1.4 Schematic diagram of core-in-cup tablet.

The inside cup cavity of the cup tablet is 0,5 mm larger than the core tablet, so that the 7 mm core tablet can easily slip into the cavity for subsequent core-in-cup compression. Once both the cores and the cups are compressed, the cores are placed inside the cups and fed into the tabletting press, equipped with 12 mm round flat punches, to finally be compressed into a single core-in-cup tablet.

16 mm

30 mm

5 mm

60 mm

25 mm

7.5 mm
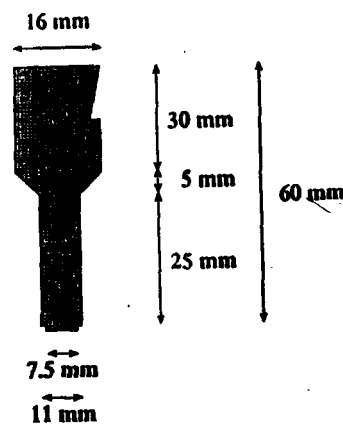
11 mm

Fig. 1.5 Sparkeroded top punch used to produce cup shaped tablets

These slightly larger punches and die cavity of 12 mm ensure that the 11 mm core-in-cup tablets can easily be fed into the final die cavity. Figure 1.6 graphically describes the production procedure that will be used to produce the core-in-cup tablets to be used in this study.

1. Cup compression
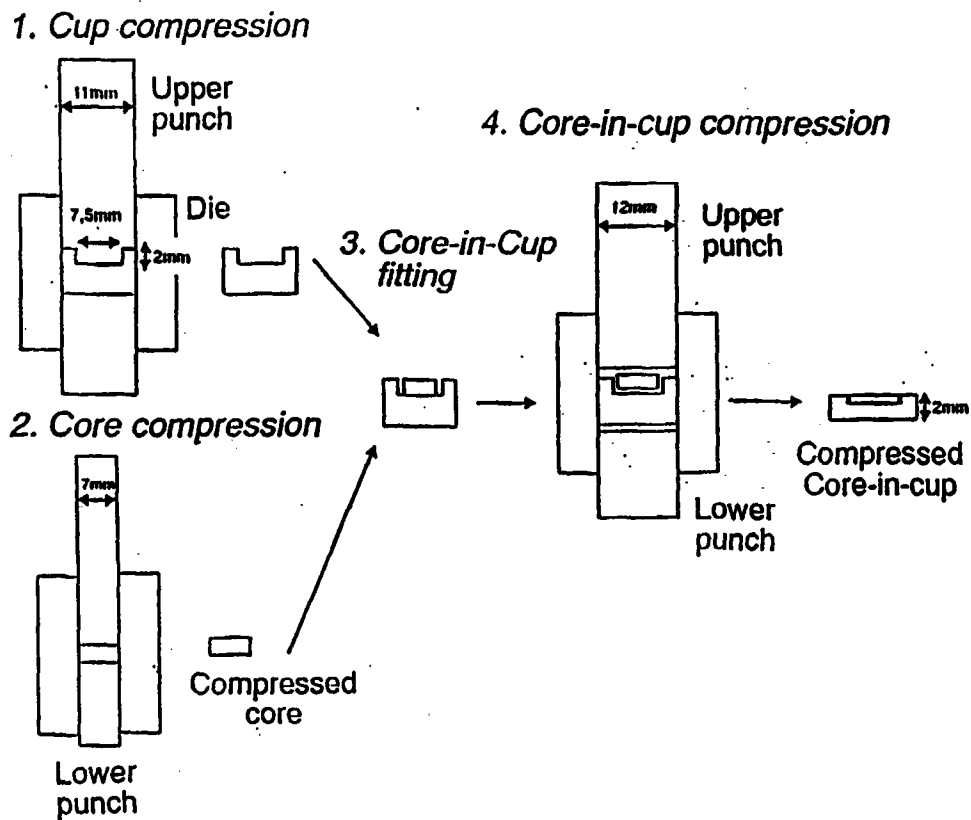
Fig 1.6 Production process of Core-in-cup tablets

The inactive cups and the active cores as well as the two being compressed together, can be accomplished automatically on a tabletting press. This tabletting press can be modified with a special feed shoe that feeds the cores into the cups and then feeds these into the die cavity to be finally compressed together. It is also a very simple method using exceedingly few adjuvants, and is applicable to a wide variety of drugs. Once it was proved that the use of such an adapted punch was feasible in producing core-in-cup tablets, a new punch with an adjustable inner rod (refer to figure 1.7 below) was made by Holland Tabletting Science, UK for the subsequent experiments. This punch has the ability to produce cup-shaped tablets of different depths.
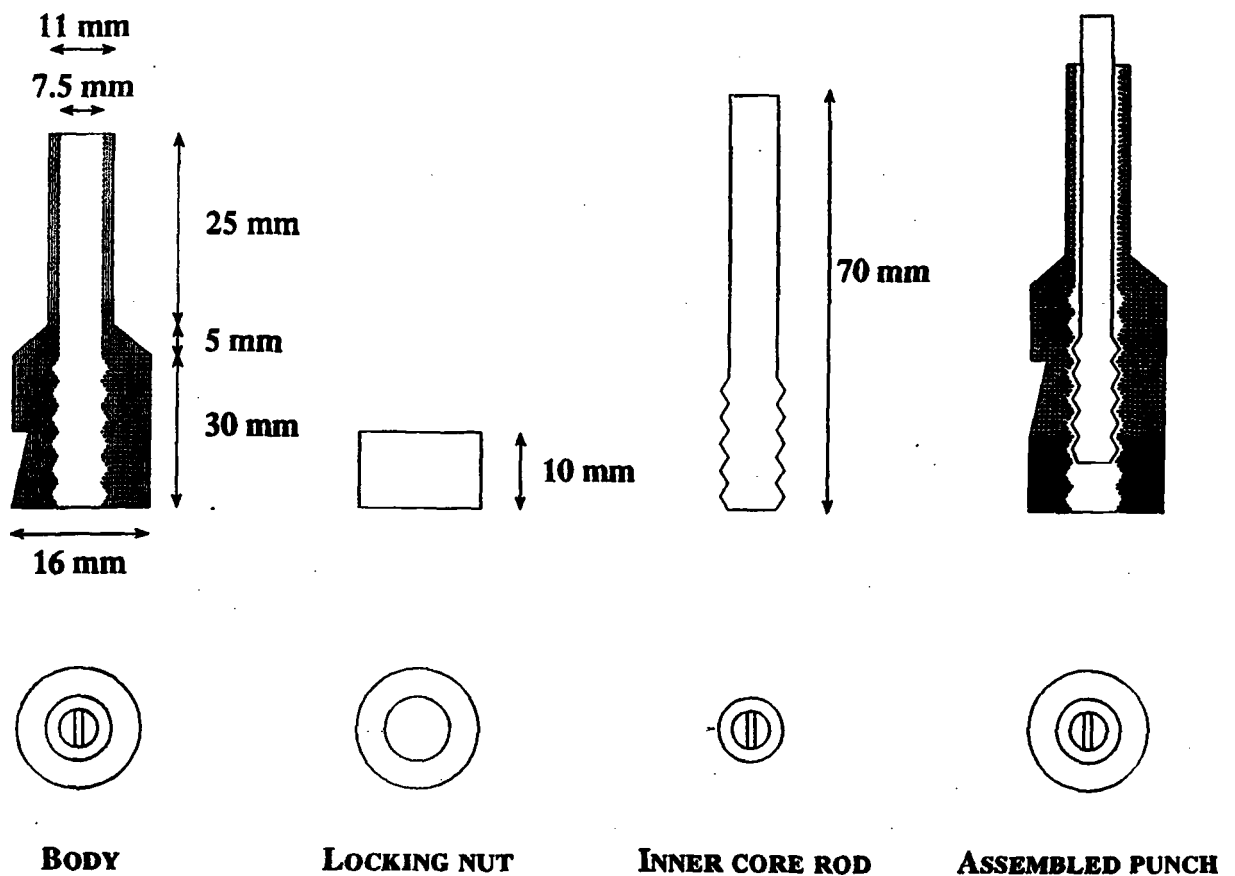
Fig. 1.7 New adjustable punch with an adjustable inner rod to produce cup shaped tablets of various depths

Core-in-cup tablets of caffeine, ibuprofen and theophylline as model drugs that represent a wide variety of physicochemical properties such as solubility, pKa's, ionisation, etc., will be used to assess the suitability of such a drug delivery system. Caffeine will be used as an aqueous soluble model drug, and ibuprofen will be used as an aqueous insoluble drug. These two drugs will be used in the preliminary investigations and the *in vitro* analysis. Theophylline, as an intermediate aqueous soluble model drug, will be used in the final *in vitro* analysis and as the model drug for the *in vivo* release studies. The drugs will only to be used as model drugs, and consequently the thesis will not cover the shelf-life stability of the core-in-cup tablets and any other stability determination. It will also not cover the purity determination and testing of any of the physicochemical properties of the drugs. The purity, particle size, and solubility as determined by the supplier will be accepted as stated on their labels. All necessary precautions will be taken to protect the purity and stability (both physical and chemical) of the model drugs throughout the research. Only one batch of each model drug will be used, and therefore, it is not necessary to determine the batch to batch variation of the formulations of the active drug. However, any variation between formulations will be rigorously tested. The model drugs were chosen mainly for their difference in solubility in aqueous solvent, as it is the major differentiating property for drug release from the core-in-cup tablets and dissolution in GIT fluids. Another major reason for choosing caffeine, ibuprofen and theophylline, is that they are readily available and much is known about their physicochemical properties.

Theophylline was chosen as the model drug for the *in vivo* analysis, because:

(1) It is stable in the GIT and well absorbed at different regions of the GIT.

(2) It interacts with very few adjuvants (Chow *et al.*, 1993; Hussein and Friedman, 1990).

(3) It is a good candidate for controlled-release formulations because of its

narrow range of effective blood concentration and short elimination half-life (Mitenko and Ogilvie, 1973; Zaske *et al.*, 1977).

(4) The absorption of theophylline in dogs from sustained-release preparations can be easily measured using plasma concentration-time data (Koritz *et al.*, 1986; McKiernan *et al.*, 1981; Munday *et al.*, 1991).

Some relevant physicochemical properties of the model drugs used in this study (The Pharmaceutical Codex, 1994), are listed in table 1.1.

TABLE 1.1.

Relevant physicochemical properties of model drugs.

Property	Caffeine (anhydrous)	Ibuprofen	Theophylline
Empirical formula	$C_8H_{10}N_4O_2$	$C_{13}H_{18}O_2$	$C_7H_8N_4O_2$
Molecular weight	194,2	206,3	180,2
Melting range °C	234-239	75-78	270-274
Solubility at 25°C			
Aqueous	1 in 60	insoluble	1 in 120
ethanol	1 in 130	1 in 1,5	1 in 80
chloroform	1 in 7	1 in 1	1 in 200
pK_a at 25°C	14,0	5,3	< 1 and 8,6
Stability	Caffeine is decomposed by solutions of strong caustic salts.	Stable in the absence of oxygen.	Sensitive to light. Stable in air.

1.6. OVERVIEW.

The first chapter of this project contains the introduction to the project and the rationale for the project. The introduction concisely describes the currently available sustained - release drug delivery systems and their formulation characteristics and finally defines the problem with current oral sustained - release drug delivery systems. The problem is then delineated, and lastly the approach and methodology of the project is described.

The second chapter of this project describes the development of the cup portion of the tablet. As it is critical that the cup portion of the tablet remains intact throughout the GIT, as well as retain the ability to be easily moulded into a cup shape that can receive the active core of the tablet, the compression properties and flow characteristics of ethylcellulose with various nonaqueous binders were investigated. The effect of (i) type of binder, (ii) concentration of binder, and (iii) particle size of ethylcellulose on the direct compression and flow of the powder blend were evaluated.

Once a suitable formula for the cup tablet was established, core-in-cup tablets of caffeine and ibuprofen were formulated to investigate the practical feasibility of such a drug delivery system. Here, the use of different grades of hydroxypropylmethylcellulose (HPMC) in the core of the tablets to release drug from the core-in-cup tablets were investigated. For this experiment, a model punch which produces a cup-shaped tablet of 2 mm depth was used. Once it was proved that the core-in-cup system was practically feasible, a new adjustable punch was made by Holland Tabletting Science, UK. For these experiments, caffeine (soluble) and ibuprofen (insoluble) were used as model drugs.

The penultimate experiment in this chapter evaluates the new adjustable punch in producing cups of different depths. It is necessary that the cup portion is developed further to be capable of producing cup tablets that can vary in their ability to accommodate various concentrations of active drug in the core portion of the tablet.

To evaluate the new punch, tests on (i) the effect of depth of cup, (ii) concentration of binder, and (iii) hardness of compression of the cup portion of the tablet, on the friability of the cup and its ability to prevent splitting when using HPMC as the core tablet polymer, were conducted. Ibuprofen was used as the model drug for this investigation.

As the HPMC used in the previous studies swells when it comes into contact with dissolution fluid, the final experiment in the chapter investigated the effect of processing variables on the release of ibuprofen and caffeine from controlled release nonswellable core-in-cup compressed tablets. In this experiment, the effect of (i) type of polymer, (ii) concentration of polymer, and (iii) hardness of compression of the core tablet on the maximum time of constant release of caffeine and ibuprofen were investigated. The purpose of the experiment therefore, was to test the effectiveness of nonswellable polymers in producing the core of a core-in-cup tablet that does not swell to any appreciable extent when it comes into contact with aqueous dissolution fluid. The second major aim of the experiment was to optimise the formulations so that they could release drug constantly over a period of at least 8 hours.

Chapter three, the formulation and *in vitro* evaluation of the new sustained-release drug delivery systems was begun. Based on the previous investigations, the effectiveness of the core-in-cup tablets to release theophylline at a zero-order rate in the presence of sequenced simulated gastrointestinal fluids was examined. The core-in-cup system was also evaluated to see if it would be unaffected by the conditions in the simulated GIT fluids and whether it was capable of releasing theophylline drug over a period of at least 8 hours at a zero-order rate.

Chapter four deals with the *in vivo* analysis of the core-in-cup tablet. Three different formulations of theophylline were tested in Beagle dogs. These were;

(i) Core-in-cup tablet.

(ii) Core only tablet.

(iii) Immediate release capsule.

The formulations were tested to determine if the core-in-cup tablet released theophylline at a zero-order rate of release, and to test whether it had any *in vivo* advantages over the core only control tablet. The dogs were dosed with immediate release capsules in order to determine the elimination rate of theophylline in each dog. The percentage area under the curve fluctuation at steady state was also calculated and compared for the different formulations.

In chapter five, the suitability of the new core-in-cup controlled-release tablets are assessed and recommendations are made for the optimization of such delivery systems for future studies.

2.0 DEVELOPMENT OF THE CUP PORTION OF THE CORE-IN-CUP TABLET.

In this section of the experimental part of the thesis, the cup portion of the core-in-cup tablet is investigated. Only once a suitable cup portion of the tablet is developed can the core and the rest of the tablet be developed. Since the cup portion of the tablet and its production process is the novel part of the tablet, much of the emphasis will be placed on this process.

2.1 THE EFFECT OF PROCESSING VARIABLES ON COMPRESSION AND FLOW PROPERTIES OF VARIOUS DIRECTLY COMPRESSIBLE ETHYLCELLULOSE/NONAQUEOUS BINDER COMBINATIONS.

2.1.1. Introduction

In order to manufacture and formulate a core-in-cup tablet, it is essential that the cup portion of the tablet adheres to the following criteria:

(i) The cup tablet must not disintegrate in its passage through the GIT. Therefore, the cup should be essentially hydrophobic.

(ii) The tablet must be produced on a tabletting press and therefore must not, cap, laminate, pit, or stick during compression.

(iii) It is also preferable that a directly compressible tabletting base be used so that cost and time savings with such systems is taken advantage of.

With the above criteria in mind, it was decided that a low viscosity grade of

ethylcellulose will be used as the directly compressible tabletting base. Ethylcellulose is an inert, hydrophobic polymer which has been widely used as a tablet excipient (Muti and Othman, 1989; Goodhart *et al.*, 1984; Shaikh *et al.*, 1987). It is also a good directly compressible base, and has been used recently in a number of direct compression applications (Katikaneni *et al.* 1995; Upadrashta *et al.*, 1994; Upadrashta, 1993; Nesic, 1987)

Although ethylcellulose itself is used as a binder, and it compresses well into a compact mass, the unusual shape of the cup tablet and its need for subsequent further recompression into a core-in-cup tablet, require the addition of an effective binder which can also add plasticity properties to the ethylcellulose. In order for the cup portion of the tablet to remain insoluble in the aqueous environment of the GIT, one cannot use normal binders which are soluble in aqueous fluid. This would lead to the premature disintegration of the cup portion of the core-in-cup tablet. Accordingly, one needs to find suitable nonaqueous binders. Very little information is available on the use and availability of nonaqueous binders. Dicalcium phosphate may be the only traditional binder that is insoluble in water. High melting point waxes could also possibly be used as binders. These waxes should also increase the plasticity of the ethylcellulose base.

The purpose of this part of the study therefore, was to test the effectiveness of low viscosity ethylcellulose together with various binders in producing an effective cup-shaped tablet. Thus, it was decided to preliminarily test the compressibility of various nonaqueous binders and select the three best ones for further study. Secondly, it was decided to examine the processing variables of type of binder (t), concentration of binder (c), and particle size range of low viscosity ethylcellulose (s) on the compressibility and flowability of the powder blends. This study then results in a 3^3 factorial design. The dependencies were explained using analysis of variance and multiple regression analysis.

A glidant/lubricant was not used in this study, because it is known to adversely affect the tablet strength (Bolhuis *et al.*, 1995, Jarosz and Parrott, 1984; Shah *et al.*, 1986; Katikaneni *et al.*, 1995). The mechanism of such decrease is thought to be due to the finer lubricant particles coating the larger excipient and drug particles and interrupting interparticulate bonding. Fragmentation of brittle particles results in large areas of new unexposed surfaces reducing the detrimental effect of a lubricant on tablet strength. Ductile deformation does not produce the same extent of new particle surfaces and the tablet strength of ductile materials is typically more sensitive to lubricants. The effect of lubricant on the compressibility, was confirmed in a preliminary study on the compressibility of ethylcellulose containing $0.5\%^w/_w$ magnesium stearate. It was found that when magnesium stearate was added to the ethylcellulose, the resultant cup tablets began to show signs of capping. Once the magnesium stearate was removed, the tendency to cap disappeared. The low viscosity ethylcellulose flows very well on its own and therefore it does not really need a glidant.

Many techniques are available to characterise the compression behaviour of powders and granules. These techniques include tablet hardness-compression force profiles (Higuchi, 1953; Fell and Newton, 1968), ejected tablet Heckel analysis (Heckel, 1961a,b), work calculations from force-displacement data (De Blaey *et al.*, 1971; Krycer *et al.*, 1982), and force-time profile analysis (Chilamkurti *et al.*, 1983; Hoblitzell and Rhodes, 1990; Martinez-Paracheo *et al.*, 1990). Of the above methods, the hardness-compression force profiles method is probably the most useful and simplest method to characterise compressibility.

Although hardness is not a central property, diametral crushing (hardness) is most typically used for in-process control and preformulation investigation of new powder or granule blends or formulations (Parrott, 1990). There is a linear relationship between tablet hardness and the natural logarithm of compression force (except at very high pressures). Plots of natural logarithm of compression force versus hardness are exponential in nature.

Therefore, a plot of tablet hardness versus the natural logarithm of compression force results in the following hardness-compression profile over the linear portion of the plot:

$$Fc = n \ln P + I \qquad \text{- equation 2.1.1}$$

where,   Fc = Hardness of tablet as measured by the diametral crushing strength.

P = Applied pressure as a measure of compression force.

n = slope of the linear portion of the plot.

I = intercept on the y-axis.

The two constants n and I are indirect measures of the compressibility of the powder mix. As the slope of the graph (n) increases, then it can be said that the powder mix has an increased ability to be compressed into a more compact mass and therefore has a better compressibility. The constant I is a measure of the inherent compressibility of a powder mix. Since the purpose of this part of the research is to estimate the compressibility of various mixtures of ethylcellulose and nonaqueous binders, it would be preferable to use a single parameter that best describes the compressibility. Factorial estimation also requires that a single parameter is used to estimate the effects of various changes in the parameters. Therefore, it was decided that the slope n was the most suitable measure for estimating the compressibility of the various powder mixtures.

As the proposed dry binders to be investigated are waxy or insoluble compounds, it is necessary to check the effect of the binders on the flow properties of the various powder mixes. Solid particles attract one another, and forces acting between particles when they are in contact are predominantly surface forces. Therefore, the action of the binder would be expected to adversely affect the flow characteristics of the directly compressible powder mix. Many methods are available to

measure the extent of interparticulate forces. Such measures are then commonly employed as an index of flow. Some of the more common methods that are used are (i) angle of repose (Carstensen and Chan, 1977; Hiestand, 1966; Jones and Pilpel, 1966), (ii) shear strength determinations (York, 1975; Hiestand and Peot, 1974), and (iii) hopper flow rate measurements (Danish and Parrott, 1971; Gold *et al.*, 1968). The angle of repose method is the simplest method and is suited to particles that are larger than 150 μm (Gordon *et al.*, 1990). Briefly, the angle of repose is a measure of the ability of an object to overcome sliding when the angle of inclination is large enough to overcome frictional forces. The method consists of allowing a powder mix to flow through an orifice under the influence of gravity and allowing it to heap on a flat surface. The angle incident to the surface is then the angle of repose.

2.1.2. Materials and Methods

2.1.2.1. *Materials*

The low viscosity (45 cps at 25°C in 80:20 toluene:ethanol) ethylcellulose with an ethoxy content of 48,5% was supplied by Sigma Chemical Company, U.S.A. The Emcompress[R] (dibasic calcium phosphate dihydrate supplied by Edward Mendell Company, Inc., U.S.A.), Suppocire C NA - 10 (hydrogenated castor oil supplied by Gattefossè, s.a., France), hard paraffin (Saarchem, Pty., Ltd., R.S.A.), cetostearyl alcohol (Saarchem, Pty., Ltd., R.S.A.), and cetyl alcohol (Saarchem, Pty., Ltd., R.S.A.) were all ground in a mortar and the fraction passing through a 355 μm aperture sieve (Endcotts Test Sieves, Ltd., London, England) was used.

2.1.2.2. *Study design*

The study followed a sequential 1^1 preliminary study followed by 3^3 factorial experimental design. In the preliminary experimental phase, the ethylcellulose in the size range of 600 μm to 850 μm was mixed with two different concentrations of the various nonaqueous binders to be tested for compression and flow properties. Once

the three most suitable binders were found, a 3^3 factorial design study was conducted. The amount of binder added to the ethylcellulose (c), particle size range of ethylcellulose (p), and type of binder (t), were used as independent variables. Type of binder and its concentration, together with the average particle size of the directly compressible tabletting base are the most critical factors in the compressibility and flow of the powder blend. The normalized factor levels of the independent variables are presented in table 2.1.1.

In the c and s central points on each level of t, and the 2^3 factorial points, the powder mixes were made in duplicate batches. Therefore, the total number of runs was 38. The compressibility and flow estimates were the dependant variables.

TABLE 2.1.1

Levels of independent variables for flow and compressibility studies.

Variable	Factor level			Units
	-1	0	1	
Concentration of binder (c)	2	4	6	$\%^w/_w$
Type of binder (t)	Encom-press	Cetyl alcohol	Carnauba wax	
Particle size μm (± class mark in range) of ethylcellulose (s)	475	725	975	μm

2.1.2.3. Formulations

For the preliminary study on the suitability of the binders, 15g of the powder blends listed in table 2.1.2 were prepared. The low viscosity ethylcellulose and binders were used as supplied and blended in a cube-shaped blender for 5 minutes. Table 2.1.2 lists the results of the preliminary study on the flow and compressibility of the various nonaqueous binders investigated. As far as compressibility is concerned, hard paraffin has the best compressibility as signified by the steepest slope value. It is then followed sequentially by carnauba wax, Emcompress^R and cetyl alcohol. The Suppocire C NA-10 exhibited sticking and pitting, even at low compression forces of 2,5 tonnes, and was therefore deemed not suitable as a directly compressible binder. When analysing the flow properties of the powder blends, Emcompress^R was the best, followed in ascending order by Suppocire C NA-10, carnauba wax, cetyl alcohol, and hard paraffin. Hard paraffin exhibits by far the worst angle of repose, at a value of 55,81 ± 7,42 and is therefore, not suitable as a binder for directly compressible tablets.

TABLE 2.1.2.

Angle of repose and compressibility of 5% $^w/_w$ binders in the preliminary powder blends

Type	Flow ± S.D. (Angle of repose) (n=3)	Compressibility ± S.D. (slope of graph) (n=3)	r^2
Carnauba wax	37,45 ± 3,31 *	30,62 ± 8,89 ##	0.873
Cetyl alcohol	46,29 ± 6,51	14,57 ± 6,09 #	0,968
Emcompress^R	34,51 ± 4,67 *	23,51 ± 7,03 ##	0,823
Hard paraffin	55,81 ± 7,42	38,76 ± 6,24 #	0,944
Suppocire CNA-10^R	34,67 ± 8,36 *	Pitting	N/A

*,# in a vertical column indicate homogenous groups that show no significant difference at the 95% confidence level using the LSD analysis of variance test.

Therefore, based on these preliminary results, it was decided that carnauba wax, Emcompress[R], and cetyl alcohol should be investigated further.

Once it was established that cetyl alcohol, Emcompress[R], and carnauba wax, were the most suitable with respect to flow and compressibility, 5g of each powder mix as listed in table 2.1.3 were prepared and tested for compressibility and flow properties. The ethylcellulose (mean particle size of 418,84 μm $\pm$ S.D. of 287,31) was separated into three different size fractions by passing the powder as supplied through a nest of sieves (Endcotts Test Sieves, Inc., London, England) with aperture sizes of 1000 μm, 850 μm, 600 μm, and 355 μm. These sieves were arranged in descending order of size in an Endcotts Octagon 200 test sieve shaker, and the powder was shaken for 15 minutes at an amplitude of 6. Before blending the fractions of ethylcellulose with each of the binders, the binders were first ground in a mortar and the fraction passing through a 355 μm sieve was used. Each powder blend to be tested was then mixed together with the specific binder to be used, for 3 minutes in a rotating cube blender and then tested, first for its flow, and then its compression properties.

2.1.2.4. *Measurement of powder flow*

The flow of the powder blends were characterised from their angle of repose measurements. This was measured by means of lightly packing 5g of each formula into a hollow glass cylinder (8 cm long with an internal diameter of 22 mm) resting on a piece of graph paper. The cylinder was then lifted vertically through a circular guide connected to a retort stand, and the powder was allowed to heap on the graph paper.

The radius and height of the powder heap were then measured and the angle of repose was calculated from the following equation;

$$\phi = \arctan \frac{H}{R} \qquad \text{- equation 2.1.2}$$

where, ϕ = angle of repose

         H = height of powder heap

         R = radius of powder heap

In order to measure the height of the powder heap without disturbing it, the distance form the bottom of the cylinder guide to the tip of the powder heap was measured, and this value was subtracted from the distance from the bottom of the cylinder guide to top of the bench.

2.1.2.5. Measurement of compressibility

After measuring the angle of repose, 700mg of each powder mix was compressed to either 2,5 tonnes, 5,0 tonnes, or 7,5 tonnes in a Beckman hydraulic press (Beckman Instruments, Inc., Fullerton, U.S.A.). The tablets were compressed into flat 13 mm diameter round disc tablets for 10 seconds at each compression force. After standing for 30 minutes, the hardness of the tablets were measured in a Pharma Test PTB 311 (Pharma Test, Hainburg, Germany). The slope of the graph of hardness (diametral crushing strength) of the tablets versus natural logarithm of compressional force was calculated using linear regression analysis. The slope was then used as the estimation of the compressibility of the powder blends tested.

TABLE 2.1.3.

Angle of repose and compressibility of powder blends (t, type of binder; s, particle size of ethylcellulose; c, concentration of binder) Subscripts $_a$ and $_b$ indicate replicates.

Run	t	s	c	Flow	Compressibility	r^2
1_a	-1	-1	-1	28.76	10.90	0,860
1_b	-1	-1	-1	35.15	10.77	0,966
2	-1	-1	0	34.77	17.38	0,998
3_a	-1	-1	1	47.95	23.98	0,874
3_b	-1	-1	1	50.77	28.27	0,998
4	-1	0	-1	30.27	2.90	0,884
5_a	-1	0	0	36.86	19.25	0,997
5_b	-1	0	0	41.71	17.21	0,966
6	-1	0	1	48.52	23.39	0,993
7_a	-1	1	-1	35.10	29.77	0,896
7_b	-1	1	-1	43.23	27.15	0,854
8	-1	1	0	39.35	20.13	0,998
9_a	-1	1	1	44.27	17.38	0,998
9_b	-1	1	1	48.70	28.35	0,888
10	0	-1	-1	26.67	22.40	0,917
11	0	-1	0	30.26	25.42	0,998
12	0	-1	1	33.32	49.77	0,897
13	0	0	-1	27.27	26.91	0,966
14_a	0	0	0	30.21	33.65	0,946
14_b	0	0	0	28.25	26.01	0,786
15	0	0	1	33.20	25.20	0,810
16	0	1	-1	26.29	40.15	0,993
17	0	1	0	29.29	28.52	0,968
18	0	1	1	31.91	59.35	0,984
19_a	1	-1	-1	30.08	30.61	0,823
19_b	1	-1	-1	28.78	34.43	0,658
20	1	-1	0	34.67	30.39	0,944
21_a	1	-1	1	35.49	34.11	0,991
21_b	1	-1	1	31.28	36.43	0,935
22	1	0	-1	31.18	57.00	0,996
23_a	1	0	0	33.15	34.30	0,966
23_b	1	0	0	28.45	44.23	0,888
24	1	0	1	34.19	70.41	0,919
25_a	1	1	-1	23.28	25.18	0,993
25_b	1	1	-1	28.56	24.87	0,990
26	1	1	0	26.93	48.43	0,968
27_a	1	1	1	28.17	55.57	0,971
27_b	1	1	1	34.13	50.66	0,854

2.1.2.6. *Statistical analysis*

Analysis of variance was performed on the data presented in Table 2.1.3 using STATGRAPHICS v 5 (Statistical Graphics Corporation, U.S.A.). The independent variables were % binder in the tablet, type of binder used in the tablet, and the average particle size (as the class mark in the particle size range) of the ethylcellulose. Because STATGRAPHICS requires that continuous variables are spaced equally apart for calculating the various outputs, the normalised values of the class mark particle size within each size range were 475 µm, 725 µm, and 975 µm instead of the actual values of 477,5 µm, 725 µm, and 925 µm. The actual class mark values were obtained because of the unavailability of 350 µm and 1100 µm sieves. As we are only using the factorial design to estimate the effects of each variable, this adjustment is quite in order for the analysis. The dependent variables were flow (through angle of repose) and compressibility. Response-surface plots were constructed for the above variables, in order to determine the optimal combination of the variables. Main effects and significant interactions were also calculated. Simple regression models for the three independent variables were also developed from the results as follows:

$$Y_l \ (c,t,s) = a_0 + a_1c + a_2t + a_3s + a_4ct + a_5cs + a_6ts + a_7c^2 + a_8t^2 + a_9s^2 \ a_{10}cts$$

$$- \text{equation 2.1.3}$$

where $a_0...,a_{10}$ are the coefficients of the system. c, t and s denote the % binder, type of binder and particle size range of the powder blends, respectively.

Each term in the final regression equation for the flow or the compressibility was only included if the t-test p value was less than 0,05. The regression coefficients for those effects that were considered insignificant were eliminated and the model was re-estimated. All statistical analysis was performed using STATGRAPHICS v 5 (Statistical Graphics Corporation, U.S.A.).

2.1.3. **Results and Discussion**

Table 2.1.4 lists the relevant statistical parameters calculated from the results of this study for the effect of the three independent variables on the compressibility and flow of the powder blends analysed. All statistical analysis was carried out on all the experimental runs.

2.1.3.1. *Powder flow*

Figures 2.1.1a - c are response surface plots of the estimated effects of the type of binder, the % concentration of binder, and the particle size of ethylcellulose on the angle of repose of the powder blends. The plots have been drawn on the basis of the model by assigning a constant value to one of the variables. All three variables play a statistically significant role in the resultant angle of repose of the powder blends. Type of binder used in the powder blends has the most significant influence on its angle of repose (Fig. 2.1.1a and 2.1.1b). This is particularly more pronounced with cetyl alcohol (Fig. 2.1.1a). Cetyl alcohol has by far the worst effect on flow (through a larger angle of repose), especially at higher concentrations (Fig. 2.1.1b). There is a similar effect on the flow of the powder blends that incorporate Encompress[R] and carnauba wax. Encompress[R] has a slightly lower angle of repose value on average over the various particle size ranges and concentrations of each binder used.

TABLE 2.1.4.

Relevant statistical parameters for flow and compressibility studies

Source effect	Estimated effects ± standard error (28 d.f.)	p-value	Regression coefficients	Regression coefficients re-estimated
Angle of repose				
average	29,211 ± 1,185			
constant			29,211	29,667
t	-9,789 ± 1,084	< 0,0001	-4,894	-4,894
s	-0,404 ± 1,126	0,7262	-0,202	
c	8,388 ± 1,126	< 0,0001	4,194	4,194
ts	-3,251 ± 1,283	0,0172	-1,626	-1,626
tc	-4,808 ± 1,283	0,0008	-2,404	-2,404
sc	-2,041 ± 1,283	0,1230	-1,021	
tt	11,225 ± 2,134	< 0,0001	5,613	5,700
ss	-1,089 ± 2,087	0,6115	-0,544	
cc	2,608 ± 2,087	0,2218	1,304	
Compression				
average	31,849 ± 4,229			
constant			31,849	31,338
t	21,414 ± 3,872	< 0,0001	10,707	10,707
s	7,742 ± 4,018	0,0642	3,871	
c	12,295 ± 4,018	0,0048	6,147	6,147
ts	0,726 ± 4,581	0,8769	0,363	
tc	3,521 ± 4,581	0,4567	1,761	
sc	0,074 ± 4,581	0,9874	0,037	
tt	-7,235 ± 7,619	0,3605	-3,612	
ss	-2,774 ± 7,450	0,7163	-1,387	
cc	9,072 ± 7,450	0,2335	4,536	

As the concentration of binder in the powder blends increase, the angle of repose increases (Fig. 2.1.1b and 2.1.1c). This increase in the angle of repose is most prominent with cetyl alcohol (Fig. 2.1.1a) and with a combination of smaller average particle size and higher concentration of binder (Fig. 2.1.1c). This is evidenced from the significant *tc* statistical interaction. Since the cetyl alcohol is a waxy binder, this adverse effect on the flow of the directly compressible powder blend is expected. Surprisingly, the effect of particle size of the ethylcellulose used in the powder blends is not statistically significant, and there was very little difference in the angles of repose over the various size ranges tested (Fig. 2.1.1a and 2.1.1c). However, as the concentration of binder used increased, the effect of increase in particle size on the angle of repose becomes a little more pronounced. At lower concentrations of binder, the opposite occurs (Fig. 2.1.1c).

In developing a regression model for the effect of the independent variables on the angle of repose dependent variable, the main effects of type of binder (*t*) and concentration of binder (*c*) as well as the second order interaction effects of *ts*, *tc* and *tt* were significant ($p < 0.05$). Therefore, the regression coefficients for these effects were included in the model. The rest of the coefficients were eliminated and the model was re-estimated by STATGRAPHICS.

$$Y_f(t,p,c) = 29,66 - 4,894t + 4,194c - 1,626ts - 2,404tc + 5,700tt$$

<div align="right">- equation 2.1.4</div>

where $Y_f(t,p,c)$ is the estimated angle of repose of the powder blends.

The squared multiple regression coefficient for this model was 0,87. This model shows that the type of binder has the major adverse effect on the friability of the cup tablet. Cetyl alcohol (signified by 0 on the type axis of the response surface plots in figure 2.1.1 a and b) is by far the worst for flow properties, which is then followed by Encompress[R], and thereafter by carnauba wax. The concentration of binder then produces the next most significant effect on the angle of repose.
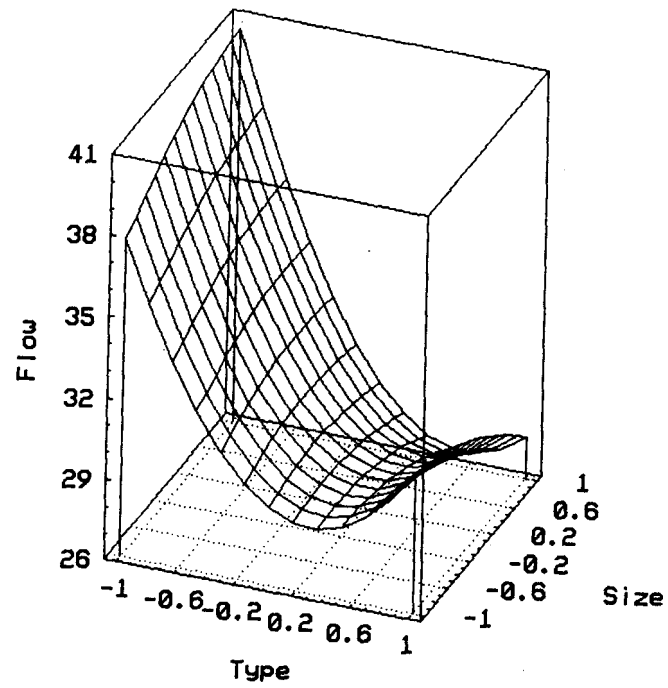
Fig. 2.1.1 a Response surface plots of the estimated effects of *t and s* on the angle of repose of powder blends.
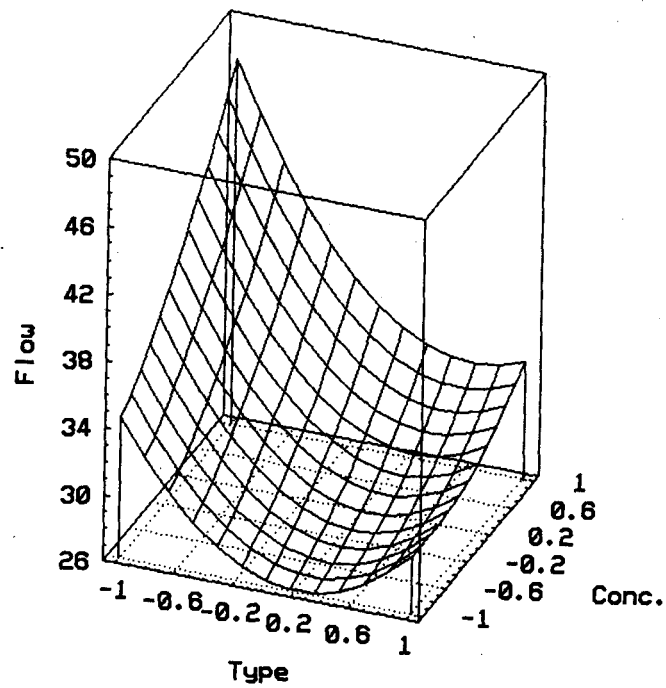
Fig. 2.1.1 b Response surface plots of the estimated effects of *t and c* on the angle of repose of powder blends.
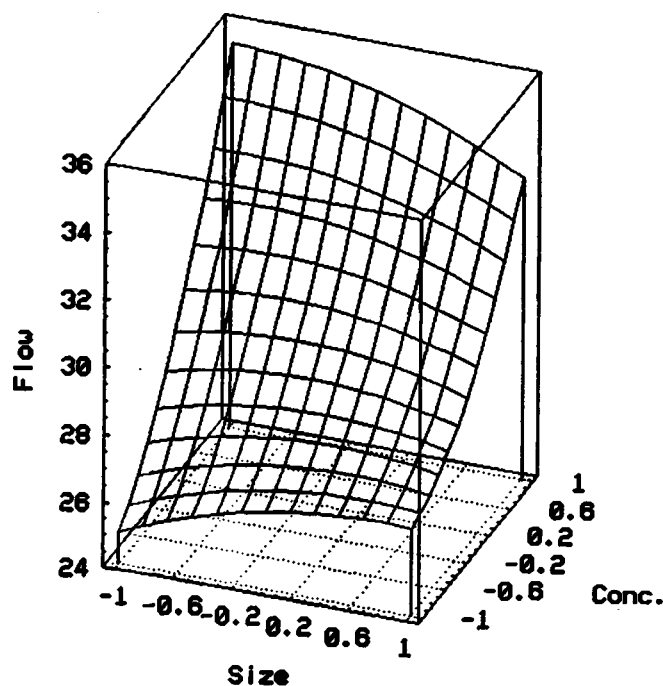
Fig. 2.1.1 c Response surface plots of the estimated effects of *s* and *c* on the angle of repose of powder blends.

As the concentration of binder increases, so does the angle of repose. From the results, it is clear that in order to produce a directly compressible powder blend with good flow properties, either Encompress[R] or carnauba wax at a low concentration range, and mixed with ethylcellulose of any size range tested in this analysis could and should be used. However, it should be noted that the angle of repose of the powder blends only becomes a problem when it is greater than $40°$.

Therefore, if we substitute the factor levels, -1 for the average particle size range, 1 for the type of binder (carnauba wax), and 40 for the maximum acceptable angle of repose range into equation 2.1.4 above, and solve for *c* (the % concentration factor level), we can obtain the maximum amount of carnauba wax that could be added to ethylcellulose. Solving the equation gives a factor level value of 4,417. This then translates to a concentration of $\pm$ 13%$^{w}/_{w}$ carnauba wax.

2.1.3.2. Compressibility

Figures 2.1.2 a - c are response surface plots of the estimated effects of the different response variables on the compressibility of the powder blends. Only the type of binder and concentration of binder play a statistically significant role in the resultant compressibility of the directly compressible powder blends (Table 2.1.4). As with the flow (angle of repose), it is the type of binder which has the most notable influence on the compressibility of the powder blend. (Fig. 2.1.2a and 2.1.2b). The response surfaces are moderately stable over the ranges of type of binder and average particle size range of ethylcellulose.
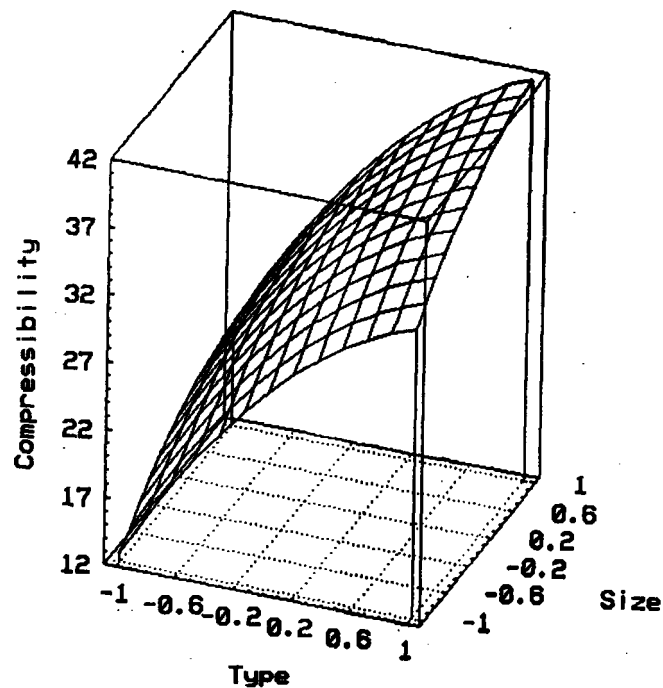
Fig. 2.1.2 a Response surface plots of the estimated effects of *t and s* on the compressibility of the powder blends.
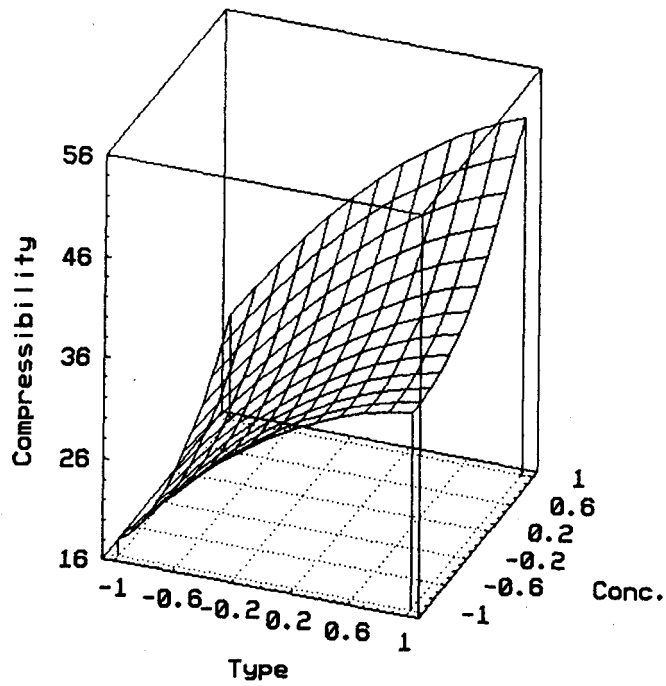
Fig. 2.1.2 b Response surface plots of the estimated effects of *t and c* on the compressibility of the powder blends.
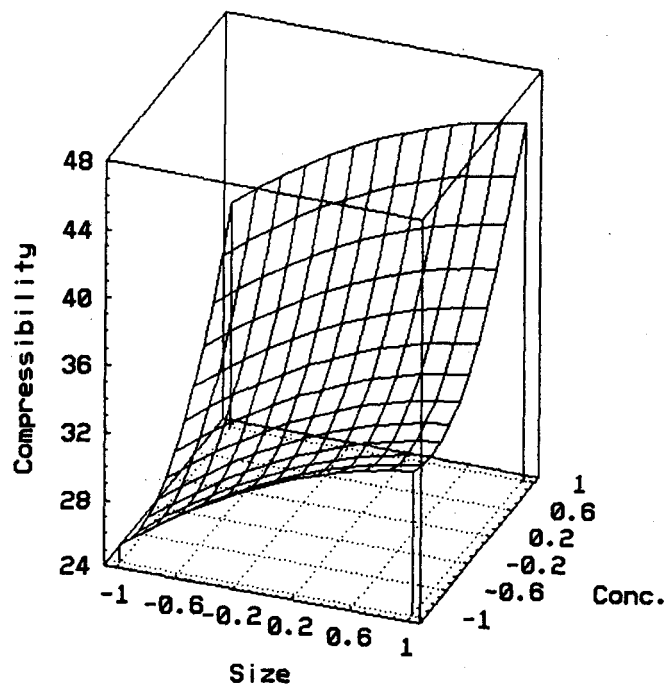
Fig. 2.1.2 c Response surface plots of the estimated effects of *s and c* on the compressibility of the powder blends.

There is a very slight improvement of the compressibility of the powder blend as the average particle size range of ethylcellulose increases. However, this does not warrant the separation of the ethylcellulose into an ideal particle size range. As the concentration of binder in the powder blends increase, so does the compressibility of the powder blends increase exponentially (Fig. 2.1.2c). This effect, however, is not as pronounced as that found with the type of binder used.　　　In developing a regression model for the effect of the independent variables on the compressibility of the powder blends, only type of binder (t) and concentration of binder (c) main effects were significant ($p < 0.05$). Therefore, only these regression coefficients were included in the model. The rest of the coefficients were eliminated and the model was re-estimated by STATGRAPHICS.

$$Y_{com} (t,c) = 31,338 + 10,707t + 6,147c \qquad \text{- equation 2.1.5}$$

where $Y_{com} (t,c)$ is the estimated compressibility of the powder blends.

The squared multiple regression coefficient for this model was 0,62. This model shows that the type of binder used has the principal effect on the compressibility of the powder blends. Carnauba wax has the best compactibility, which is then followed by Encompress[R] and cetyl alcohol. The concentration of binder then produces the next most significant effect on compressibility. In order to produce a tablet with the best compressibility (as indicated from the slope of the graph of ln compression force versus diametral crushing strength), it would be best to use carnauba wax at as high a concentration that is possible. This concentration however, will be limited by its adverse effect on the flow properties of the blend.

In conclusion, the results show that to produce a directly compressible powder blend (with the available ingredients) with good compressibility properties and minimal adverse effect on the flow of the powder, the best choice would be carnauba wax at a concentration of approximately 10% - 15%$^w/_w$. Consequently, we will use low viscosity ethylcellulose together with 10%$^w/_w$ carnauba wax for the directly

compressible powder blend was used in producing and further evaluating the cup portion of the core-in-cup tablets.

2.2 PRODUCTION AND DEVELOPMENT OF A ZERO-ORDER RELEASE ORAL COMPRESSED TABLET

2.2.1 Introduction

In the previous analysis of directly compressible powder blends, it was shown that low viscosity ethylcellulose mixed together with up to $13\%^w/_w$ carnauba wax was the most suitable combination for use as a directly compressible tabletting base for the cup portion of the tablet. Therefore, ethylcellulose together with $10\%^w/_w$ carnauba wax (so as not to adversely effect the flow of the powder too much) was used as the directly compressible base for the cup portion of the core-in-cup tablet. To produce a core tablet that would possibly release drug for a period of 8 or more hours, it was decided that HPMC would be used, as it comes in various viscosity grades and has been used extensively in matrix sustained-release preparations (Wan et al., 1993; Kumar and Banker, 1993, Melia, 1991; Alderman, 1984). The low viscosity grade is useful in that it does not swell too much in aqueous medium and erodes at a constant rate. It can also be used in low concentrations.

This experiment describes a method that can possibly be automated to produce core-in-cup tablets that have the ability to release soluble and insoluble drugs at a zero-order rate from an inert inactive cup. To check the validity of the core-in-cup drug delivery system to release both soluble and insoluble drugs at a zero-order rate, ibuprofen (insoluble) and caffeine (soluble) were used as model drugs. The experiment also investigates the release of the model drugs from two different HPMC grades (low and intermediate viscosity grades) of three different concentrations (5%, 10% and 15%), as well as from core-in-cup and core-only tablets.

The kinetics of drug release from the core-in-cup tablets are examined as to how well the rate of release fits the Korsmeyer *et al.* (1983b) relationship depicted in equation 2.2.1 or equation 2.2.2 below.

$$\frac{M_t}{M_\infty} = k. \, t^n \qquad\qquad \text{- equation 2.2.1}$$

or,

$$\log \frac{M_t}{M_\infty} = \log k + n \log t \qquad\qquad \text{- equation 2.2.2}$$

where M_t/M_∞ is the fractional release of the drug, t is the release time, k is a constant incorporating structural and geometric characteristics of the release device and n is the time exponent indicative of the mechanism of release. For example, $n = 0,5$ for square root of time kinetics and $n = 1,0$ for zero-order kinetics.

This classification has been successfully used by Ford *et al.* (1987) to characterize the release of a number of different drugs from HPMC matrices. If one plots the logarithm of the fractional release versus the logarithm of time in minutes, the slope of the graph will give one the value of the n exponent. In order for equation 2.2.2 to be applicable the intercept of the graph must pass through the origin, i.e. *log k* must be zero. The correction method, however, is applicable to the type of release of drug from the tablets.

This correction to data can be achieved via correcting the sampling time data of;

(i) cumulative fractional release versus time, for a zero-order model,

(ii) cumulative fractional release versus the square root of time, for a square root of time model, or

(iii) log of cumulative fractional release versus time, for a first-order model.

The sampling times are then corrected by linear regression so that the graph passes through the origin (Ford *et al.* 1987). The intercept on the y-axis is calculated via linear regression and the times on the x-axis are adjusted depending on whether the intercept on the y-axis is above or below zero. In this way a value is added or subtracted from the time values so that at time zero the graph goes through the origin.

2.2.2. Materials and Methods

2.2.2.1. *Materials*

HPMC K4M premium EP and HPMC K15M premium EP were supplied by Colorcon Limited, England. HPMC K4M and K15M have viscosities of 3500 - 5600 cP and 12000 - 21000 cP respectively as 2% solutions in water at 20°C. The polymers had already been screened through a No. 40 standard U.S. sieve. Caffeine (E Merck, Darmstadt) and ibuprofen (Boots Co, S.A. Pty Ltd) were ground and the fraction passing through a No. 150 standard U.K. sieve was used. Ethylcellulose (Sigma Chemical Company, U.S.A.) was used as supplied. All other reagents used were standard laboratory grade.

2.2.2.2. *Formulations*

Flat disc-shaped tablets (cores) were made consisting of 95%$^w/_w$, 90%$^w/_w$ and 85%$^w/_w$ of caffeine (soluble model drug) or ibuprofen (insoluble model drug) in either HPMC K4M or HPMC K15M. Table 2.2.1 lists all the different formulations used in this study. The codes for the different formulations tested were obtained as follows:

(i) The first number from the left, i.e. 5, 10 or 15 is the concentration of polymer used in the core tablet.

(ii) The second number from the left, separated from the first number by the letter H, i.e. H4 or H15 signifies HPMC K4M or HPMC K15M grades of polymer used in the core tablet.

(iii) The second letter from the left, i.e. c or C signifies the core only (small c) or core-in-cup (capital C) tablets.

(iii) The last letter from the left, i.e. C or I signifies the model drugs caffeine or ibuprofen respectively, used in the tablet.

Twenty grams of each combination was prepared. The cores were compressed in a tabletting press to a thickness of 2 mm and a diameter of 7 mm, therefore the weights of the cores varied slightly according to the density of the core mixture. Table 2.2.2 lists the average weights of the cores together with their standard deviations. Cups were made of 10%$^w/_w$ carnauba wax in ethylcellulose. The average weight of the cups are also listed in table 2.2.2.

TABLE 2.2.1
Codes and descriptions of different formulations tested.

Code	Formulation	
	Core %$^w/_w$ Polymer/Drug	Cup 10% Carnauba wax/ Ethylcellulose
5H4CC	5% HPMC K4M/Caffeine	Yes
10H4CC	10% HPMC K4M/Caffeine	Yes
15H4CC	15% HPMC K4M/Caffeine	Yes
5H15CC	5% HPMC K15M/Caffeine	Yes
10H15CC	10% HPMC K15M/Caffeine	Yes
15H15CC	15% HPMC K15M/Caffeine	Yes
5H4cC	5% HPMC K4M/Caffeine	
10H4cC	10% HPMC K4M/Caffeine	
15H4cC	15% HPMC K4M/Caffeine	
5H15cC	5% HPMC K15M/Caffeine	
10H15cC	10% HPMC K15M/Caffeine	
15H15cC	15% HPMC K15M/Caffeine	
5H4CI	5% HPMC K4M/Ibuprofen	Yes
10H4CI	10% HPMC K4M/Ibuprofen	Yes
15H4CI	15% HPMC K4M/Ibuprofen	Yes
5H15CI	5% HPMC K15M/Ibuprofen	Yes
10H15CI	10% HPMC K15M/Ibuprofen	Yes
15H15CI	15% HPMC K15M/Ibuprofen	Yes
5H4cI	5% HPMC K4M/Ibuprofen	
10H4cI	10% HPMC K4M/Ibuprofen	
15H4cI	15% HPMC K4M/Ibuprofen	
5H15cI	5% HPMC K15M/Ibuprofen	
10H15cI	10% HPMC K15M/Ibuprofen	
15H15cI	15% HPMC K15M/Ibuprofen	

TABLE 2.2.2

Mean weights of cores and cup used in the different formulations

Formulation	Mean weight (mg) ± SD (n=20)
HPMC K4M/Caffeine	
5H4cC	92,28 ± 2,66
10H4cC	88,27 ± 1,98
15H4cC	87,10 ± 2,09
HPMC K15M/Caffeine	
5H15cC	94,15 ± 2,45
10H15cC	90,41 ± 1,86
15H15cC	88,27 ± 2,36
HPMC K4M/Ibuprofen	
5H4cI	91,10 ± 2,62
10H4cI	90,92 ± 1,55
15H4cI	87,34 ± 3,52
HPMC K15M/Ibuprofen	
5H15cI	85,42 ± 2,57
10H15cI	86,25 ± 1,06
15H15cI	85,22 ± 2,49
Ethylcellulose/Carnauba wax	
Cup	284,06 ± 4,31

2.2.2.3. *Preparation of compressed tablets*

All powders for the cores were thoroughly mixed and granulated in an Erweka FGS granulator fitted with a 500 μm stainless steel screen. To form a coherent granule mass, 45%$^v/_v$ alcohol in water was used as granulating agent. Once the granules were dry and passed through a 500 μm screen, they were compressed into cores on a Manesty F3 tabletting press using 7 mm diameter flat round punches. The press was set to compress the cores to a thickness of 2 mm. The hardness of the cores were then measured on a Pharma Test PTB 311 hardness tester. The press was then adjusted to produce a tablet of an approximate hardness of approximately 40 N/m^2. Table 2.2.3 lists the hardness values of the cores as well as the final core-in-cup tablets.

The ethylcellulose and the carnauba wax were thoroughly mixed and directly compressed into cups with a top punch which was sparkeroded, machined, and polished so that it produces a cup-shaped tablet of 11 mm outer diameter, and an inner hollow core of 7,5 mm diameter and 2 mm depth. The bottom punch consisted of a flat round 11 mm diameter punch. The press was set to produce a tablet of an approximate hardness of 90 N/m^2. Table 2.2.3 lists the hardness values of the cups.

Once the cores and the cups were compressed, the cores were placed inside the cups and fed into the tabletting press to finally be compressed into a single core-in-cup tablet. The cores and cups were then compressed between flat round punches of 12 mm diameter. The slightly larger punches and die cavity ensured that the core-in-cup tablet of 11 mm diameter could easily be fed into the 12 mm die cavity. The press was then adjusted to produce an approximate hardness of 140 N/m^2. Cores to be tested and compared to the core-in-cup tablets were also recompressed to an approximate hardness of 140N/m^2 using flat 8 mm punches. This recompression of the cores to be tested was necessary to achieve the same relative hardness as the core portion of the tablet in the core-in-cup compressed tablet.

TABLE 2.2.3

Mean hardness of cores, and core-in-cup used in the different formulations

Formulation	Mean hardness (N/m^2) ± SD (n=9)	
	Cores	Core-in-cup
HPMC K4M/Caffeine		
5H4CC	44,61 ± 4,34	152,41 ± 7,51
10H4CC	48,61 ± 6,53	158,70 ± 4,36
15H4CC	40,70 ± 3,42	145,24 ± 5,58
HPMC K15M/Caffeine		
5H15CC	38,32 ± 9,42	145,26 ± 7,97
10H15CC	43,02 ± 3,86	150,25 ± 5,19
15H15CC	41,42 ± 4,80	147,55 ± 5,96
HPMC K4M/Ibuprofen		
5H4CI	41,98 ± 8,92	149,40 ± 8,18
10H4CI	38,16 ± 6,15	142,63 ± 7,75
15H4CI	42,94 ± 7,46	150,43 ± 6,38
HPMC K15M/Ibuprofen		
5H15CI	44,30 ± 4,07	154,79 ± 9,55
10H15CI	46,11 ± 8,48	152,12 ± 9,77
15H15CI	46,22 ± 3.09	150,65 ± 3,72
Cup		
Ethylcellulose/Carnauba wax		
Cup	90,25 ± 5,31	N/A

Figure 1.6 graphically describes the various steps in the production process of the core-in-cup compressed tablets.

The inactive cups and the active cores as well as the two being compressed together, can be accomplished automatically on a tabletting press that can be modified with feed shoes that feed the cores into the cups and then feed these into a die cavity to be compressed together. It is also a very simple method using exceedingly few adjuvants, and is applicable to a wide variety of drugs. Figure 1.6 graphically describes the compression of the core-in-cup tablets and the dimensions of the punches and dies used to produce these compressed tablets.

2.2.2.4 Release Studies

The B.P. 1988 paddle method was utilised in all the release studies. A volume of 500 ml of deionized water, equilibrated at $37°C \pm 0.5°C$, was used as the release medium. All experiments were carried out at 50 rpm. The release rates of the tablets were monitored using a 6 beaker Caleva model 7ST dissolution tester. At appropriate time intervals 2,0 ml samples were withdrawn for analysis. For the release of caffeine from the tablets, the samples were analyzed spectrophotometrically at a wavelength of 242 nm using a Beckman DU 650 spectrophotometer. Linearity was established for aqueous solutions of caffeine in the range of 6,25 - 200 µg/ml. For the release of ibuprofen from the tablets, 2 ml methanol was added to the sample withdrawn, mixed well on a vortex mixer, and measured at a wavelength of 216 nm. Linearity was established for a 50%$^v/_v$ methanol in deionized water ibuprofen solutions in the range of 6,25 - 200 µg/ml. The release profiles of a minimum of 3 tablets from each of 3 different batches (n = 9) were analyzed. The rate of release of caffeine and ibuprofen from cores only were also analyzed.

2.2.2.5 *Calculation of time exponents*

The release rate exponents of drug release from the core-in-cup tablets were examined as to how well the rate of release fits the Korsmeyer *et al.* (1983b) relationship depicted in equation 2.2.2. Plots of the logarithm of the fractional release versus the logarithm of time in minutes were plotted for each formulation. The time exponent was then calculated from the slope of the plot via linear regression. In order for equation 2.2.2 to be applicable, the intercept of the graph must pass through the origin, i.e. *log k* must be zero. This correction to data was achieved via correcting the sampling time data of cumulative fractional release versus the square root of time for the core only tablets, and via correcting time data of cumulative fractional release versus *time* for the core-in-cup tablets. The sampling times were then corrected by means of linear regression so that the graph passed through the origin, as per Ford *et al.* (1987). In order to determine whether the drug was released mainly via zero-order or square root of time kinetics, the plot with the best correlation coefficient was used. Only the linear portions of the graphs were used to calculate the time exponents. The mean release rates of the core-in-cup tablets were calculated via linear regression of the linear portion of the plot of cumulative fractional release versus time.

2.2.3 Results and Discussion

Table 2.2.4 lists the calculated time exponents as calculated from the results using equation 2.2.2 as well as the average release rates using equation 2.2.1 for the zero-order core-in-cup systems. Figures 2.2.2 and 2.2.3 show the release rate of caffeine from the core-in-cup tablets when HPMC K4M and HPMC K15M were used in the core, as well as the release from the cores without the cup coatings. These results indicate that the rate of release of caffeine (a soluble drug) is released from the core-in-cup tablets at a near zero-order rate of release for 80% of the release time. This occurred no matter which concentration of HPMC K4M was used. This near zero-order rate of release is confirmed for the release of caffeine from the HPMC matrix core-in-cups from equation 2.2.2.

TABLE 2.2.4

Mean time exponents and release rates from core only matrices and core-in-cup tablets used in the different formulations

Formulation	Exponent n value ± SD (n=9)	Mean release rate (mg/min.) ± SD (n=9)
HPMC K4M/Caffeine		
5H4CC	0,973 ± 0,046	0,174 ± 0,036
5H4cC	0,562 ± 0,041	
10H4CC	0,988 ± 0,089	0,115 ± 0,042
10H4cC	0,594 ± 0,033	
15H4CC	0,987 ± 0,057	0,105 ± 0,033
15H4cC	0,617 ± 0,023	
HPMC K15M/Caffeine		
5H15CC	1,026 ± 0,096	0,115 ± 0,045
5H15cC	0,534 ± 0,031	
10H15CC	1,056 ± 0,013	0,106 ± 0,035
10H15cC	0,516 ± 0,098	
15H15CC	1,058 ± 0,082	0,081 ± 0,048
15H15cC	0,477 ± 0,069	
HPMC K4M/Ibuprofen		
5H4CI	0,997 ± 0,032	0,126 ± 0,025
5H4cI	0,496 ± 0,031	
10H4CI	0,984 ± 0,039	0,094 ± 0,035
10H4cI	0,451 ± 0,099	
15H4CI	0,979 ± 0,019	0,081 ± 0,020
15H4cI	0,409 ± 0,026	
HPMC K15M/Ibuprofen		
5H15CI	0,987 ± 0,062	0,091 ± 0,024
5H15cI	0,540 ± 0,061	
10H15CI	1,015 ± 0,050	0,078 ± 0,016
10H15cI	0,553 ± 0,069	
15H15CI	1,041 ± 0,021	0,055 ± 0,042
15H15cI	0,499 ± 0,031	

Fig. 2.2.2 Caffeine release rates from HPMC K4M drug delivery systems.

___ Core-in-cup tablets.   _ .. Core only tablets.
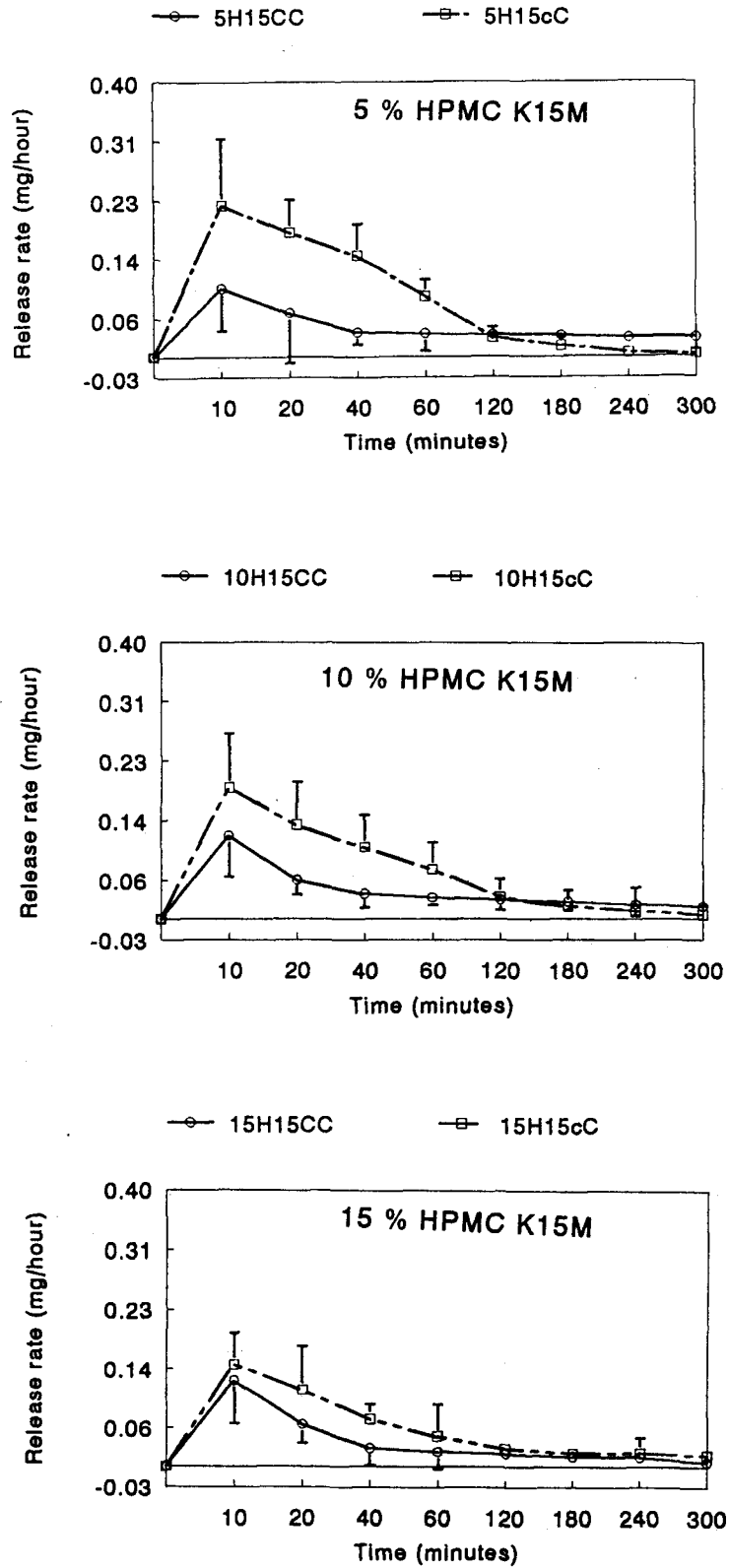
Fig. 2.2.3 Caffeine release rates from HPMC K15M drug delivery systems.

___ Core-in-cup tablets. _ .. Core only tablets

When HPMC K15M is used as the matrix polymer there is a slight negative deviation in the rate of release (i.e. the rate decreases slightly with time) which results in an exponent n of greater than 1. For these systems, the larger than 1 the exponent n is, the less closer it is to zero-order release, just as it does for a fraction less than 1 for a positive deviation. Deviation of the time exponent n away from 1 occurs more with core-in-cup tablets containing HPMC K15M than with HPMC K4M. This is because there is more swelling of the HPMC K15M in the release medium. The higher the concentration of HPMC K4M or HPMC K15M polymer in the core, the lower the rate of release and the longer the time of near zero-order release. The unique high rate of release initially is due to the occurrence of an immediate release of drug from the surface of the polymer matrix core as it comes into contact with the release medium. During manufacture some of the drug particles are exposed at the surface of the matrix and not trapped within. Also, the HPMC swells out very slightly as it comes into contact with the aqueous solution, even though its concentration in the core is low. This allows an immediate release of drug via diffusion in the initial period of release as well as a larger initial surface area exposed to the release medium. Consequently, after approximately 60 minutes this swelling above the circumference walls of the cup is eroded to a flat constant surface area. The HPMC K15M swells more than the HPMC K4M, therefore more caffeine is released via diffusion control for the HPMC K15M tablets than the HPMC K4M tablets. The release of caffeine from the tablets however, settles down to a near zero-order rate of release after 30 - 60 minutes. This is due to the fact that the release of caffeine from the polymer matrix is mainly due to erosion of the polymer and constant diffusion through the slightly swollen polymer surface.

The rates of release of ibuprofen from HPMC K4M and HPMC K15M core-in-cups and cores only are shown in figures 2.2.4 and 2.2.5. The results are very similar to that of caffeine, except that the rate of release over the linear period for both polymers are closer to zero-order than that for caffeine. The time exponents n vary from 1,041 to 0,997.
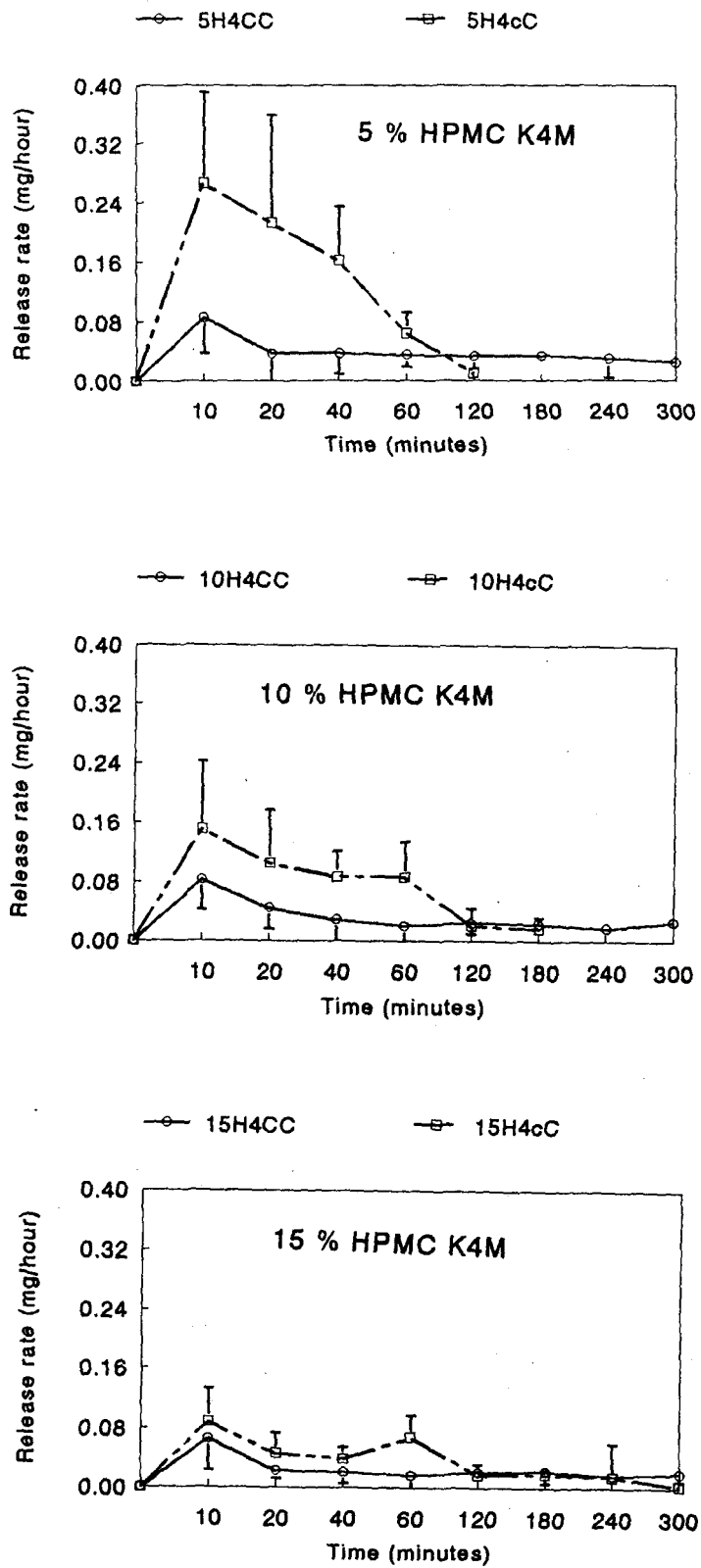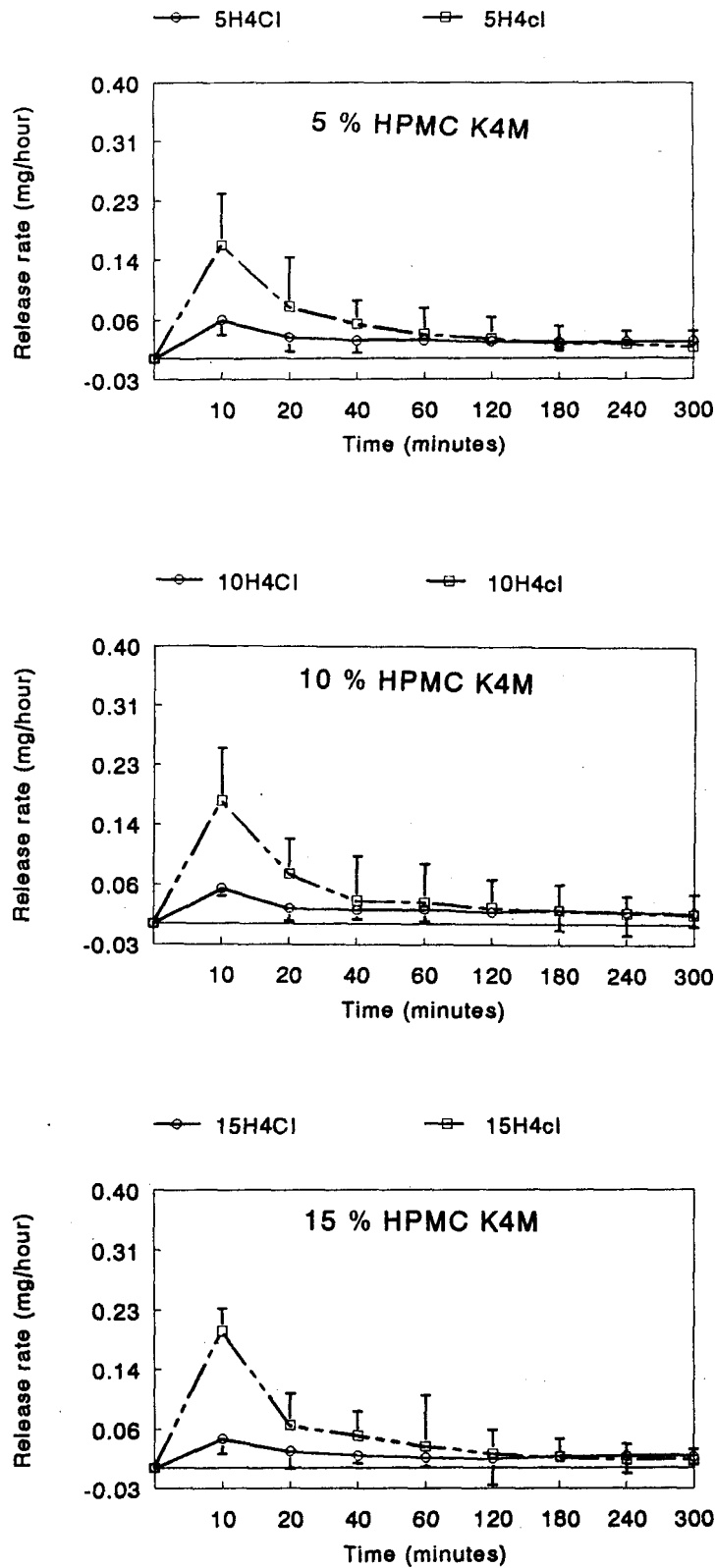
Fig. 2.2.4 Ibuprofen release rates from HPMC K4M drug delivery systems.

___ Core-in-cup tablets.   _ .. Core only tablets
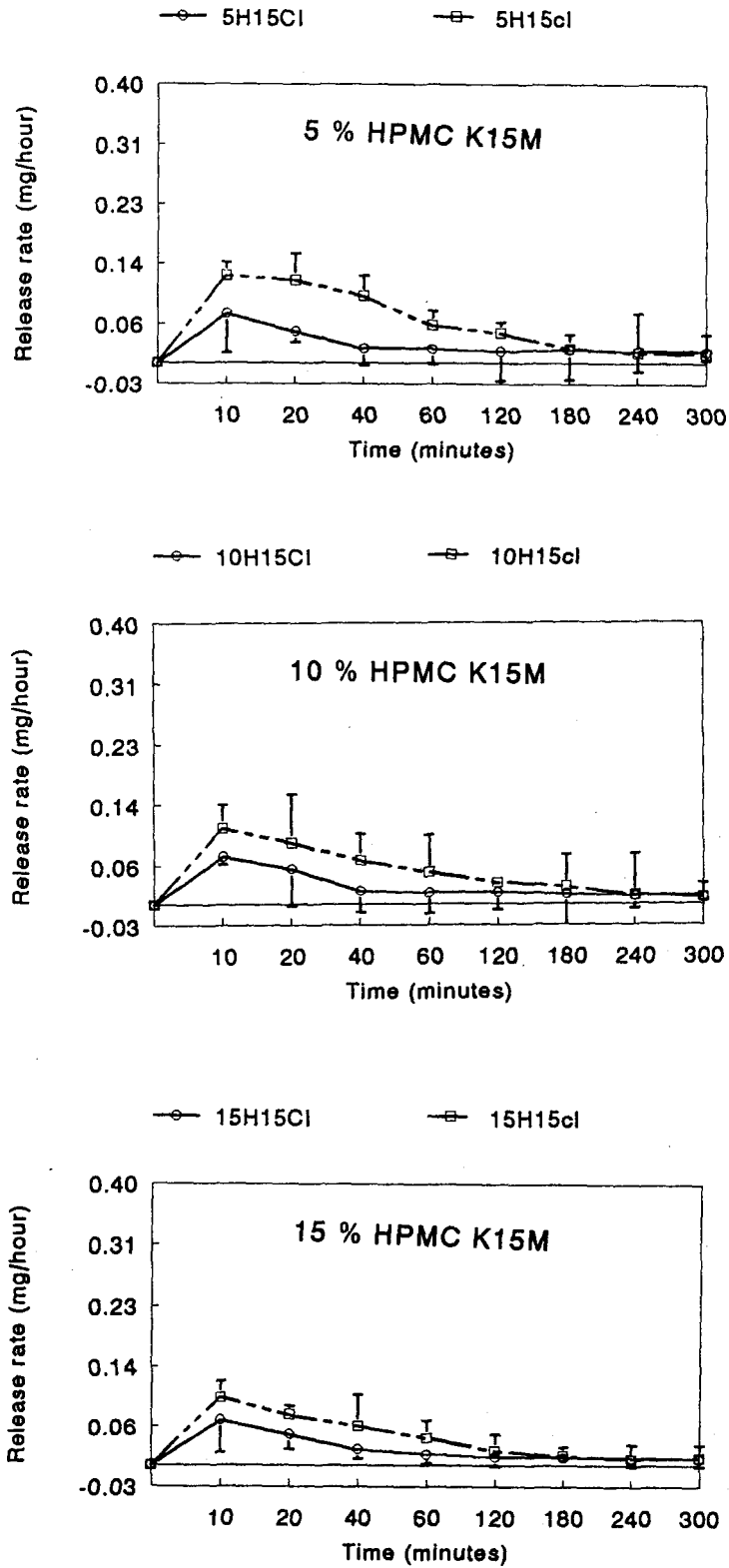
Fig. 2.2.5 Ibuprofen release rates from HPMC K15M drug delivery systems.

___ Core-in-cup tablets.   ___ .. Core only tablets

This is well in line with predicted theory in that the release of ibuprofen from the polymer matrix is predominantly through erosion of the polymer surface. The reason for this, is that ibuprofen is not very soluble in aqueous solution and negligible drug is released via diffusion from the polymer matrix.

Again, like the release of caffeine from the core-in-cup tablets, the release of ibuprofen from the HPMC K4M tablets is closer to perfect zero-order than the release of ibuprofen from the HPMC K15M tablets. The difference, however, for all practical purposes is less than the difference for the caffeine core-in-cup tablets.

In comparing all the core-in-cup tablet formulations with the core-only formulations, one can see that there is a significant difference in the release exponents of both the aqueous soluble caffeine ($p = 0,0000077$) and insoluble ibuprofen ($p = 0,0000023$). The calculated probabilities were based on the difference of the release exponents for the core only and core-in-cup tablets, and treated as a single sample test, since they were both tested in the same release fluid. The core-only formulations release drug at a rate equivalent to square root of time kinetics. This can be explained by the fact that as the core tablet erodes the surface area of the tablet decreases with time and hence less drug is released with time. Therefore, from an *in vitro* release point of view, the core-in-cup formulation is a superior formulation to the traditional matrix type of compressed tablet.

It is possible, through the manipulation of the grade of HPMC polymer used (or any other hydrophillic polymer or mixture of polymers that erodes constantly with time), the quantity of HPMC polymer used, and the exposed surface area of the core of the HPMC polymer matrix, to produce a core-in-cup compressed tablet that can release a constant amount of drug over a predetermined period of time. In this study, the time of constant release varied from approximately 8 hours for the 5%$^w/_w$ caffeine in HPMC K4M core-in-cup tablets, to approximately 23 hours for the 15%$^w/_w$ ibuprofen in HPMC K15M core-in-cup tablets. Therefore, it is possible to produce a zero-order compressed tablet that only needs to be dosed once or twice daily

depending on were the drug is absorbed in the gastrointestinal tract and its residence time. With the present advancement of robotics and automated technology it will be reasonably easy and inexpensive to fully automate the manufacture of this core-in-cup compressed tablet. Each set of punches, however, will be specific for each core-in-cup tablet, as it is the diameter and depth of the cup indentation that determine the amount of drug and polymer to be included in the tablets.

To solve the problem of only being able to produce a core-in-cup tablet that can only accommodate a specific mass of active core, a new adjustable punch that can produce cup tablets of different depths will be developed and evaluated in the next section. The ability to adjust the thickness of the core tablet will add flexibility to the dosage form, and also allow it to be adjusted to oblige powder or granule mixes that vary in their compressed density and hardness. This flexibility is critical for effective tablet manufacture.

2.3 COMPRESSION PROPERTIES OF CONTROLLED RELEASE CORE-IN-CUP COMPRESSED TABLETS FROM A NEW ADJUSTABLE PUNCH.

2.3.1 Introduction

In order to be able to produce cup tablets that have the ability to be adjusted for various core tablet thicknesses (which change in thickness according to the adjuvants used as well as the amounts of drug and adjuvants used) the new novel punch discussed in section 1.5 was designed and used in this study. By adjusting the protrusion distance of the inner central bolt, the depth of the resultant cup tablets can be adjusted to accommodate cores of different hardness and mass.

The purpose of this study, was to test the resultant effectiveness of the cup tablets produced by this new adjustable punch in producing cups of various depths for core-in-cup tablets, as well as to test whether a typical core of ibuprofen as the model drug with HPMC K4M, has any effect on the cup portion of the core-in-cup tablets produced from the punch. A friability test was also conducted on the ibuprofen in HPMC K4M core-in-cup tablets to check the intactness of the core to the cup. Finally, to check the consistency of the erosion of the core and the release from the deeper cores produced by the new punch, a release rate analysis over a period of 8 hours was conducted.

As the depth of the cup tablet is increased, it becomes more and more fragile and there is a limit to its depth. A measure of the ability of a tablet to withstand impact, as would be required in the production of the core-in-cup tablets, is its friability. The main factors that impact on the friability of these ethylcellulose and carnauba wax cup tablets include, the depth of the cup, the amount of binder in the cup, and its hardness. Since HPMC swells when it comes into contact with an aqueous environment, it could swell to such an extent that it could cause the cup to be split. Accordingly, the different cup formulations were tested for their ability to resist splitting in aqueous

dissolution medium or not. Therefore, it was decided to examine these three factors at three different levels to ascertain their effect on the friability and splitting open of the cup tablets. This study then results in a 3^3 factorial design. The dependencies were statistically analysed using analysis of variance and multiple regression analyses.

2.3.2 Materials and Methods

2.3.2.1 Materials

HPMC K4M premium EP was supplied by Colorcon Limited, England. HPMC K4M has a viscosity of 3500 - 5600 cP as a 2% solutions in water at 20°C. The HPMC had already been screened through a No. 40 standard U.S. sieve. Ibuprofen (Boots Co, S.A. Pty Ltd) was ground and the fraction passing through a No. 150 standard U.K. sieve was used.

Ethylcellulose and Carnauba wax (Sigma Chemical Company, U.S.A.) were used as supplied. All other reagents used were standard laboratory grade.

2.3.2.2 Study design

The study followed a 3^3 factorial experimental design. The amount of carnauba wax in the cup (c), hardness of the cup (h) and cup indent depth (d) were used as independent variables. The normalized factor levels of the independent variables are presented in table 2.3.1. In the 2^3 factorial points, the cup tablets were made in duplicate batches, and in the centre point, in quadruplicate batches. Therefore, the total number of runs was 38. Friability of the cup tablet and splitting of the cup in the final core-in-cup tablet were the dependant variables. This design has also been used with success by Merkku et al. (1994) to determine the influence of granulation and compression process variables on the flow rate of granules and on tablet properties.

TABLE 2.3.1

Levels of independent variables.

Variable	Factor level -1 0 1	Units
Amount of carnauba wax in cup (*c*)	5 10 15	%$^w/_w$
Hardness of compressed cup (*h*)	50 75 100	N/m^2
Depth of the cup (*d*)	2 4 6	mm

2.3.2.3. *Formulations*

Cup tablets of various depths and amounts of carnauba wax in ethylcellulose were compressed in a Manesty F3 tabletting press. The hardness of the cup tablets were then measured on a Pharma Test PTB 311 hardness tester. The press was then adjusted to produce cup tablets of approximate hardness of 50 N/m^2, 75 N/m^2, and 100 N/m^2. The ethylcellulose and the carnauba wax were thoroughly mixed and directly compressed into cup tablets by means of adjusting the protrusion of the inner bolt of the adjustable punch to the various depths tested so that it produces a cup-shaped tablet of 11 mm outer diameter, and an inner hollow core of 7,5 mm diameter. The bottom punch consisted of a flat round 11 mm diameter punch.

Production of core-in-cup tablets for release rate analysis, containing 5%$^w/_w$ HPMC K4M in ibuprofen as the core, 4 mm final cup depth, containing 15% carnauba wax in ethylcellulose as the cup, and compressed to a cup hardness of approximately 100 N/m^2 and final core-in-cup hardness of approximately 140 N/m^2, were produced as described previously in section 2.2.2.3.

2.3.2.4 Measurement of Friability

The friability of the cup tablets and the final core-in-cup tablets were measured on a Roche Friabilator (Hoffman la Roche, Basel). After weighing, 10 cup tablets from each run were rotated for 20 minutes and then re-weighed to test for % loss of weight.

2.3.2.5 Measurement of cup splitting

The core-in-cup tablets were made by compressing the different cup tablets together with cores containing $15\%^w/_w$ HPMC K4M in ibuprofen. Core tablets of approximately 100 N/m² of 2 mm, 4 mm and 6 mm thickness to match the depth of the cup tablets were produced. Core-in-cup tablets were then compressed to 1 mm, 3 mm and 4 mm for the 2 mm, 4 mm and 6 mm cup tablets respectively, to be tested for splitting. The core-in-cup tablets were placed in the dissolution apparatus as described above, and physically inspected for any splitting of the cup after 60 minutes. If any splitting of the cup tablets occurred it would occur before 60 minutes after being immersed in distilled water at 37°C and agitated at 50 rpm. The cup tablets were qualitatively adjudged to be split or not split.

2.3.2.6 Release Studies

The B.P. 1988 paddle method was utilised in all the release studies. A volume of 1000 ml of deionized water, equilibrated at 37°C ± 0,5°C, was used as the release medium. All experiments were carried out at 50 rpm. The release rates of the tablets were monitored using a 6 beaker Caleva model 7ST dissolution tester. At appropriate time intervals 2,0 ml samples were withdrawn for analysis, 2 ml methanol was added, mixed on a vortex mixer, and analyzed spectrophotometrically at a wavelength of 216 nm using a Beckman DU 650 spectrophotometer. Linearity was established for $50\%^v/_v$ methanol in deionized water ibuprofen solutions in the range of 6,25 - 200 µg/ml. The release profiles of 3 tablets from each of 3 different batches (n = 9) were analyzed.

2.3.2.7 Statistical analysis

Analysis of variance was performed on the data presented in Table 2.3.3 using STATGRAPHICS *v* 5 (Statistical Graphics Corporation, U.S.A.). The independent variables were % carnauba wax in the cup tablet, depth of the cup tablet, and hardness of the cup tablet, while the dependent variables were friability of the cup tablet and splitting of the cup tablet in aqueous medium. Response-surface plots were constructed for the above variables, in order to determine the optimal combination of the variables. Main effects and significant interactions were also calculated. Simple regression models for the three independent variables were also developed from the results as follows:

$$Y_1\ (c,h,d) = a_0 + a_1c + a_2h + a_3d + a_4ch + a_5cd + a_6hd + a_7c^2 + a_8h^2 + a_9d^2$$
$$a_{10}chd \qquad\qquad \text{- equation 2.3.1}$$

where $a_0...,a_{10}$ are the coefficients of the system. c, h and d denote the % carnauba wax in the cup tablet, hardness of the cup tablet and depth of the cup tablet, respectively.

Each term in the final regression equation for the friability or the splitting was only included if the t-test p value was less than 0,05. The regression coefficients for those effects that were considered insignificant were eliminated and the model was re-estimated.

2.3.3 Results and Discussion

Table 2.3.2 lists the hardness values, the friability and the splitting results of the cup tablets for the different runs tested in the study. Table 2.3.3 lists the relevant statistical parameters calculated from the results of this study for the effect of the three independent variables on the friability and splitting of the cup tablets analyzed. All statistical analysis was carried out on all the runs (total 38).

TABLE 2.3.2

Friability and Splitting of cup tablets (c, % carnauba wax; h, hardness; d, depth of cup). Subscripts $_{a,b,c,d}$ designate replicates.

Run	c	h	d	Mean hardness (N/m^2) $\pm$ SD (n=3)	Friability	Splitting
1_a	-1	-1	-1	53,17 $\pm$ 3,71	0,19	-1
1_b	-1	-1	-1	45,99 $\pm$ 3,79	0,51	-1
2	-1	-1	0	51,84 $\pm$ 1,67	1,06	1
3_a	-1	-1	1	63,07 $\pm$ 5,06	3,32	1
3_b	-1	-1	1	52,82 $\pm$ 4,92	2,80	1
4	-1	0	-1	72,97 $\pm$ 2,89	0,14	-1
5	-1	0	0	78,37 $\pm$ 3,72	0,48	1
6	-1	0	1	74,15 $\pm$ 6,55	1,32	1
7_a	-1	1	-1	98,16 $\pm$ 5,32	0,00	-1
7_b	-1	1	-1	106,39 $\pm$ 6,66	0,21	-1
8	-1	1	0	98,81 $\pm$ 7,43	0,18	1
9_a	-1	1	1	92,53 $\pm$ 3,73	0,67	1
9_b	-1	1	1	99,16 $\pm$ 6,06	0,41	1
10	0	-1	-1	56,91 $\pm$ 5,13	0,13	-1
11	0	-1	0	54,58 $\pm$ 5,85	0,40	1
12	0	-1	1	50,57 $\pm$ 7,03	1,13	1
13	0	0	-1	71,03 $\pm$ 7,36	0,07	-1
14_a	0	0	0	72,06 $\pm$ 3,43	0,44	1
14_b	0	0	0	78,15 $\pm$ 6,24	0,09	1
14_c	0	0	0	75,76 $\pm$ 8,47	0,26	1
14_d	0	0	0	70,19 $\pm$ 4,85	0,31	1
15	0	0	1	75,07 $\pm$ 2,88	0,64	1
16	0	1	-1	98,11 $\pm$ 6,71	0,03	-1
17	0	1	0	101,65 $\pm$ 7,83	0,06	-1
18	0	1	1	96,92 $\pm$ 8,00	0,28	-1
19_a	1	-1	-1	48,90 $\pm$ 5,89	0,04	-1
19_b	1	-1	-1	50,67 $\pm$ 7,27	0,04	-1
20	1	-1	0	56,76 $\pm$ 4,16	0,31	1
21_a	1	-1	1	48,75 $\pm$ 4,20	0,47	1
21_b	1	-1	1	55,74 $\pm$ 5,85	0,77	1
22	1	0	-1	74,99 $\pm$ 8,34	0,01	-1
23	1	0	0	69,30 $\pm$ 2,80	0,12	-1
24	1	0	1	78,49 $\pm$ 6,22	1,32	1
25_a	1	1	-1	96,24 $\pm$ 6,91	0,00	-1
25_b	1	1	-1	97,79 $\pm$ 9,37	0,00	-1
26	1	1	0	102,13 $\pm$ 5,56	0,00	-1
27_a	1	1	1	95,53 $\pm$ 7,96	0,01	1
27_b	1	1	1	103,55 $\pm$ 3,68	0,05	-1

TABLE 2.3.3

Relevant statistical parameters

Source effect	Estimated effects ± standard error (28 d.f.)	*p*-value	Regression coefficients	Regression coefficients re-estimated
Friability				
average	0,202 ± 0.096			
constant			1,375	-0,271
c	-0,713 ± 0,101	< 0,0001	-0,198	-0,095
h	-0,713 ± 0,101	< 0,0001	-0,029	-0,008
d	0,823 ± 0,101	< 0,0001	0,689	0,989
ch	0,483 ± 0,115	< 0,0005	0,002	0,002
cd	-0,606 ± 0,115	< 0,0001	-0,030	-0,030
hd	-0,640 ± 0,115	< 0,0001	-0,006	-0,006
cc	0,257 ± 0,192	0,1908	0,005	
hh	0,174 ± 0,192	0,3824	0,000	
dd	0,300 ± 0,192	0,1284	0,037	
Splitting				
average	0,600 ± 0.217			
constant			-7,041	-2,885
c	-0,462 ± 0,229	0,0543	0,061	
h	-0,615 ± 0,229	0,0122	0,084	-0,012
d	1,692 ± 0,229	< 0,0001	2,023	1,731
ch	-0,400 ± 0,262	0,1380	-0,002	
cd	-0,200 ± 0,262	0,4596	-0,010	
hd	-0,400 ± 0,262	0,1380	-0,004	
cc	0,133 ± 0,434	0,7644	0,003	
hh	-0,533 ± 0,434	0,2297	-0,000	
dd	-1,200 ± 0,434	0,0100	-0,150	-0,163

2.3.3.1 *Friability*

Figures 2.3.1a - c are response surface plots of the estimated effects of the % carnauba wax, hardness and depth of cup tablet on the friability of the tablet cups. The plots have been drawn on the basis of the model by assigning a constant value to one of the variables. All three variables play a significant role in the resultant friability of

the cup tablets. Depth of the cup tablet has the most significant influence on its friability (Fig. 2.3.1a and 2.3.1b). This is particularly pronounced at lower levels of carnauba wax (Fig. 2.3.1a).

As the % carnauba wax increases in the formulations, the cup tablets have an increased ability to withstand the increase in friability as the depth of the cup increases. There is a similar ability of the cup tablet to withstand increased friability with an increase in depth, as the hardness of the tablet is increased (Fig. 2.3.1b). This similarity in effect on the friability is evidenced from the estimated main effects of -0,713 for both c and h as well as the interaction effects of -0,606 and -0,640 for cd and hd respectively.
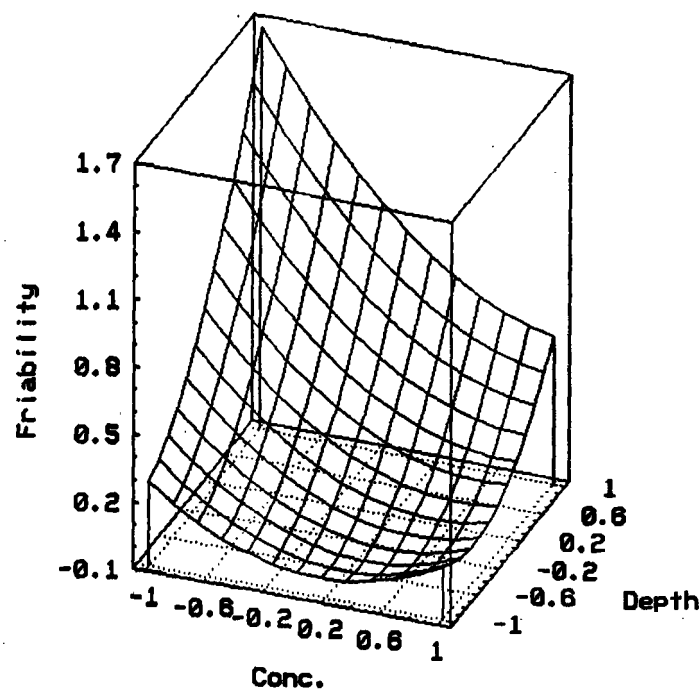
Fig. 2.3.1 a Response surface plots of the estimated effects of c and d on the friability of the tablet cups.
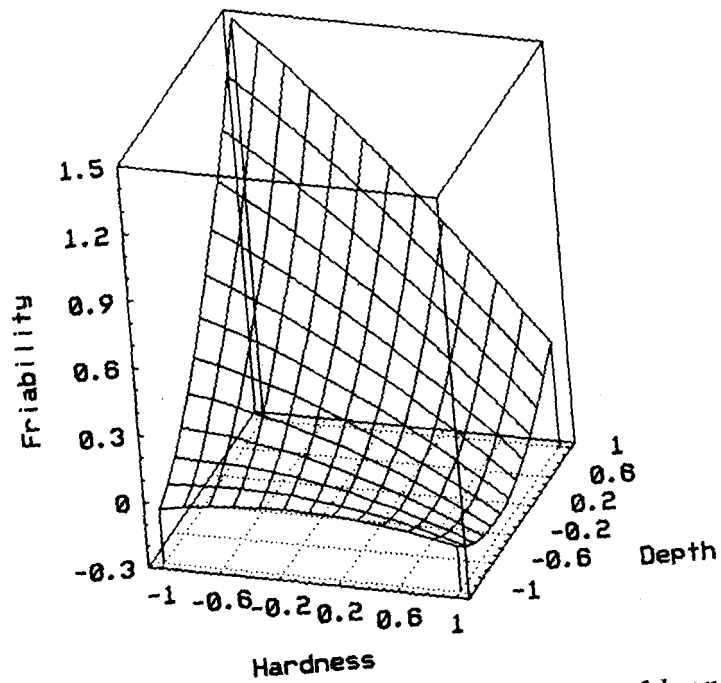
Fig. 2.3.1 b Response surface plots of the estimated effects of *h and d* on the friability of the tablet cups.
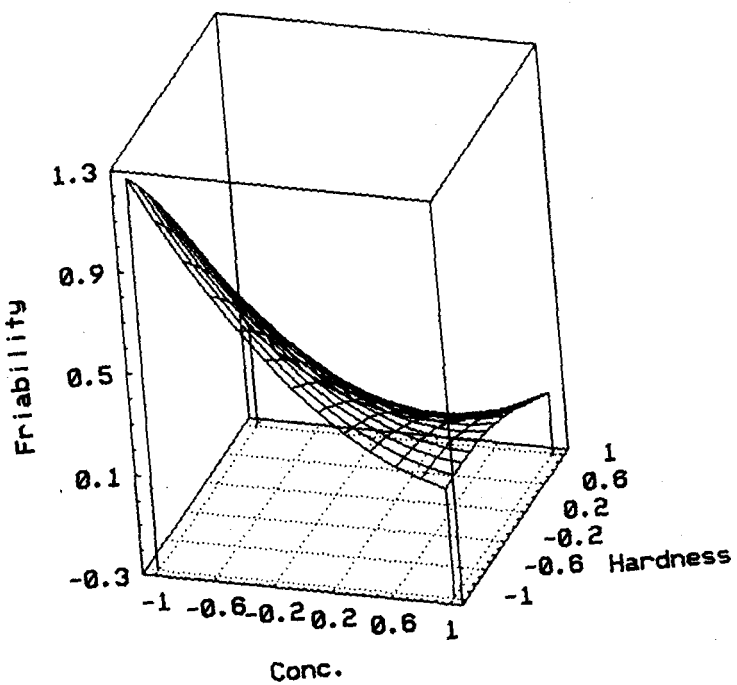
Fig. 2.3.1 c Response surface plots of the estimated effects of *c and h* on the friability of the tablet cups.

As the % of carnauba wax in the cup tablets increases, the friability of the cup tablets decreases (Fig. 2.3.1c). Since the carnauba wax acts as a binder for the ethylcellulose this effect is expected. This binding efficiency is at its maximum when the compression force is increased, and the difference in the friability at the higher compression force (equivalent to a hardness of $\pm$ 100 N/m^2) is less pronounced than that at the lower compression force (equivalent to a hardness of $\pm$ 50 N/m^2).

In developing a regression model for the effect of the independent variables on the friability dependent variable, the main effects as well as the second order interaction effects were significant ($p < 0,05$). Therefore, the regression coefficients for these effects were included in the model. The rest of the coefficients were eliminated and the model was re-estimated by STATGRAPHICS.

$$Y_f(c,h,d) = -0,271 - 0,095c - 0,008h + 0,989d + 0,002ch - 0,030cd - 0,006hd -$$
equation 2.3.2

where $Y_f(c,h,d)$ is the estimated friability of the cup tablets.

The squared multiple regression coefficient for this model was 0,902. This model shows that depth of the cup tablet has the major adverse effect on the friability of the cup tablet. As the depth increases the friability increases. The % carnauba wax then produces the next most significant effect on the friability. Carnauba wax and hardness of the cup tablet both decrease the friability of the cup tablet. Clearly, in order to produce a cup tablet with minimal friability, the compression force (tablet hardness) and % carnauba wax must be maximised, while the depth of the cup should be minimised. However, it should be noted that the friability of the cup only really becomes a problem when the % loss after 20 minutes in the friabilator becomes larger than 4%. None of the formulations in this study exceeded this value.

2.3.3.2 Splitting

Figures 2.3.2a - c are response surface plots of the estimated effects of the % carnauba wax, hardness and depth of cup tablet cup on the splitting of the cups in the core-in-cup tablets placed in an aqueous dissolution medium. Those tablets that split in aqueous dissolution medium were assigned a value of -1,0 and those that remained intact (not split) were assigned a value of 1,0. Only the hardness and depth of the cup tablets play a significant part in the resultant splitting of the cup tablets. As with the friability, depth of the cup tablet has the most significant influence on its splitting in aqueous solution. (Fig. 2.3.2a and 2.3.2b). The response - surfaces are reasonably stable over the ranges of hardness and % carnauba wax. There is a very slight decrease in the tendency to split as the % carnauba wax increases from 5% to 10%. However, as the % carnauba wax increases from 10% to 15% there is a slight tendency for the cup tablets to split at low hardness. This is made evident from the significant *dd* interaction. As the hardness of the cup tablet increases, there is a modest decrease in the tendency to split which is more pronounced at increased depths. The ability to split in aqueous medium however, decreases in a linear fashion as the hardness of the cup is increased (Fig. 2.3.2c).

In developing a regression model for the effect of the independent variables on the splitting in aqueous medium dependent variable, only depth and hardness main effects as well as the second order *dd* interaction effect were significant ($p < 0,05$). Only these regression coefficients were therefore, included in the model. The rest of the coefficients were eliminated and the model was re-estimated by STATGRAPHICS.

$$Y_f(h,d) = -2,885 - 0,012h + 1,731d - 0,163dd \qquad \text{- equation 2.3.3}$$

where $Y_f(h,d)$ is the estimated friability of the cup tablets.

The squared multiple regression coefficient for this model was 0,754.
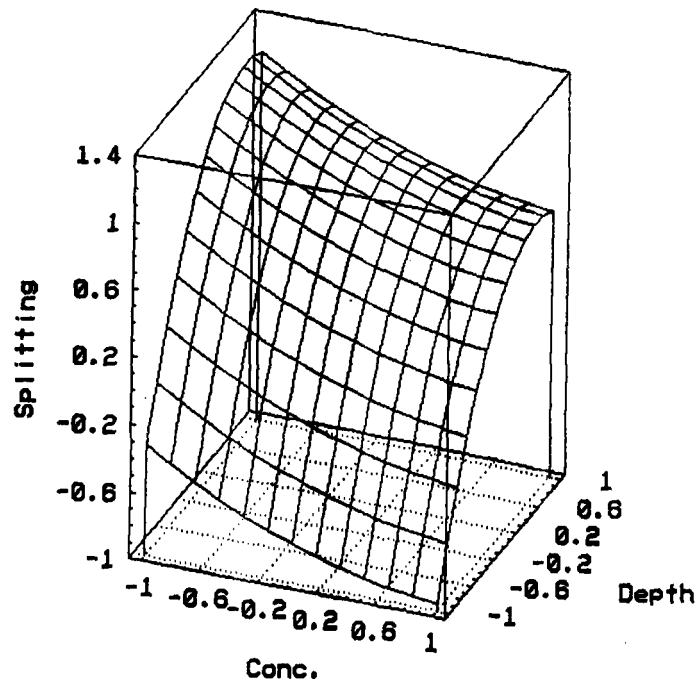
Fig. 2.3.2 a Response surface plots of the estimated effects of the *c and d* on the splitting of the cups in the core-in-cup tablets placed in an aqueous dissolution medium.
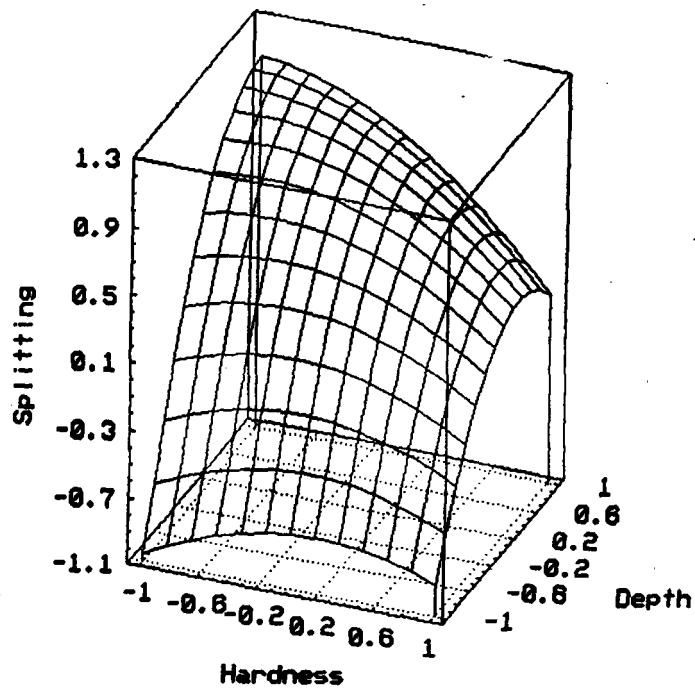
Fig. 2.3.2 b Response surface plots of the estimated effects of the *h and d* on the splitting of the cups in the core-in-cup tablets placed in an aqueous dissolution medium.
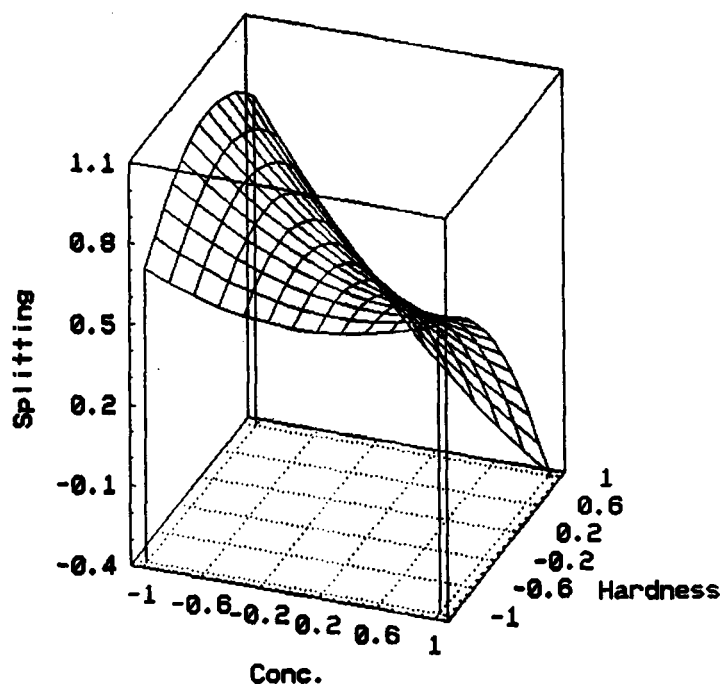
Fig. 2.3.2 c Response surface plots of the estimated effects of the *c and h* on the splitting of the cups in the core-in-cup tablets placed in an aqueous dissolution medium.

This model shows that the depth of the cup tablet has the principal adverse effect on the splitting of the tablet. As the depth increases the splitting in aqueous dissolution medium increases. The hardness of the cup tablet produces the next most significant effect on the friability. This effect however, is much less significant as compared to the depth of the cup tablet. It does however, decrease the ability of the cup tablet to split in aqueous medium. In general, splitting of the cup tablets at depths of 6 mm is a problem and will have to be investigated further. The problem of the splitting lies with the swelling of the HPMC polymer in aqueous solution.

2.3.3.3 *Release rate*

To check that the new core-in-cup tablet produced by the adjustable punch still has the ability to release drugs at a zero-order rate of release without splitting,

a core-in-cup tablet with the optimal parameters was manufactured and tested. The results above indicate that a cup tablet containing 5%$^w/_w$ HPMC K4M, compressed to a depth of 4 mm and containing 15%$^w/_w$ carnauba wax in ethylcellulose as the cup, and compressed to a hardness of 100 N/m^2 and final core-in-cup hardness of 160 N/m^2, is best from a friability and lack of splitting point of view. Therefore, a tablet of these dimensions and processing parameters was manufactured and tested. Figure 2.3.3 plots the rate of release of ibuprofen from core-in-cup tablets.

The core-in-cup system releases the ibuprofen at a near zero-order rate of 0,156 mg/min. This rate was calculated from the slope of the plot of cumulative concentration versus time from 60 minutes to 720 minutes. The correlation coefficient for this plot was 0,999.
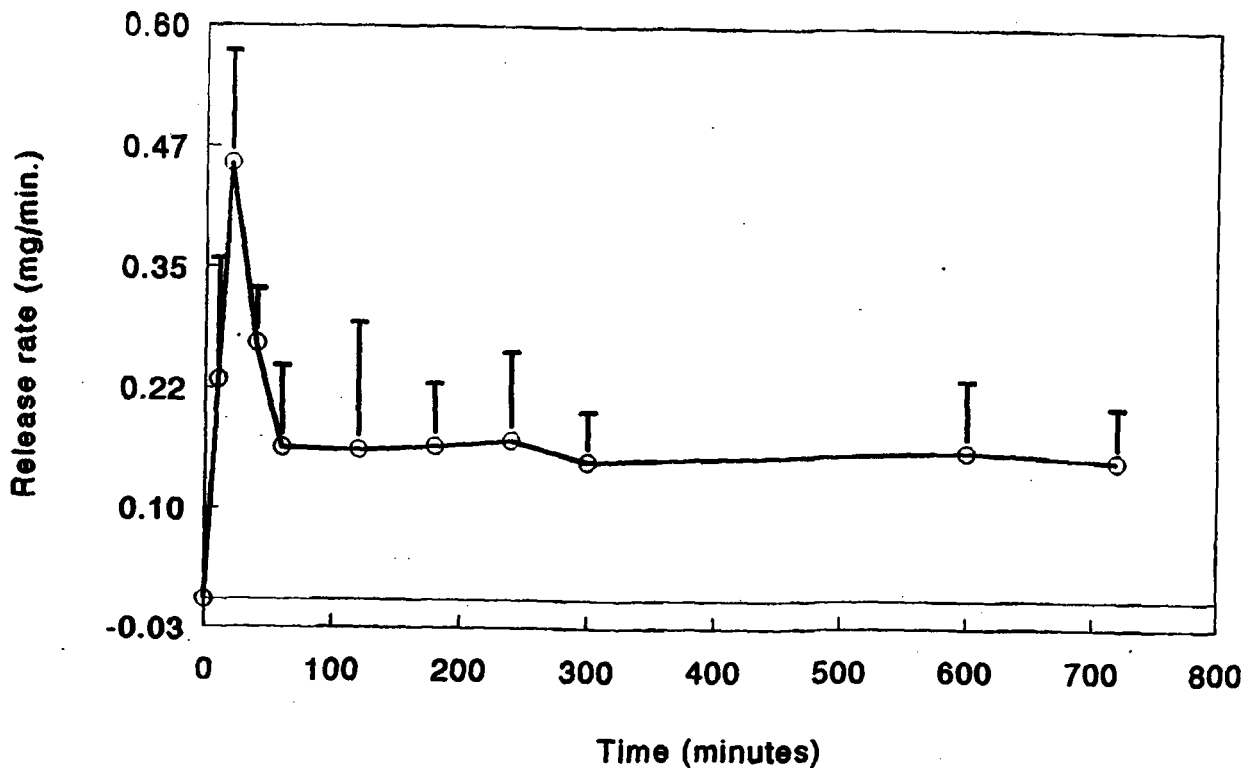
Fig. 2.3.3. Ibuprofen release rates from core-in-cup tablets.

To check whether the rate of release was zero-order, or according to the 'square root of time', plots of log of cumulative concentration versus time, and cumulative concentration versus square root of time, were plotted respectively. The correlation coefficients for these were 0,983 and 0,921 respectively. Therefore, a zero-order rate of release best describes the release rate from the ibuprofen core-in-cup system. Extrapolating the zero-order rate of release of 0,156 mg/min. the core-in-cup system can release drug for up to 18 hours. This is too long for an average oral system as gastrointestinal transit time is not much longer than 8 - 12 hours on average. Polymers that erode at a quicker rate need to be investigated, to design a system that releases drugs from the core-in-cup system at a zero-order rate for a shorter time. It would be desirable if the polymer used in the core of the tablet did not swell, but eroded at a controlled rate from the core-in-cup tablet. Therefore, in the next section the use of nonswellable polymers as sustained-release binders in the core of the tablets will be investigated.

2.3.3.4 Friability of core-in-cup

The friability test was conducted on the final core-in-cup tablet mentioned in section 2.3.3.3 above. After 20 minutes in the friabilator the percentage weight loss from the core-in-cup tablets was $1,5 \pm 0,437$ $(n = 3)$. None of the core tablets were dislodged from the core-in-cup tablets during the test. Therefore, the core-in-cup tablets do maintain their intactness during the test. They therefore, should be able to keep intact throughout their movement in the gastrointestinal tract which will be tested in Beagle dogs later.

2.4 THE EFFECT OF PROCESSING VARIABLES ON THE RELEASE OF IBUPROFEN AND CAFFEINE FROM CONTROLLED RELEASE NONSWELLABLE CORE-IN-CUP COMPRESSED TABLETS.

2.4.1 Introduction

In the previous experiment it was ascertained that the core-in-cup tablets have the ability to release soluble and insoluble drugs at a zero-order rate from an inactive cup. It was found that it is possible, through the manipulation of, (i) the grade of HPMC used (or any other hydrophillic polymer or mixture of polymers that erodes constantly with time), (ii) the quantity of HPMC polymer used, and (iii) the exposed surface area of the core of the HPMC polymer matrix, to produce a core-in-cup compressed tablet that can release a constant amount of drug over a predetermined period of time. Unfortunately, as the depth of the cup portion of the core-in-cup compressed tablet increases to 6 mm or more, some of the cups began to split in aqueous medium. This is because the efficiency of the binder in the cup portion of the tablet was not enough to overcome the swelling of the HPMC polymer when it comes into contact with aqueous medium. As the viscosity grade and concentration of the polymer used increases so does the swelling of the polymer increase (Wan *et al.*, 1993) especially in the vertical direction (Colombo *et al.*, 1990).

The purpose of these experiments thurifers to test the effectiveness of nonswellable polymers in producing the core of a core-in-cup tablet that does not swell to any appreciable extent when it comes into contact with aqueous dissolution fluid. The advantage of such a polymer would be that it would not split the cups open, and it would release the drug from a constantly eroding surface or constant diffusional area and path. It must however, be capable of releasing drugs over a period of at least 8 hours at a constant rate.

Accordingly, it was decided to first test the rate of release of a soluble drug (caffeine) and insoluble drug (ibuprofen) from polyethylene glycol 6000 (PEG 6000), acacia gum, tragacanth and hydroxyethylcellulose (HEC) from core-in-cup tablets. Secondly, it was decided to examine the processing variables of concentration of polymer (*c*) and hardness of tablet core (*h*), on the maximum time of constant release (t_{max}) of caffeine and ibuprofen from the most suitable polymers. The rate of release of caffeine was tested in 0,1 M HCl aqueous dissolution fluid. The rate of release of ibuprofen was tested in 0,2 M phosphate buffer at a pH of 7,2. This study then results in a 3^2 factorial design. The dependencies were explained using analysis of variance and multiple regression analysis.

2.4.2 Materials and Methods

2.4.2.1 *Materials*

Acacia, PEG 6000 and tragacanth gum were supplied by Saarchem (Pty) Ltd, South Africa. The acacia, PEG 6000 and tragacanth gum had viscosities of 53 cps, 43 cps, and 1250 cps, respectively, as 4% aqueous solutions at 23°C. HEC was supplied by Riedel de-Haën, South Africa and had a viscosity of 2100 cps as a 4% aqueous solution at 23°C. Ibuprofen (Boots Co, S.A. Pty Ltd) and caffeine (Sigma Chemical Company, U.S.A.) was ground and the fraction passing through a No. 150 standard U.K. sieve was used. Ethylcellulose (Sigma Chemical Company, U.S.A.) and carnauba wax (Sigma Chemical Company, U.S.A.) were used as supplied. All other reagents used were standard laboratory grade.

2.4.2.2 *Study design*

The study followed a sequential 2^1 preliminary study followed by a 3^2 factorial experimental design. In the preliminary experimental phase, the caffeine and ibuprofen were formulated in each polymer at two different concentrations in order to assess which polymer gave a constant release time closest to a maximum of 8 - 12 hours.

Once the most suitable polymer was found, a 3^2 factorial design study was conducted for each of ibuprofen and caffeine. The amount of polymer in the core (c) and hardness of the core (h) were used as independent variables. The normalized factor levels of the independent variables are presented in table 2.4.1. All the outside factorial points of the core tablets were made in duplicate batches, and in quadruplicate batches in the centre point. Therefore, the total number of runs was 20 for each drug. The maximum time of constant release (including the initial higher release rate) of drug from the core-in-cup in the relevant dissolution fluid was the dependant variable.

TABLE 2.4.1

Levels of independent variables.

Variable	Factor level			Units
	-1	0	1	
Concentration of polymer in core (c)	5	10	15	$\%^w/_w$
Hardness of compressed core (h)	40	50	60	N/m^2

2.4.2.3. Formulations

For the preliminary study on the suitability of the polymers to caffeine or ibuprofen, flat disc-shaped core tablets of 7 mm diameter and 5 mm depth were compressed on a Manesty F3 single punch tabletting press as previously discussed in section 2.2.2.3. The hardness of the core tablets were first measured on a Pharma Test PTB 311 hardness tester. The press was then adjusted to produce core tablets of approximate hardness of 50 N/m^2. Table 2.4.2 lists the composition of the different cores that were compressed and used for the preliminary study.

The cores were then compressed together with the $10\%^w/_w$ carnauba wax in ethylcellulose cups to a depth of 4 mm and not a specific hardness, as described previously in section 2.3.

TABLE 2.4.2

Maximum time of constant release (t_{max}) for caffeine and ibuprofen from different polymers

Acacia %	PEG - 6000 %	Traga - canth %	HEC %	t_{max} (hours) ± S.D. (n = 3)	
			Polymer		
Caffeine					
5				7,513 ± 0,52	
	5			3,720 ± 0,12	*
		5		1,083 ± 0,14	
			5	3,597 ± 0,31	*
10				11,523 ± 0,447	
	10			6,767 ± 0,049	#
		10		1,600 ± 0,292	
			10	6,533 ± 0,249	#
Ibuprofen					
5				18,380 ± 1,113	
	5			12,390 ± 0,399	
		5		3,800 ± 0,096	*
			5	4,320 ± 0,340	*
10				27,217 ± 1,775	
	10			8,387 ± 0,497	
		10		4,093 ± 0,156	#
			10	5,103 ± 0,190	#

*,# *in a vertical column indicate homogenous groups that show no significant difference at the 95% level of confidence using the LSD analysis of variance test.*

Once it was established that acacia was most suitable for the release of caffeine, and PEG 6000 was most suitable for the release of ibuprofen, from the core-in-cup tablets, cores of the compositions listed in table 2.4.3 were produced and compressed to a hardness of 40, 50 or 60 N/m^2. These were also compressed to a depth of 4 mm together with the cup portion of the tablet. The tabletting press was previously adjusted to produce a tablet of 4 mm thickness. Compressing the core and cup of the tablet together to a 4 mm depth was just enough compression to compress the core and cup portion of the tablet together without too adversely affecting the difference in hardness of the core tablets.

2.4.2.4 *Release Studies*

The B.P. 1988 paddle method was utilised in all the release studies. A volume of 1000 ml of 0,1 M HCl in deionized water, equilibrated at $37°C \pm 0,5°C$, was used as the release medium for the caffeine tablets. For the ibuprofen tablets, 1000 ml of 0,2 M phosphate buffer B.P. at a pH of 7,2 and equilibrated at $37°C \pm 0,5°C$, was used. All experiments were carried out at 50 rpm. The release rates of the tablets were monitored using a Caleva model 7ST dissolution tester connected to a Beckman DU 650 spectrophotometer via a flow-through cell. Dissolution medium was pumped through Elkay solvent flex PVC tubing (I.D. of 0,1 inches) with bridge tubing at a rate of 3,9 ml/min. by means of a Desaga STA peristaltic pump. The bridge tubing was connected to acid flexible manifold tubing which was connected to the flow-cell, and also from the flow-cell back into the dissolution flask. In order to constantly monitor the release of the drugs, the spectrophotometer was programmed to read the concentration of the drug in the flow cell at 10 minute intervals. Ibuprofen was measured spectrophotometrically at a wavelength of 216 nm, while caffeine was measured at a wavelength of 242 nm. Linearity was established for 0,1 M HCl aqueous solutions of caffeine, and 0,2 M phosphate buffer aqueous solutions of ibuprofen, in the range of 6,25 - 200 µg/ml.

2.4.2.7 *Statistical analysis*

Analysis of variance was performed on the data presented in Table 2.4.3 using STATGRAPHICS v 5 (Statistical Graphics Corporation, U.S.A.). The independent variables were % polymer in the core tablet (c) and hardness of the core tablet (h), while the dependent variable was maximum time of constant release (t_{max}) from the core-in-cup tablets. Response-surface plots were constructed for the above variables, in order to determine the optimal combination of the variables. Main effects and significant interactions were also calculated. Simple regression models for the two independent variables were also developed from the results as follows:

$$Y_1 \ (c,h) \ = \ a_0 + a_1c + a_2h + a_3ch + a_4c^2 + a_5h^2 \qquad \text{- equation 2.4.1.}$$

where $a_0,...,a_5$ are the coefficients of the system. c and h denote the % polymer in the core tablet and hardness of the core tablet, respectively.

Each term in the final regression equation for the maximum time of constant release was only included if the t-test p value was less than 0,05. The regression coefficients for those effects that were considered insignificant were eliminated and the model was re-estimated. All statistical analysis was performed using STATGRAPHICS v 5 (Statistical Graphics Corporation, U.S.A.).

2.4.3 Results and Discussion

Table 2.4.3 lists the t_{max} values for the release of caffeine and ibuprofen from the different formulations tested.

TABLE 2.4.3

Maximum time of constant release (t_{max}) for caffeine and ibuprofen (c, % polymer; h, hardness;)

Run	*h*	*c*	Mean hardness N/m²) ± SD (n=3)		t_{max} (hours)	
			Caffeine	Ibuprofen	Caffeine	Ibuprofen
1ₐ	-1	-1	38,16 ± 2,94	43,19 ± 3,33	4,17	12,83
1_b	-1	-1	45,99 ± 8,46	35,51 ± 7,82	4,00	11,17
2ₐ	-1	0	36,84 ± 4,43	41,06 ± 8,64	5,67	9,67
2_b	-1	0	43,07 ± 2,40	44,32 ± 5,55	7,33	6,83
3ₐ	-1	1	42,72 ± 4,94	42,80 ± 5,11	10,67	6,83
3_b	-1	1	42,94 ± 4,75	40,14 ± 7,20	11,83	6,00
4ₐ	0	-1	52,24 ± 5,66	50,48 ± 3,98	6,33	11,00
4_b	0	-1	54,55 ± 8,02	51,32 ± 6,46	5,83	12,67
5ₐ	0	0	48,16 ± 4,14	48,00 ± 9,76	10,17	9,83
5_b	0	0	51,60 ± 7,85	53,21 ± 5,68	10,50	10,67
5_c	0	0	48,81 ± 2,07	50,18 ± 9,29	11,33	10,33
5_d	0	0	52,53 ± 5,96	53,67 ± 5,47	9,50	9,83
6ₐ	0	1	49,76 ± 4,19	50,41 ± 5,80	13,33	6,67
6_b	0	1	52,91 ± 7,88	51,13 ± 8,02	12,17	6,83
7ₐ	1	-1	64,55 ± 9,95	64,40 ± 6,91	7,83	15,33
7_b	1	-1	58,27 ± 8,33	60,13 ± 8,47	8,83	14,33
8ₐ	1	0	66,56 ± 4,03	66,07 ± 4,09	11,83	8,00
8_b	1	0	62,86 ± 6,41	62,44 ± 4,16	12,50	8,83
9ₐ	1	1	68,62 ± 6,19	64,09 ± 3,27	14,83	7,33
9_b	1	1	65,69 ± 7,43	60,26 ± 5,41	13,67	7,50

Table 2.4.4 lists the relevant statistical parameters calculated from the results of this study for the effect of the two independent variables on the maximum time of constant release (t_{max}) of the core-in-cup tablets analyzed. All statistical analysis was carried out on all the experimental runs (total 20).

TABLE 2.4.4

Relevant statistical parameters

Source effect	Estimated effects ± standard error (13 d.f.)	p-value	Regression coefficients	Regression coefficients re-estimated
Caffeine release from acacia				
average constant	10,040 ± 0.381		-20,470	-7,837
c	6,583 ± 0,512	< 0,001	1,211	0,658
h	4,358 ± 0,512	< 0,001	0,629	0,218
ch	-0,609 ± 0,627	0,359	-0,006	
cc	-0,619 ± 0,825	0,474	-0,012	
hh	-0,700 ± 0,825	0,421	-0,003	
Ibuprofen release from PEG 6000				
average constant	9,2863 ± 0,514		4,775	15,626
c	-6,028 ± 0,690	0,000	-0,735	-0,603
h	1,332 ± 0,690	0,076	0,381	
ch	-0,915 ± 0,845	0,299	-0,009	
cc	1,473 ± 1,113	0,208	0,029	
hh	-0,447 ± 1,113	0,699	-0,002	

2.4.3.1 Caffeine release from acacia

Figure 2.4.1 is the response surface plot of the estimated effects of the %
acacia and hardness of the core tablet on the t_{max} of caffeine from the core-in-cup
tablets. Both the concentration of acacia and the hardness of the core tablet play a
significant role in the resultant t_{max} of the core-in-cup tablets. Concentration of acacia
in the core tablet has the most significant influence on its t_{max} (Fig. 2.4.1). Since the
acacia acts as a binder for the caffeine this effect is expected.This binding efficiency is
at its maximum when the compression force is increased, and the difference in the t_{max}
at the higher compression force (equivalent to a hardness of $\pm$ 60 N/m^2) is similar to
that at the lower compression force (equivalent to a hardness of $\pm$ 40 N/m^2). The
similarity in effect on the t_{max} is evidenced from the estimated main effects of 6,583 for
c and 4,358 for h. There were no significant ($p < 0.05$) interaction effects from the %
acacia and hardness of the tablets on the rate of release of caffeine.
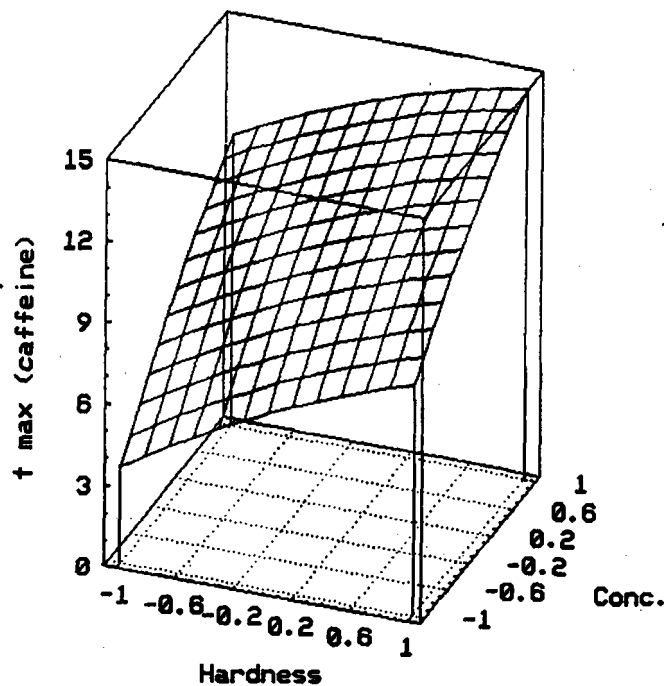
Fig. 2.4.1 Response surface plots of the estimated effects of c and h on the t_{max} of
caffeine from the core-in-cup tablets.

In developing a regression model for the effect of the independent variables on the t_{max} dependent variable, only the main effects were significant ($p < 0,05$). Therefore, the regression coefficients for these effects were included in the model.

The rest of the coefficients were eliminated and the model was re-estimated by STATGRAPHICS.

$$Y_{tc} (c,h,) = -7,837 + 0,658c + 0,218h \qquad \text{- equation 2.4.2}$$

where $Y_{tc} (c,h)$ is the estimated t_{max} of caffeine from the core-in-cup tablets.

The squared multiple regression coefficient for this model was 0,949. This model shows that % concentration of acacia in the core tablet has the major effect on the t_{max}. As the concentration increases the t_{max} increases. The hardness of compression also produces an increase in the t_{max}. Clearly, in order to produce a core-in-cup tablet that needs to release drug for a t_{max} of approximately 8 - 12 hours the concentration of acacia and hardness of compression can be adjusted to produce the required t_{max}.

2.4.3.2 Ibuprofen release from PEG 6000

Figure 2.4.2 is a response surface plot of the estimated effects of the % PEG 6000 and hardness of the core tablet cup on the t_{max} of ibuprofen from the core-in-cup tablets tested. Only the concentration of PEG 6000 in the core tablet plays a significant role in the resultant t_{max} of the core-in-cup tablets (Fig. 2.4.2). Since the PEG 6000 is water soluble it causes the ibuprofen to be released at a quicker rate than if the ibuprofen were compressed on its own. As the concentration of PEG 6000 increases from 5 to 15%$^w/_w$ the quicker is the release from the core-in-cup tablets and the shorter is the t_{max}. The t_{max} times decreased from 15,33 hours to 6,83 hours, depending on the hardness of compression of the core tablet. Hardness of compression, on the

other hand had very little significant effect on the release of ibuprofen from the tablets. As the hardness increased from 40 N/m^2 to 60 N/m^2, the t_{max} only increased on average, over all % concentration levels of PEG 6000, from 8,89 hours to 10,22 hours. The effect of hardness of compression on the t_{max} of ibuprofen from PEG 6000 was even less pronounced at the 15%$^w/_w$ PEG 6000 level. The t_{max} only increased on average from 6,42 hours to 7,42 hours. There were no significant ($p < 0,05$) interaction effects from the % PEG 6000 and hardness of the core tablets on the rate of release of ibuprofen.

In developing a regression model for the effect of the independent variables on the t_{max} dependent variable, only the concentration of PEG 6000 was significant ($p < 0,05$). Therefore, the regression coefficient for this effect only, was included in the model. The rest of the coefficients were eliminated and the model was re-estimated by STATGRAPHICS.

$$Y_{ti} (c,h,) = 15,626 - 0,603c \qquad \text{- equation 2.4.3}$$

where Y_{ti} (c,h) is the estimated t_{max} of ibuprofen from the core-in-cup tablets.

The squared multiple regression coefficient for this model was 0,8659. This model shows that the % concentration of PEG 6000 in the core tablet is the only factor that has a significant effect on the t_{max}. As the concentration increases the t_{max} decreases. The hardness of compression produces an increase in the t_{max}, but not significantly enough. In order to produce a core-in-cup tablet that needs to release ibuprofen for a t_{max} of approximately 8 - 12 hours the concentration of PEG 6000 can be adjusted to produce the required t_{max} from equation 2.4.3 above.
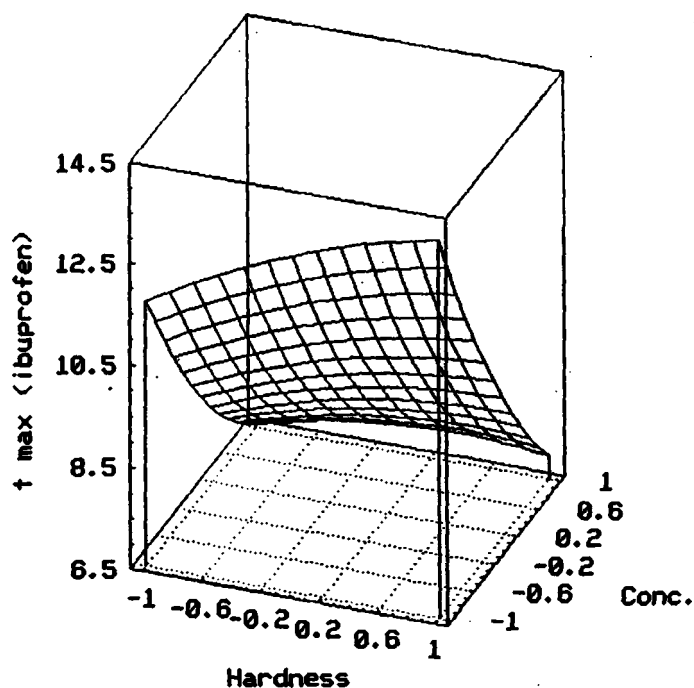
Fig. 2.4.2. Response surface plot of the estimated effects of *c* and *h* on the t_{max} of ibuprofen from the core-in-cup tablets.

From the above results it can be seen, that it is possible to produce a core-in-cup tablet that can release aqueous soluble (caffeine) and insoluble (ibuprofen) drugs at a zero-order rate, depending on the type of erodible polymer used. For insoluble drugs, it is best to use an aqueous soluble polymer such as PEG 6000, and for a soluble drug, it is best to use an erodible polymer like acacia. Neither PEG 6000 nor acacia swelled to any noticeable extent in the aqueous dissolution fluid used and therefore, there was no splitting (which could lead to dose dumping) of the cup portion of the core-in-cup tablet as can be the case with polymers that swell in aqueous fluids.

In the following section the *in vitro* dissolution rate of the model drug theophylline in simulated gastrointestinal fluids from a core-in-cup system will be evaluated. Acacia will be used as the bioerodible sustained - release polymer in the core of the tablet. As theophylline is a slightly aqueous soluble drug, acacia could be the most suitable polymer to use in the core of the tablet. Various concentrations of

acacia will be utilised, from which the ideal concentration of acacia that should be added to the core of the tablet to get a constant release of theophylline over an 8 to 12 hour period, will be determined.

3 *IN VITRO* ANALYSIS OF THE CORE-IN-CUP TABLETS

3.1 DISSOLUTION OF THEOPHYLLINE FROM CORE-IN-CUP TABLETS IN SIMULATED GASTRIC AND INTESTINAL FLUID.

3.1.1 Introduction

Sustained release of drugs in the gastrointestinal tract following oral administration is the intended rate - limiting factor in the absorption process and, in turn, the bioavailability and therapeutic response (Hussein and Friedman, 1990; Block and Banakar, 1988). It is therefore, essential in the development stages to use dissolution methods that allow pharmacokinetic screening of dosage forms, in particular, the prediction of the absorption rate from sustained - release preparations. If one wants to predict the *in vivo* release of drugs from zero-order release systems from *in vitro* data, then it is important that one chooses a model that closely approximates the conditions in the gastrointestinal tract (Skelly *et al.*, 1990; Amidon, *et al.*, 1995) for approximately 8 to 16 hours. It is also not sufficient to test the release of drugs in a single dissolution medium (Skelly *et al.*, 1986a and b). One means of effectively testing the *in vitro* release from a drug delivery system, is to first test it in simulated gastric fluid, followed immediately by simulated intestinal fluid (Lin and Ayres, 1992; Whiting *et al.*, 1991; Bodmeier and Paeratakul, 1989; Bodmeier *et al.*, 1989). Ideally, the drug delivery system should release drug at a zero-order rate in both of these simulated fluids for a time similar to the gastrointestinal residence time. This time however, can be highly variable due to many factors.

3.1.1.1 *Gastrointestinal residence time.*

After ingestion, an oral nondisintegrating dosage form will stay in the stomach for an unpredictable time. To understand the implications of this initial state of the GI

transit, it is worth mentioning the role of the stomach in terms of its anatomical structure and motor functioning during either the interdigestive or digestive phases (Code and Martlett, 1975; Kelly, 1980; Sarna, 1985; Kellow *et al.*, 1986). During the interdigestive phase, the empty stomach displays a cyclic motion called the *interdigestive migrating motor complex* (IMMC). This cyclic motion can be divided into four phases as follows:

(1) Phase I - mostly an inactive phase with little or no contractions. It lasts up to 60 minutes.

(2) Phase II - consists of irregular and intermittent sweeping contractions.

(3) Phase III - acute eruptions of peristaltic waves in distal and proximal gastric areas. It last 5 to 15 minutes. This is the phase that empties the stomach of its fasting contents and indigestible debris. This is why it is almost impossible to keep multiple-unit or monolithic dosage forms in the stomach (Müller-Lissner and Blum, 1981; Mojaverian *et al.*, 1985, 1987 and 1991; Davis, 1986).

(4) Phase IV - conversion period of decreasing activity until the next cycle.

This overall IMMC cycle lasts approximately 1,5 to 2,0 hours. The gastric residence time of solid dosage forms is thus mainly dependent on the coincidence between dosing time and phase III IMMC occurrence. The gastric emptying is consequently rather unpredictable and the residence time is usually short and highly variable. However, the ingestion of food interrupts the IMMC cycle (Thompson *et al.*, 1980) and allows the digestive phase to take place. Ingestion of food also delays the delivery of drugs to the small intestine (Davis *et al.*, 1986). The degree of delay depends on the type of formulation. Highly soluble drugs given in a conventional dosage form or drugs given as pellets, disperse in the gastric fluids and are emptied with the food. Nondispersible single units are retained in the stomach until phase III of the IMMC returns. Thus after a meal, the pylorus appears to act as a sieve allowing small particles

through but retaining larger particles (Meyer *et al.*, 1981 and 1985; Gruber *et al.*, 1987; Itoh *et al.*, 1986). This delay in the emptying of large inert particles from the stomach has been utilized to design drug delivery systems that are large enough to be retained in the stomach for longer periods of time (Cargill *et al.*). There is however, no exact cut-off size of solid particles that would not be expelled until the IMMC arrival. It is believed to be larger than 3 to 7 mm in diameter (Meyer *et al.*, 1985; Feldman *et al.*, 1984). This is probably due to interindividual variations in the diametral opening of the pylorus and in the pressure force of the propelling waves.

Numerous other factors may influence the gastric transit of sustained-release drug delivery systems (Dressman *et al.*, 1993). Among the stimulatory and inhibitory mechanisms that regulate the emptying rate of a meal, the characteristics of the diet components have first to be taken into account. These include acidity, osmolality, temperature, viscosity, volume, calorific contents, and relative fat, protein and carbohydrate concentration (Sheiner 1975).

The transit in the small intestine is more regular than in the stomach. As estimated from several studies, the mean expected transit duration of a meal marker for 95% of the population lies around 2 to 4 hours (Davis *et al.*, 1986). This transit is remarkably constant, irrespective of the presence of food or the type of drug delivery system.

Unlike the small intestine, the transit time in the colon is highly variable. Transit times vary from approximately 1 hour to more than 60 hours (Hardy *et al.*, 1985; Metcalf *et al.*, 1987). Single unit drug delivery systems such as tablet matrices and capsules tend to remain for prolonged periods of several hours not only at the ileocecal junction before entering the colon, but also at the hepatic and splenic flexures of the large bowel. They progress intermittently by acute thrusts of movement separated by periods of prolonged stasis (Metcalf *et al.*, 1987).

To sum up the physiological limitations discussed, it appears that the transit rate of a drug delivery system in the GIT may be highly variable and dependant, amongst other factors, on its size and digestibility. The transit time can be as short as a few hours and as long as 2 or 3 days. For this study, however, we will accept 8 to 16 hours as the average transit time for a normal healthy adult. Therefore, an attempt will be made to formulate a core-in-cup tablet that releases drug at a zero-order rate of release in simulated gastrointestinal fluids for a period of 8 to 16 hours.

3.1.1.2 Dissolution and bioequivalence.

In most cases, a drug must first pass into solution to be absorbed through the GIT membrane. Drugs with low solubility are absorbed with difficulty through biological membranes, and with such compounds the rate of dissolution in GIT fluids is universally the rate-controlling step for absorption. Dissolution is the process by which a chemical or drug becomes dissolved in a solvent (Shargel and Yu, 1993). In biological systems, drug dissolution in an aqueous medium is an important prior condition of systemic absorption. The rate at which drugs with poor aqueous solubility (or sustained-release preparations) dissolve (or are released, for sustained-release preparations) from an intact or disintegrated solid dosage form in the GIT often controls the rate of systemic absorption of the drug. Therefore, it is important that research includes efforts to develop *in vitro* tests that will be valid predictors of bioavailability in humans. If *in vitro* dissolution properties for a drug are found to serve as a useful index of *in vivo* absorption, the time, expense and difficulties of clinical trials may be reduced or eliminated. In some cases, *in vivo* bioavailability is not required by the Federal Drug Administration of the U.S.A., and only *in vitro* data is required for registration purposes (Stavchansky and McGinity, 1990). *In vitro* dissolution rate screening has been used (Barr, 1972; Barr and Adir, 1974; Barr *et al.*, 1972) as a sensitive quality control measure to show changes in drug release for products undergoing variable storage conditions. It is also used to warn of poor bioavailability of drugs from dosage forms that show erratic release patterns in comparative studies (Prasad *et al.*, 1983; Shah *et al.*, 1983; Levy, 1961; Levy, 1965;

Bergan *et al.*, 1973; Gibaldi and Weintraub, 1970; Wood, 1966). Therefore, it is a
valuable tool in formulation design and quality control and is a necessary test before *in
vivo* analysis is attempted.

3.1.1.3 *In vitro dissolution testing and apparatus.*

Most pharmaceutical products go through a dissolution test during their
development. Therefore, it is not unexpected that there are more than 100 apparatuses
that have been suggested for the measurement of *in vitro* drug release from solid drug
delivery systems (Parnarowski, 1974; Baun and Walker, 1969; Swarbrick, 1970;
Stricker, 1976). The many different types of apparatus can be classified into three
broad categories.

(a) *Closed-compartment systems.*

These systems usually have a large closed-compartment in which the
dissolution fluid is placed. They employ large volumes of dissolution fluid as
they assimilate sink conditions. Some examples of the equipment include the
rotating basket (USP XXI), paddle method (BP 1980), rotating flask (Gibaldi
and Weintraub, 1970), beaker method (Levy and Hayes, 1960), static disc
(Levy, 1963), circulating flow-through cell (Baun and Walker, 1969), and spin
filter (Shah *et al.*, 1973).

(b) *Open flow-through systems.*

Open flow through systems also use large volumes of dissolution fluid,
but only a small amount, is actually active in the dissolution process at any
point in time. Therefore, most of these apparatus are adaptations of the closed-
compartment models. Examples of flow-through systems include the oscillating
tube (Marshall and Brook, 1969), stationary basket (Shah and Ochs, 1974),
and sintered filter (Tingstad and Riegelman, 1970).

(c) *Dialysis and diffusion models.*

In the diffusion models, dissolved drug passes through a membrane or dividing layer into a second compartment from which the drug is analyzed. Some examples of these systems are the rotating basket (Marlow and Shangraw, 1967) and the rotating bottle (Barzilay and Hersey, 1968).

Each of the above apparatuses have their own inherent advantages and disadvantages. No matter what the specific advantages of the apparatus are, it must meet the following criteria;

(a) The apparatus must be economically viable. It should be accomplished by the use of standard laboratory equipment, so that it can be standardised as far as possible.

(b) The apparatus must be scientifically pragmatic. The inherent variability in the apparatus should be less than the inherent variability in the products being tested.

(c) The apparatus must be flexible in providing an effective degree of agitation. One must be able to alter the effective degree of agitation by altering the rate of agitation.

Of the above methods, the rotating basket and paddle methods are the only official oral drug delivery system methods in the USP and BP. They are both closed-compartment methods and comply well with the above criteria. Therefore, it is not surprising that these two methods are the most widely used methods for dissolution testing for research and quality control.

The purpose of this study is to test the dissolution rate of a standard model drug like theophylline from the core-in-cup tablets previously developed. In order for the test to be relevant and reproducible it was decided that it would be best to test the dissolution in the presence of sequenced simulated gastrointestinal fluids in the BP paddle apparatus. The effect the sequenced simulated fluids on the zero-order rate of release of drug will also be tested. A prerequisite of an effective core-in-cup system is that it must not be too affected by conditions in the GIT, and it should also be capable of releasing drugs over a period of at least 8 hours at a zero-order rate.

3.1.2 Materials and Methods

3.1.2.1 Materials

Acacia was supplied by Saarchem (Pty) Ltd, South Africa. The acacia had a viscosity of 53 cps as a 4% aqueous solution at 23°C. Theophylline anhydrous (Knoll AG, Germany) was ground in a mortar and the fraction passing through a No. 150 standard U.K. sieve was used. Caffeine (Sigma Chemical Company, U.S.A.) as internal standard was used as supplied.

Pancreatin from porcine pancreas with an activity at least equal to U.S.P. specifications, and pepsin from porcine stomach mucosa with 550 units/mg activity were obtained from Sigma Chemical Company, U.S.A. and were used as supplied. Sodium-1-octanesulfonate and sodium-1-heptanesulfonate were supplied by TCI-Ace, Tokyo Kasei Kogyo Company, Ltd., Japan. Ethylcellulose (Sigma Chemical Company, U.S.A.) and carnauba wax (Sigma Chemical Company, U.S.A.) were also used as supplied. All other reagents used were standard laboratory grade.

3.1.2.2 Formulations

Granules of 10%$^w/_w$, 20%$^w/_w$, and 30%$^w/_w$ acacia with theophylline were made as previously described in section 2.2.2.3. The press was then adjusted to produce core tablets of approximate hardness of 40 N/m^2 and thickness of 5 mm. The average weights of the core tablets and their standard deviations for each formulation are listed in table 3.1 below.

TABLE 3.1

Weights of theophylline core formulations.

%$^w/_w$ Acacia	Weight of core ± S.D. (n=10)	Intended weight of theophylline
10	158 ± 8,367	142,2 mg
20	171 ± 10,035	136,8 mg
30	182 ± 11,612	127,4 mg

The theophylline cores were then compressed together with the 10%$^w/_w$ carnauba wax in ethylcellulose cups to a depth of 4 mm as previously described in section 2.2.2.3.

3.1.2.3 Dissolution Studies

The B.P. 1988 paddle method was utilised in all the dissolution studies. Dissolution rates of the tablets were monitored using a Caleva model 7ST dissolution tester. A volume of 1000 ml of freshly prepared simulated gastric fluid TS U.S.P. XX was used as the dissolution medium during the first two hours, and then replaced by 1000 mls of freshly prepared simulated intestinal fluid TS U.S.P. XX for an additional 10 hours. At time zero, a core-in-cup tablet was placed in the simulated gastric fluid

equilibrated at 37°C ± 0,5°C. After two hours, the core-in-cup tablet was then carefully removed from the simulated gastric fluid and placed in simulated intestinal fluid pre-heated and equilibrated at 37°C ± 0,5°C for a further 10 hours. All experiments were carried out at 50 rpm. One millilitre samples were withdrawn from the dissolution media for theophylline determination after various time intervals.

3.1.2.4 Theophylline analysis

Samples withdrawn from the dissolution media were first centrifuged for 20 minutes at 5 200 r.p.m. to remove the turbidity from the pancreatin and other insoluble particles. A 200 µl aliquot of the clear supernatant was added to 200 µl of a 0,02%$^w/_v$ caffeine in distilled water internal standard solution. Theophylline/internal standard ratios in the 400 µl solutions were analyzed on a 15cm Beckman ultrasphere ODS 5 µm column connected to a Beckman System Gold HPLC consisting of a 126 programmable solvent module and 168 diode array detector module. Analytical wavelength was set at 280 nm. The mobile phase was perfused through the column at 1 ml/min and consisted of 95%$^v/_v$ 0,02 M sodium acetate buffer adjusted to pH = 4,0 with concentrated acetic acid, as well as 0,5%$^w/_v$ sodium-1-heptanesulfonate, 0,5%$^w/_v$ sodium-1-octanesulfonate, and 5%$^v/_v$ propan-1-ol (added to sharpen the chromatographic peaks). Chromatograms for theophylline and caffeine (internal standard) were completed within 10 minutes. Quantification of theophylline levels were based on comparison to standard solution curves in simulated gastric and intestinal fluid TS. The detection limit using this method was approximately 0,2 µg/ml theophylline.

3.1.2.5 Data analysis

To check that the theophylline was releasing from the core-in-cup tablets at a zero-order rate of release and hence a zero-order rate of dissolution, the cumulative amount of theophylline from both gastrointestinal solutions at various time intervals were fitted to zero-order, first-order, and square root of time models. In order to produce a

cumulative amount of theophylline released in sequenced simulated fluids, the amount released after 120 minutes was added to the amount released in the simulated intestinal fluid. These rates were then used to caluculate the amount of acacia to be added to the tablets that would would be able to release theophylline over a period of 12 hours. The correlation of the dissolution rate with each model was then calculated. The model with the highest correlation coefficient (Pearson's coefficient) was accepted as the model that best describes the rate of dissolution. The correlation coefficients for each model were then subjected to a LSD analysis of variance test, to check whether there was a significant difference (at the 95% level) between the correlation coefficients of the models applied to the data.

3.1.3 Results and Discussion

The dissolution of theophylline from the core-in-cup tablets was fairly consistent in both simulated fluids. Figure 3.1 graphically describes the dissolution of theophylline from the core-in-cup tablets over an 8 hour period from the sequenced simulated gastric and intestinal fluids. The theophylline was released and dissolved from the core-in-cup tablets at a rate that is more consistent with a zero-order dissolution rate than a first-order dissolution rate in both simulated fluids. There is no significant difference, as indicated by the LSD analysis of variance test, between the correlation coefficients of the zero-order and square root of time models applied to the data. There is, however a statistical difference between the zero-order and first-order models. Dissolution rates and the corresponding correlation coefficients of the dissolution of theophylline for zero-order, square root of time, and first-order dissolution models from the various simulated fluids, are listed in table 3.2 below. Dissolution of theophylline in the simulated gastric fluid TS is at a slightly lower rate than in simulated intestinal fluid TS. The dissolution (based on zero-order dissolution) of theophylline from the 10%, 20% and 30% acacia core-in-cup tablets were 0,8742 mg/min., 0,5255 mg/min., and 0,2688 mg/min., respectively in simulated gastric fluid TS, and 0,6114 mg/min., 0,3004 mg/min., and 0,2047 mg/min., respectively in

TABLE 3.2

Dissolution model exponents, correlation coefficients and dissolution rates of theophylline in various simulated media.

Acacia $(\%^w/_w)$	Order of model used	Correlation coefficient $\pm$ S.D. (n=3)	n for best model $\pm$ S.D. (n=3)	Rate of dissolution. $\pm$ S.D. (n=3)
Simulated gastric fluid TS				
10	zero	0,998 ± 0,002	0,973 ± 0,052	0,874 ± 0,096
	first	0,980 ± 0,008		
	√t	0,992 ± 0,005		
20	zero	0,992 ± 0,011	1,047 ± 0,046	0,526 ± 0,093
	first	0,941 ± 0,038		
	√t	0,982 ± 0,013		
30	zero	0,997 ± 0,002	1,033 ± 0,020	0,269 ± 0,028
	first	0,969 ± 0,015		
	√t	0,996 ± 0,000		
Simulated intestinal fluid TS				
10	zero	0,989 ± 0,009	1,008 ± 0,024	0,611 ± 0,102
	first	0,986 ± 0,012		
	√t	0,972 ± 0,036		
20	zero	0,968 ± 0,023		0,300 ± 0,029
	first	0,959 ± 0,042		
	√t	0,986 ± 0,011	1,058 ± 0,174	
30	zero	0,992 ± 0,003	1,021 ± 0,028	0,204 ± 0,022
	first	0,948 ± 0,029		
	√t	0,989 ± 0,008		
Simulated gastric and intestinal fluid TS				
10	zero	0,996 ± 0,002	1,026 ± 0,027	0,701 ± 0,193
	first	0,970 ± 0,002		
	√t	0,996 ± 0,002		
20	zero	0,989 ± 0,009	1,150 ± 0,098	0,388 ± 0,042
	first	0,915 ± 0,033		
	√t	0,988 ± 0,004		
30	zero	0,993 ± 0,002	1,161 ± 0,065	0,224 ± 0,027
	first	0,907 ± 0,010		
	√t	0,988 ± 0,007		
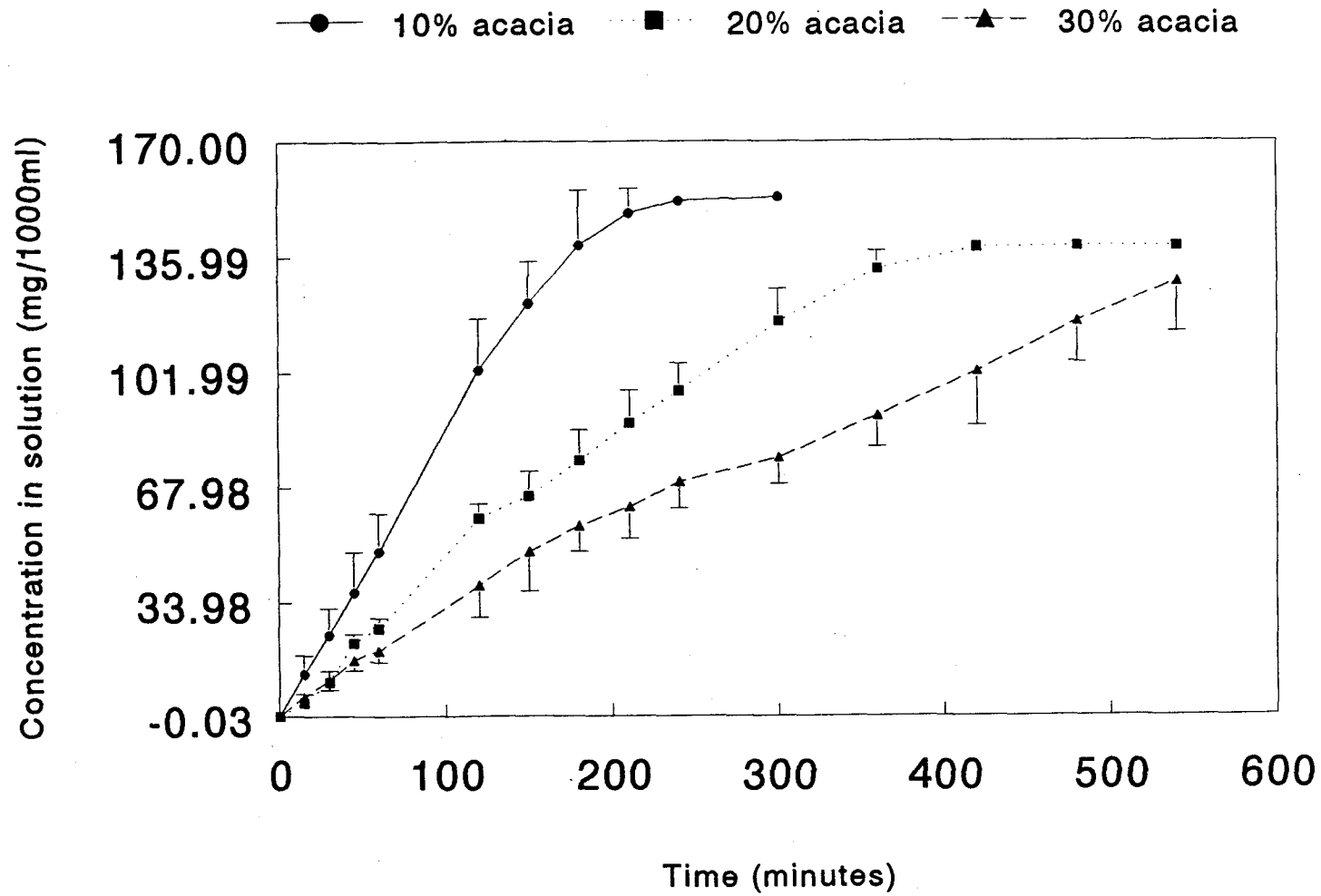
Fig. 3.1 Dissolution of theophylline from core-in-cup tablets in simulated gastrointestinal fluids.

simulated intestinal fluid TS. This is probably due to the fact that theophylline is slightly more soluble in acidic medium than it is in alkaline medium. This increase in the solubility of the embedded theophylline in the acacia makes the core portion of the tablet erode at a slightly increased rate.

The increased erosion rate then leads to an increase in the release of theophylline with a resultant increase in the rate of dissolution. Since the release of theophylline from the core-in-cup tablet is slower than the rate of dissolution, it appears that the rate of release is the rate controlling step. Therefore, this core-in-cup system is a good system for zero-order release of theophylline. The acacia does not seem to have any effect on the zero-order rate of dissolution. All three concentrations tested released theophylline at a zero-order rate of release. It also has the ability to release theophylline at a zero-order rate for a prolonged period of time, depending on the concentration of acacia used.

If one starts with a theophylline concentration of 100 mg (the intended dosage to be given to beagle dogs in the *in vivo* analysis of the core-in-cup tablets) in the core of the tablet, and wants it to be released over a period of 12 hours the rate of release would have to be 0,1389 mg/min. Therefore, the optimal concentration of acacia can be calculated by substituting this rate (the rate that releases drug over a period of 12 hours) into equation 3.1 and then solve for the concentration of acacia needed.

$$C = 37,7842 - 40,6217 \times R \qquad \text{- equation 3.1.}$$

where, R = zero-order release rate (from overall dissolution data) of theophylline from core-in-cup tablets in mg/min.

C = % $^w/_w$ concentration of acacia.

Equation 3.1 was obtained from the linear regression of the zero-order combined dissolution (cumulative release in gastric and intestinal fluid) rates versus concentration

of acacia used in the core-in-cup tablets to produce those rates. The square of the correlation coefficient for this linear relationship was 0,9688. Solving equation 3.1 then gives a value of 32,1418 for the $\%^w/_w$ acacia to add to the theophylline to release theophylline at a rate of 0,1389 mg/ min. in simulated gastric fluid TS for 2 hours followed by simulated intestinal fluid TS for 10 hours.

Therefore, in the next section, core-in-cup tablets with a concentration of 100mg theophylline and 30%$^w/_w$ acacia will be produced, and then tested *in vivo* using Beagle dogs. A 30%$^w/_w$ acacia concentration instead of a 32,1418%$^w/_w$ acacia concentration, was used so that it was possible to develop an *in vivo* to *in vitro* correlation. During the *in vitro* analysis a 30%$^w/_w$ acacia in theophylline concentration was used for the dissolution studies. The ability of the core-in-cup tablets to release drug at a zero-order rate with a resultant zero-order rate of absorption will also be checked, as well as a number of important pharmacokinetic parameters that will indicate the effectiveness of the core-in-cup tablet as a zero-order controlled release drug delivery system.

4. *IN VIVO* ANALYSIS OF THE CORE-IN-CUP TABLETS.

4.1 *IN VIVO* ANALYSIS OF THEOPHYLLINE CORE-IN-CUP TABLETS IN BEAGLE DOGS.

4.1.1. Introduction

The ideal controlled-release formulation is one which releases the drug at a constant rate, associated with a constant rate of absorption and producing sustained therapeutic concentrations over a prolonged period of time (Silber *et al.*, 1988). This period of time, should be preferably over an entire dosing interval. Therefore, the purpose of a controlled release drug delivery system is to improve therapy by maintaining uniform plasma concentrations at steady state, by reducing the ratio of maximum and minimum plasma concentrations (Theeuwes and Bayne, 1977). Although a thorough *in vitro* analysis is an important step in the formulation of new drug delivery systems, and it can supply the formulator with good relevant information, an *in vivo* analysis is always necessary. Conditions in the GIT are never ever really the same as those that can be simulated. Important pharmacokinetic parameters like rate of absorption, peak plasma concentration, extent of availability, elimination rate, and many other important parameters can only be obtained from *in vivo* studies. Therefore, it is always important in the development of drug delivery systems to conduct a thorough *in vivo* analysis. An *in vivo* analysis is necessary for the validation of *in vitro* models, specifically if one would like to develop an *in vitro/in vivo* correlation, so that the *in vitro* model can be used for further formulation studies.

4.1.1.1 *Criteria to assess in vivo performance of sustained-release products*

Many different criteria have been used to assess the performance of sustained-release drug delivery systems. Basically, from a pharmacokinetic point of view, a good

controlled-release drug delivery system should release drug at a zero-order rate for as long as is possible to maintain a level therapeutic plasma drug concentration. Therefore, the rate of absorption and peak drug level characteristics such as peak plasma time and plasma drug fluctuation are the major *in vivo* pharmacokinetic properties of drug delivery systems that need to be analyzed. The following are some of the many different parameters that have been suggested to evaluate the *in vivo* absorption and peak drug level characteristics of controlled-release drug delivery systems.

(a) *Assessment of absorption rate*

The three classical pharmacokinetic parameters used to assess bioequivalence; area under the curve (AUC), maximum plasma concentration (Cmax) and the time taken to maximum plasma concentration (tmax), are suitable to determine the extent and rate of absorption of immediate release drug delivery systems. However, they are not very useful in evaluating the pharmacokinetic performance, particularly the rate of absorption of controlled-release formulations (Bialer, 1995).

AUC is currently the ruling criterion to characterise the extent of absorption and to assess bioequivalence of standard and controlled release formulations (Welling, 1983; Dighe and Adams, 1988). AUC is a strong parameter which takes into account all the experimental points collected in each period of a bioequivalence study. It is not very likely that a new pharmacokinetic standard will substitute AUC for representation and assessment of extent of absorption. The exact selection of the proper pharmacokinetic criteria to assess the rate of absorption of controlled-release formulations is still uncertain. Cmax and tmax are single experimental point parameters which are not much use in cases of level or multiple peak concentration-time curves, as is often the case from controlled-release formulations. In addition, when Cmax and tmax are determined by visual

inspection of the data, they depend on the sample schedule times. The more readings one takes around Cmax, the more accurate the readings will be. Cmax is also unfortunately, affected by changes in the extent of absorption.

Because of the above limitations of Cmax and *t*max, the following pharmacokinetic parameters and criteria have been considered to characterise rate of absorption of controlled-release products.

(1) Mean absorption time (MAT)

The statistical moment method of analysis for the blood level profiles considers the time course of *in vivo* drug concentrations as a statistical distribution function of time (Cutler, 1978; Yamaoka *et al.*, 1978; Riegelman and Collier, 1980). The first moment estimates the mean residence time (MRT) of a drug which is calculated from equation 4.1.

$$MRT = \frac{AUMC}{AUC} \qquad \text{- equation 4.1}$$

Where AUMC is the area under the moment curve which is obtained by means of calculating the area under the curve of the plasma concentration multiplied by the corresponding time versus the time of measurement of plasma drug level.

Like AUC, MRT is also a strong parameter which takes into consideration all the experimental points in each phase of the study. Since the MRT estimates relate to both the rate and extent of absorption, they are useful in evaluating *in vivo* performance of controlled-release drug delivery systems (Lin and Yang, 1988; Block and Banakar, 1988).

If one compares the MRT of a test formulation with the MRT of a formulation that is immediately absorbed (an IV dosage form), then the mean absorption time (MAT) can be calculated from equation 4.2.

$$MAT = MRT_{oral} - MRT_{iv} \qquad \text{- equation 4.2}$$

The MRT_{iv} basically reflects the distribution and elimination rates in the body, and therefore, the difference between MRT_{oral} and MRT_{iv} is an estimation of the *in vivo* absorption rate of the drug from the test formulation. In some cases IV data is not available and an MRT for a solution may be calculated. The mean dissolution time (MDT) or an *in vivo* mean dissolution time for a solid product is given in equation 4.3 (Gillespie *et al.*, 1982; Graffner *et al.*,1984).

$$MDT = MRT_{oral} - MRT_{solution} \qquad \text{- equation 4.3}$$

MDT reflects the time for a drug to dissolve *in vivo*. Despite its usefulness, MRT has not yet gained widespread acceptability.

(2) *In vivo* mass balance absorption rate

The mass balance method is based on the additivity of the amounts of drug already excreted or still at the site of absorption, in the central compartment (including the sampling department) and, possibly, in the peripheral compartment. One of the earliest methods for the estimation of the absorption of a drug into the blood was developed by Wagner and Nelson (Wagner and Nelson, 1963, 1964). This technique was based on the assumption that the body is a single compartment from which the drug is eliminated by first-order processes. Either urinary or blood data can be collected. The method has gained wide acceptance because it does not require

prior estimate of the apparent volume of distribution and places no limitations on the order of the absorption rate constant. Equation 4.4 was derived by Wagner and Nelson for estimation of the percentage absorption of drug from a drug delivery system up until time T.

$$\% \text{ absorbed} = \underline{A_T} \times 100 = \frac{C_T + K \int_0^T C \, dt}{K \int_0^\infty C \, dt} \times 100 \text{ - equation 4.4}$$

where, A_T is the cumulative amount of drug absorbed from time zero to time T. A_∞ is the amount eventually absorbed. K is the overall elimination rate constant. C_T is blood, serum, or plasma concentration at time T.

The method using blood level data is as follows: Successive values of the top right hand side of equation 4.4 are calculated from the time of administration ($t = 0$) to some time after the peak in the blood time plot. The area under the curve for each value can be calculated using the trapezoidal rule or any other convenient method. The cumulative values of the top of the right hand side of equation 4.4 progressively increase, then reach a maximum or asymptotic value. When the individual values are expressed as percentages of the maximum or asymptotic value, the results are percent absorbed values to various times T. If the cumulative percentages absorbed are plotted against time, the resulting plots may contain linear segments up until the asymptotic value; the slope of such a linear segment is the absorption rate in percent per time unit, i.e. zero-order rate absorption. If the log of cumulative percentage absorbed up until the asymptotic value versus time is linear then a first-order rate of absorption can be suspected. The Wagner and Nelson method is particularly useful in determining the relative efficiency of absorption of a drug from different oral formulations for demonstrating *in vitro* to *in vivo* correlations (Weinberger *et al.*, 1981; Gonzalez and Golub, 1983; Chung and

Shim, 1987; Aiache *et al.*, 1989; Hussein and Friedman, 1990).

Loo and Riegelman (1968) developed a method of calculating the % drug absorbed from a two-compartment model. Their model, described by equation 4.5, is based on the assumption that a drug upon oral or intravenous administration confers upon the body the characteristics of a two-compartment model.

$$\% \text{ absorbed} = \underline{A}_T \times 100 = \frac{C_{1T} + C_{2T} + K \int_0^T C_1 \, dt}{K \int_0^\infty C_1 \, dt} \times 100$$

$$- \text{ equation 4.5}$$

where, C_{1T} is the concentration of drug in the central compartment at time T, and C_{2T} is the concentration of drug in the peripheral compartment at time T.

This method has not gained popularity amongst researchers, as it requires that the drug is given intravenously in order to estimate the apparent volume of distribution and the overall elimination rate constant. An estimate of the amount of drug in the peripheral compartment as a function of time after oral administration must also be made on the same subject under carefully replicated conditions.

(3) Deconvolution methods

Another *in vivo* mass balance technique that has gained popularity in the past few years has been the numerical deconvolution technique (Vaughn and Dennis, 1978; Langenbucher, 1982). The numerical deconvolution methods do not assume a specific compartmental model but merely linearity and time invariance of the disposition kinetics (Tucker, 1983). The disposition

kinetics are usually derived from a reference experiment with intravenous administration. Deconvolution methods reconstruct the concentration - time curve after oral administration (input function) of drug from the concentration - time curve after IV administration (response function). The input function can be considered as the cumulative distribution function after IV bolus dose, the superposition of which results in the concentration - time curve after oral administration.

As the deconvolution methods calculate the absorption rate in the n-th time interval on the basis of approximations in preceding time intervals, the choice of appropriate times of measurement is extremely important. Errors in the first value are carried over to all subsequent values. In view of this problem, numerical smoothing is frequently applied prior to deconvolution, which can become very subjective depending on the smoothing technique used.

(b) *Plateau Time.*

Data on $t$max and summarising statistics are only explicit if Cmax is obvious and described by abundant measurements in the close vicinity of Cmax. In the case of level and multiple plasma maxima, which occur with controlled-release formulations, the plateau time is a more robust characteristic than $t$max. The plateau time could be defined as the time span of one dosing series during which the serum concentration deviates from the maximum concentration by less than a clinically specified difference or percentage. In the case of a 50% deviation from the maximum, the plateau time corresponds to the half - value duration (Meier *et al.*, 1974). Some authors (Jonkman *et al.*, 1981) believe that a 50% deviation is too large and believe that it should only be a 20% (Jonkman *et al.*, 1981) or 25% (Steinijans *et al.*, 1987; Bialer, 1995).

No matter which percentage deviation is used, the longer the plateau time, the better the strength of the retardation of the release from the controlled-release product, and the less often the drug needs to be dosed.

(c) *Percent peak - trough fluctuation.*

In the case of flat or multiple maxima blood level profiles, $t$max and Cmax are of limited value. A better measure of the controlled-release characteristics in these cases, would be to describe the peak - trough variation that exists in the steady-state blood level versus time profile of the drug. This can be done by expressing the residual concentration at the end of the dosing interval, once the drug has reached steady-state, in percent of either the maximum or the average concentration (refer to equations 4.6 and 4.7).

$$\% \text{ PTF} = 100 \text{ X } \frac{(C\text{max} - C\text{min})}{C\text{av}} \qquad \text{- equation 4.6}$$

$$\% \text{ Swing} = 100 \text{ X } \frac{(C\text{max} - C\text{min})}{C\text{min}} \qquad \text{- equation 4.7}$$

where %PTF is the % peak - trough fluctuation; Cmax, Cmin and Cav are the maximum, minimum and average plasma drug concentration within the dosing interval at steady state, respectively.

Unfortunately, equations 4.6 and 4.7 are reliant on a single measurement and its potential error. To prevent this reliance on a single measurement, the percentage area under the curve fluctuation (% AUCF) around Cav is a robust measure of the fluctuation of plasma concentration (Steinijans *et al.*, 1987; Boxenbaum, 1984). Calculation of %AUCF is described in equation 4.8.

$$\%AUCF = 100 \times \frac{AUC\ (Above\ Cav) + AUC\ (Below\ Cav)}{AUC} \qquad - equation\ 4.8$$

Unlike %PTF and % Swing, the %AUCF takes into account of all values of the plasma concentration versus time curve at steady state within a dosing interval.

Two important pharmacokinetic parameters of controlled-release are the rate of absorption and the time of controlled release. The purpose of this study therefore, is to conduct an *in vivo* pharmacokinetic study of theophylline model drug from the core-in-cup tablet in Beagle dogs. Pharmacokinetic parameters that will be studied include, elimination rate, rate and kinetic order of absorption, relative availability as compared to an immediate release capsule of pure theophylline, and %AUCF at steady state.

4.1.2 Materials and Methods

4.1.2.1 *Materials*

Acacia was supplied by Saarchem (Pty) Ltd, South Africa. The acacia had a viscosity of 53 cps as a 4% aqueous solution at 23°C. Theophylline anhydrous (Knoll AG, Germany) and caffeine (Sigma Chemical Company, U.S.A.) were ground in a mortar and the fraction passing through a No. 150 standard U.K. sieve was used.

Sodium-1-octanesulfonate and sodium-1-heptanesulfonate were supplied by TCI-Ace, Tokyo Kasei Kogyo Company, Ltd., Japan. Ethylcellulose (Riedel de-Haën, South Africa) and carnauba wax (Sigma Chemical Company, U.S.A.) were also used as supplied. All other reagents used were standard laboratory grade.

4.1.2.2 *Formulations*

Three different types of dosage forms of theophylline were used in the *in vivo* study. Capsules containing 100mg pure theophylline were prepared by means of separately weighing out 100mg theophylline and filling size 2 capsules. The capsules were used as the immediate release dosage form from which the elimination rate could be calculated. Its blood profile was also used to determine the relative extent of bioavailability of the core-in-cup tablets. Core-in-cup and core only tablets containing 53,846mg (35% $^w/_w$) acacia and 100mg theophylline per tablet were also prepared and made as previously described.

4.1.2.3 Drug administration and sample collection.

Five female adult Beagle dogs, clinically healthy and hematologically normal, weighing between 16 and 22Kg, were used in this study. Each of the three dosage forms were given to each dog separately after a 14 day 'wash out' period, over a period of three months. Food, but not water, was withheld for 12 hours before and after drug administration. Dosing of each dog was staggered at 15 minute intervals so as to facilitate subsequent blood sampling. Oral administration of the drug delivery systems was achieved by opening the mouth of the dog, depressing the tongue, placing the drug delivery system in the throat region with subsequent administration of about 100 ml of water. The mouth was firmly closed and air was blown through the dog's nose in order to facilitate swallowing (Gangadharan *et al.*, 1987). Blood samples (4 - 5 ml) were withdrawn from the jugular vein at 0, 0,5, 1, 2, 4, 6, 8, 10, 16 and 24 hours. The blood samples were allowed to stand for 1 hour, centrifuged at 4 100 r.p.m. in a Hettich E.B.A. III centrifuge (Tuttlingen, Germany) for 15 minutes, and then stored at 4°C until analysis. All samples were analyzed within 48 hours from collection. The faeces of each dog was collected and checked for the presence of the cup portion of the tablet.

4.1.2.4 Theophylline extraction and analysis

The extraction and subsequent HPLC analysis of theophylline and its major metabolites from blood samples is well documented in both human (Yuen *et al.*, 1993; Tanaka, 1992; Blanchard *et al.*, 1990; Chiou *et al.*, 1987; Chung and Shim, 1987) and animal studies (Davis *et al.*, 1993; Parra and Limon, 1991; Hussein and Friedman, 1990; McKiernan *et al.*, 1981). It is by far the best method for analysis of theophylline from blood plasma, from an expense, accuracy and reliability point of view (Moncrieff, 1991). Most extraction procedures from blood plasma involve the co-elution of theophylline and its internal standard into an organic solvent/plasma protein aqueous precipitator mixture of solvents. The most common solvent combination used is a chloroform/isopropyl alcohol mixture. Therefore, the following extraction procedure was used for both the blood samples and spiked samples for standard curve preparation:

(1) A 1 ml sample of blood plasma was mixed with 1 ml of caffeine internal standard solution (5 µg/ml) on a vortex mixer for 1 minute.

(2) 3 ml chloroform and 1 ml isopropyl alcohol was then added to this mixture, vortexed for 1 minute and then centrifuged for 10 minutes at 5 200 r.p.m.

(3) The aqueous (upper) layer was carefully aspirated off, and 1 ml was withdrawn from the chloroform layer, transferred to a clean conical glass tube, and evaporated to dryness in a waterbath set at 37°C, under a gentle stream of nitrogen gas.

(4) The dry residue was reconstituted with 200 µl mobile phase, vortexed for 1 minute, and then analyzed via HPLC.

In order to construct the standard curves, plasma from fresh beagle dog blood was collected and immediately spiked with known concentrations of theophylline. Theophylline aqueous solutions of 30 µg/ml serially diluted to 1,875 µg/ml were prepared. 3 mls of plasma was then spiked with 1 ml of each of the standard solutions

and then mixed thoroughly. Plasma, instead of blood was spiked, because it was impossible to accurately measure out an exact volume of blood for the standard samples. The standard plasma solutions then resulted in a concentration range of theophylline from 7,5 µg/ml to 0,4688 µg/ml after dilution with the plasma, which were used to construct the standard curves and calculate the accuracy and reproducibility of the method. Theophylline and caffeine internal standard were then extracted and prepared for analysis as described above. The accuracy and reproducibility from spiked drug-free plasma were calculated from concentrations of 7,5 µg/ml, 1,875 µg/ml and 0,4688 µg/ml of theophylline in plasma by comparing the peak-height ratio against internal standard with those obtained for aqueous solutions containing known concentrations of theophylline. The mean extracted concentrations ($n = 3 \pm$ s.d.) calculated on the basis of peak-height ratios against the internal standard were 7,1576 ± 0,7157 µg/ml, 1,4868 ± 0,1891 µg/ml and 0,4854 ± 0,1009 µg/ml for the 7,5 µg/ml, 1,875 µg/ml and 0,4688 µg/ml spiked plasma solution of theophylline, respectively.

The theophylline concentration in the extracted blood samples and standard solutions from spiked plasma were assayed on an HPLC system as previously described under section 3.2.4.

4.1.2.5 *Data analysis.*

The plasma concentration/time curves for the core-in-cup and core only systems were analyzed to estimate the rate of absorption, the % AUCF and the relative extent of availability (%RA).

The rate of absorption was estimated from the Wagner-Nelson method discussed above. These rates of absorption for each dog and drug delivery system were then checked to see how well they fit either a zero - order (plasma concentration versus time), first - order (logarithm of plasma concentration versus time), or square root of time (plasma concentration versus square root of time) model. The applicability

of each model was done by calculating its correlation coefficient from the fraction of theophylline absorbed from time zero to 4 hours (the linear portions of the fraction absorbed versus time plots). The results from each dog were analyzed separately, because there is usually quite a large subject to subject variation in the blood levels of theophylline, as well as the fact that the dogs were not dosed on a quantity per kg basis. The elimination rate used to calculate the fraction of drug absorbed for each time interval in equation 4.4 was estimated from the last section (time 10 to 24 hours) of the plasma concentration/time curve after the immediate release capsule dose.

To estimate the %AUCF at steady state, the plasma concentrations after a single dose were extrapolated to the time interval between 50 hours and 60 hours using the method of superposition (Gibaldi and Perrier, 1982; Koritz et al., 1986) based on a 10 hour dosing interval. Plasma concentrations of theophylline after a single dose that were spoiled due to breaking of centrifuge tubes, or those values that were extraordinary, were smoothed graphically before they were extrapolated to the time interval between 50 and 60 hours. This was done to enhance the accuracy of the method. The concentration remaining at each time interval (C_r) from the previous intended dosage (the dosage regime that one would give to a patient until steady state is reached) was calculated from equation 4.9. This equation is based on the first order elimination rate calculated previously.

$$C_r = e^{K_e (T - T\text{-}1) + \ln C_{T\text{-}1}}$$
\- equation 4.9

The estimated values of plasma concentration at steady state were based on a dosing interval of 10 hours. This shorter dosing interval from the predicted 12 hour dosing interval, was used as the gastrointestinal transit time of dogs is shorter than that of humans (Bialer et al., 1988). To calculate the %AUCF below and above the average plasma concentration, the intersection point of the graph at the average plasma concentration level was estimated graphically. To test whether there is a significant

difference between the core only and core-in-cup drug delivery systems, a single paired - sample hypothesis test at a 95% confidence interval was tested on the difference in the parameter that was measured. A single paired - sample hypothesis test is used because the two drug delivery systems were each given to each dog in the study as a cross-over regimen. In order to check whether there is an *in vitro* dissolution/*in vivo* absorption rate correlation, the correlation coefficient of the fraction of theophylline dissolved *in vitro* from the 30%$^w/_w$ acacia in theophylline versus the *in vivo* fraction of theophylline absorbed from the core-in-cup tablets was calculated. The fractions dissolved or absorbed were calculated at the times of 0,5, 1, 2, 4, 6 and 8 hours.

4.1.3 Results and Discussion

Figures 4.1a to 4.1e show the theophylline plasma concentrations of the three dosage forms given to each dog. The extrapolated theophylline plasma concentrations to the steady state time interval of 50 to 60 hours is also shown.
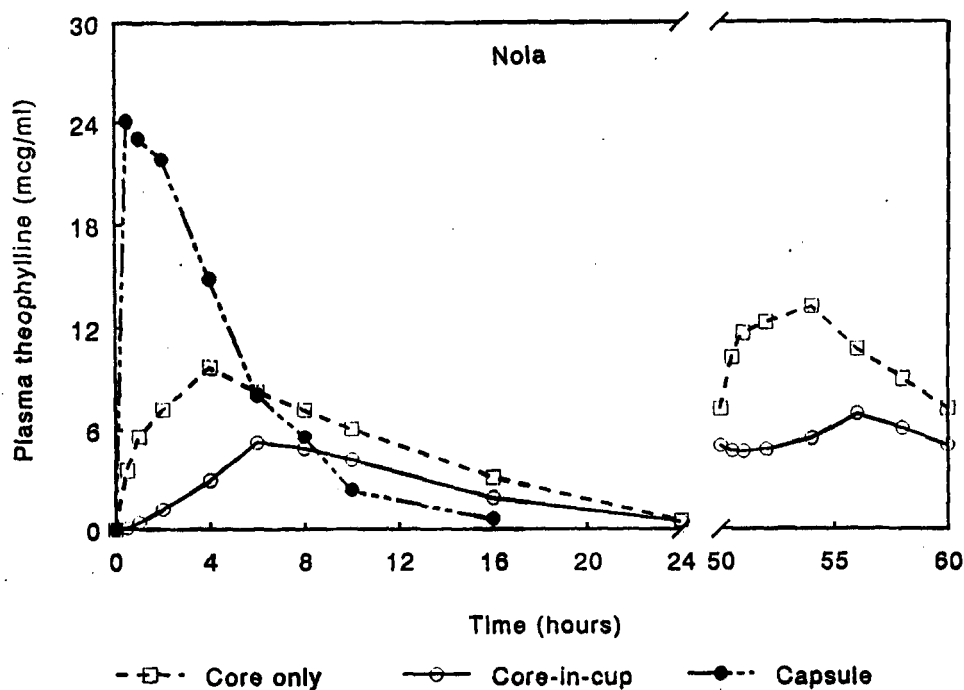
Fig. 4.1a Theophylline plasma concentrations from capsules, core only tablets and core-in-cup tablets in *Nola*.
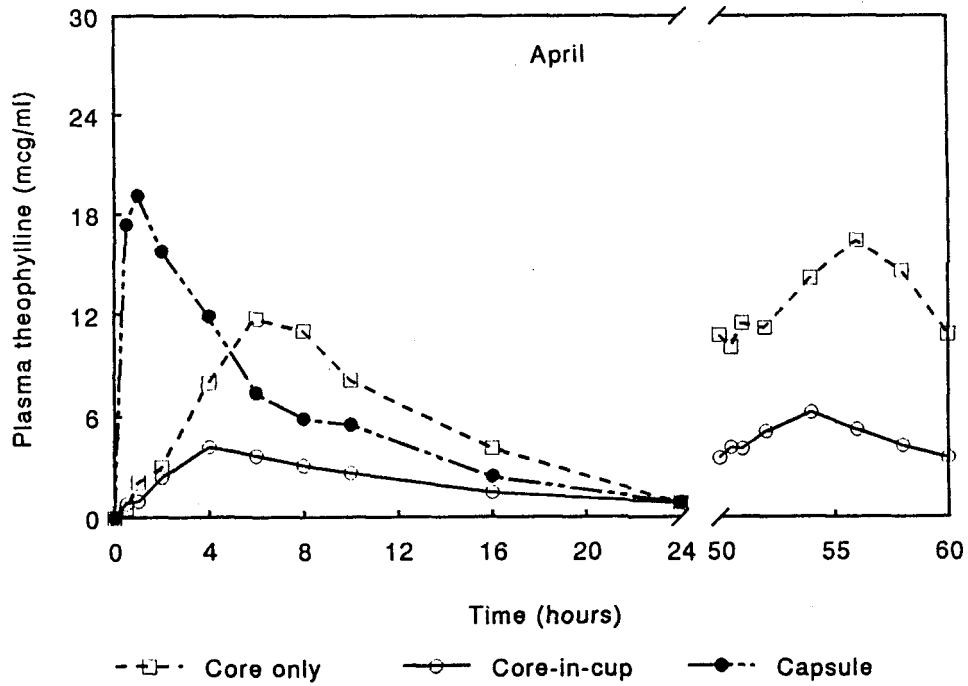
Fig. 4.1b Theophylline plasma concentrations from capsules, core only tablets and core-in-cup tablets in *April*.
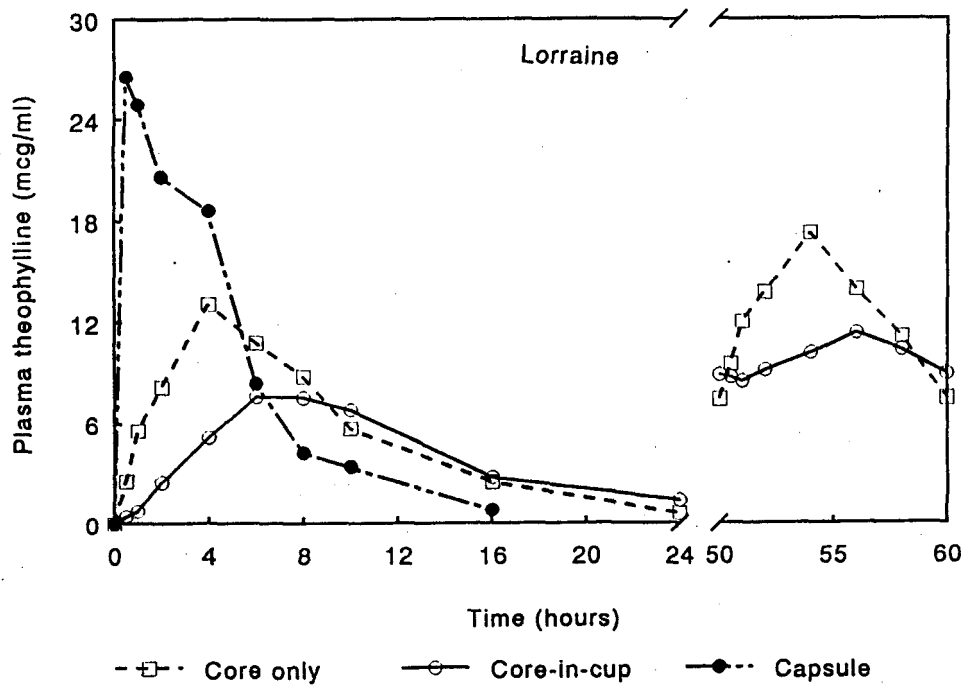
Fig. 4.1c Theophylline plasma concentrations from capsules, core only tablets and core-in-cup tablets in *Lorraine*.
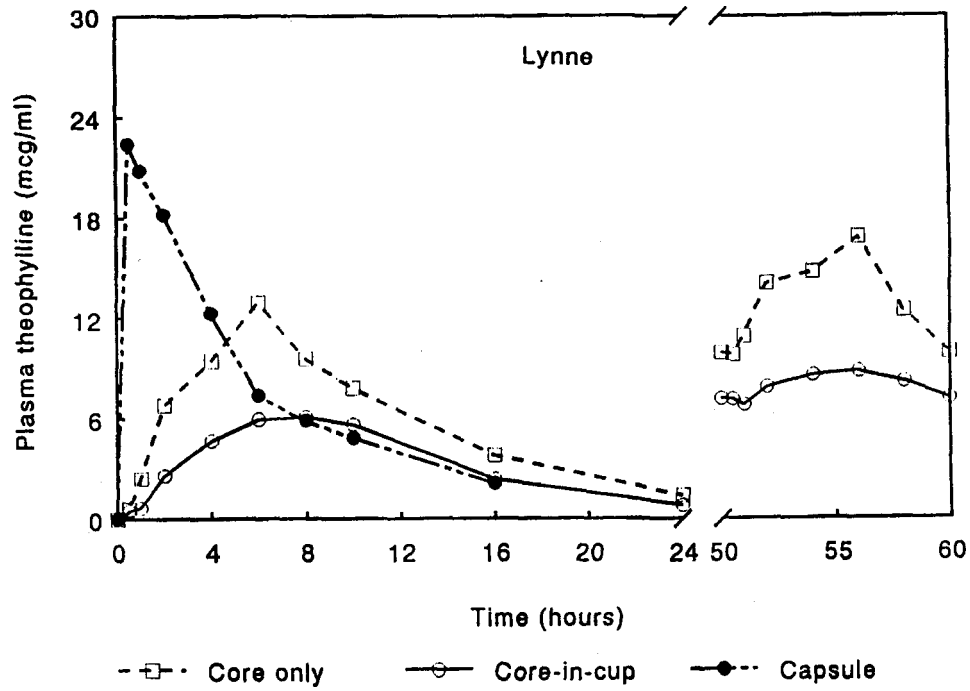
Fig. 4.1d Theophylline plasma concentrations from capsules, core only tablets and core-in-cup tablets in *Lynne*.
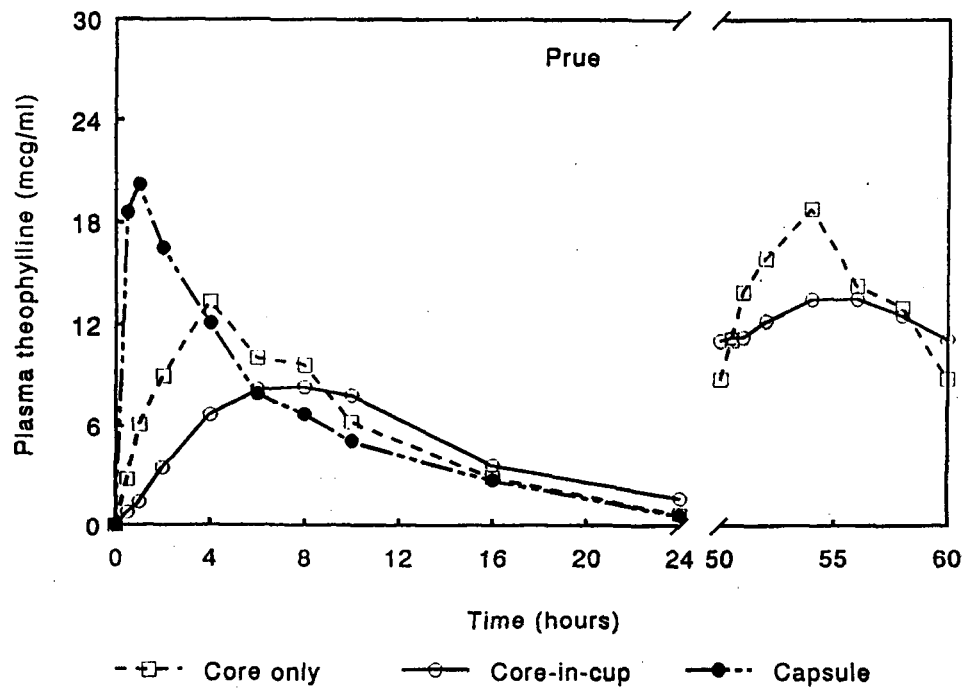
Fig. 4.1e Theophylline plasma concentrations from capsules, core only tablets and core-in-cup tablets in *Prue*.

As can be seen from the graphs, there is quite a large variation in the plasma concentrations from dog to dog. The variation, however, between the three dosage forms in each dog is much more consistent. This is also the case with the elimination rate calculated from the capsule dosage form, which varies from $0,1223$ hr^{-1} to $0,1803$ hr^{-1}.

Table 4.1 lists the results from the calculation of the relevant parameters of AUC, %AUCF, %RA and the correlation coefficients from each model for the absorption of theophylline, from the core only and core-in-cup tablets. Theophylline from both the core-in-cup and core only tablets was absorbed *in vivo* at a rate that is best described by a zero-order model. This is evidenced from the higher correlation coefficients for the zero-order model. The only exception was that for the dog Nola, where a square root of time model was most applicable with a square root of time correlation coefficient of $0,9979$ as compared to the zero-order rate correlation coefficient of $0,9887$. Even though the absorption of theophylline from the core only and core-in-cup tablets were both best described by the zero-order rate model, the correlation coefficient for this model was significantly higher ($p = 0,0314$) for the core-in-cup tablet. The zero-order rate model mean correlation coefficient for the core only and core-in-cup tablets were $0,9902 \pm 0,0034$ and $0,9952 \pm 0,0017$. Therefore, one can conclude that the core-in-cup tablet is better at releasing theophylline *in vivo* at a zero-order rate than the uncoated core only tablet. This result, of course is consistent with that predicted from the *in vitro* dissolution rate done in the previous experiment.

Although the average %AUCF for the core-in-cup tablet was less than that from the core only tablet, the difference of $6,9334$ was not quite significant at the 95% level. The probability of a significant difference was $p = 0,0545$. This is probably due to the %AUCF for the core-in-cup tablet given to one of the dogs (April) was slightly greater than that for the core only tablet.

TABLE 4.1

Relevant statistical and pharmacokinetic parameters of the in - vivo theophylline analysis from capsules, core only tablets and core-in-cup tablets.

Parameter	Nola	April	Lorra-ine	Lynne	Prue	Mean ± S.D.
Mass (Kg)	19,7	14,7	19,0	11,6	13,5	

Capsules

Parameter	Nola	April	Lorra-ine	Lynne	Prue	Mean ± S.D.
AUC	146,89	139,21	144,83	134,64	135,70	140,25 ± 4,86
Ke (hr⁻¹)	0,1803	0,1400	0,1446	0,1555	0,1223	0,1485 ± 0,0192

Core only

Parameter	Nola	April	Lorra-ine	Lynne	Prue	Mean ± S.D.
AUC	166,02	132,84	126,15	139,91	134,58	129,90 ± 8,21
%AUCF	15,49	12,69	19,97	15,65	17,14	16,19 ± 2,37
%RA	78,99	95,43	87,10	103,91	99,17	92,92 ± 8,88

Order of release correlation coefficient

Parameter	Nola	April	Lorra-ine	Lynne	Prue	Mean ± S.D.
0-order	0,9887	0,9875	0,9963	0,9870	0,9917	0,9902 ± 0,0034
1-order	0,9218	0,8943	0,9034	0,8553	0,8922	0,8934 ± 0,0217
√t	0,9979	0,9447	0,9875	0,9669	0,9881	0,9770 ± 0,0191

Core-in-cup

Parameter	Nola	April	Lorra-ine	Lynne	Prue	Mean ± S.D.
AUC	61,27	51,51	98,02	81,03	117,98	81,96 ± 24,13
%AUCF	8,81	15,40	8,02	7,38	6,67	9,26 ± 3,15
%RA	41,71	37,00	67,68	60,18	86,94	58,70 ± 18,11

Order of release correlation coefficient

Parameter	Nola	April	Lorra-ine	Lynne	Prue	Mean ± S.D.
0-order	0,9938	0,9957	0,9955	0,9930	0,9980	0,9952 ± 0,0017
1-order	0,8931	0,9403	0,9309	0,9229	0,9295	0,9233 ± 0,0161
√t	0,9494	0,9689	0,9526	0,9580	0,9673	0,9592 ± 0,0078

As could be expected, the %RA of theophylline from the core only and core-in-cup tablets were significantly different ($p = 0,0147$). There was also quite a large variation in the AUC and hence %RA from animal to animal. The difference in the %RA of theophylline from the core only and core-in-cup tablets was due to the average short gastrointestinal transit time of the dogs.

In three of the five dogs, a cup tablet with a small amount of remaining core, was found in the faeces of the dogs. The intact cups were found after 6 hours for Nola and after 8 hours for April and Lynne. The empty cups for the two remaining dogs were found in the faeces some time after 16 hours. For all the dogs, the cup portion of the core-in-cup tablet was defecated intact. The only visible change to the cups were a slight rounding off and erosion around the edges of the cups. These 12 mm diameter core-in-cup tablets should not have a problem passing through the human pylorus. Ashford et al (1993) produced a nondisintegrating 10 mm tablet which was then coated with a pH sensitive polymer, to check on the tablets transit time to reach the human colon. Through radioimaging techniques, they found that the intact tablet easily passed through the fasted stomach into the intestine.
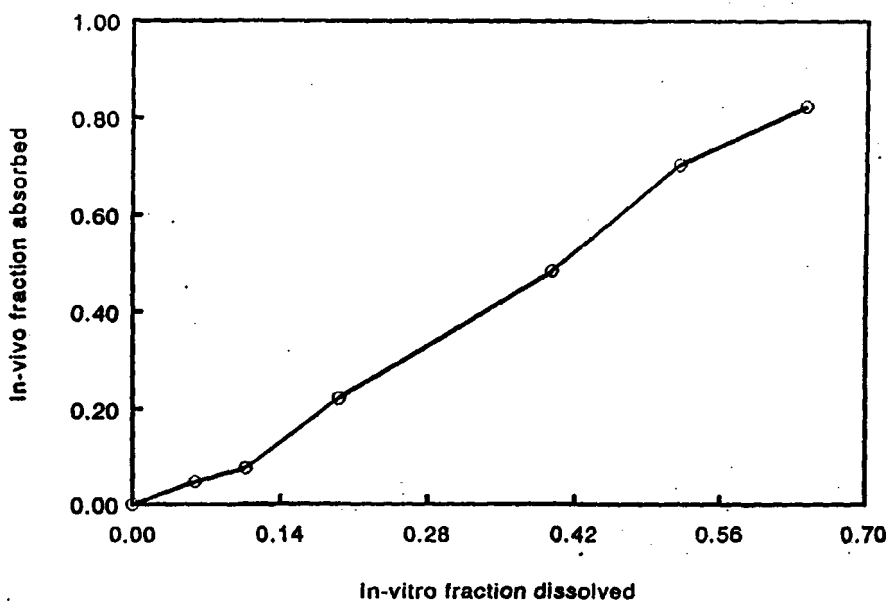
Fig. 4.2 Fraction of theophylline released into simulated gastrointestinal solution *in vitro* from the core-in-cup tablets versus the fraction of theophylline absorbed *in vivo* at various time intervals.

Figure 4.2 is a plot of the fraction of theophylline released into simulated gastrointestinal solution *in vitro* from the core-in-cup tablets versus the fraction of theophylline absorbed *in vivo* at various time intervals. The results of correlation obtained from the linear regression analysis between the fraction dissolved *in vitro* and fraction absorbed *in vivo* are presented in table 4.2.

The correlation slope values listed in table 4.2 indicate that the absorption of drug *in vivo* in dogs is on average 27,64% slower than the rate of dissolution *in vitro* in simulated gastrointestinal fluid. The mean slope was 0,7236 ± 0,012. Variability of the slopes in the *in vivo* to *in vitro* correlation, however, was very low. Slopes varied from 0,7136 to 0,7404.

TABLE 4.2

The *in vivo* to in vitro correlation parameters for the Beagle dogs obtained by linear regression analysis from the 30% $^w/_w$ core-in-cup tablets.

	Names of Beagles					
	Nola	April	Lorra-ine	Lynne	Prue	Mean ± S.D.
Slope	0,7386	0,7228	0,7194	0,7404	0,7136	0,7236 ± 0,012
Correlation coeffic-ient	0,9625	0,9603	0,9829	0,9919	0,9968	0,9789 ± 0,017

Therefore, the correlation between the *in vitro* dissolution rate in simulated gastrointestinal fluid and the *in vivo* absorption rate is very strong for theophylline from the core-in-cup tablets in Beagle dogs. However, care must be taken in extrapolating this correlation to humans. Only once effective human studies have been conducted, can one make the correlation from *in vitro* data.

5. DISCUSSION

The core-in-cup oral tablet developed throughout this research is an effective and versatile drug delivery system for releasing drugs at a zero-order rate of release. This has been established from *in vitro* and *in vivo* release studies.

5.1. Conclusion.

The core-in-cup system released a number of different drugs at a rate that was much closer to zero-order than the release from a core only matrix system. This was confirmed by the better correlation coefficients obtained from the fitting of the zero-order model as compared to the first-order or 'square root of time' models. The core-in-cup system also released a number of drugs of varying solubility properties. It released ibuprofen (insoluble), caffeine (soluble) and theophylline (intermediate) from the core-in-cup tablets at zero-order rates of release. Therefore, it could be possible to accommodate almost any drug that needs to be released at a controlled rate in the GIT. As long as the drug is formulated in a soluble polymer that erodes at a zero-order rate. This is possible since there are quite a number of different polymers available which vary according to their solubility and erosion in aqueous medium.

The core-in-cup tablet is also simple to manufacture. All that is required is a special adjustable punch (as has been described in this research) which fits to any Manesty tabletting press. Punches specific to other tabletting presses can also easily be manufactured. The adjustable punch is versatile in that it can vary the mass of the core tablet that can be manufactured and therefore, the hardness and compression weight of the tablet can be regulated as is the case for any other regular tablet.

During this research, the cores were placed by hand in the ready made cups, and then compressed together. In order to fully automate the core-in-cup tablet production, it would require an elementary adaptation to the tabletting press, from

which the cores can be fed into the cups and then fed sequentially into the final compression die. On the other hand, the cores and cups could first be produced on separate tabletting presses. Then, the cores could be fed via a tube feeder into the cups and fed into the press for final compression.

The final ethylcellulose and carnauba wax combination, used to manufacture the cup portion of the tablet, is directly compressible and has good flow and compressibility properties. This powder combination, also retains its shape and integrity throughout the release of the drug, and was defaecated with ease by the beagle dogs. It was found that a combination of $10\%^w/_w$ carnauba wax in ethylcellulose (average particle size of 925 μm) was the best combination for good compressibility and flow properties.

When considering the duration of drug release from the core-in-cup tablets, it was found that by the careful selection of the type of polymer, polymer grade , and the hardness of compression, it is possible to produce a tablet that can virtually release drug for any period up to 24 hours. This was the case for both soluble and insoluble drugs. The type of polymer had the most significant effect on the release rate. The results showed that polyethylene glycol 6000 was most suitable for ibuprofen and acacia was most suitable for caffeine and theophylline. Next, concentration of polymer and hardness of compression had the most significant effect on the release rate respectively. The release properties, type of polymer, concentration of polymer, and hardness of compression varies from polymer to polymer. Thus each of these properties would have to be tested for each new polymer that one contemplates to use.

5.2 Recommendations

The new adjustable punch and the core-in-cup system does open up a number of new opportunities in drug delivery. The core-in-cup tablet can be adapted to produced an immediate release component and a sustained-release component to the tablet. Two cores, one with the immediate release component and the other with the

sustained-release component can compressed as a multilayer core tablet into the cup tablet to produce a multilayer core-in-cup tablet. This type of system would be most suitable for the cores formulated with HPMC, which swells predominantly in the vertical direction. The immediate release component would be dissolved immediately and would then relinquish space within the cup for the HPMC to swell. This concept is graphically described in figure 6.1.
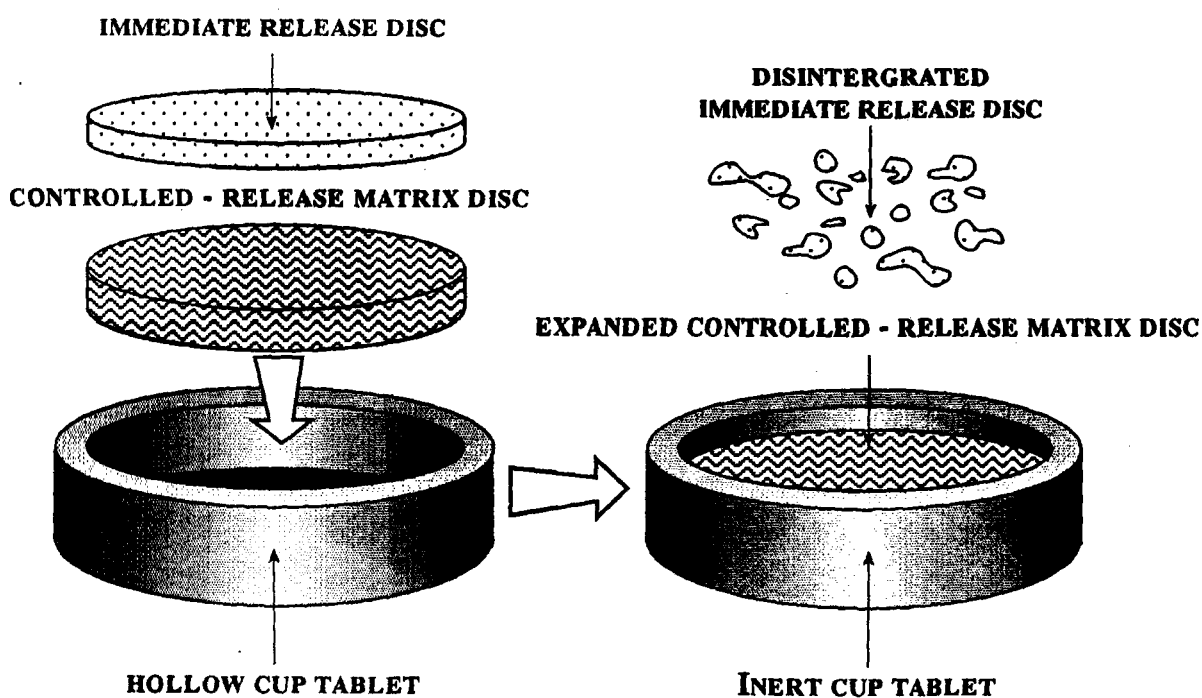
Fig. 6.1 Core-in-cup tablet with an immediate release component

In a similar manner, a pulsed-release tablet can be produced using different polymers in the layers of the core that are designed to release after predetermined times. The concentration of drug in each layer can also be varied. A zero-order enteric release core-in-cup tablet can also simply be formulated by way of making the top layer of the core from cellulose acetate phthallate, for example.

If the adjustable punch with the inner rod is used as the lower punch in the tabletting press and a similar punch without the inner rod is used as the top punch, it could be possible to manufacture a doughnut - shaped tablet with a neat large central hole. This would eliminate the wastage of drug when a hole is drilled in the centre of the tablet as reported by Kim (1995). Many tablets must also be wasted when they crack during drilling.

Presently, the cup portion of the core-in-cup tablet is formulated not to disintegrate or fundamentally change its shape during its journey through the GIT. Therefore, once the cup portion of the tablet has moved throughout the GIT, it is defaecated unchanged. As the cup portion of the tablet increases in size (which might be required from drugs which require a larger dose and hence larger punches to produce them), it could become a problem during defaecation of the tablet from the GIT. Consequently, it would be desirable that the cup portion of the tablet was designed to disintegrate once it had released the drug from it. This leaves two possibilities.

(1) The first is to formulate a cup tablet that starts to erode only once it enters the colon. Since the human colon has a high concentration of the anaerobic bacteria of the *Bacteroides* species (Simon and Gorbach, 1984) which have the ability to ferment many mucopolysaccharides and nonstarch polysaccharides (Cummings and Englyst, 1987; Bingham, 1987), it could be possible to use a polymer that is degraded by these bacteria, to achieve this end. Rubenstein and coworkers (Rubenstein *et al.*, 1993) have produced a calcium pectinate tablet that released indomethacin in the presence of pectinolytic enzymes and also in the presence of *Bacteroides ovatus*. Using calcium pectinate for the cup portion of the core-in-cup tablet, could possibly result in the cup portion of the tablet being degraded only once it enters the colon.

(2) The second way of formulating a cup tablet that disintegrates once it has

released its drug load, is to formulate the cup portion of the tablet so that it erodes at a rate that is slower than the rate of release of the drug. This can be achieved by way of utilising different grades of polymer that erode at a substantially slower rate than that of the core of the tablet. By means of careful formulation, the core could first release its active drug before the cup portion changes its shape on subsequent erosion.

Besides being applicable to a broad range of drugs, the core-in-cup drug delivery system is also applicable to an implantable tablet. A core-in-cup implantable tablet utilising different viscosity grades of polylactic glycollic acid (Resomer^R, Boehringer Ingelheim KG, Germany) has been formulated, and released a combination of levodopa and carbidopa simultaneously *in vitro* for a period of up to 100 days (Danckwerts and van der Watt, 1995). The cores of the tablet were compressed from granular Resomer^R RG 756 (i.v. of 0,8) and Resomer^R RG 858 (i.v. of 1,4). The cups of the core-in-cup tablet were compressed from granular Resomer^R L 207 (i.v. of 1,6). Most of the levodopa and carbidopa was released before the cup portion of the tablet was bioeroded to lactic and glycollic acid. It is also envisaged that this implantable core-in-cup system could be applicable to many other drugs that are characteristically released from an implantable system.

Therefore, the core-in-cup drug delivery system developed throughout this research is versatile and can be used for many different types of drugs and novel dosage forms. It is simple to produce on a large scale, and presents a number of unique possibilities for formulation of controlled - release drug delivery systems.

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