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A NOVEL TABLET DESIGN FOR ZERO-ORDER SUSTAINED-RELEASE

Erica Sundy

Dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree

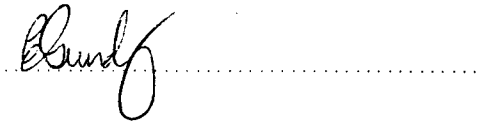
of

Master of Science in Medicine in the branch of Pharmacy

Johannesburg, 2002

DECLARATION

I, Erica Sundy declare that this dissertation is my own work. It is being submitted for the degree of Master of Science in Medicine in the branch of Pharmacy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



28th day of January, 2002

DEDICATION

This dissertation is dedicated to my parents Lynne and Sydney Gamsu to thank them for all the wonderful educational opportunities that they have given me.

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS STUDY

Presentations

A poster titled "The Production of Coated Doughnut-Shaped Tablets for Zero-Order Release" was presented at the 2nd International Conference on Pharmaceutical and Pharmacological Sciences on the 3rd – 6th October 1999.

Future Publications

A paper entitled " The development of a coated doughnut-shaped drug delivery system" is being written up.

A paper entitled " Zero-order release from a coated doughnut-shaped tablet" is being written up.

ABSTRACT

A coated doughnut-shaped tablet is evaluated as to its ability to release model drugs at a zero-order rate for 8 to 12 hours. The doughnut-shaped tablets were compressed using specially designed punches. Automated technology is thus feasible for this system. The coating material, 10% $^{w}/_{w}$ gelatin in HPMC K15M, was directly compressed and adhered to the tablet core. For the tablet cores, 5% $^{w}/_{w}$ HPMC K4M with an inner hole of 4.5 mm and 15% $^{w}/_{w}$ HPMC K4M with an inner hole of 6.5 mm was the most suitable for caffeine (soluble) and ibuprofen (insoluble) respectively to obtain zero-order release. Granule size of 0.63 μm allowed compliance with B.P standards of weight variation and friability. The coated doughnut-shaped tablet showed better zero-order release and for a longer period than the uncoated in dissolution fluid. The coated doughnut-shaped tablet is thus an easy to produce zero-order drug delivery system.

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1.0 INTRODUCTION

1.1 POPULARITY OF SUSTAINED-RELEASE DRUG DELIVERY SYSTEMS

The limitations of conventional per oral dosage forms has lead to the development of sustained-release drug delivery systems which offer several advantages, namely an increase in patient compliance, a reduction in the peaks and troughs associated with non sustained-release dosage forms, a reduction in side effects and an economy of tablets used (Madan, 1990). Sustained-release drug delivery systems can be prepared in a range of different types, which has been widely reviewed (Braybook and Hall, 1990; Krowczynski, 1987; Renade 1991; and Zahirul and Khan, 1995). These types vary from coated devices, whereby beads are coated with differing coats such as the Spansule® (Madan, 1990) or an entire core is surrounded by a rate controlling membrane, forming a reservoir device (Borodkin and Tucker, 1975) to the osmotic pump developed by Theeuwes (1975). Matrix systems, ion exchange resins and drug complexes are also used as sustained-release drug delivery systems (Madan, 1990; Krowczynski, 1987).

The matrix system is one of the most popular systems used to produce sustained-release dosage forms (Qui et al., 1998). In a matrix system the drug is usually dissolved or suspended in a support that resists disintegration. Matrix systems can be classified according to the chemical nature and properties of the material used as the support, namely, mineral matrices; hydrophilic matrices; inert matrices, lipidic matrices and biodegradable matrices. Of these different types of matrices, the hydrophilic matrix is most often used because of the

advantages it offers. It is possible for hydrophilic matrices to achieve reproducible release profiles with proper manufacturing control and they demonstrate less variability. There is less risk of dumping a large portion of the drug with hydrophilic matrices and they have the capacity to incorporate a large amount of drug, which, allows for large doses. The preparation process of hydrophilic matrices is relatively simple and conventional methods can be used. The materials used are usually inexpensive and have official acceptance (Salsa et al., 1997).

Hydroxypropylmethylcellulose (HPMC) is the cellulose ether, which is most widely used to produce hydrophilic matrices. It is inert, non-toxic and non pH-dependent (Salsa et al., 1997). HPMC is available with different substitution levels e.g. Methocel K is classified according to USP limits as having 22% methoxyl groups and 8.1% hydroxypropyl groups. HPMC is also available in a large range of molecular weights and are usually classified by the viscosity that a 2% w/w aqueous solution will form (Ford, 1999).

When HPMC is exposed to an aqueous medium, the surface particles become hydrated and undergo chain relaxation to form a viscous gelatinous layer, which is commonly referred to as the 'gel layer'. This gel layer limits water penetration into the matrix and prevents disintegration of the matrix tablet. This outer gel layer slowly erodes away exposing new particles of HPMC to the fluid, which in turn hydrate and form a new gel layer. This process of erosion and formation of a new gel layer continues until the entire tablet has dissolved (Alderman, 1984; Columbo et al., 1985; Rajabi-Siahboomi et al., 1992). The

tablet thus possesses two fronts, with the first front separating the glassy core from the rubbery state and the second front indicating the interface between the swollen polymer and the dissolution polymer. Initially the thickness of the gel layer increases as a function of the square root of time but this is followed by a synchronisation between the two fronts and the gel layer thickness becomes independent of time.

It was thought that water soluble drugs were released through diffusion through the gel layer while insoluble drugs were released by erosion of the drug layer but it is now thought that both processes contributed to drug release from the matrix. The amount that each process will contribute will depend upon the solubility of the drug (Ford et al., 1987).

1.2 ATTEMPTS TO ACHIEVE ZERO-ORDER RELEASE

The disadvantage of matrix type tablets is that generally the release of drug from such systems follows the square root of time according to the Higuchi model (Higuchi, 1963). It is desirable that the release rate of a drug from a sustained-release matrix tablet is a uniform one. To achieve this, it is necessary to either alter the type of polymer used as the matrix or to manipulate the geometry of the tablet. Altered geometry has resulted in novel drug delivery systems such as the core-in-cup shaped tablets (Seta et al., 1988; Shenouda et al., 1990; and Danckwerts, 1994), multi-layer tablets (Fassihi, 1988 and Conte et al., 1993) and doughnut-shaped tablets (Kim, 1995 and Cheng et al., 1999).

1.2.1 Control of swelling and erosion rate

If the rate the drug diffuses from the drug delivery system is balanced by the rate that the drug delivery system erodes at, then it is possible for a matrix system to release drug at a zero-order rate. This system has been extensively studied by Baveja et al. (1988a, 1988b, 1987); Devi et al. (1989); and Laicher and Profitlich (1995). These systems achieved a synchronisation of the swelling and eroding of the polymer by combining swellable polymers. Sodium carboxymethyl cellulose (SCMC) was combined with HPMC in a matrix tablet, with different beta-blockers used as the active drug. By optimising the ratios of drug, HPMC and SCMC, it was possible to reduce the burst effect in drug release and to achieve zero-order release rates for almost 100% of drug release (Baveja et al.,1988a, 1988b, 1987). The limitation with this method is that it must be confined to water soluble drugs.

1.2.2 Core-in-cup tablets

Seta et al. (1988) prepared a core-in-cup tablet, which consisted of a core containing captopril and hydroxypropyl cellulose and a cup containing a mixture of ethylcellulose and carnauba wax. The core was a bilayer tablet with a different concentration of captopril in each layer. This system released captopril at a zero-order release rate for a time period of 3-6 hours. Shenouda et al. (1990) also described a core-in-cup tablet. He formulated a core consisting of HPMC K-4000, which has the weakest gel strength and dyphylline, a water-soluble drug. Cores were produced with different concentrations of the active ingredient.

Polyethyloxazoline (PEOX) was used to produce the cup portion of the tablet because of its hydrophilicity. Cups were produced from either high molecular weight (HMW) PEOX or from medium molecular weight (MMW) PEOX. Certain cups also contained 20 mg of dyphylline. The results showed that when the majority of the drug content was included in the cup, the release kinetics followed the Hixson-Crowell cube root law but when 80% of the drug content was included in the core portion, the release rate was an apparent zero-order one. In both of these studies the core-in cup tablets were produced by first compressing the core using flat round punches, followed by press coating of the cup around the core in a larger die filled with coating mixture. This method has to be done manually and requires careful central placement of the core and visual inspections of each tablet to ensure centration and uniform thickness of the sidewall.

Danckwerts (1994) described a method for producing core-in-cup tablets that could be fully automated, easy to produce and inexpensive. This method was applicable to both the soluble and insoluble model drugs tested and demonstrated a zero-order release rate. The cups consisted of 10%$^{w}/_{w}$ carnauba wax in ethylcellulose and were compressed with a specially designed punch that produced cup-shaped tablets with an outer diameter of 11 mm, an inner hollow core of 7.5 mm and a 1mm depth. The core portion of the tablet was compressed using flat round punches with a diameter of 7 mm and a thickness of 1 mm. Caffeine and ibuprofen were used as the model soluble and insoluble drugs respectively. This study tested the effect of using two types of HPMC, HPMC K15M and HPMC K4M at concentrations of 5,10 and 15% $^{w}/_{w}$, on the kinetics

and time of release. The results of the study indicated that caffeine is released at a near zero-order rate for 80% of the time of release. A burst release effect was demonstrated for both types of HPMC although this settled down after 30 to 60 minutes. This increased release rate was higher for HPMC K15M as it swells more than HPMC K4M when it comes into contact with liquid and thus, allows an immediate release of drug via diffusion. The higher the concentration of HPMC in the core, the lower the release rate and the longer the time of release. Ibuprofen demonstrated very similar results to caffeine except that the rate of release was even closer to zero-order. The time of release varied from about 8 hours with $5\%^{w}/_{w}$ HPMC K4M in caffeine core-in-cup to 23 hours with $15\%^{w}/_{w}$ HPMC K15M in ibuprofen.

The main problem with the above study was that each core-in-cup tablet would have to have a specific set of punches, as it was the diameter and cup depth that determine the amount of polymer and drug that could be included. Danckwerts and van der Watt (1995) thus developed an adjustable punch, which could produce a cup with varying cup depths. Of course, as the cup depth is increased, the cup becomes more fragile. At a depth of 6 mm cups were prone to splitting due to the swelling of HPMC in aqueous solution. This resulted in nonswellable polymers being investigated and Danckwerts (1996) found that polyethylene glycol 6000 released insoluble drugs and acacia released soluble drugs from a core-in-cup tablet at a zero-order release rate.

1.2.3 Multi-layer tablets

Fassihi (1988) developed a concept that three-layer matrix tablets would allow for zero-order release by compensating for the zones of drug depletion via the differential dissolution/erosion of the matrix. Fassihi and Ritschel (1993) presented a direct compression method for the production of triple-layer matrix tablets. Multi-layer tablets are produced by compressing several different formulations fed into a die, one on top of another, in layers. A three-layer rotary press equipped with three die-filling and compression cycles is used to achieve this. Each punch would compress three times, once for each layer. The formulation of multi-layer tablets is more demanding than conventional tablets since bonding of the different layers is critical.

The interior layer of the tablet was composed of theophylline (55%$^{w}/_{w}$), dicalcium phosphate (30-40%$^{w}/_{w}$), Eudragit ® (8-12%$^{w}/_{w}$), talc (2%$^{w}/_{w}$) and magnesium stearate (2-5%$^{w}/_{w}$). The external layer was composed of Eudragit RS ® and ethylcellulose (25%$^{w}/_{w}$), dicalcium phosphate (20%$^{w}/_{w}$), theophylline (50% $^{w}/_{w}$) talc (2.5%$^{w}/_{w}$) and magnesium stearate (2-6%$^{w}/_{w}$). The formulations were optimised according to compressibility and release rates results. Drug release was as a result of both diffusion and dissolution but a linear release rate was shown since zero-order kinetics demonstrated the least variance when determining the goodness of fit. Controlled release of drug continued for up to 7 hours although 50% of drug release had occurred by three hours.

A novel three-layer tablet was produced by Cremer and Asmussen (1995). The matrix tablet was coated with erodible layers of drug free material with defined thickness gradients. These erodible layers would control the release profile of the drug with their geometrical shape and erosion rate. The matrix tablets were composed of theophylline, hydrogenated castor oil and microcrystalline cellulose and were granulated using gelatin solution. The tablets were compressed using a punch set with eccentric cone-shaped protrusions and a diameter of 9 mm. For the coating layers, lactose, hydrogenated castor oil, ethylcellulose and red pigment were granulated. A 50 mg quantity of granules was placed into the die of diameter 10 mm. The matrix tablet was placed on top of these granules, followed by another 50 mg of granules on top of the matrix tablet. All three layers were then compressed together. Dissolution tests were performed on both the coated and uncoated matrix tablet. The uncoated matrix followed square root of time kinetics while the coated tablet demonstrated a zero-order release profile. From half an hour the covering layers began to show signs of erosion and after 8 hours were completely eroded. The release profile is determined through the erosion of the covering layers and can be manipulated with changes in the composition, shape and compression of the covering layers.

Yang and Fassihi (1996) produced another three-layer asymmetric floatable drug delivery system as shown in figure 1.2. The asymmetric design allowed for a constant surface area at the diffusing front, which resulted in zero-order release rates. The floatability of the system prolonged gastric residence time and thus absorption time. The system could be easily manufactured using direct-compression technology.

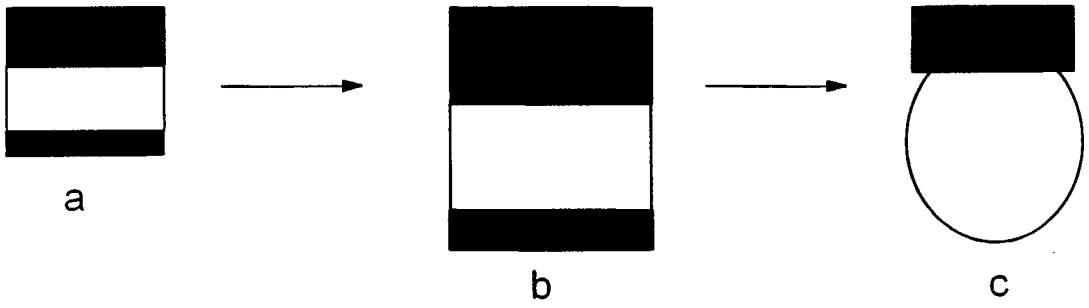


Fig 1.1 The three-layer asymmetric configuration of the tablet and the changes to the matrix following exposure to the dissolution medium: (a) before exposure (b) 15 minutes after exposure to fluid until time of 5 hours and (c) system erosion and disappearance of the third layer.

Polyethylene oxide (PEO) of average molecular weight and HPMC K4M were used as the matrix materials in each layer. In addition, the first layer contained sodium bicarbonate, a gas-generating component, while the second layer contained the active drug, theophylline. The function of the two external layers was to delay hydration of the middle layer and to restrict drug release to the cylindrical sides of the tablet. The external layers were designed to erode away at different rates. When the tablet came into contact with dissolution medium, there was simultaneous swelling of the polymer and production of resulting gas. The gas was entrapped within the swollen polymer, resulting in tablet buoyancy after a lag time of 15 minutes. The release rate of theophylline over the 16 hour dissolution study was a zero-order one.

A Geomatrix® tablet formulated by Conte et al., 1993 and Conte et al., 1994, consists of a hydrophilic matrix core, coated with either impermeable or semi-impermeable layers on either one or both sides of the core. The function of the coatings was to modify the swelling rate of the core and to reduce the surface area available for drug release. This resulted in changing the drug release profile to a zero-order one. The coatings could be applied as either a film covering or a compressed barrier. The film coatings were inert and impermeable to drug diffusion and their shape remained unchanged during dissolution. The tablet core however, swelled when it came into contact with the dissolution medium and this resulted in reducing the protective effect of the film. The compressed barriers consisted of hydrophilic swellable polymers, which were press coated to the tablet core. These barriers swelled simultaneously with the tablet core, ensuring that the protective effect of the barrier, on the tablet bases remained constant and since they were hydrophilic, they also completely dissolved.

Conte and Maggi (1996) tested barriers composed of HPMC with different viscosities. The high viscosity HMPC (Methocel K100M) demonstrated very slow hydration and swelling rates, and thus, was impermeable to drug diffusion for an extended period of time. This barrier was termed the gellable barrier. The erodible barrier was composed of low viscosity HPMC (Methocel E5) and this barrier is removed from the tablet core in a well-defined period of time. Trapidil was used as the model soluble drug and ketoprofen and nicardipine as the model insoluble drugs in order to test the effect of the different barrier layers with different drug solubility.

Both types of barrier were able to modulate drug release from the three-layer tablet. The gellable barrier was more suited for soluble drugs as it demonstrates a stronger protective effect, which results in a very slow release rate with insoluble drugs. The erodible barrier was more suited to these sparingly soluble drugs.

Qiu et al. (1998) tested the effect of having hydrophilic and /or hydrophobic barrier layers on a triple-layer tablet. The tablet core was composed of active drug embedded in a wax type matrix. Three types of tablets were produced. The first type had two hydrophilic barriers consisting of HPMC K100M while the second type had two hydrophobic barriers consisting of carnauba wax. The third type had one hydrophilic barrier consisting of HPMC K15M and one hydrophobic barrier. The layers were press coated together to form a three-layer tablet. The in vitro results showed that linearisation could be achieved with all three types, especially when compared to the uncoated layer.

1.2.4 Doughnut-shaped tablets

One of the ideas behind altering matrix geometry is to increase the surface area of drug exposed to dissolution fluid over time, so as to compensate for the increased diffusion distance that the drug must travel (Hsieh et al. 1983; Mishra and Yalkowsky, 1990). Rhine at al (1980) first showed that a hemispherical device with a hemispherical hole would follow zero-order kinetics. The influence of spherical, cylindrical and biconvex shapes on the kinetics of drug release was evaluated by Hsieh et al. (1983). This study produced hemispheres coated with

paraffin, except for a small cavity cut into the centre. The hemispheres either contained sodium salicylate in a polyethylene matrix or bovine serum albumin in ethylene vinyl acetate matrix. Zero-order release was achieved with the polymer matrices containing bovine serum albumin. Both of these devices require complex production process, which make it difficult to manufacture on a large scale.

Mishra and Yalkowsky (1990) produced a rectangular matrix with a circular hole punched out of the matrix. Silicone was mixed with progesterone and placed into a Teflon mould. When the mixture had set, it was removed from the mould and covered with sheets of aluminium from which a hole was punched out. This ensured that drug release was restricted to the central hole only. The study showed that the shape of the dissolution boundary slowly changed from flat to hemispherical over a period of time. The hemispherical boundary was only reached by the 10^{th} day of dissolution but showed significant curvature from the third day to allow for approximate zero-order release. He considered this a simpler method of production of a hemisphere than that of Hsieh et al.(1983).

Cleave (1966) proposed a mathematical theory that a tablet with a central hole or holes will provide a constant surface area, which will result in zero-order kinetics. His theory stated that if a tablet contained a cylindrical hole with radius r at time t, then at time Δt, the tablet would have eroded so that the radius of the inner cylindrical hole would be increased to r' as shown figure 1.2.

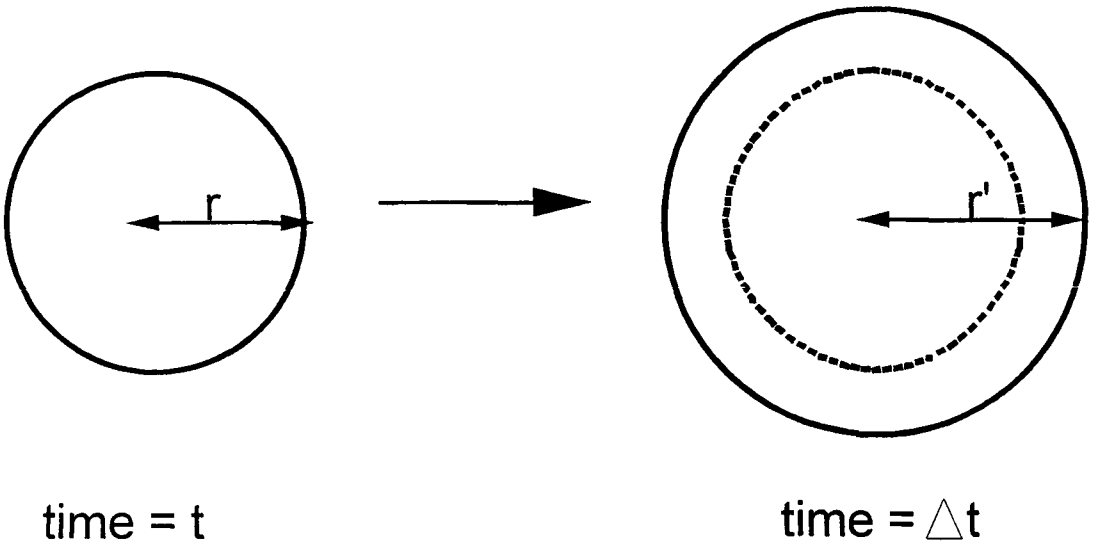


Fig 1.2. Change in radius of inner hole of tablet with time

The consequence of this increase in the inner hole radius would be an increase in the surface area of the cylindrical hole which would compensate for the decrease of the outer surface area of the tablet and thus, the surface area would remain reasonably constant. To ease the computational complexity in determining the surface area, Cleave (1966) considered the tablets in the form of parallelepipeds and checked the effect of a number of holes, ranging from one to four holes. He concluded that a tablet containing two-holes was a better structure for producing a tablet with a constant releasing surface area.

Kim (1995) produced a doughnut shaped tablet with a single central hole. PEO of various molecular weights, was mixed with active drug, either theophylline or propranol HCl, and flat round tablets of a 12 mm diameter were

prepared. A central hole was bored with a high-speed drill bit. Four hole sizes were tested ($^{3}/_{32}$", $^{7}/_{64}$", $^{1}/_{8}$", and $^{5}/_{32}$"). Kim found that the extension of linearity depended upon hole size, with the larger central hole allowing for a longer period of linear release. If the central hole was too small, then the hole was found to close during swelling of the polymer and the release kinetics were then the same as a matrix tablet without a hole. The molecular weight of PEO also affected the hole as lower molecular weight PEO swelled less and therefore, allowed for the use of a smaller hole size. As the solubility of drug increased, the release rate of the drug increased, but the duration of linear drug release was shortened to 65-70% of the total release time for propranolol as compared to 80-90% for the less soluble theophylline.

Cheng et al. (1999) also produced a doughnut-shaped tablet except that this tablet used HPMC as the matrix instead of PEO. Theophylline and diltiazem HCl were the model drugs tested. Flat round punches with a diameter of 12 mm were used and like Kim, the central holes were bored using a drill. The purpose of the study was to evaluate the effects of hole size, number of holes and solubility of drug. Hole sizes of 1 mm, 2mm and 3 mm were tested. The release profiles of the 2 and 3 mm hole tablets showed a more rapid release, with a linear release percentage of 80-90%. Tablets without a hole, only showed a linear release percentage of about 50%. The hole size of 1 mm was too small and closed due to the swelling of the HPMC. In addition to the single hole containing tablet, Cheng et al. also produced two and three-hole containing tablets. The results showed that as the number of holes increased from one to three, the more rapid, the drug release became. The linear properties also increased with an increase in the

number of holes, with the three-hole tablet demonstrating the best linear release. This conclusion was not in accordance with Cleave's (1966) results but could possibly be explained by the difference in tablet shape. The tablets considered by Cleave were rectangular but the tablets from this study were cylindrical.

Sangalli et al. (1993) produced a doughnut-shaped tablet coated with an ethylcellulose film covering. The theoretical basis for this tablet was, that if the entire erodible tablet except for the central hole was coated with a insoluble substance, then drug release would be limited to the central hole. Within the central hole, the increasing surface area of the solvent front would balance the increase in the diffusional path length, resulting in zero-order release of drug. Tablets with a 4 mm central hole, were produced with HPMC E5 as the matrix and using a specially designed punch set. The lower punch was perforated by a groove, which enabled it to glide into the die cavity. At the centre of this groove, a 4 mm cylinder was fixed and corresponded to a central hole on the bottom of the upper punch. Metoprolol tartrate and benfluorex were the model drugs chosen on the basis of their differing solubility. The tablet cores were coated in a rotating pan with ethylcellulose coating formulations containing different amounts of plasticiser. It was found that if the concentration of plasticiser in the coating formulation was decreased, a resistant continuous coating was limited to the more exposed core surface, but the central hole was only covered by a weak and irregular membrane. This could be problematic for large scale production as it is difficult to ensure uniformity of tablets. Sigmoidal drug release profiles were obtained with metoprolol at plasticiser concentrations of 6% but linear drug release was obtained for 80% of the time of release when the concentration of

plasticiser was zero. Benfluorex, which is less soluble, demonstrated linear release with low plasticiser concentrations.

Kim (1999) followed his doughnut-shaped tablet by producing a coated doughnut, because he found that for very soluble drugs, the release kinetics from a doughnut-shaped tablet changed from zero-order to anomalous (figure 1.3). He produced flat round tablets with a diameter of 12.6 mm with varying concentrations of drug (10-59%) and polymer (40-89%). A central hole of 2.38 mm was drilled with a high-speed drill. Diltiazem HCl, theophylline and nicardipine HCl were chosen as the model drugs. HPMC, polyethylene glycol (PEG) and PEO of different molecular weights and viscosities were used as the matrix material.

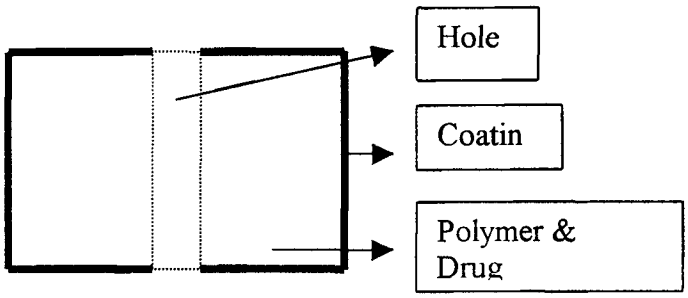


Fig 1.3 A doughnut-shaped tablet with all surfaces excepting the inner hole coated.

The tablet was coated on all surfaces except the central hole. The tablets were coated by inserting a glass rod in the hole and dipping and rolling the cores in an ethylcellulose/dichloroethane solution. After the coating was completed, the

central hole size was enlarged to either 3.18 mm or to 4.67 mm, again with a high-speed drill. When rapidly eroding polymers (HPMC E3, PEG8000, PEO with molecular weight either 100 000 or 200 000) were used, the release kinetics of diltiazem was parabolic. The slowly eroding polymers (HPMC E5, HPMC E15, PEO with molecular weight of 300 000) achieved zero-order release kinetics for diltiazem. When the drug loading was increased from 10 to 39% $^{w}/_{w}$, the drug release became faster and parabolic in a coated doughnut-shaped tablet containing HPMC E3, while the tablet containing HPMC E5 remained linear. When the drug loading was increased above 49%, the drug release rate of HPMC E5 became parabolic. As the drug solubility decreased from diltiazem to theophylline to nicardipine, the drug release rate from HPMC E3 tablets decreased but demonstrated little difference in HPMC E5 containing tablets.

1.3 OBJECTIVE OF STUDY

The objective of this study is to produce a novel drug delivery system of a coated doughnut-shaped tablet that releases its drug at a zero-order rate for approximately 8-12 hours (gastrointestinal transit time). The coating layers of the doughnut-shaped tablet will be developed first, followed by the development of the core layer which will study the effects of variables such as the concentration of polymer in the core and different hole sizes of the inner central hole.

This drug delivery system must be relatively simple and inexpensive to produce and be applicable to a wide variety of drugs. This study will therefore test both model soluble and insoluble drugs. This study will focus on automated

technology. Using specially designed tablet punches, the doughnut-shaped tablets can be easily produced with a technology suitable for manufacture on a commercial scale.

1.4 APPROACH TO STUDY

For this study, a novel shaped sustained-release drug delivery system will be produced combining the ideas behind the doughnut-shaped tablet and the multilayer tablet to produce a partially coated doughnut-shaped tablet that releases its drug at a zero-order rate.

This study proposes to produce a doughnut-shaped tablet that is coated on both the upper and lower bases. This coating of the flat ends of the tablet would restrict drug release to the lateral surfaces only. The increases in surface area of the lateral hole should now balance the decrease in surface area of the outer lateral surface (figure 1.4a and b).

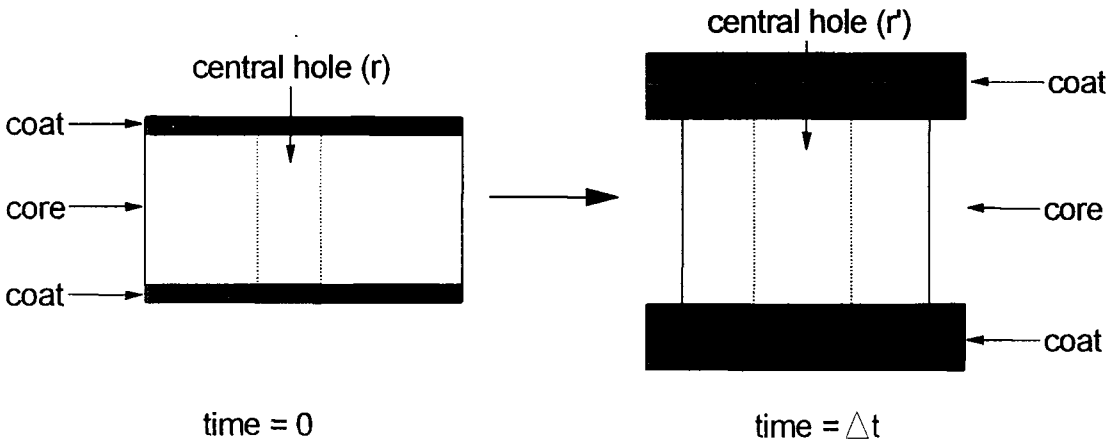


Fig. 1.4a Diagram of the changes in shape of the coated doughnut-shaped tablet over time with a profile view

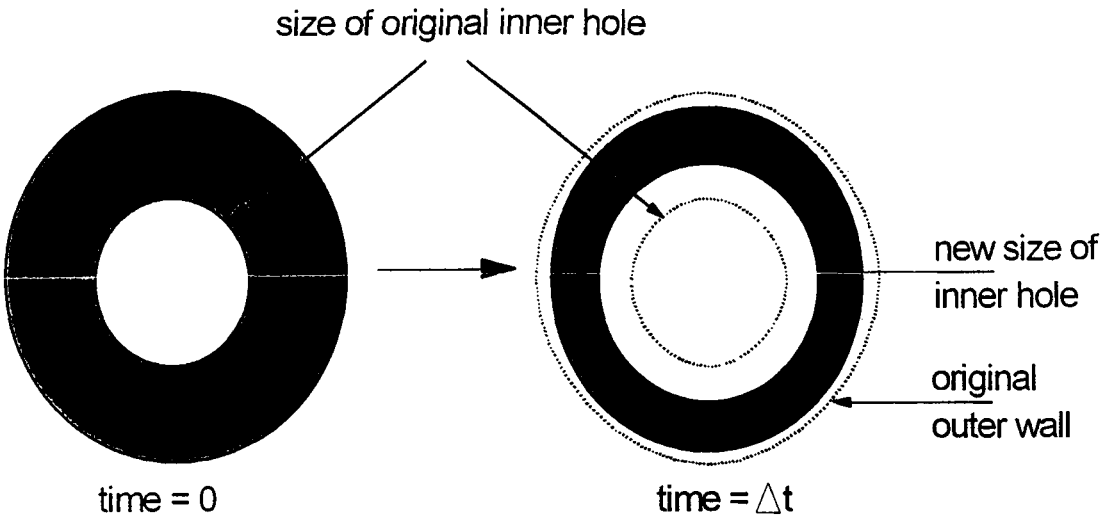


Fig. 1.4b Diagram of the changes in shape of the core layer of the coated doughnut-shaped tablet over time with a birds-eye view

Figures 1.5 a and b are pictures of the coated doughnut-shaped tablet with a core of 10% $^{w}/_{w}$ ibuprofen in HPMC K4M and a coat formula of 30% $^{w}/_{w}$ gelatin in HPMC K15M. Following recompression, the thin coating layers are not clearly visible in the pictures but after a period of two hours in the dissolution fluid of distilled water, the coating layers have swelled and are now clearly visible.

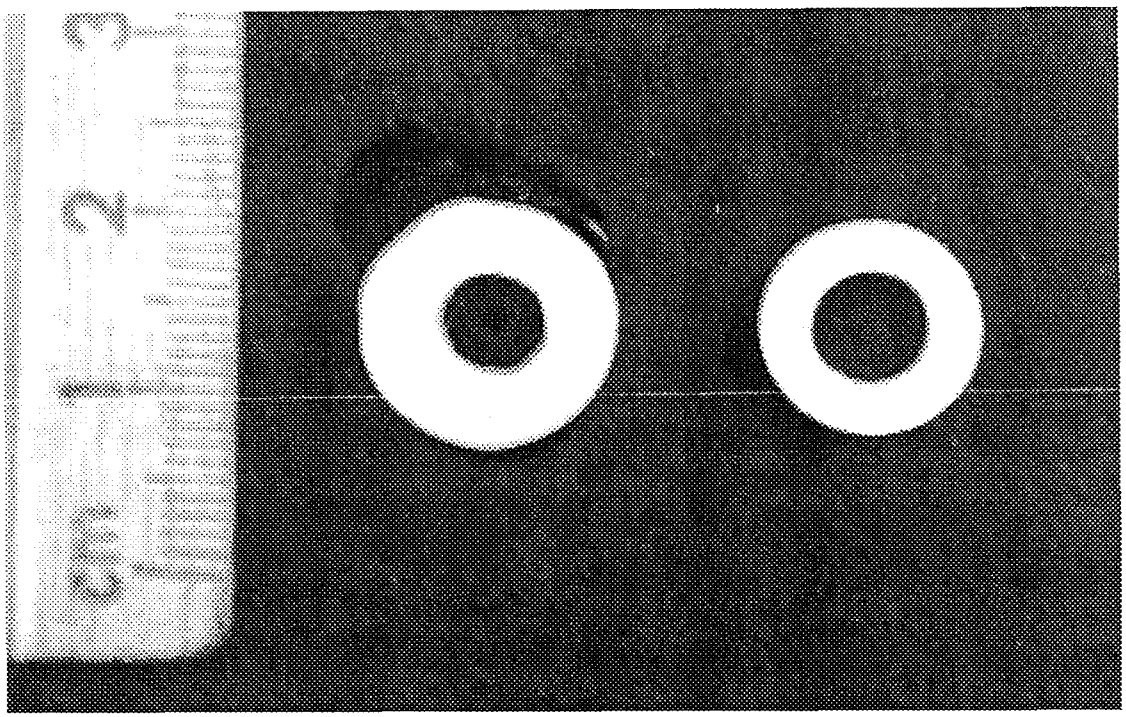


Fig 1.5 a Profile view of ibuprofen coated doughnut-shaped tablet at time =0 (right) and at time = 2 hours (left)

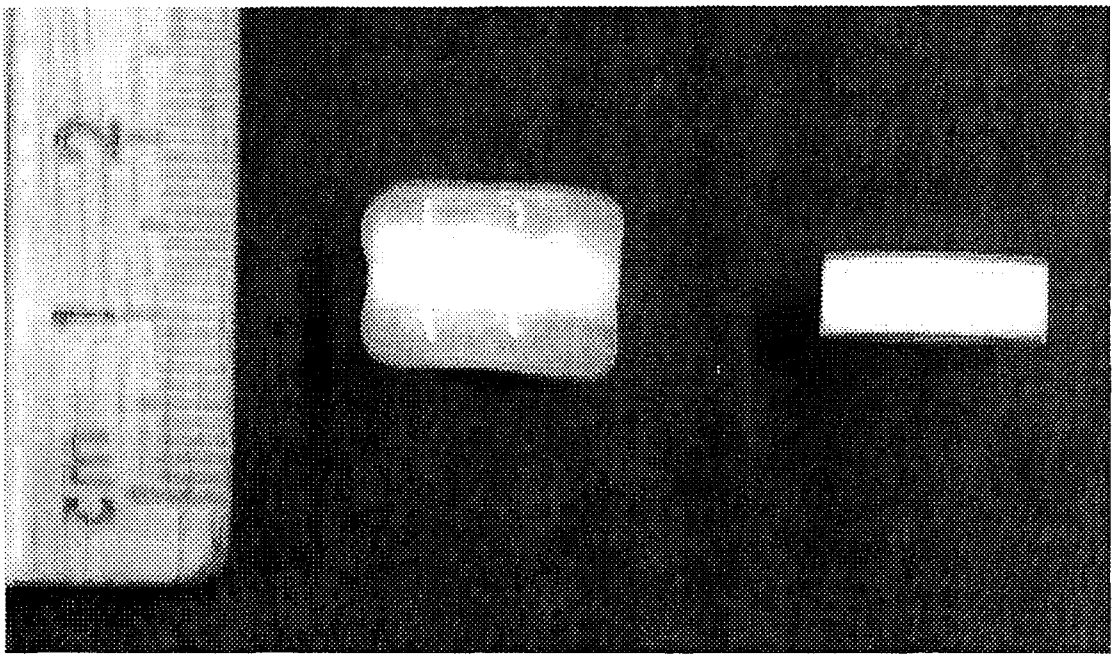


Fig 1.5 b Birds-eye view of ibuprofen coated doughnut-shaped tablet at time =0 (right) and at time = 2 hours (left)

According to experiments conducted by Colombo et al. (1990), when a tablet core is coated on both bases, then the core swells predominately in the radial direction. In figure 1.5 a, it is clear that considerable swelling of the coating layers takes place in the radial direction; however, the core layer appears to swell little in the radial direction. Figure 1.5 b, which is a birds-eye view of the coated doughnut-shaped tablet, shows that there is some swelling in the axial direction. The slight narrowing of the central is balanced by a slight increase in the outer diameter, ensuring that the surface area will remain constant and allow for zero-order release. There may be however, a small lag period before zero-order release is reached due to the time taken for the swelling of the tablet to synchronise.

The doughnut-shaped tablets developed in this study differ in their method of production from those developed by Cheng et al. (1999) and Kim (1995). These doughnut-shaped tablets are produced using a specially designed punch set as discussed in section 1.5, while those produced by Cheng et al. (1999) and Kim (1995) were drilled in order to produce the doughnut shape. In addition, this study uses the technique of compression coating in order to produce a three-layer coated doughnut-shaped tablet. With this coating technique, the coating is restricted to the upper and lower bases of the tablet. Kim (1999) and Sangalli (1993) used the technique of film coating to partially coat their doughnut-shaped tablets.

1.5 STUDY METHODS

For this study, four specially designed punch sets were provided by P.A. Cuthbert & Co (Pty) Ltd and produced by Holland Tabletting Science, UK. Each punch set consisted of punches, die and rod (figure 1.6 a and b). Both the upper and lower punches contained a longitudinal inner hole for the insertion of the rod, which enabled a doughnut-shaped tablet to be compressed around it. The specifications of the punch sets are listed in Table 1.1. Each punch set consists of the punches used to compress the tablet cores and coats as well as the punches used to recompress the three layers together, forming a three-layer doughnut-shaped tablet.

The tablet punch sets have different sized rods in order to produce doughnut-shaped tablets with different sized holes. The slightly larger punches and die cavities and smaller rods of the recompression punch sets ensure that the tablet coats and core can be easily fed into the die cavity. Figures 1.7 a - c describes the production steps to produce the core and coating layers in a Manesty F3 tabletting press. Figure 1.8 graphically describes the production procedure that will be used to produce the coated doughnut-shaped tablets.

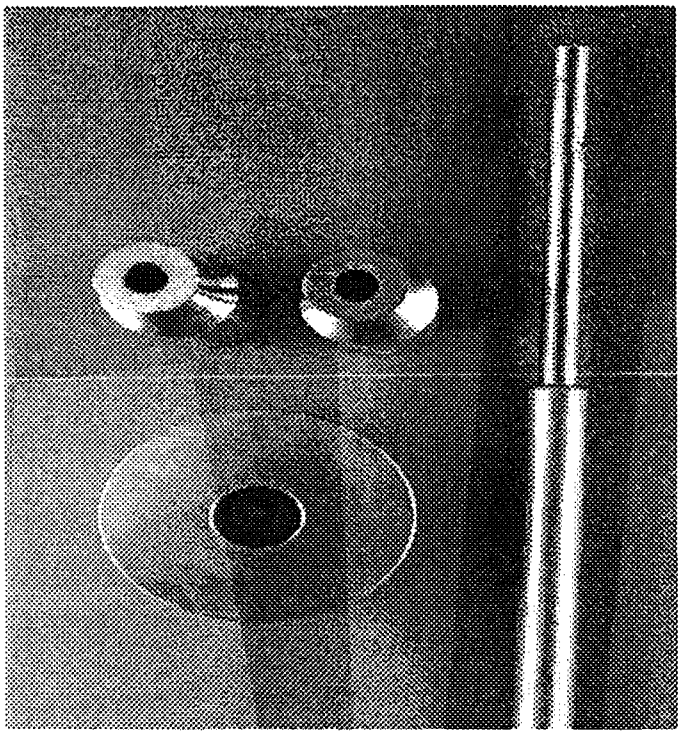


Fig 1.6 a Tabletting tools to compress doughnut-shaped tablet consisting of punches, die cavity and inner rod

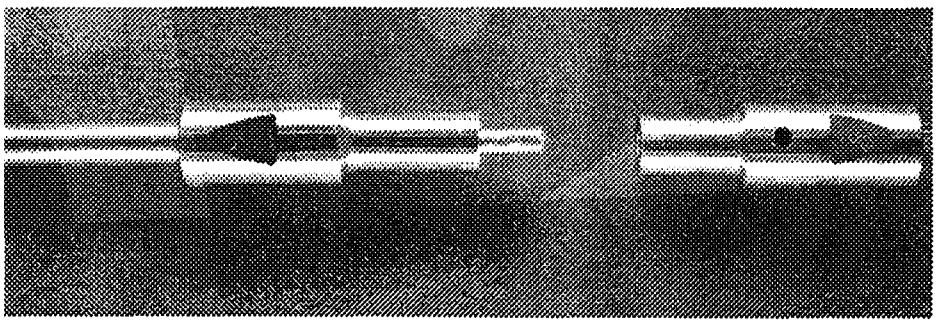


Fig 1.6 b Picture of punches and inner rod to compress a doughnut-shaped tablet.

TABLE 1.1

Specifications of punch tooling sets used to compress doughnut-shaped tablets.

Number	Punches	Rod
Set 1		
Cores and Coats	11 mm diameter	400 mm in length
	flat-faced	5 mm diameter
	5 mm inner hole	
Recompression	11.5 mm diameter	400mm in length
	flat-faced	4.5 mm diameter
	4.5 mm inner hole	
Set 2		
Cores and Coats	11 mm diameter	400 mm in length
	flat-faced	7 mm diameter
	7 mm inner hole	
Recompression	11.5 mm diameter	400 mm in length
	flat-faced	6.5 mm in diameter
	6.5 mm inner hole	

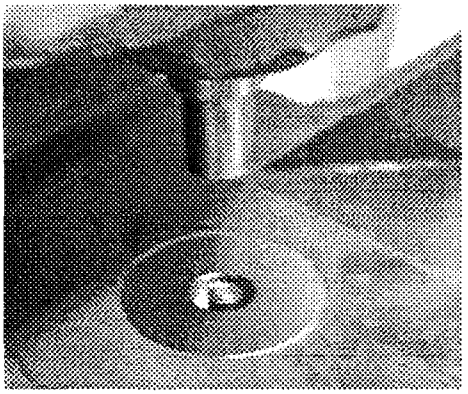


Fig 1.7a Before granule filling

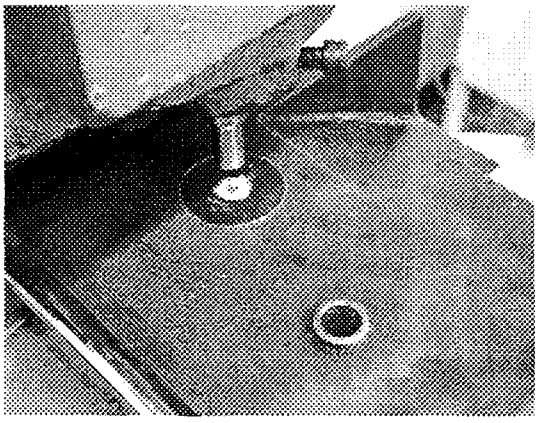


Fig 1.7b Granule filling

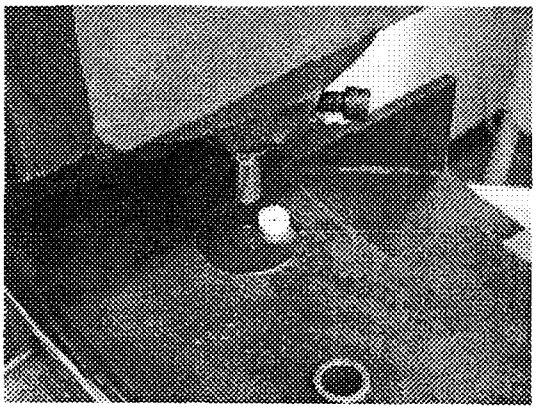


Fig 1.7c Tablet ejection

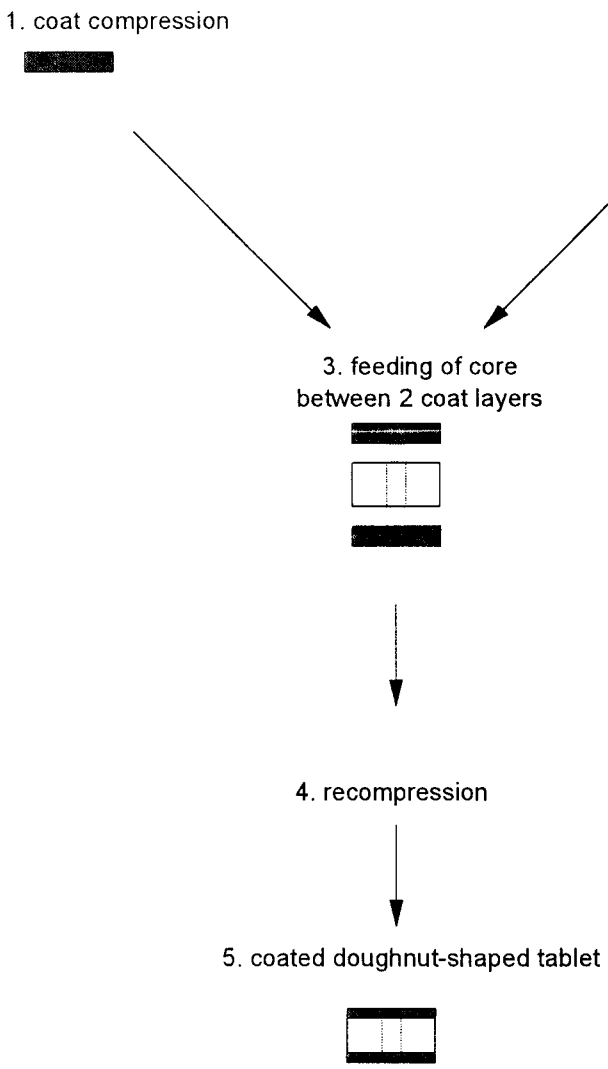


Fig 1.8 Production process of the coated doughnut-shaped tablets

Caffeine and ibuprofen will be used as the model drugs as they represent a wide variety of physicochemical properties and thus can be used to assess the suitability of the drug delivery system. The physicochemical properties of the model drugs are listed in Table 1.2. The purity, particle size and solubility were determined by the supplier and accepted as stated. Since only one batch of each model drug will be used, it is not necessary to determine batch-to-batch variation. Variations between formulas will be tested. The model drugs were chosen mainly

on the basis of their differing solubility as solubility plays a major role in drug release and dissolution.

TABLE 1.2

Relevant physicochemical properties of model drugs

Property	Caffeine (anhydrous)	Ibuprofen
Empirical formula	$C_8H_{10}N_4O_2$	$C_{13}H_{18}O_2$
pK_a at 25°C	14.0	5.3
Melting range °C	234-239	75-78
Molecular weight	194.2	206.3
Solubility at 25°C		
Aqueous	1 in 60	insoluble
Ethanol	1 in130	1 in 5
Stability	Decomposed by strong caustic salt solutions	Stable in the absence of oxygen

1.6 OVERVIEW

The first chapter contains the introduction to the project. It describes the innovations in sustained-release drug delivery systems and the approaches toward zero-order drug release. It also discusses the aim and methodology of the project.

The second chapter describes the development of the coated doughnut-shaped tablet. The study focused on determining the most suitable material to be used for the tablet coating layer. Once this was established, the coating layer was adjusted to ensure that it adhered to the tablet core and that it could be produced on an automated system.

Once the coating layers were optimised, the study focussed on developing a suitable formula for the tablet core. Concentrations of 5%$^{w}/_{w}$, 10%$^{w}/_{w}$ and 15%$^{w}/_{w}$ HPMC were tested. Tablets were also produced with two different sizes of inner hole. The formulation and tablet hole size that allowed for zero-order release with a suitable length of time of release was selected as the formula for the tablet core. The doughnut-shaped tablets were then subjected to quality control testing, namely, weight variation, hardness, and friability to ensure that automated production was possible. The flow and compressibility properties of the granulations were also checked.

In chapter three, dissolution testing was performed in order to compare the zero-order release from coated doughnut-shaped tablets to that from uncoated doughnut-shaped tablets. The dissolution testing was performed in dissolution fluid that followed the physiological gradient of the gastrointestinal tract.

Chapter four assess the suitability of the coated doughnut-shaped tablet as a sustained release drug delivery system based on the experiments in the previous chapters and discuses how to produce the coated doughnut-shaped tablet using automated technology. It also recommends future studies to be performed.

2.0 DEVELOPMENT OF THE COATED DOUGHNUT-SHAPED TABLET.

2.1 INVESTIGATION OF POLYMERS FOR PRESS COATING OF A DOUGHNUT-SHAPED TABLET

2.1.1. Introduction

In order to produce a coated doughnut-shaped tablet using the technique of compression coating, it is necessary for the coat layer to fulfil certain criteria:

(i) It is essential that the coat layer adhere to the tablet core for a large portion of the time of release.

(ii) Compression coating formulations require plasticity in order to produce a physically stable tablet.

Adhesiveness is required because the continuity of the coating depends upon its strength around the edges of the core. It ensures adequate bonding between the core and coating layers. Plasticity allows the coat to absorb the expansion of the core when the tablet is released from the die cavity during compression (Gunsel and Dusel, 1989). If the material used in the coating formulation does not possess these qualities inherently, then these must be imparted to the formulation via the addition of a binder and plasticiser (Wolff, 1956).

Both hydrophilic and hydrophobic polymers can be used as coating materials although they possess very different properties. The hydrophilic polymers swell when hydrated with water to form a gel layer which slowly erodes away. Since the coating layers are intended to act as barriers it is important that the polymer in the coating does not erode away until most of the drug has been released from the tablet core. The hydrophobic barriers will not dissolve at all and will be eliminated through excretion.

HPMC is an inert hydrophilic polymer that is widely used in matrix tablets and other types of sustained release dosage forms. It is available as a variety of viscosities and is advantageous in that it is possible to directly compress HPMC without previous granulation (Salsa et al., 1997). Conte and Maggi (1996) produced multilayer tablets with HPMC as the barrier layers. They tested two different viscosities of HPMC and demonstrated that high viscosity HPMC with its slow gelling rates is impermeable to drug diffusion for long periods of time. This restricted the area of drug release to the core and resulted in zero-order kinetics.

SCMC is suitable for use as a tablet binder or as a coating agent (Handbook of Pharmaceutical Excipients, 1986). It is also a widely used hydrophilic cellulose ether that demonstrates ease of compression (Devi et al., 1989). It differs from HPMC in that it is anionic which alters the rate of water uptake and therefore the swelling rate of the gel layer. SCMC is used often in combination with the nonionic cellulose polymers to form matrix tablets that demonstrate zero-order release. This combination of polymers is thought to synchronise the swelling and erosion rates of the gel layer, leading to a constant releasing area (Vasquez et al., 1995; Hussein et al., 1994).

Ethylcellulose is an inert hydrophobic polymer, which can be used as a binder and is directly compressible (Goodhart et al., 1984; Katikaneni et al., 1995). Ethylcellulose was used by Danckwerts et al. (1996) as the material for the cup portion of his core-in-cup tablets. It allowed the cup to be firmly recompressed around the core.

Eudragit RS, synthesised from acrylic and methacrylic acid esters, is not freely permeable to water. It is commonly used in the preparation of matrix tablets or as a tablet coat and can be directly compressed (Ribardieve et al., 1996; Kristmundsdottir et al., 1996; Torrado et al., 1996; Fassihi and Ritschel, 1993).

Usually plasticisers are used in film coating where they, reduce brittleness, improve flexibility and increase impact resistance of the polymer. The problem with many plasticisers is that they are not approved for pharmaceutical applications due to concerns with regard to their toxicity (Wu and McGinty., 1999). Wolff (1956) registered a patent for tablet formulations used in compression coating that used gelatin as a plasticiser. He found that a concentration of 1.75% $^{w}/_{w}$ of gelatin imparted satisfactory plasticity to the coating formulations for them to effectively coat the core tablets. Gunsel and Dusel (1989) stated that a plastic material such as gelatin could add softness to a formulation, which can help ensure centration of the core between the coats. In addition, gelatin also acts as a binder according to the Handbook of Pharmaceutical Excipients (1986).

2.1.2. Objective

The major objective of this experiment is to determine which materials are suitable for manufacturing the coating layers of the doughnut-shaped tablet. The coating layers are required to adhere to the core layer during a 15-minute disintegration test. Those coating layers that pass the disintegration test, will then be further subjected to adherence studies in dissolution medium, that run for a period of 300 minutes. This is done to ensure that the coats remain intact during their time of drug release.

Both hydrophilic and hydrophobic polymers will be tested for their suitability as the coating layer. HPMC and SCMC are the hydrophilic polymers tested while ethylcellulose and eudragit RSPM are the hydrophobic polymers used.

2.1.3. Materials and Methods

2.1.3.1. *Materials*

HPMC K4M premium EP and HPMC K15M premium EP were supplied by Colorcon Ltd, U.K. HPMC K4M and K15M respectively have viscosities of 3000 - 5600 and 11250 - 21000 cP, as a 2% $^{w}/_{v}$ solution in water at 20 °C. Both polymers had already been screened through a No. 40 standard sieve. Caffeine (Saarchem, S.A.) and Ibuprofen (Nicholas Piramal Ltd, India) was ground through a 212 μm aperture sieve (Endcotts Test Sieves, Ltd., England). Ethylcellulose was supplied by Riedel de-Haën (Germany); Eudragit RSPM by Röhm-Pharma (Germany); Sodium

Carboxymethylcellulose by Saarchem(South Africa), and were used as supplied. All other reagents used were standard laboratory grade.

2.1.3.2. *Formulations*

The formulation for the tablet core consisted of 10% $^{w}/_{w}$ HPMC K4M mixed with either caffeine (model soluble drug) or ibuprofen (model insoluble drug). Twenty grams of each formulation was prepared. The different formulations used as the tablet coat were HPMC K15M, SCMC, ethylcellulose (EC), and Eudragit RSPM. Each batch of coat formulation was mixed with gelatin at a concentration of 1.75% $^{w}/_{w}$ to act as plasticiser. Ten grams of each combination was prepared. 1% $^{w}/_{w}$ magnesium stearate was added to all formulations as lubricant.

2.1.3.3. *Preparation of Compressed Tablets*

All powders for the tablet core were granulated in an Erweka FGS granulator fitted with a 1.6 μm stainless steel screen. Granules were produced using distilled water as the granulating agent and dried at 60°C for 15 minutes. After drying, the granules were resieved through a 710 μm stainless steel sieve and compressed into cores on a Manesty F3 tabletting press. Flat round punches with a diameter of 11 mm and inner rod with a diameter of 5 mm were used to produce tablet cores with a thickness of 2 mm. The average weights and hardness of the cores are listed in table 2.1.1. The hardness of the tablet coating layers was not measured as the layers were too thin, and they have no impact on the release of drug from the coated doughnut-shaped tablet.

The coating formulations were thoroughly mixed using an Erweka AR 400 Cube Mixer and then directly compressed on a Manesty F3 tabletting press using 11 mm flat punches and an inner rod with a diameter of 5 mm as was used to compress the tablet core (see figure 1.8 for a schematic diagram of the production procedure). The tabletting press was set to produce the tablet coats with a thickness of 1 mm. The weights of the tablet coats differed according to the density of the coat mixture and are also listed in table 2.1.1.

Once the cores and coats were compressed, the core layer was placed between two coating layers and fed into the tabletting press to be compressed into a single three-layer tablet as described in figure 1.9b. The cores and coats were compressed with flat punches with a diameter of 11.5 mm while the diameter of the inner rod was 4.5 mm. The slightly larger punches and die cavity and slightly smaller inner rod ensured that the 11mm core and coats could be easily fed into the tabletting press for recompression. The resulting three-layer tablet thickness was 3 mm.

TABLE 2.1.1

Mean weights of the coating and core layers used in the coated doughnut-shaped tablet

Formulation	Mean weight (mg) ± SD (n=10)	Mean hardness (N) ± SD (n=10)
Core layer		
Caffeine/HPMC K4M	163.17 ± 8.91	18.26 ± 3.63
Ibuprofen/HPMC K4M	155.52 ± 7.83	9.50 ± 4.11
Coat layers		
HPMC/gelatin	64.54 ± 3.25	
SCMC/gelatin	123.40 ± 5.40	
EC/gelatin	89.14 ± 2.79	
RSPM/gelatin	107.22 ± 5.62	

2.1.3.4. *Disintegration Studies*

A Pharmatest Disintegration Tester was used in all studies. The disintegration medium used was distilled water equilibrated at 37°C. Perforated cylindrical plastic disks were placed on top of each tablet to impart a slight abrasive action to the tablets. The apparatus was operated for 15 minutes. Tablets were checked at time intervals of 5 minutes to ascertain if the coating layers remained adhered to the core layer. Nine tablets were tested from each batch. Those coating formulations that passed the disintegration test were studied further to test their adhesiveness over a longer period of time in dissolution fluid.

2.1.3.5 *Adherence Studies*

The B.P. 1999 paddle method was used in all adherence studies with a 6 beaker Caleva model 7ST dissolution tester. A volume of 900 ml of deionised water was used as the test medium, which was equilibrated at 37°C ± 0.5 °C. All experiments were carried out at 50 rpm. At selected time intervals of 30 minutes, the coated doughnut-shaped tablets were checked to ensure that the coating layers remained adhered to the core layer. Three tablets were tested from each of three batches.

2.1.4 **Results and Discussion**

2.1.4.1 *Disintegration Studies*

Table 2.1.2 lists the results of the disintegration tests performed on the coated doughnut-shaped tablets with their different coating materials. The HPMC/gelatin and SCMC/gelatin coats adhered to both the caffeine and ibuprofen tablet cores for the entire test period. The EC/gelatin coats adhered to both the caffeine and ibuprofen tablet cores for part of the time period while the Eudragit RSPM/gelatin coats did not adhere at all to either the caffeine or the ibuprofen tablet core once it come into contact with disintegration liquid.

TABLE 2.1.2.

Disintegration test results of the preliminary coating materials

Formulation	Time (minutes) (n=9)		
	5	10	15
Caffeine			
HPMC/gelatin	+	+	+
SCMC/gelatin	+	+	+
EC/gelatin	+	- (5)	- (7)
RSPM/gelatin	- (4)	- (7)	- (9)
Ibuprofen			
HPMC/gelatin	+	+	+
SCMC/gelatin	+	+	+
EC/gelatin	+	- (7)	- (9)
RSPM/gelatin	- (5)	- (8)	- (9)

+ indicating that the coats remained stuck and – indicating that the coats became unstuck (the number in brackets indicating that number of tablets missing 1 or both of the coating layers)

Based on the disintegration test results it was decided to further investigate HPMC and SCMC as the coating materials. Gunsel and Dusel, (1989) believe that it is

customary to use the same material in the tablet coat as in the core. This is based on a theory that like substances will bond to each other better than unlike substances and explains possibly why HPMC bonded to the core which consisted mainly of HPMC. SCMC contains carboxyl groups which can result in hydrogen bonding between these groups and the hydroxyl groups of the non-ionic cellulose ethers (Laicher and Profitlich, 1995) This hydrogen bonding may explain the cohesiveness of the SCMC layer to the HPMC layer.

2.1.4.2 *Adherence Studies*

Table 2.1.3 lists the results of the adherence studies performed on the coated doughnut-shaped tablets with their different coating materials. The HPMC/gelatin coats adhered to the caffeine cores for the entire test time period of 300 minutes. The ibuprofen cores were more problematic. By the time of 90 minutes, one coating layer had detached from the core for 4 of the ibuprofen tablets. These coating layers did not disintegrate but merely failed to fully adhere to the ibuprofen core. The remaining layer adhered for the entire testing time.

The SCMC/gelatin coats adhered to the caffeine cores for a period of 180 minutes after which they detached and dissolved. In the case of ibuprofen one coating layer from 2 tablets had detached by 90 minutes but again all had detached and dissolved by 180 minutes.

TABLE 2.1.3.

Adherence test results of the coated doughnut-shaped tablet

Time (mins)	*Caffeine*		*Ibuprofen*	
	HPMC/gelatin	SCMC/gelatin	HPMC/gelatin	SCMC/gelatin
30	+	+	+	+
60	+	+	+	+
90	+	+	- (4)	- (2)
120	+	+	-	-
150	+	+	-	-
180	+	- (9)	-	- (9)
240	+	-	-	-
300	+	-	-	-

+ indicating that the coats remained stuck and – indicating that the coats became unstuck (the number in brackets indicating that number of tablets missing 1 or both of the coating layers)

The HPMC/gelatin coating is thus more suitable than the SCMC/gelatin coating which dissolved too quickly. The HPMC/gelatin coating will be further investigated in the next chapter to optimise its formulation.

2.2 THE DEVELOPMENT OF COATING LAYERS THAT ADHERE TO THE CORE AND ALLOW FOR AUTOMATED TABLET PRODUCTION

2.2.1 **Introduction**

The previous experiment showed that of the materials tested, HPMC with gelatin was the most suitable coating material. The experiments with ibuprofen as the model drug in the tablet core, however demonstrated a problem with the coating layers not sticking to the core for a long enough period of time. This is problematic since this tablet design must be applicable to a wide variety of drugs. This experiment seeks to optimise the coating layer formulation so that it both adheres to the tablet core and allows for automated production. Moisture content is important with regard to adherence of the coating layers to the core; however, excess moisture can lead to manufacturing problems of pitting, sticking, and filming. Compressibility and powder flow are key variables for ensuring automated production especially when the tablet die cavity has the unusual shape of a doughnut.

2.2.1.1 *Bonding of Layer tablets and Moisture Content*

A major problem of layer tablet production is the lack of proper bonding of the layers. If the coating layers fail to adhere to the core of the doughnut-shaped tablet, then the release of drug is no longer restricted to the lateral sides of the tablet and the inner hole which will affect the zero-order release rate. Optimal moisture content of the formulations can reduce the possibility of this occurring as the moisture content improves the bonding between layers. Increased moisture content can be achieved by

increasing the amount of water used in wet granulation, changing the drying conditions (reducing either the temperature or drying time) or adding a material that retains moisture (Gunsel and Dusel, 1989).

Reliable methods of determining the moisture content of powder or granulation formulations are therefore essential (Hui and Miller, 1996). Karl Fischer (1989) proposed a method for the determination of water. He developed a reagent prepared by the action of sulphur dioxide on a solution of iodine in a mixture of anhydrous pyridine and anhydrous methanol. Water reacts with this reagent with one molecule of iodine disappearing for each molecule of water present. The end of the reaction is determined electrometrically, as current will flow between two electrodes immersed in the reaction mixture as long as iodine is present but will decrease to zero when there are no traces of iodine left.

This method was used by Stubberud et al. (1995, 1996) in a work studying moisture sorption/desorption techniques. The aim of this work was to develop an improved technique compared to the widely used desiccation method by using a climatic test chamber. The total amount of water present in the different samples was determined using the Karl Fisher titrations. The moisture levels of several materials were tested, namely anhydrous lactose, monohydrous lactose, microcrystalline cellulose (MCC), sodium starch glycolate, maltodextrin, polyvinyl pyrrolidine (PVP) and naproxen. Further work was then done to determine the relationship between moisture sorption and compactibility properties of MCC and mixtures of MCC and PVP. Karl Fisher titrations were again used to measure the total amount of water in the samples.

2.2.1.2 *Compressibility*

Information regarding compressibility and powder flow is important in tablet manufacture (Wadke et al., 1989). Hardness-compression force profiles (Higuchi, 1953; Fell, 1968) are one of the simplest and most useful methods to characterise compressibility. There is a linear relationship between tablet hardness and the natural logarithm of compression force and a plot of tablet hardness versus the natural logarithm of compression force results in the following profile over the linear portion of the plot.

$$Fc = m \ln P + I \qquad \text{-equation 2.2.1.}$$

where, Fc = tablet hardness.

P = applied pressure as a measure of compression force.

m = slope of the linear portion of the plot.

I = intercept on the y-axis.

Both the m and I constants measure indirectly the compressibility of the powder fix. It is understood that the higher the value of the slope of the graph (m), then the better the ability the powder mix has to be compressed into a compact mass. The constant I is a measure of the inherent compressibility of a powder mix.

2.2.1.3 *Powder Flow*

To measure the flow of a powder or granule mix, the angle of repose method is used as this is the simplest method. If the size of the powder or granulation particles is larger than 150 μm, then this method is not applicable (Gordon at al., 1990). This method is based on the theory that a static heap of powder under the influence of gravity will form a conical mound but this is limited by the fact that the angle to the horizontal cannot exceed a certain value, which is known as the angle of repose. The angle of repose is a measure of the ability of a particle to overcome sliding when the angle of inclination is large enough to overcome frictional forces (Cartensen, 1977; Jones, 1966). Angle of repose is calculated from the following equation:

$$\emptyset = \arctan H/R \qquad \text{- equation 2.2.2}$$

where, Ø = angle of repose

H = height of powder heap

R = radius of powder heap

2.2.2. **Objective**

The objective of this study is threefold. The first objective is to ensure that the tablet coating layers adhere to the tablet core during release studies for a period of at least 5 hours. In order to achieve the first objective, two variables will be examined:

(i) The effect of three different concentrations of plasticiser (10%, 20% and 30%) as the additional plasticity may improve coat and core adhesiveness.

(ii) The effect of producing the tablet coating layers with either wet granulation or direct compression techniques. These different techniques influence the moisture content of the powder or granule formulation, which may affect tablet cohesiveness.

The second objective is to determine if the method of manufacture can be automated by checking for suitable powder flow and compressibility properties. Since the tablet punches and die have an unusual shape, these properties are essential to ensure proper tablet manufacture.

The third objective is check if the coating layers have any effect on the release of drug from the tablet core. This is achieved by performing release studies.

2.2.3 **Materials and Methods**

2.2.3.1. *Materials*

HPMC K4M premium EP and HPMC K15M premium EP were supplied by Colorcon Ltd. HPMC K4M and K15M have viscosities of 3000 - 5600 and 11250 - 21000 cP respectively, as a 2% solution in water at 20 °C. Both polymers had already been screened through a No. 40 standard sieve. Caffeine (Saarchem, S.A.) and ibuprofen (Nicholas Piramal Ltd, India) were passed through a 212 μm aperture sieve (Endcotts Test Sieves, Ltd., England). Hydranal® composite 5 was produced by

Riedel-de-Haën (Germany). The methanol was supplied by Sigma Aldrich, S.A. All other reagents used were standard laboratory grade.

2.2.3.2 *Statistical Analysis*

Analysis of variance was used to test the different formulas for a significant difference and was performed using STATGRAPHICS v 5 (Statistical Graphics Corporation, U.S.A.). This was used to check for significant differences in the powder flow , compressibility and moisture content of the tablets. In the release studies, the release rates of the coated doughnut-shaped tablets were checked for a significant difference between the tablets. The release rates were calculated from the linear portion of the slope of concentration versus time.

2.2.3.3 *Formulations*

Flat doughnut-shaped tablet cores were produced consisting of 10%$^{w}/_{w}$ HPMC K4M mixed with either caffeine (model soluble drug) or ibuprofen (model insoluble drug) as described in section 2.1.3.2. 25 g of each formulation was produced. The weights of the core tablets are listed in table 2.2.1.

TABLE 2.2.1

Mean weights of the coating and core layers used in the coated doughnut- shaped tablet

Formulation	Mean weight (mg) ± SD (n= 20)	Hardness (N) ± SD (n= 20)
Core		
10% $^{w}/_{w}$ HPMC K4M/Caffeine	355.16 ± 10.72	21.06 ± 4.69
10% $^{w}/_{w}$ HPMC K4M/Ibuprofen	331.36 ± 11.88	7.84 ± 4.73
Coats		
Direct compression		
10% $^{w}/_{w}$ Gelatin/HPMC K15M	97.84 ± 4.64	
20% $^{w}/_{w}$ Gelatin/HPMC K15M	104.50 ± 3.71	
30% $^{w}/_{w}$ Gelatin/HPMC K15M	111.75 ± 3.50	
Wet granulation		
10% $^{w}/_{w}$ Gelatin/HPMC K15M	99.91± 2.52	
20% $^{w}/_{w}$ Gelatin/HPMC K15M	97.81± 3.62	
30% $^{w}/_{w}$ Gelatin/HPMC K15M	94.34 ± 2.58	

Tablet coats consisting of 10% $^{w}/_{w}$, 20% $^{w}/_{w}$ and 30% $^{w}/_{w}$ of gelatin in HPMC K15M were tested for their suitability. Three batches were made of each type of combination listed in table 2.2.1 according to the different production methods of either wet granulation or direct compression. Twenty grams of each granule or powder batch was produced. The weights of the different type of tablet coats differ slightly

according to the density of the core mixture. The weights of the different coats are listed in table 2.2.1. The weights and hardness of the coated doughnut-shaped tablets are listed in table 2.2.2. Magnesium stearate was added to all coating and core formulations at a concentration of $1\%^{w}/_{w}$ as a lubricant.

TABLE 2.2.2.

Mean weights of the coated doughnut-shaped tablets with both caffeine and ibuprofen cores

% Gelatin in coat	Method of Granulation	Mean weight (mg) ± SD (n= 10)	Hardness (N) ± SD (n=10)
Caffeine			
10	Wet	551.36 ± 13.04	79.01 ± 7.45
20	Wet	552.09 ± 8.04	78.59 ± 6.65
30	Wet	542.83 ± 12.54	80.41 ± 8.56
10	Dry	557.66 ± 13.04	78.91 ± 6.78
20	Dry	565.18 ± 16.95	79.70 ± 6.03
30	Dry	580.42 ± 19.59	78.44 ± 7.20
Ibuprofen			
10	Wet	521.98 ± 12.57	18.41 ± 4.56
20	Wet	513.88 ± 12.86	17.82 ± 5.22
30	Wet	510.19 ± 11.05	17.09 ± 6.32
10	Dry	509.56 ± 12.15	18.04 ± 5.51
20	Dry	522.38 ± 8.35	18.29 ± 4.78
30	Dry	543.92 ± 15.24	17.36 ± 5.96

2.2.3.4. *Preparation of Compressed Tablets*

All powders for the tablet cores were granulated using an Erweka FGS granulator fitted with a 1.6 mm stainless steel sieve. Powders for the tablet core were granulated using distilled water as the granulating agent. The granules were compressed into tablet cores using a Manesty F3 tabletting press fitted with flat round doughnut shaped punches with a diameter of 11 mm and an inner rod with a diameter of 5 mm. The press was set to compress cores of a thickness of 4 mm.

The formulations for compression of the tablet coats were produced by means of wet granulation or direct compression. For each method, 10% $^{w}/_{w}$; 20% $^{w}/_{w}$ and 30% $^{w}/_{w}$ gelatin in HPMC K15M tablets were produced. For wet granulation, a 20%$^{w}/_{v}$ solution of gelatin was used to add the required amount of gelatin to the HPMC K15M. 95%$^{v}/_{v}$ alcohol was used if any additional granulating agent was needed. Granules were produced using an Erweka FGS granulator fitted with a 1.60 μm stainless steel sieve and then compressed. For direct compression, the HPMC K15M and gelatin were mixed in an Erweka AR 400 rotary cube mixer for 5 minutes, allowed to stand for 30 minutes and then directly compressed into tablet coats. For both wet granulation and direct compression methods, the tablets were compressed on a Manesty F3 tabletting press as described in section 2.1.3.3. The press was set to produce the tablet coats with a thickness of 1.5 mm. In the previous experiment, it was found that a coat thickness of 1 mm was difficult to eject from the tablet die due to its thinness. The thickness of the core layer was also increased from 3 mm to 4mm. These thicker layers would not only aid the ease of manufacture but also allow for increased compressibility when recompressing the three layers together.

Once the tablet cores and coats were compressed, they were recompressed into a three-layer coated doughnut-shaped tablet as described in section 2.1.3.3. The coated doughnut-shaped tablets were compressed to a thickness of 5 mm.

2.2.3.5 *Measurement of Powder Flow*

The flow of the different powder or granule blends was determined using angle of repose measurements. These measurements were calculated by lightly packing 3g of each formula into a hollow glass cylinder with a length of 9.5 cm and a diameter of 15 mm). This cylinder was connected to a retort stand so that the lower end of the cylinder was at a height of 20 cm from the desk. The lower end of the cylinder was blocked with a piece of paper and when this paper was removed, the formula was allowed to heap onto graph paper placed on the desk. The radius and height of the heap were measured and the angle of repose was calculated from equation 2.2.2. In order to measure the height of the powder heap without disturbing it, the distance from the lower end of the cylinder to the top of the powder heap was measured and this value was subtracted from the distance of the lower cylinder end to the desk. Three measurements were performed for each batch.

2.2.3.6. *Measurement of Compressibility*

A mass of 700 mg of either granules or powder was weighed and then compressed to either 0.5, 0.75 or 1.0 tonnes in a Beckman hydraulic press (Beckman Instruments, Inc., Fullerton, U.S.A.). Flat round 13 mm diameter disk-shaped tablets were produced after holding for 30 seconds at each compression force. The hardness

of each tablet was then measured using a Pharma Test PTB 311 (Pharma Test, Hainberg, Germany) hardness tester. The slope of the graph of hardness versus natural logarithm of compressed force was calculated using linear regression. This slope was used as the estimation of the compressibility of the formulations tested.

2.2.3.7 *Measurement of Moisture*

All moisture studies were done using the 701 KF Titrino (Metrohm) and the Karl Fischer method for the determination of water. The solutions used were Hydranal® composite 5 and methanol. Hydranal® composite 5 is a one component reagent for volumetric Karl Fischer titration and contains imidazole, sulphur dioxide and iodine. The solubility of the substances in methanol was found to be sufficient to allow the determinations. For each batch, three measurements were determined.

2.2.3.8. *Release Studies*

The B.P. 1999 paddle method was used in all release studies with a 6 beaker Caleva model 7ST dissolution tester. A volume of 900 ml of deionised water was used as the release medium, which was equilibrated at 37°C ± 0.5 °C. All experiments were carried out at 50 rpm. At selected time intervals, 2 ml samples were withdrawn and analysed using a Beckman DU 650 spectrophotometer. For the release of caffeine, samples were diluted with deionised water, mixed on a vortex mixer and then analysed spectrophotometrically at a wavelength of 242 nm. For the release of ibuprofen, 2 ml of methanol was added to the sample, mixed with a vortex mixer and analysed at a wavelength of 216 nm. Three tablets were tested from each batch. All other excipients

showed no absorbance at the wavelengths tested. For both caffeine and ibuprofen, linearity was established in the range of 6.25 – 200 μg/ml using standard curves. The UV absorbance of a series of dilutions of both caffeine and ibuprofen solutions were obtained and the graphs of absorbance versus concentration were plotted to obtain the standard curves.

2.2.4 **Results and Discussion**

2.2.4.1 *Powder Flow and Compressibility Studies*

Table 2.2.3 lists the results of the formulation studies performed upon the different powder or granule formulations. The angle of repose decreases as the concentration of gelatin in the formula increases from 10% $^{w}/_{w}$ to 20% $^{w}/_{w}$ to 30% $^{w}/_{w}$ in those granules produced by wet granulation. The direct compression formulas show a decrease in the angle of repose as the formula changes from 10% $^{w}/_{w}$ to 20% $^{w}/_{w}$ but then increases when the formula is changed to 30% $^{w}/_{w}$. Generally the lower the angle of repose, the better the powder flow although usually all angles below 25 degrees indicate excellent powder flow. The best powder flow is exhibited by 30% $^{w}/_{w}$ gelatin produced using wet granulation and the worst by 10% $^{w}/_{w}$ gelatin produced using direct compression.

TABLE 2.2.3.

Angle of repose, compressibility and moisture values of the different granule or powder coating formulations

% $^{w}/_{w}$ Gelatin	Granulation method	Angle of repose (n=9)	Compressibility factor (*m*) (n=3)	Moisture levels (% $^{w}/_{w}$) (n=9)
10	Wet	22.01 ± 5.64#	121.91 ± 2.36#	9.12 ± 1.25
20	Wet	20.16 ± 3.60*	132.64 ± 3.60#	11.00 ± 1.41 *
30	Wet	17.08 ± 1.91	88.54 ± 11.52	11.35 ± 0.42 *
10	Dry	20.46 ± 2.30#*	164.39 ± 7.58	5.99 ± 1.22 **
20	Dry	19.17 ± 4.54*	124.51 ± 1.13#	6.19 ± 0.37 **
30	Dry	21.69 ± 4.06#	119.2 ± 14.96#	5.96 ± 0.38 **

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

With regard to the compressibility of the powder or granule blends, all demonstrate relatively good compression properties. The plots of hardness versus the natural logarithm of pressure, from which the slopes (*m*) are indicative of compressibility, are shown in figure 2.2.1 a and b. When the granules are prepared by wet granulation, there is a slight increase in compressibility from 121.91 to 132.64 as the concentration of gelatin is increased from 10% $^{w}/_{w}$ to 20% $^{w}/_{w}$, although this increase is not statistically significant (p=0.0019). The compressibility drops when the concentration is further increased to 30% gelatin. When the tablets are directly

compressed, there is a drop in the compressibility from 164.39 to 124.51 as the concentration increases from 10% $^{w}/_{w}$ to 20% $^{w}/_{w}$ gelatin. There is again a small decrease in compressibility (to 119.2) as the concentration further increases to 30% $^{w}/_{w}$ gelatin. This small decrease is not statistically significant (p=0.0019). Both the compressibility values of the formulas containing10% $^{w}/_{w}$ gelatin and 30% $^{w}/_{w}$ gelatin produced using direct compression are higher than the corresponding 10% $^{w}/_{w}$ and 30% $^{w}/_{w}$ gelatin produced using wet granulation. Overall the powder containing10 % $^{w}/_{w}$ gelatin produced by direct compression shows the greatest compressibility while the granules containing 30% $^{w}/_{w}$ gelatin produced by wet granulation shows the least. It was generally thought that wet granulation formulas were superior to direct compression formulations with regard to compressibility, although this does rely on the materials used (Shangraw, 1989). A study by Katdare (1987) comparing the different techniques when formulating norfloxacin, found that direct compression produced tablets that were more compressible.

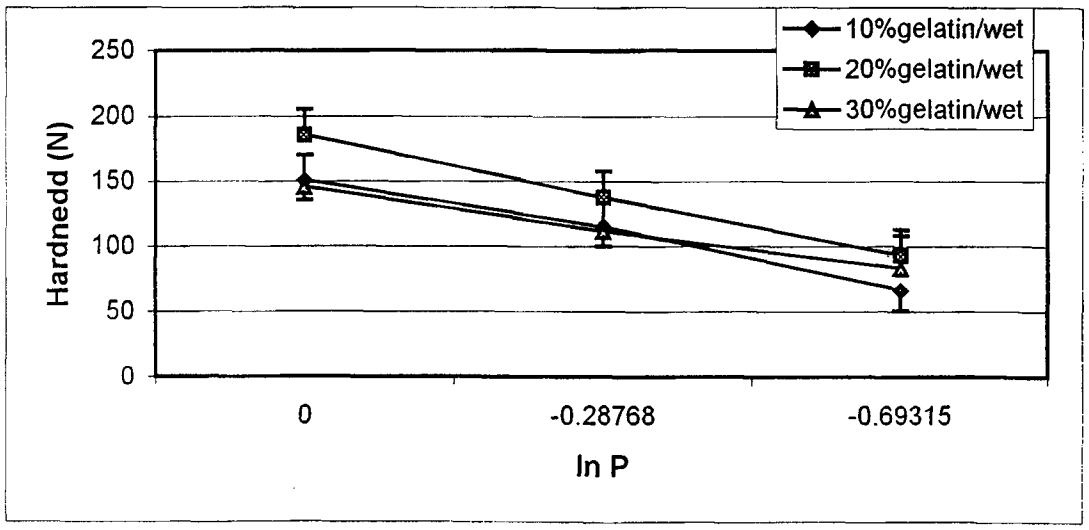


Fig 2.2.1 a Graph of hardness versus ln P for the different granulations (n=3)

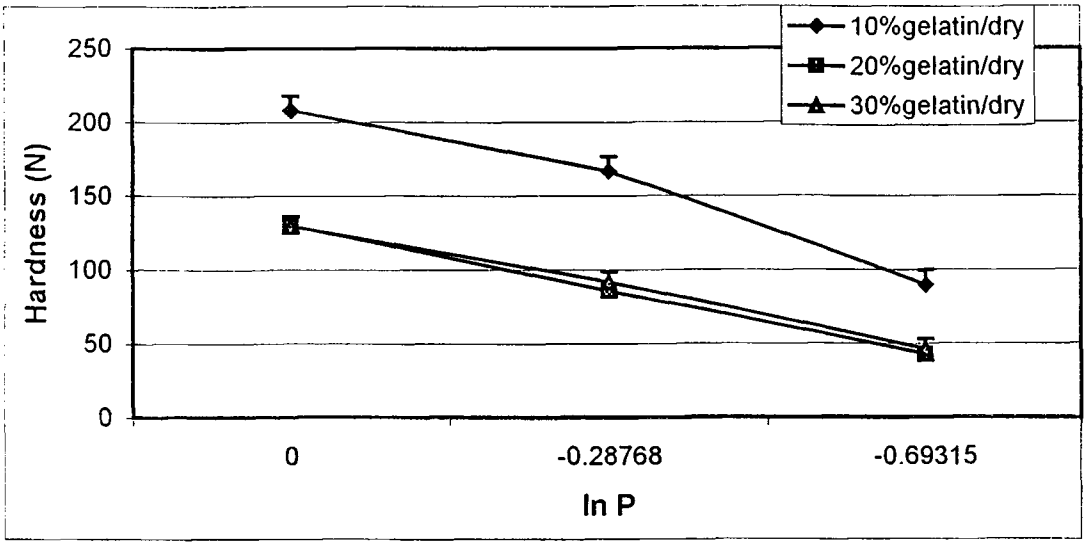


Fig 2.2.1 b Graph of hardness versus ln P for the different powders (n=3)

2.2.4.2 *Moisture Content*

The moisture level results are shown in table 2.2.3. There is a significant difference ($p \leq 0.001$) between the moisture values of the formulas produced using wet granulation and direct compression. The moisture levels of the wet granulation group (9.12; 11.00; 11.35) are much higher than those of the direct compression group (5.99; 6.19; 5.96). As the concentration of gelatin increases from 10% $^{w}/_{w}$ to 20% $^{w}/_{w}$ in the wet granulation group, the moisture levels increase from 9.12 to 11.00. However, there is no statistical difference ($p \leq 0.001$) in moisture content from 20% $^{w}/_{w}$ to 30% $^{w}/_{w}$. With the direct compression group, there is no statistical difference ($p \leq 0.001$) between the three different concentrations of gelatin.

High levels of moisture can lead to problems such as sticking, pitting and filming during tablet production (Bandelin, 1989). This is problematic for formulations intended for mass production. Based on this fact, it would suggest that the direct compression formulations are more suitable.

2.2.4.3 *Release Studies*

Table 2.2.4 lists the release rates of the different coated doughnuts for both caffeine and ibuprofen. These were calculated from the slopes of the plot of concentration versus time using linear regression. Only the linear portion of the graph was used to calculate the slope which was from a time of 90 to 300 minutes. For both caffeine and ibuprofen, there is no statistical difference in the release rates from the coated doughnut-shaped tablets regardless of the different coating layers. The lack of statistical difference in the release rates of the coated doughnut-shaped tablets indicates that the coating layers do not affect drug release and are therefore largely impermeable to either the soluble or insoluble drug.

TABLE 2.2.4

Release rates of the coated doughnut-shaped tablet.

$\%\ ^{w}/_{w}$ Gelatin	Granulation method	Release rate (ug/min) ± SD (n=9)
Caffeine		
10	Wet	0.3119 ± 0.0017 #
20	Wet	0.3397 ± 0.0045 #
30	Wet	0.3535 ± 0.0029 #
10	Dry	0.3510 ± 0.0049 #
20	Dry	0.3562 ± 0.0060 #
30	Dry	0.4141 ± 0.0080 #
Ibuprofen		
10	Wet	0.0144 ± 0.0003*
20	Wet	0.0172 ± 0.0007*
30	Wet	0.0180 ± 0.0018*
10	Dry	0.0120± 0.0012*
20	Dry	0.0087 ± 0.0009*
30	Dry	0.0084 ± 0.0012*

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

Figures 2.2.2 a – e are plots of release rate versus time of caffeine from the coated doughnut-shaped tablets. Figures 2.2.2 a and b demonstrate the effect of altering the concentration of gelatin in the tablet coat, while keeping the method of manufacture constant.

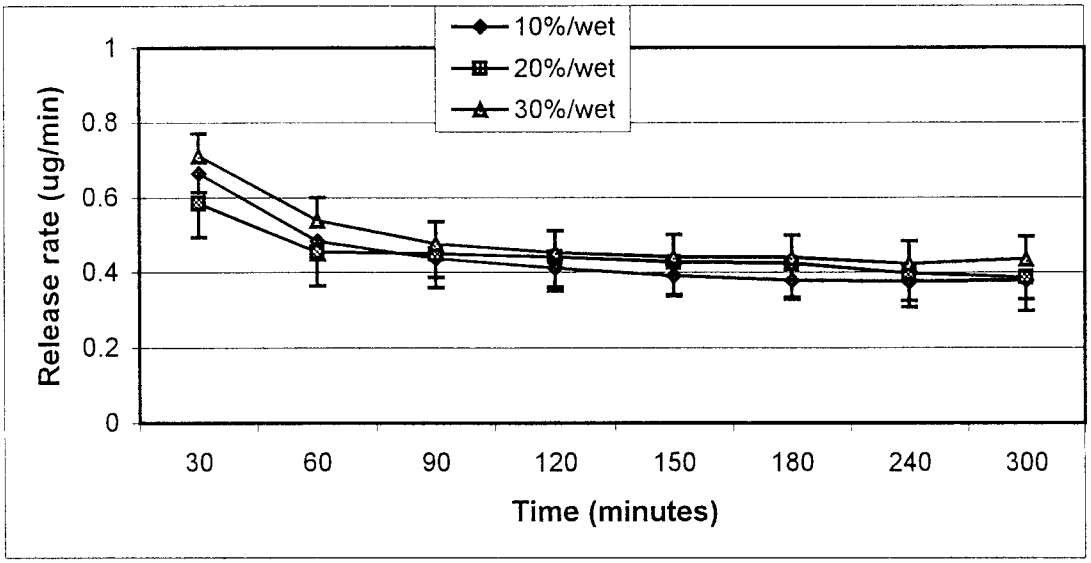


Fig. 2.2.2 a Graph of the average release rates of caffeine from coated doughnut-shaped tablets produced using a wet granulation technique (n=3).

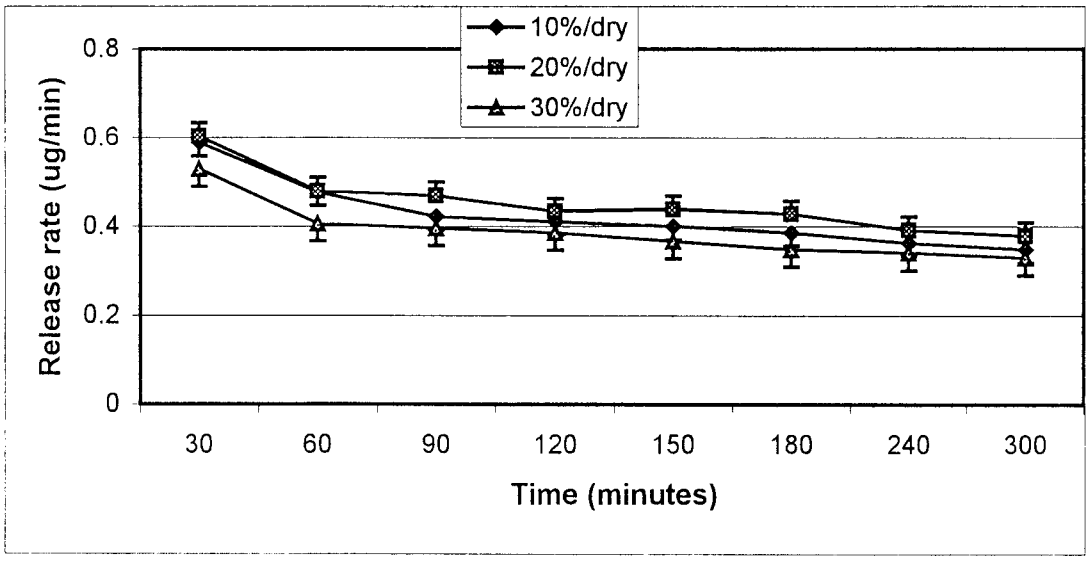


Fig. 2.2.2 b Graph of the average release rates of caffeine from coated doughnut-shaped tablets produced using a direct compression technique (n=3).

Figures 2.2.2 c – e show the effect of the method of manufacture of the coating layer on the release rate of caffeine from the core layer.

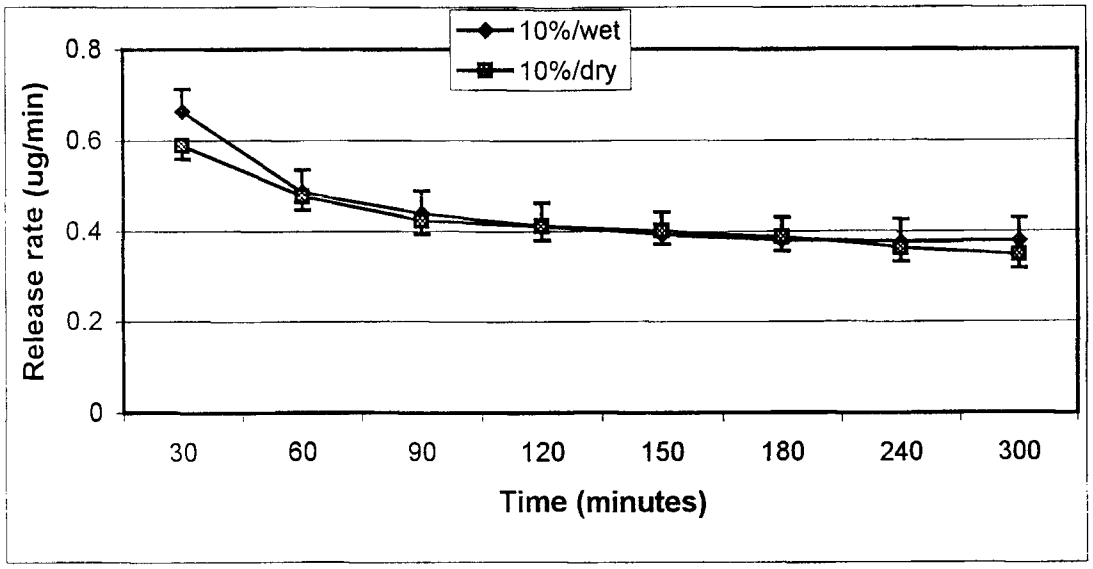


Fig. 2.2.2 c Graph of the average release rates of caffeine from coated doughnut-shaped tablets containing 10% $^{w}/_{w}$ gelatin (n=3).

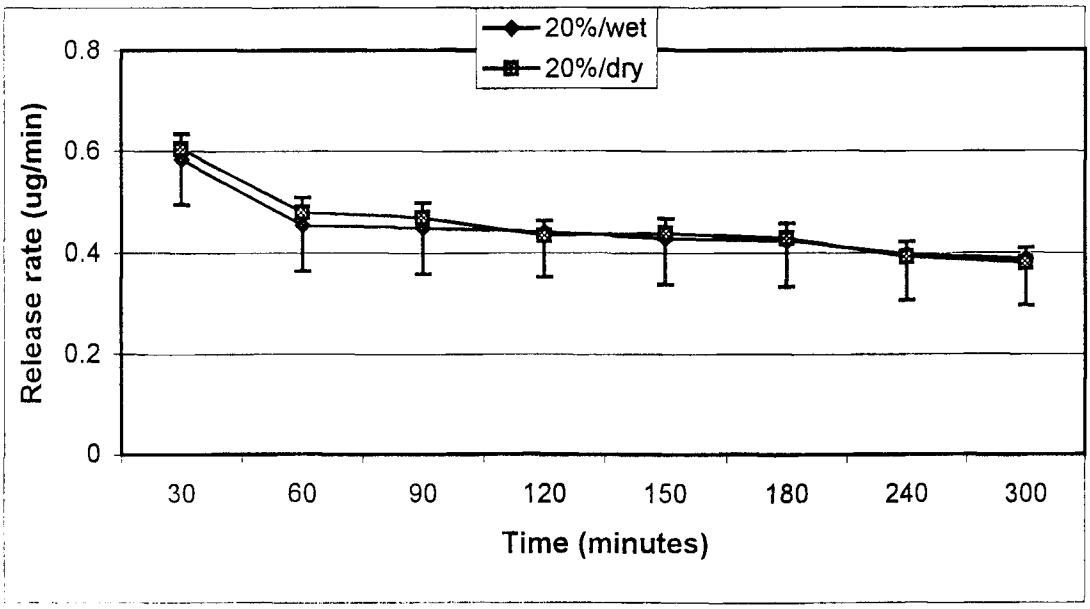


Fig. 2.2.2 d Graph of the average release rates of caffeine from coated doughnut-shaped tablets containing 20% $^{w}/_{w}$ gelatin (n=3).

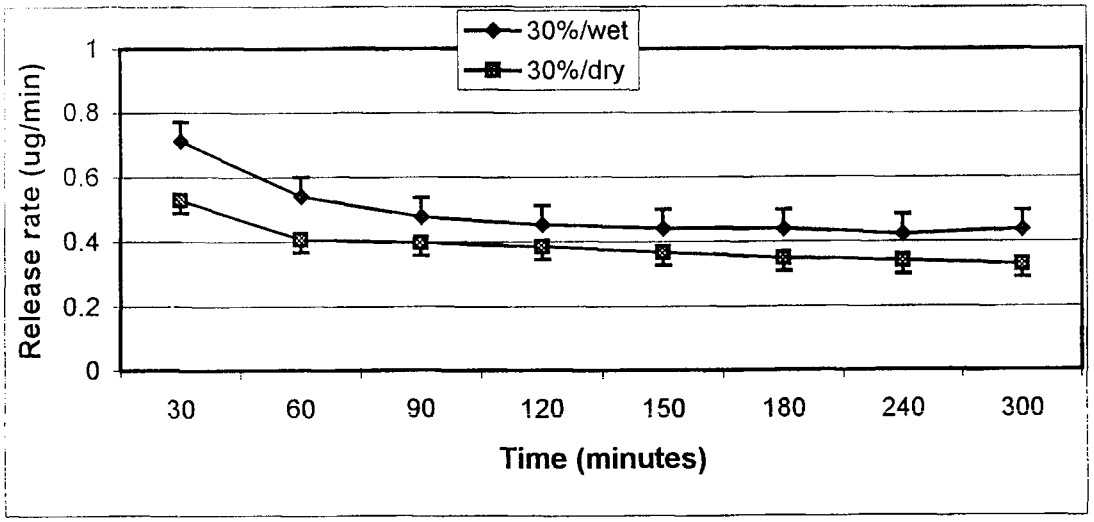


Fig. 2.2.2 e Graph of the average release rates of caffeine from coated doughnut-shaped tablets containing 30% $^{w}/_{w}$ gelatin (n=3).

Figures 2.2.2 a and b all show release profiles that follow a similar release rate. There is a "burst effect" following the initial release of caffeine from the core, which then settles into a zero-order release pattern. The burst effect is slightly greater with tablets produced by wet granulation than those produced by direct compression.

When the method of manufacture differs and the same concentration of gelatin is compared, the release rate of caffeine is very similar in both methods until the concentration reaches 30% $^{w}/_{w}$. Figure 2.2.2 c shows only a slight difference in the burst effect with 10% $^{w}/_{w}$ gelatin/wet granulation having the slightly higher burst effect. There is almost no difference between the release rate of 20% $^{w}/_{w}$ gelatin/wet granulation and 20% $^{w}/_{w}$ gelatin/direct compression as shown in figure 2.2.2 d. The release rates of 30% $^{w}/_{w}$ gelatin/wet granulation and 30% $^{w}/_{w}$ gelatin/direct compression follow the same pattern but the release rate of 30% $^{w}/_{w}$ gelatin/wet granulation is higher although not significantly different.

Figures 2.2.3 a – e are plots of release rate versus time of ibuprofen from the coated doughnut-shaped tablets. Figures 2.2.3 a and b demonstrate the effect of altering the concentration of gelatin in the tablet coat, while keeping the method of manufacture constant.

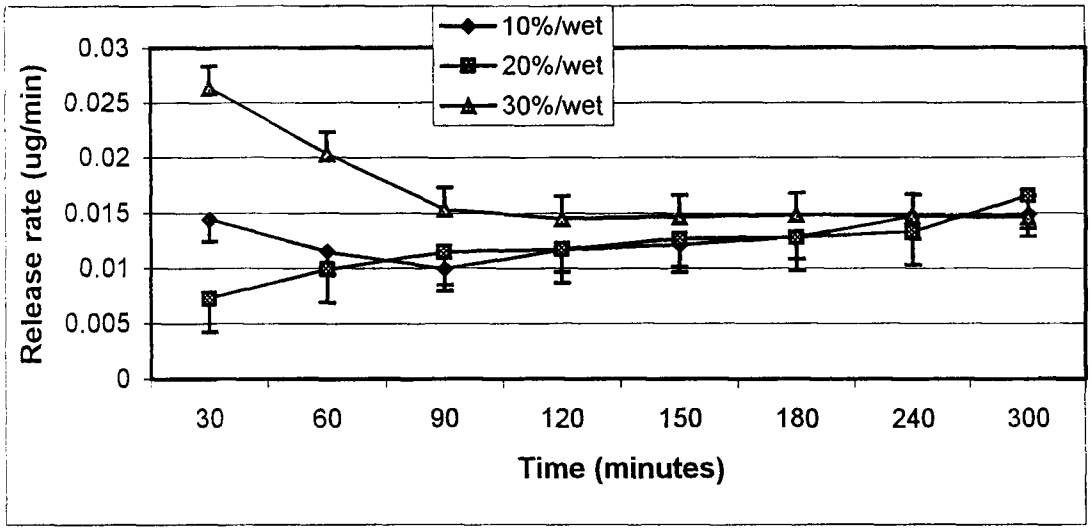


Fig. 2.2.3 a Graph of the average release rates of ibuprofen from coated doughnut-shaped tablets produced using a wet granulation technique (n=3).

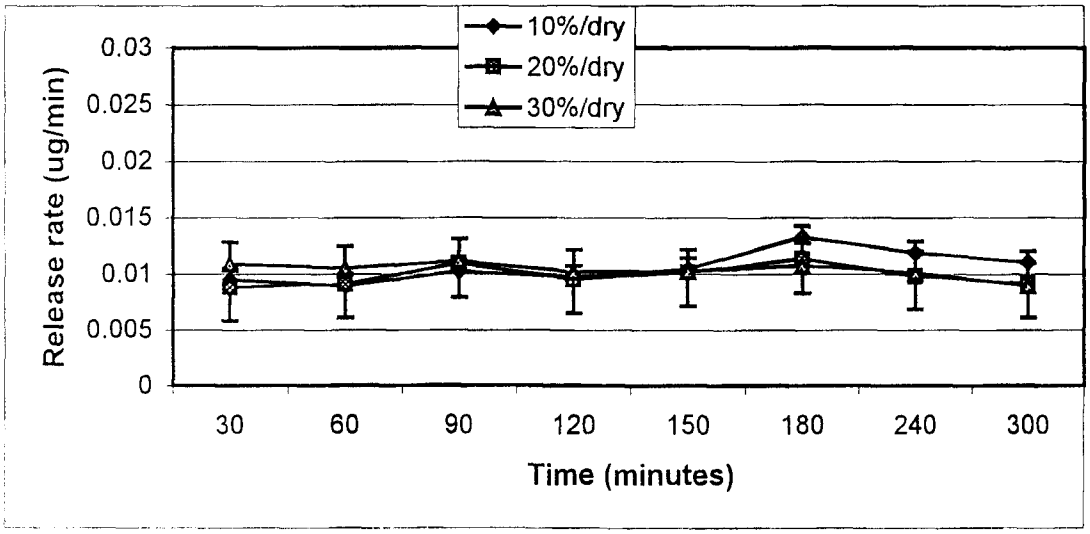


Fig. 2.2.3 b Graph of the average release rates of ibuprofen from coated doughnut-shaped tablets produced using a direct compression technique (n=3).

Figures 2.2.3 c – e show the effect of the method of manufacture of the coating layers on the release rate of ibuprofen core layer.

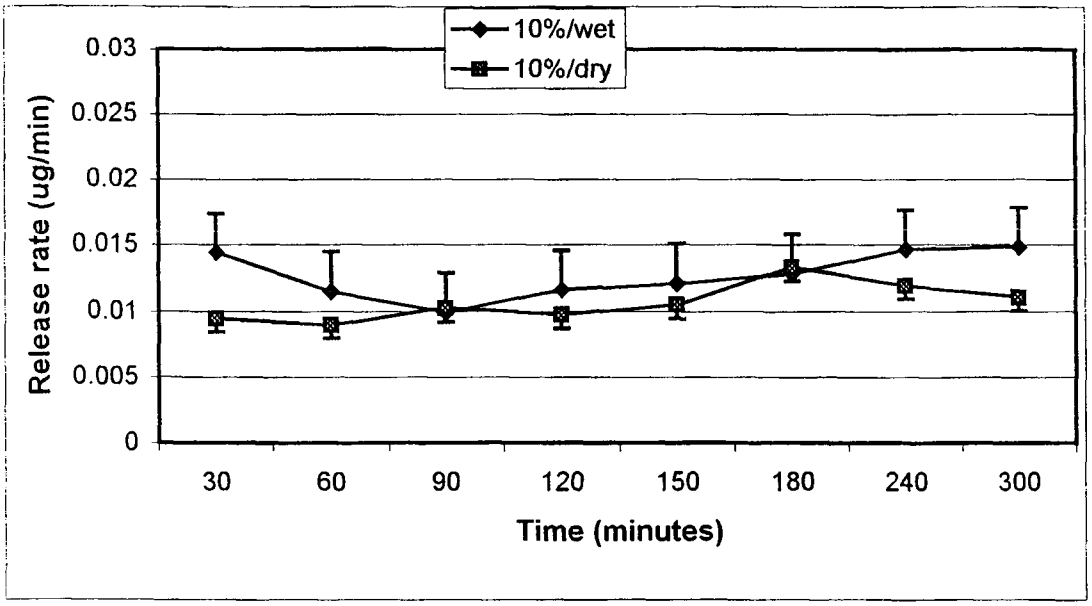


Fig. 2.2.3 c Graph of the average release rates of ibuprofen from coated doughnut-shaped tablets containing 10% $^{w}/_{w}$ gelatin (n=3).

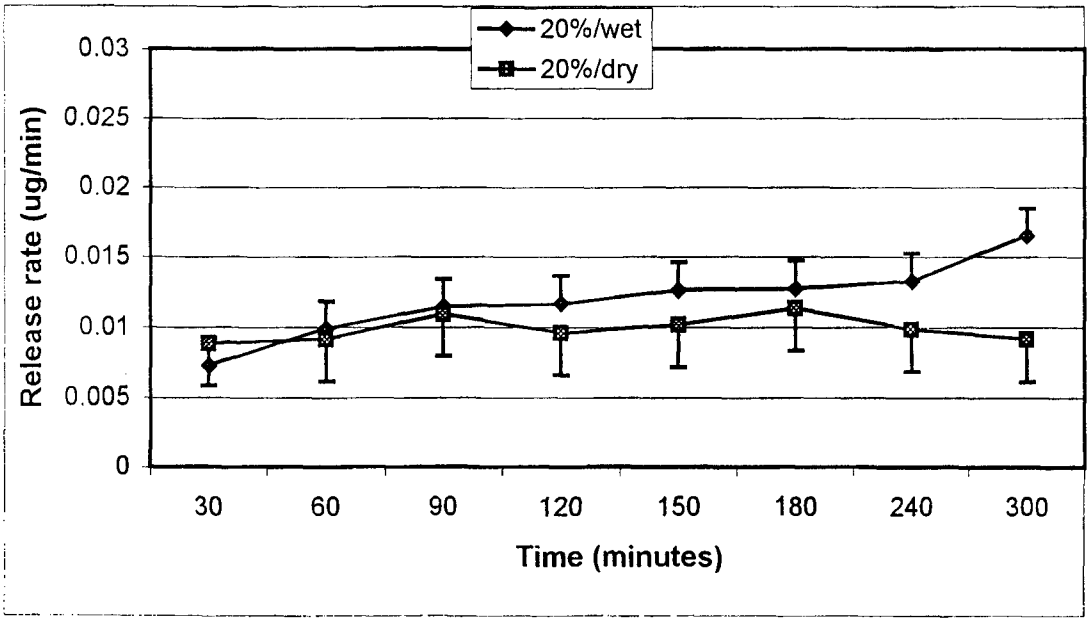


Fig. 2.2.3 d Graph of the average release rates of ibuprofen from coated doughnut-shaped tablets containing 20% $^{w}/_{w}$ gelatin (n=3).

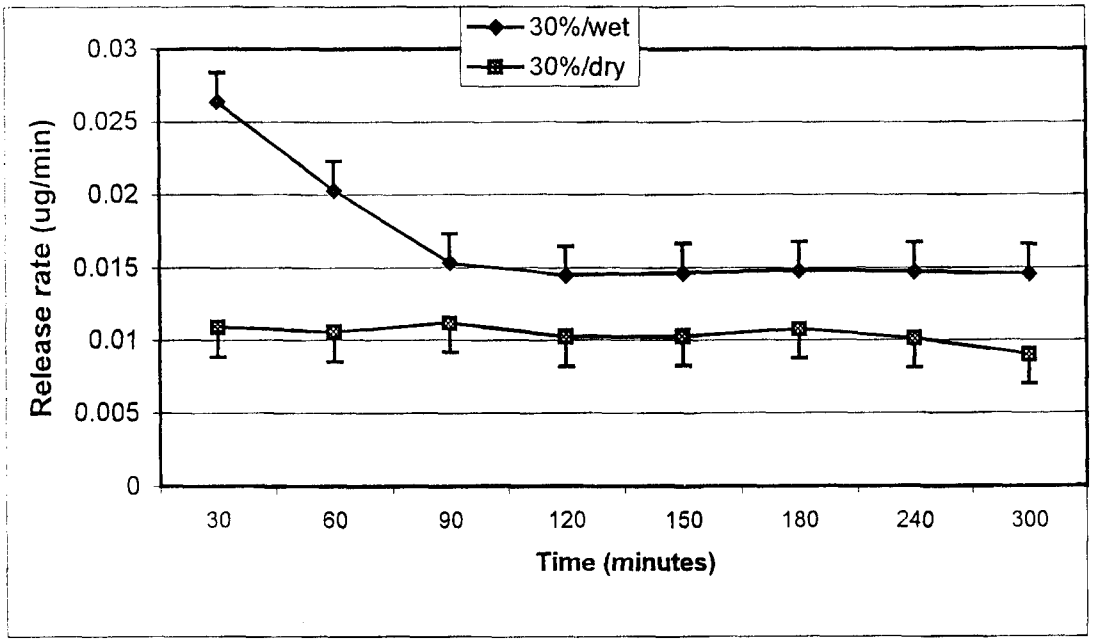


Fig. 2.2.3 e Graph of the average release rates of ibuprofen from coated doughnut-shaped tablets containing 30% $^{w}/_{w}$ gelatin (n=3).

Although the correlation coefficients indicate that there is no significant difference resulting from using a different concentration of gelatin as well as method of production, it is clear from figures 2.2.3 a – e that the release rates from the insoluble drug ibuprofen are not as similar as the release rates from the soluble drug caffeine. With regard to the release rate of ibuprofen, figures 2.2.3 a and b show that again the tablets produced using the wet granulation technique show more of a burst effect than those produced using a direct compression technique.

The coating layers adhered to both the caffeine and ibuprofen cores for the entire 5 hours of release that was studied. This adhesion to the core occurred regardless of changes in either the concentration of gelatin in the coating layer or its method of production.

Since the release rate of caffeine and ibuprofen is not significantly altered by the changes in the coat formulation, it is possible to choose the most suitable coat based upon its preformulation variables (angle of repose and compressibility) and its moisture content. According to the angle of repose results, the formula 30% $^{w}/_{w}$ gelatin produced by wet granulation indicated the best flow. The homogenous group of 20% $^{w}/_{w}$ gelatin/wet granulation, 10% $^{w}/_{w}$ gelatin/direct compression, and 20% $^{w}/_{w}$ gelatin/direct compression indicates the next best flow. The compressibility (*m*) of 10% $^{w}/_{w}$ gelatin/direct compression is significantly different from both 20% $^{w}/_{w}$ gelatin/wet granulation and 20% $^{w}/_{w}$ gelatin/direct compression, thus allowing 10% $^{w}/_{w}$ gelatin/direct compression to be distinguished from this group. 10% $^{w}/_{w}$ gelatin/direct compression is the most compressible and 30% $^{w}/_{w}$ gelatin/wet granulation is the least compressible of the group. The moisture levels of 30% $^{w}/_{w}$ gelatin/wet granulation are also too high for automated production. Direct compression is the preferred method of manufacture as it is faster, has fewer steps in manufacture and avoids the costly process of drying (Peck et al., 1989).

It is thus clear that a formula of HPMC with 10% $^{w}/_{w}$ of gelatin using a direct compression technique is the most suitable coat for the three-layer doughnut-shaped tablet. It is this formulation which will be used to produce the tablet coating layers in all subsequent experiments

2.3 EFFECT OF HOLE SIZE AND CONCENTRATION OF POLYMER ON THE RELEASE OF DRUG FROM THE COATED DOUGHNUT-SHAPED TABLET

2.3.1 Introduction

The effect of hole size on the release of drug from the doughnut-shaped tablet can be quite significant. According to both Kim (1995) and Cheng et al. (1999) the larger the size of the inner hole, the longer the rate of linear release is. Also, the release profiles of doughnut-shaped tablets with small holes are similar to that of tablets without holes (Kim, 1995; Cheng et al., 1999). This can be explained by the change of shape of the tablet during release. If the tablet is composed of a swellable polymer and has a small hole size, then the swollen polymer will close the hole.

Kim (1995) initially tested various hole sizes ranging from about 2.3 mm to a maximum of 4 mm. His later work (1999) tested hole sizes of 3.18 mm and 4.67 mm. The study by Cheng et al. (1999) tested hole sizes of 1 mm, 2 mm and 3 mm. All the tablet holes in the above studies were bored with a high-speed drill and thus these doughnut-shaped tablets cannot be produced using an automated system.

Both Kim (1995) and Cheng (1999) used the Korsmeyer et al. (1983) relationship to determine the type of release obtained from their doughnut-shaped tablets. The Korsmeyer et al. (1983) relationship is depicted in equation 2.3.1 or equation 2.3.2 below.

$$Mt/M_\infty = k.t^n \qquad \text{-equation 2.3.1}$$

or,

$$\log Mt/M_\infty = \log k + n \log t \qquad \text{-equation 2.3.2}$$

where Mt/M_∞ is the fractional release of the drug, t is the release time, k is a constant with regard to the structural and geometric characteristics of the device and n is the time exponent. It is the time exponent which indicates the type of release of drug with $n = 0.5$ for square root of time kinetics and $n = 1$ for zero-order kinetics.

Ford et al. (1987) used this classification to characterise the release of a number of drugs from HPMC matrices. According to his method, one must plot the logarithm of fractional release versus the logarithm of time in minutes so that the slope of the graph will give the value of the n exponent. However, in order for equation 2.3.2 to be applicable, the intercept of the graph must pass through the origin, i.e. log k must be equal to zero. This is achieved by correcting the sample times with linear regression. The y-axis intercept is determined and the values on the x-axis are adjusted according to whether the y-axis intercept is above or below zero. Danckwerts et al. (1996) determined that the correction method is applicable to the type of release of drug. If the model is suspected to be zero-order, then the sampling time data of cumulative fractional release versus time is corrected. If the model is suspected to be square root of time, then the sampling time data of cumulative fractional release versus square root of time is corrected and the data of log cumulative fractional release versus time is corrected for a suspected first order model.

2.3.2 Objective

In the previous analysis, it was shown that HPMC K15M mixed with 10%$^{w}/_{w}$ of gelatin and directly compressed, was the most suitable combination for the doughnut-shaped tablet coat layers. Therefore, this combination will be used for the tablet coat in this experiment which seeks to optimise the core layer of the doughnut-shaped tablet to release both soluble (caffeine) and insoluble (ibuprofen) drug at a zero-order rate.

The objective of this experiment is to determine the effect of two different sizes of the inner hole of the coated doughnut-shaped tablet and three different concentrations of HPMC in the core layer on the kinetics of drug release, the rate of drug release, and the length of time that the doughnut-shaped tablet remains intact.

2.3.3 Materials and Methods

2.3.3.1 *Materials*

HPMC K4M premium EP and HPMC K15M premium EP were supplied by Colorcon Ltd. HPMC K4M and K15M have a viscosity of 3000 - 5600 and 11250 - 21000 cP respectively, as a 2% solutions in water at 20 °C. Both polymers had already been screened through a No. 40 standard sieve. Caffeine (Saarchem, S.A.) and Ibuprofen (Nicholas Piramal Ltd., India) were passed through a 212 μm aperture sieve (Endcotts Test Sieves, Ltd., England). Methanol was supplied by Sigma Aldrich, S.A. All other reagents used were standard laboratory grade.

2.3.3.2 *Formulations*

For the core portion of the tablet, doughnut-shaped tablets were produced consisting of 5% $^{w}/_{w}$, 10% $^{w}/_{w}$ and 15% $^{w}/_{w}$ of HPMC K4M mixed with either caffeine (model soluble drug) or ibuprofen (model insoluble drug). Table 2.3.1 lists the different formulations used. Each batch of granules was prepared in triplicate with a batch size of 12 g. Tablet coats were made of 10% $^{w}/_{w}$ gelatin in HPMC K15M. All coating and core formulations contained 1% $^{w}/_{w}$ of magnesium stearate as lubricant.

TABLE 2.3.1

Descriptions of the different formulations tested

% $^{w}/_{w}$ Polymer/Drug	Hole size (mm)
5% $^{w}/_{w}$ HPMC K4M/Caffeine	4.5
10% $^{w}/_{w}$ HPMC K4M/Caffeine	4.5
15% $^{w}/_{w}$ HPMC K4M/Caffeine	4.5
5% $^{w}/_{w}$ HPMC K4M/Caffeine	6.5
10% $^{w}/_{w}$ HPMC K4M/Caffeine	6.5
15% $^{w}/_{w}$ HPMC K4M/Caffeine	6.5
5% $^{w}/_{w}$ HPMC K4M/Ibuprofen	4.5
10% $^{w}/_{w}$ HPMC K4M/Ibuprofen	4.5
15% $^{w}/_{w}$ HPMC K4M/Ibuprofen	4.5
5% $^{w}/_{w}$ HPMC K4M/Ibuprofen	6.5
10% $^{w}/_{w}$ HPMC K4M/Ibuprofen	6.5
15% $^{w}/_{w}$ HPMC K4M/Ibuprofen	6.5

2.3.3.3 *Preparation of Compressed Tablets*

All powders for the tablet core layers were granulated as described in chapter 2.2.3.4. Tablet cores with different central hole sizes were produced using two sets of flat round punches. Both sets had an outer diameter of 11 mm but the diameter of the inner rod used was respectively 5 and 7 mm. All cores were compressed to a thickness of 3.5 mm. The caffeine and ibuprofen core tablets were compressed to a hardness of approximately 20 N and 8 N respectively to achieve the same hardness as in previous studies. The weights of the core tablets varied slightly according to the density of the formulation. Table 2.3.2 lists the average weight and hardness of the cores and the average weight of the coating layers.

The HPMC K15M and gelatin used for the tablet coating layers were mixed in an Erweka AR 400 rotary cube mixer and then directly compressed into the coating layers. Again two central hole sizes of coat tablet were produced, with a central hole of either 5 or 7 mm respectively. All coats were compressed to a thickness of 1.5 mm.

Once the tablet cores and coats were compressed, they were then fed into the tabletting press so that one core was placed between two coats and then recompressed into a three-layer tablet as described in chapter 2.2.3.4. Since two sizes of central holes were produced, the inner rods were reduced respectively to 4.5 mm and 6.5 mm to ensure that the coat and cores fitted easily around them. The coated caffeine and ibuprofen doughnut-shaped tablets were recompressed to a hardness of approximately 80 N and 25 N respectively. The weights and hardness of the coated doughnut-shaped tablets are listed in table 2.3.3.

TABLE 2.3.2

Mean weights and hardness of core and coat tablets used in the different formulations

Formulation	Mean weight (mg) ± SD (n=10)	Hardness (N) ± SD (n=10)
Core Tablets		
Caffeine		
5%$^{w}/_{w}$ HPMC/5 mm hole	225.06 ± 3.31	22.74 ± 6.85
10%$^{w}/_{w}$ HPMC/5 mm hole	197.65 ± 9.02	23.92 ± 4.72
15%$^{w}/_{w}$ HPMC/5 mm hole	184.72 ± 7.49	21.34 ± 5.56
5%$^{w}/_{w}$ HPMC/7 mm hole	203.72 ± 3.94	19.65 ± 3.98
10%$^{w}/_{w}$ HPMC/7 mm hole	185.04 ± 5.70	21.45 ± 4.41
15%$^{w}/_{w}$ HPMC/7 mm hole	164.17 ± 2.78	20.12 ± 3.65
Ibuprofen		
5%$^{w}/_{w}$ HPMC/5 mm hole	180.44 ± 4.88	10.21 ± 6.51
10%$^{w}/_{w}$ HPMC/5 mm hole	191.03 ± 8.10	9.93 ± 3.09
15%$^{w}/_{w}$ HPMC/5 mm hole	197.05 ± 4.13	11.25 ± 3.86
5%$^{w}/_{w}$ HPMC/7 mm hole	171.13 ± 7.93	8.18 ± 3.72
10%$^{w}/_{w}$ HPMC/7 mm hole	152.67 ± 5.57	9.12 ± 4.42
15%$^{w}/_{w}$ HPMC/7 mm hole	146.92 ± 7.02	8.89 ± 6.07
Coat Tablets		
10%$^{w}/_{w}$ gelatin/HPMC 5 mm hole	82.91 ± 4.33	
10%$^{w}/_{w}$ gelatin/HPMC 7 mm hole	58.72 ± 2.36	

2.3.3.4 *Release Studies*

All release studies were performed as described in chapter 2.2.3.8. using the B.P. 1998 paddle method and a 6 beaker Caleva model 7ST dissolution tester.

2.3.3.5 *Calculation of Time Exponents*

This study examined the fit of the drug release rate from doughnut –shaped tablets to the Korsmeyer et al. (1983) relationship depicted in equation 2.3.2. For each formulation, plots of logarithm of the fractional release versus the logarithm of time (minutes) were plotted and the time exponent was calculated from the slope of the graph using linear regression. For equation 2.3.2 to hold true, the intercept of the graph must pass through zero and thus the data was corrected to achieve this. In order to determine whether the drug released followed zero-order or square root of time kinetics, graphs of release rate versus time or release rate versus square root of time were plotted, and the plot with the best correlation coefficient was used to correct the data. The correction to data was achieved by changing the sampling time data of cumulative fractional release versus time as per Ford et al (1987). Only the linear portions of the graphs were used to calculate the time exponents. The mean release rates from the doughnut-shaped tablets were calculated using linear regression of the linear portion of the plot of fractional release versus time.

2.3.4 Results and Discussion

Table 2.3.4 lists the calculated time exponents as calculated from the results using equation 2.3.2 and the correlation coefficients of these time exponents. The average release rates are also listed in table 2.3.4

2.3.4.1 *Caffeine release from Coated Doughnut-Shaped tablets*

Figures 2.3.1 a – e are graphs of the release rate of caffeine from the coated doughnut-shaped tablets versus time. Figures 2.3.1 a and b compare the release profiles of caffeine when the size of the inner hole remains constant but the concentration of HPMC in the doughnut core is varied. Figures 2.3. c – e compare the release profiles of caffeine when the concentration of polymer is the same but the size of the inner hole varies. These results indicate that the release rate of caffeine (soluble drug) from the coated doughnut-shaped tablets is a near zero-order one for 80% of the release time. This occurred regardless of hole size and concentration of HPMC used in the core.

TABLE 2.3.4

Mean time exponents, correlation coefficients and release rates from the coated doughnut-shaped tablets used in the different formulations.

Formulation (% $^{w}/_{w}$)	Exponent n value ± SD (n=9)	Correlation Coefficient ± SD (n=9)	Mean Release Rate (ug/hr) ± SD (n=9)
Caffeine			
5% HPMC/4.5	0.960 ± 0.032#	0.989 ± 0.006	22.979 ± 1.983 ◊
10% HPMC/4.5	1.060 ± 0.059##	0.982 ± 0.009	15.367 ± 1.488 ◊◊
15% HPMC/4.5	1.049 ± 0.067##	0.976 ± 0.019	12.77 ± 0.766
5% HPMC/6.5	0.943 ± 0.014#	0.994 ± 0.001	36.861 ± 5.331
10% HPMC/6.5	0.953 ± 0.046#	0.995 ± 0.003	22.097 ± 1.203 ◊
15% HPMC/6.5	0.957 ± 0.031#	0.996 ± 0.002	18.136 ± 0.686 ◊◊
Ibuprofen			
5% HPMC/4.5	0.932 ± 0.007*	0.993 ± 0.001	0.421 ± 0.035
10% HPMC/4.5	1.033 ± 0.009	0.993 ± 0.002	0.269 ± 0.023
15% HPMC/4.5	0.892 ± 0.002	0.984 ± 0.005	0.196 ± 0.024
5% HPMC/6.5	1.122 ± 0.006	0.991 ± 0.004	0.481 ± 0.006
10% HPMC/6.5	0.928 ± 0.009*	0.987 ± 0.006	0.441 ± 0.036
15% HPMC/6.5	1.012 ± 0.006	0.991 ± 0.002	0.349 ± 0.010

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

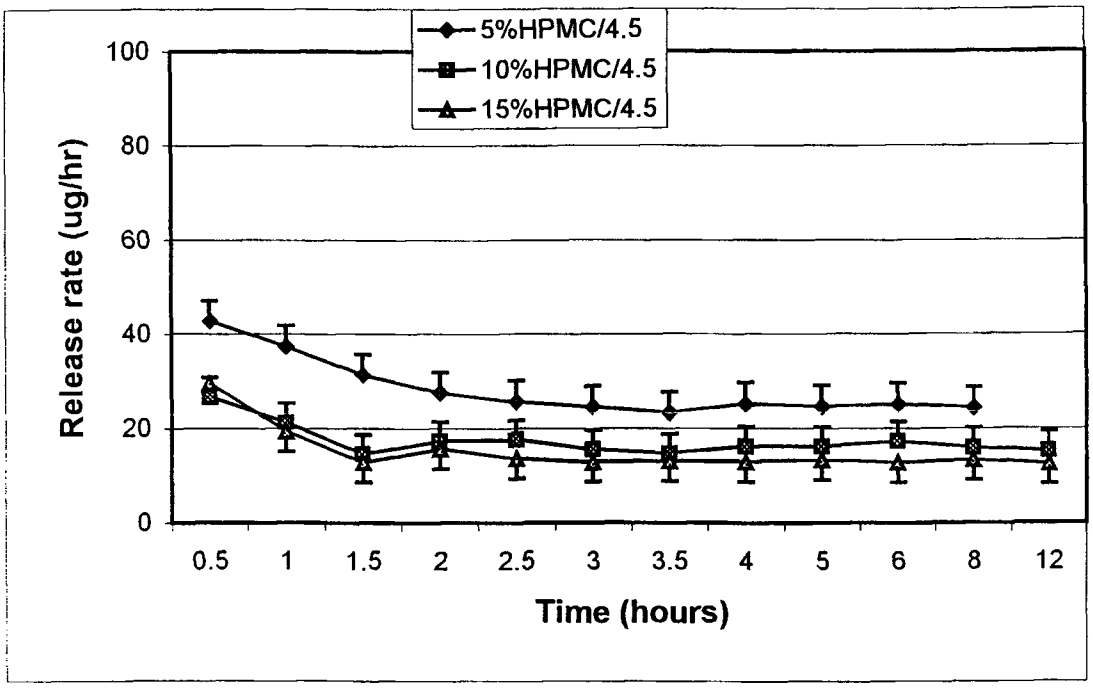


Fig. 2.3.1 a Graph of the release rate of caffeine from coated doughnut-shaped tablets with an inner hole size of 4.5mm.

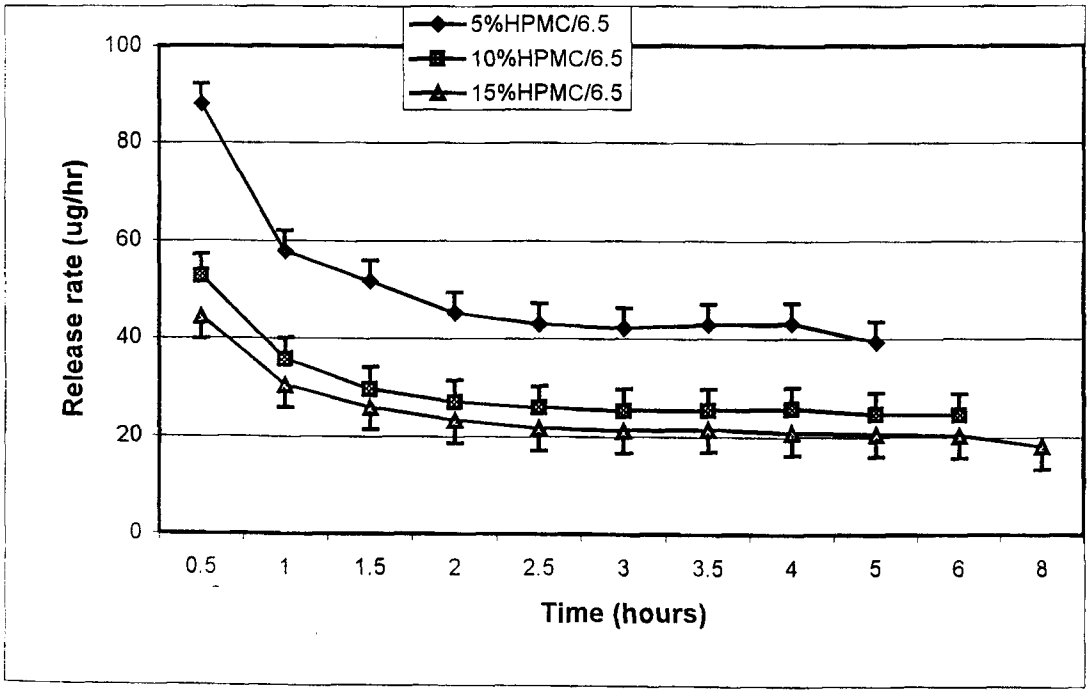


Fig 2.3.1 b Graph of the release rates of caffeine from coated doughnut-shaped tablets with an inner hole of 6.5mm.

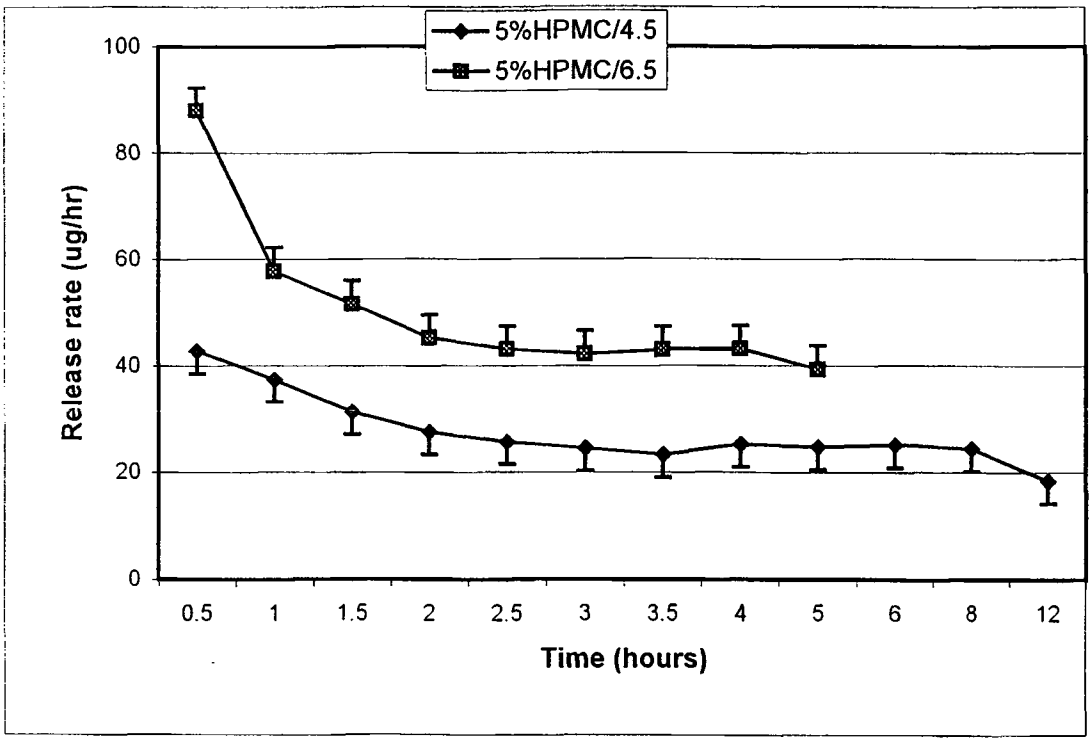


Fig 2.3.1 c Graph of the release rates of caffeine from coated doughnut-shaped tablets containing 5% $^{w}/_{w}$ of HPMC K4M in the core.

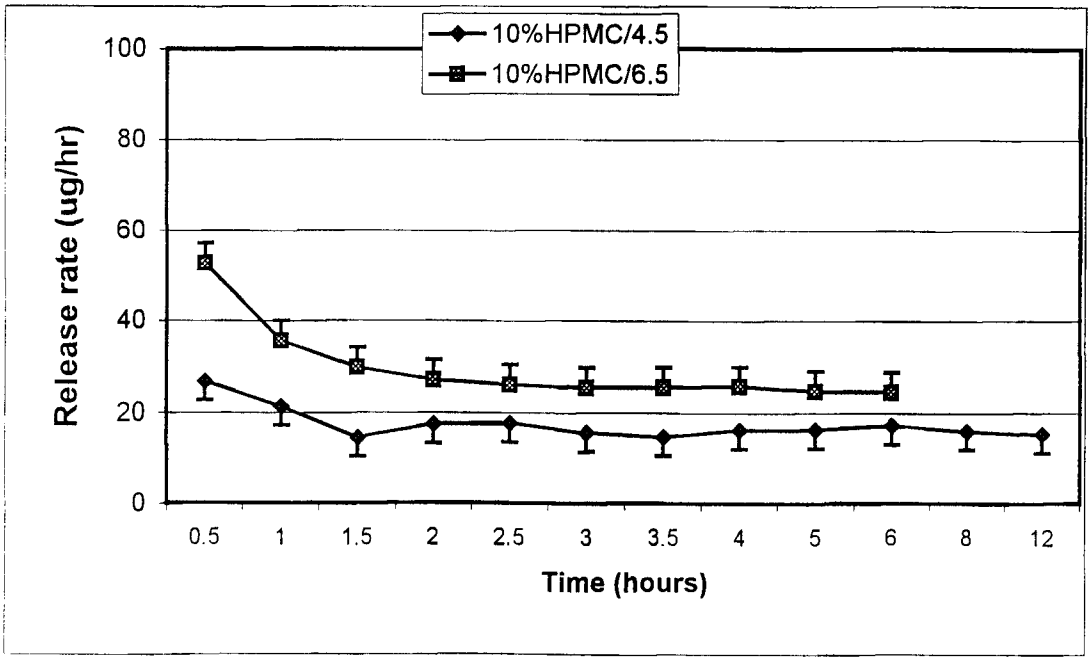


Fig 2.3.1 d Graph of the release rates of caffeine from coated doughnut-shaped tablets containing 10% $^{w}/_{w}$ of HPMC K4M in the core.

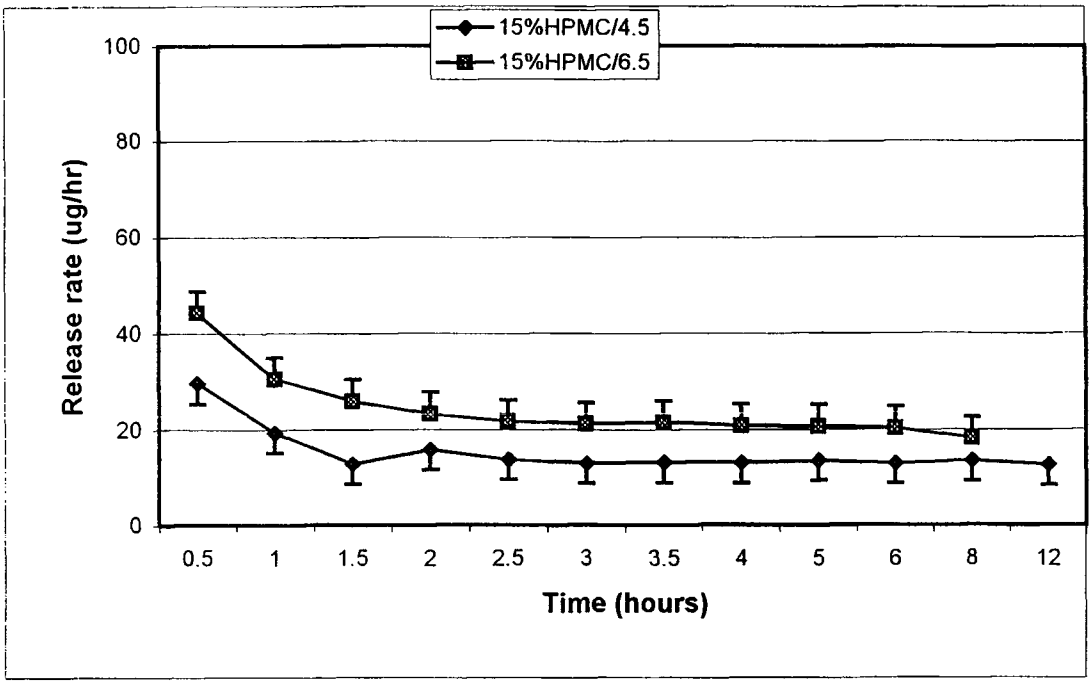


Fig 2.3. e Graph of the release rates of caffeine from coated doughnut-shaped tablets containing 15% $^{w}/_{w}$ of HPMC K4M in the core.

The near zero-order release of caffeine from the coated doughnut-shaped tablets can be confirmed using equation 2.3.2. as the time exponent *n* is close to 1.0. For the doughnut-shaped tablets with a hole size 4.5 mm and 10% $^{w}/_{w}$ and 15% $^{w}/_{w}$ concentrations of HPMC, there is a slight negative deviation in the rate of release. This means that the rate decreases slightly with time which results in an exponent *n* of greater than 1. The larger than 1, the exponent *n* is, the less closer it is to zero-order release. Likewise, the smaller than 1, the exponent *n* is for a positive deviation, the less closer it is to zero-order kinetics. The closest formula to zero-order release is 5% $^{w}/_{w}$ HPMC with a hole size of 4.5 mm, although there is no significant difference between this formula and the formulas 5% $^{w}/_{w}$ HPMC with hole size 6.5 mm, 10 % $^{w}/_{w}$ HPMC with hole size 6.5 mm and 15 % $^{w}/_{w}$ HPMC with hole size 6.5 mm.

The higher the concentration of HPMC K4M in the core, the lower the rate of release is and the longer the time of release is for both hole sizes. This is shown in figures 2.3.1 a and b. As the size of the inner hole is increased from 4.5 to 6.5 mm, the release rate of caffeine increases and the time of release is therefore shorter. The higher release rate of the doughnut-shaped tablet with hole size 6.5 mm and the same concentration of HMPC in the core is clearly demonstrated by figures 2.3.1 c – e.

The time taken for the doughnut-shaped tablet to break apart is presented in table 2.3.6. The tablet breaks apart when sufficient of the core is released or dissolved so that it is unable to hold the coating layers.

TABLE 2.3.5

Time take for the caffeine three-layer doughnut-shaped tablet to break apart

Formulation	Time (hours)
5%HPMC/4.5	8
10%HPMC/4.5	12
15%HPMC/4.5	> 12
5%HPMC/6.5	5
10%HPMC/6.5	6
15%HPMC/6.5	7

The initial high rate of release demonstrated by all formulations is due to the release of drug trapped on the surface of the polymer during manufacture. This drug is released when the polymer matrix comes into contact with the release medium. Although HMPC K4M is only of medium viscosity and at a low concentration in the core, it still swells slightly when it comes into contact with the release medium, which can result in a lag time of about 60 to 90 minutes before zero-order release is achieved.

For the release of the soluble drug caffeine, the formulas 5% $^{w}/_{w}$ HPMC/4.5, 10% $^{w}/_{w}$ HPMC/6.5 and 15% $^{w}/_{w}$ HPMC/6.5 show no significant difference with regard to the time exponent *n* (table 2.3.4) but differ with regard to the length of time of release. The formula 5% $^{w}/_{w}$ HPMC with a hole size of 4.5 mm remains intact as a coated doughnut-shaped tablet for the longest period of time.

2.3.4.2 *Ibuprofen Release from the Coated Doughnut-Shaped Tablets*

Figures 2.3.2 a – e are plots of the release rate of ibuprofen versus time. Figures 2.3.2 a and b compare the release profiles of ibuprofen when the size of the inner hole remains constant but the concentration of HPMC in the doughnut core is varied. Figures 2.3.2 c – e compare the release profiles of ibuprofen when the concentration of polymer is the same but the size of the inner hole varies. The release rates of ibuprofen from the coated doughnut-shaped tablets are much lower than those of caffeine. This is due to the fact that ibuprofen is not very soluble in aqueous solution and therefore, it is mainly released through erosion of the polymer surface with negligible amounts released via diffusion.

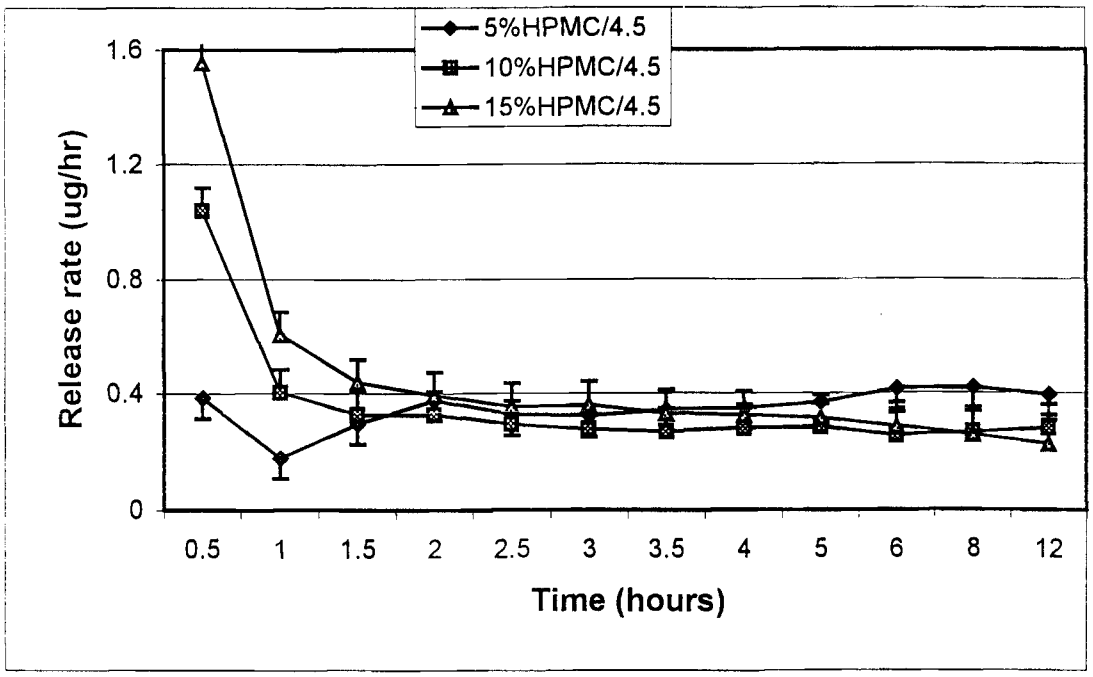


Fig. 2.3.2 a Graph of the release rate of ibuprofen from coated doughnut-shaped tablets with an inner hole size of 4.5mm.

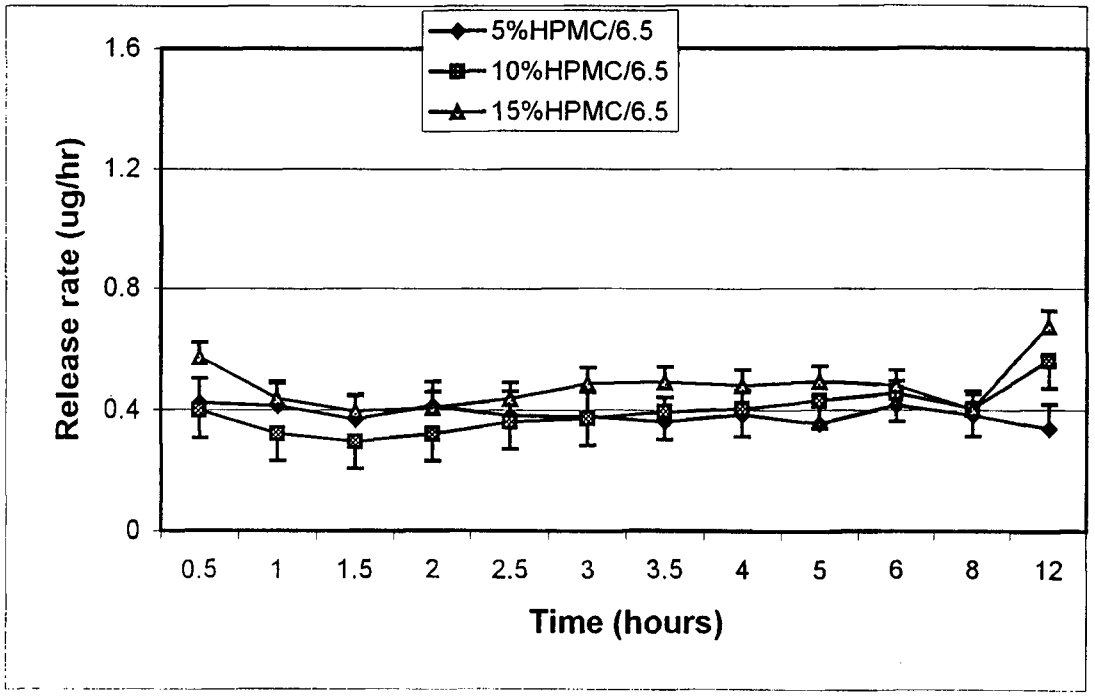


Fig 2.3.2 b Graph of the release rates of ibuprofen from coated doughnut-shaped tablets with an inner hole of 6.5mm.

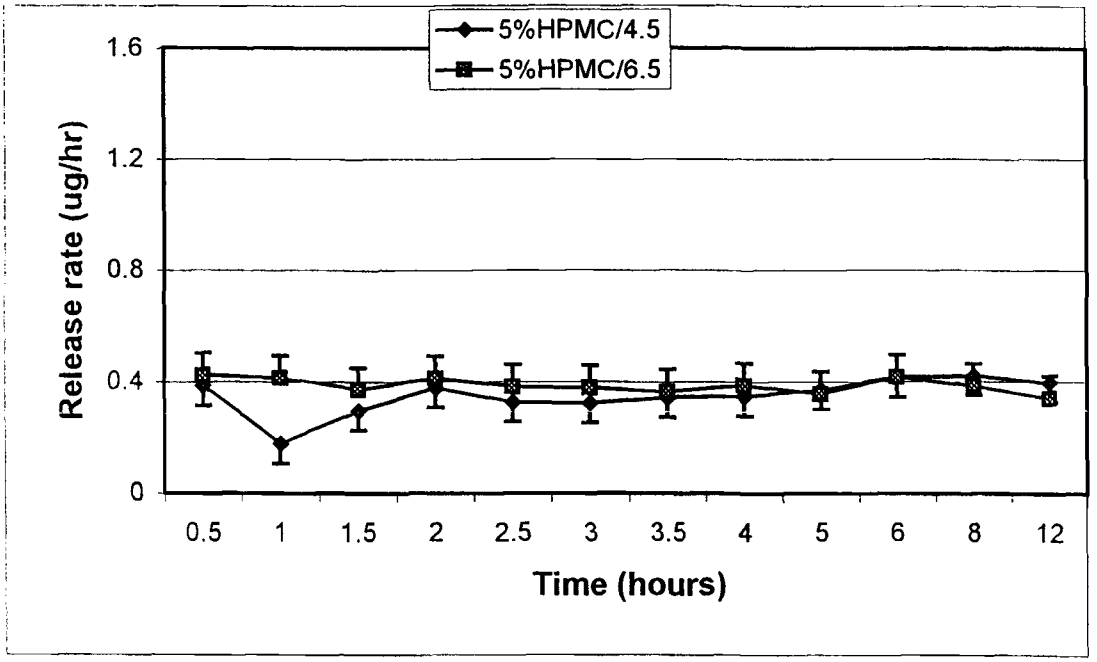


Fig 2.3.2 c Graph of the release rates of ibuprofen from coated doughnut-shaped tablets containing 5% $^{w}/_{w}$ of HPMC K4M in the core.

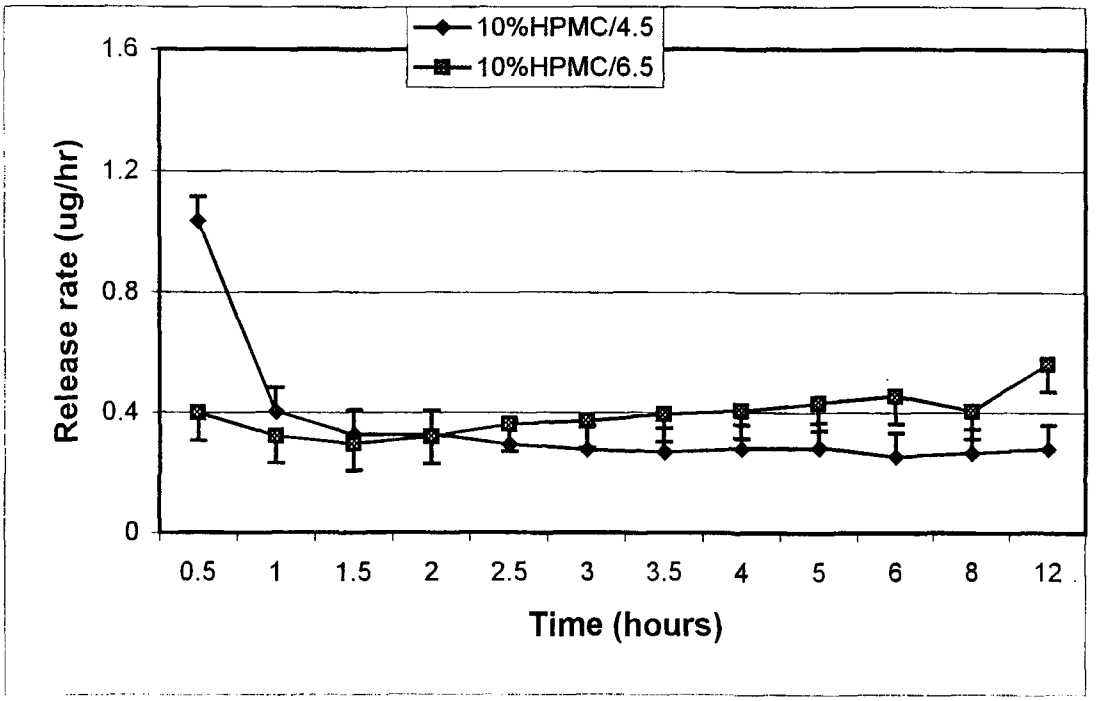


Fig 2.3.2 d Graph of the release rates of ibuprofen from coated doughnut-shaped tablets containing 10% $^{w}/_{w}$ of HPMC K4M in the core.

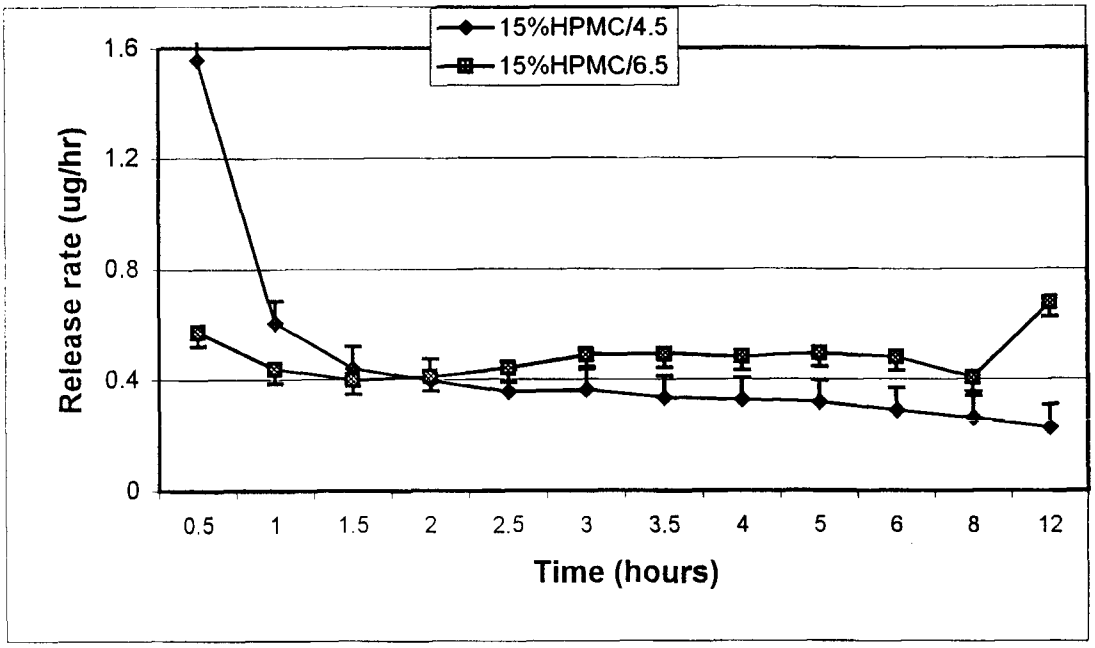


Fig 2.3.2 e Graph of the release rates of ibuprofen from coated doughnut-shaped tablets containing 15% $^{w}/_{w}$ of HPMC K4M in the core.

For the release of ibuprofen from the coated doughnut-shaped tablet, the time exponent *n* varies from 1.122 to 0.892, thus showing both large negative and positive deviation. The tablets containing10% $^{w}/_{w}$ HPMC with a hole size of 4.5 mm and 15% $^{w}/_{w}$ HPMC with a hole size of 6.5 mm have the closest time exponents to 1. Both of these formulas also demonstrate a slight negative deviation.

The size of the inner hole of the doughnut-shaped tablet, affects both the release rate of ibuprofen and the time of release. All release rates are significantly different. As the hole size changes from 4.5 to 6.5 mm, the release rate increases. Tablets with hole size 4.5 mm, show a large burst effect which increases as the concentration of HPMC in the tablet core increases as shown in figure 2.3.2 a. The greater weight of the core tablets with the hole size of 4.5 mm, allow more drug to be

trapped on the surface of the tablet, resulting in this burst effect. If the hole size is kept constant and the concentration of HPMC in the tablet core is increased, then the release rate decreases.

As the hole size increases from 4.5 to 6.5 mm, the length of time that it takes for the tablet to break apart decreases. The length of time is listed in table 2.3.6. The change in concentration of the HPMC does not affect the time that it takes the ibuprofen core to break off from the coating. Tablets with hole size 6.5 mm all show a sudden increase in release at the time of 12 hours (figure 2.3.2 b). It is at approximately this time that the core breaks away from the coating layers and the sudden increase in surface area results in an increase in the release of drug.

TABLE 2.3.6

Time take for the ibuprofen three-layer doughnut-shaped tablet to break apart

Formulation	Time (hours)
5%HPMC/4.5	> 12
10%HPMC/4.5	> 12
15i%HPMC/4.5	> 12
5%HPMC/6.5	8 - 12
10%HPMC/6.5	8 - 12
15%HPMC/6.5	8 -12

The most suitable formula for the insoluble drug ibuprofen is a concentration of 15% $^{w}/_{w}$ of HPMC with inner hole size of 6.5 mm. Although both 15% $^{w}/_{w}$ HPMC/6.5 and 10% $^{w}/_{w}$ HPMC/ 4.5 have near zero-order time exponents, 15% $^{w}/_{w}$ HPMC/6.5 has a faster release rate. Since the release rate with ibuprofen is very slow, the faster release rate is more suitable.

The formulation, which optimises the zero-order release of drug, is thus 5% $^{w}/_{w}$ HPMC with a hole size of 4.5 mm for the soluble drug caffeine and 15% $^{w}/_{w}$ HPMC with a hole of 6.5 mm for the insoluble drug ibuprofen. These respective core tablet formulations will be used for all other experiments carried out in this study.

2.4 IN-PROCESS VALIDATION

2.4.1 Introduction

Tablets must meet certain physical and biological standards. The attributes of an acceptable tablet are as follows (Bandelin, 1989):

(i) The tablet must be uniform in weight, which is measured by the weight variation test.

(ii) The tablet must be sufficiently strong enough to withstand handling manufacture, packaging, shipping and use. This property is measured by two tests, namely friability and hardness tests.

(iii) The drug content must be bioavailable which is assessed by dissolution testing.

(iv) Tablets must be elegant in appearance.

The physical, chemical and biological properties of a tablet are often interrelated and need to be assessed when evaluating a tablet (Gordon et al., 1990). Since model drugs are used in this study, the chemical properties are well known and are listed in table 1.2. The biological properties are evaluated in the next experiment. This section assesses the physical properties of a tablet required by the British Pharmacopoeia (B.P.) (1999).

2.4.1.1 *Uniformity of Weight*

A tablet is designed to contain a specific amount of drug. To check that the tablet contains the correct amount of drug, tablet weight is routinely measured (Rosanske et al.,1990). The B.P. (1999) sets limits on the acceptable deviation from the average tablet weight allowed as shown in table 2.4.1. No more than two of the individual weights can differ from the average weight by the percentage shown and none by more than twice that percentage.

TABLE 2.4.1

Deviations from tablet average allowed by B.P. (1999)

Average weight of tablets (mg)	Percentage deviation
80 mg or less	10
More than 80mg and less than 250 mg	7.5
250mg or more	5

Poor flow properties of the granulation formulation can lead to problems with weight uniformity as they can cause improper filling of the die cavity. If the granulation particle size is too large for the size of the die cavity, the dies will not be uniformly filled (Rosanske et al., 1990).

2.4.1.2 *Tablet Hardness*

The hardness of a tablet may impact on the dissolution of the tablet, and thus it is necessary to balance the hardness of tablet so that it will produce an acceptable friability value, but still achieve an adequate dissolution. Tablet hardness is defined as the force required to break a tablet in a diametrical compression test (Rosanske et al., 1990). Pressure is applied to the tablet and the pressure that just causes the tablet to break, is recorded as the tablet hardness or crushing strength. Hardness can be affected by the particle size and compression properties of the granulation formulation (Rosanske et al., 1990).

2.4.1.3 *Friability*

Friability is a measure of a tablet's ability to withstand both shock and abrasion from the time that it is produced until it is used. Friability tests are performed by utilising a plastic chamber, which rotates, dropping the tablets a distance of 12.5 cm for 100 revolutions. Tablets are then dusted and reweighed to check for weight loss. A loss of less than 1.0% is acceptable (Rosanske et al., 1990).

2.4.2 **Objective**

The objective of this experiment is to ensure that the in-process validation variables of uniformity of weight, hardness, and friability comply with standards set out in the B.P. Since, the flow and compressibility properties of the core granulations can affect the uniformity of weight, hardness and friability of the tablets, especially

due to the unusual shape of the die cavity, these properties will also be checked. In addition, the effect of granule size on the in-process validation variables will be examined. The separate core and coating layers, as well as the coated tablets will be tested for the above properties, as uniformity of weight, hardness, and friability are important during each stage of the production process.

2.4.3 **Materials and Methods**

2.4.3.1 *Materials*

HPMC K4M premium EP and HPMC K15M premium EP were supplied by Colorcon Ltd. HPMC K4M and K15M have viscosities of 3000 - 5600 and 11250 - 21000 cP respectively, as a 2% solution in water at 20 °C. Both polymers had already been screened through a No. 40 standard sieve. Caffeine (Saarchem, S.A.) and ibuprofen (Nicholas Piramal Ltd, India) were passed through a 212 μm aperture sieve (Endcotts Test Sieves, Ltd., England). All other reagents used were standard laboratory grade.

2.4.3.2 *Preparation of Compressed Tablets*

Tablets were prepared as previously discussed in section 2.3.3.3. The formula for the tablet coating layers was 10%$^{w}/_{w}$ gelatin in HPMC K15M and were directly compressed. The coating layers were compressed to a hole size of either 5 mm or 7 mm, with the 5 mm size used to coat the caffeine cores and the 7 mm size used to coat the ibuprofen cores. The core formula for caffeine consisted of 5% $^{w}/_{w}$ HPMC K4M

and was compressed with an inner hole of 5mm. The core formula for ibuprofen was 15% $^{w}/_{w}$ HPMC K4M and was compressed with an inner hole of 7 mm. Each batch of core granulation was prepared in triplicate, with a batch size of 35 g. Each batch was then divided into two and granulated using an Erweka FGS granulator, which was fitted with either a 0.63 μm aperture stainless steel sieve or with a 1.25 μm aperture stainless steel sieve. Core tablets were then recompressed with the coats to a form a coated doughnut-shaped tablet.

2.4.3.3 *Measurement of Powder Flow*

The flow of the granule blends was determined using angle of repose measurements as described in section 2.2.3.5. Three measurements were performed for each batch.

2.4.3.4 *Measurement of Compressibility*

Compressibility studies were performed as described in section 2.2.3.6. The graph of hardness versus natural logarithm of compressed force was plotted using linear regression. The slope of this graph was used as an estimation of the compressibility of the formulations tested.

2.4.3.5 *Uniformity of Weight*

20 tablets from each batch were weighed to ensure that the individual weights complied with the standards presented in table 2.4.1. Each tablet was weighed on a model TR 104 supplied by the Denver Instrument Company (Colorado, USA).

2.4.3.6 *Measurement of Friability*

The friability test was conducted on both the core and coat tablets as well as the coated doughnut-shaped tablet. Friability was measured using a Roche Friabilator (Hoffman la Roche, Basel). After weighing, 10 tablets from each batch were rotated for 100 revolutions and then re-weighed to test for % loss of weight.

2.4.3.7 *Measurement of Hardness*

The hardness of each tablet was measured using a Pharma Test PTB 311 (Pharma Test, Hainberg, Germany) hardness tester, which also measures the thickness and diameter of the tablet.

2.4.4 **Results and Discussion**

2.4.4.1 *Cores and Coats*

2.4.4.1.1 *Angle of Repose and Compressibility*

The results of the in-process validation studies of angle of repose and compressibility are listed in table 2.4.2. The size of the granulation formula does not significantly affect either the angle of repose or the compressibility for both caffeine and ibuprofen. All the angles of repose are less than 25° and therefore, indicate excellent flow. The caffeine granulation has better flow than the ibuprofen granulation, as indicated by its lower angle of repose. Caffeine is far more compressible than ibuprofen, whose low compressibility will affect the hardness of the tablet. The plots of hardness versus the natural logarithm of pressure are shown in figure 2.4.1 a and b for caffeine and figure 2.4.2 a and b for ibuprofen. The slopes of these graphs (m) indicate the compressibility of caffeine and ibuprofen respectively.

TABLE 2.4.2

Angle of repose and compressibility values of the tablet core granules

Sieve size (μm)	Angle of repose ± SD (n=9)	Compressibility (*m*) ± SD (n=3)
Caffeine		
0.63	13.229 ± 2.910 *	137.377 ± 45.096 #
1.25	15.104 ± 5.549 *	141.160 ± 33.542 #
Ibuprofen		
0.63	18.425 ± 4.343 **	38.977 ± 14.500 ##
1.25	22.620 ± 5.546 **	46.128 ± 22.188 ##

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

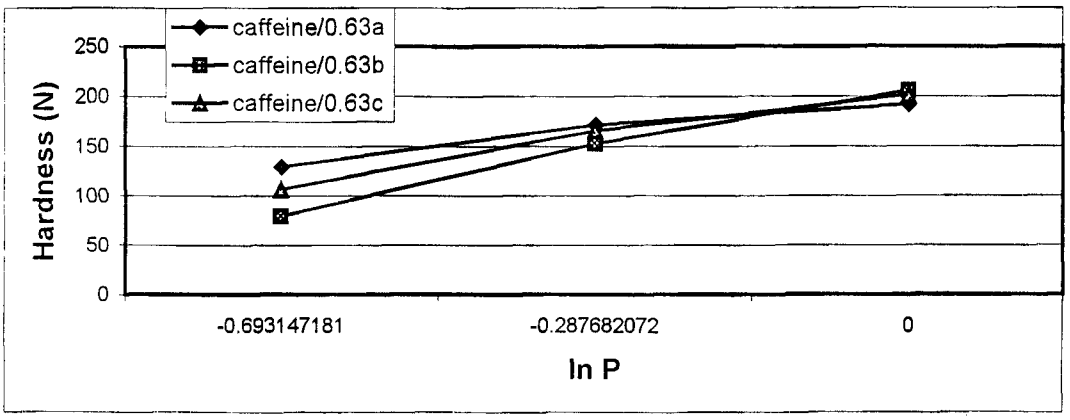


Fig 2.4.1 a Graph of hardness versus ln P for the caffeine granules produced using a sieve size of 0.63 μm.

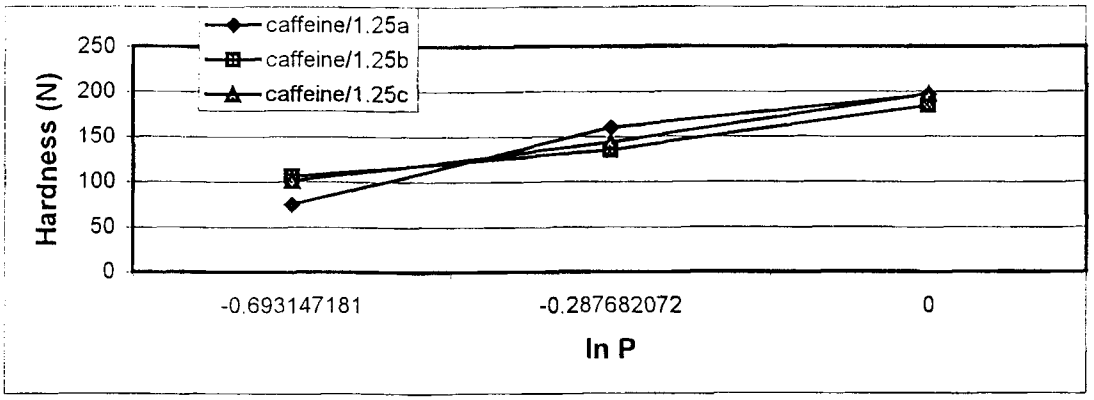


Fig 2.4.1 b Graph of hardness versus ln P for the caffeine granules produced using a sieve size of 1.25 μm.

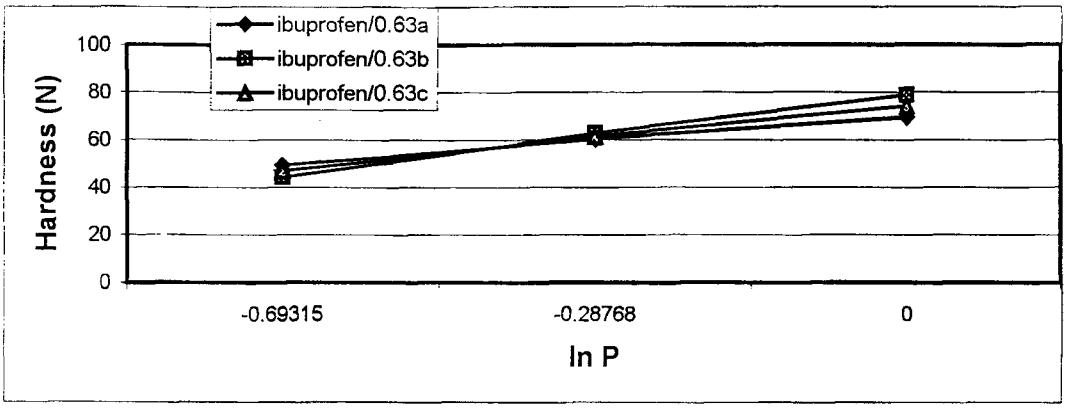


Fig 2.4.2 a Graph of hardness versus ln P for the ibuprofen granules produced using a sieve size of 0.63 μm.

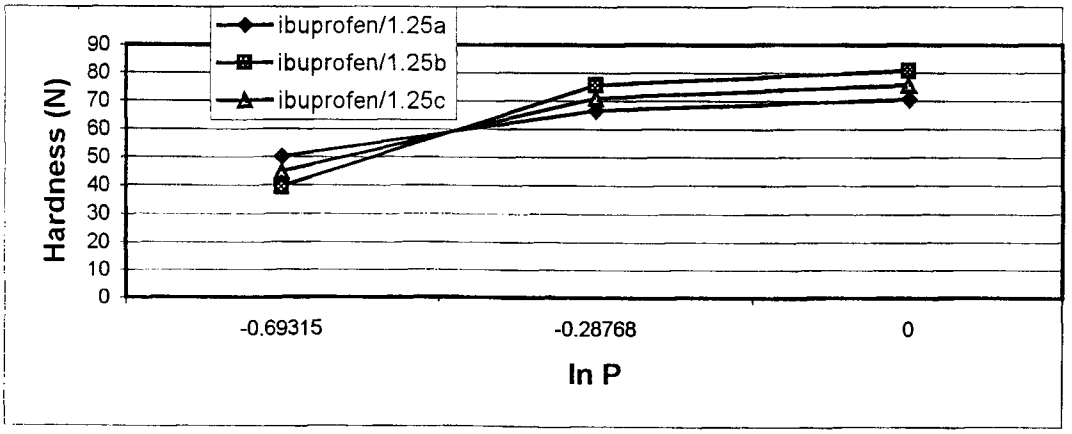


Fig 2.4.2 b Graph of hardness versus ln P for the ibuprofen granules produced using a sieve size of 1.25 μm.

2.4.4.1.2 *Weight Variation*

The average weight of the caffeine tablets produced with the granule sieve size of 0.63 and 1.25 μm was 344.427 mg (± 6.940) and 318.648 mg (± 22.950) respectively. These average weights were found to be significantly different (p=0.0025) at the 95% confidence level using the LSD analysis of variance test. The average weight of the ibuprofen tablets produced with the granule sieve size of 0.63 and 1.25 μm was 205.975 mg (± 9.515) and 199.762 mg ± (10.519) respectively. The average weights of the ibuprofen tablets showed no significant difference (p= 0.5641) at the 95% confidence level using the LSD analysis of variance test. The number of tablets that deviate from the percentage allowed by the B.P. uniformity of weight test (as shown in table 2.4.1) are listed in table 2.4.3.

TABLE 2.4.3

Uniformity of weight of the core and coating layers

Sieve Size (μm)	No of Tablets that differ by the percentage allowed	No of Tablets that differ by twice the percentage allowed
Caffeine		
0.63/batch 1	1	0
0.63/batch 2	1	0
0.63/batch 3	1	0
1.25/batch 1	5	1
1.25/batch 2	6	2
1.25/batch 3	6	1
Coat 5 mm/batch 1	1	0
Coat 5 mm/batch 2	0	0
Coat 5 mm/batch 3	1	0
Ibuprofen		
0.63/batch 1	1	0
0.63/batch 2	1	0
0.63/batch 3	1	0
1.25/batch 1	2	0
1.25/batch 2	2	0
1.25/batch 3	2	0
Coat 7 mm/batch 1	0	0
Coat 7 mm/batch 2	1	0
Coat 7 mm/batch 3	0	0

In the case of caffeine, the tablets made from the different granule sizes affects the uniformity of weight. The granules passing through a sieve size of 1.25 μm do not pass the B.P requirements of uniformity of weight as more than 2 tablets deviate from the average by more than the percentage shown in table 2.4.1. In addition, some of the tablets deviate by more than twice the percentage allowed. The uniformity of weight is acceptable for both granule sizes of ibuprofen.

2.4.4.1.3 *Hardness and Friability*

Hardness, friability, thickness and diameter of the core tablets are listed in table 2.4.4.

TABLE 2.4.4

Results of in-process validation on the core of the doughnut-shaped tablet

Sieve size (μm)	Hardness (N) ± SD (n=3)	Friability (%) ± SD (n=3)	Thickness (mm) ± SD (n=3)	Diameter (mm) ± SD (n=3)
Caffeine				
0.63	24.285 ± 3.191	0.359 ± 0.029	3.442 ± 0.067 *	10.983 ± 0.067#
1.25	20.168 ± 4.698	0.701 ± 0.329	3.480 ± 0.033 *	11.051 ± 0.010#
Ibuprofen				
0.63	9.952 ± 4.952×	0.543 ± 0.114	3.361 ± 0.051**	10.984 ± 0.024##
1.25	8.671 ± 3.988×	0.863 ± 0.106	3.392 ± 0.032**	11.012 ± 0.045##

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

With regard to caffeine, the different granule sizes affect both the friability and the hardness of the core tablets. Although the friability of the 1.25 μm sieve size granules is much higher than that of the 0.63 μm sieve size granules, it is still acceptable. Its higher friability is as a result of its lower hardness. In the case of ibuprofen, the granule size only has a significant difference on the friability of the tablet. Although the friability of both sizes is acceptable, the friability of the granules from sieve size 0.63 μm is lower. The average weight and friability of the tablet coats is listed in table 2.4.5.

TABLE 2.4.5

Average weight and friability of tablet coating layers

Size of inner hole of tablet coat (mm)	Weight (mg) ± SD (n=20)	Friability (%) (n=10)
5 mm	83.570 ± 3.485	0.843
7mm	54.210 ± 1.675	0.982

For the tablet coating layers, both the uniformity of weight (table 2.4.3) and the friability (table 2.4.5) is acceptable for both hole sizes

2.4.4.2 *Coated Tablets*

2.4.4.2.1 *Weight Variation*

The average weight of the coated caffeine tablets produced with the granule sieve size of 0.63 and 1.25 μm was 505.945 mg ± (16.166) and 484.049 mg ± (18.751) respectively. The average weight of the ibuprofen tablets produced with the granule sieve size of 0.63 and 1.25 μm was 313.975 mg ± (10.445) and 308.078 mg (± 10.108) respectively. The average weights of the caffeine tablets showed a significant difference (p= 0.0047) at the 95% confidence level using the LSD analysis of variance test but the ibuprofen tablets showed no significant difference. The number of tablets that deviate from the percentage allowed by the B.P. uniformity of weight test (as shown in table 2.4.1) are listed in table 2.4.6.

TABLE 2.4.6

Uniformity of weight results of the coated doughnut-shaped tablets

Sieve Size (μm)	No of Tablets that differ by the percentage allowed	No of Tablets that differ by twice the percentage allowed
Caffeine		
0.63/batch 1	1	0
0.63/batch 2	1	0
0.63/batch 3	1	0
1.25/batch 1	5	1
1.25/batch 2	6	2
1.25/batch 3	6	1
Ibuprofen		
0.63/batch 1	1	0
0.63/batch 2	1	0
0.63/batch 3	1	0
1.25/batch 1	2	0
1.25/batch 2	1	0
1.25/batch 3	2	0

Again, in the case of caffeine the tablets produced from the granule sieve size of 1.25 μm do not pass the B.P. uniformity of weight test as more than 2 tablets deviate from the percentage allowed and some by more than twice the percentage

allowed. The uniformity of weight tests for ibuprofen for the coated doughnut-shaped tablets from both granule sizes are acceptable.

2.4.4.2.2 *Hardness and Friability*

The hardness, friability, thickness and diameter of the coated doughnut-shaped tablets are listed in table 2.4.7.

TABLE 2.4.7

Results of in-process validation on the coated doughnut-shaped tablet.

Sieve size (μm)	Hardness (N) ± SD (n=3)	Friability (%) ± SD (n=3)	Thickness (mm) ± SD (n=3)	Diameter (mm) ± SD (n=3)
Caffeine				
0.63	82.142 ± 8.681✧	0.088 ± 0.029×	4.180 ± 0.167 *	11.472 ± 0.053#
1.25	85.589 ± 8.843✧	0.033 ± 0.011×	4.282 ± 0.176*	11.560 ± 0.025#
Ibuprofen				
0.63	14.171 ± 2.451	0.551 ± 0.192××	3.904 ± 0.158**	11.457 ± 0.021##
1.25	25.157 ± 4.180	0.448 ± 0.124××	3.947 ± 0.08**	11.436 ± 0.017 ##

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

For both granule sizes, the friability results lie within the normal B.P. limits. In the case of ibuprofen, the only significant difference ($p \leq 0.0000$) lies in the hardness of the tablets, with tablets produced from the granule sieve size of 1.25 μm producing harder tablets. The friability of the tablets containing ibuprofen for both granule sizes are acceptable.

The different granule sizes affect the caffeine tablets more than the ibuprofen tablets.The core tablets produced using a granule sieve size of 0.63 μm allow for great compliance with the B.P standards. Tablets that comply with B.P standards produce tablets that are uniform in weight and strong enough to withstand manufacturing and packaging and can be produced using automated technology. The granule sieve size of 0.63 μm therefore, will be the size of the granules used in subsequent studies.

3. *IN VITRO* ANALYSIS OF THE COATED DOUGHNUT-SHAPED TABLET

3.1 DISSOLUTION OF CAFFEINE AND IBUPROFEN USING A STEPPED-pH DISSOLUTION FLUID

3.1.1 Introduction

Dissolution testing measures the time required for a drug in a solid drug delivery system to go into solution under a specified set of circumstances (Hanna, 1990). This data can then be used to evaluate the physiological availability of the drug. In order for a drug to be absorbed through the gastrointestinal tract (GIT) membrane, it must first pass into solution in the GIT fluids. Dissolution is the rate-controlling step for the absorption of many drugs (Shargel and Yu, 1993). It is not sufficient to test the release of drugs from a drug delivery system using a single dissolution medium because the release of drug may be affected by the changes in pH of the GIT fluids as the drug passes from the stomach to the intestine (Skelly et al., 1986 a and b). It is important for *in vitro* data to closely approximate the changes in pH that occur in the GIT (Amidon, et al., 1995). The *in vitro* dissolution properties of a drug can then be used as an index of its *in vivo* absorption (Stavchansky and McGinty, 1990).

3.2.2 *Dissolution Test Apparatus*

Since most drug delivery systems are required to undergo dissolution testing during their development, it is not surprising that there are over 100 types of

dissolution apparatus, which have been published (Parnarowski, 1974.) Stricker (1976) classified the different types of apparatus into three categories:

(i) Closed-compartment systems.

These systems have a large closed-compartment in which large volumes of dissolution fluid is placed. These large volumes of dissolution fluid help to simulate sink conditions. The most well known examples of this type of apparatus are the rotating basket (USP XXI) and the paddle method (BP 1998).

(ii) Open flow-through systems

Most of these systems are adaptations of the closed-compartment models and also use large quantities of dissolution fluid. The difference of this system is that only a small amount of this fluid is active in the dissolution process at a single point in time. Examples of this system are the oscillating tube (Marshall and Brook, 1969) and the stationary basket (Shah et al., 1974).

(iii) Dialysis and diffusion models

In this system, the dissolved drug passes through a membrane or dividing layer into a second compartment from which the drug is analysed. Examples of this system are the rotating basket (Marlowe and Shangraw, 1967) and the rotating bottle (Barzilay and Hersey, 1968).

It is necessary for dissolution apparatus to fulfil certain criteria. These include:

(i) The apparatus should be economically viable and it thus should be capable of fashioning the apparatus from standard laboratory equipment.

(ii) The apparatus should be scientifically pragmatic with less inherent variability than the products being tested.

(iii) The apparatus must supply an effective degree of agitation whose rate of agitation can be altered (Stavchansky and McGinty, 1990).

(iv) The apparatus is closed to prevent solvent evaporation, thermostated to regulate temperature, transparent to observe visual observation and allow for sample withdrawal without interrupting the agitation of the system (Shah et al., 1973).

All the apparatus mentioned above offer certain advantages and disadvantages according to the above criteria. The most commonly used types are the closed-compartment model examples.

3.1.1 *Methods for Changing the pH during In Vitro Testing*

The pH of the GIT ranges from approximately 1.2 in the stomach to 7.5 in the intestine. In order to reflect these changes during a dissolution test, it is necessary to change the dissolution fluid and replace it with a different fluid buffered at a new pH.

Most methods require that the entire dissolution fluid be replaced at once although the half-change method only requires half the dissolution volume to be replaced (Ritschel and Orth, 1967). The variable-volume method starts the dissolution test with a small initial volume which corresponds to half the final volume. The pH of the initial volume is then changed by adding buffer which increases the volume to the final amount. The advantage of this method is that it has no removal of volume. Although this method is easier, it still requires the preparation of several buffers (Sallans et al., 1988)

The above methods have the following disadvantages:

(i) They require the preparation of a series of buffers corresponding to the desired pH levels. These buffers need to be prepared accurately and ahead of time.

(ii) They require special apparatus for the accurate measurement of the quantities of medium to be added, displaced or removed

(iii) The uncontrolled turbulence caused by changing the dissolution fluid affects the dosage form and may cause loss of active material

Marty et al., (1997) describes a method of changing the pH of a dissolution fluid, using a sold buffer reagent which when added to the initial acidic dissolution fluid, increases the pH of the fluid. The reagent is added in unitised doses to achieve stepped pH conditions, which more closely follow the physiological gradient. This

method does not result in any significant variation in the volume of the dissolution fluid. The solid reagent is composed of a mixture of trishydroxymethylaminomethane (tris buffer) and sodium acetate. The method was tested in two types of apparatus, the paddle method and the flow-through cell. The dissolution tests were designed for slow-release drug delivery systems. Results were analysed using high performance liquid chromatography with UV detection. The reagent showed no UV absorbance between 240 and 700 nm. The method was compared to the conventional method of changing the dissolution fluid and the two methods were found to be equivalent with the solid buffer method obtaining lower standard deviations. In addition, the easy use of the solid buffer reagent is an advantage.

3.1.2 **Objective**

The purpose of this experiment is two-fold. First is to test the dissolution of drug in a stepped pH dissolution fluid, which would provide the same physiological conditions as that experienced by a drug delivery system in the GIT. This would assess the effect of pH on the release of the model drugs from the doughnut drug delivery system. The next will be to determine if the coated doughnut-shaped tablets produce a release rate that is more closely described by the zero-order rate than an uncoated doughnut-shaped tablet.

3.1.3. **Materials and Methods**

3.1.3.1 *Materials*

HPMC K4M premium EP and HPMC K15M premium EP were supplied by Colorcon Ltd. HPMC K4M and K15M have a viscosity of 3000 - 5600 and 11250 - 21000 cP respectively, as a 2% solutions in water at 20 °C. Both polymers had already been screened through a No. 40 standard sieve. Caffeine (Saarchem, S.A) and Ibuprofen (Nicholas Piramal Ltd., India) were ground and passed through a 212 μm aperture sieve (Endcotts Test Sieves, Ltd., England). Tris buffer and sodium acetate anhydrous were supplied by Merck (S.A.). All other reagents used were standard laboratory grade.

3.1.3.2 *Preparation of Compressed Tablets*

Tablets were prepared as previously discussed in section 2.3.3.3. The formula for the tablet coating layers was 10%$^{w}/_{w}$ gelatin in HPMC K15M and were directly compressed. The coating layers were compressed to a hole size of 5 mm to coat the caffeine cores and 7 mm to coat the ibuprofen cores. The core formula for caffeine consisted of 5%$^{w}/_{w}$ HPMC K4M and was compressed with an inner hole of 5mm.The caffeine core tablets were compressed to a hardness of 24.285 N (± 3.191). The core formula for ibuprofen was 15%$^{w}/_{w}$ HPMC K4M and was compressed with an inner hole of 7mm. The ibuprofen cores were compressed to a hardness of 8.671 N (± 3.988).

Core tablets were then recompressed with the coats to a form a coated doughnut-shaped tablet. The caffeine coated doughnut-shaped tablets were recompressed to a hardness of 82.142 N (± 8.681) and the ibuprofen tablets were recompressed to a hardness of 14.171 N (± 2.451) as before in section 2.4.3.2. The uncoated cores to be tested were also recompressed using the same punches and settings as the respective coated cores in order to achieve the same relative hardness. The weights of the core and coat layers of both caffeine and ibuprofen are listed in table 3.1.1. The weights of the coated tablets are also listed in table 3.1.1

TABLE 3.1.1

Mean weight of the core layers, coating layers and coated doughnut-shaped tablets

Formulation	Mean weight (mg) ± SD (n=20)
Caffeine	
Core layer	323.655 ± 7.578
Coat layer	83.570 ± 3.485
Coated tablet	494.997 ± 16.166
Ibuprofen	
Core layer	203.775 ± 9.515
Coat layer	54.210 ± 1.675
Coated tablet	311.027 ± 10.108

3.1.3.3 *Dissolution Studies*

The B.P. 1998 paddle method was used in all dissolution studies with a 6-beaker Caleva model 7ST dissolution tester. A solid buffer reagent was used twice during the dissolution to modify the pH of the dissolution fluid. The reagent was composed of a mixture of 2.28g of tris buffer and 1.77g of anhydrous sodium acetate to form a unit dose size of 4.05g. A volume of 1000 ml was used as the dissolution medium, which was equilibrated at 37°C ± 0.5 °C. The composition of the dissolution medium was as follows: 31.6 ml of 1 N hydrochloric acid, 2g of sodium chloride and distilled water to 1000 ml. The pH of the initial dissolution fluid was 1.5. The first dose of reagent was added after 1 hour to adjust the pH of the dissolution fluid to 4.5 and the second dose was added after 3 hours to adjust the pH to 7.2. The high solubility of the buffer reagent in the moving medium ensured that the target pH was reached rapidly.

All experiments were carried out at 50 rpm. At selected time intervals 2 ml samples were withdrawn and analysed using a Beckman DU 650 spectrophotometer. Samples were only withdrawn until such time as the doughnut-shaped tablet no longer maintained its shape. All samples were filtered through a 0.45 μm filter. For the release of caffeine, samples were analysed as discussed in chapter 2.2.3.8. Ibuprofen was analysed at a wavelength of 265 nm instead of a wavelength of 216 nm because tris buffer shows U.V. absorption at wavelengths below 240 nm. The buffer reagent did not show any absorption at the wavelengths studied.

3.1.3.4 *Statistical Analysis*

The data was analysed according to the Korsmeyer et al., (1983) equation as was previously described in section 2.3.3.5. The time exponent *n* and the release rates of the coated and uncoated doughnut-shaped tablets were calculated and then subjected to a LSD analysis of variance test, to check for a significant difference.

3.1.4 **Results and Discussion**

Table 3.1.2 lists the calculated time exponents calculated using equation 2.3.2, the correlation coefficients of the time exponents, and the average release rates of caffeine and ibuprofen from both coated and uncoated doughnut-shaped tablets.

TABLE 3.1.2

Mean time exponents, correlation coefficients and release rates from the coated and uncoated doughnut-shaped tablets

Formulation	Exponent *n* value ± SD (n=9)	Correlation Coefficient ± SD (n=9)	Mean Release Rate (ug/hr) ± SD (n=9)
Caffeine			
Coated	1.002 ± 0.089	0.989 ± 0.004	24.384 ± 2.667
Uncoated	1.076 ± 0.051	0.990 ± 0.002	64.591 ± 5.342
Ibuprofen			
Coated	1.003 ± 0.048	0.986 ± 0.006	17.154 ± 2.949
Uncoated	0.989 ± 0.034	0.964 ± 0.009	25.571 ± 4.347

Both the coated and the uncoated doughnut-shaped tablets have a time exponent *n* which is close to1 indicating that zero-order release kinetics are followed. However, the time exponent *n* for both caffeine and ibuprofen is closer to zero-order with the coated tablets (*n* = 1.002 for caffeine and 1.003 for ibuprofen) than with the uncoated tablets (n = 1.076 for caffeine and 0.989 for ibuprofen). When the doughnut-shaped tablet is coated on the upper and lower bases, restricting drug release to the lateral sides of the tablet, the decrease in the outer lateral surface area is balanced by an increase in the inner lateral surface area. The surface area of a coated doughnut-shaped tablet remains constant and therefore allows for improved zero-order release.

The changes in pH of the dissolution fluid do not affect the zero-order release. This can be seen from the graphs of release rate versus time in figure 3.1 and 3.2. The solid buffer reagent method allows us to achieve these changes of pH with ease The time exponent for the uncoated caffeine tablet is greater than one, showing a slight negative deviation in the rate of release, which can be clearly seen in figure 3.1. The release rates of ibuprofen show a burst effect before settling into zero-order release for both the coated and uncoated tablet (figure 3.1).

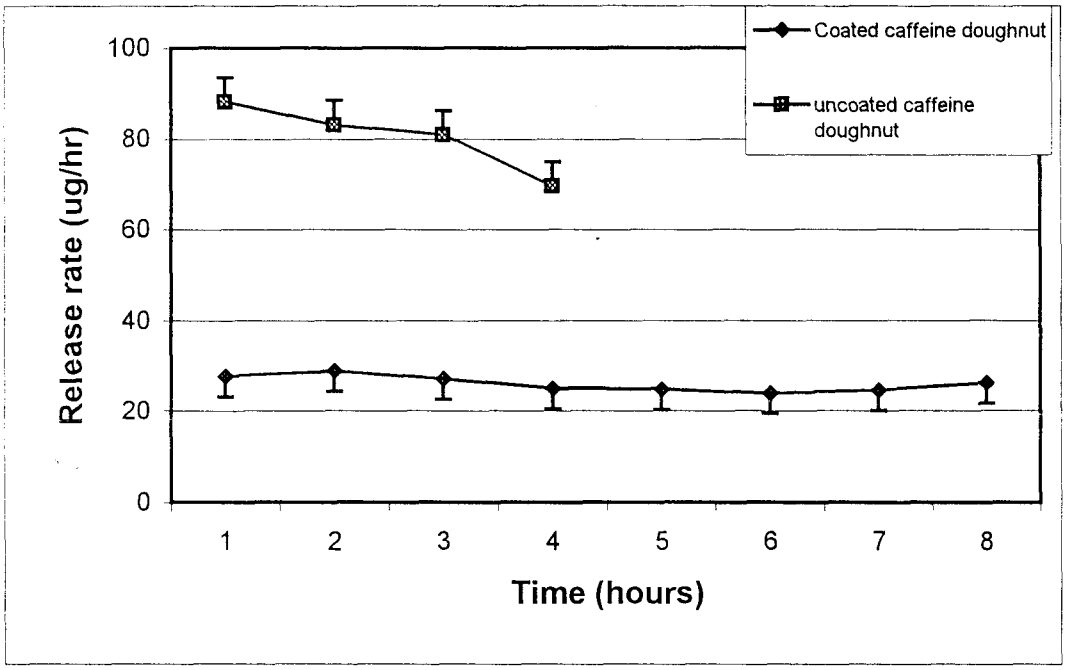


Fig 3.1 Graph of the release rate of caffeine from the coated and uncoated doughnut-shaped tablet.

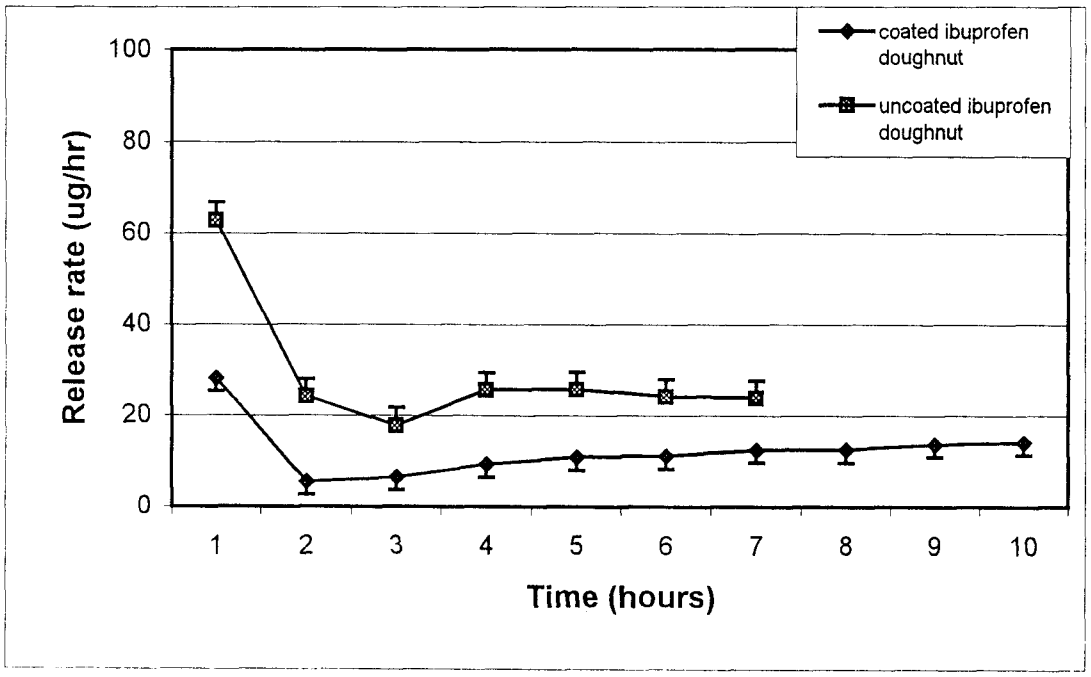


Fig 3.2 Graph of the release rate of ibuprofen from the coated and uncoated doughnut-shaped tablet.

The release rates of the uncoated tablets are significantly higher for both caffeine and ibuprofen. The uncoated caffeine tablet has an average release rate of 64.591 μg/hr as compared to 24.384 μg/hr of the coated tablet. The uncoated ibuprofen tablet has an average release rate of 25.571μg/hr as compared to 17.154 μg/hr of the coated tablet. This is due to the greater surface area available for drug release. When the doughnut-shaped tablet is partially coated, the drug release is restricted to the lateral sides of the tablet and the inner hole, but when the tablet is uncoated, drug release can take place from the top and bottom of the tablet as well. The difference in release rates of the coated and uncoated tablets is greater for caffeine than ibuprofen due to the soluble nature of caffeine. Owing to its faster release rate and greater surface area available for erosion, the uncoated tablets maintained their doughnut shape for a shorter period than the corresponding coated tablet.

Therefore, although both the coated and uncoated tablet allow for zero-order kinetics, the coated doughnut-shaped tablet shows better zero-order performance. Its time exponent is closer to 1.0 and it maintains its shape for a longer period, which allows for a longer period of zero-order release. It is thus better to produce a coated doughnut-shaped tablet for the zero-order release of both soluble and insoluble drug.

4.0 CONCLUSION

The objectives of this study were to produce a coated doughnut-shaped tablet, which released its drug at a zero-order rate and could be produced with a technology suitable for manufacture on a commercial scale. The coated doughnut-shaped tablet developed in this research study is an effective drug delivery system that allows both these objectives to be achieved.

The coated doughnut-shaped tablet released its active drug at a zero-order rate. This was confirmed using the Korsmeyer et al. (1983) relationship and the time exponent n, where the time exponent n equals 1.0 was indicative of zero-order drug release. The coated doughnut-shaped tablet released both soluble and insoluble model drugs at a zero-order rate. Caffeine, the model soluble drug, had a time exponent value of 1.002 ± 0.089 and ibuprofen, the model insoluble drug, had a time exponent value of 1.003 ± 0.048. This drug delivery system is thus applicable to a wide variety of drugs. The coated doughnut-shaped tablet was tested against the uncoated doughnut-shaped tablet and was proved advantageous in two areas. Firstly, the coated doughnut-shaped tablet produced a time exponent that was closer to 1.0 and thus zero-order drug release. Secondly, the coated drug delivery system allowed for a longer time period of zero-order release. The caffeine coated doughnut-shaped showed a zero-order release period of 8 hours as compared to 4 hours of the uncoated tablet. The ibuprofen coated doughnut-shaped tablet showed a zero-order release period of 10 hours as compared to 7 hours of the uncoated tablet.

The coating layers of the doughnut-shaped tablet were composed of 10% $^{w}/_{w}$ gelatin in HPMC K15M. This combination had both good flow and compressibility properties as well as the advantage of being directly compressible. In addition, this combination adhered to the tablet core until the core no longer maintained its shape and was relatively impermeable to drug release although it was composed of hydrophilic polymers that would eventually dissolve.

The concentration of HPMC in the core layer and the size of the inner hole were the most important factors with regard to ensuring zero-order release over an 8 to 12 hour period. The results showed that a concentration of 5 % $^{w}/_{w}$ HPMC with an inner hole size of 4.5 mm was the most suitable combination for caffeine and a concentration of 15 % $^{w}/_{w}$ HPMC with an inner hole size of 6.5 mm was the most suitable combination for ibuprofen.

The coated doughnut-shaped tablet is also easy to manufacture, as all that is required are the specially designed punches described in this research. These punches fit any Manesty tabletting press, but punches suitable for other types of tabletting press could also be manufactured. Punches could also be manufactured with larger or smaller inner rods in order to produce a coated doughnut-shaped tablet with a larger or smaller inner central hole.

Both the coating and core layers of the coated doughnut-shaped tablet can be produced automatically but the feeding of the core between two coating layers and recompression was done by hand. It is possible to automate this by adapting feed-shoes to sequentially deliver into the final compression die, first a coating layer,

followed by a core layer and then finally the second coating layer. When the tablet cores were produced from a granule sieve size of 0.63 μm, both the uncoated cores and the coated tablets passed the B.P. tests of uniformity of weight and friability. This compliance with the B.P standards also ensures that automated production of the coated doughnut-shaped tablets is possible.

4.1 **RECOMMENDATIONS**

The coated doughnut-shaped tablet has only undergone *in vitro* dissolution testing. Although *in vitro* testing can supply useful and valid information regarding the release of drug from the drug delivery system, it cannot totally simulate conditions in the GIT. *In vivo* release studies still need to be performed in order to obtain important pharmacokinetic parameters and also to develop an *in vitro/in vivo* correlation.

It is possible to examine several other variables with regard to the coated doughnut-shaped tablet. It may be desirable to test the coated doughnut-shaped tablet using other polymers. The advent of new polymers with new properties could improve the coated doughnut-shaped tablet as these new polymers could reduce the swelling that the tablet undergoes and perhaps prolong the zero-order release period to 24 hours. It is also possible to experiment with different hole sizes between the 4.5 mm and 6.5 mm used in this study.

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