University of Strathclyde
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Pulsed-Release Drug Delivery and Development of the Time-Delayed Capsule

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DEDICATION

I would like to dedicate this work to my Mum and Dad who have constantly supported me throughout my life, and to Claire who has looked after me through the entire period of these studies.

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CONTENTS

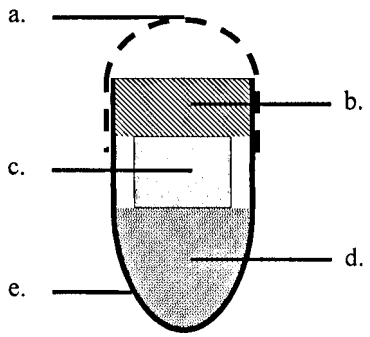
ABSTRACT

The aim of the present study was to optimise a Time-Delayed Capsule (TDC) formulation for use in clinical practice. The TDC consists of a hard gelatin capsule coated with ethyl cellulose, making it water impermeable. An expulsion excipient and drug-containing tablet is situated within the capsule, and the opening is sealed with an erodible tablet (ET) consisting of hydroxypropylmethyl cellulose and lactose. Following ingestion, gastrointestinal fluids cause the ET to erode allowing fluids to enter the capsule and the expulsion excipient swells to expel the drug tablet. The maximum force of compression (F_{max}) for coated capsules was determined pre- and post-exposure to a 90% RH and a 'capsule integrity ratio' (*CIR*) was calculated. Capsules coated with an organic solvent-based technique were found to maintain greater integrity ($CIR \approx 0.38$) than an aqueous based coated capsule ($CIR = 0.18$). ETs manufactured with 15, 24 and 30% HPMC and were found to correspond to lag-times of 1, 3 and 5 hours before drug release. A wet granulation-processing step, to prepare ETs, increased lag-times, particularly with low HPMC concentrations. Microwave dielectric analysis on the wet granulate prior to tableting gave water dipole relaxation times of 2.9, 5.4 and 7.7 $x10^{-8}$ ms for each HPMC concentration respectively. This indicated the extent of HPMC mobility within the granulation allowing spreading leading to extended ET erosion and increased TDC lag-time. Erosion kinetics of ETs was determined as a rapid first order period followed by zero order erosion. The culmination of this work was a clinical study in man, and a good *in vitro–in vivo* correlation was shown. In conclusion the Time-Delayed Capsule has been developed to allow drug delivery between lag-times of 1 and 5 hours. The TDC can exploit the potential for temporal targeting of wide range of disease states.

CHAPTER 1. INTRODUCTION

1. INTRODUCTION

The Time-Delayed Capsule (TDC) presented in this study (Figure 1.1) retains the characteristics of the original patented device (Stevens et al., 1995). It consists of a size 0 hard gelatin capsule body, coated to make it insoluble in water; a high swelling expulsion excipient; a drug containing tablet and an erodible tablet (ET).



a. Gelatin cap
b. Erodible tablet (ET)
c. Drug loaded tablet
d. Expulsion excipient
e. Insoluble coated gelatin capsule

Figure 1.1. The Time Delayed Capsule (TDC).

After ingestion, the gastrointestinal (GI) fluids erode a hydroxypropylmethyl cellulose (HPMC)/lactose erodible tablet (ET), while the capsule contents are kept dry, protected by the thick ethyl cellulose coat on the capsule. After a specific lag-time determined by erosion of the ET, water enters the TDC and causes the expulsion excipient to swell rapidly. This pushes the undissolved drug tablet free of the capsule body. Disintegration occurs outside the capsule and drug release is fast, allowing a true pulse-release profile to be obtained.

The initial part of this introduction will review various disease states and their potential to be treated with this type of technology. Two areas of pulsatile release involving temporal targeting and site-specific drug delivery will also be described. The literature reports of pulsed release technologies, and their different methods of lag-time control will be discussed before a detailed consideration of the erosion process controlling the operation of the TDC is undertaken.

The research described in this thesis culminates with the use of the TDC in a clinical study and a description of the anatomical considerations in the GI tract is given. A brief introduction of the scintigraphic and pharmacokinetic methods employed in the human study concludes this introduction.

1.1. CIRCADIAN RHYTHMS AND DISEASES

Many systems in the human body such as cardiovascular, pulmonary, hepatic and renal show variation in their function throughout a typical day. Each is controlled within a periodicity of 24-hours. They are naturally synchronised to the internal body clocks, and are controlled by the sleep-wake cycle. This synchronisation of individual circadian rhythms is important in the maintenance of health within the human body, and each bodily system exhibits a peak time of functionality in accordance with these rhythmical cycles. Disease states affect the function of some of these systems in the body, and as a consequence they too exhibit a peak time of activity within a circadian rhythm.

Disease	Peak time for appearance of symptoms (clock time)	Authors
Allergic rhinitis	Morning*	Rheinberg, A.E.
Arthritis		
Osteoarthritis	21.00	Labrecque, G., Reinberg, A.E.
Rheumatoid	06.00-09.00	
Asthma	19.00-07.00	Smolensky, M.H.
Cardiovascular disease		
Angina pectoris	06.00-12.00	Bogaty, P., Waters, D.D.
Acute myocardial infarction	08.00-11.00	
Diabetes	06.00	Jarret, R.J.
Peptic ulcer disease	21.00	Moore, J.G.

Table 1.1. Common disease states and their circadian rhythms.

*Only 60% of patients indicated acute morning symptoms.

Clinical research has been conducted with varying numbers of study subjects to determine the exact nature of the circadian rhythms associated with disease states. Peak time of disease activity is shown (Table 1.1). Knowledge of these rhythms has proved useful for diagnosis and treatment (Elliott, 2001), for example osteoarthritis may be distinguished from the rheumatoid form by the time of day at which it is most active. Conventional therapies rely on the maintenance of a constant blood plasma level of drug (Khan et al., 2000), and successful treatment often involves multiple administrations of a single dose over time. It is apparent, by observing the circadian rhythms exhibited by the above disease states that the conventional ideology of maintaining a constant drug level to treat ailments might not be suitable. A controlled variation in drug concentration may be more suitable to coincide with peak effects of the diseases. This also has implications for the minimisation of side effects (Yano et al., 2002) as targeting to a specific rhythm of a disease can result in the reduction of dosage of a specific drug. As a result those side effects associated with the drug are also reduced. In addition targeting rhythms may also prevent the interaction of certain drugs and so a wider treatment regime may become available when treating multiple ailments.

Over 100 drugs displaying temporal characteristics have been identified (Lemmer, 1991). Examples of these are theophylline, having an increased effect in the evening corresponding to the peak affect of asthma, and propranolol displaying more activity at the times indicative of cardiovascular disease. It is clear that there is an extensive opportunity for a delivery system designed to specifically target times associated with peak drug effects. This may be achieved by a strict dosing regime such as parenteral administration, as is already the case for the treatment of diabetes. However, this approach is not always convenient, particularly for overnight dosing, as a considerable degree of patient compliance is required. Clearly a simple orally administered dose would be ideal for temporal targeting to the circadian rhythms of specific diseases.

1.2. MODULATION OF ORAL DRUG DELIVERY

Two options are available for the temporal targeting of oral dosage forms: externally modulated or self-modulated. External modulation devices can alter their drug release in response to an externally generated signal such as: an electronic input to alter rate of delivery from mechanical pump, an oscillating magnetic field, ultrasound, temperature or an electronic signal. Self-modulated devices use several approaches as rate controlled mechanisms: pH sensitive polymers, enzyme substrate reaction, pH sensitive drug solubility, competitive binding, and metal concentration dependant hydrolysis (Goldbart and Kost, 1999). External modulation was rejected for the current study as the need for specialised external equipment makes it undesirable for general use.

By the options indicated above, the self-modulation method indicates that possibilities for site-specific drug delivery are available. In addition to delivering a dosage form attuned to the circadian rhythms of disease states it may also be desirable for certain therapies to be delivered to specific sites in the GI tract. For example peptic ulcer disease may either show ulceration in the stomach or the duodenum and although it may be treated by temporal means, specific targeting would provide an improved therapeutic effect. Conditions such as irritable bowel disease (IBD) (Crohn's disease or ulcerative colitis) and bowel cancer also have the potential to be treated in this way. Conventional therapies for the treatment of IBD rely on daily administration of high doses of drug. Crohn's disease is often treated with high dose anti-inflammatory agents (Van Hogezand et al., 2001), and in the case of this corticosteroid treatment there is a high risk of dependency, relapse and the development of serious irreversible adverse effects (Rutgeerts, 2001). Thus localised treatment would also reduce the dosage level and subsequent side effects. Preferential absorption of drugs has also been demonstrated for different sites of the GI tract. For example leuprolide shows absorption variability throughout the GI tract in rats, with maximum absorption available in the colon (Zheng et al., 1999).

Self-modulation, available for delivery to the large intestine focuses on protective coatings and biodegradable polymers. These polymers may be used to target specific

enzyme activity or dissolve at specific sites in the GI tract when a pH change occurs (Table 1.2).

Substance	Comments	References
Azo bond containing hydrogels	Specific enzyme activity: Azo-reductase in the colon due to resident bacteria. Swelling controlled by the localised pH of the colon.	Brønstead and Kopacek, 1992; Lee et al., 1999; Van den Mooter et al., 1994
Enteric coatings	Commercially available Eudragit® (Rohm) dissolves at specific elevated pH.	Gazzaniga et al., 1995; Gupta et al., 2001; Kao et al., 1997
Glycosidic bond containing hydrogels	Specific enzyme activity: Glycosidases in the colon. Used as a film coating onto the drug containing component	Brønstead et al., 1995; Wakerly et al., 1996
Guar gum, Pectin, Xylan	Enzymatic degradation: The result of resident bacteria in the distal GI tract	Adkin et al., 1997; Ahrabi et al. 2000; Gliko-Kabir et al., 2000; Krishnaiah et al., 1998; Macleod et al., 1999; Sinha and Kumria, 2001a
Enzyme containing substrates	Enzymatic degradation of pectin by pectinase irrespective of external environment	Krögel and Bodmeier, 1999a

Table 1.2. Manufacturing options available for self-modulation in site-specific drug delivery.

A large variety of polymers, such as pectin, xylan guar gum and azo bond containing hydrogels are susceptible to enzymatic degradation as a result of resident bacteria in the colon. Glycosidic bonds are also susceptible to elevated hydrolysis as a result of enzymatic activity in the colon; these are generally introduced as a film coating. These self-modulated systems are reliant on inter-individual uniformity of pH and/or the equal presence of microbial fauna in the colon. However variability does exist between individuals, particularly with pH (Rubinstein et al., 1995) and so much more research needs to be performed in order to finely hone these methods of modulation. As the presence of water is universal throughout the GI tract, it was this that has been the focus of control for the self-modulated pulsatile drug delivery devices, described in the next section.

Site-specific delivery may be used to protect drugs such as proteins and peptides. These may be sensitive to proteolytic enzymatic degradation or a low pH associated with gastric secretions. In addition to the protective agents indicated above, drugs may be combined with various moieties to form prodrugs (Table 1.3). These are designed to pass intact and unabsorbed in the upper GI tract, undergo a biotransformation in the colon, and then release the active drug molecule (Sinah and Kumria, 2001b). Biotransformation is carried out by enzymatic activity, usually of bacterial origin, present in the colon.

Again, further research is required to provide a wide range of treatments using the prodrug approach and therefore the use of a self-modulated device is preferable.

Prodrug types	Comments	References
Azo polymeric	Large polymeric molecules.	Brown et al., 1983
Example: N-(2-hydroxypropyl)methacrylamide (Poly) + 5-aminosalicylic acid (ASA) ↓ Poly-ASA	Enzyme: Azo reductase. Cleavage at the azo bond liberates the drug in the colon	
Glycosidic	Small molecules.	Friend et al., 1992
Examples: • Dexamethasone -β-D-glucoside • Prednisolone -β-D-glucoside	Enzyme: Glycosidase. Anaerobic microflora of the large bowel provide the highest activity of glycosidase in the intestine. Enzymatic hydrolysis liberates drug	

Table 1.3. Examples of prodrugs for site-specific drug delivery.

1.3. PULSATILE DRUG DELIVERY

1.3.1. PELLET AND TABLET DEVICES

As mentioned the presence of water throughout the GI tract is utilised in the function of the main pulsatile drug delivery (PDD) systems currently being researched. A PDD system must utilise either external or self-modulation to produce a lag-time before the complete and rapid release of drug. Three methods that use GI fluids to control lag-time are: (i) floating on the stomach contents, (ii) swelling mechanisms, and (iii) erosion/degradation of a component or outer protective agent/coating.

Floating dosage forms consist of low density materials or those that rapidly lower their density to enable buoyancy on the contents of the stomach (Figure 1.2) to increase gastric residence times. The residence time of the dose is controlled by an increase in density or complete emptying of the stomach contents (described in Section 1.5). Low-density polyvinyl pyrrolidone (Iannuccelli et al., 2000), low density hollow polycarbonate microspheres (Joseph et al., 2002) and rapidly swelling porous hydrogel composites (Chen et al., 2000), have all demonstrated floating properties. However none of these formulations have been effectively developed to produce a PDD system. Sigmoidal release and not a true pulse release has been achieved using low-density calcium alginate beads (Lee et al., 1998). These are insoluble in the stomach (Dürig et al. 1999) and dissolve as the pH rises in the small intestine (SI). Using an effervescent core to generate carbon dioxide to produce a low-density enterically coated tablet (Krögel and Bodmeier 1997; 1999b) a true PDD has been achieved. The device remains intact in the low pH of the stomach with the enteric coat dissolving at the elevated pH of the SI.

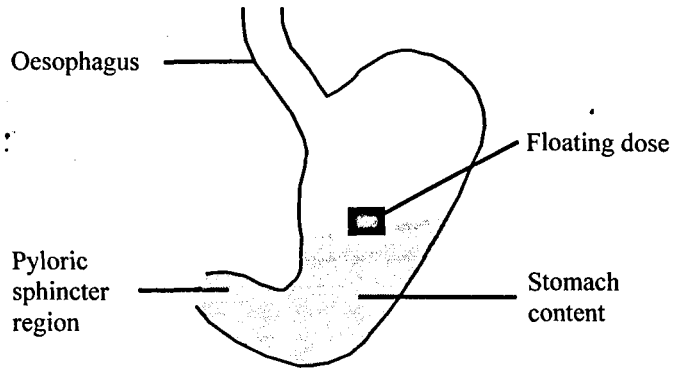


Figure 1.2. Schematic of the stomach showing retention of a floating dosage form.

Swelling mechanisms are normally associated with the incorporation of a drug containing osmotic core and a semipermeable outer layer (Figure 1.3). Water ingress into these devices causes them to swell internally resulting in a rupturing of the external coat to release the drug in a true pulsatile fashion. This type of delivery system consists of multiparticulate pellets and is summarised in Table 1.4.

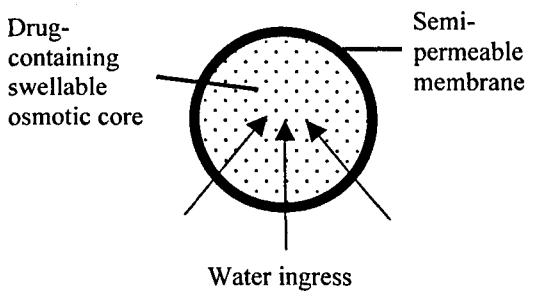


Figure 1.3. Osmotic core pulsed release pellets.

Granular based pellet systems have a major disadvantage compared to tablets or capsules due to their size. Their osmotic function is limited to a finite time as film rupturing occurs with very little water ingress. This makes it almost a necessity for them to be incorporated into a coated capsule or tablet. Site-specific delivery is also

a problem due to the variability of GI transit that may be encountered with multiple small particles, staggering dose delivery at different sites.

Osmotic system	Comments	Reference
Particulate delivery system	Permeability reducing agent and soluble component are control rate of water ingress. Swellable core ruptures outer coat.	Chen, 1993a
Multiparticulate delivery system	Diffusion of soluble core in a series of pulses* can provide multiple doses and lag-times.	Chen, 1993b
Multiparticulate	Sigmoidal release†. Eudragit® RS coating with succinic acid incorporated to vary permeability.	Narisawa et al., 1994
Time-controlled explosion system (TES)	A drug coated inert core coated with an insoluble swellable layer is in turn coated with an insoluble semi-permeable outer layer	Ueda et al, 1994a; 1994b; 1994c
Membrane coated pellet	Lipophilic plasticizers alter permeability of the coat to control water ingress.	Schultz et al., 1997; Schultz and Kleinebudde, 1997
Particulate pulse release system	Permeability of the outer coat is controlled by photo-initiation. Length of exposure to a UV source affects permeability.	Kok et al., 2000
Colon targeted	Eudragit® outer coat to dissolve at pH 6.8 then allow diffusion of drug through a diffusive coat.	Gupta et al. 2001

Table 1.4. Summary of pellet based formulations showing pulsed release.

*Outer coat remains intact;

†Sustained release following a lag-time.

Tablet devices have also been developed to produce a pulsatile release. Several types incorporate an osmotically active core as with the pellet forms listed above (Table 1.4). Others make use of erodible polymers to slowly expose a single layer or multiple layers of drug enabling multiple pulses. These are summarised in Table 1.5.

Pulsed release from the osmotically activated devices tends to approach a sigmoidal profile. An example of this is the OROS® device which provides a sustained release profile following a lag-time. This is due to the fact that the pulse is initiated from within the still intact tablet, delaying drug diffusion. This is currently the only pulse-release device available for treatment and is marketed by Covera®. It is used to deliver the drug Verapamil as a calcium channel blocker for the treatment of cardiovascular disease.

Another problem with tablet devices is the production of laminated tablets of differing component layers. This is a complex procedure requiring specific formulation for drugs of differing solubilities or powder properties.

Device	Comments	Reference
Osmotic tablet (later developed as OROS® by Covera®)	Zero order delivery of drug followed by a pulsed delivery. OROS® incorporates a hydrophilic barrier beneath a semi-permeable tablet coating.	Magruder et al., 1989.
Coated laminated tablet	Polymer layers erode in sequence with only one uncoated face.	Fujioka et al., 1991.
Time Clock®	A soluble drug-containing core coated with a variable thickness hydrophilic/hydrophobic polymer layer.	Pozzi et al., 1994.
Erosion tablet	Enteric outer coat dissolves in SI (> pH 5), then HPMC coat erodes to expose drug after a lag-time.	Gazzaniga et al., 1995.
Laminated tablet device	Laminated pH buffered layers to protect proteins erode and deliver in a series of pulses.	Jiang and Zhu, 2000.
Disintegration tablet	Drug containing core press coated with insoluble ethyl cellulose	Lin et al., 2001.
Press-coated tablets	A highly soluble drug containing core tablet is press coated with a disintegrating outer layer of L-HPC. Lag-time is controlled by varying the thickness of the outer layer.	Leokittikul et al., 2001a; 2001b.

Table 1.5. Summary of tablet formulations showing pulsed release.

1.3.2. THE DEVELOPMENT OF CAPSULE BASED DEVICES

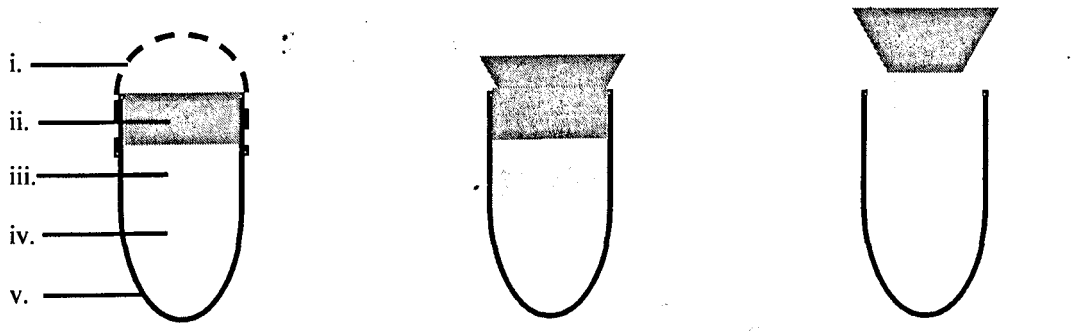
The use of a capsule based device has distinct advantages over the pellet and tablet systems described. Firstly a wide range of lag-times can be selected, to enable an increased range of temporal targeting to be available for a single device. Secondly, with the encapsulation of drugs within, their effect on the functionality of the device and its lag-time is minimal. This allows for the inclusion of a broad spectrum of therapeutic agents. Thirdly, site-specific targeting particularly to distal regions of the GI tract is possible due to the robustness of these capsular devices.

The capsule itself may be coated with a semi-permeable or water impervious layer. A semi-permeable coat provides the basis for an osmotically controlled device. The pressure caused by internal swelling can be used to force the capsule open or to allow rupturing of the capsule body to deliver the drug. This is the same mechanism shown with some of the pellet preparations. A water impervious, low-density capsule may float on the gastric contents to provide a lag-time. Whilst a non-floating device requires a barrier to external GI fluids. The capsule cap may be removed by a swelling osmotic action mechanism or in another system a seal may be inserted into the end of the capsule body, which is removed after the desired lag-time. Capsule based devices are summarised in Table 1.6.

Capsule device	Comments	References
Pulsincap™	A water impermeable capsule body consisting with hydrogel plug. Plug length and insertion depth controls lag-time control (Figure 1.4a).	McNeill et al., 1990.
Egalet™	An insoluble tube* with erodible plugs inserted at either end. Plugs are comprised of selected M_w PEG, waxy materials and surfactants. Composition controls lag-time (Figure 1.4b).	Bar-shalom and Kindt-Larson, 1993
Chronset®	An osmotically coated active compartment within a semipermeable cap This swells to pushes against a rigid barrier layer and removes the cap. Lag-time is controlled by the osmotic potential (Figure 1.4c).	Wong et al., 1994
Time-Delayed Capsule	Water impermeable coat on gelatin capsule with an erodible tablet. Erosion of the tablet allows water to enter the capsule, swelling of an expulsion excipient causes expulsion of the drug.	Stevens et al. 1995; Ross et al., 2000a; 2000b.
Programmable Oral Release Time (PORT) System®	A water-permeable coated gelatin capsule with a swellable osmotic core and sealed with an insoluble wax plug. The contents swell to remove the plug. The wall thickness and composition, concentration of the osmotic contents and the length of the hydrogel plug control lag-time (Figure 1.5a).	Amidon et al., 1995; Crison et al., 1995.
Pressure-controlled colon delivery capsule (PCDC).	Internally coated capsule. Drug is filled into the PCDC in an oily liquid base, and sealed with an insoluble waxy plug. Elevated pressure exerted by the ileocaecal junction, ruptures the device to release drug into the colon (Figure 1.5b).	Takaya et al., 1995; Jeong et al., 2001; Shibata et al., 2001.
Colon-targeted delivery capsule (CTDC).	Enteric outer coat dissolved in the SI to expose an acid soluble layer, which dissolves in the colon.	Ishibashi et al., 1999.
Hydrophilic sandwich capsule	HPMC layer sandwiched between a large outer gelatin capsule and a smaller inner gelatin capsule-containing drug. Erosion of the HPMC layer provides a lag-time, controlled by grade and/or thickness (Figure 1.5c).	Ross et al., 2000c; Stevens et al., 2000.

Table 1.6. Capsule based pulsed delivery devices.

*Capsule shaped.

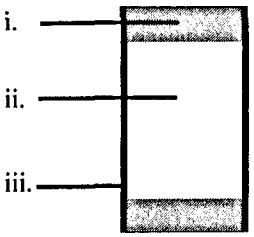


i. Soluble cap
ii. Hydrogel
iii. Drug layer
iv. Expulsion excipient
v. Insoluble coat on gelatin capsule

The plug swells in water and forms a frustro-conical shape. This pulls itself free of the insoluble body.

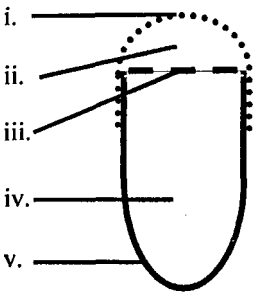
Removal of the plug causes rapid expulsion of the contents from the device.

(a) The Pulsincap™ capsule device.



i. Erodible plug
ii. Drug containing core
iii. Insoluble tube

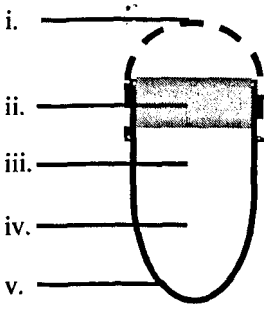
(b) The Egalet™ device



i. Semi-permeable cap
ii. Osmotic core
iii. Rigid barrier layer
iv. Drug containing compartment
v. Insoluble coat on gelatin capsule

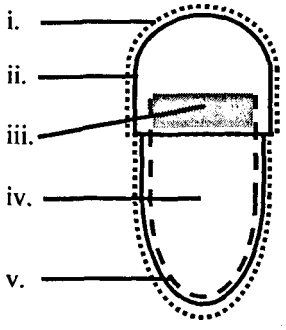
(c) The Chronset® device.

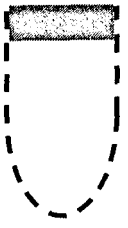
Figure 1.4. Pulsed release capsule devices.



i. Soluble gelatin cap
ii. Waxy plug
iii. Drug containing layer
iv. Osmotic compartment
v. Semi-permeable coat on gelatin capsule

(a) The PORT System®

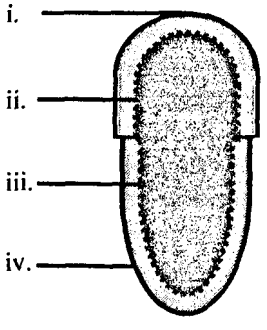




The outer enteric coat dissolved on reaching the SI, the gelatin component quickly dissolved to leave a fragile balloon like ethyl cellulose structure coated body High pressure in the colon causes rupturing

i. Enteric coat
ii. Gelatin capsule
iii. Waxy plug
iv. Drug containing core
v. Insoluble internal coat

(b) Structure and function of the PCDC.



i. Soluble gelatin outer capsule
ii. Soluble gelatin inner capsule
iii. Soluble drug containing core
iv. Methocel® layer

(c) The HS capsule

Figure 1.5. Pulsed release capsule devices.

The capsule based systems indicated above are subject to operational difficulties. The Chronset®, PORT System® and Pulsincap™ devices are all reliant on swelling mechanisms that result in the contribution of frictional forces. In the case of the Pulsincap® device the internal structure of the capsule is not of uniform surface roughness. This means that frictional forces vary as the hydrogel plug swells, leading to some degree of lag-time variability. The Chronset® device is subject to frictional forces on the external surface of the capsule as the cap is removed by an increase in osmotic pressure. In addition the rigid barrier layer, which acts as a swelling block, also has the potential to restrict the complete dissolution of drug from the core. The PORT System® is subject to the influence of frictional forces as the osmotic core swells to expel the waxy plug. However, additional studies have highlighted the importance of a tight fitting seal with the PORT System® achieved by the use of hot-melt wax plugs (Yu et. al., 1996), that prevented premature drug release.

The Egalet™ device is subject to a large amount of variability due to the reliance on uniform erosion at its terminal ends. A previous study involving a similarly constructed device highlighted the problem of asymmetrical erosion (Krögel and Bodmeier, 1999c). The formation of an ethyl cellulose pressure sensitive balloon structure in the PCDC must also provide some variability. Incidences of premature bursting due to the variability of GI pressure/force between subjects may occur. Also, owing to the flexible balloon structure formed after dissolution of the outer coat, the fit of the plug may be compromised.

The capsule based delivery system studied is an adaptation of the Pulsincap™ technology. The impracticable design of the swellable hydrogel plug and a complex mechanical insertion process led to the exploration of alternatives. An erodible tablet (ET), consisting of hydroxypropylmethyl cellulose (HPMC) and lactose was used instead. Previous studies by this group indicated the possibility of controlling the lag-time of such a device based on simple erosion experiments whilst eliminating some non-polymeric ETs. The use of HPMC still relies upon the GI fluids to control

the lag-time, and its erosion mechanisms have been well documented in sustained release formulations (Makino et al., 1996).

Many dispersible tablet formulations have made use of effervescent excipients such as sodium bicarbonate/citric acid mixtures; these may be used as expulsion excipients for pulsatile release (Gohel and Sumitra G., 2002; Krögel and Bodmeier, 1997; 1999b). The Pulsincap™ device made use of the rapidly expanding agent; low-substituted hydroxypropyl cellulose (L-HPC) used in this present study.

1.4. HYDROPHILIC POLYMER EROSION

In a HPMC matrix tablet, the basic principle of hydrophilic polymer erosion involves water ingress followed by polymer dissolution (Makino et al., 1996). This step repeats sequentially until complete erosion of the tablet has occurred. Two distinct types of erosion can occur in a polymer-based tablet: bulk and surface erosion (Burkersroda et al., 1999). During the bulk erosion process, a polymer matrix erodes from the entire cross section of the tablet. Surface erosion is confined to the matrix surface. Which type of erosion occurs depends on the velocities of two processes: firstly, the diffusion of water into a polymer matrix and secondly the degradation of that matrix. If degradation is faster than diffusion then surface erosion occurs, with bulk erosion being prevalent if the converse is the case.

Figure 1.6 represents polymer erosion of HPMC from an erodible tablet. Initially dry matrix is a non-swollen system of entangled polymer macromolecules existing within the tablet structure (Zone 0). Water ingress causes the polymer to swell and become mobile, this process is referred to as polymer relaxation and is represented by Zone 1. The extent of this water ingress is controlled by the presence of porous pathways throughout Zone 1; controlling water percolation. This movement of the polymer chains, characterised by the relaxation, permanently changes the structure of the macromolecular network (or matrix) (Siepmann et al., 1999a).

After relaxation, polymer chains are at their maximum mobility, a process of polymer chain disentanglement then begins and forms Zone 2. This new zone is a gel layer, of partially disentangled and relaxed polymer molecules. A dynamic process of chain dissentanglement and re-entanglement occurs. At the periphery of Zone 2, an excess of water causes the appearance of a concentration gradient, which extends back to Zone 1. Some disentangled, free polymer chains are able to move through the gradient and form a small-unstirred layer of un-associated polymer chains indicated by Zone 3. The polymer chains are then easily separated and dissolve into Zone 4, a well-stirred large volume of solvent.

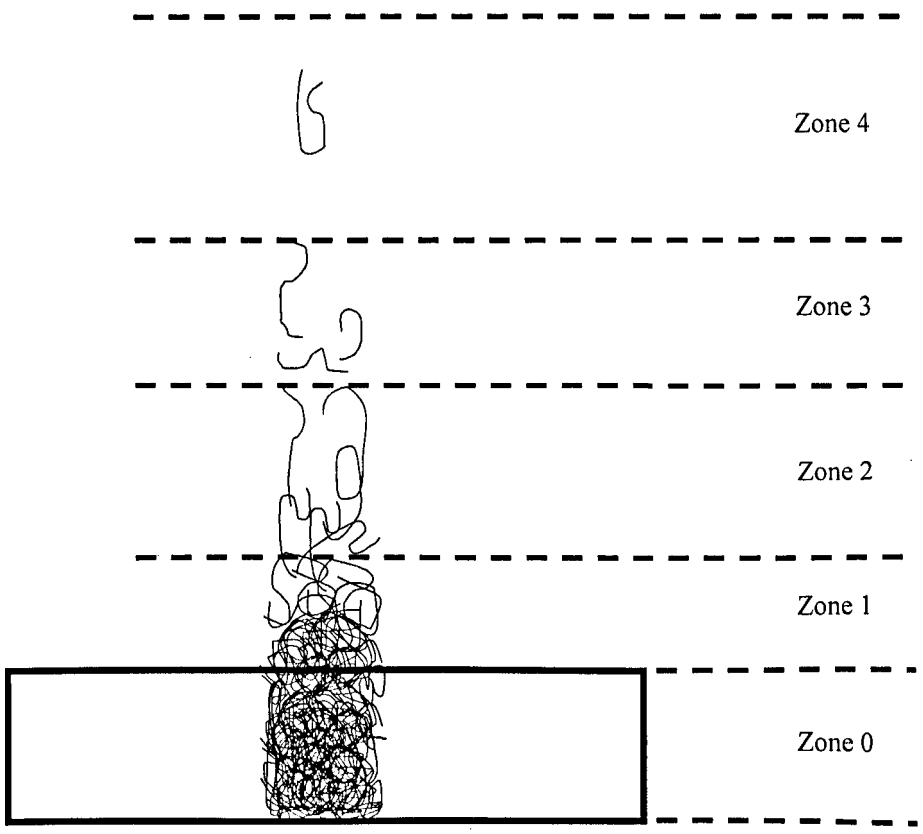


Figure 1.6. Schematic of chain dissentanglement of a HPMC polymer matrix.

In a well-stirred system, such as a dissolution vessel, sink conditions are maintained (Corbo, 1993). Below a certain polymer concentration the number of disentangling polymer chains exceeds the number of newly entangled chains resulting in destruction of the polymer network, as indicated in Zone 2. This critical

polymer concentration is known as the polymer dissentanglement concentration ($C_{p,\,diss}$) and is specific to the properties of a given polymer and its solvent. This precedes a second erosion factor (Reynolds et al., 1998), which involves the transport of the disentangled macromolecules to the bulk solution across an aqueous diffusion layer adjacent to the matrix, corresponding to Zone 3. The diffusion layer is characterised by a distinct polymer concentration gradient of variable thickness, which is dependant on the molecular weight (M_w) of the polymer. Polymer chains as well as water molecules are liberated from the matrix into the bulk solution phase (Makino et al., 1996). Convection and/or stirring leads to a homogenous distribution of the polymer chains within this bulk fluid.

The ET investigated in this study consists of HPMC and lactose. The inclusion of additives with HPMC can have a profound effect on the tortuosity of the porous pathways and hence the nature of erosion (Ford et al., 1985). Sodium ions can dehydrate the polymer and cause greater tortuosity of the gel layer, restricting polymer relaxation and hence slow erosion. Sugars such as lactose and sucrose decrease tortuosity, this causes greater erosion due to increased hydration. (Bain et al., 1991; Sungthongjeen et al., 1999). It has also been shown that drug release from HPMC matrices is affected by the pH in the surrounding media (Streubel et al., 2000a; 2000b). It might be expected that pH variation and the effect of hydrodynamic conditions through the GI tract may also affect erosion rate.

HPMC is commercially available as Methocel® and is used as a thickener, a binding agent, a film former, and water retention agent. It exists in different grades as indicated in Table 1.7.

Grade	Methoxyl substitution (%)	Hydroxypropyl substitution (%)	Viscosities available (mPa.s)
A	27.5-31.5	0.0	15, 400, 1500, 4000
E	28.8-30.0	7.0-12.0	3, 5, 6, 15, 50, 4000, 10000
F	27.0-30.0	4.0-7.5	50, 4000
J	16.5-20.0	23.0-32.0	5, 15, 100, 4000, 15000, 100000
K	19.0-24.0	4.0-12.0	3, 100, 4000, 15000, 100000

Table 1.7. Grades of Methocel® available.
(Dow Chemicals 1996a; Sheskey et al., 1994)

Each grade of Methocel® has different chemical properties owing to the different levels of substitution on the polymeric chain, and as such are recommended for different formulation purposes. A Methocel® grade is initially identified by its letter. This is then followed by its viscosity value in Millipascal-seconds (mPa.s), the letter 'C' or 'M' are often used to represent 100 or 1000 respectively. A suffix is sometimes used to denote special properties of the product. 'LV' is a low-viscosity grade, 'G' and 'S' are used to represent 'Granular' or 'Surface-treated' products. For example, K100LV is a low-viscosity K grade (4-12% hydroxypropyl substitution), and has a viscosity of 100 mPa.s.

K100LV is the lowest molecular weight HPMC grade generally recommended for use in sustained release matrix tablets (Dow Chemicals, 1996a). Higher M_w grades operate by diffusion of soluble drugs through a matrix system and show little erosion, these higher M_w grades would therefore have been unsuitable for the preparation of an ET for use in these studies.

Polymer type and composition are the main influence in gel layer thickness and its growth rate (Kim and Fassihi, 1997a). Predictions of the degree of polymer

erosion for different grades of HPMC can be made from using a scaling law equation relating to LV and 4M HPMC grades (Reynolds et al., 1998; Harland et al., 1988). These simple relationships indicated that K100LV grade afforded a suitable erosion rate under agitated conditions (80% eroded after 12 hours with no diluent). Increasing the quantity of HPMC is known to prolong erosion time (Reynolds et al., 1998; Ross et al., 2000a; Siepmann et al., 1999a) and this approach was used to provide control of erosion over shorter time range of 1-12hrs. The properties of K100LV can be modulated by the addition of a suitable soluble diluent, such as lactose.

The use of hydrophilic polymers in the preparation of sustained release formulations is well documented (Costa and Lobo, 2001). HPMC is amongst the most popular for this function and may be used in direct compression formulations to prepare sustained release tablets (Kawashima et al., 1993). The zero-order sustained release of a drug from such a tablet is indicative of the desired erosion kinetics for the ET. This can only be achieved with the maintenance of a constant surface area (SA) for erosion (Bar-Shalom et al., 1993; Conte et al. 1993; Yang and Fassihi, 1997), and release kinetics have been shown to change with SA (Bettini et al., 1994). As a result, release rates are variable with simple polymer matrix systems, making them incapable of attaining zero-order release (Yang and Fassihi, 1997). Encapsulation of a drug containing hydrophilic matrix tablet placed in the centre of a tube shields the tablet and enables disintegration to occur only at the tablet faces (Krögel and Bodmeier, 1999c). In the studies presented here with the ET situated within the coated capsule body, fluid access is restricted to the single exposed tablet face only, providing the possibility of a constant SA during erosion.

1.5. STRUCTURAL CONSIDERATIONS AND TRANSIT OF AN ORAL DOSAGE FORM IN THE HUMAN GI TRACT

1.5.1. THE STOMACH

The gastrointestinal (GI) tract consists of three sections: the stomach, the small intestine (SI) and the large intestine (colon). A pulsed release formulation must negotiate several or all of these regions before initiation of drug release. Each of these segments of the GI tract must be considered, particularly with respect to the human scintigraphic and pharmacokinetic study reported in Chapter 6.

The stomach (Figure 1.7) in its fasted state contains between 50-150 ml volume of liquid. This gastric fluid consists of greater than 99% water, produced in this fasted state at the rate of approximately 1.2 ml/min. This leaves through the pyloric sphincter to maintain a constant volume within the stomach. The lowest pH (1.5- 3) of the entire GI tract is found here and the main function of the stomach is to store and release food into the SI. This should maintain a constant calorific energy supply to the body. Upon ingestion of food there is a rapid increase in gastric fluid production, with an increase to approximately 1.7 ml/min. The appearance of a capsule in the fasted stomach is unlikely to increase gastric secretion since it has little or no nutritional value and a small volume (both stimuli for increased gastric fluid production; Seeley et al., 1995). As a result it will be subject to a continually replenishing acidic solution with an approximately 100 ml volume. The extent of the effect of the acidic medium on the function of a pulsed release capsule will depend on its gastric residence time.

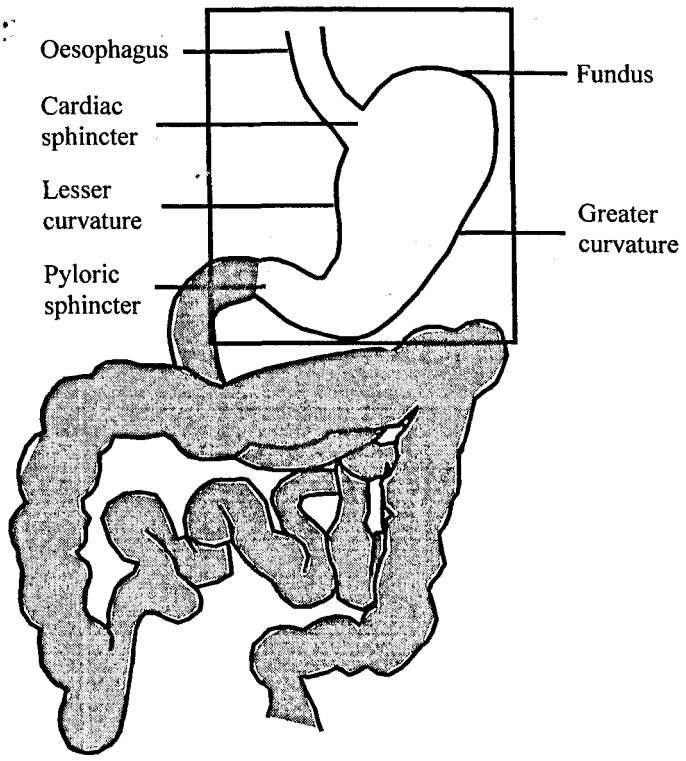


Figure 1.7. Schematic of the GI tract: The stomach (highlighted).

The stomach maintains periodical activity in order to aid digestion. This is known as the migrating myo-electric complex (MMC) and is most identifiable in the fasted state. The MMC can be divided into four phases of activity (Figure 1.8).

Phase 1 is characterised by a period of inactivity that lasts between 40 and 60 minutes and has few muscular contractions of the stomach wall. A formulation ingested at this time will have the maximum residence time of up to 2 hours in the stomach.

Phase 2, the mixing phase, also lasts 40-60 minutes and is identified by contractions of the muscular stomach wall that increase in intensity and frequency. In the presence of food the mixing process produces chyme. Throughout this period, contractions in the stomach cause a pressure rise of between 5 and 40 mmHg. This is

to enable the mixing of food with gastric fluid and to begin digestion. At this point the formulation may have between a 1 and 1.5 hour residence time.

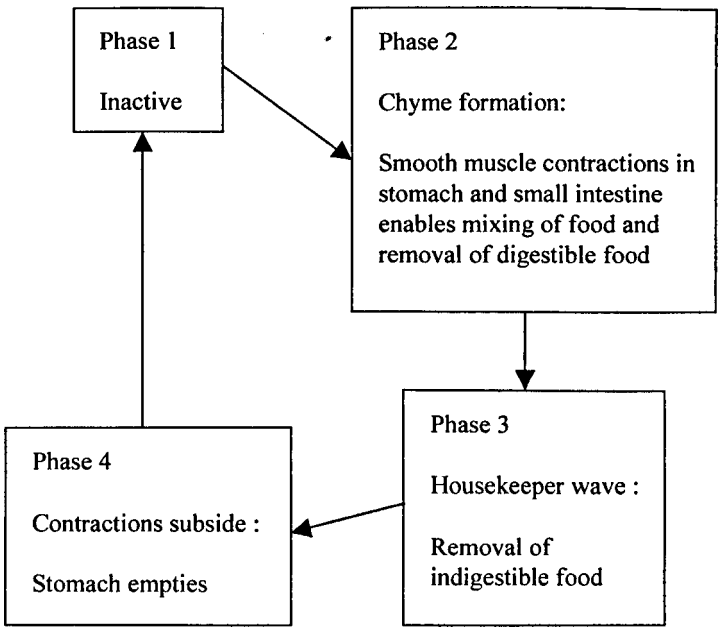


Figure 1.8. The cycle of MMC activity.

Phase 3 is known as the housekeeper wave (HW) sequence. This is short, intense and consists of regular contractions lasting 4 to 6 minutes. This enables the removal of large fragments of food, which may not be further size reduced by Phase 2. The formulation will empty from the stomach at this point, through the pyloric sphincter into the duodenum of the SI.

Phase 4 is a short transitional period between the intense activity of Phase 3 and the relatively inactive period of Phase 1. The gastric residence time of tablets or capsules has previously been shown to vary from 5 minutes to 3 hours (or even longer) in a fasted individual (Kaus et. al., 1984). Thus a formulation taken by a patient in the fasted state could empty at the moment of ingestion if the MMC was at Phase 3 of the cycle. Alternatively gastric emptying could occur anytime up to 2 hours making it difficult to predict. This must be taken into account in a clinical trial design.

In the fed state the timing of the MMC is altered. Food can be broadly classified into three categories: liquid, digestible and indigestible. The gastric retention time is 30 ±7 and 154 ±11 minutes for liquids and digestible food respectively, and 3-4 hours and for indigestible material ($T_{50\%}$ retention times; Feldman et al., 1984). Previous studies have shown that feeding 30 minutes prior to drug administration increased gastric residence time in excess of 2 hours (May et al., 1984). These variable gastric residence times must be considered when designing a viable dosage form as uncontrolled food intake leads to variable gastric emptying times (Müller-Lissner and Blum, 1981; Mazer et al., 1988). A clinical trial with several study subjects must therefore have a controlled calorific intake in order to help standardise this emptying time. In addition other factors can influence the MMC. For example increased fat content of foods can have the effect of increasing gastric emptying times by inhibiting gastric secretion and mobility. Stress has also been shown to affect gastric emptying times (McClintic, 1975). A PDD would be classified as indigestible material, and as a result would empty from the stomach at the time of the HW as previously described. During a clinical trial subjects should experience a controlled diet to try to minimise the effect of different food types on gastric emptying time.

1.5.2. THE SMALL INTESTINE

The small intestine (SI) is 6 meters in length and can be divided into 3 parts: the duodenum, the jejunum and the ileum (Figure 1.9). Each segment of the SI differs in secretion and absorption characteristics.

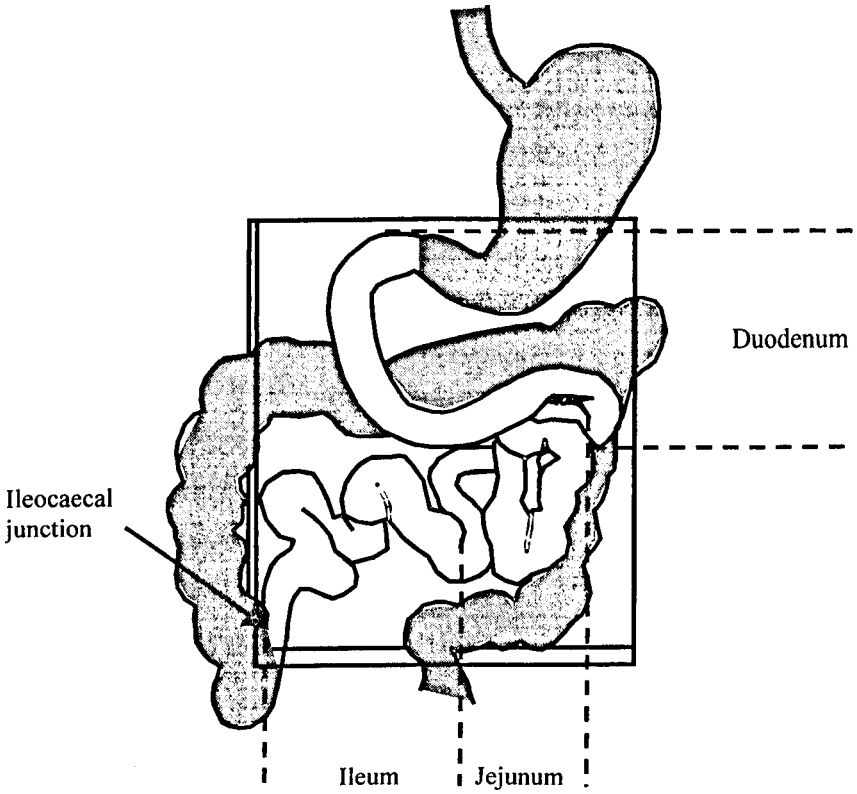


Figure 1.9. Schematic of the GI tract: The small intestine (highlighted).

The duodenum is 20-30 cm in length and consists of a thick wall and deeply folded mucus membrane. As the acidic chyme empties from the pylorus of the stomach it is neutralised by sodium bicarbonate contained within bile secretions. The buffered chyme now has a neutral pH (6.4-7.6). Peristaltic waves occurring as a result of muscle contractions move material along the SI and occur at a frequency of approximately 18 per minute. As material passes the midpoint of the duodenum secretions from the pancreas add to the volume of liquid. This contains digestive enzymes and approximately 98% water.

The jejunum is approximately 2.5 meters in length and is thicker walled and more vascous than the duodenum. This and the previous adjoining section of the duodenum are the main sites for absorption of nutritional components in the SI. The jejunum contains the most villi and has an improved blood supply for this purpose.

The jejunum empties into the ileum, which is around 3.5 meters long. This is distinguishable, as it possesses more lymphatic follicles (Peyer's patches) than the rest of the intestine. Secretion and absorption are reduced here in the ileum. There is an overall accumulation of fluid and digestive enzymes in the SI as water and electrolytes are secreted into the digestive tract. As a result conditions are favourable for a formulation that relies on an interaction with water. Drugs absorbed in the SI undergo 'first-pass metabolism'. Veins in the villi (located along the entirety of the SI) open into the portal vein, which leads to the liver.

A formulation in the SI will now be subject to a near neutral pH and an increasing volume of fluids. As the residence time in the SI is reported to be uniformly 3-4 hours (Wilding et al., 1992), this is the easiest site to target a pulsatile delivery device. *In vitro* dissolution analysis should therefore be performed at a near neutral pH, assuming the residence time in the stomach to be relatively low. As previously indicated in this chapter an enteric coating may be used to protect a pulsed delivery device from activation in the stomach.

1.5.3. THE COLON

The large bowel or colon may be divided into three sections: ascending, transverse and descending (Figure 1.10). Transit time through the small intestine is quite constant at about 3-4 hours, but the stagnation of material at the ileocaecal junction (ICJ) is the point at which considerable variation can occur. The ICJ separates small intestine from the colon and consists of the ileocaecal sphincter and the ileocaecal valve. Previous studies on the pH of the small intestine have been carried out using a telemetry capsule (Lee et. al., 1999). The 'Heidelburg' capsule consists of a pH electrode housed in a non-digestible acrylic capsule and a battery operated high frequency radio transmitter. The radio signal relays the pH to within ±0.5 pH unit accuracy. Such research has determined that there is a gradual increase in pH along the SI from the duodenum to the ileocaecal junction (pH 6.4-8). After the ICJ the formulation enters the colon and the pH drops due to increased acidity as a result of bacterial fermentation (Rubinstein, 1995).

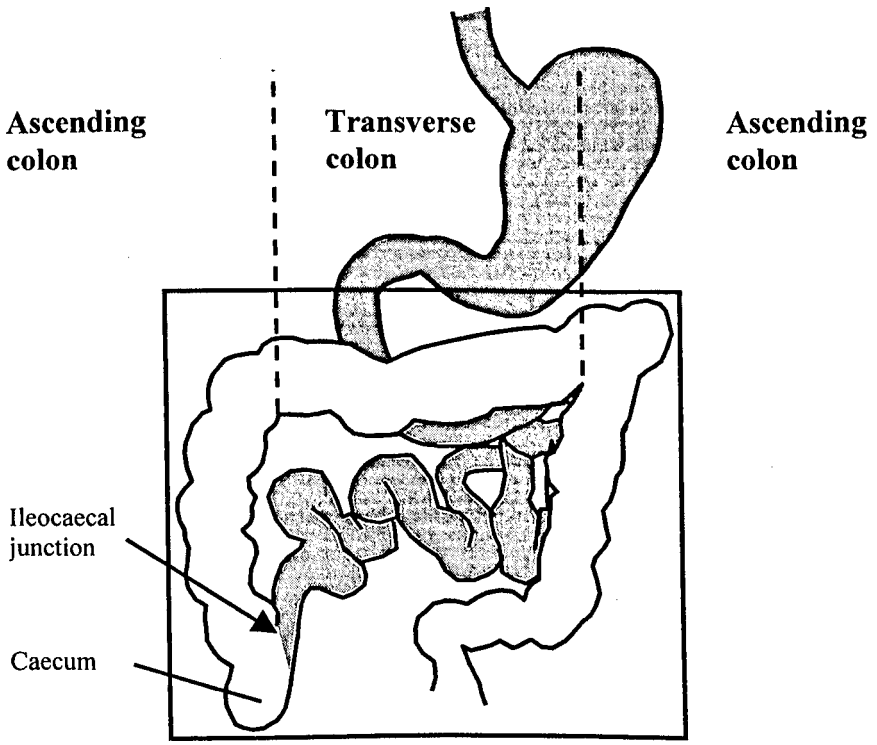


Figure 1.10. Schematic of the GI tract: The colon (highlighted).

The colon provides a less hostile environment, and is more suitable for site-specific delivery of proteins and peptides. This is due to a near neutral pH and lower intensity of enzymatic activity (Rubinstein et al., 1997). It has been shown that most therapeutic peptide and proteins are poorly absorbed due to their high hydrophilicity, large molecular size and extreme instability; this together with rapid proteolytic degradation higher up the GI tract can result in oral bioavailabilities of less than 2% (Yeh et. al., 1995). Furthermore residence times are extended in the colon, which offers opportunities for extended delivery periods.

1.6. SCINTIGRAPHY

Gamma scintigraphy is a technique that makes use of unstable radioactive isotopes that emit gamma rays upon decay to their more stable isotope. As gamma radiation passes through all but the densest of materials, the isotope may be easily tracked down the GI tract simply by using a scintigraphic detector. The use of gamma scintigraphy to track oral preparations is now well established (Christensen et al., 1985) and this non-invasive technique is preferable to those studies involving invasive intubation techniques (Chan et al., 1994) or high dose X-ray exposures (Feldman et al. 1984). Isotopes available for use with this technique include Technitium-99m (^{99m}Tc) and Indium-111 (^{111}In) (Olsson et al., 1995). Other useful isotopes may be prepared by neutron activation, allowing the preparation of dosage forms without handling radioactive isotopes and the subsequent risk of exposure. Stable isotopes of Samarium-152 (^{152}Sm) and Erbium-170 (^{170}Er) are bombarded with neutrons to form the unstable isotopes ^{153}Sm and ^{171}Er. Such systems have been used to examine the performance of oral preparations (Wilding et al., 1995). However, each has a relatively high half-life compared to the ^{99m}Tc and ^{111}In. In addition, relatively poor image quality, due to low photopeak energies associated with the use of neutron-activated isotopes.

Much of the information regarding gastric emptying and GI transit times has been gathered using scintigraphic techniques. This involves the use of the gamma emitting isotopes, which are combined with an oral preparation and detected with a

gamma camera. The progress of the oral preparation may be tracked from the stomach and through the entire length of the GI tract at regular timed intervals. Using anatomical markers, accurate positioning of the preparation may also be obtained.

The minute quantities of gamma emitting material needed mean that it does not interfere with the normal transit processes that the oral preparation would follow. It is usual to use indium-111 (^{111}In) or technecium-99m (^{99m}Tc) for this purpose as they both have a short half-life. This is important so that exposure of the patient to radiation is kept to a minimum.

When taken orally ^{99m}Tc and ^{111}In must be combined with a complexing agent to ensure that they are not absorbed into the blood stream (Rhodes and Croft, 1978). Such a complexing agent is diethylenetriaminepentaacetic acid (DTPA) (Figure 1.11). This technique allows any oral dosage form to be monitored and provides information about the transit and residence times at specific sites. Dispersion of the radioactive source within the lumen is indicative of break up of the preparation. This is generally accompanied by the absorption of drug.

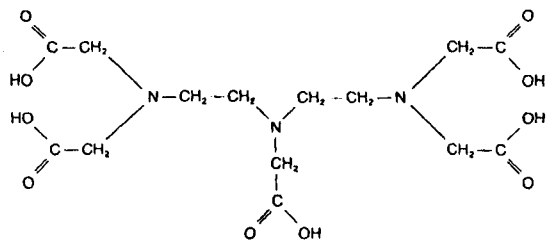


Figure 1.11. Chemical structure of DTPA.

The use of two different isotopes has been shown to aid the detection of a pulsed release (Wilding et al., 1995). Different isotopes, such as ^{111}In and ^{99m}Tc have different photopeak energies and this can be used to simultaneously to show the path of an oral dosage form and separation of the isotopes (Binns et al., 1994; 1996; Gardner et al., 1997). In this way one isotope may be incorporated into an insoluble

component of a pulsed-release device such as those described in Section 1.3. The other may be incorporated into the drug-containing dispersible component to enable the accurate detection of lag-time and drug delivery.

Blood sampling and pharmacokinetic analysis to monitor plasma levels of drug can be acquired in conjunction with the scintigraphic data, and has previously been used in the examination of pulsatile drug delivery (Binns et al, 1996; Stevens et al., 2002).

1.7. BACKGROUND OF THE CURRENT STUDY

The TDC consists of an insoluble coated size 0 hard gelatin capsule body, an expulsion excipient, a drug containing tablet and an ET. Each component is manufactured separately prior to assembly to make the complete functional device. Preparation of each component is dealt with specifically in Chapter 2. This ability to prepare and manufacture the components separately highlights the versatility of the TDC and represents an advantage over pellet or tablet based delivery devices. Also, since none of the components of the TDC involve the use of specialist precision equipment (as earlier indicated with the Pulsincap™ device, Section 1.3.2), this represents a further advance.

The TDC does not rely on the reproducibility of complex frictional forces, such as the PORT System® or the Pulsincap™ device. It relies instead on the steady erosion of HPMC (Section 1.4). With only one erosion surface, problems associated with asymmetrical erosion are avoided such as those with the Egalet™ design. Also the SA of erosion is maintained, which ensures a more uniform process.

1.7.1. THE DRUG CONTAINING TABLET

In work prior to this study (Ross; data not published) incomplete release of drug had been observed due to disintegration of the drug tablet within the TDC prior

to expulsion. This problem needed to be addressed. The model drug selected for use as the drug tablet in all dissolution studies was propranolol hydrochloride. As indicated in the early part of this introduction, cardiovascular diseases display circadian rhythms. Propranolol is often used as a first treatment drug for this condition (Lemmer, 1989).

1.7.2. ERODIBLE TABLET FORMULATIONS

The most important component of the TDC in controlling lag-time is the ET. Previous studies in this group (Ross et al., 2000b) had studied the erosion profiles of various insoluble excipients including: Compactrol® and Emcompress®. Erodible tablets prepared from these excipients revealed a non-linear erosion process related to the change in surface area of the ET during those studies. However, by varying the concentration, these excipients could afford some control of the erosion rate. But many incidences of TDC failure resulted in the selection of an erodible polymer system.

It was decided that a soluble hydrophilic polymer could be used such as HPMC. This had been shown to demonstrate suitable erosion times (Krögel and Bodmeier, 1996; 1998). Various grades of HPMC are available and previous work by this group (Ross et al., 2000b) had achieved a preliminary screening also demonstrating suitable erosion times. Methocel® (K100LV grade) was selected in the manufacture of the ET in this present study. This grade of HPMC provided some degree of swelling on contact with water, and hence a tight fit in the end of the coated capsule body allowing for a good seal to prevent premature drug expulsion.

1.7.3. THE INSOLUBLE CAPSULE BODY

The use of insoluble tubes to provide an effective barrier against water penetration has been described (Krögel and Bodmeier, 1999c). The Egalet™ device makes use of an extruded insoluble polymeric tube (Bar-shalom and Kindt-Larson, 1993). Tubular based systems have the potential disadvantages of being costly and have poor patient compliance (due to their shape). As a result capsule coating processes were investigated.

Early work involved the use of an aqueous coating technique (Ross et al., 2000b). This led to incidences of TDC failure. It was determined that ETs did not fit securely in the capsule opening due to poor internal coating. This then led to the use of an organic coating which resolved this problem.

1.7.4. EXPULSION EXCIPIENTS

While a soluble fill is necessary to facilitate drug release, without some form of expulsion excipient within a pulsed delivery device, drug release is erratic and incomplete. As previously stated many dispersible tablet formulations have made use of effervescent excipients such as sodium bicarbonate/citric acid mixtures. These may be used as expulsion excipients to facilitate drug dispersion for pulsatile release (Gohel and Sumitra G, 2002; Krögel and Bodmeier, 1997; 1999b). The Pulsincap™ device made use of the rapidly expanding agent L-HPC. Lightly compacted L-HPC (grade LH-21) was also used in the previous studies (Ross et al., 2000a; 2000b) as the expulsion excipient for the TDC.

AIMS AND OBJECTIVES

The aim of the present study was to optimise the TDC for use in clinical practice. In order to achieve this the current study had the following objectives:

1. To overcome the premature disintegration of the drug tablet within the capsule prior to expulsion.

2. To develop a series of erodible tablets capable of affording pulsatile release after 1, 3 and 5 hours.

3. To minimise the variability of lag-time and to investigate the erosion kinetics as a function of ET processing.

4. To develop an *in vitro – in vivo* correlation of performance.

CHAPTER 2. MATERIALS AND METHODS.

2.1. MATERIALS

2.1.1. SOLVENTS

Acetone	Merck-Chemicals Ltd., Poole, Dorset, UK.
Dibutylphthalate (DBP)	Sigma-Aldrich Co. Ltd., Poole, Dorset, UK.
β-Hydroxyethyl-theophylline (HiPerSolv™)	Sigma-Aldrich Co. Ltd., Poole, Dorset, UK.
Isopropyl alcohol (IPA)	Merck-Chemicals Ltd., Poole, Dorset, UK.
Methanol (HiPerSolv™)	Sigma-Aldrich Co. Ltd., Poole, Dorset, UK.
Perchloric acid (HiPerSolv™)	Sigma-Aldrich Co. Ltd., Poole, Dorset, UK.
Tetrahydrofuran	Sigma-Aldrich Co. Ltd., Poole, Dorset, UK.
Triacetin	Merck-Chemicals Ltd., Poole, Dorset, UK.

2.1.2. EXCIPIENTS

Ac-Di-Sol® (Crosscaramellose sodium)	FMC corp., Philadelphia, PA, USA; supplied by Pfizer Ltd, Sandwich, Kent, UK.
Aerosil® R728	Degussa Ltd, Macclesfield, Cheshire, UK.
Avicel® 101	FMC corp., Philadelphia, PA, USA; supplied by Pfizer Ltd, Sandwich, Kent, UK.
Emcompress® (dibasic calcium phosphate)	Penwest Pharmaceuticals, Patterson, NY, USA.
Ethocel® 100 Premium	Dow Chemicals, Midland, MI, USA.
Fast-Flo lactose	Formost Farms, Baraboo, WI, USA; supplied by Pfizer Ltd, Sandwich, Kent, UK.
Methocel® (Hydroxypropylmethyl cellulose; HPMC) K100LV	Dow Chemicals, Midland, MI, USA.
Low substituted hydroxypropyl cellulose (L-HPC) LH-21	Shin-Etsu Chemical Company Ltd, Tokyo, Japan.
Magnesium stearate (MgSt)	Merck-Chemicals Ltd., Poole, Dorset, UK.
Potassium bromide (KBr)	Sigma-Aldrich Co. Ltd., Poole, Dorset, UK.
Surelease™	Colorcon Ltd., Dartford, Kent, UK.

2.1.3. CONSUMABLES

Blu Tack®	Bostik Ltd, Leicester, Leicestershire, UK.
Coated capsule bodies ($C_{org\,(2)}$)	BWI-Manesty Ltd, Liverpool, UK.
Size 0 hard gelatin capsule bodies	Capsugel, Greenwood, SC, USA; supplied by Pfizer Ltd, Sandwich, Kent, UK.

2.1.4. DRUGS

Propranolol hydrochloride	Supplied by Pfizer Ltd, Sandwich, Kent, UK.
Riboflavin	Sigma-Aldrich Co. Ltd., Poole, Dorset, UK.
Theophylline	BASF PharmaChemikalien GmbH & Co. KG, Minden, Germany.

2.2. EQUIPMENT

2.2.1. MANUFACTURING

300 µm sieve	Endecotts Ltd., London, UK.
5 mm punch and die set	IHolland Ltd., Nottingham, Nottinghamshire, UK.
D200 Peristaltic pump	Watson-Marlow Ltd., Cornwall, Falmouth, UK.
E2 Manesty tablet press	BWI-Manesty, Liverpool, UK.
Forced-air oven	Mitchell Dryers Ltd., Carlisle, Cumbria, UK.
FP296 Mixer/granulator	Kenwood Ltd, Watford, Hertfordshire, UK.
Premier 62 Overhead stirrer	Premier Colloid Mills Ltd., Walton-on-Thames, Surrey, UK.
Strea-1 Aerocoater	Aeromatic-Fielder, Bubendorf, Switzerland.
Turbula™ mixer	Glen Creston, Stanmore, Middlesex, UK.

2.2.2. ANALYTICAL

AccuPyc Pycnometer	Micromeritics, Dunstable, Bedfordshire, UK.
Avatar 360-FTIR spectrophotometer	Nicolet Instruments Corp., Madison, WI, USA.
AXS D8 X-ray diffractometer	Brüker Instruments, Karlsruhe, Germany.
Cecil 500 UV spectrophotometer	Cecil Instruments Ltd., Cambridge, Cambridgeshire, UK.
CSL100 Rheometer	Carrimed Ltd., Dorking, Surrey, UK.
D300 Disintegration apparatus	Erweka GmbH, Hausenstamm, Germany.
DVS2000 Dynamic vapour sorption (DVS) apparatus	Surface Measurement Systems Ltd., London, UK.
HP1050 Integrated HPLC system	Agilent Technologies Ltd., Stockport, Cheshire, UK.
HP8720D Network analyser	Agilent Technologies Ltd., Stockport, Cheshire, UK.
Polaron SC515 Sputter coater	Enutech Ltd., Ashford, Kent, UK.
RDC50 Digital camera	Ricoh UK Ltd., Feltham, Middlesex, UK.
SEM500 Scanning electron microscope (SEM)	Philips Ltd, Eindhoven, Netherlands.
ST7 Dissolution apparatus	Caleva GB Ltd., Sturminster Newton, Dorset, UK.
TBH30 Tablet testing station	Erweka GmbH, Hausenstamm, Germany.
TX2000 Texture Analyser (TA)	Stable Micro Systems, Godalming, Surrey, UK.

2.3. PREPARATION OF THE WATER IMPERMEABLE CAPSULE

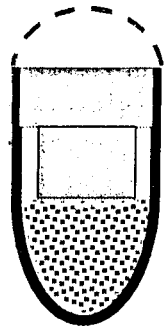


Figure 2.1.
Size 0 hard gelatin capsule body, coated with water-impermeable ethyl cellulose (red).

The insoluble capsule consists of a size 0 hard gelatin capsule body, with a layer of insoluble ethyl cellulose coated on its surface (Figure 2.1). This prevents the penetration of water into the Time-Delayed Capsule (TDC). Coating may be performed using an aqueous or organic coating solution. In conventional coatings it is generally advantageous to use an aqueous system, with the principal benefits being that they have a relatively low cost, pose little environmental hazard and are safe to use by the operator.

Two methods are used in the capsule coating process: pan or fluidised-bed coating. The pan technique makes use of a heated rotating chamber containing the capsules to be coated. A coating solution is then introduced, in the form of a spray, gradually building up coating layers onto the product. The fluidised-bed method comprises an overhead or bottom spray arrangement that introduces the coating fluid onto an agitated bed of capsule bodies. Passing a temperature-controlled stream of air directly into the sample from below causes fluidisation. Tablets, capsules and pellets may be coated in this way. A high degree of control is introduced as the temperature of the coating chamber may be manipulated by altering the temperature of the fluidising-air stream, enabling curing and drying processes to be performed after coating.

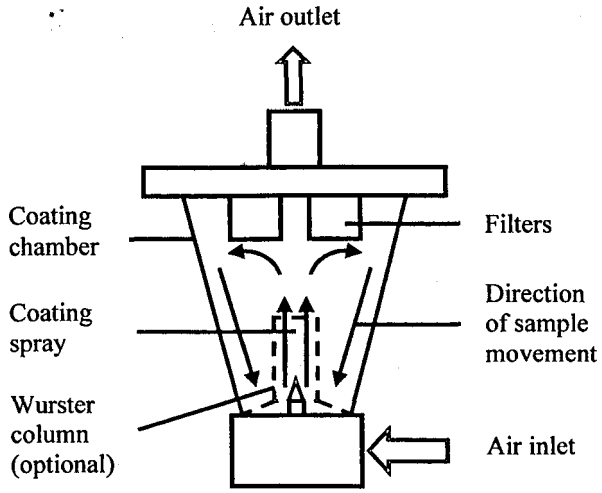


Figure 2.2. The Strea-1 Aerocoater with bottom spray arrangement.

The bottom spray fluidised-bed coating system (Figure 2.2) enables relatively small quantities of material to be coated and is therefore suitable for small-scale production. Using an aqueous or organic coating solution respectively, aqueous or organic coated capsules may be produced. Air is drawn in at the base of the apparatus and heated before passing through a gas distributor plate and into the coating chamber, fluidising the sample. A nozzle located at the centre aerosolises the coating fluid at a preset pressure dependant on the viscosity of the coating solution. This additional pressure causes the sample to be forced upwards through the coating spray plume, and a circulatory flow is initiated. The sample falls back down to the fluidised bed due to the sloped walls of the coating chamber. In this way, a uniform coating is gradually built up onto the sample. Inclusion of a Wurster column is optional, and is generally used with a small sample size or relatively large coating chamber; it acts to help maintain a suitable circulatory flow pattern by concentrating the coating spray and upward air flow within a cylindrical partition (Yang et al., 1992). Control of the spray pressure and temperature of the coating chamber enables variable coating properties to be obtained on the capsule.

In this study one aqueous capsule coating and three types of organic coated capsule bodies were prepared using the techniques outlined above for this study.

Initial batches of aqueous and organic coated capsules were prepared and used to determine which type may be more suitable for use with the TDC. Both were prepared using the same fluidised-bed coating arrangement. Once this was established, an organic coated capsule was manufactured by BWI-Manesty using a ventilated pan coating method. These were used in the TDC dissolution testing in Chapters 3 and 4, and erosion studies of the erodible tablet (ET) reported in Chapter 5. Using the fluidised-bed coating method a final batch of capsules was manufactured for use in the clinical trial in Chapter 6.

Ethyl cellulose has a high glass transition temperature (T_g) of 135°C (Porter, 1989) and is unable to form a flexible film under normal coating conditions (Oh and Luner, 1999) so suitable plasticizers also need to be considered when coating the capsule bodies. During coating, the identity of plasticizer and its concentration are critical in obtaining the optimum coating finish. The plasticizer acts by lowering the T_g of the polymer enabling polymer droplets to soften and coalesce on the surface of the product to form a continuous layer (Chang et al., 1987; Harris et al., 1986). Increased quantities of plasticizer provide improved uniformity in coating thickness over the surface of a given material, but in lowering the T_g agglomeration between the product components is also encouraged (Chang et al., 1987). Increasing plasticizer levels also has the effect of increasing film permeability (Lippold et al., 1989; Okarter and Singla, 2000; Rangaiah et al., 1997). This may be desirable when attempting to obtain a sustained release of drug from a coated tablet but is undesirable when attempting to protect the interior of the TDC from the ingress of water. The level of plasticizer used was selected to minimise these effects yet still maintain a continuous film of ethyl cellulose over the capsule bodies (i.e. greater than 5% [w/v] of DBP caused excessive agglomeration between capsule bodies).

It has been established that temperature and the spray rate, are critical in obtaining an optimally coated product (Parikh et al., 1993). After a suitable coating solution/dispersion has been prepared it is important to choose the optimal temperature and spray rate for the coating equipment. An elevated air-inlet temperature allows the T_g of the plasticized solution/dispersion to be surpassed

(Yang and Ghebre-Sellasie, 1990) to enable the coalescence of the coating. The atomised spray is produced at the centre of the fluid-bed and produces an upward flow which is varied depending on the density of the initial material to be coated. The velocity of air from the atomising spray should propel the sample to no more than three quarters the total height of the coating chamber to allow a suitable convection flow (Figure 2.2) to be obtained (Aeromatic-Fielder, 1995). The solvent must also be evaporated off of the product to prevent capsule agglomeration, so the spray rate must not be too high (i.e. greater than 12 ml/min spray rate caused excessive agglomeration).

2.3.1. AQUEOUS CAPSULE COATING

Aqueous based coating systems have been developed (as a safer alternative to organic solvents) to provide a full range of coating capabilities including enteric coatings that provide protection from dissolution in the stomach (Gordon et al., 1995), and sustained release coatings (Arwidsson, 1991). In developing the capsule body for these studies it was necessary to coat it with an insoluble layer of ethyl cellulose. However this layer must be thick enough to be impermeable to external water, at least for the duration of specific lag-times proposed. Surelease™ is a commercially available aqueous dispersion of ethyl cellulose (Colorcon, 1990), suitable for this purpose. This is pre-plasticized with dibutyl sebacate (Bodmeier and Paeratakul, 1991).

A bottom spray fluidised-bed arrangement was used to coat the capsules (Figure 2.2) with the Strea-1 Aerocoater. Hard gelatin capsule bodies (500) were separated from their caps and placed into the coating chamber. A 15% (w/v) aqueous solution of Surelease™ (2 litres) was used to coat the capsule bodies using the conditions outlined (Table 2.1). The inlet-feed was controlled using a peristaltic pump. After 1 hour of coating, coated capsules were removed at 10 minute intervals and weighed then replaced, until a constant weight gain of 300% was achieved. Capsules produced were designated C_{aq}.

Coating conditions	Setting
Drying / circulating fan	4
- Inlet temp. (°C)	60
- Outlet temp. (°C)	40
Coating gun pressure (bar)	1
Inlet feed (ml/min)	10

Table 2.1. Aqueous capsule coating conditions used with the Strea-1 Aerocoater for fluidised bed coating.

2.3.2. ORGANIC CAPSULE COATING

Organic solutions are relatively simple to prepare. Ethyl cellulose is water insoluble and shows suitable degree of solubility in many organic solvents. It is commercially available as the free flowing powder Ethocel®. The organic coating solutions need the addition of a suitable plasticizer added in order to obtain a uniform uninterrupted coating over the surface of the capsules. Initial *in vitro* studies allowed the use of dibutyl phthalate (DBP) to be used, but due to the reported toxicity of this component it was replaced with triacetin for the capsules used in the *in vivo* study.

A simple coating process, used for the coating of Eudragit® L100 as an enteric coat onto capsule (Thoma and Betchtold, 1990), was adapted for use in this study. Ethocel® (99 g) was dissolved in a 50/50 acetone/IPA solution (2 litres). An overhead stirrer was used to produce a vortex; dry powder was added to the funnel of the vortex slowly to prevent agglomeration. DBP (1 g) was introduced as a plasticizer. The Strea-1 Aerocoater was used and coating conditions were identical to that of the aqueous system (Table 2.1). After 1 hour of coating, coated capsules were removed at 10 minute intervals and weighed, until a constant weight gain of 300% was achieved. Coated capsule were designated $C_{org\ (I)}$.

2.3.3. COMMERCIALLY PREPARED CAPSULES

Organically coated capsule bodies were prepared in bulk by BWI-Manesty ltd. The method used in Section 2.3.2 was adapted for use with a ventilated pan-coater, and were prepared to a 300% weight gain. These capsules were used in the majority of the studies performed (Chapters 3-5) and were designated $C_{org\ (2)}$.

2.3.4. GMP CAPSULE COATING

Identical methods were employed as in Section 2.3.2. USP grade hard gelatin capsules were used and, USP triacetin (1 g) was substituted for DBP. Coating of the capsules using triacetin to plasticize only required a capsule weight gain of 120% due to improved internal coating (described in the results Section 3.3.1). Capsules were designated $C_{org\ (3)}$.

2.4. DRUG CONTAINING TABLETS

The drug tablet was formulated so that is would be expelled intact from the TDC before rapidly disintegrating (Figure 2.3). Model drugs of propranolol and theophylline were used in this study. Propranolol may be used to target the circadian rhythms of cardiovascular diseases in the early morning hours. Theophylline may be used in the treatment of acute asthma, and targeted to peak nocturnal symptoms during nocturnal hours.

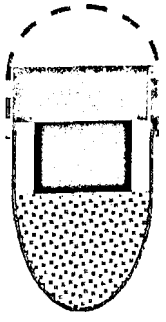


Figure 2.3.
Drug containing tablet.

May contain a suitable drug to target the circadian rhythms of disease states

2.4.1. PROPRANOLOL TABLETS

Seven different tablet formulations (with propranolol as a model drug) were prepared in order to identify an optimal formulation, having appropriate rapid disintegration following expulsion from the TDC. These were designated as P1-P7 (Table 2.2).

Blend	Propranolol (%)	Lactose (%)	Avicel® (%)	Ac-di-sol® (%)	MgSt (%)	Aerosil® (%)	Diameter (mm)
P1	51	45	-	2	2	-	6.50
P2	50	11	35	2	1	0.25	6.50
P3	40	13	45	1	0.5	0.1	6.50
P4	40	-	59	1	0.25	0.1	5.00
P5	40	13	46	-	0.25	0.25	5.00
P6	41	13	45	1	0.5	0.1	5.00
P7	51	48	-	-	1	0.1	5.00

Table 2.2. Formulation variables of propranolol containing tablets, used to determine an optimal formulation.

These were mixed (Section 2.4.1.1, below) and tableted (Section 2.4.1.2, below) using appropriate tooling indicated by the tablet diameter, and characterised (Section 5.2). The various merits of each formulation are discussed (Chapter 3, Section 3.3.2.1). This led to P3 being selected for tablet coating, and P7 was selected for all subsequent *in vitro* dissolution studies (Chapters 3-5).

2.4.1.1. Mixing

Each formulation was mixed in the Turbula™ for 20 minutes at 42 rpm. MgSt was then added to each blend and further mixed for 10 minutes (unless otherwise stated).

2.4.1.2. Tableting

Formulations were tableted using a single station E2 Manesty tablet press equipped with either 5 mm flat-faced punches for drug containing tablets (unless otherwise stated) or 6.75 mm flat-faced punches for erodible tablet formulations. The target weight was 80 ±2 mg with a crushing strength of 40 ±5 N (unless otherwise stated).

2.4.1.3. Propranolol tablet coating

One tablet formulation was coated to prevent disintegration within the TDC prior to expulsion. Propranolol (P3) tablets (100) were placed into the Strea-1 coating chamber equipped with a Wurster column. Tablets were pre-warmed to match the air-inlet temperature and dried to remove moisture by circulating for 10 minutes. Identical conditions as outlined for the organic capsule coating processes were used (Section 2.3.2). Tablets were coated for 1 minute before reversing the flow of the peristaltic pump ceased the coating fluid inlet spray. The tablets were then cured for 30 seconds and 10 were removed and weighed to assess the increase in tablet coat. This process was repeated over a 5 minute period. A standard dissolution test (Section 2.5.4) was carried out on samples taken each minute (n = 6) to determine whether a short lag-time had been achieved by this coating process.

2.4.2. RIBOFLAVIN TABLET

A riboflavin tablet was manufactured for use in the photographic study (Section 2.5.5). Emcompress® (47.5 g), riboflavin (2 g) and MgSt (0.5 g) were mixed (Section 2.4.1.1) and tableted (Section 2.4.1.2) using 5 mm punches. This highly visible yellow tablet conformed to the same dimensions as the standard P7 tablets produced to ensure duplication of expulsion from the TDC. It was formulated so as not to disintegrate during the photographic study (Section 2.7.5).

2.4.3. GMP THEOPHYLLINE TABLET

A theophylline mixture was prepared. Theophylline (60 g), Ac-di-sol® (0.22 g), MgSt (0.11 g) and lactose (0.05 g) were mixed (Section 2.4.1.1).

^{99m}Tc Labelled DTPA combined with lactose (5 mg) (Appendix II.1) was added to 85 mg of the theophylline mixture. This was tableted using a pharmacopoeial grade 5 mm punch and die set. A 1 ton compression force was applied with an IR press.

2.5. PREPARATION HPMC ERODIBLE TABLET (ET) FORMULATIONS

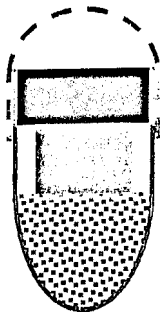


Figure 2.4.
HPMC/Lactose Erodible Tablet (red) used to control the lag-time of the TDC.

A thick 80 mg ET (Figure 2.4) was produced to incorporate a 40 mg (w/w) propranolol drug tablet and a thinner 60 mg ET was produced to incorporate a larger 80 mg (w/w) theophylline tablet.

2.5.1. 80 mg DIRECT COMPRESSION ERODIBLE TABLET

Six different concentrations of HPMC direct compression formulations were prepared (Table 2.3). Formulations were mixed (Section 2.4.1.1) and tableted (Section 2.4.1.2) as described previously.

HPMC (%)	Lactose (%)	MgSt (%)
5	94	1
10	89	1
15	84	1
24	75	1
25	74	1
30	69	1

Table 2.3. Composition of 80 mg direct compression ET formulations used for obtaining different TDC lag-times.

During tableting the use of a lubricant is necessary to facilitate the smooth ejection of the product from the tableting die. However, it has previously been reported that mixing times of lubricants can have adverse effects on disintegration, dissolution and hardness properties (Sheskey et al., 1995). This is due to the formation of a thin film of lubricant over the other excipients resulting in hydrophobic boundary effects. Mixing times of 5, 20 and 30 minutes using the 24% HPMC formulation were prepared to evaluate the extent of this possibility.

The release from HPMC controlled release tablets has been demonstrated to be dependant upon tablet crushing strength (Huber and Christenson, 1968), which is proportional to the porosity. ETs with crushing strengths of 20, 30 and 55 N were also prepared using the 24% HPMC formulation to show that the ET erosion was independent of porosity.

2.5.2. WET GRANULATED ERODIBLE TABLET

Two approaches are often used during wet granulation: either addition of a binder to a dry powder bed followed by the gradual addition of the binder vehicle (solvent), or the binder is pre-dissolved into the solvent (Danjo et al., 1992). A bulk wet mass is produced, which is usually size reduced before oven drying. A further

particle size reduction is generally required prior to tableting to ensure an even particle size distribution. During the wet granulation process used here, the dry powder bed consisted of lactose with varying amounts of HPMC acting as a binder followed by the addition of water, as recommended (Dow Chemicals, 1996b). Primary feed particles of HPMC and lactose are initially mixed in the dry state. The addition of small aliquots of water during mixing causes the surface of HPMC particles to gel. Once sufficient liquid has been added, the particles begin to adhere to each other and wet massing begins as layers of particles form around a nucleus (rich with binder) (Figure 2.5).

Gelation of the binder (HPMC) promotes particles to adhere after collision. As the granule growth increases the probability of collision of small particles with large particles increases exponentially (Sherrington and Oliver, 1981). In the first stages of particle size enlargement, it is thermodynamically favourable for small particles to adhere and larger particles to separate as stronger liquid bridges are formed due to the large SA of the small particles (Tiamraj, 1979). In this way there is a gradual and uniform growth in particle size until all fine particles have effectively been wet massed. It is apparent from this description that it is highly likely that the 'sticky' HPMC particles will also collide and 'clumping' will be an unwanted side effect, doing little to aid the homogeneity of the powder bed. To avoid this a high shear mixing force must be applied (Sheskey and Williams, 1996).

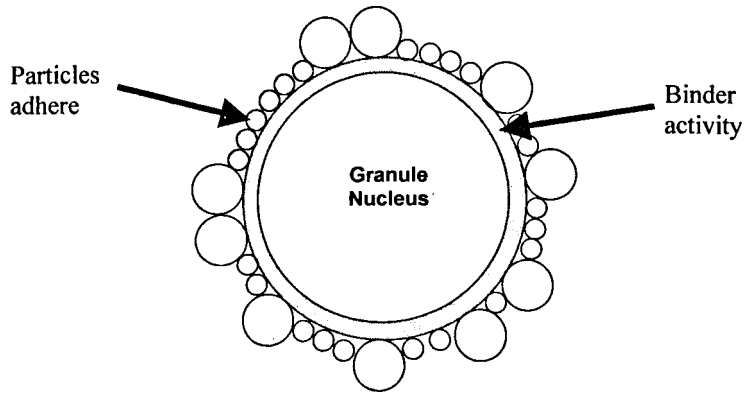


Figure 2.5. Schematic of the formation of wet-massed granules using a binder, in a high-shear mixing process.

High shear mixing provides enough mechanical energy so that suitable dispersion and powder hydration can be achieved (Ryan, 2000). This is essential with a system such as HPMC where a considerable degree of 'clumping' can occur (Liu et al., 1993), as well as poor solvent penetration into the powder bed (Shah et al., 1996). Both these granulation problems lead to a heterogeneous mixture, ultimately leading to dissolution variability. The granulation process was conducted using a twin blade mixer operating at 1350 rpm. Using [Eqn. I.2] (Appendix I) high shear properties (Knight, 1993) of the mixing process was confirmed.

Three different HPMC wet granulated (WG) ET formulations were prepared (Table 2.4). HPMC and lactose were mixed using an FP296 mixer/granulator. A total of amount of distilled water (25 ml) was added over a 5 minute period. An initial aliquot of distilled water (12.5 ml) was added over the first 2 minutes, before the mixer was stopped and mixer bowl and blades scraped using a flat edged spatula. The remaining water (12.5 ml) was added over a further 2 minute period followed by an additional scraping. Following a final mixing period of 1 minute the resultant granules were spread evenly on a tray and dried overnight in a forced-air oven (50°C). Granules (49.5 g) were then passed through a 300 μm sieve and were dry mixed in the Turbula™ with MgSt for 10 minutes, before tableting (Section 2.4.1.2).

HPMC (%)	Lactose (%)	MgSt (%)
15	84	1
24	75	1
30	69	1

Table 2.4. Composition of 80 mg WG ET formulations.

In a separate process, granulations of 15% HPMC were prepared with varying amounts of water for granulation. 5, 10, 15, 20, 25 and 30 ml of water was used in total for each wet granulation and granulated as above. ETs were then prepared and their effect on TDC lag-times determined respectively.

2.5.3. 60 mg ERODIBLE TABLET FORMULATIONS

Five formulations of 60 mg ETs were prepared (Table 2.5). Formulations were mixed (Section 2.4.1.1) and tableted (Section 2.4.1.2) but to a weight of 60 ±2 mg.

HPMC (%)	Lactose (%)	MgSt (%)
15	84	1
20	79	1
24	75	1
30	69	1
35	64	1

Table 2.5. Composition of 60 mg DC ET formulations used to incorporate the larger theophylline drug tablet.

2.5.4. 60 mg GMP FORMULATIONS

20, 24 and 35% HPMC formulations were prepared as in Section 2.5.3.

2.6. TIME-DELAYED CAPSULE ASSEMBLY

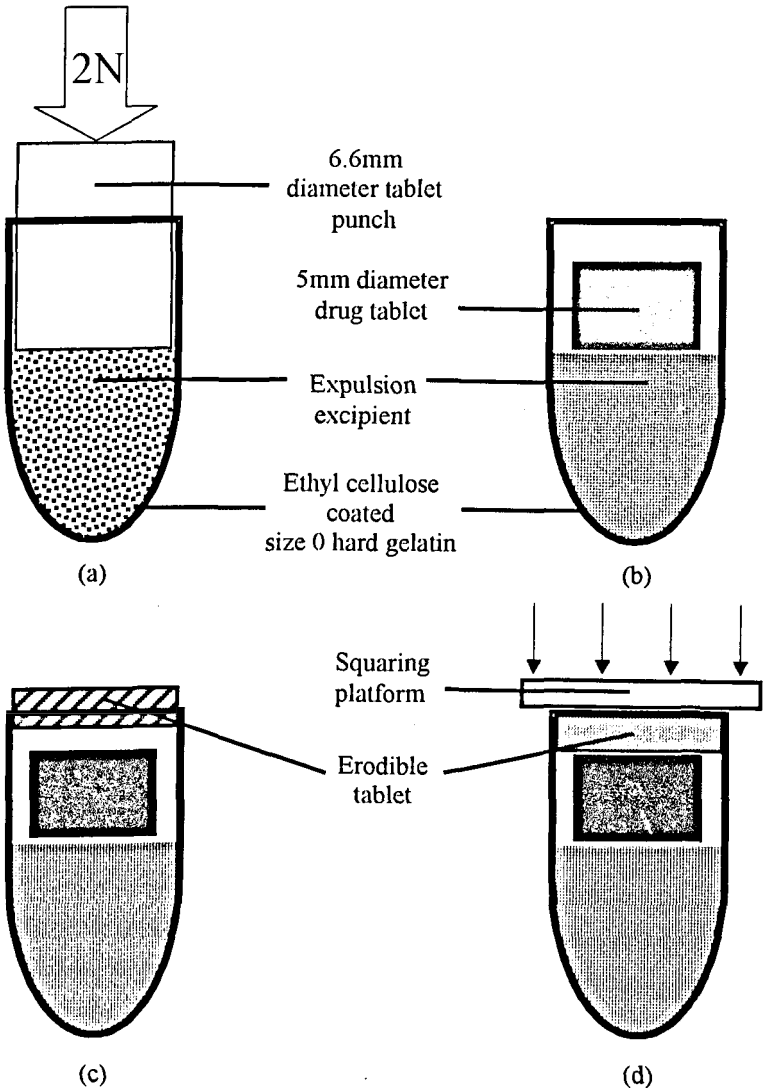


Figure 2.6. Assembly of the TDC:

(a) L-HPC (200 mg) was added to the capsule body and was tapped lightly to provide additional space at the capsule opening. A further amount of L-HPC (50 mg) was then added and tapped before consolidating with a 2 N force (200 g weight), to a total fill weight of 250 ±5 mg.

(b) A drug-containing tablet was placed on top of the compacted L-HPC.

(c) The selected ET was inserted into the end of the capsule body.

(d) The ET was pushed squarely and flush with the rim of the capsule body.

2.7. ANALYTICAL TECHNIQUES

2.7.1. CAPSULE INTEGRITY TESTING

The most effective way of coating capsules for this application is the organic solvent spray technique (Ross et al., 2000a), as a degree of coating was provided on the internal surface of the capsule bodies leading to a more effective watertight seal with the ET. In order to evaluate the suitability of the coating layer of the commercially obtained capsules and the GMP manufactured capsules, a technique was developed that assessed capsule strength using a texture analyser (TA). In this way capsules were tested for their compressibility before and after exposure to a humidity controlled environment.

Uncoated, C_{aq}, $C_{org\ (1)}$, $C_{org\ (2)}$ and $C_{org\ (3)}$ capsules (10 of each) were selected and compressed using a TX2000 TA fitted with a 20 kN load cell and poly methylmethacrylate compression stage (Figure 2.7). The maximum force of compression (F_{max}) was determined using the settings indicated (Table 2.6).

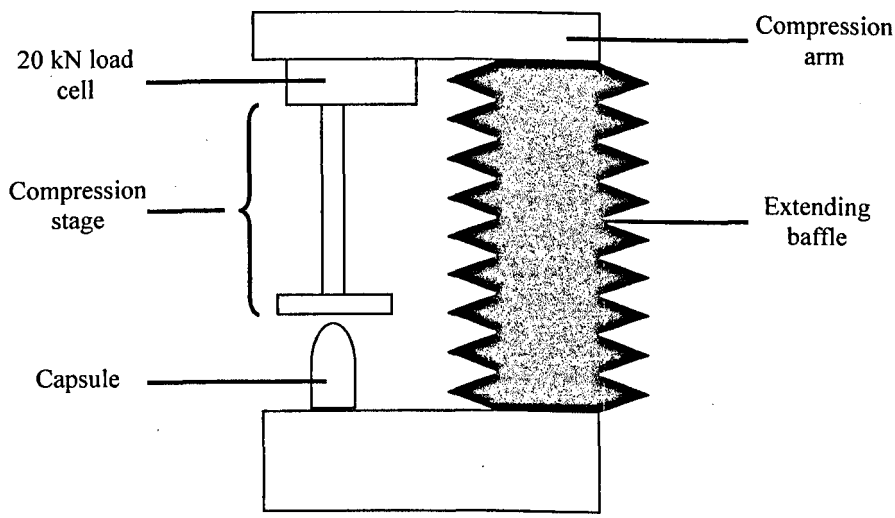


Figure 2.7. The TX2000 TA set up for the capsule compression testing to determine a 'capsule integrity ratio' (*CIR*).

Uncoated or coated capsules (10 of each) were introduced to a controlled relative humidity (RH) of 45% (representative of typical laboratory RH) at 25°C with the DVS instrument and allowed to equilibrate. This was automatically detected by the apparatus as a change in mass against time (dm/dt) of less than 0.00200 mg/s. After equilibrating at 45% RH, the sample was exposed to 90% RH for 999 minutes. The capsule was then immediately removed and analysed using an identical compression test to that described above. Maximum compression force after exposure to 90% RH ($F_{maxRH90}$) were then determined for a further 10 capsules of each type.

Variable	Setting
Test mode	Measure force in compression
Test option	Cycle until reset
Parameters	
Pre Test speed (mm/s)	2
Speed (mm/s)	1
Post test speed (mm/s)	2
Rupture test distance	-
Distance (mm)	10
Force	-
Time	-
Count	-
Trigger	
Type	Auto
Force (N)	10
Settings	
Force	Newton
Distance	Millimetres

Table 2.6. Settings for theTX2000 TA used for capsule compression testing.

2.7.2. PHYSICAL CHARACTERISTION OF TABLETS

Standard tests to determine, crushing strength, weight and thickness were performed on 10 tablets of each type using an automated TBH30 testing station. Disintegration tests were performed on the drug containing tablets in accordance with the pharmacopoeial test (British Pharmacopoeia; disintegration test A., Appendix XII, 1999).

Relative porosity ($\varepsilon_{rel.}$) values were calculated for the ET using the relationship of apparent density (ρ_A) and true density (ρ_T) [Eqn. 2.1] (Murakami et al., 2001). Gas permeation was deemed a more suitable method of porosity determination than mercury porisimetry due the polymeric nature of the tablets, making them susceptible to plastic deformation under high pressure (Westermarck et al., 1998). ρ_A was calculated using the physical parameters obtained from the TBH30 testing station, ρ_T was determined using a helium pycnometer.

$$\varepsilon_{rel.} = 1 - \frac{\rho_A}{\rho_T} \qquad \text{[Eqn. 2.1]}$$

2.7.3. CONTENT UNIFORMITY OF PROPRANOLOL TABLETS

A standard calibration curve prepared for propranolol hydrochloride (λ_{max} for propranolol of 289 nm) was prepared and the gradient and intercept were noted (Appendix I, Section I.2). Propranolol tablets (20) were dissolved into separate 100 ml volumetric flasks. An aliquot (5 ml) was removed from each and diluted to 50 ml. A Cecil 500 UV spectrophotometer set at 289 nm was used to determine the absorbance values for the tablets. A mean maximum absorbance ($A^{100\%}$) value was then determined for input into the dissolution calculation below. Drug content uniformity was calculated for each tablet (Appendix I, Section I.3).

2.7.4. DISSOLUTION TESTING

Dissolution tests were carried out on coated P3 tablets and assembled TDCs using a USP II dissolution apparatus set at 37°C with a 50 rpm paddle speed and 1000 ml water (unless otherwise stated). Samples were analysed using a 1 cm quartz flow-through cell attached to a computer, $A^{100\%}$ values were input to determine percentage dissolution. Assembled TDCs were weighted down to the bottom of the vessel with a stainless steel wire coil consisting of 9 turns, which was tightly fitted around the TDC and did not impede access of dissolution medium to the ET surface.

Different pH solutions of 0.1N HCl (pH 1) and alkaline phosphate buffer (pH 7.4) were used to test the performance of 60 and 80 mg ET in assembled TDC devices. In addition, different paddle speeds of 25 and 100 rpm were also used to provide alternative hydrodynamic conditions.

2.7.5. PHOTOGRAPHIC STUDY

A TDC comprising of a coated capsule ($C_{org\ (2)}$), a riboflavin tablet and an ET formulation of 15% HPMC was prepared (Section 2.4). A 500 ml crystallizing dish with a mounted black dissolution platform was assembled (Figure 2.8). The TDC was stuck to the surface of the platform using Blu Tack®, this provided adhesion and an angular elevation of 25° from the platform.

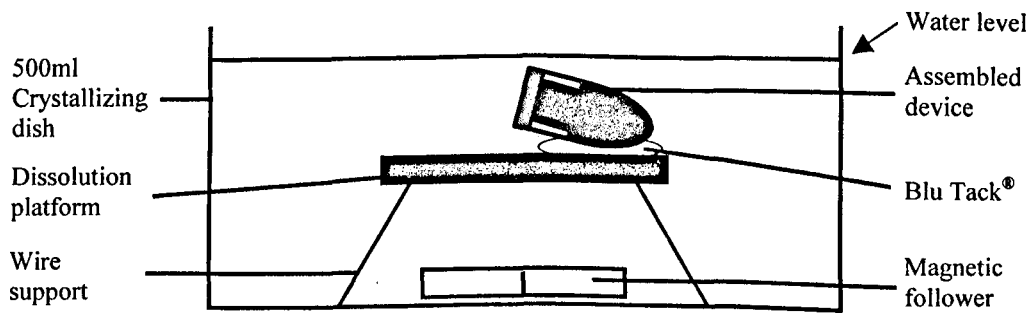


Figure 2.8. Apparatus used for the photographic study of a 1 hour TDC formulation.

De-ionised water (450 ml) pre-heated to 37°C was poured into the crystallizing dish; covering the capsule to a depth of 5 mm. An RDC50 digital camera, equipped with a 2.3M pixel supa-macro zoom facility, was positioned using a tripod to face the erodible tablet of the assembled device at a distance of 5 cm. The camera was programmed to acquire images at 5 minute intervals until the first signs of dosage expulsion were seen. Images were then acquired manually in rapid succession until complete expulsion of the riboflavin tablet was observed.

2.7.6. DIFFUSE REFLECTANCE INFRARED FOURIER TRANSFORM SPECTROSCOPY (DRIFTS)

Potassium bromide (KBr) was lightly ground and placed in a dry powder sample holder. This was levelled and inserted into the Avatar 360-FTIR spectrophotometer. A background measurement using 64 scans at 4 cm^{-1} resolution was taken and stored into the memory buffer. Lactose (10 mg) was lightly ground/mixed with KBr crystals, placed into the sample holder and scanned as above. Granulated lactose (L_{gran})(99 g) was prepared in an identical fashion to the wet granulated ET formulations (Section 2.5.2). L_{gran} (10 mg) was also treated and analysed as above.

2.7.7. X-RAY POWDER DIFFRACTION (XRPD)

Lactose was filled into a 0.7 mm borosilicate glass capillary. The capillary was mounted and aligned on a Bruker-AXS D8 X-ray diffractometer. Data were collected using CuKα_1 radiation, 1.054056 Å and 0.0145 step size at 0.5 s per step, using a Braun position sensitive detector. This analysis was repeated for L_{gran}.

2.7.8. MICROWAVE DIELECTRIC ANALYSIS (MDA)

In this study microwave dielectric analysis (MDA) was employed in a collaborative study with De Montford University, Leicester. MDA can be used to characterize the environment in which water is located (Ribeiro et al., 2001). Measurement of Capacitance (C) is the underlying principle used in MDA determination of dipole relaxation times, and a simple parallel plate arrangement is shown (Figure 2.9).

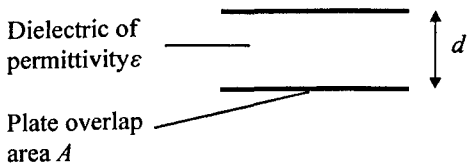


Figure 2.9. A simple parallel plate capacitance arrangement.

Each plate stores a charge (Q), which is either positive (+ve) or negative (-ve). Connecting the plates to form a circuit allows Q to dissipate as electrons flow from –ve to +ve plates. Capacitance is given by [Eqn. 2.2],

$$C = \frac{\varepsilon A}{d} \qquad \text{[Eqn. 2.2]}$$

If the dielectric between the plates is polar (i.e. water), then the molecules orientate themselves to align with the polarity of the applied field. Application of an alternating current (AC) to a capacitor changes the polarity of the plates, at a frequency (f) of the oscillating field. Provided the frequency of the field is sufficiently slow, in relation to mobility of the dipoles, then the change in polarity of the applied field, results in the dipoles following (i.e. reorientating in-phase with) the applied field.

At frequencies in the microwave region (>2 GHz), the periodicity of the alternating field is such that water dipoles are unable to reorient completely before

the field reverses. Instead of following the changes in field polarity, at these high frequencies, the dipoles instead relax to their random orientation. An absorption of energy (i.e. dielectric loss) accompanies a decrease in the dielectric constant, as the frequency of the field increases past what is known as the relaxation frequency (f_o) (i.e. the frequency at which the absorption of energy is at a maximum). In the case of a Deby-like relaxation process, it is possible to estimate the mean relaxation time (τ) from the relaxation frequency (f_o) for maximum energy absorption [Eqn. 2.3].

$$\tau = \frac{1}{2\pi f_0} \qquad \text{[Eqn. 2.3]}$$

Free water in a liquid state exhibits relaxation at a frequency of 20 GHz. It is therefore expected that relaxation of water in a granulation will occur at a lower frequency due to a more constrained environment allowing less dipolar mobility. Microwave dielectric analysis of the dielectric relaxation times for water then provides a direct measure of the mobility of water in the system.

A 3-point calibration of a HP8720D network analyser with HP85070 dielectric probe was performed:

(i) In air [ε_0],
(ii) With a metal shorting block providing no capacitance,
(iii) In 25 ml distilled water at 25°C [ε_w].

Post-calibration the dielectric probe was blotted dry to avoid scratching and/or smearing of water across its face, to ensure reproducible analysis. Calibration was necessary between each sample measurement. Wet granulations containing 15, 24 and 30% HPMC were prepared at intervals (as in Section 2.5.2) but were not dried. Immediately following each granulation, a sample was removed and placed in the polyvinyl acetate sample holder (Figure 2.10). The lid was pushed into the holder so that the granules were compacted with a reproducible force. The dielectric

probe was lowered onto the flat granule surface, and the frequency of relaxation for the water dipole was measured.

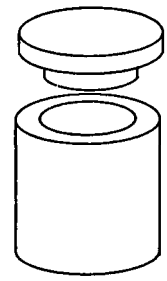


Figure 2.10. PVA dielectric analysis sample holder.

2.7.9. SOLID STATE NUCLEAR MAGNETIC RESONANCE (SSNMR)

In SSNMR two types of relaxational processes can occur. The first, spin-lattice relaxation (T_1) is a result of materials existing with weakly interacting nuclei (i.e. non-metallic). At thermal equilibrium, energy level populations of these nuclei can be described as following a Boltzman distribution and to reach this state there must be an exchange of energy from the populations with their surroundings (the lattice). T_1 is the time taken for this process to occur. The second, transverse relaxation (T_2) provides 'local field' information that can be translated to reveal details of microscopic structure and dynamics. A condition of nuclear magnetisation is that the transverse magnetisation (T_{mag}) equals zero. A pulse of electromagnetic radiation at a resonant frequency can impose coherence to produce this T_{mag}. Neighbouring nuclear dipoles producing internal fields and external fields cause the variation frequencies throughout the sample. The T_{mag} coherence is lost with the characteristic relaxation time T_2 (Smith and Strange, 1996). T_2 relaxation rates are strongly affected by the degree of chain hydration or bound water. The higher the T_2 value the greater the hydration of HPMC (Katzhendler et al., 2000). Due to the lack of motion in a large proportion of polymers the use of an elevated temperature can be used to increase motion and subsequent line narrowing (Liu et al., 1999).

This technique was used to complement the microwave study. The results indicate a reversed trend as molecular movement could be seen to be from an ordered to a disordered state (T_2) as opposed to the ordered state of dipolar alignment with MDA. The use of this technique was limited as data acquisition times were long compared to the MDA analysis times.

Enough granulate for each of the three HPMC concentrations was selected to fill the NMR tubes with 3 cm depth of sample. This was then placed in the NMR tube sample holder and analysed using the specifications outlined (Table 2.7).

Parameter	Setting	Parameter	Setting
Scans	4	H Offset	-1618
Rd [s]	2.00	NMR frequency [MHz]	20.000
Gain [dB]	90	Instrument gain [dB]	72
Digital bandwidth [Hz]	20000	H Cycles [Steps]	0
Analogue bandwidth [Hz]	Narrow	Dead time [ms]	0.007
Offset comp.	Off	Homogenous limit [ms]	0.5
Detection mode	Magnitude	Instrument Rd [s]	2.00
Digital resolution	Fast	SFC	no

Table 2.7. Instrument settings for SSNMR analysis of the wet granulate ET formulations.

2.7.10. EROSION STUDIES OF ERODIBLE TABLET FORMULATIONS

The method of erosion analysis previously used (Ross et al., 2000b) proved unsuitable for the erosion studies based on the HPMC system, as removal of ETs from baskets proved too difficult without a significant loss of ET material in transfer. This was due to the nature of the hydrophilic gel formed being 'sticky' and friable upon handling. In addition, a direct comparison between the erosion and the lag-time of TCDs could not be made directly as the surface area (SA) of the exposed ET was larger (>33%) in the erosion test, compared to the single exposed face of an ET contained within the TDC. Studies on the release rate of drug from hydrophilic matrix tablets have indicated the importance of SA exposed and the rate of drug released (Colombo et al., 1992) which parallels the lactose dissolution in the case of the ET formulations. In this present erosion study, ETs were inserted into coated capsule bodies and the dissolution apparatus used to determine erosion (as with the TDC dissolution studies). This provided identical SA exposure and allowed minimal manual contact with the ET during the study.

DC and WG erodible tablet formulations containing 15, 24 and 30% HPMC were used in the erosion study. Erodible tablets (36) were squarely inserted into $C_{org\ (2)}$ capsule bodies (36) but without expulsion excipient or drug tablets (Section 2.6). These were then weighed. Standard dissolution conditions were used (Section 2.7.4), assembled capsule/ET devices (6) were placed into each of six dissolution vessels. Individual capsules were removed at 1 minute intervals from each vessel for 6 minutes. These were oven dried at 60°C for 8 hours and re-weighed. This was repeated for capsule/ET devices (6) from each formulation but capsules were removed at 10 minute intervals from each dissolution vessel for 1 hour, before drying and re-weighing.

2.7.11. RHEOLOGICAL ANALYSIS

Solutions containing 2% HPMC were prepared using 15, 24 and 30% DC and WG erodible tablet formulations by dissolving 13.3, 8.3 and 6.7 g respectively in 100 ml deionised water at 20°C. Each sample (0.2 ml) was analysed with a CSL100 rheometer. A cone/plate arrangement of 4 cm diameter and 59μm truncation with a 2° cone angle was used, shear stress against shear rate and viscosity against time plots were obtained for each solution.

2.7.12. SCANNING ELECTRON MICROSCOPY (SEM)

DC mixtures and WG granules of 15, 24 and 30% HPMC erodible tablet formulations were mounted individually on a 1 cm cylindrical metallic stubs using double-sided copper tape. Excess powder was gently shaken off and the sample stubs were gold coated using a sputter coater for 195 seconds. Two images were obtained using an SEM at 100x and 400x magnification for each sample.

2.7.13. DYNAMIC VAPOUR SORPTION (DVS)

The DVS apparatus was set to 25°C with 10% relative humidity (RH) steps, set to increment when a change in mass against time (dm/dt) was less than 0.00200 mg/s. DC powder blends and WG granules of 15, 24 and 30% HPMC erodible tablet formulations were analysed using a single sorption-desorption cycle (sorption 0-90% RH; desorption 90-0% RH). In addition HPMC, lactose and L_{gran} was analysed using the same conditions as above.

2.8. CLINICAL TRIAL

2.8.1. SCINTIGRAPHIC ANALYSIS

Images were acquired using a single headed gamma camera. All scintigraphic images obtained for each study subject were viewed retrospectively and sequentially. By noting the relative movement of the radiolabelled TDC to the position of the radiolabelled marker placed on the abdomen gastric emptying time, site of release and gastrointestinal transit times were determined. This was confirmed by two independent trained personnel in BioImages.

Scintigraphic imaging was performed with the subject in a standing position. Anterior and posterior static acquisitions of 30 second duration were collected immediately after dosing then every 15 minutes until release of the ^{99m}Tc radiolabel from the dose has been observed then hourly until the end of the study period. The study period was dependant on the formulation used:

- 1hr time-delayed release formulation was imaged for 8 hours.
- 3hr time-delayed release formulation was imaged for 10 hours.
- 5hr time-delayed release formulation was imaged for 12 hours.

2.8.2. PHARMACOKINETIC ANALYSIS

Sampling

Pre-dose blood samples (4 ml) were taken from each subject 15 minutes before dosing. Following dosing, blood (4 ml) samples were taken according to the following schedules:

- 1hr time-delayed release formulation - every 15minutes to three hours then every 30 minutes for one hour, then hourly to 8 hours.

- 3hr time-delayed release formulation - hourly until release was observed by scintigraphy then every 15 minutes for two hours then every 30 minutes for one hour, then hourly until 10 hours.
- 5hr time-delayed release formulation - hourly until release was observed by scintigraphy then every 15 minutes for two hours then every 30 minutes for one hour, then hourly until 12 hours.

All volunteers were asked to return 24 hrs after dosing for a further blood sample. Blood samples were centrifuged at 2000 g for 10 minutes and the plasma fraction removed for assay.

2.8.2.1. HPLC Assay procedure

A HPLC assay was used to determine the concentration of theophylline in plasma samples. The assay was based on protein precipitation with perchloric acid followed by HPLC with UV detection. The assay was found to be sufficiently sensitive and selective to determine the theophylline concentration in the plasma. β-hydroxy-ethyl-theophylline was used as an internal standard.

Mobile phase preparation

10 mM sodium acetate buffer pH 4.1

Sodium acetate (1.36 g) was dissolved in 800 ml of distilled water, the pH was adjusted to 4.1 with glacial acetic acid and the solution was then made up to 1000 ml with distilled water and filtered prior to use.

Mobile phase

Mobile phase was prepared by adding tetrahydrofuran to 10 mM sodium acetate buffer pH 4.1 to give a final concentration of 1.5% (v/v).

2.8.2.2. Preparation of plasma calibrators

A 25µg/ml sub stock solution of theophylline was prepared by diluting the 0.5mg/ml stock solution 1:20 with distilled water. The calibrators were prepared by diluting the stock and sub stock solutions with theophylline-free plasma as shown in Table 2.8.

Identity	Volume (µl)	Total volume (ml)	Conc. (µg/ml)
Calibrator 1	0 (Sub-stock)	10	0
Calibrator 2	40 (Sub-stock)	10	0.1
Calibrator 3	80 (Sub-stock)	10	0.2
Calibrator 4	200 (Sub-stock)	10	0.5
Calibrator 5	200 (Sub-stock)	10	1.0
Calibrator 6	200 (Sub-stock)	10	2.0
Calibrator 7	200 (Sub-stock)	10	5.0
Calibrator 8	200 (Sub-stock)	10	10.0

Table 2.8. Preparation of plasma calibration solutions.

A typical calibration curve for plasma theophylline is shown in Figure II.1 (Appendix II).

2.8.2.3. Analysis of plasma samples

Each of the plasma sample (100 µl), internal standard solution (1 µg/ml) and 6% (v/v) perchloric acid were pipetted into a 1.5ml micro-centrifuge tube and vortexed for a few seconds. The tubes were then centrifuged at 4500g for 10 minutes. An aliquot (120 µl) of the supernatant was transferred to the insert of a labelled autosampler tube. The samples were analysed overnight at room temperature. HPLC conditions are shown in Table 2.9.

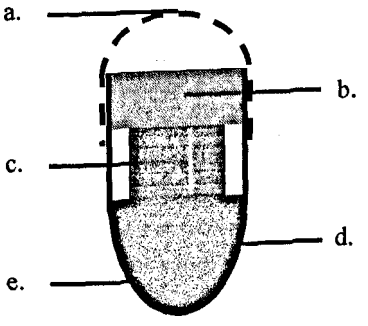
HPLC conditions	Unit
Flow rate (ml/min)	0.4
Injection volume (µl)	20
UV detection (nm)	273
Run time (min)	15

Table 2.9. HPLC condition used for pharmacokinetic analysis.

CHAPTER 3. FORMULATION AND MANUFACTURE OF THE TIME-DELAYED CAPSULE (TDC)

3.1. INTRODUCTION

The Time-Delayed Capsule (TDC) consists of a water impermeable capsule body (a size 0 hard gelatin capsule coated with ethyl cellulose); an internal swelling agent of L-HPC; a drug containing tablet as the dosage form; and an erodible table (ET), the erosion rate of which controls the lag-time of the capsule device (Figure 3.1).



a. Gelatin cap
b. Erodible tablet (ET)
c. Drug containing tablet
d. Expulsion excipient
e. Insoluble coated gelatin capsule

Figure 3.1. The Time Delayed Capsule (TDC).

The effectiveness of a coating process is generally reported as an increase in weight when compared to the original sample. This is performed at intervals during the coating process until the desired product weight is obtained. A variety of techniques to further characterise the coating process have also been used. These include: simple microscopy to view coated surfaces (Jozwiakowski et al. 1990) or examine cross sections (Arwidsson 1991); Near-IR reflectance spectroscopy to measure film thickness of coating (Kirsch and Drennen, 1996); and mechanical tests such as puncture or stress-strain (Bodmeier and Paeratakul, 1993; 1994). It was important in this study to reassess the coating process, as previous work (Ross et al. 2000a) had indicated discrepancies in capsule performance following different coating techniques (aqueous or organic spray techniques). A combination of weight gain and mechanical strength of the capsule were used to determine the suitability and effectiveness of the applied coats. A specific weight gain (i.e. the thickness of the internal coat) was required in order for the ET component of the device to be

fitted securely into the end of the capsule. In addition the mechanical strength of the capsule body after exposure to a 95% humidity was used as an indication of the effectiveness of the ethylcellulose coat in preventing exposure to moisture of the gelatin capsule body and so maintaining capsule structural integrity.

In this present study there was no further selection processes performed on the use of specific expulsion excipients, since the suitability of L-HPC had already been determined (Ross et al., 2000a). However, the quantity and compactability of this component was standardised when manufacturing the TDC throughout these studies (Chapter 2, Figure 2.6).

It was known that the dosage layer in the capsule could either consist of a drug-containing tablet, smaller than the diameter of the capsule, or alternatively pellets (Stevens et al., 1995) as both allow percolation of water through to the expulsion excipient. For ease of manufacture in this study a small uniform tablet (5 mm diameter) was produced and placed onto the surface of the consolidated L-HPC. Propranolol hydrochloride was used as a model drug throughout, and was formulated with standard tableting excipients such as lactose and microcrystalline cellulose (MCC). Initially a disintegrant was included so that rapid disintegration would follow expulsion. However, there appeared to be a problem associated with this type of tablet as incomplete levels of drug were released from the TDC. It was thought that this was due to the drug tablets disintegrating inside the capsule and becoming entrapped within the expanding L-HPC. Initial studies involving these propranolol tablets therefore focussed on creating a small lag-time (of the order of 2 minutes) to allow for expulsion from the TDC before the onset of rapid disintegration facilitated by the disintegrant. The approach of applying a thin Ethocel® coating layer to the propranolol tablets to retard disintegration had limited success. The more controllable method of decreasing the disintegrant level was later adopted.

The most important component of the TDC used to control the specific lag-time was the ET. Variation in the quantity of HPMC included in the formulation was investigated as the main method of control (thinner ETs were also studied in order to

allow the flexibility of using different size drug tablets). In this way a linear relationship could be constructed to show HPMC concentration variation for different lag-times ($T_{50\%}$ drug release) at different ET thickness, effectively allowing the experimenter to pre-program a TDC with a specific lag-time. The effect of lubricant mixing time, ET hardness, hydrodynamic conditions and pH variation were also investigated.

3.2. METHODS

Methods are summarised below (Table 3.1) and referenced to Chapter 2.

Description	Methods section
Components	
Capsules	2.3.
Drug containing tablets	2.4.
ET Formulations	
80 mg	2.5.1.
60 mg	2.5.3.
TDC Assembly	2.6.
Analysis	
Capsule coating analysis	2.7.1.
Physical characterisation of tablets	2.7.2.
Dissolution	2.7.4.
Photographic study	2.7.5.

Table 3.1. Summary of methods used in Chapter 3.

3.3. RESULTS

3.3.1. CAPSULE INTEGRITY TESTING

Compression force profiles of the coated capsule bodies are shown (Figure 3.2). An increase in compression force (F) is observed until structural collapse of the capsule (F_{max}) occurs. This is accompanied by a rapid decrease in F (omitted from the plot for clarity). Capsules coated with the organic solvent process are able to withstand a higher $F_{max\ (dry)}$ before structural collapse than the aqueous coated capsule. This is probably due to an increased flexibility associated with their structure, a function of the plasticization process during coating.

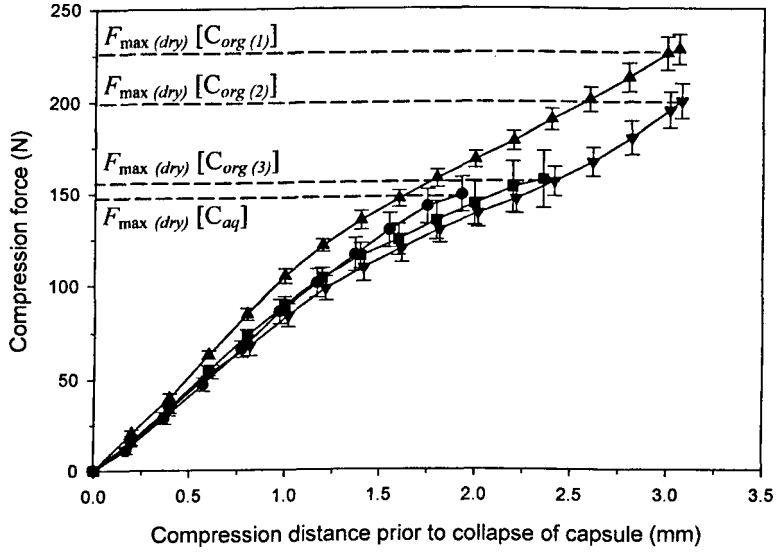


Figure 3.2. Compression force profiles of coated capsules (n =10 ± s.d).

▲ = $C_{org\ (1)}$, ▼ = $C_{org\ (2)}$, ■ = $C_{org\ (3)}$, ● = C_{aq}.

Force profiles of the coated capsule bodies following exposure to 90% RH for 999 minutes is shown (Figure 3.3). Again, all organically coated capsules are able to withstand a greater $F_{max\ (RH90)}$ than the aqueous coated capsule, which is much reduced post exposure to the 90% relative humidity (RH).

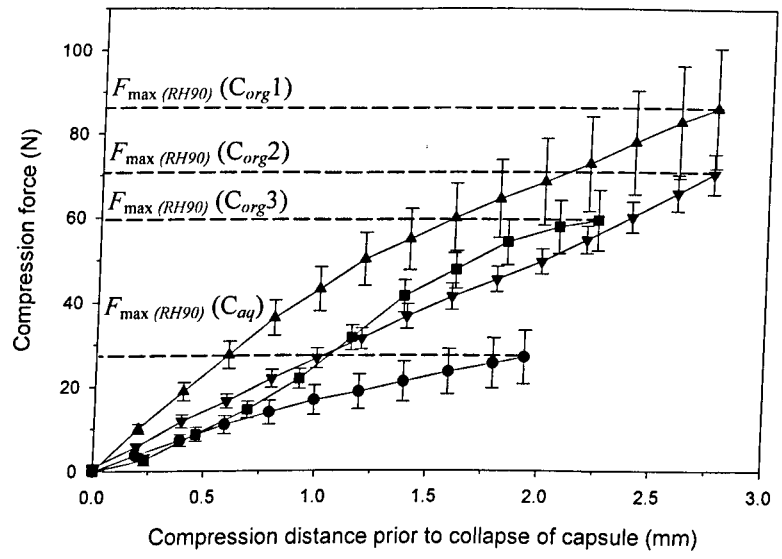


Figure 3.3. Compression force profiles of coated capsules (n =10 ± s.d).

▲ = $C_{org\ (1)}$, ▼ = $C_{org\ (2)}$, ■ = $C_{org\ (3)}$, ● = C_{aq}.

A capsule integrity ratio (*CIR*) was calculated [Eqn. 3.1].

$$CIR = \frac{F_{max\,(RH90)}}{F_{max\,(dry)}} \qquad \text{[Eqn. 3.1]}$$

Capsule type	$F_{max\ (dry)}$ [N]	(s.d)	$F_{max\ (RH90)}$ [N]	(s.d)	*CIR*
C_{aq}	148.4	(9.6)	27.0	(6.4)	0.18
$C_{org\ (1)}$	227.4	(8.0)	86.2	(14.5)	0.38
$C_{org\ (2)}$	200.0	(9.4)	74.1	(4.9)	0.37
$C_{org\ (3)}$	156.7	(15.6)	59.4	(7.2)	0.38

Table 3.2. Summary of capsule integrity ratio (*CIR*) for aqueous and organic spray coated capsules (n = 10).

CIR values (Table 3.2) for all the organic coated capsules are higher than for the aqueous coated capsules, indicating less permeability to water at 90% RH. All organic coated capsules show similar *CIR* values indicating that their structural integrity is affected to the same extent by the exposure to the RH.

In an earlier collaborative study with colleagues at Trinity College, Dublin (Ross, unpublished data) capsule surfaces were scanned with a laser spot of 1μm in a linear fashion to enable a three-dimensional surface profile to be obtained using laser profilometry (Healy et al., 1995). Surface roughness parameters were calculated to yield an average roughness parameter (R_a), which indicated the effectiveness of the coating conditions used and was a predictive tool for assessing the fit of the ET in the end of the coated capsule bodies. A profile of R_a values (Figure 3.4) from the open end of the capsule (Area segment 1) to 10 mm below the rim of the capsule (Area segment 10) indicated an improved coating level to at least 6 mm below the rim for $C_{org\ (l)}$. This data suggests improved spreading of the organic coat within the capsule body during the coating process resulting in improved coating of the gelatin with organic spray coating conditions. The resultant laminated coating (internal and external) would explain why exposure to 90% RH affects the organically coated capsule to a lesser extent than the aqueous coated capsule.

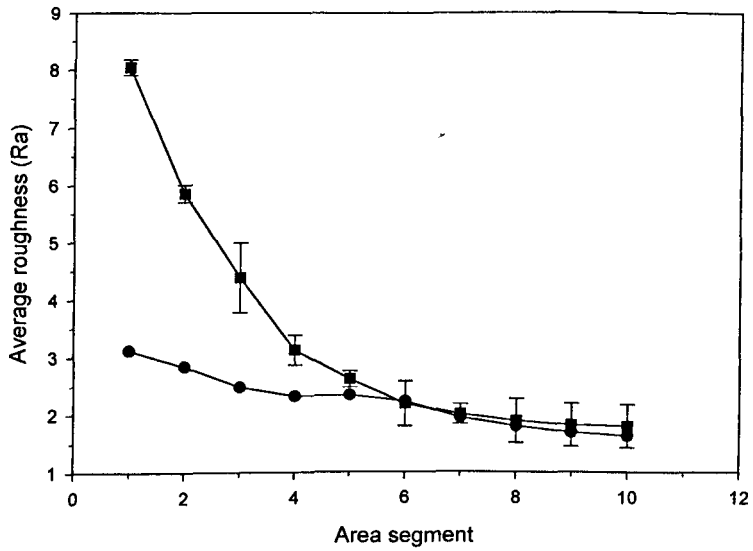


Figure 3.4. R_a profiles of coated capsule bodies.
■ $C_{org\ (l)}$, ● C_{aq}.

An improved coating on the inner surface of the capsules is therefore essential in preventing premature drug release. The provision of a good fit between the capsule and ET prevents water ingress around the capsule rim and better coating at the opening of the capsule allows for this. Aqueous coated capsules have also been shown to be susceptible to splitting prior to complete erosion of the tablet (Sutch et al., 2002). In that situation, it is reported that water penetrates into the capsule contents prior to complete erosion of the ET and leads to swelling of the L-HPC resulting in splitting of the capsule. L-HPC can force its way out of the split under pressure leaving the dosage form still intact within the malfunctioning capsule. After erosion of the ET, the already partially swollen expulsion excipient is unable to expel the drug-containing tablet, and it remains in place. Drug is then slowly released into the dissolution medium by diffusion mechanisms. The indication of the relatively low $F_{max\ (RH90)}$ for the aqueous coated capsules indicates moisture penetration through the film into the gelatin, thus weakening the coated capsule body.

3.3.2. DRUG CONTAINING TABLETS

3.3.2.1. Physical properties

Physical properties of the propranolol tablets (P1-P7), the non-disintegrating riboflavin tablet and the theophylline tablet, are shown in Table 3.3. The considerations raised with the properties of each of the propranolol formulations are outlined in Table 3.4.

Formulation	Weight [mg] (s.d.)	Thickness [mm] (s.d.)	Crushing strength [N] (s.d.)	Diameter [mm] (s.d.)	Disintegration time [mins] (s.d.)
P1	54.3 (1.7)	1.93 (0.03)	16 (6)	6.50 (0.01)	<1
P2	54.2 (0.4)	1.87 (0.04)	51 (3)	6.50 (0.00)	<1
P3	53.4 (0.3)	2.24 (0.01)	53 (2)	6.50 (0.01)	<1
P4	80.8 (0.5)	3.40 (0.01)	79 (7)	5.00 (0.00)	10
P5	81.0 (0.6)	3.49 (0.02)	98 (3)	5.00 (0.01)	3.5
P6	79.9 (0.9)	3.52 (0.02)	92 (4)	5.00 (0.00)	<1
P7	78.6 (0.4)	3.88 (0.02)	44 (3)	5.00 (0.01)	2.5
Riboflavin	132.2 (2.9)	3.30 (0.07)	97 (14)	5.00 (0.01)	>300
Theophylline	90.2 (1.3)	4.24 (0.01)	74 (5)	5.00 (0.01)	2.8

Table 3.3. Properties of drug containing tablets for use in the TDC (n=10).

The riboflavin tablet formulation showed suitable non-disintegrating properties for the photographic study (Section 3.3.3.1.5). The theophylline tablet matched the disintegration times of the *in vitro* model drug tablet.

Clinical batches of theophylline tablets manufactured using an IR press in order to conform with GMP protocols. The IR press applies a higher force to the powder blend than the E2 single station punch used earlier for *in vitro* manufacture. The result is a substantially higher crushing strength for the theophylline tablets compared to the propranolol (P7) tablets used for *in vitro* dissolution studies (indicated below). To ensure a reproducible disintegration time for this theophylline tablet, 2% disintegrant (Ac-di-sol®) was included in the GMP tablet formulation.

Formulation	Comments
P1, P2	Rejected. Crushing strength too low for coating. Should be >50 N (Wakerly et al., 1996)
P3	Accepted for coating, crushing strength >50 N. Rejected for TDC after coating (see Section 3.3.2.2, below)
P4, P5	Rejected. Lamination* occurred.
P6	Rejected. Disintegration time low.
P7	Accepted. Suitable disintegration properties. Used for all *in vitro* TDC testing.

Table 3.4. Suitability of the propranolol drug tablet formulations.

*Lamination resulted in incomplete tablet disintegration.

3.3.2.2. Tablet coating

The increase in coating level of P3 drug tablets over the 5 minute coating period is shown in Table 3.5.

Coating time (mins)	Mean tablet weight (mg)	s.d.
0	51.5	0.7
1	51.7	0.9
2	51.8	0.7
3	52.1	1.5
4	52.4	1.1
5	52.5	1.8

Table 3.5. Weight gain as a function of ethyl cellulose coat increase for P3 drug tablets (n =10).

Rapid drug release is indicated by the uncoated P3 tablets (Figure 3.5), this release becomes more sustained when coating is applied >2 minutes. Due to the variability of the coat applied during such a small time period, error bars (not shown) are large. The apparent grouping of the P3 formulations: i.e. uncoated and 1; 2 and 3; 4 and 5 minutes is an artefact, in reality a continuum of release profiles exists between uncoated and 5 minute coating levels. As a result of the development of sustained release drug profiles as coating levels increased, the further use of coating to inhibit disintegration within the capsule prior to expulsion, as abandoned.

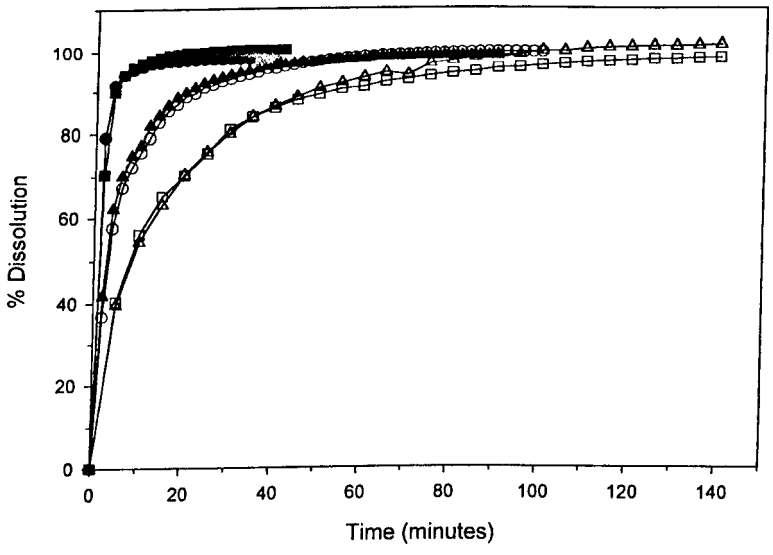


Figure 3.5. Dissolution profiles of uncoated and P3 drug tablets coated over a 5 minute period and removed at 1 minute intervals.

● Uncoated, ■ 1 minute, ▲ 2 minutes, ○ 3 minutes, △ 4 minutes, □ 5 minutes (n=6).
(Error bars omitted for clarity).

The formulation P7 was adopted as the most suitable, due to its favourable disintegration rate and the fact that its size (5 mm) was most appropriate to guarantee its expulsion.

3.3.3. ERODIBLE TABLET FORMULATIONS

3.3.3.1. 80mg Erodible tablet formulations

3.3.3.1.1. Physical properties

Physical properties of the various HPMC concentration ETs are shown in Table 3.6. Variation in lubricant mixing time of 5, 10, 20 and 30 minutes and crushing strengths of 20, 30, 40 and 50 N are indicated for the 24% ET formulations.

% HPMC	Lubricant mixing time (mins)	Weight (mg) (s.d.)	Thickness (mm) (s.d.)	Crushing strength (N) (s.d.)
5	10	80.1 (0.4)	1.62 (0.03)	48 (3)
10	10	79.9 (0.6)	1.66 (0.06)	44 (4)
15	10	81.0 (1.1)	1.64 (0.02)	43 (3)
24	10	79.6 (1.1)	1.75 (0.03)	45 (6)
24	10	80.3 (0.1)	1.89 (0.01)	20 (1)
24	10	79.7 (0.2)	1.84 (0.04)	30 (0)
24	10	80.8 (0.5)	1.68 (0.03)	55 (2)
24	5	80.5 (0.3)	1.79 (0.02)	39 (1)
24	20	80.3 (0.5)	1.78 (0.03)	41 (1)
24	30	80.1 (0.2)	1.77 (0.03)	40 (1)
25	10	79.1 (0.9)	1.65 (0.03)	44 (2)
30	10	80.5 (0.4)	1.79 (0.03)	48 (1)

Table 3.6. Lubricant mixing times and physical properties of 80 mg ET formulations (n =10).

3.3.3.1.2. Dissolution profiles

Dissolution profiles of the 80 mg ET formulations in assembled TDCs are shown in Figure 3.6. Increasing HPMC concentration shows an increase in lag-time and no apparent retardation of drug is seen once release is initiated.

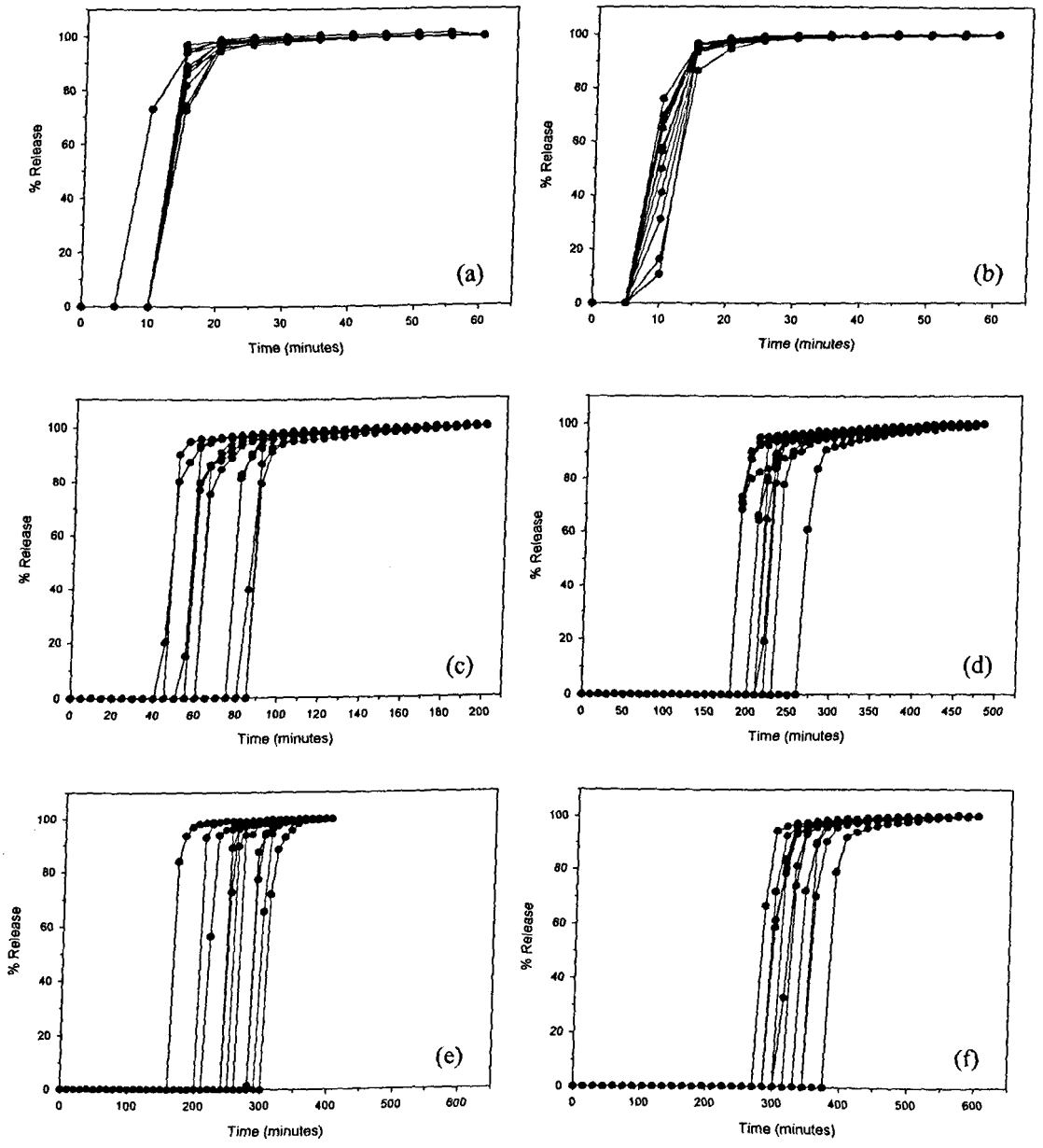


Figure 3.6. Dissolution profiles of the TDC fitted with 80 mg ETs:

(a) 5% HPMC; (b) 10% HPMC; (c) 15% HPMC; (d) 24% HPMC; (e) 25% HPMC; (f) 30% HPMC.

The results confirm that TDC lag-time ($T_{50\%}$ release) is increased by increasing the concentration of HPMC in the erodible tablet. A greater degree of polymer entanglement is seen with an increased HPMC concentration (Reynolds et al., 1998; Siepmann et al., 1999a). This is revealed as an increasing lag-time (Table 3.7).

% HPMC	Mean $T_{50\%}$ release [mins] (s.d.)
5	11.9 (0.49)
10	10.2 (0.78)
15	68.6 (13.9)
24	213 (25.4)
25	263 (32.4)
30	325 (30.3)

Table 3.7. Effect of HPMC concentration on TDC lag-time with 80 mg ETs (n = 12).

Lag-time can be controlled by varying the HPMC concentration. An 80 mg ET therefore can be formulated to provide a suitable lag-time by reference to the linear plot (Figure 3.7). However, below 15% HPMC, the linearity begins to deteriorate. The increased lactose concentration disrupts erosion of HPMC. A finite time is required before the formation of a gelled HPMC matrix provides a linear erosion rate (discussed further in Chapter 5), this cannot be achieved with elevated concentrations of lactose.

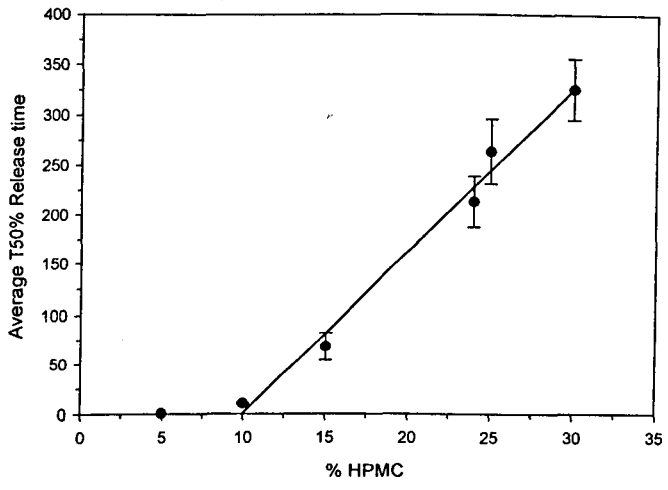


Figure 3.7. The effect of varying HPMC concentration on TDC lag-time ($T_{50\%}$ release ± s.d), $R^2 = 0.988$.

3.3.3.1.3. Effect of erodible tablet compression on Time-Delayed Capsule (TDC) lag-time

It is reported that increasing the apparent density of HPMC tablets by increased compaction pressure does not affect drug release (Huber and Christianson, 1968). This lack of effect is also shown to be the case in the present study, where by maintaining the concentration of HPMC at 24% but varying the ET crushing strength did not afford a reliable means of achieving lag-time control as shown by the $T_{50\%}$ release times (Table 3.8).

Crushing strength [N]	Mean $T_{50\%}$ release [minutes] (s.d.)
20	211.3 (32.0)
30	208.1 (33.8)
40	213.1 (25.4)
55	279.7 (22.1)

Table 3.8. Effect of ET crushing strength on TDC lag-time (n = 6).

Although the effect of tablet crushing strength seems largely ineffectual in changing the lag-time, maximum compression during tableting (55 N) does however increase lag-time. This suggests there may be a threshold effect, which is related to the very low porosity of the ET at this maximum compression force. Lowering the porosity decreases variability of the lag-time. It is difficult to predict which of the excipients is influenced most by this factor. For example, lactose may dissolve to leave pores that are occupied by the advancing HPMC matrix, however HPMC needs to be wetted sufficiently to form a gel layer prior to erosion. Either of these mechanisms may be altered significantly above the threshold crushing strength.

3.3.3.1.4. Effect of erodible tablet formulation mixing time on TDC lag-time

All observed lag-times ($T_{50\%}$ release) fall between 194 and 255 minutes and no discernable relationship is apparent between mixing time and lag-time (Table 3.9). Statistically all $T_{50\%}$ release times show significant similarity ($p > 0.05$) except for the 20 minute blending time, which shows more rapid release. This indicates that mixing times of less than 30 minutes are not sufficient to affect the lag-time of the TDCs using these formulations.

Mixing time (mins)	Mean $T_{50\%}$ release (minutes) (s.d.)
5	254.9 (30.2)
10	213.1 (25.4)
20	194.1 (10.9)
30	237.4 (26.0)

Table 3.9. Effect of lubricant mixing time on TDC lag-time (n=6).

3.3.3.1.5. Photographic study

The sequence of photographs in Figure 3.8 shows the process of erosion of a 15% HPMC ET formulation as it occurs over a 1 hour period. This is summarised in Table 3.10.

Time index (mins:secs)	Observation
5:00	Swelling of HPMC, appearance of roughened surface, expulsion of air from ET pores
10:00	Formation of a stable polymeric gel layer. No air-expulsion and smoother tablet face.
15:00	Completely smooth face, indicating HPMC erosion (described in Chapter 1, Figure 1.9)
40:00	Steady erosion has exposed internal capsule surface.
46:00	Thinning of HPMC and disruption in the upper left quadrant of the ET face.
52:30	Formation of air-bubble from the 'dead-space' between the riboflavin tablet and the inner capsule wall.
54:20	Air bubble is rapidly expelled by expanding L-HPC (not observed)
54:40	Drug tablet is completely expelled.

Table 3.10. A summary of pulsatile drug delivery from a TDC fitted with a 15% HPMC erodible tablet and highly visible riboflavin tablet.

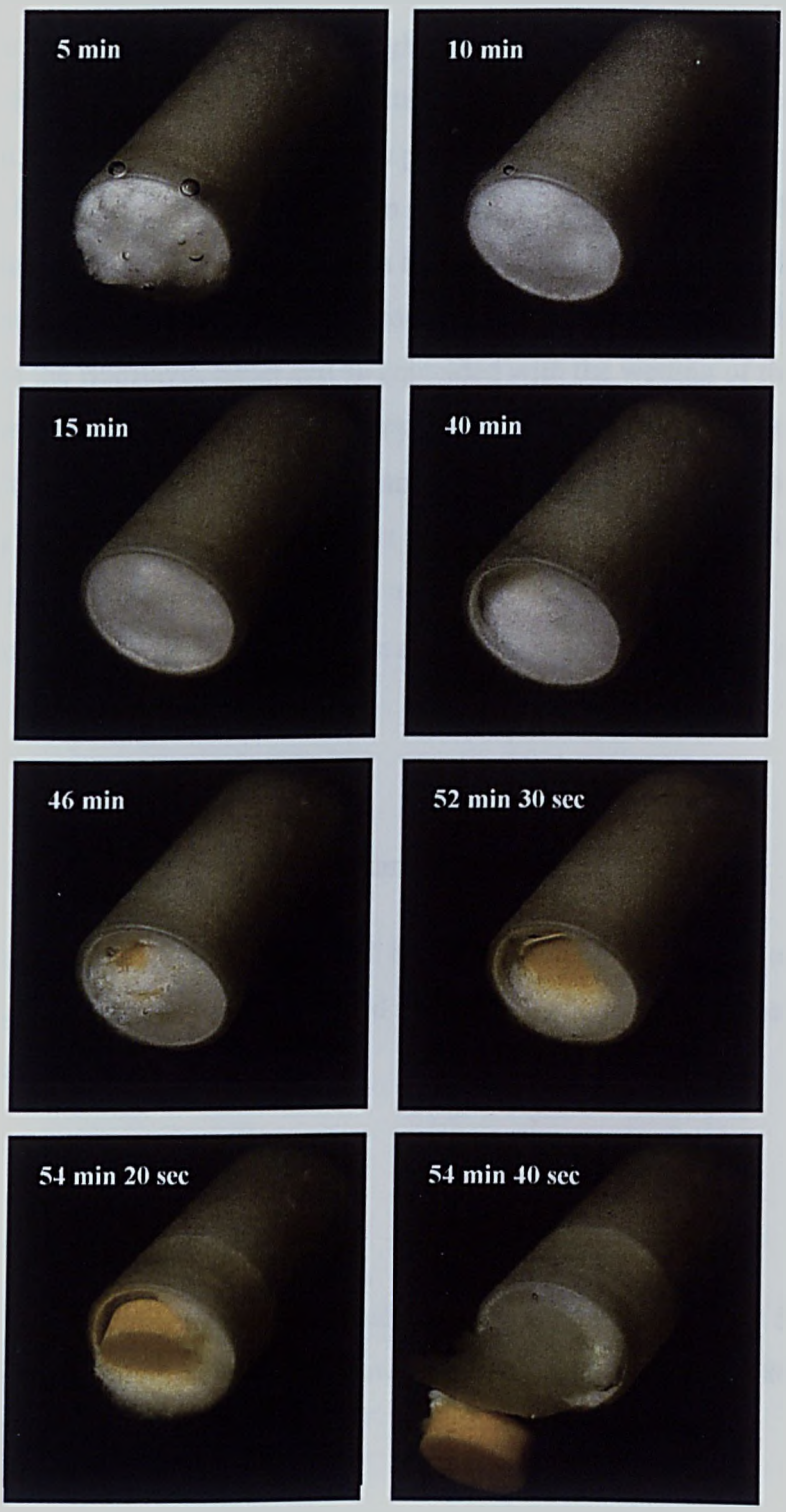


Figure 3.8. The process of pulsed release drug delivery from a TDC fitted with a 15% HPMC erodible tablet showing release of a riboflavin tablet.

At the 40 minute time point the importance of an inner coating of ethyl cellulose becomes clear. Flaws or weakness in the coat may lead to premature expulsion due to water migration through to the contents via the wall of the gelatin capsule. Remnants of the ET remain attached to the capsule body post-drug expulsion, this was consistent with data presented later (Chapter 5) which suggest that only 80% of the tablet mass need to erode before the onset of L-HPC expansion. An encroaching tidemark was also seen through the translucent coated capsule wall, initially present after 54 minutes 20 seconds. This became visible at the moment of ejection of the riboflavin tablet and so coincided with the wetting of the L-HPC. Even after final ejection the tidemark appeared no further than half way down the length of the capsule body, suggesting an excess of L-HPC was present. Indeed following many dissolution experiments the L-HPC at the base of the capsules was observed to remain dry for many hours within the dissolution vessels. This observation gives some scope for future miniaturisation of the device, and ultimately increased patient compliance.

3.3.3.2. 60 mg Erodible tablet formulations

The formulation of a thinner ET became necessary so that larger drug-containing tablets could be incorporated into the capsule for the proposed human study (Chapter 6).

3.3.3.2.1. Physical properties

Table 3.11 indicates the observed physical properties of 60 mg ET formulations, the mean thickness is shown to be 0.4 mm less than the 80 mg ET formulations (Table 3.6).

% HPMC	Weight [mg] (s.d.)	Thickness [mm] (s.d.)	Crushing strength [N] (s.d.)
15	60.5 (0.4)	1.33 (0.04)	31 (1)
20	59.8 (0.3)	1.36 (0.03)	31 (2)
24	60.2 (0.6)	1.30 (0.03)	32 (1)
30	59.7 (0.2)	1.33 (0.03)	30 (1)
35	60.0 (0.3)	1.35 (0.03)	38 (2)

Table 3.11. Physical properties of 60 mg ET formulations (n = 10).

3.3.3.2.2. Dissolution studies

As previously described (Section 3.3.3.1.2), linearity of the $T_{50\%}$ release versus HPMC content deviates with low amounts of HPMC in the erodible tablets (<10%). This was observed with the 80 mg erodible tablet with an HPMC content of <10% (equivalent to 8 mg) (Figure 3.6). When considering the lag-time of a 60 mg erodible tablet a 15% HPMC content (equivalent to 9 mg), also displays a deviation from linearity indicating that low levels of HPMC are incapable of forming reproducible gel layers permitting controlled erosion as indicated by Figure 3.9a.

As with the 80 mg ET formulations a good level of control is exhibited with the 60 mg ET formulation (Figure 3.9) by varying the levels of HPMC (>20%). This enables a thicker drug tablet to be incorporated into the capsule device while still maintaining the same content of L-HPC, hence preserving the distance between the rim of the capsule body and the expulsion excipient, and ensuring a reproducible expulsion sequence. Mean $T_{50\%}$ release times are indicated (Table 3.12). The linearity of the relationship between $T_{50\%}$ and HPMC is improved for the smaller 60 mg ETs (Figure 3.10) compared with the 80 mg ETs. This is indicated by the solid regression line (a), for concentrations of greater than 20% HPMC. The deviation of linearity below 20% concentration can be clearly seen.

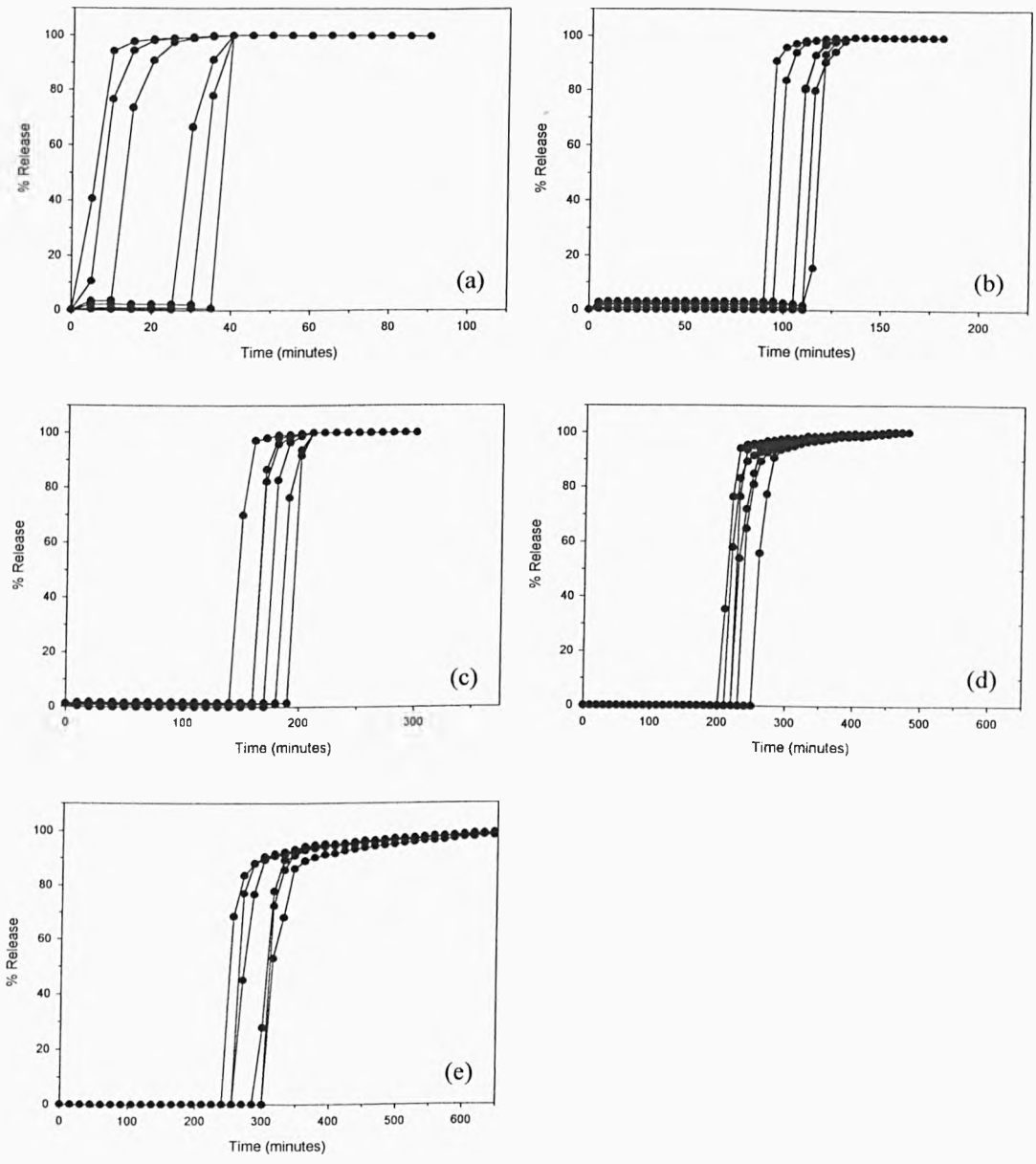


Figure 3.9. Dissolution profiles of the TDC fitted with 60 mg ETs:
(a) 15% HPMC; (b) 20% HPMC; (c) 24% HPMC; (d) 30% HPMC; (e) 55% HPMC.

% HPMC	$T_{50\%}$ release (minutes) (s.d.)
15	18.7 (13.5)
20	104.2 (9.7)
24	152.8 (17.4)
30	226.0 (19.3)
35	277.3 (28.2)

Table 3.12. Effect of HPMC concentration on TDC lag-time with 60 mg ETs (n = 6).

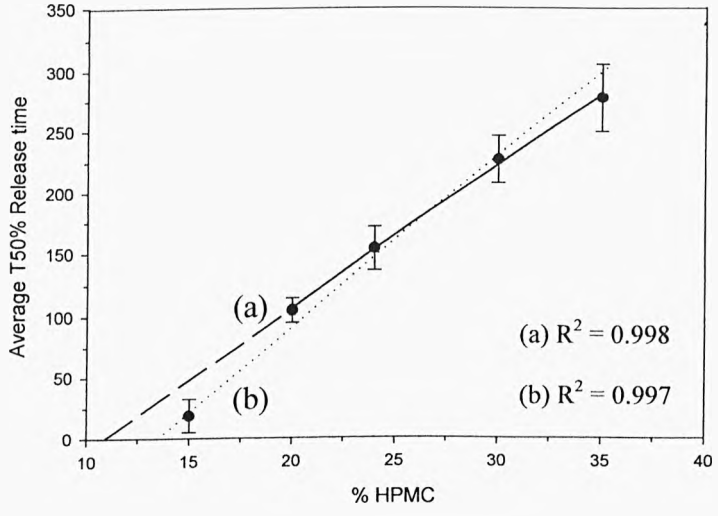


Figure 3.10. Effect of %HPMC on $T_{50\%}$ release times (± s.d).

15, 24 and 30% HPMC formulations were studied prior to the clinical study by the protocol submission deadline. This produced the linear relationship indicated by the dotted line (Figure 3.10b) with an R^2 value of 0.997. Using this plot 1, 3 and 5 hour lag-times are indicated by 20, 24 and 35% HPMC ETs respectively. It only became apparent, when the clinical trial formulations of 20 and 35% HPMC ET had been prepared, that the initial linear relationship was in error, and the correct plot could be drawn (Figure 3.10a).

3.4. EFFECT OF pH AND HYDRODYNAMIC CONDITIONS ON TIME-DELAYED CAPSULE LAG-TIME

The results of varying pH and dissolution paddle speed are summarised in Table 3.13.

% HPMC	ET weight [mg]	$T_{50\%}$ release [mins] (s.d.)				
		Standard conditions*	Paddle speed [rpm]		pH	
			25	100	1	7.4
15	80	68.6 (13.9)	110.2 (15.2)	30.3 (7.5)	35.2 (10.6)	71.6 (15.2)
24	80	213 (25.4)	294 (27.0)	156 (24.0)	165 (22.2)	225 (22.2)
30	80	325 (30.3)	415.3 (30.0)	231 (28.4)	240 (20.1)	330 (33.5)
20	60	104.2 (9.7)	140.5 (15.1)	65.4 (10.6)	68.3 (12.2)	115.3 (12.3)
24	60	152 (17.4)	231 (25.2)	90.3 (11.6)	97.3 (20.1)	162.0 (10.0)
35	60	277 (28.2)	410 (36.0)	165 (15.5)	170 (35.5)	285.4 (12.0)

Table 3.13. The effect of pH and hydrodynamic conditions on TDC lag-time.
*pH 6.5 and 50 rpm.

The data shows that the lag-time is increased with a reduced paddle speed, and decreased at lower pH values. To obtain pH 1, 0.1N hydrochloric acid was used. It has previously been shown that the chloride anion has an effect of increasing HPMC erosion (Ford et al., 1985) by reducing tortuosity of the gel layer. This is probably the mechanism involved here. The elevated pH (7.4) shows only a slight increase in erosion indicated by the lag-time. This is comparable to the pH of the GI tract, suggesting that TDC performance would be largely unaffected by GI transit. Previous *in vivo* studies have indicated this by showing that the erosion rate of HPMC is relatively constant, with pH and ionic strength only having a minor effect on the erosion (Abrahamsson et al., 1998; 1999).

The effect of paddle speed is likely to have an effect on the rate of HPMC disentanglement (Makino et al., 1996), with an increased speed leading to more rapid erosion. Well hydrated, low viscosity polymers have previously been shown to be

susceptible to hydrodynamic stress, and show elevated rates of erosion (Lindner and Lippold, 1995).

3.5. CONCLUSIONS

- Organic coated capsules maintain greater structural integrity when compared with aqueous coated capsules by observing the *CIR*. This value enabled a suitable formulation to be selected and prepared for the clinical trial (Chapter 6) when a USP approved plasticizer was incorporated in the coating process. The *CIR* was found to be consistent for all the organic coated capsules, none of which had shown incidences of failure in work prior to these studies. Coated capsule bodies could therefore be manufactured to a certain specification for consistency of operation.

- A suitable model drug-containing tablet (P7) was formulated by studying the effects of disintegrant levels and tablet coating. No incidences of sustained release (or reduced drug release) were observed with disintegrant-free formulations after desired lag-times in TDCs. An initial aim was therefore addressed by reducing inter-device variability due to the drug containing tablet.

- Accurate lag-times can be pre-programmed by variation of the concentration of HPMC in the erodible tablet formulations of 80 and 60 mgs. This allowd for the targeting of 1, 3 and 5 hours, a further aim of these studies. Lag-time variability was reduced with the thinner 60 mg formulation possibly due to a more rapid formation of Gel layer with increased concentration of HPMC.

- Varying sizes of the drug-containing tablet could be included in the TDC by varying the thickness of the ET formulations, allowing a wider range of potential treatment to be available.

- Differences in crushing strengths (porosity) do not affect erosion of the ETs and subsequent TDC lag-time. The manufacturing process therefore has an acceptable margin of error in the compression cycle.

- A visual analysis of pulsed-release drug delivery from the TDC highlighted the main processes involved in its operation. The presence of an excess of expulsion excipient suggested that a smaller preparation of the TDC might be feasible.

CHAPTER 4. THE EFFECT OF METHOD OF MANUFACTURE ON ERODIBLE TABLET PERFORMANCE

4.1. INTRODUCTION

Having established the suitability of HPMC erodible tablets for selecting specific lag-times for the Time-Delayed Capsule (TDC), the next step was to reduce the variability observed in Figures 3.5a-f. Dissolution variability of conventional dosage forms has been shown to reduce with the introduction of a wet granulation step to improve tablet homogeneity (Chowhan et al., 1982). Since the controlling factor in the TDC was the erodible tablet (ET), a wet granulation step was introduced in an attempt to improve the homogeneity and minimise lag-time variability by providing a more uniform ET.

The effect of processing on tablets has been the focus of much research (Ganderton and Selkirk, 1970; Wikberg and Alderborn, 1991, 1992; Eriksson and Alderborn, 1995). These studies indicated that the main influence on dissolution was tablet porosity as this controlled the rate of wetting, dissolution and disintegration of a tablet. In the present study the initial focus was placed on the physical properties of the ET, including crushing strength and porosity, to determine whether Wet granulation (WG) had significantly altered any of these properties.

The introduction of water during the granulation process (Chapter 2, Section 2.5.2) introduces the possibility that there might be an effect on the lactose component of the ET. As stated earlier, the grade of lactose used in the ET was Fast-Flo. This is reported to comprise a mixture of amorphous lactose (Kibbe, 2000) and α-lactose monohydrate. During exposure to a humid environment the amorphous form is very likely to change into a crystalline monohydrate form (Buckton and Darcy, 1995). As a result, some degree of an amorphous to crystalline transition may occur in the lactose during the granulation process. In order to assess whether a morphological change had occurred in the lactose Fourier transform infrared (FT-IR) spectroscopy and X-ray powder diffraction (XRPD) were used. In addition dynamic vapour sorption (DVS) was used to assess moisture uptake, which is indicative of the properties of the exposed surfaces of the particles.

Following the studies on the individual excipients, direct compression (DC) powder blends and WG granules of HPMC/lactose were visualised using scanning electron microscopy (SEM) to determine the particulate properties prior to tableting.

It has previously been shown, with high molecular weight HPMC, that no difference in drug release rates was seen between DC or WG formulations prepared by high shear mixing (Sheskey and Williams, 1996), or water spray granulation (Liu et al., 1993). As a result no overall change in TDC lag-time was expected by the introduction of the wet granulation step. The intermediate grade of HPMC (Methocel® K100LV) used in this study shares some of the properties of the low molecular weight (M_w) grades routinely used in tablet coating and higher M_w grades used for the manufacture of sustained release formulations (Dow Chemicals, 1995; 1996c). During the wet granulation process there is undoubtedly some degree of HPMC dissentanglement, and polymeric chain re-arrangement (as described in Chapter 1, Section 1.4). To assess the extent of this occurrence new innovative techniques of microwave dielectric analysis (MDA) and solid-state nuclear magnetic resonance (SSNMR) were used. In this way to the extent of water mobility within the wet granulate during the granulation stage could be assessed. It is assumed that the extent of water mobility has a direct effect on the mobility of HPMC chains, enabling them to spread and coat during the WG process. Higher M_w grades used in sustained release formulations have been shown to be susceptible to shear when in their relaxed gelatinous state, due the high shear forces imposed by mixing (Suzuki et al, 2001), consequently this would then have a direct impact on the rheological properties of granulated fluids, subsequent formation of gel layers and erosion properties (Bonferoni et. al., 1992; 1995). Viscosity is the definitive measurement used for grading HPMC and is proportional to the average polymer chain length, this was determined pre- and post-WG to assess any such effects.

4.2. METHODS

Methods are summarised below (Table 4.1) and referenced to Chapter 2.

Description	Methods section
Manufacture	
Direct compression ETs	2.5.1.
Wet granulation ETs	2.5.2.
TDC Assembly	2.6.
Analytical methods	
Physical characterisation of tablets	2.7.2.
Dissolution of TDC	2.7.4.
Lactose	
DRIFTS	2.7.6.
XRPD	2.7.7.
HPMC	
MDA	2.7.8.
SSNMR	2.7.9.
Rheology	2.7.11.
DC blends and WG granules	
SEM	2.7.12.
DVS	2.7.13.

Table 4.1. Summary of methods used in Chapter 4.

4.3. RESULTS

4.3.1. DISSOLUTION STUDIES OF TIME DELAYED CAPSULES

Dissolution profiles of the three dry blend DC erodible tablet formulations are shown (Figure 4.1). Direct compression formulations to obtain approximate release times of 1, 3 and 5 hours were designed (Chapter 3, Section 3.3.3), and were found to correspond to concentrations of 15, 24 and 30% HPMC respectively in 80 mg ETs. This demonstrates the expected trend in the dissolution properties of the three direct compression TDCs; where an increase in HPMC content in the erodible tablet shows a greater degree of polymer entanglement and hence increased lag time (Reynolds et. al., 1998; Siepmann et. al., 1999b). The increase in the degree of polymer entanglement also results in an increase in gel layer thickness, further retarding the dissolution of lactose and HPMC (Rekhi et. al., 1999).

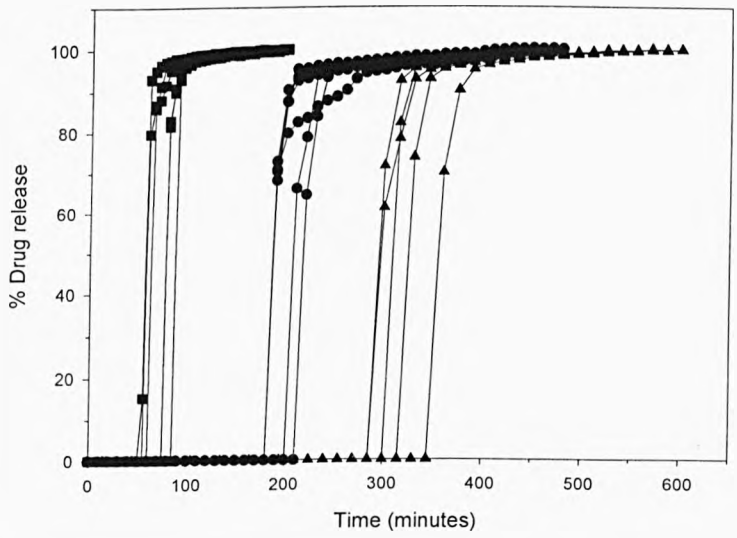


Figure 4.1. Release profiles of TDCs with 80 mg DC erodible tablets.

■ 15% HPMC; ● 24% HPMC; ▲ 30% HPMC.

(Note n =12, but n =6 on the figure for clarity).

Dissolution profiles of the corresponding TDCs with wet granulated ETs show an unexpected trend in release profiles in that all lag-times have increased to varying degrees (Figure 4.2) and have become less distinguishable between the different ET formulations. The greatest shift in lag-time occurs with the lowest concentration of HPMC (15%) in the erodible tablet.

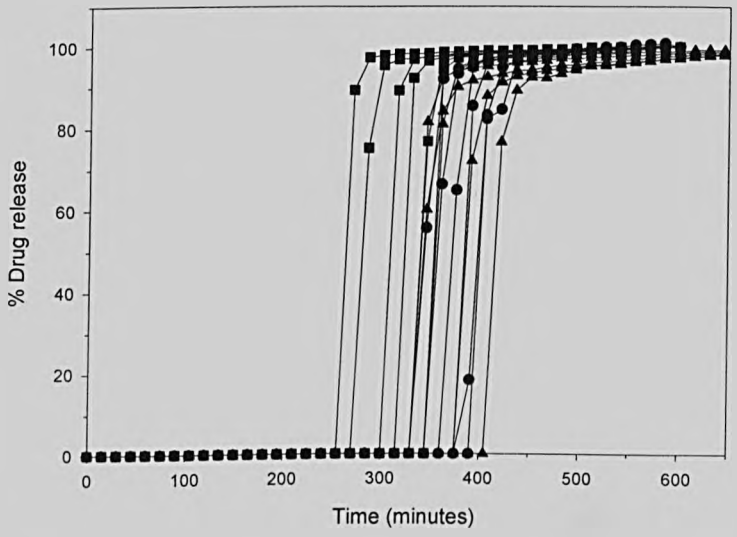


Figure 4.2. Release profiles of TDCs with 80 mg WG erodible tablets.
■ 15% HPMC; ● 24% HPMC; ▲ 30% HPMC.
(Note n =12, but n =6 on the figure for clarity).

A summary of mean $T_{50\%}$ release times (Table 4.2) indicates an increase in lag-time variability by the introduction of the WG processing step. This confirmed that the wet granulation method is unsuitable for processing ETs that are capable of varying the release of drug after pre-determined time delays.

% HPMC	$T_{50\%}$ release time [min] (s.d.)		p-value
	DC	WG	
15	67.6 (15.1)	316.7 (44.4)	<0.05
24	212.9 (24.6)	344.1 (31.2)	<0.05
30	322.7 (30.3)	345.3 (36.5)	0.214

Table 4.2. Summary of TDC lag-times for DC and WG formulations. (n = 12).

A significant difference between the DC and the WG lag-times is seen for the 15 and 24% HPMC erodible tablet formulations ($p < 0.05$), but is not apparent for the 30% HPMC Time-Delayed Capsules. Introduction of the WG processing step had a profound effect by increasing the lag-time of the TDC in this present study, when compared to the DC erodible tablet formulations. Clearly further investigation was required in order to determine the effects of WG on the erodible tablet and subsequent lag-time of the TDC.

$T_{50\%}$ release times show that the most significant prolongation of lag-time occurs with the lowest concentration of HPMC (15%), with an increase of 249.1 minutes (Figure 4.3). The 24% and 30% formulations increased by 131.2 and 22.6 minutes respectively.

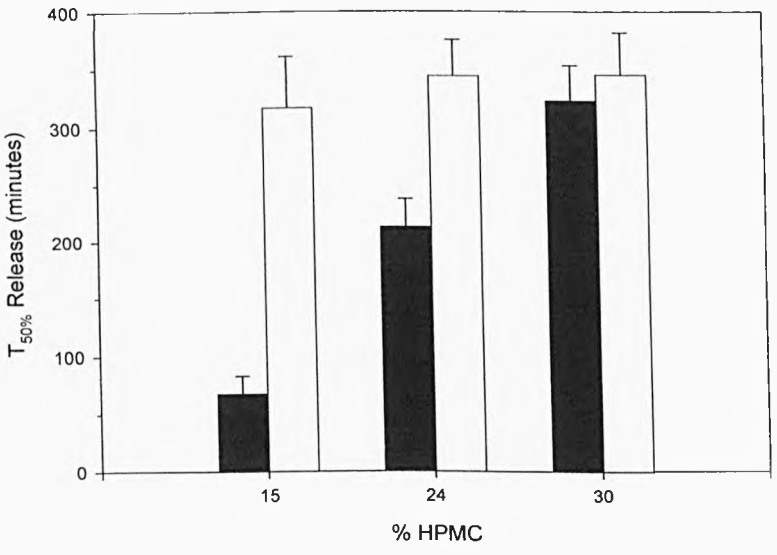


Figure 4.3. Comparison of DC and WG ET formulations.
■ DC; □ WG; (n =12; ± s.d.).

The data indicates that the WG processing step affected that lag-time of the assembled TDCs inversely to the quantity of HPMC available. The DC and WG erodible tablets were compared to see if any physical properties varied between them. HPMC and lactose excipients used in their manufacture were analysed as

previously described and the extent of water mobility and its possible effects on HPMC were assessed.

4.3.2. THE EFFECT OF VARYING WATER FOR GRANULATION ON TIME-DELAYED CAPSULE (TDC) LAG-TIME

Figure 4.4 shows the effect of varying the amount of water used in the granulation on the lag-time of TDCs fitted with 15% HPMC erodible tablets.

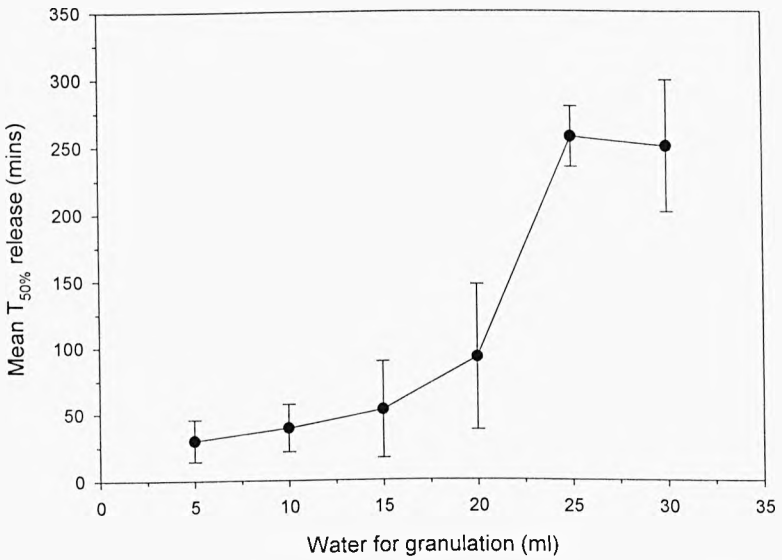


Figure 4.4. Variation of TDC lag-time, by varying the quantity of water for granulation during the manufacture of 15% HPMC erodible tablets.

The amount of water granulation added during processing has a marked effect on the erosion of ETs prepared by this method. Increasing amounts of water increased the lag-time of the TDC. Above 20 ml of water added there is a sharp increase, which appears to reach a maximum with the further addition of water. This may be due to reaching the end-point of the granulation. Further addition of water (not shown) resulted in the consolidation of the granulate forming a single mass.

This could not be processed to prepare an ET and suggests 'over-wetting' of the granulation.

4.3.3. COMPARISON OF ET FORMULATIONS

The physical parameters of 15, 24 and 30% HPMC erodible tablet formulations (Table 4.3) indicate no significant difference, whether prepared by DC or WG ($p < 0.05$) for all parameters. A constant tablet crushing strength has previously been shown to indicate that tablets have similar porosities (Carstensen, 1985) and this is true with the ET formulations, as the relative porosity values and the crushing strength show no significant difference. This has a direct impact on the wetting potential of the excipients contained within the ETs and suggests that it is not this property that is responsible for producing the shift in lag-times.

Parameter	% HPMC					
	15		24		30	
	DC	WG	DC	WG	DC	WG
Weight [mg]	80.7	79.1	80.5	80.6	80.6	81.5
(s.d.)	(0.52)	(0.61)	(0.31)	(1.11)	(0.81)	(0.66)
Thickness [mm]	1.77	1.76	1.77	1.77	1.79	1.76
(s.d.)	(0.02)	(0.03)	(0.02)	(0.01)	(0.02)	(0.03)
Crushing strength [N]	38	39	41	40	41	42
(s.d.)	(1.08)	(1.37)	(1.17)	(1.16)	(0.88)	(0.95)
Diameter	6.74	6.74	6.74	6.74	6.74	6.74
[mm] (s.d.)	(0.00)	(0.00)	(0.01)	(0.00)	(0.01)	(0.01)
Rel. Porosity [ε]	0.625	0.628	0.625	0.625	0.620	0.628
(s.d.)	(0.005)	(0.005)	(0.004)	(0.003)	(0.004)	(0.007)

Table 4.3. Physical properties of DC and WG erodible tablets.

4.3.4. THE EFFECT OF WET GRANULATION ON FAST-FLO LACTOSE

4.3.4.1. DRIFTS Analysis of lactose and granulated lactose (L_{gran}) samples

DRIFTS is a useful technique for the characterisation of molecular solids including amorphous, crystalline and solvated forms. The spectra obtained for the non-granulated lactose (Fast Flo) and the granulated lactose (L_{gran}) samples (Figure 4.5), reveals little difference in the vibrational transitions shown. Absorption, due to bound crystalline water is observed at 3524cm^{-1} (Brittain et al.,1991) and is seen in both the lactose and L_{gran} samples, which is consistent with the XRPD data presented below. These results indicate that there is no change in the physical form of lactose as a result of the granulation process. Representative spectra obtained for a pure amorphous sample of lactose indicated smooth and broad peaks (data not shown), this bore no resemblance to the lactose samples used for the manufacture of the ETs.

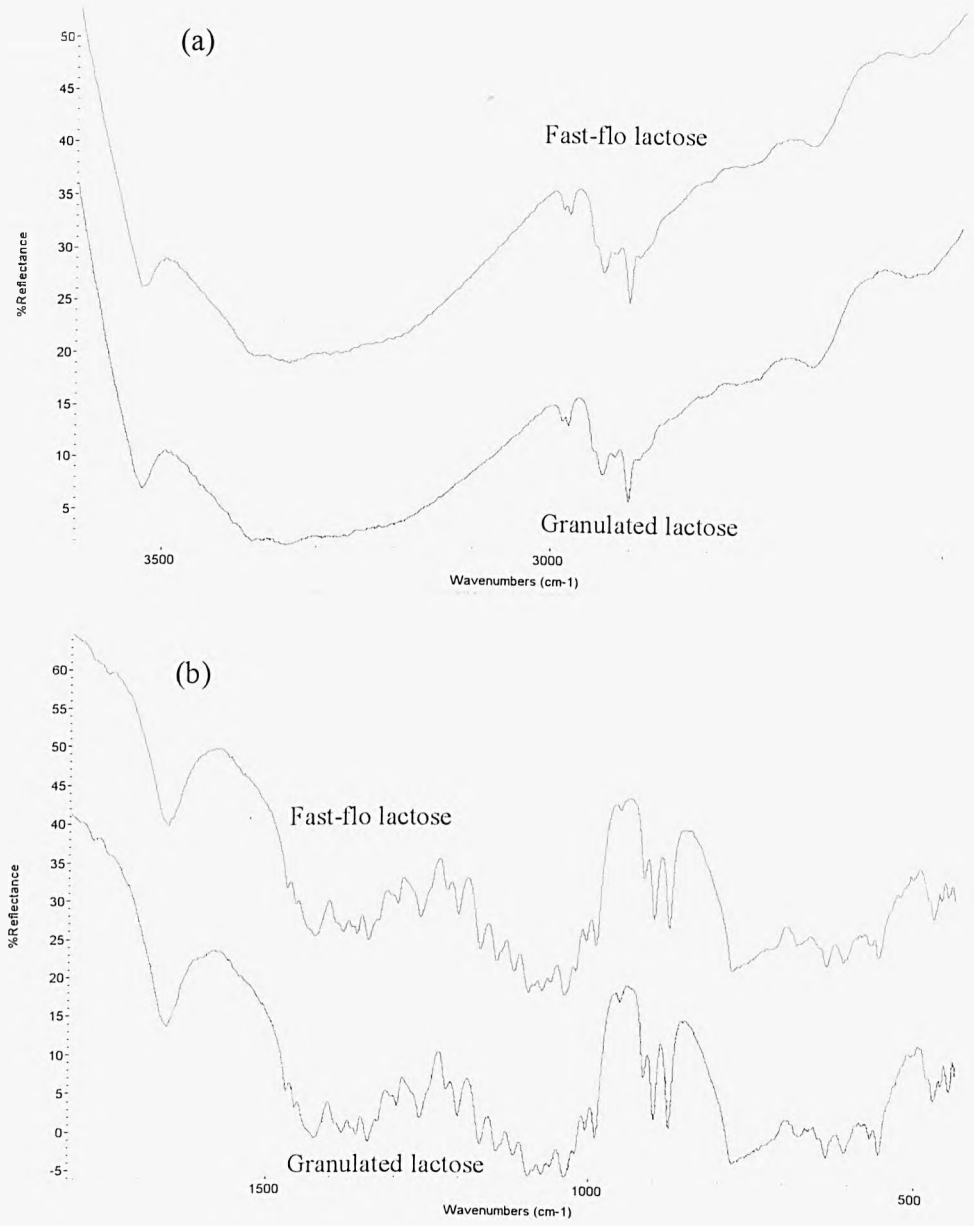


Figure 4.5. A comparison of DRIFTS spectra for Fast-flo and granulated lactose: (a) 3600 – 2400 cm^{-1}, (b) 400 – 1800 cm^{-1}.

4.3.4.2. XRPD Analysis of lactose and L_{gran} samples

The lattice parameters (Table 4.4) for both lactose and L_{gran} patterns are in good agreement with the published values from the crystal structure of α-lactose monohydrate (Noordik et al., 1984). The overlay of XRPD patterns also is consistent with a largely crystalline sample in both cases (Figure 4.6a-b) with no evidence of significant amorphous content. There is therefore no evidence from the XRPD data to indicate that granulation induces a physical transformation in the crystalline lactose present in the sample. A slightly lower signal intensity is observed with the granulated sample (Figure 4.6b) and may be due to a larger crystal size being introduced for analysis.

Crystal lattice parameter	Literature values of α-lactose monohydrate	Refined values	L_{gran} values
a [Å]	7.937	7.767	7.765
b [Å]	21.568	21.568	21.565
c [Å]	4.815	4.815	4.814
β [°]	109.77	105.92	105.97

Table 4.4. Comparison of crystal lattice values for α-lactose monohydrate and granulated lactose (L_{gran}).

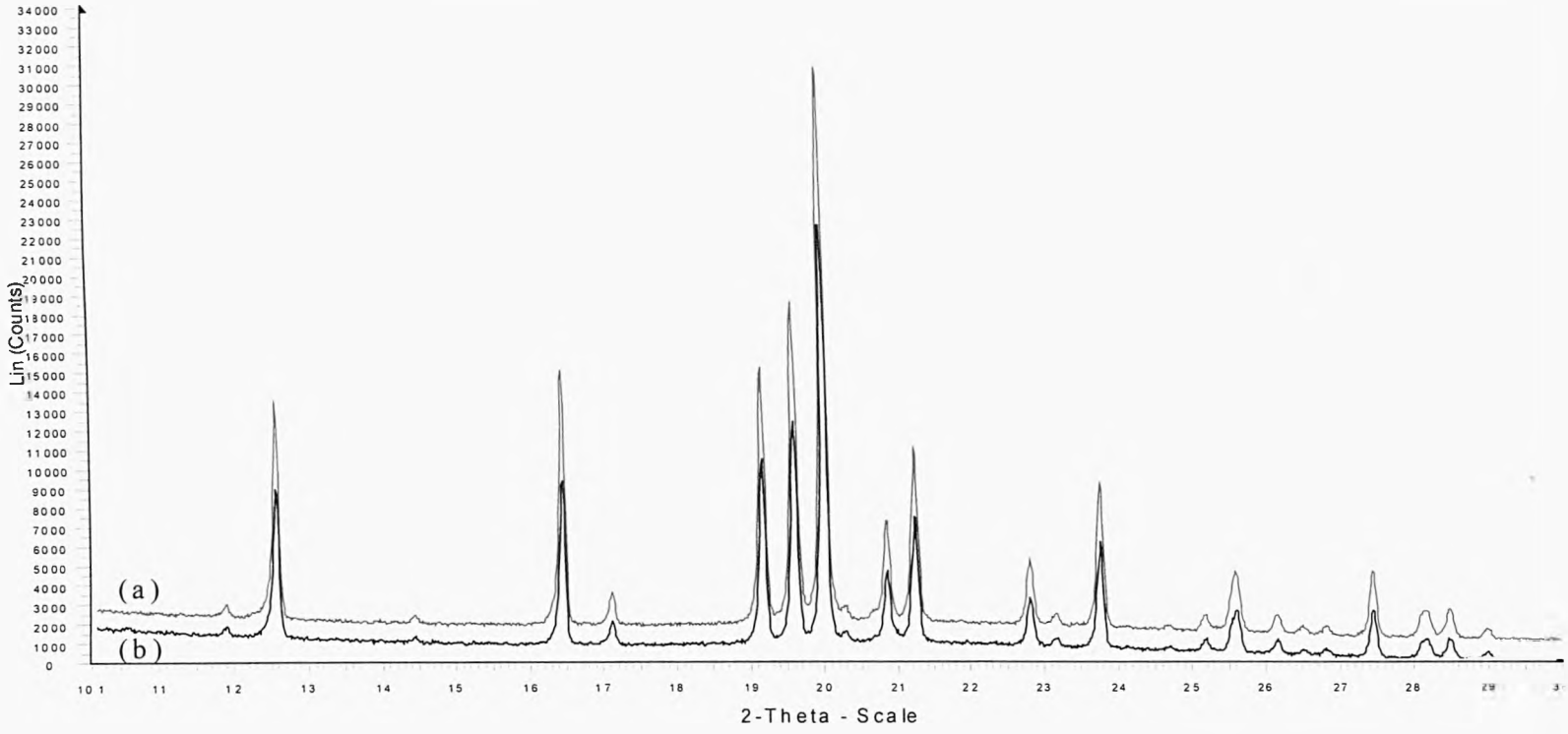


Figure 4.6. X-ray powder diffraction patterns of (a) Fast-Flo lactose, (b) Granulated lactose (L_{gran}).

4.3.5. DYNAMIC VAPOUR SORPTION

The sorption isotherms for HPMC (Figure 4.7) indicate that maximum adsorption ($Sorp_{max}$) is significantly greater (>40%) than for lactose (<3%) (Figure 4.8). This is due to an increased number of binding sites for water on the hydrophilic polymer chain of the HPMC.

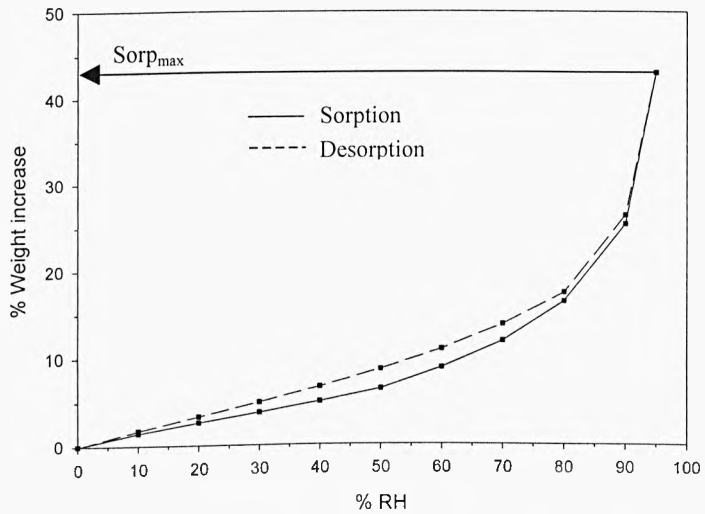


Figure 4.7. DVS Isotherms for HPMC at 25°C.

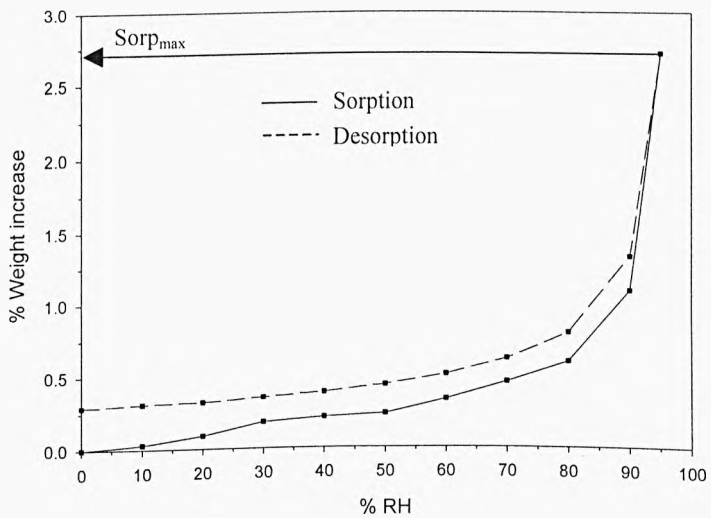


Figure 4.8. DVS Isotherms for lactose at 25°C.

At 50% RH the T_g of lactose is reduced to 25°C (Buckton and Darcy, 1996), the same as the operating temperature of the DVS chamber, used in this study. Therefore it is possible for any amorphous lactose to revert to the monohydrate form under these conditions. The theoretical post desorption (PD) weight increase of a purely amorphous sample of lactose is 5.26% (Buckton and Darcy, 1997). Using this information the degree of amorphous content can be determined by simple calculation from the DVS data:

$$amorphous\ content(\%) = \frac{PD\ weight\ increase}{5.26} \times 100 \qquad \text{[Eqn. 4.1]}$$

The degree of crystallization occurring in the sample of lactose can be calculated using [Eqn. 4.1], indicating there is a 5.46% amorphous content in the Fast-Flo lactose sample used to prepare of DC erodible tablet formulations (Table 4.5). This is consistent with the spray drying process, used in the manufacture of this type of lactose (Kibbe, 2000). Calculations to determine the amorphous content of the lactose in the DC powder blends and WG granules are also summarised in the table.

Sample	$Sorp_{max}$ (%)	PD weight increase (%)	Calculated amorphous lactose content (%)
Lactose	2.72	0.29	5.46
L_{gran}	1.57	0.07	1.33
HPMC	42.98	0.00	-
15% DC	8.09	0.20	3.84
WG	10.31	0.07	1.33
24% DC	12.62	0.26	4.94
WG	15.91	0.11	2.09
30% DC	16.00	0.07	1.33
WG	16.18	0.06	1.14

Table 4.5. Amorphous lactose content of: lactose samples, HPMC, DC powder blends and WG granulations.

As there is a degree of discrepancy between the amounts of amorphous content in the ET formulations it is perhaps due to the fact that the overall PD weight increases are very low (between 0.06 and 0.29%). This indicates amorphous lactose contents equivalent to between 1.33 and 5.46%. The largest difference in calculated amorphous lactose between DC powder blends and WG granules is with 24% HPMC. As this does not show the most significant increase in lag-time it is likely that any change in amorphous content is not the main cause of the difference in lag-time. The highest PD weight increase is greatest with WG granules from each formulation. This suggests there is a larger surface area of HPMC exposed and could indicate a coating of HPMC to be present over the samples lower than 30% HPMC (this formulation indicated similar PD weight gains for both DC powder blends and WG granules).

The sensitivity of this method must be called into question as the PD weight increase presented by the HPMC component is very large compared to that of lactose, and so it is unlikely that this technique can distinguish an amorphous transform as any detectable transition may be obscured. Alternative methods (not employed here) have been developed: a combination of near-infrared spectroscopy with DVS (Buckton et al., 1998; Hogan and Buckton, 2000a; 2001; Lane and Buckton, 2000) shows a degree of accuracy of 1%, or solution calorimetry (Hogan and Buckton, 2000b) is accurate to 0.5%; modulated temperature differential scanning calorimetry (MTDSC) (Guinot and Leveiller, 1999; Saklatvala et al. 1999) can also be used detect amorphous levels in a pharmaceutical solid.

4.3.6. THE EFFECT OF WET GRANULATION ON THE HPMC

4.3.6.1. Microwave Dielectric Analysis (MDA)

Microwave dielectric relaxation times of the water dipole are shown to be lowest for the 15% granulation formulation (Table 4.6), indicating that water is more freely able to move in a less viscous and constrained environment. It follows that the HPMC content of the wet granulated formulation is therefore able to disperse,

disentangle and swell more readily in this wetted state (as it is assumed that greater water mobility corresponds to a greater potential for HPMC movement). A more mobile system, allows for greater disentanglement and gel formation of HPMC chains. This may lead to improved coating and spreading of the HPMC resulting in a more intimate mixture of lactose and HPMC. When the granulations are dried for production of the relevant ET the degree of disorder will be fixed in the dried granules before tableting in this state.

% HPMC	Dipole relaxation time [$x10^{-8}$ ms]	s.d.
15	2.869	0.245
24	5.449	0.502
30	7.662	3.314

Table 4.6. Water dipole relaxation times for HPMC granulations obtained from microwave dielectric analysis (n =6).

As the dielectric relaxation times are proportional to the degree of HPMC motion in the formulation (as a function of water mobility), it would be expected that the fastest relaxation times would lead to an increased change in lag-time for the capsule device. This does occur, with the lag-time of the 15% HPMC wet granulated ET formulation showing the greatest variance from the equivalent DC formulation.

4.3.6.2. Solid State Nuclear Magnetic Resonance (SSNMR)

The greatest T_2 dephasing time is seen with the lowest concentration of HPMC (Table 4.7). This is consistent with increased mobility in the system. As the dephasing time is inversely related to line narrowing in the spectra obtained for the sample it therefore follows that the 15% HPMC granules must have increased mobility. A paired t-test for the data obtained for the 24% and 30% HPMC granules shows that there is no significant difference between the mean T_2 dephasing times ($p < 0.05$). This is consistent with the microwave data and the dissolution studies.

% HPMC	Dephasing time T_2 [ms]	s.d.
15	28.1	2.7
24	18.0	2.1
30	16.1	1.9

Table 4.7. SSNMR T_2 dephasing times for 15, 24 and 30% HPMC granulations (n =6)

4.3.6.3. Rheological analysis

Viscosity of HPMC (K100LV) is between 80 to 120 mPa.s at 20°C for a 2% (w/v) solution in water (Dow Chemicals, 1996b). The mean viscosity determined from 2% HPMC solutions reconstituted from the dry blends and granules are within this range (Table 4.8). Although there is some lactose present in the system, its expected contribution to the viscosity is low, and the data suggest that the high shear processing WG technique does not induce a change in the HPMC properties.

% HPMC	Viscosity mpa.s	
	DC	WG
15	106.5	105.9
24	105.9	92.5
30	100.4	98.1

Table 4.8. Mean viscosity values for 2% solutions of HPMC reconstituted from powder blends (DC) and granules (WG).

4.3.7. COMPARISON OF DIRECT COMPRESSION BLENDS AND WET GRANULATION GRANULES

4.3.7.1. Scanning Electron Microscopy (SEM)

Scanning electron micrographs (Figure 4.9) display the expected distribution of highly visible HPMC fibres interspersed with Fast Flo lactose particles, in the DC formulation. In the dry DC form the ET comprises of separate particles of lactose and HPMC. Lactose may then dissolve at the tablet surface on contact with water to leave pores, which are subsequently occupied by an advancing HPMC matrix (Korsmeyer et al., 1983). A representation of how this process may progress in ET formulations is indicated (Figure 4.10). This 'thinning' of the HPMC at the surface leads to a degree of polymer chain dissentanglement, in turn leading to relatively quick erosion of the ET followed by entry of water into the capsule, expansion of the L-HPC and expulsion of the contents.

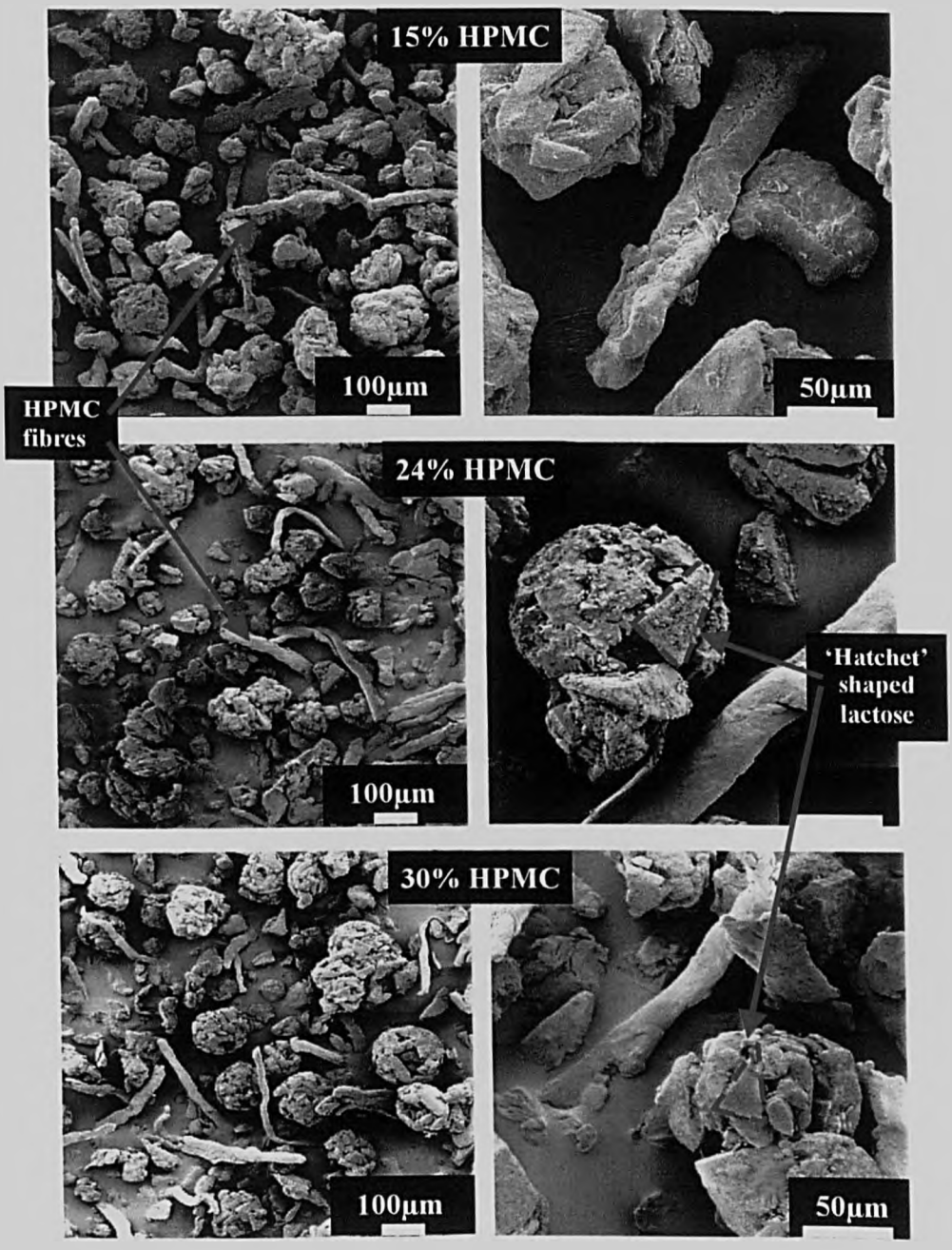


Figure 4.9. SEM images of DC powder blends prior to tableting.

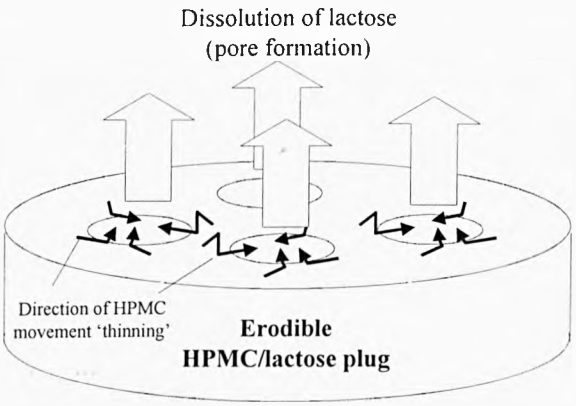


Figure 4.10. Schematic representation of pore formation and HPMC dissentanglement in an ET formulation.

During the WG process an intimate mixture of lactose and partially gelled HPMC is formed. Changes are seen to occur due to WG processing leading to the formation of aggregated granule components. On drying there are less well-defined individual particles of lactose or HPMC (Figure 4.11). SEM of 15% HPMC formulations show the presence of large uniform granules. There appear to be clearly distinctive lactose particles embedded within the granules, which have the characteristic hatchet shape of α-lactose monohydrate crystals (Raghavan et al., 2000). HPMC must also be incorporated within or onto the surface of the granules, as it is not distinguishable in isolation. In contrast the 24 and 30% HPMC wet granulated ET formulations highlight that there is still a distinction between HPMC fibres and lactose particles to be found post-processing, particularly with the increased HPMC concentration.

Tableting then leads to the formation of an improved homogenous mixture at the face of the ET. As a result fewer and/or smaller pores will form at the surface of the ET, leading to a residual degree of 'thinning' of the HPMC, less polymer dissentanglement and a slower erosion of the corresponding tablets. In addition lactose re-crystallization apparent with the 15% HPMC wet granulated granules, suggests that at least some of the lactose has been dissolved. Diffusion of lactose into the partially disentangled HPMC may lead to further retardation from the ET.

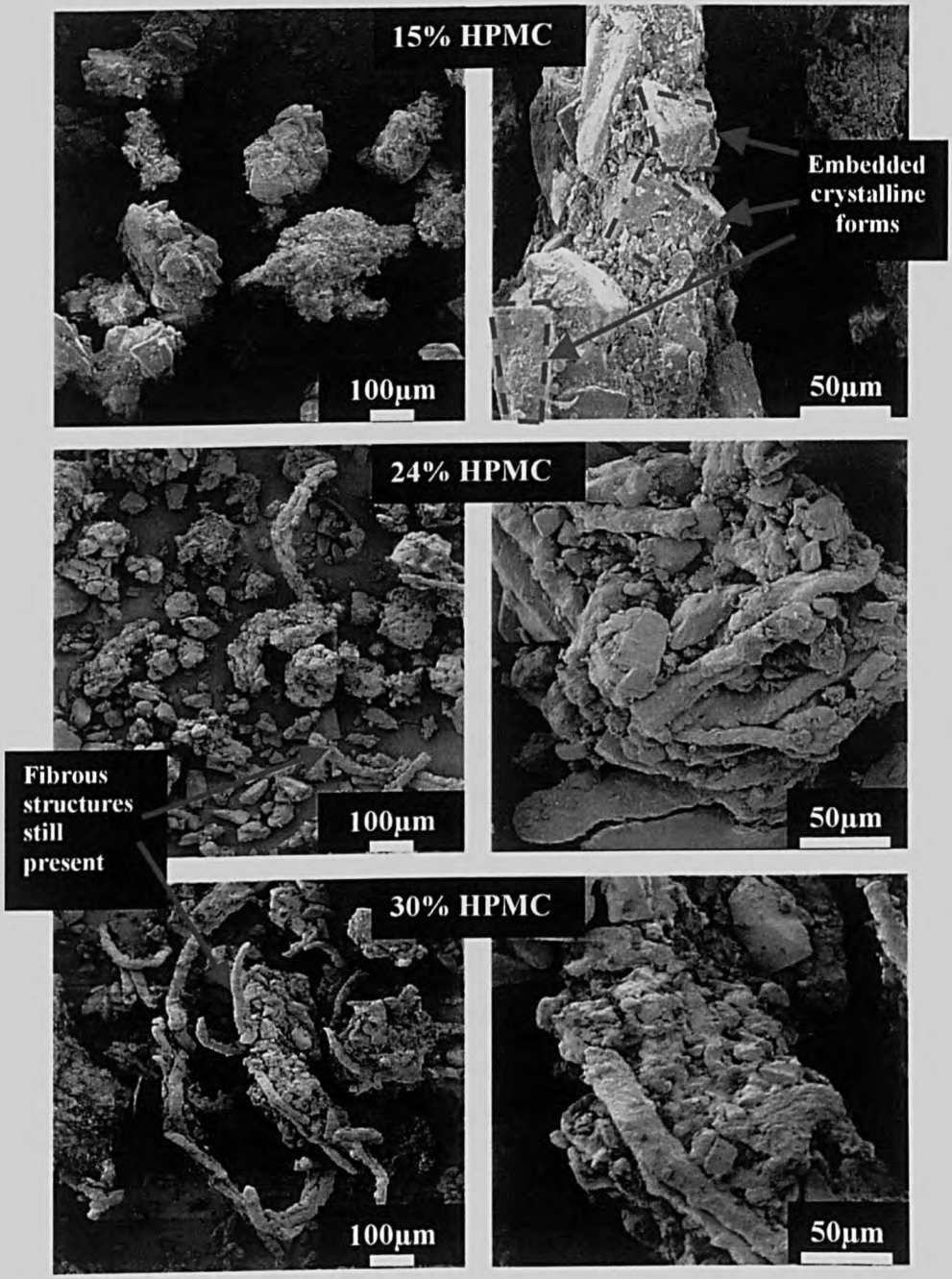


Figure 4.11. SEM images of WG granules prior to tableting.

4.4. CONCLUSIONS

- ETs formulated using a low concentration of HPMC (15%) show a greater prolongation of release time following wet granulation than those formulations containing higher HPMC concentrations (24 and 30%) as indicated by $T_{50\%}$ drug release times.

- HPMC is unaltered by shear forces involved in the high shear granulation process used and may be eliminated as a contributing factor to the increase in lag-times.

- There is no evidence of physical change in the crystalline state of lactose as demonstrated by XRPD or DRIFTS analyses. Indicating that any contribution from a change in the lactose would be very low, <10%. With the more sensitive DVS technique there is evidence for a small amorphous to crystalline transition in the lactose during wet granulation but no suggestion that this has any significant effect on the lag-time as its effects are evenly spread throughout all the WG samples.

- Water mobility during wet granulation at low concentrations of HPMC (as indicated by the MDA and SSNMR) allows greater chain mobility/swelling and spreading. This results in slower tablet erosion, and hence an increased lag-time of drug release from the assembled TDCs. This is indicated to be highest with the corresponding 15% HPMC erodible tablet formulation.

CHAPTER 5. EROSION CHARACTERISTICS AND KINETICS OF ERODIBLE TABLET (ET) FORMULATIONS

5.1. INTRODUCTION

HPMC concentration is used to control lag-time of the Time-Delayed Capsule (TDC), prior to the release of drug. To fully understand the processes involved a technique was required to assess the kinetics of erosion. Most investigations to study HPMC erosion rates have focused on the release rates of drugs (Dürig et al., 1999) rather than the rate of polymer chain dissolution itself, as it is difficult to quantify HPMC concentrations directly. Size exclusion liquid chromatography may be used (Skoug et al., 1993), but is performed retrospectively and is time consuming. An extremely useful approach has been to measure swelling and erosion fronts (Colombo et al., 1995) but this often requires the use of a highly visible water soluble drugs (Colombo et al., 1999) or fluorescein (Pham and Lee, 1994) making it unsuitable for the analysis of the drug-free erodible tablet (ET) formulations presented in this study.

In the previous collaborative study between the research groups at the University of Strathclyde and the University of Nottingham (Sutch et. al., 2002) an MRI technique was developed to monitor the change in ET thickness over time and effect of water on the insoluble capsule body. This has provided an invaluable insight into the effect of different coating types on the capsule body, and also indicated that there was zero order erosion kinetics of the ET occurring over the course of the analysis. However, a significant constraint of this method is that it only allows clear images to be obtained when the investigations were conducted under static conditions with no hydrodynamic stress. This results in considerably increased apparent erosion times for a given ET formulation. As a consequence real-time comparison between this MRI method and dissolution data of the TDC is not possible. Hydrodynamic stress and intensity of fluid flow causes greater attrition at the swelling periphery and is responsible for an increase in release rate of drugs from matrix systems (Kim and Fassihi, 1997b). In this study gravimetric analysis using a standard USP II dissolution apparatus was performed, allowing a direct comparison with dissolution data to be studied in-situ.

The ET formulations consist only of HPMC and lactose (with 1% MgSt) so therefore only two types of processes can occur when it is exposed to water: Lactose can dissolve and from the tablet, or the HPMC can relax, swell (disentangle) and dissolve. Calculation of the release exponent, *n* is generally used to determine the kinetics associated with drug release from pharmaceutical solids (Sadeghi et al., 2000) but cannot be used for analysis of the ET due to the dynamic erosion of two components, HPMC and lactose. As a result it is only the order of erosion that may be determined for the ETs using the method presented in this current study.

5.2. MATERIALS AND METHODS

Methods are summarised below (Table 5.1) and referenced to Chapter 2.

Description	Methods section
Preparation	
Direct compression ETs	2.5.1.
Wet granulation ETs	2.5.2.
Analysis	
Erosion studies	2.7.10.

Table 5.1. Summary of methods used in Chapter 5.

5.3. RESULTS

5.3.1. EROSION STUDIES OF HPMC ERODIBLE TABLETS

The erosion rates of the direct compression (DC) erodible tablets (Figure 5.1) indicate a consistent control over the 60 minute period with a highly reproducible weight loss over time.

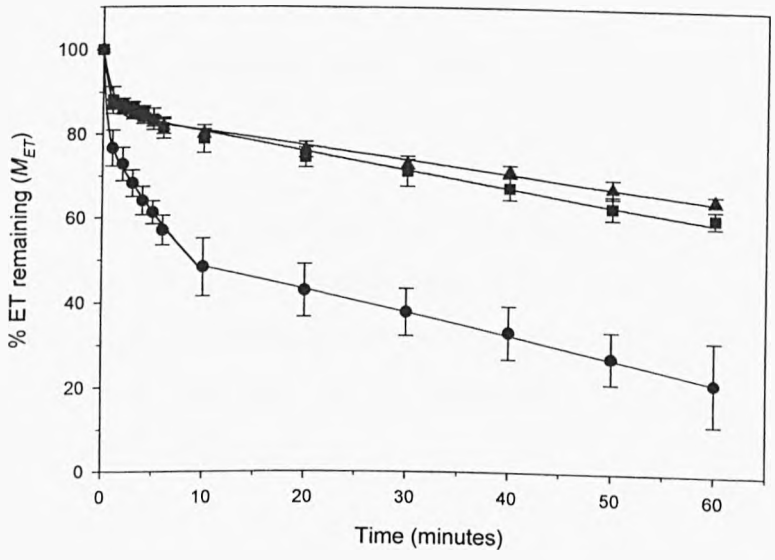


Figure 5.1. Erosion profiles of direct compression ETs.
● 15% HPMC; ■ 24% HPMC; ▲ 30% HPMC. (n = 6).

An exponential decay can be used to describe the weight loss and provide a non-linear regression fit [Eqn. 5.1].

$$M_{ET} = M_0 + a\exp^{-bt} \qquad \text{[Eqn. 5.1]}$$

Where, M_{ET} is the mass of ET remaining, M_0 is the initial mass, t is erosion time, and a, b are decay constants.

An initial weight loss occurs in each of the three formulations, confirming the findings of the photographic study (Chapter 3, Figure 3.8). This is then followed by

a linear period of weight loss. The 15% HPMC erodible tablet formulation shows the most rapid and prolonged initial weight loss period, and is due to a rapid dissolution of the lactose prior to the formation of a stable gel layer. This is analogous to the burst effect associated with high drug loading of sustained release tablets (Dürig et al., 1999; Xu and Sundana, 1995). Rapid swelling of the matrix occurs with low concentrations of the hydrophilic polymer (Wan et al., 1995), further promoting the dissolution of lactose. Approximately 45% of the total ET weight is lost before the onset of the linear period of weight loss with the 15% HPMC formulation, compared to just an initial 10% weight loss with the 24 and 30% HPMC erodible tablets. This effectively provides a 'head start' before the onset of the linear portion of the erosion.

An expression of first order kinetics is given [Eqn 5.2] (Costa and Lobo, 2001), where, A is the mass of product produced in time t, A_0 is the initial amount of product and K_1 is the first order rate constant. The expressions for mass, used in [Eqn 5.1], may be substituted into [Eqn 5.2] to give [Eqn 5.3], giving an expression for the non-linear portion of the plot.

$$A = A_0 \exp^{-K_1 t} \qquad \text{[Eqn 5.2]}$$

$$M_{ET} = M_0 \exp^{-K_1 t} \qquad \text{[Eqn 5.3]}$$

And taking the natural log,

$$\ln M_{ET} = \ln M_0 - K_1 t \qquad \text{[Eqn 5.4]}$$

Using equation [Eqn 5.4] the natural log of M_{ET} plotted against time (Figure 5.2) indicates an approximate linear relationship (R^2 =0.983); indicating a first order relationship.

In a porous polymer system produced by compression, initially pores near the surface of the matrix are filled by water and progressive swelling of the polymer

occurs leading to structural rearrangement and changes in porous structure (Korsmeyer et al., 1983). This ultimately alters the porosity and tortuosity of a given structure during swelling, and the first order diffusional loss of lactose in the early stages of release decreases when the stable gel layer is formed, leading to the observed change in erosion rate.

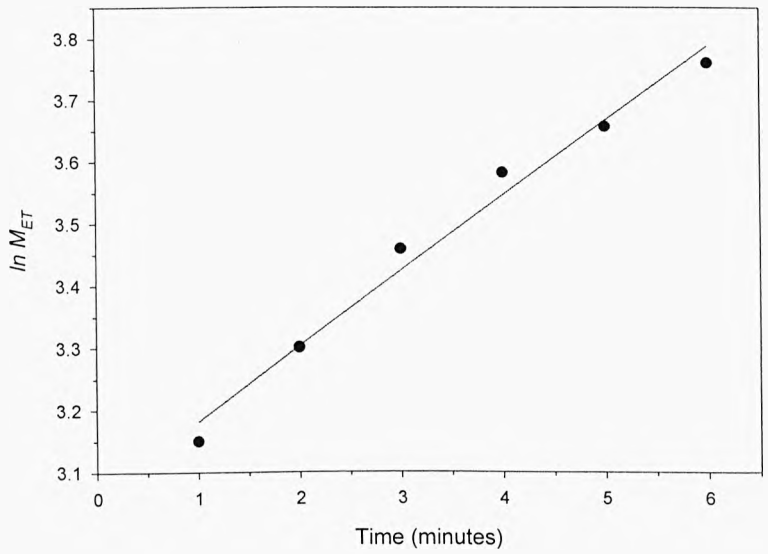


Figure 5.2. Initial weight loss of 15% HPMC DC ET formulation (n = 6).

Previous studies have shown that high levels of lactose in HPMC matrices have reduced tortuosity (Ford et al. 1985). Therefore a reduction of the lactose content and subsequent increase in HPMC gel strength will increase tortuosity. The subsequent linear zero order weight loss can be attributed to the steady erosion kinetics of the gel layer once it has been formed. At the higher concentrations of the polymer (24 and 30%) a lower initial weight loss is observed as the quantity of HPMC present enables a more rapid gel layer to be formed, and is subsequently followed by linear erosion of the ET.

The linear portion of the erosion is zero order as the reduction in mass of the ET is linear with time [Eqn 5.5], where K_0 is the zero order rate constant.

$$M_{ET} = M_0 - K_0 t \qquad \text{[Eqn 5.5]}$$

Comparing the wet granulated with the direct compression formulated ETs it can be seen that the initial first order rate of erosion is much reduced (Figure 5.3) before the onset of zero order erosion kinetics. An initial weight loss of approx. 17% is observed with all three ETs. It is worth noting that the 30% HPMC formulation indicates a more pronounced weight loss than the other two formulations (15 and 24%). However an ANOVA test reveals no significant difference ($p > 0.05$) when comparing all three concentrations of HPMC respectively.

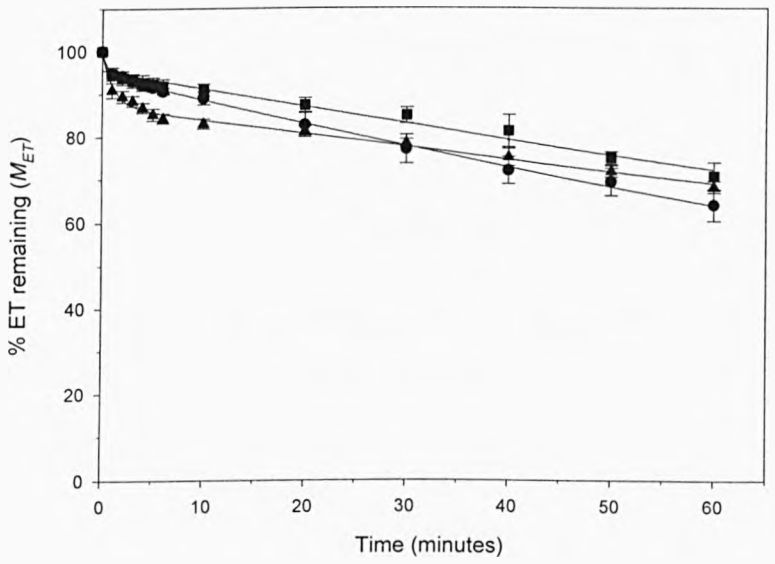


Figure 5.3. Erosion profiles of WG ETs.

● 15% HPMC; ■ 24% HPMC; ▲ 30% HPMC. (n =6).

Comparison of the 15% HPMC formulations (Figure 5.4) suggests that the gel layer inhibiting erosion is formed more rapidly following WG. The high lactose content in the 15% HPMC direct compression ET formulations may behave in a similar way to that of high drug sustained release tablets where incidences of dose dumping occur. Spheronisation has been shown to eliminate the dose dumping effect (Mehta et al., 2000) and it appears that the introduction of the WG step achieves a similar level of control of the ET thus preventing rapid lactose dissolution. The 15%

HPMC direct compression ET formulation allows the contents of the TDC to be released after a mean time of approximately one hour. After this period approximately 20% (w/w) of the DC erodible tablet remains. This is also observed with the photographic evidence (Chapter 3, Figure 3.8).

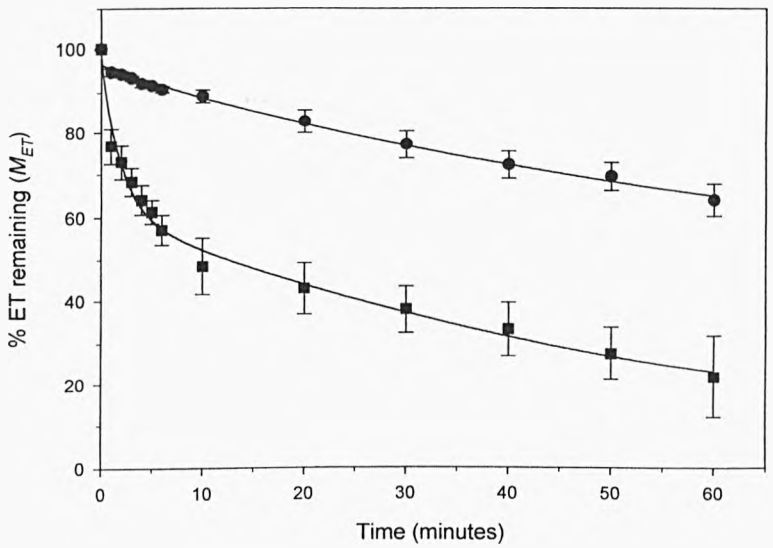


Figure 5.4. Comparison of erosion profiles of ETs.
■ DC; ● WG (n =6).

Using [Eqn. 5.1] the mass for each individually formulated ET can be extrapolated using the mean release times obtained for the respective capsule devices (Table 5.2).

% HPMC	Mean $T_{50\%}$ release (minutes)		Extrapolated ET remaining (% w/w)	
	DC	WG	DC	WG
15	67.6	312.5	20.2	12.0
24	212.9	359.6	19.6	17.5
30	322.7	360.6	23.6	20.8

Table 5.2. Extrapolated data for ET formulations.

The calculated masses of the ETs remaining after $T_{50\%}$ release suggests the DC formulations are eroded by a sufficient amount to allow water to penetrate the capsule device and subsequent expulsion of the drug tablet, when only approximately 20% of the original mass remains. The wet granulated ETs show greater variation in the mass remaining. Only 12% (w/w) of the 15% HPMC erodible tablet prepared by WG remains after expulsion, much lower than the equivalent DC formulation. This is due to increased gel strength, a more tortuous hydrophilic gel, a thicker gel layer or a combination of these factors. The 24% HPMC wet granulated ET formulation follows a similar trend. The 30% WG blend indicates a calculated value of approximately 21% which is within the same criteria as the DC formulations. Indeed, as previously discussed (Chapter4, Section 4.3.1), both 30% formulations show no significant difference in their mean lag- times, suggesting that there is very little difference between them.

5.4. CONCLUSIONS

- The period of weight loss, dependant on the natural log of the exponent, suggests that the 15% HPMC direct compression ET formulation is slowest to form a gel layer. This period can be described by first order kinetics.

- Granulation of the 15% HPMC erodible tablet formulation prior to tableting enables a more rapid onset of zero order erosion kinetics. This suggests chain relaxation and gel layer formation is quicker.

- Extrapolated data indicates that final WG erodible tablet weights are lower (except in the case of the 30% formulations), indicating that gel strength is increased and hence erosion rate is decreased by the wet granulation technique.

- The rapid onset of zero order erosion kinetics supports the data obtained by MDA (Chapter 4), suggesting spreading of HPMC occurs during wet granulation.

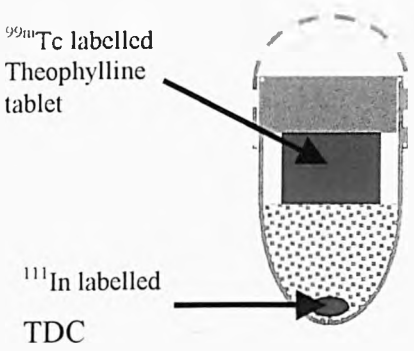
CHAPTER 6. *IN VIVO* HUMAN SCINTIGRAPHIC AND PHARMACOKINETIC STUDY

6.1. INTRODUCTION

This chapter presents the results of a human clinical study designed to investigate the *in vivo* performance of the Time-Delayed Capsule (TDC) formulations, described in Chapter 3. The study was a randomised three-way cross over design in eight healthy male volunteers and the three TDC formulations investigated were designed to release drug after 1, 3 and 5 hours.

The aim of the study, sponsored by Pfizer, was to elucidate whether the TDC could deliver a model drug (theophylline) to the site of the colon, by solely relying on a lag-time method. The erodible tablet (ET) formulations were selected to provide a range of delivery times determined by the *in vitro* analysis (1, 3 and 5 hours) of the assembled TDC. The 1 hour formulation was unlikely to reach the distal regions of the GI tract. However, given the timing of the migrating myo-electric complex (MMC) and its influence on gastric emptying times, it was anticipated that the 3 or 5 hour formulations might accomplish this. The MMC shows an approximate 2 hour variation in potential gastric emptying times as indicated in Chapter 1 (Figure 1.7). In order to minimise this variability it was proposed that the MMC could be synchronised between subjects by providing a small amount of nutrition. With the stomach containing little digestible material, the body might then be fooled into believing that it is mid-way through the MMC and the timing of the housekeeper wave may then be synchronised in all subjects.

Dual isotopes were used as described in Chapter 1, Section 1.6. In this way the TDC transit could be monitored through each section of the GI tract by reference to radiolabelled markers applied to the abdomen, and lag-time determined scintigraphically by separation of the two isotopes contained within the TDC (Figure 6.1). Blood sampling, to provide pharmacokinetic analysis, complemented the scintigraphic data.



The dual radio labelled TDC. Differentiation of the ^{99m}Tc and ^{111}In γ-sources is possible due to the higher photopeak energy of ^{111}In. Dispersion of the ^{99m}Tc source indicates the site of drug release.

Figure 6.1. The dual radio labelled TDC for use in the human studies.

6.2. METHODS

- BioImages Research Ltd conducted the study in a clinical research unit based at Glasgow Royal Infirmary. The protocol summary of the study is attached in Appendix III.

- The manufacturing process was supervised by this author and undertaken by a qualified Pharmacist from BioImages.

- All manufacture was carried out to GMP standard using pharmacopoeial grade materials.

- Analysis of the data for Subject 001 was performed by this author, while staff at BioImages performed scintigraphic and pharmacokinetic analysis for Subjects 002-008.

The manufacturing methods employed in this study are summarised below (Table 6.1) and referenced to Chapter 2.

Description	Methods section
Components	
Capsules	2.3.4.
Drug containing tablets	2.4.3.
60 mg ET Formulations	2.5.3.
TDC Assembly	2.6.
Analytical	
Scintigraphic	2.8.1.
Pharmacokinetics	2.8.2.

Table 6.1. Summary of methods used in the human study.

A study protocol summary is shown in Appendix III.1, with randomisation information (Appendix III.2). Patient information about the study (Appendix II.4), and a patient consent form (Appendix II.5) are also included.

6.3. RESULTS

6.3.1. *IN VITRO* TESTING

Dissolution profiles obtained for the 60 mg ET formulations are summarised in Chapter 3 (Table 3.12). Erodible tablet formulations of 20, 24 and 35% HPMC had been initially designed to afford TDCs with lag-times of 1, 3, and 5 hours respectively. However as previously shown (Chapter 3, Figure 3.10) this initial relationship between HPMC concentration and lag-time was flawed due to insufficient data. Formulations therefore had pulse-release times slightly different to those required. *In vitro* release times of 104, 153 and 277 minutes for 20, 24 and 35% HPMC content respectively were shown for the 1, 3 and 5 hour formulations instead.

6.3.2. SCINTIGRAPHIC ANALYSIS IN SUBJECT 001

Representative images for Subject 001 indicating gastric emptying and drug dispersion from the scintigraphic analysis are presented in Figure 6.2.

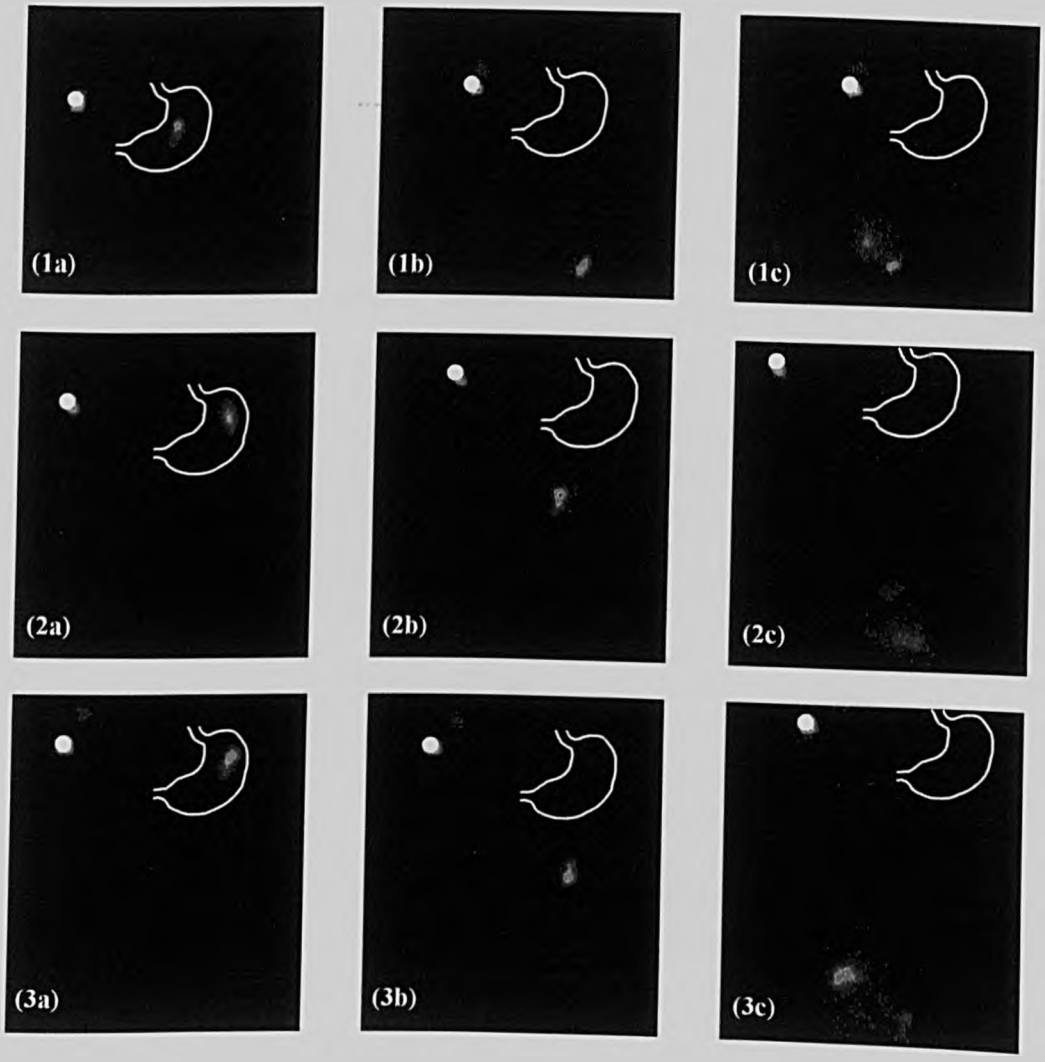


Figure 6.2. Scintiscans obtained for Subject 001 for TDC devices fitted with different ET formulations.

(1) 20% HPMC; (2) 24% HPMC; (3) 35% HPMC;

[a] Pre-gastric emptying; [b] Post-gastric emptying and [c] Release.

6.3.3. SUMMARY OF SCINTIGRAPHIC DATA FOR ALL SUBJECTS

Transit times through the GI tract and sites of dispersion of the theophylline tablet are summarised in Table 6.2. An increase in HPMC concentration is associated with a delayed ^{99m}Tc-^{111}In separation time as expected, and follows the trend observed with the *in vitro* correlation (Section 6.3.1). An overall increase in lag-time is indicated for the 20 and 24% HPMC ET formulations when compared to the *in vitro* data. *In vivo* data for the 35% HPMC formulation indicates a slightly reduced lag-time.

Subject	20% HPMC		24% HPMC		35% HPMC	
	Radiolabel separation time (mins)	Release site	Radiolabel separation time (mins)	Release site	Radiolabel separation time (mins)	Release site
001	165	SI	180	SI	255	SI
002	*210*	*SI*	*165*	*SI*	*285*	*SI*
003	*165*	*SI*	*NS*	*NS*	*195*	*SI*
004	*165*	*ICJ*	*NS*	*NS*	*225*	*SI*
005	*120*	*SI*	*180*	*ICJ*	*NS*	*NS*
006	*NS*	*NS*	*225*	*SI*	*315*	*SI*
007	*150*	*SI*	*195*	*SI*	*225*	*SI*
008	*210*	*SI*	*NS*	*NS*	*NS*	*NS*
Mean	169 (n = 7)		189 (n = 5)		250 (n = 6)	
sd	0.53		0.38		0.74	

Table 6.2. Radiolabel separation and site of release.

SI = small intestine; ICJ = ileocaecal junction; NS = No separation of isotopes.

(Data in *italics* produced by BioImages Research Ltd).

A one-way ANOVA test (using Minitab ver.13.1) revealed no significant differences between observed scintigraphic lag-times of the 20 and 24% HPMC erodible tablet formulations ($p = 0.268$). A significant difference was however observed between both these and the 35% HPMC erodible tablet formulation ($p < 0.05$).

A good correlation is observed between *in vitro* lag-times and scintigraphically observed lag-times for the 20, 24 and 35% HPMC ET formulations (Figure 6.3), R^2 =0.999. Within the HPMC range shown (20-35%) accurate *in vivo* predictions may be determined using *in vitro* data obtained for the TDC device.

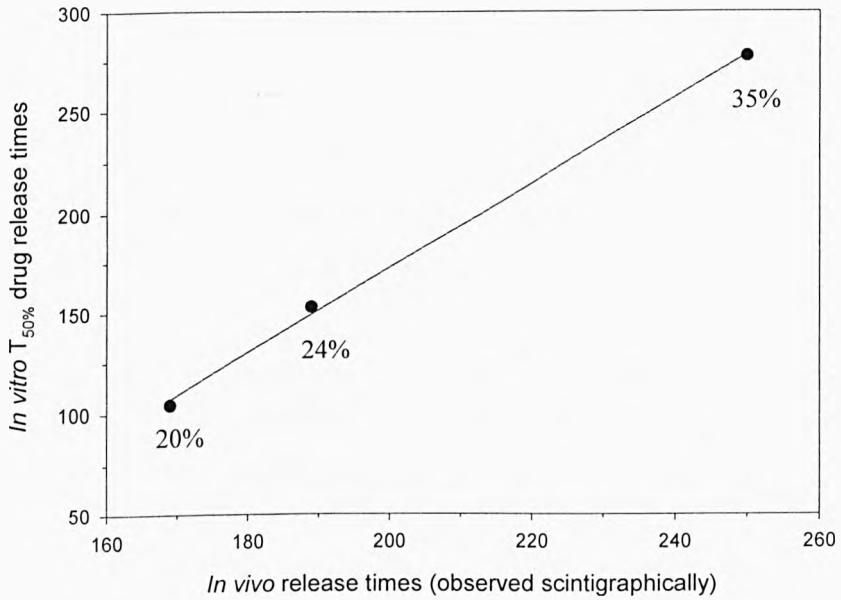


Figure 6.3. The *in vitro-in vivo* correlation between observed lag-time for 20, 24 and 35% HPMC erodible tablet formulations in GMP manufactured TDCs (R^2 =0.999).

6.3.4. GASTRIC EMPTYING TIMES AND GI TRANSIT

Gastric emptying times (Appendix II.6) summarised in Table 6.3, are variable and dependent on the stage of the MMC (Seeley 1995) encountered upon dose administration. However, a one-way ANOVA test showed no significant difference between the gastric emptying times of all formulations (p = 0.937). This indicated that the use of fasting followed by a light snack, allowed some synchronisation of the MMC. As expected the data suggests that the SI transit time is independent of erodible tablet formulation. However, a large variation in SI transit time is observed ranging from 2.25-9.75 hrs, this was unexpected as the literature reports a degree of uniformity in SI transit of 3-4 hours (Wilding et al., 1995). Residence at the site of

Residence at the site of the ICJ also varies considerably from less than 15 minutes to greater than 240 minutes. As a consequence the colonic arrival time varies from 195 minutes to greater than 600 minutes. This variation in transit time has an impact on the function of the TDC. A rapid transit time to the colon is almost certainly accompanied by increased peristalsis through the SI (McClintic, 1975), which would result in increased agitation of the Time-Delayed Capsule aiding ET erosion. However, hastening the SI transit time would expose the Time-Delayed Capsule to less GI fluids before reaching the colon and this would probably result in reduced solvation and erosion of the ET.

The scintigraphic data does not permit precise definitions of transit after isotope separation, since the imaging acquisition frequency is increased to 1 hour.

Scintigraphic observation	Mean time [hrs] (s.d.)	Range [hrs]
Gastric emptying (n =24)	1.56 (0.57)	1-2.75
SI transit (n =19)	3.98 (1.78)	2.25-9.75
Colonic arrival (n =19)	5.36 (1.86)	3.25-10.5

Table 6.3. Summary of Gastric emptying, SI transit and colonic arrival times for all TDC formulations.

6.3.5. LACK OF DISPERSION OF TECHNECIUM-99m

As shown in Table 6.2, a total of six capsules failed to release their contents. Two failures were seen with the 35% HPMC erodible tablet formulation (Subjects 005 and 008). Both showed relatively rapid colonic arrival times of 225 minutes. Three capsules failed from the 24% HPMC erodible tablet formulation (Subjects 003, 004 and 008) and of these, two had relatively rapid colonic arrival times of 225 and 240 minutes. In Subject 004, a greatly prolonged SI transit time of greater than 540 minutes was observed, which was the maximum SI transit period for this formulation. The final capsule to fail was with a 20% HPMC erodible tablet

(Subject 006); this also exhibited a prolonged SI transit time of greater than 375 minutes. Rapid colonic arrival time may have resulted in earlier exposure of the capsule to less GI fluids; this would have resulted in compromised erosion of the ET. Alternatively, GI tract content may obstruct the TDC following or during erosion of the ET to prevent expulsion of the contents.

The reason for the prolonged GI transport observed in the final two failures is not obvious. It may be due to some inter-subject variation in intestinal motility on these occasions, providing poor TDC agitation which resulted in slower erosion of the ET. It should also be noted that in Subject 004 the TDC remained stationary post-gastric emptying for a considerable period. Under those conditions the TDC would have only been exposed to minimal forces of agitation, again resulting in a slower erosion process.

6.3.6. SELECTED SCINTIGRAPHIC IMAGES

The following section shows a selection of the more significant images of GI transit and drug release of the TDC.

6.3.6.1. Rapid upper GI transit Subject 003

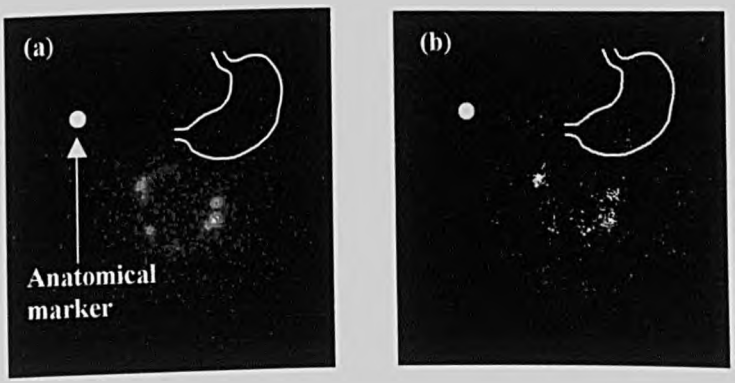


Figure 6.4. Scintiscan of Subject 003 showing rapid movement in the upper GI tract:
(a) 90 minutes post-dosing (full channels);
(b) 90 minutes post-dosing stationary intact device (^{111}In channel only).

Subject 003 at 90 minutes post dosing shows that the intact device has emptied from the stomach and is seen rapidly moving through part of the upper SI, during the period of the 30 second scan (Figure 6.4a). This could be mistaken for radiolabel separation. However, by observing the ^{111}In channel only (Figure 6.4b) it can be seen that the ^{111}In point source (having a higher photopeak energy) at the base of the TDC, is also present at each of these areas of activity. Confirming that separation had not occurred and that the images were a consequence of motility within the duodenum.

6.3.6.2. Dispersion of the theophylline tablet in Subject 005

An intact device is tracked to the ICJ (Figure 6.5a) in Subject 005, where separation of the isotopes occurs (Figure 6.5b) 225 minutes after dosing.

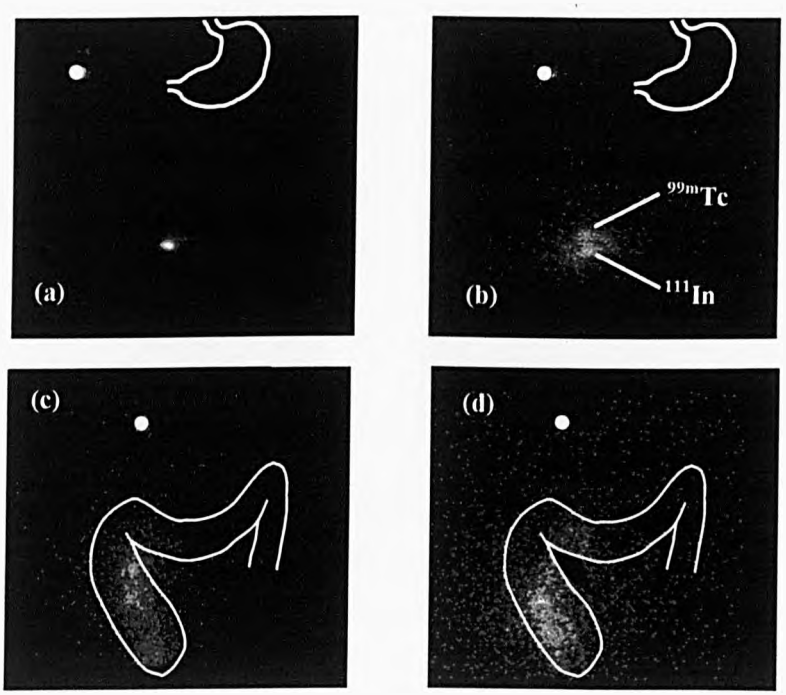


Figure 6.5. Scintiscans showing dispersion of the theophylline tablet in Subject 005: (a) 165 minutes post-dosing; (b) 225 minutes; (c) 360 minutes; (d) 600 minutes.

Dispersion of the ^{99m}Tc source can be clearly seen in the ascending colon (Figure 6.5c), which and further dispersion approaching the transverse colon after 10 hours (Figure 6.5d).

6.3.6.3. Transit of large and small units through the colon in Subject 001

Dispersion of the ^{99m}Tc label occurred in Subject 001 at the ICJ after 480 minutes (Figure 6.6a).

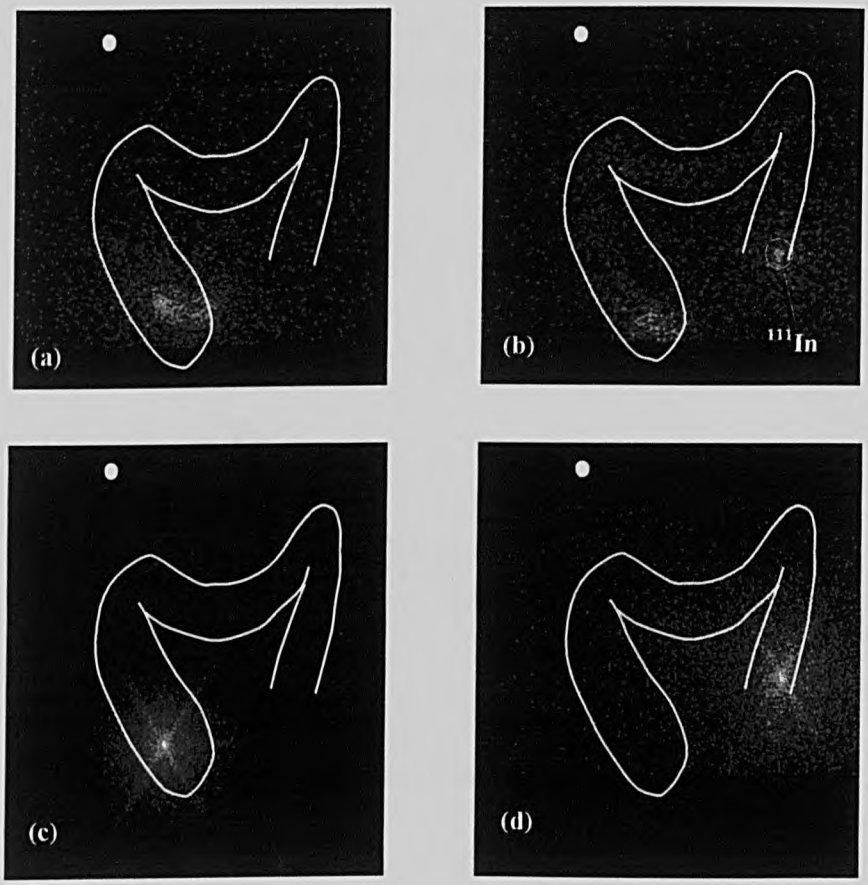


Figure 6.6. Gamma scintiscans showing dispersion of the theophylline tablet and position of the TDC body in Subject 001 with the 5 hour formulation:
(a) 480 minutes post-dosing (full channel); (b) 720 minutes (full channel);
(c) 480 minutes (^{111}In channel); (d) 720 minutes (^{111}In channel).

At this point the ^{111}In labelled capsule and the dispersed ^{99m}Tc (theophylline tablet) are at the same region. After 12 hours the entire colon is highlighted by the dispersed ^{99m}Tc, and the capsule containing the ^{111}In has moved more rapidly than the dispersed ^{99m}Tc (Figure 6.6b), this is confirmed by observing the ^{111}In channel. Previous studies have indicated the movement of small particles throughout the GI tract is slower than for larger bodies (Hunter et al., 1982).

6.4. PHARMACOKINETIC DATA

The plasma theophylline profiles determined by this author for Subject 001 are displayed in Figure 6.7. The profiles show a correlation between plasma appearance of theophylline and the HPMC content of erodible tablet formulations occurs with the three different formulations (20, 24 and 35% HPMC corresponding to first appearance of theophylline in plasma of 165, 180 and 300 minutes).

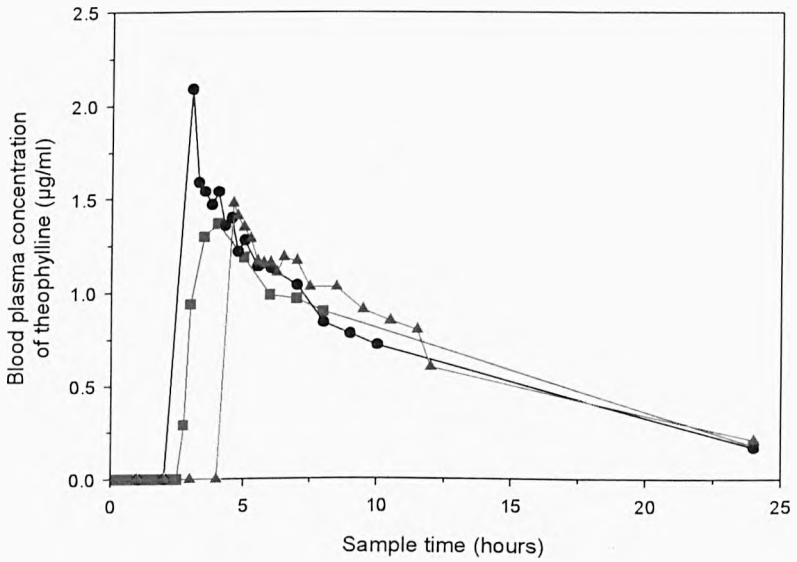


Figure 6.7. Plasma theophylline time profiles for Subject 001.
● 20% HPMC ET; ■ 24% HPMC ET; ▲ 35% HPMC ET.

Plasma theophylline levels in Subjects 002-008, were determined by BioImages. Pharmacokinetic parameters were calculated for all study subjects using the pharmacokinetic program PCModfit, these are shown in Appendix II.8. The data shows that the first appearance of theophylline within the blood plasma of the subjects corresponds well to the scintigraphic separation time indicated in the previous section (Figure 6.8).

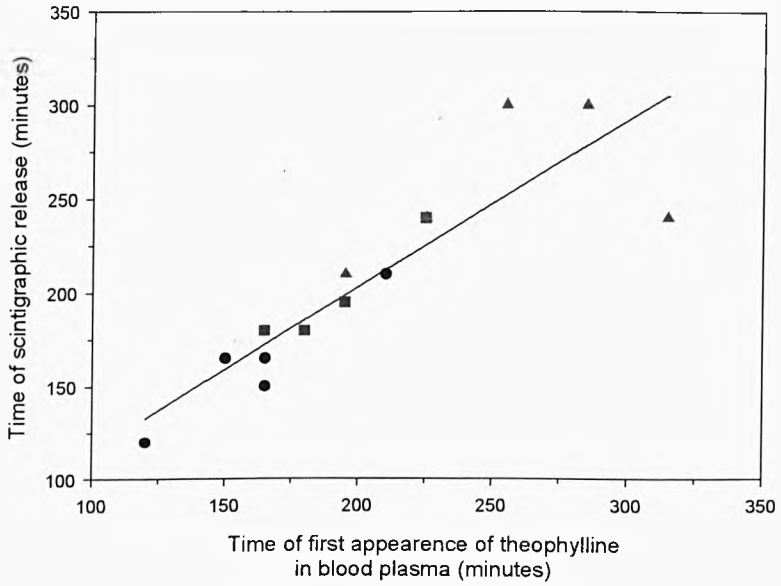


Figure 6.8. Correlation between the observed scintigraphic release times and the first appearance of theophylline in blood plasma with all TDC formulations:
● 20% HPMC ET; ■ 24% HPMC ET; ▲ 35% HPMC ET.

The plot indicates that there is a good correlation between the observed scintigraphic release and the pharmacokinetic data. However, less correlation is observed with 35% HPMC content (▲) of the ETs, and many such data points are not situated in proximity to the best-fit line. In addition, several of the data points are missing as isotope separation was not observed scintigraphically, however the trend showing that variability occurs at higher HPMC content is still apparent. This is probably due to the increased demand for water to enable erosion of the ET, as discussed below.

The scintigraphic analysis showed the failure of six formulations (Table 6.2), however the pharmacokinetic data did not support this. The 20% HPMC ET formulation taken by Subject 006 shows a first appearance in blood plasma of 300 minutes. Initial analysis on the study day suggested scintigraphic separation after 120 minutes, however re-analysis of the images after the study day suggested that this initial assessment of scintigraphic release was due to small movements of the

capsule device. However, in accordance with the protocol (Appendix II.1) the imaging time was reduced to 60 minute intervals on the study day and as a result, separation of the two radiolabels may have occurred between sampling times.

Subject 008 showed no release scintigraphically for either the 24% HPMC or 35% HPMC erodible tablet formulations, whereas release was confirmed by the appearance of theophylline in the plasma at 330 and 480 minutes respectively. Low C_{max} values were observed in each case, which may be indicative of either incomplete release of drug or release into a low fluid area. Plasma profiles (data not shown) also indicated prolonged absorption of theophylline in this subject. In earlier studies with Pulsincap™, protracted drug absorption has been attributed to low fluid levels which are inadequate to enter the capsule and cause swelling of the expulsion system and ejection of the drug (Stevens et al., 2002). It could be suggested that this Subject 008 had a relatively low fluid content within the GI tract and this could be an explanation for the increased lag-time due to slow erosion of the ET. Low fluid levels would also result in poor swelling of the expulsion excipient in the TDC and could also result in reduced disintegration and dissolution of the theophylline tablet. The result would be an extended plasma profile (T_{max}) with low C_{max}. It has been suggested (Frenning et al., 2002) that dosage forms should be tested using a novel technique in low liquid surroundings, when the dosage form is targeted to a low liquid site of administration.

The literature reports several examples of compromised absorption of theophylline. A delay in gastric emptying has been associated with a delay in the absorption of theophylline in man (Haruta et al., 2001). In another study, low C_{max} values with peak broadening were reported for theophylline in patients that had high levels of stress (Lemmer 1989). One further possibility is reaction of the drug with chemicals found within the GI tract with chemicals such as surfactants. This type of problem has previously been reported with tolbutamide (Veiga and Ahsan, 2000).

In this study the most likely explanation for TDC failure to release is a reduced exposure to GI fluids. Rapid transit of the TDC through the small intestine

results in the formulation reaching the colon more rapidly and the reduced fluid availability at that site may result in compromised erosion. Increased peristalsis of the SI due to rapid transit provides more agitation but is not sufficient to make up for the deficit of fluids in the colon required for erosion of the ET. Motility and fluid content is much reduced in the colon (Seeley et al., 1995) and so agitation and polymer erosion are likely to be minimised at this site. In addition, the extended gastric emptying times, slow SI transit and extended theophylline absorption profiles observed in Subject 008 are evidence to indicate increased stress levels may have played a part in the data obtained.

6.5. CONCLUSIONS

- Controlled gastric emptying can be achieved by dietary intake leading to synchronisation of the MMC.

- Pharmacokinetic studies provide useful confirmation of release, as indicated by the scintigraphic data.

- Good *in vivo* reproducibility has been demonstrated with this Time-Delayed Capsule (TDC) device, with only a small number of 'failures' being observed.

- SI transit time in this study was variable and prolonged. Capsule 'failure' was probably due to this and a consequence of reduced mobility and low moisture availability at distal GI sites.

CHAPTER 7. SUMMARY OF CONCLUSIONS AND FUTURE WORK.

7.1. CONCLUSIONS

A 'capsule integrity ratio' (CIR) term was developed in order to assess the suitability of capsule coating methods. This was employed in order to allow Time-Delayed Capsules (TDCs) to be developed for use in a human study using pharmacopoeial approved materials in the coating process. Organic coated capsules maintain greater structural integrity when compared with aqueous coated capsules by observing the CIR. This was supported by work conducted at the University of Nottingham (Sutch et al., 2002), which indicated a high incidence of capsule failure with aqueous coated capsules.

Propranolol often used as a first line of treatment for cardiovascular diseases, was used as a model drug in these studies. A true pulsatile release was observed by formulating this drug with suitable excipients to enable disintegration once full expulsion from the TDC had occurred. This has the potential to temporally target the early morning hours at the peak symptom time for cardiovascular disease sufferers.

Different size dosage forms can be easily incorporated into the TDC by selecting a thicker or thinner erodible tablet (ET), used to control lag-time. By varying the concentration of HPMC contained in ETs a wide range of lag-times were determined for 80 and 60 mg ETs. The ETs may be pre-programmed by observing a $T_{50\%}$ drug release versus HPMC concentration plot, and subsequently manufacture a suitable ET formulation.

Wet granulation of the ET formulations had a profound effect on the lag-time of the assembled TDCs. The greatest alteration and prolongation of release time following wet granulation was observed with the lowest concentration of HPMC (15%) within the ET. There was no evidence of physical change in the crystalline state of lactose as demonstrated by XRPD or DRIFTS analyses, indicating that any contribution from a change in morphology of the lactose would be very low. However, with the more sensitive DVS technique, evidence for a small amorphous to crystalline transition was indicated but there was no suggestion that this had a significant effect on lag-time. The recent and innovative techniques of Microwave

Dielectric Analysis (MDA) and Solid State Nuclear Magnetic Resonance revealed high levels of water mobility within granulations containing low levels of HPMC. It was believed that this allowed greater HPMC chain mobility/swelling and spreading within the wet granulate, resulting in slower tablet erosion, and hence an increased lag-time of drug release from the assembled TDCs. Increasing the water for granulation showed that a maximum increase in lag-time could be achieved, this was related to the end-point of the granulation.

The kinetics of ET erosion was determined. A period of first order weight loss, followed by an extended period of zero order weight loss associated with HPMC relaxation and dissolution, was observed. The initial period of first order weight loss was attributed to lactose dissolution from the ET prior to the formation of a gel layer by the HPMC. This period of weight loss was much reduced after the wet granulation processing, indicating that the HPMC was able to form a gel layer more rapidly following processing suggesting that its surface area had been enlarged due to spreading.

A clinical trial using eight subjects has demonstrated that the TDC performs well *in vivo* with only a small number of 'failures' being observed. Controlled gastric emptying can be achieved by dietary intake leading to synchronisation of the MMC. SI transit time showed variability and capsule 'failure' was probably due to this, a consequence of reduced mobility and low water availability at distal GI sites. The pharmacokinetic analysis provided useful confirmation of theophylline release, as indicated by the scintigraphic data. Theophylline, the drug selected for this study has the potential for temporal delivery since acute asthma has a pronounced nocturnal circadian rhythm.

In conclusion a capsule based drug delivery system, the Time-Delayed Capsule has been developed to exploit the potential for temporal targeting of disease states and an understanding of erosion processes involved in controlling the lag-time of the TDC has been demonstrated. Manufacturing and processing considerations

were also investigated to provide the optimal components for the assembly of the TDC and provide a true pulse-release drug delivery.

7.2. FUTURE WORK

The following may be applicable for the design of future work associated with the Time-Delayed Capsule:

- Multiple doses may be incorporated into the TDC to provide a series of pulses, reducing the need for multiple dosing. Patient compliance has been shown to increase by the incorporation of multiple units to give a single unit (Guichedi et. al., 1991, Cox et al., 1999).

- The presence of an excess of expulsion excipient is indicated by the photographic study (Chapter 3, Section 3.3.3.1.5) and suggests that a smaller preparation of the TDC might be feasible, further increasing patient compliance.

- Microwave dielectric analysis was a useful tool in determining the water mobility within the wet granulations prepared. It was demonstrated that an end-point was reached with the granulation process by the addition variable amounts of water. This method of analysis may be developed further to demonstrate end-points in a variety of granulation processes.

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APPENDIX I.

1.1. DEFINITION OF TERMS

%	Percentage
°C	Degrees Celsius
Å	Angstrom
a	Decay constant
$A^{100\%}$	Absorption of fully dissolved sample
AC	Alternating current
ANOVA	Analysis of variance
ASA	Aminosalicylic acid
b	Decay constant
C	Capacitance
C_{aq}	Aqueous coated capsule body
CIR	Capsule integrity ratio
cm	Centimetres
cm^{-1}	Wavelength
C_{org}	Organically coated capsule body
$C_{p,\ diss}$	Critical polymer dissentanglement concentration
DBP	Dibutyl phthalate
DC	Direct compression
DTPA	Diethylenetriamine pentaacetic acid
DRIFTS	Diffuse reflectance infra-red Fourier Transform spectroscopy
DVS	Dynamic vapour sorption
Eqn.	Equation
ET	Erodible tablet
exp	Exponent
f	Frequency
F	Force
$F_{max\ (90RH)}$	Maximum force of sample post exposure to 90% relative humidity
$F_{max\ (dry)}$	Maximum force of dry sample
FTIR	Fourier transform infrared spectroscopy
G	Giga
g	Gram
GI	Gastrointestinal
HPLC	High pressure liquid chromatography
HPMC	Hydroxypropylmethyl cellulose
hrs	Hours
HW	Housekeeper wave
Hz	Hertz
IBD	Irritable bowel disease
ICJ	Ileocaecal junction
IPA	Isopropyl alcohol
IR	Infrared
k	Kilo
K_0	Zero order rate constant
K_1	First order rate constant
KBr	Potassium bromide
kN	Kilonewton
L_{gran}	Granulated lactose
L-HPC	Low substituted hydroxypropyl cellulose
ln	Natural logarithm
LV	Low viscosity
M	Mega
m	Metres
M_0	Mass at time (0)
MCC	Microcrystalline cellulose
MDA	Microwave dielectric analysis
M_{ET}	Mass of erodible tablet remaining
mg	Milligram

MgSt	Magnesium stearate	SI	Small intestine
		$Sorp_{max}$	Maximum adsorption value
min	Minutes	SSNMR	Solid state nuclear magnetic resonance
ml	Millilitres		
mm	Millimetres	t	time
MMC	Migrating myo-electric complex	T_1	Lattice relaxation time
		T_2	Transverse relaxation time (dephasing time)
mpa.s	Millipascal seconds		
MRI	Magnetic resonance imaging	$T_{50\%}$	Time of 50% drug release (lag-time)
ms	Millisecond		
MTDSC	Modulated temperature differential scanning calorimetry	TA	Texture analyser
		TDC	Time-Delayed Capsule
		TES	Time-delayed explosion system
M_w	Molecular weight		
N	Newton	T_g	Glass transition temperature
n	Experimental number	T_{mag}	Transverse magnetisation
n	Reaction exponent	USP	United States pharmacopoeia
nm	Nanometres		
p	Probability factor	UV	Ultraviolet
PD	Post desorption	w	Weight
PDD	Pulsatile drug delivery	WG	Wet granulation
PEG	Polyethylene glycol	XRPD	X-ray powder diffraction
PMMA	Polymethyl methacrylate	ε	Permittivity
Poly	Polymer	ε_0	Permittivity of free space (air)
ρ_A	Apparent density		
ρ_T	True density	ε_r	Relative permittivity
PVA	Polyvinyl acetate	$\varepsilon_{rel.}$	Relative porosity
PVP	Polyvinyl pyrrolidone	ε_w	Permittivity of water
Q	Charge	τ	Time constant
R	Resistance	υ	Tangential velocity
r	Radius	ω	Angular velocity
R_a	Average surface roughness		
rad	Radians		
rad/s	Radians per second		
s.d.	Standard deviation		
SA	Surface area		
sec	Seconds		
SEM	Scanning electron microscopy		

I.1. UV SCAN FOR PROPRANOLOL

A 0.0055% (w/v) solution was prepared by weighing propranolol hydrochloride (55 mg) and dissolving in distilled water (1000 ml). This was then scanned using the Cecil 500 UV/VIS spectrophotometer, with a slit width of 2.0 nm, between 200 and 400 nm (Figure I.1).

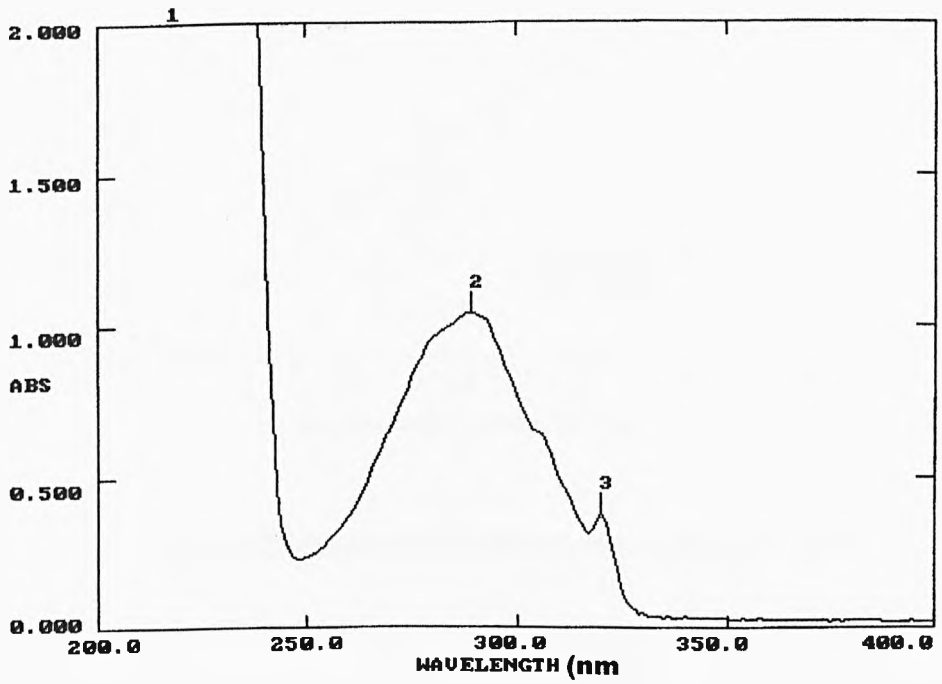

Figure I.1. Wavelength scan of propranolol hydrochloride.

Three peaks were detected (Table I.1) and the second was selected as the lambda maximum (λ_{max}) at 289 nm.

Peak designation	Wavelength (nm)	Absorbance
1	217	2.55
2	289	1.036
3	320	0.376

Table I.1. Absorption peaks for propranolol hydrochloride.

I.2. PROPRANOLOL CALIBRATION

Standard solutions of 0.1, 0.2, 0.3, 0.4 and 0.5 mg/ml propranolol hydrochloride were prepared and analysed at 289 nm. A calibration curve was constructed (Figure I.2).

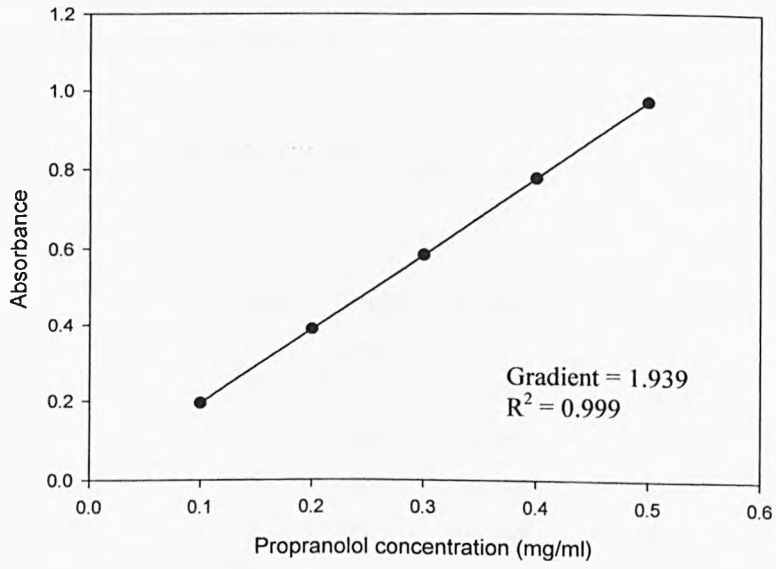

Figure I.2. Propranolol hydrochloride calibration curve.

I.3. CONTENT UNIFORMITY OF FORMULATION P7 PROPRANOLOL TABLETS

Individual tablets (10) were dissolved in distilled water (100 ml). Aliquots (10 ml) of each solution were further diluted (100 ml). Using the calibration curve constructed above (Figure I.2) [Eqn. I.1] was used to calculate the drug content of each tablet as shown in Table I.2.

$$Content(mg) = \frac{Absorbance}{Gradient} \times \frac{100}{10} \times 100ml \qquad \text{[Eqn. I.1]}$$

Tablet	Weight (mg)	Absorbance	Drug content (mg)
1	78.3	0.738	38.2
2	78.0	0.749	38.8
3	78.9	0.778	40.3
4	77.1	0.740	38.3
5	77.5	0.727	37.7
6	79.3	0.826	42.8
7	78.9	0.752	39.0
8	79.0	0.771	39.9
9	77.8	0.737	38.2
10	79.5	0.825	42.7
Average	78.43	0.764*	39.6
s.d..	0.81	0.035	1.9

Table I.2. Content uniformity of propranolol tablets.

*$A^{100\%}$ absorbance value.

I.4. CALCULATION OF SHEAR PROPERTIES OF THE MIXER/GRANULATOR

Calculation of the rotational velocity of the impellor tips contained within an FP296 mixer/granulator is shown [Eqn I.2-I.4]. An impellor tip speed >10 ms^{-1} has high shear properties (Knight, 1993).

Blade rotation ≡ angular velocity (ω) [Eqn. I.2]

$$\omega = \frac{1350\ rev}{1\min} \times \frac{2\pi rad}{1\min} \times \frac{1\min}{60\sec} = 141.3\ rad\sec^{-1} \quad \text{[Eqn. I.3]}$$

Tangential velocity (v_t) of the 90 mm radius (r) blade,

$$v_t = r\omega \quad \text{[Eqn. I.4]}$$

v_t = 0.09 m x 141.3 rad/s

= 12.72 ms^{-1}

APPENDIX II.

II.1. STUDY SUMMARY

Protocol Title:	A study to investigate oral time-delayed delivery of theophylline in healthy volunteers using gamma scintigraphy
Objective:	To characterise release of scintigraphic markers and the marker drug theophylline from three novel formulations designed to release drug after 1, 3 and 5 hours
Study Design:	The study is single centre, open-label, randomised The study will be split into two phases: Three-way cross-over study in 8 volunteers using a time delay of 1, 3 and 5 hours Follow-on study using one of the above formulations in 12 volunteers
Active Ingredient:	Theophylline BP
Treatment:	Administration of time-delayed (1, 3 &5 hours) formulations each containing: 4.0MBq ^{99m}Tc-DTPA in an 80mg theophylline tablet 0.25MBq ^{111}In-DTPA labeled capsule body
Assignment:	Randomised
Population:	Healthy male volunteers aged between 18-45 years inclusive
Sample size:	20 subjects

Adverse Events:	Volunteered and elicited
Data Analysis:	Scintigraphic analysis of time and site of release and gastrointestinal transit, if applicable. Analysis of plasma theophylline concentration.
Proposed Start Date:	September 2001

II.2. STUDY RANDOMISATION

Table II.1 indicates the randomisation schedule used to assign assembled TDCs with patients on specific study days.

Subject No	Study Day 1	Study Day 2	Study Day 3
1	1hr	5hr	3hr
2	5hr	3hr	1hr
3	3hr	1hr	5hr
4	5hr	1hr	3hr
5	3hr	5hr	1hr
6	1hr	3hr	5hr
7	1hr	3hr	5hr
8	3hr	5hr	1hr

Table II.1. Randomisation schedule used to determine the dosing regime:

1 hr = 1 hour time delayed release formulation;

3 hr = 3 hour time delayed release formulation;

5 hr = 5 hour time delayed release formulation.

II.3. PHARMACOKINETIC ANALYSIS

A HPLC calibration curve of theophylline in blood plasma is shown in Figure II.1.

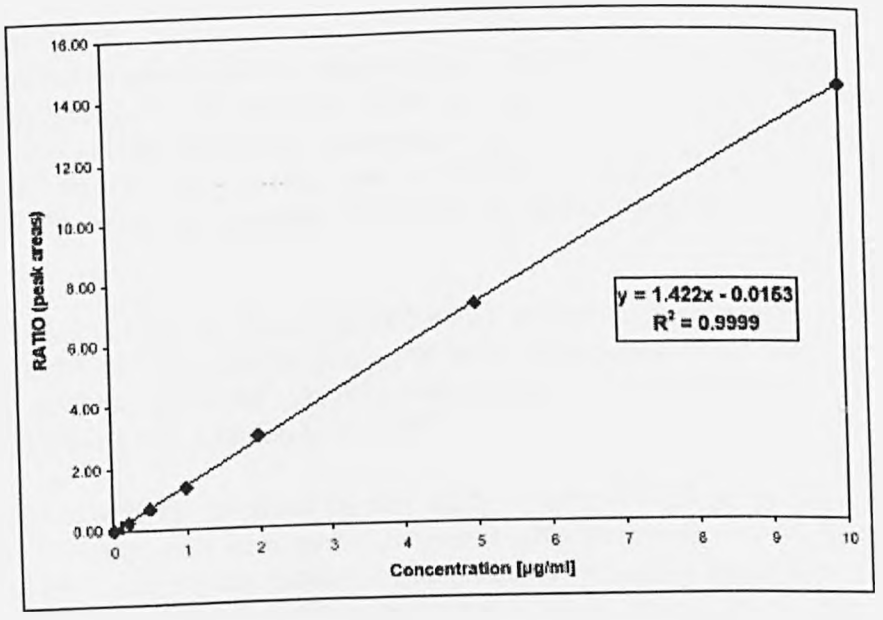

Figure II.1. Calibration curve for theophylline in plasma.

A STUDY TO INVESTIGATE ORAL TIME-DELAYED DELIVERY OF THEOPHYLLINE IN HEALTHY VOLUNTEERS USING GAMMA SCINTIGRAPHY

BACKGROUND

You are invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Consumers for Ethics in Research (CERES) publish a leaflet entitled 'Medical Research and You'. This leaflet gives you more information about medical research and looks at some questions you may want to ask. A copy may be obtained from CERES, PO Box 1365, London N16 OBW

Eight subjects will be involved in this study. They will all be people who have volunteered to take part, in response to poster advertisements that we have placed. They must all satisfy certain inclusion and exclusion criteria in order to participate in this study. These study eligibility requirements relate mainly to the age, sex and medical history of the volunteers.

AIMS

This study aims to investigate a new way of delivering a drug using a capsule which is taken at night and releases the drug at a set time point several hours later. This could be used to treat disease such as asthma, rheumatoid arthritis and heart disease which are worse in the early morning.

The medicine resembles a small capsule similar to the kind you may take for a headache. We will be measuring:

- Stomach (gastric emptying) and gastrointestinal transit time (the length of time it takes to travel from the small and large bowel).
- The blood levels of the test drug (theophylline)

Gastric emptying and gastrointestinal transit time is measured by taking pictures with a gamma camera. This piece of equipment detects and records gamma rays given off by radioisotopes which are incorporated into the capsule. A small amount of the gamma-emitting radioisotopes Technetium-99m and Indium-111 are added into the capsule. These radioisotopes are used routinely in nuclear medicine clinics for patient diagnosis, in much larger doses than volunteers will receive in this study. The gamma camera does not emit X-rays or radioactivity.

Eight volunteers will take part in this study and each volunteer will participate in three study periods, of up to twelve hours each. It is up to you to decide whether or

not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive. During the course of the study you will be informed immediately of any important information that that may come to light about any of the products being used. Your general practitioner will be informed of your participation in this study.

WHAT WILL HAPPEN TO ME IF I TAKE PART?

ENROLMENT

After you have read this volunteer information sheet, study personnel will be available to answer any questions that you may have. They will thoroughly explain the purpose and method of the study and any expected effects and potential risks to you. You will be asked to attend a medical examination at the Bio-Imaging Centre during the three weeks before the first study day to establish your fitness to participate in the study. This will include a medical history, physical examination, and the assessment of blood pressure and pulse. It is important that you tell us accurately about your full medical history and any previous problems you may have had after taking any medicines. You will be excluded from this study if the physician is not satisfied that you are fit to participate. Blood samples will be taken for testing to assess, your health. These tests will include blood biochemistry haematology and tests for Hepatitis B and C. The amount of blood taken will be about 20ml, which is less than a twentieth of a pint. Additionally, a urine sample will be taken for urinalysis.

STUDY DESIGN

This will be a randomised, non-blinded three-way cross-over study involving eight subjects. These terms are explained below.

Randomised Trial

The medicine you receive on each study day is selected by a computer which has no information about the individual - i.e. by chance. All volunteers will receive the same study medication, but in a different sequence.

Non-blinded:

This study is a non-blinded trial. You will know what medicine you are taking.

Cross-over trial:

This is a cross-over study; all volunteers who complete the study will receive the same treatments.

WHAT DO I HAVE TO DO?

You will also be expected to agree to the following:

- You must not eat any food from 10pm on the evening before the study day, although water will be allowed until 2 hours before dosing
- You must not take any medication within 21 days prior to study day and for the duration of the study
- You must refrain from unusual strenuous activity 24 hours prior to the study period
- You must not consume alcoholic drinks or caffeine for 24 hours prior to the study period

At each study period you will receive a capsule which contains theophylline. The capsule will also contain a small amount of both Technetium-99m and Indium-111. There are three study days, with at least a week between each one.

STUDY SCHEDULE

We will ask you to arrive at the Bio-Imaging Centre at 8am in the morning of the study day. We will insert a needle into your arm to enable us to take blood samples, and attach markers to your abdomen to help us take images. We will give you a hot drink and a biscuit thirty minutes before dosing. We will ask you to swallow one capsule with a small amount of water. After dosing we will ask you stand in front of the gamma camera. Images will be taken at regular intervals throughout the study day. We will measure your blood pressure and pulse throughout the day. We will also take regular blood samples during this time. The total amount of blood we will take from you per study day will be 120ml. The length of study day will vary from 8 to 12 hours depending on the medicine you receive that day. You will be provided with a schedule before the start of the study.

We will provide lunch, an afternoon snack. An evening meal will be provided on the 12 hour study day. Liquid refreshments will be provided on all study days. There is also a television and video provided for your entertainment.

POST STUDY MEDICAL

Several days after your treatment you will be asked to return to the centre to have another physical examination, and blood and urine samples will be taken for laboratory testing. Again, the amount of blood taken will be about 20 ml.

WHAT ARE THE POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART?

The risks involved relate to:

Theophylline

Theophylline is used to treat nocturnal asthma with a single daily dose of 300mg. During the course of the study you will receive a total of 240mg of theophylline. Side effects of theophylline are rare but may include arrhythmias, tachycardia, palpitation, flushing, giddiness, headache, tremor, anxiety, restlessness, insomnia, muscular weakness, nausea, vomiting, dyspepsia, thirst, sweating, difficulty in

micturition. However, we do not expect any side effects with this low dose. We will, nonetheless, be monitoring volunteers during the course of the study. Those who experience any adverse effects will be excluded from the remainder of the trial.

Radioactivity
The total radiation exposure you will receive from this study will be 0.55 mSv, which is less than what you would receive if you had a hip X-ray.

Blood Sampling
The total amount of blood taken from you over the three study days will be not exceed 400 ml, which is around three quarters of a pint.

WILL I BE COMPENSATED FOR TAKING PART?
For the time and inconvenience involved in participating in this study you will be paid the sum of £320, which is broken down as follows: £10 for the pre-study medical examination and £100 for each study day and £10 for the post-study medical examination. If you choose to withdraw from the study, you will be paid for the period that you have completed. If, however, having started the study, your participation is terminated by the study doctor for medical reasons, you will receive the full amount.

Studies in normal people have a very good safety record. This study is subject to the guidelines relating to compensation for injury arising in the course of clinical trials developed by the ABPI (Association of British Pharmaceutical Industry). If you require a copy please ask.

Will information remain confidential?
The investigators will ensure that the information that is obtained from this study, which can be identified with you, will remain confidential. This information will be stored on computer. In any written reports and publications you will be referred to by a code number only and, in signing your consent, you give permission for this. The investigator reserves the right to stop the trial at any time.

WHO IS ORGANISING AND FUNDING THE RESEARCH?
This research project is organised by Bio-Images Research Ltd in conjunction with The University of Strathclyde.

QUERIES
For any further information you require about this study please contact:
Dr. Bridget O'Mahony or Dr Blythe Lindsay
Phone: (0141) 552 8791

II.5. CONSENT FORM

Bio-Images Research Ltd
Dalycarraghy
Burnside Road
Drymen G63 0BX
Scotland UK

Registered in Scotland
N° 212808

Bio-Images

Operating from the Bio-Imaging Centre in Glasgow Royal Infirmary

Study Number: BC-018-01

Patient Identification Number: _____

CONSENT FORM

Title of project: A STUDY TO INVESTIGATE ORAL TIME-DELAYED DELIVERY OF THEOPHYLLINE IN HEALTHY VOLUNTEERS USING GAMMA SCINTIGRAPHY

Name of Researcher: _____

Please initial box

1. I confirm that I have read and understand the information sheet dated.....(version.....) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reasons, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I agree to take part in this study ☐

_____	_____	_____
Name of volunteer	Date	Signature
_____	_____	_____
Name of person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

II.6. SCINTIGRAPHIC DATA

Tables II.2 and II.3 show the transit times obtained from scintigraphic studies for all study subjects.

Subject	% HPMC	Stomach	Small Intestine			Colon		
		Emptying time (hrs)	Transit time (hrs)	ICJ residence (hrs)	Arrival time (hrs)	Regional transit times A (hrs)	T (hrs)	D (hrs)
001	20	1.75	>6.75	>1	-	-	-	-
	24	1.5	>8.3	>5	-	-	-	-
	35	1.25	7.75	<1	9	<1	<1	>3
002	20	3	>5	>1	-	-	-	-
	24	2	4	<2	6	<4	-	-
	35	2.5	4.5	<1	7	>5	-	-
003	20	1.75	3.5	<1	5	>3	-	-
	24	1	2.75	0.5	3.75	>6.25	-	-
	35	1	4	<1	5	>7	-	-
004	20	1	3	<2	4	>4	-	-
	24	1	>9	-	-	-	-	-
	35	1.25	4.75	<2	6	>6	-	-

Table II.2. Subjects 001-004 GI transit times obtained by scintigraphic analysis.

A = Ascending; T = Transverse; D = Descending.

Subject	% HPMC	Stomach	Small Intestine			Colon		
		Emptying time (hrs)	Transit time (hrs)	ICJ residence (hrs)	Arrival time (hrs)	Regional transit times A (hrs)	T (hrs)	D (hrs)
005	20	1	2.25	<2	3.25	>4.75	-	-
	24	1.25	3.75	<2.5	5	>5	-	-
	35	1	3.25	<1	4.25	>7.75	-	-
006	20	1.75	>6.25	-	-	-	-	-
	24	2.75	>7.25	>4	>10	-	-	-
	35	1.75	9.75	<1	10.5	>1.5	-	-
007	20	1.75	3.25	<1	10	>3	-	-
	24	1.25	3.75	<1	10	>5	-	-
	35	2	3	<1	10	<5	<1	-
008	20	1	4	<1	10	>3	-	-
	24	1.5	2.5	<1	4	>6	-	-
	35	1.5	2.25	<1.5	3.75	<8	>1.5	-

Table II.3. Subjects 005-008 GI transit times obtained by scintigraphic analysis.

A = Ascending; T = Transverse; D = Descending.

II.7. REPRESENTATIVE CHROMATOGRAMS FROM CLINICAL STUDIES

Figures II.2-II.4 show representative chromatograms of clinical samples from one subject taken at pre-dose, 4.75 and 24 hours after administration of a TDC fitted with a 35% HPMC formulation.

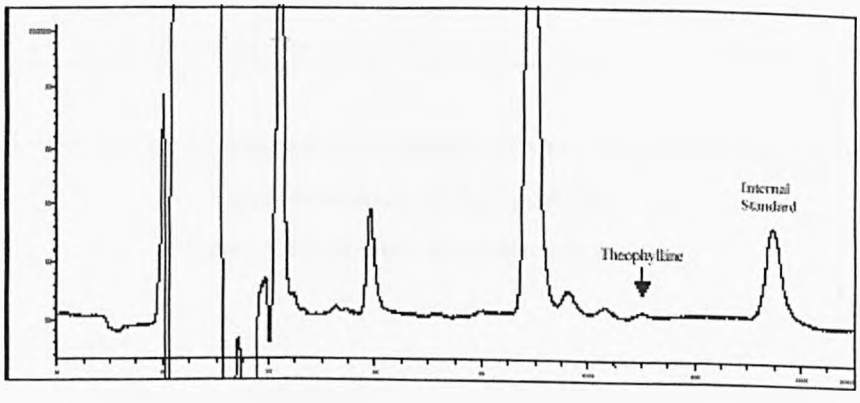

Figure II.2. HPLC chromatogram of extracted plasma sample taken pre-dose.

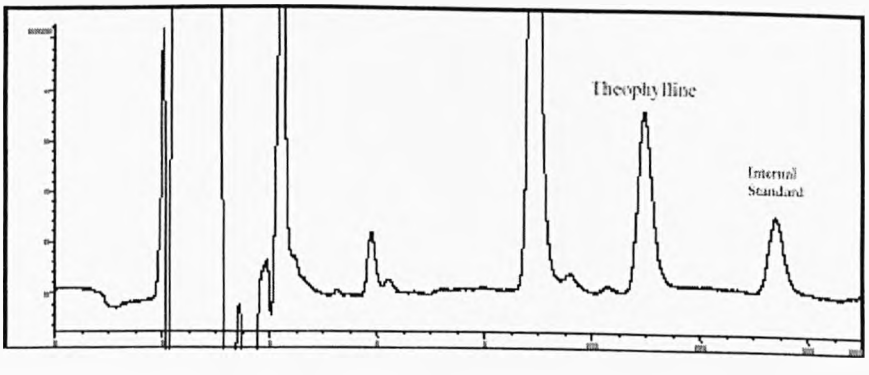

Figure II.3. HPLC chromatogram of extracted plasma sample taken at 4.75 hours after administration of theophylline.
(conc. of theophylline in plasma: 1.58 μg/ml).

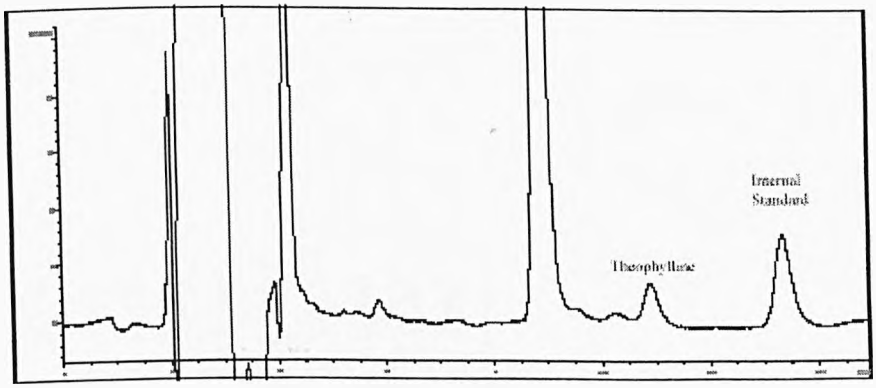

Figure II.4. HPLC chromatogram of extracted plasma sample taken at 24 hours after administration of theophylline.
(conc. of theophylline in plasma: 0.26 μ/ml).

II.8. PHARMACOKINETIC PARAMETERS FOR ALL STUDY SUBJECTS

Tables II.4-II.6 show the pharmacokinetic parameters for all study subjects.

Subject	Scintigraphic release (hrs)	First appearance in plasma (hrs)	T_{max} (hrs)	C_{max} (μgml^{-1})	$AUC_{(0-24)}$	$AUC_{(0-inf.)}$	Elimination rate constant	Half-life (hrs)
001	2.75	2.75	4	1.37	14.34	16.15	0.099	6.979
002	3.5	3.5	5	0.96	10.88	12.72	0.092	7.531
003	2.75	2.5	2.75	1.38	18.08	27.94	0.048	14.439
004	2.75	2.75	4	1.37	17.91	22.40	0.073	9.441
005	2	2	3	1.02	9.92	11.37	0.094	7.393
006	NS	5	6	1.58	22.40	49.21	0.032	21.674
007	2.5	2.75	3	1.46	14.19	16.23	0.095	7.313
008	3.5	3.5	4	1.58	21.51	32.36	0.051	13.549
Mean	2.82	3.09	3.97	1.34	16.15	23.55	0.073	11.04
sd	0.53	0.92	1.11	0.23	4.60	12.71	0.026	5.203

Table II.4. Pharmacokinetic parameters for 1hr formulation.

Subject	Scintigraphic release (mins)	First appearance in plasma (mins)	T_{max} (mins)	C_{max} (μgml^{-1})	$AUC_{(0-24)}$	$AUC_{(0-inf.)}$	Elimination rate constant	Half-life (mins)
001	3	3	3	2.09	14.98	16.41	0.111	6.257
002	2.75	3	4	1.07	11.10	12.05	0.115	6.051
003	NS	-	-	-	-	-	-	-
004	NS	-	-	-	-	-	-	-
005	3	3	3.25	2.42	21.19	24.02	0.099	7.019
006	3.75	4	4.5	1.60	18.52	24.71	0.068	10.239
007	3.25	3.25	3.5	1.17	12.49	14.77	0.087	7.942
008	NS	6	10	0.59	7.35	11.96	0.054	12.719
Mean	3.15	3.71	4.71	1.49	14.27	17.32	0.089	8.37
sd	0.38	1.19	2.65	0.68	5.05	5.71	0.024	2.62

Table II.5. Pharmacokinetic parameters for 3hr formulation.

Subject	Scintigraphic release (mins)	First appearance in plasma (mins)	T_{max} (mins)	C_{max} (μgml^{-1})	$AUC_{(0-24)}$	$AUC_{(0-inf.)}$	Elimination rate constant	Half-life (mins)
001	4.25	5	5	1.48	12.87	15.11	0.096	7.208
002	4.75	5	7	1.25	13.56	18.10	0.074	9.423
003	3.25	3.5	5.25	1.16	14.92	22.94	0.051	13.644
004	3.75	4	4.33	1.46	15.65	20.40	0.07	9.897
005	NS	-	-	-	-	-	-	-
006	6.25	4	8	1.13	16.96	35.41	0.034	20.206
007	3.75	4	4.25	1.48	12.72	14.63	0.099	6.979
008	NS	8	24	0.53	7.19	-	-	-
Mean	4.33	4.79	8.26	1.21	13.41	21.10	0.071	11.23
sd	1.07	1.52	7.08	0.34	3.15	7.69	0.025	5.01

Table II.6. Pharmacokinetic parameters for 5hr formulation.

APPENDIX III.

III.1. ABSTRACTS AND PRESENTATIONS

1. McConville, J., Florence, A., Stevens, H., Ross, A. Effect of process variables on the time-delayed release from a capsule based delivery device. *23rd Joint Research Seminar.* Trinity College Dublin (2000).

2. McConville, J.T., Florence, A.J., Stevens, H.N.E., Ross, A.C. Effect of process variables on drug release from a time-delayed capsule delivery system. *J. Pharm. Pharmacol.* **52**: S7 (2000).

3. McConville, J.T., Stevens, H.N.E., Florence, A.J., Ross, A.C. Processing induced variability of time-delayed delivery from a pulsatile capsule device. *AAPS PharmSci* **1**(4): #1678 (2000).

4. McConville, J.T., Florence, A.J., Stevens, H.N.E., Smith, G. Microwave Dielectric Analysis of Wet Granulations for Erodible HPMC Tablets. *138th BPC Sci. Proceed.* S262 (2001)[*†].

5. McConville, J.T., Smith, G., Florence, A.J., Stevens, H.N. The use of microwave analysis to describe the effect of a wet granulation processing technique. *AAPS PharmSci* **3**(3): #1843 (2001).

6. O'Mahony, B., McConville, J.T., Lindsay, B., Jones, T., Wilson, C.G., Stevens, H.N.E. Gamma scintigraphic visualisation of drug release from a Time-Delayed Capsule. *Procced. 6th US-Japan Drug Del. Symp.* (2001).

7. McConville, J.T., O'Mahony, B., Lindsay, B., Jones, T., Stanley, A., Vennart, B., Buchanan, T., Humphrey, M.J., Wilson, C.G., Stevens, H.N.E. Gamma scintigraphic investigation of drug release from a Time-Delayed Capsule. *Cont. Rel. Soc.* (2002).

8. McConville, J.T., Ross, A.C., Healy, A.M., Florence, A.J., Stevens, H.N.E. Preparation of water-impermeable capsule bodies for a pulsatile drug delivery system. *139th BPC Sci. Proceed.* (2002) – Accepted.

9. McConville, J.T., O'Mahony, B., Lindsay, B., Jones, T., Stanley, A., Vennart, B., Buchanan, T., Humphrey, M.J., Wilson, C.G., Stevens, H.N.E. Time delayed delivery of theophylline. *J. Pharm. Pharmacol.* **54**: S137 (2002).

10. McConville, J.T., Ross, A.C., Healy, A.M., Florence, A.J., Stevens, H.N.E. The suitability of a capsule component for use with a pulsed release drug delivery device. *AAPS PharmSci* (2002) – Accepted.

11. O'Mahony, B., Lindsay, B., Jones, T., McConville, J.T., Stanley, A., Vennart, B., Buchanan, T., Humphrey, M.J., Wilson, C.G., Stevens, H.N.E. Gastrointestinal transit and release of Time-Delayed Delivery Capsules. *AAPS PharmSci* (2002) – Accepted.

III.2. FULL-PAPERS

1. McConville, J.T., Ross, A.C., Chambers, A.R., Smith, G., Florence, A.J., Stevens, H.N.E. The effect of processing on erodible matrix controlled pulsatile drug delivery. – To be submitted.

2. McConville, J.T., Ross, A.C., Florence, A.J., Stevens, H.N.E. Erosion characteristics and kinetics of an erodible tablet used to control a time-delayed capsule (TDC). – To be submitted.

*Runner-up research day presentation, Department of Pharmaceutical Sciences, University of Strathclyde, Glasgow.

†Commended poster presentation 138th British Pharmaceutical Conference, Glasgow.