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Erosion Characteristics of an Erodible Tablet Incorporated in a Time-Delayed Capsule Device

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ABSTRACT A time-delayed oral drug delivery device was investigated in which an erodible tablet (ET), sealing the mouth of an insoluble capsule, controlled the lag-time prior to drug release. The time-delayed capsule (TDC) lag-time may be altered by manipulation of the excipients used in the preparation of the ET. Erosion rates and drug release profiles from TDCs were investigated with four different excipient admixtures with lactose: calcium sulphate dihydrate (CSD), dicalcium phosphate (DCP), hydroxypropylmethyl cellulose (HPMC; Methocel® K100LV grade) and silicified microcrystalline cellulose (SMCC; Prosolv® 90 grade). Additionally, the compressibility of different insoluble coated capsules was tested at different moisture levels to determine their overall integrity and suitability for oral delivery. Erosion rates of CSD, DCP, and SMCC displayed a nonlinear relationship to their concentration, while HPMC indicated rapid first-order erosion followed by zero-order erosion, the onset of which was dependent on the HPMC concentration. Capsule integrity was confirmed to be most suitable for oral delivery when the insoluble ethyl cellulose coat was applied to a hard gelatin capsule using an organic spray coating process. $T_{50\%}$ drug release times varied between 245 (±33.4) and 393 (±40.8) minutes for 8% and 20% DCP, respectively, $T_{50\%}$ release times of 91 (±22.1) and 167 (±34.6) were observed for 8% and 20% CSD; both formulations showed incidence of premature drug release. The SMCC formulations showed high variability due to lamination effects. The HPMC formulations had $T_{50\%}$ release times of 69 (±13.9), 213 (±25.4), and 325 (±30.3) minutes for 15%, 24%, and 30% HPMC concentrations respectively, with no premature drug release. In conclusion, HPMC showed the highest reproducibility for a range of time-delayed drug release from the assembled capsule formulation. The method of capsule coating was confirmed to be important by investigation of the overall capsule integrity at elevated humidity levels. The erosion characteristics of ETs containing HPMC may be described by gravimetric loss. The novel time-delayed capsule device presented in this study may be assembled to include an erodible tablet with a known concentration of HPMC. A variety of suitable drugs for targeted chronopharmaceutical therapy can be

incorporated into such a device, ultimately improving drug efficacy and patient compliance, and reducing harmful side effects.

KEYWORDS Chronopharmaceutical lag-time, Erodible tablet, Erosion kinetics, Pulled release

INTRODUCTION

Time-delayed release preparations have been the subject of much interest since the importance of circadian rhythms in disease states was described (Lemmer, 1991). It is known that targeting a specific delivery window greatly improves drug efficacy (Lemmer, 1989), and a decrease in dose reduces harmful patient side effects (Yano et al., 2002). Additionally, a reduction in dosing frequency improves patient compliance (Campbell, 1999). Pellets, tablets, and capsules have all been investigated as potential temporal delivery systems. Pellet-based systems generally consist of a drug containing core surrounded by, or mixed with, a swellable or osmotically active excipient that is coated with a semipermeable or porous insoluble layer (Chen, 1993; Schultz & Kleinebudde, 1997; Stevens et al., 1992; Ueda et al., 1994). The osmotic core induces water ingress to cause rupturing of the pellets, thereby releasing the drug contained within. Tablet formulations usually incorporate a drug-containing layer formulated with excipient, the drug layer may then be sandwiched between inert excipient layers (Jiang & Zhu, 2000). Drug release occurs as the outer layers of soluble excipient slowly dissolve. This type of arrangement for a tablet provides a convenient method of producing multiple drug release reservoirs, which may be manipulated to release drug sequentially. However, tablet formulations can be susceptible to lamination effects leading to premature drug expulsion or dose dumping (Efentakis & Buckton, 2002), and incomplete or sustained drug dissolution that is unsuitable for pulsed release delivery.

Capsule devices can be constructed in several ways. The PORT® System consists of an osmotic core within a porous/semipermeable capsule body. This facilitates water ingress to subsequently swell the contents of the capsule, which in turn displace a sealing plug allowing the release of drug (Crison et al., 1995). Another device, the Chronset® device, makes use of an osmotic cap that swells and removes itself from the capsule body exposing the drug-containing core to the dissolution media (Wong et al., 1994). A different capsule device, Pulsincap™, utilizes a self-removing sealing plug contained within a water-impermeable capsule (McNeill et al., 1994). The plug consists of a hydrogel polymer that swells slowly in contact with water to form a frusto-conical shape, which initiates its ejection from the capsule and results in the exposure of the drug-containing core to allow dissolution. Release studies have been carried out on another time-delayed capsule formulation where the hydrogel plug, present in the Pulsincap™ system, has been replaced by an erodible tablet (ET) (Krogel & Bodmeier, 1998; McConville et al., 2004; Ross et al., 2000). This modification eliminates the need for tight control of frictional forces associated with the hydrogel plug expulsion system in the Pulsincap™ formulation and the lag-time prior to drug release is simply controlled by the erosion charactersitics of the ET. The incorporation of an expulsion agent inside the capsule facilitates rapid expulsion of the contents upon exposure to dissolution media (Krogel & Bodmeier, 1998). Thus, manipulation of the ET composition provides a means of controlling lag-time (McConville et al., 2004; Ross et al., 2000). In this present study, the erosion characteristics of ETs composed of different pharmaceutical excipients are examined by measuring the gravimetric loss from the ETs over time. Additionally, the coating process used to apply the water impermeable ethyl cellulose coating to the size 0 hard gelatin capsule, was examined by investigating the coated capsule integrity, as determined by force of compression following exposure to different humidity conditions. The erosion characteristics of ETs were compared, and dissolution results from assembled TDCs were also examined. The usefulness of erosion characteristics to determine the most suitable compositions for inclusion in the TDC,

and for predicting the lag-time prior to drug release is discussed.

MATERIALS AND METHODS

Hydroxypropylmethyl cellulose (Methocel®; K100LV grade) and ethyl cellulose (EC; Ethocel® 45 premium grade) were obtained from Dow Chemical Company, Midland, MI. Low-substituted hydroxypropyl cellulose (L-HPC; LH-21 grade) was obtained from Shin-Etsu Chemical Company, Tokyo, Japan. Propranolol hydrochloride and all tablet excipients: Magnesium stearate, croscarmellose sodium (Ac-Di-Sol®; FMC BioPolymer, Philadelphia, PA), colloidal silica (Aerosil R728®; Degussa-Hüls Ltd., Macclesfield), dicalcium phosphate (Emcompress®; JRS Pharmaceuticals LP), calcium sulphate dihydrate (Compactrol®; JRS Pharmaceuticals LP), silicified microcrystalline cellulose (SMCC: Prosolv® 90 grade; JRS Pharmaceuticals LP, Patterson, NY) and Fast-Flo® lactose (Foremost Farms USA, Baraboo, WI) were obtained as gifts from Pfizer Limited, Sandwich, UK. Size 0 gelatin capsules were obtained as a gift from Capsugel, Basle, Switzerland. Dibutyl phthalate (DBP), acetone, and propan-2-ol (IPA) were purchased from Sigma-Aldrich Company Ltd., Gillingham. Triacetin was obtained from Merck-Chemicals Ltd. (Poole, Dorset, UK). Surelease® was obtained from Colorcon Ltd. (Dartford, Kent, UK).

Erodible Tablet Preparation

The following quantities of DCP or CSD were weighed and added to lactose (where appropriate) to make 99 g: 8, 20, 30, 50, 79, 90, or 99 g. For the HPMC formulations: 5, 10, 15, 24, 25, or 30 g of HPMC was added to 94, 84, 75, 74, or 68 g of lactose, respectively. Finally for SMCC: 10, 30, or 50 g SMCC was added to 89, 69, or 49 g lactose, respectively. Each individual formulation was mixed for 20 minutes in a Turbula™ mixer (Glen Creston, Middlesex, UK) at 42 rpm. Magnesium stearate (1 g) was then added to each mixture and mixed for a further 10 minutes. Each mixture was tableted to 80±1 mg (160±5 mg for 8% and 20% [w/w] CSD; and 120±5 mg for 8% and 20% [w/w] DCP) using 6.75mm diameter, flat-faced shape tooling (I Holland Ltd., Nottingham, UK) with an E2 Manesty single-punch tablet press (BWI-Manesty Ltd., Liverpool, UK) to produce DCP/lactose, CSD/lactose, SMCC/lactose or HPMC/lactose erodible tablets.

Preparation of Propranolol Tablets

Propranolol hydrochloride (45% [w/w]), lactose (53% [w/w]), and croscarmellose sodium (1% [w/w]) were mixed for 20 minutes in the Turbula™ mixer at 42 rpm. Magnesium stearate (1% [w/w]) was then added to each mixture and mixed for a further 10 minutes. The mixture was then compressed on a Manesty E2 single-punch tablet press using a 5 mm punch and die set to a weight of 56 mg (equivalent to 25 mg propranolol hydrochloride).

Tablet Characteristics

Tablets were measured for uniformity of weight, thickness, diameter, and crushing strength using a D200 tablet testing station (Erweka GmbH, Hausenstamm, Germany).

Capsule Coating

Size 0 capsule bodies for use in erosion studies were coated with ethyl cellulose using a Strea-1 Aerocoater (Aeromatic-Fielder AG, Bubendorf, Switzerland) and a coating process that utilized an organic solvent or a process that used an aqueous dispersion of ethyl cellulose (Surelease®), as previously described (Ross et al., 2000). The organic solution of ethyl cellulose coating comprised: EC (95% [w/w]) plasticized with DBP (5% [w/w]) as a 3% w/v solution in a 50:50 mixture of acetone: IPA. The following types of capsules were: 1) Aqueous coated capsules (CA) prepared using using Surelease (an aqueous dispersion of ethyl cellulose preplasticized with dibutyl sebacate), 2) organic coated (CO1) (ethyl cellulose 5% [w/v] dissolved in a 50/50 acetone/IPA solution plasticized with 0.05% [w/v] dibutylphthalate), 3) organic coated (CO2) (prepared as with CO1 using a ventilated pan-coater and supplied by BWI-Manesty), 4) organic coated [CO3] (prepared as with CO1 but using 0.05% [w/v] triacetin as the plasticizer).

Capsule Integrity Testing

The most effective way of coating capsules for use in the TDC is the organic solvent spray technique (Ross et al., 2000), as a degree of coating is 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, a technique was developed that assessed capsule strength using a TX2000 texture analyzer (Stable Micro Systems, Godalming, Surrey). In this way capsules were tested for their compressibility before and after exposure to a humidity controlled environment.

Uncoated capsules, CA, CO1, CO2, or CO3 capsules (10 of each) were selected and compressed using the texture analyzer fitted with a 20 kN load cell and polymethylmethacrylate compression stage. The maximum force of compression (F_{max}) prior to structural collapse was determined. Uncoated capsules, CA, CO1, CO2, or CO3 capsules (10 of each) were introduced to a controlled relative humidity (RH) of 45% (representative of typical laboratory RH) at 25°C with a dynamic vapor sorption (DVS) apparatus (Surface Measurement Systems Ltd., London, UK) 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 analyzed using an identical compression test to that described above. Maximum compression forces after exposure to 90% RH $F_{max(RH90)}$ were then determined for a total of 10 capsules of each type.

Time-Delayed Capsule Assembly

Assembly of the TDC device proceeded as previously published (Ross et al., 2000; McConville et al., 2004). Briefly: L-HPC (250 mg) was weighed into the precoated capsule body and lightly compacted using 2 N force; a propranolol tablet was placed centrally onto the compacted L-HPC layer; finally, an erodible tablet was inserted into the mouth of the capsule and positioned flush with the end of the coated body.

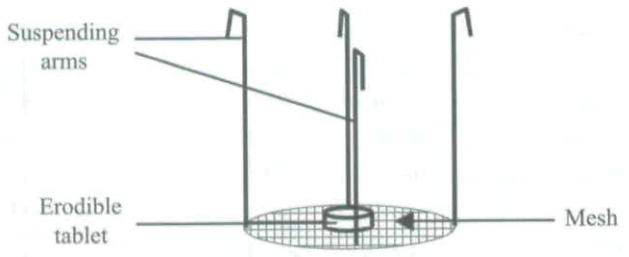

FIGURE 1 Erosion Support Arrangement with Erodible Tablet.

Erosion Studies

Erodible Tablets Containing: DCP, CSD, or SMCC

Supports for the ETs during the erosion test (Fig. 1), were prepared to enable ETs to be suspended in a model ST7, standard USP II paddle apparatus (Copley Scientific Ltd., Nottingham, UK) at 37°C in 1000 mL water and a paddle speed of 50 rpm. The supports consisted of a 5 cm diameter, 2 mm stainless steel mesh, suspended by four fixing arms attached to the top of standard 1000 mL dissolution vessels. The ETs (six in total) were weighed initially and placed individually onto six erosion supports. Each support was placed into a dissolution vessel and then removed sequentially at times of 0.25, 0.5, 1, 2, 3, and 4 hours. Each ET was then placed on a weighing boat and dried at 60°C overnight in an oven. Samples were then reweighed and weight loss at each sample time was determined.

Additionally, a study was conducted to determine the influence of tablet crushing strength on erosion for 30% w/w DCP, CSD, or SMCC formulations. Each sample was removed when approximately 10% of the original ET was remaining after visual inspection (up to 4 hours).

Erodible Tablets Containing HPMC

The method described above proved unsuitable for the erosion studies on ETs prepared with HPMC. This was due to the fact that the adhesive nature of the hydrophilic gel layer formed by the hydration of the polymer, led to a significant loss of material during their removal from the support mesh used in the study. Thus, a different approach that minimized contact of the HPMC containing ET was developed.

The ETs (36 in total) from each formulation containing 15%, 24%, or 30% w/w HPMC were selected and weighed. Each ET was fitted flush (as previously described with the capsule assembly procedure) into the mouth of an ethyl cellulose coated

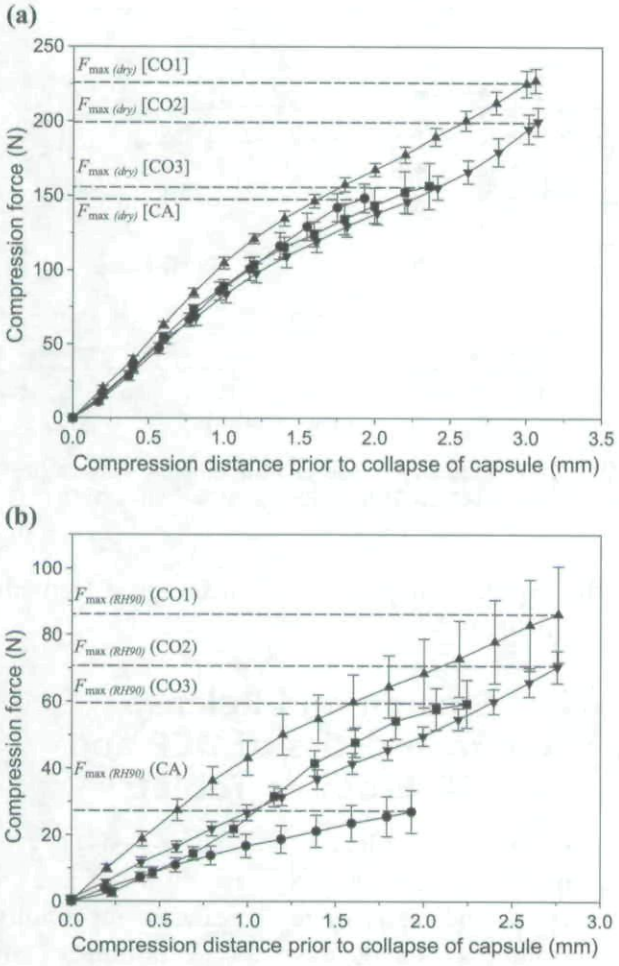

FIGURE 2 **(a) Compression Force Profiles of Dry Coated Capsules; (b) Compression Force Profiles of Coated Capsules at 90 Relative Humidity (n=10±s.d.). ▲=CO1, ▼=CO2, ■=CO3, ●=CA.**

size 0 hard gelatin capsule. The weight of each capsule together with ET was determined, and six assembled capsule/ET devices were placed into each of the six individual dissolution vessels (using a standard USP II paddle apparatus at 37°C in 1000 mL deionized water). A single capsule was removed from each of the six vessels at 1 minute intervals over an initial 6 minute period. These were oven dried at 60°C overnight and reweighed. The change in mass was calculated at each time point over the 6 minute period. This procedure was repeated using six more capsules for each of the three HPMC/lactose formulations with samples being removed at 10 minute intervals over a 1-hour period. In this way, 12 time points were obtained for each HPMC ET formulation.

Dissolution Studies

The capsules were tested in the model ST7, USP II paddle apparatus at 37°C in 1000 mL water at 50 rpm. Release of propranolol from the tablet following expulsion from the capsule was measured by UV spectrophotometry at 289 nm in a 10 mm quartz flow-through cell (Cecil Instruments Ltd., Cambridge, UK). It should be noted that the inorganic calcium salts demonstrate a pH-dependent solubility, this study was solely concerned with comparative dissolution profiles for each individual excipient and not dissolution rates that may occur at different sites of the gastrointestinal tract, thus dissolution studies were conducted in deionized water (at a pH of 6.5). $T_{50\%}$ values for dissolution profiles are indicated due to the fact that $T_{10\%}$ or $T_{90\%}$ values demonstrate less than a 5% deviation away from $T_{50\%}$ values. The values vary little as there is an immediate ejection and subsequent disintegration (<10 seconds) of the drug-containing tablet once the TDC begins to eject its contents.

RESULTS AND DISCUSSION

Capsule Integrity Testing

Compression force profiles of the coated capsule bodies are shown (Fig. 2a). An increase in compression force (F) is observed until structural collapse of the

TABLE 1 **Summary of Capsule Integrity Ratio (*CIR*) for Aqueous and Organic Spray Coated Capsules**

	$F_{max\ (dry)}$		$F_{max\ (RH90)}$		
Capsule type	[N]	(s.d.)	[N]	(s.d.)	*CIR*
CA	148.4	(9.6)	27.0	(6.4)	0.18
CO1	227.4	(8.0)	86.2	(14.5)	0.38
CO2	200.0	(9.4)	74.1	(4.9)	0.37
CO3	156.7	(15.6)	59.4	(7.2)	0.38

Note: n=10.

capsule (F_{max}) occurs. This is accompanied by a rapid decrease in F (omitted from the plot for clarity). Capsules coated using 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. Force profiles of the coated capsule bodies following exposure to 90% RH for 999 minutes are shown (Fig. 2b). Again, all capsules coated using the organic feed solution are able to withstand a greater $F_{\max\ (RH90)}$ than the aqueous coated capsules. The capsules coated using the aqueous feed solution demonstrate a greatly reduced F_{max} value following exposure to the 90% RH conditions.

A capsule integrity ratio (*CIR*) was calculated Eq. (1).

$$CIR = \frac{F_{\max(RH90)}}{F_{\max(dry)}} \qquad (1)$$

The *CIR* values (Table 1) 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. Maintainence of a high capsule integrity is important when considering the exposure of the capsule to mechanical forces associated with the gastrointestinal tract. A force of compression could not be obtained for the uncoated capsule following exposure to the elevated humidity levels as the capsule disintegrated when removed from the DVS apparatus.

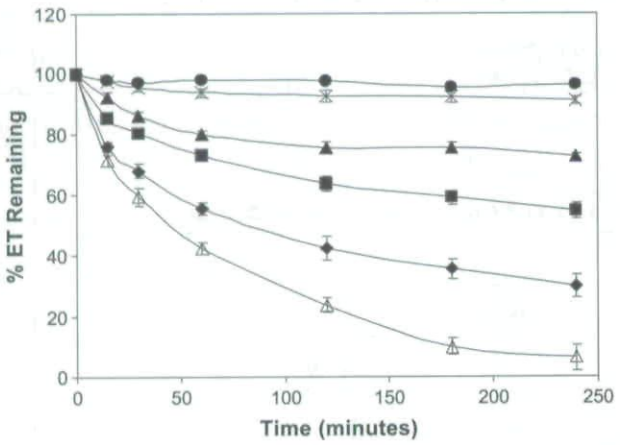

FIGURE 3 Erosion Profiles of DCP Erodible Tablets (n=6). Key: ● 99%; × 90%, ▲ 70%, ■ 50%, ◆ 30%, △ 10% DCP.

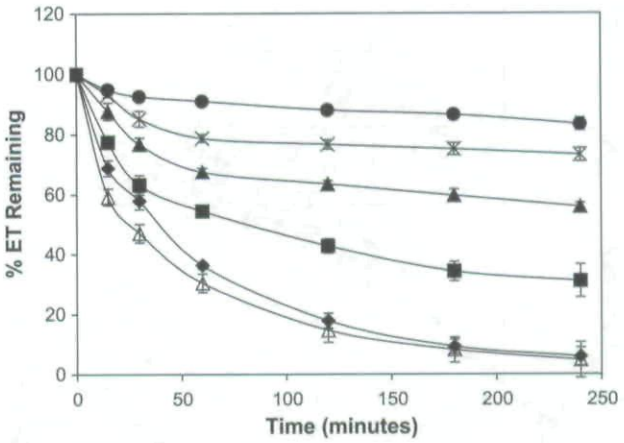

FIGURE 4 Erosion Profiles of CSD Erodible Tablets (n=6). Key: ● 99%; × 90%, ▲ 70%, ■ 50%, ◆ 30%, △ 10% CSD.

Erosion and Release Characteristics of DCP and CSD Erodible Tablets

The erosion profiles of ETs composed of varying ratios of lactose and DCP are shown (Fig. 3). It is clear that the erosion rate decreases as the amount of insoluble excipient increases. A nonlinear relationship is evident between the ET weight and time due to a decrease in surface area of the ET. It has been reported that drug release from tablets composed of degradable polymers exhibiting surface erosion drug release is a zero-order process confined to the surface of the system (Cooney, 1972; Hopfenberg, 1976). Although DCP is not a degradable polymer, erosion occurs by surface detachment and the kinetics are similar to those demonstrated by surface eroding polymers. Furthermore, when only one face of a DCP containing ET is exposed to the

TABLE 2 Dissolution Lag-Times of Time-Delayed Capsule Formulations with Erodible Tablets Containing CSD, DCP or SMCC

ET formulation	Mean $T_{50\%}$ drug release (mins)	S.D.
8% (w/w) DCP	245	33.4
20% (w/w) DCP	393	40.8
8% (w/w) CSD	91	22.1
20% (w/w) CSD	167	34.6
10% (w/w) SMCC	182	32.1

dissolution media, erosion is linear and follows zero-order kinetics (Sutch et al., 2003). This type of erosion has been observed for amoxicillin release from HPMC matrixes by maintaining a constant surface area (Katzhendler et al., 1997).

The underlying trend of erosion is the same as that of DCP for CSD ETs (Fig. 4). Erosion is more rapid, probably as a result of an increased porosity of ETs containing CSD and the less hydrophobic nature of this excipient. This is not surprising as CSD and DCP are both water-insoluble, inorganic salts, used widely as tablet and capsule diluents.

The effect of tablet hardness on the erosion rates of both CSD and DCP ETs revealed that ET hardness did not affect the rate of erosion; this observation was found to be true for all the CSD and DCP containing ETs tested.

Close inspection of the ET surfaces during the study revealed random large pore formation or pronounced "pitting" of the tablet surface for both CSD and DCP containing ETs. This could result in large areas of the ET becoming detached from the main body of the ET (which may still be loosely associated) at the surface, and due to the experimental design this did not affect the overall weight change. This type of large detachment is due to the random mixing with lactose prior to direct compression, resulting in uneven lactose dissolution around the hydrophobic excipients and the potential formation of large erosion pockets at the surface. This problem may result in premature expulsion of the contents of a fully assembled TDC and variable drug release times with CSD and DCP formulations.

Dissolution experiments were performed on TDCs comprising CSD and DCP ETs to test their ability to provide a controlled pulsatile release of propranolol (Table 2). During the experiments, it was observed that in some cases large pieces of the ET surface became detached from the bulk ET, resulting in large variations in the observed drug dissolution times for those TDCs (confirming what had occurred in the erosion study of the CSD and DCP formulations).

Erosion and Release Characteristics of SMCC Erodible Tablets

The erosion mechanism of SMCC ET formulations was different from those observed with CSD and DCP ETs. Rapid erosion follows from rapid expansion and lamination of the ET to expose a large surface area to the dissolution media. With SMCC (10% w/w) the ET completely disintegrated within 30 minutes irrespective of ET hardness (data not shown). However ET hardness did influence the rate of erosion considerably when the SMCC level increased to 30% (w/w) (Table 3), as rate of erosion was found to be proportional to ET hardness. The increase in compression force produced a more compact tablet reducing the rate of water ingress and slowing down subsequent ET lamination. The erosion mechanism is found to be more complex than for ETs comprising CSD and DCP and erosion kinetics could not be assigned without further, more detailed studies.

Dissolution profiles of TDCs with SMCC ETs were also studied. The mean dissolution time of propanalol from a capsule with a 10% (w/w) SMCC ET (weight=120 mg) was 182 (32.1) minutes (Table 2). The complete erosion time of 30 minutes observed for this ET formulation does not correlate with the dissolution time. This is due to the capsule preventing radial ingress of water into the ET so precluding

TABLE 3 The Relationship Between Tablet Crushing Strength and Erosion/Dissolution Characteristics of 30% SMCC ETs

Tablet crushing strength (N)	ET retrieval time (mins)	ET remaining (%)	Mean dissolution time $T_{50\%}$ drug release (mins) [S.D.]
13	15	5	178 [36]
28	30	10	355 [30]
50	60	7.5	670 [108]
63	180	10	[a]
81	240	22	[b]

Note: n=6.
[a]Only 1 capsule released after 600 min.
[b]No release observed after 900 min.

erosion by lamination of the tablet. The influence of ET hardness on the lag-time prior to drug dissolution from the TDC was also studied using 30% (w/w) SMCC ETs with various tablet crushing strengths (Table 3). The dissolution time was found to be directly proportional to ET crushing strength. Although the relative dissolution times follow the same trend as ET erosion (Table 3), the lag-times are far in excess of those predicted from those erosion times. The variability in lag-time from the SMCC containing ETs was considered to be unacceptable. Erosion of SMCC ETs is therefore a poor predictor for the lag-time prior to drug dissolution from assembled TDCs. It is probable that excellent control of tablet crushing strength (not afforded by the E2 single-punch tableting machine used in the study) would be necessary in order for SMCC to be of any value in this controlled-release device and it can be concluded that this excipient is not suitable for the production of ETs for use in an assembled TDC.

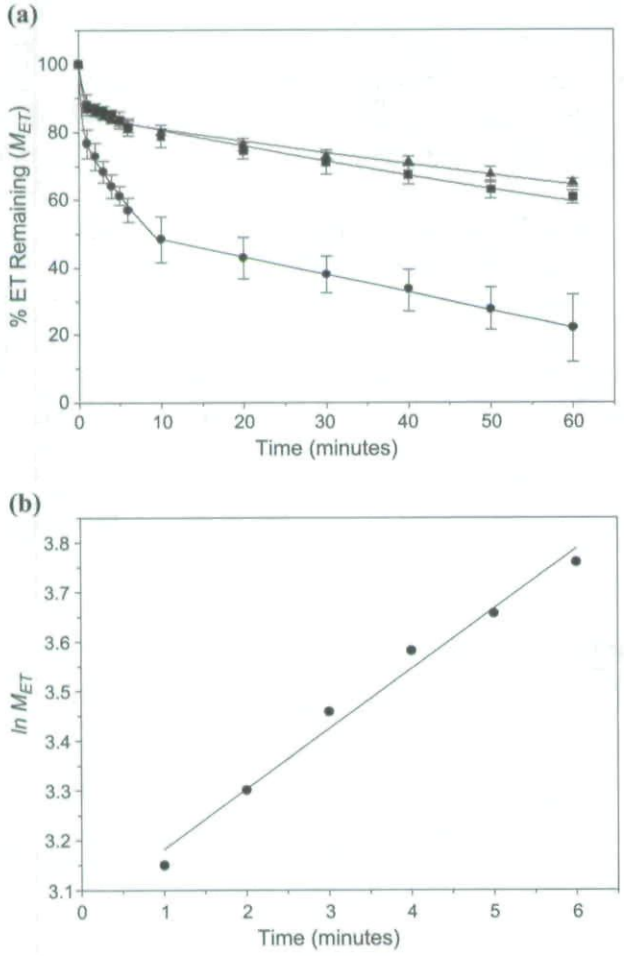

FIGURE 5 Erosion Profiles of HPMC/Lactose Erodible Tablets. (a) ● 15%; ■ 24%; ▲ 30% HPMC; (b) Initial Weight Loss of 15% Direct Compression Formulation (n=6).

Erosion and Release Characteristics HPMC Erodible Tablets

The erosion profiles obtained for ETs containing HPMC (Fig. 5a) show a more complex erosion process than was evident for the CSD and DCP ETs. An initial "burst" period of weight loss occurs with each of the three HPMC formulations investigated, this is followed by a linear, approximately zero-order weight loss period. HPMC erosion indicated a good degree of uniformity over a 60 minute period as indicated by a small standard deviation.

The 15% HPMC formulation shows the most rapid and prolonged initial phase of weight loss, due to rapid dissolution of the lactose. This is analogous to the burst effect associated with sustained release dosage forms that incorporate a high hydrophilic drug loading (Durig et al., 1999; Xu & Sundana, 1995). For a controlled-release hydrophilic matrix tablet containing a hydrophilic drug, the initial stages of hydration involve rapid swelling of the HPMC matrix. High hydrophilic drug loading and low polymer concentrations improve the surface wetting of the HPMC matrix (Wan et al., 1995). In this present study, the hydrophilicity of lactose is likely to improve the surface wetting of the HPMC in a similar way to promote rapid dissolution. Approximately 45% of the total ET weight loss occurs before the onset of the linear period of weight loss in the 15% (w/w) HPMC formulation, compared to a much lower initial 10% weight loss with the 24% and 30% (w/w) HPMC ETs. A simple first-order expression can be used to describe the initial period of erosion [Eq. (2)], and a linear plot may be obtained by taking the natural log [Eq. (3)].

$$M_{ET} = M_0 \exp^{-K_1 t} \tag{2}$$

$$\ln M_{ET} = \ln M_0 - K_1 t \tag{3}$$

The R^2 value (Fig. 5b) of 0.983 indicates a linear relationship associated with first-order kinetics. Thus we can assume the early stages of erosion follow a first-order exponential process, which occurs during the formation of a stable gel layer. It is clear (Fig. 5a) that the order of erosion changes and this is reflected by the onset of a

linear period, indicative of zero-order kinetics. It has previously been shown that zero-order drug release occurs with insoluble drugs from high molecular weight HPMC matrices, due to polymer erosion following the formation of a gel layer (Costa et al., 2001; Fyfe & Blazek-Welsh, 2000). This is also the case with the ET formulations containing K100LV grade HPMC. Zero-order erosion only occurs after a significant gel layer has been formed. Therefore, as the K100LV has a low molecular weight and viscosity, it hydrates and swells to form a gel layer rapidly, and rapid erosion of the polymer is observed as a consequence. While the erosion process is progressing, lactose will diffuse through the gel matrix in accordance with the Higuchi model (Costa et al., 2001). However, the linear relationship observed (Fig. 5b) indicates that lactose diffusion occurs at a slower rate than the erosion of the polymer. Consequently, its contribution to ET mass loss will be minimal. At higher polymer concentrations (24% and 30% [w/w]), a lower initial weight loss is observed as

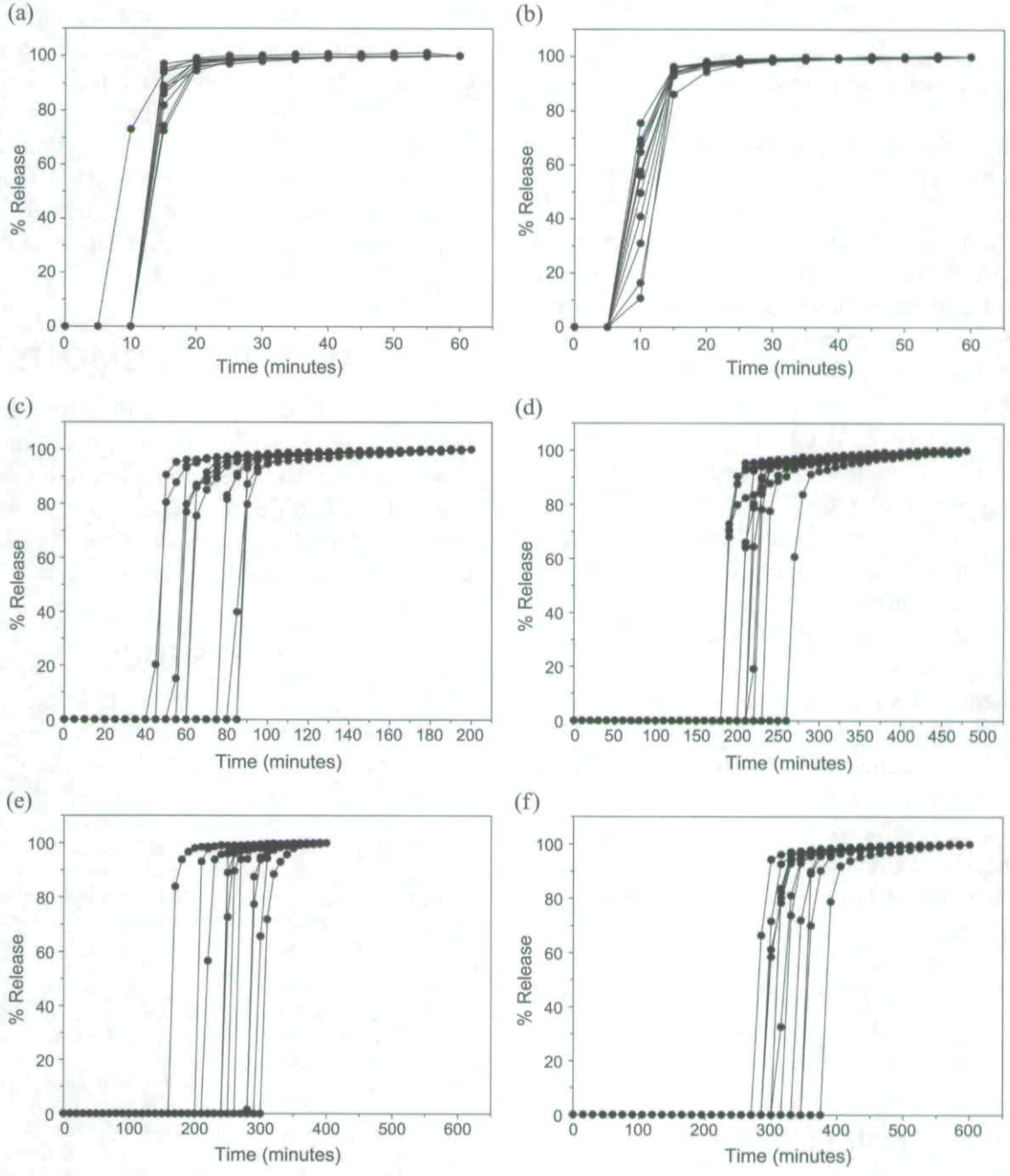

FIGURE 6 Dissolution Profiles of the TDC Fitted with 80 mg ETs: (a) 5% HPMC; (b) 10% HPMC; (c) 15% HPMC; (d) 24% HPMC; (e) 25% HPMC; (f) 30% HPMC.

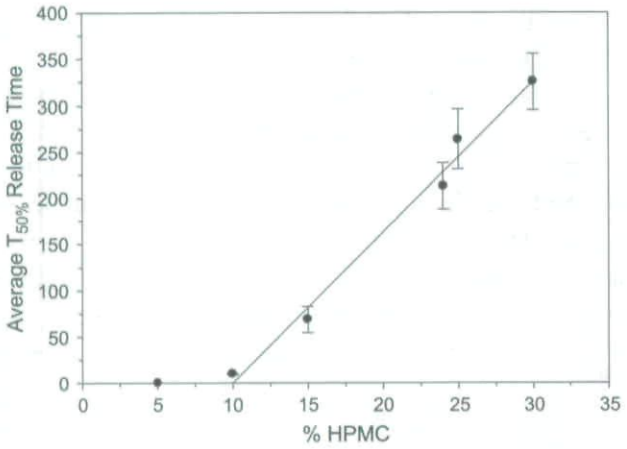

FIGURE 7 The Effect of Varying HPMC Concentration on TDC Lag-time ($T_{50\%}$ Release ± s.d.), $R^2 = 0.988$.

the quantity of HPMC present enables more rapid gel layer formation, which is quickly followed by linear erosion of the ET.

Dissolution profiles of the HPMC ET formulations in assembled TDCs are shown (Fig. 6). Increasing HPMC concentration shows an increase in lag-time and no apparent retardation of drug is seen once release is initiated. It is clear varying the HPMC concentration in the ET can effectively control that lag-time of the TDC. An ET containing HPMC therefore can be formulated to provide a suitable lag-time by reference to the linear plot (Fig. 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 (as previously discussed). This is not readily achieved with elevated concentrations of lactose and low concentration of HPMC.

Overall, incorporation of HPMC containing ETs in the TDC results in a controlled pulsatile release, as indicated by the low range of $T_{50\%}$ drug release times. A correlation is also evident between erosion of the HPMC ETs and the lag-time prior to drug release from the corresponding TDCs. Erosion studies of ETs composed of HPMC and lactose can therefore be used as predictors for the dissolution time obtained from the corresponding TDCs and subsequent drug release is less variable than with other ET compositions.

CONCLUSION

Capsules that were prepared using an organic feed solution exhibited superior integrity and high crushing strengths when exposed to elevated humidity levels compared to those prepared from an aqueous dispersion. This demonstrates their suitability for oral delivery. The use of a pharmaceutically acceptable plasticizer in the organic coating process also confirmed to demonstrate good capsule integrity and subsequent appropriateness for oral delivery when exposed to high humidity and force of compression.

HPMC is the material of choice when preparing tablets to be used as an erodible barrier in the pulsed release capsule device described in this study. The erosion characteristics of ETs containing HPMC may be described by gravimetric loss. The novel, time-delayed capsule device presented in this study may be assembled to include an erodible tablet with a known concentration of HPMC. A variety of suitable drugs for targeted chronopharmaceutical therapy can be incorporated into such a device, ultimately improving drug efficacy and patient compliance, and reducing harmful side effects.

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