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Chronopharmaceutical Drug Delivery from a Pulsatile Capsule Device based on Programmable Erosion

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Abstract

We report the development of a chronopharmaceutical capsule drug delivery system capable of releasing drug after pre-determined time delays.

The drug formulation is sealed inside the insoluble capsule body by an erodible tablet (ET). The release time is determined by ET erosion rate and increases as the content of an insoluble excipient (dibasic calcium phosphate) and of gel-forming excipient (hydroxypropylmethylcellulose; HPMC) increases. The time-delayed release of a model drug (propranolol HCl) was investigated by dissolution testing (USP XXIII paddle method). Both composition and weight of ET influence the time of drug release. Moreover it was found that drug release was controlled by the quantity of HPMC, irrespective of lactose content within the tablet weight range 80–160 mg, when above a threshold concentration of 20% HPMC.

Programmable pulsatile release has been achieved from a capsule device over a 2–12-h period, consistent with the demands of chronotherapeutic drug delivery. The time of drug release can be controlled by manipulation of tablet formulation.

Over the past two decades there has been a growing appreciation of the importance of circadian rhythms on gastrointestinal tract physiology and on disease states, together with the realisation of the significance of time-of-day of drug administration on resultant pharmacokinetic and pharmacodynamic parameters (Lemmer 1989; Smolensky & D'Alonzo 1994; Lamberg 1996). The significance of these day–night variations has not been overlooked from the drug-delivery perspective (Hrushesky et al 1990; Lemmer 1991; Stevens 1998) and pharmaceutical scientists have displayed considerable ingenuity in the development of time-delayed drug-delivery systems to address emerging chronotherapeutic requirements. Technologies studied include tablet (Ishino et al 1992), pellet (Ueda et al 1994) and capsule (Bakhshaee et al 1992) formulations.

Capsule-based delayed-release formulations have been extensively studied by this group. An early prototype formulation comprising a water-permeable body with a moisture-sensitive core (Rashid 1990) generated internal pressure as water diffused through the capsule. This led to expulsion of a plug sealing the drug in the capsule and successfully delivered captopril to the colon (Wilding et al 1992). The Pulsincap device (McNeil et al 1994) comprised a water-insoluble body with drug formulation contained within the capsule and sealed within this region by means of a hydrogel polymer plug. When the Pulsincap formulation was swallowed, the cap dissolved in the gastrointestinal fluids, exposing the hydrogel plug which swelled at a constant rate. At a pre-determined time after ingestion, the swollen plug was ejected and the drug formulation released (Binns et al 1993, 1996; Wilson et al 1997; Hebden et al 1999).

In an attempt to simplify the Pulsincap technology, the complex synthetic hydrogel polymer whose ejection was controlled by a sliding friction-controlled mechanism, has been replaced (Figure 1) by an erodible tablet (Stevens et al 1995a; Ross et al 1999). While the tablet must have a tight fit in the capsule opening to prevent entry of fluid, it does

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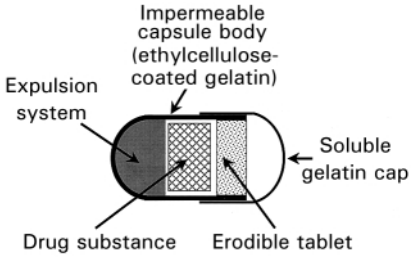

Figure 1. Configuration of the pulsatile capsule formulation.

not move relative to the capsule body during the release process but erodes away from the mouth of the capsule. It does not, therefore, require the same precise dimensional tolerances previously necessary for the sliding hydrogel polymer employed in Pulsincap formulations. Recent studies by Krögel & Bodmeier (1998, 1999) examined time-delayed drug release from polypropylene capsules and tubes sealed with erodible, swellable or enzymatically activated tablets. This report discusses the influence of formulation factors on the erosion of the tablet leading to the time-delayed release of a model drug (propranolol) from a delivery system based on an impermeable, coated gelatin capsule .

Materials and Methods

Materials

Hydroxypropylmethylcellulose (HPMC; Methocel E3, E5, E15, K100LV and K4M) and ethylcellulose was obtained from the Dow Chemical Company, USA. Low-substituted hydroxypropylcellulose (LH-21) was obtained from Shin-Etsu Chemical Company, Japan. Propranolol HCl and all tablet excipients (magnesium stearate, dibasic calcium phosphate, cross-linked carboxymethycellulose (Ac-Di-Sol) and lactose) were obtained as gifts from Pfizer Central Research, Sandwich, UK. Gelatin capsules (size 0) manufactured by Capsugel were obtained from Pfizer. Dibutyl phthalate, acetone and propan-2-ol were obtained from Sigma-Aldrich, Gillingham, UK.

Preparation of erodible tablets

Excipients were used as received and weighed to give the desired composition. Each formulation contained magnesium stearate (1%) as lubricant. Mixing was carried out in a Turbula mixer (Glen Creston, England) for 30 min. Tablets were directly compressed at different weights and at a range of diameters (6·5, 6·6, 6·75, 6·9 and 7·0 mm), using a single-punch tablet press (Model E2, Manesty, Liverpool, England).

Characterisation of erodible tablets

Compressed erodible tablets (ET) were fully characterised for weight, diameter, thickness and hardness (Erweka TGB 30 tablet tester, Copley Instruments, Nottingham, England).

Determination of erosion rate

ET erosion rates were determined by placing 6 tablets in a USP dissolution bath modified by being fitted with a suspended stainless steel mesh grid of diameter approximating to the vessel diameter and which rested at the start of the curvature at the bottom of the vessel. Weighed tablets were placed on the grid and immersed in 500 mL water at 37°C, paddle speed 50 rev min^{-1}. The grid was removed at pre-determined times and oven dried. Tablet residues were re-weighed and percentage erosion calculated.

Preparation of propranolol tablets

Tablets containing propranolol HCl (45%), lactose (53%), Ac-Di-Sol (1%) and magnesium stearate (1%) were prepared by blending the drug and excipients in a Turbula mixer and compressing on a Manesty E2 single-punch tablet press at a diameter 5 mm and weight of 56 mg ($\equiv$ 25 mg propranolol).

Capsule coating

Size 0 capsule bodies (separated from the caps) were coated in a Strea-1 Aerocoater with ethyl cellulose (95%) plasticised with dibutyl phthalate (5%) as a 3% solution in a 50 : 50 v/v mixture of acetone and propan-2-ol.

Assembly of capsule delivery system

LH-21 (200 mg) was weighed into the previously coated capsule body and lightly compacted using a rod. A propranolol tablet was placed onto the LH-21 layer and ET inserted into the mouth of the capsule and positioned flush with the end of the coated body. A soluble gelatin cap was optionally placed over the end of the capsule.

Dissolution studies

Delayed release of propranolol was determined (UV spectrometry) by dissolution testing (USP XXIII paddle method; 50 rev min^{-1}) using 500 mL distilled water at 37°C. A manual sampling method (Erweka dissolution apparatus) or an automated technique (Caleva automated apparatus) was used. In certain studies, the dissolution medium (0·1 M

HCl and pH 7·4 phosphatebuffered saline; PBS) and stirring rate (25 and 100 rev min^{-1}) was varied.

Results and Discussion

The objective of this study was to investigate the potential of ET to replace the swelling hydrogel polymer employed in the earlier Pulsincap technology. For this mechanism to work effectively it must be ensured that ET forms an effective seal in the mouth of the capsule, keeping the contents dry until ET erosion is complete. It is also essential to ensure that water cannot penetrate through the capsule wall otherwise any water that migrates from the exterior may cause swelling of the contents, which may lead to premature expulsion of ET before the erosion process is complete. When configured optimally, following complete dissolution and erosion of ET, fluid will then enter the capsule and make contact with the high-swelling expulsion excipient at the base of the capsule. This will swell rapidly and, by this active mechanism, expel the propranolol tablet from the capsule into the gastrointestinal-tract lumen.

To identify the most appropriate ET formulation with respect to erosion rates, tablets containing lactose together with a second excipient (either dibasic calcium phosphate or HPMC) were produced (7 mm diameter, 250 mg weight) at a range of hardness values (4–10 kp). Each ET contained magnesium stearate (1%). The results of the erosion studies show that rates of erosion decreased as the content of the insoluble dibasic calcium phosphate excipient increased (Figure 2). The erosion of HPMC formulations is more complex. For the low-viscosity E grades, the rate of erosion is similar to that of lactose alone; however, where higher-viscosity grades of HPMC with greater gel-forming potential were used, the rates of erosion decreased (Figure 3). The erosion profiles tended towards first order, with an initial rapid rate of erosion followed by a slower phase and were consistent with reports of first-order swelling kinetics of hydrophilic-matrix tablets (Wan et al 1993). This was particularly prominent with formulations based on HPMC E grades. However, interestingly, the K100LV grade ET formulations demonstrated a more linear erosion profile. With all the formulations it was observed that tablet hardness did not influence erosion rate within the ranges studied (data not shown).

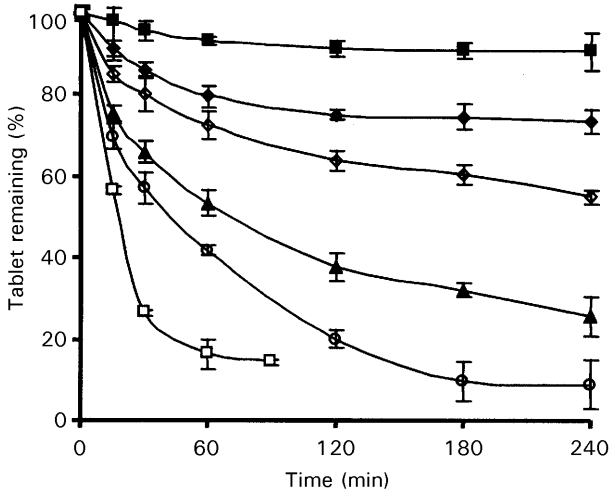

Figure 2. Erosion profiles of lactose–dibasic calcium phosphate tablet formulations with unrestricted surface and ratial exposure to water: ■, lactose-dibasic calcium phosphate 9%/90%; ◆, 29%/70%; ◇, 49%/50%; ▲, 69%/30%; ○, 89%/10%; □, lactose 99%. Values are expressed as mean ± s.d., n = 6.

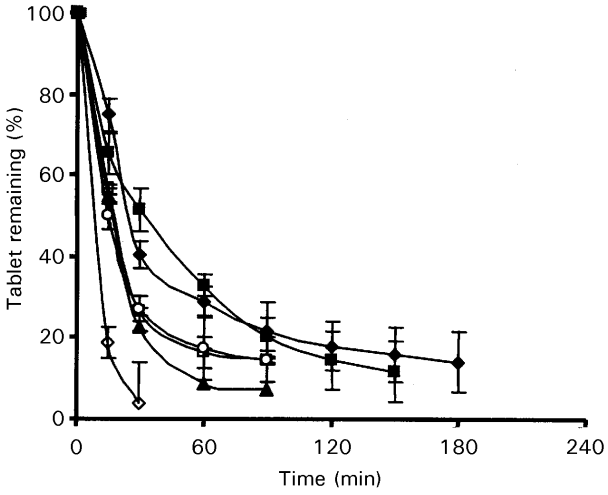

Figure 3. Erosion profiles of lactose–HPMC tablet formulations with unrestricted surface and radial exposure to water: ■, lactose–HPMC K100LV 84%/15%; ◆, lactose-HPMC K4M 70%/29%; ◇, lactose-HPMC E15 LV 84%/15%; ▲, lactose-HPMC E3 89%/10%; ○, lactose-HPMC E5 89%/10%; □, lactose 99%. Values are expressed as mean ± s.d., n = 6.

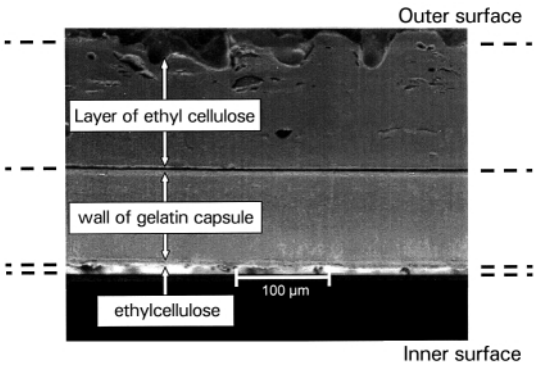

Figure 4. Freeze fractured SEM of section through coated capsule showing outer ethyl cellulose layer (100 μm) and thin inner layer of coating (5 μm).

Fluid bed coating technology using organic solvent coating solution afforded a uniform ethylcellulose coating on the outside of the gelatin capsule body as well as a thin coat on the inner surface of the capsule. At the preferred outer-layer coating thickness of 100 μm, a thin intact film (estimated thickness 5 μm using scanning electron microscopy) was deposited on the inner capsule surface (Figure 4). Of particular importance was the fact that the area around the mouth of the capsule body was completely coated. The 100-μm coating was found to be impermeable during at least a 12-h immersion period. Such coated gelatin capsules were considered to be more pharmaceutically acceptable than polypropylene capsules and tubes used earlier (Krögel & Bodmeier 1998, 1999). With the level of coating discussed above, it was found that an ET diameter of 6·75 mm formed a tight fit and these were used for subsequent studies with assembled capsule formulations.

A small number of studies were performed using lactose–dibasic calcium phosphate formulations, and release of propranolol from ET (weight = 162 mg) containing 8% dibasic calcium phosphate is shown in Figure 5. Discrete insoluble particles were observed to detach from the surfaces of ET during the dissolution process as the surrounding soluble lactose support dissolved. At the end of the process a few small discrete holes in ET were visible, allowing entry of water which, in turn, provoked expansion of the expulsion system and ejection of the drug tablets and any residual portions of non-dispersed ET. However, in some instances the close proximity of the holes led to collapse of a large area of the tablet, resulting in irreproducible erosion.

The majority of assembled capsule studies were therefore performed with ET formulations based on HPMC. Furthermore, ET swelling during the dissolution process was thought likely to enhance the seal between ET and the capsule wall and so assist in maintaining the dry integrity of the capsule contents during the entire dissolution–erosion process. ET based on K100LV were selected for particular study in fully assembled capsule devices because they demonstrated the most linear properties during the tablet erosion studies.

Visual observation during the dissolution process revealed the detachment of gelled plumes from the swollen ET surface. Eventually, at a point at which only the smallest of gel layers remained, a small hole appeared in ET with the development of an air bubble that then detached from the surface. Water ingress then followed leading to expansion of the expulsion system and ejection of the drug, as discussed above. The release profiles were sharp in nature demonstrating that the expulsion system selected showed rapid swelling following ingress of fluid, affording complete and rapid ejection of the propranolol tablet formulation. Low-substituted hydroxypropylcellulose has previously been shown to have excellent expansion potential for applications such as bursting pellets (Ueda et al 1994) and to enable complete drug expulsion from Pulsincap formulations (Stevens et al 1995b) and was successfully employed as an expulsion system in these studies. This overcame some of the disadvantages of premature expulsion seen with effervescent fills discussed by Krögel & Bodmeier (1998).

Time of release could be controlled by modifying the composition of HPMC-based ET or by chan-

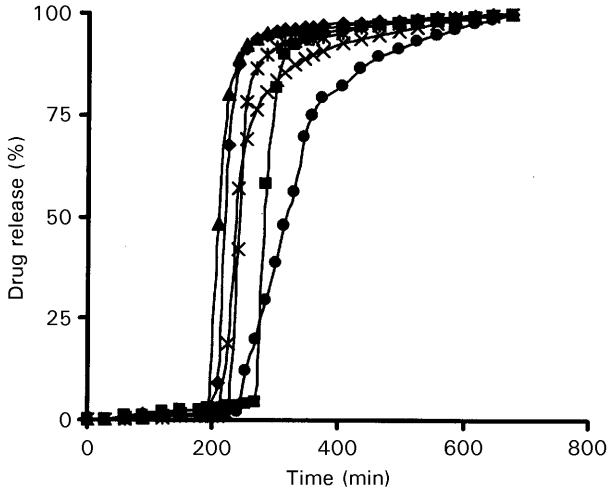

Figure 5. Dissolution profile of drug release from individual capsules where the lag time prior to drug release is controlled by lactose-dibasic calcium phosphate 91%/8% formulation (tablet weight 162 mg).

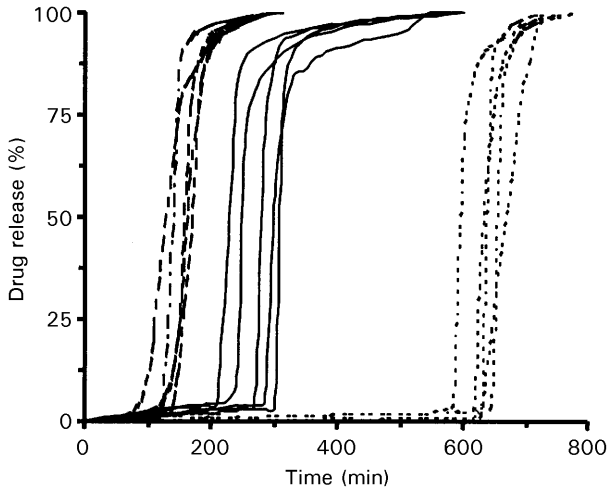

Figure 6. The influence of erodible tablet weight and composition on the lagtime prior to dissolution of lactose–HPMC K100LV formulations: -·-·-, lactose-HPMC 91%/8%, weight 160 mg; –, 84%/15%, weight 120 mg; ···, 69%/30%, weight 130 mg (each curve represents a single capsule).

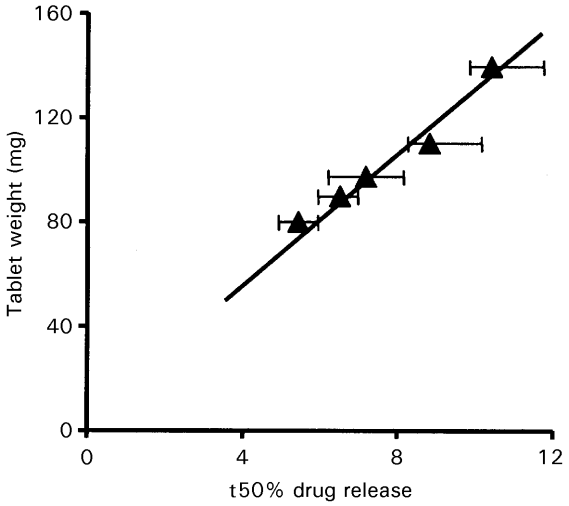

Figure 7. Relationship between t50% drug release from the pulsatile capsule and erodible tablet weight for lactose-HPMC K100LV 74%/25% formulation, (▲, mean value and range; n = 5 or 6).

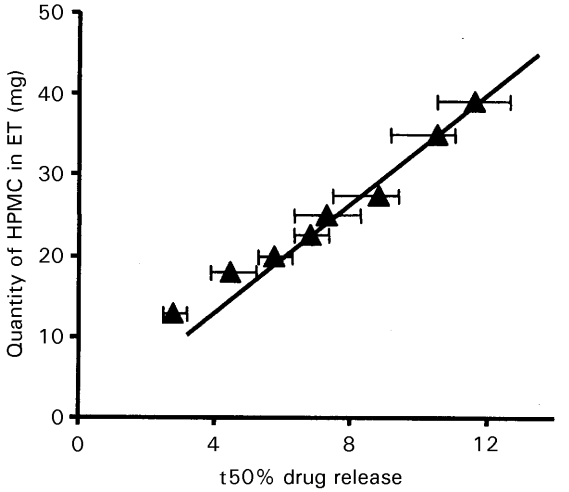

Figure 8. Relationship between t50% drug release from the pulsatile capsule and HPMC quantity in the erodible tablet for lactose–HPMC formulations ▲, mean value and range; n = 5 or 6.

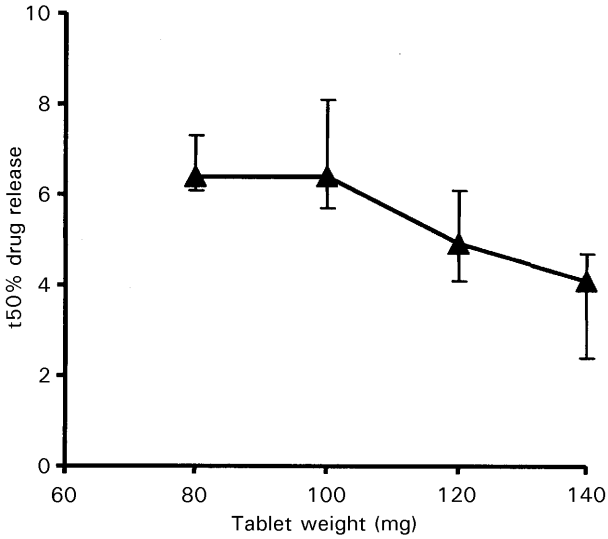

Figure 9. The influence that erodible tablet formulations containing a constant quantity of HPMC and an increasing level of lactose on t50% drug release from the pulsatile capsule, (▲, mean value and range; n = 5 or 6).

ging the weight (tablet thickness) of a given formulation. Dissolution studies on different composition lactose–K100LV ET formulations (Figure 6), showed that a 160-mg tablet containing 8% K100LV released after 150 min, whereas a 120-mg ET containing 15% K100LV released after 270 min and a 130-mg formulation containing a high-level (30%) K100LV demonstrated pulsatile release after 630 min.

For constant ET composition containing 25% K100LV, release times were found to be dependent on tablet weight (over the 80–140 mg range studied) and a near linear relationship between release time and ET weight was observed (over a 5–11-h period) (Figure 7). This confirmed previous findings with lactose tablets (Stevens et al 1995a) and with Gelucire moulded tablets (Krögel & Bodmeier 1998).

For the various ET studied (weight range 80–160 mg), containing various ratios of lactose–K100LV (HPMC 8–35%), a near linear relationship was observed between pulse-time and quantity of K100LV (mg) contained in ET, irrespective of tablet weight and lactose content (Figure 8). The dominant role of HPMC content was further investigated when ET containing 24 mg K100LV were compressed at varying weights (80, 100, 120 and 140 mg) and release times determined (Figure 9). Over the tablet weight range 80–140 mg, release was less consistent (4·25–6·5 h) than expected. It is suggested that as the HPMC percentage was diluted by lactose, release times accelerated due to less effective formation of the gel-matrix structure.

Many analogies can be drawn from previous reports of the mechanisms of drug release from HPMC-matrix tablets and the observed performance of HPMC ET formulations in our studies. It has been demonstrated by Gao et al (1996) that lactose and drug release from HPMC-matrix tablets were superimposed, indicating a diffusional release mechanism. It can be concluded that following lactose dissolution from ET, HPMC erosion then takes place by the established mechanism of detachment of polymer chains from the gel-matrix surface as proposed by Reynolds et al (1998). This is independent of the original lactose content of the ET formulations when above a threshold concentration of 20% HPMC. Below this value the gel

Table 1. Effect of dissolution media and the paddle speed on the t50% drug dissolution from the pulsatile capsule.

Formulation	Condition	Mean t50% dissolution (min)
Lactose–HPMC 74%/25%, 80 mg	25 rev min^{-1}, distilled water	447 (412–484)
Lactose–HPMC 74%/25%, 80 mg	50 rev min^{-1}, distilled water	330 (301–361)
Lactose–HPMC 74%/25%, 80 mg	100 rev min^{-1}, distilled water	221 (174–259)
Lactose–HPMC 74%/25%, 80 mg	50 rev min^{-1}, 0·1 M HCl	242 (145–259)
Lactose–HPMC 74%/25%, 80 mg	50 rev min^{-1}, PBS pH 7·4	412 (370–457)
Lactose–dibasic calcium phosphate 79%/20%, 120 mg	25 rev min^{-1}, distilled water	332 (308–398)
Lactose–dibasic calcium phosphate 79%/20%, 120 mg	50 rev min^{-1}, distilled water	280 (238–319)
Lactose–dibasic calcium phosphate 79%/20%, 120 mg	100 rev min^{-1}, distilled water	222 (166–272)

Range given in parentheses.

structure was inadequate and dispersed more rapidly. Studies of drug release from HPMC-matrix tablets have previously shown that drug release occurs mainly by Fickian diffusion and polymer relaxation (Vigoreaux & Ghaly 1994) and medium infiltration rate (Tahara et al 1995). As in our studies, these latter authors noted that low-viscosity HPMC grades were most desirable for surface erosion of the tablet matrix. It can be expected that similar general mechanisms control the rate of lactose dissolution from the ET formulations as well as the erosion characteristics of those tablets.

Although HPMC-based ET formulations show both radial and axial swelling during the tablet erosion studies (Figure 3), due to the configuration of ET positioned within the impermeable capsule body, swelling can only occur in an axial direction during the capsule dissolution studies. In similarly constrained HPMC partially coated matrix tablets, Bettini et al (1994) noted that the impermeable coating modified the swelling kinetics and as a consequence, the systems became more liable to erosion. It can be proposed that a similar mechanism contributes to the linearity of ET release times shown in Figure 8.

The effect of paddle speed and dissolution medium would be expected to exert an influence on erosion from HPMC-based ET surfaces during dissolution studies and this was shown to be the case (Table 1), with an HPMC formulation containing 25% K100LV being more sensitive to agitation rate than a formulation containing 20% dibasic calcium phosphate. The effect of acidic and alkaline pH media on dissolution rate is also shown in Table 1, where more rapid release was observed in acidic dissolution medium at pH 1·1 and slower release in pH 7·4 phosphate-buffered saline than when water was used as the medium. The effect in acidic medium is likely to be due to the presence of the chloride anion rather than to pH (Ford et al 1985; Mitchell et al 1991). Whether such effects will have an influence on in-vivo performance remains to be determined and is the subject of an ongoing investigation. The in-vivo erosion of HPMC-matrix tablets has been studied by Ödman et al (1997) and Abrahamsson et al (1998, 1999). These authors concluded that factors such as pH and ionic strength had minor effects and that erosion and in-vivo dissolution were practically constant and had no tendency to be affected by the location of the tablet in the gastrointestinal tract.

In conclusion, pulsatile drug release over a period of 2–12 h, consistent with the requirements for chronopharmaceutical drug delivery, was achieved from a coated gelatin capsule where drug was sealed within the capsule body by means of an erodible tablet based on either lactose–dibasic calcium phosphate or lactose–HPMC formulations. Classical tablet formulation parameters could be manipulated to modulate the drug release time in accordance with chronotherapeutic objectives.

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