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RESEARCH PAPER

Investigation of Cyclobenzaprine Hydrochloride Release from Oral Osmotic Delivery Systems Containing a Water-Swellable Polymer

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ABSTRACT

Oral osmotic delivery systems containing polyethylene oxide (PEO, a water-swellable polymer) were designed and the release of cyclobenzaprine hydrochloride (model drug) from the devices was investigated. The systems consisted of model drug, mannitol (osmotic agent), and increasing amounts of PEO surrounded by a semipermeable membrane drilled with a delivery orifice. There was a decrease in drug release rate with PEO in the core. This may be due to solubility-modulating properties of the polymer. Visual inspection of the devices with PEO showed significant swelling during dissolution testing. Swelling (internal pressure) may influence water imbibition rate into the core and subsequently drug release rate. The release rates were a function of membrane thickness. The release rates were independent of orifice size (range of 150–510 μm diameter) and hydrodynamic conditions for the devices. This would be advantageous in the delivery of drugs in man.

Key Words: *Osmotic delivery system; Cyclobenzaprine hydrochloride; Water-swellable polymer; Dissolution*

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INTRODUCTION

Over the past 40 years, with the recognition of the therapeutic advantages of controlled drug delivery systems, greater attention has been dedicated to development of controlled-release delivery systems. Among various technologies that have been used in the development of controlled drug delivery systems, osmotic pumps hold an important position (1–4). These are devices that use osmotic pressure as an energy source to deliver drug at predetermined zero-order rates for extended periods of time. Though different types of oral osmotic systems have been reported in the literature (5), the single most important osmotic delivery system is Theeuwes' elementary osmotic pump (6). In this system, the osmotic core is surrounded by a semipermeable membrane drilled with a drug delivery orifice. Once this system comes in contact with the gastrointestinal fluids, the osmotically driven water enters the system through the semipermeable membrane, dissolves the soluble agents, and exits through the delivery orifice. Because these systems use osmotic pressure for the controlled delivery of the active compound(s), delivery rates are expected to be independent of gastrointestinal condition (6).

The rate of drug release from osmotic pumps is dependent on the total solubility and the osmotic pressure of the core. Therefore, poorly water-soluble drugs do not create sufficient osmotic pressure and are delivered at low rates. To overcome this problem, other types of osmotic pumps for poorly water-soluble drug have been designed (7,8). In contrast, highly water-soluble drugs may create considerable osmotic pressures and may release the active drug at undesirable high rates. In some cases, this problem may be solved by addition of a solubility-modulating agent to the core (9–11). However, this approach is not satisfactory for cases where large amounts of the modulator are necessary. In addition, rapid depletion of the modulator from the system will cause the device to release the drug at non-uniform rates.

Polyethylene oxide (PEO) is a non-ionic homopolymer of ethylene oxide and is available in several molecular weights. These polymers are water-swellable/soluble, and because of their low toxicity have been widely used in diverse industrial applications.

In pharmaceutical preparations, they are used as tablet binder and viscosity-modifying agent (12). Their application in design and manufacture of controlled-release devices is also available in recent publications. Zero-order drug release kinetics are reported for PEO-based simple and triple-layer tablets (13,14). Their excellent flow and direct compressibility (15), along with their singular swelling and erosion properties, have made these polymers a prime excipient candidate for design/research and development of new controlled-release delivery systems.

The objectives of this study were to investigate the release of cyclobenzaprine hydrochloride (model drug) from osmotic tablets containing a water-swellable polymer, PEO. Mannitol was used as the osmotic agent. In addition, experiments were conducted to investigate the effects of membrane thickness, orifice size, and hydrodynamic conditions on drug release from these osmotic pumps.

EXPERIMENTAL

Materials

Cyclobenzaprine hydrochloride was purchased from Sigma (St. Louis, MO). Mannitol (Pearlitol®) was supplied by Roquette America, Inc. (Keokuk, IA). Polyethylene oxide (WSRN-1105, molecular weight 900,000) was received as a gift from Union Carbide Corporation (Danbury, CT). Magnesium stearate was obtained from Mallinckrodt, Inc. (Hazelwood, MO). Two grades of cellulose acetate (394-60S and 320-S) were obtained from FMC (Newark, DE). Polyethylene glycol (molecular weight 400) was purchased from Sigma (St. Louis, MO). Acetone and methanol, both HPLC grades, were obtained from Fisher Scientific (Pittsburgh, PA). All materials were used as received.

Preparation of Core Tablets

Core tablets were prepared by direct compression of a dry blend of cyclobenzaprine hydrochloride (25 mg, model drug), varying amounts of mannitol (osmotic agent), polyethylene oxide (water-swellable polymer at 0, 5, and 15% w/w), and magnesium stearate (lubricant) using an instrumented Manesty F-press equipped with an 11.11-mm diameter round, plain, and standard concave tooling. The core compositions are summarized in Table 1.

Table 1

Core Tablet Compositions

Ingredients (mg/ta)	Device I	Device II	Device III
Cyclobenzaprine hydrochloride	25	25	25
Polyethylene oxide (MW = 900,000)	—	30	90
Mannitol	569	539	479
Magnesium stearate	6	6	6
Total core weight	600	600	600

Coating of the Tablets

Tablets were coated using a film-coating solution prepared by dissolving 120 g of cellulose acetate 394-60S, 40 g of cellulose acetate 320S, and 40 g of polyethylene glycol 400 in a binary solvent mixture of acetone (3000 g) and methanol (1000 g). The water-insoluble components of the membrane, the cellulose acetates, were water-permeable polymers. Polyethylene glycol 400 was selected as a plasticizer. The core tablets were coated to target film thicknesses of 110, 200, and 340 μm using a fluidized bed (Glatt column with Wurster insert) spray-coating technique. Various tablet coats were examined with an environmental scanning electron micrograph, Electro Scan 2010 (FEI Company, Hillsboro, OR). The films appeared uniform without any detectable defects. Electron micrographs of a tablet cross-section and film surface are shown in Figs. 1 and 2, respectively.

Creation of Delivery Orifice

A mechanical microdrill (Servo Product, Co., Pasadena, CA), equipped with cobalt microdrill (Guhring, Germany) was used to create the orifices for the delivery of the drug. To investigate the effects of the orifice size on the release of the active, orifices of 150 and 510 μm diameter were drilled on the tablets. In all cases, the shape and diameter of the created orifice was visually inspected and measured using a 50× microscope.

Dissolution Testing

Dissolution testing was carried out using USP dissolution method 2 (Vankel Industries, USA) with 900 mL deionized water at 37°C and 75 rpm paddle speed. To investigate the effects of hydrodynamics on drug release, different paddle speeds were used. Cyclobenzaprine hydrochloride release from the tablets was measured spectrophotometrically at 290 nm wavelength.

Experiments were performed to study the effect of (a) core polymer content, (b) coating thickness, (c) orifice size, and (d) hydrodynamic conditions on drug release from the tablets.

GENERAL DISCUSSION

The mechanisms governing the release of drug from an elementary osmotic tablet can be summarized as the following.

1. Osmotic imbibition of water into the core tablet. When the osmotic pump is placed in gastrointestinal fluids, water imbibition through the semipermeable membrane occurs at controlled rates and is dependent on the osmotic pressure difference and the hydraulic permeability of the membrane.
2. Dissolution and release of drug through the delivery orifice. As water penetrates into the core, dissolving the drug, further water uptake forces a saturated drug solution flow through the orifice.
3. Decline and eventually end of drug release from the device. As the osmotic agent(s) get exhausted, osmotic water imbibition declines and eventually approaches zero. Once this stage is reached, drug release into the dissolution medium only occurs by a slow diffusion process through the membrane and the delivery orifice.

The drug release (dm/dt) from the elementary osmotic tablets is described by Eq. (1) (6):

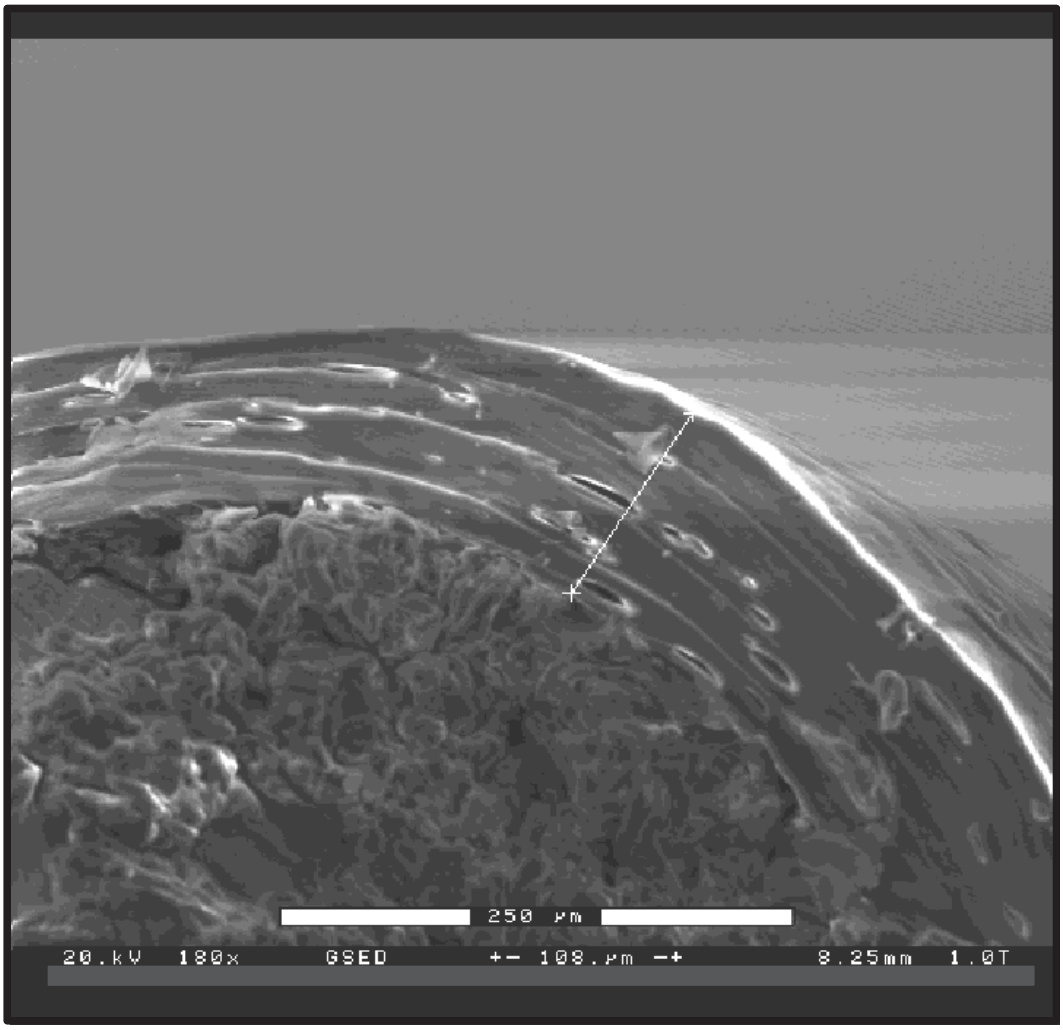

Figure 1. Scanning electron micrograph of the film coat at 180× magnification. The film appears uniform and non-porous.

$$\left(\frac{dm}{dt}\right) = \frac{A}{h}\sigma L_p(\Delta\pi - p)C + \frac{PAC}{h} \quad (1)$$

where A is the tablet surface area, h is the membrane thickness, C is the drug concentration, $\Delta\pi$ is the osmotic pressure difference across the film, σL_p is the hydraulic permeability of the membrane, and P is the drug permeability coefficient of the membrane. The term p is the hydrostatic pressure and can be neglected for tablets with rigid walls due to its small value compared to $\Delta\pi$.

Because of osmotic action, drug release from osmotic pumps is independent of agitation rate and pH of the dissolution medium (6). Also of note for osmotic pumps is the lag time observed prior to drug release. This is the time for water to diffuse across the semipermeable membrane, moisten and dissolve the drug, and begin the drug release process.

RESULTS AND DISCUSSION

The devices in Table 1 have the common features of a water-soluble core surrounded by a semipermeable membrane with a 150-µm diameter drug delivery orifice. However, they differ in the amount of water-swellable polymer PEO. Devices I, II, and III have 0, 5, and 15% w/w of PEO in the core composition, respectively. These formulations were designed to investigate the effect of the water-

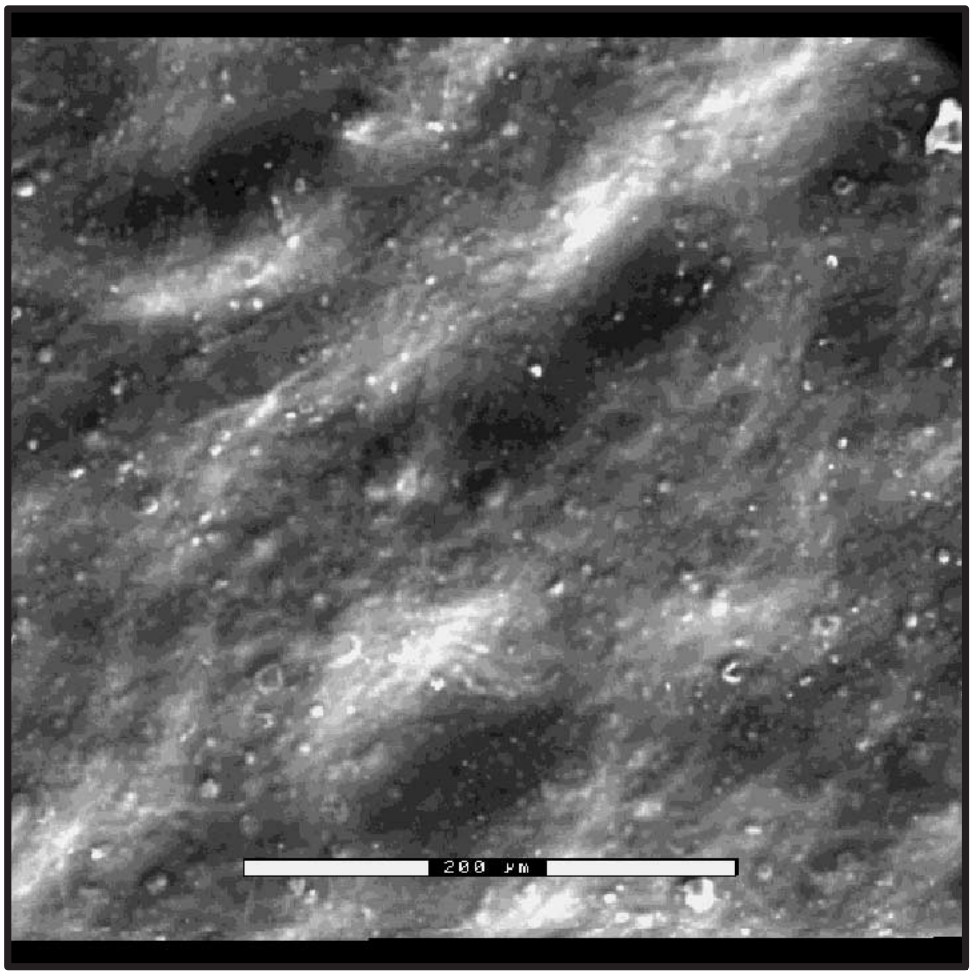

Figure 2. Scanning electron micrograph from film surface at 180 × magnification.

swellable polymer on drug release from osmotic pumps.

Cyclobenzaprine hydrochloride was chosen as model drug. This compound has a reported aqueous solubility of 664 mg/mL at 37°C (1). Mannitol (Pearlitol, a direct compression grade) was chosen as the osmotic agent. The aqueous solubility of this compound is reported as 1 g in approximately 5.5 mL water (12).

The release of cyclobenzaprine hydrochloride from devices I, II, and III, coated to 200 µm target film thickness with 150-µm diameter drug delivery orifice into deionized water, is shown in Fig. 3. For all devices, there was a lag time followed by a longer zero-order release period. As described in the previous section, this is characteristic of osmotic pumps. The devices with 0, 5, and 15% w/w polymer released 63±2.2, 39±2.3, and 36±3.1% drug, respectively, at 10 hr [with no statistically significant difference ($p < .05$) between devices II and III]. With a total load of 25 mg cyclobenzaprine hydrochloride in core tablets, it is reasonable to assume that the drug release is controlled by the osmotic pressure gradient created by the major component mannitol.

The release rates for devices I, II, and III were calculated from a linear regression fit of all points in the zero-order portion of the release profiles ($r^2 > 0.99$) and the calculated drug release rates were 1.90, 0.82, and 0.81 mg drug/hr, respectively. There was a decrease in drug release rates with polymer content. However, there was no statistically significant difference ($p < .05$) between release rates for devices II and III.

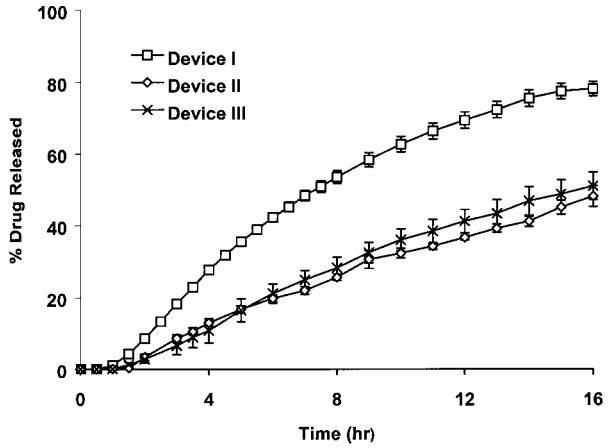

Figure 3. Cyclobenzaprine hydrochloride release from devices coated to a target thickness of 200 μm.

The rate of drug release for osmotic delivery systems is controlled through (1) the total solubility and osmotic pressure of the core, (2) the hydraulic permeability of the membrane, (3) the thickness and surface area of the membrane, and (4) the internal pressure.

The decrease in drug release rate with swelling polymer gives an indication of the solubility-modulating properties of the polymer in the core. A similar trend was observed in a study using potassium chloride and PEO (unpublished data). In that study, independent measurements of core potassium chloride concentrations showed a decrease in salt concentrations with increasing amount of core PEO. The decrease in the concentration of potassium chloride (model drug and osmotic agent) reduced the osmotic pressure gradient across the membrane, resulting in a depressed potassium chloride release rate.

It appears that addition of PEO to mannitol/cyclobenzaprine hydrochloride also behaves as a solubility-modulating agent, leading to a decrease in the osmotic pressure gradient and drug release rate from the osmotic pumps. At the same time, addition of PEO to core tablets caused extensive swelling of the devices during dissolution testing. For device I (no PEO), visual inspection showed no significant volume change during dissolution testing. This suggests that during the zero-order release period, the rate of water inflow into the device was similar to the rate of water outflow. For this device, the internal pressure (p) inside the core was negligible and can be ignored. However, significant tablet swelling (internal pressure) was observed for devices II and III during dissolution testing. Swelling may create significant internal pressure within the device, leading to a reduced imbibition and drug release rate.

In addition a swelling device is a complex system and the physical changes that the device undergoes during swelling must be considered for explanation of drug release. For example, for a swelling device, as the surface area is increasing, the membrane thickness is decreasing, both encouraging a faster water imbibition into the tablet. Swelling may also cause significant changes to the internal structure of the membrane, thus changing the membrane permeability characteristics.

In general, the physical changes that a swelling device undergoes during release testing are of significance in explaining the drug release. However, for these devices, the osmotic pressure gradient difference remains the dominant factor controlling the drug release rate. That is the reason behind decreased drug release rates for devices II and III compared to device I. However, the similarity between release rates for swelling devices II and III may be explained by the complex interactions among all the factors.

Influence of Membrane Thickness on Drug Release

The dependence of cyclobenzaprine hydrochloride release on coating thickness was also investigated. For these experiments, devices I, II, and III coated to target thicknesses of 110 and 340 μm (with 150-μm diameter delivery orifice) were manufactured. Dissolution testing on these devices was performed using deionized water at 37°C and 75 rpm paddle speed.

The release profiles for devices I, II, and III with 110 μm film thickness are given in Fig. 4. Again, all release profiles showed a lag time, followed by a longer period of zero-order drug release. The release rates were calculated from the linear portion of the profiles ($r^2 > 0.99$) and for devices I, II, and III were 3.38, 1.15, and 1.15 mg drug/hr, respectively.

The release profiles for devices I, II, and III coated to a target thickness of 340 μm are shown in Fig. 5, and present similar trends as shown previously for devices with lower membrane thickness. Due to the larger membrane thickness for these devices, longer lag times are observed. The steady-

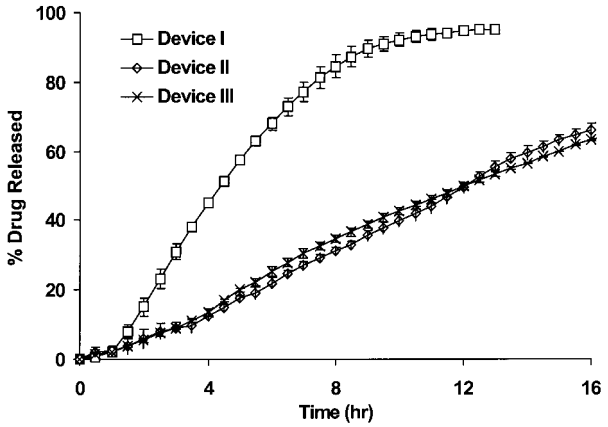

Figure 4. Cyclobenzaprine hydrochloride release from devices coated to a target thickness of 110 μm.

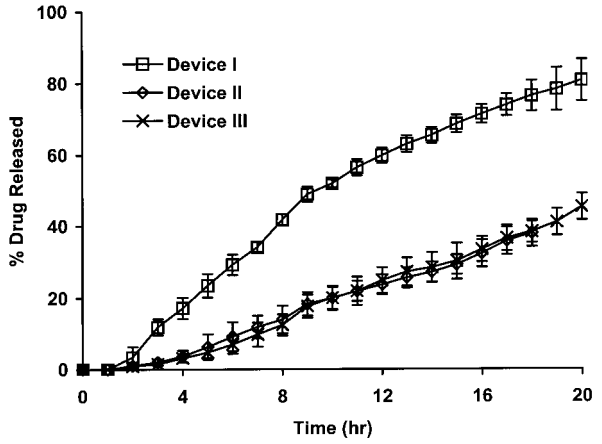

Figure 5. Cyclobenzaprine hydrochloride release from devices coated to a target thickness of 340 μm.

Table 2

Cyclobenzaprine Hydrochloride Release Rates from Devices Coated to Different Thicknesses

Device	% PEO (w/w)	Film Thickness (μm)	Release Rate (mg/hr)
I	0	110	3.38
I	0	200	1.90
I	0	340	1.28
II	5	110	1.17
II	5	200	0.82
II	5	340	0.63
III	15	110	1.15
III	15	200	0.81
III	15	340	0.63

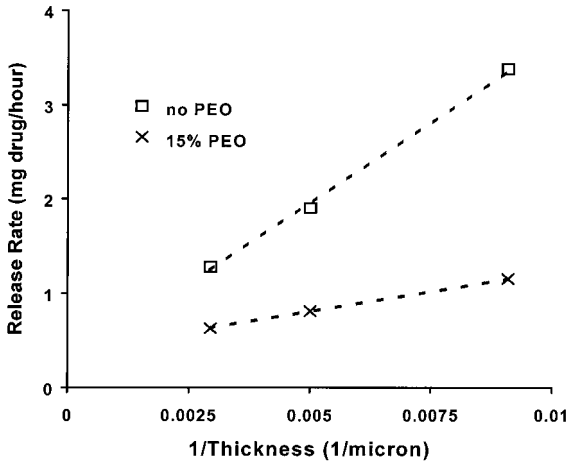

Figure 6. Cyclobenzaprine hydrochloride release rate from devices I and III coated to various thicknesses.

state release rates calculated from the linear portions of the profiles ($r^2 > 0.99$) for devices I, II, and III were 1.28, 0.63, and 0.63 mg drug/hr, respectively (see Table 2).

Figure 6 is a plot of drug release rates for devices I and III against the inverse of the membrane thickness. The plots are linear ($r^2 > 0.99$) with slopes of 344 and 84 mg μm/hr for devices I and III, respectively. The linearity of the plots is in good agreement with the theoretical prediction [see Eq. (1)] and illustrates the dependency of release rates on membrane thickness. The slopes give an indication of the faster release rate for device I vs. device III. This is due to the faster osmotic water imbibition rate (larger osmotic pressure difference) for device I.

Influence of Orifice Size on Drug Release

To investigate the effects of orifice size on cyclobenzaprine hydrochloride release, device I (no PEO) and device III (15% w/w PEO) coated to a target 200 μm thickness with 150 and 510-μm diameter delivery orifice were prepared. Dissolution testing on these devices was performed using deionized water at 37°C and 75 rpm paddle speed.

For elementary osmotic tablets, the size of delivery orifice must satisfy two conditions: (1) it must be sufficiently large to minimize internal pressure inside the tablet and (2) it must be small enough to minimize its contribution to total drug release by

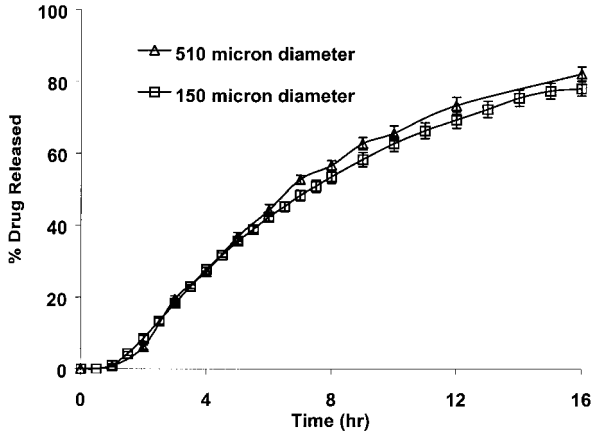

Figure 7. Cyclobenzaprine hydrochloride release from device I (no polymer) coated to a target thickness of 200 μm and drilled with different drug delivery orifice size.

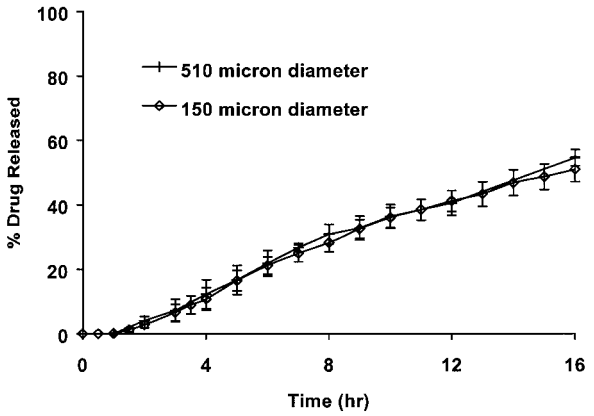

Figure 8. Cyclobenzaprine hydrochloride release from device III (15% w/w polymer) coated to a target thickness of 200 μm and drilled with different drug delivery orifice size.

simple drug diffusion through the orifice. There are equations available for estimating the minimum and maximum range of the orifice area (6).

The release profiles for device I (no PEO) with 150 and 510-μm diameter delivery orifice are given in Fig. 7 and were similar. This indicated that the contribution to drug release by simple diffusion through the orifice is minor compared to dominant osmotic pumping. Also, during dissolution testing, tablets with different orifice sizes showed minimal change in tablet volumes, demonstrating insignificant internal pressure within the tablets. Therefore, it was concluded that for device I, the delivery rate was independent of orifice size within that range.

The drug release profiles for device III (15% w/w PEO) with 150 and 510-μm diameter are given in Fig. 8. The profiles for the tablets were also similar, indicative of the independence of the delivery rate on orifice size within the range. As mentioned earlier, the drug release rates may have been affected in the devices with significant observed swelling (hydrostatic pressure) during dissolution testing [see Eq. (1)]. However, visual inspection of these devices (both orifice sizes) during dissolution testing showed a similar rate and extent of tablet swelling. Therefore, it appears that the larger diameter orifice does not reduce appreciably the extent of internal pressure when compared to the smaller diameter orifice; hence the total drug delivery rate was not significantly changed.

Effects of Hydrodynamics on Drug Release

The release of cyclobenzaprine hydrochloride from the osmotic devices under different hydrodynamic conditions was also investigated. To this end, dissolution testing was performed on devices I and III with 200 μm film thickness and 510-μm diameter orifice size. Dissolution testing on these devices was performed using deionized water at 37°C and 25, 75, and 150 rpm paddle speed. Figure 9 shows the release profiles for device I (no PEO) at different paddle speeds; release profiles during zero-order release period are similar under all conditions.

Generally, because in osmotic delivery systems delivery rate is governed by osmotic action, release rates are expected to be independent of hydrodynamic conditions. The release profiles for device III (15% w/w PEO) are given in Fig. 10. The release profiles were almost identical at 25 and 150 rpm paddle speed. Again, the results indicated that for these swelling devices, the drug release rates were independent of hydrodynamic conditions.

SUMMARY AND CONCLUSIONS

In this study, release of cyclobenzaprine hydrochloride from swelling osmotic delivery systems was investigated. The osmotic tablets contained cyclobenzaprine hydrochloride (model drug), mannitol

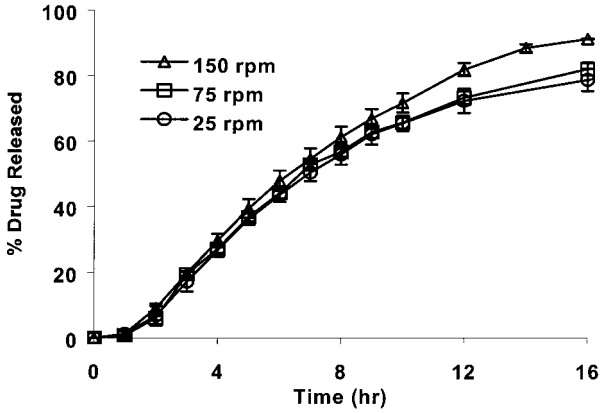

Figure 9. Cyclobenzaprine hydrochloride release from device I (no polymer) coated to target thickness of 200 μm and drilled with 510-μm diameter drug delivery orifice size, tested at different hydrodynamic conditions.

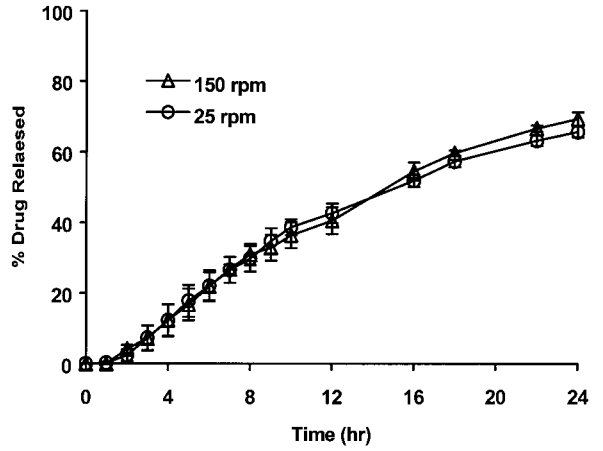

Figure 10. Cyclobenzaprine hydrochloride release from device III (15% w/w polymer) coated to a target thickness of 200 μm and drilled with 150-μm diameter drug delivery orifice size, tested at different hydrodynamic conditions.

(osmotic agent), and polyethylene oxide, a water-swellable polymer surrounded by a semipermeable membrane with a drug delivery orifice. There was a decrease in drug release rate with PEO in the core. This may be due to solubility-modulating properties of the polymer.

Visual inspection of the devices with PEO showed significant swelling during dissolution testing. Swelling (internal pressure) may influence water imbibition rate into the core and subsequently drug release rate.

There was no significant difference in release rates for devices with 5 and 15% w/w polymer. This may be explained by the complex interactions between various parameters (i.e., membrane hydraulic permeability, tablet surface area, membrane thickness, and swelling pressure) as they may change during release testing.

The release rates were a function of membrane thickness. Graphs of release rates against inverse of membrane thickness were linear and in agreement with theoretical prediction.

The release rates were independent of orifice size (range of 150–510 μm diameter) and hydrodynamic conditions for swelling and non-swelling devices. This would be advantageous in the delivery of drugs in man.

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