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RESEARCH PAPER

Release of Cyclobenzaprine Hydrochloride from Osmotically Rupturable Tablets

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ABSTRACT

Osmotically rupturable systems were developed and the release of cyclobenzaprine hydrochloride (model drug) from the systems was investigated. Systems were designed using mannitol (osmotic agent) and increasing amounts of polyethylene oxide (PEO, a water-swellable polymer) surrounded by a semipermeable membrane. When placed in an aqueous environment, osmotic water imbibition into the systems distended and swelled the systems until the membrane ruptured and released the active compound to the outside environment. Tablets with increasing amount of PEO exhibited longer rupture times. This may be due to osmotic pressure-modulating properties of the polymer, changing the rate of water imbibition into the systems.

The integrity of the membranes was investigated using high-pressure mercury intrusion porosimetry. Minimal mercury intrusion into the membrane structure and core tablet indicated membrane integrity and lack of defective areas or pinholes. The results were in agreement with the release profiles where no drug release was detected prior to membrane rupture. Mercury intrusion porosimetry appears to be a promising technique for evaluation of membrane integrity.

Once the systems ruptured, drug was released by osmotic pumping and diffusion mechanisms through the ruptured area. There was a decrease in drug release rate with inclusion of PEO in the core.

The effects of film thickness on rupture and release times were also investigated. Devices with thicker films produced longer rupture times. This is in agreement with the theoretical prediction.

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INTRODUCTION

A controlled-release delivery system utilizing an osmotic bursting mechanism was invented by Baker (1). This system comprises (1) a water-permeable membrane surrounding the osmotic device, (2) active drug, and (3) if necessary, additional osmotic agents. When placed in an aqueous environment, osmotic water imbibition into the device distends and swells the membrane until the membrane ruptures. Once rupture occurs, active agent is released to the outside environment (1).

There are several reasons for the attractiveness of these devices. In humans, a device of this nature could be used to deliver an active agent only after a certain period of time, for example for colonic delivery of drugs (2). Also, a number of osmotically rupturable devices can be designed to deliver drugs in pulses. Pulsed delivery systems have applications in different protein and hormone therapies (3). In agriculture, insecticide-containing devices can release the active drugs at a predetermined time after a rainfall. For these devices, the membrane should be relatively impermeable to the contents of the core, so drug release occurs only after the membrane has ruptured. The rupture times and drug release can be altered by varying the membrane material, membrane thickness, or changing the choice and amount of the osmotic agent(s) (1). In general, large changes in the rupture times are best achieved by varying the membrane material and/or membrane thickness. If the osmotic agent is changed, it must be capable of creating an internal pressure that exceeds the pressure required to rupture the membrane.

Polyethylene oxides (PEOs) are water-swellable/soluble resins that are white, free-flowing powders supplied in several molecular weights. These resins are non-ionic, which minimizes polymer–drug interactions, and because of their low toxicity have extensive industrial applications, including pharmaceuticals, food packaging, and cosmetics (4). Because of their unique properties, PEOs can be used in a variety of pharmaceutical applications: mucosal bioadhesives, transdermal drug delivery, wound dressings, lubricious coatings, and tablet binders (4,5). In addition, PEOs have been used in controlled oral drug delivery systems (6,7), several of which have been successfully marketed (8,9).

In this paper, we report the development of osmotically rupturable tablets containing the water-swellable polymer PEO. Systems were prepared with cyclobenzaprine hydrochloride (model drug), mannitol (osmotic agent), and PEO. To investigate the effect of PEO on rupture times and drug release, systems without PEO were also prepared and drug release profiles compared. The effects of membrane thickness on rupture times and drug release were also investigated.

EXPERIMENTAL

Materials

Cyclobenzaprine hydrochloride was purchased from Sigma (St. Louis, MO). Mannitol (Pearlitol) was supplied by Roquette (America, Inc., Keokuk, IA). 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 grade, were obtained from Fisher Scientific (Pittsburgh, PA). Polyethylene oxide (WSRN-1105, molecular weight 900,000), a water-swellable polymer, was received as a gift from Union Carbide Corporation (Danbury, CT). 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), varying amounts of mannitol, polyethylene oxide (water-swellable polymer at 0, 5, and 15% w/w), and magnesium stearate using an instrumented Manesty F-press equipped with a 11.11-mm diameter round, standard concave tooling. The core compositions are summarized in Table 1.

Table 1

Core Tablet Compositions

Ingredients (mg/tablet)	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 tablet weight (mg)	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 320-S, and 40 g of polyethylene glycol 400 in a binary solvent mixture of acetone (3000 g) and methanol (1000 g). The insoluble components of the membrane, the cellulose acetates, were permeable to water. 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.

All tablets were visually inspected using a 50× microscope for any film defect. Also, various tablet coats were examined using an environmental scanning electron micrograph (ESEM), Electro Scan 2010 (FEI Company, Hillsboro, OR).

High-Pressure Mercury Intrusion Porosimetry

Mercury intrusion was followed on a computer-controlled automatic high-pressure porosimeter (Poremaster 60, Quantachrome, Boynton Beach, FL). Core and film-coated tablets were placed in sample cells and low-pressure (15–50 psi) and high-pressure (15,000–20,000 psi) mercury intrusion was performed.

Dissolution Testing

Dissolution testing was conducted using USP dissolution method 2 (Vankel Industries, USA) with 900 mL deionized water at 37°C and 75 rpm paddle speed. Cyclobenzaprine hydrochloride release from the tablets was measured spectrophotometrically at 290 nm.

RESULTS AND DISCUSSION

Drug release from osmotically rupturable delivery systems occurs in the following steps:

1. Water absorption and swelling of the system;
2. Rupture of the membrane;
3. Subsequent drug release from the ruptured area.

These steps are shown schematically in Fig. 1. During the first step, water is imbibed as the system is placed in an aqueous environment. The water imbibition occurs through the semipermeable membrane and is dependent on the hydraulic permeability of the membrane and the osmotic pressure gradient. As the water is imbibed, it produces an internal pressure inside the system, which distends the membrane, and the system begins to swell. Water imbibition and system swelling continue until the internal pressure becomes greater than the cohesive strength of the membrane. At this point, the membrane ruptures and the contents of the system are released to the environment.

The rate at which the system swells (dv/dt) is equal to the flux rate of water through the semipermeable membrane, and is described by Eq. (1) (10):

$$\frac{dv}{dt} = \frac{A}{h}\sigma L_p(\Delta\pi - p) \quad (1)$$

where A is the membrane surface area, h is the membrane thickness, σL_p is the hydraulic permeability of the membrane, $\Delta\pi$ is the osmotic pressure difference across the membrane, and p is the internal pressure.

The time that it takes for the system to absorb water, swell, and rupture is called "rupture time." As the equation describes, rupture times can be controlled by (i) varying the membrane area, thickness, and/or material of composition to change the hydraulic permeability and/or cohesive strength of

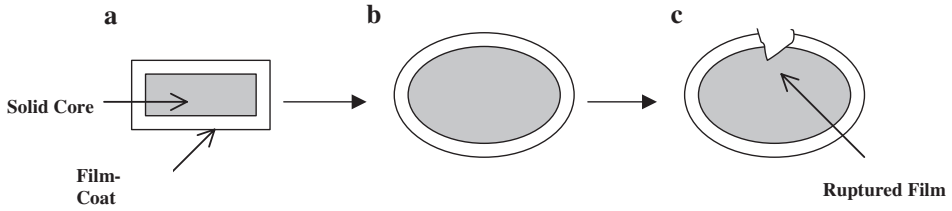

Figure 1. Schematic presentation of changes in osmotically rupturable tablet with time in deionized water at 37°C. (a,b) The process of water imbibition and swelling of the device with time. Once internal pressure (swelling pressure) overcomes the cohesive strength of the film coat it ruptures, releasing the drug to the outside environment (c).

the membrane and (ii) addition of agents to the system that can alter the osmotic pressure inside the membrane.

Once the system ruptures, it releases its contents to the outside environment. The mechanisms governing drug release from ruptured systems are similar to elementary osmotic pumps. Elementary osmotic pumps are devices that use osmotic pressure as an energy source to release drug at controlled rates. These devices have a solid core surrounded by a semipermeable membrane with a drug delivery orifice (10). When placed in an aqueous environment, the water penetrates into the core, dissolves the drug, and further water uptake forces a saturated drug solution to flow through the orifice.

The drug release (dm/dt) from the elementary osmotic tablets is described by Eq. (2) (10):

$$\frac{dm}{dt} = \frac{A}{h}\sigma L_p(\Delta\pi - p)C + \frac{PAC}{h} \tag{2}$$

where C is the drug concentration, P is the drug permeability coefficient of the membrane, and the other parameters have been described earlier.

The first term of this equation describes the dominant drug release mechanism by osmotic pumping and the second term describes the minor contribution to drug release by simple diffusion through the membrane.

This equation also describes drug release from osmotically ruptured systems. However, depending on the extent of the membrane rupture, the contribution to total drug release by simple diffusion through the ruptured area may become significant. For elementary osmotic pumps, equations are available that describe the minimum and maximum range of the orifice area (10). Within this range, the contribution to drug release by simple diffusion through the orifice is minimal.

Evaluation of Film Integrity

For osmotically rupturable systems, the initial integrity of the membrane is of paramount importance. Drug release should only occur after osmotic imbibition of water has caused excessive swelling and membrane rupture. Obviously, any core exposure to the outside environment (through membrane defect) will prevent the internal pressure from becoming fully developed and will influence the dynamics of tablet swelling, rupture, and drug release. In addition, drug will be released from the exposed areas as soon as enough osmotic pressure gradient has been created.

For this study, the integrity of the membranes was investigated visually using light microscopy and environmental scanning electron microscopy. In general, the film coats appeared uniform with no detectable defects.

In addition, high-pressure mercury intrusion porosimetry was performed on the film-coated tablets to monitor film integrity. The theory of mercury intrusion porosimetry is based on the Washburn equation (11), which describes the relationship between the pressure and the radius of the pores:

$$Pr = -2\gamma\cos\theta \tag{3}$$

where P is pressure, r is radius, γ is surface tension (480 mN/m), and θ is contact angle (140°C) of mercury. The equation dictates that as the pressure is increased, mercury intrudes into narrow pores.

This method can provide a good measure of the integrity of the film, as well as a quantitative description of the membrane pore structure (12). For comparison purposes, mercury intrusion porosimetry was also performed on core tablets.

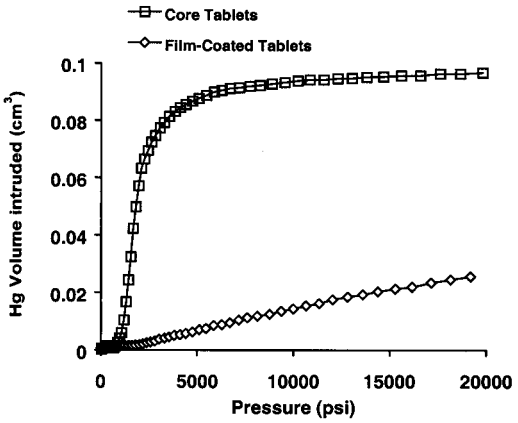

Figure 2. Mercury volume intrusion vs. pressure for core and film-coated cyclobenzaprine hydrochloride tablets (device I) determined by mercury intrusion porosimetry.

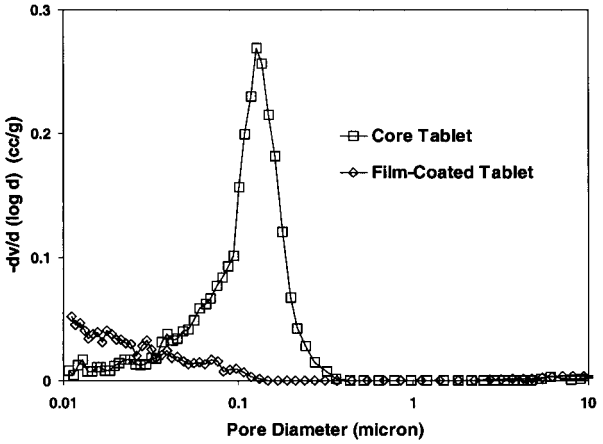

Figure 3. Pore volume size distribution of core and film-coated cyclobenzaprine hydrochloride tablets (device I) determined by mercury intrusion porosimetry.

Mercury volume intrusion vs. pressure measurements for core and film-coated tablets (device I) are given in Fig. 2. Approximately 0.02 and 0.1 cm^3 of mercury intruded into the core and film-coated tablets, respectively. The results gave an indication of good integrity and barrier properties of the membrane to mercury intrusion at high pressures. Visual inspection of the tablets also confirmed the above conclusion. Core tablets appeared completely dark and stained with mercury. However, film-coated tablets were only slightly stained with mercury on the surface and, when broken into halves, showed no sign of mercury intrusion into the core.

The pore volume size distribution for the same core and film-coated tablets are shown in Fig. 3. The pore volume size distribution also shows minimal mercury intrusion into the film-coated tablets with pores smaller than 0.1 μm in diameter. Core tablets showed significant mercury intrusion, with a large peak where pores are about 0.1–0.5 μm in diameter.

Based on the results obtained from ESEM images and mercury intrusion porosimetry, it was concluded that the films on the tablets had good uniformity and integrity.

Cyclobenzaprine Hydrochloride Release from Osmotically Ruptured Devices

Cyclobenzaprine hydrochloride release from devices coated to 200 μm film thickness are shown in Fig. 4. The release profiles for devices I, II, and III show rupture times of approximately 1, 2, and 5 hr, respectively, followed by a drug release period. No drug release was detected prior to membrane rupture, indicating membrane impermeability to cyclobenzaprine hydrochloride.

The driving force for the mechanism of action of this device is osmotic imbibition of water through the semipermeable membrane causing swelling, rupture, and drug release (see Fig. 5). Since osmotic imbibition is dependent on the solubility and osmotic pressure of the core, any change in these parameters will change the rate of water imbibition, and subsequent swelling and rupture times.

Based on the results, it appears that inclusion of PEO reduced the core osmotic pressure causing slower imbibition rate and consequently longer rupture times. In another study, inclusion of PEO in

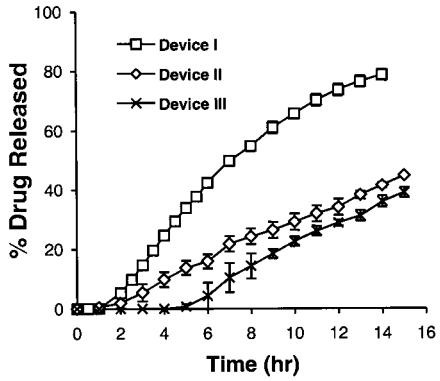

Figure 4. Cyclobenzaprine hydrochloride release from devices coated to target thickness of 200 μm.

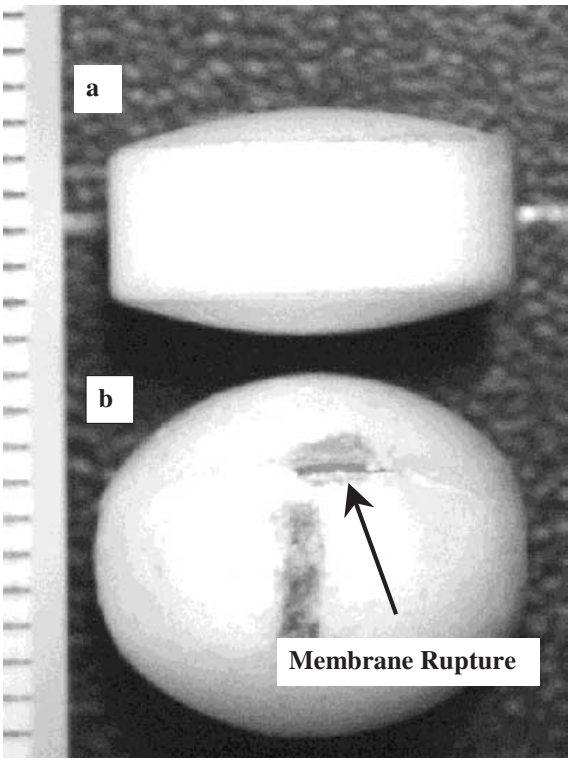

Figure 5. Digital photographs of cyclobenzaprine hydrochloride (device II) tablets (side view) before (a) and after dissolution testing; (b). Each unit of the scale is 1 mm.

elementary osmotic pumps containing cyclobenzaprine hydrochloride and mannitol also showed the same effect (13). For those devices, increasing the amount of PEO in the core reduced the drug release rates. It was postulated that PEO reduced the core osmotic pressure, causing a depressed drug release rate.

In general, one method of controlling the release times for osmotically rupturable devices is by varying the osmotic pressure of the core. This is possible by the choice and amount of the osmotic agent. Osmotic agents must be chosen so the total osmotic pressure exceeds the pressure required to rupture the membrane. It is also important that appropriate amounts are incorporated such that excess osmotic agent remains after membrane rupture. The excess osmotic agent will ensure the creation of sufficient osmotic pressure and drug release by osmotic pumping. Obviously, rapid depletion of the osmotic agents once rupture occurs will also be detrimental to device operation and will produce erratic results.

Given the results, it appears that PEO has osmotic pressure-modulating properties and changing the amount of PEO in the device can control the rupture times. This is of value since altering the rupture and release times does not require a change in the choice of the osmotic agent. Only small changes in the amount of PEO (the minor component) can produce the desired rupture and release times. In addition, once the device is ruptured, PEO prevents rapid depletion of the osmotic agent and ensures a prolonged drug release period.

The Effects of Film Thickness on Rupture Times

Another method of altering the rupture times and drug release is by varying the membrane thickness. To investigate the effects of film thickness on rupture times and drug release, devices I, II, and III were prepared and coated to 340 μm target film thickness. The release of cyclobenzaprine hydrochloride from these devices in deionized water is shown in Fig. 6. As expected, the release profile showed extended rupture times, followed by a zero-order drug release period. Devices I, II, and III ruptured at approximately 5, 6, and 10 hr, respectively. There was an increase in rupture times with increasing amount of core PEO.

The same trend was observed for the devices with 200 μm membrane thickness. However, for

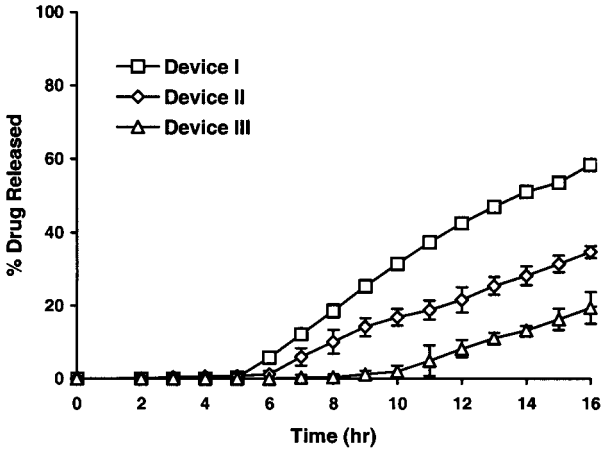

Figure 6. Cyclobenzaprine hydrochloride release from devices coated to target thickness of 340 μm.

these devices the rupture times were significantly shorter. Inspection of Eq. (2) shows that the rate of water imbibition is inversely proportional to the film thickness. As a result, the thinner the film, the shorter the rupture time. However, it must be taken into consideration that varying the membrane thickness may change the mechanical properties of the film. Films with different thicknesses may not exhibit the same elastic behavior or tensile strength. Given that rupture occurs when internal pressure overcomes the cohesive strength of the film, the relationship between film thickness and mechanical properties becomes significant.

In summary, for these devices rupture times can successfully be altered by varying the thickness of the membrane.

SUMMARY

Controlled drug delivery systems with an osmotic rupturing mechanism were developed. Systems were designed with and without the water-swellable polymer, PEO. Systems with PEO showed longer rupture times. It appears that inclusion of PEO in the core reduces the rate of water imbibition, thus longer rupture times are produced. This may be due to the osmotic pressure-modulating properties of the polymer.

No drug release was detected prior to membrane rupture. This indicated integrity of the film, as well as relative membrane impermeability to the active compound. The results were in agreement with high-pressure mercury intrusion profiles. Minimal mercury intrusion at high pressures into the membrane structure was indicative of good membrane integrity and lack of defective areas or pinholes. Mercury intrusion porosimetry appears to be a promising technique for evaluation of membrane integrity.

Once the systems ruptured, drug was released by osmotic pumping in a zero-order fashion. There was a decrease in drug release rate with inclusion of PEO in the core. The effects of film thickness on rupture and release times were also investigated. Devices with thicker films produced longer rupture times. This is in agreement with the theoretical prediction. However, the effects of thickness on film mechanical properties must be investigated prior to design of osmotically rupturable devices.

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