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Development and evaluation of osmotic drug delivery system for calcium channel blocker drug

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Abstract

Osmotic drug delivery systems are new approach for a controlled release dosage form. Nifedipine is a calcium channel blocker used in the treatment of hypertension. Nifedipine was selected as a model drug for investigation because it required 2-3 doses daily. So controlled release formulation is require. Controlled release of drug is achieved by adding a suitable polymer in dosage form. In present studied we prepared different dosage form using a Polyethylene oxide controlled release polymer. From the result it was cleared that higher concentration of water swell able polymer give optimum controlled release. Devices were prepared by two membrane thickness 110 µm and 340 µm. Nifedipine drug in osmotic tablet dosage form gives controlled release with 340 µm membrane thickness compare to 110 µm. Nifedipine drug release is similar from 250 µm and 510 µm diameter orifice size contained dosage form.

Key words: Osmotic drug delivery, Nifedipine, Zero order release, PEO, Membrane thickness, VPO

INTRODUCTION

Oral osmotic delivery systems have been used in a variety of therapeutic areas and have produced significant clinical benefits in the field of medicine. First latest osmotic drug delivery device is Rose Nelson pump, comprises an osmotic core surround by a semipermeable membrane drilled with a drug delivery orifice [1-4]. This system becomes especially unsuitable in the case of active compounds that must be administered in high doses. In order to solve this problem, other types of osmotic systems for poorly water-soluble drugs have been designed [5-7]. On the other hand, highly water-soluble drugs create considerable osmotic pressure

gradient and are released at high rates that may not be desirable. It is reported that candidate drugs for osmotic delivery have solubility of 50 to 300 mg/mL [8]. To overcome this problem, solubility-modulated osmotic pumps have been designed [9-12]. In these pumps, desired release rates are achieved by addition of appropriate solubility-modulating agents to the core. This approach, when feasible, allows the formulator to design an osmotic pump for highly water-soluble drugs, without altering the chemical structure of the drug. However, two problems are associated with this design,

1. Generally, the amount of required solubility modulator is large and creates the problem of formulating a highly dosed active and its solubility-modulator in a small enough tablet for oral administration.
2. Rapid depletion of the solubility-modulating agent that causes the device to release the drug at non-uniform rates.

To prevent rapid depletion of the solubility-modulating agent from the core, a pump-in-a-pump osmotic delivery system has been designed [13]. This design employs film-coated sodium chloride crystals as the solubility-modulating agent. By film-coating the crystals, rapid depletion of the sodium chloride from the device is prevented. Apart from the processing difficulties associated with the film-coating of sodium chloride crystals, this design has the limitation of maintaining the integrity of the film-coated crystals during the compression step. In this research, we report the design of osmotic systems containing a water swellable polymer for delivery of highly water-soluble drugs. The first system is a modified elementary osmotic pump that works on the principal of osmosis and consists of a swelling osmotic core surrounded by a semipermeable membrane drilled with a delivery orifice. It is hypothesized that inclusion of a water-swellable polymer, polyethylene oxide, into the design of these osmotic pumps acts as a solubility modulator (osmotic pressure modulator) of the osmotic core, thus controlling the rate of drug release from the device. The specific strategy to examine this hypothesis is as follows. Modified elementary osmotic systems will be designed and the release of highly water-soluble actives from the devices containing different amounts of the polymer will be evaluated.

MATERIALS AND METHODS

Materials

Nifedipine was obtained from Arch PharmaLabs Ltd., India. Various grade Polyethylene oxides were gifted by Colorcon Asia Pvt Limited, Goa. Various osmogents like sodium chloride, potassium chloride, mannitol, spray-dried lactose, and fructose was purchased from Chemedyes India. Acetone and methanol, both HPLC grades were obtained from S.D.Fine India. All other chemicals, reagents and solvents used are of A.R. grade.

Methods

Preparation of Potassium Chloride Core Tablets

Core tablets were manufactured by direct compression of a dry blend of potassium chloride crystals (model drug and osmotic agent), microcrystalline cellulose (compression aid) and varying amount of polyethylene oxide (water swellable polymer at 0, 5, 10 and 15% w/w) on using a 11.11 mm diameter, round, plain and standard concave tooling. Microcrystalline

cellulose was added to produce tablets of >15 kg hardness. The core compositions have been summarized in Table I. The physical properties of the core tablets are given in Table II [14-15].

Preparation of Nifedipine Tablets

Core tablets were prepared by direct compression of a dry blend of Nifedipine (model drug), varying amount of mannitol (osmotic agent), polyethylene oxide (water swellable polymer at 0, 5 and 15% w/w), and magnesium stearate (lubricant) with an 11.11 mm diameter round, plain and standard concave tooling. The core compositions are summarized in Table III. The core tablets physical properties are given in Table IV [16-18].

Preparation of Film Coated Tablets

Both potassium chloride and Nifedipine tablets were coated using a film-coating solution prepared by dissolving 120 grams of cellulose acetate 394- 60S, 40 grams of cellulose acetate 320S and 40 grams of polyethylene glycol 400 in a binary solvent mixture of acetone (3000 grams) and methanol (1000 grams). The water insoluble components of the membrane, the cellulose acetates, were water permeable polymers. Polyethylene glycol 400 was selected as a plasticizer. Potassium chloride tablets were coated to target film-thicknesses of 130 and Nifedipine tablets were coated to target film-thicknesses of 110, 200 and 340 µm using a fluidized bed spray coating technique.

Tablets were film-coated in a 4" diameter column with a 2" diameter Wurster insert. The tablets were film-coated using the following conditions: 45°C inlet air temperature maintaining an exhaust air temperature of 35°C, inlet dew point of 15°C, 120 cfm process air volume, 2.5 bar atomizing air pressure and a spray rate of 18 g/min [19].

Table I. Nifedipine core tablet compositions

Ingredients(mg/tablet)	Device I	Device II	Device III
Nifedipine	25	25	25
PolyethyleneOxide (MW=200,000)	--	30	90
Mannitol	569	539	479
Magnesium Stearate	6	6	6
Total Core Weight	600	600	600

Table II. Physical properties of nifedipine core tablets

Physical Properties	Device I	Device II	Device III
Weight (mg)	602±4 [a]	602±5 [a]	600±6[a]
Hardness (kg)	17.6±1.1 [b]	17.7±0.8 [b]	20.3±0.8 [b]
Thickness (mm)	5.94±0.06 [b]	6.07±0.07 [b]	5.98±0.04 [b]
True Density (g/mL)	1.451	1.438	1.417
% Tablet Porosity	12.6	12.3	11.2
Tablet Bulk Density (g/mL)	1.27	1.27	1.25

[a] Average of ten measurements ± SD.; [b] Average of six measurements ± SD.

Creation of Drug Delivery orifice

A mechanical drill with a cobalt micro drill was used to create the orifices for the delivery of the drug. To minimize the effect of orifice size on the release of the active, orifice of 150

µm diameter was drilled on the tablets. To evaluate the effects of orifice size on drug release tablets with orifices of 250 and 510 µm diameters were also prepared. In all cases, the shape and diameter of the created orifice was visually inspected and measured using a 50 X light microscope [20].

Dissolution Testing

Dissolution studies were performed using USP dissolution method 2 in 900 mL deionized water at 37°C and 75-rpm paddle speed.

Potassium chloride release from the tablets into deionized water was measured using a potassium-specific-electrode. Calibration curves were constructed by plotting the electrode reading against known potassium concentrations (0.1-0.0001 mole/L corresponding to 7.456-0.007456 mg/mL, respectively) on semi logarithmic paper and were linear (r2>0.99) over the potassium chloride concentration range of interest (0-600 mg/liter). A typical calibration curve had a logarithmic regression formula of y=24.182 ln(x) + 9.3389 with a correlation coefficient of 0.9991.

Nifedipine release from the tablets into deionized water was measured spectrophotometrically at 235 nm wavelength. Calibration curves were constructed by plotting the spectrophotometer reading against known amounts of Nifedipine dissolved in deionized water and were linear (r2>0.99) over the Nifedipine range of interest (0.00125-0.025 mg/mL). The calibration curve had a linear regression formula of C=0.29782 A with a correlation coefficient of 0.9999, and an uncertainty of 0.45%

Osmotic Pressure Measurements

Osmotic pressure of the solution inside the potassium chloride tablet was measured at 37°C using a vapor pressure osmometer [21].

Helium Pycnometry

The true densities of the tablets were measured using a helium pycnometer.

RESULTS AND DISCUSSION

Release of Nifedipine from Osmotic Tablets

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 swellable polymer on drug release from osmotic pumps. Nifedipine was chosen as model drug. Mannitol (direct compression grade) was chosen as osmotic agent. The aqueous solubility of this compound is a reported one gram in -5.5 mL water [23].

The release of Nifedipine from Devices I, II and III coated to 200 µm target film-thickness with 150 µm diameter drug delivery orifice. For all Devices, there was a lag-time followed by a longer zero-order release period. As described in previous section, this is characteristic of osmotic pumps. Devices I, II and III released 63 ± 2.2, 39 ± 2.3 and 36 ± 3.1 % drug respectively, at 10 hour time-point [with no statistically significant difference ($p<0.05$) between Devices VI and VII]. With a total load of 25 mg Nifedipine 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 ± 0.085, 0.82 ± 0.030, and 0.81 ± 0.034 mg drug/hr, respectively. There was a decrease in drug release rates with polymer content. The rates of drug release for osmotic delivery systems are controlled through:

1) Total solubility and osmotic pressure of the core.
2) Hydraulic permeability of the membrane.
3) Thickness and surface area of the membrane.
4) Hydrostatic pressure.

The decrease in drug release rate with swelling polymer, gives indication of Solubility modulating properties of the polymer in the core. Similar trend was observed in previous study using potassium chloride and PEO.

The Effects of Film-Thickness on Nifedipine Release

The dependence of nifedipine release on coating thickness was also investigated. For these experiments, Devices I, II and III coated to target thickness of 110 and 340 µm (with 150 µm diameter delivery orifice) were manufactured. A scanning electron micrograph of Device I with 110 µm film thickness is given in Dissolution testing on these Devices was performed using deionized water at 37°C and 75 rpm paddle speed.

The release profiles for Device I, II and III with 110 µm film-thickness are given in Fig. 1 Again, all release profiles showed a lag-time, followed by a longer period of zero-order drug release.

Table III. Nifedipine Release Rates from Device I-III coated to Different Film Thicknesses

Device	% w/w PEO	Film Thickness (µm)	Release Rate mg/hr)	r^2
I	0	110	3.38±0.128	0.99
II	5	110	1.17±0.031	0.99
III	15	110	1.15±0.035	0.99
I	0	200	1.90±0.085	0.99
II	5	200	0.82±0.030	0.99
III	15	200	0.81±0.034	0.99
I	0	340	1.28±0.133	0.99
II	5	340	0.63±0.067	0.99
III	15	340	0.63±0.039	0.99

The release rates calculated from the linear portion of the profiles (r2>0.99) for Devices I, II and III were 3.38±0.128, 1.17±0.031 and 1.15±0.035 mg drug/hr, respectively. The release profiles for Device I, II and III coated to a target thickness of 340 µm are shown in Fig. 2 and show similar trends as previously shown for Devices with lower membrane thickness. Due to larger membrane thickness for these devices, longer lag-times are observed. The steady-state release rates calculated from the linear portions of the profiles (r2>0.99) for Devices I,

II and III were 1.28±0.133, 0.63±0.067 and 0.63±0.039 mg drug/hr, respectively. The results are summarized in Table III.

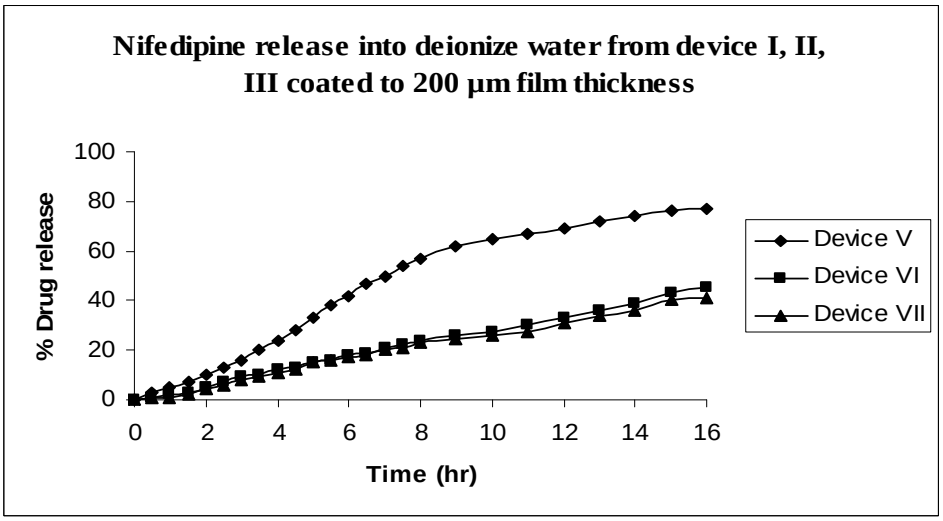

Figure 1

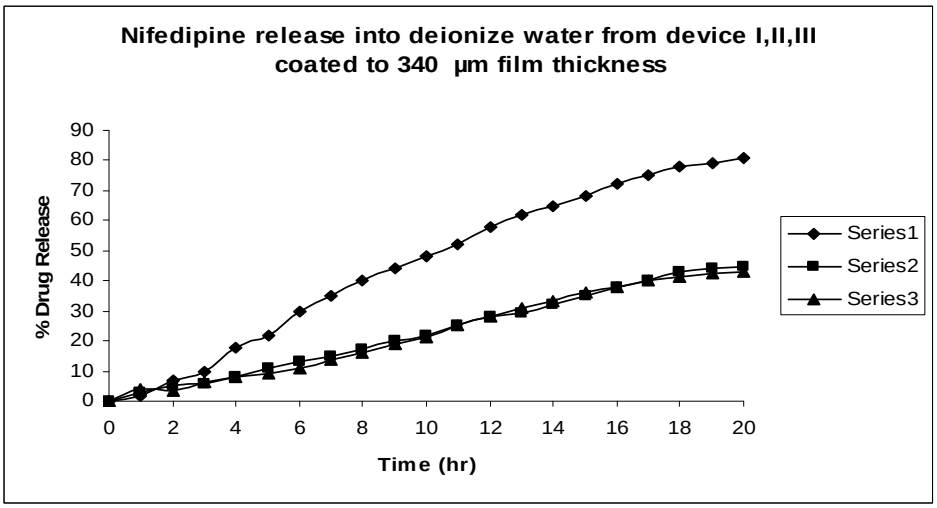

Figure 2

The Effects of Orifice Size on Drug Release

To investigate the effects of orifice size on nifedipine release, Device I (no PEO) and Device III (15% w/w PEO) coated to a target 200 µm thickness with 150 and 510 tm diameter delivery orifice were prepared. Dissolutiontesting 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 hydrostatic pressure inside the tablet.
2) It must be small enough to minimize its contribution to total drug release by simple drug diffusion through the orifice. There are equations available for estimating the minimum and maximum range of the orifice area.

The release profiles for Device I with 150 and 510 µm diameter delivery orifices are given in Fig. 3 and were similar. This indicated that 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 mm diameter are given in Fig. 4. The profiles for the tablets were also similar, indicative of independence of delivery rate on orifice size within the range. As it was mentioned earlier, for PEO containing devices, significant swelling (hydrostatic pressure) was observed during dissolution testing that might have affected the drug release rate. However, visual inspection of these devices (both orifice sizes) during dissolution testing showed 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 smaller diameter orifice; hence the total drug delivery rate was not significantly changed.

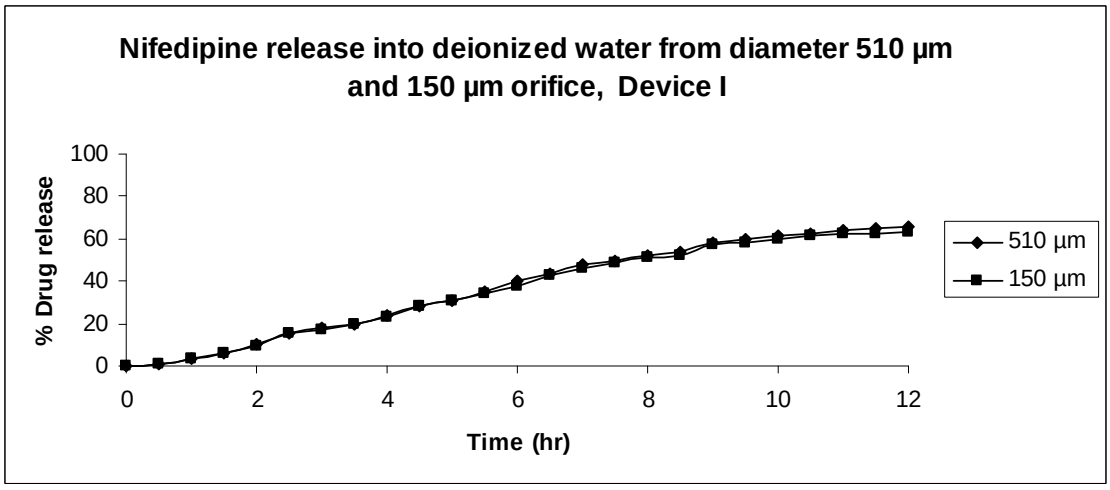

Figure 3

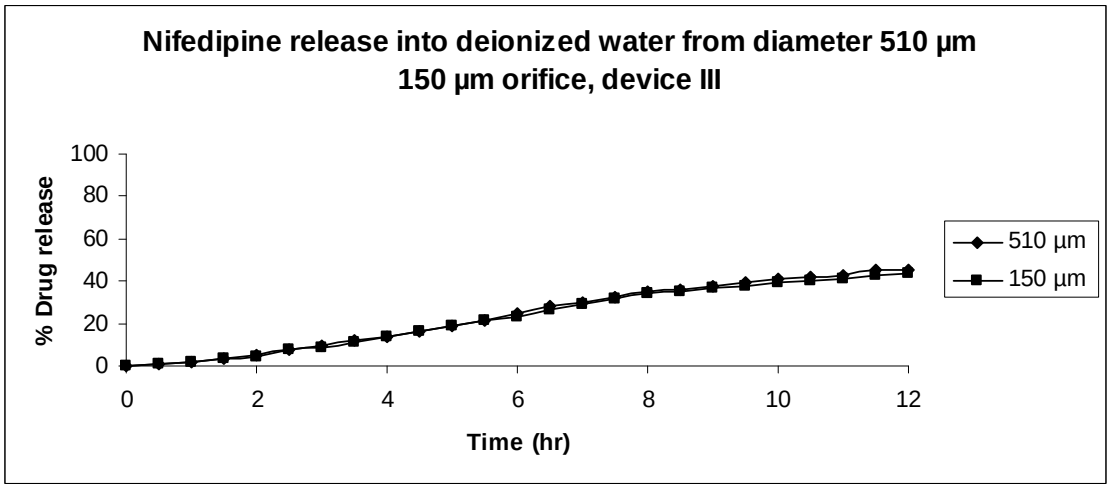

Figure 4

CONCLUSION

In this study, release of Nifedipine from swelling osmotic delivery systems was investigated. The osmotic tablets contained Nifedipine (model drug), mannitol (osmotic agent) and PEO (a water-swellable polymer), 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 (hydrostatic pressure) may influence osmotic water imbibitions and subsequently the drug is released at a slower 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 (ie. 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. Plots of release ray against inverse of membrane-thickness were constructed. The plots were linear and 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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