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Effect of hydrophilic polymers on the release of diltiazem hydrochloride from elementary osmotic pumps

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Abstract

Diltiazem hydrochloride (DLTZ) is a freely water-soluble drug, because of its higher aqueous solubility, the suitability of the drug with elementary osmotic pumps is restricted. Plain DLTZ elementary osmotic pump had shown higher release rate. Drug entrapment in polymer matrix or addition of release retardant materials (various polymers) can reduce the release rate of drug. In present study, effect of appropriate hydrophilic polymers (HP) on the release pattern was investigated. Ingredients of the system were optimized for parameters like drug:polymer ratio and amount of osmogent, for the desired release pattern. Two optimized formulations were selected for further characterization. Theoretical release rate of the formulations were also determined and compared. Different dissolution models were applied to drug release data in order to establish release mechanism and kinetics. Criteria for selecting the most appropriate model were based on best goodness of fit and smallest sum of squared residuals.

Keywords: Osmotic pumps; Hydrophilic polymers; Diltiazem hydrochloride; Release kinetics

1. Introduction

Osmotic pumps are controlled drug delivery devices based on the principle of osmosis. A wide spectrum of osmotic devices are in existence, out of them osmotic pumps are unique, dynamic and widely employed in clinical practice (Santus and Baker, 1995; Singh et al., 1999). Osmotic pumps offer many advantages like they are easy to formulate and simple in operation, improved patient compliance with reduced dosing frequency, more consistent and prolonged therapeutic effect is obtained with uniform blood concentration and moreover they are inexpensive and their industrial adaptability vis-a-vis production scale up is easy.

Elementary osmotic pumps essentially contain an active agent having suitable osmotic pressure, contained into a tablet, coated with a semipermeable membrane usually of cellulose acetate (Theeuwes, 1975). A small orifice is drilled through the coating by using LASER or high-speed mechanical drill. In fact, this system represents a coated tablet with an aperture. When exposed to an aqueous environment, the soluble drug within the tablet draws water through the semipermeable coating, resulting in formation of a saturated aqueous drug solution within the device. The membrane is non-extensible and increase in volume due to imbibition of water raises inner hydrostatic pressure, eventually leading to flow of saturated solution of active agent out of the device through small orifice. Solubility of drug in water plays a criti-

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cal role in functioning of osmotic pump. Typically the solubility of drug delivered by these pumps should be at least 10–15% (w/v).

The drug is pumped out of the system through the orifice at a controlled rate dm/dt, which is equal to the multiple of volume flow rate of water (dv/dt) into the core and drug concentration C_S.

$$\frac{dm}{dt} = \left(\frac{dv}{dt}\right) C_S$$

In principle, this delivery system dispenses drug continuously at a zero order rate until the concentration of the osmotically active salt in the system decreases below saturation solubility, where upon a non-zero order release pattern results. Recently, controlled release oral osmotic pump of naproxen sodium (Ramakrishna and Mishra, 2001) and ibuprofen (Ozdemir and Sahin, 1997) have been developed.

Diltiazem hydrochloride (DLTZ) is a calcium channel blocker widely used for the treatment of angina pectoris, arrhythmia and hypertension. Its short biological half-life and thus frequent administration (usually three to four times a day) makes it a suitable candidate for controlled release and/or sustained release (CR/SR) preparations (Chaffman and Brogden, 1985). DLTZ is a freely water-soluble drug and the release rate of DLTZ from oral osmotic pumps is usually high. Controlled porosity osmotic pump of DLTZ was developed, in which solubility of drug was reduced by adding sodium chloride (1 M concentration) to the core (McClelland et al., 1991). Sodium chloride reduced the solubility of DLTZ significantly and a constant release rate of drug was achieved. Further, Zentner et al. (1991) prepared controlled porosity solubility and resin-modulated osmotic drug delivery systems for the release of DLTZ. Hydrophilic polymers (HPs) are frequently added to the core to form polymer matrix. HPs can also be used (at lower to moderate concentration) to retard the release rate of highly water-soluble drugs from oral osmotic pumps to get desired zero order release rate. The designing essentially involves a mechanism, wherein the HPs control the release by producing hydrogel within the core which may restrict and delay the solvent contact with drug molecules and may increase the diffusional path length of solvent.

The objective of the present study was to investigate the effect of appropriate HPs on the release of DLTZ from elementary osmotic pump. The drug:HP ratio was optimized on the basis of release rate of DLTZ. The mechanism and kinetics of drug release from the optimized formulations was established by fitting drug release data into different dissolution models.

2. Materials and methods

2.1. Materials

DLTZ was a gift sample from USV (P) Ltd., Mumbai, India. Cellulose acetate (320 S) was obtained from Sun Pharmaceutical Advanced Research Centre, Mumbai, India (manufactured by FMC Corp., USA). Hydroxy propyl methyl cellulose (HPMC, 200–300 cps, medium viscosity grade), polyethylene glycol (PEG) 400 and polyvinyl pyrrolidine (PVP K-25) were purchased from Himedia, India. Sodium carboxy methyl cellulose (NaCMC, medium viscosity 400–800 cps) and mannitol were procured from Loba Chemie, India.

2.2. Methods

2.2.1. Drug analysis

DLTZ was analyzed by ultraviolet (UV) spectrophotometric method at λ_{max} 237 nm (Sood and Panchagnula, 1998). Calibration curves were prepared in distilled water, simulated gastric fluid (SGF pH 1.2) and simulated intestinal fluid (SIF pH 7.4) in the concentration range of 2–20 μg/ml (Shimadzu 1601 UV/visible spectrophotometer). No enzymes were added to both SGF (pH 1.2) and SIF (pH 7.4). Correlation coefficients were found to be $r > 0.9994$ for all media and no interference of additives used in formulation was observed.

2.2.2. Formulation design

To optimize the content of HPs various formulations of DLTZ (coded as DIL 1–10) containing HPMC and NaCMC mixture (1:1 ratio and 5, 10, 15, . . . , 50% w/w of drug) were prepared and the dose of DLTZ was kept constant (100 mg, i.e. thrice of conventional dose 30 mg with excess of 10 mg). Total weight of each core tablet was 350 mg and mannitol (also having osmogenic properties) was used as diluent. Mannitol content varied with varying amount of HP. Apart from

these, a plain formulation, which contained only DLTZ and mannitol (DIL P) was prepared for comparison study.

2.2.3. Granulation and punching

The granules were prepared by wet granulation method by using isopropyl alcohol as granulating solvent. PVP K-25 (25% w/w of drug) was used as a binder. Appropriate concentration of magnesium stearate and talc were added as lubricant and glidant, respectively. The granules were punched by an automated single punching machine (CIP machinaries, Ahmedabad and Bro-Shell Remedies, Sagar, India) with concave punches (diameter, −10 mm). The punched tablets were of $7.4 \pm 0.22\,kg/cm^2$ average hardness. The drug content of the tablets was found to be within the limits of 95–105%.

2.2.4. Coating and drilling of the formulations

5% (w/v) coating solution of cellulose acetate (320S) polymer for casting semipermeable membrane and polyethylene glycol 400 (15% w/w based on polymer weight) as plasticizer in solvents, methylene chloride and methanol (80:20 ratio) (Ayer and Theeuwes, 1980, 1981; Zaffaroni et al., 1978) was used as an optimized formula. The coating was carried out by spray pan coating machine with hot air blower (Rowland chem. and machinaries, Hyderabad, India). Pan was made up of stainless steel, having diameter of 22 cm and rotating speed of 25 rpm. The spray rate was fixed at 4 ml/min. Coated tablets were dried at 50 °C for 12 h. After coating, the formulations were evaluated for the percent weight increase. An orifice was mechanically drilled in the center of each pump. The aperture diameter and coating thickness were measured microscopically using empty shells obtained after complete dissolution of the contents (Table 1).

Table 2
Composition of optimized formulations

Ingredients	Quantity (mg)	
	DIL 3	DIL 5
Diltiazem hydrochloride	100	100
HPMC and NaCMC mixture (1:1)	15	25
PVP	25	25
Magnesium stearate	6	6
Talc	6	6
Mannitol	198	188

2.2.5. In vitro drug release

In vitro drug release of the formulations was conducted by using USP paddle type apparatus (rotation speed of 100 rpm and at 37 ± 1 °C). The dissolution medium was SGF (pH 1.2; 1000 ml) for first 2 h and SIF (pH 7.4; 1000 ml) for subsequent hours (Theeuwes et al., 1982). The samples were withdrawn at intervals of 1 h and analyzed immediately by UV spectroscopic method. The amount of DLTZ released was determined by measuring the absorbance at 237 nm.

According to the in vitro release profiles the formulations were optimized. Two formulations (DIL 3 and DIL 5, Table 2) that gave the desired release profile (near zero order) were selected for further characterization along with formulation that did not contain any polymer (DIL P). Formulation DIL 4 was not studied further for it exhibited almost similar release rate and profile as was recorded in the case of DIL 5. Minor changes in basic formula were incorporated for the preparation of optimized formulations.

2.2.6. Determination of theoretical release rate of DLTZ

The solubility of DLTZ at room temperature in the presence of potassium bicarbonate was determined. Excess amount of each material was added to the media in glass vials, the vials were capped tightly and

Table 1
Coating evaluation data of the formulations ($n = 5$)

Formulation	Average percentage weight increase (%)	Average coating thickness (μm)	Average aperture diameter (μm)
DIL 3	14.71 ± 0.96	600 ± 19	605 ± 7
DIL 5	14.3 ± 0.73	595 ± 23	612 ± 12
DIL P	14.46 ± 0.42	593 ± 15	598 ± 9

equilibrated at room temperature for 24 h. Aliquots of the resulting solutions were withdrawn from the vials and filtered. The DLTZ content was determined by UV analysis after appropriate dilution. The solubility of DLTZ in distilled water, SGF (pH 1.2) and SIF (pH 7.4) were found to be 611.16 ± 2.96 mg/ml, 636.63 ± 3.41 mg/ml and 606.38 ± 1.68 mg/ml, respectively.

Zero order release rate of the drug $(dm/dt)_z$ from an elementary osmotic pump, assuming a negligible osmotic pressure of the environmental fluid, is given by (Theeuwes et al., 1982),

$$Z = \left(\frac{dm}{dt}\right)_z = \frac{kA\pi_r S_d}{h}$$

where S_d is solubility of the agent inside the system (621.21 mg/ml), π_r is the total osmotic pressure of system, A is the surface area of the system (2.59 cm^2); k is the membrane permeability (1×10^{-5} cm^3 cm/cm^2 h atm), and h is membrane thickness. π_r and h values are shown in Table 3.

The osmotic pressure of the system can be calculated from equation (Martin et al., 1994),

$$\pi v = nRT, \quad \text{where, } \frac{n}{v} = C$$

Therefore $\pi = CRT$,

where π is the osmotic pressure, C is the molar concentration of drug inside the system, R is the gas constant, T is the absolute temperature, n is the number of moles of drug and v is the volume of system. The calculated values are recorded in Table 3.

2.2.7. Release models and kinetics

Generally the release of drug from oral osmotic systems is controlled by various factors such as osmotic pressure, aperture diameter, coating thickness, permeability of membrane, solubility of drug, etc. The in vitro release from system DIL P (which did not contain any polymer) was very fast, and $t_{80\%}$ was determined to be 2 h. But, the release from other formulations (containing polymers) was comparatively more controlled, where $t_{80\%}$ was found to be more than 10 h. The findings led to a conclusion that retardance in release was due to the addition of HPs, therefore, it is necessary to find the kinetics in order to elucidate the mechanism of drug release from the systems containing HPs.

Table 3
The variables and theoretical release rate of DLTZ pumps

Formulations	Osmotic pressure (atm)	Coating thickness (μm)	Theoretical release rate (mg/h)
DIL 3	144.35	600	66.58
DIL 5	126.11	595	58.57
DIL P	169.48	593	83.49

In order to describe the kinetics of drug release from controlled release preparations various mathematical equations have been proposed. The zero order rate Eq. (1) describes the systems, where the drug release is independent of its concentration (Najib and Suleiman, 1985). The first order equation Eq. (2) describes the release from systems, where release rate is concentration dependent (Desai et al., 1966). According to Higuchi model Eq. (3), the drug release from insoluble matrix is directly proportional to square root of time and is based on Fickian diffusion (Higuchi, 1963). The Hixson–Crowell cube root law Eq. (4) describes the release from the systems, where it depends on the change in surface area and diameter of the particles or tablets with time and mainly applies in case of system, which dissolute or erode over time (Hixson and Crowell, 1931; Abdou, 1989).

$$Q_t = k_0 t \tag{1}$$

$$\ln Q_t = \ln Q_0 - k_1 t \tag{2}$$

$$Q_t = k_H t^{1/2} \tag{3}$$

$$Q_0^{1/3} - Q_t^{1/3} = k_{HC} t \tag{4}$$

where Q_t is the amount of drug release in time t, Q_0 is the initial amount of the drug in tablet and k_0, k_1, k_H and k_{HC} are release rate constants for zero order, first order, Higuchi model and Hixson–Crowell rate equations, respectively.

In order to define a model, which will represent a better fit for the formulations, dissolution data can be further analyzed by Peppas and Korsenmayer equation Eq. (5) (Korsenmeyer et al., 1983; Ritger and Peppas, 1987a,b).

$$\frac{M_t}{M_\alpha} = kt^n \tag{5}$$

where M_t is the amount of drug released at time t and M_α is the amount released at time α (18 h), thus M_t/M_α

is the fraction of drug released at time t, k is kinetic constant and n is diffusional co-efficient. The exponent 'n' value can be used to characterize the mechanism of drug release (Peppas, 1985; Schwartz et al., 1968).

Drug release data obtained was applied to different drug release models in order to establish the drug release mechanism and kinetics. Criteria for selecting the most appropriate model was based on best goodness of fit and smallest sum of squared residuals (Parab et al., 1986).

3. Results and discussion

3.1. Formulation optimization

According to the in vitro release profile obtained, two optimized formulations of DLTZ (DIL 3 and DIL 5, Table 2) were further prepared. Punching, coating and drilling were carried out. Coating evaluation confirmed uniform thickness of film and the uniformity of aperture diameter (Table 1). In vitro drug release was determined and was reproducible. The prepared formulations were working well with total intactness of semipermeable membrane during the dissolution. In case of formulation DIL 5 negligible swelling of the system was observed, which might be due to higher content of HP. The empty shells obtained after 24 h of dissolution were left out with nearly 5% of drug inside. The empty shells were semitransparent, however, absolutely intact during the course of dissolution.

3.2. In vitro drug release

The formulation DIL P, which did not contain polymer, however, showed burst release where 90% of the drug was released within 2 h. It was further confirmed by $t_{80\%}$ values (time to release 80% of the drug content, Fig. 1). Formulation DIL 5 showed comparatively slower release rate than formulation DIL 3 probably due to higher content of hydrophilic polymer. Both the formulations showed no burst release and gave satisfactory controlled release. The curve between percent cumulative drug release and time confirmed that almost 80–90% of the drug released in 18 h (Fig. 1). The average release rates of the formulations for first 10 h were calculated. They were 6.88 ± 1.5 mg/h and 5.97 ± 1.3 mg/h for DIL 3 and DIL 5, respectively. The release rate was almost constant up to a time period of 10–12 h followed by gradual decrease in the release rate with decreasing osmotic pressure of the system (Fig. 2).

3.3. Effect of hydrophilic polymers on the release

The $t_{80\%}$ values determined from percent cumulative drug release versus time plots and release rate diagrams confirmed the effect of hydrophilic polymer on the release of DLTZ from the pumps (Figs. 1 and 2). Formulation DIL 5 showed slower release compared to DIL 3 and both the formulations gave relatively slower release rate than formulation DIL P that devoid of any polymer. The comparison of theoretical release rate with actually determined in vitro release rate also

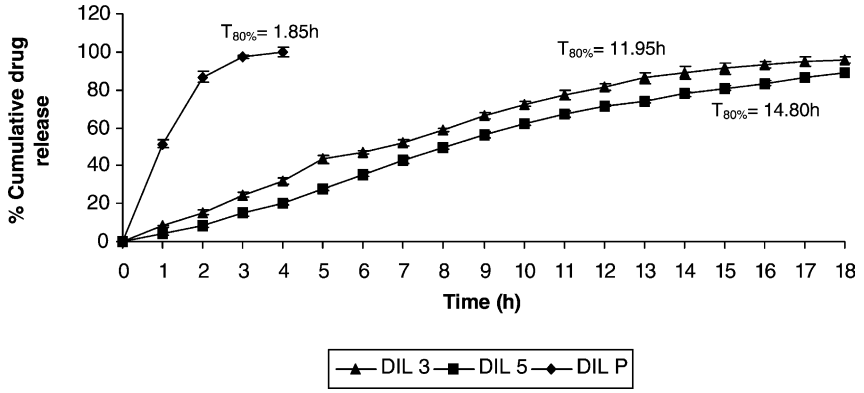

Fig. 1. In vitro cumulative release of DLTZ from optimized formulations.

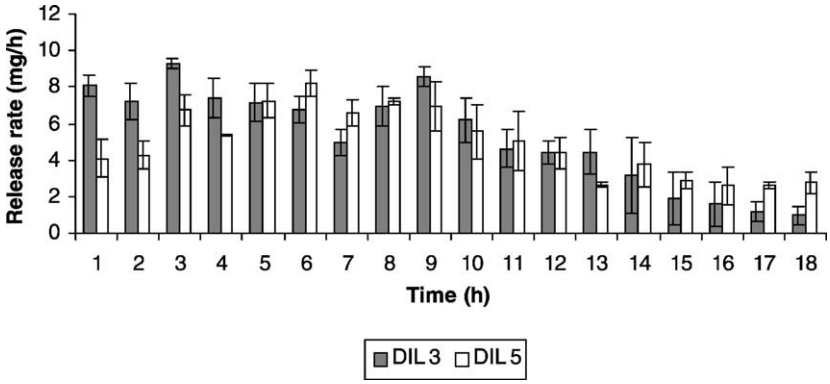

Fig. 2. In vitro release rate of DLTZ from optimized formulations.

confirmed the role of HPs in the slower and controlled release. The results suggest that appropriate addition of release retardants especially HPs can successfully control the release of highly water-soluble drugs from the elementary osmotic pumps.

3.4. Drug release kinetics

The linear nature of the plots between percent cumulative drug release and time suggests that none of the formulations follow first order kinetics, which is confirmed by the higher sum of squared residuals and comparatively less correlation co-efficient (Table 4).

Table 4
Regression analysis and correlation co-efficient values for dissolution data of formulations according to various kinetic models

Kinetic models	Parameters	Formulations	
		DIL 3	DIL 5
Zero order	r	0.9785	0.9869
	SSQ	17844.9	16401.8
	k_0	5.48	5.29
First order	r	−0.9939	−0.9878
	SSQ	2147.7	2155.8
	k_1	−0.0555	−0.0795
Higuchi model	r	0.9796	0.9883
	SSQ	18465.5	15857.9
	k_H	5.58	5.21
Hixson–Crowell model	r	0.9982	0.9986
	SSQ	15.29	9.99
	k_{HC}	0.1773	0.1434

The linear nature of the curves obtained for zero order, Higuchi model and Hixson–Crowell model suggests that the release from the formulations may follow any one of these models (not shown). While considering the higher correlation co-efficient values and less sum of squared residual (SSQ) values (Table 4), the release data seem to better fit with Hixson–Crowell model. Zero order and Higuchi model, moreover show higher SSQ values and comparatively small correlation co-efficients. Applicability of the release curves to the Hixson–Crowell equation indicated a change in surface area and diameter of the particles with progressive dissolution of the matrix as a function of time. Also, the change in diffusional path length along with the change in surface area and diameter of the particles during dissolution process follows cube root law.

Based on Korsenmayer–Peppas Power model Eq. (5), drug release data further analyzed for curve fitting and the results (DIL 3: $n = 0.5477$, $r = 0.9894$ and $k = 1.836$, DIL 5: $n = 0.6726$, $r = 0.9913$ and $k = 0.614$) confirmed that the formulations followed non-Fickian diffusion kinetics (because $n > 0.5$).

4. Conclusion

From the results obtained, it can be inferred that the release of freely water-soluble drug DLTZ from elementary osmotic pump can be controlled efficiently by the addition of HPs in to the core formulations. The oral osmotic pumps possess many advantages over the simple matrix type of SR/CR oral dosage forms.

The pumps gave better controlled release and time duration for the release can be extended up to 24 h. This can lead to the development of these formulations as potential candidate for once a day dosage form. The kinetics of drug release from formulations follow Hixson–Crowell cube root model and mechanism of release would follow non-Fickian diffusion process. It can be concluded from the study that HPs can play a considerable role in controlling the release of DLTZ (or other highly water-soluble drugs) from elementary osmotic pumps.

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