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Preparation and Dissolution Characteristics of Sustained Release Diltiazem Hydrochloride Tablets

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In the present study, the applicability of Eudragit to produce matrix tablet by a wet granulation technique was evaluated. The effect of various formulation variables on the release of drug from these tablets was examined. Release profiles of diltiazem hydrochloride were investigated using the rotating basket method described in the USP 24 with 1000 ml buffer solution (pH 1.2 and 6.8) maintained at 37 °C. *In vitro* findings showed that matrix tablets prepared with Eudragit gave prolonged release of diltiazem hydrochloride. In order to understand the drug release mechanism better, the release data was tested assuming common kinetic models. In the present study, for the optimized formulation, the correlation coefficients were low for first order, zero order and Hixon-Crowell models. When the goodness of fit of release data to Matrix and Peppas equation was evaluated, the difference between these two models was found to be minimal. For the optimized formulation, the best-fit kinetic model was the Matrix model.

Keywords: Diltiazem hydrochloride, Matrix tablet, Sustained release, Eudragit, *In vitro* release studies.

INTRODUCTION

Diltiazem hydrochloride is a calcium channel blocker that is widely used in the treatment of variant angina, hypertension and arrhythmias. Diltiazem reduces blood pressure predominately through its vasodilator actions, without causing tachycardia [1,2]. Its water solubility, short elimination half-life and therapeutic use in chronic diseases make it a suitable candidate for formulation as a sustained release dosage form. Thus, various techniques have been employed to develop prolonged release preparations containing this drug.

Hydrophilic matrices containing polyethylene oxide and carbopol [3], hydroxypropyl-methylcellulose (HPMC) [4], combination of hydroxypropyl methyl cellulose and xanthan gum [5] have been used for the preparation of modified release tablets of diltiazem HCl. In addition, Guar gum and polyacrylamide-grafted-guar gums were used to prepare sustained release tablets of drug [6,7]. Other techniques employed for preparing sustained release preparation of drug are physical mixtures or polyelectrolyte complexes of chitosan-alginate or chitosan-carrageenan [8], and alginate beads prepared by the ionotropic gelation method [9]. A new approach for *in situ* interactions between diltiazem hydrochloride and electrolyte(s) to control the release of highly water-soluble drugs from oral hydrophilic monolithic systems has also been tried [10]. The characteristics of methylcellulose can be changed by reacting it with succinic acid and the resultant product can be used as a hydrophilic matrixing agent for diltiazem hydrochloride [11].

Controlled release drug delivery systems are dosage forms from which the drug is released at a predetermined rate which is based on a desired therapeutic concentration and the pharmacokinetic characteristics of the drug. The formulation of the controlled release drug delivery systems employing manufacturing technologies such as wet granulation is attracting increasing attention. The purpose of this study was to prepare controlled release diltiazem matrix tablets by wet granulation using Eudragit RS 100, Eudragit L 100 and Eudragit RL 100 in varying ratios

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together with the plasticizer dibutyl phthalate. Release profiles of diltiazem hydrochloride from different series were investigated. Model equations, intended to elucidate the drug release mechanism, were fitted to the release data.

EXPERIMENTAL

Materials

Diltiazem hydrochloride, Eudragit RS 100, Eudragit L 100 and Eudragit RL 100 were generous gifts from Ranbaxy Research Laboratories, Ahamadabad, India. All other chemicals and reagents were of analytical grade. A UV Spectrophotometer was used for the assay of diltiazem hydrochloride.

Preparation of sustained release diltiazem hydrochloride tablets

The normal release granules of diltiazem hydrochloride were prepared using weighed quantities of initial dose of the drug and subjected to wet granulation using acetone: methanol (90:10). The sustained release granules of drug were made from weighed quantities of sustained release portions of dose of drug and polymers, granulated in acetone: methanol (90:10) and subsequently dried at 30 °C. The total dose of diltiazem hydrochloride was 170 mg comprising an initial and maintenance dose of 60 mg and 110 mg respectively.

Sample I: Eudragit RS 100 and Eudragit L 100 (70:30) were used as the binder and the polymers were added to the maintenance dose of the drug. Acetone and methanol in the ratio of 90:10 were added to the mixture of polymers and drug to make a coherent mass which was passed through the sieve and the resultant granules dried at 30 °C. The sustained release granules thus obtained were mixed with normal release granules of the drug. Talc (0.1%) and magnesium stearate (0.1 %) were then added to the granules before compression to the tablets. For Sample II, Eudragit RS, Eudragit L 100 and Eudragit RL 100 (60:20:20) were used as the binder and the procedure followed for sample I repeated. To obtain sample III, Eudragit RS 100, Eudragit L 100 and Eudragit RL 100 (60:20:20) were used along with the plasticizer dibutyl phthalate (10 % of the dry weight of the polymers). The composition of different samples of the matrix tablets are given in Table 1.

Table.1: Compositions of Matrix tablet formulations

Sample	Formula (polymer concentration)	Diltiazem.HCl (mg)		Eudragit RS 100 (mg)	Eudragit L 100 (mg)	Eudragit RL 100 (mg)	Dibutyl phthalate (mg)
		Initial dose	Maintenance dose				
Sample I	A-1 (15 %)	60.00	110.88	21.10	9.04	---	---
	A-2 (30 %)	60.00	110.88	51.26	21.96	---	---
	A-3 (45 %)	60.00	110.88	97.86	41.94	---	---
Sample II	B-1 (15 %)	60.00	110.88	18.09	6.03	6.03	---
	B-2 (30 %)	60.00	110.88	43.93	14.64	14.64	---
	B-3 (45 %)	60.00	110.88	83.88	27.96	27.96	---
Sample III	C-1 (15 %)	60.00	110.88	18.09	6.03	6.03	3.01
	C-2 (30 %)	60.00	110.88	43.93	14.64	14.64	7.32
	C-3 (45 %)	60.00	110.88	83.88	27.96	27.96	13.98

Talc = 0.1%, magnesium stearate = 0.1%, acetone:methanol (90:10) = q.s.

Assay of diltiazem hydrochloride tablets

The content of diltiazem hydrochloride in tablets was determined spectrophotometrically at 237 nm.

In vitro release studies

The *in vitro* release studies were carried out according to the USP 24 [12] rotating paddle method using Simulated Gastric Fluid (SGF) pH 1.2 for the first two hours followed by Simulated Intestinal Fluid (SIF) pH 6.8 for the next 10 hours, stirred at 50 rpm. At regular intervals, 2.0 ml aliquots of dissolution media were withdrawn and replaced with equal quantities of fresh buffer. The amount of drug released was determined spectrophotometrically at 236 nm & 237 nm respectively using SGF pH 1.2 and SIF pH 6.8 as blanks.

Release kinetics

The optimized formulation was subjected to kinetic analysis using the Dissolution software PCP Disso Version 2.04 to obtain the best-fit kinetic model. The goodness of fit of the release data was tested with the following mathematical models:

First Order:

$$\log (\text{Fraction unreleased}) = (k/2.303)t$$

Zero Order:

$$\% \text{ Released} = kt$$

Matrix (Higuchi Matrix):

$$\% \text{ Released} = k\, t^{0.5}$$

Peppas-Korsmeyer Equation:

$$\log (\% \text{ Released}) = \log k + n \log t$$

Hixson-Crowell Equation:

$$(\text{Fraction unreleased})^{1/3} = 1 - kt$$

Where t = time

RESULTS AND DISCUSSION

The present study was an attempt to develop oral sustained release matrix tablets of diltiazem hydrochloride. Matrix formulations effectively control the rate of drug availability for drugs of either low or high availability in depot fluid. Matrix tablets were prepared using different concentrations of Eudragit polymers. The Eudragit system fulfills two functions in the matrix tablet formulation acting as a binding agent and as a sustained release medium. After compression to matrix tablets, the polymer will create a sponge-like structure in which the active ingredients are distributed and embedded. The release of active ingredients will take place by diffusion or by erosion. This depends on the kind of Eudragit polymer used. In the case of pH independent Eudragit polymers (Eudragit RS and RL), the release will be mainly by diffusion, whereas in the case of pH dependent Eudragit, the release will be by erosion or by a combination of diffusion and erosion.

In this study, polymers were used at concentration of 15 %, 30 % and 45 %. Further increase in polymer content beyond 45 % resulted in the formation of rubbery masses upon addition of solvent and made granulation impossible. Hydrophobic polymers with high glass transition temperatures tend to be brittle and lack adhesiveness. Addition of plasticizer to the polymer improves the ability of the polymer to interact with hydrophilic excipients.

Release of diltiazem hydrochloride from tablets

The results of dissolution tests with diltiazem hydrochloride matrix tablets of formulation A-1, A-2 and A-3 are shown in Figure 1. Practically, dissolution of the initial dose (30 %) occurred during the first 2 h and no differences could be noted between the samples. Conversely, the maintenance dose (110 mg) was released very slowly. Within 12 h about 65 % of diltiazem hydrochloride had been released from formulation A-1, 68 % from formulation A-2 and 65 % from formulation A-3.

The results of the dissolution test with the diltiazem hydrochloride matrix tablets of formulations B-1, B-2 and B-3 are shown in Figure 2. The initial dose of 30 % was released from all the formulations in the first 2 h. Within 12 hours, 72 % of drug had been released from formulation B-1, 77 % from formulation B-2 and 74 % from formulation B-3. This increase in release of maintenance dose was due to the incorporation of Eudragit RL 100 in the formulations.

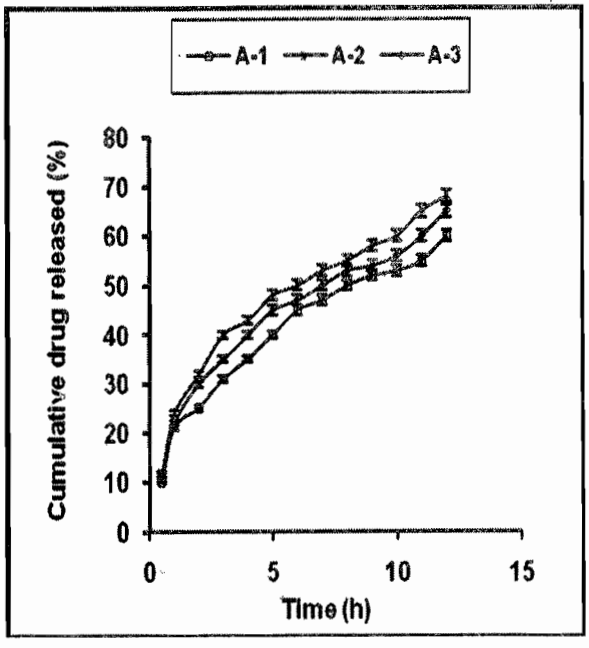

Figure 1: Cumulative drug released versus time for formulations A-1, A-2 and A-3

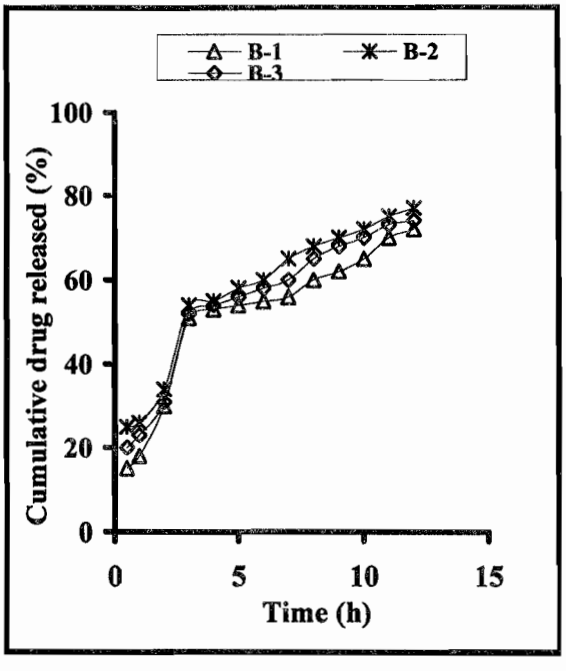

Figure 2: Cumulative drug released versus time for formulations B-1, B-2 and B-3

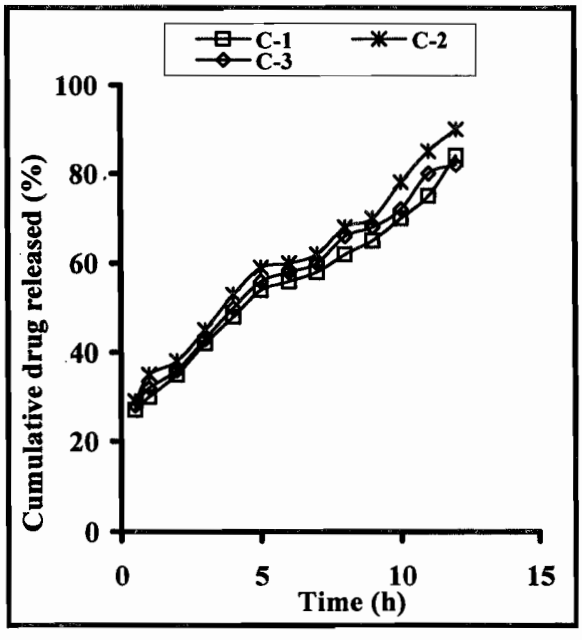

Figure 3: Cumulative drug released versus time for formulations C-1, C-2 and C-3

As can be seen from Figure 3, 35 % of drug was released in 2 h from all the formulations. The releasing rate depends on the concentration of polymers used in the formulation. Within 12 h, 84 % of drug was released from formulation C-1, 90 % from C-2 and 82 % from formulation C-3.

The low amount of drug released from formulation A-1, A-2 and A-3 was due to the presence of high concentrations of a polymer with low water permeability, Eudragit RS 100. These formulations also contained Eudragit L 100. Formulations B-1, B-2 and B-3 showed comparatively higher drug release which was due to the presence of Eudragit RL 100, which is a readily permeable polymer, in addition to Eudragit RS 100 and Eudragit L 100 in the formulations. The highest drug release rates were obtained with formulations C-1, C-2 and C-3, which contained a plasticizer, dibutyl phthalate (10%) in addition to polymers (Eudragit RS 100: Eudragit L 100: Eudragit RL 100 in the ratio 60:20:20). It was found that the drug release rate was dependent on the concentration of polymers in the formulations. The drug release rate was low when the concentration of polymers was 15 %

(Formulations A-1, B-1 and C-1) and high in formulations containing 30 % of polymers (Formulations A-2, B-2 and C-2). Further increase in the polymer concentrations to 45 % resulted in a decrease in drug release rates (Formulations A-3, B-3 and C-3). The formulation C-2 showed highest drug release rates (90 %) for 12 hours, hence it was chosen as an optimized formulation. It contained 30 % of polymers (Eudragit RS 100: Eudragit L 100: Eudragit RL 100) and dibutyl phthalate (10% of the dry weight of the polymers).

Kinetics of diltiazem hydrochloride release from tablets

In the present study, for formulation A-2 zero order, first order and Hixon-Crowell equations were not linear and linearity was most closely approached by using the Matrix model and Korsmeyer-Peppas equation. The best-fit kinetic model was Peppas (Table 2). For formulation B-2, the best-fit kinetic model was the Matrix model and minimal differences were noted with Peppas model. There was no sufficient linearity for zero order, first order and Hixon-Crowell equations. The release pattern for formulation C-2, which contained 30 % of the three polymers, Eudragit RS 100, Eudragit L 100 and Eudragit RL 100 along with plasticizer, dibutyl phthalate, corresponded best to the Matrix model, and correlation coefficients for other kinetic models were low (Table 2).

The diltiazem release rate from this pharmaceutical system was not constant, and diminished with the square root of time (Higuchi model) showing that the phenomenon controlling drug release was the diffusion occurring inside the swelled polymeric matrix.

Table 2: Kinetic models for formulation A-2, B-2 and C-2

Model	Formulation A-2			Formulation B-2			Formulation C-2		
	R	k	Constant	R	k	Constant	R	k	Constant
Zero order	0.8816	0.0187	0.057	0.9100	0.0146	0.045	0.9203	0.0144	0.036
T-test	5.283 (Passes)			7.282 (Passes)			7.802 (Passes)		
1st order	-0.8817	-0.0002	2.000	-0.9101	-0.0001	2.000	-0.9204	-0.0001	2.000
T-test	5.286 (Passes)			7.285 (Passes)			7.806 (Passes)		
Matrix	0.9744	0.0635	0.018	0.9801	0.0574	0.003	0.9796	0.0559	-0.004
T-test	12.247 (Passes)			16.389 (Passes)			16.153 (Passes)		
Peppas	0.9780	0.0843	-	0.9719	0.0511	-	0.9726	0.0390	-
T-test	13.250 (Passes)			13.703 (Passes)			13.873 (Passes)		
Hixon-Crowell	-0.8817	-0.0001	1.000	-0.9101	0.0000	1.000	-0.9203	0.0000	1.000
T-test	5.285 (Passes)			7.284 (Passes)			7.804 (Passes)		
t-Table at P=0.05 (two tails), d.f. = n-2	2.306			2.201			2.201		
Best fit model	Peppas			Matrix			Matrix		
Parameters for Korsmeyer Peppas Equation	n= 0.4058, k = 0.0843			n= 0.5852, k = 0.0511			n= 0.6858, k = 0.0390		

CONCLUSION

The results of the study showed that the diltiazem hydrochloride sustained release matrix tablets produced by wet granulation demonstrated sustained release *in vitro* for 12 h and the drug release from the optimized formulation followed Fickian diffusion (Higuchi Matrix model).

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