DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 18(15), 1649-1661 (1992)

PREPARATION AND DISSOLUTION CHARACTERISTICS OF CONTROLLED RELEASE DILTIAZEM PELLETS

Katerina Vasilevska[1] Zorica Djurić [2],
Milica Jovanović [2] and Angel Simov [1]

[1] Instiututes of Pharmacy at a Faculty of Medicine,
91000 Skopje, Vodnjanska 17, Yugoslavia

[2] Faculty of Pharmacy, 11000 Belgrade,
Dr Subotića 8 , Yugoslavia

ABSTRACT

Different series of Diltiazem pellets with slow release of the active substance were prepared, by pan coating technique, using different mixtures of acrylic polymers (Eudragit E, Eudragit L, Eudragit RL and Eudragit RS) as film coating agents. The thickness of the coatings were varied by different amounts of Eudragit. Release profiles of Diltiazem hydrochloride were investigated using USP XX rotating basket method (Erweka DT-D6) with 1000 ml buffer solution (pH values 1.5 ; 2.2 ; 5.5 ; 6.8 ; 7.0) at 37 ° C as solvent. In vitro dissolution findings showed that Eudragit coatings gave prolonged release of Diltiazem hydrochloride. The permeability of coatings in gastric and intenstinal juices was found to be influenced by the

amount of Eudragit L in the formulation. Also, the drug release rate was found to be dependent on the amount of coating applied. In order to understand the drug release mechanism better, the release data were tested assuming common kinetic models. In the present study square - root of the time plots and Weibull plots were not sufficiently linear, although several correlation coefficients were high. When the goodness of fit of release data to first - order kinetics and Hixson - Crowell 's equation was evaluated, the difference between these two models was often noted to be minimal.

INTRODUCTION

Diltiazem hydrochloride is a Calcium channel blocker widely prescribed for the treatment of angina pectoris, arrhytmia and hypertension (1-4). Its watersolubility, short elimination half - life and therapeutic use in chronic diseases, make it suitable as a candidate for prolongation of its release from dosage forms. Thus, attempts have been made to develop both twice and once - a - day prolonged release preparations that contain this drug (5-7).

Controlled release drug delivery systems are dosage forms from which the drug is released by a predetermined rate which is based on a desired therapeutic concentration and the drug 's pharmocokinetic characteristics (8). The formulation of the controlled release drug delivery systems employing manufacturing technologies such as film coating of small particles, which contain or are coated with drug substance, is attracting increasing attention.

The purposes of this study were to prepare controlled release Diltiazem pellets using different mixtures of acrylic polymers as film coating agents and varying the thickness of the coating by different amounts of Eudragit. Release profiles of Diltiazem hydrochloride from different series were investigated.

EXPERIMENTAL

Materials

Eudragit RS 100, Eudragit RL 100, Eudragit E 100 (Röhm Pharma) , Diltiazem hydrochloride (Lusofarmaco, Ital.), inert pellets (Upjohn, Italy).

Preparation of coated pellets

Batches of 200g of inert pellets were coated by using pan coating technique (Erweka DK 3/UG). The speed of rotation was 30-50 rpm and the pan angle at 30°. The inlet air temperature was 40-60°, and coating solutions were sprayed continuously, operating at a spray pressure of 0.2-0.5 bar, with a spray nozzle orifice of 2mm. The pellets were dried in the coating pan for another five minutes at the same temperature and air flow.

Preparation of Eudragit Coating solutions

The film coating agents were acrylic polymers (Eudragit E 100, Eudragit L 100, Eudragit RL 100 and Eudragit RS 100). The concentration of plasticizer Castor oil (10%) was given as a percentage of the amount of filmcoating polymers. Coating solutions (6%) were prepared using alcohol (96%) as a solvent.

The total dose of Diltiazem hydrochloride was 170 mg (initial dose was 60 mg, and the maintance dose was 110 mg).

Samples type I: The maintenance dose (110 mg) was added in the form of coating solution prepared with 1% Eudragit L in diluted alcohol. The pellets were coated primarly with this solution. After that, the pellets were coated with different mixtures of Eudragit RS and L (Table 1). The initial dose was then added by coating of pellets with 1% solution of Eudragit E in diluted alcohol.

TABLE 1
The composition of Eudragit's solutions

Film forming agent		Amount of coating mg/cm²	Samples
RS :L	70:30	4,5	Ia
	60:40	4,5	Ib
	50:50	4,5	Ic
RS :L	70:30	4,5	IIa
	60:40	4,5	IIb
	50:50	4,5	IIc
RS:RL:L	20:60:20	5,0	IIIa
	20:60:20	3,0	IIIb
	20:60:20	2,0	IIIc

In the samples II and III total dose of Diltiazem hydrochloride (170 mg) was coated on inert pellets with Eudragit L solutions (1%) in diluted alcohol. Afterwards, the pellets were coated with different mixtures of Eudragit polymers (Table 1).

The composition of Eudragit solutions is described in Table 1.

The determination of Diltiazem hydrochloride in pellets

The content of Diltiazem hydrochloride in pellets was determined spectrophotometricaly (LKB) at 242 nm. The content of Diltiazem hydrochloride in pellets was measured in weight of pellets which contains 170 mg of drug substance.

Dissolution test

The dissolution test was carried out using USP XX rotating basket method (Erweka DT-D6) with 1000 ml of buffer solutions (pH

values 1.5 ; 2.2 ; 5.5 ; 6.8 ; 7.0) at 37°C ± 0.5°C as solvent. The speed of stirring was 120 rpm. The amounts of Diltiazem hydrochloride released were determined spectrophotometricaly (LKB) at 236 nm.

Release kinetics

The goodness of fit of the release data was tested with following mathematical models:

(A) first - order kinetics - eqn.1 (9,10)

(B) square - root of time equation - eqn.2 (11)

(C) Hixson - Crowel 's cube - root equation - eqn.3 (12)

(D) Weibull distribution function - eqn. 4 (13)

$$\ln Q = \ln Q_o - k_1 t \quad (1)$$

$$Q = k\sqrt{t} \quad (2)$$

$$m^{1/3} = m_o^{1/3} - Kt \quad (3)$$

$$m = 1 - \exp\left[-(t - Ti)^{b/a}\right] \quad (4)$$

RESULTS AND DISCUSSION

Content of Diltiazem hydrochloride in pellets

The contents of Diltiazem hydrochloride in pellets are presented in table 2.

Release of Diltiazem hydrochloride from pellets

The results of dissolution tests with coated Diltiazem pellets of formulation Ia-c are shown in Figure 1. Practically, dissolution of initial dose (35%), occured during the first 30 minutes, and no difference between samples can be noted.

But, maintance dose (110mg) released very slowly. In 12 hours about 100% of Diltiazem hydrochloride was released from formulation Ic, and more than 80% from formulation Ib. But, from

TABLE 2

The determination of Diltiazem hydrochloride in pellets

Series	mean weight ± SD (mg) n = 20	mean Diltiazem. HCl content ± SD (mg) n = 10
Ia	432,9 ± 1,8	169,00 ± 1,60
Ib	437,5 ± 1,5	170,00 ± 1,00
Ic	430,0 ± 1,2	169,00 ± 1,00
IIa	569,0 ± 2,0	169,80 ± 1,60
IIb	567,2 ± 3,0	168,95 ± 1,50
IIc	564,2 ± 2,2	169,00 ± 2,00
IIIa	577,6 ± 3,5	169,50 ± 2,20
IIIb	519,3 ± 1,8	168,00 ± 1,90
IIIc	478,2 ± 3,0	169,00 ± 2,00

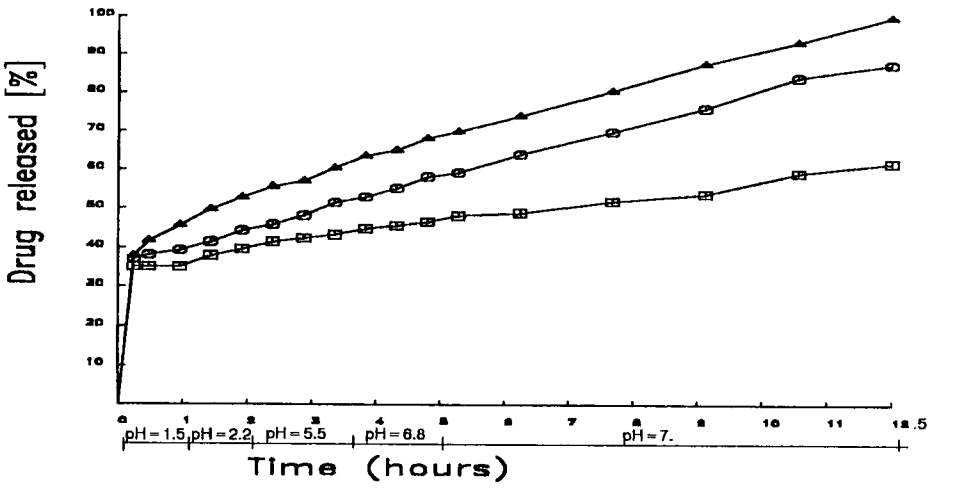

FIGURE 1

Cumulative amounts of Diltiazem hydrochloride released from series Ia, Ib and Ic. Each point represents the mean (n = 5-10).
Symbols : □ Ia, ○ Ib, △ Ic.

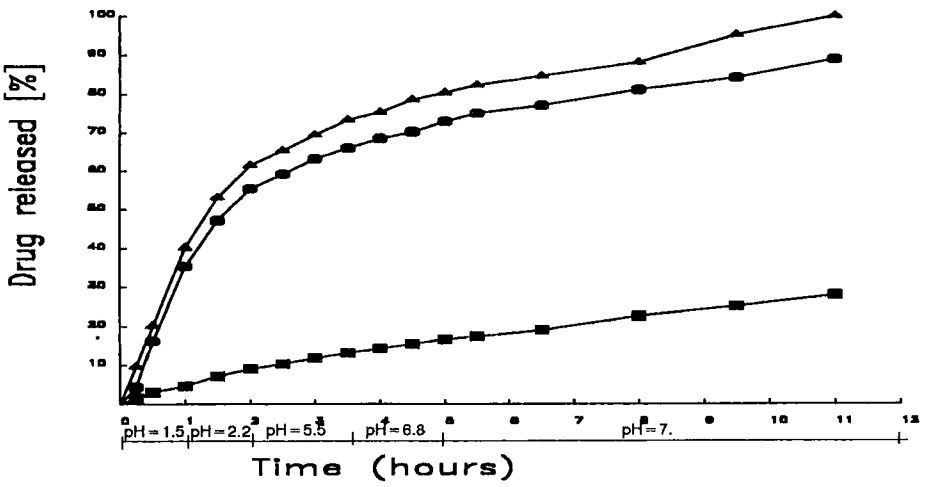

FIGURE 2

Cumulative amounts of Diltiazem hydrochloride released from series IIa, IIb and IIc. Each point represents the mean (n = 5-10).
Symbols : ■ IIa, ● IIb, ▲ IIc.

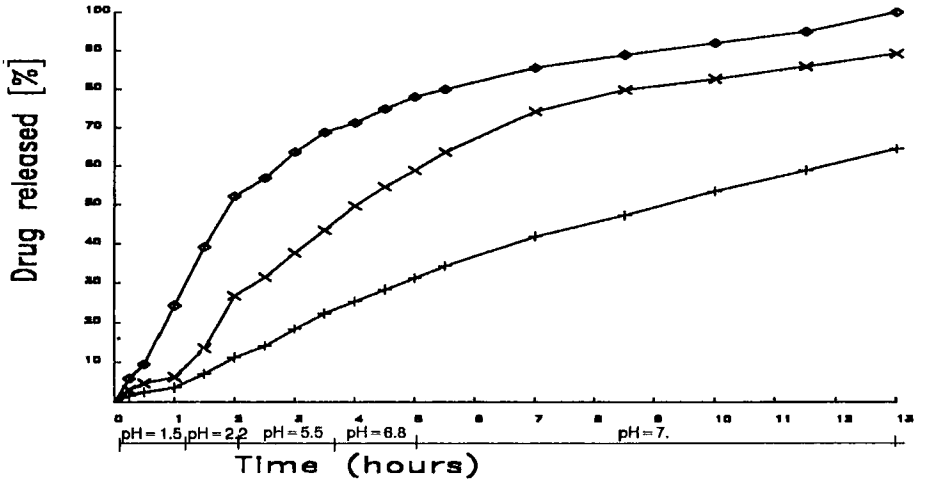

FIGURE 3

Cumulative amounts of Diltiazem hydrochloride released from series IIIa, IIIb and IIIc. Each point represents the mean (n = 5-10).
Symbols : + IIIa, × IIIb, ◆ IIIc.

formulation Ia, after 12th hour was released only 60% of Diltiazem hydrochloride, which was not satisfactory.

The results of dissolution test with the coated Diltiazem pellets of formulations IIa-c are shown in Figure 2. Permeability of coatings in gastric juice depends on percentage of Eudragit L in formulation. As can be seen from Figure 2, an initial release of drug in first two hours was different, due to the different percentage of Eudragit L in formulations. There was no sufficient initial drug quantity released from samples IIa, but increasing the percentage of Eudragit L in formulation, a sufficient initial drug quantity was released from formulations IIb and IIc. Also, the permeability of coatings in intestinal juices depends on the percentage of Eudragit L in formulation. The releasing rate for samples IIa was very low, and only about 25% of drug was released for 11 hours. From samples IIb and IIc there was released about 90% and 100% of Diltiazem hydrochloride for 11 hours, respectively. Increasing percentage of Eudragit L from 30 to 40 and 50%, better dissolution characteristics were developed, but there is always a danger of unsuitable initial drug quantity released in gastric juice.

The results of dissolution tests with the coated Diltiazem pellets of formulations IIa-c are shown in Figure 3.

As can be seen from Figure 3, an initial drug quantity released from samples was very low for formulation IIIa, low for formulation IIIb, and sufficient for samples IIIc, where the amount of coating was 2mg/cm^2. The releasing rate depends on the amount of coating, and for 13 hours about 65% was released from formulation IIIa, about 90% was released from samples IIIb and about 100% Diltiazem hydrochloride was released from samples IIIc.

Kinetic of Diltiazem hydrochloride release from pellets

In the present study, for formulation Ia, diffusion model (square-root) was not sufficiently linear, and the linearity was best by using first-order kinetic, Hixon-Crowell's equation and Weibull's

TABLE 3

Kinetic models for samples Ia, Ib and Ic

series	pH	First-order kinetic		Hixson-Crowell 's eq.		Diffusion model		Weibull function	
		k,min^{-1}	f	k,$\%^{1/3}min^{-1}$	f	k,$\%min^{-1/2}$	f	Td.63,2% (min)	f
Ia	1,5	0,0168	0,9966	0,0284	0,9949	6,6485	0,9875	810	0,9967
	2,2	0,0048		0,0081		3,8049			
	5,5	0,0031		0,0053		3,1789			
	6,8	0,0023		0,0038		2,7919			
	7,0	0,0016		0,0025		2,3997			
Ib	1,5	0,0184	0,9907	0,0316	0,9968	7,2176	0,9866	340	0,9761
	2,2	0,0048		0,0082		4,0532			
	5,5	0,0034		0,0056		3,5538			
	6,8	0,0029		0,0047		3,3659			
	7,0	0,0025		0,0037		3,1917			
Ic	1,5	0,0199	0,9769	0,0335	0,9314	7,7534	0,9950	225	0,9752
	2,2	0,0069		0,0114		5,0340			
	5,5	0,0049		0,0083		4,3267			
	6,8	0,0039		0,0062		4,0016			
	7,0	0,0037		0,0056		3,6692			

Symbols : k - release rate constant, f - correlation coefficient

TABLE 4

Kinetic models for samples IIa, IIb and IIc

series	pH	First-order kinetic		Hixson-Crowell's eq.		Diffusion model		Weibull function	
		k,min^{-1}	f	k,$\%^{1/3}min^{-1}$	f	k,$\%min^{-1/2}$	f	Td.63,2% (min)	f
IIa	1,5	0,0008	0,9883	0,0015	0,9983	0,5940	0,9972		0,9861
	2,2	0,0008		0,0014		0,8210			
	5,5	0,0007		0,0012		0,8970			
	6,8	0,0006		0,0011		0,9580			
	7,0	0,0016		0,0009		1,0767			
IIb	1,5	0,0054	0,9861	0,0095	0,9553	2,8746	0,9577	166	0,9781
	2,2	0,0064		0,0113		5,0065			
	5,5	0,0051		0,0079		4,5470			
	6,8	0,0043		0,0065		4,2090			
	7,0	0,0037		0,0051		3,7740			
IIc	1,5	0,0076	0,9879	0,0136	0,9844	3,7940	0,9632	116	0,9742
	2,2	0,0082		0,0131		5,6010			
	5,5	0,0063		0,0093		5,0510			
	6,8	0,0054		0,0077		4,6300			
	7,0	0,0052		0,0066		4,1170			

Symbols : k - release rate constant, f - correlation coefficient

TABLE 5

Kinetic models for samples IIIa, IIIb and IIIc

series	pH	First-order kinetic		Hixson-Crowell's eq.		Diffusion model		Weilbull function	
		k,min^{-1}	f	k,$\%^{1/3}min^{-1}$	f	k,$\%min^{-1/2}$	f	Td.63,2% (min)	f
IIIa	1,5	0,0008	0,9984	0,0015	0,9989	0,4350	0,9919	780	0,9989
	2,2	0,0009		0,0016		0,8700			
	5,5	0,0012		0,0021		1,5200			
	6,8	0,0012		0,0021		1,7800			
	7,0	0,0013		0,0021		2,2250			
IIIb	1,5	0,0014	0,9969	0,0026	0,9988	1,0233	0,9829	360	0,9973
	2,2	0,0026		0,0045		2,6970			
	5,5	0,0029		0,0047		3,3670			
	6,8	0,0032		0,0048		3,6000			
	7,0	0,0031		0,0045		3,4267			
IIIc	1,5	0,0040	0,99 19	0,0072	0,9852	2,1173	0,9639	180	0,9579
	2,2	0,0058		0,0096		4,4050			
	5,5	0,0054		0,0084		4,7000			
	6,8	0,0049		0,0072		4,4600			
	7,0	0,0042		0,0058		3,8825			

Symbols : k - release rate constant, f - correlation coefficient

distribution function. The differences between these models was noted to be minimal, as presented in Table 3. For formulation Ib, the best fit kinetic model was cube-root equation , also minimal differences were noted with first-order kinetic model. There was no sufficient linearity for diffusion model and Weibull's distribution function (Table 3) . The release pattern for formulation Ic, including the highest proportion of Eudragit L (50%), corresponded best to first-order equation, and correlation coefficients for other kinetic models were low (Table 3).

For formulation IIa the best fit kinetic models were cube-root equation and diffusion model, and the difference between these two models was noted to be minimal. But, there were no significant correlation coefficients with the presented kinetic models for other two series, IIb and IIc (Table 4).

As can be seen from Table 5, on plotting logarithms of undissolved drug versus time, linearity was best for samples IIIa, and correlation coefficients for other kinetic models were low. For samples IIIb there was minimal difference between first-order kinetic model and Hixson-Crowell's equation, and they were the best fit kinetic models for these formulations. Also the correlation coefficients for other kinetic models were low. For samples IIIc correlation coefficients for all four kinetic models were low.

CONCLUSIONS

The results of the study showed that it is possible to produce coated pellets with prolonged Diltiazem hydrochloride release, by a pan coating method. The release rate of Diltiazem hydrochloride was depended on the ratio of Eudragit polymers. The coating thickness also had significant effects on drug release rate.

REFERENCES

1. J.R. Kilborn, S. Battellocchi, J. Larribaud and P.L. Morselli in "New drug therapy with acalcium antagonists", J.R. Bing, eds., Excerpta Medica, Amsterdam, 1978, p.129.
2. R. Zelis, N. Engl. J. Med., 306,926 (1982).
3. M. Chaffman, R. N. Brogden, Drugs, 29, 387 (1985).
4. P.E. Pool, S.C. Seagren, Am. J. Cardiol., 49, 573 (1982).
5. K. Murata, H. Yamahara, M. Kobayashi, K. Noda, M. Samejima, J. Pharm. Sci., 11, 960 (1989).
6. K. Vasilevska, Z. Djurić, M. Jovanović, M. Stupar, A. Simov, Pharmazie, 46 (1991)H.1
7. F. Ferrari, M.C. Bonferoni, C. Caramella, M. De Bernardi di Valsera, F. Feletti, M.R. Galmozzi, 9th Pharmaceutical Technology Conference, April 1990.
8. W.A. Ritchael, DDIP, 15(6&7), 1073 (1989).
9. B. Hecquet, C. Fornier, G. Depadt, P.J. Cappelaere, J. Pharm. Pharmacol., 36, 803 (1984).
10. M. Donbrow, S. Benita, J. Pharm. Pharmacol., 34, 547 (1982).
11. S. Benita, M. Donbrow, Int. J. Pharm., 12, 251 (1982).
12. A.W. Hixson, J.H. Crowell, Ind. Engin. Chem., 23, 923 (1931).
13. F. Langenbucher, J. Pharm. Pharmacol., 24, 979 (1972).