DESIGN AND EVALUATION OF DILTIAZEM MUCOADHESIVE TABLETS FOR ORAL CONTROLLED RELEASE

K. P. R. Chowdary*, B. Suresh, B. Sangeeta and G. Kamalakara Reddy

تم إجراء دراسة استقصائية على أقراص هلامية لاصقة من عقار ديلتيازيم والتي تم صياغتها كأقراص منبت (منشأ أو أرضية) بواسطة صوديوم كاربوكسي ميثيل سليولوز، وهيدروكسي بروبيل ميثيل سليولوز، وإيثيل سليولوز. وقد تآكلت ببطء الأقراص المُصاغة بالصوديوم كاربوكسي ميثيل سليولوز، والهيدروكسي بروبيل ميثيل سليولوز وذابت تماماً خلال 4-5 ساعات. وعندما تم وضع إيثيل سليولوز، بقيت الأقراص كاملة وأعطت إطلاقاً بطيئاً ممتداً للدلتيازم على مدى 10-12 ساعة. أما الأقراص المصاغة بالصوديوم كاربوكسي ميثيل سليولوز مع 5% من إيثيل سليولوز فأعطت إطلاقاً بطيئاً وكاملاً على مدار 12 ساعة وتبين أنها مناسبة للجزء التعويضي من الأقراص الفموية المحكومة الإطلاق. وقد تبين من دراسات الأشعة السينية أن هذه الأقراص قد أظهرت التصاقاً هلامياً جيداً في المعي لمدة 10-12 ساعة. كما ثبت أن الإطلاق لا يتبع قانون "فِكْ" في معظم التراكيب. وفي حالة تركيبه ذات طبقتين إحداها ذات إطلاق مباشر تتكون من الدلتيازم وكروسكارميلوز صوديوم (مُفكَك سريع جداً)، وأرضية (مطرس) تتكون من الدلتيازم وصوديوم كاربوكسي ميثيل سيليولوز وايثيل سليولوز كطبقة تعويضية ثانية، أعطت إطلاقاً قريباً من الإطلاق الممتد المفعول النظري المطلوب للدلتيازم.

Mucoadhesive tablets of diltiazem were formulated as matrix tablets employing sodium carboxymethylcellulose (Sodium CMC), hydroxypropylmethylcellulose (HPMC) and ethyl cellulose and were investigated. Tablets formulated employing sodium CMC and HPMC alone were slowly eroded and were dissolved completely within 4-5 hr. When ethyl cellulose was incorporated, the tablets remained intact and provided slow release of diltiazem for over 10-12 hr. Tablets formulated employing sodium CMC with 5% ethyl cellulose gave slow and complete release over a period of 12 hours and were found suitable for the maintenance portion of oral controlled release tablets. These tablets exhibited good mucoadhesion in the intestine for 10-12 hr in the x-ray studies. Non-Fickian release was observed from most of the formulations. A two-layered tablet formulation, an immediately releasing layer consisting of diltiazem and croscarmellose sodium, (a superdisintegrant) and a matrix consisting of diltiazem, sodium CMC and ethyl cellulose as a second maintenance layer, gave release close to the theoretical sustained release (SR) needed for diltiazem.

Key Words: Mucoadhesive tablets, diltiazem, ethyl cellulose, controlled release (CR), mucoadhesive polymers.

Introduction

Diltiazem is a calcium channel blocker, which has been used in the treatment of various cardiovascular disorders, particularly angina pectoris and systemic hypertension (1). It has a short biological half-life of about 3.5 hr (2) and is rapidly eliminated. The oral bioavailability of diltiazem is 40 % in humans (3). Because of its low bioavailability and short biological half-life attempts have been made to develop sustained release products with extended clinical effects and a reduced dosing frequency (4). As diltiazem hydrochloride is a highly water-soluble drug, its formulation into SR products is rather difficult. There are a few reports on the formulation of oral controlled release products of diltiazem employing coated beads (5),

Department of Pharmaceutical Sciences, Andhra University, Visakhapatnam- 530 003, INDIA.
e-mail: profkprc@rediffmail.com
* To whom correspondence should be addressed

pan coating (6), microencapsulation (7) and complexation (8) techniques. In the present investigation mucoadhesive tablets of diltiazem were formulated employing sodium CMC and HPMC as mucoadhesive materials. These materials are reported (9) to have good mucoadhesive properties. Mucoadhesive polymers prolong the residence time of the dosage form in the gastro-intestinal tract and hence they are more suitable as matrix material for oral controlled release (10). The tablets were evaluated for drug release kinetics and mechanisms and *in vivo* mucoadhesive property.

Experimental

Materials and Methods

Diltiazem hydrochloride, USP, croscarmellose sodium (Ac-Di-Sol) and HPMC (having a viscosity of 50 cps in 2 % by weight aqueous solution at 20°C) were gift samples from M/s Natco Pharma Pvt. Ltd., Hyderabad, India. Sodium CMC (having a viscosity of 1500-3000 cps in a 1 % w/v aqueous solution at 25°C), ethyl cellulose (having an ethoxyl content of 47.5 % by weight and a viscosity of 22 cps in 5 % concentration by weight in 80:20 toluene-ethanol solution at 25°C), methanol GR, talc I.P. and magnesium stearate I.P. were procured from M/s Loba Chemie, Mumbai, India. Dilzem SR tablets (M/s Torrent Pharmaceuticals Ltd, Indrad; Batch No. 1006011; Mfg. date: 6-2000; Exp. date: 5-2003) were procured from local market.

Estimation of diltiazem

An Ultraviolet (UV) spectrophotometric method based on the measurement of absorbance at 237 nm in water was used for the estimation of diltiazem (1). The method obeyed Beer's law in the concentration range of 0-20 µg/ml. When a standard drug solution was assayed repeatedly (n=6) the relative error (accuracy) and relative standard deviation (precision) were found to be 0.9% and 1.2% respectively.

Preparation of Mucoadhesive Tablets

Mucoadhesive matrix tablets each containing 90 mg of diltiazem hydrochloride were prepared by conventional wet granulation method employing sodium CMC and HPMC as mucoadhesive materials as shown in the formulae given in Table 1. A batch of 100 tablets was prepared in each case. A blend of diltiazem hydrochloride (9.0 g) and the required amounts of sodium CMC or HPMC and ethyl cellulose were granulated with a solvent blend of water and ethyl alcohol (1:1). The wet masses were passed through 12 mesh sieve and the wet granules produced were dried at 60°C for 4 hours. The dried granules (16 mesh) after blending with talc (0.5 g) and magnesium stearate (0.5 g) in a laboratory cube blender for 5 minutes were compressed into 250 mg tablets of hardness 7-8 kg/sq. cm on a Cadmach single punch tablet machine (M/s Cadmach machinery Co., Pvt. Ltd., Ahmedabad, India) using 9 mm flat surface tablet tools. The tablets were tested for hardness, friability, disintegration time and drug content.

Hardness of the tablets was tested using a Monsanto hardness tester (M/s Campbell Electronics, Mumbai, India.). Friability of the tablets was determined in a Roche friabilator (M/s Campbell Electronics, Mumbai, India). Disintegration times were determined in a Thermonic tablet disintegration test machine (M/s Campbell Electronics, Mumbai, India) using water, 0.1 N HCl and phosphate buffer of pH 7.4 as the test fluids according to USP method for uncoated tablets.

Table 1. Formulae of Diltiazem Mucoadhesive Tablets Prepared

No.	Ingredient	Formulation							
	(mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8
1.	Diltiazem	90	90	90	90	90	90	90	90
2.	*Ethyl cellulose*	-	5	12.5	25	-	5	12.5	25
3.	Sodium CMC	150	145	137.5	125	-	-	-	-
4.	HPMC	-	-	-	-	150	145	137.5	125
5.	Talc	5	5	5	5	5	5	5	5
6.	Magnesium stearate	5	5	5	5	5	5	5	5

Table 2. Release Profiles of Diltiazem from Mucoadhesive Tablets

Formulation	Percent Diltiazem Released at Times (hr) $\bar{X}$ ± s.d.					T_{50} (hr)	Release rate (mg/hr)
	1.0	2.0	4.0	8.0	12.0		
F1	14.42 ± 1.16	25.98 ± 2.75	61.66 ± 1.83	99.72 ± 0.44	-	3.4	13.37
F2	14.05 ± 3.51	23.19 ± 3.04	40.73 ± 2.06	82.23 ± 1.01	93.47 ± 1.07	4.8	8.075
F3	13.93 ± 3.89	21.17 ± 0.24	37.51 ± 1.70	75.05 ± 4.63	99.67 ± 0.24	5.1	7.635
F4	4.08±1.44	6.81±1.89	23.54±0.08	56.89±1.08	86.32±1.93	7.2	6.760
F5	46.48 ± 1.23	68.80 ± 1.95	84.64 ± 2.49	-	-	1.1	8.27
F6	37.64 ± 2.48	55.16 ± 2.91	82.00 ± 1.94	-	-	1.7	9.94
F7	51.13 ± 1.11	80.57 ± 1.91	90.38 ± 1.02	-	-	0.9	12.86
F8	59.39±2.09	68.86±1.87	86.76±1.34	-	-	0.8	8.18
Two layered tablet as described in text	34.31 ± 2.33	39.82 ± 3.37	47.91 ± 1.89	71.34 ± 1.82	95.2 ± 0.69	4.4	5.193
Theoretical SR profile needed	33.3	40.0	53.33	80.0	100	-	5.605

Table 3. Correlation Coefficient (r) Values in Various Kinetic Models Tested to Describe Drug Release from the Mucoadhesive Tablets Formulated.

Formulation	Zero	First	Higuchi	Weibull	Korsmeyer-Peppas	n
F1	0.995	0.926	0.978	0.995	0.995	1.11
F2	0.963	0.988	0.981	0.992	0.992	0.858
F3	0.997	0.941	0.992	0.996	0.996	0.833
F4	0.996	0.955	0.982	0.994	0.994	1.28
F5	0.949	0.984	0.980	0.984	0.984	0.397
F6	0.997	0.989	0.998	0.999	0.999	0.554
F7	0.918	0.956	0.932	0.951	0.951	0.421
F8	0.998	0.993	0.997	0.992	0.992	0.272
CR	0.996	0.940	0.977	0.961	0.962	0.403
CP	0.967	0.995	0.989	0.994	0.991	0.569

n: diffusional exponent derived from Peppas equation.
CR: Controlled release formulation designed as a two layered tablet; CP: Commercial product

Drug Release Study on Mucoadhesive Tablets

Release of diltiazem from the tablets was studied in water (900 ml) as prescribed for diltiazem extended release tablets in USP XXIV employing apparatus 2. A 3-station dissolution rate test apparatus (Model DR-3, M/s Campbell Electronics, Mumbai, India) was used. One tablet containing 90 mg of diltiazem, at paddle speed of 100 rpm and a temperature of 37 ± 0.5°C were employed in each test. Samples were withdrawn through a filter (0.45 μ) at different time intervals, suitably diluted and assayed spectrophotometrically at 237 nm using a Shimadzu UV-150 double beam spectrophotometer. For comparison drug release from Dilzem SR tablets was also studied as described above. Drug release experiments were conducted in triplicates.

In vivo Mucoadhesion Testing

The *in-vivo* evaluation of the mucoadhesive property of the tablets formulated was performed in human subjects by X-ray studies. For this purpose tablets containing barium sulphate (instead of diltiazem) were prepared employing sodium CMC and HPMC as matrix materials. These tablets were administered to healthy human subjects along with a glassful of water after overnight fasting. X-ray photographs were taken at different time intervals (0, 2, 4, 6, 8 and 10 hr) and observed for the position of the tablets.

Analysis of Release Data

The release data obtained were fitted to zero-order (11), first order (12), Higuchi (13), Korsmeyer-Peppas (14-16) and Weibull (17-19) equations to determine the corresponding release rate and mechanism of drug release from the mucoadhesive tablets.

Results and Discussion

All the prepared mucoadhesive matrix tablets were found to be non-disintegrating in water, 0.1 N HCl and phosphate buffer of pH 7.4. Hardness of the tablets was in the range 7-8 kg/sq.cm. Percentage weight loss in the friability test was found to be 0.2 % in all the cases. The tablets in all the prepared batches contained diltiazem within 100 ± 5 % of the labeled content. As such all the batches of tablets prepared were of good quality with regard to hardness, friability and drug content.

Diltiazem release from the tablets was slow and extended over longer periods of time. The release profiles are shown in Table-2. When the tablets were formulated employing mucoadhesive polymer alone the tablets were slowly eroded and they completely dissolved in 4-5 hr. Whereas when ethyl cellulose was incorporated along with the mucoadhesive polymer the tablets were found to be intact over a period of 12 hr due to the water insoluble nature of ethyl cellulose and the diltiazem release was spread over a longer period of time. The release was relatively fast from tablets formulated with both HPMC alone and with ethyl cellulose and was complete within 4-5 hr. Whereas sodium CMC gave slow controlled and complete release of diltiazem over a period of 12 hr.

The X-ray studies (20) showed that (Fig. 1) the tablets formulated with sodium CMC and ethyl cellulose (5 %) were intact and remained in the intestinal region even after 10 hr of administration indicating good adhesion of the tablets in the intestinal region.

Several kinetic models describe drug release from immediate and modified release dosage forms (11-19). The model that best fits the release data was evaluated by correlation coefficient (r). The correlation coefficient (r) value was used as criteria to choose the best model to describe drug release from the mucoadhesive controlled release tablets. The r-value in various models is given in Table 3. The r-values ($r>0.932$) obtained for fitting the drug release data to the Higuchi equation, indicated that the drug release mechanism from these tablets was diffusion controlled. In most of the formulated tablets the r values were higher in zero order model than in first order model indicating the drug release from most of the tablets was according to zero order kinetics. The values of n in Peppas model also indicated that most of the products followed non-Fickian release i.e. zero order. Thus drug release from the mucoadhesive tablets formulated was diffusion controlled and followed zero order kinetics.

The mucoadhesive tablets formulated with sodium CMC were found suitable for the maintenance portion of oral controlled release tablets. Due to small initial release burst effect, an immediately releasing loading dose may be applied either as a coat or as a layer on these tablets. Oral controlled release tablets each containing 90 mg of diltiazem were designed as two layered tablets, an immediately releasing layer consisting of diltiazem (30 mg) and croscarmellose sodium (Ac-Di-Sol), a super disintegrant and a matrix consisting of diltiazem (60 mg), ethyl cellulose (5 %), sodium CMC (91 %), talc (2 %) and magnesium stearate (2 %) as a second layer. The release profile of this controlled release formulation is shown in Table 2.

Theoretical sustained release profile needed for diltiazem was evaluated based on its pharmacokinetic parameters (21). An oral controlled release formulation of diltiazem should contain a total dose of 90 mg and should provide a release of 33.3 % in 1 hr, 40.0 % in 2 hr, 53.3 % in 4 hr, 80.0 % in 8 hr and 100 % in 12 hr according to theoretic sustained release profile. Oral controlled release formulation designed as a two layered tablet gave release close to the theoretical SR needed for

diltiazem. Diltiazem release from this formulation was also comparable to that of a commercial SR tablet tested.

Conclusion

Slow, controlled and complete release of diltiazem over a period of 12 hr was obtained from matrix tablets (F3) formulated employing sodium CMC and ethyl cellulose (5 %). These tablets exhibited good mucoadhesion in the intestine for over 10 hr. Good oral controlled release two layered mucoadhesive tablet formulation of diltiazem could be developed using sodium CMC and ethyl cellulose.

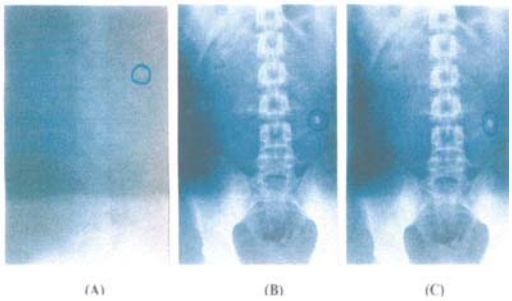

Fig. 1. X-Ray photographs taken at 2 hr (A), 6 hr (B) and 10 hr (C) after oral administration of matrix tablets of barium sulphate similar in composition to diltiazem formulation F3.

References

1. United States Pharmacopoeia, XXIV, United States Pharmacopoeial Convention, Inc., Rockville, M.D., 2000; 573-576.
2. Kinney E, Moskovitz RM and Zelis RF. Pharmacokinetics and pharmacology of oral diltiazem in normal volunteers. J. Clin. Pharmacol., 1981; 21: 337-342.
3. Chaffman M and Brogden RN. Diltiazem: a review of its pharmacological properties and therapeutic efficacy. Drugs., 1985; 29: 387-454.
4. Murata K, Yamahara H, Kobayashi M, Nodak K and Samejima M. Pharmacokinetics of an oral sustained release diltiazem preparation. J. Pharm. Sci., 1989; 78: 960-963.
5. Deboeck, A M. and Raymond, B P. Extended release form of diltiazem, PCT Int. Appl. WO 93, 00, 093. Through CA: 1993; 118: 132163v.
6. Vasilevska K, Djuric Z, Jovanovic M and Simov A. Preparation and dissolution characteristics of controlled release diltiazem pellets. Drug Dev. Ind. Pharm., 1992; 18(15): 1649-1661.
7. Chowdary KPR and Ramesh KVRNS. Studies on Microencapsulation of Diltiazem, Indian J. Pharm. Sci., 1993; 55(2): 52-54.
8. Horiuchi Y, Hirayama F and Uekema K. Slow release characteristics of diltiazem from ethylated beta-cyclodextrin complexes. J. Pharm. Sci., 1990; 79: 128-.132.
9. Lee, J W., Park, J H. and Robinson, J R. Bioadhesive-based dosage forms: The next generation. J. Pharm. sci., 2000; 89(7): 850-863.
10. Chowdary KPR, Kamalakara Reddy G and Bhaskar P. Mucoadhesive polymers – promising excipients for controlled release. Int. J. Pharma Excip., 2001; 2: 33-38.
11. Najib N and Suleiman M. The kinetics of drug release from ethyl cellulose solid dispersions. Drug Dev. Ind. Pharm., 1985; 11: 2169-89.
12. Desai SJ, Singh P, Simonelli AP and Higuchi WI. Investigation of factors influencing release of solid drug dispersed in wax matrices III. Quantitative studies invovling polyethylene plastic matrix. J. Pharm. Sci., 1966; 55: 1230-1234.
13. Higuchi T. Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci., 1963; 52: 1145-1149.
14. Korsmeyer RW, Gunny R, Doelker EM, Buri P and Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int. J. Pharm. 1983; 15: 25-35.
15. Ritger PL and Peppas NA. Simple equation for description of solute release. I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or disks. J. Control Release 1987; 5: 23-26.
16. Ritger PL and Peppas NA. A Simple equation for description of solute release. II Fickian and anomalous release from swellable devices. J. Control. Release 1987; 5: 37-42.
17. Langenbucher F. Linearization of dissolution rate curves by the Weibull distribution. J. Pharm. Pharmacol. 1972; 24: 979-981.
18. Goldsmith JA, Randall N and Ross SD. Methods of expressing dissolution rate data. J. Pharm. Pharm. 1978; 30: 347-349.
19. Romero P, Costa JB, Castel-Maroteaux X and Chulia D. Statistical optimization of a controlled release formulation obtained by a double compression process: application of a hdamard matrix and a factorial design. In: Wells JI, Rubin stein MH. (Eds.), Pharmaceutical Technology, Controlled Drug Release, 1991; Vol. 2, Ellis Harwood. New York, pp. 44-58.
20. Madhusudhan Rao Y, Vani G and Bala Ramesha Chary R. Studied the mucoadhesive property of bioadhesive tablets by X-ray studies in rabbits. Indian Drugs. 1998; 35: 558-561.
21. Wagner JG. Biopharmaceutics and Pharmacokinetics. Ist ed. Drug Intelligence Publications. 1971; 22: 148-157.