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Research Article

FORMULATION AND EVALUATION OF SINTERED MATRIX TABLETS OF DILTIAZEM HYDROCHLORIDE

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ABSTRACT

In the present work, sustained release (SR) sintered matrix tablets of Diltiazem hydrochloride were prepared by trituration method using 4% and 8% HPMC K_4M and HPMC $K_{15}M$ and then sintered. The prepared tablets were transferred to the sintering chamber (dessicator filled with acetone in the bottom and equilibriated for 24 hours with vapour) and exposed to different sintering time like 3 hours and 6 hours. The release characteristics study was carried out in USP XXI model.

900ml dissolution medium of 0.1N HCI (pH 1.2) was used for the first 2 hours and pH 6.8 phosphate buffer for remaining 8 hours. The revolutions at 50rpm and temperature at 37±1°C were maintained. From *In vitro* drug release profile, formulations F_5, F_6 and F_9 exhibited sustained drug release profiles with maximum sustaining effect when compared with unsintered formulation in about 8 hours. By using sintering technique, friability of tablets was found to decrease with increasing sintering time and hardness was increased with increasing sintering time.

Keywords: Diltiazem HCL, Sintering, HPMC K_4M, HPMC $K_{15}M$, Sustained release tablets.

INTRODUCTION

Diltiazem HCl is a 'calcium channel blocker' which is widely used in the treatment of hypertension, angina pectoris and cardiac arrhythmias. In the present study, an attempt has been made to prepare sustained drug delivery of Diltiazem HCl by using sintering technique to improve patient compliance, better therapeutic efficacy, less side effects and reduced dosage regimen with less toxicity for the treatment of many diseases. The drug as hydrochloride is readily soluble in water, and its elimination half-life is short enough for it to be a suitable candidate for SR formulation.

The term sintering means fusion of particles or formation of welded bonds between particles of polymer. The SR oral dosage forms can be developed by sintering the polymer matrix by exposing to temperature above glass transition point of the polymer or exposing these matrix systems to solvent vapours. As the temperature treatment method may be a limiting factor for many drugs that get degraded at elevated temperature, therefore, in the present investigation, solvent casting method was followed in which the above mentioned problems were eliminated.

MATERIAL AND METHODS

Materials

Diltiazem HCl was a gift sample from Cipla Mumbai. HPMC K_4M and HPMC $K_{15}M$ (Ipca Laboratories, Mumbai) were used as received. All other chemicals used were of analytical grade and were used as received.

Methods

Preparation of SR sintered matrix tablets of Diltiazem HCl was done by trituration method using different drug:polymer ratio. HPMC K_4M and HPMC $K_{15}M$ were used as matrix forming material. Formulations F_1 to F_{12} were prepared by using 4% and 8% polymer. The prepared tablets were transferred to the sintering chamber (dessicator filled with acetone in the bottom and equilibrated for 24 hours with vapour) and exposed to different sintering time like 3 hours and 6 hours.

Evaluation of Sintered Matrix Tablets

All prepared matrix tablets were evaluated for the following parameters:

Hardness or tablet crushing strength (the force required to break a tablet in diametric compression) was measured using Monsanto tablet hardness tester.

Friability of the tablets was determined using Roche friabilator (Electrolab, Mumbai). This device subjects the tablets to the combined effect of abrasions and shocks in a plastic chamber revolving at 25rpm and dropping the tablets at a height of 6 inches in each revolution.

Pre-weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were de-dusted using a soft muslin cloth and re-weighed. A loss of less than 0.5-1% in weight is generally considered acceptable.

Weight variation

Average weight was determined by weighing 20 tablets. Not more than two tablets deviated from the average weight by a percentage greater than that given and no tablet deviated by more than double that percentage.

Content uniformity

Ten tablets were triturated and the weight equivalent to one average tablet was dissolved in a suitable quantity of methanol. The solution was filtered and the filtrate was dried. Dried powder was dissolved in a suitable quantity of glacial acetic acid and titrated with freshly prepared and standardized 0.1N perchloric acid using crystal violet as an indicator. A blank was performed in the same manner omitting the drug.

In vitro drug release studies

The dissolution of dosage form acts as a rate limiting factor in determining the physiologic availability. The release characteristic study was carried out in USP XXI rotating basket dissolution apparatus. 900ml dissolution medium of 0.1N HCl (pH 1.2) was used for the first 2 hours and pH 6.8 phosphate buffer for the next 8 hours. The revolutions at 50rpm and temperature at 37±1°C were maintained.

The sink condition was maintained by replacing 5ml aliquot with fresh equal amount of dissolution media of the same pH at the end of every hour. These aliquots were assayed at 240nm Spectrophotometrically. The cumulative percentage release of Diltiazem HCl at regular time interval was calculated.

RESULTS AND DISCUSSION

A simple technique of sintering method was used in present investigation. SR matrix tablets of Diltiazem HCl were prepared using hydrophilic polymers like HPMC K_4M and HPMC $K_{15}M$ and

unsintered formulations were compared with sintered formulations. The formulation variables and various physico-chemical properties of prepared unsintered and sintered matrix tablets are shown in Tables 1*, 2* and *3.* The dissolution rate studies were performed by using USP XXI tablet dissolution tester. The data from the dissolution profiles are shown in the tables and graphs. The cumulative percentage release at 8th hour for formulations F_1 to F_{12}(Table 3) are: F_1-95.70 , F_2-85.30, F_3-86.30, F_4-82.40, F_5-81.42, F_6-78.66, F_7-71.00,
F_8-60.66, F_9-74.00, F_{10}-72.73, F_{11}-57.20 and F_{12}-61.16.

Based on the results obtained for the drug release, the unsintered formulations F_1, F_2, F_3, F_4 were comparable to the drug release profile of sintered formulations F_5, F_6, F_7, F_8, F_9, F_{10}, F_{11}, F_{12}. Since, formulations F_1, F_2, F_3,, F_4 were unsintered, it showed the maximum drug release and had tendency to greater percentage friability as compared to sintered formulations and thus proved to be better formulations.

From the *Figures 1, 2, 3 and 4,* the increase in the amount of HPMC K_4M and HPMC $K_{15}M$ decreases the cumulative percentage of drug release. Also, increase in sintering time causes the decrease in the cumulative percentage of drug release.

Amongst all formulations, sintered formulations F_5, F_6, F_7, F_8, F_9, F_{10}, F_{11}, F_{12} exhibited sustained drug release profiles with maximum sustaining effect when compared with unsintered formulations F_1, F_2, F_3, F_4 in about 8 hours.

Table 1: Composition of various formulations F_1 to F_{12}

Sr. No.	Ingredients	Formulations											
		F_1 (US) (mg)	F_2 (US) (mg)	F_3 (US) ((mg)	F_4 (US) (mg)	F_5 (S_3) (mg)	F_6 (S_3) (mg)	F_7 (S_6) (mg)	F_8 (S_6) (mg)	F_9 (S_3) (mg)	F_{10} (S_3) (mg)	F_{11} (S_6) (mg)	F_{12} (S_6) (mg)
1.	Diltiazem HC1	120	120	120	120	120	120	120	120	120	120	120	i20
2.	HPMC K_4M	19.2	38.4	-	-	19.2	38.4	19.2	38.4	-	-	-	
3.	HPMC $K_{15}M$	-	-	19.2	38.4		- -	-	-	19.2	38.4	19.2	38.4
4.	Dicalcium Phosphate	288.96	269.76	288.96	269.76	288.96	269.76	288.96	269.76	288.96	269.76	288 96	269.76
5.	Talc 4%	19.2	19.2	19.2	19.2	19.2	19.2	19.2	19.2	19.2	19.2	19.2	19.2
6.	Magnesium Stearate 0.8%	38.4	38.4	38.4	38.4	38.4	38.4	38.4	38.4	38.4	38.4	38.4	38.4
7.	Starch 6%	28.8	28.8	28.8	28.8	28.8	28.8	28.8	28.8	28.8	28.8	28.8	28.8

F_1, F_5, F_7 = 4% HPMC K_4M formulation. F_2, F_6, F_8 = 8% HPMC K_4M formulation.
F_3, F_9, F_{11} = 4% HPMC $K_{15}M$ formulation. F_4, F_{10}, F_{12} = 8% HPMC $K_{15}M$ formulation.
(US) = Unsintered. (S_3) and *(S_6) = Sintered for 3 hours and 6 hours respectively.*

(Weight of each tablet: 480mg)

Table 2: Physicochemical properties or prepared tablets

Formula code	Friability (%)	Hardness (kg/cm²)	Content uniformity (%)
F_1	0.69	5.5	98.26
F_2	0.65	5.4	98.00
F_3	0.63	5.3	96.98
F_4	0.64	5.5	97.07
F_5	0.62	5.4	99.10
F_6	0.54	5.5	99.22
F_7	0.57	5.2	98.72
F_8	0.53	5.6	99.28
F_9	0.56	5.4	97.15
F_{10}	0.52	5.3	97.42
F_{11}	0.55	5.7	96.03
F_{12}	0.48	5.8	96.90

F_1= Unsintered, 4% HPMC K_4M. F_2 = Unsintered 8% HPMC K_4M.
F_3 = Unsintered 4% HPMC $K_{15}M$. F_4 = Unsintered 8% HPMC $K_{15}M$.
F_5 = Sintered 3 hours 4% HPMC K_4M. F_6 = Sintered 3 hours 8% HPMC K_4M.
F_7 = Sintered 6 hours 4% HPMC K_4M. F_8 = Sintered 6hours 8% HPMC K_4M.
F_9 = Sintered 3 hours 4% HPMC $K_{15}M$. F_{lo} = Sintered 3 hours 8% HPMC $K_{15}M$. F_{11} = Sintered 6 hours 4% HPMC $K_{15}M$.F_{12} = Sintered 6 hours 8% HPMC $K_{15}M$.

Table 3: Comparison of cumulative % drug release of Diltiazem HCL sintered, unsintered matrix tablets prepared with various concentrations of HPMC K_4M AND HPMC $K_{15}M$

Sr. No.	Time in hrs.	Cumulative % drug release											
		F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
1.	0.5	24.20	26.30	18.26	18.16	18.00	19.26	15.11	13.20	11.00	11.60	13.10	13.00
2.	1	40.30	30.40	20.18	30.28	24.12	23.22	20.13	19.22	17.19	23.13	15.10	17.10
3.	2	52.40	50.22	27.13	40.11	35.24	31.64	27.88	24.16	24.13	36.88	19.11	22.34
4.	3	60.42	61.33	40.22	49.20	41.14	39.66	38.16	33.88	32.33	40.30	24.16	27.99
5.	4	72.20	72.80	47.99	55.60	53.22	44.76	45.13	38.66	37.66	50.66	29.44	35.44
6.	5	86.20	74.10	59.60	62.70	64.90	52.90	52.66	45.11	44.11	54.36	34.66	41.67
7.	6	88.10	77.90	71.80	65.37	73.44	60.22	58.19	50.00	56.20	59.99	42.49	47.00
8.	7	92.60	83.22	82.20	75.22	77.80	66.13	64.77	54.86	66.99	67.11	48.99	54.22
9.	8	95.70	85.30	86.30	82.40	81.42	78.66	71.00	60.66	74.00	72.73	57.20	61.16
10.	9	98.40	90.44	88.60	83.20	86.33	80.14	73.40	65.70	82.20	75.44	60.22	62.88

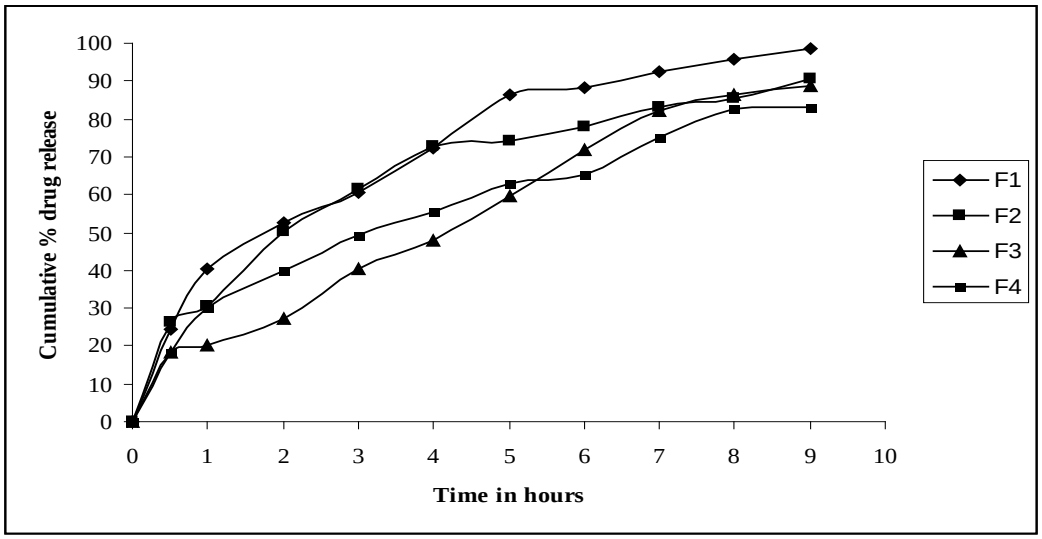

Fig. 1: In vitro release profile of unsintered matrix tablets (formulation F_1, F_2, F_3, F_4)

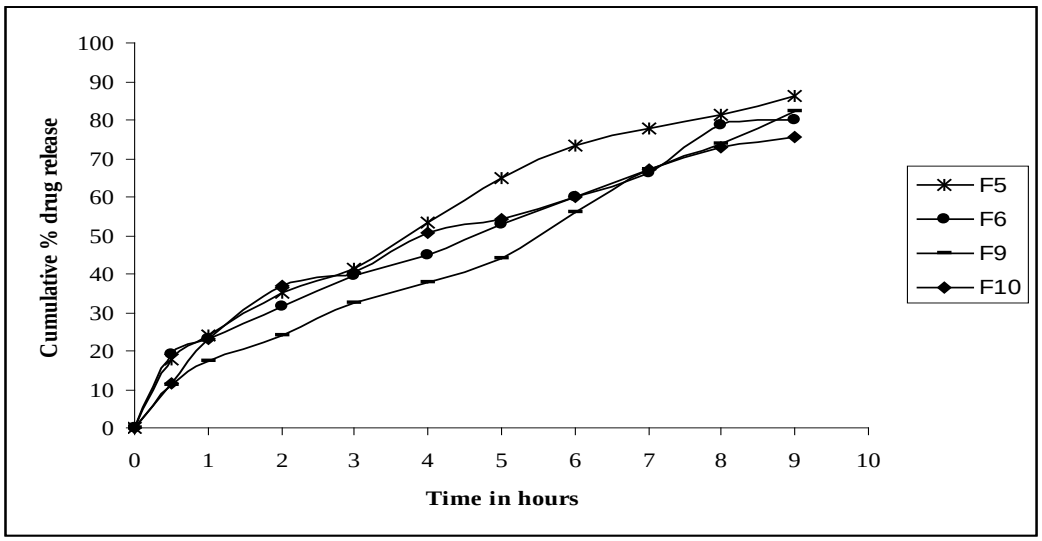

Fig. 2: In vitro release profile of unsintered matrix tablets (formulation F_5, F_6, F_9, F_{10})

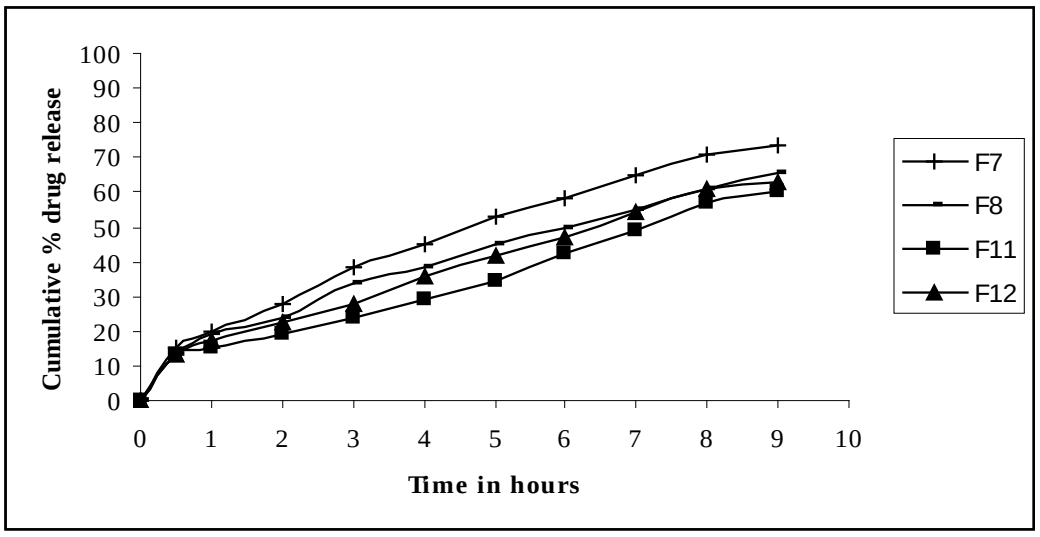

Fig. 3: In vitro release profile of unsintered matrix tablets (formulation F_7, F_8, F_{11}, F_{12})

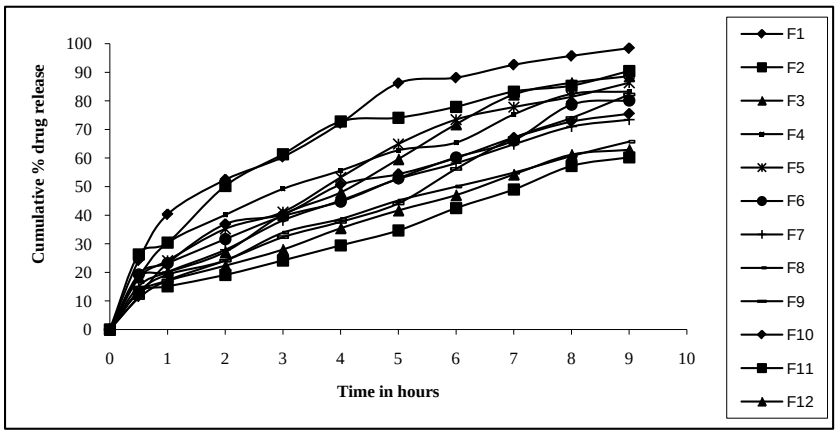

Fig. 4: Comparison of *in vitro* release profile of formulations F_1 TO F_{12}

CONCLUSION

Asimple technique of sintering method was used in the present investigation. Sustained release matrix tablets of Diltiazem HCl were prepared using hydrophilic polymers. Two polymers used were hydroxy propyl methyl cellulose K_4M and $K_{15}M$. Prepared unsintered formulations were compared with sintered formulations.

Approximately all the matrix tablets (unsintered, sintered) prepared with two different polymers exhibited concentration dependent release retardation effect. However, the required releases were better with sintered formulations from 1 to 8 hours, when compared with unsintered formulations.

By using sintering technique, friability of tablets was found to decrease with increasing sintering time and hardness was increased with increasing sintering time. Thus, on the basis of results obtained, sintering technique proved to be effective than unsintering technique by further retarding the release profile of drug.

Thus, the sintered matrix tablets are easy to prepare and have sound technology. They are cost effective and exhibit predictable release behaviour. The authors, therefore, presume that the future controlled release products could be developed on these lines rather than multi-unit pellet preparation which are not only sophisticated in their technology but also comparatively uneconomical than sintered matrix products.

REFERENCES

1. Sreenivasa RB, Seshasayana A, Himasankar K, Prasanna RV and Ramanamurthy KV. The Design and Evaluation of Ethylene Vinyl Acetate Sintered Matrix Tablets. Indian J Pharm Sci 2003; 65:496-502.
2. Kondaiah A and Prakash K. Design of Controlled Release Non-erodible Polymeric Matrix Tablets of Theophylline using Sintering Technique. Indian J Pharm Sci 2001; 64 : 239-241.
3. Telikapalli P, Patel MM, Sheth MN, Gohel MC, Chauhan GM. Sustained Release Formulation of Verapamil Hydrochloride using Hydrophilic Matrices. The Eastern Pharmacist 1995; 11 : 185-187.
4. Aithal KS, Udupa N. Controlled Fluoride Release-Tablets using Methyl Cellulose and Hydroxy Propyl Methyl Cellulose. The Indian Drugs 1994; 31: 298-301.
5. Haririan J, Ghaffari A, Mohammed PM. Formulation of Controlled Release Matrix of Isosorbide Dinitrate. Indian J Pharm Sci 2001; 63 : 24-29.
6. Kurmala VP, Amar K, Shivakumar HG. Studies on Drug Release from A Carbomer Tablet Matrix. Indian Drugs l999; 36 : 200-202.
7. Balaramesha CR, Madhusudan RY. Formulation and Evaluation of Methocel $K_{15}M$ Bioadhesive Matrix Tablets. Drug Development and Industrial Pharmacy 2000; 26 : 901 -906.