ORIGINAL ARTICLE

Formulation and evaluation of floating matrix tablets of diltiazem hydrochloride

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This study was performed to design floating tablets of diltiazem as a model drug for prolongation of gastric residence time. A simple visible spectrophotometric method was employed for the estimation of diltiazem at 236 nm and Beer's law is obeyed in the concentration range of 2-20 mg/ml. Preformulation studies were carried out to optimize the ratios required for various grades of HPMC-SCMC and HPMC- Carbopol P934. Total 10 formulations (five each) were prepared using HPMC (K4M). The prepared floating tablets were evaluated for hardness, weight variation, thickness, friability, drug content uniformity, buoyancy lag time, total floating time, water uptake (swelling index), and *in vitro* dissolution studies. SEM and stability studies were carried out only for best release formulations (A1 and B1). Among the five formulations with HPMC K4M and A1-A4 showed drug release ranging from 99.89 to 77.52%. Similarly five formulations with HPMC K4M and Carbopol P934 (B1-B4) showed drug release ranging from 97.9 to 80.35% in 0.1 N HCl dissolution medium. Formulations A1 and B1 gave maximum drug release upto 100% within 12 hrs. SEM for A1 and B1 formulations revealed that surface was smooth upto 4 hrs after that swelling and porosity of tablet increased indicating the diffusion and erosion mechanism of release.

Key words: *Controlled release, diltiazem, floating tablets, flotation, total floating time*

INTRODUCTION

Development of oral controlled release systems has been a challenge to formulation scientists because of the difficulty in localizing the system in target areas of the gastrointestinal tract. Controlled/sustained release preparations using alternating routes have also been formulated but oral route still remains preferable.[1,2] In recent years, peroral dosage forms for gastric retention have attracted more attention for their theoretical advantage in gaining control over time and the site of drug release. This would be particularly valuable for drugs that exhibit an absorption window in the upper part of the small intestine. Various approaches have been used to prepare dosage forms for gastric retention.[3] These systems mainly consist of swelling and expanding systems,[4,5] floating capsules,[6-8] floating pellets,[9] and floating granules.[10] Gastric retention of the drugs provides such advantages as better delivery of the drugs with narrow absorption windows in the small intestinal region and longer residence time in the stomach, which could be advantageous for local action in the upper part of small intestine. The current investigation aims at development of floating matrix tablets of different release patterns for diltiazem using a gas generating agent. Diltiazem is a member of the group of drugs known as benzodiazepines, which are a class of calcium channel blockers, used in the treatment of hypertension, angina pectoris, and some types of arrhythmia. Formulation of floating tablets containing diltiazem HCL as a drug candidate, which would remain in stomach and/or upper part of GIT for prolonged period of time thereby maximizing the drug release at the desired site within the stipulated time, and the oral bioavailability has been reported to be 40%. The human jejunal permeability to diltiazem and the extent of absorption is low.[11,12] Thus, it seems that an increase in gastric retention time may increase the extent of absorption and bioavailability of the drug. In the present study, we have attempted to formulate a floating system of diltiazem.

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EXPERIMENTAL

Materials

Diltiazem was obtained from Cipla Pharmaceutical Ltd, Vikhroli (Mumbai, India). HPMC K4M, Sodium CMC and Carbopol P934 were obtained as gift samples from Torrent Pharmaceutical Ltd, (Ahmedabad, India). Other materials were purchased from commercial sources: magnesium stearate (Loba chemicals, Mumbai, India), sodium bicarbonate (S.D. Fine Chemicals, Mumbai, India) and Lactose Indchem International Ltd, (Mumbai, India).

MATERIALS AND METHODS

Preparation of floating tablets

Floating tablets were prepared by direct compression using HPMC K 4M, Sodium CMC, and Carbopol P934 as the release controlling polymers, and sodium bicarbonate as a gas generating agent. The optimum concentrations of the above ingredients were determined under experimental conditions and on the basis of trial preparation of the tablets.[13]

The controlled release matrix tablet contained uniform mixture of drug, polymers, and excipients including gas-generating agent. Equivalent amount of diltiazem HCl and polymer namely HPMC K4M, using variable amount of sodium CMC and carbopol P934 was mixed properly in a mortar with weighed amount of polymers and excipients as shown in [Table 1]. The well-mixed powder was compressed by direct compression technique. Tablets were compressed on RIMEK multi station punching machine using 12.5 mm flat punches, with the hardness of 5.5 kg/cm^2.

Physical parameters of the tablet

Tablet weight: 450 mg ± 30 mg
Thickness: 3.83 ± 0.5 mm
Hardness: 5.5 ± 0.5 kg/cm^2
Friability: Not more than 1%

Floating property study

The time taken for dosage form to emerge on surface of medium is called buoyancy lag time (BLT). Duration of time by which the dosage form constantly emerges on surface of medium is called total floating time (TFT).

Tablets were placed in a 400 ml flask of 0.1 N HCl solution (pH 1.2), time needed to go upward and float on surface of the liquid and floating duration were determined.[14]

Water uptake study

The swelling of the polymers can be measured by their ability to absorb water and swell. The swelling property of the formulation was determined by various techniques. The water uptake study of the tablet was done using USP dissolution apparatus II. The medium used was distilled water, 900 ml rotated at 50 rpm. The medium was maintained at 37 ± 0.5°C throughout the study.[15] After a selected time intervals, the tablets were withdrawn, blotted to remove excess water, and weighed. Swelling characteristics of the tablets were expressed in terms of water uptake (WU).

$$WU(\%) = \frac{\text{Weight of the swollen tablet} - \text{initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100$$

In vitro Dissolution studies

Dissolution of the tablet of each batch was carried out using USP XXIII dissolution type II apparatus using paddles at 75 rpm. A total of 900 ml of 0.1 N HCl was filled in a dissolution vessel and the temperature of the medium was set at 37 ± 0.5°C. 1 ml of sample was withdrawn at predetermined time interval of 1 hr, 2 hr, 3 hr and thereafter every hour for 12 hrs and same volume of fresh medium was replaced. The withdrawn samples were diluted to 10 ml in volumetric flask and analyzed by an UV spectrophotometer at 236 nm.

The drug content was calculated using the equation generated from standard calibration curve. The % cumulative drug release was calculated.[16,17]

Details of dissolution test

Dissolution test apparatus: USP XX III (DTD – 06P).
Speed: 75 rpm
Stirrer: Paddle type
Volume of medium: 900 ml 0.1 N HCl
Aliquot taken at each time interval: 1 ml
Temperature: 37 ± 0.5°C

Table 1: Formulation of floating tablets of diltiazem HCl

Ingredients	A1	A2	A3	A4	B1	B2	B3	B4
Diltiazem HCl	120	120	120	120	120	120	120	120
HPMC K4M	130	130	130	130	130	130	130	130
Sodium CMC	13.50	18	22.50	27	-	-	-	-
Carbopol p934	-	-	-	-	9	13.50	18	22.50
Lactose	127.5	123	118.5	114	132	127.5	123	118.5
$NaHCO_3$	54	54	54	54	54	54	54	54
MgS	5	5	5	5	5	5	5	5

All the amounts are shown as milligrams. Total weight of the tablet = 450 mg

Hardness

Hardness values of the prepared formulations were determined using Monsanto hardness tester.[18]

Scanning electron microscopy analysis

The Scanning electron microscopy (SEM) analysis was conducted using Jeol, Japan (Model - JSM 5610LV) scanning electron microscope for the optimized formulation in the following states:

Dry tablet surface and tablets after swelling of 4, 8, and 12 hrs.

As with SEM high vacuum is required for image formation and samples must be thoroughly desiccated before entering the vacuum chamber, therefore samples were thoroughly dried after swelling for analysis. The dried samples were mounted on sample holder using double-sided adhesive carbon tape.

The SEM was operated at 15 KV. The condenser lens position was maintained at a constant level. The photomicrographs were recorded at 500×.

Stability

Stability studies were carried out according to ICH guidelines. All formulations were sealed in aluminum packaging coated inside with polyethylene, and samples were kept in humidity chamber at 40°C and 75% RH for 6 months. At the end of the period, samples were analyzed for drug content, floating characteristics, hardness values, and *in vitro* dissolution studies.[19,20]

RESULTS

Floating characteristics

All formulations floated more than 12 h with a lag time of up to 1 to 1.30 min. During floating duration, formulations maintained matrix integrity. Swelling of the tablets was observed, which gave floating ability to formulations. Floating duration and lag time were found to be dependent to the amounts of polymers incorporated in formulations.

In vitro drug release

The release of diltiazem was found to be a function of the polymer concentration. All formulations retarded the release of drug for 12 h. The effect of sodium CMC and carbopol P934 at different concentrations on the release of diltiazem from tablet matrices was studied. Figures 1 and 2 show the drug release profile of drug from sodium CMC and carbopol P934 matrices, respectively, at different concentrations of polymer.

DISCUSSION

Oral drug delivery system represents one of the frontier areas of controlled drug delivery system; such dosage forms are having a major advantage of patient compliance. Floating drug delivery system belongs to oral controlled drug delivery system group that are capable of floating in the stomach by bypassing the gastric transit. These dosage forms are also defined as gastro retentive drug delivery system or hydro dynamically balanced dosage form or gastric floating drug delivery system, which can float in the contents of the stomach and release the drug in a controlled manner for prolonged period. The release rate will be controlled depending upon the type and concentration of the polymer that swells, leading to diffusion and erosion of the drug.[21,22]

Diltiazem HCl is a synthetic broad-spectrum antimicrobial agent for oral administration.

It is considered to be soluble in aqueous solutions with pH between 2 to 5; it is sparingly to slightly soluble in aqueous solutions with pH 7 (solubility falls to 4 mg/ml). At the pH conditions in the small intestine the molecule exists as a zwitterions, also precipitation of active compound occurs, which adversely arrests absorption in the lower section of the intestine.[23,24]

In view of this absorption characteristic, the hypothesis of current investigation is that if the gastric residence time of diltiazem HCl containing formulation is prolonged and allowed to float in the stomach for a long period, the oral bioavailability might be increased.[25]

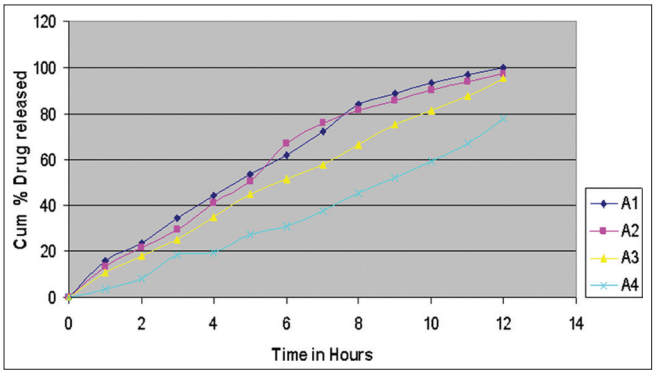

Figure 1: *In vitro* release profile of diltiazem from formulations A1, A2, A3, and A4 (with sodium CMC)

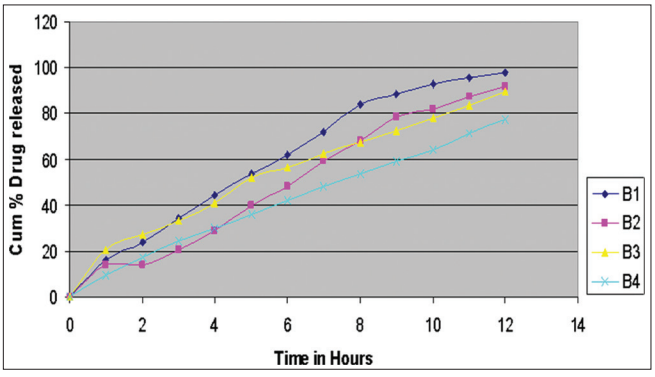

Figure 2: *In vitro* release profile of diltiazem from formulations B1, B2, B3, and B4 (with carbopol P934)

To enhance the bioavailability, an attempt was made to prepare the gastro retentive floating tablet of diltiazem HCl using polymers such as HPMC K4M (28.88%), carbopol P934 (2-5%), SCMC (3-6%), $NaHCO_3$ (12%), and lactose (25.33-28.32%)

Hence, the present research work was to study systematically the effect of formulation variables on the release and floating properties of diltiazem HCl.[26,27]

Floating property study reveals that all formulations had good floating property.

Floating lag time varied from 1 to 6 minutes in all the 8 formulations, and the total floating time varied from 12 to 19 hours [Table 2].

The prepared tablets were subjected to preliminary characterization such as hardness, thickness, % weight variation, friability, and drug content. The evaluated parameters were within acceptable range for all the ten formulations. The values are indicated in [Table 3].

SEM for A1 and B1 formulations revealed that surface was smooth upto 4 hrs after that the swelling and porosity of tablet increased indicating the diffusion and erosion mechanism of release [Figures 3-10].

Stability studies were carried out for two formulations (A1 and B1). Both the formulations showed good stability and the values were within permissible limits [Tables 4 and 5].

From the results of *in vitro* release study it was observed that,

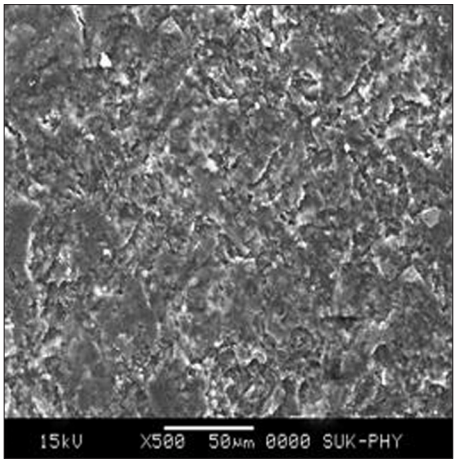

Figure 3: SEM of optimized formulation A1 at dry state

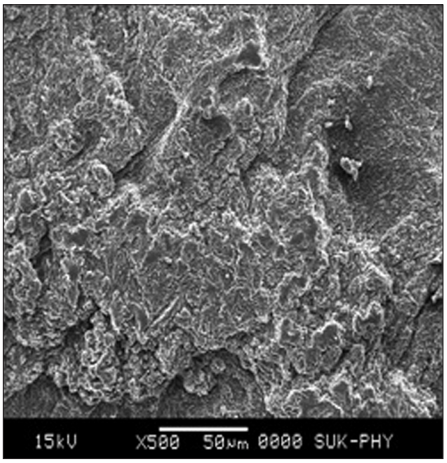

Figure 4: SEM of optimized formulation A1 after 4 hr swelling

Table 2: Floating characteristics of floating tablets of diltiazem HCl

Floating characteristics						
Formulation code	Lag time (min)		Floating duration (h)		Matrix integrity	
	A	B	A	B	A	B
A1	1	3	17	15	+	+
A2	3	5	15	12	+	+
A3	2	3	18	15	+	+
A4	4	6	16	13	+	+
B1	2	3	19	16	+	+
B2	3	4	17	14	+	+
B3	3	5	15	13	+	+
B4	4	6	16	12	+	+

A. Before stability studies B. After stability studies

Table 3: Evaluation of physicochemical parameters

Formulation code	Thickness ± S.D. (mm)	Evaluation parameters					
		Hardness ± S.D. (kg/cm^2)		Friability (%)	Average weight variation	Drug content (%)	
		A	B			A	B
A1	3.80 ± 0.043	5.2 ± 0.4	5.1 ± 0.8	0.221	0.603 ± 0.011	95.76	94.80
A2	3.84 ± 0.055	5.4 ± 0.2	5.2 ± 0.5	0.133	0.603 ± 0.010	97.96	95.90
A3	3.82 ± 0.085	5.2 ± 0.2	5.1 ± 0.3	0.099	0.602 ± 0.010	96.61	95.36
A4	3.85 ± 0.067	5.4 ± 0.1	5.2 ± 0.9	0.352	0.601 ± 0.135	96.44	94.27
B1	3.81 ± 0.048	5.3 ± 0.3	5.2 ± 0.3	0.344	0.601 ± 0.010	96.61	95.20
B2	3.82 ± 0.028	5.2 ± 0.2	5.1 ± 0.8	0.298	0.602 ± 0.008	95.42	94.73
B3	3.83 ± 0.039	5.3 ± 0.3	5.1 ± 0.9	0.245	0.599 ± 0.008	99.15	97.39
B4	3.82 ± 0.026	5.5 ± 0.4	5.3 ± 0.3	0.355	0.602 ± 0.008	97.62	96.42

A. Before stability studies B. After stability studies

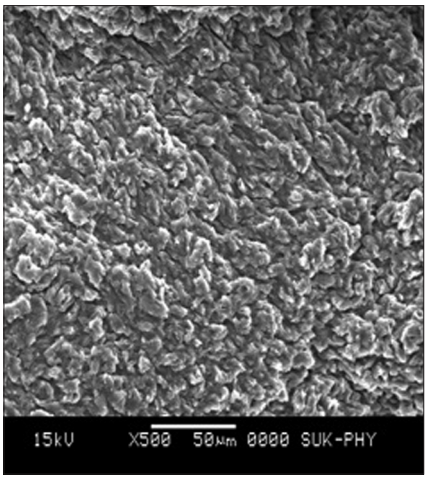

Figure 5: SEM of optimized formulation A1 after 8 hr swelling

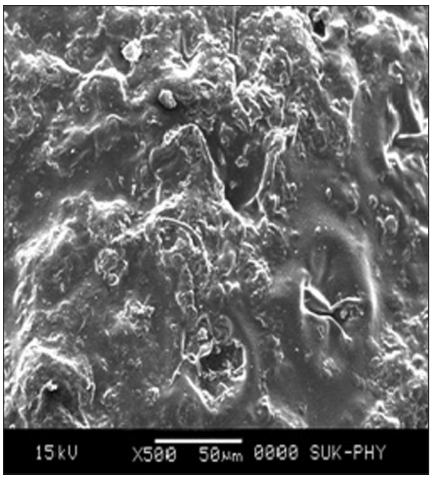

Figure 6: SEM of optimized formulation A1 after 12 hr swelling

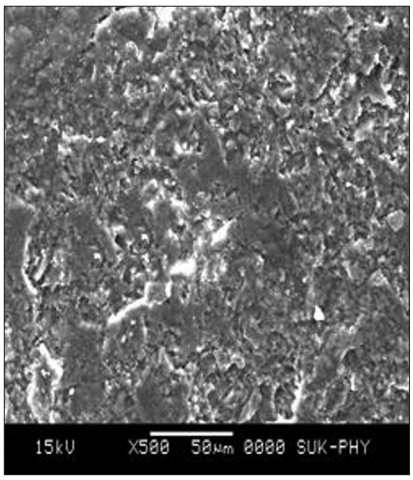

Figure 7: SEM of optimized formulation B1 at dry state

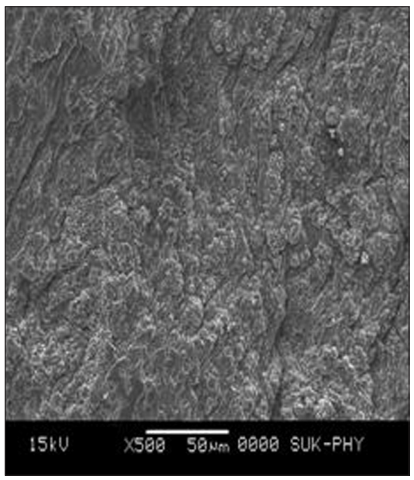

Figure 8: SEM of optimized formulation B1 after 4 hr swelling

Table 4: Stability studies of optimized formulation A1

Time	Hardness ± S.D. (kg/cm²)	Drug content Uniformity ± S.D. (%)	% CDR
After 0 month	5.15 ± 0.2	97.61 ± 0.9	99.89
After 2 month	5.10 ± 0.4	98.03 ± 0.7	98.11
After 4 month	5.20 ± 0.3	97.49 ± 1.0	97.89
After 6 month	5.10 ± 0.5	97.88 ± 0.8	97.11

Table 5: Results of the stability studies of optimized formulation B1

Time	Hardness ± S.D. (kg/cm²)	Drug content Uniformity ± S.D. (%)	% CDR
After 0 month	5.30 ± 0.3	98.3 ± 0.5	97.89
After 2 month	5.25 ± 0.7	97.18± 1.2	97.38
After 4 month	5.20 ± 0.5	97.10 ± 0.8	96.89
After 6 month	5.20 ± 0.9	97.41 ± 0.9	97.22

Table 6: *In vitro* release profile

Formulation code	% Diltiazem released at 12 hrs	
	A	B
A1	99.89672	97.14262
A2	97.328	94.157
A3	95.16754	91.22467
A4	77.52278	75.38982
B1	97.89672	95.421151
B2	91.94232	89.73514
B3	89.56632	85.77145
B4	77.41208	74.62458

A. Before stability studies **B.** After stability studies

the order of release was found to be:
A series: A1>A2>A3>A4.
B series: B1>B2>B3>B4 [Table 6].

CONCLUSION

From the above experimental results it can be concluded that sodium bicarbonate has predominant effect on the buoyancy lag time, while HPMC K4M has predominant effect on total floating time and drug release. Lactose also shows significant effect on drug release.

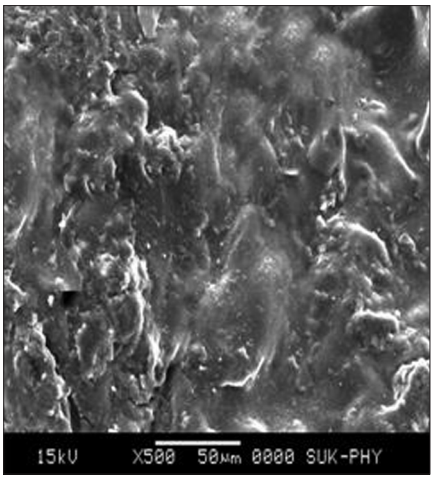

Figure 9: SEM of optimized formulation B1 after 8 hr swelling

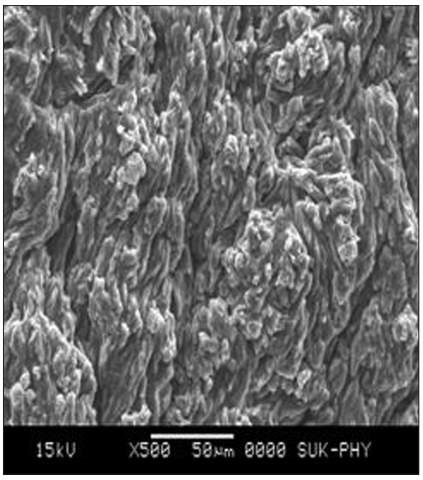

Figure 10: SEM of optimized formulation B1 after 12 hr swelling

Sodium CMC and carbopol P934 have given extra adhesion property and helped to maintain the integrity of the tablet.

Floating matrix tablet give good floating and a controlled release.

In vitro release rate studies showed that the maximum drug release was observed in A1 and B1 formulations upto 12 hrs.

Formulations A1 and B1 were found to be stable at room temperature for a period of 6 month.

From the present study, it is evident that a promising controlled release floating tablets of diltiazem HCl can be developed. Further detailed investigations are required to establish efficacy of these formulations.

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