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Research Article

Formulation and evaluation of bilayer floating tablets of Diltiazem hydrochloride for bimodal release

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ABSTRACT

In the present investigation concern, the formulation and evaluation of bilayer floating tablet of diltiazem hydrochloride which after an oral administration increase gastric residence time, to increase the bioavailability. Diltiazem HCl is the Ca^{2+} channel blocker which used in ischemic heart disease and hypertension. It has a half-life of 3 – 4 h and bioavailability of 40%. Moreover, after administration of 60 mg of sustained release dose it required 3.9 h to reach peak plasma concentration. So to overcome these drawbacks it is advantageous to formulate bilayer floating tablet of diltiazem hydrochloride helps to increase bioavailability, decreases the frequency of administration and also to reach peak plasma concentration rapidly. Bilayer floating tablets comprised of two layers, immediate and control release layers. The immediate release layer is comprised of gas generating system sodium bicarbonate and citric acid, control release layer comprised of low density release retardant polymers like HPMC K4M, K15M, E50LV. The prepared powder blends were subjected to FT-IR for any interaction. The tablets were prepared by direct compression. First, the powder blends of controlled release layer was precompressed and then powder blends of immediate release layer was added. The tablets were evaluated for hardness, friability, drug content, floating lag time, total floating time, swelling index and *in vitro* drug release. In the present study, it was found that formulation F3 showed maximum release retardant capacity, F4, F5, F2 were next in sequence. The release data were fitted to various mathematical models such as Higuchi, first order and zero order to evaluate kinetics and mechanism of drug release, and it was and best fitted to first order and Higuchi's model. Stability studies revealed no significant changes.

Keywords: Diltiazem HCl; Bilayer Floating Tablets; Gas Generating Agent; Low Density Polymers

INTRODUCTION

The aim of any drug delivery system is to afford a therapeutic amount of drug to the proper site in the body to attain promptly, and then maintain the desired drug concentration. In an oral drug delivery system not all drugs or therapeutic agents are absorbed uniformly throughout the gastrointestinal tract (GIT). Some drugs are absorbed in a particular portion of GIT. One of the novel approaches in the area of oral sustained release drug delivery is gastroretentive drug delivery system (GRDDS). Drugs those are having a narrow absorption window and having more solubility in the gastric region are suitable candidates for GRDDS (Hoffman A *et al*., 2004). GRDDS prolongs the retention time of dosage forms in the stomach or upper gastrointestinal tract, as to improve solubility, bioavailability and the therapeutic efficacy of the drugs (Talukder R *et al*., 2004)**.** Several techniques have been proposed to increases the gastric residence time of dosage forms such as buoyancy or floating system (Tanwar Y *et al*., 2007), hydrodynamically balanced system (Ali J *et al*., 2007)**,** expanding or swelling system, bio/mucoadhesive system (Varsosaz *et al*., 2006)**,** sedimentation or high density system, geometry or modified shape system may also use to increase gastric residence time. The biphasic system is used mostly when maximum relief needs to be achieved quickly followed by a sustained release phase. It also avoids repeated administration of drug. In the biphasic system mainly coronary vasodilator, antihypertensive, antidiabetics, analgesics, etc. agents are used. The biphasic system may contain one or two drugs for immediate and sustained release. Diltiazem hydrochloride is calcium channel blocker used in the treatment of angina pectoris and hypertension. Diltiazem hydrochloride is mainly absorbed from stomach and upper part of intestinal tract, but it has low bioavailability 40%. It has biological half life 3-4 h. Moreover with 60 mg sustained release dosage form time require to reach peak plasma concentration is about 3.9 h. So an administration of the loading dose also becomes beneficial to reach peak plasma concentration rapidly. The present work concern with formulation and evaluation of bilayer floating tablets having immediate release and floating sustain release layer.

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Table 1: Formulation of bilayer floating tablet of Diltiazem HCl

Ingredient	F1	F2	F3	F4	F5	F6	F7
	Immediate release layer						
DiltiazemHCl(mg)	40	40	40	40	40	40	40
Sod. Bicarbonate (mg)	50	50	50	50	50	50	50
Citric acid(mg)	10	10	10	10	10	10	10
	Floating layer						
DiltiazemHCl(mg)	60	60	60	60	60	60	60
HPMC E50LV(mg)	150	-	-	-	75	75	50
HPMC K4M(mg)	-	150	-	75	-	75	50
HPMC K15M(mg)	-	-	150	75	75	-	50
MCC(mg)	30	30	30	30	30	30	30
Mg. Sterate(mg)	5	5	5	5	5	5	5
Talc(mg)	5	5	5	5	5	5	5
Total wt.	**350**	**350**	**350**	**350**	**350**	**350**	**350**

These tablets showed the biphasic drug release means an immediate release layer releases the drug immediately after come in contact with dissolution medium which is a loading dose. Floating sustained release layer releases the drug for prolong period of time which is maintenance dose. All other chemicals used were of analytical grade.

MATERIALS AND METHODS

Materials

Diltiazem hydrochloride was received as a gift sample from J.B. Chemicals (Ankleshwar, India), HPMC K4M, K15M, microcrystalline cellulose (MCC) were obtained from Yerrowchem products (Mumbai, India), HPMC E50LV, sodium bicarbonate, citric acid, magnesium stearate and talc were obtained from LobaChemical Pvt Ltd (Mumbai, India). Hydrochloric acid was obtained from Merck Chemicals Ltd., (Mumbai, India).

PREFORMULATION STUDIES

FT-IR

The powdered samples of upper and floating layer were mixed with previously dried potassium bromide (IR grade) to form pallets of mixture. The spectral smoothening and baseline correction were done, and then samples are scanned from 4000cm^{-1} to 400cm^{-1} in FT-IR spectrophotometer (Alpha, Bruker) at an ambient temperature (Sathiyaraj S *et al*., 2011).

Angle of repose

The accurately weighed powder blends were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder blend. The powder blends were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation (Cooper and Gunn, 1986).

$$\theta = \tan^{-1}h/r$$

where, θ = angle of repose, h=height of pile, r=radius

Bulk density

Powder blends of both upper and floating layer were accurately weighed 5 gm and transferred in to measuring cylinder. Volume of the powder blend in the measuring cylinder was noted, and bulk density was calculated as per following equation (Lachmann L, 1990).

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{Bulk volume of powder}}$$

Tapped density

Accurately weighed powder was taken in measuring cylinder, and it was subjected for 100 or until no further change in volume was observed in mechanical tapping apparatus. Tapped density was calculated as per following equation(Lachmann L, 1990).

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped volume of powder}}$$

Carr's index

Carr's index is a one-point determination and does not always reflect the ease or speed with which the powder consolidates. The compressibility index of the granules was determined by Carr's compressibility index as per the following equation(Aulton ME, 2002).

$$\textit{Carr's Index}\ (\%) = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

FORMULATION OF BILAYER FLOATING TABLETS

Bilayer tablet contains two layers one immediate and second floating sustained release layer of diltiazem hydrochloride. The powder blends of upper and floating layer were prepared by accurately weighing the quantities of drug, polymers and other ingredients as per Table 1. These powders blends were then kept for drying in a hot air oven at 40 °C to remove moisture. The tablets were prepared by direct compression method using Remak Minipress I using 10 mm flat face punch in two stages. First powder blend of floating layer was filled in die cavity, and it was precompressed after that upper layer was added on the floating layer

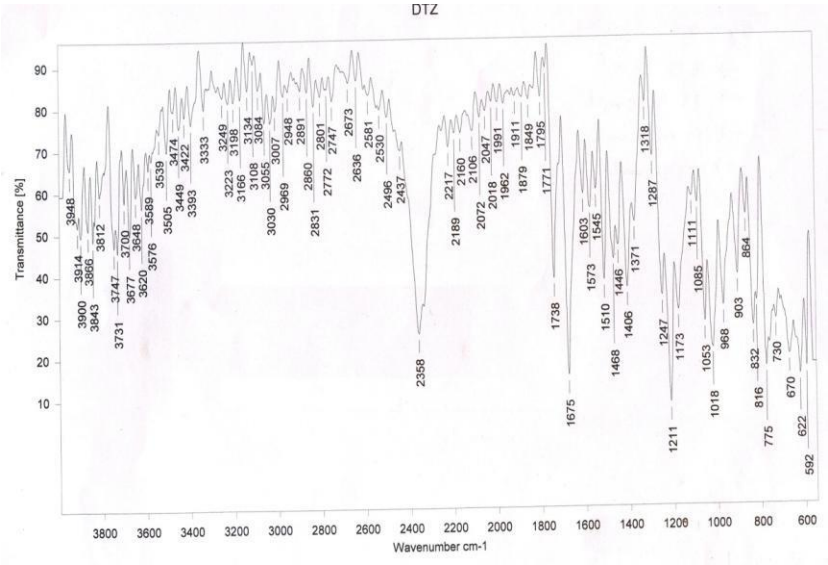

Figure 1: IR spectrum of Diltiazem HCl

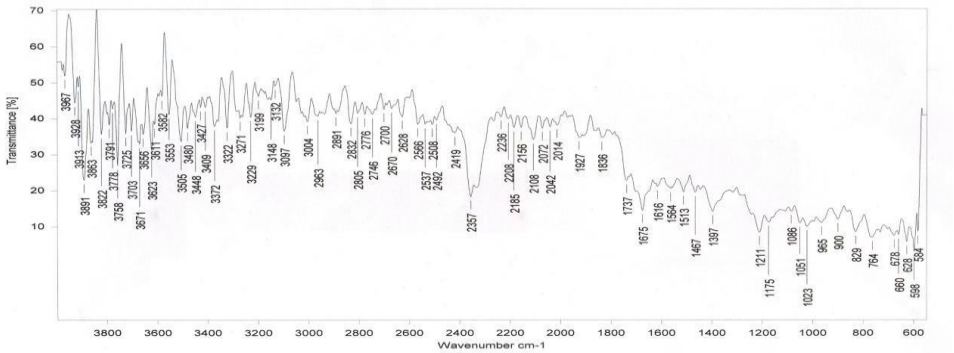

Figure 2: IR spectrum of upper layer

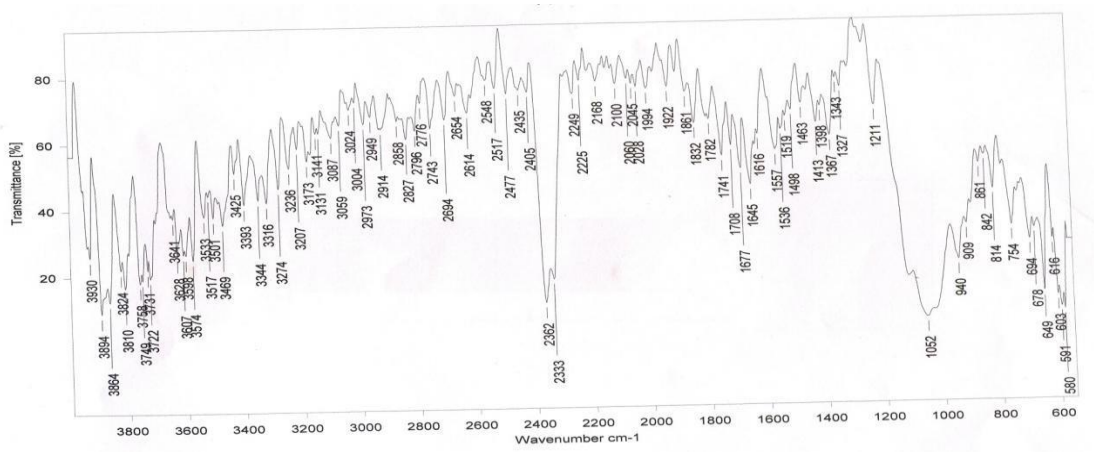

Figure 3: IR Spectrum of DTZ with HPMC E50LV, HPMC K4M, HPMC K15M

and full compression was given to prepare bilayer floating tablet of diltiazem hydrochloride.

EVALUATION OF BILAYER FLOATING TABLETS

Hardness test

For each formulation, the hardness of five randomly selected tablets was determined by the Monsanto hardness tester (Campbell electronics). The force of fracture is recorded, and values were reported in Kg/cm^2. The average mean and SD were calculated (Lachmann L, 1990).

Friability test

Six tablets from each formulation were randomly selected, weighed together and then placed in the Roche friabilator chamber (Campbell electronics). The friabilator was operated for 100 revolutions at 25 rpm. The tablets were then dedusted and re-weighed. The friability was calculated as the percentage weight loss (Lachmann L, 1990).

Weight variation test

To study weight variation, randomly selected 20 tablets from each formulation were weighed individually using an electronic balance (AR2130, Ohaus Corp.), and the test was performed according to the official method. The percentage deviation from average weight was reported (Lachmann L, 1990).

Drug content estimation

Ten tablets from each formulation were randomly selected and powdered. A quantity of powder equivalent to 100 mg of diltiazem hydrochloride was accurately weighed and extracted with 0.1N HCl. This solution was filtered through Whatmann filter paper (0.22 µm size). 1 ml of this solution was transferred to a 100 ml volumetric flask and diluted to 100 ml with 0.1 N HCl and the absorbance was measured at 237 nm using an UV / visible spectrophotometer. The percentage of diltiazem hydrochloride was determined using calibration curve (Lachmann L, 1990).

Buoyancy test

The *in vitro* buoyancy is determined to find out floating ability of the tablet in the dissolution medium. The tablet was placed in the 100ml beaker containing 0.1N HCl and the time required for the tablet to rise to the surface, and float was determined as floating lag time by using a stop watch (Kalaria D *et al*, 2011)

Swelling index

Swelling index was done on the prepared tablets by using 200 ml beaker containing 0.1N HCl. The temperature maintained at 37°C. The tablets were tested for 9 h. The tablets were carefully removed using a small basket, and the weight of each tablet was determined. Swelling index was calculated using the following equation (Kalaria D *et al*., 2011).

$$\%\ Swelling\ Index = \frac{W_2 - W_1}{W_1} \times 100$$

W_1= initial wt of tablet

W_2= wt. of swollen tablet

***In vitro* drug release**

In vitro dissolution study was performed by using USP type II apparatus (paddle type, Electrolab TDT-08L) at 50 rpm. The drug release profile was studied in 900 ml of 0.1 N HCl, which was maintained at 37 ± 0.5°C. Aliquots of 5 ml of the dissolution medium was withdrawn at the interval of 5 min up to 30min to know the release of drug from immediate release layer after that at 1 h interval up to 10 h to know the release pattern of drug from floating layer. The same volume of the dissolution medium was replaced after each withdrawal. The amount of drug dissolved was determined by UV / visible spectrophotometer (Schimadzu, UV-1700) by measuring the absorbance of the sample at 237 nm against a blank. 3 trials for each batch were performed, and an average percentage drug release with standard deviation was calculated and recorded (Anil G *et al*., 2011).

Drug release kinetics

Different mathematical models are applied for describing the kinetics of the drug-release process from matrix tablets, the most suited being the one which best fits the experimental results and it was calculated using Microsoft® Office Excel. The kinetics of diltiazem release from formulations was determined by finding the best fit of the dissolution data (drug-released fraction vs. time)to distinct models: zero-order, first-order and Higuchi (Sanghvi G *et al*., 2011).

Stability studies

The optimized formulation was subjected to stability studies as per ICH guidelines at 40 ± 2°C and 75 ± 5 % RH in a stability chamber (LPC-170G, Labtop Instruments) for the period of six months and at room temperature (25 ± 2°C) in a desiccator. After each month tablet, sample was analyzed for physical characteristics and percentage drug content.

RESULTS AND DISCUSSIONS

FT-IR

The FT-IR spectrum of the diltiazem HCl shown in Figure 1 – 3. The FT-IR spectrum of the diltiazem HCl showed short bend of C-H starching at 2948 cm^{-1}, the absorption bend of C=O starching at 1738cm^{-1}, $OCOCH_3$ group showed absorption at 1675 cm^{-1}, the starching bend of C=C seen at 1603cm^{-1}, the absorption bend of the amine group seen at 1252cm^{-1}, 1053cm^{-1}. All these absorption bends of the drug were also found in the IR spectrum of the all formulations which indicates there were no interaction between drug and polymer.

Preformulation studies

It was done for upper and lower floating layer. The data obtained from preformulation studies indicated that powder mixtures had good flow properties, which are necessary for the direct compression method employed in tablet preparation. Results are shown in Table 2.

Table 2: Preformulation studies

Powder Properties	Upper Layer	F1	F2	F3	F4	F5	F6	F7
Bulk Density (gm/cc)	0.5263	0.4032	0.3875	0.4	0.4065	0.4	0.3906	0.3968
Tapped Density (gm/cc)	0.6493	0.4629	0.4424	0.4587	0.4672	0.4629	0.4504	0.4587
Angle of Repose (°)	32.61	28.22	28.95	28.64	27.95	26.16	25.22	26.12
Carr's Index	18.94	12.89	12.40	12.89	12.99	13.58	13.27	13.49

Table 3: Evaluation of bilayer floating tablets

Formulation	Hardness (kg/cm^2) N=5	Friability N=6	Weight variation N=20	Drug content N=10	Buoyancy lag time (sec)	Total buoyancy time (h)
F1	4.18±0.19	0.77%	345.1±2.86	97.96±0.093	76	>10
F2	4.46±0.13	0.82%	347±2.59	98.57±0.063	48	>10
F3	4.54±0.1	0.58%	346.5±4.49	99.62±0.04	57	>10
F4	4.32±0.16	0.67%	347.3±3.36	97.69±0.057	53	>10
F5	3.92±0.07	0.48%	347±3.18	98.98±0.036	62	>10
F6	4.42±0.11	0.57%	347.7±3.07	98.35±0.066	65	>10
F7	4.52±0.07	0.86%	348.6±2.97	99.83±0.086	43	>10

Evaluation of bilayer floating tablets

The data obtained by evaluation of bilayer floating tablets shown in Table 3. The hardness of all the formulation found to be in the range of 3.92-4.54 kg/cm^2. The friability was found in the range of 0.48-0.86% which indicated good mechanical strength. Weight variation was also found in the range as described in IP. Drug content of the prepared tablets was found to be in the range of 97.96-99.83%. Buoyancy lag time was found in range of 43 – 76 sec and all tablets remained floated for more than 10 h.

Swelling index

The purpose of swelling index is to determine water uptake capability of the polymer. When the polymer comes in contact with water, it takes up water molecule and swells. Swelling of the polymer is important for the retardation of drug release from the tablet. Moreover, the viscosity of the polymer is also affect polymer swelling. Higher viscosity grade polymers show more swelling. The highest swelling index was found in the formulation F3 which contains HPMC K15M and lowest swelling index found in the formulation F1 which contains HPMC E50LV, which is the low viscosity grade. The results are shown in Figure 4.

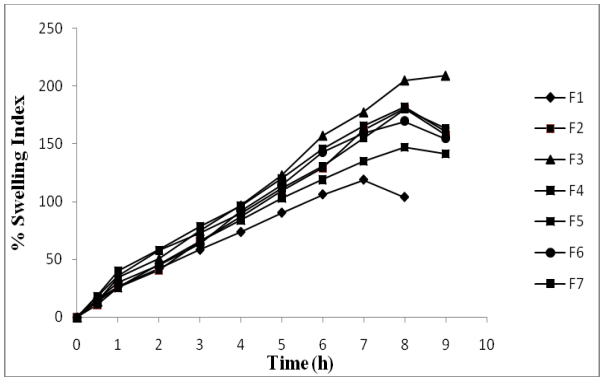

Figure 4: Comparative swelling index of different formulations

***In vitro* drug release**

In vitro drug release of diltiazem HCl tablets was carried out in 0.1N HCl at 50 rpm. Temperature was maintained 37±0.5°C. It was found that loading dose from all the tablets was released within 30 min which because when the tablet came in contact with dissolution medium upper layer immediately releases CO_2, which was made up of gas generating agents. Concurrently floating layer releases drug up to 10 h. The results showed in Figure 5.

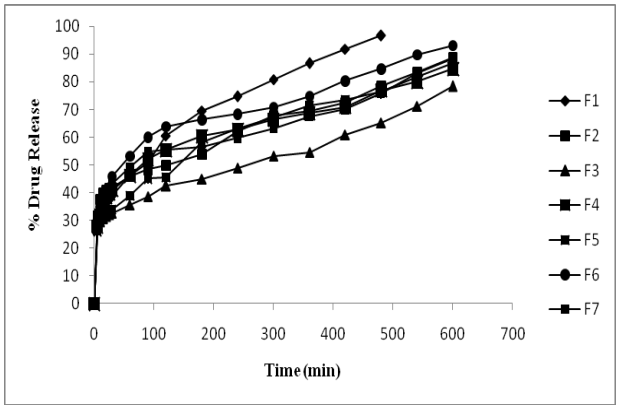

Figure 5: Comparative in vitro drug release profile of different formulations

Drug release kinetics

The hydrophilic polymers like HPMCs highly swell when they come in contact with dissolution medium, which is characterized by formation of gel like network surrounding the system. In the present investigation drug release mechanism is best fitting to first order (0.901-0.962) and Higuchi model (0.906-0.974) because the regression coefficient was seen closest to 1in these models. In the case of controlled release formulations, they should follow zero order release kinetics. However, in present work release, kinetic is best fitting to first order, which is because of the hydrophilic matrix. In the case of hydrophilic matrix tablets swell upon ingestion and a gel layer form on the surface. This gel layer retards further ingress of the fluid and subsequent drug release. In case of hydrophilic matrices, swelling and erosion of the polymer occurs simultaneously and both contribute to the overall drug release rate. So that it showed a typical time dependent profile, i.e. decrease release with time because of increased diffusion path length, which lead to first order release kinetics (Sanghvi G *et al.,* 2011). In the present investigation drug, release also followed Higuchi's model, which conforms to diffusion assisted mechanism of release. The results of drug release kinetics shown in table 4.

Table 4: Comparison of drug release kinetics of different formulations

Code	Zero-Order	First-Order	Higuchi Model
F1	R^2=0.878	R^2=0.944	R^2=0.974
F2	R^2=0.842	R^2=0.935	R^2=0.921
F3	R^2=0.838	R^2=0.929	R^2=0.915
F4	R^2=0.812	R^2=0.948	R^2=0.931
F5	R^2=0.859	R^2=0.962	R^2=0.957
F6	R^2=0.805	R^2=0.918	R^2=0.927
F7	R^2=0.816	R^2=0.908	R^2=0.906

Stability studies

Stability study was done as described in methodology for 8 weeks. It was revealed that all the formulations were stable throughout the stability studies, and no significant change was observed in drug content of tablets.

CONCLUSION

Bilayer floating tablets of diltiazem hydrochloride was prepared by direct compression method. The FT-IR study did not show any spectral changes. The powder blends of different formulations have good flow properties. The tablets containing HPMC K15M polymer showed the high degree of swelling. All the formulations remain buoyant up to 10 h with undergoing disintegration. *In vitro, vitro* drug release was carried out up to 10 h and showed a sustained release. The drug release form all the formulations were found to be first order and best fitted to Higuchi's model conforming to be diffusion assisted mechanism. This is one of the encouraging observations. Stability study was carried out for all the formulations, and it was revealed that there were no significant changes.

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