Digest Journal of Nanomaterials and Biostructures Vol. 6, No 4, October-December 2011, p. 1841-1850

FORMULATION AND EVALUATION OF FLOATING MATRIX TABLET FOR CONTROLLED DRUG RELEASE

U.D.SHIVHARE*, P.M.CHILKAR, K.P.BHUSARI, V.B.MATHUR
Sharad Pawar College of Pharmacy, Wanadongri, Hingna road, Nagpur-441110. (M.S.)INDIA

The present investigation concerns the development of floating drug delivery system (FDDS) of diltiazem hydrochloride, which is designed to increase the gastric residence time, thus prolonging the drug release with localized drug action. Hydroxy propyl methyl cellulose (HPMC) of different viscosity grades and drug in different ratios were used to prepare floating matrix tablets by wet granulation technique. The prepared floating matrix tablets were evaluated for various parameters like hardness, friability, uniformity of weight, uniformity of drug content, drug-polymer interaction studies, *in vitro* floating studies, *in vitro* drug release and short term stability studies. The drug-polymer ratio, viscosity grades of HPMC and gas generating agents were found to influence the drug release and floating properties of the prepared floating matrix tablets. The floating properties and drug release characteristics were determined for the prepared floating matrix tablets in 0.1N HCl as dissolution media. All the floating tablet formulations showed good *in vitro* floating properties with an optimum concentration of gas generating agents, sodium bicarbonate and citric acid. The rate of drug release decreased with increased polymer concentration. It was found that HPMC viscosity had a significant impact on the drug release from the prepared floating matrix tablets. The decrease in the release rate was observed with an increase in the polymeric system. Among the three viscosity grades of HPMC (K4M, K15M and K100M), HPMC K4M along with microcrystalline cellulose as diluent was found to be beneficial in improving the drug release rate and floating properties. Regression analysis of drug dissolution profiles on the basis of Higuchi's and Korsmeyer peppas model indicated that diffusion is the predominant mechanism controlling the drug release.

(Received October 10, 2011; Accepted December 2, 2011)

Keywords: Floating drug delivery system (FDDS), Diltiazem hydrochloride, Hydroxy propyl methyl cellulose, *In vitro* floating, Higuchi's model, Korsmeyer peppas model.

1. Introduction

Various approaches have been worked out to improve the retention of an oral dosage form in the stomach e.g. floating system, swelling and expanding system, bioadhesive system, modified shape system, high-density system and other delayed gastric emptying devices [1]. Floating drug delivery systems (FDDS) or hydrodynamically balanced systems have a bulk density lower than gastric fluids and therefore remain floating in the stomach without affecting the gastric emptying rate for a prolonged period. These systems are useful for drugs acting locally in the gastrointestinal tract, drugs which are poorly soluble and unstable in intestinal fluid. While the system is floating on gastric contents, the drug is slowly released at a desired rate from the floating system and after the complete release; the residual system is expelled from the stomach. This leads to an increase in the gastric residence time and better control over fluctuations in plasma drug concentrations [2].

* Corresponding author: udshivhare@gmail.com

Gastric retention drug delivery systems can be retained in the stomach for a long time. Such retention systems are important for drugs that are degraded in intestine or for drugs like antacids or certain antibiotics and enzymes that should act locally in the stomach. If the drugs are poorly soluble in intestine its retention in gastric region may increase the solubility before they are emptied, resulting in increased bioavailability. Such systems are more advantageous in improving GI absorption of drugs with narrow absorption windows as well as for controlling release of the drugs having site-specific absorption limitation. Retention of drug delivery systems in the stomach prolongs overall GI transit time, there by resulting in improved bioavailability for some drugs [3].

The rate of gastric emptying depends mainly on viscosity, volume and caloric content of meals. Nutritive density of meal helps to determine the rate of gastric emptying, increase in acidity and caloric values slows down the gastric emptying rate. Biological factors such as age, body mass index, gender, posture and diseased states influence gastric emptying. Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down. Gastric emptying of dosage form is different in fasted and fed condition. Volume of liquids affects the gastric emptying i.e. larger the volumes faster the emptying. Fluids taken at body temperature leave the stomach more quickly than either colder or warmer fluids. The gastric residence time may increase by the ingestion of a meal prior to administration of liquids. Park *et al* have reported the residence time for both liquid and solid foods in each segment of the GIT.

Diltiazem hydrochloride is one of the new generation calcium channel blocker with peripheral and coronary vasodilator properties, which is used in the management of classical, Vasosplastic angina pectoris and also in the treatment of essential hypertension. The plasma half life of the Diltiazem HCl is 3 - 4 h. The success of a therapy depends on selection of the appropriate delivery system as much as it depends on the drug itself. Controlled release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action. Diltiazem is rapidly and almost completely absorbed from the gastrointestinal tract following oral administration, but undergoes extensive first pass hepatic metabolism. The bioavailability has been reported to be about 40%, although there is considerable inter-individual variation in plasma concentrations.

Diltiazem is around 50% bound to plasma protein. It is extensively metabolized in the liver, one of the metabolites desacetyl diltiazem has been reported to have 25 to 50% of the activity of the parent compound. Approximately 60% of the dose is excreted in the bile and 35-40% in the urine, 2-4% as unchanged diltiazem [4].

2. Experimental

Preparation of standard calibration curve of Diltiazem hydrochloride in pH 1.2 buffer:

Accurately weighed 100 mg of Diltiazem hydrochloride was dissolved in pH 1.2 buffer and the volume was made up to 100 ml with the pH 1.2 buffer to give solution of 1000 µg/ml concentration (SS I). 5 ml of SS I was then made up to 200 ml with the pH 1.2 buffer to give solution of 25 µg/ml concentration (SS II). Aliquots of 1, 2, 3, 4, ,5, 6, 7, 8, 9, 10 ml of SS II was pipetted into 25 ml volumetric flask and volume was made upto 25 ml with pH 1.2 buffer. The absorbance was measured at 237 nm against blank (pH 1.2 buffer).

Preparation of 0.1 N HCl: 8.5 ml of concentrated HCl was diluted with 1000 ml of distilled water to get 0.1 N HCl [5].

Standard calibration curve of diltiazem hydrochloride:

Standard calibration curve of Diltiazem Hydrochloride was determined by plotting absorbance v/s concentration at 237 nm and it follows the Beer's law.

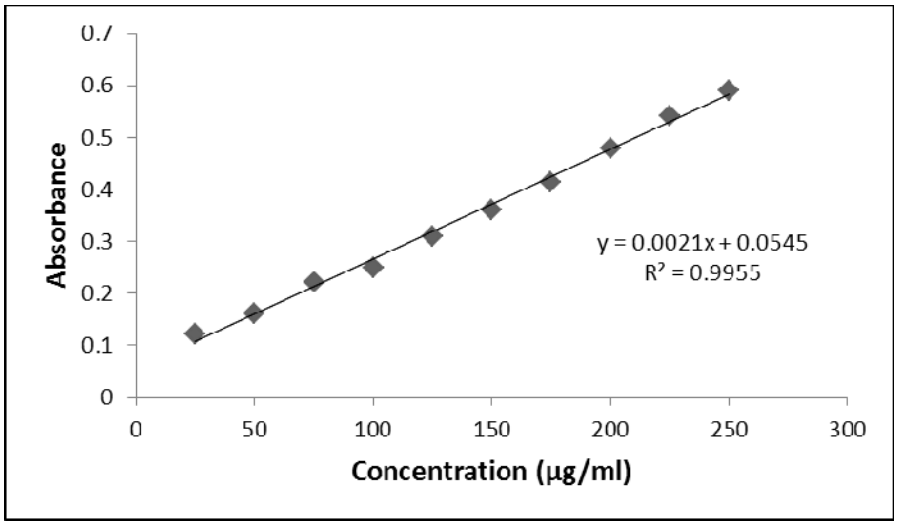


Fig. 1: Standard calibration curve of Diltiazem hydrochloride in pH 1.2 buffer

Infrared Spectroscopic Studies:

Identification of the pure drug and polymers were performed using infrared spectroscopy. IR spectroscopy by potassium bromide pellet method was carried out on drug and polymer. They are compressed under 10 tones pressure in a hydraulic press to form a transparent pellet. The pellet was scanned from 4000 to 400 cm^{-1} in a spectrophotometer and peaks obtained were identified.

Method of preparation of floating matrix tablet of Diltiazem hydrochloride:

All the ingredients were accurately weighed and sieved through sieve No. 60. In order to mix the ingredients thoroughly, drug and all the excipients shown in table 1 and 2 except the lubricants (magnesium stearate and talc) were blended geometrically in mortar and pestle for 15 min and granulated using PVP K30 dissolved in sufficient isopropyl alcohol by passing through sieve No. 12. Granules were dried at 60°C for 4 h. The dried granules were sized through sieve No. 18 and lubricated by adding magnesium stearate and talc. Tablets were compressed on a single punch tablet machine using flat surfaced, round shaped punches of 12.5 mm diameter [6].

Evaluation of floating matrix tablets

Evaluation of tablets:

Tablets were evaluated for both its pre-compression parameters like bulk density, tapped density, Carr's index, Hausner ratio, angle of repose as well as their post compression parameters tablet hardness, friability, uniformity of weight and content uniformity of drug and other specific evaluation tests for GFDDS like floating lag time, total floating time and release rate of drug.

Precompression Parameters

I. Bulk density and Tapped density:

Both bulk density (BD) and tapped density (TD) was determined. A quantity of 2 g of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced into 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. BD and TD were calculated using the following equations.

$$\text{Bulk density} = W/V_0$$

$$\text{Tapped density} = W/V_f$$

Where, W - wt. of powder, V_0 - initial volume, W - wt. of powder, V_f - final volume.

II. Compressibility index and Hausner ratio:

The compressibility index and Hausner ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently

greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the compressibility Index and the Hausner Ratio. The compressibility index and Hausner ratio may be calculated using measured values for bulk density (D_b) and tapped density (D_t) as follows:

$$\text{Compressibility index} = D_t - D_b / D_t \times 100$$

$$\text{Hausner ratio} = D_t / D_b$$

Where D_b- Bulk density, D_t - Tapped density

III. Angle of repose:

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated.

$$\tan \Theta = h/r \quad \text{or} \quad \Theta = \tan^{-1}(h/r)$$

Where h = height of pile, r = radius of the base of the pile, Θ = angle of repose [7].

Post- compression parameters

1. Tablet Hardness:

The crushing strength ($kg/cm^{2)}$ of prepared tablets was determined for tablets of each batch by using Monsanto tablet hardness tester. Hardness indicates the ability of a tablet to withstand mechanical shocks while handling [8].

II. Weight variation test:

Twenty tablets were selected randomly from each batch and weighed individually. The average weight of each batch of tablet was calculated. Individual weights of the tablets were compared with the average weight. Since the tablets weighed over 250 mg, I.P. specifies that the tablets pass the test if not more than two of the individual weights deviate from the average weight by more than 5 % and none should deviate from the average weight by more than 10% [9].

Average weight of tablet (X mg)	Percentage deviation
$X \leq 80$ mg	10
$80 < X < 250$ mg	7.5
$X \geq 250$ mg	5

III. Friability Test:

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W_0) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. [10] The tablets were weighed again (W_f). The % friability was then calculated by

$$\% \text{ Friability} = (1 - W_f / W_0) \times 100$$

Where, W_0 -Weight of tablet before test, W_f -Weight of tablet after test.

IV. Drug content uniformity:

The tablets were weighed and taken in a mortar and crushed to powder. A quantity of powder equivalent to 100 mg of Diltiazem hydrochloride was taken in a 100 ml volumetric flask and 0.1 N HCl was added. It was then heated at 60°C for 30 min. The solution was filtered using Whatmann filter paper and then its absorbance was measured at 237 nm [11]. The amount of drug was calculated using standard calibration curve.

V. 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 swelling

capacity study of the tablet was done using USP XXII type I dissolution apparatus. The medium used was 0.1 N HCl (900 ml) and rotated at 100 rpm. The medium used was maintained at 37 ± 0.5 ^{o}C throughout the study. After 8 h, the tablets were withdrawn and blotted to remove excess water and weighed [12]. Swelling characteristics of the tablets were expressed in terms of swelling index (%).

$$\text{Swelling index (\%)} = W_f - W_i / W_i \times 100$$

Where, W_f - Weight of swollen tablet, W_i - Initial weight of table.

VI. *In vitro* buoyancy study:

The time, tablets took to emerge on the water surface i.e. floating lag time (FLT) and the time, tablets constantly float on the water surface i.e. total floating time (TFT) were evaluated. The buoyancy of the tablets was studied in USP XXII type II dissolution apparatus at 37 ± 0.5^{o}C with paddle rotation at 100 rpm in 900 ml of simulated gastric fluid at pH 1.2. The measurements were carried out for each formulation of tablets. The time of duration of floatation was observed visually [13].

VII. *In vitro* Drug release studies:

The Diltiazem hydrochloride released from different floating tablet formulations was determined using a USP XXII paddle apparatus under sink condition (Lab India Disso 2000). The dissolution medium was 900 ml simulated gastric fluid (pH 1.2, no enzyme) at 37 ± 0.5^{o}C; paddle speed 100 rpm, to simulate *in vivo* conditions. The formulation prepared was subjected to dissolution tests for 12 h. At every 1 h interval, Sample was withdrawn, filtered through Whatmann filter paper and replaced by an equal volume of dissolution medium. Drug content in the dissolution sample was determined at 237 nm by UV Spectrophotometer (UV – 1700). Cumulative percent drug release was found out at each time interval and graph was plotted between cumulative % drug released and time in h [14].

Table 1: Composition of floating matrix tablets.

Ingredients (mg)	**Formulation Code**							
	F1	F2	F3	F4	F5	F6	F7	F8
Diltiazem HCl	90	90	90	90	90	90	90	90
HPMC K4M	90	180	225	-	-	-	-	-
HPMC K15M	-	-	-	90	180	225	-	-
HPMC K100M	-	-	-	-	-	-	90	180
Microcrystalline cellulose	-	-	-	-	-	-	-	-
Sodium bicarbonate	25	25	25	25	25	25	25	25
Citric acid	-	-	-	-	-	-	-	-
PVP K 30	14	16	18	14	16	18	14	16
Carbopol 934P	20	30	40	20	30	40	20	30
Talc	2	2	2	2	2	2	2	2
Magnesium stearate	4	4	4	4	4	4	4	4

Ingredients (mg)	Formulation Code							
	F9	F10	F11	F12	F13	F14	F15	F16
Diltiazem HCl	90	90	90	90	90	90	90	90
HPMC K4M	-	180	180	180	180	180	180	180
HPMC K15M	-	-	-	-	-	-	-	-
HPMC K100M	225	-	-	-	-	-	-	-
Microcrystalline cellulose	-	-	35	35	35	35	35	35
Sodium bicarbonate	25	50	50	50	25	50	25	25
Citric acid	-	-	-	-	15	30	10	5
PVP K 30	18	16	16	16	16	16	16	16
Carbopol 934P	40	40	30	30	30	30	30	30
Talc	2	2	2	2	2	2	2	2
Magnesium stearate	4	4	4	4	4	4	4	4

Table 2: Precompression parameters for formulations F1- F16

Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (%)	Hausner ratio	Angle of repose (^{o}) *
F1	0.509	0.555	8.22	0.92	24.56 ± 0.21
F2	0.517	0.564	8.33	0.92	23.62 ± 1.12
F3	0.510	0.555	8.17	0.92	23.89 ± 0.26
F4	0.513	0.575	10.68	0.89	22.84 ± 0.62
F5	0.521	0.564	7.52	0.92	25.64 ± 0.21
F6	0.500	0.553	9.57	0.90	21.58 ± 0.15
F7	0.526	0.555	5.19	0.95	22.46 ± 0.21
F8	0.490	0.565	13.20	0.87	23.76 ± 0.10
F9	0.516	0.567	8.89	0.91	25.26 ± 1.20
F10	0.526	0.572	8.07	0.92	24.29 ± 0.32
F11	0.515	0.566	9.04	0.91	26.48 ± 0.12
F12	0.494	0.576	14.16	0.86	24.35 ± 0.23
F13	0.517	0.556	7.05	0.93	24.80 ± 0.45
F14	0.515	0.573	10.22	0.90	22.15 ± 0.21
F15	0.536	0.557	3.77	0.96	24.26 ± 0.14
F16	0.516	0.564	8.51	0.91	26.75 ± 0.10

* All values are expressed as mean ± SD (n=5).

Table 3: Postcompression parameters for formulations f1-f16

Batch code	Hardness^ (Kg/cm^2)	Weight variation* (mg)	Friability# (%)	Content uniformity^ (%)	% Cumulative drug release at the end of 12 h^
F1	4.5 ± 0.04472	261 ± 1.6050	0.99 ± 0.0621	97.8 ± 0.0345	93.66 ± 0.14
F2	5.0 ± 0.04472	348 ± 1.8467	0.55 ± 0.0616	98.3 ± 0.0134	92.59 ± 0.13
F3	5.1 ± 0.05477	391 ± 1.7770	0.46 ± 0.0153	98.6 ± 0.0532	91.76 ± 0.10
F4	4.8 ± 0.05477	260 ± 1.0954	0.84 ± 0.0265	98.0 ± 0.0243	92.68 ± 0.12
F5	4.9 ± 0.05477	348 ± 1.2258	0.51 ± 0.0355	97.7 ± 0.0326	90.48 ± 0.05
F6	5.1 ± 0.04472	390 ± 1.1697	0.43 ± 0.0391	98.2 ± 0.0326	88.14 ± 0.04
F7	4.7 ± 0.04472	260 ± 1.3168	0.80 ± 0.0265	98.1 ± 0.0134	93.26 ± 0.09
F8	5.2 ± 0.08366	349 ± 2.5726	0.51 ± 0.0399	97.9 ± 0.0709	91.75 ± 0.09
F9	5.3 ± 0.08944	390 ± 2.2820	0.43 ± 0.0268	98.0 ± 0.0435	89.45 ± 0.07
F10	5.1 ± 0.05477	379 ± 3.5703	0.42 ± 0.0378	99.4 ± 0.0219	95.28 ± 0.04
F11	5.4 ± 0.04472	416 ± 2.3951	0.38 ± 0.0089	98.6 ± 0.0219	96.25 ± 0.58
F12	5.2 ± 0.07071	419 ± 2.1343	0.45 ± 0.0190	99.1 ± 0.0326	97.25 ± 0.07
F13	5.3 ± 0.04472	431 ± 2.5808	0.30 ± 0.0348	99.5 ± 0.0251	96.35 ± 0.12
F14	5.2 ± 0.07071	450 ± 2.4767	0.38 ± 0.0157	99.8 ± 0.0324	99.70 ± 0.13
F15	5.2 ± 0.04472	430 ± 2.3004	0.28 ± 0.0185	98.8 ± 0.0435	95.08 ± 0.07
F16	4.9 ± 0.05477	424 ± 2.5731	0.40 ± 0.0377	98.6 ± 0.0532	96.47 ± 0.18

* All values are expressed as mean ± SD (n=20).
^ All values are expressed as mean ± SD (n=5).
# All values are expressed as mean ± SD (n=10).

Table 4: Swelling and floating properties of tablets

Formulation code	Swelling index (%)	Floating lag time (s)	Total floating time (h)
F1	85.06 ± 1.12	96.1 ± 1.2	> 24
F2	99.41 ± 3.21	89.3 ± 2.6	> 24
F3	106.66 ± 4.25	85.6 ± 3.1	>24
F4	68.76 ± 6.28	95.7 ± 4.4	>24
F5	101.39 ± 3.47	86.2 ± 3.3	>24
F6	125.67 ± 3.53	82.9 ± 5.8	>24
F7	85.22 ± 4.59	98.3 ± 2.7	>24
F8	92.28 ± 1.37	90.3 ± 6.1	>24
F9	114.33 ± 2.53	85.2 ± 3.2	>24
F10	93.57 ± 6.45	60.0 ± 6.8	>24
F11	89.82 ± 3.32	51.2 ± 4.2	>24
F12	98.36 ± 1.56	53.1 ± 5.3	>24
F13	100.29 ± 3.12	45.3 ± 1.9	>24
F14	101.23 ± 2.87	30.1 ± 1.7	>24
F15	91.96 ± 3.12	53.2 ± 4.1	>24
F16	92.65 ± 4.12	60.1 ± 1.1	>24

Kinetic modeling of drug release:

Analysis of drug release from floating matrix tablets was performed with a flexible model that can identify the contribution to overall kinetics, mechanism of drug release and the dissolution data obtained for optimized formulation was treated with the different release kinetic equations [15]. Zero order release equation:

$$Q = K_0 t \quad (1)$$

First order equation:

$$\ln Q = K_f t \quad (2)$$

Higuchi's square root of time equation:

$$Q = K_H t^{1/2} \quad (3)$$

Korsmeyer and Peppas equation:

$$F = (M_t / M) = K_m t^n \quad (4)$$

Where,

Q = Amount of drug release at time t

M_t = Drug release at time t

M = Total amount of drug in dosage form

F = Fraction of drug release at time t

K_0 = Zero order release rate constant

K_f = First order release rate constant

K_H = Higuchi square root of time release rate constant

K_m = Constant depend on geometry of dosage form

n = Diffusion exponent indicating the mechanism of drug release [16].

Table 5: Kinetic treatment of drug release data of various Batches

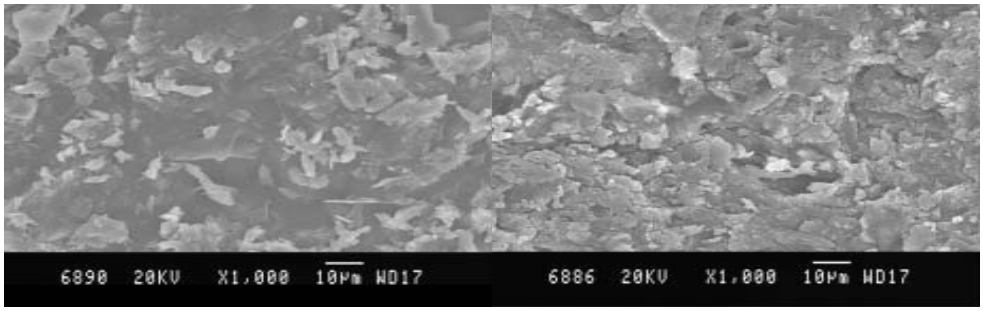
Formulation code	Zero order	First order	Higuchi's matrix	Peppas model	Diffusion coefficient (n)
	R^2				
F1	0.969	0.871	0.964	0.992	0.68
F2	0.988	0.886	0.961	0.998	0.68
F3	0.965	0.872	0.957	0.986	0.65
F4	0.965	0.908	0.968	0.991	0.65
F5	0.988	0.884	0.959	0.997	0.68
F6	0.979	0.965	0.973	0.997	0.68
F7	0.971	0.943	0.983	0.993	0.67
F8	0.961	0.963	0.988	0.997	0.68
F9	0.977	0.978	0.973	0.996	0.69
F10	0.981	0.960	0.972	0.998	0.68
F11	0.973	0.960	0.978	0.993	0.68
F12	0.992	0.932	0.951	0.997	068
F13	0.990	0.826	0.957	0.996	0.69
F14	0.961	0.817	0.991	0.994	0.68
F15	0.982	0.975	0.969	0.996	0.68
F16	0.963	0.923	0.979	0.989	0.67

Stability studies:

Stability studies were carried out for optimized batch (F14) of floating matrix tablets of Diltiazem hydrochloride. The tablets were packed in aluminum foil placed in airtight container and kept at 4^o in refrigerator, 40^o/75% RH and 60^o for 60 days. At the interval of 15 days, the tablets were withdrawn and evaluated for physical properties and *in-vitro* drug release [17].

Morphological characterization of optimized batch:

Tablet sample (Batch F14) was removed from the dissolution apparatus at predetermined time interval, the specimen was then position on the sample holder so as to present a cross-section of the tablet under the microscope. Sample were coated with platinum and visualized under scanning electron microscope (SEM).



[a] **[b]**

Fig. 2: S.E.M. image of [a] Dry floating tablet [b] Wet floating tablet

3. Results

The preformulation studies shows that Diltiazem hydrochloride possesses all requisite qualities required for controlled drug delivery system in the form of floating tablet. The FTIR spectra obtained indicated no change in chemical identity of the drug and polymers. The floating matrix tablets of Diltiazem hydrochloride were formulated by using different viscosity grades of HPMC (K4M, K15M and K100M) by wet granulation technique. Microcrystalline cellulose was used as diluent. Sodium bicarbonate and citric acid were used as gas generating agents either alone or in combination. All the prepared tablets were found to be good without chipping, capping and sticking. The drug content was uniform (97.7 to 99.8%) and well within the accepted limits with low values of standard deviation indicating uniform distribution of drug within the tablets of same batch. The drug: polymer ratio, viscosity grades of HPMC and gas generating agents were found to influence the release of drug from the prepared floating tablets and their floating characteristics. The amount of drug released for a particular drug polymer ratio was found to be in the order of K4M > K15M > K100M.

The prepared tablets showed excellent *in vitro* floating properties. Addition of gas generating agent sodium bicarbonate alone resulted in the reduction of floating lag time. Addition of citric acid to the floating tablet with sodium bicarbonate has produced a marked reduction in the floating lag time. All the floating matrix tablets have showed a floating time of 24 h. The floating lag time is depended upon the concentration of gas generating agent i.e. an optimum concentration of sodium bicarbonate (50 mg per tablet) and citric acid (≈30 mg per tablet) were found to be essential to achieve an optimum *in vitro* floating. The *in vitro* dissolution profiles of all the prepared floating matrix tablets of Diltiazem hydrochloride were found to control the drug release over a period of 12 h and the drug release decreased with increase in polymer concentration.

Release of Diltiazem hydrochloride from most of the formulations was found to follow zero order kinetics (0.96 to 0.99) and derived correlation coefficient 'R^2' (0.99) indicated good fit of Higuchi model suggesting that diffusion is the predominant mechanism controlling the drug release. When drug release data fitted to Korsmeyer equation, the values of slope 'n' (0.65 to 0.69) indicated that the drug release was by Non-Fickian mechanism.

Among the various floating tablet formulations studied, formulation F14 containing drug-polymer ratio (1:2) prepared with HPMC K4M showed promising results releasing 99.70% of the drug in 12 h with a floating lag time of 30 s and floating time of 24 h has been considered as an ideal formulation. Optimized batch of floating tablet of Diltiazem hydrochloride (F14) was further subjected for short term stability studies and found to be stable for 60 days. SEM study further confirmed both swelling and diffusion mechanisms to be operative during drug release from the optimized formulation of batch F14.

4. Discussion

Gastroretentive drug delivery system offers a simple and practical approach to achieve increased gastric residence and to modify drug release profiles essential for controlled, site specific

and localized drug action. The approach of the present study was to develop floating matrix tablets of Diltiazem hydrochloride and henceforth evaluate the release profiles of these formulations. Diltiazem hydrochloride possesses all requisite qualities required for controlled drug delivery system in the form of floating matrix tablet. The floating matrix tablets of Diltiazem hydrochloride were formulated using the wet granulation process using isopropyl alcohol as a granulating fluid. The evaluation data for properties such as hardness, friability, weight variation, drug content uniformity, floating lag time and water uptake indicated that the prepared floating tablets were well within the specified standards. The results proved that prepared tablets exhibited excellent *in vitro* drug release as well as controlled the drug release over 12 h. The drug/polymer mass ratio can affect the drug release and *in vitro* floating. Among the various formulation, the formulation F14 was found to be optimum formulation. The formulation F14 containing drug: polymer ratio (1:2.0), HPMC K4M and PVP K30 as granulating agent fulfilled all desirable requirements for formulation of floating matrix tablet. Formulation F14 was found to release the drug for 12 h (99.7%) and followed Korsmeyer-Peppas model in dissolution studies. From the stability studies, it is clear that the formulation was stable for sixty days and the FTIR spectra obtained indicated no change in chemical identity of the drug.

5. Conclusion

Gastroretentive drug delivery system offers a valuable dosage form which delivers the drug at a controlled rate and at a specific site. The floating matrix tablets of Diltiazem hydrochloride provides a better option for increasing the bioavailability and reliability for treatment of hypertension by allowing a better control of fluctuations observed with conventional dosage forms. Formulation F14 appears suitable for further pharmacodynamic and pharmacokinetic studies to evaluate clinical safety of these floating tablets in suitable animal and human models.

References

[1] A. A. Deshpande, N. H. Shah, C. T. Rhodes, Pharm. Res., 815 – 819 (1997).
[2] S. K. Jhain, N. K. Jhain, G. P. Agarwal, Drug delivery technology **5**, 21-31 (2005).
[3] Mathiowitz, Editors, Encyclopedia of controlled drug delivery, 1st edition, New York: John Wiley, 9 – 11 (1999).
[4] S. C. Sweetman, Martindale. The complete drug reference, 32nd edition, Pharmaceutical press London,854-855 (2000).
[5] Indian Pharmacopoeia 2007, Vol. 2, The Indian Pharmacopoeia Commission. Ghaziabad, 241, 244.
[6] R. Kumar, M. B. Patil, S. R. Patil, M. S. Paschapur, Int. J. Pharm. Tech. Res. **1**(3), 754 (2009).
[7] M. E. Aulton. In; Pharmaceutics: The science of dosage form design, 2nd edition, Churchill Livingstone, 113-114 (1989).
[8] H. A. Liberman, L. Lachman, J. B. Schwartz. In; Pharmaceutical dosage forms: Tablets. 2nd edition, Vol I, Marcel Decker, New York, 411 (1989).
[9] Indian Pharmacopoeia 1996, Vol. 2, The Indian Pharmacopoeia Commission Ghaziabad, 734.
[10] J. I. Wells, In: Swarbick J, Boylan JC, editors, Encyclopedia of pharmaceutical technology, 2nd edition, Vol X, New York: Marcel Decker, 411 (1996).
[11] X. Xiaoqiang, S. Minjie, Z. Feng, H. Yiqiao, Int. J. Pharm. **310**,139-145 (2006).
[12] V. Agarwal, B. Mishra, Drug Dev. Ind. Pharm. **25**(6), 701-709 (1999).
[13] S. Baumgartner , J. Kristl, F. Vrecer, P. Vodopivec, B. Zorko, Int. J. Pharm. **195**, 125 (2000).
[14] Z. Rahman, M. Ali, R. K. Khar, Design and evaluation of bilayer floating tablets of captopril, Acta Pharm. **56**, 49-57 (2006).
[15] S. Kumar, M. Pandey, S. A. Saraf, J. Pharm. Res. **2(4)**, 717-722 (2009).
[16] K. R. Reddy, S. Mutalik, S. Reddy, AAPS Pharm. Sci. Tech. **4,** 61 (2003).
[17] J. Dumpeti, L. Meka, K. M. Chinnala, Int. J. Pharm. Sci. Nanotech **1**(3)**,** 227 (2008).