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FORMULATION AND EVALUATION OF FLOATING GASTRORETENTIVE DRUG DELIVERY SYSTEM OF DILTIAZEM HYDROCHLORIDE

G. SURESH*[1], P. PAVAN [2], D.V.R.N. BIKSHAPATHI[3] AND Y. MADHUSUDAN RAO[1].

[1]Vaagdevi College of pharmacy, Kakatiya University, Warangal, INDIA.
[2]Centre for Biopharmaceutics, Kakatiya University, Warangal, INDIA.
[3] Vijaya College of Pharmacy, Jawaharlal Nehru Technological University, Hyderabad, INDIA.

ABSTRACT

The present investigation describes the design and evaluation of monolithic gastro retentive dosage forms of diltiazem. Hydrophilic cellulose derivatives, Sodium alginate, Sodium carboxy methyl cellulose, Polyox, Methocel K100M in combination with Methocel E6LV are used as the rate controlling polymers. Sodium bicarbonate was incorporated as gas generating agent. Tablets were prepared by employing a wet granulation process and evaluated for the different evaluation parameters such as thickness, diameter, drug content uniformity, friability, floating lag time, in-vitro buoyancy, in-vitro drug release studies and stability studies were performed. All the evaluation parameters results were significant. DSC studies indicated absence of interaction between the drug and excipients. The release rate, extent and mechanisms were found to be governed by polymer and floating agent content. Kinetics of drug release from tablet followed Higuchi and Korsmeyer equations. Both Formula F-5 & F-6 were stored at 40°C/75% RH for 3 months according to ICH guidelines. From all the formulations F6 was found to be optimized formulation based on the results obtained from the studies. Abdominal X-ray imaging of formula F-6, loaded with barium sulfate, in eight healthy human volunteers revealed a mean gastric retention period of 5.50 ± 0.55 h. It is concluded that the gastro retentive tablet of diltiazem HCl can be prepared via floating mechanism to increase its residence time and thereby increasing its availability for absorption from the stomach or upper gastrointestinal tract (GIT).

KEYWORDS:Hydrophilic Polymers, Mean Dissolution Time, Floating drug delivery system, Diltiazem HCl, Sustained Release Tablets.

G. SURESH
Vaagdevi College of pharmacy, Kakatiya University, Warangal, INDIA.

**Corresponding author*

INTRODUCTION

The present investigation describes the design and development of diltiazem hydrochloride gastroretentive dosage forms. The purpose of these dosage forms is to improve the state of disease management by modifying the pharmacokinetic profiles of therapeutic agents normally administered as conventional tablets or capsules. However, the issue in the development of oral controlled release dosage forms is to prolong the residence time of dosage forms in the stomach or upper gastrointestinal (GI) tract until the drug is completely released[1]. Rapid GI transit could result in incomplete drug release from the drug delivery device in the absorption zone leading to diminished efficacy of the administered dose[2]. The principle of buoyant preparation offers a simple and practical approach to achieve increased residence time for the dosage form in stomach and sustained drug release. Diltiazem, a calcium channel blocker, is indicated in the long-term treatment of hypertension, angina pectoris and arrhythmias[3]. Diltiazem undergoes an extensive biotransformation, mainly through the cytochrome p-450 CYP3A[4], which results in less than 4% of its oral dose being excreted unchanged in urine[5]. Bioavailability of diltiazem is approximately 30% - 40% owing to first pass metabolism[3, 5, 6]. The half-life of the drug is ~3.5 hours. In addition, many reports stated that it has an absorption zone from the upper intestinal tract[5, 6]. Therefore, gastric and intestinal transient times have a significant effect on the rate and extent of oral absorption of the drug. As a result, variable oral bioavailability may be expected.Diltiazem has absorption window in upper G.I tract, efficacy of the administered dose may get diminished due to incomplete drug release from the dosage form above the absorption zone and due to this often display low bioavailability. Diltiazem requires multiple daily dosage to maintain adequate plasma concentrations (three to four times a day) makes it suitable model candidate for gastroretentive formulation. The gastroretentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. Therefore in the present investigation efforts have been made to increase the residence of diltiazem at or above the absorption window by preparing Gastro retentive tablet for gastric retention considering fact that it is stable at gastric condition.The aim of the present study was to prepare and characterize sustained release floating matrix tablets of diltiazem using various hydrophilic cellulose derivatives; Methocel K 100M and Methocel E6LV, Sodium carboxy methyl cellulose, sodium alginate and polyethylene oxide. High molecular weight Polyox and HPMC K100M was used since it is reported that it swells to a great extent and forms a stronger gel that is less prone to erosion. The rate of drug release from hydrophilic matrix is dependent on various factors such as types of polymer, solubility of drug, polymer content, particle size of drug and polymer as well as types and amount of filler used in the formulation[7]. The adjustment of polymer concentration, viscosity grade and addition of different types and levels of excipients to the polymer matrix can modify the kinetics of drug release[8]. Investigations were performed to see the effect of floating agent content and diltiazem content upon the floating lag time of the tablets. The impact of formulation variables upon the release rate and release mechanism was also evaluated with the help of various mathematical models.

MATERIALS AND METHODS

MATERIALS

Diltiazem was a generous gift from Dr. Reddy's Laboratories Limited, (Hyderabad, India), Hydroxy propyl methyl cellulose (HPMC E6LV and 100M) were obtained from Colorcon Asia Private Limited, India), PVPK 30 was obtained from BASF, Germany. Sodium carboxy methyl cellulose and sodium alginate were used. All excipients were of USP/NF grade and all other chemicals used were of analytical grade.

Radiographic studies

The study protocol was approved by the Institutional Human
Ethics Committee (IHEC), University College of Pharmaceu-
tical Sciences, Kakatiya University, Warangal, India.

Solubility studies

The equilibrium solubility of diltiazem hydrochloride was measured in 0.1M hydrochloric acid (pH 1.2), acetate buffer (pH 4.5), and phosphate buffers (pH 7.4 and 8.0). Excess amounts of the drug were added to 50 mL-stoppered conical flasks (n = 3). The flasks were shaken mechanically at 37 °C ± 0.5 °C for 48 hours. After 2 days of equilibrium, aliquots were withdrawn and filtered (0.22 µm pore syringe filter). Then, the filtered samples were diluted with an appropriate amount of suitable buffers and the final solutions were measured by spectrophotometer at 237 nm, (SL159 UV-Visible spectrophotometer, Elico SL159, Elico Private Limited Hyderabad).

Drug-excipient compatibility

The physicochemical compatibilities of the drug and the used excipients were tested by differential scanning calorimetric (DSC) analysis. DSC thermograms of the drug alone and drug-excipient physical mixture and tablets were derived from a DSC (2-C, Perkin-Elmer, New York, NY) with a thermal analysis data station system, computer, and plotter interface. The instrument was calibrated with an indium standard. The samples (2-4 mg) were heated (50 °C-300 °C) at a constant scanning speed (10 °C/min) in sealed aluminum pans, using nitrogen as purging gas.

Preparation of diltiazem hydrochloride sustained release matrix tablets

All the tablet formulations were prepared by using wet granulation technique. The composition of a 90 mg diltiazem HCl tablet compositions were given in table 2. Polyvinyl pyrrolidone was accurately weighed and dissolved in isopropyl alcohol. All excipients except magnesium stearate were accurately weighed and passed through No. 40 mesh ASTM. Calculated amount (required to prepare a 50 tablet batch) of the drug, polymer (HPMC K 100M, 6 cps, Polyox or Sodium alginate etc) and filler Microcrystalline cellulose (Avicel pH101) was mixed thoroughly. A sufficient volume of the specified granulating agents were added slowly to achieve the granulation endpoint. After enough cohesiveness was obtained, the granules were dried at room temperature to evaporate the IPA and dried the granules at 50 °C for 30 minutes. The semi-dried granules were passed through No. 10 mesh ASTM and continued the drying for another 1 hour 30 minutes. The granules were collected and passed through # 22 mesh ASTM. Lubricated the granules with # 80 mesh ASTM passed magnesium stearate. The tablets were compressed using 8 mm round standard concave punches. The composition of the different formulations was shown in Table 2.

Evaluation of tablets

Thickness

The thickness of the tablets was determined using a vernier caliper (Mitutoyo, New Delhi, India). Ten tablets from each batch were used. Thickness values were reported in millimeters. Mean and SD were calculated.

Average weight of the dosage Unit

To study weight variation, 10 tablets of each formulation were weighed using an electronic balance (Mettler Toledo, Switzerland). Values were reported in milligrams. Mean and SD were calculated.

Drug content

Five tablets were weighed individually, then placed in a mortar and powdered with a pestle. An amount equivalent to 90 mg drug (100 mg) was extracted with 100 mL of 0.1 M hydrochloric acid and sonicated intermittently for 30 minutes. The solution was filtered through a 0.22 µm PVDF syringe filter SLGV Millipore, properly diluted with 0.1 M hydrochloric acid, and then the drug content was measured.

Hardness test

For each formulation, the hardness of 6 tablets was determined using a hardness tester (Sotax HT_1, Sotax, Switzerland). Hardness values were reported in Newton's (N). Mean and SD were calculated.

Friability test

For each formulation, 6 tablets were weighed. The tablets were placed in a friabilator Electrolab, Mumbai, India) and subjected to 100 rotations in 4 minutes. The tablets were then dedusted and reweighed. The friability was calculated as the percentage weight loss.

In vitro release studies

In vitro release studies of diltiazem HCl matrix tablets were monitored. The release experiments were performed in a 900-mL dissolution medium of hydrochloric acid pH 1.2 kept at 37 C ± 0.5 C and stirred at 50 rpm, using USP dissolution apparatus II. A 5-mL sample was withdrawn through a 0.45-μm filter and replaced with another 5 mL of a suitable fresh dissolution medium at preselected intervals up to 12 hours. The amount of the drug was determined as mentioned previously.

Kinetic modeling of drug release

The dissolution profiles of all the batches were fitted to zero order, first order, Higuchi and Peppas equations (Higuchi, 1961[9] (equation 1-4 respectively).

$M_t = M_0 + k_0t$ (1)

$\ln M_t = \ln M_0 + k_1t$ (2)

$M_t = M_0 – k_Ht^{1/2}$ (3)

$M_t/M_\alpha = K_t^n$ (4)

In these equations, M_t is the cumulative amount of drug released at any specified time (t) and M0 is the dose of the drug incorporated in the delivery system and M_t/M_α is a fraction of drug released at time (t). k_0, k_1, k_H and K are rate constants for zero order, first order, Higuchi and Korsmeyer model respectively, n is the release exponent. The n value is used to characterize different release mechanisms as given in table 1 for cylindrical shaped matrices[10].

Table 1
Diffusion exponent and solute release mechanism for cylindrical shape

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

The dissolution data were also fitted according to the well-known exponential Zero Order equation, which is often used to describe drug release behavior from polymeric systems. The best fit with higher correlation (r^2 > 98) was found with Higuchi's equation for all the formulations.

Determination of In-vivo gastric residence time

To make the best achieved formula (F-6) X-ray opaque, 90 mg of the drug was replaced with barium sulfate and all other ingredients were kept constant. This amount was determined experimentally to allow X-ray visibility but not to hinder tablet buoyancy. After overnight fasting, the volunteers were fed with a low calorie food. After half an hour, a barium sulfate-labeled tablet was given to every subject with 200 mL of water. The volunteers were asked to take 200 mL water after every 1 hour. At different time intervals (0, 0.5, 2, 4 and 6 h post-administration of tablets), the volunteers were exposed to abdominal X-ray imaging (Genesis 50, Josef Betschart AG, Brunnen, Switzerland) in standing position.A radiograph was made just before the administration of the tablet, at zero time, to ensure the absence of radio-opaque material in the stomach. The distance between the source of X-rays and the subject was kept constant for all images. Thus, the observation of the floating tablet movements could be easily noticed[11]. The mean gastric retention period was estimated.

Solubility studies

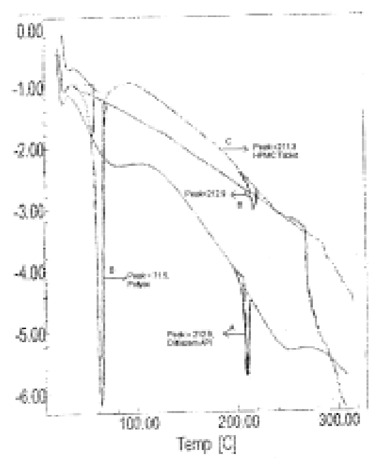
Diltiazem is a water soluble drug. The results of diltiazem solubility in physiological solutions of pH 1.2, pH 4.5 and pH 7.4 and 8.0 were 653, 585, 590 and 515 mg/mL, respectively, at 37°C (n=3) with increase in pH the solubility decreased.

Drug-excipient interaction

Figure 1 shows thermograms of diltiazem HCl and its physical mixtures (1:1 ratio wt/wt) with the physical mixtures used in this study. The DSC analysis of the drug alone elicited an endothermic peak at 210°C, very close to the reported value of diltiazem melting point, which is 210 °C, it was found that the endothermic peaks of physical mixture as well as tablet reflected the characteristic features of diltiazem alone. Thus, there was no evidence of interactions between diltiazem HCl and the used excipients.

Figure 1

DSC Thermograms of (A) Pure Drug (B) Physical Mixture (C) Tablet.



Preparation and evaluation of diltiazem HCl gastro retentive floating tablets

Different formulations (Table 2) were prepared using approximately 48.5%, 46.0%, 43.0% and 43.0% of floating agent with the tablet weight of 350 mg for F-1, F-2, F-3 and F-4 and 23.0%, 40.0%, 34.5% and 23.5% of floating agent with the tablet weight of 260 mg for F-5, F-6, F-7 and F-8 to get the floating lag time within 4 minutes. Tablets compressed with 260 mg tablet weight with combination of 23.0% of methocel K100 M and 23.0% HPMC E6 LV floating agents floating lag time was found to be higher side. Tablets were compressed without any problem. The physical evaluation parameters of the prepared tablets are presented in Table 3. Tablets prepared were smooth, shiny and do not require coating (for patient compliance and palatability aqueous coating can be preferred). For all prepared tablets, the relative SD of weight was under 6% and SD's were quiet uniform, ranging from 1.8 to 3.1. It was observed that the variation in thickness of the tablets was minimal. It was also observed that increasing tablet weight resulted in a slight increase in the thickness of the tablet formulations. The friability values of the prepared tablets are in the range of 0.10% to 0.27% and the friability is in compliance with the

US and European pharmacopeia which state that the acceptable loss of weight up to 1.0%. Hardness of the prepared tablets fell into the range 9.0 to 18 Kp. Increase in tablet weight resulted in increase in thickness. All these results were in good agreement with those of thickness and friability.

Table 2
Composition of different formulations of floating tablets

Formula	F-I	F-2	F-3	F-4	F-5	F-6	F-7	F-8
Diltiazem (mg)	90	90	90	90	90	90	90	90
Avicel 101 (mg)	15	20	5	25	42.5	17.5	22.5	42.5
Methocel K 100M (mg)	120	80	-	-	30	75	-	-
HPMC E6-LV (mg)	50	-	-	-	-	30	-	-
Sodium CMC (mg)	-	-	-	150	-	-	-	-
Polyox (mg)	-	80	-	-	30	-	-	60
Sodium alginate	-	-	150	-	-	-	90	-
Sodium bicarbonate (mg)	55	60	85	65	50	30	40	50
PVPK 30 (mg)	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5
Total (mg)	350	350	350	350	260	260	260	260
Remarks	Floated	Floated	Floated	Floated	Floated	Floated	Floated	Floated

Table 3
Compression force, Hardness, Friability, Thickness, weight and Drug content of the Prepared Hydrophilic Matrix Tablets, Expressed as Mean SD

Formula	Compression Force (Tonnage)	Hardness (Kp)	Friability (%)	Thickness (mm)	Weight (mg)	Drug Content (%)
F-1	3	17.7±1.5	0.18	5.40 ± 0.05	348 ± 2.2	55.50± 0.64
F-2	3	16.5±1.0	0.19	5.42 ± 0.08	350 ± 1.9	45.70± 0.82
F-3	3	17.0±1.5	0.17	5.41 ± 0.06	354 ± 3.1	50.60± 0.55
F-4	3	16.0±1.5	0.23	5.43 ± 0.04	351 ± 2.2	98.10± 1.41
F-5	3	9.0±1.0	0.27	4.47 ± 0.12	260 ± 1.9	99.68 ± 0.92
F-6	3	9.6±2.5	0.14	4.44 ± 0.24	260 ± 2.4	99.04 ± 1.47
F-7	3	9.8±2.0	0.12	4.45± 0.36	260 ± 1.8	95.50± 0.82
F-8	3	9.5±2.0	0.10	4.48 ± 0.28	260 ± 2.1	97.50± 0.91

In vitro release studies

Table 4 shows the floating lag time and % release of all the 8 formulations. Figures 2 and 3 shows the in vitro release profile of diltiazem HCl from the prepared 90 mg floating matrix tablets at pH 1.2.

Table 4
Floating lag time and release parameters of floating tablets of Diltiazem HCl

Formula	Floating Lag time (Sec)	% Release
F-1	40±20	55.50
F-2	35±15	45.70
F-3	40±15	50.60
F-4	35±15	91.10
F-5	210±15	97.53
F-6	40±15	95.89
F-7	40±15	91.00
F-8	50±15	89.53

Figure 2
Dissolution profile of GRDDS floating tablets F-1, F-2 and F-3.

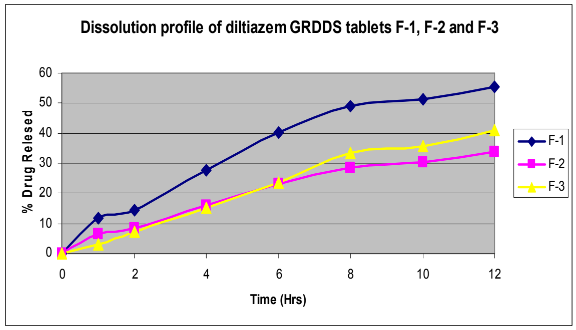
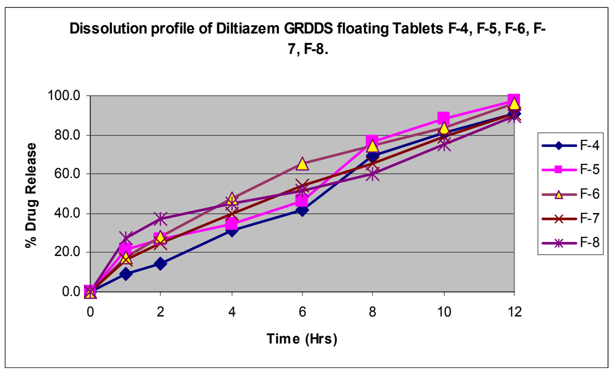


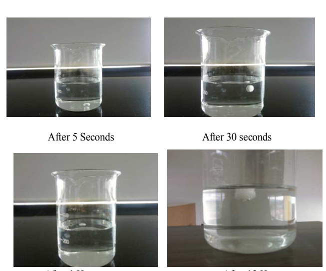
Figure 3
Dissolution profile of GRDDS floating tablets F-4, F-5, F-6, F-7 and F-8.



In vitro buoyancy study

Formulations were evaluated for *in vitro* buoyancy and all formulations had floating lag times below 4 minutes and constantly floated on dissolution medium for more than 10 hours. Floating lag times were found to be significantly controlled by sodium hydrogen carbonate content. Floating lag time was reduced due to increase of amount of floating agent (Figure 4). Increased amount of floating agent caused rapid formation as well as entrapment of CO_2 gas into the hydrophilic polymeric gel which eventually resulted in reduction of floating lag time.

Figure 4
Pictorial presentation of in vitro floating behavior of a representative tablet of Methocel K 100M.



Effect of polymer grade on release of diltiazem HCl

All the formulations containing Methocel K100M and Methocel E6-LV and in combination with Polyox polymers were compared to explore the effect of polymer grade and amount on the drug release from the formulations. To evaluate the effect of viscosity on the drug release variation of product F-1 which contained 120 mg Methocel K 100M and 50 mg HPMC E6 agent was compared with F-2 which contained 80 mg Methocel K 100M and 80 mg of polyox (Table 2). At the end of twelve hour products F-3 and F-4 showed the release of drug was 50.60% and 91.1%. R^2 value obtained from zero order equation for F-3 and F-4 was 0.982 and 0.988 respectively (Table 5). The best linearity was found in Higuchi's equation plot 0.935 and 0.911 for F-3 and F-4 respectively indicating the release of drug from matrix as a square root of time dependent process based on diffusion mechanism. Then value was found to be 0.31 and 0.57 for F-3 and F-4 indicating fickian diffusion.For F-5 and F-6 the percent drug release at the end of twelve hour was 97.5% and 96.0%. R^2 value obtained from zero order equation for F-5 and F-6 was 0.974 and 0.967 respectively (Table 5). The best linearity was found in Higuchi's equation plot (F-5) 0.925 indicating the release of drug from matrix as a square root of time dependent process based on diffusion mechanism. Formula (F-6) value is near zero order release. values for (F-5, F-6) were found to be 0.77 and 0.49 respectively, indicating non fickian (anomalous) release, coupled diffusion.In case of F-7 and F-8 the percent release at the end of ten hour was 91.0% and 89.5%. R2 values obtained from the zero order equation for F-7 and F-8 are 0.963 and 0.92 respectively (Table 5). The best linearity was found in Higuchi's equation plot (F-7) 0.973 indicating the release of drug from matrix as a square root of time dependent process based on diffusion mechanism. Formula (F-8) value is near to the zero order release. The n values for (F-7, F-8) were found to be 0.51 and 0.87 respectively, indicating non fickian (anomalous) release, coupled diffusion.The formulations F-5 and F-6 containing methocel K100M polymer in lower concentrations 11.5 and 29.0% respectively showed zero order release and was found to follow predominantly non fickian (anomalous release), coupled diffusion mechanism.Influence of gas generating agent (with 20.0% of sodium hydrogen carbonate with 260 mg of tablet weight) in combination with low concentrations of hydrophilic polymer methocel k100M and polyox of the formulations resulted in the increase of drug release rate and extent possibly due to the formation of channels which simulated water penetration into the inner part of the matrix and thus exposure of new surfaces of tablet matrix to the dissolution medium. In the formulation F-5, an increase in the lag time was observed with low concentrations of methocel polymer in combination with polyox comparable to the formulation F-6.

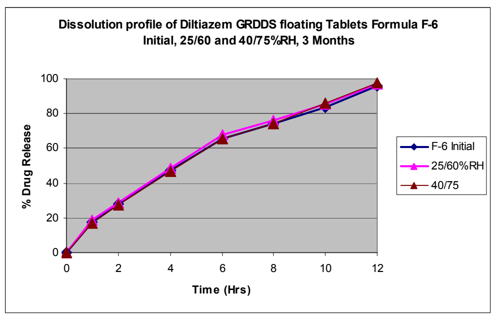
Table 5
Release parameters of diltiazem HCl gastro retentive floating tablets

Formula	Zero Order (r^2)	K_0	First Order (r^2)	K Values	Higuchi (r^2)	K_h	Peppas (r^2)	N Value
F-3	0.982	0.05	0.812	0.4	0.935	12.9	0.922	0.3
F-4	0.988	0.05	0.753	0.66	0.911	14.9	0.822	0.57
F-5	0.974	6.54	0.61	0.85	0.925	9.37	0.65	0.77
F-6	0.967	10.55	0.593	0.87	0.985	6.87	0.677	0.49
F-7	0.963	7.56	0.62	0.83	0.973	7.92	0.692	0.51
F-8	0.92	15.1	0.49	0.95	0.967	0.56	0.54	0.87

Stability studies

The stability of floating tablets prepared from formulation F-5 containing Methocel K100M (30 mg, 11.5%), with Sodium bicarbonate 50 mg, and F-6 containing methocel K100M (75mg, 29%) and methocel E6 LV 30 mg, (11.5%) was tested for stability at 25°C/60% RH and 40°C/75%RH in properly closed HDPE bottles along with 1 g desiccant for 3 months. The diltiazem HCl release (Figure 5) rate from the floating tablets showed no significant change in formulation F-6 during storage, but floating time was increased in the formulation F-5 during storage. For buoyancy testing, the formulations stored in both conditions for 3 months floated on the surface of the media (0.1N HCl) for 12 h. Thus, it was found that the diltiazem HCl floating tablets prepared from the formulation containing Methocel K100M, methocel E6 LV and sodium bicarbonate were stable under these storage conditions for at least 3 months. Based on the above, Formula F-6 was chosen for further *in vivo* studies.

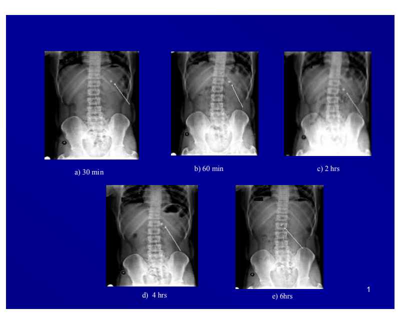
Figure 5
Release profile of diltiazem HCl tablets (F-6) stored at 25°C /60% RH and 40°C /75%RH for 3 months.



The mean gastric retention period

The in vitro buoyancy lag time of the barium sulfate-loaded tablet was 260 ± 10 s. The increase in the lag time, compared to the original formula F-5 (210 ± 15 s), was expected because barium sulfate, as reported by its manufacturer, has a high density (4.5 g/cm3). Figure 6 shows the radiographic images taken at different periods post-administration of the barium sulfate-loaded tablet in three volunteers. It is clear that the tablet appears more or less at the same position in the stomach for the first 4 h. This could be related to its floating ability. Later on, the tablet slightly moved downwards, yet, remained within the stomach till the end of 6 h. The mean gastric retention period was 5.50±0.55 h

Figure 6
Radiographic images showing the presence of a $BaSO_4$ loaded floating tablet in the stomach at a different time periods (the location of the tablet is indicated with an arrow).



CONCLUSION

Gastroretentive drug delivery systems of Diltiazem HCl could be successfully prepared. It was observed that the increase of amount of floating agent caused the decrease of floating lag time. At relatively higher viscosity polymer grade containing formulations displayed better fitting with zero order release kinetics and n values shows that all the formulations followed case II transport Anomalous (non-fickian) diffusion.The combination of methocel K100M, methocel E6LV and polyox polymer delayed the floating time where as floating lag time and drug release was not affected without the combination of polyox polymer. All these results indicate that a high amount of combination of hydrophilic polymer in the presence of sodium bicarbonate favored the sustained release of diltiazem HCl from gastro retentive floating formulations. The polymer type and concentration of the matrix tablets affected the floating lag time release profile of diltiazem HCl from hydrated methocel K100M, methocel E6LV and polyox matrices significantly. These studies indicated that the proper balance between a hydrophilic matrix former and in situ gas generating agent component can produce a drug dissolution profile. From all the formulations F6 was found to be optimized formulation based on the results obtained from the in-vitro dissolution and buoyancy studies. Abdominal X-ray imaging of formula F-6, loaded with barium sulfate, in eight healthy human volunteers revealed a mean gastric retention period of 5.50 ± 0.55 h. It was concluded that the gastro retentive tablet of diltiazem HCl can be prepared via floating mechanism to increase its residence time and thereby increasing its availability for absorption from the stomach or upper gastrointestinal tract.

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