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Development of gastroretentive systems for famotidine: *in vitro* characterization

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Abstract

Floating tablets of famotidine were developed to prolong gastric residence time, leading to an increase in drug bioavailability. Tablets were prepared by direct compression technique, using polymers hydroxypropyl methylcellulose (HPMC K4M and HPMC K15M). Tablets were evaluated for physical characteristics, weight, thickness, hardness and friability; drug content, swelling, floating properties and *in vitro* drug release characteristics for 12 h. Tablets exhibited sustained and prolonged drug release profiles while floating over the dissolution medium. The release pattern followed was anomalous non-fickian type, indicating that water diffusion and polymer rearrangement played an essential role in drug release. The best formulation was selected based on *in vitro* characteristics and was subjected for *in vivo* radiographic studies. These studies revealed that the tablets remained in stomach for more than 4.5 h in fed condition indicated that gastric retention time was increased by floating principle.

Keywords: famotidine, gastroretentive drug delivery system, floating tablets, gastric residence time

Introduction

Drug absorption from gastrointestinal tract is a complex procedure and is subject to many variables and the absorption is related to contact time with the small intestinal mucosa (Hirtz 1985). Gastro retentive systems can remain in the gastric region for several hours and therefore significantly prolong the gastric residence time of drugs. Many approaches have been reported in the literature for the gastro retentive systems viz. mucoadhesion (Ponchel and Irache 1998), floatation (Deshpande et al. 1997), sedimentation (Rednick and Tucker 1970), expansion (Mamajek and Moyer 1980, Urguhart and Theeuwes 1994), and modified shape systems (Fix et al. 1993, Fedzierewicz et al. 1999) or by the simultaneous administration of pharmacological agents (Groning and Heun 1984 and 1989) which delay gastric emptying. Both single unit systems (tablets or capsules) and multiple unit systems (multi particulate systems) have been reported in the literature (Soppinath et al. 2001, Arora et al. 2005). Floating drug delivery offers a number of applications for drugs having poor bioavailability because of narrow absorption window in the upper part of gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability (Ali et al. 2006).

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Famotidine is a histamine H_2-receptor antagonist, widely prescribed in gastric ulcers, duodenal ulcers, Zollinger-Ellison syndrome and gastroesophageal reflux disease (Reynolds 1996). The low bioavailability (20-60%) and short biological half life (2.5-4.0 h) of famotidine following oral administration favors development of a sustained release formulation. It is also reported that oral treatment of gastric disorders with an H_2-receptor antagonist like ranitidine or famotidine used in combination with antacids promotes local delivery of these drugs to the receptor of the parietal cell wall (Coffin and Parr 1995).

Local delivery also increases the stomach wall receptor site bioavailability and increases the efficacy of drugs to reduce acid secretion. This principle may be applied for improving systemic as well as local delivery of famotidine, which would efficiently reduce gastric acid secretion (Coffin and Parr 1995).

In context of the above principles, a strong need was recognized for the development of a dosage form to deliver famotidine in the stomach and to increase the efficiency of the drug, providing controlled release action. The present investigation applied a systematic balance between floating lag time, floating duration, and in vitro drug release for the development of gastroretentive dosage forms of famotidine suitable for a once daily formulation.

Materials and Methods

Materials

Famotidine was a gift from Dr.Reddys laboratory, Hyderabad, India. Hydroxypropyl methylcellulose K4M and 15M were gift samples of Colorcon, Mumbai, India. Sodium bicarbonate and barium sulphate were purchased from Merck, Mumbai, India. Purified talc and magnesium stearate were purchased from S.D. Fine-Chem Ltd, Mumbai, India. All other chemicals used were of analytical grade.

Preparation of famotidine floating tablets

All formulations were prepared by direct compression method by changing the drug polymer ratio and keeping all other ingredients constant. Presifted (#40) drug was mixed geometrically with polymer, guar gum and sodium bicarbonate for 10 min in a mortar. The blend was passed through sieve 40# to get uniform particle size and required quantities of magnesium stearate (# 80) and talc were added and mixed for 3 min. The lubricated blend was compressed into tablets with 8 mm punches on rotary compression machine (Riddhi, Ahmedabad, India). The composition of tablets was shown in Table 1.

Tablets for radiographic studies were prepared by incorporating a radio opaque high density (4.48 g cm^{-3}) component. Barium sulphate (15% w/w) was incorporated as radio opaque compound in tablets meant for radiographic studies (Table 1).

Table 1. Formulae of famotidine floating tablets

Ingredient (mg)	Formulation code						
	F1	F2	F3	F4	F5	F6	F5R
Famotidine	40	40	40	40	40	40	-
HPMCK4M	40	80	120	-	-	-	-
HPMCK15M	-	-	-	40	80	120	80
$BaSO_4$	-	-	-	-	-	-	30
Sodium bicarbonate	25	25	25	25	25	25	25
MCC	80	40	-	80	40	-	50
Guargum	10	10	10	10	10	10	10
Talc	3	3	3	3	3	3	3
Magnesium stearate	2	2	2	2	2	2	2

Characterization

Mass, thickness, hardness and friability determination

The mass of tablets were determined using a digital balance (Denver APX 60, Denver Instrument GmbH, Germany) and thickness with a digital screw gauge (Mitutoyo, Japan). Crushing strength and friability were measured with Pfizer hardness tester and with Roche friabilator respectively.

Assay of famotidine

Twenty tablets were taken and powdered; powder equivalent to one tablet was taken and was allowed to dissolve in 100 mL of 0.1N hydrochloric acid (HCl) by sonicating for 5 min followed by shaking for 30 min on a rotary shaker. The solution was filtered through 0.45 µm membrane filter, diluted suitably and analyzed using UV/visible spectrophotometer (Elico SL 164, Hyderabad, India) at 265 nm.

Determination of swelling index

The swelling index of tablets was determined in 0.1N HCl at room temperature. The swollen weight of the tablet was determined at predefined time intervals. The swelling index was calculated by the following equation:

$$\text{Swelling index} = \frac{W_t - W_0}{W_0}$$

Where W_0 is the initial weight of tablet, and W_t is the weight of tablet at time t. Each experiment was performed in triplicate and the mean and standard deviation (SD) were calculated.

In vitro buoyancy studies

The *in vitro* buoyancy was determined by floating lag time. The tablets were placed in a 100 mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was taken as the floating lag time. The experiments were conducted in triplicate.

In vitro drug release studies

The release of famotidine was studied using USP dissolution apparatus II (Labindia, India). The dissolution media was 900 mL 0.1N HCl maintained at 37±0.5°C with rotation speed of 50 rpm. Aliquots of 5 mL was collected at predetermined time intervals and replenished with an equivalent volume of fresh medium. The samples were filtered through a 0.45 µm membrane filter and diluted suitably with 0.1N HCl and were analyzed using UV/visible spectrophotometer at 265 nm. The results are expressed as mean ± S.D (n=6).

Kinetic modeling of drug release

The suitability of several equations, which are reported in the literature to identify the mechanism(s) for the release of famotidine, was tested with respect to the release data. The data were evaluated according to the following equations:

S. No.	Model	Equation
1	Zero order (Chen and Hao 1998)	$F = k\,t$
2	First order (Shah et al. 1987)	$\ln F = k\,t$
3	Higuchi (Higuchi 1961)	$F = kt^{0.5}$
4	Korsmeyer and Peppas model (Korsmeyer et al. 1983)	$F = kt^{n}$

Where F is the fraction of drug release, k is the release constant, t is the time, n diffusion coefficient

Drug – excipient compatibility studies

FTIR

The infrared spectra of famotidine, physical mixture of drug and excipients which was kept for stability for 30 days, at 40°C and 75%RH, and compressed tablet were recorded between 400 to 4000 cm^{-1} on FTIR. The IR spectra for the test samples were obtained using KBr disk method using an FTIR spectrometer (Perkin Elmer, USA).

Differential scanning calorimetry

DSC was performed on pure drug (6.56 mg), physical mixture of drug and excipients (11.1 mg) which were kept for stability for 30 days at 40°C / 75% RH, and compressed tablet powder (12.2 mg). Differential scanning calorimetry (DSC) measurements were carried out on a Mettler DSC 822e/TGA SDTA 851e (Switzerland) instrument equipped with a thermal data system. Samples were placed in aluminum pans (Al-crucibles) and sealed. The probes were heated from 25° C to 350°C at a rate of 10°C min^{-1} under nitrogen atmosphere.

In vivo assessment of gastroretentivity

The experimental protocol was approved by the Ethics Committee, Kakatiya University, India. Gastroretentivity of the dosage form were evaluated in healthy volunteer. The tablet was administered to a healthy male volunteer (age 25 years, weight 62 kg). The tablet was administered with 200 mL water and a 360 kcal bread following an overnight fast. Other wise, no food was allowed (with *ad libitum* access to water,) during the experiment. The first x-ray photo graphs were taken at time points of 0.5, 1.5, 3 and 4.5 h.

Results and Discussion

Physical properties of the compressed floating tablet systems

The floating tablets of famotidine were prepared by effervescent technique using HPMC K4M, HPMC K15M, guar gum, microcrystalline cellulose, sodium bicarbonate, along with magnesium stearate and talc as lubricant and glidant, respectively. The results mass, thickness variation and assay of floating tablets are shown in Table 2. The mass and thickness of the all the formulations were uniform as it was evidenced from RSD values, which were less than 3 indicating uniformity of mass and thickness. Hardness of tablets was found to be between 4.05 to 5.10 kg cm^{-2} indicating sufficient crushing strength. The friability was below 1% for all formulations, indicating good mechanical resistance of the tablet. The drug content varied between 39.1 to 39.7 mg in all tablets with low standard deviation indicating content uniformity of the prepared batches.

Table 2: Physicochemical parameters and buoyancy study of the prepared formulations

Code	Hardness (kg cm^{-2})	Thickness (mm)	weight (mg)	Friability (%)	Drug content (mg)	Floating lag time (sec)	Floating time (h)
F1	4.6 ± 0.3	3.4 ± 0.1	200.1 ± 1.5	0.73 ± 0.1	39.4 ± 0.1	55 ± 6	>12
F2	4.0 ± 0.4	3.4 ± 0.1	200.4 ± 1.9	0.63 ± 0.1	39.7 ± 0.3	73 ± 7	>12
F3	4.5 ± 0.1	3.4 ± 0.1	201.1 ± 1.1	0.45 ± 0.1	39.6 ± 0.3	450 ± 13	>12
F4	5.1 ± 0.2	3.4 ± 0.1	200.7 ± 1.2	0.67 ± 0.1	39.3 ± 0.2	69 ± 8	>12
F5	4.8 ± 0.3	3.5 ± 0.1	201.2 ± 1.6	0.54 ± 0.1	39.4 ± 0.3	87 ± 4	>12
F6	5.0 ± 0.2	3.5 ± 0.1	199.5 ± 1.4	0.57 ± 0.1	39.1 ± 0.5	467 ± 13	>12

Buoyancy studies

The formulated tablets on immersion in 0.1N HCl media, they remain buoyant for more than 12 h with a lag time of 55 to 467 sec. Sodium bicarbonate was added as a gas-generating agent. The optimized concentration of effervescent mixture utilized aided in the buoyancy of all tablets. This may be due to the fact that effervescent mixture in tablets produced carbon dioxide that was trapped in swollen matrix, thus decreasing the density of the tablet below 1 making the tablets buoyant. Results are shown in Table 3. All the batches showed good in vitro buoyancy. The results of the in vitro buoyancy study of batch F5 are shown in Fig.1. That clearly indicates the floating lag time (87 sec) of the famotidine tablet and the floating and swelling tendency of the formulation. The tablet swelled radially and axially. Formulation F5R composed of barium sulphate showed a lag time of 12±2 min with a floating duration of more than 8 h.

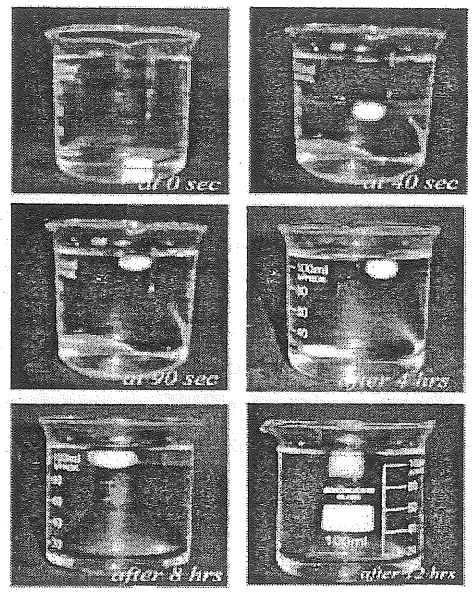

Figure 1. *In vitro* buoyancy study of batch F5

Table 3: Famotidine floating tablets release kinetics

Code	R^2				Peppas n
	Zero	First	Higuchi	Peppas	
F1	0.994	0.531	0.9794	0.978	0.67
F2	0.989	0.511	0.9888	0.982	0.69
F3	0.991	0.592	0.9841	0.977	0.60
F4	0.989	0.629	0.9882	0.988	0.64
F5	0.990	0.693	0.9957	0.998	0.54
F6	0.981	0.573	0.9938	0.993	0.53

Both MCC and magnesium stearate present in the formulation improve the floating properties of the tablet. The addition of MCC to effervescent tablets will allow more air to be entrapped in the tablets as it is very porous structure. While magnesium stearate slows down the water uptake and penetration, tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release. Kinetics of

swelling is important because the gel barrier is formed with water penetration. Swelling is also a vital factor to ensure floating. To obtain floating, the balance between swelling and water acceptance must be restored (Timmermans and Moes 1990, Baumgartner et al. 1998). Results were shown in Fig. 2.

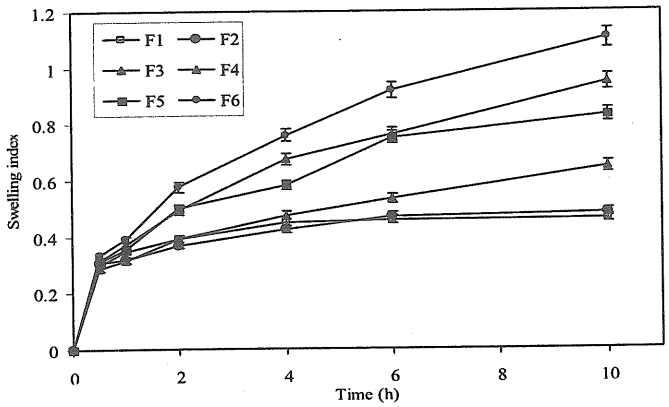

Figure 2. Swelling index

In vitro drug release studies

The *in vitro* release pattern of famotidine in 0.1N HCl are shown in Fig. 3. The drug release from floating tablets was found to be 94.8 to 97.8% for F1 to F3 with HPMC K4M. The drug release from formulations containing high-viscosity grade HPMC K15M (F4 to F6) varied between 90.9 to 101.9%. The prepared formulations sustained the drug release for a period of 8-12 h. Comparing the two different grades of HPMC, it was found that low-viscosity grade HPMC (K4M) provided better-sustained release characteristics with excellent *in vitro* buoyancy.

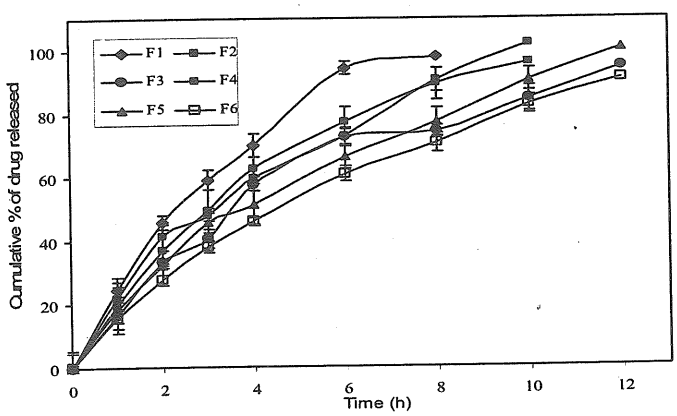

Figure 3. Drug release profiles of famotidine floating tablets composed of HPMC K4M (F1, F2 and F3) and HPMCK15M (F4, F5, andF6)

The release of famotidine from floating tablets was fit in to kinetic models and is shown in Table III. The correlation coefficient (R^2) was used as an indicator of the best fitting, for each of the models considered. From table III, it is clear that all formulations containing, famotidine are best fit in zero-order model. This was found to be fairly linear as indicated by their high regression values $R^2 = 0.981$ to 0.994. The release pattern from the tablets was found to be anomalous non-fickian transport as it was evidenced from *n* values in the range of 0.53 to 0.69 (transport

corresponding to coupled drug diffusion in the hydrated matrix and polymer relaxation) (Higuchi 1961, Korsmeyer et al. 1983).

FTIR Studies

The IR spectra of pure famotidine drug showed the characteristic band of non conjugated C=C vibration at 1638cm-1, strong absorption band at 3402 cm^{-1} belonging to the 1° amine group (N-H), characteristic band at 1535 cm^{-1}(C=N), C-C stretching at 1288 cm^{-1},and 781 cm^{-1} (Fig. 4a). The IR spectra of powder mixture which was kept at 40 °C/75% RH for 30 days, showed all the above mentioned bands of famotidine. So it is concluded that there is no interaction (Fig. 4b). The IR spectra of mixture of compressed tablet powder also showed the above mentioned characteristic bands, so it was concluded that there is no interaction (Fig. 4c).

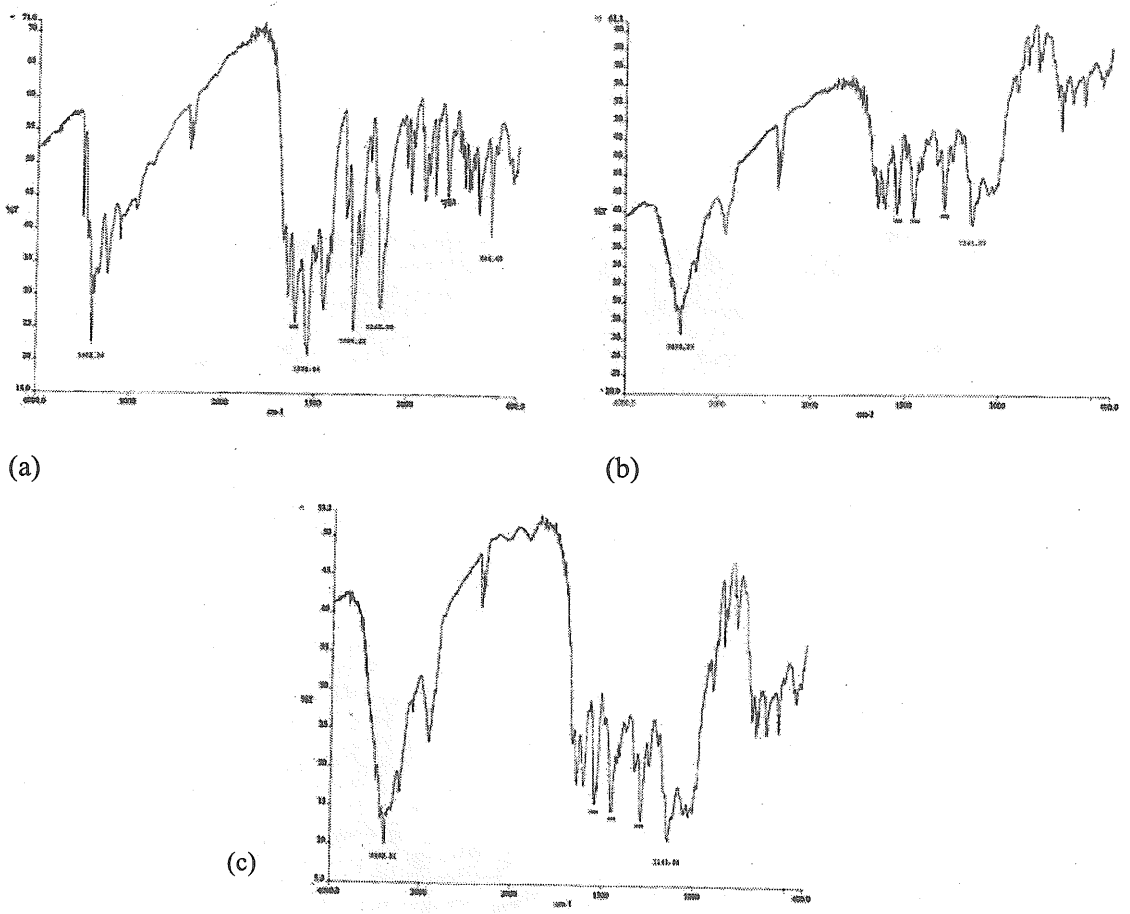

Figure 4. The FTIR spectra of (a) pure drug (b) physical mixture and (c) compressed tablet powder

DSC studies

The DSC thermogram of pure drug, compressed tablet, physical mixture of drug polymer which was kept at 40°C / 75% RH revealed that an endothermic peak of melting of drug appears at about 171.52°C indicates that there is no incompatibility between drug and excipients (Fig. 5).

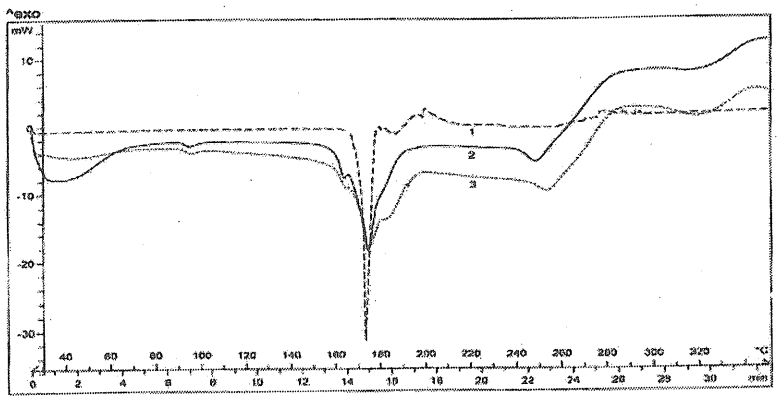

Figure 5. Thermogram of (1) famotidine (2) compressed tablet powder and (3) physical mixture

In vivo assessment of gastroretentivity

The X-radiograms, showing the position of tablets, were given in Fig. 6. The radiograms were taken for every 1.5 h and the tablet was found floating on the gastric content for more than 4.5 h.

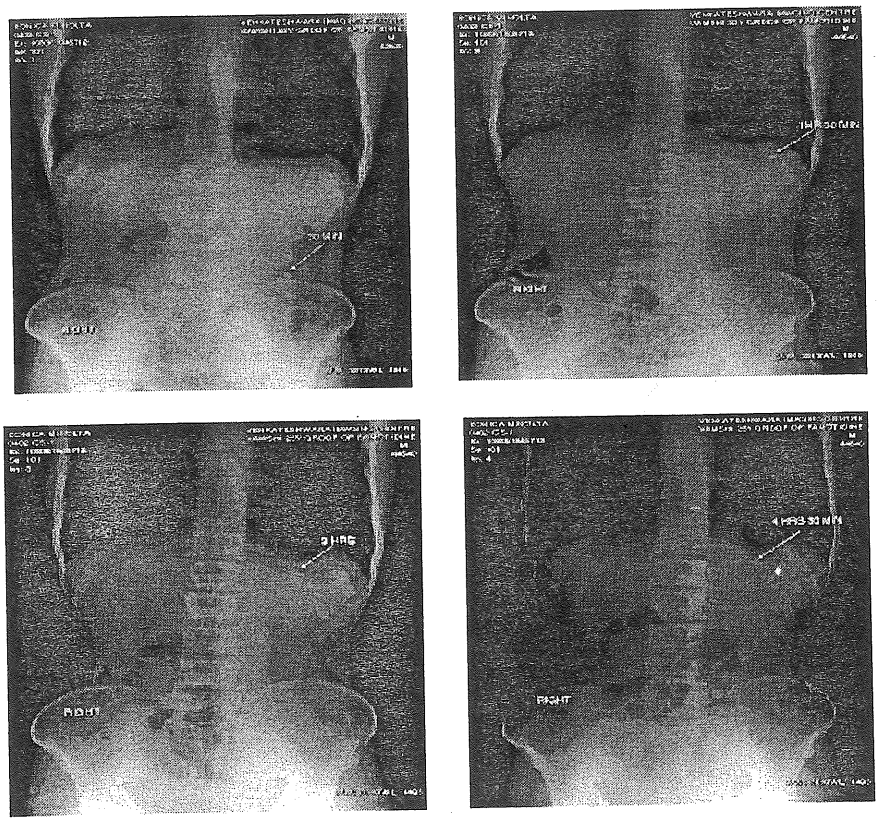

Figure 6. Representative of radiographic images showing the presence of $BaSO_4$-loaded floating tablet in the stomach at different time periods in fed state (The tablet is pointed by an arrow).

Conclusions

An attempt was made to develop a floating drug delivery system of famotidine using HPMC K4M and HPMC K15M as gel-forming polymer, sodium bicarbonate, as gas-generating agent. Drug excipient study was carried out to investigate the possible interactions between drug and polymers. Results of FTIR, DSC analysis indicated that there is no incompatibility, can be used to manufacture the tablet formulation with desired *in vitro* floating time and dissolution. *In vivo* radiological studies revealed that the floating tablet could be retained for more than 4.5 h in fed state.

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