ORIGINAL ARTICLE

Formulation development and *in vitro* and *in vivo* evaluation of gastroretentive floating drug delivery system of Lafutidine

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Lafutidine a newly developed histamine H2-receptor antagonist was retained in the stomach and assist in improving the oral sustained delivery of drugs in the gastrointestinal tract. A floating drug delivery system (FDDS) was developed using the gas forming agents, such as sodium bicarbonate, citric acid with hydrochlorides, such as hydroxyl propyl methyl cellulose (HPMCK 4M, HPMCK15M) and novel Carbopol 71G. Polymer with lower viscosity was found to be beneficial than higher viscosity polymer in improving the release properties of gastroretentive FDDS. The prepared tablets of various formulations were evaluated for a total floating time, buoyancy lag time, and percentage drug released. The formulation code HF3 having HPMCK4M showed better results it may be useful for prolonged drug release in the stomach to improve the bioavailability and reduced the dose frequency. Non-Fickians release transport was confirmed as the drug release mechanism from the optimized formulation by Korsmeyer-Peppas. *In vivo* study was per formed using the rabbits by X-ray imaging technique; radiological evidences suggest that, a formulated tablet was well floated more than 10 h in rabbit's stomach. Optimized floating tablets showed no significant changes in the physical appearance, drug content, total buoyancy time, and also *in vitro* dissolution pattern after storage at 40°C/75% relative humidity for 3 months.

Key words: *Floating drug delivery system, in vitro and in vivo study, Lafutidine, sustained release*

INTRODUCTION

Lafutidine, (±)–2-(furfurylsulfinyl)–N-(4-[4-[piperidinomethyl]–2–pyridyl] oxy-(Z)-2-butenyl) acetamide is a newly developed 2nd generation histamine H2-receptor antagonist.[1] It is used in the treatment of gastriculcers, duodenal ulcers, and gastric mucosal lesions associated with acute gastritis and acute exacerbation of chronic gastritis.[2] It is absorbed in the small intestine, reaches gastric cells via the systemic circulation, and rapidly binds to gastric cell histamine H2 receptors, resulting in immediate inhibition of gastric acid secretion.[3] Lafutidine has been shown to increase the gastric mucosal blood flow[4] and gastric mucus secretion[5,6] also accelerate sepithelial restitution in rats. Lafutidine has a receptor binding affinity, which is 2-80 times higher than famotidine, ranitidine and cimetidine.[7,8]

The development of an oral floating drug delivery system (FDDS) should be primarily aimed at achieve more predictable and increased bioavailability of drugs. The development process is precluded by several physiological difficulties, such as an inability to restrain and localize the FDDS within desired regions of the gastrointestinal tract and the highly variable nature of gastric emptying process.[9] Depending upon the physiological state of the subject and the design of pharmaceutical formulation the emptying process can last from a few minutes to 12 h. This variability, in turn, may lead to unpredictable bioavailability and times to achieve the peak plasma levels since the majority of drugs are preferentially absorbed in the upper part of the small intestine. Thus, control of placement of FDDS in a specific region of the gastrointestinal tract offers numerous advantages, especially for the drugs

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Access this article online

Quick Response Code:

Website: www.asiapharmaceutics.info

DOI: 10.4103/0973-8398.115969

exhibiting an absorption window in the GI tractor drugs with stability problem. Overall, the intimate contact of the FDDS with the absorbing membrane maximizes drug absorption and may also influence the rate of drug absorption. These considerations have led to the development of oral controlled-release (CR) dosage forms possessing the gastric retention capabilities.

Floating drug delivery is one of the approaches for gastroretention. FDDS or hydro dynamically balanced system shave a bulk density lower than gastric fluids and thus, remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, drug is released slowly at a pre-determined rate.[10]

This research work is with new active pha rmaceutical ingredient alongwith new and novel polymer, i.e., Carbopol 71 Ggranular grades. Prolonged gastric retention improves bioavailability and improves solubility of drugs that are less soluble in the high pH environment. Thus, aim to develop hydro dynamically balanced systems for the treatment of ulcer, which attempts to increase the gastric retention time of the Lafutidine.

MATERIALS AND METHODS

Hydroxy propyl methylcellulose K4M (HPMCK4M), hydroxyl propyl methyl cellulose K15M (HPMCK15M) were supplied by Colorcon Asia Pvt. Ltd. (Goa, India), Lafutidine was a sample from Alkem Laboratories Ltd. (Kacchigam, India), Carbopol 71G from Lubrizol, MCCKG-100 from Torrent Laboratory (Ahmadabad, India), sodium bicarbonate, an hydrous citric acid, purified talc, magnesiums tea rate were gifts ample from S.D. Fine chemicals (Mumbai, India). All other chemicals were of analytical grades as required.

Preparation of floating tablets of Lafutidine

Each tablet containing about 50 mg of Lafutidine was prepared by direct compression method. The ingredients were weighed accurately and sieved through 40 meshes then mixed thoroughly for 15 min, finally lubricated for 3 min with magnesium stearate by passing through 60 meshes. The granules were then compressed into tablets by direct compression method using the single-punch tablet compression machine (Cadmach, Ahmadabad, India) using 9.00 mm standard concave punches. Tablet blend was evaluated for their bulk density, tapped density, flow properties, and compressibility index.

In vitro buoyancy studies

The *in vitro* buoyancy was determined by buoyancy lag time as per the method described by Rosa *et al*.[11] The test was performed by placing each of the tablet in a 250-mL of beaker, containing 200 mL of 0.1 NHCl, pH 1.2, maintained at 37 ± 0.5° Cinawaterbath. Physical state of the tablet was observed for 12 h. The time between the introduction of the tablets its buoyancy on the 0.1 NHCl (lag time) the time during, which the tablets remains buoyant (total buoyancy time) were determined visually. Three replicates of each formula were performed.

Swelling study

The Lafutidine floating tablets were weighed individually (Labeledas W1) placed separately in a glass beaker containing 200 mL of 0.1 NH Clincubated at 37 ± 1°C. At regular 1 h time intervals until 12 h, the tablets were removed from beaker and the excess surface liquid was removed carefully using the paper. The swollen Lafutidine tablets were then re-weighed (W2) and the swelling index (SI) was calculated using the following formula.[12]

$$SI=(W2 - W1)/W1 \quad (1)$$

In vitro dissolution studies

The *in vitro* drug release studies of various formulations (HF1, HF2, HF3, MF1, MF2, MF3, and CF1, CF2, CF3) were performed using the paddle with the sinker at 100 rp min 900 mL of 0.1 NHCL medium was maintained at 37 ± 1°C.Then, 10 mL of the sample was withdrawn at a predetermined time intervals until 12 h replaced with same dissolution medium.[13,14] The samples were analyzed by the High Performance Liquid Chromatography (HPLC) (Agilent) at 236 nm.

In vivo study

The protocol for *in vivo* study was approved by the Institutional Animal Ethics Committee of R.C, Patel Institute of Pharmaceutical Education and Research, Shirpur and is in accordance with guidance of Committee for the Purpose of control and supervision of experiments on animals, Ministry of social justice and empowerment, Government of India. All the *in vivo* experiments were performed under permission from animal ethical committee. *In vivo* study of the final formulation (HF3) was performed using the New Zeal Albino rabbit by an X-ray imaging method.[15,16] Tablets containing barium sulfate were selected for *in vivo* study given to rabbit followed by 30 mL of water. Rabbit was placed in supine posture to check the position of the tablet in the gastric region by X-ray machine at the pre-determined time intervals. In each experiment, the animals were fasted overnight with free access of water and a radiograph was made just before the administration of the Lafutidine floating tablet to ensure the absence of any radio-opaque material in the stomach. The formulation was administered by the natural swallowing by the rabbit followed by 50 mL of water. The radiographic imaging was taken in a supine position and the distance between the sources of X-rays and the animal was kept constant for all imaging; thus, the observation of the Lafutidine floating tablet movement could be easily noticed. Gastric radiography was carried out at 2 h time intervals for a period of 12 h using an X-ray machine (WiproGEDX-300 with the horizontal X-ray system, model SI-0146-3128 capacity 300 MA-100 KVP, Pune, India).

Kinetic modeling of drug release

The dissolution profile of all the batches were fit to zero order, first order,[17] Higuchi,[18] Hixon, and Crowell,[19] Korsmeyer-Peppas model.[15,20] To ascertain the kinetics modeling of drug released by PCP Dissolution version 2.08 Software model with the high correlation coefficient was considered to be the best model.

Stability studies

Stability studies were performed to check the effect of environmental condition or storage conditions on formulation. Optimized batch HF3 was kept in accelerated stability condition at 40ºC temperature 75 ± 5% relative humidity for a period 3 months as per International Conference on Harmonization (ICH) guidelines.[21] The samples were withdrawn at 1, 2, and 3 months intervals evaluation was carried out for appearance, thickness, hardness, friability, buoyancy lag time, drug content, floating behavior, and cumulative% drug released.

RESULTS AND DISCUSSION

Gastroretentive floating tablets of Lafutidine were developed to increase the gastric residence time of the drug, which could be retained in the stomach for a longer time, improving the buoyancy and drug release characteristics also help in CR of drug upto 12 h. The gastroretentive floating tablets were made using the gel-forming polymers such as HPMCK4M, HPMCK 15 M and novel Carbopol 71G. They are known to be beneficial when taken in a combination with gas generating agent, i.e., Sodium lauryl sulfate. The composition of gastroretentive floating tablets of Lafutidine (HF1, HF2, HF3, MF1, MF2, MF3 and CF1, CF2, CF3) is shown in Table 1.

Evaluation of pre-compression parameters of powder blend

Prepared powder blend of all formulations of the Lafutidine (HF1, HF2, HF3, MF1, MF2, MF3 andCF1, CF2, CF3) were evaluated for their physical properties such as the angle of repose, bulk density, tapped bulk density, Hausner's ratio, loss on drying Carr's index, it can be clearly concluded that the powder blend with different formulations components were having good flow properties, good compressibility, which allow these formulations to be directly compressed into tablets. Results of pre-compression evaluations of formulations were shown in Table 2.

Physico chemical characterization of gastroretentive floating tablets of Lafutidine

The Physico chemical characterization of gastroretentive floating tablets (HF1, HF2, HF3, MF1, MF2, MF3 and CF1, CF2, CF3) were evaluated for average weight, thickness, hardness, friability, and drug content the results were shown in Table 3. All physicochemical parameters of all the formulations (HF1, HF2, HF3, MF1, MF2, MF3 and CF1, CF2, CF3) were within the acceptance limit. The drug content was found to be within an arrow range as specified in pharmacopoeia (90-110%) in all the formulations.

Table 1: Composition of gastroretentive floating tablets of Lafutidine

Formulation code	HF1	HF2	HF3	MF1	MF2	MF3	CF1	CF2	CF3
Ingredients (mg)									
Lafutidine	50	50	50	50	50	50	50	50	50
HPMC (K4M)	30	60	90	-	-	-	-	-	-
HPMC K115M	-	-	-	30	60	90	-	-	-
Carbopol 71G	-	-	-	-	-	-	30	60	90
MCC KG-100	116	86	56	116	86	56	116	86	56
Citric acid	15	15	15	15	15	15	15	15	15
Sodium bicarbonate	80	80	80	80	80	80	80	80	80
Magnesium stearate	6	6	6	6	6	6	6	6	6
Talc	3	3	3	3	3	3	3	3	3
Total weight (mg)	300	300	300	300	300	300	300	300	300

HPMC: Hydroxylpropylmethyl cellulose, MCC: Microcrystalline cellulose, HF: Formulation code-HPMCK4M, MF: HPMCK15M, CF: Carbopol

Table 2: Evaluation of pre-compression parameters of gastroretentive floating tablets of Lafutidine

Formulation code	HF1	HF2	HF3	MF1	MF2	MF3	CF1	CF2	CF3
Parameters (*n*=3)									
LOD (%)	1.50	1.54	1.56	1.60	1.68	1.63	1.57	1.58	1.59
Bulk density (g/ml)	0.333	0.345	0.350	0.351	0.335	0.332	0.335	0.350	0.336
Tapped density (g/ml)	0.455	0.475	0.480	0.497	0.450	0.465	0.480	0.495	0.482
Hausner's ratio	1.366	1.378	1.371	1.415	1.343	1.400	1.432	1.414	1.434
Carr's compressibility index (%)	20.0	27.36	27.08	29.37	25.55	25.50	30.20	29.29	30.25
Angle of repose (degree)	47	46	48	45	45	46	48	49	49

LOD: Loss on drying, HF: HPMC K4M, MF: HPMC K15M, CF: Carbopol

In vitro dissolution studies

To evaluate different polymers such as HPMCK4M, HPMCK15M, and Carbopol 71G used to prepare the gastroretentive floating tablets of Lafutidine and their individual % cumulative drug released profile was evaluated and showed in Figures 1-3. The Lafutidine floating tablets of formulations HF1, HF2, HF3, MF1, MF2, MF3, CF1, CF2 andCF3 exhibited cumulative % drug released shown in Table 4.

HPMCK4M containing gastroretentive formulation HF3 exhibited 99.20% cumulative drug released and good floating time for 12 h. Although, HF1, HF2 could not maintain its matrix integrity for more than 8h. HPMCK15M containing formulation MF1, MF2, MF3 forms a thick gel structure that delayed drug released i.e., 79.71, 61.71, 44.10% respectively over a period of 12h. Also, Carbopol 71G containing formulation CF1, CF2, CF3 showed drug released upto 10 h. A significantly higher rate extended release of the drug was found to be near required theoretical profile value (which was calculated using the equations for an immediate release dose maintenance dose) from batch HF3 and CF3 compared with other batches. The Lafutidine floating tablets containing HPMCK4M (HF3) showed a higher rate extended released upto 12h as compared to the formulation with Carbopol 71G (CF3), which was upto 10h. The data obtained from *in vitro* dissolution studies were fitted to zero order; first order, Higuchi Korsmeyer–Peppas equations data was analyzed n value of optimized formulation was found to be 0.622, which in the range of $0.5 < n < 1$ and k value was found to be 11.20. The diffusion exponent value indicates that the drug release follows non-Fickian transport.

Swelling study

Swelling is also a vital factor to ensure buoyancy drug dissolution of the floating tablet. The gastroretentive floating tablets of Lafutidine composed of polymeric matrices build age layer around the tablet core when they come in contact with water. This gel layer governs the drug release from the matrix tablet. The floating tablets containing HPMCK4M showed constant increased in swelling because HPM Care more hydrophilic than the Carbopol 71G, this can be shown by released pattern of the batches HF3 and CF3. This erosion

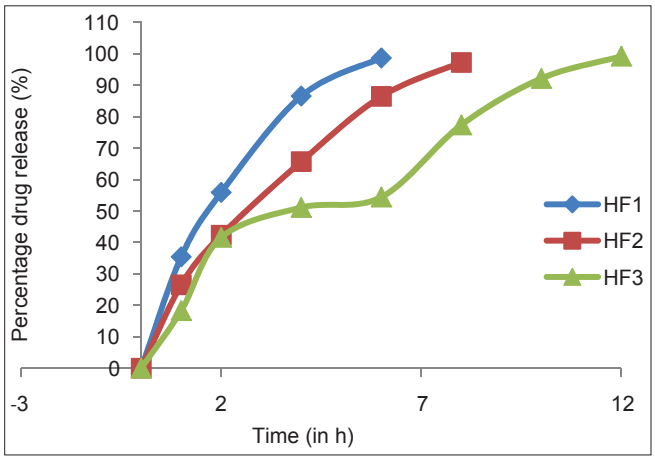

Figure 1: % Cumulative released of Lafutidine floating tablets comprising of HPMCK4M

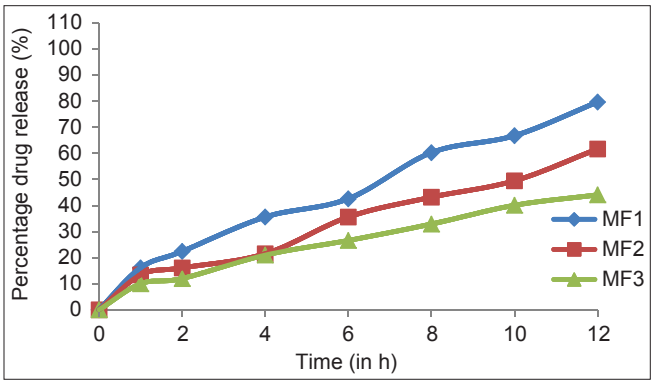

Figure 2: % Cumulative released of Lafutidine floating tablets comprising of HPMCK15M

Table 3: Physico chemical characterization of gastroretentive floating tablets of Lafutidine

Formulation code	HF1	HF2	HF3	MF1	MF2	MF3	CF1	CF2	CF3
Parameters									
Average weight (mg) (*n*=3)	300	300	300	300	300	300	300	300	300
Thickness (mm) (*n*=3)	4.35	4.34	4.35	4.35	4.36	4.35	4.36	4.38	4.38
Hardness (N) (*n*=3)	70	80	65	87	68	80	88	80	75
Friability (%) (*n*=3)	0.28	0.29	0.31	0.24	0.46	0.24	0.24	0.25	0.34
Drug content (%)	100.87	100.01	99.99	99.48	98.51	98.0	99.77	99.38	100.27

HF: HPMC K4M, MF: HPMC K15, CF: Carbopol

Table 4: Determination of cumulative % drug released, buoyancy lag time and floating time of Lafutidine floating tablets

Formulation code	HF1	HF2	HF3	MF1	MF2	MF3	CF1	CF2	CF3
Parameters									
Cumulative % drug released	98.60± 0.45	97.20± 0.26	99.20± 0.50	79.7± 0.70	61.70± 2.25	44.10± 0.82	101.90± 0.41	99.60± 0.27	98.80± 0.31
Buoyancy lag time (s)	15	16	12	15	18	13	18	19	19
Floating time (h)	6	8	12	12	12	12	8	10	10

HF: HPMC K4M, MF: HPMC K15M, CF: Carbopol

of polymers dominates over water sorption after 6h. Hence, the reduction in tablet weight occurs after 7 h because of erosion of matrix. In case of increasing concentrations of Carbopol (CF3) showed an increase in swelling, but not to the extent of HPMC (HF3). The formulation CF3 containing HPMCK4M showed less SI at the beginning, but was found higher at the end of 7 h also maintains their matrix integrity upto 6-7 h. The SI of Lafutidine floating tablets of formulations HF3 was 140 ± 2-1% and CF3 was 115 ± 2.1% at the end of 7 h.

In vivo study

The prepared gastroretentive floating tablets of Lafutidine containing hydroxyl propyl methylcellulose (HPMC) (CF3) were selected for evaluation of gastric retention using X-ray imaging. *In vivo* study of the final formulation (CF3) was performed using New Zeal Albino rabbits by X-ray imaging technique. Prepared tablets of various concentration of barium sulfate were evaluated for *in vitro* floating study. It was observed that tablets showed good floating property and sufficient integrity of Lafutidine floating tablets.

Radiological evidences suggest that the formulated gastroretentive floating tablets of Lafutidine (CF3) was well floated more than 10 h in rabbit stomach; hence, we can conclude that the gastroretentive floating tablets was satisfactory floated to the rabbit stomach [Figure 4a-d].

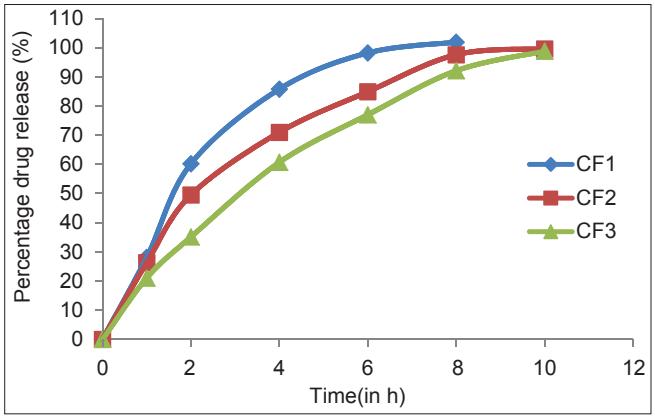

Figure 3: % Cumulative released of Lafutidine floating tablets comprising of Carbopol71G

Stability studies

The prepared gastroretentive floating tablets of Lafutidine containing HPMCK4M were selected for stability study on the basis of *in vitro* buoyancy and *in vitro* drug dissolution studies. The gastroretentive floating tablets of Lafutidine were stored at 40°C/75% RH in closed high-density polyethylene bottles for 3 months. The gastroretentive floating tablets did not showed any significant changes in physicochemical parameters and drug contents as shown in Table 4. Thus, it was found that the CF3 formulation of Lafutidine tablets were stable under 40°C/75% RH storage conditions for a period of 3 months. Formulation CF3 results was found satisfactory were shown in Table 5.

CONCLUSION

From the results of the study, it is evident that the gastroretentive floating tablets prepared from HPMCK4M with the gas generating agent sodium bicarbonate was crucial to achieve *in vitro* buoyancy also addition of citric acid to achieve buoyancy under elevated pH of the stomach, caused an enhancement of drug release. The gastroretentive floating tablets of Lafutidine were formulated by using gelling polymer HPMCK4M, which showed pleasing results with short buoyancy lag time, total buoyancy time more than 10 h controlled drug released upto 12 h comparing with HPMCK15M and Carbopol 71G. On the whole, this concluded that viscosity of polymer is a key factor affecting the release and floating properties of drug and this would be a feasible alternative to conventional oral dosage form of Lafutidine in order to retain the drug at the site of absorption and to increases the bioavailability of the drug there by reducing the dose or dosing interval. Lafutidine has a receptor binding affinity, which is 2-80 times higher than the famotidine, ranitidine and cimetidine. Thus, it was brought into being that the gastroretentive floating tablets of Lafutidine (HF3) were stable at 40°C/75% RH for a period of 3 months results were found satisfactory.

ACKNOWLEDGMENTS

The authors are thankful to Alkem Laboratories Ltd. (Kacchigam, India) for providing a gift sample of drug, Colorcon Asia Pvt.

Table 5: Evaluation of gastro retentive floating tablets of Lafutidine kept in stability at 40°C/75% RH

Formulation	HF3				CF3			
Parameters	Initial	1 month	2 months	3 months	Initial	1 month	2 months	3 months
Appearance	White to off white colored tablet							
Average weight (mg)	303	301	302	301	303	302	301	301
Thickness (mm)	4.35±0.08	4.36±0.07	4.35±0.05	4.35±0.08	4.35±0.07	4.34±0.07	4.35±0.08	4.36±0.08
Hardness (*N*)	60-70	60-70	60-70	60-70	60-65	60-65	60-65	60-65
Buoyancy lag time (s)	12±2.0	14±2.0	15±2.0	15±2.0	19±2.90	20±2.90	20±3.10	20±3.50
Total buoyancy time (h)	12	12	12	12	10	10	10	10
Drugcontent (%)	100.05±1.20	99.50±1.10	99.12±1.47	99.73±1.81	92.80±1.25	92.20±1.15	97.00±1.20	96.00±0.180
% Drug released (mean±SD)	99.7.0±1.97	99.7.0±1.97	98.7±1.14	98.0±1.24	96.5±1.50	96.0±2.20	93.0±2.60	87.0±1.30

All values are mean±SD of three determinations, RH: Relative humidity, HF: HPMC K4M, CF: Carbopol

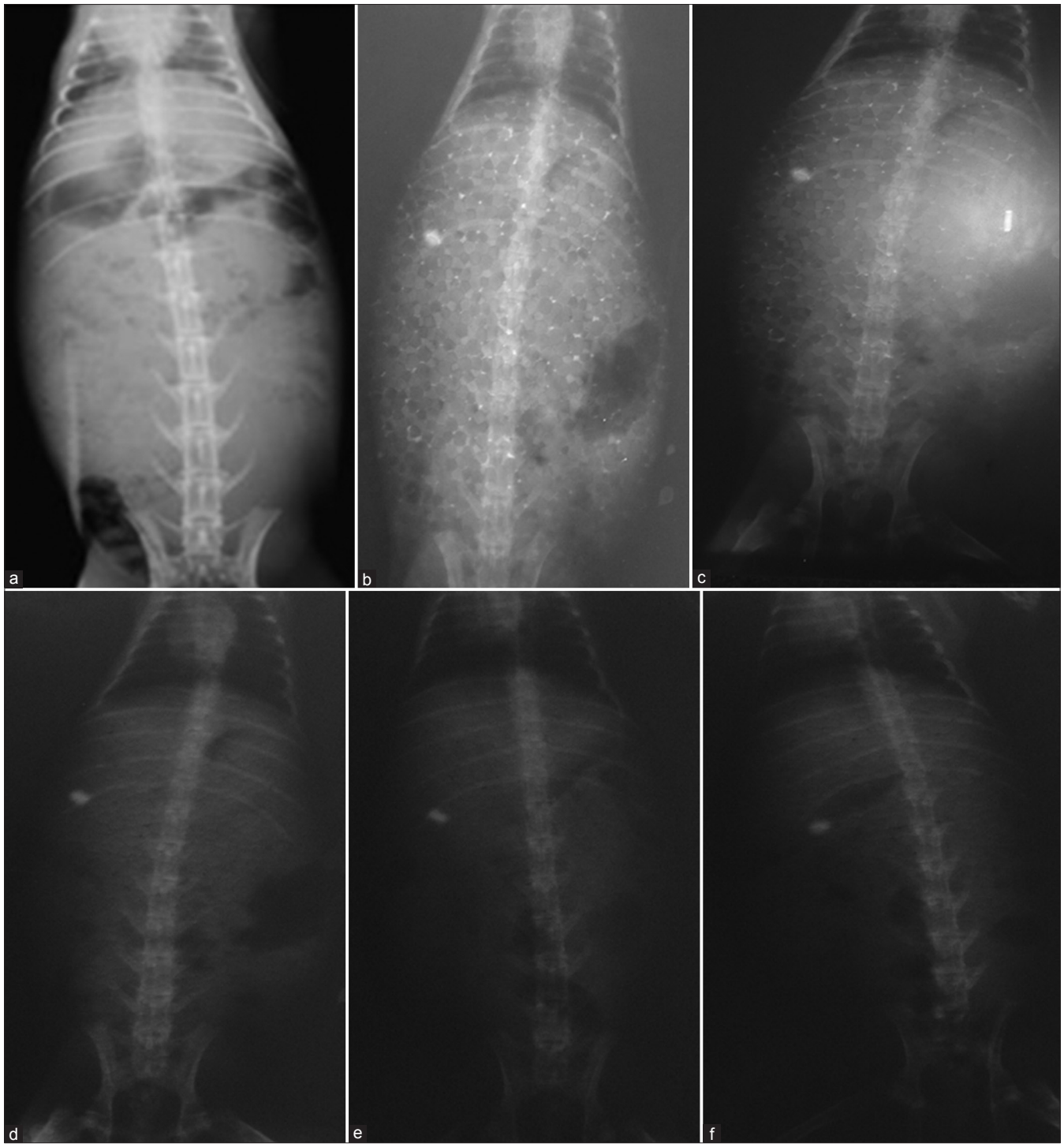

Figure 4: X-ray photographs at different time intervals of gastroretentive floating tablets of Lafutidine (a) X-ray at 0 h. (b) X-ray after 2 h. (c) X-ray after 4 h. (d) X-ray after 6 h. (e) X-ray after 8 h. (f) X-ray after 10 h

Ltd. (Goa, India) for providing gift samples of polymers, Torrent Laboratory, (Ahmadabad, India) and Lubrizol (Mumbai, India) for providing gift samples of excipients.

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How to cite this article: Patil SH, Talele GS. Formulation development and *in vitro* and *in vivo* evaluation of gastroretentive floating drug delivery system of Lafutidine. Asian J Pharm 2013;7:68-74.

Source of Support: Nil. **Conflict of Interest:** None declared.