

HOSTED BY



ELSEVIER

Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Biomedicine

journal homepage: www.elsevier.com/locate/apjtb

Document heading

doi:10.12980/APJTB.4.201414B73

© 2014 by the Asian Pacific Journal of Tropical Biomedicine. All rights reserved.

Formulation and evaluation of novel stomach specific floating microspheres bearing famotidine for treatment of gastric ulcer and their radiographic study

Rishikesh Gupta^{1*}, Sunil Kumar Prajapati¹, Snigdha Pattnaik², Peeyush Bhardwaj¹¹Institute of Pharmacy, Bundelkhand University, Jhansi, Uttar Pradesh, India²School of Pharmaceutical Sciences, Siksha O Anusandhan University, Bhubaneswar, Orissa, India

ARTICLE INFO

Article history:

Received 20 Feb 2014

Received in revised form 26 Mar 2014

Accepted 15 May 2014

Available online 28 Jun 2014

Keywords:

Floating microspheres

Famotidine

Floating drug delivery

Stomach targeting

ABSTRACT

Objective: To develop and characterize multiple-unit-type oral floating microsphere of famotidine to prolong gastric residence time and to target stomach ulcer.

Methods: The floating microspheres were prepared by modified solvent evaporation method. Eudragit S-100 was used as polymer. Microspheres were characterized for the micromeritic properties, floating behavior, entrapment efficiency and scanning electron microscopy. The *in-vitro* release studies and floating behavior were studied in simulated gastric fluid at pH 1.2. Different drug release kinetics models were also applied for all the batches. Selected formulations were also subjected for X-ray radiographic study.

Results: Floating microspheres were successfully prepared by modified solvent evaporation technique. Microspheres showed passable flow properties. The maximum yield of microspheres was up to (95.11±0.35)%. On the basis of optical microscopy particle size range was found to be ranging from (52.18±182.00) to (91.64±5.16) μm. Scanning electron microscopy showed their spherical size, perforated smooth surface and a cavity inside microspheres. Microspheres were capable to float up to 20 h in simulated gastric fluid. X-ray radiographic studies also proved its better retention in the stomach.

Conclusions: On the basis of the results, such dosage forms may be a good candidate for stomach targeting and may be dispensed in hard gelatin capsules.

1. Introduction

Oral route of administration is the most convenient and widely used method of drug administration, and the development of stomach specific oral controlled-release drug delivery systems is a challenging job due to the variation of pH in different segments of the gastrointestinal tract, the fluctuation in gastric emptying time and the difficulty of localizing an oral delivery system in a selected region of the gastrointestinal tract. Rapid gastrointestinal transit can prevent the absorption of complete drug in the absorption zone and reduce the efficacy of the administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine^[1,2].

To overcome the above discussed issues, many types of oral controlled drug delivery systems having prolonged gastric residence times have been reported such as: floating drug dosage systems (FDDS)^[3–7], swelling or expanding system^[8], mucoadhesive systems^[9,10], modified-shape systems^[11], high-density systems and other delayed gastric emptying devices^[12].

FDDS have lower density than gastric fluids and thus remain buoyant in the stomach fluid without affecting the gastric emptying for a prolonged period of time. While the system is floating in the gastric fluid, the drug is released slowly from the system at a desired rate. Materials used for FDDS include carbon dioxide gas-forming agents (carbonate or bicarbonate compounds)^[8,13], highly swellable hydrocolloids and light mineral oils^[14,15]. Multiple unit systems and floating systems prepared by solvent evaporation methods have also been developed^[12,16–20].

However, it has been shown that products based on a multiple unit system comprising many small units have

*Corresponding author: Rishikesh Gupta, Institute of Pharmacy, Bundelkhand University, Jhansi, Uttar Pradesh, India.

Tel: 09450040567

E-mail: rishikeshgupt@gmail.com

Foundation Project: Supported by Institute of Pharmacy, Bundelkhand University, Jhansi (U.P.), India (Grant No. BU/SF/PHARM/IAEC/10/031).

advantages over single-unit preparations such as matrix tablets^[21]. The gastric emptying of multiple unit dosage forms occur gradually, in a more consistent manner, with less individual variation^[2,22]. Multiple unit dosage forms also have the potential to distribute widely over a large area in the stomach and small intestine, thus yielding a more predictable drug release by suppressing the effect of many variables in the gastrointestinal environment. As multiple unit dosage forms consist of many small units, less risk of dosage dumping is expected^[23].

Famotidine, a competitive histamine H_2 -receptor antagonist is used to treat gastrointestinal disorders such as gastric or duodenal ulcer, gastroesophageal reflux disease, and pathological hypersecretory conditions. Famotidine inhibits many of the isoenzymes of the hepatic CYP450 enzyme system. Other actions of famotidine include an increase in gastric bacterial flora such as nitrate-reducing organisms^[24].

Famotidine is widely used as the treatment of peptic ulcer disease and gastroesophageal reflux disease. Famotidine binds competitively to H_2 -receptors located on the basolateral membrane of the parietal cell, blocking histamine affects. This competitive inhibition results in reduced basal and nocturnal gastric acid secretion and a reduction in gastric volume, acidity, and amount of gastric acid released in response to stimuli including food, caffeine, insulin, betazole and pentagastrin^[25].

Floating microspheres are one of the multiparticulate delivery system and are prepared to obtain prolonged or controlled drug delivery to improve bioavailability and to target drug to specific sites. Microspheres can also offer advantages like limiting fluctuation within therapeutic range, reducing site effects, decreasing dosing frequency and improving patient compliance^[26].

In the present study, the multiple-unit-type oral floating microspheres bearing famotidine were developed by modified solvent evaporation technique. Eudragit S-100 was used as polymer.

The high surface tension of stirring phase causes the solidification and aggregation of polymer on the surface when the polymeric solution is poured from upside. To minimize the contact of polymer solution with interface, a new method of introducing the polymer solution into stirring phase was adopted as established by Lee *et al*^[27].

2. Materials and methods

Famotidine was obtained as a gift sample from Cadila Pharmaceutical Ltd., Mumbai (Maharashtra). Eudragit S100 (Rohm Pharma GmbH, Germany) was used as polymers. All other chemicals and reagents were of analytical grade and were used without further purification.

2.1. Preparation of floating microspheres

Floating microspheres were prepared by the method reported by Kawashima *et al.* with slight modifications^[19]. Ten formulations of floating microspheres were developed. Different ratios of famotidine and Eudragit S-100 were mixed

in a mixture of dichloromethane (DCM) and ethanol (Table 1). The resulting suspension was added slowly into stirring to 0.25% w/v 400 mL solution of polyvinyl alcohol (PVA) at room temperature from the bottom side as shown in Figure 1^[27]. The stirring was continued for 2 h by mechanical stirrer equipped with four blade propellers in order to evaporate the solvent. After evaporation of solvent, microspheres were collected by filtration and washed repeatedly with water. The collected microspheres were dried at room temperature and stored in a desiccator.

Table 1

Batch specifications for floating microspheres.

Code	Drug: polymer (mg)	Speed	Solvent ratio (DCM: ethanol, mL)
FS-1	1:1	900	1:1
FS-2	1:2	900	1:1
FS-3	1:3	900	1:1
FS-4	1:4	900	1:1
FS-5	1:5	900	1:1
FS-6	1:3	1000	1:1
FS-7	1:3	1200	1:1
FS-8	1:3	1300	1:1
FS-9	1:3	900	1:3
FS-10	1:3	900	3:1

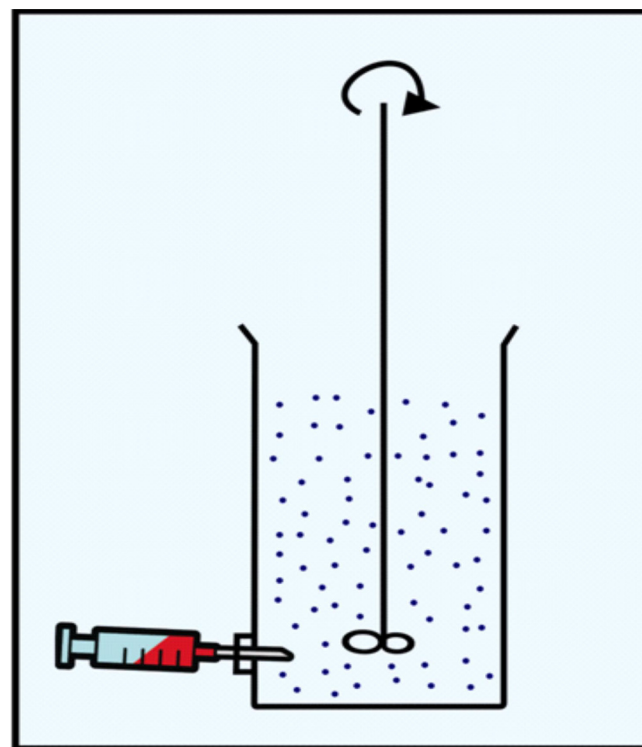


Figure 1. Method of injection of volatile phase into PVA solution.

2.2. Characterization of floating microspheres

2.2.1. Morphology

The morphology of microspheres was studied by scanning electron microscopy (SEM). The samples for SEM were prepared by sprinkling the microspheres on a both side adhesive tape stuck to a stub. Gold palladium coating on the prepared stub was done by using sputter coater (POLARON model SC-76430). The thickness of coating was 200 Å. The coated stubs were randomly scanned under electron microscope (LEO-430, UK). The photomicrograph of prepared microspheres are presented in Figure 2.

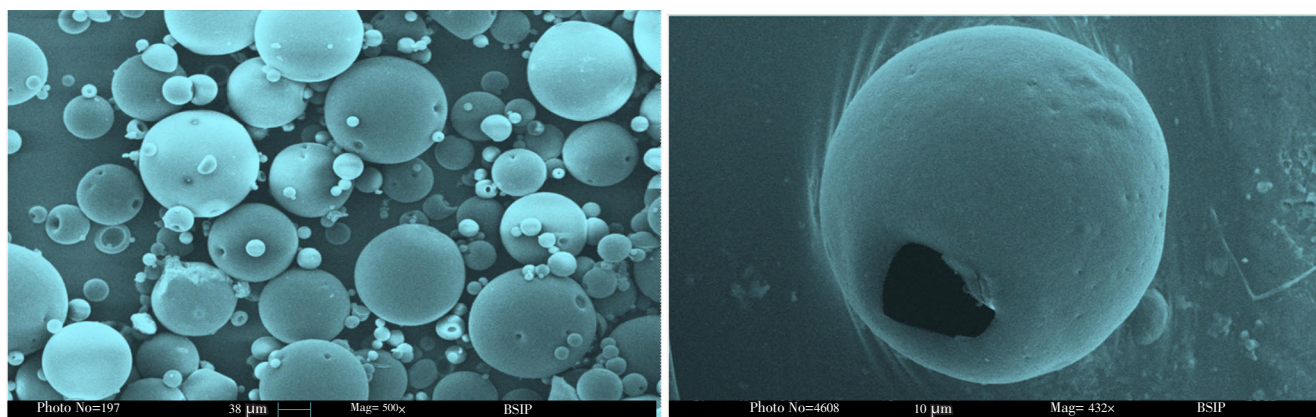


Figure 2. Scanning electron micrograph of floating microsphere.

A: Photo micrograph showing population of batch FS-3; B: Photo micrograph showing a floating cavity and porous surface in microsphere of batch FS-5.

2.2.2. Particle size analysis

The size of microspheres was determined by using an optical microscope (Magnus MLX-DX, Olympus, India) fitted with an ocular micrometer and a stage micrometer. The mean particle size was calculated by measuring 200–300 particles.

2.2.3. Micromeritic properties

The prepared microspheres were characterized for their micromeritic properties such as true density, tapped density and % compressibility index. The tapping method was used to calculate tapped densities and % compressibility index using following equations^[28]:

$$\text{Tapped density} = \frac{\text{Mass of microspheres}}{\text{Volume of microspheres after tapping}}$$

$$\text{Compressibility index (\%)} = (1 - V/V_0) \times 100$$

Where V and V₀ are the volumes of the samples after and before the standard tapping respectively.

True density of floating microspheres was determined by immersing the microparticles in 0.02% Tween 80 solution for three days in a metal mesh basket. The microparticles that were sunk after the process were used for density measurement as carried out by the displacement method^[29].

2.2.4. Angle of repose

Flow characteristic such as angle of repose (θ) of the microspheres, which measures the resistance to particle flow, was determined by fixed funnel method using following equation^[28]:

$$\tan \theta = \frac{h}{r}$$

Where, h is the height of pile, r is the radius of the base of pile on the graph paper.

2.2.5. Yield of microspheres

The prepared microspheres were collected and weighed. The actual weight of obtained microspheres divided by the total amount of all drug and polymer solid material that was used for the preparation of the microspheres^[30]:

$$\text{Yield (\%)} = \frac{\text{Actual weight of the product}}{\text{Total weight of the excipients and drug}} \times 100$$

2.2.6. Incorporation efficiency

To determine the incorporation efficiency 50 mg microspheres were taken and dissolved in 25 mL of methanol. The solution was filtered to separate shell fragments. The estimation of drug was carried out at the λ_{max} of 264 nm by using a UV double-beam spectrophotometer (Shimadzu UV-1800 series). The incorporation efficiency was calculated using following equation^[30]:

$$\text{Incorporation efficiency} = \frac{\text{Calculated drug content}}{\text{Theoretical drug content}} \times 100$$

2.2.7. In-vitro floating ability

Floating microspheres (50 mg) were placed in 100 mL beaker. A total of 10 mL of 0.1 mol/L HCl containing 0.02% Tween 20 was added to that. The beaker was shaken horizontally in a water bath at (37.0±0.1) °C. Floated particles were collected after 20 h and dried in a desiccator till constant weight. This process was applied to all the batches. Floating microspheres are shown in Figure 3. The percentage of floating microspheres was calculated using following equation^[30]:

$$\text{Floating ability (\%)} = \frac{\text{Weight of floating microspheres}}{\text{Initial weight of microspheres}} \times 100$$

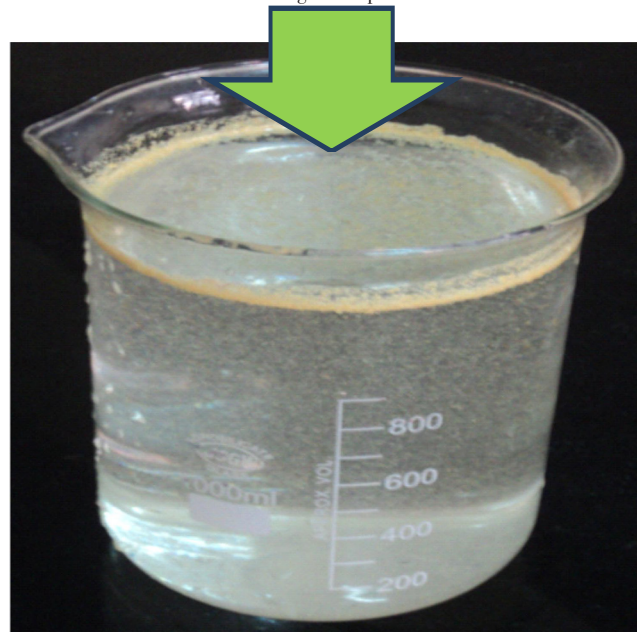


Figure 3. Floating microspheres.

2.3. *In-vitro* drug release

In-vitro drug release studies were performed in 0.1 mol/L HCl (pH 1.2) for floating microspheres. The drug release rate of the floating microspheres was determined in 900 mL 0.1 mol/L HCl at 100 r/min by using USP XXIII dissolution apparatus (paddle type). A weighed amount of floating microspheres equivalent to 50 mg drug was placed in a non-reacting muslin cloth having a smaller mesh size than the microspheres. The mesh was tied with a nylon thread to avoid the escape of any microspheres and a glass bead was placed in the mesh to induce sinking of microspheres in the dissolution medium^[31]. The temperature of dissolution medium was maintained at (37.0±0.5) °C.

At specified time intervals, 5 mL aliquots were withdrawn, filtered, diluted with the same medium and assayed at 264 nm for famotidine using a UV double-beam spectrophotometer (Shimadzu UV-1700 series). Samples withdrawn were replaced with equal volume of the same dissolution medium. All the experiments as specified above were conducted in triplicate.

2.4. Kinetics of drug release

The zero-order rate (equation 1) describes systems where drug release is independent of its concentration and this is applicable to the dosage forms like transdermal system, coated forms, osmotic system as well as matrix tablets with low soluble drugs. The first-order equation (equation 2) describes systems in which the release is dependent on its concentration (generally seen for water-soluble drugs in porous matrix). The Higuchi model describes the release of the drug from an insoluble matrix to be linearly related to the square root of time and is based on Fickian diffusion (equation 3). The Hixson-Crowell cube root law (equation 4) describes the release of drug from systems where it depends on the change in surface area and diameter of the particles or tablets with time and mainly applies in the case of systems that dissolve or erode over time. In order to authenticate the release model, dissolution data can further be analyzed by Peppas and Korsmeyer equation (equation 5).

$$Q_t = k_0 t \quad (\text{equation 1})$$

$$\ln Q_t = \ln Q_0 - k_1 t \quad (\text{equation 2})$$

$$Q_t = k_{HC} t^{1/2} \quad (\text{equation 3})$$

$$Q_0^{1/3} - Q_t^{1/3} = k_{HC} t \quad (\text{equation 4})$$

$$M_t/M_\infty = k t^n \quad (\text{equation 5})$$

Where Q_t is the amount of drug released at time t ; Q_0 is the initial amount of the drug in the formulation; k_0 , k_1 , k_H , and k_{HC} are release rate constants for zero-order, first-order, Higuchi model and Hixson-Crowell rate equations. In equation 5, M_t is the amount of drug released at time t , and M_∞ is the amount of drug released at time ∞ ; k is the kinetic constant, and n is the diffusion coefficient^[32].

The release data of various formulations were fitted in various models to ascertain the mechanism of drug release.

2.5. Preparation of dosage form for radiographic study

The optimized formulations which showed good *in-vitro* buoyancy and sustained release behavior were finally selected for radiography study. The drug in all selected formulations was replaced with the same amount of barium sulphate while all other ingredients were kept constant. These formulations were analyzed for their physical properties. The analysis confirmed that the developed dosage forms were similar to those containing drug.

2.5.1. Radiographic studies

The experimental protocol to carry out *in-vivo* radiographic studies were reviewed and approved by the Institutional Animals Ethical Committee of Institute of Pharmacy, Bundelkhand University, Jhansi, India (Registration No. BU/Pharm/IAEC/10/031). The *in-vivo* radiographic studies were conducted in young and healthy male albino rabbits weighing 2.0 kg to 2.2 kg. The animals were kept under standard laboratory conditions [temperature (25±2) °C]. Rabbits were kept for one week in animal house to acclimatize them and were fed a fixed standard diet. The 4 healthy male albino rabbits were used to monitor the *in-vivo* transit behavior of the prepared floating microspheres. None of the animal had symptoms or past history of gastro-intestinal disease. In order to standardize the conditions of gastrointestinal motility, the animals were fasted for 12 h prior to the commencement of each experiment. In each experiment, the first radiographic image of the animal subjects was taken to ensure the absence of radio-opaque material in the gastrointestinal tract. One of each dosage form (capsule containing microspheres) prepared for radiography was orally administered to rabbits with sufficient amount of water. During the study the rabbits were not allowed to eat, but water available with *ad libitum*^[33,34].

For radiographic imaging, the legs of the rabbit were tied over a piece of plywood (20 inch×20 inch), and location of the formulation in the stomach was monitored by keeping the subjects in front of X-ray machine (Allengers, Bharat Electricals, India, model No. E-080743). The distance between the source of X-rays and the object was kept same during the imaging process. Gastric radiography was done at the intervals of 0 h, 1 h, 3 h, 5 h and 6 h. In between the radiographic imaging, the animals were freed and allowed to move and carry out normal activities but were not allowed to take any food.

3. Results

The formulations of famotidine loaded floating microspheres were developed by modified solvent evaporation method. In this method, the drug-polymeric suspension was introduced into stirring 0.25% w/v solution of PVA from bottom side to reduce the aggregation of polymer on the top of PVA. This technique produced more spherical microspheres and good yield of product could be achieved.

The formulation mechanism of polymeric floating microspheres is well documented in the literature (Figure 4). The polymer and drug were dissolved in solvent mixture such

as dichloromethane and ethanol. The polymeric mixture at different ratio were dissolved in a volatile solvent (ethanol, dichloromethane combined) as given in Table 1. This polymeric drug solution was poured in 0.25% w/v solution of PVA. Thus, an O/W emulsion was formed. The ethanol present in oil droplet diffuse, to water thus polymer and drug mixture solidified on dichloromethane droplet. Now the temperature was raised up to 45 °C–50 °C. After evaporation of solvent, microspheres were collected by filtration, washed with water, and dried at room temperature. As a result, hollow cavity

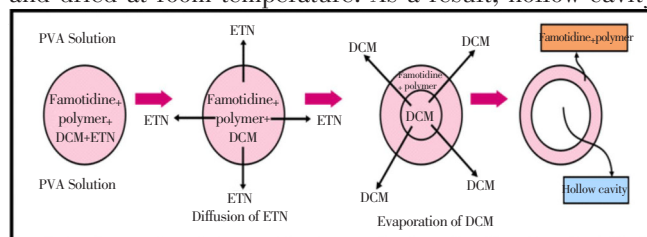


Figure 4. Mechanism of formation of floating microspheres.

ETN: Erythryl tetranitrate; DCM: Methylene chloride.

SEM photo micrograph confirmed that prepared microspheres were spherical with smooth perforated surface (Figure 2). The formation of perforation may be attributed to evaporation of alcohol from embryonic microspheres. The prepared microspheres were found to be spherical in shape with smooth perforated surface as indicated by photomicrographs. Floating cavities could also be observed on some micrographs.

The mean particle size of the floating microspheres was found to be ranging from (52.18±1.82) μm to (91.64±5.16) μm. It was observed that, on increasing the polymer amount, the average particle size increased. This may be due to diminished shearing efficiency at higher concentration of the polymer (higher viscosity). It was also observed that on increasing the volume of DCM, average particle size was found to be increased (Table 2).

Table 2

Micromeritic properties of floating microspheres.

Formulation code	Mean particle size ^a (μm)	Bulk density ^b (g/cm ³)	Tapped density ^b (g/cm ³)	Compressibility index ^b	Angle of repose ^b
FS-1	52.18±1.82	0.185±0.070	0.165±0.120	25.07±1.23	32.56±0.85
FS-2	60.32±3.01	0.166±0.030	0.154±0.340	28.31±4.65	20.89±0.38
FS-3	77.75±6.84	0.160±0.090	0.145±0.070	34.21±4.01	21.16±1.10
FS-4	82.24±7.94	0.151±0.080	0.131±0.090	41.01±2.25	23.04±0.42
FS-5	91.64±5.16	0.145±0.040	0.124±0.060	49.31±0.36	24.01±0.94
FS-6	78.02±2.67	0.155±0.060	0.149±0.130	35.94±1.45	25.00±0.71
FS-7	71.31±0.89	0.169±0.040	0.175±0.640	29.02±2.64	29.74±1.48
FS-8	63.94±4.23	0.188±0.040	0.191±0.010	21.14±6.02	30.07±0.58
FS-9	56.30±0.78	0.195±0.300	0.199±0.070	19.84±0.08	19.31±0.89
FS-10	85.18±6.54	0.175±0.020	0.188±0.610	32.01±1.34	32.70±2.95

^a: Mean±SD, n=200–300; ^b: Mean±SD, n=3.

The measured tapped density was found to be in the range of (0.124±0.06) g/cm³ to (0.199±0.070) g/cm³. Compressibility index ranged from (19.84±0.08) to (49.31±0.36) (Table 2).

The angle of repose was found to be in the range of (19.31±0.89) to (32.56±0.85). All the batches showed good flow properties except bathes FS-1 and FS-8 which exhibited higher angle of repose (Table 2).

The yield was found to be ranging from (69.74±1.35)% to (95.11±0.35)%. The drug entrapment/incorporation efficiency of microspheres was found to be satisfactory (55.75±2.94)% to (75.35±1.96)% (Table 3).

Table 3

Various formulation parameters of floating microspheres.

Formulation code	Yield ^a (%)	Incorporation efficiency ^a	Buoyancy % ^a
FS-1	69.74±1.35	55.75±2.94	68.84±2.15
FS-2	78.94±2.65	57.35±1.75	73.16±1.76
FS-3	81.75±0.45	60.70±2.94	86.46±1.64
FS-4	88.94±1.75	62.94±2.67	88.64±2.99
FS-5	95.11±0.35	65.74±2.94	95.81±2.46
FS-6	78.45±2.31	68.94±1.75	83.46±2.81
FS-7	79.44±2.03	70.88±3.16	75.11±2.41
FS-8	81.91±1.66	75.35±1.96	79.78±2.38
FS-9	70.46±1.74	57.68±1.09	61.64±2.67
FS-10	73.45±1.81	59.64±2.97	96.15±2.46

^a: Mean±SD, n=3.

All floating microspheres showed good floating ability/buoyancy (61.64±2.67)% to (95.81±2.46)% up to 20 h. This could be attributed to insolubility of used polymers in the gastric fluid. It was observed that the floating ability increased with increasing average particle size (Table 3).

It was also observed that the formulation prepared with higher volume of DCM (batch FS-10) showed better floating ability as compared to other batches. The reason behind this may be the formation of larger air core, which made them lesser dense than that of gastric fluid.

The release of famotidine from the developed floating microspheres was studied in 0.1 mol/L HCl (pH 1.2) up to 20 h. Since the acrylic polymers are insoluble in acidic medium, the microspheres retained their integrity during *in-vitro* dissolution studies. The cumulative % drug release for microspheres was found to be between 85–98% (Figures 5– 7).

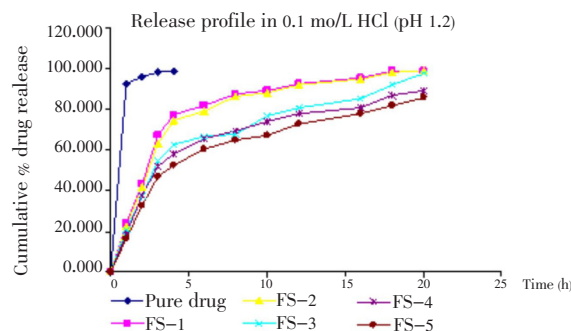


Figure 5. Effect of polymer ratio on release profile of drug in 0.1 mol/L HCl.

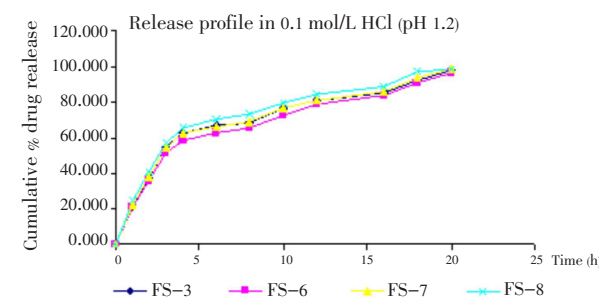


Figure 6. Effect of stirring ratio on release profile of drug in 0.1 mol/L HCl.

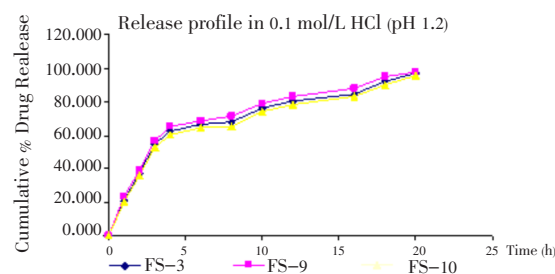


Figure 7. Effect of solvent ratio on release profile of famotidine in 0.1 mol/L HCl.

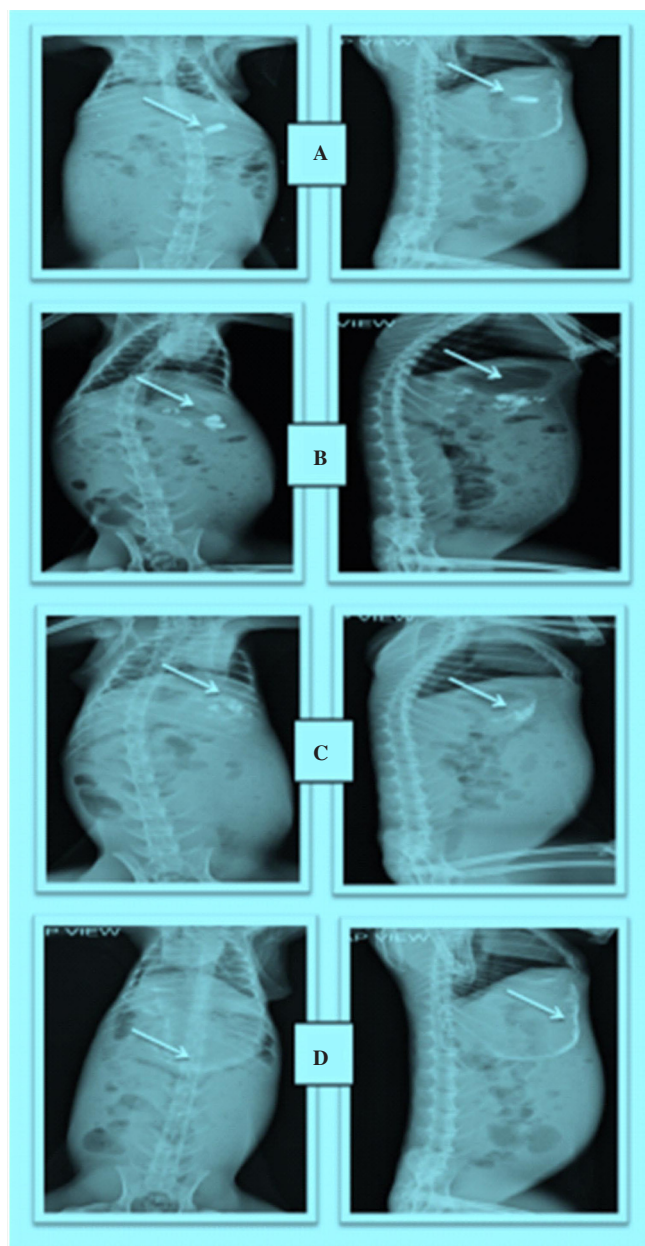


Figure 8. Radiographic images showing the presence of BaSO₄ loaded floating microspheres in the stomach at different time intervals. Images were taken after a: 0 h, b: 1 h, c: 3 h, d: 5 h.

The release profile data of all the developed formulations were fitted in kinetic model using PCP Disso software. The best model was selected on the basis of goodness of fit the values of residual sum of squares (RSS).

Table 4

Drug release kinetics for different formulations.

Formulation code	Zero-order			First order			Higuchi				Hixon-Crowell			Peppas and Korsmeyer		Best fit model	
	R	RSS	k ₀	R	RSS	k ₁	R	RSS	k _H	R	RSS	k _{HC}	R	RSS	k		n
FS-1	0.0071	11334	6.7027	0.9740	849	-0.221	0.895	2252	26.44	0.869	3251	-0.044	0.911	1342	33.74	0.410	FO
FS-2	0.3195	10186	6.6340	0.9802	666	-0.213	0.915	1833	26.06	0.894	2778	-0.043	0.923	1222	31.65	0.431	FO
FS-3	0.5710	6305	6.0150	0.9530	928	-0.151	0.959	7460	23.35	0.921	2219	-0.034	0.958	412	28.16	0.430	M
FS-4	0.5170	6190	5.7000	0.9320	1543	-0.118	0.949	8250	22.22	0.849	2685	-0.030	0.942	561	25.90	0.447	M
FS-5	0.6290	4764	5.3800	0.9400	1272	-0.103	0.967	5100	20.85	0.873	2130	-0.0270	0.950	466	22.30	0.482	M
FS-6	0.6530	5245	5.8500	0.9610	799	-0.139	0.973	4830	22.63	0.935	1840	-0.0330	0.966	304	25.97	0.450	M
FS-7	0.5940	6165	6.0500	0.9530	765	-0.158	0.964	6690	23.48	0.933	2025	-0.0350	0.962	366	28.10	0.433	M
FS-8	0.5090	7277	6.2500	0.9610	736	-0.178	0.952	9070	24.35	0.932	2253	-0.0380	0.961	394	30.87	0.409	M
FS-9	0.5340	6990	6.1900	0.9630	800	-0.168	0.955	8610	24.09	0.929	2246	-0.0370	0.958	435	29.68	0.421	FO
FS-10	0.6090	5721	5.8600	0.9590	1000	-0.137	0.964	6430	22.74	0.918	2141	-0.0328	0.955	427	26.26	0.448	M

RSS: Residual sum of squares; K: Release constant; n: Diffusion coefficient; H: Higuchi (Matrix); HC: Hixon-Crowell; FO: First order; M: Matrix.

The drug release of batches FS-1, FS-2 and FS-9 showed first order drug release and remaining all the batches showed Higuchi (Matrix) model (Table 4).

The hard gelatin capsule containing BaSO₄ loaded floating microspheres were clearly visible in stomach after oral administration of dosage form. In radiographic image taken after 1 hour, all microspheres were found to be scattered in stomach. Dense images of microspheres were seen at initial hours, but as time passed on the images of microspheres became lighter. It may be because of distribution and scattering of microspheres within gastrointestinal region. The radiographic images indicated that these floating microspheres retained successfully in the stomach up-to 6 hours (Figure 8).

4. Discussion

Novel floating microspheres were successfully prepared by solvent evaporation method with modified technique of administration of polymeric solution from bottom side, for prolonged as well as stomach specific action of famotidine. Due to their low densities, this multi particulate drug delivery system showed good floating ability.

It was noted, on increasing the polymer ratio the cumulative % drug release decreased gradually. It may be because of increased partitioning of drug in polymer (Eudragit S-100). It was also observed that the release of famotidine decreased significantly ($P < 0.05$) on increasing the amount of polymers.

Further, a significant increase was found in drug release on increasing the stirring rate. It may be because of increased surface area of microspheres due to reduced size.

On increasing the volume of ethanol in solvent phase the release was found to be increased. On the other hand, when the volume of DCM was increased, the release of drug was found to be decreased. The reason behind this may be the size of microspheres which increases on increasing the volume of DCM.

From *in-vitro* drug release studies, it can be concluded that by changing the ratio of polymer and solvent, drug release can be controlled. These floating microspheres containing famotidine could be dispensed by filling them in the empty capsule shell.

In-vivo radiographic images were also helpful to locate the position of floating micro spheres in gastrointestinal tract. And this study also confirmed that the prepared microspheres were able to retain in stomach for prolonged

release of famotidine.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgements

We are thankful to Cadila Pharmaceutical Ltd., Gujarat, for providing gift sample of famotidine and Degussa India Pvt. Ltd. for providing Eudragit S–100 polymer as a gift sample. We also wish to thank to the Director, Birbal Sahni Institute of Palaeobotany, Lucknow, India, for providing us SEM facility.

References

- [1] Kaushik K, Chaurasia D, Chaurasia H, Mishra SK, Bhardwaj P. Development and characterization of floating alginate beads for gastroretentive drug delivery system. *Acta Pharma Sci* 2011; **53**(4): 551–562.
- [2] Tadros MI. Controlled–release effervescent floating matrix tablets of ciprofloxacin hydrochloride: development, optimization and *in vitro–in vivo* evaluation in healthy human volunteers. *Eur J Pharm Biopharm* 2010; **74**(2): 332–339.
- [3] Baumgartner S, Kristl J, Vrečer F, Vodopivec P, Zorko B. Optimisation of floating matrix tablets and evaluation of their gastric residence time. *Int J Pharm* 2000; **195**(1–2): 125–135.
- [4] Bulgarelli E, Forni F, Bernabei MT. Effect of matrix composition and process conditions on casein–gelatin beads floating properties. *Int J Pharm* 2000; **198**(2): 157–165.
- [5] Davoudi ET, Noordin MI, Kadivar A, Kamalidehghan B, Farjam AS, Javar HA. Preparation and characterization of a gastric floating dosage form of capecitabine. *Biomed Res Int* 2013; doi: 10.1155/2013/495319.
- [6] Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. *J Control Release* 2000; **63**(3): 235–259.
- [7] Garg R, Gupta G. Progress in controlled gastroretentive delivery systems. *Trop J Pharm Res* 2008; **7**(3): 1055–1066.
- [8] Chen J, Park K. Synthesis of fast–swelling, superporous sucrose hydrogels. *Carbohydr Polym* 2000; **41**(3): 259–268.
- [9] Shaikh R, Singh TRR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. *J Pharm Bioallied Sci* 2011; **3**(1): 89–100.
- [10] Boddupalli BM, Mohammed ZNK, Nath RA, Banji D. Mucoadhesive drug delivery system: an overview. *J Adv Pharm Technol Res* 2010; **1**(4): 381–387.
- [11] Kedzierewicz F, Thouvenot P, Lemut J, Etienne A, Hoffman M, Maincent P. Evaluation of peroral silicone dosage forms in humans by gamma–scintigraphy. *J Control Release* 1999; **58**(2): 195–205.
- [12] Rouge N, Allémann E, Gex–Fabry M, Balant L, Cole ET, Buri P, et al. Comparative pharmacokinetic study of a floating multiple–unit capsule, a high density multiple–unit capsule and an immediate–release tablet containing 25 mg atenolol. *Pharm Acta Helv* 1998; **73**(2): 81–87.
- [13] Prajapati PH, Nakum VV, Patel CN. Formulation and evaluation of floating matrix tablet of stavudine. *Int J Pharm Investig* 2012; **2**(2): 83–89.
- [14] Chaturvedi K, Umadevi S, Vaghani S. Floating matrix dosage form for propranolol hydrochloride based on gas formation technique: development and *in vitro* evaluation. *Sci Pharm* 2010; **78**(4): 927–939.
- [15] Murata Y, Sasaki N, Miyamoto E, Kawashima S. Use of floating alginate gel beads for stomach–specific drug delivery. *Eur J Pharm Biopharm* 2000; **50**(2): 221–226.
- [16] Jagtap YM, Bhujbal RK, Ranade AN, Ranpise NS. Effect of various polymers concentrations on physicochemical properties of floating microspheres. *Indian J Pharm Sci* 2012; **74**(6): 512–520.
- [17] Jain AK, Jain CP, Tanwar YS, Naruka PS. Formulation, characterization and *in vitro* evaluation of floating microspheres of famotidine as a gastro retentive dosage form. *Asian J Pharm* 2009; **3**(3): 222–226.
- [18] El–Kamel AH, Sokar MS, Al Gamal SS, Naggar VF. Preparation and evaluation of ketoprofen floating oral delivery system. *Int J Pharm* 2001; **220**(1–2): 13–21.
- [19] El–Kamel AH, Sokar MS, Al Gamal SS, Naggar VF. Development of floating microspheres to improve oral bioavailability of cefpodoxime proxetil. *Int J Pharma* 2001; **220**: 13–21.
- [20] Wakde PH, Kasliwal RH, Mane SB. Design and fabrication of gastroretentive bilayer floating tablet of propranolol HCl using natural polymer. *Int J Pharm Sci Res* 2013; **4**(12): 4715–4728.
- [21] Pandya N, Pandya M, Bhaskar VH. Preparation and *in vitro* characterization of porous carrier–based glipizide floating microspheres for gastric delivery. *J Young Pharm* 2011; **3**(2): 97–104.
- [22] Jagdale SC, Agavekar AJ, Pandya SV, Kuchekar BS, Chabukswar AR. Formulation and evaluation of gastroretentive drug delivery system of propranolol hydrochloride. *AAPS PharmSciTech* 2009; **10**(3): 1071–1079.
- [23] Hussain MN, Masum MAA, Akhter S, Sharmin F, Reza MS. Formulation and evaluation of gastro retentive floating tablets of simvastatin using hydrophilic rate retardant. *Bangladesh Pharm J* 2012; **15**(2): 119–126.
- [24] Al–Omar MA, Al–Mohizea AM. Famotidine, analytical profile. In: Brittain HG, editor. *Profiles of drug substances, excipients and related methodology*. Burlington: Academic Press; 2009, p. 115–151.
- [25] Muzib YI, Ch Rekha. Development and evaluation of mineral oil entrapped emulsion gel beads of famotidine. *Int J Pharmacol Technol* 2011; **3**(2): 83–90.
- [26] Haznedar S, Dortunc B. Preparation and *in vitro* evaluation of eudragit microspheres containing acetazolamide. *Int J Pharm* 2004; **269**(1): 131–140.
- [27] Lee JH, Park TG, Choi HK. Development of oral drug delivery system using floating microspheres. *J Microencapsul* 1999; **16**(6): 715–729.
- [28] Bhardwaj P, Singh R, Swarup A. Development and *in–vitro* evaluation of floating microspheres of 5–fluorouracil. *Int J Pharm Sci Res* 2012; **3**(3): 934–941.
- [29] Soppimath KS, Kulkarni AR, Aminabhavi TM. Development of hollow microspheres as floating controlled–release systems for cardiovascular drugs: preparation and release characteristics. *Drug Dev Ind Pharm* 2001; **27**(6): 507–515.
- [30] Patel A, Ray S, Thakur RS. *In–vitro* evaluation and optimization of controlled release floating drug delivery system of metformin hydrochloride. *DARU* 2006; **14**(2): 57–64.
- [31] Chaurasia D, Kaushik K, Bhardwaj P, Chaurasia H, Jain SK, Shobhna S. Development and *in–vitro* characterization of floating microsphere bearing tramadol HCl. *Acta Pol Pharm–Drug Res* 2011; **68**(5): 795–801.
- [32] Bhardwaj P, Chaurasia D, Chaurasia H, Gupta R, Prajapati SK. Development and *in–vitro* evaluation of site–specific floating multiparticulate drug delivery system for stomach. *Int J Pharmagenesis* 2011; **2**(1): 5–13.
- [33] Jagdale SC, Bari NA, Kuchekar BS, Chabukswar AR. Optimization studies on compression coated floating–pulsatile drug delivery of bisoprolol. *Biomed Res Int* 2013; doi: 10.1155/2013/801769.
- [34] Shah SS, Pandya SJ, Waghulade MK. Development and investigation of gastro retentive dosage form of weakly basic drug. *Asian J Pharm* 2010; **4**(1): 11–16.