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Research Article

PREPARATION AND IN-VITRO ESTIMATION FOR GASTRORETENTIVE FLOATING HOLLOW – MICROSPHERES OF FAMOTIDINE

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ABSTRACT

Objective: The present study's objectives were to prepare and evaluate gastroretentive floating hollow-microspheres (HM) of the selected Famotidine (FM) to enhance its retention time within the stomach.

Methods: HM was prepared by solvent emulsion diffusion technique utilizing various polymers such as ethyl cellulose, eudragit L100, eudragit S100 as polymers, and Dichloromethane and methanol as solvents. The formulated HM was estimated for their particle-size, entrapment efficiency, floating ability, scanning electron microscopy, and *in vitro* drug release of drug.

Results: The average particle-size of the formulated HM was within the range of 262.3±3.5 to 323.1±2.1µm. The SEM confirmed the smooth surface, sphere shape, and hollow cavity within it. The formulated microspheres showed good floating behavior for up to 8 h because of their low particle size. The *invitro* release profile of the HM displayed a controlled-release of FM microspheres in pH1.2 for up to 8 h.

Conclusion: The result depicts that the formulated HM of FM by virtue of good floating time and sustained release properties is likely to improve the retention time within the stomach and thereby the oral bioavailability.

Keywords: Famotidine, Microballoons, Floating drug delivery system, Scanning electron microscopy, Solvent emulsion diffusion method.

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INTRODUCTION

The primary limitations of oral administration are the short residence period of pharmaceutical medications at the absorption site and inadequate drug release out of the system, leading to poor gastrointestinal absorption [1]. Gastroretentive drug delivery system (GRDDS) is a strategy that allows the controlled release of medications over time by retaining them in the stomach for an extended length of time, hence increasing the gastric residence time. This system would be beneficial for medications that display pH-dependent solubility and stability in gastric fluids [2]. GRDDS would be of great benefit to the therapeutic agents that possess absorption window in the upper part of the gastrointestinal tract. Some of the common benefits of using these systems are improved patient compliance by decreasing dosing incidence thereby enhancing the therapeutic value of drugs with shorter half-life. Moreover, other advantages include site-specific delivery, constant and continuous release of drug within the stomach, increased residence time of drug at the absorption site, improved oral bioavailability. Enabling reduction of dosage and avoiding dumping of medications [3]. Extending the time of emptying is seen to be beneficial therapeutic agents that are known to exhibit variable bioavailability due to variable gastric emptying of dosage forms [4].

Development of floating Drug Delivery System may involve several approaches such as hydrodynamically regulated, low-density system that owns enough buoyancy to float on the content of the stomach thereby slowing down the gastric emptying process [5]. When the system remains suspended in the stomach proximal to the absorption window the therapeutic agents is likely to get slowly releases in a controlled manner for a prolonged period of time. This results in improved gastric retention time and greater control over changes in plasma medication concentrations for drugs that possess absorption site in the upper past of small intestine [6]. Such systems are ideal for medications with improved acid solubility and medications with a particular site of absorbance in the upper intestine [7]. Floating hollow microspheres are a novel delivery system that possesses a spherical cavity having a low density. This would help the dosage form float in the gastric fluid for longer period, enable controlled release thereby helping in drug absorption [8]. It is a non-effervescent approach with free-flowing particles of 1–1000 µm in size and a specific density of <1 [9].

Famotidine (FM), potent histamine H2 receptor antagonist frequently used for the treatment of gastroesophageal reflux disease, gastric ulcers, and Zollinger Ellison syndrome. The recommended dosage of FM is 20-40 mg/day. Conventional dosage of 20 mg can inhibit gastric secretion upto 5 h but not more than that and leads to fluctuation in plasma concentration and require frequent dosing. FM is absorbed from the initial part of the small intestine that is the stomach and thus it has a narrow absorption window [10]. It exhibits a low bioavailability (40–45%) and a short biological half-life (1–3 h) following oral administration, which prompted the evolution of sustained release formulations. Local administration of FM boosts medication efficacy in decreasing acid secretion through increasing availability at the GI wall receptors site [11].

METHODS

Chemicals

FM procured from Yarrow Chemicals, Mumbai. Eudragit L100 and Eudragit S100 were obtained from Central Drug House, New Delhi, and Ethyl Cellulose obtained from S D Fine Chem Ltd, Mumbai, was used as polymers. Polyvinyl alcohol was also obtained from S D Fine Chem Ltd. All other ingredients employed in the study were of analytical grade.

Calibration curve of FM

Accurately weighed 10 mg of FM was transferred into 10 ml volumetric flask. After that, add 0.1N HCl buffer was added up to the mark and

sonicated the buffer solution until drug is dissolved completely. The concentration of this standard solution was 1000 µg/mL. About 1 ml of standard solution was pipetted and transferred into another 10 mL volumetric flask and frame the volume was made up to the mark with 0.1 N HCl buffer. Appropriate dilutions were made from 5 to 30 µg/mL concentration range. The photometric absorbance was recorded using UV-VIS Spectrophotometer (Shimadzu-1700, Japan) using 0.1N HCl as blank at the lambda max of 265 nm [12].

pH solubility analysis of FM

The solubility of FM in buffer of varying pH was determined to identify the right solvent. The study was performed using five different buffers with varying pH conditions. Excess amount of drug was added to 5 mL buffer in pH 1.2, 4.4, 5.4, 6.8, and 7.4 in a series of glass vials. The samples were then sonicated and left overnight to attain equilibrium. After equilibration, suitable samples were made and analyzed for drug content against respective buffer as blank by UV-VIS Spectrophotometer [13].

Preparation of Floating Microballoons (MB)

The floating hollow microspheres/MB were developed using the emulsion solvent diffusion process and compositions are given in Table 1. The drug and the polymer were weighed in different proportions (1:1, 1:2) and dissolved in a combination of methanol and dichloromethane in a ratio of 1:1 containing 0.5–1% tween 80. The resultant solution was added into an aqueous solution of 0.75% w/v PVA at 40°C. The dispersion was stirred for 1 h at 500 rpm with a three-bladed mechanical stirrer propeller to vaporize the volatile solvent. After vaporization, the hollow-microspheres (HM) were separated by filtration, washed with water, and dried at room temperature overnight [14].

Characterization of floating MB

Particle size

The particle size of HM was visualized using an optical microscopic method and observations was given in Table 2. The HM was dispersed in glycerine, then a drop of the solution was taken on a glass slide and observed by an optical microscope under steady bright light, and the mean particle size was determined by measurement of 200 MB in triplicate by the use of a calibrated eyepiece micrometer and a stage micrometer [15].

Surface morphology

The scanning electron microscopy (SEM) was used to study surface morphology characteristics of the MB. The MB was gold coated using an ion sputtering device in a atmosphere of argon. After that, SEM was used to study the surface morphology of MB on microscopic scale under appropriate magnification [16].

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectroscopy was used to assess the possible drug-polymer interactions and the stability of the drug during formulation process. It was used to record spectra for pure drug and drug-loaded MB. Approximately 10 mg of drug sample was mixed in equal quantity of potassium bromide and loaded into a diffused reluctance sampler. The scanning range was between 1000 and 4000 cm^{-1} to identify the different functional groups. The FTIR spectra of the FM, ethyl cellulose, eudragit L100, and floating MB formulation were recorded using FTIR spectrometer (JASCO FTIR 460 plus) [17].

Differential scanning calorimetry (DSC)

DSC studies were done to detect any possible interactions between the drug and the excipient within the formulation. The thermoanalytical technique is also used to characterize the solid state of the drug in the polymer. The sample was taken in concealed aluminum pan and analyzed by a differential scanning calorimeter instrument (DSC-60 Shimadzu, Japan). The sample was heated in the presence of nitrogen and thermograms was acquired by heating at a constant rate of 10°C/min in a temperature range of 10–350°C. Throughout the run, a nitrogen outflow of 20 mL/min was kept flowing. Thermograms of FM and the formulation were obtained [18].

Drug entrapment efficiency

To determine the percentage of drug entrapped within the formulation, drug entrapment efficiency was performed by dissolving 10 mL of MB in 5 mL of methanol. Then, the resulting solution was centrifuged at 2500 rpm for 5 min. After centrifugation, 1 mL of supernatant liquid was pipette out and diluted with 0.1N HCl buffer and was estimated using a UV Spectrophotometer (Shimadzu-1700, Japan) at a lambda max (λmax) of 265 nm using methanol as a blank. The entrapment efficiency was calculated as per equation 1 [19]:

$$\%\,Entrapment\ Efficiency = \frac{Calculated\ Drug\ Content}{Theoratical\ Drug\ Content} \times 100 \quad (1)$$

Floating time

To record the floating time of the MB, the formulated MB was placed in a glass beaker containing 0.1N HCl and their time of floating was recorded for up to 8 h. The floating behavior of the prepared MB is shown in Fig. 1. The figure depicts lesser that the particle size of the MB greater is the floating time [12].

***In vitro* floating ability**

Ten milligram of formulated MB was taken in a 100 mL beaker and 50 mL of 0.1N HCl containing 0.02 % tween 80 was added and the beaker was shaken at room temperature. After 8 h, each proportion of the MB floating on the surface of the beaker and those sinking down were collected and weighed after drying. All the measurement was done in triplicate, and the average was plotted. The proportion of floating MB was counted by the equation 2 [20]:

$$\%\ Floating\ ability = \frac{weight\ of\ \ floating\ microballoons}{Initial\ weight\ of\ microballoons} \times 100 \quad (2)$$

Table 1: Formulation table; FM-famotidine microballoons

Formulation	Drug (mg)	Ethyl cellulose (mg)	Eudragit L 100(mg)	Eudragit S 100(mg)	DCM: MTH Ratio
FM1	100	200	-	-	1:1
FM2	100	100	100	-	1:1
FM3	400	-	-	400	1:1
FM4	50	-	100	-	1:1
FM5	100	-	-	100	1:1
FM6	100	50	50	-	1:1

Table 2: Various formulation parameters of MB. The mean±SD, n=3

Formulation	Particle size (µm)	Entrapment efficiency (%)	Floating ability (%)
FM1	271.33±2.9	70.58±2.7	73.14±2.1
FM2	262.30±3.5	74.20±3.2	78.35±3.6
FM3	323.10±2.1	69.33±2.1	38.20±2.8
FM4	293.21±3.3	58.10±3.5	68.93±3.3
FM5	311.18±2.5	64.15±2.7	35.82±2.6
FM6	283.14±4.2	67.46±3.8	73.40±3.2

Table 3: The optimized composition of MB

Variables	Values
Polymer ratio	1:1
Drug: Polymer	1:2
Emulsifier concentration	1%
Stirring speed (rpm)	500
Stirring time (h)	1

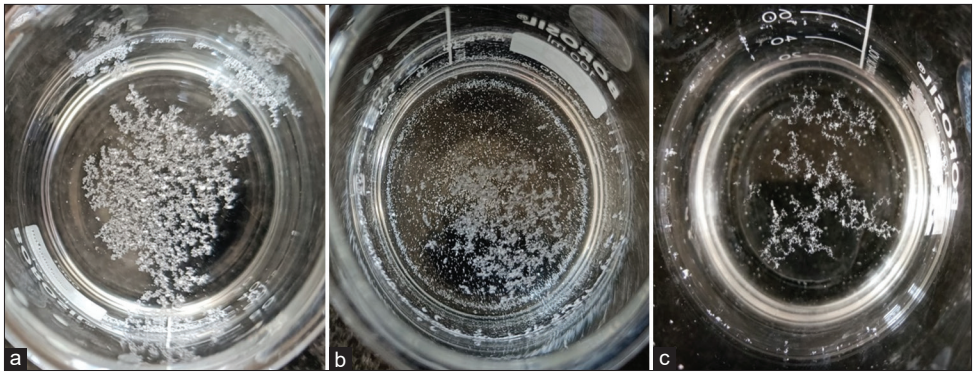

Fig. 1: (a-c) Floating behavior of optimized MB in 0.1N HCl with 0.02% tween 80

***In vitro* drug release**

The drug release rate from the floating MB was determined using dissolution equipment USP type I. The samples were taken with a muslin cloth and placed in a wire basket of the tester. The dissolution was carried out with 0.1N HCl of pH1.2 in dissolution fluid of 900 ml maintained at 37±0.5°C at 100 rpm. Five milliliters of sample was withdrawn from the dissolution media for 8 h and replaced with a fresh media every time to maintain the sink condition. The samples withdrawn was diluted with 0.1N HCl buffer appropriately before analysis at 265 nm with a UV VIS Spectrophotometer (Shimadzu UV-1700). All the measurement was done in triplicate, and the average was plotted [21-23].

RESULTS AND DISCUSSION

Formulation of MB

FM MB was formulated using different ratios (1:1, 1:2) of polymers by solvent emulsion diffusion method [14]. According to the method, the polymer and drug were dissolved in a mixture of Dichloromethane: Methanol in a ratio of 1:1. Then, the polymer solution was added in an aqueous solution of 0.75% (w/v) PVA that was used a stabilizer. Methanol was found to diffuse into the aqueous phase to form the embryonic microspheres. On the other hand, dichloromethane, which cannot disperse, is reserved as a core of the MB. When these MBs were equilibrated at 40°C, dichloromethane vaporizes leaving the MB with hollow cores. The optimized batch formulation was given in Table 3 and selected based on the particle size, drug polymer ratio, and floating time. It was noticed that the lower the emulsifier concentration (0.5%) higher the particle size of MB. The particle size of the MB decreased with an increase in the concentration of emulsifier (1%). It is noted that higher the concentration of the emulsifier more is the drop in the interfacial tension that will eventually result in decreased globule size [24]. Higher stirring speed initiates the formulation of small-sized MB. It is well-known, as the stirring speed increases the globule size decreases producing finer microparticles. It was also noticed that batches formulated with lower polymer concentration resulted in finer particles [25]. This can be attributed to the fact that lower polymer concentration would produce organic solutions having lower viscosities that would be easily dispersed leading to the formation of smaller microparticles. On the other hand, solutions containing higher polymers resulted in the formulation of lumps and therefore resulted in bigger particle size.

Calibration curve of FM

The calibration curve of FM that was performed in 0.1N HCl and was observed to be linear in a concentration range of 5–30 µg/mL as illustrated in Fig. 2. The regression value was of 0.9965. The high regression value indicates the linearity of the curve and shows that it follows Beer's Lambert's law [26].

pH solubility analysis of FM

The solubility profile of FM studied in of pH 1.2, 4.4, 5.4, 6.8, 7.4 indicated that the maximum amount of the drug was soluble in acidic pH 1.2 and the least was soluble in pH 4.4. The pH solubility profile is depicted in Fig. 3. The solubility of FM in pH 1.2 indicates that the drug is highly soluble in gastric acid conditions while it remains poor in higher pH values. The good solubility in pH 1.2 can be explained by the pKa value of FM (pKa = 6.69). Similar solubility profiles for FM have been reported earlier in the literature [27].

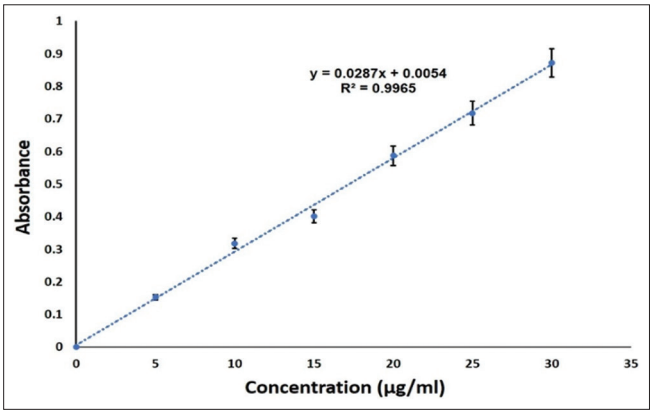

Fig. 2: Calibration curve of FM in 0.1N HCl. (n=3)

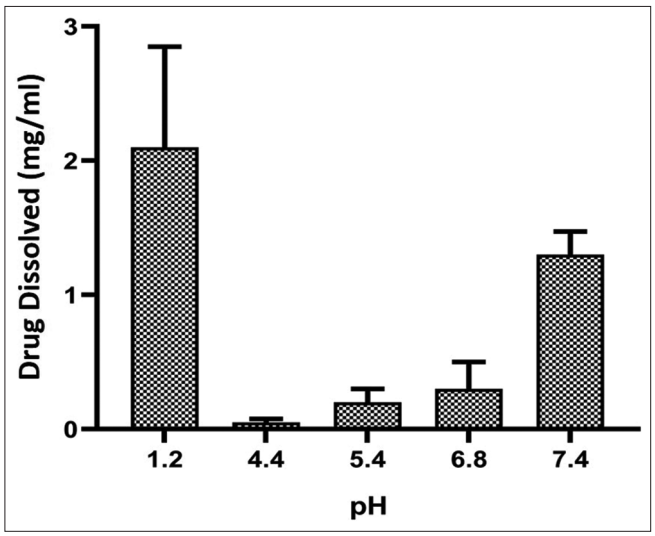

Fig. 3: pH solubility profile of Famotidine (n=3)

FTIR

FTIR spectroscopy was utilized to observe any possible interactions between the medication and the polymer utilized in the formulation due to manufacturing conditions. FTIR spectra of the FM showed the

presence of functional group NH2, C=N and S=N at 2365.26 cm^{-1}, 1540.85 cm^{-1}, and 1311.61 cm^{-1}, respectively. The FTIR spectra of the drug and the formulation is shown in Fig. 4. There was no evidence of any loss or the formation of any additional peak in the formulation's FTIR spectra when compared with the characteristic FTIR spectra of pure FM. The major peak values of the drug remained unaltered during the formulation, showing that there were no chemical interactions. Thus, the study proved the chemical integrity of the drug in the polymer matrix [28].

DSC

Differential scanning colorimetry studies were performed to assess the potential interaction in an excipient and pharmacological core in the

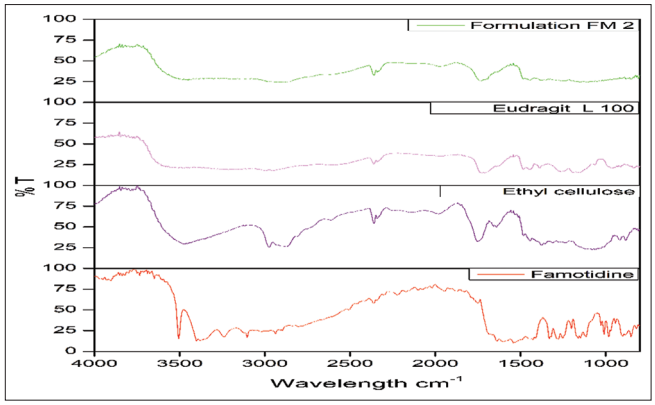

Fig. 4: FTIR spectra of famotidine, Ethyl cellulose, Eudragit L100, optimized formulation

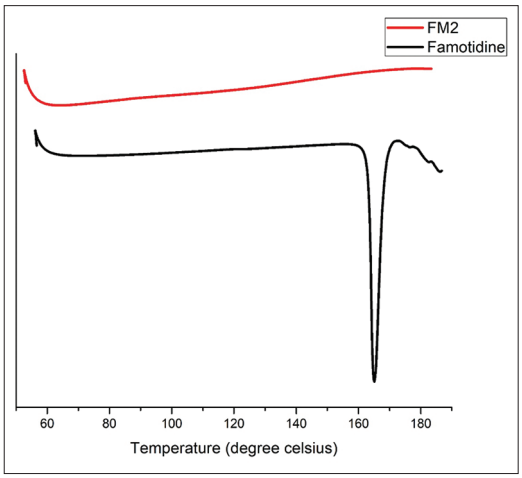

Fig. 5: DSC thermographs of drug and optimized formulation

MB. FM in its purest form has a distinguishing peak at 165.11°C, which is a key sign of the drug's crystalline composition. However, the thermal behavior of the FM MB demonstrates no characteristic peak of the drug in the formulation as showing in Fig. 5. It suggests that the drug's crystalline nature entirely transforms into an amorphous form. The presence of the drug as a solid solution in the polymer matrix is likely to control the release from the insoluble polymeric matrix in pH 1.2. This ends up resulting in a substantial change in the peak endothermic temperature of the resultant formulation [29].

SEM

SEM was used to investigate the shape and external morphology of the produced MB, as shown in Fig. 6. The SEM indicated that the MB displayed a spherical shape with a rough surface. The rough surface can be due to the deposits of the polymers on the MB due to rapid diffusion of the solvent [30]. The hollow cavity is likely to be formed result of the evaporation of water, methanol, and Dichloromethane [31].

***In vitro* floating ability**

The percentage floating was reported above 60% for all the batches except for formulations FM3, and FM5 which was prepared using Eudragit S100. The floating time was observed to be dependent on the type of polymer employed and amount of polymer used to produce the MB. The result of the floating studies is portrayed in Fig. 7. After comparing all the formulations, it was observed that batches prepared with Eudragit L100 showed increased floating ability as they were found to possess low particle size. In general, it was observed that the MB produced with a higher amount of polymer displayed bigger particle size due to agglomeration that reduced the total floating time as noted with formulation FM3 [32].

***In vitro* drug release**

The drug release studies were executed in simulated gastric fluid pH 1.2 for 8 h. The profile of dissolution of all the formulations prepared using different polymer concentrations is shown in Fig. 8. The drug release was found to depend on the type and amount of polymer used to produce the MB. As per the figure, batches made with Eudragit S100 showed the least release while their 8 h retention time in pH1.2. It should be noted that FM3 was produced with a higher amount of polymer displayed poor release of 62.775 in the given time span. The poor release can be due to the bigger microparticle size due to high amount of polymer used which lead to agglomeration. The highest proportion of drug release from the FM MB was recorded from formulation FM2 which was 86.78% made with Eudragit L100 and the least release was from formulation FM3 of 62.77%. The complete release of FM from F1 indicated that pH 1.2 would be able to maintain the necessary sink condition that ensures the complete release of drug. Thus, the MB remains afloat proximal to the absorption window and releases the drug in a sustained manner. The prolonged floatation noted with FM2 indicated that the drug release could happen locally in the stomach. The prolonged gastric retention is likely enhancing the action of FM on the receptors in the

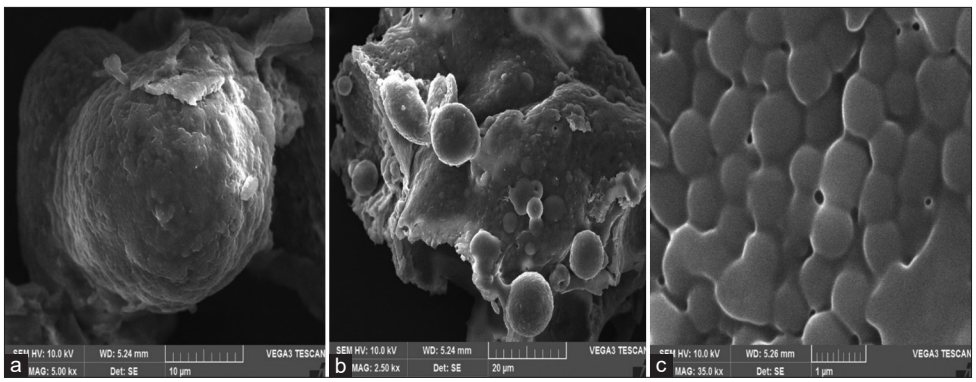

Fig. 6: Scanning electron micrograph of optimized MB: (a) spherical MB with smooth surface, (b) population of spherical MB, and (c) section of MB showing a hollow cavity

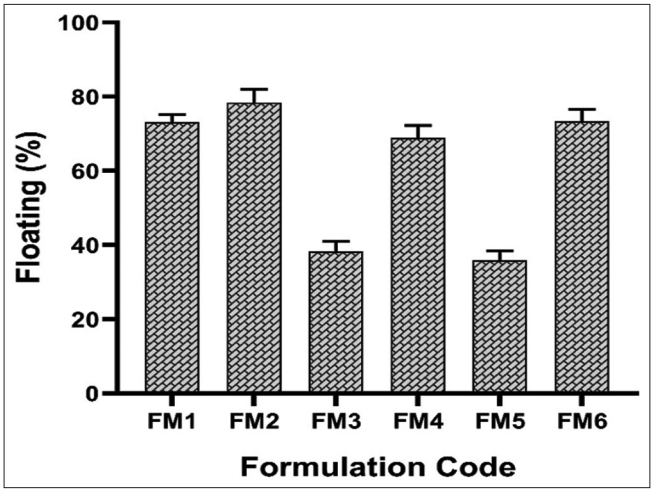

Fig. 7: *In vitro* floating ability of Famotidine MB

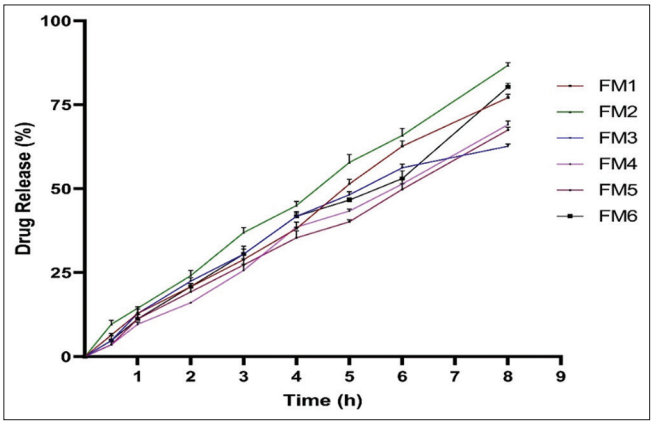

Fig. 8: *In vitro* release profile of Famotidine MB (n=3)

gastrointestinal wall thereby that acts by reducing the secretion of HCl. The controlled release of the drug is likely to improve the absorption and enhance the oral bioavailability. Gastroretentive floating MB has been employed for controlled release of drugs in the past to improve the drug absorption [33].

CONCLUSION

Gastroretentive floating HM of FM was successfully formulated by solvent emulsion diffusion method using different concentrations of polymers in methanol and dichloromethane. The developed MB showed good floating behavior due to their low densities for up to 8 h. The SEM established the presence of a smooth surface, spherical shape, and hollow cavity in the MB. The FT-IR and DSC results showed no drug-polymer interactions. After comparing all the formulations, batches prepared with Eudragit L100 displayed superior floating time than batches with Eudragit S100. The formulation FM2 was found to display prolonged floating time and better release in a controlled way for a longer duration. Hence, floating MB is likely to display better efficacy by acting locally on the receptors in the gastrointestinal wall and improve the drug absorption as well.

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CONFLICTS OF INTEREST

In the manuscript, the authors reveal that they do not have any conflicts of interest.

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