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Optimization Studies on Floating Multiparticulate Gastroretentive Drug Delivery System of Famotidine

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The objective of this study was to optimize floating microballoons of famotidine by the emulsion solvent diffusion technique using central composite design. Formulations F_1–F_{15} were prepared using three independent variables (pH of medium, drug: Eudragit® S100 ratio and ethanol : dichloromethane ratio) and evaluated for dependent variables (shape, percentage buoyancy, and encapsulation). The optimized formulation F_9 was fractionated and a polymer combination of (Eudragit® S100 : Eudragit® L100-55, 9.5:0.5) resulted in microballoons that exhibited zero order release (94.73%) with 84.20% buoyancy at the end of the eighth hour when studied in the mesh-designed modified USP type II apparatus.

Keywords famotidine; microballoons; emulsion solvent diffusion method; fractionation; mesh designed apparatus

INTRODUCTION

Oral controlled release (CR) dosage forms are not suitable for a variety of important drugs characterized by a narrow absorption window in the upper part of the gastrointestinal tract as one requisite for successful performance of oral CR dosage forms is that drug should have good absorption throughout the gastrointestinal tract (GIT), preferably by passive diffusion (Patil, Hirlekar, Gide, & Kadam, 2006). This is due to the relatively short transit time of the dosage form in these anatomical segments. Various attempts have been made to prolong the retention time of the dosage form in the stomach. One such method is the preparation of a device that remains buoyant in the stomach contents because of its lower density than that of the gastric fluids (Desai & Bolton, 1993; Deshpande, Rhodes, Shah, & Malick, 1996; Kawashima, Niwa, Takeuchi, Hino, & Itoh, 1992; Whitehead, Fell, Collett, Sharma, & Smith, 1998). Porous carriers have also been used in preparation of gastroretentive dosage forms (Jain, Acanthi, Jain, & Agrawal, 2005; Sriamornsak, Thirawong, & Puttipipatkhachorn, 2004). Low-density systems are superior than the gas-generating systems as gas-generating systems inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter whereas low-density systems (<1.004 g/cm^3) show immediate buoyancy as most of them entrap oil or air (Bardonnet, Faivre, Pugh, Piffaretti, & Falson, 2006). On the contrary, a floating system made up of multiple unit forms has relative merits compared with a single unit preparation as (a) these avoid "all or none" emptying from the stomach during migrating motor complex, (b) reduction in chances of dose dumping, (c) reduction in intersubject variability in absorption, (d) reduction in producing irritation, and (e) reduction in obstruction in the GIT.

In general, the gastroretention time of dosage form is longer in the fed state in comparison with that in the fasting state as the dosage forms are retropelled from the pyloric-antrum for further digestion and evacuation in the end of the fed state, or are retained until the arrival of the subsequent "house keeper wave." Thus theoretically, continuous feeding can prolong the gastroretention time of the dosage form for more than 24 h (Read & Sugden, 1987). The pH of the stomach in fasting state is 1.2–2.0 and in the fed state it ranges from 2.0 to 6.5 depending on the intake. As the stomach does not get enough time to produce sufficient acid when the liquid empties the stomach, generally basic drugs have a better chance of dissolving in the fed state than in the fasting state (Arora, Ali, Ahuja, Khar, & Baboota, 2005). Weakly basic drugs have lower pK_a values and remain in unionized form at intestinal pH having lower solubility (Kostewicz et al, 2004). According to pH partition theory (Allen, Popovich, & Ansel, 2004), the drug is absorbed in unionized form; thus, for a weakly basic drug incorporated in the conventional CR dosage forms, only a fraction of the drug is dissolved due to lesser solubility at its absorption site, such as the intestine. Incorporation of weakly basic drug in a gastroretentive dosage form is beneficial over a conventional CR dosage form so that released drug continuously reaches its absorption site such as the intestine.

Famotidine, a H_2-receptor antagonist, antiulcerative drug was chosen as the drug candidate to be formulated as a gastroretentive multiparticulate system as it is a weakly basic drug with a short half-life of 3 h, low bioavailability (40–45%), and is incompletely absorbed from the GIT (Sweetman, 2002).

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The objective of this study was to optimize the microballoons of famotidine prepared with Eudragit® S100 alone and in combination of different polymers so that a CR may be obtained in the fed state conditions. Eudragit polymers were selected to form the floating microballoons, as these are generally recognised as safe (GRAS) listed, FDA approved rate controlling excipient and very widely used in pharmaceutical industry (Rowe, Sheskey, & Oven, 2006).

MATERIALS AND METHOD

Famotidine was provided by Sun Pharmaceuticals (Mumbai); different grades of Eudragit® were provided by Degussa India Pvt. Ltd. (Mumbai); ethylcellulose and ethanol were obtained from S. D. Fine Chemicals Ltd. (Mumbai), dichloromethane was obtained from Qualigens Fine Chemicals (Mumbai) and poly vinyl alcohol was provided by Qualikems Fine Chemicals Pvt. Ltd. (New Delhi). All other ingredients used were of analytical grade and were used without further purification. Spectrophotometeric studies were carried out by using double-beam UV spectrophotometer, Pharmaspec 1700, Shimadzu (Japan).

Experimental Design

Preliminary trials for response surface optimization of method and formulation were conducted using a Central Composite Design (CCD) for preparation of microballoons (Bolton, 1997; Jain, 2004). A CCD consists of a central core of two-level factorial design (2^n) (denoted as +1 and –1), one central point (0) and 2*n* outer points (+a and –a). The CCD was given in Table 1. The independent variables used were pH of medium, drug : Eudragit® S100 ratio and ethanol : dichloromethane ratio whereas the dependant variables were shape of microballoons, percentage encapsulation and percentage buoyancy. The five levels of independent variables were +1, –1, 0, +a and –a, and the levels of pH of aqueous medium were 5, 1.2, 3, 4, and 2, levels of drug : Eudragit® S100 ratios were 1:12, 1:4, 1:8, 1:10, and 1:6 and levels of ethanol : dichloromethane ratios were 2:1, 0.5:1, 1:1, 1.25:1, and 0.75:1, respectively.

TABLE 1
Various Formulations with the Levels of Independent Variables used in Central Composite Design

Formulation Code	pH of Aqueous Medium	Drug : Eudragit® S100	Ethanol: Dichloromethane
F_1	–1	–1	–1
F_2	+1	–1	–1
F_3	–1	+1	–1
F_4	+1	+1	–1
F_5	–1	–1	+1
F_6	+1	–1	+1
F_7	–1	+1	+1
F_8	+1	+1	+1
F_9	–a	0	0
F_{10}	+a	0	0
F_{11}	0	–a	0
F_{12}	0	+a	0
F_{13}	0	0	–a
F_{14}	0	0	+a
F_{15}	0	0	0

Optimized Method for Preparation of Microballoons

Microballoons of famotidine were prepared by modified emulsion solvent diffusion method established by Kawashima et al. Drug and Eudragit® S100 in a ratio of 1:8 (80:640 mg) were dissolved or dispersed in a mixture of ethanol and dichloromethane (1:1) at room temperature (10 mL). To this 0.5 mL of dimethyl formamide (DMF) was added, and the solution was introduced to an aqueous solution (pH 2.0) of poly vinyl alcohol (0.75%, wt/vol, 132 mL) at 40°C, forming oil in water-type emulsion. The resultant emulsion was stirred, employing a mechanical stirrer at 1065279.6 m/s. The finally dispersed droplets of the polymer solution of drug were solidified in the aqueous phase by diffusion of the solvent. Dichloromethane, evaporated from the solidified droplets, was removed by an aspirator (Buchi type rotary vacuum evaporator, HICON, Grover Enterprises, Delhi), leaving water-filled microspheres. After agitating the system for 1 h at 1065279.6 m/s, the resulting polymeric particulate systems were filtered and dried overnight at room temperature to produce microballoons.

Selection of Optimized Formulation

Formulations from F_1 to F_{15} were prepared and evaluated for dependent variables (shape, percentage encapsulation and percentage buoyancy). Shape of microballoons was observed visually and percentage encapsulation and percentage buoyancy were determined by following method.

Determination of Percentage Encapsulation

Ten milligram of floating microballoons was taken in a test tube and drug was extracted with DMF. The samples were assayed for drug content by UV-spectrophotometer at 265 nm after suitable dilution. The percentage encapsulation was calculated as follows:

$$\text{Percentage encapsulation} = \frac{Q_p}{Q_t} \times 100$$

where Q_p is quantity of drug in grams encapsulated in microballoons and is the product of drug content per gram of

microballoons and yield of microballoons in grams. Q_t is quantity of drug in grams added for encapsulation.

Determination of Floating Behavior by Percentage Buoyancy

Fifty milligram of floating microballoons was placed in simulated gastric fluid (pH 2.0, 100 mL) containing 0.02% (wt/vol) tween 20. The mixture was stirred at 11836.44 m/s on a magnetic stirrer. After 8 h, the microballoons that floated and those settled were collected and dried overnight in dessicator. Both the fractions of microballoons were weighed and buoyancy was determined by the following formula:

$$\text{Percentage buoyancy} = \frac{W_f}{W_f + W_s} \times 100$$

where W_f and W_s are weights of the floating and settled microballoons, respectively

Evaluation of Optimized Microballoons

The optimized formulation was fractionated into three different fractions using british standard sieves (BSS) arranged in ascending order i.e., from sieve no. 10–16 (1,000–2,000 μm), 16–22 (710–1,000 μm) and 22–44 (355–710 μm) and coded f_1, f_2, and f_3 fractions, respectively. These fractions were collected, weighed, and evaluated for different parameters. Studies for shape, drug content, and percentage buoyancy for f_1, f_2, and f_3 were conducted as described in previous section.

Micromeritic Properties

The different fractions of optimized formulation were characterized by their micromeritic properties, such as bulk density, tapped density (50 tappings) using bulk density apparatus (HICON, Grover Enterprises). The density determinations were used to determine the Hausner's ratio (Wells, 2002).

Characterization of Hollow Structure of Microballoons

The porosity (ε) and the ratio of diameter to thickness (*D/T*) of the microballoons were used as the parameters for characterizing the microballoons (Jain et al., 2005)

$$\varepsilon = \left(1 - \frac{\rho_P}{\rho_t}\right) \times 100$$

$$\frac{D}{T} = \frac{2}{\left(1 - \frac{\varepsilon}{100}\right)^{\frac{1}{3}}}$$

where ρ_P is particle density and ρ_t is true density.

Scanning Electron Microscopy

The external and internal morphology of the microballoons were studied by scanning electron microscopy (SEM) using scanning electron microscope (Zeiss EVO® 50, UK). The samples for SEM were prepared by adhering to the microballoons on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with silver in a vacuum evaporator. The internal cavity of the microballoons was examined by cutting them in three pieces with a steel blade.

In Vitro Drug Release Studies

The drug release rate from different fractions of formulation F_9 was determined using USP type II apparatus with modification (Burns, Attwood, & Barnwell, 1994). The standard dissolution vessel was modified by the insertion of a circular stainless-steel mesh (no. 44) of similar diameter in the dissolution vessel at 72 mm from the base. This effectively divides the vessel into a lower portion, which represents approximately one-third of vessel volume, and an upper portion. A standard USP paddle is rotated immediately above the mesh to cause agitation of the dosage form. A weight of microballoons corresponding to 20 mg of famotidine was placed in the dissolution vessel and the sieve was placed. Dissolution medium (phosphate buffer pH 2.50, 900 mL) with 0.02% (wt/vol) tween 20 maintained at 37 ± 0.5°C was than filled in the dissolution vessel and stirred at 50 rpm. Aliquot samples were withdrawn at every hour till 8 h and the samples analyzed spectrophotometrically at 265 nm.

Modification of the Optimized Batch

The microballoons of famotidine were prepared with Eudragit® S100 alone and in combination with Eudragit® L100-55 (EL100-55), Eudragit® L100 (EL100), and Ethyl cellulose (EC) in a ratio of 9:1. The different formulations were than evaluated for percentage buoyancy and in vitro drug release study. Additionally, the release of f_1 fraction of F_9 formulation in pH 2.50, 4.50, 6.50, and 7.40 were studied and compared.

Interaction Studies of Optimized Formulation

The optimized formulation was analyzed for any interaction between the drug and the formulation ingredients by UV spectrophotometry and X-ray diffraction studies. The drug and optimized formulation were dissolved in DMF and the polymer was dissolved in ethanol and made up the volume to 10 ml with phosphate buffer pH 2.5 and the spectra were recorded in the Ultra violet range of 200–400 nm and then analyzed. X-ray diffraction analysis for pure famotidine, polymer mixture, and optimized formulation was done by X-ray powder diffractometry (PW 3040/60X'Pert PRO, Netherlands). The X-ray diffraction patterns were recorded automatically using Cu Kα radiations (λ = 1.5405980 Å), a current of 30 mA, and a voltage of 40 kV. The samples were analyzed over the 5–40 *2θ* range with a scan step

size of 0.02 and time per step of 0.50 s. The recorded diffraction patterns were evaluated for interaction, if any.

Statistical Analysis

In vitro drug release of famotidine from microballoons, prepared with different polymers, was statistically analyzed by two-way analysis of variance (ANOVA). Statistically significant differences between in vitro drug releases of formulations were defined as $p < .05$ (Bolton, 1997).

RESULTS AND DISCUSSION

CCD used for response surface optimization of method for preparation of microballoons of famotidine as CCD is an effective second-degree design that combines the advantages of factorial design and axial design and ascertains the possibility of curvature in the response. Thus, formulations F_1–F_{15} were prepared according to CCD and evaluated for dependent variables—shape, percentage encapsulation and percentage buoyancy, and the data are recorded in Table 2. F_2–F_6 and F_8 could not be formulated, as the experimental conditions did not favor formation of microballoons. F_9 and F_{13}–F_{15} exhibited buoyancy of more than 80% with encapsulation efficiencies of 22.89, 18.55, 9.43, and 19.40%, respectively. The F_9 formulation that showed maximum percentage encapsulation was selected as optimized formulation keeping in view of the fact that higher the encapsulation efficiency lower will be the dose size. F_1, F_7, and F_{10}–F_{12} were rejected based on low values of percentage buoyancy and percentage encapsulation. On this basis, the optimized experimental conditions for preparation of famotidine microballoons were identified as drug : polymer ratio of 1:8 in ethanol : dichloromethane ratio (1:1) at pH 2.0.

TABLE 2
Observation Table of Various Formulations for Dependent Responses

Formulation Code	Shape	Percentage Buoyancy	Percentage Encapsulation
F_1	Spherical	75.8	1.26
F_2[a]	–	–	–
F_3[a]	–	–	–
F_4[a]	–	–	–
F_5[a]	–	–	–
F_6[a]	–	–	–
F_7	Spherical	79.5	2.28
F_8[a]	–	–	–
F_9	Spherical	87.0	22.89
F_{10}	Spherical	77.4	12.54
F_{11}	Spherical	57.6	9.30
F_{12}	Spherical	77.6	2.31
F_{13}	Spherical	96.6	18.55
F_{14}	Spherical	93.0	9.43
F_{15}	Spherical	81.2	19.40

[a]Formulation could not be formed.

At pH 5.0, the microballoons were not formed because the polymer was precipitated out as very fine particles. It is suggested that the drug : Eudragit® S100 ratio should be kept at 1:8, as at higher polymer concentrations (1:10 and 1:14), ethanol was not sufficient to solubilize the polymer and led to aggregation of the polymer on addition to poly vinyl alcohol (PVA) solution. However, higher levels of ethanol supported formation of microballoons when the drug : polymer ratio was at higher levels as observed for formulation F_7. Furthermore, a drug : polymer ratio less than 1:8 was insufficient to produce spherical shaped microballoons (F_3, F_4). It was also observed that the ethanol : dichloromethane (E : D) ratio affected the shape and rigidity of microballoons and a ratio of 1:1 yielded spherical and rigid microballoons, whereas in 0.5:1 and 2:1 ratios, microballoons could not be not formed. It is suggested that as Eudragit® S100 is soluble in ethanol, thus the concentration of ethanol will have a definite role in formulation. In a ratio of E : D, 0.5:1 Eudragit was insufficiently soluble to produce spherical shaped microballoons and in 2:1 ratio polymer was completely soluble in ethanol and could not be solidified in aqueous phase to form spherical shape floating microballoons. The mechanism of microballoon formation is the ethanol : dichloromethane solution with the drug and polymer when poured into aqueous solution with stirring was finely dispersed into discrete droplets forming an o/w type emulsion. As the stirring continued, all ethanol diffused out of the droplets into the aqueous phase in contrast to dichloromethane that partially resided in the droplets. Evaporation of dichloromethane formed an internal cavity in the microsphere of the polymer with the drug that on aspiration, left water filled microspheres. On drying, the microspheres overnight at room temperature resulted in formation of microballoons.

In an attempt to increase the percentage encapsulation of formulation F_9, DMF was added to drug polymer mixture, as famotidine is not soluble in the mixture of ethanol and dichloromethane used for preparation of microballoons. A quantity of 0.25 mL per 40 mg of famotidine was used and it was observed that on addition of DMF, the percentage encapsulation increased from 22.89 to 49.47% thus improving the process. However, the drug content determination was not reproducible as the particle distribution of microballoons was in a wider range. To achieve reproducibility in drug content determinations, optimized formulation F_9 was subjected to fractionation and three different fractions were collected in size ranges 1,000–2,000, 710–1,000, and 355–710 μm. All the three fractions were evaluated for variable parameters such as bulk density, tapped density, particle density, hausner's ratio, percentage porosity, D/T ratio, percentage buoyancy, and drug content (Table 3). The particle density, measured by liquid displacement method, ranged from 0.0778 to 0.0817 g/cm^3, which is less than 1.004 g/cm^3 (Vyas & Khar, 2002), the specific

TABLE 3
Evaluation Parameters of Fractionated Optimized Formulation (F_9)

Parameters	(F_1) 1000–2000 μm	(F_2) 710–1000 μm	(F_3) 355–710 μm
Bulk density (g/cm^3)	0.098	0.097	0.0819
Tapped density (g/cm^3)	0.099	0.098	0.0847
Particle density (g/cm^3)	0.0817	0.0796	0.0778
Hausner's ratio	1.010	1.010	1.034
Percentage porosity	90.66	90.99	91.11
D/T ratio	4.373	4.425	4.445
Percentage buoyancy	92.5	89.6	77.6
Drug content (mg/10 mg)	0.9428	1.0651	0.4967

gravity of the gastric fluid, substantiating the buoyant properties of the microballoons. The Hausner's ratio in the range of 1.010–1.034 indicated good flow property. The microballoons floated instantaneously on introduction into the test media displaying zero lag time. Percentage buoyancy for fraction f_1 was found to be highest in comparison with other two fractions but drug content was highest for fraction f_2. In fraction f_1, Eudragit® S100 was present in higher amount as compared with fraction f_2, resulting in a higher value for percentage buoyancy for fraction f_1. The percentage buoyancy is a factor of polymer concentration in the wall of the microballoons, and consequently, D/T ratio becomes a significant parameter for defining the thickness of the wall of microballoons. D/T ratio and percentage porosity increased as the size range decreased, and this could be interpreted as—a decrease in size range resulted in a decrease in the thickness of wall and hence the rigidity, which consequently affected percentage buoyancy at the end of 8 h. This possibly explained the decrease in buoyancy of microballoons of smaller size range. The porosity values of more than 90% and D/T ratio greater than 4 proved a high cavity volume within the microballoons in all size ranges.

The buoyancy test was carried out to investigate the floatability of the prepared microballoons. The floating ability differed according to the formulation tested and the medium used. Fraction f_1 exhibited maximum floating ability (92.5%) till the end of 8 h in simulated gastric fluid pH 2.0 containing tween 20 (0.02%, wt/vol). It is suggested that tween 20 counteracted the downward pulling at the liquid surface by lowering surface tension because of relatively high surface tension of simulated gastric fluid that causes decrease in surface area at the air fluid interface (Jain et al., 2005).

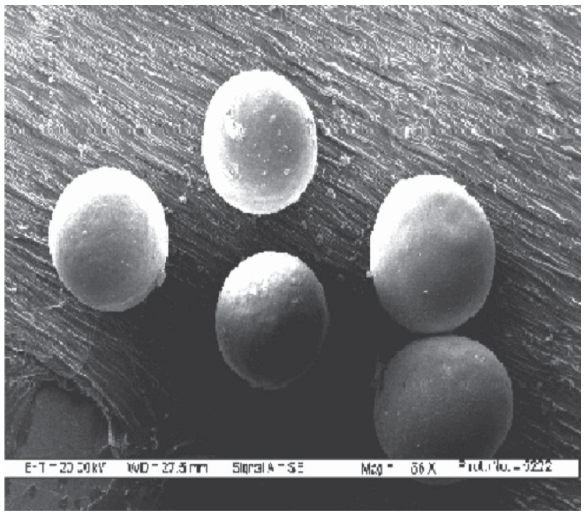
The microballoons of famotidine were predominantly spherical (Figure 1A) in appearance, which was conformed in SEM photomicrographs. The surface (Figure 1B) was observed to be smooth with numerous depressions that are expressions of evaporation of water, ethanol, and dichloromethane. The cavity formed is clearly visible (Figure 1C) in the cross-sectional view of the microballoons.

In vitro drug release studies were carried out for f_1, f_2, and f_3 using mesh designed USP type II-modified apparatus. The apparatus is suggested to overcome a number of shortcomings and drawbacks of USP type II conventional apparatus such as adherence of dosage form to the paddle shaft or sample withdrawn aids (pipets), incomplete exposure to the dissolution medium and failure to mimic in vivo conditions. The fraction f_1 showed a higher release (82.99%) in 8 h as compared with f_2 and f_3 fractions (Figure 2). Thus, f_1 fraction was selected as optimized fraction on the basis of release profile and floating behavior and used for further studies to obtain zero order release profile.

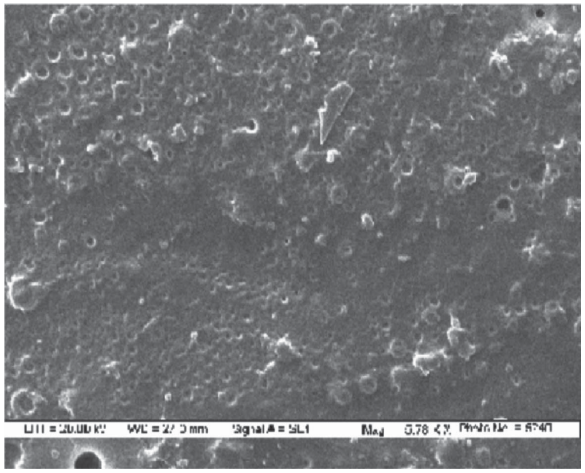
The release kinetics of fraction f_1 did not follow the zero order release and exhibited Hixon Crowell fitting (r = .9935). To achieve the zero order release, microballoons were attempted with variable polymer combinations such as ES100 in combination with EL100-55, EL100, and EC in 9:1 ratio. Hydroxy propyl methyl cellulose (HPMC) was rejected on the basis of drug excipient compatibility screening carried out by storing the samples for 15 days at 55°C in the presence of water (0.45%, wt/wt) as a worst case. HPMC showed physical incompatibility (discoloration and caking) and chemical incompatibility fourier transform infra red (FTIR) with famotidine whereas the drug displayed no incompatibility with other polymers (data not shown). Microballoons prepared with ES100:EL100-55 in 9:1 ratio showed highest release (95.28%) at the eighth hour with lowest percentage buoyancy whereas those prepared with ES100:EC (9:1) showed lowest release (48.34%) with highest percentage buoyancy (Figure 3). This may be attributed to hydrophobic nature of EC that was poorly penetrable by the medium, whereas EL100-55 facilitated penetration of the medium through the surface of the microballoons resulting in higher release that followed Peppas model (r = .9932).

To improve percentage buoyancy and the order of release of the formulation made with ES100:EC (9:1), the ratio was manipulated to ES100:EC (9.5:0.5) and an increase from 71.5 to 84.2% was observed for percentage buoyancy (Table 4), whereas the percentage release remained almost same (94.73%) and followed zero order kinetics (r = .9959). The

(A)



(B)



(C)

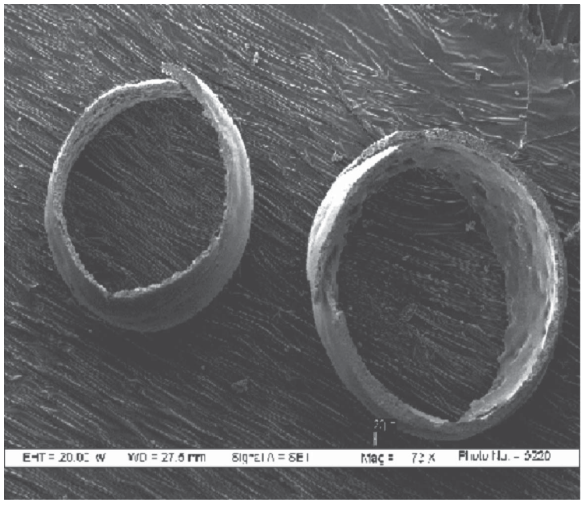


FIGURE 1. (A–C) Scanning electron micrographs of the whole and cross-section of optimized formulation.

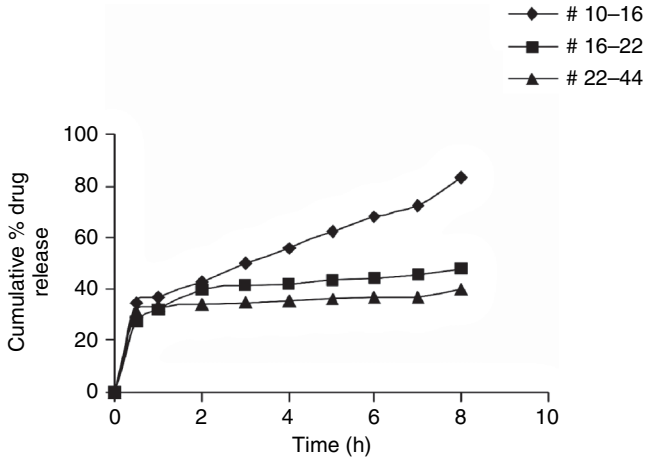


FIGURE 2. Cumulative percentage drug release from fractionated microballoons of F_9 (optimized formulation) in phosphate buffer pH 2.5 containing 0.02% (wt/vol) tween 20 using mesh-designed modified USP type II apparatus.

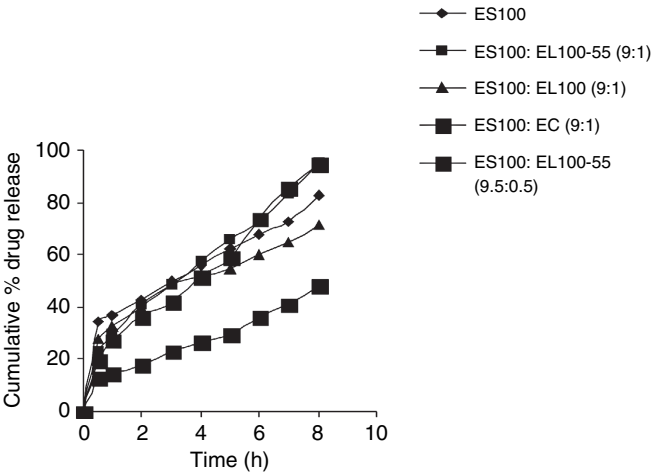


FIGURE 3. Cumulative percentage drug release from optimized fractionated microballoons prepared with different polymers in phosphate buffer pH 2.5 containing 0.02% (wt/vol) tween 20 using mesh-designed modified USP type II apparatus.

cumulative percentage drug release profile when subjected to model fitting using PCP disso software v 2.08, Pune, India, indicated that the release profile of the drug from the microballoons could be controlled by use of different polymers combinations. On application of two-way ANOVA, a significant difference was observed between the in vitro drug release profiles of famotidine from the microballoons prepared with different polymers at 95% confidence interval ($p < .05$) as the calculated F-value was found to be greater than the tabulated value substantiating the role of release-controlling polymers. On the basis of release profiles, the polymer combination ES100:EL100-55 prepared in 9.5:0.5 ratios exhibited maximum drug release in zero order fashion and hence was selected as the final optimized formulation.

The release of fraction f_1 was studied in pH 2.5, 4.5, 6.5, and 7.4 (Figure 4). In the fed state, gastric pH ranges from

TABLE 4
Percentage Buoyancy and *r*-value for Model Fitting on Drug Release form f_1 Fraction using Variable Polymer Ratio

Polymer Used	Percentage Buoyancy	*r*-Value				
		Zero Order	First Order	Matrix	Peppas	Hixon Crowell
ES100	92.5	.9844	–.9891	.9887	.9712	–.9935
ES100: EL100-55 (9:1)	71.5	.9617	–.9727	.9873	.9932	–.9801
ES100:EL100 (9:1)	85.2	.9836	–.9953	.9960	.9911	–.9960
ES100: EC (9:1)	95.6	.9940	–.9923	.9749	.9653	–.9939
ES100: EL100-55 (9.5:0.5)	84.2	.9959	–.9448	.9753	.9829	–.9708

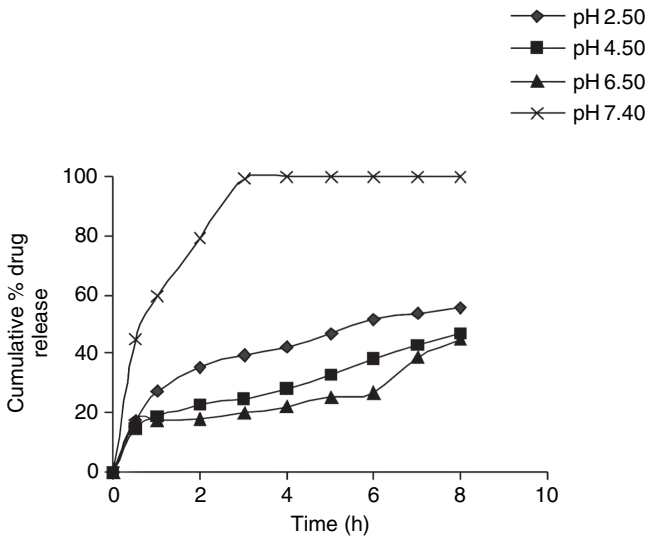


FIGURE 4. Cumulative percentage drug release from optimized fractionated microballoons of F_9 formulation in different dissolution mediums (pH 2.5, 4.5, 6.5, and 7.4) using mesh-designed modified USP type II apparatus.

more than pH 2.0 to pH 6.5 (Arora et al., 2005); therefore, pH 2.5 and 6.5 were selected as extreme fed state gastric pH whereas pH 4.5 was taken as intermediate fed state gastric pH and pH 7.4 represented the intestinal pH. At the end of 8 h at pH 2.5, fraction f_1 showed higher release (55.86%), and release decreased as the pH increased to 6.5 (44.09%). The reduction in release may be attributed to the basic nature of famotidine (pK_a 6.89) that showed higher solubility at lower pH values. At intestinal pH (7.4), microballoons showed initial burst release (44.70%) within 30 min and were completely dissolved within 3–4 h as Eudragit® S100 is an enteric coating polymer that gets dissolved at pH 7.0 because of ionization of carboxylic acid group, thus allowing penetration of solvent and liberation of the drug. This indicated that there should be not be any cumulation of microballoons or polymer in the body as no residue could be observed visually at the end of dissolution. Thus, it can be concluded that microballoons of famotidine release the drug in a zero order pattern till 8 h thereafter as the system transits to intestine the residual famotidine if any should be released, leading to an increase in bioavailability.

UV spectroscopy and X-ray diffraction studies were carried out to ascertain that the processing conditions have not led to any interaction between the drug and the polymer in the optimized formulation. The UV absorption spectra for pure drug and optimized formulation (stored for 30 days at room temperature) exhibited absorption maxima at 265 nm clearly indicating absence of any degradation of famotidine in the presence of polymers or because of processing conditions. The XRD spectra (Figure 5A–D) of pure famotidine, polymer mixture, physical

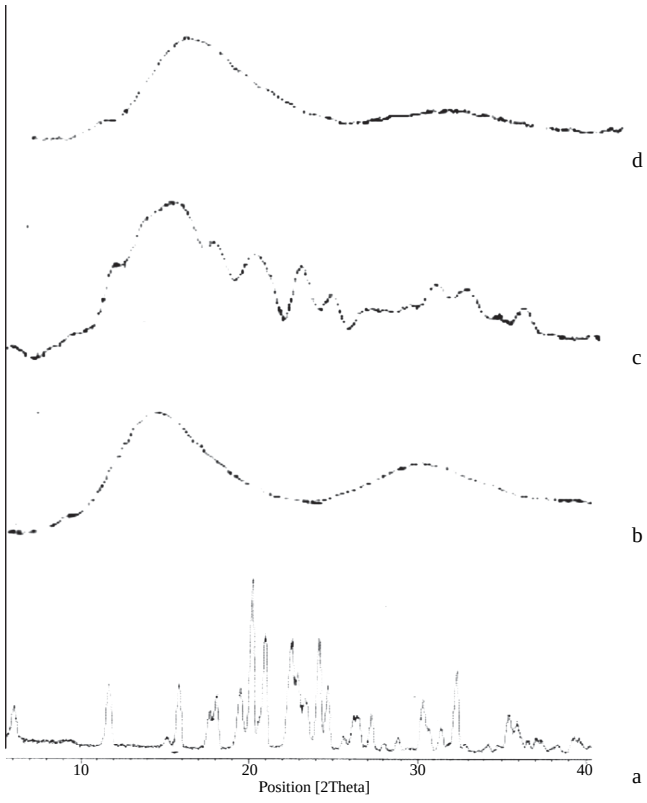


FIGURE 5. X-ray powder diffraction pattern. (A) Pure famotidine, (B) Eudragit S100, (C) Physical mixture [drug : polymer mixture (Eudragit S100 : Eudragit L100-55, 9.5:0.5) in 1:8 ratio], and (D) Optimized formulation.

mixture, and optimized formulation revealed the disappearance of the crystalline form of famotidine (pure form) in the optimized formulation indicating that the drug was present either in amorphous form or as solution in the polymeric matrix. This was further confirmed by the similarity in the spectra of formulation with that of the spectrum obtained for polymer.

CONCLUSION

The floating microballoons of famotidine were designed and successfully prepared by modified emulsion solvent diffusion method. Famotidine (H_2 antagonist) was enclosed in the shell of microballoons containing enteric acrylic polymers such as Eudragit® S100 forming a matrix-like structural wall. A drug : polymer ratio (1:8) and ethanol : dichloromethane ratio (1:1) favored buoyancy and encapsulation. Fractionation of selected formulation (F_9) and its modification by use of polymer combinations resulted in the zero order release profile. Microballoons prepared with Eudragit® S100 : Eudragit® L100-55 in a ratio of 9.5:0.5, in a size range 1–2 mm exhibited highest release with zero order pattern and was selected as optimized formulation. Thus, this approach provides an opportunity and potential for the development of a gastroretentive drug delivery system for peptic ulcer in the stomach by maximizing the bioavailability and improving the drug therapy.

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