Original Research Article

Formulation development and *in vitro* evaluation of gastroretentive hollow microspheres of famotidine

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Abstract

Background: The main aim of this study was to develop a gastroretentive, multiple-unit floating drug delivery system for a drug which is poorly absorbed from the lower gastrointestinal tract. Such a dosage form may provide an extended retention of drug in the upper gastrointestinal tract resulting in enhanced absorption and improved bioavailability. **Materials and Methods:** Microspheres were prepared by the emulsion solvent diffusion method. Four different ratios (1:1, 1:2, 1:3, and 1:4) from each polymer, i.e., Eudragit RL 100 (E1–E4) and cellulose acetate (C1–C4) were prepared. **Results:** Hollow microspheres were characterized by particle size using optical microscopy. The *in vitro* release data obtained for the formulations E1–E4 and C1–C4 showed good entrapment efficiency, good percentage buoyancy, and prolonged drug release. The *in vitro* drug release showed the highest regression coefficient values for Higuchi's model, indicating diffusion to be the predominant mechanism of drug release. The surface and cross-sectional morphology of the formulations E1-A and C1-A were determined using scanning electron microscopy. **Conclusions:** Thus, prepared floating hollow microspheres of famotidine may prove to be potential candidates for the multiple-unit drug delivery device adaptable for any intragastric condition.

Key words: Cellulose acetate, emulsion solvent diffusion, Eudragit RL 100, Higuchi's model, scanning electron microscopy

INTRODUCTION

An effective drug therapy not only depends on the inherent therapeutic activity of the drug molecule but also the efficiency of its delivery at the site of action. Drug absorption at the desired rate means, first, to reach the effective plasma level within an acceptable short time period, second, to avoid an overshoot in the case of rapidly absorbed drugs, and third, to maintain effective plasma levels over the desired time period.[1] Oral drug administration has been the predominant route for drug delivery. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. The reasons for this are essentially physiological and usually affected by the GI transit of the form, especially its gastric residence time (GRT), which appears to be one of the major causes of the overall transit time variability.[2-6]

Gastroretentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged periods. As the system floats over gastric contents, the drug is released slowly at a desired rate resulting in increased gastric retention with reduced fluctuations in the plasma drug concentration. When microspheres come in contact with gastric fluid, the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However, a minimal gastric content is needed to allow proper achievement of buoyancy.[7,8]

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MATERIALS AND METHODS

Materials

Famotidine, Eudragit RL100, and cellulose acetate was obtained as a gift sample from Madras Pharmaceuticals, Chennai. Glyceryl monostearate was purchased from Loba Chemie Pvt. Ltd.,

Mumbai. Ethyl acetate was purchased from Paxmy Specialty Chemicals, Chennai. All other chemicals and reagents used were of analytical grade.

Methods

Preparation of famotidine's floating hollow microspheres using Eudragit RL 100

Microspheres were prepared by the emulsion solvent diffusion method.[9] Four different ratios [E1 (1:1), E2 (1:2), E3 (1:3), E4 (1:4)] of floating hollow microspheres of famotidine were prepared by using Eudragit RL 100 as the polymer. Calculated quantities of Eudragit RL 100 and glyceryl monostearate were dissolved in 20 ml of a mixture of ethanol and dichloromethane (1:1) to get a homogenous polymer solution [Table 1]. Famotidine was dispersed uniformly in the polymer solution and then it was poured slowly into 200 ml of 0.75% w/v polyvinyl alcohol in distilled water. The emulsion formed was stirred continuously for 2 h using a propeller-type agitator at 1500 rpm. The temperature was maintained at 40°C. The finely dispersed droplets of the polymer solution of drug were solidified in an aqueous phase via the diffusion of the solvent, leaving the cavity of microspheres filled with water. Hollow microspheres formed were filtered using a nylon cloth and washed repeatedly with distilled water.

Preparation of famotidine's floating hollow microspehers using cellulose acetate

Four different ratios [C1 (1:1), C2 (1:2), C3 (1:3), C4 (1:4)] of floating hollow microspheres of famotidine were prepared using cellulose acetate. They were prepared by same procedure as that for Eudragit RL 100. The solvent system used was acetone and ethyl acetate in a ratio of 1:1 [Table 2].

Identification of drug by infrared spectra

The infrared (IR) spectrum of famotidine in KBr dispersion was analyzed using ABB Bomen model MB104 Fourier transform IR spectrophotometer. From the IR spectrum obtained, interpretations were made and compared with those of standard.

The IR spectrum of the drug sample was found to comply with that of standard famotidine USP. The IR spectra of famotidine are shown in Figure 1[(a) 2000–500/cm and (b) 4000–2000/cm] and interpretations are given in Table 3.

Table 1: Formulation of floating hollow microspheres, E1–E4, of famotidine

Ingredients	Quantity			
	E1 (1:1)	E2 (1:2)	E3 (1:3)	E4 (1:4)
Famotidine	500 mg	250 mg	250 mg	250 mg
Eudragit RL 100	500 mg	500 mg	750 mg	1000 mg
Glyceryl monostearate	250 mg	250 mg	375 mg	500 mg
Ethanol: dichloromethane (1:1)	20 ml	20 ml	20 ml	20 ml
Polyvinyl alcohol (0.75% w/v)	200 ml	200 ml	200 ml	200 ml

Table 2: Formulations of famotidine's floating hollow microspheres, C1–C4

Ingredients	Quantity			
	C1 (1:1)	C2 (1:2)	C3 (1:3)	C4 (1:4)
Famotidine	500 mg	250 mg	250 mg	250 mg
Cellulose acetate	500 mg	500 mg	750 mg	1000 mg
Glyceryl monostearate	250 mg	250 mg	375 mg	500 mg
Acetone: ethyl acetate (1:1)	20 ml	20 ml	20 ml	20 ml
Polyvinyl alcohol (0.75% w/v)	200 ml	200 ml	200 ml	200 ml

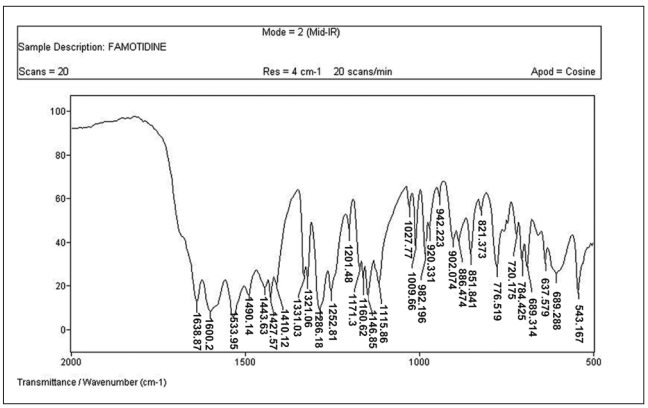

Figure 1a: IR spectrum of famotidine (500-2000 cm^{-1})

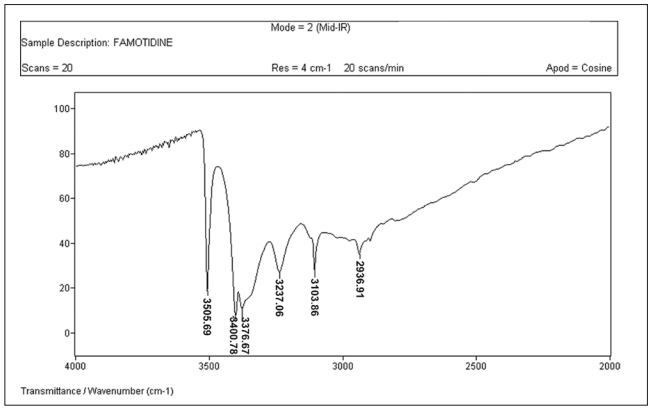

Figure 1b: IR spectrum of famotidine (2000-4000 cm^{-1})

Drug excipients' compatibility study

Each polymer used in the formulation was mixed with the drug at levels similar to those of the realistic with respect to the final dosage form. Drug–polymer mixtures were stored at 40°C and 75% relative humidity (RH). After 1 and 2 months, each mixture was tested for its stability by physical observation and by Fourier transform infrared spectroscopy. The IR spectra of the physical mixtures containing the drug and polymer in various ratios show similar spectra as obtained for famotidine's pure sample. Therefore, the active molecule is not altered by the addition of polymer substances. This study helps in assuming the stability of the drug and in further development of the dosage form [Figures 2-5].

Table 3: Interpretation of the IR spectrum of famotidine

Wave number (per cm)	Type of vibrations (groups)
3505.69	N-H stretching (amides)
3376.67 3237.06	N-H asymmetric (sulfonamide) symmetric vibration
3103.86 2936.91	C-H stretching (alkene)
1331.03 1321.06	Asymmetric (– SO_2 stretching vibration)
1171.3 1160.62	Symmetric (– SO_2 stretching vibration)
902.074	S-N stretching

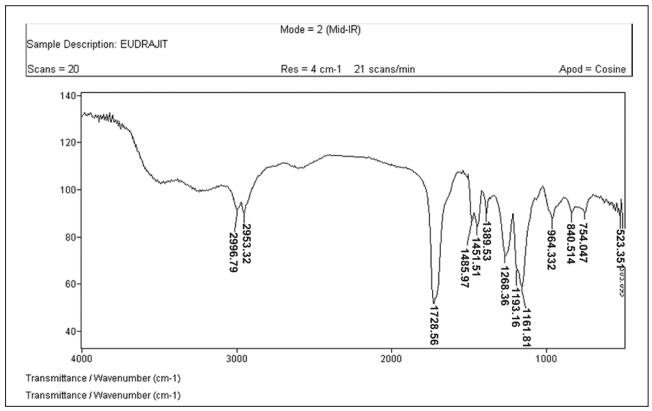

Figure 2: IR spectrum of Eudragit RL 100

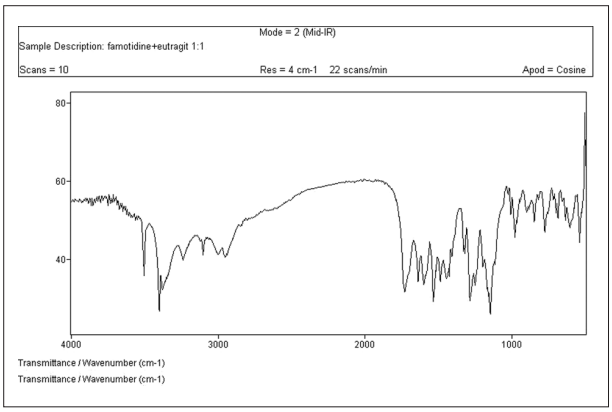

Figure 3: IR spectrum of famotidine + Eudragit RL 100 (1:1)

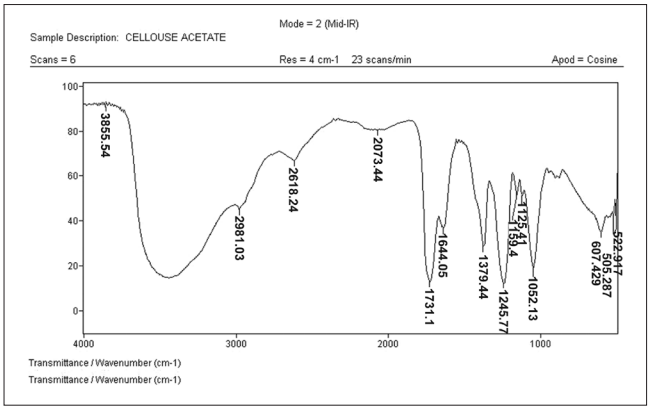

Figure 4: IR spectrum of cellulose acetate

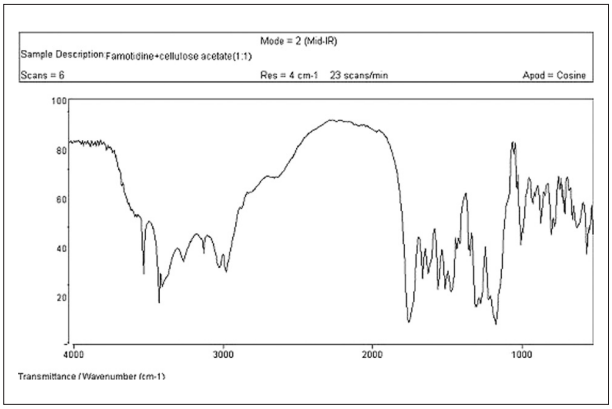

Figure 5: IR spectrum of famotidine + cellulose acetate (1:1)

Characterization of microspheres

Particle size

The size distribution in terms of $d_{(avg)}$ of microspheres of formulations E1–E4 and C1–C4 was done using an optical microscopic method with the help of a calibrated ocular micrometer.[10]

Entrapment efficiency

To determine the entrapment efficiency, 50 mg of microspheres was taken in a 50 ml standard flask; 10 ml of methanol was added for solubilization and the mixture was made up to the volume with distilled water. The drug content was determined by measuring the absorbance at 265 nm using Shimadzu UV 1601 spectrophotometer.[11]

The percentage drug entrapment efficiency of microspheres was calculated by using the following formula:

$$\%\text{Entrapment efficiency} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

Buoyancy percentage

The floating behavior of hollow microspheres was studied in a USP XXIV dissolution apparatus (Type II) by spreading the microspheres (300 mg) on a 0.1 mol/L HCl containing 0.02% tween

80 as a surfactant. The medium was agitated with a paddle rotating at 100 rpm and maintained at 37°C. After 12 h, both the floating and the settled portions of microspheres were collected separately. The microspheres were dried and weighed. The buoyancy percentage was calculated using the following formula:[12]

$$\%\text{Buoyancy of microspheres} = \frac{\text{Weight of buoant microspheres}}{\text{Initial weight of buoyant microspheres}} \times 100$$

In vitro drug release study

The release rate of famotidine from microspheres was determined using USP dissolution testing apparatus I (basket type). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5°C, at 100 rpm.[9] Withdrawn samples (5 ml) were analyzed spectrophotometrically at 265 nm. The volume was replenished with the same amount of fresh dissolution fluid each time to maintain the sink condition. All experiments were performed in triplicate. Linear regression was used to analyze the *in vitro* release mechanism.[13]

Mechanism of drug release

The *in vitro* data were treated according to zero order, first order, and Higuchi, Korsmeyer–Peppas, and Hixson–Crowell equations, and the coefficient of correlation was determined:

Zero order equation – % released = K.time

First order equation – log (fraction unreleased) = K/2.303 × time

Higuchi equation – % released = $K.time^{0.5}$

Korsmeyer–Peppas equation - %released = $K.time^{n}$

Hixson–Crowell equation – $(\text{fraction of unreleased})^{1/3} = 1 - K.time$.

Scanning electron microscopy

The external and internal morphology of the microspheres was studied by scanning electron microscopy (SEM). The samples for SEM were prepared by lightly sprinkling the microspheres on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with platinum to a thickness of about 10 Å under argon atmosphere using a gold sputter module in a high-vacuum evaporator. Afterward, the stubs containing the coated samples were placed in a scanning electron microscope (JSM-6360A, JEOL, Tokyo, Japan) chamber. The samples were then randomly scanned and photomicrographs were taken at the acceleration voltage of 15 kV to investigate the internal morphology of hollow microspheres by laser technique.

RESULTS AND DISCUSSION

Particle size

The results indicated that the mean particle size or average diameter $d_{(avg)}$ of microspheres was in the range of 153.6–201.9μm. Cellulose acetate polymer-containing microspheres were smaller in size than Eudragit RL 100-coated microspheres [Table 4].

Table 4: Particle size of formulations E1–E4 and C1–C4

Formulations	Mean particle size (μm)[a]
E1	177.4 ± 1.914
E2	185.6 ± 1.328
E3	195.9 ± 1.318
E4	201.9 ± 2.132
C1	171.2 ± 1.818
C2	188.3 ± 2.164
C3	172.2 ± 1.154
C4	153.6 ± 1.931

Values are expressed as mean ± SD, *n* = 3.

Table 5: Drug entrapment efficiency of formulations (E1–E4 and C1–C4)

Formulation code	Entrapment efficiency (%)			Mean ± SD
	1	2	3	
E1	71.05	70.28	69.95	70.42 ± 0.56
E2	71.2	69.18	69.98	70.12 ± 1.01
E3	69.24	70.18	68.25	69.22 ± 0.96
E4	69.03	67.04	67.29	67.78 ± 1.08
C1	72.25	71.11	73.21	72.19 ± 1.05
C2	68.98	69.01	68.64	68.87 ± 0.20
C3	67.19	66.91	67.34	67.14 ± 0.21
C4	67.56	66.14	66.92	66.87 ± 0.71

Values are expressed as mean ± SD, *n* = 3

[a]Values are expressed as mean ± SD, *n* = 3

Drug entrapment efficiency

The drug content of all formulations was determined spectrophotometrically. The entrapment efficiency of formulations E1–E4 were 70.42%, 70.12%, 69.22%, and 67.78% respectively and for the formulations C1–C4 were 72.19%, 68.67%, 67.14%, and 66.87% respectively. The results show that cellulose acetate-containing microspheres showed a desirable high drug content and entrapment efficiency [Table 5].

Buoyancy percentage

The percentage buoyancies of formulations E1–E4 at the end of 12 h were found to be 69.21%, 67.24%, 66.46%, and 64.3%, and for the formulations C1–C4 at the end of 12 h were 71.23%, 65.35%, 60.14%, and 59.45%. The result indicates that with an increase in the concentration of polymers, Eudragit RL 100 and cellulose acetate decrease the floating time [Table 6]. Formulations C1 of cellulose acetate-coated microspheres and E1 of Eudragit RL 100-coated microspheres were found to be the best.

In vitro drug release

The cumulative percentage drug releases of E1–E4 at the end of

10 h were 62.53%, 50.64%, 45.86%, and 36.41%; it indicates that an increase in the concentration of Eudragit RL 100 decreases the release rate of the drug. The cumulative drug release of C1–C4 at the end of 10 h was 63.30%, 52.60%, 47.37%, and 39.42%. An increase in the concentration of cellulose acetate tends to control the release of famotidine from the formulations. The *in vitro* drug release profile for formulations E1–E4 [Table 7] and their comparisons are shown in Figure 6. The *in vitro* drug release profile for formulations C1–C4 [Table 8] and their comparisons are shown in Figure 7.

Mechanism of drug release

The data obtained for the *in vitro* release were fitted into equations

Table 6: Buoyancy percentage of formulations E1–E4 and C1–C4

Formulation code	Buoyancy (%) after 12 h			Mean ± SD
	1	2	3	
E1	70.17	69.11	68.36	69.21 ± 0.09
E2	67.15	68.05	66.52	67.24 ± 0.76
E3	66.16	67.29	65.95	66.46 ± 0.72
E4	64.29	64.64	63.99	64.30 ± 0.32
C1	71.11	70.75	71.84	71.23 ± 0.55
C2	65.34	64.61	66.1	65.35 ± 0.74
C3	59.26	59.97	61.21	60.14 ± 0.98
C4	58.86	59.12	60.37	59.45 ± 0.80

Values are expressed as mean ± SD, $n = 3$

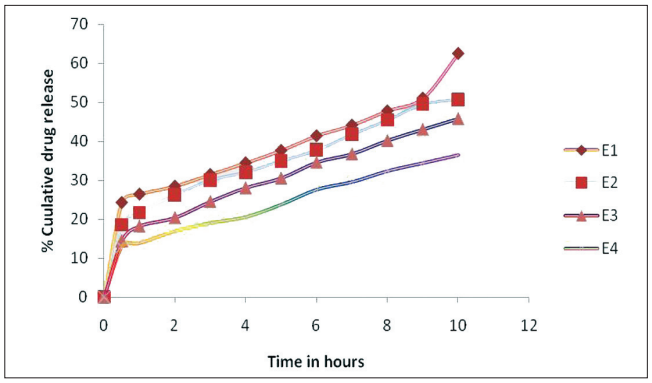

Figure 6: Comparison of the *in vitro* drug release profiles for formulations E1–E4

Table 7: *In vitro* drug release profile for formulations E1–E4

Sampling time (h)	Cumulative % drug release			
	E1	E2	E3	E4
0.5	24.32 ± 0.57	18.57 ± 0.46	14.46 ± 0.22	12.87 ± 0.85
1	26.48 ± 0.05	21.69 ± 0.29	18.28 ± 0.65	13.80 ± 0.14
2	28.51 ± 0.23	26.23 ± 0.17	20.43 ± 0.61	16.89 ± 0.26
3	31.53 ± 0.65	29.95 ± 0.62	24.57 ± 0.57	18.99 ± 0.12
4	34.49 ± 0.18	32.01 ± 0.54	28.10 ± 0.16	20.52 ± 0.82
5	37.68 ± 0.54	34.92 ± 0.23	30.58 ± 0.68	23.72 ± 0.17
6	41.45 ± 0.71	37.70 ± 0.11	34.63 ± 0.74	27.57 ± 0.66
7	44.18 ± 0.11	41.70 ± 0.98	36.80 ± 0.50	29.51 ± 0.71
8	47.84 ± 0.47	45.36 ± 0.41	40.25 ± 0.40	32.32 ± 0.52
9	51.10 ± 0.22	49.39 ± 0.12	43.08 ± 0.52	34.36 ± 0.55
10	62.53 ± 0.96	50.57 ± 0.83	45.86 ± 0.26	36.41 ± 0.32

Values are expressed as mean ± SD, $n = 3$

Table 8: *In vitro* drug release profile for formulations C1–C4

Sampling time (h)	Cumulative % drug release			
	C1	C2	C3	C4
0.5	19.74 ± 0.25	15.66 ± 0.18	13.26 ± 0.48	10.39 ± 0.32
1	22.66 ± 0.27	19.27 ± 0.38	15.88 ± 0.24	12.33 ± 0.48
2	28.00 ± 0.23	22.32 ± 0.83	18.79 ± 0.69	15.33 ± 0.71
3	33.23 ± 0.37	26.69 ± 0.14	22.15 ± 0.10	17.93 ± 0.68
4	37.73 ± 0.85	30.29 ± 0.67	26.08 ± 0.85	20.06 ± 0.15
5	41.92 ± 0.44	34.85 ± 0.64	29.62 ± 0.32	22.19 ±0. 74
6	45.30 ± 0.90	37.77 ± 0.44	34.02 ± 0.48	26.51 ± 0.49
7	49.53 ± 0.45	41.93 ± 0.62	37.17 ± 0.74	30.56 ± 0.73
8	53.78 ± 0.21	44.96 ± 0.93	40.70 ± 0.87	33.94 ± 0.73
9	57.64 ± 0.23	50.03 ± 0.18	43.25 ± 0.29	35.87 ± 0.78
10	63.30 ± 0.19	52.60 ± 0.34	47.37 ± 0.26	39.42 ± 0.51

Values are expressed as mean ± SD, $n = 3$

for the zero order, first order, and Higuchi release models. The interpretation of data was based on the value of a resulting regression coefficient. The *in vitro* drug release showed the highest regression coefficient values for Higuchi's model, indicating diffusion to be a predominant mechanism of drug release [Table 9].

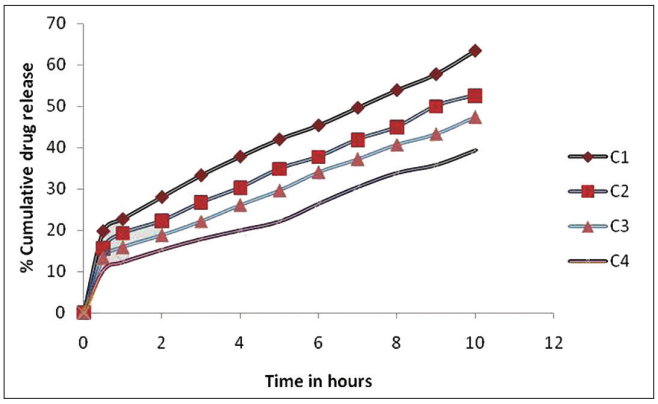

Figure 7: Comparison of *in vitro* drug release profiles for formulations C1–C4

Values are expressed as mean ± SD, $n = 3$.

Scanning electron microscopy

The surface topography [Figure 8] revealed a spherical surface and a round cavity enclosed by an outer shell composed of the drug and polymer of the refabricated formulations E1-A and C1-A. They appeared to be hollow presumably because of the rapid escape of the volatile solvent from the polymeric matrix. This hollow nature was responsible for the floating capability of microspheres in gastric fluids.

CONCLUSIONS

Floating hollow microspheres of famotidine were prepared by the emulsion solvent diffusion technique. Famotidine is a slightly water soluble drug which has good absorption in gastric pH. Famotidine suffers from poor oral bioavailability (22–66%) since it is less soluble in water and shows poor absorption in lower GIT. Hence, such a drug requires a novel gastroretentive drug delivery system which can provide an extended period of time in stomach and improve oral bioavailability. Hollow microspheres are the suitable drug delivery system for the

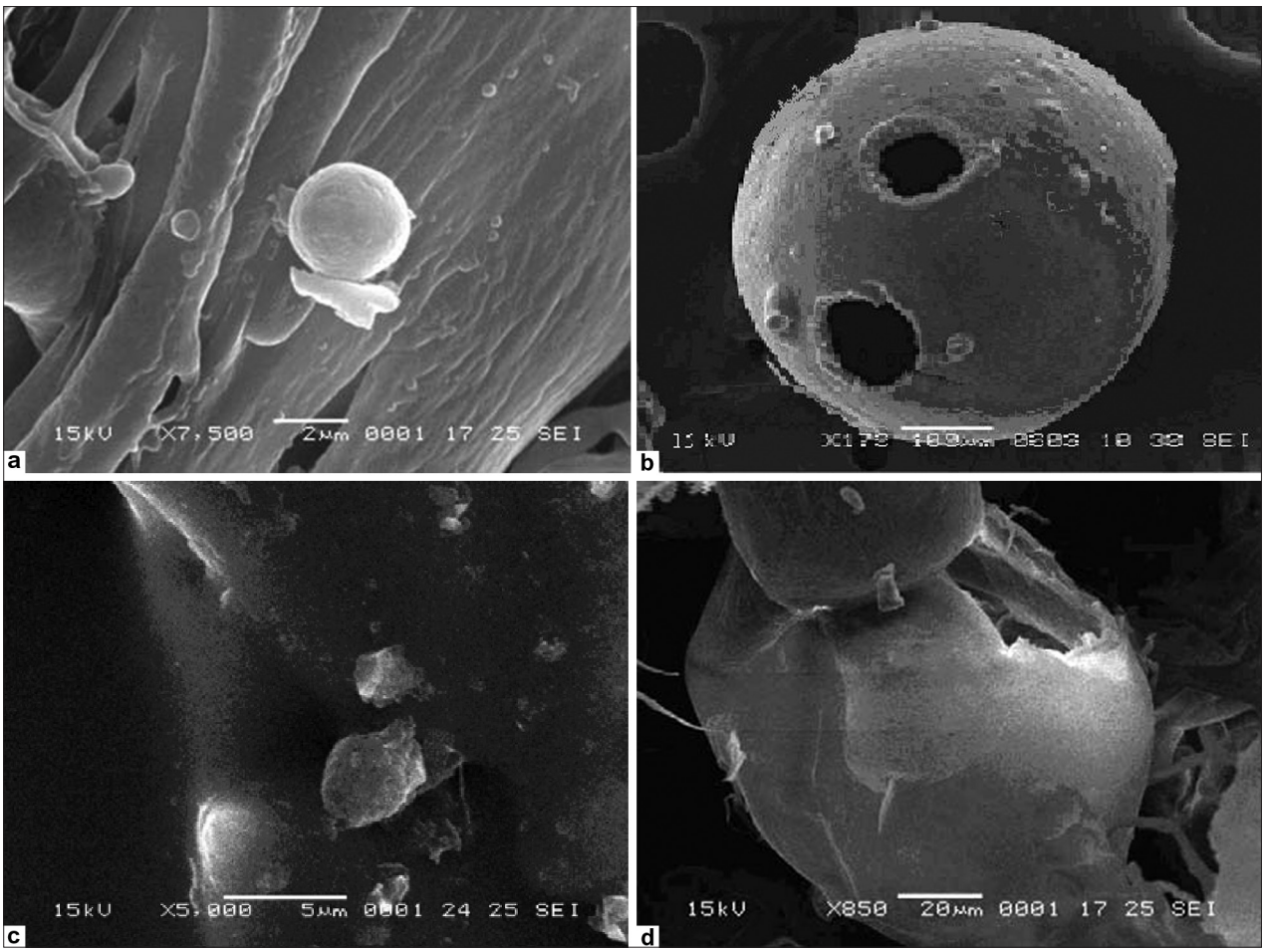

Figure 8: Scanning electron microphotographs of floating hollow microspheres of famotidine: (a) and (b) surface and cross-sectional morphology of C1-A, respectively; (c) and (d) surface and cross-sectional morphology of the formulation E1-A, respectively

Table 9: *In vitro* kinetics data for formulations E1–E4 and C1–C4

Formulation code	Coefficient of correlation (r^2)					
	0 order	1st order	Higuchi's model	Korsmeyer–Peppas equation		Hixson–Crowell equation
				r^2	*n* value	
E1	0.8585	0.9903	0.990	0.865	0.285	0.8910
E2	0.8848	0.9407	0.974	0.966	0.337	0.9253
E3	0.9175	0.9579	0.986	0.968	0.384	0.9466
E4	0.9184	0.9486	0.974	0.932	0.365	0.9398
C1	0.9238	0.991	0.995	0.865	0.285	0.9612
C2	0.9359	0.9718	0.984	0.963	0.408	0.9631
C3	0.9503	0.9764	0.982	0.956	0.434	0.9700
C4	0.9585	0.9733	0.969	0.963	0.408	0.9698

drugs that have poor absorption from lower GIT. Hollow microspheres were formed via an o/w type emulsion by rapid diffusion of volatile solvents. Hollow microspheres were studied for characterization, compatibility study, particle size and shape, *in vitro* drug release, entrapment efficiency, and buoyancy time. The formulation using Eudragit RL 100 and cellulose acetate showed a constant rate of release. Thus, prepared floating hollow microspheres of famotidine may prove to be potential candidates for a multiple-unit drug delivery device adaptable for any intragastric condition.

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