ABSTRACT

Floating microballoons of famotidine for improving the bioavailability by prolongation of gastric residence time was prepared by emulsion solvent diffusion method using Eudragit - S100 polymer in ethyl alcohol and dichloromethane organic solvent system. The response surface methodology was followed to study the influence of rate of stirring, polymer concentration and temperature on the drug entrapment and drug release features. Better entrapment and drug release was attained at lower possible polymer concentration and stirring rate at 40°C. The drug encapsulation was found to be 74 against the predicted 71 %. The formation of a sphere and hollow within the sphere was confirmed by SEM photographs. The micromeritic properties indicated better flowability and packability of the spheres. The in vitro percentage buoyancy was around 92 ± 0.18 with good floatability up to 12 h. In vitro dissolution profile showed prolonged release of drug up to 91 % over 12 h demonstrating non-Fickian diffusion mechanism of drug release. Acute oral toxicity studies as per OECD guidelines performed on wistar rats showed no mortality with normal haematological and biochemical values. Histopathogical studies also ruled out prevalence of any toxicity. Residual solvent analysis for dichloromethane and ethanol by gas chromatography was found to be within the limits as prescribed by ICH guidelines for impurities. Long term and accelerated stability studies showed the intactness of the drug without any significant change in the physical properties.

Keywords: Microballoons, central composite design, antulcer activity, residual solvent.

INTRODUCTION

The oral route offers multiple advantages like ease of administration and enormous surface area for passive diffusion of drugs. Another great advantage that the oral route offers for formulation design is it has variable and versatile physiological conditions at different parts starting from mouth thus enabling developing formulations that can selectively release the medicament for optimal absorption and therapeutic advantage. However, it is a well accepted fact that it is difficult to predict the real in vivo time of release with solid, oral controlled release dosage forms. Thus, drug absorption in gastrointestinal tract may be very short and highly variable in certain circumstances. Single unit oral formulations have no control over drug delivery leading to fluctuations in plasma drug level. These have a disadvantage of release all or nothing emptying process, while the multiple unit particulate system pass through the gastrointestinal tract to avoid the vagaries of gastric emptying and thus release the drug more uniformly. Various approaches have been worked out to improve retention of oral dosage form in the stomach e.g. floating systems, swelling an expanding system, bioadhesive systems and high density systems.

One such approach is floating microspheres (hollow microspheres). Floating microspheres are low density gastro-retentive drug delivery systems based on non-effervescent approach with sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. The drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.

Indeed, the gastric emptying of a multiparticulate floating system would occur in consistent manner with small individual variations. On each subsequent gastric emptying, such particles will spread over a large area of absorption sites, increases the opportunity for drug release profile and absorption in a more or less predictable way. Since, each dose consists of many subunits; the risk of dose dumping is reduced. Famotidine, a H2 receptor antagonist is widely used for the short term treatment of acute duodenal ulcer, gastric ulcer and gastro-oesophagal reflux. It is also indicated for maintenance therapy of duodenal ulcer and management of Zollinger-Ellison syndrome and multiple endocrine adenomas. Famotidine is rapidly but incompletely absorbed with low bioavailability (20 to 60 %) from the gastrointestinal tract. The poor bioavailability and short biological half-life of 2.5 to 4 hours suffice the development of controlled release formulation as floating microballoon.

Keywords: Microballoons, central composite design, antulcer activity, residual solvent.
MATERIALS AND METHODS

Preparation of Microballoons of Famotidine with Eudragit S-100

Microballoons were prepared by emulsion solvent diffusion method as follows:

Famotidine and Eudragit S-100 were incorporated into a mixture of dichloromethane and ethanol at room temperature separately. The polymeric suspension of famotidine was added into an aqueous solution of polyvinyl alcohol (0.75% w/v, 15 cps, and 200ml) that was thermally controlled at 40°C. The representative formulations for preparation of microballoons are given in Table 1. The above resultant suspension was stirred with a propeller type agitator at 300 rpm. The finely dispersed droplets of the polymer solution of drug were solidified in the aqueous phase via diffusion of the solvent. The dichloromethane that evaporated from the solidified droplet was removed by a fabricated aspirator flask, leaving the cavity of the microspheres filed with water. After agitating the system for one hour, the microspheres were filtered, washed repeatedly with distilled water and dried in an oven at 40°C. The representative

<table>
<thead>
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<th>Factor 1</th>
<th>Factor 2</th>
<th>Factor 3</th>
<th>Response 1</th>
<th>Response 2</th>
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<tr>
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<td>81</td>
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<tr>
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<td>400</td>
<td>500.00</td>
<td>50.00</td>
<td>97</td>
<td>83</td>
</tr>
</tbody>
</table>

Optimization

Preliminary runs were conducted to assess the impact of independent variables on the physical characteristics of microballoons. The three independent variables stirring rate, polymer concentration and temperature were maintained constant. The dependent response variables measured was the drug entrapment and drug release. Experiments were conducted in random sequence in a face-centered manner in order to evaluate the interaction

X1 - Rate of Stirring (RPM) - 200 (-1) & 800 (+1), X2 - Concentration of polymer (mgs) - 500 (-1) & 2000 (+1), X3- Temperature 25°C (-1) & 5 °C (+1).Response - Drug entrapment (Y1) and Drug release (Y2) - (dependent variables)

Physico-Chemical Properties of Microballoons

Roundness or sphericity

The morphology (outer surface and sphericity) of microballoons was examined using a scanning electron microscope (GEOL 5400, USA). Completely dried microballoons were coated with gold-palladium alloy for 45 Sec under an argon atmosphere in an ion sputter before observation.

X-Ray diffraction patterns

The drug polymer compatibility and any change in the physical form of the drug in the formulation were studied by XRD (Philips). The diffraction patterns were obtained separately for pure drug, polymer and formulation

Differential Scanning Calorimetry

Thermal analysis of famotidine, Eudragit S-100 and famotidine loaded microballoons were studied by differential scanning calorimeter (Mettler Toledo DSC, USA). Accurate amount of samples were weighed into aluminium pans and sealed. All samples were run at a heating rate of 10 °C/min over a temperature range of 25-300 °C in atmosphere of nitrogen.
Micromeritic Studies

The size of microspheres was determined using optical microscope (Olympus NWF 40X, Educational Scientific Stores, India) fitted with an ocular micrometer and stage micrometer. The images were taken in an optical microscopy to characterize the surface and for the confirmation of formation of hollow microspheres. The arithmetic mean diameter was determined with MicroLite Image software attached to optical microscope. The flow properties of microspheres were characterized in terms of angle of repose, Carr’s index and hausner’s ratio. Accurately weighed microspheres were poured gently through a glass funnel into a graduated cylinder cut exactly to 10 ml mark. Initial volume was noted. Bulk density ($\rho_b$) and tapped density ($\rho_t$) were calculated by tapping method using 10 ml measuring cylinder. Hausner’s ratio ($H_r$) and Carr’s index ($I_c$) were calculated according to the two equations given below:

$$H_r = \frac{\rho_b}{\rho_t}$$

$$I_c = \frac{\rho_{t \times \rho_b}}{\rho_b}$$

In-Vitro Buoyancy

Microspheres (100 mg) were spread over the surface of a USP dissolution apparatus type II filled with 900 ml of 0.1 N hydrochloric acid containing 0.02%w/v tween 80. The use of tween 80 was to account for the wetting effect of the natural surface-active agents in the GIT. The medium was agitated with a paddle rotating at 100 rpm for 12 h. The floating and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the microspheres that remained floating and the total mass of the microspheres.  

$$Buoyancy \% = \frac{W_f}{W_f + W_s} \times 100$$

Where $W_f$ and $W_s$ are the weights of the floating and settled microspheres. All the determinations are made in triplicate.

In Vitro Drug Release Studies

The release rate of famotidine from optimized microballoons of Eudragit S and Eudragit L was determined in a United States Pharmacopoeia XXI111 basket apparatus (Electrolab, Mumbai) in simulated gastric fluid (300 ml) pH 1.2 hrs containing Tween 20 (0.02% w/v) for 2 hrs and phosphate buffer (900 ml) pH 6.8 containing Tween 80 (0.5% w/v). The extent drug released was determined spectrophotometrically at 265 nm using Shimadzu UV-VIS 1601 in triplicate.

ANTIULCER ACTIVITY OF OPTIMIZED FORMULATIONS

The animal experiments were carried out with prior permission from the Institutional Animal ethics Committee approval (IAEC NO: MSRPC/P-08/2008).

Pyloric ligation model: The ulcer protective effect of the optimized formulations were studied as per the method of Shay et al. The ulceration is caused by accumulation of acidic gastric juice in the stomach and by this method several parameters can be estimated. In this method albino rats were fasted in individual cages for 24 h. Care was being taken to avoid Coprophagy. Control vehicle, three doses of optimized formulations and reference drug (Ranitidine 30 mg/kg) were administered by oral route. The pyloric ligation was carried out 30 minutes and 4h after the drug administration in each group animals. Under light ether anesthesia, the abdomen was opened and the pylorus was ligated. The abdomen was then sutured. They are deprived of both food and water during the post-operative period and are sacrificed at the end of 19 hours with excess of anesthetic ether. Stomach was dissected out and gastric contents subjected to analysis for volume, pH, free acidity and total acidity. The glandular portion of the stomach was opened along the greater curvature, and the severity of hemorrhagic erosions in the acid secreting mucosa was assessed on a scale of 0 to 5. Ulcer index and percentage ulcer protection was determined for all the five groups.

Mean ulcer score for each animal is expressed as Ulcer Index. The percentage protection was calculated using the formula:

$$\text{Percentage of ulcer protection} = \frac{U_t}{U_c} \times 100$$

Where $U_t$ = Ulcer index of treated group

$U_c$ = Ulcer index of the control group

Determination of free and total acidity

One ml of supernatant liquid was pipetted into a 100 ml conical flask and diluted to 10 ml with freshly prepared distilled water. Added 2 or 3 drops of Topfer’s reagent and titrated against 0.01N Sodium hydroxide until all traces of red colour disappears and the colour of the solution turns yellowish orange. The volume of alkali (0.01N Sodium hydroxide) added was noted, which corresponds to free acidity of the gastric juice. Titration was further continued with 2 to 3 drops of freshly prepared phenolphthalein solution (1% in 50% absolute ethanol) till the solution regained pink colour. Again the total volume of alkali added was noted and was taken as corresponding to the total acidity.

Acidity was expressed as:

$$\text{Acidity} = \frac{-\text{Volume of NaOH x Normality of NaOH x 100mEq/l}}{100 \ g}$$

RESIDUAL SOLVENT ANALYSIS

Residual solvents present in traces in the optimized formulations were determined as per ICH Harmonised Tripartite Guideline on Impurities: Guideline for Residual Solvents Q3C (R4). Since there is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications or other quality-based requirements. The presence of volatile solvents ethanol (Class 3) and dichloromethane (Class 2) in all the three optimized formulations was determined by Gas Chromatography; concentration limit was expressed in terms of ppm.
STABILITY STUDIES
The stability studies of the finalized formulations were designed and carried out as per ICH ‘Q1AR2’ guidelines. The optimized formulations filled in capsule were stored in vial covered with aluminium foil in order to minimize the accidental exposure of the sample to the light. The packed formulations were stored at 25 ± 2°C and 65 ± 5% RH in a stability chamber for a period of 12 months (long term storage conditions) and at 40 ± 2°C and 75 ± 5% RH for a period for 6 months (accelerated storage condition). Periodical testing of the stored samples for drug content and for any physical change was done at 3 month intervals for both the studies to ascertain the physical integrity of the drug product.

RESULTS AND DISCUSSION
The scanning electron microphotographs and optical photographs of microspheres have proved the spherical shape with hollow cavity in the sphere (Fig 3). The outer surface was found to be porous in nature. The XRD pattern of the formulation showed physical integrity of famotidine without any signs of drug polymer interaction (Figure 1). DSC thermograms of famotidine, Eudragit S-100 and FAS-D1 are shown in the Figure 2. It was clearly evident from the thermogram of FAS-D1 that the drug has not undergone any physical change being in its natural form. The drug entrapment and drug release optimization data for famotidine Eudragit S-100 was fitted to quadratic model for drug release and linear model for drug entrapment as it showed the maximum values of R2 and model sum of squares for drug entrapment. The result of DOE (design of experiment) is shown in the Table 1 with 15 batch runs. Numerical optimization solutions of famotidine eudragit S-100 hollow microsphere is indicated in Table 2, out of which FAS-D1 was selected for further studies as the desirability value was around 0.935. Summary of ANOVA results in the analysis of lack of fit and pure error of surface linear model for drug entrapment and quadratic model for drug release are summarized in Table 3. ANOVA proved that the model was significant (with a probability F value of <0.0001) and polymer concentration most significantly affected the drug entrapment as indicated by a probability F value of <0.0001 and obeyed linear model. The three-dimensional response surface graph along with the contour graph indicated that with the lower polymer concentration maximum drug release and drug entrapment could be achieved. It was observed that an increase in the ratio of drug to polymer concentration resulted in a decrease in the entrapment efficiency (Figure 4 and 5). From the numerical optimization results (Table 2), solution 1 was selected randomly as the optimized formula for the preparation of famotidine eudragit S-100 microsphere as it showed maximum drug entrapment and drug release efficiency. The influence of stirring rate, polymer concentration and temperature on drug entrapment and drug release from microspheres are shown in the Table 4. There was a considerable increase in drug entrapment and drug release from the optimized formulation over the predicted values.

Table 2: Numerical optimization solutions of famotidine eudragit S-100 hollow microsphere

<table>
<thead>
<tr>
<th>Number</th>
<th>Stirring rate (rpm)</th>
<th>Polymer Conc (mgs)</th>
<th>Temp (°C)</th>
<th>Drug release (%)</th>
<th>Drug Entrapment (%)</th>
<th>Desirability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>300.00</td>
<td>937.63</td>
<td>40.00</td>
<td>88.2766</td>
<td>71.4335</td>
<td>0.935 (FAS-D1)</td>
</tr>
<tr>
<td>2</td>
<td>300.00</td>
<td>967.62</td>
<td>40.00</td>
<td>87.7827</td>
<td>71.8614</td>
<td>0.934 (FAS-D2)</td>
</tr>
</tbody>
</table>

Table 3: Summary of ANOVA results in the analysis of lack of fit and pure error of Surface linear model for drug entrapment and Quadratic model for drug release

<table>
<thead>
<tr>
<th>Response</th>
<th>Model</th>
<th>Sum of Squares</th>
<th>F Value</th>
<th>Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Entrapment</td>
<td>Surface Linear</td>
<td>1151.70</td>
<td>31.85</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Drug Release</td>
<td>Quadratic</td>
<td>190.07</td>
<td>24.02</td>
<td>&lt; 0.0001</td>
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</table>

Table 4: Model validation chart of predicted and actual values for optimized formulations of acrylic polymers Eudragit S-100

<table>
<thead>
<tr>
<th>Observations</th>
<th>Polymer</th>
<th>RPM</th>
<th>Polymer conc. (mgs)</th>
<th>Temp (°C)</th>
<th>Drug entrapment (%)</th>
<th>Drug release (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted values</td>
<td>Eudragit S-100</td>
<td>300</td>
<td>967.62</td>
<td>40</td>
<td>71.86</td>
<td>87.38</td>
</tr>
<tr>
<td>Actual values</td>
<td>Eudragit S-100</td>
<td>300</td>
<td>1000</td>
<td>40</td>
<td>74.00</td>
<td>90.64</td>
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</table>

Table 5: Micromeritic properties of coded optimized formulations

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Mean particle size (µm)</th>
<th>Angle of repose (θ)</th>
<th>Tapped density (gm/cm³)</th>
<th>Porosity (%)</th>
<th>Hausner ratio (Hₕ)*</th>
<th>Carr index (Iₖ)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure Drug (Famotidine)</td>
<td>255.84 ± 4.56</td>
<td>53° 13’</td>
<td>0.816</td>
<td>34.8</td>
<td>1.28 ± 0.020</td>
<td>0.168 ± 0.014</td>
</tr>
<tr>
<td>FAS-D1</td>
<td>398.23 ± 44</td>
<td>36° 88’ ± 0.10</td>
<td>0.802</td>
<td>48.56</td>
<td>1.182 ± 0.017</td>
<td>0.1480.010</td>
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</table>

* Each value is ± of three independent determinations
Table 6: Comparison of various calculated parameters of the formulations with the control

<table>
<thead>
<tr>
<th>S.No</th>
<th>Treatment</th>
<th>% ulcer protection</th>
<th>Ulcer Index</th>
<th>Mean volume of gastric juice (ml)</th>
<th>pH</th>
<th>Free acidity (mEq/l/100 g)</th>
<th>Total acidity (mEq/l/100 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Control</td>
<td>------</td>
<td>4.28 ± 0.137**</td>
<td>6.516 ± 0.199**</td>
<td>1.83± 0.088**</td>
<td>57.66±2.275**</td>
<td>180.33±1.145**</td>
</tr>
<tr>
<td>2</td>
<td>Famotidine</td>
<td>70.86</td>
<td>3.033 ± 0.08 **</td>
<td>4.016 ± 0.130**</td>
<td>3.83 ± 0.071**</td>
<td>44.83±1.662**</td>
<td>134.83±1.424**</td>
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<tr>
<td>3</td>
<td>FAS-D1</td>
<td>62.68</td>
<td>2.683 ± 0.06 **</td>
<td>3.450 ± 0.092**</td>
<td>5.05 ± 0.117**</td>
<td>46.00±2.19**</td>
<td>140.66±0.843**</td>
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Values are mean ± SEM of 6 animals (n=6); Statistical comparision was performed by using ANOVA

Table 7: Residual solvent limits for optimized formulations

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<thead>
<tr>
<th>S.No</th>
<th>Formulation code</th>
<th>Prescribed limit (ppm)</th>
<th>Detected limit (ppm)</th>
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<td></td>
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<td>Ethanol</td>
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<tr>
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<td>5000</td>
<td>600</td>
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Table 8: Observations of stability test studies in real time storage conditions (25 ± 2°C and 65 ± 5 % RH)

<table>
<thead>
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<th>Formulation code</th>
<th>Drug content (%) Months</th>
<th>Particle size (µm)</th>
<th>Physical change (12 months)</th>
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<tr>
<td></td>
<td>0</td>
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<td>6</td>
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<tr>
<td>FAS-D1</td>
<td>99.36</td>
<td>99.12</td>
<td>98.78</td>
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</table>

* No significant physical change

Table 9: Observations of stability test studies in accelerated storage conditions (40 ± 2°C and 75 ± 5 % RH)

<table>
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<th>Formulation code</th>
<th>Drug content (%) Months</th>
<th>Particle size (µm)</th>
<th>Physical change (6 months)*</th>
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<td></td>
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<td>2</td>
<td>4</td>
</tr>
<tr>
<td>FAS-D1</td>
<td>99.12</td>
<td>98.12</td>
<td>96.02</td>
</tr>
</tbody>
</table>

* No significant physical change

Figure 1: X Ray diffraction patterns of famotidine, Eudragit S-100 and Formulation FAS-D1
Figure 2: DSC thermograms of famotidine, Eudragit S-100 and FAS-D1.

Figure 3: Optical (Panel A) and SEM photographs (Panel B) of optimized formulation FAS-D1 with porous outer surface and hollow cavity.
Figure 4: 3D RSM graph of famotidine hollow microsphere (FAS-D1) – Drug release

Figure 5: 3D RSM graph of famotidine hollow microsphere (FAS-D1) – Drug entrapment

Figure 6: Gas chromatogram of standard (ethanol and dichloromethane) - STANDARD
The micromeritic property of optimized formulations projects improved flowability, packability, porosity and density lesser than unity for floatation in the gastric contents (Table 5). The tapped density values were 0.816 and 0.802 g/cc respectively for drug and formulation. Optimized formulations showed better buoyancy (up to 92 %) till 12 hrs over. Eudragit S-100 (92.38 %) showed a better drug release up to 12 hours (Table 4, Figure 8). Regression analysis suggests that the release of famotidine from microballoons followed zero order with non-Fickian diffusion mechanism (Figure 9).

The percent ulcer protection of the formulations was found to be 62.68 % which is statistically significant as there was a significant reduction in the ulcer index of the formulations over the pure drug and control. The values of various pathological parameters are shown in the Table 6. The mean pH of the control was very high (1.833 ± 0.088) compared to pure drug famotidine (3.833 ± 0.071).
and found to be decreasing in the acidic pH with the mean pH of 5.05 ± 0.117 for the optimized formulations (Table 6). The mean free and total acidity of FAS-D1 was found to be 46 ± 2.19 and 140.66 ± 0.843 mEq/l/ 100 g respectively. Appreciable decline in the mean gastric juice (3.450 ± 0.092 ml) of the optimized formulation over the control and pure drug (6.51 ± 0.199 and 4.016 ± 0.130 ml) confirms the ulcer protective activity of FAS-D1.

The amount of ethanol and dichloromethane in the formulations were found be within the limits as prescribed by the ICH guideline for impurities 'Q3C for the residual solvents. It can be inferred that the formulations were safe for oral administration (Table 7). The related chromatograms of the standard and FAS-D1 are shown in Figures 6 and 7.

Long term and accelerated stability studies carried out as per ICH guidelines showed that there was no drastic changes in the drug content (not more than 5 %) as well as in the particle size. The values are presented in the Table 8 and 9 for both the studies.

CONCLUSION

The microballoons of famotidine prepared by emulsion-solvent diffusion method exhibited excellent in vitro buoyancy and zero order drug release with non-Fickian transport mechanism. The surface response central composite design methodology could be successfully employed for assessing the influence of formulation parameters on the desired response. The drug polymer concentration and stirring rate played a vital role in achieving the desirable designed product. Ulcer protection activity of the formulation was found to be superior with significant reduction in the gastric juice volume, free and total acidity and gastric pH towards alkalinity. Hence the floating hollow microspheres of famotidine prepared with acrylic polymers may provide a convenient dosage form for achieving better floating and drug release.

REFERENCES


