Formulation, *In Vitro* Characterization And Comparison Of Famotidine Loaded Effervescent Sustained Release Floating Microspheres Using Natural And Synthetic Polymers

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**Objective:** The present study was aimed to formulate and evaluate gastro retentive floating microspheres of famotidine, a H₂-receptor antagonist. The gastric retention of the drug was prolonged in order to obtain a better efficacy of the administered dose. The influence of drug:polymer ratio, type of polymer, concentration of calcium chloride on entrapment efficiency, floating ability and *in vitro* release characteristics of the drug were investigated.

**Methods:** The microspheres were prepared by ionotropic gelation technique using calcium chloride as cross linking agent, sodium bicarbonate as gas generating agent and gum ghatti, HPMC K100M and xanthan gum as release retardant polymers. Alginates are non toxic and biodegradable polymers commonly used in pharmaceutical industry. These microspheres are formulated in such a way that they remained buoyant in the stomach for a longer time. Different drug release kinetic models were applied to the different batches of formulations.

**Results:** The prepared microspheres were analyzed for their micromeretic properties, drug entrapment efficiency, *in vitro* floating ability and dissolution studies. FTIR and DSC studies have shown absence of any significant interactions between the drug and the polymers used. The yield and encapsulation efficiency was high for all the formulations. All the formulations were found to float for a period of greater than 12 hours and the release of drug was sustained. F7 showed a release of 99% of drug over a period of 12hours. SEM studies have revealed that the microspheres were uniform, spherical and discrete in nature.

**Conclusion:** Data obtained in this study concluded that floating microspheres of famotidine can sustain drug release for a period of 12 hours and showed an enhanced bioavailability. It was found that drug release followed zero order kinetics indicating that release was independent of concentration.
INTRODUCTION:
In case of humans, the average gastric emptying time ranges between 2-3h through the major absorption zones on oral administration i.e., stomach and upper part of intestine. Rapid gastro intestinal transit of the drug may lead to incomplete release and absorption resulting in reduced bioavailability and therapeutic benefit of the drug thus abolishing the effectiveness of administered dose [1, 2]. Gastro retentive drug delivery systems (GRDDS) are an important approach to overcome such a drawback and increase the gastric residence time of the drug, to target drug to specific sites and to reduce fluctuations in plasma drug concentration. GRDDS are of significance in conditions where the drug is poorly soluble in gastric pH, possess narrow absorption window, degrades at intestinal pH or in case a local and sustained action is required in the stomach [3-5].

Floating dosage forms or hydro-dynamically balanced systems are a category of GRDDS which remain buoyant in the stomach for a prolonged time period as they possess lesser density when compared to the gastric fluids. As the dosage form floats on the gastric contents, the drug is released slowly over a longer period of time at a desired rate. It retains the dosage form at the site of absorption and hence enhances its bioavailability [6, 7].

Famotidine acts by binding competitively to H₂-receptors thus blocking histamine affects. This decreases secretion of gastric acid, reduces gastric volume and acidity. The low bioavailability and shorter biological half life of the drug lead to development of a sustained release formulation for it [8].

MATERIALS AND METHODS
Materials
Famotidine, gum ghatti, calcium chloride were obtained from Yarrow Chem Products, sodium alginate, sodium bicarbonate were obtained from Finar Chemicals.
Preparation of floating microspheres
The microspheres were preparation by external ionotropic gelation method. Sodium alginate in combination with different ratios of xanthan gum, gum ghatti, HPMC K100 M (125, 250, 500mg), were considered. 1g of sodium alginate was dissolved in distilled water to form homogenous solution. The drug famotidine (500mg) was added to the polymer solution after complete mixing sodium bicarbonate (250mg) was added and the resulting dispersion was added manually drop wise into 5% w/v calcium chloride solution.
through a syringe with a needle size no.21. The added droplets were retained in the calcium chloride solution to complete the curing reaction. The microspheres were collected by the traces of liquid paraffin oil. The microspheres were dried and at hot air oven [9].

\[ \text{Percentage yield (\% yield) =} \frac{\text{Weight of the microspheres}}{\text{Total weight of the drug and polymer taken}} \times 100 \]

**Table 1: Formulation for famotidine loaded microspheres**

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Drug (mg)</th>
<th>Sodium alginate (g)</th>
<th>Xanthan gum (mg)</th>
<th>Gum ghatti (mg)</th>
<th>HPMC K100 M (mg)</th>
<th>Sodium bicarbonate (mg)</th>
<th>Calcium chloride (% w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>500</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>250</td>
<td>5</td>
</tr>
<tr>
<td>F2</td>
<td>500</td>
<td>1</td>
<td>125</td>
<td>-</td>
<td>-</td>
<td>250</td>
<td>5</td>
</tr>
<tr>
<td>F3</td>
<td>500</td>
<td>1</td>
<td>250</td>
<td>-</td>
<td>-</td>
<td>250</td>
<td>5</td>
</tr>
<tr>
<td>F4</td>
<td>500</td>
<td>1</td>
<td>500</td>
<td>-</td>
<td>-</td>
<td>250</td>
<td>5</td>
</tr>
<tr>
<td>F5</td>
<td>500</td>
<td>1</td>
<td>-</td>
<td>125</td>
<td>-</td>
<td>250</td>
<td>5</td>
</tr>
<tr>
<td>F6</td>
<td>500</td>
<td>1</td>
<td>-</td>
<td>250</td>
<td>-</td>
<td>250</td>
<td>5</td>
</tr>
<tr>
<td>F7</td>
<td>500</td>
<td>1</td>
<td>-</td>
<td>500</td>
<td>-</td>
<td>250</td>
<td>5</td>
</tr>
<tr>
<td>F8</td>
<td>500</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>125</td>
<td>250</td>
<td>5</td>
</tr>
<tr>
<td>F9</td>
<td>500</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>250</td>
<td>250</td>
<td>5</td>
</tr>
<tr>
<td>F10</td>
<td>500</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>500</td>
<td>250</td>
<td>5</td>
</tr>
</tbody>
</table>

**Compatibility studies**

**FTIR analysis**
The FT-IR spectra of prepared solid dispersions were scanned over a frequency range 4000-400 cm-1. A little quantity of sample was placed on diamond ATR and analyzed for the presence of characteristic peaks.

**Differential scanning Calorimetry**
The DSC analysis of pure drug, drug- loaded microspheres and blank microspheres without drug were carried out using to evaluate any possible drug polymer interaction. The analysis was performed at a rate 10 °C min⁻¹ from 20 °C to 30 °C temperature range under nitrogen flow of 25 ml min⁻¹ [10].

**X-Ray powder diffractometry (X-RD)**
The X-ray diffraction patterns of pure drug and the drug loaded formulations were recorded using Philips X-ray diffractometry (Ultima-III, Rigaku, Japan) with copper target to investigate the effect of microencapsulation on crystallinity of drug.

**Characterization of microspheres**

**Determination of micromeretic properties**
The microspheres were characterized by their bulk density, tapped density, compressibility index, Hausner’s ratio and angle of repose.
Estimation of drug content and entrapment efficiency
A weighed quantity of microspheres (equivalent to 100 mg of a drug) was crushed into powder and added to 100 ml of 0.1N HCl buffer. The resulting mixture was kept stirring at 2hrs and kept it over night. Then the solution was filtered through the membrane whatman’s filter and 1ml of this solution was diluted using 0.1N HCl buffer and analyzed spectrophotometrically at 265nm to get practical drug content.

\[
\text{Drug entrapment efficiency (\%)} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100
\]

Determination of particle size distribution by sieve analysis
A mechanical sieve shaker was employed for partitioning the microspheres into different size mesh. A stack of 5 numbers of standard stainless steel sieves (Ajantha sieves, Chennai, India) were placed in a sequence of their increasing pore size (bottom to top) over a sieve shaker. Accurately 10g of microspheres from different formulated batches were loaded on the top most sieves. Then the sieve shaker was operated for a 10 min period. The sieves were shaken for a period of 10 min. Microspheres retained over each sieve were collected and weighed accurately [11].

Surface morphology
Scanning electron micrographs of famotidine microspheres and pure drug powder were taken using a scanning electron microscope (JSM 6360, Joel make, UK). Samples were fixed on an aluminium stub with conductive double side adhesive tape.

Total floating time and floating lag time
The time taken for microspheres to emerge on surface of medium after they are added in to the medium is called Floating Lag Time (FLT) are Buoyancy Lag Time (BLT). Total duration of time for which the microspheres remain buoyant is called Total Floating Time (TFT). The test was performed using 250ml glass beaker filled with 0.1N HCl. The time required for the microspheres to rise to the surface of the medium and duration for which the formulation constantly floated on the medium were noted as floating lag time and total floating time respectively.

In vitro floating ability
Fifty milligrams of microspheres were placed in 100 ml simulated gastric fluid (SGF, pH 1.2) containing 0.02% Tween20 and the contents were stirred at a speed of 100 rpm on a magnetic stirrer. After 8 h, the floating and settled microspheres were collected separately, dried at 40 C and weighed [12].

\[
\text{Buoyancy (\%)} = \frac{\text{Weight of the floating microspheres}}{\text{weight of the floating microspheres} + \text{Weight of the settled microspheres}} \times 100
\]

In vitro drug release studies
Dissolution studies of Famotidine loaded microspheres were carried out for a period of 12 hrs using basket type dissolution apparatus (USP-XXIII Electrolab, Mumbai) containing 900 ml of simulated gastric fluid (0.1N HCl) maintained at 37±0.5 ⁰C and speed of agitation at 50 rpm. Accurately weighed quantity of microspheres was added to the dissolution medium and 5 ml aliquots were withdrawn at preset time intervals. The
withdrawn volume of dissolution fluid was replaced by an equal volume of fresh pre warmed dissolution medium. After suitable dilutions, the samples were analyzed spectrophotometrically at 265 nm [13].

**Kinetics of drug release**

Mathematical modeling is a significant approach in optimization of a formulation because its development utilizes comprehension of all the parameters affecting drug release kinetics. The various model dependent approaches include zero order, first order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas.

\[
Q_t = Q_0 + k_0 t \quad (1)
\]

\[
\log Q = \log Q_0 - kt/2.303 \quad (2)
\]

\[
Q = k_{HC} t^{1/2} \quad (3)
\]

\[
Q_0^{1/3} - Q^{1/3} = kt \quad (4)
\]

\[
M_t / M_\infty = k t^n \quad (5)
\]

Where \(Q_t\) is the amount of drug released at time \(t\); \(Q_0\) is the initial amount of the drug in the formulation; \(k_0\), \(k_1\), \(k_H\), and \(k_{HC}\) are release rate constants for zero order, first order, Higuchi model and Hixson-Crowell rate equations. In equation 5, \(M_t\) is the amount of drug released at time \(t\), and \(M_\infty\) is the amount of drug released at time \(\infty\); \(k\) is the kinetic constant, and \(n\) is the diffusion coefficient. The release data of various formulations were fitted in various models to ascertain the mechanism of drug release [14, 15].

**RESULTS AND DISCUSSION**

**Preparation of floating microspheres:**

Ten formulations of gastro retentive effervescent floating microspheres were formulated using different ratios of xanthan gum, gum ghatti and HPMC K100M.

**Compatibility studies**

**FTIR analysis**

The IR spectrum of famotidine showed characteristic peaks corresponding to the functional groups present in the drug structure. IR spectra of famotidine showed peaks at 3354.6cm\(^{-1}\)(N-H stretching), 1597.26cm\(^{-1}\)(aromatic-C=C-stretching), 1530.16cm\(^{-1}\)(aromatic-C=C stretching and bending). Presence of any interaction between drug and polymers used often leads to significant changes in IR spectra of the drug-polymer mixture. From the IR spectra of drug-polymer mixture, it was found that there occurred no major shift in the frequencies of the characteristic functional groups of the drug. Absence of significant shifting in intensity of peaks and band width the excipients showed that no incompatibilities occurred between the drug and polymers used.
Differential scanning Calorimetry

DSC thermogram of famotidine showed a sharp endothermic peak at 163.8 °C corresponding to its melting point. The obtained value matched with the value given in literature. In the DSC curve of famotidine and gum ghatti mixture, the original peaks were retained and no additional peaks were obtained. This indicated that famotidine and gum ghatti are compatible with each other.
**X-Ray diffractometry (X-RD)**
Famotidine exhibited a series of intense peaks at 11.390, 15.499, 17.636, 19.072, 20.657, 23.706, 29.894, 31.902, and 35.014 which were indicative of crystalline nature of famotidine. The diffractogram of famotidine microspheres showed a slight decrease in intensity of peaks, which suggested that the drug was dispersed homogeneously in the formulated batches.

**Fig. 5: XRD of (A) Famotidine, (B) Famotidine and gum ghatti**

**Characterization of microspheres**

**Determination of micromeretic properties**
Flow properties like angle of repose, bulk density, tapped density; Carr's index and Hausner's ratio of the drug were studied and were tabulated in table. The microspheres have good flow property.

**Table 2: Micromeretic properties of microspheres**

<table>
<thead>
<tr>
<th>Formulation codes</th>
<th>Angle of repose(θ°)</th>
<th>Bulk density(g/cm³)</th>
<th>Tapped density(g/cm³)</th>
<th>Hausner's ratio</th>
<th>Carr's index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>24.75±0.14</td>
<td>0.472±0.03</td>
<td>0.581±0.03</td>
<td>1.23</td>
<td>18.76</td>
</tr>
<tr>
<td>F2</td>
<td>21.56±0.11</td>
<td>0.481±0.01</td>
<td>0.570±0.01</td>
<td>1.18</td>
<td>15.61</td>
</tr>
<tr>
<td>F3</td>
<td>25.71±0.43</td>
<td>0.451±0.01</td>
<td>0.511±0.02</td>
<td>1.05</td>
<td>11.97</td>
</tr>
<tr>
<td>F4</td>
<td>27.68±0.04</td>
<td>0.464±0.02</td>
<td>0.504±0.01</td>
<td>1.12</td>
<td>12.43</td>
</tr>
<tr>
<td>F5</td>
<td>32.89±0.32</td>
<td>0.474±0.02</td>
<td>0.502±0.02</td>
<td>1.05</td>
<td>5.57</td>
</tr>
<tr>
<td>F6</td>
<td>26.73±0.12</td>
<td>0.463±0.04</td>
<td>0.497±0.01</td>
<td>1.07</td>
<td>6.84</td>
</tr>
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</table>
Percentage Yield (% yield) and entrapment efficiency
Percentage yield of microspheres of different batches were in the range of 74.00% to 87.5%. Entrapment efficiency of all the formulations ranged from 63.61 to 83.05%.

Table 3: Percentage yield and entrapment efficiency

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Percentage yield (%)</th>
<th>Drug entrapment efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>74.10</td>
<td>83.05</td>
</tr>
<tr>
<td>F2</td>
<td>79.64</td>
<td>67.22</td>
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<tr>
<td>F3</td>
<td>77.92</td>
<td>69.41</td>
</tr>
<tr>
<td>F4</td>
<td>78.74</td>
<td>73.22</td>
</tr>
<tr>
<td>F5</td>
<td>78.51</td>
<td>63.61</td>
</tr>
<tr>
<td>F6</td>
<td>81.86</td>
<td>71.66</td>
</tr>
<tr>
<td>F7</td>
<td>87.5</td>
<td>79.16</td>
</tr>
<tr>
<td>F8</td>
<td>76.89</td>
<td>77.77</td>
</tr>
<tr>
<td>F9</td>
<td>74.00</td>
<td>68.33</td>
</tr>
<tr>
<td>F10</td>
<td>84.25</td>
<td>64.16</td>
</tr>
</tbody>
</table>

Determination of particle size distribution by sieve analysis
Particle size distribution of all the formulated batches of microspheres was performed by using a set of standard sieves (#10, #22, #30, #44, #60). All the microspheres passed through sieve #10 but were retained on sieve #22. So the particle size of the microspheres was in the range of 710-1700 μm with an average size of 1205 μm.

Surface morphology
SEM photographs of famotidine drug clearly showed existence of drug in crystalline form.
SEM photographs of optimized formulation of famotidine indicated that the microspheres were discrete, spherical and uniform in shape. There indicate their free flowing nature. It also showed that microspheres had a smooth outer surface and was porous.

Fig. 6: SEM images of (A) Famotidine, (B) Gum ghatti, (C) Microspheres of F7

**Total floating time and floating lag time**

All the formulations of microspheres floated for a period of 12hrs when dispersed in 0.1N HCl solution.

Fig. 7: Floating lag time of F7

**In vitro floating ability**

The floating ability of prepared microspheres was evaluated in acidic buffer (pH 1.2). Floating capacity of all the formulation ranged from 93.7% to 98.73%. All the formulations showed a total floating time of more than 12hrs.
In vitro drug release studies
The cumulative in vitro release studies of different formulations of famotidine were performed in 0.1N HCl buffer for 12 hrs. The samples were spectrophotometrically analyzed at 265 nm. A total of ten formulations were designed i.e., (F1 to F10) with different polymers and varying concentration of polymers in each formulation. Formulation F1 was prepared with sodium alginate only. Due to absence of polymer, formulation showed 100.78% drug release in 5hrs without any sustained action. So in order to sustain the drug release polymers like xanthan gum, gum ghatti and HPMC K100M were utilized along with sodium alginate.

### Table 4: Total floating time, buoyancy

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Lag time (sec)</th>
<th>Total floating time (hrs)</th>
<th>Buoyancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>30</td>
<td>&gt;12 hrs</td>
<td>95.0</td>
</tr>
<tr>
<td>F2</td>
<td>96</td>
<td>&gt;12 hrs</td>
<td>96.17</td>
</tr>
<tr>
<td>F3</td>
<td>47</td>
<td>&gt;12 hrs</td>
<td>94.14</td>
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<tr>
<td>F4</td>
<td>54</td>
<td>&gt;12 hrs</td>
<td>95.71</td>
</tr>
<tr>
<td>F5</td>
<td>57</td>
<td>&gt;12 hrs</td>
<td>97.3</td>
</tr>
<tr>
<td>F6</td>
<td>131</td>
<td>&gt;12 hrs</td>
<td>97.9</td>
</tr>
<tr>
<td>F7</td>
<td>98</td>
<td>&gt;12 hrs</td>
<td>98.73</td>
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<tr>
<td>F8</td>
<td>33</td>
<td>&gt;12 hrs</td>
<td>95.10</td>
</tr>
<tr>
<td>F9</td>
<td>40</td>
<td>&gt;12 hrs</td>
<td>94.16</td>
</tr>
<tr>
<td>F10</td>
<td>130</td>
<td>&gt;12 hrs</td>
<td>94.7</td>
</tr>
</tbody>
</table>
Kinetics of drug release
Several kinetic models like zero order, first order, Higuchi model, Korsemeyer-Peppas model, Hixson Crowell etc were applied to the dissolution profiles of famotidine floating microspheres (F7) and compared in order to find out the most probable kinetics of drug release. Various parameters like correlation coefficient, release rate constant and diffusion coefficient values estimated after linearization of dissolution data.

Comparing the correlation coefficient values of zero order (0.969) and first order (0.797), it was found that drug release follows zero order kinetics indicating that drug release was independent of concentration. In order to find out the release component (n) value, the release data was analyzed as per Korsemeyer-Peppas model. The 'n' value of F7 batch was found to be 0.508 ensuring that the drug release followed non-Fickian or anomalous diffusion mechanism. This type of release behaviors was generally exhibited by swelling controlled drug delivery systems where solvent up take determines the swelling rate of the polymer and drug release.

Fig. 9: Dissolution data of all formulations
CONCLUSION
From the results we can conclude that design of microspheres employing natural gums like gum ghatti by ion gelation technique can be widely used to encapsulate wide range of drugs to achieve sustained drug delivery.

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