Formulation and *in vitro* evaluation of salbutamol sulphate floating microspheres

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**Abstract**

The objective of the present study was to develop once daily sustained release floating dosage form of salbutamol sulfate. The study involves the preparation of floating microspheres of salbutamol sulfate coated with Eudragit L100 using solvent evaporation method and its *in vitro* characterization. Three batches (F1, F2 & F3) of microspheres were prepared taking three drug: polymer ratios (1:1, 1:2 & 1:3). The entrapment efficiency was increased with the increment in polymer concentration. The microspheres remained buoyant in acidic medium containing surfactant for 8-12 hours *in vitro*. The mean particle size increased and the drug release rate decreased at higher polymer concentration. The surface morphology of microspheres characterized by SEM showed microspheres with smooth surface. The *in vitro* drug release studies were carried out for 12 hours both in 0.1N HCl (pH 1.2) and pH 6.8 buffers. The release studies showed the drug release was faster in intestinal pH as compared to gastric pH due to the polymer solubility in pH from 6.

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Introduction

Gastro retentive systems are such type of arrangements that increase the gastric retention time of the drugs enabling site-specific absorption in the gastrointestinal tract. Floating dosage forms that utilize a non-effervescent system have a bulk density lower than gastric fluids and therefore remain buoyant in the stomach without getting affected by the gastric emptying rate for a prolonged period. The drug is released at a desired rate from the floating system and after complete release of the drug; the residual system is expelled from the stomach. The sustained or controlled release of the drug from these systems at preferred absorption sites optimizes delivery of drugs, improves its bioavailability, maximizes its therapeutic benefit, minimizes drug waste and reduces side effects by permitting a large portion of the drug to be absorbed before passing through the lower GI tract.\(^1\)

Asthma is characterized by hyper responsiveness of tracheo-bronchial smooth muscle to a variety of stimuli, resulting in narrowing of the air tubes, often accompanied by increased secretion, mucosal edema and mucus plugging.\(^2\) Drugs like salbutamol, ephedrine, theophylline, corticosteroids are generally used for the treatment of asthma.

In the present investigation, salbutamol sulfate, a potent bronchodilator, was selected as a drug for the design of GRDDS in the form of floating multiparticulate system i.e., floating microspheres. The \(P^\text{Ka}\) value (9.3) of salbutamol sulphate indicates it as a weak acid, i.e, it is predominantly absorbed from the stomach and upper part of intestine. Its oral bioavailability is 50\%\), plasma half life is short (2.7-5 hrs.) and plasma protein binding is very low (10\%) which are the important factors for a drug candidate to be fabricated into a sustained release floating dosage form.\(^3\)

The aim of this work was to investigate the possibility of obtaining a prolonged, relatively constant effective plasma-level of salbutamol sulfate through floating microsphere formulation using Eudragit L100 as the carrier. Eudragit L 100 is an anionic copolymer of methacrylic acid and methyl methacrylate.\(^4\)

Materials and methods

Materials

Salbutamol sulfate was gifted by M/s. Nebula healthcare, Chennai, Eudragit L100 was gifted by M/s. GVK Pharma, Ahmedabad and all other chemicals were of analytical grade.

Preparation of floating microspheres\(^5\)

Three formulations were prepared by taking drug:polymer ratio 1:1, 1:2, and 1:3. Eudragit L 100 was dissolved in 15ml of acetone by using a magnetic stirrer and powdered Salbutamol sulfate was dispersed in the polymer solution (Table 1). The resulting dispersion was mixed with 50ml light liquid paraffin and 1\% span80 and stirring was continued with a triple blade propeller. Stirring was continued for 30 minutes to 45 minutes with 300 r.p.m. until acetone was evaporated completely. After the evaporation of acetone, the formed microspheres were collected by filtration in vacuum, washed 4-5 times with 30ml n-hexane each time and dried at room temperature for 24h.

Characterization of microspheres

1. Yield of microspheres

The prepared microspheres were collected and weighed.

Percentage of yield= (actual weight of product / total weight of excipient and drug) \(\times 100\)
Table 1: Formulations for different batches of floating microspheres

<table>
<thead>
<tr>
<th>Sr.No.</th>
<th>Ingredients</th>
<th>Batches of microspheres prepared</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>1.</td>
<td>Drug : Polymer Ratio</td>
<td>1:1</td>
</tr>
<tr>
<td>2.</td>
<td>Salbutamol sulphate (mg)</td>
<td>80</td>
</tr>
<tr>
<td>3.</td>
<td>Eudragit L 100 (mg)</td>
<td>80</td>
</tr>
<tr>
<td>4.</td>
<td>Light liquid paraffin (ml)</td>
<td>50</td>
</tr>
<tr>
<td>5.</td>
<td>Acetone (ml)</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Span 80 (%)</td>
<td>1</td>
</tr>
</tbody>
</table>

2. Entrapment efficiency

Drug entrapment efficiency for each batch was calculated in terms of percentage drug entrapment (PDE) as per the following formula:

\[ \text{PDE} = \left( \frac{\text{Actual drug loading}}{\text{Theoretical drug loading}} \right) \times 100 \]

3. Particle size analysis

Particle size was determined by optical microscopy.

4. In vitro evaluation of floating ability

A weighed amount of microspheres was spread over the surface of a dissolution apparatus filled with 900 ml of simulated gastric fluid (0.1 N HCl) at 37°C containing 0.02% Tween 20. The medium was agitated with a paddle rotating at 100 RPM for 12 h. The buoyant and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained buoyant and the total mass of the microspheres.

\[ \text{Percentage buoyancy} = \left( \frac{\text{weight of buoyant microspheres}}{\text{initial weight of floating microspheres}} \right) \times 100 \]

5. Morphology and surface characteristics

Scanning electron microscopy (SEM) was performed to characterize the morphology and surface of the formed microspheres.

6. In vitro release study

The in vitro release studies were carried out using paddle type dissolution apparatus. Drug loaded microspheres containing 15 mg of drug were introduced into the 900 ml of dissolution medium, maintained at 37±0.5°C with paddle rotating at 100 r.p.m. Aliquots were withdrawn at regular intervals and analyzed spectrophotometrically. The dissolution studies were carried out in triplicate in 0.1N HCl (pH 1.2) and pH 6.8 phosphate buffers. The mean values were plotted as percentage cumulative drug release (%CDR) versus time.
Results and Discussions
Characterization of floating microspheres

Percentage yield and Entrapment efficiency

The F3 showed maximum entrapment efficiency (67.5±1.36%) in comparison to F2 (63±1.42 %) and F1 (58±0.98%). For maximum entrapment efficiency the drug-polymer ratio was found to be 1:3. The entrapment efficiency for all the batches was increased with increasing polymer concentration. This can be explained by an increment in the polymer concentration in a fixed volume of organic solvent resulted in an increase in the entrapment efficiency. The results have been shown in Table 2.

Table 2: Percentage yield, percentage drug loading and entrapment efficiency

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Drug: polymer</th>
<th>% Yield</th>
<th>% Loading</th>
<th>% Entrapment</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1:1</td>
<td>63 ± 0.79</td>
<td>46 ± 0.88</td>
<td>58 ± 0.98</td>
</tr>
<tr>
<td>F2</td>
<td>1:2</td>
<td>64.5 ± 0.96</td>
<td>33 ± 1.06</td>
<td>63 ± 1.42</td>
</tr>
<tr>
<td>F3</td>
<td>1:3</td>
<td>67 ± 1.08</td>
<td>25 ± 0.98</td>
<td>67.5 ± 1.36</td>
</tr>
</tbody>
</table>

Values are expressed in mean ± standard deviation (n=3)

Mean particle size

Particle size was determined by optical microscopy and the mean particle sizes for all batches of microspheres are shown in Table 3. The results indicate that the mean particle size was increased with an increment in the polymer concentration. As the polymer concentration was increased, the microspheres’ diameters were also increased due to deposition of more polymer over the primary coat of the spheres. Mean particle size of the spheres is graphically represented in Fig.1 and values are tabulated in Table. 3.

Percentage buoyancy

Floating ability or % buoyancy for all three formulations was determined. The F3 showed the highest buoyancy (82±1.10%) in comparison to F2 (79±1.70%) and F1 (75±1.64%). The results confirm that 1:3 ratio had the maximum percentage buoyancy and remained buoyant for a longer period of time. It also indicates that larger the particle size, longer the floating time. The results are tabulated in the Table 3.

Table 3: Mean particle size and percentage buoyancy

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Formulations</th>
<th>Mean particle size (μm)</th>
<th>% buoyancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>F1</td>
<td>77.5 ± 1.09</td>
<td>75 ± 1.64</td>
</tr>
<tr>
<td>2.</td>
<td>F2</td>
<td>103 ± 1.11</td>
<td>79 ± 1.70</td>
</tr>
<tr>
<td>3.</td>
<td>F3</td>
<td>135.6 ± 1.16</td>
<td>82 ± 1.10</td>
</tr>
</tbody>
</table>

Mean ± Standard deviation (n =3)
Surface morphology

For the external morphological studies, air dried particles were visualized using scanning electron microscopy (SEM). The scanning electron microphotographs revealed that the microspheres were spherical in shape and had a smooth surface. The microphotograph of F3 has been shown in Fig. 2.

**Fig. 2: Scanning electron microphotograph of F3**

In vitro release studies

Eudragit L 100 is an enteric polymer which is soluble in intestinal pH 6. So a rate of drug release from microspheres altered significantly above and below pH 6. At intestinal pH, the drug release was faster and continuous as compared to the amount released at gastric pH. From the results, it was observed that F1 and F2 released more or less 30% of the drug like 33.50±0.50% and 29.50±1.25% respectively at the end of 12th hour in acidic medium (pH1.2) in comparison to F3 which released around 25% (25.25±1.00%) only. Again the F1 released more than 86% (86.64±1.00%) at the end of 12th hour where as F2 and F3 released roughly 82% (82±1.25%) and 79% (79.1±0.73%) respectively in phosphate buffer (pH6.8). Hence, F3 showed the most retarded release at the end of 12th hour in both media. In all batches, the drug release rate decreased with increasing polymer concentration. This can be explained that the amount of uncoated drug decreased with higher polymer concentration and decreased amount of drug was present closer to the surface. Release profiles were graphically represented in Fig. 3 & 4.
**Fig. 3:** Graph for *In Vitro* release profiles of microspheres in 0.1N HCl

![Graph for In Vitro release profiles of microspheres in 0.1N HCl](image1)

**Fig. 4:** Graph for *In vitro* release profiles of microspheres in pH 6.8 buffer

![Graph for In vitro release profiles of microspheres in pH 6.8 buffer](image2)

**Conclusion**

It can be concluded that F3 can be considered as an optimized formula for delivering the drug at a slower and sustained release rate over an extended period of time to achieve the goal of the preparation of FDDS. Moreover, F3 showed highest entrapment efficiency and the maximum percentage buoyancy. So, floating microspheres of salbutamol sulfate may treat asthma more efficiently than the conventional dosage forms and enhance patients’ compliance.

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References


