Preparation and Evaluation of Ofloxacin Sustained Released Gastro Retentive Floating Microspheres

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Abstract
Floating microspheres of Ofloxacin were prepared by emulsion cross linking method in which form two phase solution. A total of six formulations were prepared i.e. F1, F2, F3, F4, F5 and F6. Microsphere were evaluated for various rheological properties like bulk density, tapped density, Hausner's ratio, angle of repose, shows satisfactory results. The prepared microsphere were then evaluated for various physical tests like particle size, drug content, drug entrapment efficiency, swelling index and buoyancy test by using standard procedures. The particle size of all the formulations was ranged between 158.6±0.62 and 205.1±0.42 μm. The drug content and entrapment efficiency was ranged between 18.4±0.48 to 31.1±1.02% and 53.0±1.48 to 76.6±0.94%, respectively. The swelling index and buoyancy were ranged from 79.9±1.42 to 110.6±1.37 and 94.2±0.29 to 121.9±0.19, respectively. The prepared microspheres exhibited good spherical geometry with smooth surface as evidence by scanning electron microscopy. The in vitro release studies exhibited that F3 displayed better sustained effect over a period of 16 hours.

1 Introduction
The drug release from conventional oral dosage form cannot be control and it leads to fluctuations in plasma drug level. It is one of the major disadvantages of a release all or nothing emptying process while the multiple unit particulate system pass through the Gastro intestinal transit to avoid the vagaries of gastric emptying and thus release the drug more uniformly. Hence different techniques have been applied for the improvement of the retention of oral dosage form in the stomach, e.g. floating systems, swelling and expanding systems, bioadhesive systems, high density systems.

In floating drug delivery system, the floating microsphere is best option to deliver drug in the body. The floating microspheres are gastro-retentive drug delivery systems based on effervescent and non-effervescent approach. The size of microsphere is less than 200 mm and is available in free flowing powders. Gastro-retentive floating microspheres are low-density systems that have 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. Floating microspheres to improve patient compliance by decreasing dosing frequency, better therapeutic effect of short half-life drugs can be achieved. Enhanced absorption of drugs which solubilize only in stomach, gastric retention time is increased because of buoyancy.

Ofloxacin exhibits pH dependant solubility, where the drug is readily soluble in the acidic environment of the stomach; however, in the intestine, where neutral to slightly alkaline pH prevail, precipitation of the active compound occurs, which adversely affects absorption in the lower sections of the intestine. Therefore, these drugs have been found to be good candidates for the development of a gastroretentive drug delivery system aiming to increase their bioavailability.

The gastroretentive microsphere drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. The local delivery of Ofloxacin by this approach will also promote a fast and effective potency along with increase in bioavailability of drug rather than a conventional tablet containing Ofloxacin.
Keeping these factors in view it is aimed to formulate and evaluate sustained release of floating microspheres of Ofloxacin, which after oral administration could prolong the gastric residence time and increase the drug bioavailability.

2 Materials and Methods

2.1 Formulation of Ofloxacin floating microspheres

The floating microspheres of Ofloxacin were prepared by mixing with different concentration of polymers. Floating microspheres were formed by emulsion cross linking method in which form two phase solution. One phase contained solvent as dichloromethane drug and polymer (HPMC and PVA) in different concentration. Now slurry was formed then second phase has water and gas forming agent like sodium bicarbonate and calcium carbonate. These second phase poured in a beaker and heated by placing it on magnetic stirrer after that first phase solution was poured in to beaker by a syringe drop by drop to form fine microsphere. Now microspheres was filtered and collected, then washed with ethanol and dried at room temperature. The compositions of ingredient of microsphere are shown in table 1.

2.2 Physicochemical characterization of the microspheres

2.2.1 Micromeretic Properties

Microsphere were evaluated for various rheological properties like bulk density, tapped density, Hausner's ratio, angle of repose by using standard procedures. All these properties were carried out in triplicate (n=3) and average values were reported.

2.2.1.1 Bulk density

Bulk density was determined by placing the powders blend in a measuring cylinder and the total volume is noted. The weight of powder bed was determined by using digital weighing balance. Bulk density was calculated using the following formula:

\[ \text{Bulk Density} = \frac{\text{Weight of the powder}}{\text{Volume of the powder}} \]

2.2.1.2 Tapped density

Tapped density was determined by taking the dried powders in a measuring cylinder and measures the volume of powders after 100 tapping's and take weight of the total powders.

Tapped Density = \( \frac{\text{Weight of the powder}}{\text{Tapped Volume of powder}} \)

2.2.1.3 Angle of repose

Angle of repose was determined by measuring the height and radius of the heap of the powder bed. A cylindrical two side open tube of 6 cm length is place on graph paper. Powders are placed in the tube and slowly removed the tube vertically. With the help of scale the height and radius of the heap were measure and note.

\[ \theta = \tan^{-1} \frac{h}{r} \]

Where, \( h \) = height of heap of granular bed, \( r \) = radius of heap of granular bed.

2.2.1.4 Hausner's ratio

It is expressed in percentage and is expressed by

\[ H = \frac{D_t}{D_b} \]

Where \( D_t \) is the tapped density of the powder and \( D_b \) is the bulk density of the powder.

2.2.2 Determination of particle size

The mean particle size of the drug and the formulations was analyzed by laser light scattering technique using Ankersmid CIS-50.

2.2.3 Drug Content

For the determination of drug content, formulations (50 mg) were triturated with 0.1N HCl and finally the volume was made up to 50 ml with the same. The solution was filtered through Whatmann No.1 filter paper and suitable dilutions were carried out with 0.1N HCl. The concentration of Ofloxacin is then determined using UV spectrophotometer at wavelength of 294 nm.

2.2.4 Surface morphology

The surface characteristics of the drug powder and that of the formulations before and after dissolution were studied by scanning electron microscope at 1600X. The samples were mounted on double-sided tape that has previously been secured on copper stubs and then analyzed at different magnifications.

2.2.5 Swelling index

Swelling properties of floating microspheres is studied by soaking the known weight of microspheres at 37±0.5°C in 0.1N HCL in a glass beaker for the required period of time. The microspheres are allowed to swell and removed at different time interval. Their changes in weight are measured and calculated from the formula.

\[ \text{Swelling index} = \frac{W_e - W_o}{W_o} \]

Where, \( W_o \) is the initial weight of dry microspheres, \( W_e \) is the weight of swell microspheres.

2.2.6 Buoyancy studies

This study is carried out by USP type II dissolution test apparatus by spreading the floating microspheres on a simulated gastric fluid (pH 1.2) containing surfactant. The media is stirred at 100 rpm at 37±0.5°C. After specific interval of time, both the fraction of microspheres (floating and settled microspheres) were collected and
buoyancy of the floating microspheres is determined by using formula:

$$\text{Buoyancy(%)} = \frac{Q_f}{Q_s} \times 100$$

Where, $Q_f$ is floating microspheres and $Q_s$ is settled microspheres

2.2.7 Drug entrapment efficiency

Estimation of drug content in floating microspheres can be carried out by dissolving the weight amount of crushed microspheres in required quantity of 0.1N HCL and analysed spectrophotometrically at a particular wavelength using the calibration curve. Each batch should be examined for drug content in a triplet manner. The entrapment efficiency of floating microspheres is calculated by dividing the actual drug content by the theoretical drug content of microspheres.

2.2.8 In-vitro dissolution study

The in vitro dissolution studies were carried out using USP type II dissolution apparatus (Paddle Type). The study was carried out in 900 ml of 0.1N HCl. The Dissolution medium was kept in a thermostatically controlled water bath, maintained at 37±0.5 °C. The basket was rotated at 100 rpm. At predetermined time intervals i.e. 1, 2, 4, 6, 8, 10, 12, 14 and 16 hours 5 ml of sample was withdrawn and replaced with fresh media. The drug concentration was analyzed by using UV spectrophotometer at 294 nm.

3 Results and Discussions

3.1 Micrometric property of microsphere

The bulk density of the formulation F1 to F6 containing different ratio of HPMC K4M and PVA was in the range of 0.47±0.83 to 0.71±0.57g/cm³ as shown in table 6.10. The tape density of the formulation F1 to F6 containing different ratio of HPMC K4M and PVA was in the range of 0.54±1.12 to 0.85±0.91g/cm³ as shown in table 2.

The Carr’s index and Hausner’s ratio of the formulation F1 to F6 containing different ratio of HPMC K4M and PVA was in the range of 14.89±0.68 to 20.00±1.07 and 1.14±0.92 to 1.20±0.78 respectively.

The angle of repose of the formulation F1 to F6 containing different ratio of HPMC K4M and PVA was in the range of 22.44±0.54 to 28.23±1.17 as shown in table 2. The values of Carr’s index, Hausner’s ratio and angle of repose indicate excellent flow properties.

3.2 Particle size determination

The results of particle size analysis of Ofloxacin and various formulations are given in table 3. The particle size of the formulation F1 to F6 containing different ratio of HPMC K4M and PVA was in the range of 158.6±0.62 µm to 205.1±0.42 µm. The size of microsphere of formulation F3 was smaller than other formulations. The outcomes of particle size exhibited that on increasing the sodium alginate and polymer it decreases the particle size of microspheres.

3.3 Drug content and entrapment efficiency

From the results presented in table 3, it was observed that ionotropic gelation technique produced microspheres of high encapsulation efficiency. The drug entrapment efficiency value ranged from 53.0±1.48% to 76.6±0.94%. The formulation F3 revealed maximum drug content and drug entrapment efficiency. The findings exhibits that on increasing the concentration of sodium alginate it increases the drug entrapment efficiency. This may be explained by the fact that at higher concentration sodium alginate and polymer forms matrix with Calcium Chloride and gelling property of polymer enhance the incorporation of drug. The above statement can be confirmed from drug content outcomes.

3.4 Scanning electron micrograph

Scanning electron microscopy (SEM) was performed for surface morphology of the prepared microspheres. Images of formulation indicate the surface morphology of formulation (Fig 1). Surface smoothness of the Ofloxacin microspheres was increased by increasing the polymer concentration, which was confirmed by SEM. The numerous channels and pores visible in the micrograph showed the pathway through which dissolution medium could permeate into the drug-polymer matrix, swell the polymers, and widen the pore diameter which in turns would help the drug molecule to diffuse from the matrix into the dissolution medium.

3.5 Swelling index

The swelling index of the formulation F1 to F6 containing different ratio of HPMC K4M and PVA was in the range of 79.9±1.42 to 110.6±1.37% (Table 3). The formulation F3 has highest swelling index as compared to other formulations. On increasing the concentration of polymer it increases the swelling index of microsphere leading to spongy property of polymers.

3.6 Buoyancy study

The purpose of preparing floating microsphere was to extend the gastric residence time of a drug. The buoyancy test was carried out to investigate the floatability of the prepared microsphere. The microsphere spread over the surface of simulated gastric fluid and the force of microsphere buoyant and settled down as a function of time was quantitated. The percentage of buoyancy of formulation F1 to F6 containing different ratio of HPMC K4M and PVA was in range from 94.2±0.29 to 121.9±0.19% (Table 3). Among all the formulations F3 has highest percentage of buoyancy as compared to other formulations.
3.7 In vitro drug release studies

Figure 2 exhibited *in-vitro* dissolution of Ofloxacin microsphere, it revealed that 92.21 to 97.29% of drug release from various formulations. The 50% of the drug was released from the F4 within 4 hrs, while other formulation release 50% drug after 4 hrs. The maximum *in vitro* release was evaluated to be 97.29% over a period of 16 hrs for formulation F3.

Table 1 Quantity of raw materials for preparation of microspheres (in mg)

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofloxacin</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>HPMC K4M</td>
<td>200</td>
<td>300</td>
<td>400</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PVA</td>
<td>-</td>
<td>-</td>
<td>200</td>
<td>300</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Sodium Alginate</td>
<td>100</td>
<td>200</td>
<td>300</td>
<td>100</td>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>50</td>
<td>100</td>
<td>150</td>
<td>50</td>
<td>100</td>
<td>150</td>
</tr>
<tr>
<td>Calcium Carbonate</td>
<td>50</td>
<td>100</td>
<td>150</td>
<td>50</td>
<td>100</td>
<td>150</td>
</tr>
<tr>
<td>Theoretical Weight</td>
<td>600</td>
<td>900</td>
<td>1200</td>
<td>600</td>
<td>900</td>
<td>1200</td>
</tr>
</tbody>
</table>

Table 2: Micrometric property of formulated microspheres

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Angle of Repose</th>
<th>Bulk density g/cm³</th>
<th>Tap density g/cm³</th>
<th>Compresibility Index (%)</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F 1</td>
<td>22.44±0.54</td>
<td>0.59±0.95</td>
<td>0.68±0.38</td>
<td>15.25±0.73</td>
<td>1.15±0.67</td>
</tr>
<tr>
<td>F2</td>
<td>24.54±0.36</td>
<td>0.63±1.05</td>
<td>0.74±0.86</td>
<td>17.46±0.61</td>
<td>1.17±0.78</td>
</tr>
<tr>
<td>F3</td>
<td>27.05±0.95</td>
<td>0.71±0.57</td>
<td>0.85±0.91</td>
<td>19.71±0.58</td>
<td>1.19±0.43</td>
</tr>
<tr>
<td>F4</td>
<td>23.78±0.84</td>
<td>0.47±0.83</td>
<td>0.54±1.12</td>
<td>14.89±0.68</td>
<td>1.14±0.92</td>
</tr>
<tr>
<td>F5</td>
<td>26.98±1.02</td>
<td>0.56±0.49</td>
<td>0.65±0.59</td>
<td>16.07±0.49</td>
<td>1.16±0.61</td>
</tr>
<tr>
<td>F6</td>
<td>28.23±1.17</td>
<td>0.65±0.75</td>
<td>0.78±0.67</td>
<td>20.00±1.07</td>
<td>1.20±0.78</td>
</tr>
</tbody>
</table>

Table 3: Physicochemical characteristics of Ofloxacin microspheres

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Particle size (µm)</th>
<th>Drug content</th>
<th>Entrapment efficiency (%)</th>
<th>Swelling index (%)</th>
<th>Buoyancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>205.1±0.42</td>
<td>23.2±0.36</td>
<td>65.7±1.02</td>
<td>94.5±1.62</td>
<td>105.4±0.15</td>
</tr>
<tr>
<td>F2</td>
<td>192.5±0.36</td>
<td>28.5±0.59</td>
<td>69.5±1.26</td>
<td>103.2±1.18</td>
<td>117.8±0.72</td>
</tr>
<tr>
<td>F3</td>
<td>168.3±0.53</td>
<td>31.1±1.02</td>
<td>76.6±0.94</td>
<td>110.6±1.37</td>
<td>121.9±0.19</td>
</tr>
<tr>
<td>F4</td>
<td>195.7±0.18</td>
<td>18.4±0.48</td>
<td>53.0±1.48</td>
<td>79.9±1.42</td>
<td>94.2±0.29</td>
</tr>
<tr>
<td>F5</td>
<td>179.4±0.24</td>
<td>21.8±1.14</td>
<td>60.4±0.46</td>
<td>85.4±1.19</td>
<td>101.7±0.48</td>
</tr>
<tr>
<td>F6</td>
<td>158.6±0.62</td>
<td>25.3±0.91</td>
<td>65.8±1.31</td>
<td>89.3±1.53</td>
<td>107.4±0.37</td>
</tr>
</tbody>
</table>
Fig 1: Scanning electron micrograph of Ofloxacin floating microspheres

The F2 and F6 release maximum drug from microsphere at 14 hrs. Further the F1, F4 and F5 release maximum drug from microsphere at 12 hrs. This decrease in the rate and extent of release with relative increase in the polymer concentration in microspheres can be attributed to the increase in the density of the polymer matrix with increased polymer concentration. The formulation F3 showed better sustained release at the end of the 16 hrs as compared to other batches. This may be due to better loading, encapsulation efficiency and spherical particle size as compared to other batches. Hydrophilic polymers microspheres swell in water and form gel which retards the drug release this could be attributed due to gel strength of the alginate microspheres in the dissolution media might be too high and prevented the release of drug from formulation. While in acidic environment alginate microspheres shrink due to tightening of the gel meshwork. At basic environment polymer is eroded and the contents are released in a sustained manner by both diffusion and slow erosion of polymer matrix. Additionally, the effect of variation in drug to polymer concentration on drug release was due to the increase in wall thickness that results in longer diffusion path.

4 Conclusion

It was concluded that microsphere of Ofloxacin can be successfully prepared by emulsion cross linking method using polymers HPMC K4M and PVA for sustained release of drug. Higher concentration of drug content and drug entrapment was found on increasing the concentration of polymer. The formulation F3 exhibited better results as compared to other formulations. Further these formulations can be select for in vivo study.

5 References

