INTRODUCTION

To develop oral drug delivery systems, it is necessary to optimize both the residence time of system within the gastrointestinal tract and release of drug from the system. Drugs that are easily absorbed from the gastrointestinal tract and have a short half life are eliminated quickly from the blood circulation and require frequent dosing. To avoid this problems, the oral controlled release formulations have been developed in an attempt to release the drug slowly into the gastrointestinal tract and maintain a constant drug concentration in the serum for a longer period of time. Such oral drug delivery devices have a restriction due to the gastric retention time (GRT), a physiological limitation. Therefore prolonged gastric retention is important in achieving control over the GRT because this helps to retain the controlled release system in the stomach for a longer time in a predictable manner. Various attempts have been made to prolong the residence time of the dosage forms within the stomach. The prolongation of the GRT of delivery devices could be achieved by adhesion to the mucous membranes, by preventing their passage through the pylorus or by maintaining them in buoyant fashion in gastric juice. Unfortunately floating devices administered in a single unit form (tablet) such as hydrodynamically balanced systems are unreliable in prolonging the GRT owing to their “all or none” emptying process and thus, they may cause high variability in bioavailability and local irritation due to a large amount of drug delivered at a particular site of GRT. In contrast, multiple unit particulate dosage form (e.g., microspheres) have the advantages that they pass uniformly through the gut to avoid the vagaries of gastric emptying and provide an adjustable release, thereby reducing intersubject variability in absorption and risk of local irritation. Ketoprofen (2-aryl propionic acid derivative) is an important analgesic and nonsteroidal antiinflammatory drug, also with antipyretic properties, whose mechanism of action is the inhibition of prostaglandin synthetase. This drug is used in therapy of rheumatic disorder and its plasma elimination half life is 1 to 3 hours, and in order to maintain therapeutic plasma level drug must be administered at least thrice a day. On the other hand, eudragit (methacrylate copolymers) have been recently received increased attention for preparing modified dosage forms because of their inertness, solubility, in relatively non toxic solvents of resins with different properties.

The aim of present work is to prepare floating microspheres of ketoprofen using Eudragit S 100 and Eudragit L 100 as polymer. Floating drug delivery system have a bulk density less than gastric fluids and so remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. Ketoprofen is nonsteroidal antiinflammatory drug with short elimination half life 1-3 hours. The short half life of ketoprofen and multiple administration dose make ketoprofen a very good candidate for formulation of floating drug delivery system. Floating microspheres of ketoprofen were prepared by emulsion solvent diffusion method using Eudragit S 100 and Eudragit L 100 as polymer. The floating microspheres was evaluated such as micromeritic properties, particle size, percentage yield, in vitro buoyancy, incorporation efficiency, drug polymer compatibility (IR study), scanning electron microscopy and drug release of microspheres. The micromeritic properties was found to be good and scanning electron microscopy confirmed their hollow structure with smooth surface. Formulation EU: prepared with Eudragit S 100 drug:polymer ratio (1:2) which exhibited excellent micromeritic properties, percentage yield, in vitro buoyancy, incorporation efficiency and percentage drug release 92.26 % for a period of 12 hrs. Results show that as increase in drug:polymer ratio affects the particle size, percentage yield, in vitro buoyancy and drug release of microspheres.

The data obtained in this study thus suggest that a floating microspheres of ketoprofen are promising for sustained drug delivery which can reduce dosing frequency.

Keywords: Ketoprofen, Eudragit S 100, Eudragit L 100, Floating microspheres.

ABSTRACT

The aim of present work is to prepare floating microspheres of ketoprofen using Eudragit S 100 and Eudragit L 100 as polymer. Floating drug delivery system have a bulk density less than gastric fluids and so remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. Ketoprofen is nonsteroidal antiinflammatory drug with short elimination half life 1-3 hours. The short half life of ketoprofen and multiple administration dose make ketoprofen a very good candidate for formulation of floating drug delivery system. Floating microspheres of ketoprofen were prepared by emulsion solvent diffusion method using Eudragit S 100 and Eudragit L 100 as polymer. The floating microspheres was evaluated such as micromeritic properties, particle size, percentage yield, in vitro buoyancy, incorporation efficiency, drug polymer compatibility (IR study), scanning electron microscopy and drug release of microspheres. The micromeritic properties was found to be good and scanning electron microscopy confirmed their hollow structure with smooth surface. Formulation EU: prepared with Eudragit S 100 drug:polymer ratio (1:2) which exhibited excellent micromeritic properties, percentage yield, in vitro buoyancy, incorporation efficiency and percentage drug release 92.26 % for a period of 12 hrs. Results show that as increase in drug:polymer ratio affects the particle size, percentage yield, in vitro buoyancy and drug release of microspheres.

The data obtained in this study thus suggest that a floating microspheres of ketoprofen are promising for sustained drug delivery which can reduce dosing frequency.

Keywords: Ketoprofen, Eudragit S 100, Eudragit L 100, Floating microspheres.

INTRODUCTION

To develop oral drug delivery systems, it is necessary to optimize both the residence time of system within the gastrointestinal tract and release of drug from the system. Drugs that are easily absorbed from the gastrointestinal tract and have a short half life are eliminated quickly from the blood circulation and require frequent dosing. To avoid this problems, the oral controlled release formulations have been developed in an attempt to release the drug slowly into the gastrointestinal tract and maintain a constant drug concentration in the serum for a longer period of time. Such oral drug delivery devices have a restriction due to the gastric retention time (GRT), a physiological limitation. Therefore prolonged gastric retention is important in achieving control over the GRT because this helps to retain the controlled release system in the stomach for a longer time in a predictable manner. Various attempts have been made to prolong the residence time of the dosage forms within the stomach. The prolongation of the GRT of delivery devices could be achieved by adhesion to the mucous membranes, by preventing their passage through the pylorus or by maintaining them in buoyant fashion in gastric juice. Unfortunately floating devices administered in a single unit form (tablet) such as hydrodynamically balanced systems are unreliable in prolonging the GRT owing to their “all or none” emptying process and thus, they may cause high variability in bioavailability and local irritation due to a large amount of drug delivered at a particular site of GRT. In contrast, multiple unit particulate dosage form (e.g., microspheres) have the advantages that they pass uniformly through the gut to avoid the vagaries of gastric emptying and provide an adjustable release, thereby reducing intersubject variability in absorption and risk of local irritation.

Ketoprofen (2-aryl propionic acid derivative) is an important analgesic and nonsteroidal antiinflammatory drug, also with antipyretic properties, whose mechanism of action is the inhibition of prostaglandin synthetase. This drug is used in therapy of rheumatic disorder and its plasma elimination half life is 1 to 3 hours, and in order to maintain therapeutic plasma level drug must be administered at least thrice a day. On the other hand, eudragit (methacrylate copolymers) have been recently received increased attention for preparing modified dosage forms because of their inertness, solubility, in relatively non toxic solvents of resins with different properties.

The aim of present work was to develop and evaluate floating microspheres of Ketoprofen using Eudragit S-100 & Eudragit L-100 as polymer and emulsion solvent diffusion as a method of preparation. Ketoprofen whose physicochemical properties and short half life make it suitable candidate for floating drug delivery system.

MATERIALS AND METHODS

Materials

Ketoprofen was received as gift sample from Ciron Drugs and Pharmaceutical Pvt. Ltd. Mumbai (India), Eudragit S 100 and Eudragit L 100 was received as gift sample from Degussa india pvt. Ltd., Mumbai. ethanol, methanol, dichloromethane, tween 20 was obtained from SD fine chemicals Ltd., Mumbai (India). All other chemical and reagent used in this study were of analytical grade.

Method of preparation

Floating microspheres were prepared by emulsion solvent diffusion method. Weighed amount (as shown in table 1) of ketoprofen was mixed with Eudragit S 100 and Eudragit L 100 drug:polymer ratio (1:1, 1:2, 1:3) in a solution of ethanol : dichloromethane (1:1) at room temperature. The resulting drug polymer solution was poured slowly using glass tube into 200 ml of water containing 0.75 % w/v polyvinyl alcohol, maintained at constant temperature of 40°C and preparation was stirred at 300 rpm for 1 hr. The finely developed floating microspheres were then filtered, washed with water and sieved between 50 and 30 mesh size and dried overnight at 40°C.

Evaluation of floating microspheres

Yield of floating microspheres

The prepared floating microspheres with a size range of 102 - 192 μm were collected and weighed. The measured weight was divided by total amount of all non-volatile components which were used for the preparation of microspheres.

% yield = (Actual weight of product / Total weight of excipient and drug) x 100

ABSTRACT

The aim of present work is to prepare floating microspheres of ketoprofen using Eudragit S 100 and Eudragit L 100 as polymer. Floating drug delivery system have a bulk density less than gastric fluids and so remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. Ketoprofen is nonsteroidal antiinflammatory drug with short elimination half life 1-3 hours. The short half life of ketoprofen and multiple administration dose make ketoprofen a very good candidate for formulation of floating drug delivery system. Floating microspheres of ketoprofen were prepared by emulsion solvent diffusion method using Eudragit S 100 and Eudragit L 100 as polymer. The floating microspheres was evaluated such as micromeritic properties, particle size, percentage yield, in vitro buoyancy, incorporation efficiency, drug polymer compatibility (IR study), scanning electron microscopy and drug release of microspheres. The micromeritic properties was found to be good and scanning electron microscopy confirmed their hollow structure with smooth surface. Formulation EU: prepared with Eudragit S 100 drug:polymer ratio (1:2) which exhibited excellent micromeritic properties, percentage yield, in vitro buoyancy, incorporation efficiency and percentage drug release 92.26 % for a period of 12 hrs. Results show that as increase in drug:polymer ratio affects the particle size, percentage yield, in vitro buoyancy and drug release of microspheres.

The data obtained in this study thus suggest that a floating microspheres of ketoprofen are promising for sustained drug delivery which can reduce dosing frequency.

Keywords: Ketoprofen, Eudragit S 100, Eudragit L 100, Floating microspheres.
In vitro Buoyancy

Floating microspheres (equivalent to 100 mg) were dispersed in 90 ml of 0.1 N hydrochloric acid solution (pH 1.2) containing tween 20 (0.02 W/V%) to simulate gastric fluid at 37℃. The mixture was stirred with a paddle at 100 rpm and after 12 hr, the layer of buoyant microspheres (Wb) was pipetted and separated by filtration simultaneously. Floating microspheres (Wf) were also separated. Both microspheres type were dried at 40℃ over night. Each weight was measured and buoyancy was determined by the weight ratio of the floating microspheres to the sum of floating and sinking microspheres.

Incorporation efficiency

Floating microspheres were dissolved in a minimum amount of methanol and drug was extracted into suitable aqueous media (0.1 N hydrochloric acid) by evaporating methanol. The solution was filtered through whatman filter paper, diluted suitably and analyzed for drug content spectrophotometrically at 254 nm using Shimadzu UV visible spectrophotometer.

Micromeritic properties

The floating microspheres were characterized by their micromerletic properties such as particle size, bulk density, tapped density, Hausner’s ratio, Carr’s index and angle of repose.

Drug release

Drug release from Floating microspheres having a size range between 102 - 192 μm and floating microspheres equivalent to 150 mg of drug was carried out using paddle method at 100 rpm, for the first 2 hrs in pH 1.2 with tween 20 (0.02 W/V%) to simulate gastric fluid and 10 hrs in phosphate buffer pH 7.4 with tween 20 (0.02 W/V%) to simulate gastric fluid. Each time 5 ml of samples were withdrawn at different time intervals and replaced with fresh phosphate buffer, the amount of drug release was analyzed at 254 nm using a Shimadzu UV visible spectrophotometer.

Table 1: Formulation table of floating microspheres of ketoprofen

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulation code</th>
<th>EU1</th>
<th>EU2</th>
<th>EU3</th>
<th>EU4</th>
<th>EU5</th>
<th>EU6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit S 100</td>
<td>0.500</td>
<td>1.000</td>
<td>1.500</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Eudragit L 100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.500</td>
<td>1.000</td>
<td>1.500</td>
<td>-</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>0.500</td>
<td>0.500</td>
<td>0.500</td>
<td>0.500</td>
<td>0.500</td>
<td>0.500</td>
<td>-</td>
</tr>
<tr>
<td>Ethanol</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 2: Percentage yield, in vitro buoyancy and incorporation efficiency of floating microspheres of ketoprofen

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Percentage yield</th>
<th>In vitro buoyancy</th>
<th>Incorporation efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU1</td>
<td>62.40 ± 0.72</td>
<td>80.66 ± 2.08</td>
<td>61.59 ± 1.58</td>
</tr>
<tr>
<td>EU2</td>
<td>86.13 ± 2.00</td>
<td>87.00 ± 1.00</td>
<td>81.70 ± 2.02</td>
</tr>
<tr>
<td>EU3</td>
<td>89.45 ± 1.50</td>
<td>91.66 ± 1.52</td>
<td>79.94 ± 2.28</td>
</tr>
<tr>
<td>EU4</td>
<td>65.26 ± 2.05</td>
<td>71.66 ± 4.04</td>
<td>61.07 ± 0.98</td>
</tr>
<tr>
<td>EU5</td>
<td>77.73 ± 1.51</td>
<td>90.33 ± 1.52</td>
<td>71.78 ± 2.34</td>
</tr>
<tr>
<td>EU6</td>
<td>81.08 ± 1.97</td>
<td>91.33 ± 3.05</td>
<td>79.03 ± 2.00</td>
</tr>
</tbody>
</table>

All values are represented as mean ± standard deviation (n=3).

In vitro buoyancy

The in vitro buoyancy test was carried out to investigate buoyancy of prepared microspheres. The microspheres formulations EU1 to EU6 showed good floating ability range from 80.66 ± 2.08 to 91.66 ± 1.52 (as shown in table 2). The results also showed a tendency that, larger the particle size longer the floating time.

Incorporation efficiency

The incorporation efficiency of formulation F1 to F6 was carried out and found to be in a range 61.07 ± 0.98 to 81.70 ± 2.02 (as shown in table 2).

Micromeritic properties

The mean particle size of floating microspheres formulation EU1 to EU6 was found to be 102.33 ± 15.27 to 192.33 ± 27.50 (as shown in table 3). The effect of polymer concentration on the particle size of floating microspheres was determined. The mean particle size of the microspheres was found to be increase with increasing Eudragit concentration (as shown in table 1). The viscosity of medium increases at a higher Eudragit concentration resulting in enhanced...
interfacial tension. Shearing efficiency is also diminished at higher viscosities. This results in the formation of larger particles. The bulk density, tapped density, Hausners ratio of formulation EU1 to EU6, ranges from 0.591 ± 0.04 to 0.722 ± 0.02 gm/cm³, 0.652 ± 0.05 to 0.773 ± 0.016 gm/cm³, 1.04 ± 0.02 to 1.10 ± 0.03 respectively. The Carr’s index ranges between 5.00 ± 2.34 to 10.01 ± 1.05 %. The angle of repose of microspheres ranges from 13.25 ± 2.40 to 20.07 ± 1.68 (as shown in table 3). The values of Carr’s index and angle of repose indicate excellent flow properties.

Infrared spectroscopy
The FT-IR spectra study showed no change in the fingerprint of pure drug spectra, thus confirming absence of drug and polymer interaction.

Table 3: Micromeritic properties of floating microspheres of ketoprofen

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Mean particle size (µm)</th>
<th>Bulk density (gm/cm³)</th>
<th>Tapped density (gm/cm³)</th>
<th>Hausners ratio</th>
<th>Carr’s index</th>
<th>Angle of repose (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU1</td>
<td>123.33±15.27</td>
<td>0.622±0.05</td>
<td>0.692±0.07</td>
<td>1.10±0.01</td>
<td>10.1±1.05</td>
<td>16.77±1.43</td>
</tr>
<tr>
<td>EU2</td>
<td>161.33±1.01</td>
<td>0.632±0.02</td>
<td>0.684±0.03</td>
<td>1.07±0.03</td>
<td>7.63±2.66</td>
<td>19.11±2.42</td>
</tr>
<tr>
<td>EU3</td>
<td>192.33±27.50</td>
<td>0.674±0.03</td>
<td>0.725±0.05</td>
<td>1.04±0.02</td>
<td>5.00±2.34</td>
<td>20.07±1.68</td>
</tr>
<tr>
<td>EU4</td>
<td>102.33±1.12</td>
<td>0.591±0.04</td>
<td>0.652±0.05</td>
<td>1.10±0.01</td>
<td>9.16±0.80</td>
<td>16.79±1.59</td>
</tr>
<tr>
<td>EU5</td>
<td>122.66±19.60</td>
<td>0.658±0.03</td>
<td>0.707±0.05</td>
<td>1.07±0.03</td>
<td>6.80±3.29</td>
<td>20.07±1.68</td>
</tr>
<tr>
<td>EU6</td>
<td>156.66±27.53</td>
<td>0.722±0.02</td>
<td>0.773±0.01</td>
<td>1.06±0.02</td>
<td>4.73±2.73</td>
<td>13.25±2.40</td>
</tr>
</tbody>
</table>

All values are represented as mean ± standard deviation (n=3)

Fig. 2: in vitro buoyancy of floating microspheres of ketoprofen: (A) formulation EU1 to EU3 (B) EU4 to EU6

Fig. 3: Image showing drug polymer interaction study by FT-IR: (A) Ketoprofen (B) Eudragit S 100 (C) Eudragit S 100 (D) EU2 (E) EU4
Scanning electron microscopy (SEM)

Morphology of floating microspheres was examined by scanning electron microscopy. The view of the microspheres showed hollow structure with a smooth surface morphology (fig. 3 a, b, c) exhibited range of sizes within each batch. The outer surface of microspheres was smooth and dense, while the internal surface was porous. The shell of microspheres also showed some porous structure (fig. 3d) it may be caused by evaporation of solvent entrapped within the shell of microsphere after forming smooth and dense layer.

Drug release

The drug release from formulation EU1 TO EU6 (as shown in fig 5) was as follows. EU1, EU3, EU4, EU6 show percentage drug release 82.66 ± 0.95 to 90.31 ± 2.11 at end of 12 hour and formulation EU2 and EU5 show percent drug release 92.26 ± 1.96 and 90.31 ± 2.11 at end of 12 hr. Among all formulation EU2 was found to be the best formulation as it release ketoprofen in a sustained manner with constant fashion over extended period of time (after 12 hr). it was observed as the concentration of Eudragit S 100 and Eudragit L 100 was increased percent release of ketoprofen decreases. The increase in Eudragit S 100 and Eudragit L 100 concentration leads to the increased density of polymer matrix into the microspheres which result in an increased diffusional path length. This may decrease the overall drug release from polymer matrix. Furthermore smaller microspheres are formed at lower polymer concentration and have larger surface area exposed to dissolution medium.

Fig. 4: Scanning electron microphotographs of floating microsphere of ketoprofen: (a) & (b) smoothness of the surface of spherical shaped microsphere (c) & (d) internal view of the shell having porous structure.

Fig. 5: In vitro drug release profile of floating microspheres of ketoprofen formulation EU1 to EU6
CONCLUSION

Floating microspheres of ketoprofen with enteric acrylic polymers such as Eudragit S 100 and Eudragit L 100 were successfully prepared by the emulsion solvent diffusion method. The formulation EU2 with drug-polymer ratio (1:2) was found to be satisfactory in terms of excellent micromeritic properties, yield of microspheres (86.13%), incorporation efficiency (81.70%), in vitro buoyancy (87.00%) and highest in vitro drug release of 92.26% in sustained manner with constant fashion over extended period of time for 12 hrs. From the results it was observed that Drug: Polymer ratio influences the particle size, in vitro buoyancy, as well as drug release pattern of floating microspheres.

ACKNOWLEDGEMENTS

Authors are thankful to Principal Luqman College of Pharmacy, Gulbarga (India) for providing research laboratory to carry out this project work and also extend thanks to Ciron Drugs and Pharmaceutical Pvt. Ltd., Mumbai for providing gift sample of ketoprofen and thanks to Deggusa india pvt. Ltd., Mumbai for providing gift sample of Eudragit S 100 and Eudragit L100.

REFERENCES