Design and Evaluation of Floating Tablets of Pioglitazone
Employing Selected Natural and Synthetic Polymers

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ABSTRACT

Floating tablets of pioglitazone were formulated employing (i) olibanum (a natural gum resin) (ii) HPMCK15M (a synthetic polymer) and (iii) cross-linked starch urea (a new modified starch) with an objective of evaluating them as matrix formers in the design of floating tablets of pioglitazone. Floating tablets of pioglitazone were designed employing the above mentioned three polymers as matrix formers, sodium bicarbonate as gas generating agent and bees wax and ethyl cellulose as floating enhancers and the tablets were evaluated for floating and drug release characteristics. Floating tablets formulated employing (i) olibanum (a natural gum resin) (ii) HPMCK15M (a synthetic polymer) and (iii) cross-linked starch urea (a new modified starch) as matrix formers and sodium bicarbonate as gas generating agent, beeswax and ethyl cellulose as floating enhancers (PF7, PF8, PF9) exhibited a floating time of more than 44 hours after a floating lag time in the range 2 – 6 min. These floating tablets also provided slow and complete release of pioglitazone over 24 hours. Release was diffusion controlled and followed zero order kinetics. Non – Fickian diffusion was the release mechanism from all the floating tablets formulated. As such these tablets (PF7, PF8, PF9) are considered as good floating tablets for controlled release of pioglitazone. Olibanum and cross-linked starch urea are suitable as matrix formers for floating tablets and are comparable to HPMC K15M, a widely used polymer for floating tablets and for controlled release.

Key words: Floating tablets, Pioglitazone, HPMCK15M, Olibanum, Cross-linked Starch Urea

INTRODUCTION

The oral route of drug administration is the most convenient and commonly used method of drug delivery. However, this route has certain problems such as unpredictable gastric emptying rate, short gastrointestinal transit time (8 – 12 h) and existence of an absorption window in the gastric and upper small intestine for several drugs1,2 leading to low and variable oral absorption over shorter period of time. The real issue in the development of oral drug delivery systems is to prolong the residence time of the dosage form in the stomach or upper g. i. tract until the drug is completely released and absorbed.

Several approaches are currently used to retain the dosage form in the stomach. These include bioadhesive systems3, swelling and expanding systems4,5, floating systems6,7 and other delayed gastric emptying devices8–9. The principle of floating tablets offers a simple and practical approach to achieve increased gastric residence time to enhance the bioavailability and to obtain controlled release. Floating tablets are designed based on gas generating principle. Design of floating tablets needs a strong matrix forming polymer. In the present study three polymers namely (i) olibanum (a natural gum resin) (ii) HPMCK15M (a synthetic polymer) and (iii) cross-linked starch urea (a new modified starch) were evaluated as matrix formers in the design of floating tablets of pioglitazone. Floating tablets of pioglitazone were designed employing the above mentioned three polymers as matrix formers, sodium bicarbonate as gas generating agent and bees wax and ethyl cellulose as floating enhancers and the tablets were evaluated for floating and drug release characteristics. Pioglitazone is an effective oral anti diabetic agent that belongs to the thiazolidinediones drug class. Pioglitazone belongs to BCS class II and exhibits low and variable oral bioavailability. It majorly absorbs from stomach10. Pioglitazone has a short biological half life of 3-5 hours and is eliminated rapidly11. Hence controlled release floating formulations are needed for pioglitazone to improve its oral bioavailability and also to prolong its duration of action and to improve patient compliance.

EXPERIMENTAL

Materials: Pioglitazone was a gift sample from M/s Dr. Reddys Labs Ltd., Hyderabad. Cross-linked starch urea (prepared in the laboratory), Olibanum (procured from Girijan Cooperative Corporation, Govt. of AP, Visakhapatnam), Hydroxy propyl methyl cellulose (K15M, Colorcon) Bees wax, LP and ethyl cellulose were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Preparation of Cross linked Starch urea

Potato starch (9 parts) was dispersed in purified water (10 parts) to form starch slurry. Urea (1 part), calcium chloride (1 part) were dissolved in purified water (40 parts) and the solution was heated to boiling. While boiling, the starch slurry was added and mixed. Mixing while heating was continued for 20 minutes to form cross-linked starch urea polymer. The mass formed was spread on to a stainless steel plate and dried at 85°C for 6-8 h. The dried polymer was powdered and passed through mesh No. 120.

Preparation of floating tablets: Matrix tablets each containing 30 mg of pioglitazone were formulated employing (i) olibanum (a natural gum resin) (ii) HPMCK15M (a synthetic polymer) and (iii) cross-linked starch urea (a new modified starch) as per the formulae given in Table 1. Sodium bicarbonate was used as gas generating agent at 15% strength in each case. Bees wax (15%) and ethyl cellulose (5%) were used as floating enhancers in all the formulations.

The required quantities of pioglitazone, olibanum, cross-linked starch urea, HPMC K15M, bees wax, ethyl cellulose and lactose as per the formulae were thoroughly mixed in a mortar by following geometric dilution technique. The granulating fluid (a mixture of water and alcohol in 1:1 ratio) was added and mixed thoroughly to form dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60°C for 2 h. The dried granules were passed through mesh No.16 to break the aggregates. The lubricants, talc (2%) and magnesium stearate (2%) were passed through mesh No. 60 on to the dry granules and blended in a closed
polyethylene bag. The tablet granules were compressed into tablets on a 16-station tablet punching machine (M/s Cadmach Machineries Pvt. Ltd., Ahmedabad) to a hardness of 8 – 10 kg/sq.cm.

**Evaluation of tablets:** Hardness of the tablets was tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Disintegration time of the tablets was determined using a thermonic tablet disintegration test machine using water, 0.1 N HCl and phosphate buffer of pH 7.4 as the test fluids.

**Estimation of pioglitazone:** An ultraviolet (UV) spectrophotometric method based on the measurement of absorbance at 269 nm in 0.1N hydrochloric acid was used for the estimation of pioglitazone. The method obeyed Beer-Lambert’s law in the concentration range of 1-10 μm/ ml. When a standard drug solution was assayed repeatedly (n = 6), the relative error (accuracy) and coefficient of variation (precision) were found to be 0.60% and 1.2% respectively. No interference from the excipients used was observed.

**Floating lag time and floating time:** In vitro buoyancy was determined by measuring floating lag time and duration of floating. The tablets were placed in a 250 mL glass beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration during which the tablet remains floating was determined as floating time.

**Drug release study:** Drug release from the matrix tablets was studied using 8-station dissolution rate test apparatus (Labindia, Disso 2000) employing a paddle stirrer at 50 rpm and at temperature of 37±1°C. Hydrochloric acid, 0.1 N (900 mL) was used as dissolution fluid. A 5 mL aliquot of dissolution medium was withdrawn through a filter (0.45 μm) at different time intervals and assayed spectrophotometrically by measuring absorbance at 269 nm. All drug release experiments were conducted in triplicate (n=3).

**Data analysis:** Drug release data were analyzed as per zero order, first order, Higuchi12 and peppas13 equation models to assess drug release kinetics and mechanism from the tablets.

**RESULTS AND DISCUSSION**

Floating tablets of pioglitazone were prepared employing (i) olibanum (a natural gum resin) (ii) HPMC K15M (a synthetic polymer) and (iii) cross-linked starch urea (a new modified starch) with an objective of evaluating them as matrix formers in the design of floating tablets of pioglitazone. Floating tablets of pioglitazone were designed employing the above mentioned three polymers as matrix formers, sodium bicarbonate as gas generating agent and bees wax and ethyl cellulose as floating enhancers and the tablets were evaluated for floating and drug release characteristics. Floating tablets of pioglitazone were designed in the present study to enhance its oral bioavailability and to achieve controlled release over 24 h for once a day administration.

Olibanum is a natural gum resin obtained from Boswellia serrata, Roxburgh and other species of Boswellia. Olibanum consists4 chiefly an acid resin (50-60%), gum (30-36%) and volatile oil (3-8%). The resin contains5 mainly a resin acid (boswellic acid) and a resin (olibanoresene) in equal proportions. Chowdary, et al.14-15 reported first time olibanum gum and resin as efficient matrix formers and microencapsulating agents for controlled release.

Modified starches are promising and having good potential as release retardants and rate controlling polymers for controlled release. Cross-linked starch urea is a modified starch prepared by gelatinization of starch in the presence of urea and cross linking by treatment with calcium chloride. The cross linked polymers generally swell in water and aqueous fluids to form gelatinized matrices suitable for controlled release. Cross-linked starch urea is reported16-20 as an efficient rate controlling matrix former for controlled release.

The matrix formers were used at strength of 50% in the matrix tablets. The matrix tablets were prepared by wet granulation method employing water - alcohol (1:1) as granulating fluid. A total of 9 floating tablet formulations of pioglitazone were prepared employing sodium bicarbonate as gas generating agent at 15% strength in the tablets, beeswax (15%) and ethyl cellulose (5%) as floating enhancers. The formulae of these matrix tablets are given in Table 1. All the matrix tablets prepared were evaluated for hardness, friability, floating characteristics, disintegration and drug release characteristics.

Drug content, hardness, friability and disintegration time of various tablet formulations are given in Table 2. Hardness of the matrix tablets was in the range 7.0-8.5 kg/sq.cm. Weight loss in the friability test was less than 0.3% in all the cases. All the tablets prepared contained pioglitazone within 100±5% of the labeled claim. All the matrix tablets prepared were found to be non-disintegrating in water and aqueous fluids of acidic pH (1.2) and alkaline pH (7.4). As such all the matrix tablets prepared employing HPMC K15M, olibanum and cross-linked starch urea were of good quality with regard to drug content, hardness and friability.

Floating characteristics of various matrix tablets formulated are given in Table 2. Tablets formulated with sodium bicarbonate (15%) alone exhibited floating time in the range 5-8.5 h with all the three polymers. Floating lag time was relatively longer, 21.6±2.88 min with olibanum and 13±1.73 min with cross-linked starch urea and HPMC K15M tablets exhibited a short floating lag time in the range 4-6 min. The floating characteristics of the formulations PF1, PF2 and PF3 which contain sodium bicarbonate (15%) were not satisfactory with all the three polymers and need to be improved. Beeswax and ethyl cellulose, which are lipophilic materials having density less than one, are tried to decrease the hydrophilic property of the formulation to increase the buoyancy. Beeswax (15%) was incorporated in formulations PF4, PF5 and PF6 retaining sodium bicarbonate (15%) in these formulations. Floating time was in the range 23-42 h and floating lag time was in the range 2-11 min. Among the three polymers, HPMC K15M exhibited better floating characteristics than the other two. Based on the floating characteristics, the order of performance of various polymers tested was HPMC K15M > Cross-linked starch urea > Olibanum.

Formulations PF7, PF8 and PF9 contain ethyl cellulose (5%) in addition to beeswax (15%). These formulations exhibited excellent floating characteristics. Floating time was in the range 44-48 h and floating lag time 1-3 min with HPMC; 4-7 min with cross-linked starch urea and 5-6 min with olibanum. The floating characteristics of matrix tablets formulated with olibanum (PF7) and cross-linked starch urea (PF8) are comparable with those of tablets formulated with HPMC K15M (PF9) when floating enhancers (beeswax, ethyl cellulose) are included in the tablet formulations.

Pioglitazone release from the floating tablets was studied in 0.1 N hydrochloric acid. The release characteristics are shown in Tables 3. Pioglitazone release from all the floating tablets prepared was slow and spread over 24 h and depended on the polymer used and composition of the tablets. Release data were analyzed by zero order, first order, Higuchi12 and Peppas13 equation models. The correlation coefficient (r) values in various models are given in Table 4. When the release data were analyzed as per zero and first order models, the ‘r’ values were relatively higher in zero order model with all the floating tablets formulated indicating that the drug release from all these tablets followed zero order kinetics. Pioglitazone release data also obeyed Higuchi12 and Peppas13 equation models with ‘r’ values greater than 0.913. When percent release was plotted against time, linear regressions with ‘r’ > 0.943 were observed with all the floating tablets prepared indicating that the drug release from all these tablets was diffusion controlled. When the release data were analyzed as per Peppas13 equation, the release exponent ‘n’ (Table 4) was found in the range 0.481 to 0.955 indicating non fickian (anamalous) diffusion as the release mechanism from all the floating tablets prepared with various polymers.

Pioglitazone release from the floating tablets prepared with the three polymers alone (i.e. PF1, PF2, PF3) was relatively rapid. T50% (time for 90% release) was 5.6, 6.4 and 9.4 respectively with floating tablets prepared employing olibanum, cross-linked starch urea and HPMC alone. As such these tablets (i.e. PF1, PF2, and PF3) are considered not suitable for con
Floating Tablets Prepared Employing Various Polymers

Table 1: Formulae of Floating Matrix Tablets of Pioglitazone Prepared Employing Various Polymers

<table>
<thead>
<tr>
<th>Ingredient (mg/tablet)</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PF1</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>30</td>
</tr>
<tr>
<td>Lactose</td>
<td>47.5</td>
</tr>
<tr>
<td>Olibanum</td>
<td>125</td>
</tr>
<tr>
<td>Cross-linked Starch Urea</td>
<td>—</td>
</tr>
<tr>
<td>HPMC</td>
<td>—</td>
</tr>
<tr>
<td>Sodium Bicarbonate (15%)</td>
<td>—</td>
</tr>
<tr>
<td>Beeswax (15%)</td>
<td>—</td>
</tr>
<tr>
<td>Ethyl Cellulose (5%)</td>
<td>—</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>—</td>
</tr>
<tr>
<td>Talc</td>
<td>5</td>
</tr>
<tr>
<td>Weight of the Tablet (mg)</td>
<td>250</td>
</tr>
</tbody>
</table>

These tablets also exhibited good floating characteristics apart from controlled release over 24h. Based on the release characteristics of tablets PF7, PF8 and PF9, which contain sodium bicarbonate (15%), beeswax (15%), ethyl cellulose (5%), the order of release retarding efficiency of various polymers was olibanum > cross-linked starch urea > HPMC (based on Kp). The results, thus, indicated that both olibanum and cross-linked starch urea are suitable as matrix formers for floating tablets and are comparable to HPMC K15M, a widely used polymer for floating tablets and for controlled release.

Table 2: Drug Content, Hardness, Friability and Floating Characteristics of the Pioglitazone Floating Tablets Prepared Employing Various Polymers

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Hardness (Kg/sq.cm)</th>
<th>Friability (%)</th>
<th>Pioglitazone Content (mg/tablet)</th>
<th>Floating Lag Time (min)</th>
<th>Floating Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF1</td>
<td>8.0</td>
<td>0.30</td>
<td>28.8</td>
<td>21.6±2.88</td>
<td>6.6±0.57</td>
</tr>
<tr>
<td>PF2</td>
<td>7.5</td>
<td>0.25</td>
<td>30.3</td>
<td>13±1.73</td>
<td>5.3±0.57</td>
</tr>
<tr>
<td>PF3</td>
<td>8.5</td>
<td>0.30</td>
<td>28.5</td>
<td>5±1</td>
<td>8.3±1.53</td>
</tr>
<tr>
<td>PF4</td>
<td>8.5</td>
<td>0.25</td>
<td>28.8</td>
<td>10±1.15</td>
<td>23.3±1.15</td>
</tr>
<tr>
<td>PF5</td>
<td>8.0</td>
<td>0.20</td>
<td>29.4</td>
<td>8.3±2.51</td>
<td>28.3±2.51</td>
</tr>
<tr>
<td>PF6</td>
<td>7.5</td>
<td>0.20</td>
<td>30.0</td>
<td>2±1.5</td>
<td>41.3±3.09</td>
</tr>
<tr>
<td>PF7</td>
<td>8.5</td>
<td>0.26</td>
<td>28.8</td>
<td>5.3±0.57</td>
<td>44±3.46</td>
</tr>
<tr>
<td>PF8</td>
<td>8.0</td>
<td>0.27</td>
<td>29.1</td>
<td>5.6±1.52</td>
<td>45±3.05</td>
</tr>
<tr>
<td>PF9</td>
<td>7.0</td>
<td>0.25</td>
<td>28.8</td>
<td>2±1</td>
<td>47±3.15</td>
</tr>
</tbody>
</table>

CONCLUSIONS
Floating tablets formulated employing (i) olibanum (a natural gum resin) and (ii) HPMC K15M (a synthetic polymer) and (iii) cross-linked starch urea (a new modified starch) as matrix formers and sodium bicarbonate as gas generating agent, beeswax and ethyl cellulose as floating enhancers (PF7, PF8, PF9) exhibited a floating time of more than 44 hours after a floating lag time in the range 2 – 6 min. These floating tablets also provided slow and complete release of pioglitazone over 24 hours. Release was diffusion controlled and followed zero order kinetics. Non – Fickian diffusion was the release mechanism from all the floating tablets formulated. As such these tablets (PF7, PF8, PF9) are considered as good floating tablets for controlled release of pioglitazone. Olibanum and cross-linked starch urea are suitable as matrix formers for floating tablets and are comparable to HPMC K15M, a widely used polymer for floating tablets and for controlled release.

REFERENCES

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