FORMULATION AND EVALUATION OF BILAYERED FLOATING TABLETS OF CAPTOPRIL USING OLIBANUM GUM - A NATURAL POLYMER

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ABSTRACT

The main objective of the present study is to study the rate controlling efficiency and release retarding efficiency of olibanum gum – a natural polymer obtained from Boswellia serrata, Roxburgh and other species of Boswellia. Captopril is an antihypertensive drug and has a half life of 2hrs and requires a daily dose of 37.5-75 mg to be taken three times. So, a controlled release form is required. Floating tablets of Captopril (25mg) were prepared employing olibanum as matrix former, sodium bicarbonate, tartaric acid as gas generating agent and HPMC K4M as floating enhancers by direct compression method and the tablets F1 to F8 were formulated with varied proportions of olibanum gum. The formulations were evaluated for various pre compression, post compression parameters, floating and drug release characteristics. All the prepared formulations were of good quality. Formulation (F7) exhibited a floating time of more than 8 hours and with a floating lag time less than 70sec and provided slow and complete release of Captopril over 12 hours. Release was diffusion controlled and followed zero order kinetics. Non – Fickian diffusion was the release mechanism from all the floating tablets formulated. FTIR studies reports indicate no interaction between drug and polymer. Hence Olibanum gum was found suitable as release retarding polymer for better controlled release of Captopril over a period of 12h and also cost effective.

Keywords

Floating Tablets, Captopril, Olibanum.

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INTRODUCTION

In the recent years of development in pharmaceutics, increasing attention is being given for administering drugs in a more challenging and controlled manner for better therapeutic end point. 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 drugs[1, 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. Various approaches are used to retain the dosage form in the stomach. These include bioadhesive systems [3], swelling and expanding systems [4, 5], floating systems [6, 7] and other delayed gastric emptying devices[8, 9]. A floating drug-delivery system floats in the gastric juice without affecting the gastric emptying rate. It forms a cohesive gel barrier that serves as a reservoir and releases the drug over the desired period of time. This technique helps to increase a drugs gastric residence time and reduces the variability in bioavailability [10].

Regular research is going on in field of use of natural occurring biocompatible polymeric material in designing of dosage form for oral controlled release administration. Natural gums are biodegradable and nontoxic, which hydrate and swell on contact with aqueous media, and these have been used for the preparation of dosage form[11]. Floating tablets are designed based on gas generating principle. Design of floating tablets needs a strong matrix forming polymer. In the present study a natural gum namely olibanum was evaluated as matrix formers in the design of floating tablets. Olibanum is a natural gum resin obtained from Boswellia serrata, Roxburgh and other species of Boswellia. Olibanum consists [12] of chiefly an acid resin (50-60%), gum (30-36%) and volatile oil (3-8%). The resin contains [13] mainly a resin acid (boswellic acid) and a resene (olibanoresene) in equal proportions. Chowdary, et al. [14-23] reported first time olibanum gum and resin as efficient matrix formers and microencapsulating agents for controlled release. So, present study is aimed to use olibanum gum as matrix former as it is cost effective. Captopril is an antihypertensive agent, has been widely used for the treatment of hypertension and congestive heart failure. Captopril is rapidly absorbed and has bioavailability of about 75% and half life is approximately 2 hours [24]. It has been reported, however, that the duration of antihypertensive action after a single oral dose of Captopril is only 6-8 hours, so clinical use requires a daily dose of 37.5-75 mg to be taken three times. It is most stable at pH 1.2 and as pH increases; it becomes unstable and undergoes a degradation reaction. The virtue of the prolonged release dosage form of Captopril has been reviewed. The present study is aimed to evaluate release retarding efficiency of olibanum gum at different concentrations for controlled release of Captopril by prolonging its gastro residence time.

MATERIALS AND METHODS

Materials:

Captopril was a gift sample from Micro Labs Ltd, Olibanum (procured from Nutritroma, Hyderabad), Hydroxy propyl methyl cellulose (HPMCK4M), Tartaric acid, I.P and Sodium bicarbonate were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Methods:

Preparation of olibanum gum powder:

Olibanum is available in crystal form. The crystal form of Olibanum gum was dried at 60°C for 4hrs in hot air oven. Then the dried form was crushed in a mortar to make it powder. Then it was passed through 200# size to obtain fine powder.

Preparation of floating tablets:

Matrix tablets each containing 25 mg of captopril were formulated employing olibanum gum as per the formulae given in Table 1. Sodium bicarbonate (12%) and tartaric acid (2%) was used as gas generating agent in each case. HPMCK4M (12%) was used as floating enhancer in all the formulations.

Preparation of floating Layer:

Floating layer was formulated with HPMCK4M and by adding an effervescent mixture of sodium bicarbonate and tartaric acid. Floating and effervescent mixture were blended in a mortar. To that PVPK-30 and microcrystalline cellulose were added. Finally this was compressed using direct compression technique.

Preparation of Bilayered tablets:

Captopril, olibanum gum and PVPK-30 were employed in the release layer formulation for the controlled delivery of Captopril. Various formulations of Bilayered floating tablets were given in Table 1. Matrix tablets were prepared by direct compression technique. Before compression magnesium stearate was added. At the beginning floating layer was placed in dye cavity and compression was done. There after release layer was added and subjected to compression using RIMEK tabletting machine with a compression force of about of 5-6 kg/cm². These tablets are evaluated for thickness, hardness, friability, drug content and in vitro buoyancy studies.
he matrix tablets
the concentration range of 1
ared powder blend was evaluated for various pre compression parameters like Angle of repose, Bulk density,

Evaluation of powder blends:
The prepared powder blend was evaluated for various pre compression parameters like Angle of repose, Bulk density, Tapped density, Carrs index and Hausners ratio and results were given in Table 2.

Table 2: Pre-compression parameters for the powder blend F1-F8.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Bulk density (g/cm³)*</th>
<th>Tapped density (g/cm³)*</th>
<th>Carr’s index (%)*</th>
<th>Hausner’s ratio</th>
<th>Angle of repose (°)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.287±0.024</td>
<td>0.362±0.026</td>
<td>16.08±0.034</td>
<td>1.22</td>
<td>26.19±0.014</td>
</tr>
<tr>
<td>F2</td>
<td>0.362±0.016</td>
<td>0.434±0.022</td>
<td>15.06±0.028</td>
<td>1.16</td>
<td>23.24±0.017</td>
</tr>
<tr>
<td>F3</td>
<td>0.294±0.018</td>
<td>0.354±0.024</td>
<td>14.54±0.021</td>
<td>1.21</td>
<td>22.15±0.013</td>
</tr>
<tr>
<td>F4</td>
<td>0.285±0.026</td>
<td>0.342±0.032</td>
<td>17.47±0.027</td>
<td>1.22</td>
<td>21.65±0.019</td>
</tr>
<tr>
<td>F5</td>
<td>0.276±0.032</td>
<td>0.336±0.034</td>
<td>16.58±0.038</td>
<td>1.23</td>
<td>19.47±0.016</td>
</tr>
<tr>
<td>F6</td>
<td>0.273±0.022</td>
<td>0.332±0.024</td>
<td>17.44±0.024</td>
<td>1.23</td>
<td>24.85±0.026</td>
</tr>
<tr>
<td>F7</td>
<td>0.282±0.025</td>
<td>0.362±0.027</td>
<td>16.22±0.025</td>
<td>1.24</td>
<td>22.35±0.023</td>
</tr>
<tr>
<td>F8</td>
<td>0.290±0.017</td>
<td>0.382±0.022</td>
<td>15.25±0.028</td>
<td>1.26</td>
<td>21.23±0.019</td>
</tr>
</tbody>
</table>

Evaluation of tables [25-26]:
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 thermionic tablet disintegration test machine using water, 0.1 N HCl and phosphate buffer of pH 7.4 as the test fluids. The results were given in Table 3 and all the tablets prepared were within the official limits.

Table 3: Uniformity of weight, Hardness, Friability, Thickness, Drug content, Disintegration time of the matrix tablets prepared.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Uniformity of wt(mg) (A.M±S.D)*n=20</th>
<th>Hardness (kg/cm²) (A.M±S.D)* n=5</th>
<th>%Friabilityn=6</th>
<th>Thickness(mm) (A.M±S.D)*n=5</th>
<th>%Drug content</th>
<th>Disintegration Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>502.81±1.2</td>
<td>5.533±0.11</td>
<td>0.69</td>
<td>4.28±0.046</td>
<td>95±0.02</td>
<td>Non-disintegrating</td>
</tr>
<tr>
<td>F2</td>
<td>502.46±1.1</td>
<td>5.067±0.11</td>
<td>0.3</td>
<td>4.177±0.02</td>
<td>94.5±0.0</td>
<td>Non-disintegrating</td>
</tr>
<tr>
<td>F3</td>
<td>502.17±1.3</td>
<td>6.201±0.112</td>
<td>0.5</td>
<td>4.53±0.025</td>
<td>94.8±0.0</td>
<td>Non-disintegrating</td>
</tr>
<tr>
<td>F4</td>
<td>502.36±1.5</td>
<td>6.467±0.23</td>
<td>0.227</td>
<td>4.2±0.036</td>
<td>97±0.02</td>
<td>Non-disintegrating</td>
</tr>
<tr>
<td>F5</td>
<td>502.82±1.5</td>
<td>5.133±0.11</td>
<td>0.465</td>
<td>4.467±0.02</td>
<td>99.8±0.0</td>
<td>Non-disintegrating</td>
</tr>
<tr>
<td>F6</td>
<td>501.79±0.7</td>
<td>6.067±0.11</td>
<td>0.342</td>
<td>4.5±0.026</td>
<td>98.7±0.0</td>
<td>Non-disintegrating</td>
</tr>
<tr>
<td>F7</td>
<td>502.54±2.1</td>
<td>6.333±0.23</td>
<td>0.278</td>
<td>4.13±0.04</td>
<td>96.0±0.0</td>
<td>Non-disintegrating</td>
</tr>
<tr>
<td>F8</td>
<td>502.16±1.4</td>
<td>6.733±0.11</td>
<td>0.764</td>
<td>4.1±0.026</td>
<td>99.1±0.0</td>
<td>Non-disintegrating</td>
</tr>
</tbody>
</table>
Floating behavior of the tablets:
The in vitro buoyancy was determined by the floating lag time (time period between placing the tablet in the medium and the floating time) method described by Rosa et al, 1994. Tablets were placed in a 100 ml beaker containing 0.1 N HCL. The time required for the tablets to rise to the surface and float was taken as the floating lag time [27-29]. The results given in Table4.

<table>
<thead>
<tr>
<th>S. No</th>
<th>Buoyancy lag time</th>
<th>Total floating time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>180 sec</td>
<td>9</td>
</tr>
<tr>
<td>F2</td>
<td>180sec</td>
<td>11</td>
</tr>
<tr>
<td>F3</td>
<td>120sec</td>
<td>&gt;12</td>
</tr>
<tr>
<td>F4</td>
<td>110sec</td>
<td>&gt;12</td>
</tr>
<tr>
<td>F5</td>
<td>&lt;50 sec</td>
<td>&gt;12</td>
</tr>
<tr>
<td>F6</td>
<td>&lt;70sec</td>
<td>&gt;12</td>
</tr>
<tr>
<td>F7</td>
<td>&lt;50sec</td>
<td>&gt;16</td>
</tr>
<tr>
<td>F8</td>
<td>&lt;70sec</td>
<td>&gt;8</td>
</tr>
</tbody>
</table>

Drug release study:
Drug release from the matrix tablets was studied using 8-station dissolution rate test apparatus employing a paddle stirrer (USP Type II) 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 205 nm given in Table 5 and drug release profiles given in Fig 1&2.

Table 5: Drug Release Profiles of Captopril (25mg) Floating Matrix Tablets Employing Olibanum Gum and Commercial Products.

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>49.0452</td>
<td>47.8774</td>
<td>45.5419</td>
<td>40.871</td>
<td>42.0387</td>
<td>40.871</td>
<td>37.3677</td>
<td>33.8645</td>
</tr>
<tr>
<td>4</td>
<td>72.4</td>
<td>70.0645</td>
<td>68.8968</td>
<td>59.5548</td>
<td>57.2194</td>
<td>56.0516</td>
<td>53.7161</td>
<td>49.0452</td>
</tr>
<tr>
<td>8</td>
<td>99.419</td>
<td>89.7484</td>
<td>86.4129</td>
<td>78.7097</td>
<td>72.4</td>
<td>71.2323</td>
<td>67.729</td>
<td>63.0581</td>
</tr>
<tr>
<td>10</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>91.81</td>
<td>85.2452</td>
<td>84.0774</td>
<td>80.5</td>
<td>77.071</td>
</tr>
<tr>
<td>12</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>96.9226</td>
<td>94.5871</td>
<td>89.112</td>
<td>86.4129</td>
</tr>
</tbody>
</table>

Fig 1: Zero order Drug Release Profiles of Captopril (25mg) Floating Matrix Tablets Employing Olibanum Gum.
Data analysis:

Drug release data were analyzed as per zero order, first order, Higuchi [30] and Peppas [31] equation models to assess drug release kinetics and mechanism from the tablets given in Table 6 and Fig 3&4.

Table 6: Regression Coefficient (R^2) Values in Analysis of Release Data.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>R^2</th>
<th>Slope(n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zero Order</td>
<td>First Order</td>
</tr>
<tr>
<td>F1</td>
<td>0.9931</td>
<td>0.7305</td>
</tr>
<tr>
<td>F2</td>
<td>0.9964</td>
<td>0.9320</td>
</tr>
<tr>
<td>F3</td>
<td>0.9942</td>
<td>0.9531</td>
</tr>
<tr>
<td>F4</td>
<td>0.9947</td>
<td>0.9313</td>
</tr>
<tr>
<td>F5</td>
<td>0.9857</td>
<td>0.9685</td>
</tr>
<tr>
<td>F6</td>
<td>0.9937</td>
<td>0.9685</td>
</tr>
<tr>
<td>F7</td>
<td>0.9937</td>
<td>0.9685</td>
</tr>
<tr>
<td>F8</td>
<td>0.9980</td>
<td>0.9685</td>
</tr>
</tbody>
</table>
Drug-Excipients interaction study

Infrared Spectrophotometric is an analytical technique utilized to check the chemical interaction between the drug and other excipients used in the formulation. One milligram of the sample was powdered and intimately mixed with 10mg of dry powdered potassium bromide. The powdered mixture was taken in a diffuse reflectance sampler and the spectrum was recorded by scanning in the wavelength region of 4000-400cm\(^{-1}\) in an FTIR spectrophotometer (Jasco 460 plus, Japan). The IR spectrum of the drug was compared with that of the physical mixture to check for any possible drug-excipients interaction given in Fig 5,6&7 and in Table 7.

Fig 4: Log Cumulative Percentage Release Vs Log Time Plots of Captopril

FTIR Spectroscopy

Fig 5: FTIR spectra of captopril
Fig 6: FTIR spectra of olibanum gum

Fig 7: FTIR spectra of Captopril and olibanum gum

Table 7: FTIR Drug-Excipient studies.

<table>
<thead>
<tr>
<th>Functional groups</th>
<th>Pure drug (cm⁻¹)</th>
<th>Drug+Olibanum gum (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-H(Thiol)</td>
<td>2567</td>
<td>2562.96</td>
</tr>
<tr>
<td>C=O(in COOH)</td>
<td>1747</td>
<td>1742.51</td>
</tr>
<tr>
<td>C=O(in amide)</td>
<td>1591</td>
<td>1583.63</td>
</tr>
<tr>
<td>CH₃ (symmetric)</td>
<td>2877</td>
<td>2872.78</td>
</tr>
<tr>
<td>CH₃(asymmetric)</td>
<td>2981</td>
<td>2978.45</td>
</tr>
<tr>
<td>CH₂</td>
<td>2949</td>
<td>2934.23</td>
</tr>
</tbody>
</table>
RESULTS AND DISCUSSION

Olibanum is a natural gum resin obtained from *Boswellia serrata*, Roxburgh and other species of Boswellia. Olibanum consists (12) of chiefly an acid resin (50-60%), gum (30-36%) and volatile oil (3-8%). The resin contains (13) mainly a resin acid (boswelliacid) and a resin (olibanoresene) in equal proportions. Chowdary, et al.(14-23) reported first time olibanum gum and resin as efficient matrix formers and microencapsulating agents for controlled release. Bilayered Floating tablets of captopril were designed in the present study to enhance its oral bioavailability and to achieve controlled release over 12 h.

The matrix tablets were prepared by direct compression technique. A total of 8 floating tablet formulations of captopril were prepared employing olibanum gum with different proportions in the formulation. sodium bicarbonate, tartaric acid as gas generating agent at 12% and 2% strength respectively in the tablets, HPMCK4M as floating enhancer. The formulae of these matrix tablets are given in Table 1. All the matrix tablets prepared were evaluated for pre formulation properties given in Table 2 revealed that all are within the limits. All the tablets were evaluated for post compression properties like hardness, friability, floating characteristics, disintegration and drug release characteristics.

Drug content, hardness, friability and disintegration time of various tablet formulations are given in Table 3. Hardness of the matrix tablets was in the range 5-6 kg/sq.cm. Weight loss in the friability test was less than 0.6% in all the cases. All the tablets prepared contained captopril within 90±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 olibanum were of good quality with regard to drug content, hardness and friability.

Floating characteristics of various matrix tablets formulated are given in Table 4. Tablets formulated with sodium bicarbonate (12%), tartaric acid (2%) with floating lag time of 70sec to 180sec with olibanum.

Captopril release from the floating tablets was studied in 0.1 N Hcl. The release characteristics are shown in Table 5 & Fig 1&2. Captopril release from all the floating tablets prepared was slow and spread over 16 h and depended on the polymer used and composition of the tablets. Release data were analyzed by zero order, first order, Higuchi and Peppas equation models. The correlation coefficient (R²) values in various models are given in Table 6. When the release data were analyzed as per zero and first order models, the R² 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. Captopril release data also obeyed Higuchi equation model with R² values greater than 0.9318. When percent release was plotted against √time, linear regressions with ‘r’ > 0.97 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 Peppas equation, the release exponent ‘n’ (Table.4) was found in the range 0.70 to 0.87 indicating non-fickian (anomalous) diffusion as the release mechanism from all the floating tablets prepared with olibanum polymer. FTIR studies reported that Olibanum gum is compatible with drug as there are no interactions. The results, thus, indicated that olibanum was suitable as better release rate retarding polymer for controlled release of Captopril.

CONCLUSIONS

Floating tablets formulated employing olibanum (a natural gum) as a matrix former, sodium bicarbonate, tartaric acid as gas generating agent and HPMCK4M as floating enhancers exhibited a floating time of more than 16 hours after a floating lag time in the range 70 –180 sec. These floating tablets also provided slow and complete release of Captopril over 16 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 (F1- F8) are considered as good floating tablets for controlled release of Captopril. Olibanum was found to be suitable as matrix formers for better controlled release of Captopril from the tablets. It was found that increase in concentrations of polymer concentration there is increase in drug release efficiency and that in future it can be used in place of other commercial polymers as its cost was less and of natural origin.

Once daily sustained release bilayer tablet of Captopril has achieved the objective of controlled drug delivery with prolonged drug release, cost effective, low dose and frequency of administration and hence improved patient compliance.

REFERENCES