Formulation and Evaluation of Effervescent Floating Matrix Tablet of Losartan Potassium

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Abstract

Gastroretentive system can remain in the gastric region for several hours. In this present investigation delayed release tablets of Losartan Potassium were formulated using two different grades of methocel K100 and K15 by effervescent technique. Sodium bicarbonate was employed as gas generating agent. Tablets prepared by wet granulation method were further evaluated for hardness, friability, weight variation, drug content, in-vitro buoyancy and dissolution studies. All the prepared tablets showed good in-vitro buoyancy. The effect of citric acid and two different grades of methocel on drug release profile and floating property were investigated. A combination of sodium bicarbonate and citric acid was found to achieve optimum in vitro buoyancy. It was observed that tablet remain float for 8-10 hrs. The tablets with high grades of methocel (K100) were found to float for longer duration as compared with formulations containing methocel K15M. It is evident from this investigation that gas powered floating matrix tablet could be promising delivery system for Losartan Potassium with sustained release action.

Key words- Effervescence, Losartan Potassium, Granulation, GRT, GRDF

Introduction

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDF or GRDS). [1] GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form. [2]

Dosage form with prolonged GRT, i.e. gastro retentive dosage form (GRDF), will bring about new and important therapeutic options such as (Longer et al., 1985) –

1) This application is especially effective in sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug

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dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To override this problem, erodible, gastro retentive dosage forms have been developed that provide continuous, controlled administration of sparingly soluble drugs at the absorption site.

2) GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa. (For e.g. Eradicating Helicobacter pylori from the submucosal tissue of stomach) making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis, reduce the risk of gastric carcinoma and administer non-systemic controlled release antacid formulations (calcium carbonate).

3) GRDFs can be used as carriers for drugs with so-called absorption windows. These substances for e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillin’s, cephalosporin’s, amino glycosides, tetracycline’s etc.), are taken up only from very specific sites of the GI mucosa.

Materials and Methods

Materials

Losartan Potassium was a kind gift from Cadila Pharma, Ahemdabad, India. Methocel K 15M and Methocel K 100M were received as a gift sample by Colorcon Asia Pvt. ltd. (Mumbai, India). Polyvinyl Pyrrolidine K30 (PVP K 30), lactose and talc were purchased from S.D. Fine chemicals Ltd., Mumbai. Magnesium stearate, sodium bicarbonate and citric acid were purchased from Ases Chem. Works, Jodhpur. All other ingredients were of laboratory grade.

Methods

Preparation of Losartan Potassium floating tablets

The ingredients (except glidets and lubricant) were thoroughly mixed in poly bag and passed through sieve # 60 (Table-1). Granulation was done with a solution of calculated quantity of PVP K-30 in sufficient isopropyl alcohol. The wet mass was passed through sieve no. 12, and dried at 45-55°C for 2 hours. The dried granules were sized by sieve no.18 and mixed with magnesium stearate and talc. The granules thus obtained were compressed into tablets on a Cadmach machine.

Evaluation of Granules

1. Angle of repose

Angle of repose was determined by using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height, h, was obtained. Diameter of heap, D, was measured. The repose angle (θ) was calculated by following formula.\[\tan \theta = \frac{2h}{D}\]

2. Carr’s index and Hausner ratio

Tapped density was determined by placing a graduated cylinder containing a known mass of the prepared granules on a mechanical tapping apparatus, which was operated for a fixed number of taps until the bed volume reached to a minimum.\[\frac{D}{P}\]
Poured density was determined by pouring weighed quantity pre-sieved granules into a graduated cylinder and measuring the volume.
The Carr's index and Hausner's ratio were calculated using following formula:

\[
\text{Carr's Index} = \frac{D_T - D_p}{D_T} \times 100
\]

\[
D_T = \text{Tapped density}
\]

\[
D_p = \text{Poured Density}
\]

\[
\text{Hausner’s ratio} = \frac{D_T}{D_p}
\]

**Evaluation of Tablets**

1. **Weight Variation**

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the percentage shown in Table-2 and none deviate by more than twice the percentage shown.\(^6\)

2. **Hardness**

The hardness of ten tablets was measured using Monsanto Hardness tester. Mean and standard deviation were computed and reported. It was expressed as kg/cm\(^2\).\(^7\)

3. **Friability**

The friability of the tablets was determined using Roche friabilator. It was expressed in percentage (%). 10 tablets were initially weighed and transferred to the friabilator. The friabilator was operated at 25 rpm for four minutes. After four minutes the tablets were weighed again.\(^7\)

The % friability was then calculated using the formula:

\[
\% \text{ Friability} = \frac{W_{in} - W_f}{W_{in}} \times 100
\]

\[
W_{in} = \text{Initial weight}
\]

\[
W_f = \text{final weight}
\]

4. **Drug Content**

Ten tablets were weighed; average weight was calculated and crushed to powder in mortar-pastel. Powder equivalent to average weight was dissolved in 100ml 0.1N hydrochloride solution and stirred on a magnetic stirrer. Solution was filtered through whatman filter paper no. 42 and 1 ml of the filtrate was diluted to the 20ml using a 0.1N hydrochloride. Absorbance of resultant solution was measured at 265 nm using 0.1 N hydrochloride as blank.

5. **In vitro floating behaviour:**

The time taken for tablet to emerge on surface of medium is called the floating lag time (FLT) and duration of time the dosage form constantly remain on surface of medium is called the total floating time (TFT). The tablets were placed in a beaker containing 0.1N hydrochloride solution (200 ml). The time required for the tablet to rise to the surface and float was determined as floating lag time.\(^8\)

6. **Dissolution study:**

The release of drug from floating tablets were determined using *United States Pharmacopoeia* (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl, at 37 ± 0.5°C and 75 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus at different time intervals and the samples were replaced with fresh dissolution
medium. The samples were filtered through a 0.45µ membrane filter and diluted to methanol. Absorbance of these solutions was measured using a UV/Vis. double-beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve. \(^9\)

**Result and discussion**

Gastroretentive tablets of losartan potassium were developed to increase the gastric retention time of drug, so that they can be retained in stomach for longer time. The floating tablets of Losartan Potassium were made using gel forming polymers such as Methocel K100M and Methocel K15M (Table-1). They are known for improving the buoyancy characteristics and drug release. The floating Tablets of Losartan Potassium were prepared by effervescent technique employing methocel (K-100 & K-15), sodium bicarbonate, citric acid, PVP K-30. Magnesium stearate and talc was used as lubricant and glidant respectively in the granules prepared for compression (Table-1).

The prepared floating Tablets were evaluated for weight variation, hardness, friability, drug content, floating characteristics, in-vitro drug release studies (Table-3). All the Tablets were prepared by effervescent approach. Sodium bicarbonate was added as a gas generating agent. Sodium bi-carbonate induced carbon dioxide generation in presence of dissolution medium (0.1 N hydrochloric acid). The combination of sodium bicarbonate and citric acid provided desired floating ability and therefore this combination was selected for the formulation of the floating Tablets. Tablets were found to exhibit short floating lag times due to presence of sodium bicarbonate and citric acid. Tablets with methocel K-100 were found to float for longer duration as compared with formulation containing methocel K-15 (Table-3). The coefficient of regression and release constant values for zero order first order kinetics, and Korsmeyer - Peppa's model were computed. Comparing and analyzing the release data it was found that the release of Losartan Potassium from floating matrix Tablets followed non fickian diffusion. Hence the *in-vitro* release observed for various formulation of Losartan Potassium floating tablets showed well controlled and sustained release. Formulation F6 with methocel K-100 was found to exhibit better drug release characteristics at the end of 18 hrs (Table-3 & Figure-1).

**References:**


[3].Longer M.A., Ch’ng H.S., Robinson J.R. Bioadhesive polymers as platforms for oral controlled drug delivery III: Oral


Table 1: Formulations of floating tablets of Losartan Potassium

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
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<tbody>
<tr>
<td>Losartan Potassium</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Methocel K-15</td>
<td>60</td>
<td>80</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Methocel K-100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>60</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>Sodium Bicarbonate</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Citric Acid</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>PVP K-30</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>10</td>
<td>10</td>
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<tr>
<td>Magnesium Stearate</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Talc</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>35</td>
<td>35</td>
<td>35</td>
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<tr>
<td>Lactose</td>
<td>35</td>
<td>35</td>
<td>35</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 2: The weight variation tolerance for uncoated tablets

<table>
<thead>
<tr>
<th>Average weight of tablets (mg)</th>
<th>Maximum % difference allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>130 or less</td>
<td>10</td>
</tr>
<tr>
<td>130-324</td>
<td>7.5</td>
</tr>
<tr>
<td>More than 324</td>
<td>5</td>
</tr>
</tbody>
</table>
Table 3: Physicochemical Characterization of Floating Tablets of Losartan Potassium

<table>
<thead>
<tr>
<th>Code</th>
<th>Thickness (mm.)</th>
<th>Average Weight (mg)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Drug Content (mg/Tablet)</th>
<th>Total Floating Time (hr.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>4.15 ± 0.15</td>
<td>258 ± 2.33</td>
<td>5.25 ± 0.45</td>
<td>0.58 ± 0.20</td>
<td>49.2 ± 0.25</td>
<td>8.00 ± 0.49</td>
</tr>
<tr>
<td>F2</td>
<td>3.85 ± 0.20</td>
<td>247 ± 3.25</td>
<td>5.50 ± 0.25</td>
<td>0.64 ± 0.23</td>
<td>48.5 ± 0.35</td>
<td>10.15 ± 0.61</td>
</tr>
<tr>
<td>F3</td>
<td>4.10 ± 0.35</td>
<td>262 ± 3.47</td>
<td>4.25 ± 0.45</td>
<td>0.45 ± 0.17</td>
<td>48.7 ± 0.15</td>
<td>9.30 ± 0.60</td>
</tr>
<tr>
<td>F4</td>
<td>3.85 ± 0.34</td>
<td>256 ± 3.43</td>
<td>5.00 ± 0.50</td>
<td>0.45 ± 0.25</td>
<td>48.3 ± 0.52</td>
<td>10.35 ± 0.42</td>
</tr>
<tr>
<td>F5</td>
<td>4.40 ± 0.53</td>
<td>265 ± 3.32</td>
<td>5.35 ± 0.35</td>
<td>0.58 ± 0.15</td>
<td>47.5 ± 0.45</td>
<td>11.50 ± 0.27</td>
</tr>
<tr>
<td>F6</td>
<td>4.15 ± 0.22</td>
<td>260 ± 2.48</td>
<td>4.5 ± 0.45</td>
<td>0.70 ± 0.19</td>
<td>49.0 ± 0.68</td>
<td>14.20 ± 0.34</td>
</tr>
</tbody>
</table>

Figure 1: Zero order kinetic plots of different formulations