DESIGN AND DEVELOPMENT OF STOMACH SPECIFIC DRUG DELIVERY SYSTEM OF VALSARTAN BY USING SEED MUCILAGE OF OCIMUM BACILICUM LINN

INTRODUCTION:

Oral administration is the most convenient and preferred means of any delivery to the systemic circulation. Oral controlled release drug delivery has recently been of increasing interest in the pharmaceutical field to achieve improved therapeutic advantages such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastro intestinal tract (GIT) have short half life are eliminated quickly from systemic circulation. Frequent dosing of these drugs is required to achieve therapeutic activity. To avoid these limitations, the development of oral sustain release formulation is an attempt to release the drug slowly into the gastrointestinal tract and maintain an effective drug concentration in the systemic circulation for long time. Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site specific drug release in the upper gastro intestinal tract for local and systemic effect.

Plant products serve as an alternative to synthetic products because of local accessibility, eco-friendly nature and lower prices compared to important synthetic products. Natural gums and mucilage have been widely explored as pharmaceutical excipients. Thus the aim of this study was to evaluate mucilage of ocimum bacilicum linn as pharmaceutical excipient by formulating stomach specific drug delivery system of valsartan.

Hypertension:

Hypertension (HTN) or high blood pressure, sometimes arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is elevated. This requires the heart to work harder than normal to circulate blood through the blood vessels. Blood pressure involves two measurements, systolic and diastolic, which depends on whether the heart muscle is contracting (systole) or relaxed (diastole) between beats. Normal blood pressure is at or below 120/80 mmHg. High blood pressure is said to be present if it is persistently at or above 140/90 mmHg. Valsartan belongs to the family of angiotensin II type1 receptor (AT1) antagonists and possess about 20,000 fold greater affinities for it than for the angiotensin II type 2 receptor (AT2). This action exert effects on blood pressure (BP) reduction, as well as decreases vascular smooth muscle contraction, inhibits sympathetic outflow, improves renal

ABSTRACT

Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site specific drug release in the upper gastro intestinal tract for local and systemic effect. Sustained release tablets for Valsartan were successfully prepared using mucilage extract of ocimum bacilicum linn seed. The prepared tablets were evaluated for Weight Variation, Thickness, Hardness, Friability, Drug content, Swelling studies and In vitro drug release and stability studies. Among all the formulations prepared the formulation F-6 with 45mg of Ocimum showed drug release of 95.9% at 12hr which follows super case II transport type. Stability studies of F-6 formulation have revealed that there are no significant changes during the period.

Key Words: Valsartan, HPMC, Ocimum Bacilicum Linn, In vitro drug release studies, Stability Studies.
function and also leads to reduction in progression of atherosclerosis lesions. The aim of the present study is to prepare gastro retentive tablets of valsartan which is a non-peptide, selective angiotension type II (AT II) receptor antagonists. It is used in the treatment of hypertension.

**MATERIALS AND METHODS:**

**MATERIALS USED:**

Valsartan was obtained as a gift sample from Aurabindo Pharma pvt.ltd, Hyderabad. Ocimum basilicum purchased from local market.

**METHODS:**

Mucilage was extracted from seeds of ocimum basilicum linn by soaking seeds in distilled water (for about 12hrs) then blending and finally precipitated with acetone. 2,5,6

**Formulation of floating tablets of valsartan using ocimum basilicum linn. seed mucilage:** 7

Preparation of Valsartan tablets by wet granulation method by using the compositions as mentioned in given table 1.

**Step1: Weighing**

All the ingredients were weighed accurately as per the manufacturing formula.

**Step 2: Pre sieving & mixing**

Valsartan, Oscimum seed mucilage and HPMC was passed through #40 mesh sieve and collected in a poly bag. Above sifted materials was loaded in a planetary mixer and mixed for 15min at slow speed.

**Step 3: Binder preparation**

0.5gm of Starch was added in a 55ml of purified water.

**Step 4: Dry Granulation**

The above prepared binder solution was added to the contents of planetary mixer and obtained the wet dough mass

**Step 5: Drying**

Wet mass was dried at 50ºC-55ºC by using tray drier for 6 to7hrs, till desired LOD is achieved.

**Step 6: Sieving milling**

Dried granules were passed through #16 mesh sieve and over sized granules passed through 2.0mm multi mill at medium speed in forward direction. Finally milled granules were passed through #16 mesh sieve and loaded in a double cone blender

**Step 7: Blending**

Magnesium stearate was passed through #40 mesh and it was added to the contents of double cone blender and mixed for 10 min

**Step 8: Compression**

Blended material was loaded in a hopper and powder compressed into tablets by using (cad mach) compression machine with (9mm) mm standard flat punches.

**PRE FORMULATION STUDIES:** 8

The following characterization studies were carried out for 6 different formulations of Granules.

**Angle of repose:**

Angle of repose for different formulations was measured according to fixed funnel standing method. Granules were weighed passed through the funnel, which was kept at a height ‘h’ from horizontal surface. The passed granules formed a pile of the height ‘h’ above the horizontal surface and the pile was measured and the angle of repose was determined for all the formulation using the formula (n=3).

\[
\text{Angle of repose} = \tan^{-1}\left(\frac{h}{r}\right)
\]

Whereas, ‘h’ is the height of pile and ‘r’ is the radius.

**Bulk density and Tapped density:**

Bulk density and Tapped density were measured by using 10ml graduated cylinder. The sample poured in the cylinder was tapped mechanically for 100 times, then tapped volume was noted and bulk density and tapped density were calculated. Each experiment was performed in triplicate.

\[
\text{Bulk density} = \frac{\text{Mass of powder}}{\text{Bulk volume}}
\]

\[
\text{Tapped density} = \frac{\text{Mass of powder}}{\text{Tapped density}}
\]

**Carr’s index and Hausner’s ratio:**

Compressibility index and Hausner’s ratio were determined according to following equations.

\[
\text{Carr’s index} = \left(\frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}\right) \times 100
\]

\[
\text{Hausner’s ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}
\]

**PHYSICO CHEMICAL EVALUATION OF FORMULATED TABLETS**

The tablets were evaluated for Appearance, Weight variation, Thickness, Diameter, Hardness and Friability to meet the Pharmacopoeial standards.

**Determination of Weight Variation of the tablets**

Ten tablets were selected at random from each batch and were weighed accurately and average weights were calculated. Then the deviations of individual weights from the average weight and the standard deviation were calculated by using the formula,

\[
\text{Percentage deviation} = \left(\frac{X - X^*}{X}\right) \times 100
\]

Where as,

\[
X \rightarrow \text{Actual weight of the tablet}
\]

\[
X^* \rightarrow \text{Average weight of the tablet}
\]

Limit for weight variation is ± 10%

**Determination of Thickness of the tablets**

Thickness of ten randomly selected tablets from each batch was measured with a Slide Calipers. Then the average diameter and thickness and standard deviation were calculated.

**Determination of Hardness of the tablets**

Hardness was determined by using Monsanto Hardness Tester. Then average hardness and standard deviation was calculated.

**Determination of Friability of the tablets**

Ten tablets were sampled randomly from each batch and the friability was determined using Roche type Friabilator. A pre-weighed tablet sample was placed in Friabilator which was then operated for 100 revolutions (25 rpm). The tablets were then dusted and reweighed. Then percentage friability was calculated by using the formula, 

\[
\text{Friability index} = \left(\frac{I - F}{I}\right) \times 100
\]

Where as,

\[
I \rightarrow \text{Initial weight}
\]

\[
F \rightarrow \text{Final weight}
\]
Drug content
Three tablets were selected randomly from each batch and taken separately into three 100 ml volumetric flasks. In each flask 100 ml of Phosphate buffer pH 6.8 was poured and kept for 24 hrs. After filtering the solutions, the absorbance of the filtrate was measured at 251 nm. From this absorbance, drug content was determined and average and standard deviations were calculated.

Swelling studies: Prepared formulations were weighed individually (designated as W$_1$) and placed separately in Petri dishes containing 0.1 N HCl. At regular intervals (1, 2, 3, 4, 5 and 6hr), the CR tablets were removed from the Petri dishes and excess surface water was removed carefully by using the filter paper. The swollen tablets were then reweighed (designated as W$_2$). This experiment was performed in triplicate. The swelling index (water uptake) calculated according to the following Equation:

\[
\text{Swelling index} = \frac{W_2 - W_1}{W_1} \times 10
\]

Where, W$_1$ = Initial weight of tablet
W$_2$ = Swollen tablet

IN-VITRO DRUG RELEASE STUDIES

Dissolution Parameters:
- Wave length : 251nm
- Volume : 900 ml
- Apparatus : USP Type-II (Paddle)
- RPM : 50 RPM
- Temperature : 37.0 ± 0.5°C

Sample preparation:
Transferred one tablet into each dissolution bowel and operated the dissolution apparatus as per dissolution parameters. 10 ml of sample solutions were withdrawn at regular sampling time intervals. Replace aliquots withdrawn for analysis with equal volumes of fresh dissolution medium which was maintained at 37 ± 0.5°C.

Standard solution:
An accurately weighed 100 mg of Valsartan was dissolved in 0.1N HCl and volume was made up to 100 ml in a volumetric flask (Stock Solution: I, 1000 µg/ml). From this 10 ml of solution were pipetted out and volume was made up to 100 ml (Stock Solution: II, 100µg/ml). Then the aliquots were prepared, whose concentration ranging from 2 to 20µg/ml and the absorbance was measured at 251nm by using UV Spectrophotometer.

Stability studies:
The stability studies were conducted using ICH guidelines for best formulation. The tablets were evaluated for appearance, Weight variation, Thickness, Diameter, Hardness and Friability, floating capacity, swelling index, in vitro dissolution studies to meet the Pharmacopoeical standards. All formulations were evaluated for different physico chemical evaluations and results were shown in the table 3. The in-vitro drug release studies were conducted using 0.1N HCl as dissolution medium and the results were tabulated and also represented graphically by taking Time (hrs) on X-axis and Cumulative percentage drug release on Y-axis.

Kinetic release data
Dissolution of Valsartan from all the formulations developed was slow and spread over 12hrs. Release followed Zero order kinetics. Release data of the tablets more obeyed Zero order, Higuchi, Peppa’s equation models. Higuchi plots were linear indicating that the drug release from these tablets was diffusion controlled. (Table 5)

STABILITY STUDIES
The stability study results were mentioned in the following Table 6, 7 and Figure 3

Discussion:
After first month the tablets showed the same results as that of initial result at conditions. After second month the tablets showed the same results as that of initial at accelerated stability condition a slight variation in assay and dissolution i.e. ±2%. After third month the tablets showed the same results as that of initial result in accelerated condition the assay and dissolution results were deviating ±4% of the initial result in accelerated condition the assay and dissolution results were deviating ±5% of the initial result.

CONCLUSION:
Sustained release tablets for Valsartan were successfully prepared using natural polymers Ocimum sanctum by wet granulation technique. The prepared tablets were evaluated for Weight Variation, Thickness, Hardness, Friability, Drug content, Swelling studies and Invitro drug release and stability studies. The In vitro drug releases from all formulations were governed by Zero order and peppa’s plot it is confirmed that super case II transport type. Among all the formulations prepared the formulation with 45mg of Ocimum showed dug release of 95.9% at 12hr. Hence it is optimized formulation. Stability studies have revealed that there are no significant changes during the period.

ACKNOWLEDGEMENTS
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Table 1: Composition of drug and polymers (in mg)

<table>
<thead>
<tr>
<th>S.No</th>
<th>Ingredients</th>
<th>F-1</th>
<th>F-2</th>
<th>F-3</th>
<th>F-4</th>
<th>F-5</th>
<th>F-6</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Valasartan</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
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<td>30</td>
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<tr>
<td>2</td>
<td>HPMC</td>
<td>15</td>
<td>30</td>
<td>45</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Ocimum</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>15</td>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>Sodium bicarbonate</td>
<td>102</td>
<td>87</td>
<td>72</td>
<td>102</td>
<td>87</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>Magnesium stearate</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>6</td>
<td>Talc</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td><strong>Total wt (mg)</strong></td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
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Table 2: Micromeritic properties of granules

<table>
<thead>
<tr>
<th>S.No</th>
<th>Angle of Repose (Mean±SD)</th>
<th>Bulk density (Mean±SD)</th>
<th>Tapped density (Mean±SD)</th>
<th>Carr’s Index (Mean±SD)</th>
<th>Hausner’s Ratio (Mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>29.9±0.25</td>
<td>0.424±0.03</td>
<td>0.487±0.012</td>
<td>12.93±1.82</td>
<td>1.141±0.05</td>
</tr>
<tr>
<td>F2</td>
<td>30.1±0.32</td>
<td>0.436±0.018</td>
<td>0.507±0.01</td>
<td>11.03±1.74</td>
<td>1.162±0.07</td>
</tr>
<tr>
<td>F3</td>
<td>30.7±0.64</td>
<td>0.471±0.021</td>
<td>0.524±0.01</td>
<td>12.11±1.61</td>
<td>1.111±0.03</td>
</tr>
<tr>
<td>F4</td>
<td>28.7±0.91</td>
<td>0.454±0.018</td>
<td>0.536±0.015</td>
<td>13.29±2.12</td>
<td>1.183±0.01</td>
</tr>
<tr>
<td>F5</td>
<td>29.1±0.69</td>
<td>0.412±0.011</td>
<td>0.492±0.02</td>
<td>12.52±2.32</td>
<td>1.16±0.03</td>
</tr>
<tr>
<td>F6</td>
<td>28.5±0.52</td>
<td>0.425±0.026</td>
<td>0.485±0.09</td>
<td>12.03±2.01</td>
<td>1.23±0.09</td>
</tr>
</tbody>
</table>

Table 3: Physicochemical parameters of tablets

<table>
<thead>
<tr>
<th>S.No</th>
<th>Weight Variation (mg)</th>
<th>Thickness (mm)</th>
<th>Hardness Kg/cm²</th>
<th>Friability (%)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>148 ± 0.13</td>
<td>2.60 ± 0.03</td>
<td>3.93 ± 0.11</td>
<td>0.67 ± 0.04</td>
<td>99.47±0.36</td>
</tr>
<tr>
<td>F2</td>
<td>149 ± 0.45</td>
<td>2.53 ± 0.31</td>
<td>3.81 ± 0.07</td>
<td>0.92 ± 0.02</td>
<td>98.49±0.61</td>
</tr>
<tr>
<td>F3</td>
<td>148 ± 0.16</td>
<td>2.59 ± 0.23</td>
<td>3.97 ± 0.14</td>
<td>0.87 ± 0.05</td>
<td>98.03±0.15</td>
</tr>
<tr>
<td>F4</td>
<td>150 ± 0.21</td>
<td>2.50 ± 0.08</td>
<td>4.01± 0.16</td>
<td>0.69 ± 0.01</td>
<td>99.53±0.99</td>
</tr>
<tr>
<td>F5</td>
<td>152 ± 0.17</td>
<td>2.52 ± 0.16</td>
<td>3.83 ± 0.04</td>
<td>0.59 ± 0.03</td>
<td>99.26±0.30</td>
</tr>
<tr>
<td>F6</td>
<td>151 ± 0.32</td>
<td>2.51 ± 0.12</td>
<td>3.89 ± 0.02</td>
<td>0.61 ± 0.04</td>
<td>98.50±0.45</td>
</tr>
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</table>

Table 4: Swelling studies of F-1 to F-6 formulations

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Swelling index profile of all formulations</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>1</td>
<td>41.42</td>
</tr>
<tr>
<td>2</td>
<td>84.14</td>
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<td>3</td>
<td>167.49</td>
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<td>4</td>
<td>182.43</td>
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<td>5</td>
<td>197.54</td>
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<tr>
<td>6</td>
<td>218.68</td>
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</table>

Figure 1: Swelling Index Data For Formulation F1-F6

Figure 2: *In Vitro* drug release profile of F-1 to F-3 formulations.

![Comparative In vitro drug release F1-F3](image)

Figure 3: *In Vitro* drug release profile of F4 to F6 formulations.

![Comparative In vitro drug release F4-F6](image)

Table 5: Release kinetics and mechanism of formulations

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Mathematical models</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zero order ( R^2 )</td>
<td>Higuchi’s ( R^2 )</td>
<td>Peppa’s Model ( R^2 )</td>
</tr>
<tr>
<td>F-1</td>
<td>0.970</td>
<td>0.977</td>
<td>0.962</td>
</tr>
<tr>
<td>F-2</td>
<td>0.993</td>
<td>0.992</td>
<td>0.984</td>
</tr>
<tr>
<td>F-3</td>
<td>0.998</td>
<td>0.996</td>
<td>0.997</td>
</tr>
<tr>
<td>F-4</td>
<td>0.998</td>
<td>0.998</td>
<td>0.999</td>
</tr>
<tr>
<td>F-5</td>
<td>0.998</td>
<td>0.993</td>
<td>0.996</td>
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<tr>
<td>F-6</td>
<td>0.995</td>
<td>0.998</td>
<td>0.996</td>
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Table 6: Drug Content of the Formulations Developed Before and After Storage for 3 Months

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Percent Drug Content (( \bar{X} \pm s.d ))</th>
<th>Significance of Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Storage</td>
<td>After 3 months</td>
</tr>
<tr>
<td>F-1</td>
<td>99.47 ± 0.07</td>
<td>98.23 ± 0.27</td>
</tr>
<tr>
<td>F-2</td>
<td>98.49 ± 0.06</td>
<td>97.08 ± 0.04</td>
</tr>
<tr>
<td>F-3</td>
<td>98.03 ± 0.11</td>
<td>97.90 ± 0.13</td>
</tr>
<tr>
<td>F-4</td>
<td>99.73 ± 0.37</td>
<td>98.03 ± 0.30</td>
</tr>
<tr>
<td>F-5</td>
<td>99.26 ± 0.86</td>
<td>98.02 ± 0.16</td>
</tr>
<tr>
<td>F-6</td>
<td>98.50 ± 0.81</td>
<td>97.90 ± 0.31</td>
</tr>
</tbody>
</table>

REFERENCES:


4. Meghana S Kamble,. Evaluation of binding properties of ocimum tenuiflorum linn seed mucilage isolated by defatting method. Journal of biomedical and pharmaceutical research, 1(3); 22-27.


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