FORMULATION AND EVALUATION OF SUSTAINED RELEASE VALSARTAN MATRIX TABLETS BY USING NATURAL POLYMERS

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ABSTRACT
The present study was aimed to develop antihypertensive sustained release matrix tablets of valsartan Angiotensin II receptor antagonist, using natural polymers (guargum and pectin) as the matrix material in different proportion by direct compression method. The tablets were prepared by Guar gum different formulations FG1, FG2, FG3 (1:0.5, 1:1, 1:1.5) and same as with Pectin different formulations FP4, FP5, FP6 (1:0.5, 1:1, 1:1.5). The tablets were subjected to weight variation test, drug content, hardness, friability, and in vitro release studies. In vitro dissolution studies indicate that among all the formulations FG3 (1:1.5) significantly reduced the rate of drug release compared to other formulations. The result of dissolution study indicate that the formulation prepared by guar gum (1:1.5) ratio showed maximum drug release up to 23 hrs. Mathematical treatment of the in vitro drug release data suggest that, optimized formulation FG3 fitted in to zero order and Peppas release kinetic shows R2 value 0.982. Drug release from the matrix occurred by combination of two mechanism, diffusion and erosion of tablet. So when compared to Pectin the Guargum is the best polymer to control the release of Valsartan tablet.

Key words: Valsartan, Guargum, Pectin, Sustained Release, Matrix Tablet.

INTRODUCTION
The goal of designing sustained or controlled release drug delivery systems of Valsartan matrix tablets is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required, or providing controlled drug delivery.
Valsartan is an angiotensin II receptor antagonist class of drug used for the treatment of hypertension, myocardial infarction and congestive heart failure. It treats the hypertension by blocking the vasoconstrictor and aldosterone secreting effect of angiotensin II selectively by blocking the binding of angiotensin II and angiotensin1 receptor in many tissues. Valsartan drug was comes under BCS class III, low bioavailability (approximately 20-25%), and shorter half-life (nearly 6 hours). The treatment of anti hypertension therapy need long duration and to maintain plasma concentration the constant drug release due to over come of toxic effects. so to design controlled delivery system of Valsartan for gradual release of drug in amounts sufficient to maintain therapeutic response for a specific period of time and to maintain dose frequency. In vitro dissolusion study conducting different mediums 0.1N Hcl for 2 hrs, 7.4 phosphate buffer up to 22hrs. The
selection of natural polymers than synthetic polymers as matrix system for sustained drug delivery is to obtain desired drug release, patient compliance, cost effectiveness and to enhance compatibility with the drug. Hence in the present study an attempt has been made to develop sustained release matrix tablet of Valsartan using natural polymers. Matrix materials such as Guar gum and Pectin are used in the formulation. The natural polymer Guar gum the concentration increase to delay the drug release up to certain extent. After the concentration increase the drug release will be constant so, we are optimize (1:3) ratio of the Guar gum to fulfill our object.

**Material and Methods**

Valsartan was a gift sample from Aurabindo pharma pvt.ltd, Hyderabad. Guar gum was purchased from S.Kant. Healthcare Ltd Vapi, Gujarat. Pectin was purchased from Coax Bioremedies Pvt. Ltd., Hisar. Other ingredient lactose was obtained from Qualigens Fine Chemicals, Mumbai, magnesium stearate from S. D Fine Chem. Ltd., Mumbai and talc was obtained from Nice Chemicals Pvt. Ltd., Cochin. The other entire chemical used was of high analytical grade.

**Preparation of matrix tablet**

Initially, valsartan tablets with different concentration of hydrophilic polymer were prepared by direct compression technique. Required quantities of all ingredients were weighed individually on electronic balance (citizen India). All ingredients were first sieved through sieve #44 and mixed for 5 min by adding lactose then blended with talc and magnesium stearate for lubrication which were then compressed on rotatory tablet compression machine using circular 6.5mm tooling set (cadmech Ahmadabad India).

**Formulation of valsartan sustained release tablets**

<table>
<thead>
<tr>
<th>S. No</th>
<th>Ingredients</th>
<th>FG1 (mg)</th>
<th>FG2 (mg)</th>
<th>FG3 (mg)</th>
<th>FP1 (mg)</th>
<th>FP2 (mg)</th>
<th>FP3 (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Valsartan</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>Guar gum</td>
<td>15</td>
<td>30</td>
<td>45</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>3</td>
<td>Pectin</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>15</td>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>Lactose</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>Mg stearate</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>6</td>
<td>Talc</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Total tablet weight</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
</tbody>
</table>

FG: valsartan with guar gum ; FP: valsartan with pectin

**Evaluation of tablets**

**Weight variation test**

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Citizen, India), and the test was performed according to the official method.

**Hardness and friability**

For each formulation, the hardness and friability of 6 tablets were determined using the Hardness tester (Monsanto, India) and the friabilator (Roche Friabilator India), respectively.

**In Vitro release studies**

Release of the prepared tablets was determined up to 24 hour using U.S.P type II paddle type dissolution rate test apparatus (VEEGO, India). 900 ml of 0.1 N HCl (pH 1.2) was used as dissolution medium for first 2 hrs and (pH 7.4) phosphate buffer for up to 24 hrs the test of the period as dissolution medium. The paddle was adjusted at 75 rpm and the temperature of 37±0.5°C was maintained throughout the experiment. Samples of 5 ml were withdrawn at known time intervals and were replaced with same volume of fresh dissolution media after each withdrawal. The samples were analyzed for drug contents by measuring absorbances at 251 nm using UV-VIS double beam spectrophotometer thermo scientific, India.

**Drug content**

Three tablets were selected randomly from each batch, powderer separately and then taken into three volumetric flasks of 100 ml. In each flask 100 ml of phosphate buffer pH
7.4 was poured and kept for 24 hrs. After filtering the solution and making suitable dilutions, the absorbance of the filtrate was measured at 251nm using UV-Vis double beam spectrophotometer thermo scientific, India. From this absorbance, drug content was determined. Drug content was determined according to the following formula

\[
\text{Drug content} = \frac{\text{Actual drug content}}{\text{theoretical drug content}} \times 100
\]

**Swelling index**

Measurement of the swelling index was carried out to gain an insight into the phenomenon of polymer hydration and to evaluate the extent of media penetration within the tablets. The swelling index was determined by equilibrium weight gain method the study was carried out in the USP dissolution apparatus type 1. The tablets were accurately weighed, placed in dissolution basket, immersed in phosphate buffer (pH 7.4) and maintained at 37±0.5°C in the dissolution vessel. At regular intervals of 2, 4, 6, 8, 10 up to 24 hrs. The weighted basket matrix system was withdrawn from the dissolution vessel, lightly blotted with the tissue paper to remove excess test liquid and re-weighed. The swelling index (SI) of each tablet was calculated according to the following equation.

\[
\text{S.I.} = \left( \frac{W_t - W_0}{W_0} \right) \times 100
\]

Where, \(W_0\) = initial weight, \(W_t\) = final weight

**Release kinetics**

In order to examine the release mechanism of drug sample from the prepared matrix tablets of the optimized formulation (FG3), the results of the dissolution study was examined in accordance to the kinetic models such as zero-order, first order, Higuchi equation, Korsemeyer–Peppas equation and Hixson–Crowell equation.

**Stability study**

Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously. The selected formulations were packed in yellow-color PVDC/ALU, Blister. They were then stored at 40°C / 75% RH for 3 months and evaluated.

**RESULTS AND DISCUSSION**

The tablets of different formulation were evaluated for hardness, weight variation, friability and drug content. The result of tablets of formulation FG1 to FP6 where weight variation ranging from 1.25±0.22 to 1.29±0.22, hardness were maintained 5.5kg/cm², friability 0.78% to 0.8%, drug content values ranging from 93% to 98%. The results of tablets are concluded that all the parameters are within the acceptance range.

Drug release studies were found to be increase in concentration of polymers, Guargum there was an increase in time drug release. From the optimization studies it was concluded that with increase in concentration of Guargum, there was an increase in time of release of drug was observed in FG3 (1:1.5) the drug release was up to 23 hrs. But increased concentration of Pectin does not seem to influence the release profile of drug when compared to Guargum as same concentration of Pectin FP6 (1:1.5) the drug release was up to 9 hrs. Finally the control release of Valsartan failed to extend the release of drug with Pectin. Therefore formulation FG3 was selected to fulfil our object. Drug release data and comparison of drug release curve of formulation are shown in graph respectively.

Measurement of the swelling index was carried out to gain an insight into the phenomenon of polymer hydration and to evaluate the extent of media penetration within the tablets. Formulation FG3 showed 195.73±0.79 % swelling index and result concluded that formulation FG3 showed good swelling index property. Release kinetic was showed that in vitro release curve fitted under zero order and Peppas model which show R2 value 0.982 is highest as compared to other models. The regression coefficient R2 value nearer to 1
indicated the model fitting of the release mechanism. R2 value and curve of different model are shown in table respectively. Stability studies were carried out at 40°C / 75% RH for the selected formulation for the period of 3 months there was slightly acceptable changes was observed in physical and chemical parameter and slightly acceptable changes in drug release. FG3 formulation was showed 98.46±0.16, 97.48±0.06 and 97.48±0.22 up to 24 hrs in 1 month, 2 month, and 3 month respectively. Result was concluded that formulation was stable under specific temperature and humidity condition.

**Evaluation parameters**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Parameter</th>
<th>FG1</th>
<th>FG2</th>
<th>FG3</th>
<th>FP4</th>
<th>FP5</th>
<th>FP6</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Hardness(kg/cm²)</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>2</td>
<td>Weight variation(%)</td>
<td>1.25±0.22</td>
<td>1.28±0.22</td>
<td>1.30±0.22</td>
<td>1.25±0.22</td>
<td>1.27±0.22</td>
<td>1.29±0.22</td>
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<tr>
<td>3</td>
<td>Swelling index(%)</td>
<td>0.024</td>
<td>0.035</td>
<td>0.051</td>
<td>0.026</td>
<td>0.042</td>
<td>0.063</td>
</tr>
<tr>
<td>4</td>
<td>Drug content(%)</td>
<td>96</td>
<td>97.5</td>
<td>98</td>
<td>92.4</td>
<td>94</td>
<td>96.3</td>
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**Coefficient values and drug release parameters**

<table>
<thead>
<tr>
<th>S. No</th>
<th>Formulation</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi</th>
<th>Peppas</th>
<th>Ke</th>
<th>T50</th>
<th>T90</th>
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<tbody>
<tr>
<td>1</td>
<td>F1</td>
<td>0.988</td>
<td>0.964</td>
<td>0.958</td>
<td>0.980</td>
<td>83.5</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>F2</td>
<td>0.974</td>
<td>0.916</td>
<td>0.928</td>
<td>0.995</td>
<td>41.7</td>
<td>9</td>
<td>15.5</td>
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<tr>
<td>3</td>
<td>F3</td>
<td>0.982</td>
<td>0.808</td>
<td>0.881</td>
<td>0.999</td>
<td>31.8</td>
<td>13</td>
<td>23</td>
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<tr>
<td>4</td>
<td>F4</td>
<td>0.980</td>
<td>0.899</td>
<td>0.944</td>
<td>0.995</td>
<td>68.4</td>
<td>4</td>
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<tr>
<td>5</td>
<td>F5</td>
<td>0.983</td>
<td>0.849</td>
<td>0.951</td>
<td>0.997</td>
<td>74.2</td>
<td>3.5</td>
<td>5</td>
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<tr>
<td>6</td>
<td>F6</td>
<td>0.992</td>
<td>0.859</td>
<td>0.964</td>
<td>0.994</td>
<td>85.9</td>
<td>2.8</td>
<td>6</td>
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</table>

**CONCLUSION**

The approach of the present study was to make Valsartan sustained release matrix tablets by using natural polymers with different ratios. Among all the six formulations, F3 formulation with drug polymer (Guargum) ratio (1:1.5) for sustained release formulation of valsartan showing 23 hr drug release. By this our objective of sustained release of valsartan from matrix tablet has been fulfilled.

**ACKNOWLEDGEMENTS**

We are sincerely thankful to Aurabindo pharma pvt.ltd for providing gift sample of Valsartan drug and we would also like to thank the management and staff of Vikas College of pharmacy, vissannapeta for encouraging us and providing all facilities to proceed on the work.

**REFERENCES**