RESEARCH ARTICLE

FORMULATION AND EVALUATION OF VALSARTAN SUSTAINED RELEASE MATRIX TABLETS

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The present work was aimed to develop novel oral antihypertensive sustained release matrix tablets of Valsartan using HPMC K15M as polymer in different proportion by wet granulation method. Compatibility among the formulation components was assessed by DSC analysis. Compressed tablets were evaluated for various parameters like weight variation, drug content, hardness, friability, in vitro drug release and swelling behaviour. Release kinetics showed that in vitro release curve fitted under Korsmeyer and Peppas model which shows R² value 0.9930 highest as compared to other models. The results of dissolution study indicated that the formulation prepared by HPMC K15M at high concentration would produce better results.

Key words: Valsartan, HPMC, Sustained release, Matrix tablet, Antihypertensive.

INTRODUCTION

Valsartan is an angiotensin II receptor antagonist that is used for the treatment of hypertension. It treat the hypertension by blocking the vasoconstrictor and aldosterone secreting effect of angiotensin II selectively by blocking the binding of angiotensin II and angiotensin I receptor in many tissues. The most preferred route for this drug is oral delivery in form of tablets. Valsartan have poor water solubility, low bioavailability (approximately 20-25%), and shorter half-life (nearly 6 h) (Abdelbary et al 2004).

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reason that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is as well absorbed as the food stuffs that are ingested daily (Bandelin, 2008). The low bioavailability and short half-life of valsartan make the development of sustained-release forms desirable. Sustained release system is a type of modified drug delivery system that can be used as an alternative to conventional drug delivery system (Armstrong and James, 1996).

These systems sustain the release of drug and maintain the plasma drug concentration in therapeutic window except any fluctuation and increase the therapeutic efficacy of drug. They show their action by avoiding peak and trough in dosing and show constant plasma drug concentration in therapeutic window. Sustained release system have benefits like patient compliance and avoidance of multiple dosing, increased plasma drug concentration, avoidance of side effects and overcoming the problems associated with conventional system (Hingmire et al 2008).

Among various approaches used for novel drug delivery systems (Dahiya and Gupta, 2011; Tripathi et al 2011; Khan et al 2012; Mishra et al 2013; Verma et al 2014), matrix tablet is one of the most widely used and popular method. 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 dose required, or providing controlled drug delivery.

EXPERIMENTAL

Materials
Valsartan (Val) was obtained as a gift sample from Torrent pharmaceuticals Private Limited, Ahmedabad. HPMC K15M was purchased from S. Kant. Healthcare Limited, Vapi, Gujarat. Lactose was obtained from Qualigens Fine Chemicals, Mumbai. Magnesium stearate was procured from S. D. Fine Chemicals Limited, Mumbai and Talc was obtained from Nice Chemicals Pvt. Limited, Cochin. Other chemicals used were of analytical reagent grade.

Methods

Drug excipients interaction (Rowe et al 2006)
Compatibility of the drug with excipients was determined by differential scanning calorimeter (Perkin Almer, USA). This study was carried out to detect any change on chemical constitution of the drug after combination with the excipients. The samples taken for DSC study were physical mixtures of Val : HPMC K15M (1 : 1).

Preparation of matrix tablets
Valsartan tablets with different concentrations of polymer were prepared by the wet granulation technique. All ingredients in required quantities were weighed individually (Jha et al 2009). All the ingredients were first sieved and mixed for 5 min. Isopropanol alcohol was added drop wise till suitable mass for granulation was obtained. Then wet mass was granulated through sieve 8# and prepared granules were dried at 60°C for 1 h. The dried granules were passed through sieve 10# and fractions of granules retained on the sieve were discarded then blended with talc and magnesium stearate for lubrication of granules which were then compressed on single punch tablet machine using circular 4 mm punch. The weight of tablet adjusted to 300 mg, each tablet containing 20 mg Valsartan and other excipients listed in Table 1.

Table 1. Formula for Valsartan matrix material

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredients</th>
<th>Quantity of Ingredients/Tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SR1</td>
</tr>
<tr>
<td>1</td>
<td>Valsartan</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>HPMC K15M</td>
<td>60 (20%)</td>
</tr>
<tr>
<td>3</td>
<td>Magnesium stearate</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>Talc</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>Lactose</td>
<td>216</td>
</tr>
</tbody>
</table>

Evaluation of granules

Angle of repose
The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface (Hingmire et al 2008). The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

\[ \tan \theta = \frac{h}{r} \]

where \( h \) and \( r \) are the height and radius of the powder cone, respectively.

Bulk density

Both bulk density (BD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals (Karasulu et al 2003). The tapping was continued until no further change in volume was noted. BD and TBD were calculated using the following formulas:

BD = weight of the powder/volume of the packing

TBD = weight of the powder/tapped volume of the packing

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index:

Carr's index (%) = \[ \frac{(\text{TBD} - \text{BD}) \times 100}{\text{TBD}} \]
EVALUATION OF TABLETS

Weight variation
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.

Drug content (Karasulu et al 2003)
Three tablets were selected randomly from each batch, powdered separately and then taken into three volumetric flasks of 100 ml. In each flask, 100 ml of phosphate buffer pH 6.8 was poured and kept for 24 h. After filtering the solution and making suitable dilutions, the absorbance of the filtrate was measured at 251 nm using UV-VIS Pharmaspec spectrophotometer (Shimadzu 1700, Japan). From this absorbance, drug content was determined according to the following formula:

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

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

In vitro release studies
Release of the prepared tablets was determined up to 24 h using USP type II paddle type dissolution rate test apparatus (Veego, India). 0.1 N HCl (900 ml) was used as dissolution medium for first 2 h and phosphate buffer pH 6.8 for the rest of the period as dissolution medium. The paddle was adjusted at 50 rpm and the temperature of 37±0.5°C was maintained throughout the experiment. Samples were withdrawn at known time intervals and were replaced with same volume of fresh dissolution media after each withdrawal. The samples were analysed for drug contents by measuring absorbance at 251 nm using UV spectrophotometer (Higuchi, 1963).

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 6.8 and maintained at 37±0.5°C in the dissolution vessel. The weighed basket matrix system was withdrawn from the dissolution vessel, lightly blotted with tissue paper to remove excess test liquid and re-weighed. The swelling index (SI) of each tablet was calculated according to the following equation:

\[
\text{S.I.} = \frac{(W_f - W_o)}{W_o} \times 100
\]

where \(W_o\) = initial weight, \(W_f\) = final weight

Release kinetics
In order to examine the release mechanism of drug sample from the prepared matrix tablets of the optimized formulation, the results of the dissolution study were examined in accordance to the kinetic models such as zero-order, first order, Higuchi equation, Korsemeyer-Pappas equation and Hixson-Crowell equation (Higuchi, 1963).

RESULTS AND DISCUSSION

Drug excipient interaction
DSC thermogram showed endothermic peaks at 117°C due to melting of drug and at 116°C due to melting of polymer HPMC K15M. Drug and polymer displayed their characteristic individual melting trends without appreciable deviation. It is observed that there is no interaction between drug and polymer (Figure 1, 2).

Evaluation of granules
Formulation of granules is the key factor in the production of tablet dosage form involving sustained release of drug from matrix type particle. The granules of different formulation were evaluated for BD, TBD, compressibility index, angle of repose (Table 2). Generally compressibility index values up to 15% result in good to excellent flow properties but reading above 25% indicates poor flow properties and angle of repose rarely less than 20°, and value up to 40° indicate reasonable flow properties. All the results indicated that the formulated granules possessed satisfactory flow property and compressibility.

Evaluation of tablet Physical parameter
The tablets of different formulations (SR1 and SR2) were evaluated for hardness, weight variation, friability, drug content and thickness (Table 3). The result concluded that all the parameters were in acceptable range.
Fig. 1. DSC thermogram of Valsartan

Fig. 2. DSC thermogram of Valsartan and HPMC

Table 2. Pre-compression characteristics of Valsartan and polymer blend

<table>
<thead>
<tr>
<th>Tests</th>
<th>SR1</th>
<th>SR2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk density (g/cm³)</td>
<td>0.45±0.01</td>
<td>0.47±0.01</td>
</tr>
<tr>
<td>Tapped density (g/cm³)</td>
<td>0.51±0.01</td>
<td>0.52±0.01</td>
</tr>
<tr>
<td>Hausner's ratio</td>
<td>1.13±0.03</td>
<td>1.11±0.12</td>
</tr>
<tr>
<td>Carr's index (%)</td>
<td>11.11±0.09</td>
<td>10.20±0.92</td>
</tr>
<tr>
<td>Angle of repose (°)</td>
<td>27.34±2.49</td>
<td>27.63±0.88</td>
</tr>
</tbody>
</table>

Table 3. Post-compression characteristics of Valsartan sustained release tablets

<table>
<thead>
<tr>
<th>Tests</th>
<th>SR1</th>
<th>SR2</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Weight variation</td>
<td>300.12±1.21</td>
<td>299.99±1.91</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>3.13±0.15</td>
<td>3.17±0.06</td>
</tr>
<tr>
<td>Hardness (kg/cm²)</td>
<td>4.67±0.24</td>
<td>4.83±0.24</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>0.42±0.02</td>
<td>0.41±0.05</td>
</tr>
<tr>
<td>Drug content (%)</td>
<td>99.66±0.05</td>
<td>99.8±0.01</td>
</tr>
</tbody>
</table>

**Drug release study**

It was concluded from drug release studies that with increase in concentration of low viscosity grade polymer HPMC K15M (SR1) (99.42% in initial 5 h), there was an increase in time of cumulative % release of drug, up to 8 h and in the case of HPMC K15M (SR2) (67.35% in initial 5 h) also increases time of cumulative % release of drug up to 12 h (Figure 3).

**Swelling index**

The swelling index measurement is usually performed to have an idea about polymer hydration as well as evaluation of the extent of media penetration within tablets. Formulation SR2 showed 195.73±0.79% swelling index thus, possess good swelling property (Figure 4).

**Release kinetics**

Release kinetics showed that *in vitro* release curve fitted under Korsmeyer and Peppas model which showed R² value 0.9930, highest as compared to other models. The regression coefficient R² value nearer to 1 indicated the model fitting of the release mechanism (Table 4).

**CONCLUSION**

The present study was carried out to perform the preformulation and formulation of valsartan pure drug. The preformulation result showed that the drug was authentic and found to be pure and hence there was no indication of any variation in drug. Valsartan showed poor flow property and good compressibility. It was found to be soluble in organic solvent and slightly soluble in water and portioning of drug in lipophillic phase was maximum compared to hydrophilic phase. The physicochemical compatibility of drug with HPMC K15M was
established through DSC. The study indicated that the drug had good compatibility with it. From results it is concluded that formulation of sustained release tablet of Valsartan containing HPMC K15M can be taken as an ideal formulation of sustained release tablets for 24 h release as it fulfils all the requirements for sustained release matrix tablet.

REFERENCES

Table 4. Drug release behaviour of Valsartan sustained release tablets

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Model</th>
<th>R²</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Zero Order</td>
<td>0.9798</td>
</tr>
<tr>
<td>2</td>
<td>First Order</td>
<td>0.8026</td>
</tr>
<tr>
<td>3</td>
<td>Higuchi</td>
<td>0.9600</td>
</tr>
<tr>
<td>4</td>
<td>Hixson-Crowell</td>
<td>0.9061</td>
</tr>
<tr>
<td>5</td>
<td>Korsmeyer and Peppas</td>
<td>0.9930</td>
</tr>
</tbody>
</table>

Fig. 3. Drug release profiles of SR1 and SR2

Fig. 4. Swelling index curve