FORMULATION DEVELOPMENT AND OPTIMIZATION OF VALSARTAN TABLETS EMPLOYING βCD STARCH 1500 AND SOLUPLUS

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ABSTRACT
The objective of the present study is optimization of Valsartan tablet formulation employing βCD, Starch 1500, and Soluplus by 2³ factorial design to achieve NLT 85% dissolution in 10 min. Eight Valsartan tablet formulations were prepared using selected combinations of the three factors as per 2³ factorial design. Valsartan tablets were prepared by direct compression method and were evaluated. The individual and combined effects of the three factors βCD, Starch 1500 and Soluplus are highly significant (P < 0.01) in influencing the dissolution rate of Valsartan tablets. Valsartan tablet formulations F₁,F₁,F₂,F₂,F₃,F₃,F₄,F₄,F₅,F₅,F₆,F₆,F₇,F₇,F₈,F₈ disintegrated rapidly and gave very rapid dissolution of Valsartan, 92.4%, 99.4%, 96.2% and 99.2% in 10 min respectively. The increasing order of dissolution rate (K₁) observed with various formulations was F₁< F₂< F₃< F₄< F₅< F₆< F₇< F₈. The polynomial equation describing the relationship between the response, percent drug dissolved in 10 min (Y) and the levels of βCD (X₁), Starch 1500 (X₂) and Soluplus (X₃) based on the observed results was found to be Y = 68.625 + 4.375(X₁) + 27.375(X₂) - 2.375(X₁X₂) + 3.375(X₃) + 0.125(X₁X₃) - 1.875(X₂X₃) - 0.625(X₁X₂X₃) Based on the above equation, the formulation of optimized Valsartan tablets with NLT 85% dissolution in 10 min require βCD at 1:3.5 ratio of drug: βCD, Starch 1500 at 24.37% of drug and βCD content, and Soluplus at 1% of drug and βCD content. The optimized Valsartan tablet formulation gave 85.75% dissolution in 10 min fulfilling the target dissolution requirement. Hence formulation of Valsartan tablets with NLT 85% dissolution in 10 min could be optimized by 2³ factorial design.
KEYWORDS: Formulation Development, Valsartan tablets, Optimization, Factorial Design, βCD, Starch 1500, Soluplus.

INTRODUCTION
Optimization\(^1\) of pharmaceutical formulations involves choosing and combining ingredients that will result in a formulation whose attributes confirm with certain prerequisite requirements. The choice of the nature and qualities of additives (excipients) to be used in a new formulation shall be on a rational basis. The application of formulation optimization techniques is relatively new to the practice of pharmacy. The optimization procedure is facilitated by applying factorial designs and by the fitting of an empirical polynomial equation to the experimental results. The predicted optimal formulation has to be prepared and evaluated to confirm its quality. In a few studies\(^{2-8}\) optimization by factorial designs was employed in the formulation development of BCS Class II drugs.

About 95% of all new potential therapeutic drugs (APIs) exhibit low and variable oral bioavailability due to their poor aqueous solubility at physiological pH and consequent low dissolution rate. These drugs are classified as class II drugs under BCS with low solubility and high permeability characters. These BCS class II drugs pose challenging problems in their pharmaceutical product development process. Valsartan, a widely prescribed anti hypertensive drug belongs to class II under BCS classification and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Because of poor aqueous solubility and dissolution rate it poses challenging problems in its tablet formulation development. It needs enhancement in the dissolution rate in its formulation development.

Several techniques\(^9\) such as micronisation, cyclodextrin-complexation, use of surfactants, solubilizers and super disintegrants, solid dispersion in water soluble and water dispersible carriers, microemulsions and self emulsifying micro and nano disperse systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble BCS class II drugs. Among the various approaches cyclodextrin complexation and use of superdisintegrants such as Crosspovidone and Sodium starch glycolate, carriers such as Starch 1500\(^{10-13}\) are simple industrially useful approaches for enhancing the dissolution rate of poorly soluble drugs in their formulation development. Surfactants such as SLS, Soluplus are also used for enhancing the solubility of poorly soluble drugs in formulation development.
In the present study complexation with \( \beta \)-cyclodextrin (\( \beta \)CD) along with Starch 1500 and Soluplus (a non ionic surfactant) was tried to enhance the dissolution rate of Valsartan in its tablet formulation development. Valsartan tablets with NLT 85% dissolution in 10 min was aimed in its formulation development. A \( 2^3 \) factorial design employing \( \beta \)CD, Starch 1500 and Soluplus was used for Valsartan tablet formulation development to achieve NLT 85% dissolution in 10 min. Thus the objective of the present study is optimization of Valsartan tablet formulation employing \( \beta \)CD, Starch 1500, and Soluplus by \( 2^3 \) factorial design to achieve NLT 85% dissolution in 10 min.

**EXPERIMENTAL**

**Materials**

Valsartan was a gift sample from M/s Kekule Pharma Ltd., Hyderabad. \( \beta \)-cyclodextrin, Starch 1500 and Soluplus were gift samples from M/s Natco Pharma Ltd., Hyderabad. Talc and magnesium stearate were procured from commercial sources. All other materials used were of pharmacopoeial grade.

**Estimation of Valsartan**

An UV Spectrophotometric method based on the measurement of absorbance at 250 nm in 0.1N HCl acid was used for the estimation of Valsartan. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer’s law in the concentration range of 0 -10 \( \mu \)g/ml. When a standard drug solution was repeatedly assayed \((n=6)\), the relative error and coefficient of variance were found to be 0.65% and 1.15% respectively. No interference by the excipients used in the study was observed.

**Formulation of Valsartan Tablets**

For optimization of Valsartan tablets as per \( 2^3 \) factorial design the \( \beta \)CD, Starch 1500 and Soluplus are considered as the three factors. The two levels of the factor A (\( \beta \)CD) are 1:1 and 1:6 ratio of drug: \( \beta \)CD, the two levels of the factor B (Starch 1500) are 2% and 30% of drug and \( \beta \)CD content, and the two levels of factor C (Soluplus) are 0 and 2% of drug and \( \beta \)CD content. Eight Valsartan tablet formulations employing selected combinations of the three factors i.e. \( \beta \)CD, Starch 1500 and Soluplus as per \( 2^3 \) factorial design were formulated and prepared by direct compression method.
Preparation of Valsartan Tablets

Valsartan (40 mg) tablets were prepared by direct compression method as per the formula given in Table 1. The required quantities of Valsartan, βCD, Starch 1500 and Soluplus as per the formula in each case were blended thoroughly in a closed polyethylene bag. Talc and magnesium stearate were then added by passing through mesh no.80 and blended. The blend of ingredients was then compressed directly into tablets using an 8 - station RIMEK tablet punching machine employing 9mm or 12mm round and flat punches.

Evaluation of Tablets

All the Valsartan tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate as follows.

Hardness

The hardness of prepared tablets was determined by using Monsanto hardness tester and measured in terms of kg/cm².

Friability

The friability of the tablets was measured in a Roche friabilator using the formula

\[ \text{Friability (\%)} = \frac{(\text{Initial weight} - \text{Final weight})}{(\text{Initial weight})} \times 100 \]

Drug Content

Weighed tablets (10) were powdered using a glass mortar and pestle. An accurately weighed quantity of powder equivalent to 40 mg of Valsartan was taken into 100 ml volumetric flask, dissolved in 0.1N HCl acid and the solution was filtered through Whatman filter paper no. 41. The filtrate was collected and suitably diluted with 0.1N HCl acid and assayed for Valsartan at 250 nm.

Disintegration time

Disintegration time of the tablets was determined using single unit disintegration test apparatus (Make: Paramount) employing water as test fluid.

Dissolution Rate Study

Dissolution rate of Valsartan tablets prepared was studied in 0.1N HCl acid (900 ml) employing eight station dissolution rate test apparatus (LABINDIA, DS 8000) using paddle stirrer at 50 rpm and at a temperature of 37°C ± 1°C. One tablet was used in each test. Samples of dissolution fluid (5 ml) were withdrawn through a filter at different time intervals.
and assayed for Valsartan at 250nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh drug free dissolution fluid and a suitable correction was made for the amount of drug present in the samples withdrawn in calculating percent dissolved at various times. Each dissolution experiment was run in triplicate (n=3).

**Analysis of Data**
The dissolution data were analyzed as per zero order and first order kinetic models. Dissolution efficiency (DE$_{30}$) values were estimated as suggested by Khan$^{14}$. Dissolution rate (K$_1$) values were analyzed as per ANOVA of 2$^3$ factorial experiments.

**RESULTS AND DISCUSSION**
The objective of the present study is to optimize the Valsartan tablet formulation employing βCD, Starch 1500 and Soluplus by 2$^3$ factorial design to achieve NLT 85% dissolution in 10 min. For optimization of Valsartan tablets as per 2$^3$ factorial design the βCD, Starch 1500 and Soluplus are considered as the three factors. The two levels of the factor A (βCD) are 1:1 and 1:6 ratio of drug: βCD, the two levels of the factor B (Starch 1500) are 2% and 30% of drug and βCD content, and the two levels of factor C (Soluplus) are 0 and 2% of drug and βCD content. Eight Valsartan tablet formulations employing selected combinations of the three factors i.e. βCD, Starch 1500, and Soluplus as per 2$^3$ factorial design were prepared. The tablets were prepared by direct compression method as per the formulae given in Table 1 and were evaluated for drug content, hardness, friability, disintegration time and dissolution rate characteristics. The dissolution rate (K$_1$) values were analyzed as per ANOVA of 2$^3$ factorial design to find out the significance of the individual and combined effects of the three factors involved on the dissolution rate of Valsartan tablets formulated.

**Table 1: Formulæ of Valsartan Tablets Prepared Employing β-CD, Starch 1500 and Soluplus as per 2$^3$ Factorial Design**

<table>
<thead>
<tr>
<th>Ingredient (mg/tablet)</th>
<th>F1</th>
<th>F a</th>
<th>F b</th>
<th>F ab</th>
<th>F c</th>
<th>F ac</th>
<th>F bc</th>
<th>F abc</th>
<th>F opt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsartan</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>β-cyclodextrin</td>
<td>40</td>
<td>240</td>
<td>40</td>
<td>240</td>
<td>40</td>
<td>240</td>
<td>40</td>
<td>240</td>
<td>140</td>
</tr>
<tr>
<td>Starch 1500</td>
<td>1.6</td>
<td>5.6</td>
<td>24</td>
<td>84</td>
<td>1.6</td>
<td>5.6</td>
<td>24</td>
<td>84</td>
<td>43.87</td>
</tr>
<tr>
<td>Soluplus</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.6</td>
<td>5.6</td>
<td>1.6</td>
<td>5.6</td>
<td>1.8</td>
</tr>
<tr>
<td>Talc</td>
<td>1.6</td>
<td>5.7</td>
<td>2</td>
<td>7.2</td>
<td>1.6</td>
<td>5.8</td>
<td>2.1</td>
<td>7.3</td>
<td>5.0</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.6</td>
<td>5.7</td>
<td>2</td>
<td>7.2</td>
<td>1.6</td>
<td>5.8</td>
<td>2.1</td>
<td>7.3</td>
<td>5.0</td>
</tr>
<tr>
<td>Total Weight (mg)</td>
<td>84.8</td>
<td>297</td>
<td>108</td>
<td>378.4</td>
<td>86.4</td>
<td>302.8</td>
<td>109.8</td>
<td>384.2</td>
<td>235.7</td>
</tr>
</tbody>
</table>

F opt: Optimised Formulation to achieve NLT 85% Dissolution in 10 Minutes
Table 2: Physical Properties of Valsartan Tablets Prepared Employing βCD, Starch 1500 and Soluplus as per 2³ Factorial Design.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Hardness (Kg(sq.cm))</th>
<th>Friability (% wt Loss)</th>
<th>Disintegration Time (Sec)</th>
<th>Drug Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F 1</td>
<td>5.5</td>
<td>0.65</td>
<td>95</td>
<td>98.6</td>
</tr>
<tr>
<td>F a</td>
<td>4.0</td>
<td>0.70</td>
<td>90</td>
<td>98.2</td>
</tr>
<tr>
<td>F b</td>
<td>5.0</td>
<td>0.90</td>
<td>35</td>
<td>99.6</td>
</tr>
<tr>
<td>F ab</td>
<td>5.0</td>
<td>0.65</td>
<td>30</td>
<td>100.2</td>
</tr>
<tr>
<td>F c</td>
<td>4.5</td>
<td>0.80</td>
<td>85</td>
<td>100.6</td>
</tr>
<tr>
<td>F ac</td>
<td>4.5</td>
<td>0.90</td>
<td>90</td>
<td>101.8</td>
</tr>
<tr>
<td>F bc</td>
<td>5.0</td>
<td>0.55</td>
<td>22</td>
<td>98.2</td>
</tr>
<tr>
<td>F abc</td>
<td>5.5</td>
<td>0.65</td>
<td>30</td>
<td>98.4</td>
</tr>
<tr>
<td>F opt</td>
<td>4.5</td>
<td>0.80</td>
<td>20</td>
<td>99.2</td>
</tr>
</tbody>
</table>

The physical parameters of the Valsartan tablets prepared are given in Table 2. The hardness of the tablets was in the range 4.0-5.5 kg/cm². Weight loss in the friability test was less than 0.90% in all the cases. Valsartan content of the tablets prepared was within 100±2%. Much variations were observed in the disintegration and dissolution characteristics of the Valsartan tablets prepared. The disintegration times were in the range 22 to 95 sec. Valsartan tablet formulations Fb, Fab, Fbc and Fabc disintegrated rapidly within 35 sec. However, all the Valsartan tablets prepared fulfilled the official (IP 2010) requirements with regard to drug content, hardness, friability and disintegration time. Dissolution of Valsartan tablets prepared was studied in 0.1N HCl acid. The dissolution profiles of the tablets are shown in Fig.1 and the dissolution parameters are given in Table 3.

Table 3: Dissolution Parameters of Valsartan Tablets Prepared Employing βCD, Starch 1500 and Soluplus as per 2³ Factorial Design.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>PD₁₀ (%) (X ± S.D)</th>
<th>T₅₀ (min)</th>
<th>DE₃₀ (%)</th>
<th>K × 10⁻² (min⁻¹) (X ± S.D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F 1</td>
<td>30.2 ± 1.06</td>
<td>20</td>
<td>28.6</td>
<td>3.12 ± 1.43</td>
</tr>
<tr>
<td>F a</td>
<td>42.1 ± 1.23</td>
<td>12</td>
<td>45.2</td>
<td>5.52 ± 1.12</td>
</tr>
<tr>
<td>F b</td>
<td>92.4 ± 0.24</td>
<td>3.0</td>
<td>81.5</td>
<td>25.40 ± 4.14</td>
</tr>
<tr>
<td>F ab</td>
<td>99.4 ± 0.18</td>
<td>2.0</td>
<td>90.4</td>
<td>47.20 ± 1.23</td>
</tr>
<tr>
<td>F c</td>
<td>38.9 ± 0.27</td>
<td>15</td>
<td>37.5</td>
<td>4.25 ± 0.21</td>
</tr>
<tr>
<td>F ac</td>
<td>54.2 ± 1.33</td>
<td>9.0</td>
<td>52.5</td>
<td>6.10 ± 1.23</td>
</tr>
<tr>
<td>F bc</td>
<td>96.2 ± 0.46</td>
<td>3.0</td>
<td>85.6</td>
<td>26.20 ± 1.02</td>
</tr>
<tr>
<td>F abc</td>
<td>99.2 ± 0.74</td>
<td>2.0</td>
<td>91.6</td>
<td>169.36 ± 2.0</td>
</tr>
<tr>
<td>F opt</td>
<td>85.5 ± 1.25</td>
<td>2.0</td>
<td>85.7</td>
<td>48.12 ± 1.27</td>
</tr>
</tbody>
</table>
Dissolution of Valsartan from all the tablets prepared followed first order kinetics with coefficient of determination ($R^2$) values above 0.920. The first order dissolution rate constant ($K_1$) values were estimated from the slope of the first order linear plots. Much variations were observed in the dissolution rate ($K_1$) and $DE_{30}$ values of the tablets prepared due to formulation variables. ANOVA of $K_1$ values indicated that the individual and combined effects of the three factors, βCD, Starch 1500 and Soluplus are highly significant ($P < 0.01$).

Valsartan tablet formulations $F_{abc}$, $F_{bc}$, $F_{ab}$ and $F_{b}$ gave very rapid dissolution of Valsartan than others. These tablets ($F_{abc}$, $F_{bc}$, $F_{ab}$ and $F_{b}$) gave more than 90% drug release in 10min. Higher levels of βCD and lower levels of Starch 1500 gave low dissolution of Valsartan tablets. The increasing order of dissolution rate ($K_1$) observed with various formulations was $F_1 < F_c < F_a < F_{ac} < F_b < F_{bc} < F_{ab} < F_{abc}$.

![Fig.1: Dissolution Profiles of Valsartan Tablets Prepared using βCD, Starch 1500 and Soluplus as per $2^3$ Factorial Design.](image)

Optimization

The optimization procedure is facilitated by applying factorial designs and by the fitting of an empirical polynomial equation to the experimental results. The predicted optimal formulation has to be prepared and evaluated to confirm its quality. The polynomial equation describing the relationship between the response, percent drug dissolved in 10min ($Y$) and the levels of βCD ($X_1$), Starch 1500 ($X_2$) and Soluplus ($X_3$) based on the observed results was found to be

$$Y = 68.625 + 4.375(X_1) + 27.375(X_2) - 2.375(X_1 X_2) + 3.375(X_3) + 0.125(X_1 X_3) - 1.875(X_2 X_3) - 0.625(X_1 X_2 X_3).$$

Based on the above equation, the formulation of optimized Valsartan tablets with NLT 85% dissolution in 10 min require βCD at 1:3.5 ratio of drug: βCD, Starch 1500 at 24.37% of drug and βCD content, and Soluplus at 1% of drug and βCD content.
To verify Valsartan tablets were formulated employing the optimized levels of βCD, Starch 1500 and Soluplus. The formula of the optimized Valsartan tablets is given in Table 1. The optimized Valsartan tablet formulation was prepared by direct compression method and the tablets were evaluated. The physical parameters of the optimized formulation are given in Table 2 and dissolution parameters are given in Table 3. The hardness of the optimized Valsartan tablets was 4.5 kg/sq.cm. Friability (percent weight loss) was less than 0.80%. Disintegration time of the tablets was 20 sec. The optimized Valsartan tablet formulation gave 85.75% dissolution in 10 min fulfilling the target dissolution requirement. The dissolution results also indicated validity of the optimization technique employed. Hence formulation of Valsartan tablets with NLT 85% dissolution in 10 min could be optimized by 2³ factorial design.

CONCLUSIONS

1. The individual and combined effects of the three factors, βCD, Starch 1500 and Soluplus are highly significant (P < 0.01) in influencing the dissolution rate of Valsartan tablets.
2. Valsartan tablet formulations $F_{abc}$, $F_{bc}$, $F_{ab}$ and $F_b$ disintegrated rapidly within one minute and gave more than 90% dissolution in 10 minutes.
3. The increasing order of dissolution rate ($K_1$) observed with various formulations was $F_1 < F_c < F_a < F_{ac} < F_b < F_{bc} < F_{ab} < F_{abc}$.
4. The polynomial equation describing the relationship between the response, percent drug dissolved in 10 min ($Y$) and the levels of βCD ($X_1$), Starch 1500 ($X_2$) and Soluplus ($X_3$) based on the observed results was found to be $Y = 68.625 + 4.375(X_1) + 27.375(X_2) - 2.375(X_1X_2) + 3.375(X_3) + 0.125(X_1X_3) - 1.875(X_2X_3) - 0.625(X_1X_2X_3)$. Based on the above equation, the formulation of optimized Valsartan tablets with NLT 85% dissolution in 10 min require βCD at 1:3.5 ratio of drug: βCD, Starch 1500 at 24.37% of drug and βCD content, and Soluplus at 1% of drug and βCD content.
5. The optimized Valsartan tablet formulation gave 85.75% dissolution in 10 min fulfilling the target dissolution requirement.
6. Formulation of Valsartan tablets with NLT 85% dissolution in 10 min could be optimized by $2^3$ factorial design.
REFERENCES


