FORMULATION DEVELOPMENT OF VALSARTAN TABLETS: OPTIMIZATION BY $2^3$ FACTORIAL DESIGN, IN VITRO AND PHARMACOKINETIC EVALUATION

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ABSTRACT

Valsartan, a widely prescribed anti hypertensive drug belongs to class II under BCS classification and needs enhancement in the dissolution rate in its formulation development. The objective of the present study is optimization of Valsartan tablet formulation with NLT 85% dissolution in 10 min employing βCD, Crospovidone and SLS by $2^3$ factorial design. The optimized valsartan tablets developed were evaluated for in vitro dissolution and in vivo pharmacokinetics. Eight valsartan tablet formulations employing selected combinations of the three Factors i.e., βCD, Crospovidone and SLS as per $2^3$ Factorial design were formulated, prepared by direct compression method and were evaluated by in vitro and in vivo methods. Valsartan tablet formulations $F_b$ and $F_{bc}$ disintegrated rapidly with in 45 sec and gave very rapid dissolution of valsartan, 100% in 10 min. Higher levels of βCD and lower levels of Crospovidone gave low dissolution rates of valsartan tablets. The increasing order of dissolution rate ($K_1$) observed with various formulations was $F_b = F_{bc} > F_{ab} > F_{abc} > F_a > F_{ac} > F_{1} > F_{c}$. The polynomial equation describing the relationship between the response i.e. percent drug dissolved in 10 min ($Y$) and the levels of βCD ($X_1$), Crospovidone ($X_2$) and SLS ($X_3$) based on the observed results is $Y = 60.05 + 5.34 (X_1) + 33.88 (X_2) - 8.95 (X_1 X_2) - 3.18 (X_3) - 2.38 (X_1 X_3) + 2.80 (X_2 X_3) + 1.95 (X_1 X_2 X_3)$. Based on the above polynomial equation, the optimized valsartan tablet formulation with NLT 85% dissolution in 10 min (Fopt1) could be formulated employing βCD at 1:3 ratio of drug: β CD, Crospovidone at 26.31% of drug content, and SLS at 1% of drug content.
optimized valsartan tablet formulation (Fopt1) gave 85.86% dissolution in 10 min fulfilling the target dissolution set. In the pharmacokinetic evaluation the biological half – life (t½) was found to be 5.06 h and 4.66 h respectively following the administration of optimized valsartan tablets formulated (Fopt2) and Market product. With both the two products tested valsartan was absorbed rapidly and peak concentration is achieved in 1 h. The absorption rate constant (Ka) was 2.275 h⁻¹ and 1.409 h⁻¹ respectively with Fopt2 and Market product. The relative bioavailability (BA) of valsartan from the Fopt2 formulation was 105.7% when compared to Market product (100%). The optimized valsartan tablets formulated employing βCD, Crospovidone and SLS (Fopt2) are comparable to the market product with regard to in vivo performance.

**KEYWORDS:** Valsartan tablets, Optimization, β-cyclodextrin, Crospovidone, SLS, Factorial Design, Pharmacokinetics.

**INTRODUCTION**

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[1] 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[2,3] and use of superdisintegrant[4,5] such as Crospovidone and sodium starch glycolate (Primojel) and surfactant such as sodium lauryl sulphate (SLS) are simple industrially useful approaches for enhancing the dissolution rate of poorly soluble drugs in their formulation development. Complexation with β-cyclodextrin (βCD) and use of Crospovidone and SLS are tried in the present study for enhancing the dissolution rate of Valsartan in its formulation development. The objective of the present study is optimization of Valsartan tablet formulation with NLT 85% dissolution in 10 min employing βCD, Crospovidone and SLS by 2³ factorial design. The optimized valsartan tablets developed were evaluated for in vitro dissolution and in vivo pharmacokinetics.
EXPERIMENTAL

Materials
Valsartan was a gift sample from M/s Hetero Drugs Ltd., Hyderabad. Crospovidone, sodium lauryl sulphate (SLS) and β-cyclodextrin were gift samples from M/s. Eisai Pharma Technology Ltd, Visakhapatnam. Talc and magnesium stearate were procured from commercial sources. All other materials used were of pharmacopoeial grade.

METHODS

Estimation of Valsartan
An UV spectrophotometric method based on the measurement of absorbance at 250 nm in phosphate buffer of pH 6.8 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 µg/ ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.95% and 1.25% 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 designs the βCD, Crospovidone and SLS are considered as the three Factors. The two levels of the Factor A (βCD) are 1:1 and 1:5 ratio of drug: βCD, the two levels of the Factor B (Crospovidone) are 2% and 30% of drug content; and the two levels of Factor C (SLS) are 0% and 2% of drug content. Eight valsartan tablet formulations employing selected combinations of the three Factors i.e., βCD, Crospovidone, and SLS as per $2^3$ Factorial design were formulated and were prepared by direct compression method.

Preparation of Valsartan Tablets
Valsartan (80 mg) tablets were prepared by direct compression method as per the formula given in Table1. The required quantities of valsartan, βCD, Crospovidone and SLS as per the formula in each case were blended thoroughly in a closed polythene 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/cm$^2$.[2]

Friability
The friability of the tablets was measured in a Roche friabilator using the formula
Friability (%) = [(Initial weight - Final weight) / (Initial weight)] x 100

Drug Content
Weighed tablets (5) were powdered using a glass mortar and pestle. An accurately weighed quantity of powder equivalent to 20 mg of valsartan was taken into 100 ml volumetric flask, dissolved in phosphate buffer of pH 6.8 and the solution was filtered through Whatman filter paper no.41. The filtrate was collected and suitably diluted with phosphate buffer of pH 6.8 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 phosphate buffer of pH 6.8 (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 250 nm. 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). 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.[6]
Pharmacokinetic Evaluation

Pharmacokinetic evaluation of the following valsartan products was done in healthy rabbits weighing 1.5 – 2.5 kg (n=6) of either sex in a cross over study at a dose of 40 mg of valsartan per tablet.

(i) Optimized valsartan tablets containing 40 mg of valsartan per tablet

(ii) Commercial valsartan tablets (Valent-40) containing 40 mg of valsartan per tablet.

In vivo study protocols

In vivo study protocols were approved by the Institutional Animal Ethics Committee (Regd. No. CPCSEA / CH/ ORG /2013-035). A wash out period of one month was given between testing of two products.

After collecting the zero hour blood sample (blank), the product in the study was administered orally with 10 ml of water. No food or liquid other than water was permitted until 4 hours following the administration of the product. Blood samples (2 ml) were collected from marginal ear vein at 0.5, 1, 2, 3, 4, 6, 8 and 12 hours after administration. The blood samples were collected in heparinized test tubes and were centrifuged at 20000 rpm for 10 min and the plasma separated was collected into dry test tubes. All the samples were stored under refrigerated conditions prior to assay on the same day. Plasma concentrations of valsartan were determined by a known revalidated HPLC method[7] as follows.

Estimation of Valsartan in Plasma Samples by HPLC Method

HPLC used: Waters Alliance HPLC System, Model: e2695 with PDA Detector (Photodiode Array), Model: 2998.

Chromatographic conditions

Column : Inertsil ODS (150x4.6 mm)
Flow rate : 1.0ml/minute
Wavelength : 230nm
Injection volume : 10µL
Program : Isocratic
Internal Standard : Atorvastatin
Retention time (Valsartan) : 3.821 minutes
Retention time (Atorvastatin) : 4.787 minutes

Mobile Phase: ACN: Phosphate buffer pH 3.5(65:35v/v)
Construction of Calibration Curve
For the estimation of Valsartan in plasma sample, a calibration curve (Fig.3) was constructed initially by analyzing plasma samples containing different amounts of valsartan as follows.

To a series of tubes containing 0.5 ml of drug free plasma in each, 0.1 ml of internal standard solution and 0.1 ml of drug solution containing 0.5, 2, 4, 6, 8, 10, and 12 micrograms of internal standard and valsartan respectively were added and mixed. To each tube 1 ml acetonitrile was added, mixed thoroughly and centrifuged at 5000 rpm for 2.0 min. The organic layer (0.5ml) was taken in to a dry test tube and acetonitrile was evaporated. To the dried residue 0.5 ml mobile phase was added and mixed for reconstitution. Subsequently 10 µl were injected in to the HPLC columns for analysis. A model HPLC Chromatogram is shown in Fig.2. Plasma (0.5ml) collected in the pharmacokinetic study was used for the estimation of valsartan as described above.

Data Analysis
From the time versus plasma concentration data, various pharmacokinetic parameters such as peak concentration (C_{max}), time at which peak occurred (T_{max}), Area under the curve (AUC), elimination rate constant (K_{el}), biological half - life (t_{1/2}), percent absorbed to various times and absorption rate constant (K_{a}), were calculated in each case assuming one compartment open model as per known standard methods.[8,9]

RESULTS AND DISCUSSION
The objective of the present study is to optimize the valsartan tablet formulation employing βCD, Crospovidone and SLS by 2³ Factorial design to achieve NLT 85% dissolution in 10 min. For optimization of Valsartan tablets as per 2³ Factorial design the βCD, Crospovidone and SLS are considered as three Factors. The two levels of the Factor A (βCD) are 1:1 and 1:5 ratio of drug: βCD , the two levels of the Factor B (Crospovidone) are 2% and 30% of drug content ; and the two levels of Factor C (SLS) are 0% and 2% of drug content. Eight valsartan tablet formulations employing selected combinations of the three Factors i.e., βCD, Crospovidone , and SLS as per 2³ Factorial design were formulated and prepared by direct compression method as per the formula given in Table 1 .

The hardness of the tablets was in the range 4.5-5.0 kg/cm². Weight loss in the friability test was less than 0.94 % in all the cases. Valsartan content of the tablets prepared was within 100±3%. Many variations were observed in the disintegration and dissolution characteristics of the valsartan tablets prepared. The disintegration times were in the range 25 sec. to 8 min.
30 sec. Valsartan tablet formulations (Fb, Fbc, and Fabc) disintegrated rapidly with in 1 min. All other tablets disintegrated rather slowly in about 3 min to 8 min 30 sec. As βCD level was increased the disintegration time is increased, whereas as Crospovidone concentration is increased the disintegration time is reduced.

Dissolution rate of valsartan tablets prepared was studied in phosphate buffer of pH 6.8. The dissolution profiles of the tablets are shown in Fig.1 and the dissolution parameters are given in Table 2. Dissolution of valsartan from all the tablets prepared followed first order kinetics with coefficient of determination (R²) values above 0.945. Valsartan tablet formulations Fb and Fbc gave very rapid dissolution of valsartan than others. They gave 100% dissolution in 10 min. Higher levels of βCD and lower levels of Crospovidone gave low dissolution of valsartan tablets. The increasing order of dissolution rate (K) observed with various formulations was Fb = Fbc > Fabc > F<sub>a</sub> > F<sub>c</sub>.

**Optimization**

For optimization, percent drug dissolved in 10 min was taken as response (Y) and level of βCD as (X<sub>1</sub>), level of Crospovidone as (X<sub>2</sub>) and level of SLS as (X<sub>3</sub>). The polynomial equation describing the relationship between the response, Y and the variables, X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> based on the observed data was found to be:

\[ Y = 60.05 + 5.34 (X_1) + 33.88 (X_2) - 8.95 (X_1 X_2) - 3.18 (X_3) - 2.38 (X_1 X_3) + 2.80 (X_2 X_3) + 1.95 (X_1 X_2 X_3) \]

Based on the above polynomial equation, the optimized valsartan tablet formulation with NLT 85% dissolution in 10 min could be formulated employing βCD at 1:3 ratio of drug: βCD, Crospovidone at 26.31% of drug content, and SLS at 1% of drug content. To verify, valsartan tablets (Fopt1) were formulated employing the optimized levels of βCD (240 mg/tablet), Crospovidone (21.05 mg/tablet) and SLS (0.8 mg/tablet). The formulae 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 hardness of the optimized valsartan tablets was 4.5 kg/sq.cm. Friability (percent weight loss) was less than 0.85%. Disintegration time of the tablets was 40 sec. The optimized valsartan tablet formulation gave 85.86% dissolution in 10 min fulfilling the target dissolution set.

Valsartan optimized tablets with NLT 85% dissolution in 10 min (Fopt.2) containing 40 mg of valsartan per tablet were also prepared employing optimized levels of βCD (120 mg/tablet), Crospovidone (10.52 mg/tablet) and SLS (0.4 mg/tablet) as per the formulae given in Table 1.
for in vivo pharmacokinetics studies. These optimized valsartan tablets (Fopt2) gave 86.10% dissolution in 10 min.

**Pharmacokinetic Evaluation**

Pharmacokinetic evaluation was done on optimized valsartan tablets formulated (Fopt2) with a view to evaluate their in vivo performance in comparison to a market product. Plasma concentrations of valsartan following the oral administration of valsartan products in rabbits (n=6) are shown in Fig.4.

A summary of the pharmacokinetic parameters estimated following the oral administration of valsartan products tested is given in Table 3.

The elimination rate constant (K_{el}) for valsartan was found to be 0.1368 h^{-1} and 0.1486 h^{-1} respectively following the administration of optimized valsartan tablets formulated (Fopt2) and Market product. The corresponding half-life was found to be 5.06 h and 4.66 h respectively.

The absorption rate constant (K_{a}) was found to be 2.275 h^{-1} and 1.409 h^{-1} respectively with Fopt2 and Market product. With both the two products tested valsartan was found to be absorbed rapidly and peak concentration is achieved in 1 h and later the plasma concentrations were also decreased rapidly. Based on AUC_{0\rightarrow \infty} the relative bioavailability (BA) of valsartan from the Fopt2 formulation was found to be 105.7 % when compared to Market product (100%)

Table 1: Formulae of Valsartan Tablets Prepared Employing β CD, Crospovidone and SLS as Per 2^3 Factorial Design

<table>
<thead>
<tr>
<th>Ingredient (mg/tab)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F12</th>
<th>F13</th>
<th>F23</th>
<th>F123</th>
<th>Fopt1</th>
<th>Fopt2</th>
</tr>
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<tbody>
<tr>
<td>Valsartan</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>βCD</td>
<td>80</td>
<td>400</td>
<td>80</td>
<td>400</td>
<td>80</td>
<td>400</td>
<td>80</td>
<td>400</td>
<td>240</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>1.6</td>
<td>1.6</td>
<td>24</td>
<td>24</td>
<td>1.6</td>
<td>1.6</td>
<td>24</td>
<td>24</td>
<td>21.05</td>
</tr>
<tr>
<td>SLS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.6</td>
<td>1.6</td>
<td>1.6</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Talc</td>
<td>3.2</td>
<td>9.6</td>
<td>3.6</td>
<td>10</td>
<td>3.3</td>
<td>9.7</td>
<td>3.7</td>
<td>10.1</td>
<td>6.8</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>3.2</td>
<td>9.6</td>
<td>3.6</td>
<td>10</td>
<td>3.3</td>
<td>9.7</td>
<td>3.7</td>
<td>10.1</td>
<td>6.8</td>
</tr>
<tr>
<td>Total weight (mg)</td>
<td>168</td>
<td>500.8</td>
<td>191.2</td>
<td>524</td>
<td>169.8</td>
<td>502.6</td>
<td>193</td>
<td>525.8</td>
<td>355.45</td>
</tr>
</tbody>
</table>
Table 2: Dissolution Parameters of Valsartan Tablets Prepared Employing βCD, Crospovidone and SLS as per $2^3$ Factorial Design

<table>
<thead>
<tr>
<th>Formulation</th>
<th>PD$_{10}$ (%$\bar{x}$ ± s d)</th>
<th>T$_{50}$ (min)</th>
<th>T$_{90}$ (min)</th>
<th>DE$_{30}$ (%$\bar{x}$ ± s d)</th>
<th>K$_1$ X 10$^2$ (min$^{-1}$)</th>
<th>K$_1$ X 10$^2$ (min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F$_1$</td>
<td>16.04 ± 0.83</td>
<td>35</td>
<td>&gt;60</td>
<td>22.75 ± 0.83</td>
<td>1.64 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>F$_a$</td>
<td>50.69 ± 1.92</td>
<td>10</td>
<td>35.5</td>
<td>57.45 ± 1.92</td>
<td>7.44 ± 1.06</td>
<td></td>
</tr>
<tr>
<td>F$_b$</td>
<td>100 ± 0.83</td>
<td>0.5</td>
<td>2.5</td>
<td>91.66 ± 0.83</td>
<td>78.2 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>F$_{ab}$</td>
<td>91.04 ± 1.89</td>
<td>2</td>
<td>4</td>
<td>87.19 ± 1.89</td>
<td>26.8 ± 1.91</td>
<td></td>
</tr>
<tr>
<td>F$_c$</td>
<td>12.63 ± 0.14</td>
<td>42.5</td>
<td>&gt;60</td>
<td>15.85 ± 0.14</td>
<td>1.23 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>F$_{ac}$</td>
<td>30.15 ± 1.47</td>
<td>17</td>
<td>52</td>
<td>42.04 ± 1.47</td>
<td>4.07 ± 0.15</td>
<td></td>
</tr>
<tr>
<td>F$_{bc}$</td>
<td>100 ± 0.83</td>
<td>2.5</td>
<td>4</td>
<td>91.66 ± 0.83</td>
<td>78.2 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>F$_{abc}$</td>
<td>89.51 ± 0.35</td>
<td>3.5</td>
<td>10</td>
<td>84.25 ± 0.35</td>
<td>20.2 ± 1.36</td>
<td></td>
</tr>
<tr>
<td>F$_{opt}$</td>
<td>85.86 ± 0.41</td>
<td>2.5</td>
<td>12</td>
<td>85.25 ± 0.41</td>
<td>24.25 ± 0.03</td>
<td></td>
</tr>
</tbody>
</table>

Fig.1: Dissolution Profiles of Valsartan Tablets Prepared Employing βCD, Crospovidone and SLS as per $2^3$ Factorial Design
Fig. 2: HPLC Chromatogram of Valsartan (0.5 µg/0.5ml of plasma)

<table>
<thead>
<tr>
<th>Peak Name</th>
<th>RT</th>
<th>Area</th>
<th>Height</th>
<th>USP Plate Count</th>
<th>USP Resolution</th>
<th>USP Tailing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsartan</td>
<td>3.822</td>
<td>151722</td>
<td>19671</td>
<td>3869</td>
<td>1.33</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>4.771</td>
<td>46817</td>
<td>4262</td>
<td>4481</td>
<td>3.5</td>
<td>1.13</td>
</tr>
</tbody>
</table>

Fig. 3: Calibration Curve for Estimation of Valsartan in the Plasma Sample

\[ y = 1.7896x + 2.8507 \]
\[ R^2 = 0.9987 \]

Fig. 4: Plasma Concentrations of Valsartan Following the Oral Administration of Valsartan Products in Rabbits (n=6)
Table 3: Summary of Pharmacokinetic Parameters Estimated Following the Oral Administration of Valsartan Products

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Optimized Valsartan Tablets Formulated (Fopt2)</th>
<th>Commercial Valsartan tablet (Valent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (µg/ml)</td>
<td>24.52±1.4</td>
<td>22.86±1.2</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>K&lt;sub&gt;el&lt;/sub&gt; (h&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.1368</td>
<td>0.1486</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>5.06</td>
<td>4.62</td>
</tr>
<tr>
<td>(AUC)&lt;sub&gt;0→12h&lt;/sub&gt;</td>
<td>165.63</td>
<td>160.44</td>
</tr>
<tr>
<td>(AUC)&lt;sub&gt;0→α&lt;/sub&gt;</td>
<td>208.39</td>
<td>197.11</td>
</tr>
<tr>
<td>Rel. BA (%)</td>
<td>105.7</td>
<td>100.0</td>
</tr>
<tr>
<td>K&lt;sub&gt;a&lt;/sub&gt; (h&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>2.275</td>
<td>1.409</td>
</tr>
</tbody>
</table>

Percent Drug Absorbed to Various times Estimated as per Wagner –Nelson Method

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Optimized Values</th>
<th>Commercial Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 h</td>
<td>79.17</td>
<td>72.1</td>
</tr>
<tr>
<td>1.0 h</td>
<td>95.51</td>
<td>86.2</td>
</tr>
<tr>
<td>2.0 h</td>
<td>99.0</td>
<td>94.0</td>
</tr>
</tbody>
</table>

CONCLUSIONS

1. Valsartan tablet formulations F<sub>b</sub> and F<sub>bc</sub> disintegrated rapidly with in 45 sec and gave very rapid dissolution of valsartan, 100% in 10 min.
2. Higher levels of βCD and lower levels of Crospovidone gave low dissolution rates of valsartan tablets.
3. The increasing order of dissolution rate (K<sub>1</sub>) observed with various formulations was F<sub>b</sub> = F<sub>bc</sub> > F<sub>ab</sub> > F<sub>abc</sub> > F<sub>a</sub> > F<sub>ac</sub> > F<sub>c</sub>.
4. The polynomial equation describing the relationship between the response i.e. percent drug dissolved in 10 min (Y) and the levels of β CD (X<sub>1</sub>), Crospovidone (X<sub>2</sub>) and SLS (X<sub>3</sub>) based on the observed results is Y = 60.05 + 5.34 (X<sub>1</sub>) + 33.88 (X<sub>2</sub>) - 8.95 (X<sub>1</sub>X<sub>2</sub>) - 3.18 (X<sub>3</sub>) - 2.38 (X<sub>1</sub>X<sub>3</sub>) + 2.80 (X<sub>2</sub>X<sub>3</sub>) + 1.95 (X<sub>1</sub>X<sub>2</sub>X<sub>3</sub>).
5. Based on the above polynomial equation, the optimized valsartan tablet formulation with NLT 85% dissolution in 10 min (Fopt1) could be formulated employing βCD at 1:3 ratio of drug: βCD, Crospovidone at 26.31% of drug content, and SLS at 1% of drug content.
6. The optimized valsartan tablet formulation gave 85.86% dissolution in 10 min fulfilling the target dissolution set.
7. The biological half – life (t<sub>1/2</sub>) 5.06 h and 4.66 h respectively following the administration of optimized valsartan tablets formulated (Fopt2) and Market product.
8. With both the two products tested valsartan was absorbed rapidly and peak concentration is achieved in 1 h. The absorption rate constant (Kₘₐₓ) was 2.275 h⁻¹ and 1.409 h⁻¹ respectively with Fopt2 and Market product.

9. The relative bioavailability (BA) of valsartan from the Fopt2 formulation was 105.7 % when compared to Market product (100%).

10. The optimized valsartan tablets formulated employing βCD, Crosspovidone and SLS (Fopt2) are comparable to the market product with regard to in vivo performance.

REFERENCES