PHARMACOKINETIC EVALUATION OF OPTIMIZED VALSARTAN TABLETS FORMULATED EMPLOYING β CD, CROSPOVIDONE AND SLS IN COMPARISON TO A MARKET PRODUCT

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ABSTRACT

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. It needs enhancement in the dissolution rate in its formulation development. Optimized valsartan tablet formulation with NLT 85% dissolution in 10 min could be developed employing βCD, Crospovidone and SLS by $2^3$ factorial design. In the present study pharmacokinetic evaluation was done on optimized valsartan tablet formulation developed in comparison to a market product of valsartan tablets with an objective to evaluate their in vivo performance. Pharmacokinetic evaluation of the Optimized valsartan (40 mg) tablets in comparison to commercial valsartan (40 mg) tablets (Valent-40) 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. The biological half – life (t ½) was found to be 5.06 h and 4.66 h respectively following the administration of optimized valsartan tablets formulated (Vopt) and Market product. With both the two products tested valsartan was found to be absorbed rapidly and peak concentration is achieved in 1 h. The absorption rate constant (K_a) was found to be 2.275 h⁻¹ and 1.409 h⁻¹ respectively with Vopt and Market product. The relative bioavailability (BA) of valsartan from the Vopt formulation was found to be 105.7 % when compared to Market product (100%). The optimized valsartan tablets formulated employing βCD, Crospovidone and SLS are comparable to the market product with regard to in vivo performance.

KEYWORDS: Valsartan tablets, Pharmacokinetic evaluation, Optimization.
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 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 superdisintegrant 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. In our earlier report complexation with β-cyclodextrin (βCD) and use of Crospovidone and SLS were tried for enhancing the dissolution rate of valsartan in its formulation development. Optimized valsartan tablet formulation with NLT 85% dissolution in 10 min could be developed employing βCD, Crospovidone and SLS by $2^3$ factorial design. The results are reported earlier. In the present study pharmacokinetic evaluation was done on optimized valsartan tablet formulation developed in comparison to a market product of valsartan tablets with an objective to evaluate their in vivo performance.

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.

Formulation of Optimized 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, prepared by direct compression method and were evaluated.

For optimization, percent drug dissolved in 10 min was taken as response (Y) and level of βCD as ($X_1$), level of Crospovidone as ($X_2$) and level of SLS as ($X_3$). The polynomial equation describing the relationship between the response, Y and the variables, $X_1$, $X_2$ and $X_3$ 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. Valsartan tablets containing 40 mg of valsartan per tablet were formulated and prepared employing the optimized levels of βCD (120 mg/tablet), Crospovidone (10.52 mg/tablet) and SLS (0.40 mg/tablet) and were used in the pharmacokinetic evaluation.

**Preparation of Optimized Valsartan Tablets**

Valsartan (40 mg) tablets were prepared by direct compression employing the optimized levels of βCD (120 mg/tablet), Crospovidone (10.52 mg/tablet) and SLS (0.40 mg/tablet). The required quantities of valsartan, βCD, Crospovidone and SLS 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.

**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 as follows.

Estimation of Valsartan in Plasma Samples by HPLC Method

**Instrumentation**

**Instrument Make**: Waters Alliance HPLC System, Model: e2695  
**Software**: Empower Chromatography Data Software  
**Detector**: 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  
- **Pump Pressure**: 1500psi  
- **Run time**: 10minutes  
- **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 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 into 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 into the HPLC columns for analysis. A model HPLC Chromatogram is shown in Fig.1. 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\text{max}), time at which peak occurred (T\text{max}), Area under the curve (AUC), elimination rate constant (K\text{el}), biological half-life (t\text{1/2}), percent absorbed to various times and absorption rate constant (K\text{a}), were calculated in each case assuming one compartment open model as per known standard methods.[8,9]

RESULTS AND DISCUSSION
Pharmacokinetic evaluation was done on optimized valsartan tablets formulated with a view to evaluate their \textit{in vivo} performance in comparison to a market product. A summary of the pharmacokinetic parameters estimated following the oral administration of valsartan products tested is given in Table1.

The elimination rate constant (K\text{el}) for valsartan was found to be 0.1368 h\textsuperscript{-1} and 0.1486 h\textsuperscript{-1} respectively following the administration of optimized valsartan tablets formulated (Vopt) and Market product. The corresponding half-life was found to be 5.06 h and 4.66 h respectively. The absorption rate constant (K\text{a}) was found to be 2.275 h\textsuperscript{-1} and 1.409 h\textsuperscript{-1} respectively with Vopt 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 $AUC_0^\infty$ the relative bioavailability (BA) of valsartan from the Vopt formulation was found to be 105.7 % when compared to Market product (100%).
Fig. 1: HPLC Chromatogram of Valsartan (0.5 µg/0.5ml of plasma)

Fig. 2: Calibration Curve for Estimation of Valsartan in the Plasma Sample
Fig. 3: Plasma Concentrations of Valsartan Following the Oral Administration of Valsartan Products in Rabbits (n=6)

Table 1: Summary of Pharmacokinetic Parameters Estimated Following the Oral Administration of Valsartan Products

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Optimized Valsartan Tablets Formulated</th>
<th>Commercial Valsartan tablet (Valent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (µg/ml)</td>
<td>24.52±1.4</td>
<td>22.86±1.2</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>$K_{\text{el}}$ (h$^{-1}$)</td>
<td>0.1368</td>
<td>0.1486</td>
</tr>
<tr>
<td>$t_{\frac{1}{2}}$ (h)</td>
<td>5.06</td>
<td>4.62</td>
</tr>
<tr>
<td>$(\text{AUC})_{0-12\text{h}}$</td>
<td>165.63</td>
<td>160.44</td>
</tr>
<tr>
<td>$(\text{AUC})_{0-\infty}$</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>$K_a$ (h$^{-1}$)</td>
<td>2.275</td>
<td>1.409</td>
</tr>
<tr>
<td>Percent Drug Absorbed to Various times Estimated as per Wagner–Nelson Method</td>
<td></td>
<td></td>
</tr>
<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. The biological half–life ($t_{\frac{1}{2}}$) was found to be 5.06 h and 4.66 h respectively following the administration of optimized valsartan tablets formulated (Vopt) and Market product.
2. With both the two products tested valsartan was found to be absorbed rapidly and peak concentration is achieved in 1 h. The absorption rate constant ($K_a$) was found to be 2.275 h$^{-1}$ and 1.409 h$^{-1}$ respectively with Vopt and Market product.
3. The relative bioavailability (BA) of valsartan from the Vopt formulation was found to be 105.7% when compared to Market product (100%).
4. The optimized valsartan tablets formulated employing βCD, Crosspovidone and SLS are comparable to the market product with regard to in vivo performance.

REFERENCES