FAST DISSOLVING ORAL DISINTEGRATING FILMS OF VALSARTAN

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III. INTRODUCTION

Valsartan is an angiotensin II receptor antagonist used in the management of hypertension. It improves symptoms and quality of life in patients with chronic heart failure. Valsartan treatment had no demonstrable negative effects on growth and development and is used safely as an antihypertensive agent in children less than 6 years old.

Valsartan is rapidly absorbed following oral administration. It has a systemic availability of 0.25, which is reduced to about 0.15 by food. It is 95% protein bound and is mostly excreted as unchanged drug via the bile. It is given in doses of 40–160 mg once daily; this dosage is reduced in hepatic impairment, intravascular volume depletion, and renal impairment. The drug is available commercially as conventional tablets 40, 80, and 160 mg. Trials were done to formulate valsartan as a transdermal dosage form to overcome its low oral bioavailability.

Orodispersible tablets are those tablets dispersing upon contact with the moist mucosal surfaces of the oral cavity and quickly release their components without mastication or water before swallowing. The primary benefit of the orodispersible tablets is improved patient compliance due to ease of swallowing and no need for water. Difficulties with and resistance to tablet taking are common in all patient groups but are particularly prevalent in geriatric, pediatric, and psychiatric patients. Physical problems with swallowing (dysphagia) can exacerbate compliance problems and undermine treatment efficacy. Other benefits of orodispersible tablets include accuracy of dosage, rapid onset of action, and increase in bioavailability. The increased bioavailability of some orodispersible tablets compared to conventional tablets could be due to the dispersion in saliva and pregastric absorption. This pregastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo a great deal of hepatic metabolism. However, many orodispersible tablets showed nearly identical plasma concentration profiles as conventional tablets but with the major advantage of convenience.

The present work is concerned with the formulation and characterization of valsartan orodispersible tablets for oral administration. Different drug compatible excipients were tried as fillers and binders. An in vivo study was conducted to assess the bioavailability of the selected formula in comparison with that of the conventional commercial tablets.

Go to:

IV. MATERIALS AND METHODS

Materials

Valsartan (particle size 2.91 μm) was obtained as a gift from International Drug Industries, Egypt. Mannitol was purchased from Winlab Laboratory Chemicals, UK. Spray-dried lactose, sucrose, and pregelatinized starch were a gift from Chemical Industries Development Company, Egypt. Sorbitol, xanthan gum, pectin (from citrus peel), gelatin (approximately 300 bloom), and acetonitrile (high-performance liquid chromatography (HPLC)) were obtained from Sigma, USA, β-cyclodextrin was purchased from Cerestar Inc., USA, sodium alginate (low molecular weight) was purchased from CDH Labs., India, Tareg® tablets, 40 mg, Novartis, Egypt. All other chemicals were of analytical grade and used as received.

Drug–Excipient Compatibility Study

This study was done to evaluate the compatibility of valsartan with pharmaceutical excipients of common use as fillers and binders. Differential scanning calorimetry (DSC) was used for screening. The specified samples were hermetically sealed in a flat bottomed aluminum pans and heated in the differential scanning calorimeter (Shimadzu Corporation, Japan) in an atmosphere of nitrogen, and the rate of flow was 25 ml/min. A temperature range of 0°C to 250°C was used, and the heating rate was 10°C/min.

Experiment Design

A 3^3 randomized full factorial design was used in the present study. In this design, three factors are evaluated, each at three levels, and experimental trials are performed at all the 27 possible combinations. The filler type (X1), the binder type (X2), and the binder concentration (X3) were selected as independent variables. The composition of the different tablet formulas is listed in Table I. The oral disintegration time, percentage drug dissolved after 4 min (DP_{4 min}), dissolution rate at 4 min (DR_{4 min}), and dissolution efficiency at 30 min (DE_{30 min}) were selected as dependent variables.
## Table I - Composition and Responses for a $3^3$ Factorial Design

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<thead>
<tr>
<th>Tablet formula</th>
<th>Variables</th>
<th>Response values</th>
<th>Disintegration time (s)</th>
<th>$\text{DR}_{4\text{min}}$ (μg/min)</th>
<th>$\text{DP}_{4\text{min}}$ (%)</th>
<th>$\text{DE}_{30\text{min}}$ (%)</th>
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<td>$X_1$</td>
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<td>$X_3$</td>
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<td>1</td>
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<td>Mannitol</td>
<td>Spray-dried lactose</td>
<td>Sorbitol</td>
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Variables

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<th>X&lt;sub&gt;2&lt;/sub&gt;</th>
<th>X&lt;sub&gt;3&lt;/sub&gt;</th>
<th>Response values</th>
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<td>Percentage pushed through blister intact</td>
<td>Disintegration time (s)</td>
<td>DR&lt;sub&gt;4&lt;/sub&gt; min (µg/min)</td>
<td>DP&lt;sub&gt;4&lt;/sub&gt; min (%)</td>
</tr>
<tr>
<td></td>
<td>X&lt;sub&gt;2&lt;/sub&gt; = binder type</td>
<td>X&lt;sub&gt;3&lt;/sub&gt; = binder concentration (%)</td>
<td>to</td>
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<td>Xanthan gum</td>
<td>0.5</td>
<td>1</td>
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</tr>
</tbody>
</table>

Transformed values: −1

Open in a separate window

All values are mean of three readings ± S.D

Preparation and Characterization of Valsartan Orodispersible Tablets

A suspension containing valsartan together with other components of the preparation, filler (60 mg/tablet), and binder (0.5%, 1%, or 2% w/w of the total tablet weight) was prepared in distilled water using a magnetic stirrer (200 rpm). The tablet mix suspension was dispensed into tablet polyvinyl chloride (PVC) blister packs to result in a valsartan dose of 40 mg in each tablet. Tablet blister packs containing prepared tablets were then frozen in the freezer for 24 h. The frozen tablets were then lyophilized for 24 h using a Novalyphel NL 500 Freeze Dryer (Savant Instruments, Holbrook, NY, USA).

Physical Properties

Twenty tablets of each formula were examined visually for their appearance. The tablet friability was expressed in terms of the percentage pushed through the PVC blister intact, and weight variation was described as the relative standard deviation (% R.S.D.) among each tablet formula.

Oral Disintegration Time

Three human subjects were involved in the determination of the disintegration time for each tablet formula; the time required for complete disintegration of the tablet when placed on the tongue was determined by tactile feedback using a stop watch.

In vitro Dissolution Study

The dissolution of valsartan from the prepared tablets was performed using the United States Pharmacopia XXVIII rotating basket, at a speed of 50 rpm in 400 ml Sorensen’s phosphate buffer (pH 6.8) and at a temperature of 37 ± 0.5°C. The study was conducted for 30 min, and aliquots each of 3 ml were withdrawn, at time intervals of 2 min, from the dissolution medium and replaced with an equivalent amount of the fresh medium. The samples were analyzed spectrophotometrically for valsartan content by measuring the absorbance at λ<sub>max</sub> 250 nm against Sorensen’s phosphate buffer pH 6.8 as a blank. Each experiment was carried out in triplicate.

For assessment and comparison, the dissolution rate of the drug during the first 4 min (DR<sub>4</sub> min) was used. For this mean, the amount of drug dissolved per minute presented by each tablet was calculated by dividing the amount of drug dissolved in microgram by the corresponding time. Additionally, the dissolution profiles were evaluated on the basis of the dissolution efficiency parameter at 30 min (DE<sub>30 min</sub>) as described by Khan et al. according to the following equation:

\[
DE = \int_{0}^{t} \frac{y_{100} \cdot dt}{y_{100} \cdot t} \times 100
\]

Where the integral in Eq. 1 is the area under the dissolution curve up to the dissolution time t, and y<sub>100</sub> is the area of the rectangle described by 100% dissolution at the same time.

Wetting Test

The time required for a water soluble dye to diffuse throughout the entire tablet (at 2% w/w binder concentration) and reach its surface (wetting time) was measured by a slight modification of the procedure mentioned by Bi et al..

Scanning Electron Microscopy
Scanning electron micrographs of the fracture plane of tablets were taken using electron microscope (Joel, 100S, Japan).

**Oral Bioavailability Study**

**Subjects**

Four male subjects aged 18 to 45 years were involved in the study. They were in good health based on medical history, vital signs (sitting systolic and diastolic blood pressure, heart rate, body temperature), and physical examination. Exclusion criteria included known hypersensitivity to any ingredient in the valsartan tablet, use of other drugs within 14 days before or during the trial, history of cardiovascular or pulmonary disorders, diabetes mellitus, or any other disease or condition that could interfere with the study results, a known tendency toward bleeding and a recent history of drug abuse.

**Study Design**

The study was a randomized, open-label, two-way crossover trial on healthy volunteers. Two treatments were used in a single dose with a washout period of 14 days. Treatment A consisted of two 40-mg tablets of the selected orodispersible valsartan tablets (formula number 6) taken without water. Treatment B consisted of two 40-mg tablets of the commercial conventional oral valsartan tablets (Tareg®) taken with 180 ml water. Both treatments were administered after an overnight fast of 10 h. The protocol was approved by the University Protection of Human Subjects Committee, and it complies with the Declaration of Helsinki and Tokyo for Humans.

**Blood samples for pharmacokinetic analysis** were obtained immediately before drug intake and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 24 h after dosing. Blood samples were collected in heparinized tubes and were centrifuged for 10 min at 3,000 rpm at room temperature within 1 h of collection. Separated plasma was aspirated and transferred into plastic tubes and were stored at −20°C until assayed.

**Pharmacokinetic and Statistical Methods**

Peak plasma concentration (Cmax, microgram per milliliter), time to Cmax (Tmax, hour), the area under the plasma concentration–time curve from time zero to the last quantifiable time point (AUC(0–t), microgram per hour per milliliter), AUC extrapolated to infinity (AUC(0–∞), microgram per hour per milliliter), and t1/2 (hour) were estimated by noncompartmental analysis using WinNonlin® software (version 1.5, scientific consulting, Inc, Cary, NC, USA). The differences in average of data were compared by simple analysis of variance (one-way ANOVA) using the software SPSS (SPSS Inc., Chicago, USA). The significance of the difference was determined at 95% confidence limit (α = 0.05).

**Method of Assay**

The assay of valsartan in plasma was performed by slight modifications for the high-performance liquid chromatography method adapted by Satana et al. A thermo BDS hypersil C18 column (5 μ, 150 × 4.6 mm, Hypersil) and a mobile phase consisting of 0.02 M phosphate buffer (pH 3.2): acetonitrile (55:45 v/v) mixture were used. The flow rate was 1 ml/min, and the effluent was monitored at 225 nm using a SPD-10AVP, ultraviolet–visible detector. Diclofenac sodium was used as an internal standard. Before assay, the linearity, the precision, the selectivity, and the accuracy of the method were demonstrated.

Go to: V. RESULTS AND DISCUSSION

**Drug–Excipient Compatibility Study**

The thermogram of valsartan showed a sharp characteristic peak at 107°C (T_onset = 104.39°C, T_endset = 116.94°C, and ΔHf = −249.13 J/g) due to the melting of the solid drug. This peak was reserved in the thermograms of the 1:1 physical mixtures of the drug with spray-dried lactose, mannitol, sorbitol, xanthan gum, gelatin, and pectin, Fig. 1a, which confirms the compatibility of valsartan with those excipients. Other excipients showing incompatibilities with the drug (β-cyclodextrin, pregelatinized starch, sodium alginate, and sucrose) were avoided in the development of our tablets, Fig. 1b.
Factorial Design
During the preparation of all the tablets, the drug:filler ratio was fixed to reduce the residual variation and increase the sensitivity of the experiment in detecting effects or changes in response due to the factors under investigation. Our preliminary work showed that drug loadings more than 40% resulted in friable tablets. The choice of the levels of the \( X_1 \) and \( X_2 \) factors was based on results of the previous drug excipients compatibility study. The levels for factor \( X_3 \) were determined based on the data collected from previously published studies.

Preparation and Characterization of Valsartan Orodispersible Tablets
Fast-dissolving drug delivery systems can be manufactured by a variety of technologies, including direct compression, wet granulation, and freeze drying. Freeze drying was selected here because it results in porous tablets with rapid reconstitution in small amount of saliva in the mouth.

Physical Properties
All the prepared tablets were evaluated visually for their appearance, ease of removal of the blister, and integrity during removal, as well as weight variation. Percentage pushed through blister intact values are listed in Table I. The filler type (factor \( X_1 \)) showed the most pronounced effect on the physical characters of the tablets. Tablet formulas number 19–27, which contained sorbitol, shrank after freeze drying. They were sticky, friable, and not easily removed from blisters (their percentage pushed through blister intact values ranged from 20% to 50%). This is probably due to the hygroscopic properties of sorbitol. Even though variations in the levels of the other two factors (binder type and binder concentration) highly affected the percentage pushed through blister intact values, but all these values remained very low and unacceptable for handling and administration by patients. Contrary to that, tablets prepared using mannitol and spray-dried lactose as fillers showed smooth nonsticky surfaces with high integrity. It is clear that almost all the percentage pushed through blister intact values were acceptable (65–100%).

Studying the effect of the binder type (\( X_2 \)) on the physical properties of the tablets, at each level of factors \( X_1 \) and \( X_3 \), showed that pectin recorded the best appearance and the easiest removal and the highest percentage pushed through blister intact values. Pectin was followed by xanthan gum and then gelatin, which recorded the lowest percentage pushed through blister intact values. Increasing the amount of the binder (factor \( X_2 \)) improved the tablet appearance and integrity and increased the percentage pushed through blister intact. Increasing the binder amount increased the viscosity of the tablet mix suspension during preparation and resulted in more compact tablets. % R.S.D. values for the mean tablet weights ranged from 1.3% to 3.7% for all the 27 formulas indicating high weight uniformity, data are not shown. This is because the used
binders increased the viscosity of the tablet mix suspension during preparation, and the magnetic stirring kept all the tablet components homogenously suspended. The drug content obeyed the official limits, ranged from 97.43% to 101.2%.

**Oral Disintegration Time**

The results of the disintegration time are shown in Table I. Statistical analysis of these data was performed using the statistical software (StatView version 4.57, Abacus Concept). The analysis of variance including sum of squares, subsequent significant tests, and the calculation of the average values was also obtained using this software. The calculated F ratios exceeded their tabulated values for the three tested variables, filler type, binder type, and binder concentration, (p ≤ 0.05). Additionally, all the interactions between the factors under investigation were found to have a significant effect on the disintegration time. The mean difference values between each two levels of the three factors exceeded the critical value calculated by Fisher’s test (0.174) at p ≤ 0.05, indicating a significant difference between the three levels of all factors on disintegration time as follows:

Tablets containing sorbitol as a filler recorded the lowest mean values for disintegration time 4,650 s (3.358), followed by mannitol 7.189 s (5.417) then spray-dried lactose 7.878 s (5.257), numbers between parenthesis represent S.D. This low value of sorbitol-based tablets was expected due to their poor integrity and high friability. Concerning the binder type (factor X3) effect on disintegration time, xanthan gum tablets had the highest mean value 12.728 s (3.337) probably due to its ability to absorb water and swell-hindering disintegration. Pectin showed the lowest mean value 3.122 s (1.200). Increasing the binder amount (factor X1) significantly prolonged the time required for complete disintegration of the tablets in mouth.

**In vitro Dissolution**

The calibration curve of valsartan in Sorensen’s buffer pH 6.8 at λ_{max} 250 nm was linear over the range from 5 to 50 μg/mL with the determination coefficient of 0.99967. The initial drug dissolution rates during the first 4 min (DR_4 min) and the extent of dissolution after 4 min (DE_4 min) were calculated and shown in Table I. Additionally, the dissolution efficiency, based on 30 min, was calculated as a measure of both the rate and extent of drug dissolution. The statistical analysis revealed that the three factors (X1, X2 and X3), as well as the interactions between them, exhibited a highly significant effect on the three dissolution parameters (DP_4 min, DR_4 min, and DE_30 min) at p ≤ 0.05, Fig. 2.

Interaction bar plot for the drug dissolution parameters showing the effect of filler type × binder type × binder concentration; error bars indicate 95% confidence interval. X.G xanthan gum, SDL spray-dried lactose

Concerning the effect of filler type on drug dissolution profile, tablets containing sorbitol showed significantly lower release rate and extent than those containing spray-dried lactose and mannitol at p ≤ 0.05. The mean difference values between mannitol and spray-dried lactose did not exceed the critical differences calculated by Fisher’s test for each of the dependant variables indicating a nonsignificant difference between the two fillers on the drug dissolution profile.

The binder type (factors X2) and binder concentration (factors X1) showed the most significant effect on the drug dissolution profile as evidenced by the highest calculated F values for the two factors on DP_4 min, DR_4 min, and DE_30 min (data are not shown). Xanthan gum (as a binder) showed the lowest release rate and extent (Fig. 3), DE_30 min was 42.769% (27.705) in relation to 92.849% (8.711) and 95.466% (1.473) in case of pectin and gelatin, respectively. Most of the xanthan gum tablets remained intact after the in vitro dissolution test (30 min), although those tablets disintegrated in mouth in less than 12 s, this could be due to the mechanical force applied on tablets in mouth. Additionally, the presence of large volume of
dissolution medium in vitro facilitated the water absorption and swelling of the tablets, the formed hydrated mass hindered the tablet disintegration and drug release from the tablet. Fisher’s test for DP$_{4\text{min}}$, DR$_{4\text{min}}$, and DE$_{30\text{min}}$ ($p \leq 0.05$) showed a significant difference between the three levels of factor $X_2$ on the drug dissolution profile.

Effect of the binder type on the drug dissolution from valsartan orodispersible tablets prepared using mannitol and different binders at 2% concentration; error bars indicate S.D, $n = 3$

To further investigate the effect of the binder type (factor $X_2$) on the drug dissolution profile, the wetting test results were compared for the three binders. The time required for water to diffuse throughout the entire tablet and reach its surface (wetting time) was 3 (0.010), 5.2 (0.004), and 57 (0.103) s for tablets containing gelatin, pectin, and xanthan gum, respectively. These differences in the wetting time values were easily justified by the scanning electron microscope images for a longitudinal section of the tablets (Fig. 4). Tablets containing pectin and gelatin as binders showed highly porous textures with deep wide pores. These pores formed channels, through which the dissolution medium penetrated facilitating tablet disintegration and drug diffusion (all the tablets completely dissolved in less than 6 min releasing 100% of their loadings; Fig. 4a, b). On the other hand, xanthan gum tablets showed a less porous sectional surface with narrow shallow pores (Fig. 4c).
Scanning electron images of valsartan orodispersible tablets prepared using mannitol and a 2% gelatin, b 2% pectin, and c 2% xanthan gum

It is clear that the higher the binder amount, the lower the drug dissolution rate and extent from the tablets. Fisher’s test proved significant differences between the three levels of factor $X_3$ on $DP_{4\text{ min}}$, $DR_{4\text{ min}}$, and $DE_{30\text{ min}}$.

The above results show that, for factor $X_1$ (filler type), both mannitol and spray-dried lactose showed the best physical properties, acceptable disintegration time values, and the highest rate and extent of drug dissolution. Mannitol has more pleasant taste and feeling on dissolving in mouth than spray-dried lactose.

For binder type (factor $X_2$), pectin was superior concerning the physical properties and the disintegration time. Both pectin and gelatin had the fastest dissolution profiles.

Although the high level of factor $X_3$ (2% binder) showed longer disintegration time values and slower drug dissolution from the tablets comparative to the low and the medium levels, it recorded the best physical properties.

Based on the above discussion, formula number 6 (consisting of 4:6 valsartan:mannitol and 2% pectin) was selected to be tested in vivo. This formula fulfilled all the requirements for an orodispersible tablet. The tablets showed uniform smooth surfaces and pleasant taste, they were removed from blisters with 0% breakage, they had a disintegration time of 4.29 s, and they dissolved in vitro releasing 100% of their drug loading in 6 min with dissolution efficiency ($DE_{30\text{ min}}$) of 96.45% and initial dissolution rate of 24.86 μg/min.

Oral Bioavailability Study

Validation of the Method of Assay

The calibration curve of valsartan was linear over the range from 20 to 3,000 ng/mL with the determination coefficient of 0.9997. The calibration curve had the regression equation of $y = 0.0067x + 0.087$, where $y$ was the peak area ratio of valsartan to internal standard, and $x$ was the concentration of valsartan. The within-run and between-run reproducibility of the method for plasma was calculated by analysis of replicates ($n = 3$) of samples containing known concentrations of 20, 400, and 3,000 ng/mL of valsartan. The precision of the method was described as % R.S.D. among each assay. The within-run % R.S.Ds were always below 7.9% and the between-run % R.S.Ds below 10.8%.

The accuracy of the method was expressed as a percentage error of measured concentrations versus nominal concentrations according to the following equation:

$$\text{Mean relative error} = \frac{\text{mean measured concentration} - \text{added concentration}}{\text{nominal concentration}} \times 100$$

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The within-run percentage mean relative error values were always below 8% and the between-run percentage mean relative error values below 10%. No interference with the internal standard and drug with plasma was found which proves the selectivity of the method.

Pharmacokinetic and Statistical Methods

The mean plasma concentration–time profiles for the prepared orodispersible tablets (treatment A) and the commercial conventional Tareg® tablets (treatment B) are shown in Fig. 5. In crossover design, each treatment appears an equal number of times in each period, the balancing of order of administration compensates for the period effect. If any extraneous variables affect the outcome differently in one period compared to another, all treatments may be affected equally the difference in means of the two treatments due to within and between treatment variability could be simply compared either by one-way ANOVA or paired t test. The pharmacokinetic parameters for both formulas in addition to the statistical analysis comparing the two formulas is summarized in Table II with $p$ values and confidence intervals.
Mean plasma concentration–time profiles of valsartan tablets; error bars indicate S.D., n = 4

Table II
Mean and 95% Confidence Intervals (in Parenthesis) for Pharmacokinetic Parameters of Valsartan Orodispersible Tablets and the Commercial Traditional Targ ® Tablets Administered to Four Healthy Volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Orodispersible tablets</th>
<th>Traditional tablets</th>
<th>Statistical tests (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (µg/ml)</td>
<td>2.8792 ± 0.244 (2.6028–3.1556)</td>
<td>1.4711 ± 0.553 (0.8448–2.0974)</td>
<td>0.016</td>
</tr>
<tr>
<td>AUC$_{0-24}$ (µg h/ml)</td>
<td>14.7099 ± 4.4369 (9.6892–19.7306)</td>
<td>10.8703 ± 1.3003 (9.3989–12.3417)</td>
<td>0.224</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$ (µg h/ml)</td>
<td>15.2218 ± 4.7039 (9.8988–20.5447)</td>
<td>12.1265 ± 1.6627 (10.2445–14.0075)</td>
<td>0.343</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>1.08 ± 0.382</td>
<td>2.167 ± 0.288</td>
<td>0.017</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>4.88 ± 1.14 (3.59–6.17)</td>
<td>7.073 ± 2.778 (3.926–10.217)</td>
<td>0.275</td>
</tr>
</tbody>
</table>

Data are mean values ± S.D, n = 4
The mean maximum plasma concentration ($C_{\text{max}}$) of the prepared orodispersible tablets was significantly higher (nearly twofold) than the conventional tablets. The mean time to maximum plasma concentration ($t_{\text{max}}$) of treatment A was significantly shorter than that of treatment B. Thus, the estimates of both $C_{\text{max}}$ and $t_{\text{max}}$ showed an improved rate of absorption and hence bioavailability, which may be due to the rapid disintegration of the orodisperisible tablets in the mouth and the dispersion in saliva.

The ratio of mean total area under the curve AUC$_{\text{0-24}}$ of treatment A to treatment B was 135%, which reflects higher amount of drug absorption over 24 h. This could be due to some pregastric absorption of the drug. No statistically significant difference ($p = 0.224$) was found between the mean AUC$_{\text{0-24}}$ values for the two formulas, this statistically nonsignificant difference could be due to the small population size. Statistical comparison of half-life values did not indicate a significant difference between the test and the reference formulas.

Similarly, it was reported by Thurmann P.A. that valsartan is rapidly absorbed with maximal plasma concentrations occurring 1–2 h after oral administration. The terminal half-life of valsartan was reported in various studies in the range of 3–7 h. The maximum plasma concentrations after single oral dose of valsartan reach 2–4 µg/ml.

The above results reveal that the valsartan orodispersible tablets would be advantageous with regards to improved patient compliance, rapid onset of action, and increase in bioavailability. Go to:

**VI. REFERENCES**


