

Comparative Dissolution Study of Various Brands of Valsartan Tablets Marketed in Pakistan

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ABSTRACT

The purpose of this study was to perform a comparative dissolution study of various brands of valsartan tablets marketed in Pakistan. This drug belongs to BCS class II, which has high permeability and low solubility. Four different brands of valsartan tablets (80 mg) were collected from the local market of Rawalpindi and Islamabad, labeled as A, B, C, and D. All brands were evaluated for weight variation, hardness, friability, disintegration, and dissolution. Brand A (multinational brand) was selected as a reference for having a good dissolution profile. A model-independent approach, f_1 (difference factor), f_2 (similarity factor), and dissolution efficiency were used to compare the brands. Results of the dissolution study showed that f_1 and f_2 for all brands were within the specified limits of 0–15 for f_1 and 50–100 for f_2 . Mean dissolution efficiency and 95% confidence intervals were within the acceptable range of $\pm 10\%$ for all brands. All other quality control test results were within the acceptable ranges, except hardness of brand C. Dissolution profiles of brands B, C, and D were comparable with brand A (and have much lower prices). Therefore, brands B, C, and D can be prescribed in place of brand A, which will be more cost-effective for the patients.

KEYWORDS: Valsartan, dissolution, f_1 and f_2 factor analysis, dissolution efficiency, bioavailability

INTRODUCTION

Valsartan is an angiotensin-II type-I receptor blocker that prohibits the binding of angiotensin-II on angiotensin-II type 1 receptors in vascular smooth muscles and adrenal glands, resulting in decreasing blood pressure by vasodilation and inhibiting aldosterone production in adrenal glands. Valsartan is used to treat patients with hypertension, diabetic nephropathy, left ventricular failure, and heart failure (1).

Solubility and permeability are the most important factors for determining drug bioavailability in the Biopharmaceutical Classification System (BCS). Comparable dissolution profiles of various valsartan brands ensure maximum solubility and permeability of the drug in physiological fluids, indicating good bioavailability. Malpractices in manufacturing generic valsartan may reduce solubility and absorption of the drug from the gastrointestinal tract, resulting in low bioavailability and therapeutic effect. Therapeutic effectiveness and quality of generic drugs is a major concern in Pakistan. Comparable bioavailability of various valsartan brands allows clinicians to prescribe any available brand as a replacement for the innovator brand (2, 3).

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Model independent factors (f_1 and f_2) demonstrate the difference and similarity between reference and generic drugs by comparing percentage drug release curves. Similar drug release profiles have f_1 values 0–15 and f_2 values 50–100 (4, 5). Differences in dissolution efficiency and 95% confidence intervals should lie within 10% of the mean for comparable dissolution profiles (6, 7).

METHODS

Materials

Sodium hydroxide and phosphoric acid of analytical quality from Sigma-Aldrich were used as well as double distilled water. Four different brands of valsartan tablets (80 mg) were collected from the local market. All brands were manufactured in Pakistan by multinational and local companies and were within their expiration date. Brand A was Diovan (batch BAFL3, Novartis Pharma Pakistan Ltd.), Brand B was Valken (batch KH21023, Kanel Pharma), Brand C was Valstar (batch MY46, Consolidated Chemical Laboratories), and Brand D was Valtec (batch 288, Tabros Pharma). Brand A was selected as the reference brand.

Weight Variation Test

From each brand, 20 tablets were used to analyze the weight variation. These tablets were weighed by using an analytical balance (Shimadzu ATX 224). According to *United States Pharmacopeia (USP)*, the percentage deviation should be within $\pm 7.5\%$ of the average weight (8).

Hardness Test

From each brand, 10 tablets were randomly collected to analyze the crushing strength using ERWEKA hardness tester. The force is applied on the edge of tablets, while gradually increasing the force and analyzing the hardness of tablets. The crushing strength should be within official *USP* limits, 5–10 kg/cm² (9).

Friability Test

From each brand, 10 tablets were used to analyze the percentage friability. Their initial weights were recorded by using the analytical balance. Then 10 tablets were placed in a friabilator (Roche) at 25 rpm for 4 minutes (100 revolutions). Tablets fall from 6-inch height in every rotation and are observed for any cracking or chipping of tablets. The percentage friability must be $< 1\%$, as given by *USP* official limits (10).

Disintegration Test

From each brand, six tablets were placed in a single basket rack assembly (Pharma Test PTZ-S tablet disintegration tester) with phosphate buffer (pH 6.8) as medium at 37 ± 2 °C and analyzed for disintegration for 30 minutes as specified by *USP* (11).

Dissolution Test

The dissolution test was performed to analyze the percentage of drug release from each brand of valsartan tablets using *USP* dissolution apparatus 2 (Galvano Scientific Tablet Dissolution Tester Beta - 8L) (12, 13). The dissolution apparatus was calibrated with a performance verification test using *USP* Prednisone tablets, and all mechanical parameters (i.e., alignment, component

conformance, temperature control, motor, and transmission) were within permissible limits. The dissolution medium was 900 mL of phosphate buffer (pH 6.8, PHS-3CT automatic pH meter) maintained at 37 ± 0.5 °C (14). The test ran for 60 minutes at 50 rpm. Samples (5-mL) were collected at 15, 30, 45, and 60 minutes, and the same volume of dissolution medium was replaced to maintain the sink conditions. The withdrawn samples were suitably diluted with dissolution medium and filtered through 0.45- μ m syringe filter (Millex), then analyzed in a UV/Vis spectrophotometer (Jasco V-530) at 250 nm. The UV spectrophotometer was calibrated by an independent calibration company. The UV analytical method was validated by ICH guidelines to evaluate linearity, precision, accuracy, specificity, and other parameters. (15, 16).

Standard Curve of Valsartan

Stock solution was prepared by adding 4 mg of valsartan in 50 mL of phosphate buffer (pH 6.8), to make an initial concentration of 80 μ g/mL. The stock solution was then diluted to make the required concentrations of 40, 20, 10, 5, 2.5, and 1.25 μ g/mL. Using the UV spectrophotometer, absorption vs time was plotted to make the standard curve (Fig. 1). Sample concentration was measured by $y = 0.03x + 0.0464$.

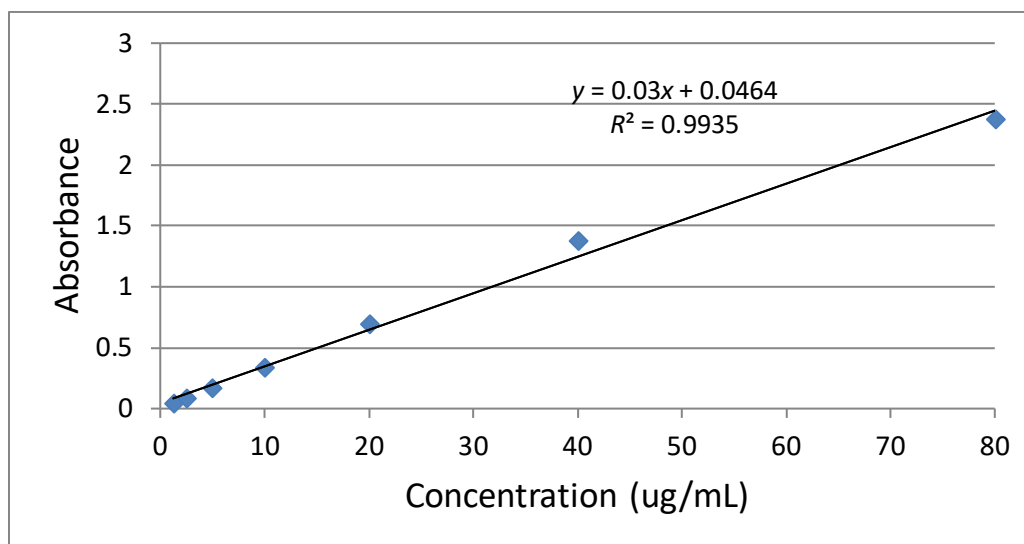


Figure 1. Standard curve of valsartan.

Data Analysis

Drug release profiles of reference and test brands were compared using f_1 and f_2 factors with the Microsoft Excel add-in program, DDsolver (17–19). These factors provide data that clearly states the similarity between two dissolution curves. When reference and sample brands have similar dissolution profiles, the value of f_1 (difference factor) should be 0–15 and f_2 (similarity factor) should be 50–100 (20–22).

Dissolution efficiency was also calculated using DDsolver (23, 24). The concept of dissolution efficiency was proposed by Khan and Rhodes in 1975 (7). Dissolution efficiency is the percentage of a rectangle representing the area under the curve up to a specific time point indicating maximum dissolution of 100%.

RESULTS AND DISCUSSION

Results from weight variation, hardness, friability, and disintegration tests are presented in Table 1. All tablet brands were within acceptable limits for weight variation, friability, and disintegration. The individual weight of 20 tablets ranged from 130–324 mg. All brands had crushing strength within the given range of 5–10 kg/cm², except brand C which was 14.96 ± 1.94 kg/cm². All brands disintegrated within 1–2 minutes.

Table 1. Summarized Quality Control Test Results of Tested Brands of Valsartan

Brand Code	Hardness, kg/cm ² (mean ± SD)	Friability, %	Weight Variation, mg (mean ± SD)	Disintegration, min (mean ± SD)
A	8.81 ± 0.97	0.34	159.36 ± 6.71	1.59 ± 0.31
B	9.70 ± 0.96	0.45	174.74 ± 2.12	0.63 ± 0.52
C	14.96 ± 1.94	0.14	216.43 ± 3.64	1.39 ± 0.22
D	5.51 ± 0.72	0.10	202.89 ± 1.80	0.94 ± 0.34

Dissolution profiles are shown in Figure 2. The percentage drug release of all brands was more than 85% within 15 minutes, as shown in Table 2. The f_1 and f_2 values were within the acceptable range, as shown in Table 3. Differences in mean dissolution efficiency values and 95% confidence intervals were within acceptable range of 10% as shown in Table 4.

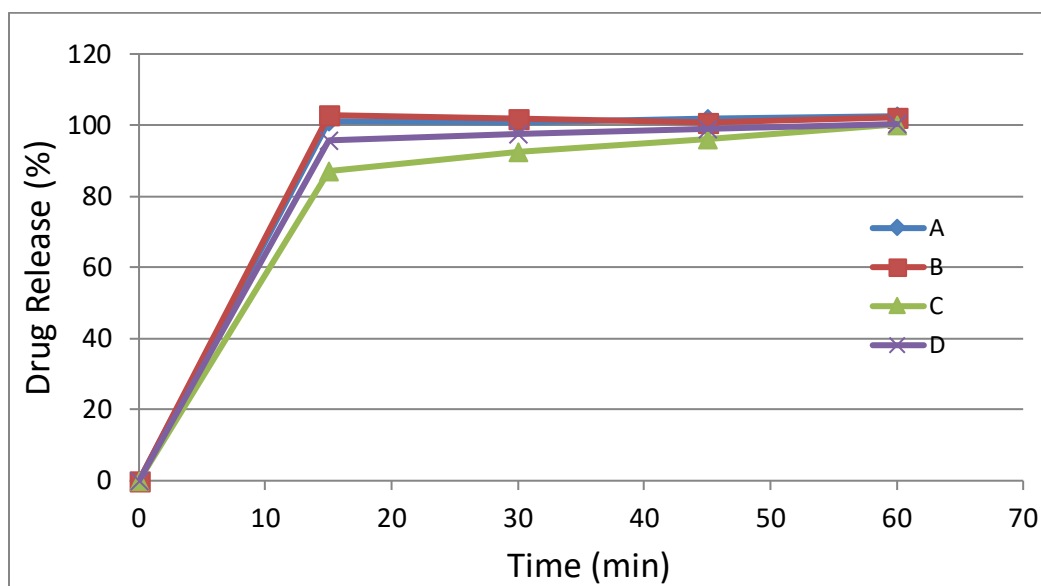


Figure 2. Dissolution profiles of different brands of valsartan tablets.

Table 2. Dissolution Profile Results of Tested Valsartan Brands

Time Point (min)	Mean Drug Release (%)			
	Brand A	Brand B	Brand C	Brand D
0	0	0	0	0
15	101.1	102.8	87.0	95.6
30	100.6	102.0	92.6	97.5
45	102.0	100.9	96.0	99.0
60	102.5	102.1	100.2	100.3

Table 3. Similarity Factor Analysis of Tested Valsartan Brands

Brand Code	Difference Factor, % (f_1)	Similarity Factor, % (f_2)
A vs. B	1.13	91.22
A vs. C	7.48	55.22
A vs. D	3.40	73.26

Table 4. Dissolution Efficiency (DE) with 95% Confidence Intervals (CI) of Tested Valsartan Brands

Brand Code	Mean DE, %	95% CI	Difference In DE	Corresponding Critical Values	10% Limit of Mean DE
A	88.77	88.50–89.05	Ref	0.27	8.87
B	89.23	87.28–91.16	0.45	1.94	8.92
C	81.39	79.46–83.31	7.38	1.92	8.14
D	85.59	85.18–85.99	3.18	0.40	8.56

CONCLUSION

Comparative dissolution analysis of four brands of valsartan tablets was performed. All quality control tests for weight variation, hardness, friability, disintegration, and dissolution were within acceptable ranges except hardness of brand C. Statistical analysis by fit factors f_1 and f_2 confirmed similarity of the dissolution profiles. Differences in dissolution efficiency were also within the acceptable limit. These findings indicate that the tested brands are interchangeable with the reference product (brand A).

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CONFLICTS OF INTEREST

The authors disclosed no conflicts of interest related to this article.

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