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**Mehnaz Ali**
Department of Pharmacy, University of Asia Pacific, 74/A Green Road, Farmgate, Dhaka, Bangladesh

**Fabiha Faizah Ali**
Department of Pharmacy, University of Asia Pacific, 74/A Green Road, Farmgate, Dhaka, Bangladesh

**Nazma Akhter Rita**
Department of Pharmacy, University of Asia Pacific, 74/A Green Road, Farmgate, Dhaka, Bangladesh

**Mohiuddin Ahmed Bhuiyan**
Department of Pharmacy, University of Asia Pacific, 74/A Green Road, Farmgate, Dhaka, Bangladesh

**Correspondence**
**Mehnaz Ali**
Department of Pharmacy, University of Asia Pacific, 74/A Green Road, Farmgate, Dhaka, Bangladesh

# Comparative *in vitro* evaluation of some commercial brands of valsartan tablets marketed in Bangladesh

**Mehnaz Ali, Fabiha Faizah Ali, Nazma Akhter Rita and Mohiuddin Ahmed Bhuiyan**

**Abstract**
The availability of numerous brands of valsartan tablets in pharmacies of Bangladesh today places health practitioners in a problem of generic substitution. The aim of the present study was the evaluation and comparison between different brands of valsartan manufactured by various pharmaceutical companies of Bangladesh with different trade names in order to minimize health risk factors and maximize safety of local people. General quality assessments of these tablets like diameter, thickness, hardness, weight variation, friability, disintegration test were also performed according to the established protocols. Dissolution study of the collected commercial samples were performed using a validated UV spectrophotometric method. Active ingredients were also assayed. Dissolution study showed that brand B was the fastest (83.24%) and brand A was the slowest (77.24%) in terms of drug release and assay value of the brands were recorded within 89.1% to 96.3%. This type of study is a good pointer for the evaluation of the idealness of commercial products.

**Keywords:** Valsartan, *In vitro* evaluation, dissolution study, disintegration test

## 1. Introduction
Bangladesh, a developing country in South East Asia, is the 9th most populous country in the world having around 156 million people and the pharmaceutical industry in Bangladesh is one of the most developed sectors within Bangladesh. This sector provides 97% of the total medicinal requirement of the local market and so monitoring of post market medicines is crucial to judge the quality, therapeutic efficacy and safety of medicine [1-2]. Therefore, information obtained from such monitoring could play an important role for product development and upgrading of existing regulations [3-5]. In this research physical parameters of commercially available valsartan tablets were evaluated.

Hypertension is one of the most widespread chronic illnesses today and cannot be cured, but itcan be controlled. Various drug therapies, single doses or associations of diuretics, beta-blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor (AT1) antagonist (ARA) are utilized for the pharmacological management or control of hypertension [6]. Valsartan (VAL) is one of the potent angiotensin II receptor antagonist (more commonly called an ARB, or angiotensin receptor blocker) which is recommended for treatment of hypertension, post-myocardial infarction or congestive heart failure [7]. It is administered at a dose of 80 mg or 160 mg per day [8].

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme. Angiotensin II is the main pressor agent of the rennin angiotensin system and it has effect on vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Valsartan blocks the vasoconstriction and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the angiotensin II type 1(AT1) receptor, thereby relaxing blood vessels and causing them to widen which lowers blood pressure and improves blood flow [9-11]. After oral administration, only 25% of valsartan is absorbed [12]. The low bioavailability of valsartan is related with its poor water solubility. Despite of having reduced water solubility valsartan is freely soluble in alkaline solution as the corresponding salt.

According to the Biopharmaceutics Classification System (BCS), aqueous solubility and permeability are the most important variables affecting drug bioavailability. Valsartan is classified as Class II that is drugs that have low solubility and high permeability characteristics after oral administration [7]. The challenge of increasing absorption of such type of drugs in the gastrointestinal tract is to improve the dissolution profile. Therefore, constant surveillance on marketed valsartan tablets is necessary to ensure availability of quality medicines.

Quality of pharmaceutical product is the most significant for efficacy and safety of product. Drug products that are chemically and bio-pharmaceutically equivalent must be equal in strength, quality, purity, active ingredient release profile and should be in the same dosage form, for the same route of administration; and to ensure that quality control tests are performed by drug manufacturers on tablets throughout manufacturing and on the final product batches. Such type of evaluation is required to make sure that the generic and branded drugs products are pharmaceutically equivalent. Thus, the current study is carried out to assess the quality of some commercially available valsartan brands in the Bangladeshi market with special importance dissolution study due to their enormous prominence in predicting bioavailability and product quality. Other general quality parameters of these tablets like diameter, thickness, hardness, friability, weight variation, disintegration time were also determined according to the established protocols.

## 2. Materials and Methods

### 2.1 Materials

#### 2.1.1 Drug

Standard of valsartan was a kind gift from Popular Pharmaceuticals Ltd., Bangladesh.

#### 2.1.2 Dosage form

Valsartan tablets (80 mg) from three different brands were purchased from local drug store of Dhaka city. The samples were accurately checked for their manufacturing license numbers, batch numbers, production and expiry dates. They were randomly coded as A, B, C and stored properly.

#### 2.1.3 Solvents and reagents

Potassium dihydrogen phosphate and sodium hydroxide that were used in this study were of analytical-reagent grade and distilled water was also used during the study.

### 2.2 Methods

#### 2.2.1 Determination of diameter and thickness

20 tablets from 3 brands were taken and both the diameter and thickness of the tablets was measured with an electronic digital caliper (MEGA Digital Clipper) in order to determine the average diameter and thickness.

#### 2.2.2 Hardness test

Tablets require a certain amount of strength or hardness and resistance to friability and to withstand mechanical shocks from handling in packaging and shipping. To perform this test, ten tablets were randomly selected from each brand were placed between two anvils, force was applied to the anvils and the pressure at which each tablet crushed was recorded. Hardness is thus sometimes termed the tablet crushing strength.

#### 2.2.3 Friability test

Ten tablets from each brand were taken and their weight was measured. Then 10 tablets were placed to the Roche Friabilator and the machine was run at 25 rpm for 4 minutes. After 100 revolutions, the tablets were taken out from the machine and weighted again. The loss in weight indicated the friability.

#### 2.2.4 Weight variation test

20 tablets from each of the 3 brands of valsartan were weighed individually with an analytical weighing balance (Ohaus, USA) and the average weight for each brand was determined as well as the percentage deviation from the mean value were calculated utilizing the formula given by Banker and Anderson [13].

#### 2.2.5 Disintegration test

At first the vessel of Tablet Disintegration Tester (Veego, India) was filled with 900 ml distilled water and temperature was set to $37\pm0.5^0$C. Six tablets from each brand were taken and placed in the basket of disintegration chamber and the disk was placed appropriately. The machine was started and the disintegration time (DT) was taken as the time when no particle remained on the basket of the system.

#### 2.2.6 Dissolution test

The dissolution tester (Electrolab, India) involving USP apparatus type II (paddle) at 50 RPM was used for the dissolution study of three brands of valsartan. The dissolution medium was 900 ml of phosphate buffer ($p^H$ 5.8) which was maintained at 37±0.5°C. In all the experiments, 10 ml of dissolution sample was drawn out at 0, 10, 20, 30, 40, 50 and 60 minute and replaced with equal volume of phosphate buffer to maintain an ideal sink condition. Samples were filtered and then assayed by UV-VIS spectrophotometer (Shimadzu, Japan) at 250 nm. For the determination of the concentration of sample, standard curve of pure API (Figure 1) was utilized and using the $Y= mX + C$ equation, sample concentration was calculated.

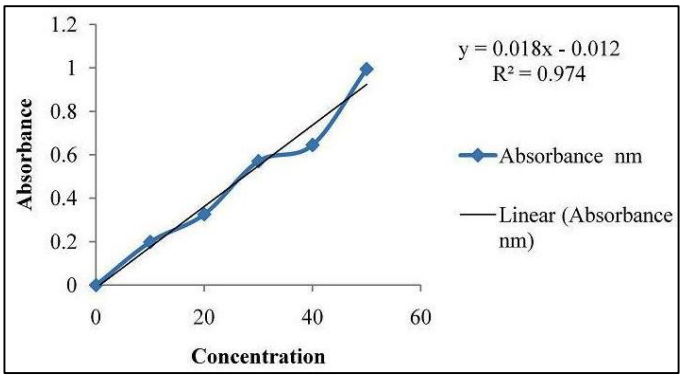


**Fig 1:** Standard Curve of Valsartan

#### 2.2.7 Assay

Twenty tablets from each brand were weighed and then finely powdered. The powder equivalent to 80 mg of valsartan was taken and dissolved in phosphate buffer ($p^H$ 5.8) and flasks were subjected to sonication to dissolve the powdered material. Then the solution was filtered and the filtrate was suitably diluted. Absorbance values were then measured at the maximum wavelength ($\lambda_{max}$) of these concentrations using a UV-VIS spectrophotometer (Shimadzu, Japan). Maximum wavelength ($\lambda_{max}$) was obtained by scanning samples from 200 to 400 nm and it was found 250 nm.

## 3. Results and Discussions

### 3.1 Diameter test

By measuring the diameter and thickness of the tablets at regular intervals, potential problems relating to tablet weight and hence content uniformity can be detected at an early stage [14]. From the data mentioned in Table 1, it has been revealed that among three brands, brand-B had highest average diameter (12.12 mm) whereas brand-A had lowest average diameter (8.14 mm).

**Table 1:** A summary of the quality control tests undertaken on different brands of valsartan tablets (values are expressed as mean ± SD)

| Brand Code | Diameter (mm)* | Thickness (mm)* | Hardness (kgf)* | Friability | Weight Variation (mg) | DT (min)* | % Drug content |
|---|---|---|---|---|---|---|---|
| A | 8.14±0.01 | 3.40±0.03 | 2.0±0.66 | 0.49% | 162.64±2.4 | 5.50±3.01 | 89.1% |
| B | 12.12±0.02 | 4.32±0.04 | 4.1±0.60 | 0.20% | 248.51±50.2 | 6.16±1.72 | 92.7% |
| C | 10.30±0.04 | 3.05±0.03 | 2.6±1.10 | 1.69% | 167.00±2.2 | 11.16±3.97 | 96.3% |

### 3.2 Thickness test
The thickness of tablets is critical to their therapeutic effectiveness as with increasing thickness, there is a decrease in hardness due to compression force, on the other hand with decreasing thickness there is an increase in hardness. So, tablets of the same batch which have lower thickness show greater hardness. The average thickness of brand A, B and C were found 3.40 mm, 4.32 mm and 3.05 mm respectively as shown in Table 1. In consideration of average thickness, the variation of thickness was acceptable for all brands.

### 3.3 Hardness test
To develop into quality products, tablets should have adequate hardness. Tablet hardness has influence on disintegration. If the tablet is hard then it cannot disintegrate within the specified time and if the tablet is soft then it becomes difficult to withstand the handling during coating or packaging [15]. Oral tablets normally have a hardness of 4 to 8 or 10kgf. In general, if the tablet hardness is too high, disintegration test is performed before rejecting the batch and if the disintegration is within limit, the batch is usually accepted. Hardness also has influence on density and porosity of tablets. According to Table 1, brand-B had maximum hardness of 4.1 kgf whereas brand-A and brand C had the hardness of 2.0 and 2.6 kgf respectively. Here, only one brand was within the range but since the hardness test is an unofficial test [16] and later their disintegration time (DT) was found acceptable, the batches were considered as of good quality.

### 3.4 Friability test
Friability is a propensity of the tablet to crumble. It is significant for the tablet to resist attrition. For the duration of manufacturing and handling, tablets are usually introduced to stresses from collision and tablet sliding towards one another and other solid surfaces which can cause removal of small fragments and particles from the surface of tablet. So, friability test is performed to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting as it reveals good mechanical strength of the tablets [17]. The compendial specification for friability is not more than 1% [18]. Usually harder the tablets less will be the percentage friability and vice versa. As shown in Table 1, two brands (A and B) had percent friability below 1% which indicates that tablets from remaining one brand (C) may face difficulty during storage or transportation. Among three brands, brand-C showed maximum friability (1.69%) whereas brand-B showed minimum friability (0.20%).

### 3.5 Weight variation test
Weight variation serves as an indicator to good manufacturing practices (GMP) sustained by the manufacturers as well as amount of active pharmaceutical ingredient (API) contained in the formulation. The limit of deviation of weight variation is ±10% for tablets weighing 130 mg or less, ±7.5%for tablet weighing more than 130 mg to 324 mg and ±5% for tablet weighing more than 324 mg. According to USP, not more than two tablets should cross the single limit and none of them should cross the double of the limit. The weight variation for all the tablets utilized in this study showed compliance with the official specifications of USP. Here, as shown in Table 1, weight variation of three brands A, B and C were within the limit of USP specification.

### 3.6 Disintegration test
After oral administration a solid dosage form, a drug must be in solution to become absorbed and the first important step towards this condition is usually the breaking up of the tablet which is known as disintegration that plays an important role in a tablet's dissolution. Thus disintegration test is a measure of the time required under specific conditions for a group of tablets to disintegrate into particle. If disintegration time is not perfect, the effectiveness of drug is not considered good. Therefore, type, concentration, and efficiency of disintegrates to a great extent affects the dissolution [19]. BP specifies that uncoated tablets should disintegrate within 15 minute which is 30 minute in case of USP. Table 1 shows all the three brands met the official criteria. Here, brand C took maximum time of 11.16 minute and brand A took the minimum time of 5.50 minute to disintegrate.

### 3.7 Dissolution test
Dissolution testing of drug products plays an important role as quality control tool to observe batch to batch consistency of drug release. In addition, it can be used as a qualitative and a quantitative tool which can provide significant information about biological availability of a drug. Dissolution tests are used to identify formulations which will meet the prerequisite requirements of quality as well as to verify batch-to-batch reproducibility. *In vitro* release profile (Table 2) showed that only one brand achieved 80% dissolution within 60 minutes. Intra-brand (within a brand) dissolution profile in Figure 2 and inter-brand (brand to brand) dissolution profile in Figure 3 reveals that brand B showed maximum % of drug release (83.24%) whereas brand A showed minimum % of drug release (77.24%) in 60 minutes. The evaluation showed that release pattern of drugs was different among the three brands and brand A and C failed to comply the official specification (not less than 80% within 60 minutes).

**Table 2:** Dissolution profile of three brands of valsartan tablets (values are expressed as mean±SD)

| Time (min) | % Drug Release | | |
|---|---|---|---|
| | Brand A | Brand B | Brand C |
| 0 | 0±0 | 0±0 | 0±0 |
| 10 | 49.50±6.75 | 20.62±1.71 | 18.37±2.82 |
| 20 | 55.49±2.83 | 55.50±8.51 | 24.00±4.68 |
| 30 | 57.37±4.50 | 67.87±9.70 | 40.87±5.31 |
| 40 | 60.75±5.95 | 71.99±7.87 | 56.99±4.54 |
| 50 | 64.12±8.50 | 80.62±2.34 | 62.99±5.62 |
| 60 | 77.24±7.65 | 83.24±3.37 | 78.74±11.41 |

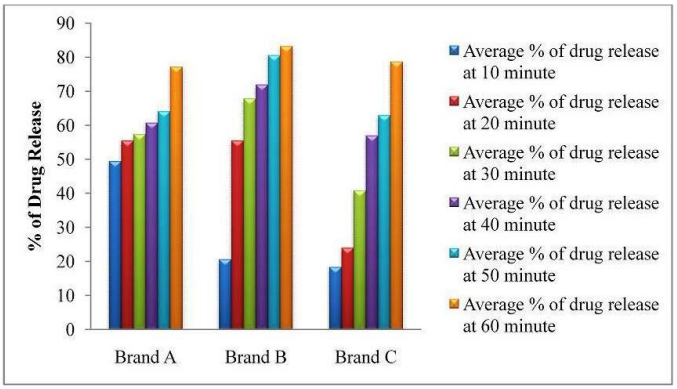


**Fig 2:** Intra-brand Dissolution Profile of Three Brands of Valsartan Tablets

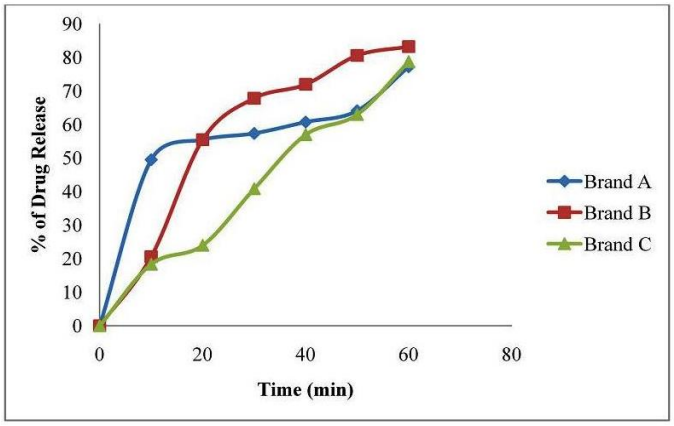


**Fig 3:** Inter-brand Dissolution Profile of Three Brands of Valsartan Tablets

### 3.8 Assay

Analysis of drug potency in tablets indicates the presence of drug in dosage form and their stability is indicated by analysis of drug potency in tablets. As shown in Table 1, the active content of all the brands were in between 89.1% (brand-A) and 96.3% (brand-C). The result indicates there was no significant variation in content of active moiety in two brand B and C which were 92.7% and 96.3% respectively that were within the USP specification of 100±10% except one brand (A) which was out of specification.

## 4. Conclusion

In the current industrial practice, *in vitro* tests play a significant role to compare the quality of multi brand generic drugs and to provide enough therapeutic effectiveness of the dosage form. The presented data exhibits that only one brand of valsartan tablet included in the study seem to have sufficient dissolution rate and satisfied potency rather than the other two brands used in the study which represents the current scenario of different quality parameters of drug products manufactured by local companies. This study emphasized the need of constant inspection on marketed drug product by the government, manufacturers and independent research groups to ensure supply and availability of quality medicines for safe, effective and economic treatment of the patients. However, *in vivo* testing may be required for final comments regarding the quality of marketed brands of valsartan.

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