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Quality Attributes Comparison of Selected Brands of Rosuvastatin Calcium Tablets Marketed in the US and Bangladesh

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Authors' contributions

This work was carried out in collaboration among all authors. Author FIR designed the study and supervised the project. Authors STM, KNE and RI carried out the experiment. Author STM wrote the first draft of the manuscript and managed the analyses of the study with support from authors SAE, KNE and RI. Author STM and FIR managed the literature searches. Author SAE proof read the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: This study investigated whether locally marketed rosuvastatin calcium tablets in Bangladesh have comparable physical and chemical attributes, including *in vitro* bioequivalence profiles, to the proprietary brand.
Methodology: Nine generic products (G1-G9) containing 10 mg of rosuvastatin calcium were compared to the proprietary brand Crestor® (R1) and an FDA approved generic rosuvastatin calcium tablet (R2). Weight variation, diameter, thickness, friability, drug content, disintegration time and dissolution profiles were tested according to United States Pharmacopeia (USP) guidelines. *In vitro* bioequivalence requirements were assessed by calculating difference (f_1) and similarity (f_2) factors.

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Results: The generic products complied with the pharmacopeial requirements for weight variation, disintegration time and friability. All the tablets had drug ranging between 92%-105% and released more than 80% of rosuvastatin within first 15-30 minutes. However, for brands G5, G7 and G8 the f_1 values were 15.7%, 15.82% and 25.21% respectively and their f_2 values were 41.8, 41.6 and 32.6 respectively whereas for G9 the f_2 value was 43.4. These brands have thus failed to meet *in vitro* bioequivalence requirements.
Conclusion: We conclude that few substandard generics of rosuvastatin calcium has somehow found its way to the market and further studies are required to ascertain their noncompliance.

Keywords: Rosuvastatin; bioequivalence; comparative study; crestor; generic drugs; usp-nf specifications.

1. INTRODUCTION

Therapeutic effectiveness of any pharmaceutical preparation depends on its formulation properties, methods of manufacturing and stringency of quality control [1]. According to the United States Food and Drug Administration (USFDA), the major challenge in maintaining pharmaceutical product quality is the lack of post market quality surveillance of currently marketed products [2]. This is even more applicable for Bangladesh, where the industry comprises of mostly generic drugs and substandard and counterfeit drugs often makes its place in the market [3]. Thus, post market quality evaluation of generic drugs can be a great tool for evaluating quality, efficacy and safety of commercially available brands. It can also help to ensure that the marketed generics are therapeutically equivalent to innovator brands and be safely interchanged.

Hypercholesterolemia is accounted for an estimated 4.4 million deaths worldwide per year and is one of the main reasons behind ischemic strokes and heart disease [4]. A major risk factor behind the development of cardiovascular diseases (CVD) and atherosclerosis is elevated low density lipoprotein cholesterol (LDL-C) levels that occurs mostly in hypercholesterolemia patients [5]. As a result, several lipid lowering agents have been discovered, among which the statins demonstrated the highest efficacy in reducing serum cholesterol levels [6]. Lovastatin (Mevacor®, Merck) was the first statin to be marketed in 1987. In August 2003, FDA approved rosuvastatin calcium (Crestor®, Astrazeneca) as the seventh drug in the statin class for treating hypercholesterolemia by reducing low density lipoprotein cholesterol (LDL-C) levels [7]. Rosuvastatin is considered as one of the most potent statins till date. After Astrazeneca's patent expiry of Crestor® in 2016, a number of FDA approved generics became available in the US market which are sold at a lower price. These generics are preferred because they have similar efficacy compared to that of the proprietary brand and are available at a much more affordable price [8]. In the US market, generic products gain approval for marketing only after strict documentation of bioequivalence criteria fulfillment has been provided to FDA. In Bangladesh, however, there is lack of proper bioequivalence testing facilities and there is very limited amount of studies that have comprehensively tested and compared the safety and efficacy of generic drugs to their proprietary brand counterpart [9]. Specially in the case of statin drugs this is even more important because low-quality, substandard or contaminated generic statins are a matter of growing concern in treating cardiovascular patients [10].

To date, there has been no published studies on the comparison of quality attributes of locally available generic rosuvastatin calcium tablets with proprietary brand. The aim of this study was to investigate the different physical quality parameters as well as *in vitro* dissolution profile of different generic rosuvastatin calcium tablets available in Bangladesh market using proprietary brand Crestor® as the reference product. We also included an FDA approved rosuvastatin calcium marketed by Aurobindo Pharma USA, as a secondary reference to compare how much the dissolution profile of an FDA approved bioequivalence tested generic varied from our locally available generic products. Physical and chemical quality attributes such as weight variation, drug content, friability and disintegration time were comprehensively tested and analyzed according to United States Pharmacopeia standards.

2. MATERIALS AND METHODS

2.1 Drug

Reference standard of rosuvastatin calcium pure was kindly gifted from ACI Pharmaceuticals

Limited (Dhaka, Bangladesh). Nine generic brands (denoted as G1-G9) of rosuvastatin calcium (10 mg) were purchased from local Bangladesh pharmacies through University of Asia Pacific purchasing department. These brands are all approved for sale by the Directorate General of Drug Administration (DGDA) of Bangladesh, as they comply to their standards. Crestor® (AstraZeneca, United Kingdom; denoted as R1) and rosuvastatin Tablets USP (Aurobindo Pharma USA, Inc.; denoted as R2) were imported from USA through a local pharmaceutical. The collected drugs were properly screened for their manufacturing date, shelf-life, batch numbers and manufacturing license numbers after which they were stored in proper storage conditions.

2.2 Solvents and Reagents

Analytical grade Citric acid anhydrous was obtained from Merck (Darmstadt, Germany). Sodium hydroxide pellets was obtained from Qualikems Fine Chem Pvt. Ltd (Gujarat, India). Double distilled water was used to dissolve the solvents and during the analytical tests.

2.3 Determination of Weight Variation

Weight variation test according to USP was performed to measure the uniformity of dosage units [11]. The test involved weighing 20 tablets from each of the 11 brands (G1-G9, R1 and R2) individually with an analytical balance (Ohaus, USA). The average weights for each brand along with the percentage deviation from the mean value were measured to demonstrate the individual deviations of the tablet weight from that brand's average tablet weight.

2.4 Determination of Diameter and Thickness

Diameter and thickness of 20 tablets from each of the brands were individually measured through an electronic digital slide calipers (Shanghai, China) in order to determine average diameter and thickness. The maximum and minimum deviations from the mean value were then determined.

2.5 Friability Test

Friability of the tablets were tested according to the general USP method of friability testing [12]. Twenty tablets of each brand were collectively dedusted, weighted and exposed to rolling and repeated shocks by employing an Electrolab friabilator (EF-2, India) at 25 revolutions per minute for total of 4 minutes. The tablets were then dusted to remove all loose particles from the surface and observed for any cracks or broken parts. The tablets were collectively weighed again and compared with their initial weights. The percent loss of mass was then calculated as friability.

2.6 Disintegration Test

Six tablets from each brand were submerged in distilled water at 37°C using an Electrolab tablet disintegration tester (ED-2L, India) to evaluate the disintegration time of the tablets. The disintegration time was measured as the time required for a tablet to completely dissolve in such a way that no trace of particle remained in the basket of the machine.

2.7 Calibration Curve and Assay of Drug Content

For determining the drug content, a simple and selective UV spectrophotometric assay was used. To prepare the standard solution, 100µg of drug equivalent to standard rosuvastatin calcium was taken and dissolved in up to 100ml of 0.05M citric acid buffer (pH 6.6). For preparing the sample solution, ten tablets from each brand were weighed and crushed to fine powder using mortar and pestle. Powder containing 100 µg of drug was then dissolved in the citric acid buffer media. The standard and sample solutions were then sonicated using Hwashin 410 Ultrasonicator bath (Seoul, South Korea) followed by filtration using Whatman filter paper (Sigma-Aldrich, USA). Then the solution was diluted up to 4 times and the final concentration of the stock solution was obtained 25 µg/ml. The stock solution was diluted into 10 individual concentration ranging from 5-25 µg/ml respectively. The absorbance values of the solutions were taken at maximum wavelength (λmax) of 241.3 nm using a UV Spectrophotometer (UV1280, Shimadzu, Japan). By scanning the samples from 200 nm to 400 nm, the maximum absorbance value of 241.3 nm was obtained.

Through MS Excel (Microsoft Corporation, Washington, USA), a ten-point calibration curve was obtained which is shown in Fig. 1.

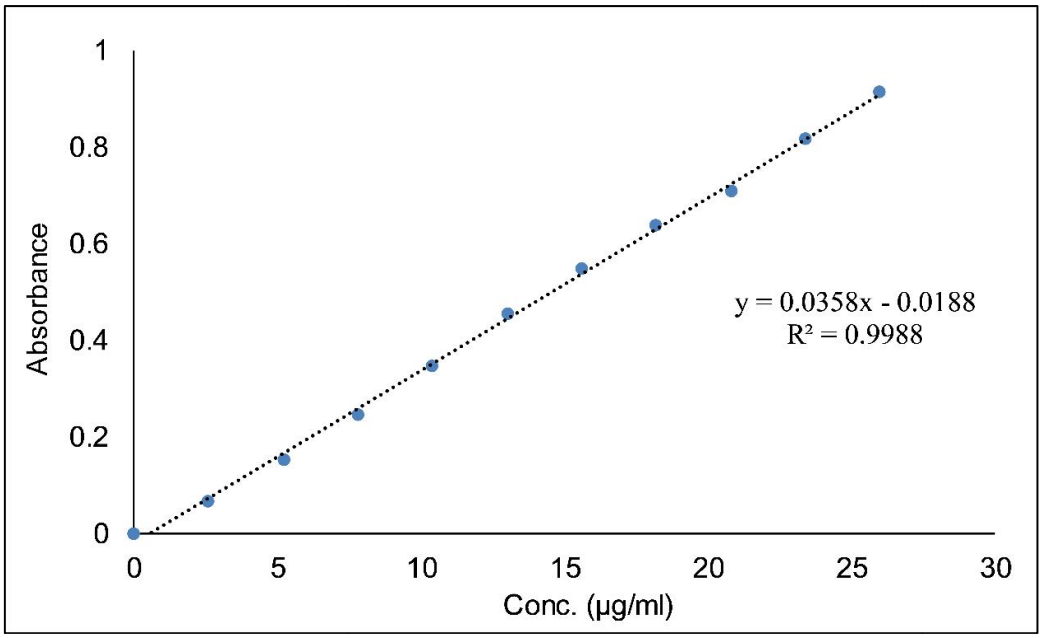

Fig. 1. Ten-point calibration curve of standard rosuvastatin calcium (R2 indicates correlation coefficient)

2.8 Dissolution Test

Tablets of reference and generic brand were tested for determining their dissolution profile using a USP apparatus II tablet dissolution tester EDT-08LX (Electrolab, India) at a pedal speed of 50 rpm. 900 ml citric acid buffer was used as dissolution media at 37±2ºC temperature for testing each unit of each brand (*n* = 6). 10 ml of dissolution sample was withdrawn from the dissolution medium at 5, 15, 30, 45 and 60 minutes while simultaneously being replaced with equal volume of citric acid buffer solution to maintain sink condition. Collected sample were filtered and analyzed by UV- Spectrophotometer (UV1280, Shimadzu, Japan) at λmax =241.3 nm against vessel citric acid buffer as blank. The percent drug release of each brand was determined by comparing with the reference drug release at each time intervals which included any rosuvastatin calcium lost due to prior sample withdrawals.

2.9 Statistical Analysis

Statistical analyses, calculations, graphical presentations were all performed using MS Excel 2019 (Microsoft Corporation, Washington, USA). For comparing dissolution profiles of the different generic brands with the reference brands, the model independent mathematical approach of Moore and Flanner was used [13]. According to this model, difference factor (f_1) and similarity factor (f_2) were studied where f_1 represents as a measurement of relative error between two dissolution curves and difference between two curves is calculated as percentage at each point. Values up to 15% stipulate little difference between the two curves. On the contrary, the similarity factor (f_2) is an estimate of the similarity in the percent (%) dissolution between the two curves and presented as a logarithmic reciprocal square root transformation of the sum of squared error [14]. The following equations were applied to calculate f_1 and f_2.

$$f_1 = \left\{\frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n} R_t}\right\} \times 100$$

$$f_2 = 50\log\left\{\left(1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right)^{-0.5} \times 100\right\}$$

where n is the number of sampling times, R_t is the dissolution value of reference product at time t, T_t is the cumulative dissolution percentage for the test product at time *t* and T_t is the cumulative dissolution percentage for the test products. Similarity factor (f_2) is considered by both FDA and European Agency for the Evaluation of Medicinal Products (EMEA) as standard measures for comparing dissolution profiles

[15,16]. According to FDA standards, for generic product's dissolution profile to be considered similar and bioequivalent to innovator product, it is suggested that if f_1 should be between 0 and 15 and f_2 should be between 50 and 100. Any deviation from this range indicates possible difference in the *in vivo* performance of the generic product.

3. RESULTS AND DISCUSSION

3.1 Physical Appearance

Visual inspection of the tablets showed that the tablets of each brand slightly varied in their physical appearance. The tablets were all film coated and tablets of each respective brand officiated from the same batch and had been labeled with a shelf life greater than two years from the time of this study. Details of the generic and reference products are given in Table 1.

3.2 Diameter and Thickness Testing

Potential irregularities relating to tablet weight and uniformity of dosage can be detected at an early level of production through analysis of the diameter and thickness of marketed tablets at regular intervals. From the data shown in Table 2, it can be demonstrated that average diameters of the tablets ranged between 5.1 mm to 7.8 mm and average thickness of the different brands ranged between 2.46 mm to 3.17 mm. All the brands had low variation in both diameter and thickness from their average value which is evident from their low standard deviation values.

3.3 Test of Uniformity of Weight

Weight variation serves as a good tool for estimating the amount of active pharmaceutical ingredient (API) contained in a formulation and is considered as an indicator of Good Manufacturing Practice (GMP) by the manufacturers [17]. According to USP specifications for content uniformity, tablets weighing less than or equal to 130 mg should have no more than ±10% deviation in their weight and for tablets weighing between 130 mg to 324 mg should have no more than ±7.5% deviation. No more than 2 tablets can cross this limit and not a single tablet may cross double of this specified limit [11]. Analyzing the data in Table 2 it is clear that average weight of all the brands except brand G6 were clearly less than 130 mg. The lowest average weight was 66.1 mg for brand G8 and the highest average weight was 180.08 mg for brand G6. The weight variation ranges from average of the tested brands did not exceed ±5% and in case of brand G6 it did not exceed ±1.5%. Not a single tablet of any of the brands had a deviation greater than the USP specified limit of ±20%.

3.4 Friability Test

Friability test is done to measure the mechanical strength of the tablet, its ability to endure transportation via vehicles and other physical shocks. The USP specification for friability is that it should not exceed 1%. All the brands tested complied with this specification and showed friability way lesser than 1% as shown in Table 2.

Table 1. Rosuvastatin calcium tablets (10 mg) of different brands purchased from local Bangladesh market and USA

No.	Code	Manufacturing Country	Tablet Characteristics (Shape, Color, Coating)	Manufacture Date	Expiry Date
1	R1	USA	Spherical, pink, film coated	06/2019	06/2021
2	R2	USA	Round, white, film coated	05/2019	05/2021
3	G1	Bangladesh	Spherical, pink, film coated	09/2019	09/2021
4	G2	Bangladesh	Spherical, pink, film coated	08/2019	08/2022
5	G3	Bangladesh	Spherical, gray, film coated	05/2019	05/2021
6	G4	Bangladesh	Round, white, film coated	01/2019	01/2021
7	G5	Bangladesh	Triangular, brown, film coated	09/2019	09/2022
8	G6	Bangladesh	Heart, yellow, film coated	08/2019	08/2021
9	G7	Bangladesh	Round, orange, film coated	07/2019	07/2021
10	G8	Bangladesh	Round, white, film coated	06/2019	06/2021
11	G9	Bangladesh	Oval, pink, film coated	05/2019	05/2021

Table 2. Summary of the physical attributes of different brands of rosuvastatin calcium (10 mg) tablets (*Mean ± Standard deviation)

No.	Code	Diameter (mm ± SD)*	Thickness (mm ± SD)*	Avg. Weight (mg ± SD)*	Wt. Variation Range (% from average)	Friability (%)
1	R1	6.62 ± 0.002	2.54 ± 0.010	110.2 ± 0.32	98.0% - 99.8%	0.004%
2	R2	5.50 ± 0.012	2.46 ± 0.03	83.6 ± 0.27	96.89% - 99.28%	0.003%
3	G1	6.55 ± 0.005	3.17 ± 0.005	112.1 ± 0.49	98.13% - 99.91%	0.002%
4	G2	5.98 ± 0.007	2.64 ± 0.006	81.92 ± 0.49	97.66% - 100.0%	0.011%
5	G3	6.09 ± 0.008	2.77 ± 0.03	82.5 ± 1.04	98.18% - 100.6%	0.001%
6	G4	7.09 ± 0.001	2.84 ± 0.013	123.3 ± 1.03	98.13% - 101.4%	0.02%
7	G5	7.35 ± 0.012	3.09 ± 0.006	126.08 ± 2.22	95.18% - 101.5%	0.012%
8	G6	7.80 ± 0.01	3.17 ± 0.013	180.08 ± 1.44	98.84% - 101.1%	0.09%
9	G7	6.02 ± 0.004	2.90 ± 0.07	102.45 ± 0.79	98.58% - 101.5%	0.003%
10	G8	5.10 ± 0.011	2.56 ± 0.013	66.1 ± 0.62	100% - 103.03%	0.001%
11	G9	7.02 ± 0.008	3.11 ± 0.013	72.1 ± 0.79	100% - 102.78%	0.013%

Different generic brands of rosuvastatin calcium showed satisfactory physical attributes which includes uniform weight, diameter and thickness (Table 2). The generic products showed excellent mechanical strength demonstrated by their nearly 0% loss of weight after friability testing. Utilizing optimized formulation and modern machineries, generic products can certainly be manufactured within a desired weight range, supplanting the minimal requirements set by the pharmacopeias.

3.5 Disintegration Testing

Tablet disintegration is considered as the first stage of the bioavailability cascade because a faster disintegration time can result in quicker dissolution of the API inside the body and provides faster onset of action of the desired therapeutic effect. USP recommends that all film coated and uncoated tablets should disintegrate within 30 minutes (1800sec). All the brands tested were film coated and disintegrated within 7 minutes as shown in Table 3. Lowest average disintegration time was demonstrated by brand G2 which was only 17 seconds whereas the highest disintegration time was shown by brand G5 which was approximately 6 minutes and 43 seconds. As disintegration time directly affects the subsequent dissolution of tablets, a faster disintegration time is necessary to ensure good bioavailability of the generic drugs.

Table 3. Average disintegration time and mean percent of rosuvastatin calcium in each tested tablet calculated by means of claimed amount ± Standard deviation

No.	Code	Disintegration Time (seconds ± SD)	Drug Content (% mean ± SD)
1	R1	22 ± 3	102.11 ± 1.32
2	R2	20.5± 2.5	104.70 ± 0.65
3	G1	95 ± 31.03	96.77 ± 0.98
4	G2	17 ± 3.74	101.5 ± 1.21
5	G3	278 ± 14.7	93.54 ± 0.78
6	G4	89.33 ± 3.29	96.99 ± 0.62
7	G5	403.33 ± 36.42	91.94 ± 1.15
8	G6	47.67 ± 1.25	105.48 ± 1.34
9	G7	58.33 ± 4.42	99.56 ± 1.75
10	G8	21.67 ± 4.49	93.73 ± 0.88
11	G9	45.67 ± 5.78	98.14 ± 1.11

3.6 Assay of Drug Content

Analysis of drug content in tablets indicates the amount of active ingredient present in dosage form. The data presented in Table 3 outlines that the active drug content of all the brands were in between 91.94% (brand G5) and 105.48% (brand G6). The result shows there was no significant variation in active drug content of the dosage forms among the tested brands and all are within the USP specification of 100±10% for rosuvastatin calcium tablets [18].

The different disintegration times observed in the tablets were certainly well within the specified limit of USP standards (Table 3). A faster disintegration time is desired for satisfactory dissolution of a drug and influences how quickly it will be released from its solid dosage form. USP allows a small variation in the allowable range of drug content, no less than 90% and no more than 110% of claimed active drug is allowed in a unit dosage form. Though there were variations among the brand, all the products complied with the drug content test in accordance with USP.

3.7 Dissolution of Rosuvastatin Calcium Tablets

A comparative study of percent drug release between all the generic brands along with the innovator and FDA approved brand were done according to Dissolution Test 3 of USP for rosuvastatin calcium tablets which was included in the revision bulletin [18]. According to USP specifications, each brand must be dissolved no less than 80% (Q) of its labelled claim within 45 minutes of the test. Analyzing the data, it was observed that all the drugs had dissolved by more than 80% of the labeled claim within 15-30 minutes of testing. The two reference products R1, R2 and generic drugs G1, G2, G4, G6 all had dissolved more than 80% within just 5 minutes. These drugs also had quite low disintegration time which could have also contributed to this rapid dissolution. On the other hand, generic drugs G3, G7, G9 had dissolved more than 80% within 15 minutes. G5 and G8 took 30 minutes to reach 80% dissolution. It should be noted that G5 had the longest disintegration period and though it released more than 60% within 5 minutes, it still took the longest time to dissolve more than 80% among all the generic brands. Finally, it can be observed that all the products complied with the dissolution test 3 standards which is illustrated in Fig. 2.

Table 4 exhibits the f_1 and f_2 values of different brands (G1-G9) in respect to our reference innovator brand R1 (Crestor®). The FDA approved brand R2 showed the least f_1 value of 2.53% and highest f_2 value of 80.75 which indicates closes dissolution profile to the innovator Crestor®. For generic products G1, G2, G3, G4 and G6 the f_1 values did not exceed 15% and the f_2 values were within the acceptable range of 50-100. So, these 5 generic products can be used interchangeably with innovator brand Crestor®. However, for brands G5, G7 and G8 the f_1 values exceeded 15% and the f_2 values were less than 50, whereas for brand G9 the f_2 value was not within acceptable limit. It clearly means that all these brands had poorer dissolution rate compared to that of innovator brand.

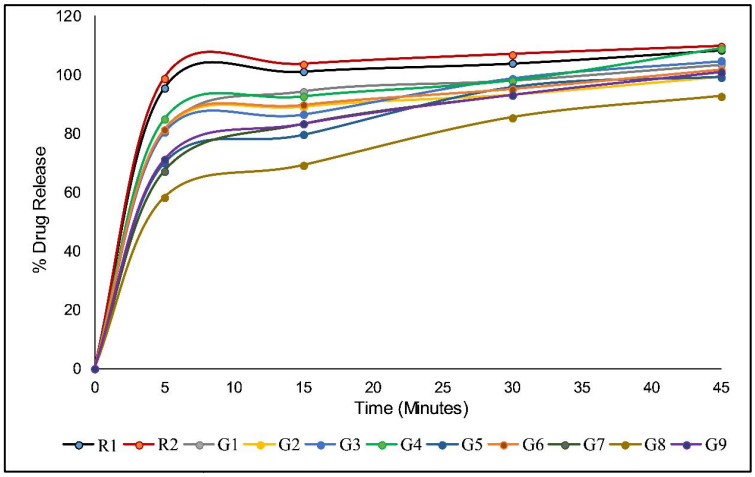

Fig. 2. Dissolution profiles of different brands of rosuvastatin calcium 10 mg tablets

Table 4. Difference factor (f_1) and similarity factor (f_2) of different generic products (G1-G9) and FDA approved product (R2) in respect to innovator brand Crestor®

Products	Difference factor (f_1)	Similarity factor (f_2)
R2	2.53%	80.75
G1	7.91%	56.45
G2	11.31%	50.83
G3	9.35%	52.37
G4	6.25%	60.68
G5	15.73%	41.84
G6	10.05%	52.91
G7	15.82%	41.57
G8	25.21%	32.57
G9	14.88%	43.41

Dissolution plays an important role in predicting *in vivo* bioavailability and has been applied to predict bioequivalence of generic tablets so that they can be prescribed interchangeably [19]. It is often considered by FDA to be more useful than *in vivo* tests for distinguishing between a bioequivalent generic and substandard one [15]. f_1 and f_2 are often applied in *in vitro* bioequivalence studies for comparing dissolution profiles of generic products to proprietary brand not only by FDA but the Human Medicines Evaluation Unit of EMEA as well [20]. Rosuvastatin calcium belongs to the Biopharmaceutics Classification System (BCS) group II drugs which means it has high permeability but low solubility [21]. Thus, for a generic rosuvastatin calcium tablet to be considered as bioequivalent, it must have rapid dissolution. A study published in 2020 found a generic rosuvastatin to be equally effective and safe in lowering LDL-C levels compared to the proprietary rosuvastatin [22]. Our *in vitro* study demonstrates that four out of the nine locally available generic brands tested may not be therapeutically equivalent with the reference product Crestor®. The other five generic brands were within the f_1 and f_2 acceptable limits but none of them came close to the similarity in dissolution profile shown by the FDA approved generic product. This indicates that there are several generic rosuvastatin calcium available in the local market which should not be used interchangeably with the proprietary brand and those that can be interchangeably used lag behind in comparison to an FDA approved generic.

The impact of prescribing these four generic brands on the safety and health of patients requires further investigation. The current study included only the 10 mg strength of rosuvastatin calcium and did not analyze tablet dissolution in different pH media. Our study employed the FDA recommended dissolution process, including dissolution apparatus, pedal speed and dissolution medium as well as incorporating the rosuvastatin calcium tablet USP monograph specific dissolution test 3 directions [23]. This study hopes to encourage continuous independent investigation of approved drug products so that inferior or substandard brands can be detected.

4. CONCLUSION

Quality attributes investigation of marketed drugs play a vital role in analyzing whether these products comply with standards set by their authorizing organization. These studies work as a post market quality assurance, ensuring the safety and efficacy of sensitive drugs like the lipid lowering statins used by CVD patients. Different physical and chemical attribute tests indicate that the locally available rosuvastatin calcium brands have satisfactory standards, demonstrating desirable uniformity of weight, friability, disintegration time and drug content. However, this is not sufficient to provide proof of a generic product's *in vivo* performance. *In vitro* dissolution testing suggests that four generic rosuvastatin calcium products in the Bangladesh local market may lack in their efficacy and safety. These drugs may fail to achieve therapeutic outcome in patients, thus leading to more serious complications. The manufacturers were notified of the test results and they assured to further investigate this by retesting on a larger scale. Impact of such substandard drugs on therapeutic outcome needs to be further investigated.

5. STUDY LIMITATIONS

The study aimed to measure the bioequivalence of generic rosuvastatin calcium brands by

comparing *in vitro* dissolution characteristics with the innovator and FDA approved generic brand. While *in vitro* tests can give preliminary assumptions on bioequivalence, no concrete conclusion can be made without *in vivo* studies. Each of the generic brands chosen for this study belonged to a single batch only. Therefore, it could not assess the between batch bioequivalence of these brands.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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