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Post-marketing quality assessment of some brands of rosuvastatin tablets available in Jos, North-Central Nigeria

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Abstract

Rosuvastatin is a synthetic statin medication approved for the management of lipid disorders and also for preventing cardiovascular disease in at-risk individuals. Generic rosuvastatin formulations have been developed which are comparatively lower in cost and also assumed to be bio-similar to the innovator brand Crestor®. The present study investigated the chemical and physical attributes together with the in vitro bioequivalence profiles of four generic brands of rosuvastatin calcium tablets marketed in Jos, Nigeria in comparison to the reference brand. The tablet dimensions (thickness and diameter), weight variation, friability, hardness, disintegration time and dissolution profiles were evaluated in accordance to standard procedures. The samples were also assayed using Ultraviolet–Visible spectrophotometry at wavelength of 242.5 nm in methanol. In vitro bioequivalence was evaluated by determining the difference (f_1) and similarity (f_2) factors. The generic brands all complied with the pharmacopoeial specifications for weight variation, friability and disintegration. In addition, the tablet brands tested all had active drug content ranging from 94.92 to 109.2% and released over 80% of rosuvastatin calcium within the first twenty minutes of the dissolution studies thereby complying with pharmacopoeial requirements for content and dissolution respectively. All brands had similarity factor (f_2) values ranging from 50 to 100 and difference factor (f_1) values between 0 to 15% at pH 6.6, thus implying that the brands can be used interchangeably with the innovator brand. The chemical and physical tests carried out reveal that the locally marketed brands of rosuvastatin calcium are of good quality and meet the required regulatory standards.

Keywords Rosuvastatin, Bioequivalence, Quality, Nigeria, Dyslipidemia

Introduction

Dyslipidemias are multifactorial disorders of lipoprotein metabolism which are characterized by abnormalities in the blood concentration of lipids [1–3]. These derangements may take the form of raised plasma concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TGs), lowered level of high-density lipoprotein cholesterol (HDL-C) within the blood or a combination of two or more of the above mentioned features [4]. Depending on the disease aetiology, dyslipidemias may be classified as primary (which is linked to genetics) or secondary (caused by exogenous factors) [5]. Dyslipidemia is

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well recognized as an important risk factor for the development of atherosclerosis and cardiovascular disease [6]; which are leading causes of death globally [7]. Together with dietary interventions and lifestyle modification such as cessation of smoking [8], pharmacotherapy remains a key part of the strategy for management of dyslipidemia which has the attendant benefit of reducing the associated risk of cardiovascular complications.

Statins are considered first-line agents for the management of dyslipidemias [9]. They act to decrease biosynthesis of cholesterol via competitive inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase [10]; an important enzyme in the mevalonate pathway. Rosuvastatin is one of the synthetic, enantiometrically pure statins. Chemically, it is named (E,3R,5S)-7-[4-(4-Fluorophenyl)-2-[methylsulfonyl) amino]-6-propan-2-ylpyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid [11]. Rosuvastatin calcium has very poor water solubility but is freely soluble in dichloromethane and basically insoluble in anhydrous ethanol [12]. It is used to manage hypercholesterolemia and also for preventing cardiovascular diseases together with other measures such as diet and exercise [13]. Rosuvastatin is considered a high-intensity statin because of its ability to cause a marked reduction (at least 50%) in LDL-C [14] and it is being prescribed more frequently [15]. Sequel to the expiration of Astrazeneca's patent for Crestor® in the year 2016, numerous generic brands of rosuvastatin calcium have received regulatory approval by the United States Food and Drug Administration (FDA). It is therefore important to establish the bioequivalence of these generics to the innovator product. The drug is official in the United States Pharmacopoeia [16] which requires Rosuvastatin tablets to contain between 90—110% of the labelled claim while the British Pharmacopoeia [12] specifies a content of 93- 105% of the labelled claim of Rosuvastatin. The quality control tests and methods used in this study are based on the United States Pharmacopoeia specifications which requires tests to be conducted for disintegration, hardness, dissolution, dosage uniformity, identification, and friability tests. A product that fails any of the tests mentioned is usually considered sub-standard. In addition, a validated Ultraviolet (UV) spectrophotometric method was used for the assay of the Rosuvastatin tablets, instead of the HPLC method specified by the USP. This was due to a number of practical and scientific considerations including the fact that the UV spectrophotometric method used in this study has been previously been validated [17] according to established pharmacopoeial guidelines, demonstrating high accuracy, precision, and specificity for Rosuvastatin. In addition, the HPLC assay requires more complex instrumentation with greater operational costs and in this post-marketing surveillance study which was conducted in a resource constrained setting, UV spectrophotometry offers a more cost-effective, efficient, and readily available alternative without compromising analytical accuracy. UV spectrophotometric method is also widely accepted in the literature [17–20] and in many pharmaceutical quality control labs for the analysis of Rosuvastatin, particularly for routine analysis.

Due to changing diets and lifestyle patterns which have become more westernized, recent studies have shown an increasing prevalence of dyslipidemias in Africa [21] and this increase is also reflected globally [22]. This trend has been accompanied by increasing prescription and use of Statins with a recent study reporting them as been among some of the most prescribed medication in the United States [23]. Rosuvastatin was found to be among the top three most prescribed statin in studies conducted in Nigeria [24] and also in Ethiopia [25]. A Chinese time trend analysis study of statin prescription pattern from 2012 to 2018 showed that Rosuvastatin had the highest rate of prescription for yearly use of statins among new users [26]. Due to increasing incidence of obesity, sedentary lifestyles and a host of other factors, It has been projected that Statins will likely gain a greater share of the market within the period forecasted from 2023 to 2030 [27]. Increased prescription and use of rosuvastatin has been accompanied by reports of falsification of this important medication in different parts of the world such as in Taiwan where a batch of the genuine product was found to have been adulterated with counterfeits thereby leading to its recall [28, 29]. Counterfeit rosuvastatin tablets were similarly found and seized by law enforcement agents in India [30]. There have also been reports of substandard generic statins linked to poor manufacturing practices and violations of current good manufacturing practice (cGMP) guidelines [31, 32]. Substandard and falsified medicines can be harmful to patients in addition to causing treatment failure. They can also cause loss of confidence in medicines, healthcare workers and even the healthcare system. They affect every region of the world and both generic and innovator brands can be falsified. Routine quality checks are therefore important to curtail these consequences of counterfeit medicines. The aim of this work is to carryout quality control tests and in vitro bioequivalence studies on some brands of rosuvastatin calcium found in Jos metropolis thus contributing to surveillance of the drug status in the Nigerian market.

Methods

Equipment/Apparatus

UV/Visible spectrophotometer (Jenway, United kingdom, Model 6305), Monsanto hardness tester (Indian Equipment Corporation, New Delhi, Model 04215), Roche Friabilator (Eagle scientific Ltd, Model, 1024), Mettler electronic balance (Greifense-Zurich Switzerland, Model CH-8606), Disintegration tester (Tianjin Optical Instrument Factory, China, Model RC-6), Dissolution Apparatus (SR6 SRII 6-FLASK Dissolution test station Hanson Research Corporation Chatsworth, California USA), Vernier caliper (Drapper Ltd, Germany).

Reagents

Citric acid monohydrate (Kermel Industries, China), Ethyl acetate (Lobachemie, India), Methanol (Lobachemie, India), Sodium hydroxide (Kermel Industries, China), Ammonia (Sigma Aldrich, Germany), Distilled water. All the reagents used were of Analytical grade.

Drugs

Pure Rosuvastatin Calcium Reference standard was a donation from Prof. J.O. Onah while the Innovator brand Crestor® and four other generic brands of Rosuvastatin Calcium (10 mg) were purchased from registered and licensed retail Pharmacy premises in Jos, Plateau state, North-Central, Nigeria.

Methods

Physical inspection

The purchased drugs were closely examined and details such as manufacturer, country of manufacture, batch number, manufacturing and expiry dates were recorded. Tablet physical features such as shape, colour, and type of coating of the different brands were visually inspected and recorded after which the tablets were stored under the appropriate storage conditions prior to further experiments.

Identification test

The Ultraviolet (UV) absorption spectra of sample solutions in methanol were recorded in the region of 200 nm to 400 nm and compared with the absorption spectrum of the standard reference solution of same concentration.

Evaluation of tablet properties

The various brands of rosuvastatin tablets were subjected to both official and non-official methods of analysis for tablets as described below:

Determination of uniformity of weight

Weight uniformity test according to the United States Pharmacopoeia (USP) guidelines was performed to measure the uniformity of dosage unit. The test involved weighing 20 tablets from each of the five (5) brands individually with an analytical balance. The average weight for each of the brands together with the percent deviation from the mean value were calculated to establish the deviation of the weight of individual tablets from that particular brand's average tablet weight.

Determination of diameter and thickness uniformity

Diameter and thickness of 20 tablets from each of the brand were individually measured using a Vernier caliper and the average results were recorded. The maximum and minimum deviations from the mean value were then determined [16].

Friability tests

Ten (10) tablets were randomly selected from each brand. They were weighed together and then placed inside the friabilator chamber and rotated at 25 revolutions per minute (RPM) for four minutes. The tablets were then cleaned to eliminate all loose particles from their surface and similarly examined for fissures and cracks. The tablets were collectively weighed again and compared with their initial weights. The percent loss of mass was then calculated as friability.

$$\%\ \text{Friability} = \left[\left(\frac{\text{Wi} - \text{Wf}}{\text{Wi}}\right) x100\right]$$

where:

W_i = initial weight of ten tablets.

W_f = final weight of ten tablets.

Hardness test

Five (5) tablets from each brand were randomly selected, each tablet was then placed between the fixed and movable jaws of the hardness tester. Pressure supplied by a screw driver spring was applied until the tablet was crushed. The crushing strength of each tablet was recorded in Kg force /cm [12].

Disintegration test

This test is official in both the British Pharmacopoeia (BP) and USP. It was conducted by placing six (6) tablets from each brand individually in the separate chambers of the disintegration apparatus containing distilled water at 37 °C. The period of time it took for the tablets or their fragments to completely disintegrate and disperse in the water so that no agglomerates of particles remained was noted and recorded [16].

Preparation of calibration curve

Pure rosuvastatin calcium (40 mg) was accurately weighed and dissolved in 40 ml methanol to give a stock solution (1000 $\mu g/ml$). The stock solution was further diluted with methanol to get the working standard solution and this was scanned in the UV range (200—400 nm) to determine absorption maximum which was found to be 242.5 nm. Aliquots of the working standard solution were taken and used to prepare a series of solutions corresponding to 2, 6, 10, 14, 18, 22 $\mu g/ml$ in triplicates each, with methanol used as the diluent in all cases. The absorbance of these solutions was measured at the maximum against methanol as blank. A calibration curve of absorbance versus concentration of rosuvastatin calcium was then plotted.

Method validation

The method was validated according to International Conference on Harmonization (ICH) Q2 (R1) guidelines for validation of analytical procedures [33].

Precision The precision of the method was determined by conducting intra-day and inter-day precision studies. Intra-day precision was carried out by performing three replicate analysis at different times (8 h apart) within the same day at three different concentrations (8, 12, and 16 µg/mL) and percent relative standard deviation (%RSD) was calculated. Inter-day precision study was similarly evaluated by analysis of the afore mentioned concentrations of the drug substance on three different days in triplicate, and % RSD was calculated.

Accuracy Accuracy of the method was assessed using recovery studies which was carried out by employing the standard addition method whereby known amounts of standard at three different levels 80%, 100% and 120% were added to known sample of the tablet formulation and the final concentration of Rosuvastatin determined. The recovery studies were performed in triplicate and the mean percentage recovery and % RSD were calculated thereafter.

Linearity The linear relationship between concentration and absorbance for Rosuvastatin was evaluated over the concentration range of 2–22 µg/mL. The experiment was replicated 5 times.

Sensitivity The sensitivity of the method was evaluated in terms of the limit of detection (LOD) and limit of quantification (LOQ). LOD and LOQ of the developed method were calculated from the standard deviation (σ) of the Y intercept of the regression lines and slope of the calibration curve (S) using the formula, limit of detection = 3.3*σ/S; Limit of quantitation = 10*σ/S.

Assay of the various brands

Ten (10) tablets of each of the brands of rosuvastatin from the samples collected were weighed and crushed uniformly with the help of a mortar and pestle. The average weight of sample powder equivalent to 10 mg of rosuvastatin were transferred into a 10 ml volumetric flask. A 5 ml portion of methanol was used to dissolve the powdered drug with manual agitation for 5 min and the volume was subsequently made up to 10 ml with methanol to give a concentration of 1000 $\mu g/ml$. This filtrate was further diluted to a concentration of 10 $\mu g/ml$ prepared in triplicate. The absorbance was measured at 242.5 nm against methanol as blank and their corresponding concentrations were determined from the regression equation. The concentrations obtained were then used to determine the percentage content of the drug using the formular:

$$\%\ \text{Content} = \left[\left(\frac{\text{Actual Content (mg)}}{\text{Label Claim (10 mg)}}\right)x100\right]$$

In vitro dissolution test

The dissolution profile of the reference and generic brands were determined using a USP apparatus II dissolution tester (paddle) at speed of 50 revolutions per minute (RPM). 900 ml of 0.05 M Sodium citrate buffer pH 6.6 was used as dissolution media at $37^0 \pm 0.5\ ^0$C temperature for testing each unit of each brand. It was prepared by dissolving 63.0 g of citric acid monohydrate and 35.2 g of sodium hydroxide in 6 Liters of distilled water and the pH adjusted to 6.6 with citric acid. Six (6) tablets from each brand were tested in the dissolution studies. 10 ml of dissolution sample was withdrawn from the dissolution medium at 3, 10, 20, 30, 40, 50, 60 and 90 min while simultaneously being replaced with equal volume of sodium citrate buffer solution to maintain sink condition. Collected sample were filtered and analyzed using the validated UV/VIS spectrophotometric method to get the drug concentration. The percent drug release at the various time intervals were calculated and plotted against time to generate the dissolution profile. The test was done in triplicates and the average of the readings used to prepare the dissolution profile.

$$\text{Amount of drug released(mg)} = \left[\left(\frac{\text{Concentration } \mu\text{g/ml x Dilution Factor x Volume of Dissolution Medium}}{1000}\right)\right]$$

$$\%\ \text{Drug Released} = \left[\left(\frac{\text{Amount of Drug Released (mg)}}{\text{Label Claim (10 mg)}}\right)x100\right]$$

Determination of In Vitro bioequivalence

The dissolution test profile was used as a surrogate basis for determination of bioequivalence of generics in comparison to the innovator brand Crestor®. The dissolution profiles of the generic and innovator brand were compared using a similarity (f_2) and difference (f_1) factor of the model independent mathematical approach whereby f_2 values from 50–100 and f_1 values from 0–15% would imply sameness or equivalence of the generics curve to the innovator curve and thus equivalence of the in vitro performance [34].

Determination of similarity (f_1) and difference factor (f_2)

$$f_2 = 50log\left\{\left(1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right)^{-0.5} x100\right\}$$

$$f_1 = \left\{\frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n} R_t}\right\} x100$$

where n is the number of sampling times, Rt is the mean percentage drug release value of the reference product at time t, Tt is the mean percentage drug release value for the test product at time t. f_1 is difference factor and f_2 is the similarity factor.

Statistical analysis

The data obtained from the study was expressed using descriptive statistics including mean, standard deviation, and percentages. Statistical analysis, graphical presentations and calculations were all performed with Microsoft Excel®. A model independent mathematical approach was used for comparison of the dissolution profiles of the generic products with the reference brand [34].

Result

Figures 1, 2

Discussion

Rosuvastatin is one of the first line agents recommended for the management of lipid disorders. A number of generics of this drug have been approved and these generics are preferred in developing countries due to their cheaper cost and the assumption that they should have comparable efficacy to the innovator brand [35]. Most clinicians and patients welcome the decreased costs of generic drugs but it is imperative that their safety and efficacy are similar to that of the innovator.

Organoleptic/ visual inspection

This test involves examination of the physical appearance of the drug in its package and is useful as an early/ preliminary indicator of product quality especially during procurement of the drug. Damaged drugs with dents pose a problem of loss of elegance and poor acceptability by patients. The tablets of each of the brands examined showed very minimal variations in their physical appearance upon visual inspection. Four of the tablets were film coated and one brand was uncoated and were all within their expiration dates during the course of the investigation. All five brands had acceptable physical appearance with no sign of coating defects and details of the properties are shown in Table 1.

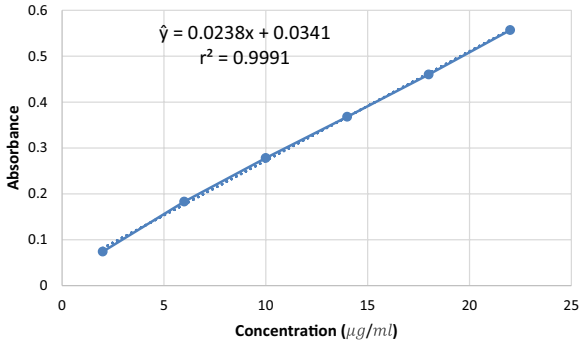

Fig. 1 Six-point calibration curve for the reference rosuvastatin in methanol at 242.5 nm. $\hat{y} = mx + c$ (where x is the concentration of Rosuvastatin (µg/mL); y is the absorbance for UV spectrophotometric method; m is the slope and c is the intercept and r^2 is the correlation coefficient

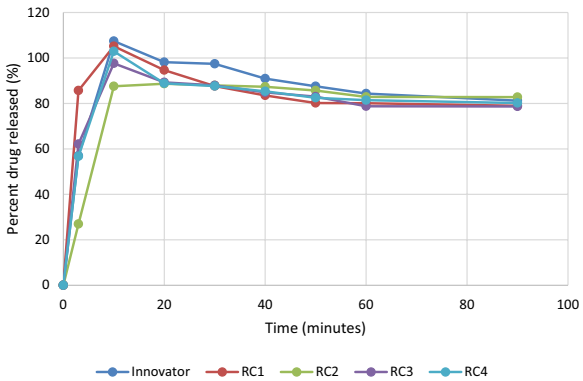

Fig. 2 A dissolution rate profile for the five brands of Rosuvastatin 10 mg tablet in 0.05 M sodium citrate buffer pH 6.6

Table 1 General information about the various Rosuvastatin brands sampled in the study

S/N	Brand	Country of origin	Description (Shape, color, coating)	Batch No	Manufacture date	Expiry date
1	Innovator	Turkey	Round biconvex, pink, film coated	A0236021	11/2019	10/2023
2	RC1	India	Round, white, uncoated	WG22082	02/2022	01/2025
3	RC2	India	Round biconvex, brown, film coated	GT22193	04/2022	03/2025
4	RC3	India	Round biconvex, yellow, film coated	BM112	08/2021	07/2024
5	RC4	Spain	Round biconvex, pink, film coated	18871	03/2021	02/2025

Weight uniformity test

Weight variation test is a pointer to the manufacturers' adherence to good manufacturing practices (GMP) in addition to indicating the consistency in the API content in the product. For tablets that weigh 130 mg or less, the deviation permitted is ± 10%; for tablets weighing between 130 and 324 mg, it is ± 7.5% while for tablets whose weight is greater than 324 mg, it is ± 5%. The USP states that no tablet should exceed the double limit and that no more than two tablets should exceed the single restriction. All the tablet brands evaluated in this study complied with the USP specifications with respect to weight variation (Table 2). The percent deviation in weight across the different brands ranged from 0.87% to 2.92%. This result was in agreement with a post market evaluation of some rosuvastatin calcium tablet brands available in the Pakistani city of Karachi where the tablet weights did not exceed the USP specified limit of ± 10% and had a range of deviation between 0.7% and 2.26% [36].

Uniformity of diameter and thickness test

Periodic evaluation of the dimensions (thickness and diameter) of marketed tablets can help in the detection of anomalies related to the weight and dosage uniformity of tablets which would have originated earlier in the production process. A tablet is said to pass this test for diameter and thickness if percentage deviation in diameter or thickness of the tablet is within limit of ± 5% [16]. The data in Table 2 shows that percent deviation in thickness of the different brands ranged between 0.48 to 3.52% while percent deviation in diameters of the brands ranged between 0.16 and 0.50%. As can be seen from their low percent deviation figures, all of the Rosuvastatin calcium tablet brands evaluated exhibited little variance from their average values in terms of thickness and diameter. The values obtained in another study were quite similar where the nine brands evaluated had percent deviation in diameter between 0.13 and 0.22% and percent deviation in thickness between 0.41 and 1.22% [35].

Friability

The purpose of friability testing is to evaluate the mechanical strength of tablets and their resistance to physical shocks they may encounter such as during transportation and handling. The USP specifies that friability should not be more than 1%. As indicated in Table 2, every brand that was tested met this requirement and all had friability of less than 1%. This agrees with a study where the generic rosuvastatin tablets tested demonstrated exceptional resistance as indicated by their practically negligible (near zero percent) weight loss during friability testing [35]. Friability test is usually recommended for only uncoated tablets as coating gives tablets extra strength and protects them from been chirped but all the tablets in this study (both coated and uncoated) were subjected to the test and they all met the pharmacopoeial requirements.

Table 2 Results of some quality control tests on the various Rosuvastatin brands (presented as Mean ± standard deviation)

Brand	Uniformity of Weight (g)	Tablet Diameter (mm)	Tablet Thickness (mm)	Hardness/ Crushing Strength (KgF)	Percentage (%) Friability	Disintegration time (Sec)
Innovator	0.154 ± 0.00293	7.10 ± 0.03557	3.88 ± 0.0515	9.40 ± 1.158	0.10 ± 0.03	29.17 ± 2.409
RC1	0.147 ± 0.00366	7.09 ± 0.03468	3.09 ± 0.0606	5.00 ± 0.707	0.10 ± 0.03	29.19 ± 1.772
RC2	0.160 ± 0.00467	7.17 ± 0.01374	3.20 ± 0.1129	6.00 ± 1.049	0.01 ± 0.04	29.83 ± 1.572
RC3	0.283 ± 0.00554	9.61 ± 0.01526	3.98 ± 0.0563	11.30 ± 1.166	0.01 ± 0.06	150.83 ± 1.737
RC4	0.151 ± 0.00132	7.13 ± 0.02498	3.44 ± 0.0166	8.10 ± 1.200	0.04 ± 0.05	23.67 ± 2.211

Tablet hardness

The disintegration of a tablet is markedly impacted by its hardness. A tablet that is too soft will be difficult to handle during coating, packaging, or transportation, and a tablet that is too hard will not disintegrate in the stipulated time limits. It is therefore important that tablets possess sufficient hardness and resistance to powdering in order to maintain good quality. The hardness of oral tablets is usually between 4 and 8 kg/F. Generally speaking, a disintegration test is conducted before a tablet batch is rejected if their hardness is very high; if the disintegration time is however found to be within acceptable bounds, the batch is typically approved [13]. Table 2 shows that RC3 had the highest hardness of 11.3 kg/F while RC1 had the lowest hardness of 5 kg/F. Although there were only two brands whose hardness fell in the range of 4 to 8 kg/F, the products were deemed to be of good quality because the test of hardness is an unofficial test and their disintegration time were found to be acceptable. This result was similar to a previous study evaluating the interchangeability of generics and innovator brand of the drug via in vitro bioequivalence study where one of the generics failed the hardness test but passed the disintegration test [37]. Another study on rosuvastatin brands in Saudi Arabia also found all three brands evaluated as having hardness of between 8.15 and 8.85 kg/F [18].

Disintegration test

Disintegration of a tablet is the first step in the sequence of processes that leads to absorption of a drug into systemic circulation and faster disintegration leads to more rapid dissolution of the drug in the body thereby providing quicker onset of therapeutic action [35]. According to USP guidelines, tablets that are uncoated should disintegrate in 15 min and film-coated tablets in 30 min. Four out of the five Rosuvastatin brands tested were film-coated while one was uncoated and they all disintegrated in less than three minutes (Table 2). The film-coated brand RC4 had the smallest mean disintegration time of 23.67 s while RC3 had the longest mean disintegration time which averaged 150.83 s and this is likely due to the material used for its film coating. Timely disintegration of tablets is required to guarantee the bioavailability of generic medications because it has a direct impact on the subsequent dissolution step which is a precursor to absorption of the drug. The different disintegration times observed for all six tablets from each brand were all within the limits of the USP specification for this parameter. This test result was in line with a study done on comparative evaluation of some brands of rosuvastatin tablets sold in Bangladesh and the United States of America (USA). In that study, all the tablet brands assessed were film-coated and had disintegration time of less than seven minutes [35].

Method validation

The results of the method validation experiments signify that the UV spectrophotometric method used in this study was accurate, precise and sensitive (Table 3), hence it is considered suitable for its use in the assay and dissolution studies. The data for regression analysis of the calibration curves revealed strong linear relationship between absorbance and concentration over the range of 2–22 µg/ml for Rosuvastatin with an excellent correlation coefficient (r^2) of 0.991. Percentage relative standard deviation (% RSD) was used to express the method's precision and the study findings demonstrate the assay's reproducibility. The percent RSD determined

Table 3 Summary of Method Validation data for the UV Spectrophotometric Analysis of Rosuvastatin

S/n	Parameter	Result
1	Accuracy from Recovery Studies	100.55—103.80%
2	Precision:	
	Intra-day precision	0.63—1.50% RSD
	Inter-day precision	0.42—1.12% RSD
3	Correlation Coefficient (r^2)	0.9991
4	Linear Range	2–22 µg/ml
5	Limit of Detection	0.1290 µg/ml
6	Limit of Quantitation	0.3900 µg/ml

Table 4 Precision of the UV Spectrophotometric Method for Analysis of Rosuvastatin

Concentration (µg/ml)	Intra-Day Found (µg/ml)	% RSD	Inter-Day Found (µg/ml)	% RSD
8	7.98 ± 0.12	1.50	8.05 ± 0.09	1.12
12	12.01 ± 0.08	0.67	11.99 ± 0.05	0.42
16	15.97 ± 0.10	0.63	16.14 ± 0.13	0.81

n = 3 for intra-day and n = 9 for inter-day, *S.D.* Standard Deviation

Table 5 Accuracy of the UV Spectrophotometric Method for Analysis of Rosuvastatin

Concentration Added (µg/ml)	Found (µg/ml)	% Recovery	% RSD
5	5.19 ± 0.09	103.80	1.73
10	10.06 ± 0.18	100.60	1.79
20	20.11 ± 0.22	100.55	1.09

n = 3, *S.D.* Standard Deviation

were all observed to be below 2 (Table 4) for both intra and inter-day evaluations thus demonstrating the excellent precision of the method and making it suitable for the determination of Rosuvastatin. Furthermore, when the methods' accuracy was assessed by means of recovery studies, the method showed good recovery between 100.56% and 101.23% (Table 5) with low values of percent RSD indicating the accuracy of the method. The limits of quantitation (LOQ) and detection (LOD) of the method for Rosuvastatin were determined to be 0.390 µg/ml and 0.129 µg/ml respectively (Table 3) thereby indicating its sensitivity even down to low Rosuvastatin concentration levels.

Assay of rosuvastatin

This is a test carried out to ensure that the content of the medication falls within the specified limit as stated in the individual monographs. The test ensures that drugs produce the desired therapeutic effect while toxicity due to overdose is avoided. The results presented in Table 6 reveal that the content of active ingredient in the brands ranged between 94.92% (RC3) and 109.2% (RC4). The results also show that all the tested brands met USP requirements for API content of 90–110% for Rosuvastatin calcium tablets [16] and no significant variance of active ingredient content was observed among them. This assay result is similar to that gotten in a past study where there were no major disparities in the active drug content among tested brands and all conformed to the USP specifications of ± 10% for rosuvastatin calcium tablets. Specifically, the API content of all the brands were in between 98.75% to 107.5% in that study [38].

Table 6 Average Percent drug content for the rosuvastatin brands

Tablet Brand	Average % Content ± C.I.)
Innovator	102.90 ± 4.743
RC1	99.02 ± 5.556
RC2	99.54 ± 2.745
RC3	94.92 ± 4.310
RC4	109.20 ± 0.926

n = 3, C.I. = 95% Confidence Interval, Acceptance criteria: 90—110% (USP 2024)

Dissolution rate and In Vitro bioequivalence test

Dissolution is a major factor that influences the in vivo bioavailability of drugs and has been routinely used for predicting the bioequivalence of generic medicines in order to support their interchangeable prescription and use. For a brand of Rosuvastatin Calcium tablets to meet USP specifications, it must release a minimum of 80% of the label claim of Rosuvastatin inside 45 min of the dissolution test. Data analysis revealed that all the brands of the drug evaluated, released over 80 percent of their label claim within twenty minutes (Table 7). These brands displayed quick disintegration which may have been a contributory factor to their swift dissolution. The products were also all found to comply with the standards specified in dissolution test three. The model independent mathematical approach was employed for comparison of the dissolution profile of the reference (innovator) brand with those of the various Rosuvastatin generics [34]. The similarity factor (f_2) and difference factor (f_1) were estimated using this model. Difference factor (f_1) is a measure of the relative error between two curves and is calculated using the percentage difference between them at each of the time points when sampling was done. Conversely, similarity factor (f_2) on the other hand measures how similar the two curves' % dissolution is and is a logarithmic reciprocal square root translation of the sum of squared errors. Generally, in assessing the similarity of two curves, values of f_1 from 0 to 15 and f_2 values between 50 and 100 imply equivalence or sameness of the curves and therefore performance of the test. The f_1 and f_2 values calculated for the various brands in comparison to the reference brand Crestor® are displayed in Table 8. The smallest f_1 value of 1% and largest f_2 of 93% were obtained with brand RC1 which indicates that its dissolution profile is the closest to the reference brand Crestor®. The other generics evaluated had f_1 values below 15% while their f_2 values fell between 50 to 100% which is acceptable. Although the brand RC2 had acceptable f_1 and f_2 values, the difference in percent release was more than twenty percent

Table 7 Dissolution profile showing percentage drug release for five brands of rosuvastatin tablet at various time intervals

Time (Min)	3	10	20	30	40	50	60	90
Innovator	56.98 ± 0.09	107.45 ± 0.13	98.16 ± 0.05	97.44 ± 0.24	90.94 ± 0.17	87.53 ± 0.63	84.33 ± 0.26	81.24 ± 0.08
RC1	85.67 ± 0.12	105.18 ± 0.10	94.65 ± 0.31	87.63 ± 0.08	83.51 ± 0.36	80.20 ± 0.52	80.10 ± 0.60	78.96 ± 0.55
RC2	26.94 ± 0.04	87.53 ± 0.16	88.67 ± 0.45	87.94 ± 0.36	87.33 ± 0.30	85.67 ± 0.48	82.89 ± 0.22	82.78 ± 0.09
RC3	62.14 ± 0.33	97.66 ± 0.47	89.29 ± 0.14	87.94 ± 0.29	84.85 ± 0.18	82.99 ± 0.08	78.76 ± 0.41	78.65 ± 0.15
RC4	56.77 ± 0.22	102.91 ± 0.18	88.87 ± 0.17	87.63 ± 0.14	85.36 ± 0.35	82.47 ± 0.23	81.44 ± 0.34	80.20 ± 0.17

Acceptance criteria: Not less than 80% of the labelled amount of Rosuvastatin is released after 45 min (USP 2024)

at the first sampling point and more than ten percent at the second time point compared to the innovator drug release profile. This brand also had the largest difference (f_1) value thus, it's interchangeability with the innovator in terms of efficacy cannot be guaranteed to be same [34]. The other three generics can be used interchangeably with the innovator Crestor® from the results obtained. A number of regulatory bodies including the American Food and Drug Administration (FDA) and the European Medicines Agency (EMA) often apply f_1 and f_2 for comparing the dissolution profiles of generic drugs with their proprietary brands during in vitro bioequivalence studies. Rosuvastatin calcium has low solubility and high permeability and consequently belongs to Class II in the biopharmaceutical classification system (BCS) of drugs. Generic brands of rosuvastatin calcium tablet must therefore exhibit rapid dissolution to be considered bioequivalent to the reference brand. Pharmaceutical products that contain active ingredients which are highly soluble at pH 6.8, having high permeability, and which are weakly acidic like rosuvastatin (BCS class II), are eligible for a biowaiver if the generic brand dissolves quickly enough to release eighty-five percent or more of the labelled amount of active ingredient in standard or appropriate medium at pH 6.8, in 30 min and with the use of the paddle type apparatus set at speed of 75 revolutions per minute (RPM). The generic products should in addition, show dissolution profiles that are comparable to the reference brand in buffers at all 3 pH values of 1.2, 4.5, and 6.8, as measured by the f_2 value or using any statistical method that is equivalent [39]. However, for rosuvastatin calcium tablets, the Food and Drug Administration (FDA) guidelines recommends carrying out its dissolution studies at only pH of 6.6 due to the acid instability of the drug and the observation that it will degrade at the other two pH values earlier mentioned for the biowaiver dissolution studies (pH 1.2 and 4.5) [11]. Generics used for this study fulfilled the criteria of solubility at pH 6.6, are rapidly dissolving i.e. > 85% labelled claim dissolved in less than 30 min in standard buffer and exhibited similar dissolution profiles as determined by f_2 values to that of the innovator at pH 6.6. Thus, these generics can be used interchangeably with the innovator drug product via IVIVC. From the generics performance during this study, there is likelihood for them to also meet up to dissolution test in the other pH media in comparison to the innovator brand, however, degradation of the drug will affect their profiles thus tests in the two other media were avoided. The findings of this study aligns with a similar study on comparative evaluation of some rosuvastatin calcium tablet brands sold in Bangladesh and the United States of America where three generic brands showed greater than 80% dissolution within just 5 min [35] (Table 8).

Table 8 Similarity and difference factor for generic brands of Rosuvastatin

Tablet Brand	SIMILARITY FACTOR (f_2)	DIFFERENCE FACTOR (f_1)
RC1	93	1
RC2	51	11
RC3	63	6
RC4	66	5

Impurity profiling is well recognized as an important aspect of ensuring on-going safety and efficacy of marketed drugs during post market surveillance. However, the scope and focus of the present study was concentrated on the evaluation of critical quality attributes such as identity, dosage uniformity, hardness, friability, disintegration, and dissolution. These parameters were selected based on their direct relevance to the drug products quality and performance, as elucidated in the United States Pharmacopeia guidelines. The omission of impurity testing in this study was primarily due to our inability to access the impurities mentioned in the USP and this is one of the limitations of the study.

Conclusion

Investigation of the quality parameters of marketed pharmaceutical products plays an important role in determining if they meet the standards set by the regulatory bodies thus ensuring that sensitive drugs like the statins are safe and efficacious for use by patients with cardiovascular disease. The different chemical and physical properties evaluated demonstrate that the brands of rosuvastatin calcium tablets available in Jos, North-Central Nigeria possess acceptable quality in terms of their API content, friability, uniformity of weight and disintegration time. The data from this study also supports the conclusion that the generic brands of rosuvastatin evaluated are of good quality and are bioequivalent to the innovator product.

Abbreviations

TC	Total cholesterol
LDL-C	Low-density lipoprotein cholesterol
TG	Triglycerides
HDL-C	High-density lipoprotein cholesterol
HMG-CoA	3-Hydroxy-3-methylglutaryl coenzyme A
FDA	Food and Drug Administration
cGMP	Current good manufacturing practices
UV	Ultraviolet
USP	United States Pharmacopoeia
RPM	Revolutions per minute
BP	British Pharmacopoeia
API	Active pharmaceutical ingredient
EMA	European Medicines Agency
BCS	Biopharmaceutical classification system
IVIVC	In vitro—In vivo correlation

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Author contributions
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References

1. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2):S1-45.
2. Pirillo A, Casula M, Olmastroni E, Norata GD, Catapano AL. Global epidemiology of dyslipidaemias. Nat Rev Cardiol. 2021;18(10):689–700. https://doi.org/10.1038/s41569-021-00541-4.
3. de Brito Alves JL, Trindade da Costa PC. Probiotic for dyslipidemia prevention and treatment. London: Academic Press; 2022.
4. Dybiec J, Baran W, Dąbek B, Fularski P, Młynarska E, Radzioch E, et al. Advances in treatment of dyslipidemia. Int J Mol Sci. 2023. https://doi.org/10.3390/ijms241713288.
5. Mosca S, Araújo G, Costa V, Correia J, Bandeira A, Martins E, et al. Dyslipidemia diagnosis and treatment: risk stratification in children and adolescents. J Nutr Metab. 2022;2022:4782344.
6. Sarfo FS. Dyslipidaemia among African adults. Lancet Glob Heal. 2018;6(9):e940–1. https://doi.org/10.1016/S2214-109X(18)30305-X.
7. Murphy A, Faria-Neto JR, Al-Rasadi K, Blom D, Catapano A, Cuevas A, et al. World heart federation cholesterol roadmap. Glob Heart. 2017;12(3):179-197.e5.
8. Aronow WS. Lipid Disorders in the Elderly. Oxford: Academic Press; 2014.
9. Fiorentino R, Chiarelli F. Treatment of dyslipidaemia in children. Biomedicines. 2021. https://doi.org/10.3390/biomedicines9091078.
10. Tokgözoğlu L, Carl O, Saseen JJ. Statins. New Delhi: Elsevier; 2024.
11. Zaid AN, Al Ramahi R, Cortesi R, Mousa A, Jaradat N, Ghazal N, et al. Investigation of the bioequivalence of Rosuvastatin 20 mg tablets after a single oral administration in Mediterranean Arabs using a validated LC-MS/MS method. Sci Pharm. 2016;84(3):536–46.
12. BP. British Pharmacopoeia. London: The Pharmaceutical Press, Her Majestys Stationary Office. 2024.
13. Radwany NY. In vitro and in vivo Post-marketing Surveillance of Rosuvastatin among Palestinian Patients. 2021.
14. Rahhal A, Khir F, Orabi B, Chbib S, Al-Khalaila O, Abdelghani MS, et al. A comparative study of high-intensity rosuvastatin versus atorvastatin therapy post-acute coronary syndrome using real-world data. Curr Probl Cardiol. 2022;47(7):100956.
15. Shaheen S, Elserafy ASH, Amin M, Hassan R, Issak ER. Brand versus generic rosuvastatin in egyptian patients with hyperlipidemia cost-minimization analysis. Int J Clin Med. 2019;10(12):631–8.
16. USP. The United State Pharmacopeia. Rockville (MD): The United States Pharmacopeial Convention. 2024.
17. Uyar B, Celebier M, Altinoz S. Spectrophotometric determination of rosuvastatin calcium in tablets. Pharmazie. 2007;62(6):411–3.
18. Alam AM, Alhazmi HA, Najmi A, Zoghebi K, Sultan MH, et al. Comparison of Rosuvastatin calcium tablets marketed in Saudi Arabia under Biowaiver conditions in vitro quality control dissolution study. Dissolution Technol. 2023;30(4):19–27.
19. Navale S, Pingale M, Bhosale S, Patil P, Ghongade A. Development and validation of UV spectrophotometeric technique for estimation of rosuvastain drug in bulk and pharmaceutical dosage form. J Re Attach Ther Dev Divers. 2023;6(9):1590–5.
20. Sikdar KYK, Nazir MS, Alam MM, Sarkar MR, Rahman SAR. Evaluation of in vitro dissolution profile and physicochemical characterization of polymer based formulations of sparingly soluble rosuvastatin. Dhaka Univ J Pharm Sci. 2021;20(2):199–211.
21. Noubiap JJ, Bigna JJ, Nansseu JR, Nyaga UF, Balti EV, Echouffo-Tcheugui JB, et al. Prevalence of dyslipidaemia among adults in Africa: a systematic review and meta-analysis. Lancet Glob Heal. 2018;6(9):e998-1007.
22. Ali N, Kathak RR, Fariha KA, Taher A, Islam F. Prevalence of dyslipidemia and its associated factors among university academic staff and students in Bangladesh. BMC Cardiovasc Disord. 2023;23(1):366.
23. Matyori A, Brown CP, Ali A, Sherbeny F. Statins utilization trends and expenditures in the US before and after the implementation of the 2013 ACC/AHA guidelines. Saudi Pharm J. 2023;31(6):795–800.

24. Akunne OO, Godman B, Adedapo AD, Truter I, Fadare J. Statin prescribing among hypertensive patients in southwest Nigeria: findings and implications for the future. J Comp Eff Res. 2016;5(3):281–8.
25. Demoz GT, Wahdey S, Kasahun GG, Hagazy K, Kinfe DG, Tasew H, et al. Prescribing pattern of statins for primary prevention of cardiovascular diseases in patients with type 2 diabetes: insights from Ethiopia. BMC Res Notes. 2019;12(1):386.
26. Liu Y, Lv X, Xie N, Fang Z, Ren W, Gong Y, et al. Time trends analysis of statin prescription prevalence, therapy initiation, dose intensity, and utilization from the hospital information system of Jinshan Hospital, Shanghai (2012–2018). BMC Cardiovasc Disord. 2020;20(1):201.
27. Data Bridge. HealthCare. 2023. p. 1–350 Global Statin Market – Industry Trends and Forecast to 2030. https://www.databridgemarketresearch.com/reports/global-statin-market
28. Chia LI. All Crestor recalled after more counterfeits found. Taipei Times. 2017
29. Taylor P. Securing Industry. 2017 Taiwan FDA seeks Crestor recall after counterfeit finds. https://www.securingindustry.com/pharmaceuticals/taiwan-fda-seeks-crestor-recall-after-counterfeitfind/%0As40/a3433/#.XXHZ2CgzblU. Accessed 13 Jan 2024
30. The News Himachal. The News Himachal. 2022. Drugs Control Administration seizes counterfeit medicines in Baddi. https://thenewshimachal.com/2022/11/drugs-control-administration-seizes-counterfeit-medicines-in-baddi/. Accessed 5 Jan 2024
31. Loftus P. Wall Street Journal. 2012. Ranbaxy Halts Production of Generic Lipitor. https://www.wsj.com/articles/SB10001424127887323751104578149383396925280. Accessed 20 Jan 2024
32. US Department of Justice. Press Release. 2013. Generic Drug Manufacturer Ranbaxy Pleads Guilty and Agrees to Pay $500 Million to Resolve False Claims Allegations, cGMP Violations and False Statements to the FDA. Available from: https://www.justice.gov/opa/pr/generic-drug-manufacturer-ranbaxy-pleads-guilty-and-agrees-pay-500-million-resolve-false. Accessed 18 Jan 2024
33. ICH. International conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use. Validation of analytical procedures: text and methodology Q2(R1). 2005.
34. Moore JW, Flanner HH. Mathematical comparison of curves with an emphasis on in vitro dissolution profiles. Pharm Technol. 1996;20:64–74.
35. Monisha ST, Ela KN, Islam R, Ether SA, Rahman FI. Quality attributes comparison of selected brands of rosuvastatin calcium tablets marketed in the US and Bangladesh. J Pharm Res Int. 2021;33(39):46–55.
36. Alam S, Dilshad H, Khan B, Farooq N, Zehra A. Post marketing in-vitro relative analysis of diverse brands of rosuvastatin calcium accessible in urban Karachi (Pakistan). World J Pharm Sci. 2021;9(8):114–9.
37. Hasin F, Al MMAR, Alam ME, Saha CK, Rahman MdH, Akter S. Cost Effective formulation development of rosuvastatin in compared to innovator brand & evaluation of interchangeability via in-vitro bio-equivalence study. World J Pharm Res. 2017;6(15):72–86.
38. Naveed S, Qamar F. Simple UV spectrophotometric assay of rosuvastatin formulations. Glob J Pharm Res. 2014;3(3):1985–90.
39. World Health Organization (WHO). Proposal to waive in vivo bioequivalence requirements for the WHO model list of essential medicines immediate release, solid oral dosage forms. Geneva: World Health Organization; 2006.

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