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Comparison of Rosuvastatin Calcium Tablets Marketed in Saudi Arabia Under Biowaiver Conditions: In Vitro Quality Control Dissolution Study

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ABSTRACT

Rosuvastatin (RST) calcium is used to treat hyperlipidemia, and several generic brands of RST calcium are available in Saudi Arabia along with the innovator. The current study aimed to compare two generic brands of RST with the innovator with respect to physicochemical parameters and dissolution data under biowaiver conditions. Two generic brands of RST calcium tablets, Resova and Ivarin, were purchased from the local market. Their pharmaceutical equivalence with the innovator brand, Crestor, was determined according to United States Pharmacopeia (USP) methods for assessment of various parameters, including weight, friability, hardness, disintegration, and in vitro dissolution in three different mediums. Drug content was highest for Crestor (104.14%), and Ivarin had the lowest (99.7%). Dissolution of RST calcium tablets in 0.1 N hydrochloric acid (HCl) (pH 1.2) revealed that Crestor released the highest amount of drug (88.9%) at the end of 60 min; Resova and Ivarin released 88.7% and 75.2%, respectively. The amount of drug released was higher in 0.05 M phosphate buffer (pH 6.8) for all the brands, showing 98.5%, 98.8%, and 98.4% release at 60 min for Crestor, Resova, and Ivarin, respectively. In 0.05 M sodium citrate buffer (pH 6.6), maximum release of the drug was achieved, showing 99.1%, 102.1%, and 99.8% for Crestor, Resova, and Ivarin, respectively. Similarity factor analysis demonstrated equivalence of the generic brands with the innovator brand. In conclusion, the tested brands of RST calcium tablets passed the standards set by USP, allowing interchangeability of generic and brand name products.

KEYWORDS: Rosuvastatin, pharmaceutical equivalence, disintegration, dissolution, quality control, biowaiver

INTRODUCTION

The Saudi Arabian pharmaceutical market is considered one of the largest markets among Middle Eastern and African countries, with an estimated market value of 8.2 billion US dollars, according to data collected in 2018 (*1, 2*). Competition among drug manufacturers to develop generic and innovative products is increasing. Approval of generic medications is

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established after verifying the claim of the generic drug to be identical, efficacious, authorized, and safe compared with the innovator drug or the reference product. The generic formulation needs to have similar levels of active ingredients, comparable dosage forms, and a similar route of drug delivery. The generic product should also fulfil the stipulated requirements of integrity, potency, durability, and purity (*3*).

In vivo bioequivalence studies are used to assess drugs exhibiting similar bioavailability profiles (*2, 3*). The World Health Organization (WHO) promotes evaluating varying dosage forms to guarantee that all pharmaceuticals are certified and have similar clinical benefits to the patients (*4–6*). Although many generic medicine brands are readily accessible in the market, they lack comprehensive control and quality monitoring, especially in underdeveloped nations. Simultaneously, expanding generic pharmaceuticals has contributed to a broad supply of unsatisfactory and fraudulent pharmaceutical items in this sector (*7*).

According to WHO, these substandard drugs are legitimate medications made by authorized manufacturers that do not exceed the quality parameters imposed by national or global guidelines (*4*). Approximately 10% of pharmaceutical products are observed to be of low quality or are misrepresented. Possible causes of substandard drugs include improper storage conditions, technical hindrances, manufacturing drawbacks, distribution problems, and weak management by local councils over regulations concerning pharmaceutical products (*4*). Implementing strict quality control methods for drugs from various production sources is essential to demonstrate the intended clinical benefits (*8*).

Several quantitative analyses of pharmacological products are available, especially for capsule or tablet drug forms that are self-administered. Evaluations are required to precisely identify the physicochemical features of different forms and doses including bioavailability and stability profiles, which are often performed throughout the early phases of designing a drug and are constantly monitored for quality control. Chemical interactions or degradation of the components of a tablet may change the physicochemical characteristics, possibly decreasing bioavailability (*9*). Tablets shall be manufactured to resist breaking, cracking, and erosion. Every tablet within a provided batch should have the active pharmaceutical ingredient (API) within an acceptable range of the indicated dose. The primary physical features are mechanical stability, drug concentration, and tablet weight. The dissolution profile, uniformity of doses, and hardness can be used to compare the units (*10–14*). The drug is absorbed in vivo after the API is released from the tablet. For immediate-release (IR) formulations, tablet disintegration is the primary stage of drug release (*15, 16*). The in vitro dissolution profile reflects the in vivo bioavailability of many orally administered compositions. Such investigations are critical quality assurance methods for assessing uniformity of drug delivery systems using a specific dosage form (*17–19*). To obtain a biowaiver for a generic drug, WHO and the United States Food and Drug Administration (FDA) require in vitro dissolution testing to show bioequivalence with the innovator brand (*20, 21*). Thus, dissolution analysis is vital throughout the drug development process, and the results can predict the dissolution behavior with respect to solubility and time, thereby serving as a crucial component in seeking regulatory authorization (*17, 22*).

RST belongs to the statins drug group, which is used to treat excessive cholesterol and associated diseases and prevent cardiovascular complications. RST calcium, a Biopharmaceuticals

Classification System (BCS) class 2 medication, treats hyperlipidemia by lowering LDL cholesterol, apolipoprotein B, and triglycerides while increasing HDL cholesterol. The increasing cost of the innovator drug has made it difficult for patients to afford. Introduction of a generic form after bioequivalence testing is the most significant way to reduce pharmaceutical costs, and many generic drugs are introduced into the market every year. As a result, the healthcare system's fundamental difficulty is understanding the safety and efficacy criteria of these generic products (*23*). Quality control studies can help identify pharmaceutical products that may be fraudulent, poor quality, and harmful to consumers (*24*).

The current research aims to perform quality control testing, including comparison of in vitro dissolution profiles, of generic and innovator brands of RST calcium tablets and to determine their pharmaceutical equivalence. *USP* general chapters <1216> Friability, <1217> Tablet Breaking Force, 701 <Disintegration>, and <711> Dissolution were followed to assess weight, friability, hardness, disintegration, and drug release (*25–28*).

METHODS

Tablet Samples

Three brands of RST calcium (20 mg) tablets were acquired from different pharmacies in Jazan, Saudi Arabia. These included the innovator drug Crestor (batch no: PF067P1, exp date: 03/31, IPR Pharmaceuticals –Inc. Puerto Rico) and generic drugs Resova (batch no: 9114, exp date: 9/20, Jazeera Pharmaceuticals, Saudi Arabia) and Ivarin (batch no: 82M111, exp date: 8/20, Tabuk Pharma, Saudi Arabia).

Chemicals and Reagents

RST calcium as a standard reference was obtained from IPR Pharmaceuticals Incorporations, Puerto Rico. The reagents used in the study, potassium dihydrogen phosphate (KH_2PO_4), disodium hydrogen phosphate (Na_2HPO_4) and hydrochloric acid (HCl), were obtained from Sigma Aldrich, Germany.

Preparation of Standard Curve

The stock solution of RST with a 100 µg/mL concentration was prepared by dissolving the appropriate amount of RST in 0.1 N HCl. The prepared stock solution was then taken in aliquots, and serial dilutions of concentrations 2–14 µg/mL were prepared using 0.1 N HCl. The absorbances of obtained solutions were measured using a UV/Visible spectrophotometer (Jenway 6705, London, UK) at 243 nm, and a graph was plotted using absorbance values versus concentration.

Price Comparison

The price of the different brands of RST calcium tablets was compared according to Akinleye et al (*29*).

Weight Variation Test

Twenty tablets of each brand were separately weighed. The percentage variation of individual tablet from the average value was calculated according to *USP* <1216> Friability (*25*).

Friability Test

Ten tablets of each brand were arbitrarily selected, dusted, weighed, and placed inside the friabilator (Roche) and rotated for 4 min at 25 rpm. For repeatability and accuracy, the tablets were re-weighed, and the difference in the weight was measured as friability percentage according to *USP* <1216> Friability (*25*).

Hardness Test

A hardness tester (Monsanto) was used to test the hardness on 10 tablets of each brand according to the guidelines of *USP* <1217> Tablet Breaking Force (*28*). The amount required to break a tablet throughout its diameter was measured in kp (kilopounds).

Disintegration Test

Following the guidelines of *USP* <701> Disintegration, six tablets from each brand were separately kept within individual tubes of the disintegration apparatus basket (Copley) (*26*). Distilled water was used as the medium, and the test was performed at 37 $\pm$ 0.5 °C after the basket assembly was mounted. Disintegration time was recorded as the length of time required for the tablets to break down into small particles or granules. The brands passed the test only if all six tablets from the brand were completely dissolved in the medium. If one or two tablets could not wholly disintegrate, then 12 more tablets were tested, and only two of the 18 tested tablets are permitted to fail the test (*26*).

Preparation of Calibration Curve

A series of concentrations (2–14 g/mL) of RST calcium in methanol was prepared and analyzed at a wavelength of 244 nm, and the corresponding absorbance values were recorded. The calibration curve was plotted using concentration at the x-axis and absorbance values at the y-axis (*30*).

Drug Content

The UV-Vis spectrophotometer was used to determine the amount of drug present in the final solution. The percentage purity was calculated at 244 nm using methanol as the medium (*31*).

In Vitro Dissolution Study

Following *USP* <711> Dissolution, a Copley USP dissolution apparatus 2 (basket) was used to perform the in vitro dissolution tests in 900 mL of dissolution medium (*27*). The dissolution medium used was 0.05 M $Na_3C_6H_5O_7$ (sodium citrate) buffer (pH 6.6), sodium phosphate buffer (pH 6.8), and 0.1 N HCl buffer (pH 1.2). The HCl and phosphate buffer mimics the conditions in the stomach and the small intestine, respectively. The sodium citrate buffer is suggested by the FDA for RST calcium dissolution studies (*32*). This study was conducted at 37 $\pm$ 0.5 °C with a speed of 50 rpm. Samples (10-mL) were drawn at 5, 10, 15, 30, 45, and 60 minutes and refilled with the same fresh medium to maintain sink conditions. The samples obtained were filtered using 0.45-mm Whatman filter paper, and absorbance values were determined at 244 nm.

Statistical Analysis

The difference factor (f_1) and the similarity factor (f_2) were calculated for all the generic brands

using the innovator brand as the reference (*33*). The statistical analyses were conducted using the Graph Pad Prism program, version 6.01 software. The dissolution data were analyzed using two-way ANOVA followed by Dunnett's post-hoc testing. The modeling data for dissolution comparison of generic and innovator brand profiles were obtained using DD Solver version 1.0 using Microsoft Excel. The coefficient of determination (R^2), Akaike information criteria (AIC) of DD Solver, and fit characteristics were used to employ the most reliable drug-release model.

RESULTS AND DISCUSSION

Physiochemical Properties

Crestor was the most expensive brand, with 28 tablets per box for 145.25 Saudi Arabian Riyals (SAR) ($38.73 USD). Resova and Ivarin were comparatively cheaper and provided 30 tablets per box for 115.45 and 128.30 SAR ($30.78 and $34.21 USD, respectively), respectively (i.e., 20.51% and 11.67% lower than Crestor, respectively).

The primary goals in assessing dosage form uniformity are to verify proper manufacturing procedures, suitable tablet sizes, drug content, and formulation consistency (*34*). To achieve this, weight variability and friability tests were conducted. All tablet brands had slight weight variations, but the results were within the acceptable limit according to *USP* (*25*). Ivarin had the largest weight variation and the hardest tablets (8.15–8.85 kp) among the three brands. Friability test results were within the acceptable limit according to *USP* (*25*). Variations in friability might be connected to batch flaws, such as changes in the composition of excipients and inappropriate drug transit or storage circumstances (*9, 13*).

The physicochemical properties of the innovator and generic RST calcium tablets are provided in Table 1. The dissolution of drugs affects their bioavailability, which is directly related to tablet disintegration, as faster disintegration results in faster drug release. All brands were within the disintegration time standards set by *USP* (*28*). Resova had the fastest disintegration time compared to other brands.

Table 1. Physicochemical Properties of RST (20 mg) Calcium Tablets

Brand	Weight, mg (*n* = 20)[a]	Hardness, kgf (*n* = 10)[a]	Friability, % (*n* = 10)[a]	Disintegration time (min: sec) (*n* = 6)	Drug Content, %
Crestor (Innovator)	307.62 ± 1.82	8.15 ± 0.24	0.29 ± 0.0063	2:38	104.14
Resova	305.04 ± 5.42	8.35 ± 1.18	0.032 ± 0.0007	1:22	103.90
Ivarin	303.30 ± 2.59	8.85 ± 0.24	0.098 ± 0.0021	2:00	99.27

[a]*Values are presented as mean ± SD.*

Dissolution Profiles

The calibration plot was observed to be linear with an R^2 value of 0.998 and linear regression equation of $y = 0.0413x - 0.0024$. Drug content purity was highest for Crestor (104.14%), followed

by Resova (103.9%), then Ivarin (99.3%). The percentage purity was within the *USP* limit for all brands. The UV method developed was validated as per the ICH guidelines and reported in our earlier study (*35*).

The in vitro dissolution test results are presented in Table 2 and compared in Figure 1. In 0.1 N HCl medium (pH 1.2), Crestor released the most drug by the end of 60 min, and Ivarin released the least amount (Fig. 1A). Resova had a dissolution profile that was similar to Crestor. The differences in drug release were not statistically significant ($p > 0.05$ for all). In 0.05 M phosphate buffer (pH 6.8) medium, Ivarin showed a burst release profile as it released highest amount of drug within 5 min of dissolution, whereas Crestor and Resova maintained a low profile at the beginning (Fig. 1B). By the end of 60 min, all the three brands exhibited similar drug release effects. In 0.05 M sodium citrate buffer (pH 6.6), Crestor released the most amount of drug within 5 min of dissolution, and Resova released the least amount (Fig. 1C). After 60 min of dissolution, Resova released the highest amount of drug in comparison to Crestor and Ivarin.

Table 2. In Vitro Dissolution Rates (Mean Cumulative Drug Release ± SD) for RST (20 mg) Calcium Tablets

	Crestor (Innovator)			**Resova**			**Ivarin**		
Media	**0.1 N HCl (pH 1.2)**	**0.05 M PB (pH 6.8)**	**0.05 M SCB (pH 6.6)**	**0.1 N HCl (pH 1.2)**	**0.05 M PB (pH 6.8)**	**0.05 M SCB (pH 6.6)**	**0.1 N HCl (pH 1.2)**	**0.05 M PB (pH 6.8)**	**0.05 M SCB (pH 6.6)**
5 min	18.076 ± 0.020	75.966 ± 0.001	80.869 ± 0.002	18.458 ± 0.022	73.351 ± 0.003	69.429 ± 0.004	16.587 ± 0.001	79.889 ± 0.013	79.235 ± 0.003
10 min	43.845 ± 0.031	80.215 ± 0.023	94.271 ± 0.023	46.496 ± 0.008	89.695 ± 0.008	89.368 ± 0.003	39.487 ± 0.021	88.061 ± 0.024	85.772 ± 0.002
15 min	60.389 ± 0.022	88.518 ± 0.021	96.886 ± 0.001	59.735 ± 0.009	90.676 ± 0.007	94.271 ± 0.025	51.763 ± 0.023	90.022 ± 0.020	93.291 ± 0.014
30 min	61.642 ± 0.025	97.867 ± 0.009	97.540 ± 0.013	59.535 ± 0.002	91.656 ± 0.028	96.232 ± 0.012	58.209 ± 0.021	94.598 ± 0.024	95.579 ± 0.018
45 min	76.878 ± 0.002	98.194 ± 0.006	97.867 ± 0.034	75.316 ± 0.036	92.637 ± 0.024	98.847 ± 0.003	64.565 ± 0.020	95.252 ± 0.016	97.867 ± 0.017
60 min	88.918 ± 0.087	98.521 ± 0.002	99.174 ± 0.054	88.736 ± 0.007	98.847 ± 0.022	102.116 ±0.009	75.243 ± 0.021	98.466 ± 0.017	99.828 ± 0.002

RST: rosuvastatin; PB: phosphate buffer; SCB; sodium citrate buffer.

Table 3. Similarity Factor Analysis of Generic RST Calcium Tablets Compared to Innovator Brand (Crestor)

Brand	**Hydrochloric acid pH 1.2 (0.1 N)**		**Phosphate Buffer pH 6.8 (0.05 M)**		**Sodium Citrate Buffer pH 6.6 (0.05 M)**	
	f_1	f_2	f_1	f_2	f_1	f_2
Resova	2.18	86.65	5.0	63.26	4.47	63.13
Ivarin	14.49	53.08	3.64	68.97	3.01	69.66

RST: rosuvastatin; f1: difference factor; f2: similarity factor

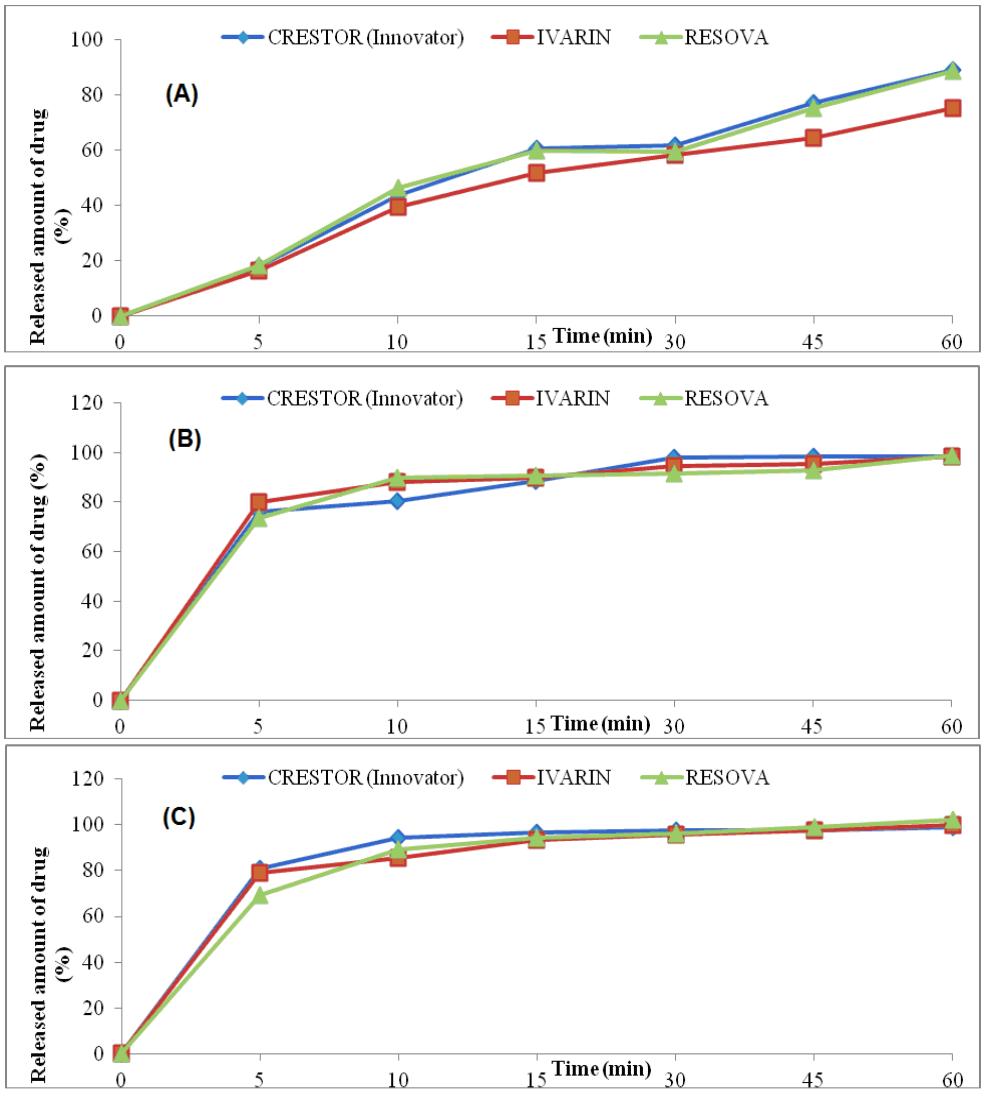

Figure 1. Comparison of drug release profiles of the innovator brand (*Crestor*) *and generic brands* (*Ivarin and Resova*) *in 0.1 N HCl* (***A***)*, 0.05M phosphate buffer* (*pH 6.8*) (***B***)*, and 0.05 M sodium citrate buffer* (*pH 6.6*) (***C***)*.*

To further compare the dissolution profiles of the generic products with the innovator, Table 3 presents the similarity factor analysis results, which confirms that the dissolution profiles of Resova and Ivarin are similar with Crestor.

CONCLUSION

The two generic brands (Resova and Ivarin) of RST (20 mg) calcium tablets met USP guidelines for having similar physicochemical properties and dissolution profiles with respect to the innovator brand (Crestor). Resova was more similar to Crestor than Ivarin; however, both generic brands passed the in vitro bioequivalence tests and can be used as a substitute for the innovator brand. These findings can help design guidelines and policies for ensuring interchangeability and bioequivalence of RST calcium tablet brands.

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CONFLICT OF INTEREST

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

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