Study of Drug Release Kinetics of Rosuvastatin Calcium Immediate-Release Tablets Marketed in Saudi Arabia

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ABSTRACT

Rosuvastatin (RST), a BCS class II drug, is a poorly water-soluble antihyperlipidemic agent. The aim of the present work was to determine and compare the drug release kinetics from the RST calcium innovator (Crestor) and generic products (Ivarin and Resova) marketed in Saudi Arabia by employing various drug release kinetic mathematical models. A dissolution study was performed on all RST calcium immediate-release tablets. The in vitro drug release profiles were determined in three different dissolution media: 0.1 N HCl (pH 1.2), 0.05 M phosphate buffer (pH 6.8), and 0.05 M citrate buffer (pH 6.6). Drug release data were obtained, correlated quantitatively, and interpreted with the help of mathematical models, then the drug release kinetics were analyzed. The criterion for selecting the most suitable model was based on the highest coefficient of correlation ($R^2$) with the dissolution profile in each respective media. The innovator product followed the Hixson-Crowell model ($R^2 = 0.955$) only in 0.1 N HCl (pH 1.2), whereas in other media all the formulations followed first order release kinetics with non-swellable matrix Fickian diffusion, which is considered ideal for an immediate-release tablet formulation.

KEYWORDS: Rosuvastatin, immediate-release tablets, dissolution, mathematical models, drug release kinetics

INTRODUCTION

Rosuvastatin (RST) is an antihyperlipidemic drug that lowers low-density lipoprotein (LDL) cholesterol, apolipoprotein B, and triglycerides and increases high-density lipoprotein (HDL) cholesterol in the clinical management of hyperlipidemia (1). Therefore, it can be used to reduce the progression of atherosclerosis and for primary prevention of cardiovascular diseases. Owing to its low solubility in water, which is 0.33 mg/mL, RST exhibits poor solubility in gastrointestinal fluids and undergoes extensive first pass metabolism, limiting oral bioavailability to only 20% (2). Different brands of RST calcium immediate-release (IR) tablets are marketed in Saudi Arabia, including Crestor (innovator), Ivarin (generic), and Resova (generic). Crestor is manufactured by AstraZeneca (UK) and is available in 20-mg film-coated tablets in Saudi Arabia. Ivarin is manufactured locally by Tabuk Pharmaceuticals in Riyadh, Saudi Arabia, and is available as film-coated tablets in strengths of 10, 20, and 40 mg. Resova is manufactured in by Jazeera Pharmaceutical Industries, also in Riyadh, and is available as 10- and 20-mg tablets. The film-coating on these tablets is used to provide stability during manufacturing, transport, storage, and
clinical uses of the drug. Various polymers are used for the film coating, which can control drug release from the formulation. The type of polymer, coating technology, and coating uniformity have significant effects on the release of drugs, as well as excipients used in the tablet formulation.

Dissolution and release of a drug in vivo is an important process for solid dosage forms such as tablets and capsules in order to deliver the correct concentration of drug over an intended period of time (3). Dissolution of a solid into a medium involves the transfer of mass from solid to a liquid phase, and this process is governed by the Noyes-Whitney equation. Drug release kinetics are directed by one or more mechanisms that depend on the composition of matrix and dissolution media (4, 5). There are various factors affecting the mechanism of drug release kinetics, and it is of utmost importance to identify these factors. An ideal drug delivery system delivers the drug at a rate dictated by the body during the entire course of treatment, thereby increasing the therapeutic efficacy and safety of drugs. Factors related to drugs such as solubility, dose, content, molecular weight and size, particle size and shape, physical state, and diffusion in polymer and medium are capable of influencing the release kinetics of a formulation (6). Factors related to formulations such as geometry (size and shape), excipients or additives, and other processing variables also influence the release kinetics. Therefore, release of a drug from the formulation plays a vital role in modified-release or immediate-release dosage forms (7).

Various release models are used to study the release pattern of a drug from the formulation in order to design an effective formulation. The Higuchi model describes drug release from a matrix system, and the Hixson-Crowell model deals with the release from systems where there is a change in surface area and diameter of particles (8). The Korsmeyer–Peppas model analyzes both Fickian and non-Fickian release of a drug from swelling and non-swelling polymeric delivery systems (9). These mechanistic mathematical models are based on real phenomenon such as diffusion, dissolution, swelling, erosion precipitation and/or degradation. These models can explain the release kinetics with desired or required predictive ability and accuracy (9). These models are also used to fit in vitro release data and to describe the release kinetics (10–13). The release data can be fitted into kinetic models such as zero order, first order, Higuchi, Hixon-Crowell, and Korsmeyer-Peppas, and the coefficient of correlation ($R^2$) can be determined, which reflects the extent to which the regression line represents the data. The model that best fits the release data is determined by its $R^2$ value (14, 15).

Therefore, it is important to study the drug release kinetics of different generic formulations present in the market and to compare them with the innovator brand to identify formulations that fail to deliver the correct concentration of an active ingredient over a period of time. It is desirable to check the quality of generic brands that are available in the market to assess their equivalence with the innovator brand. Generic brands are sometimes associated with counterfeit drugs in which the desirable activity of the drug is compromised. The drug release kinetics of generic products should be similar to the innovator product to have equivalent therapeutic efficacy. This study aims to evaluate the drug release kinetics of innovator and generic brands of RST calcium tablets and compare them using various drug release kinetic models.
MATERIALS AND METHODS

The three brands of RST calcium tablets (Crestor, Ivarin, and Resova) were purchased from the local market of Jazan, Saudi Arabia. All chemicals were purchased from Sigma Aldrich (Steinheim, Germany) and were used without further purification. All the buffers were prepared fresh before the commencement of each experiment. The product information for selected brands of RST calcium tablets is shown in Table 1.

Table 1. Product Information of Rosuvastatin Calcium Tablets (20 mg)

<table>
<thead>
<tr>
<th>Brand</th>
<th>Batch No.</th>
<th>Manufacture Date</th>
<th>Expiration Date</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crestor (Innovator)</td>
<td>PF067P1</td>
<td>04/19</td>
<td>03/21</td>
<td>IPR Pharmaceuticals Inc., Puerto Rico</td>
</tr>
<tr>
<td>Resova (Generic)</td>
<td>9114</td>
<td>09/19</td>
<td>08/21</td>
<td>Jazeera Pharmaceuticals, Saudi Arabia</td>
</tr>
<tr>
<td>Ivarin (Generic)</td>
<td>82M111</td>
<td>08/19</td>
<td>07/21</td>
<td>Tabuk Pharma, Saudi Arabia</td>
</tr>
</tbody>
</table>

Preparation of Calibration curve

A UV-Vis spectrophotometer (UV1800, Shimadzu, Japan) was used for the analysis of drug concentration in all samples. A stock solution (20 mg/100 mL) of pure RST calcium prepared in methanol was further diluted to 2, 4, 6, 8, 10, 12 and 14 µg/mL concentrations. The calibration plot was constructed by taking the absorbance of the solutions at 244 nm. The equation for linear regression was obtained to be $y = 0.0413x - 0.0024$, with an $R^2$ value of 0.998. Concentrations of drug in unknown samples were determined using the regression equation.

Validation of the Analytical Method

The method used for the analysis of RST calcium was validated with respect to stability, linearity, sensitivity, precision, accuracy, specificity, robustness, and ruggedness according to the International Council for Harmonisation (ICH) guidelines Q2B (16).

Determination of Drug Content

The average weight of 10 randomly selected tablets from each brand was determined, then the tablets were crushed into powder. Powder equivalent to 20 mg of RST calcium was transferred into a 100 mL volumetric flask. The mixture was sonicated (WiseClean sonicator, WUC-A03H, Witeg, Germany) for 30 minutes by adding 50 mL of methanol. The final volume of 100 mL was obtained by adding methanol, then filtered using a nylon filter (0.45 µm, Chrom Tech F30-NY045, MN, USA); 100 ± 10% was considered the acceptable limit per USP (17).

In Vitro Dissolution Studies

The in vitro dissolution studies were performed in three different dissolution media (0.1 N HCl buffer, pH 1.2; 0.05 M sodium citrate buffer, pH 6.6; 0.05 M phosphate buffer, pH 6.8) using the standard method described in USP General Chapter <711> Dissolution (18). A USP apparatus 2 (paddle) (Copley, Nottingham, UK) was used to perform dissolution tests. The conditions for the dissolution procedure are summarized in Table 2.
For each of the three brands, one tablet was placed in each of the six dissolution vessels containing 900 mL of dissolution medium maintained at 37 ± 0.5 °C. The rotational speed was set at 50 rpm. At set time intervals (5, 10, 15, 30, 45, 60, 90, 120, and 150 minutes), a 10-mL sample was withdrawn and replaced with 10 mL fresh dissolution media. The concentrations were adjusted mathematically to deal with the dilution occurring with each addition of dissolution medium. The samples were filtered with a 0.45-µm nylon filter. Absorbance was checked using UV-Vis spectrophotometry at 244 nm. The standard calibration curve of pure RST calcium was used to calculate the drug released at each time of sampling. All the experiments were performed in triplicate.

Table 2. Dissolution Test Parameters and Specifications for Rosuvastatin Calcium Tablets

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissolution equipment</td>
<td>USP apparatus II (paddle)</td>
</tr>
<tr>
<td>Dissolution media</td>
<td>0.1 N HCl buffer (pH 1.2), 0.05 M phosphate buffer (pH 6.8), 0.05 M sodium citrate buffer (pH 6.6)</td>
</tr>
<tr>
<td>Media volume</td>
<td>900 mL</td>
</tr>
<tr>
<td>Media temperature</td>
<td>37.0 ± 0.5 °C</td>
</tr>
<tr>
<td>Paddle speed</td>
<td>50 rpm</td>
</tr>
<tr>
<td>Sampling procedure</td>
<td>Aliquots of 10 mL were drawn at 5, 10, 15, 30, 45, 60, 90, 120, and 150 min, and filtered via 0.45-µm nylon filter.</td>
</tr>
<tr>
<td>Ultraviolet absorbance</td>
<td>244 nm</td>
</tr>
</tbody>
</table>

Application of Drug Release Kinetic Models

Various mathematical models were employed to investigate the drug release kinetics of different RST brands. The drug release models included zero order, first order, Higuchi, Hixon-Crowell, and Korsmeyer-Peppas models. $R^2$ values were used to determine the best fitting model.

**Zero Order Release Kinetics Model**

Zero order kinetics implies a constant drug release from a formulation, resulting in a constant level of drug in blood throughout the process (11, 19). The fraction of drug release was plotted against time, and the slope of the curve obtained gives the zero-order rate constant and $R^2$.

**First Order Release Kinetics Model**

First order release kinetics can be defined as the process in which the rate of reaction is directly proportional to the concentration of drug, so the greater the concentration, the faster the release (20, 21). The log of the percentage of drug remaining was plotted against time, and the slope gives the rate constant and $R^2$.

**Higuchi Model**

The Higuchi model is one of the most widely employed and well-known models used to study the release of water soluble and less soluble drugs that are incorporated in solid and/or semisolid matrices (22–24). This model describes the release of a drug from a drug delivery system (DDS) involving both dissolution and diffusion. The fraction of drug release was plotted against the square root of time, and $R^2$ was obtained from the curve.
**Korsmeyer-Peppas Model**

In the Korsmeyer-Peppas model, the drug release and elapsed time are exponentially related, which describes the release of a drug from a polymeric system (24). The release exponent ($n$) is used to characterize the release mechanisms of the drug, and $n$ less than 0.5 indicates Fickian diffusion, whereas values between 0.5 and 1.0 indicate a non-Fickian mechanism (26, 27). To test this model, the log of the percentage of drug release was plotted against log time, and $R^2$ was calculated from the curve.

**Hixson-Crowell Model**

The Hixson-Crowell model is applied when the drug release is a function of change in surface area or the diameter of drug particles (27, 28). This model was tested by plotting the cubic root of the amount of drug remaining in the tablet matrix versus time, then calculating $R^2$.

**RESULTS**

The developed UV-Vis spectroscopic method was validated as per the ICH guidelines, and the parameters assessed were found to be within prescribed range. The stock solution of RST calcium was stored at two temperatures (low and high) for 1 month to check the stability of the solution. No significant differences were observed in the UV spectra, showing good stability of the stock solution in methanol. The calibration curve was plotted using 2–14 µg/mL concentrations, and good linearity was observed up to 50 µg/mL concentration. The limit of detection (LOD) and limit of quantification (LOQ) vales were 0.33 and 0.99 µg/mL, respectively.

Inter-day and intraday precision were calculated by measuring the quality control samples (10, 25, and 50 µg/mL) in triplicates on the same day (intra-day) and three consecutive days (inter-day). The relative standard deviation (%RSD) values were 0.24–1.21 for intra-day and 0.33–0.65 for inter-day measurements, showing high precision of the method. The accuracy of the method was determined using recovery experiments on the medium quality control sample by standard addition method. High recovery values in the range of 98.3–101.2% were observed for six measurements, showing excellent accuracy of the method.

The percentage drug content present in the selected brands was in the range of 99.27–104.15%, which is within the USP acceptance limit of 100 ± 10%. Highest drug content was present in the Crestor brand, showing 104.15%, followed by Resova, having 103.35%. The lowest drug content was observed for Ivarin, showing 99.27%.

In this study, three different dissolution media were used to study the effect of pH on the release kinetics of RST calcium IR tablets. The buffers used were 0.1 N HCl (pH 1.2), 0.05 M sodium citrate buffer (pH 6.6), and 0.05 M phosphate buffer (pH 6.8). The HCl buffer and phosphate buffer mimic the stomach and small intestine conditions, respectively, whereas citrate buffer is recommended for the dissolution studies of RST by the U.S. Food and Drug Administration (FDA) (29). The in-vitro release data from all three media were fitted in the mathematical models and best fit model was determined.
Dissolution in 0.1N HCl Buffer (pH 1.2)

Dissolution of the innovator formulation in 0.1 N HCl buffer was performed, and 99.69% of drug was released at 150 min. The highest $R^2$ value was observed with the Hixon-Crowell drug release kinetic model (Fig. 1A).

When the generic formulations of RST were subjected to dissolution under the same conditions using 0.1 N HCl, 89.79% and 96.65% of drug was released from Ivarin and Resova, respectively, after 150 min. Comparison of $R^2$ values showed that the best fit model was the first order model for Ivarin ($R^2 = 0.965$) and Resova ($R^2 = 0.925$) (Fig. 1B and 1C).

The $R^2$ values obtained in each kinetic model for all three products are presented in Table 3 for comparison purposes. In the Korsmeyer-Peppas model, the release exponent was 0.185, 0.186, and 0.177 for Crestor, Ivarin, and Resova respectively, indicating Fickian diffusion of these drugs in 0.1 N HCl at pH 1.2.

Dissolution in 0.05 M Phosphate Buffer (pH 6.8)

For the innovator brand, cumulative drug release in 0.5 M phosphate buffer (pH 6.8) after 150 min was 99.92%. The best fit model for Crestor at pH 6.8 was the first order model, as it showed highest $R^2$ value (0.959) (Fig. 2A).

The dissolution profile of the generic brands in 0.05 M phosphate buffer revealed that 99.89% and 99.27% of RST was released after 150 min for Ivarin and Resova, respectively. For both brands, the best fit model was the first order model, with $R^2$ values of 0.958 and 0.901 for Ivarin and Resova, respectively (Fig. 2B and 2C).

In the Korsmeyer-Peppas model, the release exponent was found to be 0.03, 0.02, and 0.03 for Crestor, Ivarin, and Resova respectively, indicating Fickian diffusion of these drugs in 0.5 M phosphate buffer at pH 6.8.
Figure 2. Drug release profile (Log % drug remaining over time) obtained for (A) Crestor (Innovator), (B) Ivarinm (Generic), and (C) Resova (Generic) in 0.05 M phosphate buffer (pH 6.8) showing the best-fit mathematical models and $R^2$ values.

Dissolution in 0.05 M Citrate Buffer (pH 6.6)

The cumulative drug release upon dissolution of the innovator brand in 0.05 M citrate buffer (pH 6.6) was 99.83%. The best fit model was the first order model, with $R^2 = 0.900$ (Fig. 3A).

Upon dissolution of generic brand tablet in 0.05 M citrate buffer (pH 6.6), 99.43% and 99.99% of RST was released for Ivarin and Resova, respectively, over 150 min. The best fit model for both was the first order model, with $R^2$ values of 0.891 and 0.879 for Ivarin and Resova, respectively (Fig. 3B and 3C).

In the Korsmeyer-Peppas model, the release exponents were 0.02, 0.02, and 0.03 for Crestor, Ivarin, and Resova respectively, indicating Fickian diffusion of the drug in 0.05 M citrate buffer, pH 6.6.

Figure 3. Drug release profile (Log % drug remaining over time) obtained for (A) Crestor (Innovator), (B) Ivarinm (Generic), and (C) Resova (Generic) in 0.05 M citrate buffer (pH 6.6) showing the best-fit mathematical models and $R^2$ values.
Table 3. Comparative Release Model Analysis of Rosuvastatin Calcium Tablets at pH 1.2, 6.8, and 6.6

<table>
<thead>
<tr>
<th>Dissolution Media and Product</th>
<th>Coefficient of Correlation ($R^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zero Order</td>
</tr>
<tr>
<td>0.1 N HCl Buffer (pH 1.2)</td>
<td></td>
</tr>
<tr>
<td>Crestor (Innovator)</td>
<td>0.737</td>
</tr>
<tr>
<td>Ivarin (Generic)</td>
<td>0.771</td>
</tr>
<tr>
<td>Resova (Generic)</td>
<td>0.710</td>
</tr>
<tr>
<td>0.05 M phosphate buffer (pH 6.8)</td>
<td></td>
</tr>
<tr>
<td>Crestor (Innovator)</td>
<td>0.644</td>
</tr>
<tr>
<td>Ivarin (Generic)</td>
<td>0.664</td>
</tr>
<tr>
<td>Resova (Generic)</td>
<td>0.557</td>
</tr>
<tr>
<td>0.05 M citrate buffer (pH 6.6)</td>
<td></td>
</tr>
<tr>
<td>Crestor (Innovator)</td>
<td>0.468</td>
</tr>
<tr>
<td>Ivarin (Generic)</td>
<td>0.509</td>
</tr>
<tr>
<td>Resova (Generic)</td>
<td>0.380</td>
</tr>
</tbody>
</table>

*Diffusion or release exponent given in parentheses.

DISCUSSION

Dissolution profiles of three RST calcium IR tablet formulations were compared and analyzed using drug release kinetic models. At pH 1.2 (0.1 N HCl), the highest $R^2$ value for the innovator brand was observed for the Hixon-Crowell cube root law model ($R^2 = 0.955$), which shows that the dissolution rate was normalized for the decrease in solid surface area as a function of time. Drug is released from the system where there is a change in surface area and diameter of particles or tablets (30). Provided there is no change in shape as the suspended solid dissolves, its surface area decreases to two-thirds power of its weight. Whereas the generic brands showed first order release kinetics with $R^2$ values 0.965 and 0.925 for Ivarin and Resova, respectively. The first order equation describes a system where the release rate is concentration-dependent. The dosage forms containing water soluble drugs in porous matrices follow this profile such that the amount of drug released per unit time diminishes (31).

Korsmeyer et al developed a relationship to describe drug release from a polymeric delivery system to analyze both Fickian and non-Fickian diffusion from swelling and non-swelling (25). The release exponent is indicative of the mechanism of drug transport through the polymer. Crestor, Ivarin, and Resova showed non-swellable matrix Fickian diffusion with release exponents less than 0.5 at pH 1.2.

In 0.05 M phosphate buffer (pH 6.8), all three brands followed a first order release model, with $R^2$ values of 0.901–0.959. In the Korsmeyer-Peppas model, release exponents were less than 0.05, indicating non-swellable matrix Fickian diffusion. Similarly, dissolution in 0.05 M citrate buffer followed first order release kinetics for all three brands, with $R^2$ values of 0.879–0.900 and release exponents less than 0.5.

The FDA guidance for stability testing emphasizes the importance of release kinetics in the determination of a product’s shelf life for both the drug substance and drug products (32). The
FDA guidance for dissolution testing describes the model-dependent approaches and gives step by step procedures to select the appropriate model to fit the dissolution profiles (33). Similarly, ICH guidelines explain the importance of mathematical modeling and explanation of release mechanisms for establishing the stability and shelf life of a product for human use (34).

Mathematical models of drug release kinetics are useful in predicting in vivo dissolution profile of a drug. These models help to determine the exact transport mechanisms involved in the release of drugs. Drug release kinetics is crucial for controlled-release formulations, where the release of drug is controlled by polymer matrix behavior; however, study of drug release kinetics in immediate-release formulations is also important because release of the drug from a tablet matrix not only depends upon the polymer but also on other factors. For example, formulation variables can affect drug release from IR tablets. Formulation geometry (size and shape), processing techniques and manufacturing variables, as well as excipients and additives can influence physical characteristics of the formulation and thus impact drug release. For example, the presence of hydrophobic additives can hinder the infiltration of aqueous medium, whereas insoluble fillers may result in blocking the surface pores of the formulation. Also, binding agents and lubricants used in the tablet can retard the drug release, whereas the plasticizers are known to enhance it. Therefore, studying drug release kinetics in immediate-release formulations is important even if it is going to release the drug in a short time.

Various mathematical models are used to predict the overall drug release behavior and to design drug delivery systems. The zero order kinetic model is used to describe the dissolution of drugs present in modified-release dosage forms, such as transdermal systems, matrix tablets containing poorly water-soluble drugs, coated dosage forms, and osmotic systems. Formulations following this model release the same amount of drug per unit of time. This model is ideal for drug release to have a prolonged pharmacological action (35). In the first order model, the plot between log drug release versus time is linear, so the release of a drug depends on the amount of drug remaining in its matrix. Dosage forms containing water-soluble drugs in porous matrices follow first order kinetics (31).

The Higuchi model explains the dissolution of drugs in semisolid planar dosage forms, such as suspension and ointments as well as other geometric and porous dosage forms. This model is based on the several conditions including: the initial drug concentration in the dosage form matrix is higher than its solubility; there is one-dimensional drug diffusion taking place; the diameter of drug particles is much less than the system thickness; there is negligible matrix swelling; there is constant drug diffusivity; and perfect sink conditions are attained (36).

The Korsmeyer-Peppas model describes the relationship concerning drug release from a polymeric matrix. The release exponent, $n$, is used to characterize the release mechanism. For thin film (slab) geometry, an $n$ value less than 0.5 indicates Fickian diffusion. For other geometries such as cylindrical and spherical, an $n$ value less than or equal to 0.45 denotes a Fickian diffusion mechanism; $n$ more than 0.45 and less than 0.89 corresponds to non-Fickian transport; $n$ equal to 0.89 relates to case II diffusion (relaxational); and $n$ greater than 0.89 denotes super case II transport (37). This model is used for the analysis of drug release from dosage forms where the release mechanism is not fairly known and there could be more than one release phenomena involved.
Finally, the Hixson-Crowell model is used when the regular area of drug particles is proportional to the cubic root of its volume. This model applies to various dosage forms including tablets, where dissolution takes place in planes that are parallel to the surface of drugs. The initial geometrical form of tablets remains constant all the time and the dimensions diminish proportionally. The graph of the cubic root of unreleased drug fraction versus time will be linear, provided that the equilibrium conditions are not achieved (8).

CONCLUSIONS

Drug release kinetics models were used to evaluate and compare the dissolution profiles of three brands of RST calcium IR tablets (one innovator and two generic brands) in three media. All the brands followed first order kinetics in all dissolution media except the innovator brand which followed Hixson-Crowell kinetics in 0.1 N HCl (pH 1.2). This means that in 0.1 N HCl, the change in surface area and diameter of tablets with progressive dissolution of the tablet matrix was a function of time. Dissolution occurred in planes, parallel to the tablet surface, and the initial geometrical form remained constant.

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CONFLICT OF INTEREST

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

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