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Comparative Dissolution Study of Branded and Generic Ritonavir Tablets in the Indian Market as a Quality Control Tool

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ABSTRACT

Introduction: Ritonavir (RIT) is classified as a BCS class IV drug due to its poor solubility and limited permeability. The goal of this study was to utilize a model-independent method to compare the dissolution profiles of branded (B-1) and generic (G1–G5) Ritonavir tablets currently marketed in India. **Methods:** USP apparatus 2 (paddle, 75 rpm) with 0.06 M polyoxyethylene-10 lauryl ether as the dissolution medium (37.0 ± 0.5 °C) provided the optimal conditions for testing. Although the primary focus was the model-independent technique, a concurrent investigation of the model-dependent strategy was used for comparison. Analytical method development with validation was also performed. **Results:** The difference factor (f_1) value, similarity factor (f_2), and percentage of drug release fell within the acceptable range for all products except one (G-4: f_1 18.0, f_2 42.1). When compared with the reference product (B-1), G-5 was the most suitable (f_1 3.4, f_2 74.5) and considered fully interchangeable. **Conclusion:** The validated analytical method is suitable for future industry adoption for routine analytical testing of RIT tablets. The dissolution profiles obtained under these conditions demonstrated capability for comparative assessment.

Keywords: Ritonavir, dissolution, analytical validation, difference factor (f_1), similarity factor (f_2)

INTRODUCTION

The promotion of generic drugs and the implementation of replacements from various sources in health care policies aim to strengthen public health while maintaining long-term cost effectiveness. As a result, cost savings and accessibility facilitate significant improvements in health care delivery systems (*1*). The prevalence of generic medications can be attributed to economic factors. Therefore, it is imperative to conduct in vivo bioequivalence studies to ascertain whether the generic medication and original drug product are therapeutically equivalent. Generic medicines have the same active components as brand-name versions and are chemically indistinguishable. In addition, the inactive ingredients are the same in both type and amount (qualitatively and quantitatively) as the reference listed drug (RLD) (*2*). In recent times,

there has been a notable surge in the use of generic pharmaceuticals, prompting several nations to implement rules aimed at ensuring the provision of secure, efficient, and high-quality medications (*3*–*5*). The Biopharmaceutics Classification System (BCS) has shown significant advantages in several areas of drug discovery, drug product development, and regulatory sciences (6–9). BCS categorizes pharmaceuticals according to their aqueous solubility, intestinal permeability, and dissolution, all of which impact the absorption of active pharmaceutical ingredients (APIs) in immediate-release solid oral formulations (*7*–*10*).

Ritonavir (RIT), which was originally designed to inhibit proteases, functions primarily to enhance the efficacy of other protease inhibitors. It effectively inhibits the process of HIV-1 replication (*11*–*13*). Formerly designated ABT-538, RIT functions as an inhibitor of HIV-1 protease, an enzyme that is indispensable for the viral life cycle to reach its culmination (*14*–*16*). The Gag and Gag-Pol polyproteins are cleaved by the protease into viral enzymes and core proteins (*15*–*17*). Mutagenesis-induced inactivation of protease and drug-induced inhibition both lead to the generation of noninfectious particles (*18*–*21*). Ritonavir is classified as a BCS class IV drug due to its poor solubility and limited permeability (*20*–*23*).

A literature review revealed that several analytical techniques have been used for the evaluation of RIT bulk drugs and combination drug products, both for qualitative and quantitative analysis. Mantripragada et al. reported the estimation of impurity levels in combination products using the RP-HPLC method (*24*). Hiremath et al. studied the stability-indicating method in a combination product of RIT and lopinavir, and Patil et al. reported the use of stability-indicating assays is essential for distinguishing ritonavir from its degradation products (*25*, *26*). Pham et al. reported a study of lopinavir/RIT nanoparticles (*27*). Xu et al. conducted research on in vitro characterization of RIT (*28*). However, there is no existing research that compares the drug release profile of RIT alone, in either tablets or capsules, or in combination with other drug products.

There are three distinct analytical approaches that can be employed for in vitro drug release studies: analysis of variance (ANOVA), model-dependent, and model-independent. Drug release data may be assessed either in their original format or using fundamental ANOVA-based techniques, which are excellent for analyzing variation in both the level and shape of profiles (*29*). Model-dependent approaches, including zero and first-order, Hixson-Crowell, Higuchi, quadratic, Weibull, Gompertz, and logistic methods, are used to determine the mathematical equations that describe the release pattern of a pharmaceutical dosage form, taking into account its unique qualities. These frameworks facilitate the straightforward understanding of quantitative data and are frequently used throughout the formulation development process (*30*–*42*).

This study aimed to analyze and compare the drug release profiles of one branded (B-1) and five generic (G1–G5) RIT tablets (100 mg) supplied in India. This was accomplished by analyzing the in vitro dissolution profiles according to the guidelines laid forth in the United States Pharmacopeia (USP) monograph for RIT tablets (*43*).

METHODS

Chemicals and Reagents

Methanol, monobasic potassium phosphate, acetonitrile and phosphoric acid were high-performance liquid chromatography (HPLC) quality and obtained from Merck. Polyoxyethylene

10 lauryl ether (POE10LE) was of analytical grade and obtained from Sigma Aldrich. The water used for the preparation of buffers and other solutions originated from the Milli-Q system. RIT tablets were acquired from a local Indian market.

Standard Preparation

A stock standard concentration of 1110 µg/mL was achieved by weighing and dissolving 111 mg of the RIT working standard in 100 mL of a volumetric flask using 30% methanol followed by dissolution medium (0.06 M POE10LE) to mark the volume. To create the final working standard solution, which was 111 µg/mL, the same solution was further diluted with dissolution medium and mixed well.

Analytical Methodology

An ultraviolet (UV) detector coupled with HPLC technique was chosen for the analytical procedure (Prominence-I, Shimadzu, Japan). The preliminary method development was conducted using a trial-and-error approach, involving the injection of blank, standard, and sample solutions for peak detection, as well as assessing any interference from the placebo at the peak of interest, with various trials on solvent, flow rate, and column. The reversed phase chromatographic conditions employed a Waters Symmetry C18 column (150 x 4.6 mm, 5 µm) as the stationary phase, utilizing composition of methanol and buffer (4.1 g/L monobasic potassium phosphate) in a 45:55 (% v/v) ratio as mobile phase, adjusted to pH 4.0 with phosphoric acid, at a flow rate of 1.5 mL/min in isocratic separation mode. The chromatogram was generated using a 25-µL injection volume and monitored at 215 nm, and the column oven was maintained at 40 °C.

Analytical Method Validation

The developed reversed phase HPLC technology has been validated in accordance with ICH recommendations Q2(R1) for several criteria, including specificity, linearity, solution stability, precision and accuracy (*44*).

System suitability was assessed by injecting five replicates of the RIT standard solution (111 µg/mL) to evaluate chromatographic parameters, including peak area repeatability (%RSD), peak symmetry, and column efficiency, with a %RSD threshold of less than 2%.

The method's specificity was measured by evaluating its ability to precisely quantify RIT, ensuring that interference from dissolution media and placebo remained below 2% from a 100% sample concentration.

Linearity was established by preparing series of standard solutions within the concentration range of 11.1–200 µg/mL, corresponding to 10–175% of the sample concentration.

Method precision was studied by conducting the dissolution test with six replicates and further confirmed by performing the dissolution test on a different day by a different analyst using a different column and alternate HPLC system. Recovery was studied with the standard addition method at three concentration levels (50%, 100%, and 150%) in triplicate, yielding acceptable values between 95% and 105%.

The compatibility of the filter was studied to evaluate the percent drug release of standard and sample solutions in comparison to a control solution (centrifuged), ensuring minimal drug

absorption through various filters.

The stability of RIT solutions was examined at room temperature by analyzing freshly prepared solutions and monitoring them till 24 hours.

Dissolution Test Procedure

The percentage dissolution of each generic version and brand of RIT tablet was determined through a dissolution test utilizing a USP paddle dissolution apparatus (EDT 08Lx, Electrolab, Country). Prior to study initiation, the dissolution apparatus was calibrated successfully, and all physical parameters were meeting the acceptance criteria. The experiment was conducted in accordance with the guidelines outlined in the USP, with 900 mL of 0.06 M POE10LE as the dissolution medium at 75 rpm (*43*). Six tablets from each brand were used to perform the drug release study. The samples were withdrawn at 15, 30, 45, 60, 90, and 120 min and replaced with an equal volume of dissolution medium to ensure that sink conditions were maintained throughout the experiment. The samples underwent filtration through a 0.45-µm syringe filter (polyvinylidene fluoride [PVDF]) by first discarding 2 mL of filtrate, then analyzing using HPLC instrument equipped with UV detector (Prominence-I, Shimadzu).

The dissolution profile of RIT was studied utilizing a model-independent approach that incorporates fit factors: the similarity factor (f_2) and difference factor (f_1) (*34–36*, *41*, *42*). Comparable dissolution profiles must have f_1 values between 0 and 15 and f_2 values between 50 and 100.

A model-dependent approach was also used to analyze the drug release data across the different brands, i.e., calculation of the dissolution constant (k) and coefficient of determination (r^2) for the zero-order, first-order, Higuchi, and Hixson-Crowell models. The Weibull model was used to determine the curve shape factor (β), its r^2 value, and the td parameter, which represents the time required for 63.2% drug transfer to the systemic circulation.

RESULTS AND DISCUSSION

Optimization of Analytical Methodology

Chromatographic conditions have been optimized by an approach involving trial and error. Initial composition of 50 mM monobasic potassium phosphate buffer with acetonitrile in different ratios (70:30, 50:50, 30:70, v/v) using USP L1 column (150 x 4.6 mm, 5 µm and 250 x 4.6 mm, 5 µm) showed poor peak of symmetry for peak of interest. This composition also caused high column back pressure due to precipitation of mobile mixture composition while increasing ratio of acetonitrile. To counter such issues, acetonitrile was replaced with methanol to continue trials using a different mobile phase composition and USP L1 column. The 30 mM monobasic potassium phosphate buffer with methanol in equal ratio (50:50, v/v) using Zorbax SB C18 (150 x 4.6 mm, 5 µm) showed improved peak response and symmetry but ended with interference of placebo at peak of interest. Subsequent investigations explored multiple mobile phase compositions and alternative column types, finally ended up with mobile phase composition of methanol and buffer (4.1 g/L monobasic potassium phosphate) in a ratio of 45:55 (v/v) adjusted to pH 4.0 with phosphoric acid and Waters Symmetry C18 column (150 x 4.6 mm, 5 µm) showed proper peak shape and symmetry with no interference from dissolution medium and placebo. The optimal

chromatographic conditions were established at a flow rate of 1.5 mL/min, injection volume of 25 µL, and column temperature of 40 °C. These conditions provided stable and reproducible performance for the analysis. The analyte peak was eluted in time span of 18 minutes with retention time of about 10.0 min for RIT.

HPLC Method Validation

The HPLC method validation results are summarized as below, offering an overview of the established parameters and their compliance with validation criteria.

System Suitability

System suitability was established using five replicate of standard solution samples with 1.2% relative standard deviation (RSD) for RIT. The USP chromatographic parameters were within the acceptance criteria, with an average retention time of 9.95 min for RIT.

Specificity

The method was specific as the blank, placebo preparation, and standard solution demonstrated no interference from the dissolution media and excipients at the peak of interest.

Linearity

A linear correlation was determined between the mean peak area and the concentration of RIT within the range of 11.1–200 µg/mL. The calibration curve was obtained by plotting the mean peak area vs the relevant drug concentration (µg/mL), resulting in a correlation coefficient (R^2) of 0.9991, suggesting excellent linearity. The calibration curve's y-intercept at 100% linearity level was 1460.9, within the acceptable limit of ±2%.

Recovery

Recovery was conducted within a range of 50–150% at drug concentration for RIT of 55.5–166.5 µg/mL). The recovery values were 98.77–98.97%, which is within the anticipated range of 95–105%. The relative error was under 2.0% at each level.

Precision

The RSD values of precision and intermediate precision of the developed HPLC method must be less than 2.0%, and absolute difference between both should not more than 3.0%. The RSD of six replicates of RIT was 1.13% and 1.30% for both tests, which was within the specification level.

Filter Compatibility

Filter compatibility was performed by comparing the percentage of drug release from sample solutions (filtered through different syringe filters) to a centrifuged control. Both the 0.45-µm and 0.22-µm PVDF syringe filters demonstrated negligible drug adsorption, as resulted by an absolute percentage drug release variation of less than 1.5%, and the 0.45-µm nylon filter (SY25NN) showed a difference beyond 2% relative to the control. Thus, the 0.45-µm PVDF syringe filter was selected and used for all sample solution filtration throughout the study.

Solution Stability

The stability of the solution was confirmed with an absolute area percentage difference of 0.9%

and 0.6% after 24 hours for RIT standard and sample solutions, respectively, showing ambient stability.

Comparative Dissolution Study

In accordance with the dissolution test for RIT tablets as specified in the *USP* and U.S. Food and Drug Administration's dissolution database, 900 mL of 0.06 M POE10LE and USP apparatus 2 (paddle) were selected for the drug release study, considering 75% (Q) of drug should dissolve within 120 minutes. The average percentage drug release data are shown in Table 1. Figure 1 shows the different dissolution profiles, indicating that each brand meets the acceptable standards for drug release.

Product G-4 had the slowest release rate, although it was within the acceptable limit of 75% (Q), compared to other generic products and the reference drug (B-1). Moreover, product G-5 demonstrated superior performance compared to the other brands, with an f_1 value of 3.4 and an f_2 value of 74.5, relative to B-1, rendering G-5 the most suitable generic product.

Except for G-4, every drug product's f_1 and f_2 values were inside the permissible range (Table 2). Compared to B-1, G-4 had f_1 and f_2 values of 18.0 and 42.1, respectively, which fall short of the acceptance criteria. These data demonstrate that except for the G-4 brand, all other generic products can be interchangeable with the reference drug product.

A model-dependent approach was essential for thoroughly analyzing the drug release data across all the different brands tested. The kinetic modeling data are presented in Table 3.

Table 1. Mean (± SD) Percentage Drug Release of Branded (B-1) and Generic (G1–G5) Ritonavir Tablets

Time (min)	B-1	G-1	G-2	G-3	G-4	G-5
15	36.0 ± 2.1	29.9 ± 3.4	27.4 ± 2.3	35.1 ± 2.6	27.7 ± 4.5	37.3 ± 3.7
30	53.8 ± 2.7	49.2 ± 3.4	47.0 ± 4.1	51.3 ± 3.5	43.9 ± 7.8	52.2 ± 5.2
45	76.8 ± 2.1	68.8 ± 2.3	67.6 ± 2.5	71.8 ± 3.1	54.1 ± 5.5	72.3 ± 4.1
60	84.0 ± 1.6	80.6 ± 2.0	78.8 ± 2.3	80.2 ± 2.0	67.4 ± 4.9	82.9 ± 2.8
90	96.0 ± 1.3	91.2 ± 1.6	88.4 ± 1.9	89.1 ± 2.8	81.7 ± 3.6	90.6 ± 2.0
120	100.0 ± 0.9	97.3 ± 1.6	96.7 ± 1.2	97.1 ± 1.5	91.3 ± 2.7	98.6 ± 2.1

Table 2. Fit Factors of Branded (B-1) and Generic (G1–G5) Ritonavir Tablets

Comparison	Difference Factor (f_1)	Similarity Factor (f_2)
B-1 vs G-1	6.6	63.7
B-1 vs G-2	9.1	57.3
B-1 vs G-3	4.9	68.3
B-1 vs G-4	18.0	42.1
B-1 vs G-5	3.4	74.5

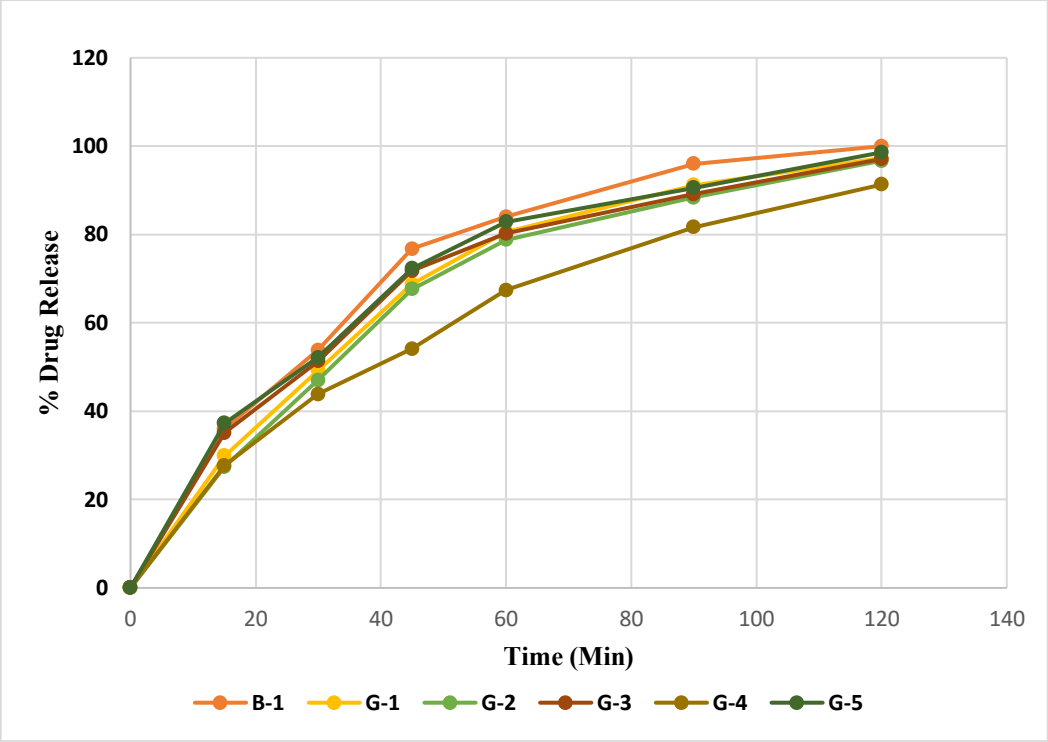

Figure 1. Comparative dissolution study of branded (B-1) and generic (G1–G5) ritonavir tablets.

Table 3. Summary of Dissolution Model Characteristics and Statistical Fit

Model	Statistics	B-1	G-1	G-2	G-3	G-4	G-5
Zero Order	r^2	0.0739	0.3757	0.4624	0.0978	0.6017	0.0326
	k_0	1.070	1.017	0.997	1.018	0.907	1.037
	AIC	49.8108	47.8694	47.1444	48.9434	44.1790	49.3561
First Order	r^2	0.9829	0.9904	0.9883	0.9902	0.9921	0.9858
	k_1	25.8499	22.8448	24.1873	21.8220	20.6762	24.0336
	AIC	0.030	0.025	0.024	0.027	0.019	0.028
Hixon-Crowell	r^2	0.9877	0.9929	0.9891	0.9653	0.9732	0.9666
	k_{HC}	0.008	0.007	0.007	0.007	0.005	0.008
	AIC	23.8627	21.0070	23.7550	29.4008	27.9836	29.1580
Higuchi	r^2	0.9237	0.9473	0.9454	0.9416	0.9851	0.9371
	k_H	10.017	9.451	9.237	9.524	8.355	9.714
	AIC	34.8307	33.0410	33.4220	32.5137	24.4475	32.9575
Weibull	r^2	0.9934	0.9977	0.9955	0.9917	0.9982	0.9909
	t_d	35.532	40.491	42.212	38.461	55.089	37.390
	β	1.785	1.298	1.142	1.165	1.375	1.436

B-1: reference product, G1–G5: generic drug products; AIC: Akaike information criterion.

CONCLUSION

The validated analytical method is suitable for future industry adoption for routine analytical testing of RIT tablets. The dissolution profiles obtained under these conditions demonstrated capability for comparative assessment. All RIT tablet brands met the acceptability requirements for the release rate at the final time point of 120 min, as specified by the USP. The f_1 and f_2 values were within the acceptable criteria, with the exception of one brand (G-4).

DISCLOSURES

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