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Comparative Dissolution Study of Enzalutamide Capsules in India

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ABSTRACT

Introduction: The objective was to conduct a comparative dissolution study of several brands of enzalutamide capsules available in the Indian market using a model-independent approach. Enzalutamide is classified as a Biopharmaceutical Classification System class 2 medicine due to its limited solubility in water and high ability to pass through the intestines. **Methods:** A United States Pharmacopeia apparatus 2 (paddle) was used with 0.3% cetyl trimethyl ammonium bromide (CTAB) in 0.1 N HCl as dissolution medium at 37.0 ± 0.5 °C and 50 rpm to provide the most favorable conditions for testing. Four generic brands of enzalutamide capsules were compared to the reference brand product. Because the focus was mostly on the model-independent technique, a concurrent study of the model-dependent strategy was conducted for comparison. **Results:** The Weibull model provided the most optimal fit for all brands. For every brand, the difference factor (f_1) and cumulative drug release were within the acceptable range. However, generic brand 2 failed to meet the acceptance criteria for the similarity factor (f_2) and difference in dissolution efficiency. Generic brand 4 was the most similar to the reference product based on the model-independent approach. **Conclusion:** Three out of four generic products were found to be interchangeable with the reference product, and generic product 4 is the preferred generic substitution for ENZ capsules in India.

Keywords: Enzalutamide capsule, comparative dissolution, difference Factor (f_1), similarity factor (f_2), dissolution efficiency (DE)

INTRODUCTION

Enzalutamide (ENZ) is primarily used to treat metastatic castration-resistant prostate cancer (mCRPC) in adults. The chemical name of ENZ is 4-{3-[4-cyano-3-(trifluoromethyl) phenyl]-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl}-2-fluoro-N-methylbenzamide. ENZ is an androgen receptor inhibitor that targets steps in the androgen receptor signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors, inhibit activated androgen receptor nuclear translocation, and inhibit activated androgen receptor association with DNA. ENZ works by blocking the androgen receptor, a protein found in prostate cells that is activated by androgens (male sex hormones like testosterone). Androgens

can stimulate the growth of prostate cancer cells. ENZ inhibits the binding of androgens to the androgen receptor and prevents the receptor from moving into the cell nucleus, ultimately suppressing the growth of prostate cancer cells. ENZ is a Biopharmaceutics Classification System (BCS) class 2 drug, having low aqueous solubility and high intestinal permeability (*1–6*).

Encouragement of generic medications and substitution from many sources into the healthcare system aims to maximize population health while keeping costs low. As a result, the overall healthcare delivery system may improve. When a generic duplicate of a reference drug contains identical levels of the same active component, a generic replacement may be considered if it is the same dose formulation and route of administration and if it meets standards for strength, purity, quality, and identity (*1–3*). However, recent publications have indicated that marketed medications containing the same amount of active component exhibit considerable variances in therapeutic results. There have been reports of generic products that are not interchangeable with the reference brand and/or with each other (*4–7*).

The BCS has proven to be quite beneficial in a variety of sectors of drug research, product development, and drug product regulatory sciences. It categorizes medications according to their dissolution, water solubility, and intestinal permeability, all of which affect the absorption of active pharmaceutical ingredients (API) from immediate-release solid oral formulations (*1–12*).

Various analytical methods have been reported for qualitative or quantitative estimation of ENZ bulk drug and drug product. Benoist et al. reported a bioanalytical method to quantitate ENZ in human plasma (*13*). Prajapati et al. studied stability in bulk and a synthetic mixture (*14*). Guo et al. studied in vitro and in vivo characteristics of ENZ nanocrystals, and Taraka et al. studied ENZ nanoparticles (*15*, *16*). There are no comparative dissolution studies of ENZ in either dosage forms, tablets or capsules. The current study aims to evaluate and compare the in vitro dissolution profiles of different generic brands of ENZ capsules available in the Indian market.

A comparative drug release study of various brands of ENZ establishes the maximum medication solubility and penetration into body fluids, indicating bioavailability. For an in vitro drug release study, three different statistical approaches can be used: (A) analysis of variance (ANOVA), (B) model-dependent, and (C) model-independent. Drug release data can be evaluated in its raw form or through basic ANOVA-based methods, which is a handy approach for detecting changes in level and shape amongst dissolution profiles. Model-dependent methods such as zero and first-order, Hixson-Crowell, Higuchi, quadratic, Weibull, Gompertz, and logistic investigate the mathematical equations that determine the dissolution profile as a function of certain characteristics of the pharmacological dosage form. These frameworks make quantitative data interpretation simple. These techniques are always used in the formulation development phase (*12, 17–19*).

Model-independent approaches yield a single value from a drug release study, allowing for direct comparison of data with a reference formulation. The fit factors, namely the difference and similarity factor (f_1 and f_2, respectively) demonstrate the difference and similarity between reference and generic drugs by comparing the drug release profile. Similar drug release profiles have f_1 values of 0–15 and f_2 values of 50–100 (*13*, *15*, *20*).

METHODS

High-performance liquid chromatography (HPLC)-grade methanol, acetonitrile, trifluoroacetic acid (TFA), and phosphoric acid were obtained from Merck. Cetyl trimethyl ammonium bromide (CTAB) and hydrochloric acid (HCl) were of analytical grade. Water used to prepare buffers and other solutions was made from Milli-Q.

ENZ capsules were purchased from the local Indian market, including one branded product (B-1 [reference]) and four generic brand products (G1–G4). The study was conducted with 2 months of the expiration date for each product.

Procedure

Dissolution tests were performed to measure percentage of drug release from each brand of ENZ capsules using a United States Pharmacopeia (USP) type 2 dissolution apparatus (paddle) with sinkers. The apparatus was calibrated according to the USP performance verification test using Prednisone Tablets USP 10 mg, and all physical parameters were within the acceptance limit. The dissolution medium was 900 mL of 0.3% CTAB in 0.1 N HCl (*21*). The spinning rate was set at 50 rpm. The experiment was conducted using an Electrolab dissolution apparatus (EDT 08Lx) fitted with an autosampler. Six capsules of each brand were analyzed. Samples (10 mL) were collected at specified time intervals at a distance not less than 1 cm from the wall of vessel and top of paddle and were replenished with same volume of dissolution medium to maintain sink conditions. Samples were filtered through 0.45-µm polytetrafluoroethylene (PTFE) syringe filter and analyzed using HPLC coupled with an ultraviolet (UV) detector.

The dissolution profiles of ENZ capsules were compared using a model-independent method (f_1 and f_2). The factor f_1 is proportional to the average difference between the two profiles, and factor f_2 is inversely proportional to the average squared difference between the two profiles, with emphasis on the larger difference among all sampling time points. To assure consistency in product performance, regulators are particularly interested in how comparable the two curves are when comparing dissolution profiles. Thus, regulatory agencies are more focused on the similarity factor, f_2.

RESULT AND DISCUSSION

Dissolution is defined as the amount of substance that goes into solution per unit time under conditions of liquid/solid interface, solvent composition, and temperature. It can be used as a tool to offer detailed information about the biological activity of a drug product as well as batch to batch consistency.

The dissolution test for ENZ capsules is not officially mentioned in *USP 45–NF 40*. According to the U.S. Food and Drug Administration (FDA) dissolution database, 900 mL of 0.3% CTAB in 0.1 N HCl and USP apparatus 2 with sinkers was chosen for this drug release study, considering that 75% (Q + 5%) of drug should be dissolved in 30 minutes (*21*). Dissolution test results are shown in Table 1 and Figure 1. All ENZ brands met the acceptance criteria. A detailed study on the development and validation of ENZ capsule dissolution would be a subject for a separate study.

Table 1. Dissolution Data for Enzalutamide Capsules

Brand	Mean Drug Release, %		RSD, %		Minimum		Maximum	
	30 min	45 min	30 min	45 min	30 min	45 min	30 min	45 min
B-1	92.8	99.9	1.8	1.1	91.2	98.7	95.3	101.2
G1	91.5	97.7	4.4	1.8	86.9	95.6	96.7	100.1
G2	85.2	94.0	2.7	1.5	82.3	92.3	87.8	96.4
G3	87.5	95.6	2.4	2.2	85.0	93.8	91.2	99.8
G4	88.5	97.2	2.3	1.0	85.3	95.7	91.0	98.1

B-1: reference product; G1–G4): generic drug products 1–4; RSD: relative standard deviation.

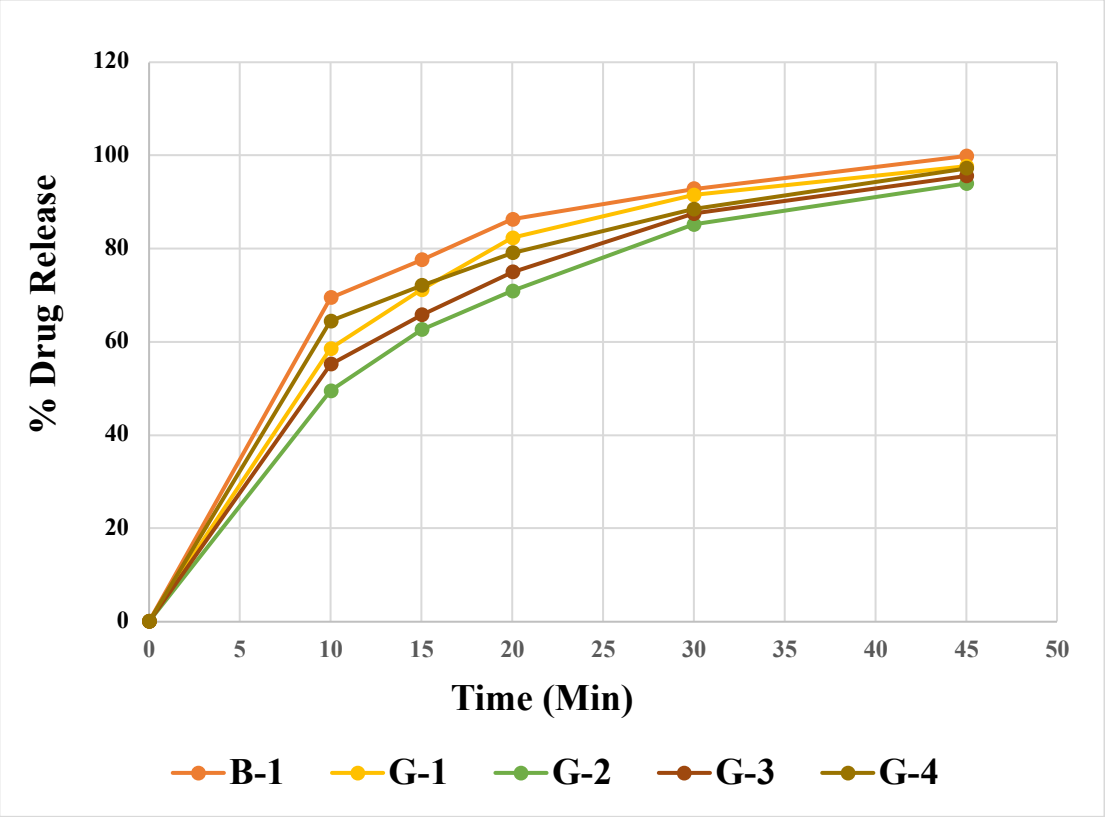

Figure 1. Comparative drug release profile of different brand of enzalutamide capsules. B-1: reference product; G1–G4: generic drug products 1–4.

The results of the model-dependent approach are shown in Table 2, including dissolution constant (k) and coefficient of determination (r^2) for zero and first order, Higuchi, and Hixon Crowell models, and curve shape factor (β), r^2, and td (the time necessary to transfer 63.2% of the administered drug into the systemic circulation) for the Weibull model. Having the lowest AIC and highest r^2 values (> 0.99), the Weibull model produced the best fit for dissolution profile for brands that were tested, though the β values had notable differences. The model-dependent approach data were elaborated for supportive study purposes only.

Table 2. Characteristics of Mathematical Models and Descriptive Statistics for Dissolution Data

Model	Statistics	B-1	G1	G2	G3	G4
Zero Order	r^2	-6.8586	-2.3720	-0.6290	-1.4537	-4.3903
	k_0	2.977	2.861	2.641	2.730	2.832
	AIC	44.1172	42.5452	40.1066	41.2894	42.9681
First Order	r^2	0.9415	0.9967	0.9944	0.9836	0.8950
	k_1	0.106	0.085	0.065	0.073	0.087
	AIC	19.6156	7.8744	11.7634	16.2639	23.2768
Hixon-Crowell	r^2	0.7758	0.9414	0.9332	0.8985	0.6875
	k_{HC}	0.028	0.023	0.018	0.020	0.023
	AIC	26.3340	22.2827	24.1350	25.3608	28.7287
Higuchi	r^2	-0.1652	0.6587	0.9275	0.8336	0.3560
	k_H	17.373	16.547	15.111	15.711	16.448
	AIC	34.5735	31.0931	24.5426	27.8354	32.3450
Weibull	r^2	0.9929	0.9982	0.9990	0.9997	0.9992
	AIC	13.0517	8.8276	7.2534	-0.5322	3.0460
	β	1.984	1.076	1.150	1.412	2.160

r^2: coefficient of determination; k: dissolution constant; β: curve shape factor; AIC: Akaike information criterion; B-1: reference product; G1–G4: generic drug products 1–4.

This study mainly focused on dissolution comparison using fit factors for quantitative comparison of drug release profiles of different brands to establish interchangeability (model-independent approach). For any degree of interchangeability with the reference product, all generic brands must have similarity factors between 50 and 100 and difference factors below 15. Also, dissolution efficiency (DE) should be within a 10% limit. Generic brand 2 had an f_1 value of 15, an f_2 value of 43, and thus was not considered interchangeable with the reference brand based on the f_2 value (Table 3). Generic brand 2 also exceeded the 10% limit for DE (Table 4). The other three generic brands were considered interchangeable with the reference based on f_1 and f_2 values and DE. Generic brand 4 was the most similar to reference product, having the highest similarity score (f_2 = 64) and smallest difference in DE (4.29%).

Table 3. Fit Factor Analysis of Enzalutamide Capsules

Brand	f_1	f_2
B-1 vs G1	6	61
B-1 vs G2	15	43
B-1 vs G3	11	50
B-1 vs G4	6	64

f_1: difference factor (acceptable: 0–15); f_2: similarity factor (acceptable: 50–100); B-1: reference product; G1–G4: generic drug products 1–4.

Table 4. Dissolution Efficiency (DE) for Enzalutamide Capsules

Brand	DE, %	Difference in DE	95% CI
B-1	77.02	Reference	9
G1	73.09	3.93	12
G2	66.36	10.66	14
G3	69.25	7.77	13
G4	72.73	4.29	9

CI: confidence interval; B-1: reference product; G1–G4: generic drug products 1–4.

CONCLUSION

A comparative dissolution study of different brands of ENZ capsules available in India was performed using fit factors. The Weibull model provided the optimal fit for all brands. The percentage of drug release and f_1 values were within the acceptance criteria for all brands; however, generic product 2 was not considered interchangeable with the reference product based on having an f_2 value below 50 and a difference in DE above 10%. Generic product 4 is the most similar to the reference product, making it the more preferred generic substitution for ENZ capsules.

DISCLOSURES

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