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Pharmaceutical Equivalence of Some Conventional Carbamazepine Tablets Marketed in Sudan

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ABSTRACT

Background: Carbamazepine (CBZ) is commonly used in the treatment and control of epilepsy, seizures, and neuropathic pain. Due to its limited water solubility, CBZ have slow and variable absorption following oral administration. Effective CBZ plasma levels are achieved through multiple-dose administration of conventional CBZ tablets which may result in serious side effects because of its narrow therapeutic index and toxicity levels. Objectives: This work aimed at comparing four commercial brands of CBZ tablets (A, B, C and D) manufactured by multinational and national companies including the originator (A) through evaluation of their pharmaceutical equivalence using pharmacoepial and nonpharmacoepial standard tests. **Methods:** Model-independent approach was used for determination of dissolution efficiency (%D.E) and fit factors. Difference between brands was demonstrated through analysis of difference (f_1) and similarity (f_2) data. In addition, various quality tests including weight variation, thickness, diameter, hardness, friability and disintegration time were carried out. **Results:** The study revealed that all brands complied with the USP specifications regarding weight variation, friability disintegration and drug content. The amount of drug released within 45 minutes were found satisfactory and ranged from 83.44% to 94.5%. Although clear differences in release profiles exist, all brands released about 90% of the labeled CBZ within 30 minutes, which can satisfy the patient need. Only brand B failed to pass the nonpharmacoepial hardness test. **Conclusion:** Although all selected brands complied with pharmacoepial quality specifications, only brands C and D could be used interchangeably with the originator brand (A) based on the dissolution profile (f_2).

KEYWORDS *Carbamazepine, Narrow therapeutic index, Dissolution, Brands*

1. INTRODUCTION

In recent years, the number of generic products of essential prescription medicines has increased significantly. Generic products and their usage are generally promoted in many countries. The importance of assessing bioequivalence between generic products of the same drug has been long recognized [1-5]. For conventional immediate-release tablets, *in vitro* dissolution test is often used for prediction of *in vivo* performance. As generic products are approved via comparison against the reference only, switching from one generic product to another might lead to complications such as therapeutic failures and /or adverse drug reactions that are life threatening or may result in persistent or significant disability. Such complications are more encountered in narrow therapeutic index (NTI) drugs generics due to the potential differences between two generic products than between any single generic product and the reference. According to the Bio pharmaceutics Classification System (BCS), class II (low solubility and high permeability) drugs such as carbamazepine, phenytoin and warfarin have a strong correlation between the *in vitro* rate or extent of drug dissolution and *in vivo* performance, i.e. the bioavailability [6-7]. For class II drugs, dissolution often considered as rate-limiting step for absorption from the gastrointestinal tract (GIT) [7,8]. Based on the FDA definition of bioequivalence [9], generic approval generally ensures that all approved products are similar in safety and effectiveness, as in clinical practice the bioavailability range for most drugs is wider than 80-125% of the mean value. For narrow therapeutic index (NTI) drugs, minimal change in drug systemic absorption can lead to marked changes in pharmacodynamics response. Therefore, generic equivalence of NTI drugs represents a serious concern [10]. In particular, such concerns have focused on special drug groups such as, anti-arrhythmic (Lithium), anticoagulants (Warfarin) and neurologic (CBZ) for which dose titration and patient monitoring are required to ensure both safety and effectiveness [11,12].

Economic reason accounts for the widespread use of more affordable generic medicines. Except for class I BCS drugs (highly soluble and highly permeable), *in vivo* bioequivalence studies are necessary to ensure the therapeutic equivalence of the generic medicines compared to the original drug product. Mainly the quality of excipients and manufacturing practices are the determinants of drug release of generic products compared to the reference product at predefined conditions. Adequate release profiles of generic drugs promotes interchangeability of such products at a lower cost with the same pharmacological effect [13]. Dissolution test is one of the official pharmacoepial test during drug development and as quality control test for finished products. *In vitro* dissolution profiles generally evaluated through: (i) analysis of variance, (ii) model dependent approaches, (iii) model-independent approaches [14].

Carbamazepine (CBZ) is a widely used antiepileptic drug. It is used for the control of grand mal seizures as well as in the treatment of neuralgia. According to BCS, Carbamazepine belongs to class II (low solubility/ high permeability). Its absorption through GIT might be limited by the dissolution rate [15]. In clinics, single daily dose of conventional tablets of CBZ is insufficient, effective CBZ plasma levels can be achieved by multiple administration. Due to the narrow therapeutic index for CBZ (from 5 to 12 µg/ml) multiple dosing may cause inconsistent plasma CBZ levels leading to serious side effects when toxic levels reached. Previous studies showed significant differences in dissolution profiles of CBZ commercial brands [16], as well as loss of seizure

control upon products exchange [17]. Break through seizures were reported after generic substitution of CBZ [18]. This work was conducted to compare four commercial brands of CBZ tablets marketed in Sudan and manufactured by different multinational and national companies. The present study aimed at comparing the dissolution profile of four commercial brands of CBZ tablets on the basis of their *in vitro* dissolution characteristics using the dissolution conditions in the USP. In addition, tablets hardness, friability and disintegration were conducted as important tests often employed for the analysis of an immediate release solid dosage forms, they have direct/ indirect impact on dissolution profile of the drug products [19].

2. MATERIALS AND METHODS

2.1 MATERIALS

CBZ powder was kindly gifted by General Medicine Company (GMC) (Khartoum, Sudan). Sodium Lauryl Sulphate (SLS) 1% and methanol were obtained from SDFCL (India). CBZ Brands used were purchased from pharmacies located at Wadmedani city and randomly coded as B, C and D against Tegretol® as a reference, which coded as A. Analysis was performed before the product expiration dates, which were similar among brands.

2.2 METHODS

2.2.1 *In vitro* dissolution studies

2.2.1.1 Calibration curve construction

CBZ standard stock solution was prepared by dissolving accurately weighed 10 mg CBZ in 10 ml methanol, then the volume was made up to the mark in 100 ml volumetric flask with distilled water to obtain final concentration of 100 µg/ml CBZ stock solution from which 2.5 ml was added to 25 ml volumetric flask and completed to the mark with distilled water. Then concentrations of 1, 3, 5, 7 and 9 µg/ml of CBZ was prepared using serial dilution and the UV absorbance at λ_{max} of each solution was recorded in triplicate using 7315 UV/VIS spectrophotometer, (Jenway®, England). For determination of λ_{max} for CBZ, stock solution was further diluted with distilled water to obtain the concentration of 10µg/ml and scanned at UV range of 200 - 450 nm in 1.0 cm quartz cell against methanol-distilled water as a blank using 7315 UV/VIS spectrophotometer, (Jenway®, England).

2.2.1.2 Validation of the analytical method for CBZ determination

Validation of the UV method was performed according to the bioanalytical method validation guidelines (2015) recommended by European Medicine Agency. Analysis was conducted in three consecutive days and all the experiments were carried out in triplicates. All the results were expressed as a mean ± SD.

2.2.1.3 Apparatus and procedure

All dissolution studies were performed according to (USP 38 – NF 33) using USP apparatus II RC-6 Dissolution tester manual-sampling dissolution bath (Gouming®, China). The dissolution of carbamazepine tablets was performed at 75 ± 1 rpm in 900 ml water containing 1% Sodium Lauryl Sulfate solution at pH 6.6 adjusted using

pH-meter (Jenway®, England). The dissolution medium was maintained at 37 ± 0.5°C. In all experiments, 10 ml sample was withdrawn at 5, 10, 15, 30, 45 and 60 min and replaced with an equal volume of the dissolution medium to maintain sink conditions. Samples were filtered through 0.45µm membrane filter and assayed by measuring absorbance at 230 nm using 7315 UV–VIS spectrophotometer (Jenway®, England). Six tablets of each brand were studied to obtain statistically significant results (20).

2.2.2 Model-dependent approach

In vitro drug release data were fitted to four release kinetic models including; zero-order, first-order, Higuchi square law and Korsmeyer- Peppas model employing the following set of equations in order to verify the release kinetics of carbamazepine as various qualitative and quantitative changes in a formulation altered drug release and *in vivo* performance (14):

Zero-order model $M_0 - M_t = K_0 t$

First-order model $\text{Ln}\ (M_0/M_t) = K_1 t$

Higuchi model $M_t = K_h \sqrt{t}$

Hixson–Crowell cube root model $(W_0)^{1/3} - (W_t)^{1/3} = K_{1/3} t$

Weibull model $m = 1 - exp^{\frac{[-(t-Ti)]^{\beta}}{\alpha}}$

Korsemeyer–Peppas model $M_t/M_\infty = K_{kp}{}^{n}\, t$

Where M_0, M_t, and M_∞ correspond to the drug amount taken at time equal to zero, dissolved at a particular time, t, and at infinite time, respectively. Various other terms; k_0, k_1, K_h and K_{kp} refer to the release kinetic constants obtained from the linear curves of zero-order, first-order, Higuchi and Korsemeyer–Peppas model, respectively.

2.2.3 Model-independent approach

2.2.3.1 Dissolution efficiency (%D.E)

Dissolution efficiency (% D.E) is the area under the dissolution curve within a time range (t_1 - t_2) expressed as a percentage of the dissolution curve at maximum dissolution, over the same time frame (21). This was calculated from the following equation.

$$(\%\text{D.E}) = \frac{\int_{t1}^{t2} Y.dt}{Y100.(t1-t2)} \times 100\%$$

Where y is the percentage of dissolved product. D.E. is then the area under the dissolution curve between time points t_1 and t_2 expressed as a percentage of the curve at maximum dissolution, y100, over the same time period.

2.2.3.2 Fit factors

Fit factors, namely, the difference factor *f1*, and the similarity factor *f2* contrast the difference between the percent of drug dissolved per unit time of a test with that of a reference formulation. Difference factor (f_1) is the percentage difference between two curves at each point and is a measurement of the relative error between the two curves. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared

error and is a measurement of the similarity in the percent (%) dissolution between two curves. Fit factors were calculated using the software DD solver program. According to FDA dissolution profiles are considered similar when f_1 is 0 - 15 and f_2 is 50 – 100.

2.2.4 Other quality tests

2.2.4.1 Weight variation test

Twenty tablets from each CBZ brand were selected randomly and weighed individually using four decimal sensitive balance (Kern®, Germany). The average weight of each brand as well as the percentage deviation from the mean value were calculated. Tablets were considered complying with the USP standards if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit which was 5% for tablets weighing more than 324 mg (22).

2.2.4.2 Content uniformity test

Ten CBZ tablets were powdered using mortar and pestle. A quantity equivalent to 10 mg of the powdered tablets was accurately weighed using sensitive balance (Kern®, Germany) and then transferred to a 50 ml volumetric flask. 20 ml of methanol was added and sonicated for 5 minutes then, the solution was completed to 50 ml with methanol. The resulting solution was filtered through 0.45 µm membrane filter, suitably diluted and analyzed spectrophotometrically at 230 nm using 7315 UV–VIS spectrophotometer (Jenway®, England) (23). Conformity with content uniformity test achieved when the % amount of CBZ found not less than 85% and not more than 115% of the labeled quantity.

2.2.4.3 Disintegration test

Disintegration test is a measure of the time required for a group of tablets to break up into particles under a given set of conditions. Six tablets were randomly selected from each brand, one tablet was placed in each tube of the basket. The basket rack was positioned in one liter beaker containing distilled water (as the disintegration medium) maintained at 37°C. The apparatus was started to move the basket assembly containing the tablets and the time required for the six tablets to break into particles and to pass the screen to the disintegration medium was recorded. The tablets considered complying with USP standards if all tablets disintegrate between 5 to 30 minutes (24).

2.2.4.4 Hardness test

Tablet hardness tester (Gouming®, China) was used to determine the crushing strength of the tablets. Ten tablets were randomly selected from each brand and the pressure at which each tablet broken was measured (25).

2.2.4.5 Friability test

Friability test was performed to monitor the resistance of the tablets to abrasions or fractures during manufacturing, packaging and transportation. 20 tablets were randomly selected from each formulation, dedusted, weighed using sensitive balance (Kern®, Germany) and then subjected to a uniform tumbling motion in a friability tester (Gouming®, China) at 25 rpm for 4 min. Tablets were dedusted again after the end of rotation and reweighed. The friability loss was determined as a percentage weight loss and calculated as follow:

$$\% \text{ weight loss} = \frac{W1 - W2}{W1} \times 100 \qquad (3.1)$$

Where W_1 is the initial weight of tablets prior to the test and W_2 is the final weight of tablets at the end of the test.
A maximum weight loss of less than 1% is considered acceptable according to USP standards (22).

3. RESULTS

3.1 Calibration curve of CBZ

The wavelength of maximum absorption (λmax) for CBZ was found to be 230 nm. Linear calibration curve (Figure 1) was obtained at the conc. range between 1-9 µg/ml as *Absorbance = 0.115 ∗ Concentration+ 0.0137*, with a regression coefficient $(R^2) = 0.999$.

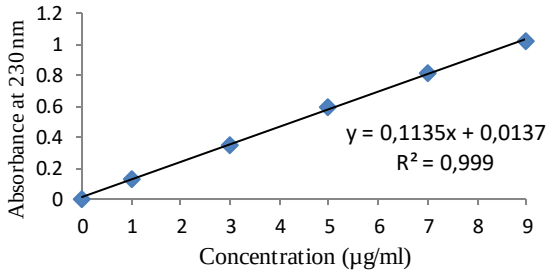

Figure (1) Calibration curve of CBZ

3.2 *In vitro* dissolution studies

Figure 2 below shows the dissolution profile of the four brands of CBZ. Brand A was taken as a reference product. More than 90% of the labeled CBZ was released in 30 min. in all brands. Great difference was noticed in the % released at 5 mins, 10 mins and 15 mins for brand B compared to other brands. Standard deviations in the % dissolved recorded for each brand are become smaller after 30 mins.

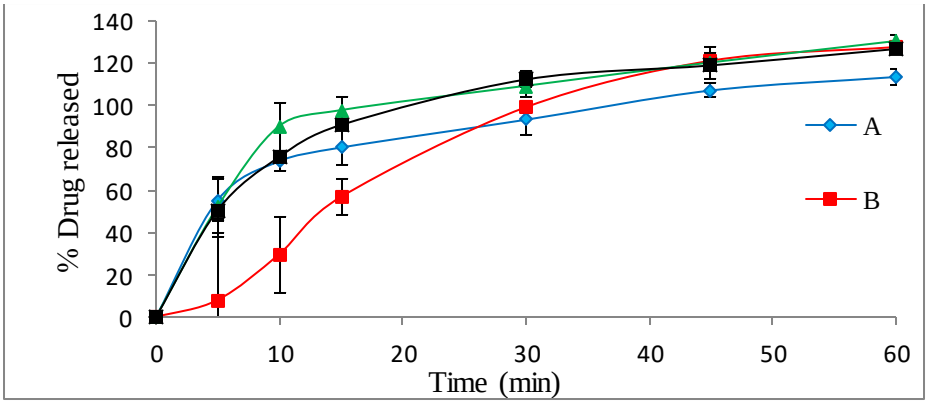

Figure (2) Dissolution profiles of CBZ brands

3.2.1 Determination of drug release kinetics

Data were fitted to different release kinetic models (Table 1) in order to verify the release kinetics of CBZ as various qualitative and quantitative changes in a formulation altered drug release and *in vivo* performance (14). The Korsmeyer-Peppas model provided the best fitting for all brands, since highest determination coefficients (R^2) and smallest AIC values were achieved for all brands tested .

The Korsmeyer-Peppas parameters are shown in Table (2), k is the constant comprising the structural geometric characteristics and n is the diffusion exponent. K value for brand A, C and D were similar , but it was different for brand B in correspond to the independent models, n was less than 0.5 for brand A, C and D which mean their release mechanism follows a Fickian diffusion, and n was more than 0.5 for brand B which indicates a non-Fickian diffusion.

Table (1): Kinetic parameters obtained from the dissolution data for conventional CBZ tablets

CBZ Brands	Para-meters	Zero-order	First-order	Higuchi	Hixson-Crowell	Weibull	Korsmeyer-Peppas
CBZ A	**R^2**	0.1373516	0.961304	0.856905	0.917916	0.9677	**0.9969**
	AIC	64.610196	42.880125	52.034667	48.144295	43.6092	**29.1549**
CBZ B	**R^2**	0.9074533	0.8538	0.908302	0.89513	0.9291	**0.9561**
	AIC	53.512462	56.715409	53.447965	54.387543	53.6432	**52.2967**
CBZ C	**R^2**	0.149294	0.8787	0.844311	0.870022	0.8884	**0.9707**
	AIC	66.785373	53.151789	54.897943	53.634445	54.5670	**47.1975**
CBZ D	**R^2**	0.2986364	0.8941	0.904724	0.921343	0.8962	**0.9840**
	AIC	65.350131	52.114999	51.376361	50.034654	53.9737	**42.8971**

Table (2) The Korsmeyer-Peppas's parameters (k, n) derived from the data adjustment to this kinetic

CBZ Brands	K	n
CBZ A	37.892	0.270
CBZ B	07.304	0.720
CBZ C	42.107	0.279
CBZ D	35.744	0.319

3.2.2 Dissolution profile comparison of marketed brand of Carbamazepine

3.2.2.1 Dissolution efficiency (%DE) and mean dissolution time (MDT)

Dissolution efficiency (%D.E) and mean dissolution time of the commercial brands and the reference are illustrated in (Table 3). Brand C and brand D showed increased dissolution efficiency (101.45%), (99.42%) respectively over the reference brand A (88.3%).

3.3.2.2 Fit factors

Results obtained for each brand are shown in Table (3). The similarity factor f_2 is considered more sensitive to find dissimilarities between dissolution curves than the difference factor f_1. Fit factor values are dependent on the number of sampling time point selected.

Table (3): Statistical comparison of the Dissolution Efficiency (DE), Mean Dissolution Time (MDT) and fit factors among the commercial brands compared to brand A as a reference tablets

CBZ Brands	MDT (min.)	DE (%)	Fit Factors	
			f_1	f_2
CBZ A	13.27	088.30	-	-
CBZ B	20.67	083.57	28.37	26.90
CBZ C	13.13	101.49	15.62	43.61
CBZ D	12.19	099.42	11.90	47.99

3.3 Other Pharmacoepial and Nonpharmacoepial tests of CBZ tablets brands

3.3.1 Content uniformity test

Content limits for CBZ tablets are 92-108% of the labeled amount. All brand tested fit within the content uniformity limits (Table 4).

3.3.2 Disintegration test

Table 4 showed that none of the marketed CBZ brands exceeds the specifications and they are complying with the pharmacopeia specifications of disintegration time. The tablets comply with USP standards if all tablets disintegrate as low as 5 minutes and maximum disintegration time of 30 minutes.

3.3.3 Weight variation test

Tablets comply with the USP standards if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit which was 7.5% for tablets weighing between 130mg and 324mg and 5% for tablets weighing 325 mg and more. Weight of all tested commercial brands were within the acceptance limits, the results are given in Table (4).

3.3.4 Hardness test

Results in Table (4) show that hardness was satisfactory for all commercial CBZ brands except for brand B. Tablets comply with the USP standards if a crushing strength in the range of 4-8 Kg. The dissolution profile for brand B is directly affected by its hardness. When compared to other brands, brand B showed a delayed release with the lowest % dissolved within 30 Figure (2).

Table (4) Pharmacoepial and nonpharmacoepial tests of CBZ tablets brands

3.3.5 Uniformity of thickness and diameter

Variation in tablet's size and weight can be determined by measuring their thickness and diameter. As shown in Table (4), the standard deviations for both diameter and thickness are very small indicating that the size and shape of all brands are consistent.

3.3.6 Friability test

Friability test was performed to monitor the resistance of the tablets to abrasions or fractures during manufacturing, packaging and transportation. A maximum weight loss of less than 1% is generally considered acceptable for most pharmaceutical tablets. As shown in Table (4), all brands were within the allowed friability limit.

Table (4) Pharmacoepial and nonpharmacoepial tests of CBZ tablets brands

CBZ Brands	Content (%)	Weight ± RSD (mg)	Diameter ± RSD (mm)	Thickness ± RSD (mm)	Hardness ± RSD (Kg)	Disintegration Time (min)	Friability (%)
CBZ A	102	280.4 ± 1.3	9.1 ± 0	3.52 ± 0.08	5.41 ± 0.67	2.08	0.4 %
CBZ B	096	258.46 ± 0.6	9.8 ± 0	3.51 ± 0.03	13.49 ± 3.05	7.50	0.1%
CBZ C	103	576.53 ± 0.6	9.0 ± 0	4.38 ± 0.06	7.72 ± 1.15	6.17	0.1%
CBZ D	102	278.82 ± 1.6	12.9 ± 0	3.43 ± 0.05	7.23 ± 0.58	5.20	0.6%

4. DISCUSSION

In vitro dissolution testing is a fundamental analytical test during solid dosage forms development and thereafter during industry. This test allows for quality assurance of oral solid pharmaceutical dosage forms. Formulation optimization during the development phase is mainly judged by the dissolution tests results, then further stability studies, manufacturing processing and quality control testing could be carried out [26]. Switching from one generic product to another might lead to therapeutic failures and /or adverse drug reactions that are sometimes life threatening or may result in persistent or significant disability. Such complications are more encountered with narrow therapeutic index (NTI) drugs. The dissolution test for CBZ tablets described in the USP indicates that not less than 70% of the API should be dissolved in 30 min. Dissolution curves indicated the mean percentage of drug dissolved at each time point and the relative standard deviation (RSD), the analyzed products presented different dissolution profiles but all brands fulfilled the USP specifications (Figure 2). More than 90% of the labeled CBZ was released in 30 min. in all brands. Great difference was noticed in the % released at 5 mins, 10 mins and 15 mins for brand B compared to other brands. Standard deviations in the % dissolved recorded for each brand are become smaller after 30 mins. Different dissolution profiles below 30 mins. may be due to the formulation excipients and the hardness of the tablets.

In order to determine the suitable drug release kinetic model, the *in vitro* release data of CBZ brands were fitted to different release models representing zero order, first order, Higuchi, Korsmeyer-Peppas, Hixson-crowell and Weibull using the Excel add-in DDSolver program [27]. Determination of % DE and MDT values are useful methods since reduction of each dissolution curve into a single number took place. To compare the dissolution profile of CBZ marketed brands and reference brand A, a model independent approach of dissolution efficiency (% D.E), difference factor (f_1) and similarity factor (f_2) were employed. Increased dissolution efficiency for Brands C and D (101.45% and 99.42%) respectively over the reference brand A (88.3%) proved the role of the excipients in retarding the release of the active ingredient from the formulation. Fit factors are a quantitative parameters recommended by the FDA to compare dissolution profiles of different brands. According to the FDA,

f_1 values less than 15 and f_2 values greater than 50 should ensure equivalence between the dissolution curves, indicating an average difference of no more than 10% at the sample time points. The similarity factor f_2 is considered more sensitive to find dissimilarities between dissolution curves than the difference factor f_1. According to this guideline, the dissolution curves corresponding to brand C and brand D would be somewhat similar to that obtained with the reference formulation (Tables 1-3). This study was in accordance to a study carried out by Yasin *et al.* in 2019. In such study, authors mentioned the brands names; the same dissolution profile for brand (B) was obtained. In both studies hardness was found satisfactory for all commercial CBZ brands, except for brand B which was harder than the other brands, this may be due to the difference in excipients used for manufacturing or in the compression force used [23]. In another study carried out in Peru, the same findings were obtained. The biopharmaceutical equivalence study of two generics and one commercial brand of CBZ 200 mg tablets revealed that all samples were meeting the official specifications for quality control tests, despite that, the evaluated samples are not *in vitro* biopharmaceutical equivalents with the innovator brand based on the dissolution profiles (f2) [28]. For satisfactory tablet, hardness should not be so high that disintegration and dissolution are delayed. Conversely, hardness should not be so low that tablets are soft and friable. For satisfactory tablet, hardness should be between 4 and 8 kg. Other pharmacoepial and nonpharmacoepial quality tests for all brands were found in accordance with the specification and limits (Table 4).

5. CONCLUSION

Carbamazepine brands C and D could be used interchangeably with the originator brand (A) since they showed pharmaceutical equivalence in all tests performed. Brand B failed to pass the hardness test which affects the dissolution profile especially in the first 30 mins. More than 90% of the labeled CBZ was released within 30 min. in all brands. Release mechanism for brands A, C and D was found to follow Fickian diffusion, while brand B demonstrated non-Fickian diffusion. Further pharmacokinetics and/or bioequivalence studies should be done to confirm the use of all brands tested interchangeably.

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