In Vitro Bioequivalence of Pregabalin Capsules (150 mg): An Alternative to In Vivo Bioequivalence Studies

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ABSTRACT

Introduction: We aimed to study the dissolution behavior of available brands of pregabalin in the United Arab Emirates (UAE) (Ras Al Khaimah) market and to report efficiency and fungibility data for generic brands under biowaiver conditions. **Methods**: The pharmaceutical parameters of five brands of pregabalin 150 mg capsules were analyzed, including the reference product and four generic products. Dissolution tests were performed as per WHO and FDA recommendations (pH 1.2, 4.5, and 6.8). United States Pharmacopeia (USP) apparatus 2 (paddle, 50 rpm) was used to assess drug release. Multiple time points were measured to estimate the drug release profile of the capsules. Pharmacokinetic models and similarity factor analysis were performed. **Results**: The percentage of drug release within 15 minutes was 95–102% at pH 1.2, 86–95% at pH 4.5, and 89–98% at pH 6.8. Different kinetic models were used to analyze the suitability level of drug release from the different capsules. In all the three buffers, first order kinetics and the Korsmeyer–Peppas model demonstrated the drug release with $R^2 \geq 0.95$, which helps to predict and evaluate the acceptability level of drug release. The similarity and difference factor results were within the acceptable range for all capsules. **Conclusion**: The dissolution profiles of all tested capsules of pregabalin in the UAE market are pharmaceutically and therapeutically equivalent. The results indicate that the post-market analysis is essential for determining interchangeability of different brands of the same drug.

KEYWORDS: Pregabalin capsules, dissolution behavior, comparative study, biowaiver studies

INTRODUCTION

Pregabalin is an alpha2 delta ligand having analgesic, anxiolytic, and anticonvulsant properties. The real mechanism of action is not known, but nonclinical studies suggest that binding of voltage-gated calcium channels to the alpha2 delta auxiliary subunit in the central nervous system tissues may be involved in its anti-nociceptive and anti-seizure effects. In vitro studies indicate that pregabalin, due to intonation of calcium channel, reduces the calcium-dependent release of several neurotransmitters. Pregabalin is a new gabapentinoid, which trailed the use of gabapentin (GBP). GBP was initially used as an antiepileptic drug (*1–3*). After the establishment of randomized controlled studies in neuropathic pain conditions, it is widely used for the treatment of neuropathic pain (*4*, *5*). Pregabalin is a highly soluble and highly permeable compound; the oral absorption is almost 90% and is not dependent of dose and rate of administration. Pregabalin is categorized as a class 1 compound in the Biopharmaceutics Classification System (BCS).

Regulatory agencies and health organizations have taken advantage of the BCS system to allow in vitro dissolution to be used to establish bioequivalence (BE) studies among the different brands containing the same compounds. For the establishment of pharmaceutical products equivalency, a dissolution test could be adopted as the surrogate basis for the decision instead of conducting expensive and time-consuming in-vivo studies. The BCS approach to waive in vivo studies of pregabalin have been approved by the United States Food and Drug Administration (US FDA) (*6*).

Pregabalin is marketed in the US by Pfizer under the brand name, Lyrica. The biowaiver study for pregabalin capsules was approved by FDA in the phase 3 of its development, which undoubtedly edited the timeline for the submission of new product and eliminated the costs related to in vivo

BE studies (6). Mylan Pharmaceuticals (USA) has received approval to manufacture generic pregabalin capsules based on the BCS class 1 biowaiver approach (7).

Pregabalin is also classified as a schedule V drug in the US (8). Pregabalin has narrow therapeutic index and is a highly potent drug. It may cause serious side effects such as fatal allergic reactions, waves of suicidal thoughts, swelling of hands, legs, and feet, dizziness, and sleepiness. Widespread use of this medicine without BE studies is alarming.

In this study, we aimed to assess the interchangeability of different brands of pregabalin to establish the pharmaceutical and therapeutic equivalency. We also studied the effect of different pH on the releasing behavior of drug from the different capsules to inform the basic concept and strategy for biowaiver studies. Pregabalin capsules are errant in nature, so we compared the amount of active component in the different brands.

MATERIALS AND METHODS

Materials
Five brands of pregabalin capsules from the United Arab Emirates (UAE) market were used in this study including the reference product (Lyrica, Pfizer). The five brands were labeled P-1, P-2, P-3, P-4, and P-5, with P-1 being the reference product. Pregabalin powder (reference) was obtained as gift sample from Dr Reddy Laboratories (Hyderabad, India). The five brands of generic and reference pregabalin capsules (150 mg) were randomly purchased from local market of Ras Al Khaimah, UAE. All selected capsules were under their expiry date. Analytical grade products were used including potassium hydroxide (KOH, LabChem), hydrochloric acid (HCl, Merck), Potassium dihydrogen phosphate KH_2PO_4, Merck), and Sodium Hydroxide (NaOH, Sigma Aldrich). Distilled water was prepared onsite by distillation method.

Equipment
An electronic balance (Mettler Toledo, England) and pH meter (Hanna) were used in the study. The dissolution test assembly was a United States Pharmacopeia (USP) apparatus 2 (paddle) (D5 8000, Labindia Instruments).

The high-performance liquid chromatography (HPLC) system (Shimadzu) used comprised an LC-20AD liquid chromatography pump equipped with an SPD-20A UV-VIS detector. Chromatographic separations were performed on C18 column (3.9 × 300 mm; 10 μm packing), which was attached with a 20-μL loop to the HPLC system.

Preparation of Dissolution Medium
Three dissolution media were prepared with a pH of 1.2, 4.5, and 6.8, as specified in the USP (9). The pH 1.2 buffer was prepared by transferring 8.5 mL HCL to 1000 mL distilled water and shake. The pH 4.5 medium was prepared by dissolving 6.8 g KH_2PO_4 (0.2 M) into 1000 mL distilled water. The pH 6.8 medium was prepared by dissolving 27.22 g KH_2PO_4 (0.2 M) into 1000 mL distilled water. Next, a solution was mixed with 250 mL of KH_2PO_4 and 112 mL NaOH (0.2 M), then diluted with distilled water up to a final volume of 1000 mL.

Preparation of Mobile Phase
The mobile phase was a mixture of acetonitrile and KH_2PO_4 buffer (pH 6.9) in a ratio of 50:950. The mobile phase was filtered through a 0.45-μm (pore size) filter (Millipore) and degassed before use.

Preparation of Diluent
In accordance with *Indian Pharmacopeia*, 1.2 g of KH_2PO_4 was dissolved in 900 mL of distilled water (10). The pH was adjusted to 6.9 ± 0.05 with 5 N KOH, and volume was made up to 1000 mL with distilled water.

Preparation of Standard Solutions
Pregabalin (20.0 mg) powder was accurately weighed and carefully transferred into 25-mL volumetric flask. Diluent, 1.2, 4.5, or 6.8 buffer was added separately to reach a volume of 25 mL. After proper shaking, 5 mL of solution was pipetted out and diluted to 25 mL to get a final concentration of 160 μg/mL. It was then filtered through 0.45-μm (pore size) filter paper.

Preparation of Working Solutions
Six capsules of each brand were dissolved in 900 mL of each dissolution medium. The final concentration of working solutions was 166.67 μg/mL.

Chromatographic Conditions (HPLC)

Mobile Phase:	Acetonitrile: KH_2PO_4 (50:950)
Column (C_{18}):	3.9 x 300 mm (10 μm packing)
Flow Rate:	1.5 mL/min
Wavelength:	210 nm
System Suitability:	Theoretical Plate numbers > 2000
	Tailing Factor < 2.0 (allows for
	higher sample load)

Resolution > 2.0 (allows for method variation variation and column aging)

RSD of replicate injections < 2.0% (checks system performance)

Calibration Curve of Pregabalin in Diluent
The calibration curves were constructed for the diluent and three dissolution media with different concentrations

(500–100 µg/mL) by using pregabalin (reference) powder. A series of dilutions were made for the pH 1.2, 4.5, and 6.8 buffers and diluent separately. The absorbance (peak area) of solutions was measured by using HPLC (Fig. 1).

Physiochemical Parameters

y = 423.01x + 290.4
$R^2 = 0.999$

y = 575.16x
$R^2 = 0.997$

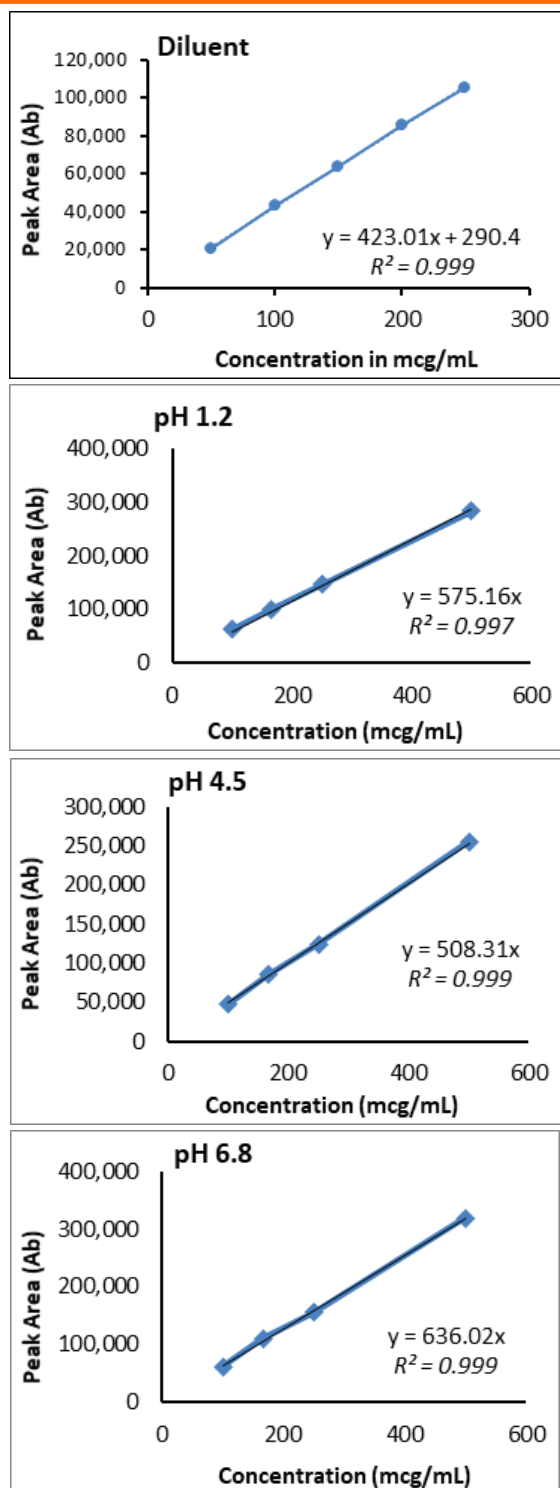y = 508.31x
$R^2 = 0.999$

y = 636.02x
$R^2 = 0.999$

Figure 1. Calibration Curve (Linearity) of pregabalin in diluent and pH 1.2, 4.5, and 6.8.

One of the most important steps is to study the physiochemical properties of the finished product before performing the dissolution of drug. Any dissimilarity in the physical parameters of dosage form leads to variance in the pharmaceutical equivalency consequently it indicates the deviation in the dissolution profile. The pharmaceutical evaluation of capsules included uniformity of weight, length, diameter, disintegration test, and content assay (*9, 11*).

Dissolution Analysis

A USP apparatus 2 was used in this study at 50 rpm and 37 ± 0.5 °C; 900 mL of dissolution medium (pH 1.2, 4.5, 6.8) was transferred each time to the dissolution vessel. First, the dissolution test was done in 0.06 N HCl as per USP, and then the tests were performed again for all dissolution media. A 5-mL sample was withdrawn at each time interval: 10, 15, 20, 30, 45, and 60 minutes with replacement. Samples were filtered and injected into the HPLC injector. The dissolution profiles of different capsules were constructed on the basis of average and cumulative percentages drug release.

Statistical Analysis

One-way analysis of variance (ANOVA) was used for the statistical analysis of the dissolution profile for the tested products. ANOVA was used to compare the pattern of drugs release from different brands of pregabalin capsules to estimate the variation at different time points. It was also used to determine means and relative differences. Similarity (f_2) and difference (f_1) factor analysis was also conducted. Microsoft Excel (Office 365 version) was used, and a *p* value less than 0.05 was considered significant.

In addition, pharmacokinetic modeling with DDSolver (Simulations Plus add-in) was used to evaluate the dissolution profile including zero order, first order, Higuchi, Hixson Crowell and Korsmeyer–Peppas models.

RESULTS

All the capsules were assessed and were found to have suitable organoleptic properties. Results of the pharmaceutical evaluation are presented in Table 1. The weight variations were intended to assess indirectly the homogeneity of amount of drug in capsule dosage form. No major divergence was observed in the capsules. Disintegration time of capsules was within 2–4 minutes, which is within the acceptance criteria set by pharmacopeias (15 minutes). The estimation of content uniformity of drug was done by HPLC analytical method. HPLC System suitability analysis was performed before starting the dissolution and content assay testing. Results

were within 97–102%, which meets USP acceptance criteria (90–110%).

The percent release of pregabalin from the dissolution medium was within 95%–102% for pH 1.2, 86–95% for pH 4.5, and 89–98% for pH 6.8 within 15 minutes (Figure 2). The calculated value of F for all the three media is smaller than 0.05, indicating that there is no significant difference in samples means (Table 2).

All five brands failed to obey the zero order, Higuchi, and Hixson-Crowell models, with $R^2 \leq 0.95$. On the other hand, the drug release profiles were adequately described by first-order and Korsmeyer–Peppas models with R^2 value ≥ 0.95 in pH 1.2, 4.5, and 6.8 buffers (Table 3). The R^2 value for the Korsmeyer–Peppas model was almost equal to 1.0 at all three pH levels.

In the present study to verify the similarity factors f_2, P-1 capsules (innovator) were taken as reference product.

Table 1. Pharmaceutical Evaluation of Pregabalin Capsules

Product No.	Weight Variation, mg (n = 20)	Length, mm (n = 20)	Diameter, mm (n = 20)	Disintegration Time, min (n = 6)	Drug Content, % (n = 4)
P-1 (Ref)	261.63 ± 2.63	17.45 ± 0.175	6.05 ± 0.10	2.09 ± 0.27	99.69 ± 0.81
P-2	275.98 ± 9.41	17.33 ± 0.151	6.53 ± 0.12	3.97 ± 1.18	97.02 ± 1.20
P-3	363.54 ± 9.12	18.74 ± 0.147	6.56 ± 0.09	2.57 ± 0.48	98.49 ± 1.48
P-4	263.28 ± 3.79	17.40 ± 0.114	6.06 ± 0.08	3.33 ± 0.13	101.58 ± 0.88
P-5	352.52 ± 7.19	18.34 ± 0.166	6.54 ± 0.12	2.27 ± 0.57	101.13 ± 0.80

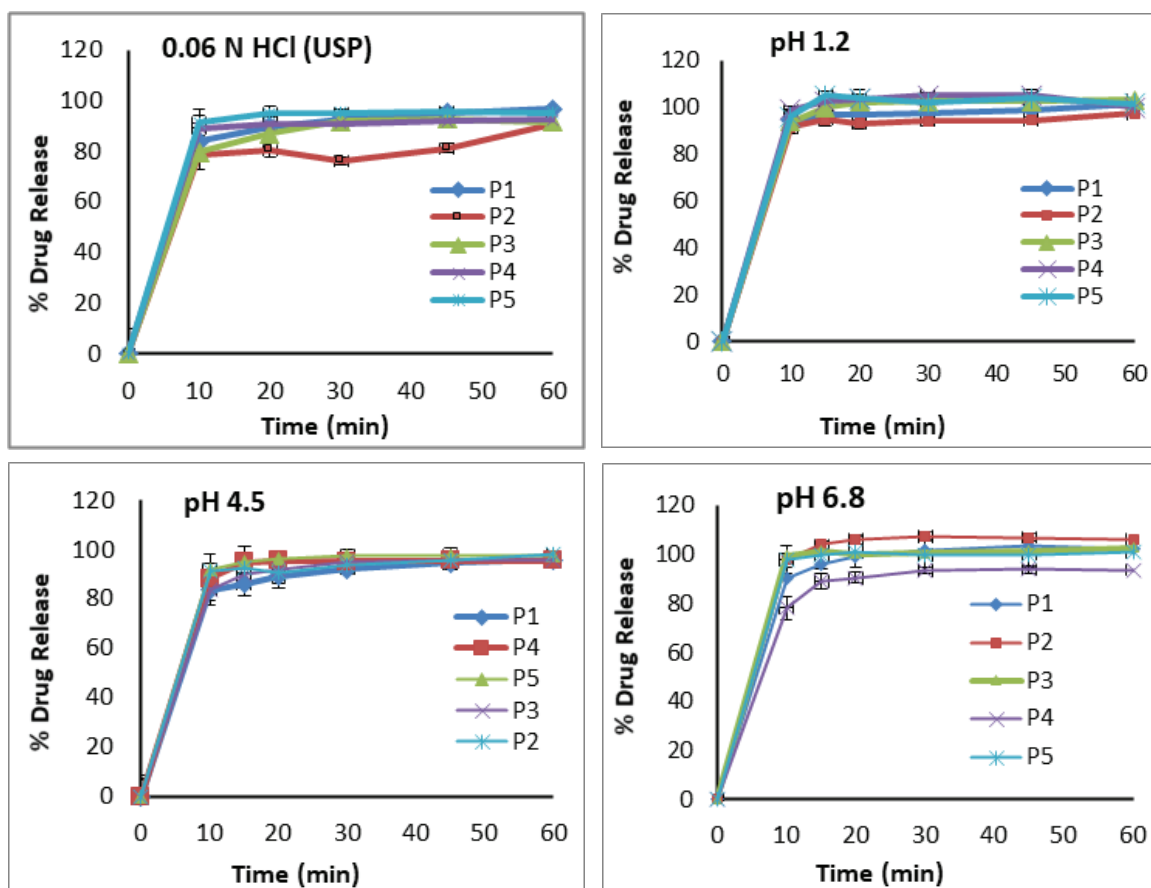*Data are presented as mean ± standard deviation.*

Figure 2. Percentage release of drug from five brands (P1-P5) in 0.06 N HCL, pH 1.2, 4.5, and 6.8 buffers. Result based on n = 6. P-1 = reference product; P-2–P-5 = generic products.

Table 2. Analysis of Variance for In Vitro Dissolution of Capsules in pH 1.2, 4.5, and 6.8 Buffers

Buffer	Source of Variation	SS	df	MS	F	P-Value	F crit
pH 1.2	Between Groups	216.81	4	54.20	0.03835	0.99704	2.68963
	Within Groups	42,406.84	30	1413.56			
pH 4.5	Between Groups	97.11	4	24.28	0.01933	0.99923	2.68963
	Within Groups	37,684.53	30	1256.15			
pH 6.8	Between Groups	360.04	4	90.01	0.06595	0.99159	2.68963
	Within Groups	40,945.79	30	1364.86			

SS: sum of the squares; df: degrees of freedom; MS: mean square; F: ratio of the mean squares.

Table 3. Dissolution Data Evaluated with Kinetic Models in pH 1.2, 4.5, and 6.8 Buffers

Parameter	Product P-1 (Ref)	Product P-2	Product P-3	Product P-4	Product P-5
pH 1.2 Buffer					
First-Order Model					
k_1	0.286	0.226	0.298	0.228	0.367
R^2	0.9988	0.9961	0.9988	0.9967	0.9989
KP Model					
k_{KP}	87.946	87.651	88.026	95.113	93.000
R^2	0.9997	0.9977	0.9987	0.9999	0.9984
pH 4.5 Buffer					
First Order Model					
k_1	0.165	0.239	0.179	0.234	0.243
R^2	0.9944	0.9916	0.9961	0.9969	0.9984
KP Model					
k_{KP}	71.548	83.050	74.355	85.016	87.403
R^2	0.9985	0.9984	0.9979	0.9956	0.9997
pH 6.8 Buffer					
First Order Model					
k_1	0.165	0.365	0.144	0.234	0.243
R^2	0.9943	0.9985	0.9950	0.9969	0.9984
KP Model					
k_{KP}	79.384	68.817	68.817	89.632	95.922
R^2	0.9984	0.9958	0.9958	0.9993	0.9996

KP: Korsmeyer–Peppas.

Results for all brands were within the acceptance limit in all three buffers, i.e., $f_2 \geq 50$. The difference between the two curves at each time point was measured by f_1 factor. These results were also within the acceptable limit and are presented in Table 4.

DISCUSSION

For estimation of pharmaceutical equivalence of generic and brand name / reference products, a dissolution test could be acquired as a substitute tool instead of conducting expensive and time-consuming in vivo studies (*12–14*). On the other hand, we cannot ignore the possibility of therapeutic inequivalence of two immediate-release products that can never be reduced to zero.

Pregabalin is used for the treatment of anxiety because it has significant mechanism for the inhibition of calcium currents. It is also used for the treatment of pain of diabetic neuropathy and post-herpetic neuralgia in Europe (*15*). It plays an important role as an antiepileptic medication in USA, approved by the FDA in 2005 for partial epilepsy, painful diabetic polyneuropathy, post-herpetic neuralgia, and fibromyalgia (*16–18*).

Safe and effective response to this medicine should be achieved when the concentration of drug in the body is maintained at a constant level. Non-compliance of drug or misbranded capsules can create a worse condition (such as seizures, difficulty in sleeping, nausea, headache, and diarrhea) or may lead to addiction in some patients.

Table 4. Similarity (f_2) and Differences (f_1) Data of Generic Pregabalin Capsules (P-2–P-5) Compared to the Reference Product (P-1)

Dissolution Medium	P-2	P-3	P-4	P-5
f_2 Values				
0.06 N	70	74	50	74
pH 1.2	72	71	69	64
pH 4.5	67	79	65	60
pH 6.8	70	51	61	67
f_1 Values				
0.06 N	4	3	11	3
pH 1.2	4	3	4	4
pH 4.5	4	2	4	6
pH 6.8	3	9	6	3

To prevent these situations, the concentration of the drug in the body must be monitored to ensure that it remains in a stable and consistent state throughout the duration of treatment. In this regard, it is necessary to monitor the quality of pregabalin capsules available in the market.

The UAE is emphasizing to launch generic brands of medicine in the market to reduce the cost of treatment (19). For example, the reference product of pregabalin (Lyrica, Pfizer) is available as 200–300 Arab Emirate Dirham (AED) for 28 capsules whereas the generic products are available in the range of 65–95 AED for the same quantities. This will be supportive for low-income patients who may not have sufficient insurance to cover the cost of the brand name product.

The new health regulation (NHR) of UAE dictates the dispensing of generic medicines as the first choice to support the local and regional pharmaceutical industry as well as to provide more options and convenient supply to patients. The NHR is also endorsing the incentive for generic companies to invest in UAE (20).

In 2016, there were 14 native pharmaceutical factories in UAE, according to the statistics from the Ministry of Health and Prevention. That number is expected to reach 34 by the end of 2020. Drug manufacturers process, package, and market products, but they may not undergo clinical trials. For that reason, generic pharmaceuticals must have the same efficacy and potency as the original patented medicine. At this stage, the in vivo BE studies are prohibitively time consuming and expensive. To support the usage of generic drugs, the UAE government makes it sure that patients are receiving high-quality medicines for optimal treatment outcomes (21). In view of rising concerns, it is prudent to assess and regulate the available marketed brands in the UAE for interchangeability.

The main purpose of the current study was to examine the release behavior of pregabalin from capsules as it is affected by different pH levels found in the gastrointestinal tract (pH 1.2, 4.5, and 6.8). In vitro dissolution testing plays a critical role in the life cycle of a generic drug product. According to the BCS guidelines, in vitro dissolution testing may be a useful tool to forecast the in vivo performance of drug products and potentially reduce the number of bioavailability and bioequivalence studies required.

In the current study, five brands of pregabalin were selected from the local market, including the brand name product, and compared. There were no differences observed between the capsules based on physical parameters (i.e., weight, length, diameter, disintegration time, and drug content). All the tested products released more than 85% of drug within 15 minutes, with no statistically significant differences in the similarity (f_2) and difference (f_1) factors. Dissolution test results are consistent with the work of Arayne et al. in 2014 and Pai et al and Hasin et al. in 2017 (22–24). In terms of pharmacokinetic modeling, the best fit model was Korsmeyer–Peppas. This model helps us understand the exact mass transport mechanisms involved in the drug release, which is useful for quantitative estimation of drug release kinetics. Our study shows that generic pregabalin can be substituted for the innovator product in clinical use.

CONCLUSION
All the five commercial brands of pregabalin capsules available in local market satisfy the USP specifications. The results of dissolution tests can help to estimate the effectiveness and clinical outcome of pregabalin and aid in achieving biowaiver approval. The results were verified and evaluated by different independent and dependent models.

The World Health Organization's model list of drugs does not recommend a single analgesic medicine as a first-line treatment for neuropathic pain (*25*). So, it is essential to analyze the pregabalin products rigorously to estimate the availability of quality medicine for the treatment of neuropathic pain to avoid possible serious consequences for patients, especially for non-proprietary drug products.

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CONFLICT OF INTEREST

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

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