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Research Article

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Quality Assurance and Comparative Studies of Different Brands of Pregabalin in Nigerian Pharmacies

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Abstract Pregabalin, a neuropsychotropic agent, is a drug of choice for the treatment of epilepsy and neuropathic pain. Several brands are available in the Nigerian drug market which raises the challenge of determining the products that could be interchanged with the innovator brand or with other generics. Therefore, the current study was carried out to evaluate and compare the quality and physicochemical characteristics of five different pharmaceutical brands of Pregabalin (75 mg) capsules available in the pharmacies of some southern states in Nigeria. For the brands studied, physical examination, drug content, weight variation, disintegration, dissolution, amongst other quality control tests were carried out. Results showed that most of the samples complied with the standards specified for capsules. Drug contents were not exactly the same with the reference sampleas two brands (P3 and P5) had their drug contents to be less than 80%. There was a consistency in drug release carried out within 30min at intervals of 5, 10, 15, and 30min. Thus, the results of the study indicated that all brands of pregabalin tested conformed with the pharmacopeial standards for disintegration, weight uniformity and dissolution tests, while two brands (P3 and P5) failed the content uniformity test. Also, the samples were found to be interchangeable with the innovator brand (P1) as their dissolution profiles showed that they all released more than 85% of their active content within 30 min. The study therefore underscored the need for constant post-market surveillance and quality assurance of multisource essential drug agents, especially in developing countries such as Nigeria.

Keywords Quality Assurance, Pregabalin, Quality Control, Comparative Studies, Bioequivalence

Introduction

Pregabalin marketed under the innovator brand name Lyrica® is a medication used to treat epilepsy, neuropathic pain, fibromyalgia, and generalized anxiety disorder [1]. The drug is a structural analogue of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), but not functionally related to it. Like its predecessor, gabapentin, it binds to the α-2 γ subunit of voltage-gated calcium channels reducing the release of several exciting generalized anxiety neurotransmitters and blocking the development of hyperalgesia and central sensitization [2].

Figure 1: Structure of Pregabalin

Pregabalin is chemically known as (S)-3-(aminomethyl)-5-methyl-hexanoic acid and it is commonly indicated in the treatment of central and generalized anxiety disorders [1]. It has been found effective both at controlling post-operative pain and preventing chronic neuropathic pain [3]. When taken before surgery, pregabalin does not appear to affect pain after surgery but may decrease the use of opioids [4-6].

Different generics of pregabalin are available in Nigeria pharmacies, and are interchangeably utilized in the management of indicated health conditions. These generic products, though assumed to be chemically equivalent, should be identical in strength, quality and purity, while as pharmaceutical equivalents, should be assessed by being similar in terms of content uniformity, disintegration and dissolution rates [7]. The National Agency for Food and Drug Administration and Control (NAFDAC) which is the regulatory authority responsible for the regulation and control of drugs in Nigeria, has been at the forefront in ensuring standards for quality, efficacy and safety in line with WHO guidelines aimed at getting quality and safe drugs to the consumers. Another major driving interest in carrying out quality evaluation on the drug arises partly from the fact that pregabalin, apart from its use as an anticonvulsant, is also used in the treatment of neuropathic pain which remains a significant challenge for medical workers [8].

There is therefore urgent need to regularly evaluate the quality and interchangeability of available brands of multisource preparations such as pregabalin in the Nigerian healthcare delivery system so as not to jeopardize the expected therapeutic outcome [9].

Materials and Methods

Sample Procurement and Assessment

a) **Samples**: Fivecapsule brands of pregabalin (encoded as P1, P2, P3, P4, and P5) used for this study were procured from various pharmacy premises in some Nigerian cities located at the southern region of the country in the first quarter of2018.

b) **Reference Sample**: The innovator brand, P1, was used as the reference standard. It was procured from Pfizer Global Pharmaceuticals, Lagos, Nigeria.

Methods:

Preliminary Tests:

General Appearance

The organoleptic properties which included the size, shape, colour, odour, packaging and overall dosage form conformity of the different brands of pregabalin tablets were examined and recorded.

Packaging and Labelling Inspection

Information about the various brands such as brand name, producers, country of manufacture, manufacturing/expiry dates, batch /lot number, product registration status with National agency for Food and Drug Administration and Control (NAFDAC) were assessed.

Preparation of Pregabalin Stock Solution

A stock solution was prepared by dissolving the equivalent content of a capsule (75mg) of pregabalin in 100ml of distilled water. This was vigorously shaken and allowed to stand for 30 min to completely dissolve, after which it was filtered. This was used to prepare the working solution by suitable dilutions [10].

Determination of maximum wavelength (λ_{max}) of absorption

An aliquot from pregabalin stock solution and suitable dilutions were scanned in the UV-Visible Spectrophotometer using distilled water as blank. The determinations were carried out within the range of 190 to 223 nm wavelength and the maximum wavelength of absorbance was obtained at 221 nm [10].

Preparation of 0.1N HCl

A 10 mL volume of concentrated HCL was measured using a 10 mL measuring cylinder into 500 mL distilled water in a 1000 mL measuring cylinder. This was made up to 1000 mL with distilled water. This preparation was employed as the simulated gastric fluid (SGF) [11].

Official Tests

Uniformity of Weight

Twenty capsules from each brand of pregabalin were selected randomly and weighed with Acculab® analytical balance (ALC210.4, Germany) individually. The weights were recorded in triplicates, and the mean, standard deviation, percentage standard deviation and coefficient of variance were calculated and recorded. The capsule batches passed the test if not more than two of the individual weights deviate from the average weight by more than ± 7.5%, and none deviated by twice ± 7.5% [11].

Disintegration test

The disintegration test for the different brands of pregabalin were carried out according to the method described in the BP [10]. Six capsulescarefully selected from each formulation were used for the test. Each of the capsules from each batch was weighed and placed in different baskets. The apparatus (Erweka® ZT122) was operated using distilled water (pH 8) as immersion fluid at 37 ˚C ± 1 ˚C. The capsules were observed for any form of disintegration, cracking or softening. The capsules were then removed and the fluid replaced by another under same condition of operation for the various batches [11].

Dissolution Test

The dissolution test for the different brands of pregabalin capsules were carried out according to United States Pharmacopoeia using Erweka® dissolution apparatus (Germany, paddle type) set at 100rpm per minute for 30min in 0.1 N HCl as dissolution medium at 37 ± 1˚C [11]. After an interval of 5, 10, 15, 20, 25 and 30 min respectively, 5 ml of the solutions were taken out and 5 ml fresh dissolution medium added to keep the volume of dissolution medium constant. The sample was analysed using UV-Spectrophotometer at 221 nm and the percentage drug release was calculated [11].

Content of Active Ingredient

The contents of ten capsules from each brand of pregabalin were emptied into a mortar. The equivalent of 75mg of the pregabalin powder was weighed out and transferred into a volumetric flask and dissolved to make 100ml solution with 0.1N HCl. This was filtered and the absorbance obtained at 221 nm wavelength and used to calculate the percentage drug release. Mean percentage drug release was further calculated for each brand [10].

Bioequivalence Determination Using Dissolution Profiles

Similarity factor (f_2) was determined to compare the dissolution efficacy of the various brands of pregabalin. F_2 is a logarithmic reciprocal square root transformation of the sum of square error and is a measurement of the similarity in the percent (%) dissolution between two dissolution curves at each point [12].

F_2 was determined using the equation:

$$F_2 = 50\log\{1 + \frac{1}{n}\sum_n (R_t - T_t)^2\}^{-0.5} \times 100$$

Where:
n = number of time points
R_t = dissolution value of reference product at time t and
T_t = dissolution value for the test product at time t.

Results and Discussion

The results of the product information and physical examination of the respective brands of Pregabalin used for this study are presented in Tables 1 & 2. The preliminary evaluation showed that the samples complied with basic physical assessment requirements by displaying the label claim, batch number, date of manufacture and expiration, manufacturer, country of manufacture and registration status with the National Agency for Food and Drug administration and control, (NAFDAC). All the brands were within their shelf-life as at the time of study.

Table 1: Product information for various brands of pregabalin capsules

Brand Name	Country of Manufacture	Manufacturing Date	Expiry Date	NAFDAC Status	Label Content
P1	USA	02/2017	08/2020	Registered	75 mg
P2	India	07/2017	06/2019	Registered	75 mg
P3	France	03/2018	04/2019	Registered	75 mg
P4	UK	11/2017	09/2019	Registered	75 mg
P5	UK	08/2017	08/2020	Registered	75 mg

Table 2: Physical Assessment of the various brands of pregabalin capsules

Brand Name	Colour	Packaging	Dosage Form
P1	White and red	Aluminium foil blister	Capsule
P2	White and brown	Aluminium foil blister	Capsule
P3	Red and white	Aluminium foil blister	Capsule
P4	Yellow and brown	Aluminium foil blister	Capsule
P5	White and brown	Aluminium foil blister	Capsule

The results of weight variation and disintegration tests for the pregabalin brands (Table 3) were found to comply with the official standard as all the brands passed the tests. Both British pharmacopoeia (BP) and United State Pharmacopoeia (USP) stipulate that the percentage weight variation for capsules and tablets should not be more than 10% for capsule or tablet weights of less than 80mg, 7.5% for weights within 130-324 mg and 5% for greater than 325mg weights [10,11]. The reference standard for disintegration test of capsules and tablets was found to be 15min for both tablets and capsules. Thus, the pregabalin brands passed the test as their disintegration time did not exceed 15min.

Out of the five brands, two brands (P3 and P5) failed the test for uniformity of content (Table 3). Compendial specification for most solid dosage forms requires that at least 80% of active drug content should be released within 30 min by each brand [10]. The variation in the amount of active ingredients contained in these samples could result in unpredictable treatment outcomes [13].

Table 3: Results of some Pharmaceutical tests of the samples

Brands	Mean Weight (mg)	Disintegration time (min)	Actual content (%)
P1	133.8 ± 2.63	6.85 ± 2.26	100
P2	140.1 ±1.41	8.52 ±1.83	95.19
P3	148.1 ±2.04	11.47± 2.92	79.79
P4	297.5 ±4.32	7.00 ±2.77	91.43
P5	131.9 ±1.72	3.67 ±2.85	71.88

The result on table 4 showed the assay result for the dissolution profile of pregabalin and it indicated that all the samples used in this analysis complied with the official standards. The USP specified that capsules should release not less than 85% of their active drug within 30 min [11]. The timely release of active ingredients from solid dosage forms, as determined by dissolution tests could be used to predict the rate and extent to which the drug would be absorbed or distributed in the body when taken by patients [14].

Table 4: Release Rate of various samples

Time	% drug release				
	P1	**P2**	**P3**	**P4**	**P5**
0	0	0	0	0	0
5	50.2	51.92	52.11	51.95	50.60
10	53.2	52.94	60.53	56.70	59.21
15	66.26	68.16	63.79	72.30	70.04
20	80.10	80.37	76.63	74.51	78.05
25	84.47	86.10	83.12	87.00	86.62
30	89.18	91.42	95.41	98.46	98.50

The bioequivalent corelation of different brands of pregabalin samples was to be determined using their similarity factors (F_2). The similarity factor stresses on the comparison of closeness or the similarity between two formulation dissolution profiles. Where the percentage release profiles of the samples showed values equal or greater than 85%, the FDA specified that the calculation of F_2 factor might not be necessary for the samples [12]. Thus, the results of the dissolution profiles in this study suggested that the generic samples of pregabalin could be bioequivalent with the innovator P1 and can be interchanged with them.

Conclusion

This study indicated that all brands of pregabalin tested conformed with the pharmacopeial standards for disintegration, weight uniformity and dissolution tests, while two brands (P3 and P5) failed the content uniformity test. Also, the samples were found to be interchangeable with the innovator brand (P1) as their dissolution profiles showed that they all released more than 85% of their active content within 30 min. The study thus underscored the need for constant post-market surveillance and quality assurance of essential drug agents with multiple generics, especially in developing countries.

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