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EVALUATION OF THE PHYSICOCHEMICAL PROPERTIES AND QUALITY INDICES OF MULTISOURCE FLUOXETINE CAPSULES MARKETED IN NIGERIA

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ABSTRACT

The need to constantly evaluate the quality of multisource drugs to ascertain their pharmaceutical equivalence and interchangeability cannot be overemphasized. Fluoxetine, a selective serotonin re-uptake inhibitor antidepressant, is one of the commonly utilized multisource psychotropic agents in many parts of the globe, with an equally great potential for abuse. This study examined the extent to which commonly available brands of fluoxetine hydrochloride in Nigeria comply with quality and safety standards. Different brands of fluoxetine hydrochloride capsules obtained from retail pharmacies located in some parts of Nigeria were assessed using official BP and USP and unofficial methods. Tests for uniformity of weight, disintegration, dissolution, content of active ingredients and similarity factor determination for capsules were employed. The content of active ingredient test was carried out using UV-spectrophotometer at a wavelength of 241 nm for fluoxetine. The innovator brand (Prozac®) was used as primary standard. The results showed that all the brands passed the uniformity of weight (< 5 mg), disintegration (< 10 min), and dissolution tests (> 85% after 30 min). However, one sample failed the assay for active ingredient (75%), while only one brand had a similarity factor greater than 50. Thus, only one brand was found to be interchangeable with the innovator brand. Therefore, the random therapeutic use of multisource fluoxetine in Nigeria can potentially affect therapeutic outcome.

KEYWORDS: Substandard, Counterfeit, Fluoxetine, Interchangeability, Multisource medicines.

1.0 INTRODUCTION

Despite the effort of drug regulatory agencies, the incidence of fake, counterfeit, or substandard medicines in developing countries has continued to plaque their population. There is the need to constantly evaluate the quality of multisource drugs to ascertain their pharmaceutical quality, equivalence and interchangeability.[1] Quality control (QC) of pharmaceutical dosage forms is very important in the pharmaceutical industry. It involves the totality of procedures employed in ensuring the quality of all factors involved in the production of medicines. It is aimed at guaranteeing the safety and efficacy of medicines as well as protecting the manufacturer against compensation claims. QC utilized numerous tests done at every stage of production to ensure that Good Manufacturing Practices protocol is followed and quality is not compromised and is optimized through the independence of QC from production.[2]

Fluoxetine is a selective serotonin re-uptake inhibitor (SSRIs) antidepressant used for the treatment of depression and anxiety disorder.[3] It is one of the commonly prescribed antidepressant agents prescribed in Nigeria. The SSRIs generally produce a less toxic side effect, and fewer deaths have been attributed to overdose compared to more traditional antidepressants, such as tricyclic antidepressants.[4] Among SSRIs, fluoxetine has been reported to be the least toxic by hazard index measures.[4] However, reports have shown that most common effects of fluoxetine overdose were signs of serotonin syndrome such as tachycardia, drowsiness, tremor, nausea, and vomiting. Other serious and life threating effects include seizures, cardiac toxicity, rapid onset, ascending sensorimotor paralysis, bilateral hearing loss, respiratory failure, cardiac arrest and death, while overdose can occur as a result of accident, medical error or poor quality of dosage form.[5]

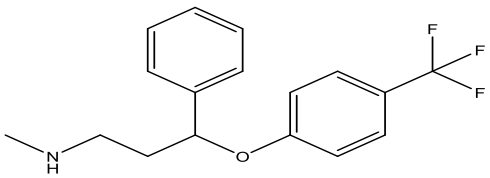

Fig 1: Structure of Fluoxetine.

Predictability of therapeutic outcome and lowering of chances of inaccurate dosage associated with the use of multisource brands of fluoxetine underscores the need to ensure that the quality of various generics of fluoxetine comply with specified standards as the innovator brand. The efficacy and safety of any pharmaceutical dosage form can only be guaranteed when its quality is reliable. Efficacy of pharmaceutical dosage forms is generally determined by the manufacturing methods and also by their formulation properties, therefore it is likely that the quality of dosage form may vary slightly, however, this variability must comply with those contained in reference books such the USP and B.P [6]. The aim of this work was to investigate the pharmaceutical quality, equivalence and interchangeability of different brands of fluoxetine hydrochloride capsules in Nigeria.

2.0 MATERIALS AND METHOD

2.1 Sample Collection and Organoleptic Analysis

The respective brands of fluoxetine 20mg capsules used in this study were procured from various pharmacy premises in south-south states of Nigeria. Each brand was identified by brand name, manufacturer's name, country of manufacture, manufacturing / expiry dates, batch number / or lot number, manufacturing and expiry dates and label claim of potency. There capsules were coded as F1, F2 and F3; and physically examined for shape, colour, packaging and overall dosage form conformity. The innovator brand of fluoxetine, Prozac® manufactured by Eli Lilly and Company was used as the standard.

2.2 Instruments/Reagents used in the study

Laboratory instruments such as dissolution tester (DT 600 High head), Erweka disintegration tester (ZT122), Jenway 6405 UV/Vis Spectrophotometer, Erweka Friabulator, Monsanto Hardness Tester and Acculab analytical weighing balance were used in this study. Distilled water, Methanol, 5% NaOH, NaOH Pellets and Potassium dihydrogen phosphate were used. All reagents were of analytical grade.

2.3 Uniformity of Weight

Twenty capsules of fluoxetine were randomly selected and accurately weighed individually using Acculab analytical balance (ALC210.4, Germany). The mean, standard deviation, and percentage standard deviation of the weights were obtained.[7]

$$\text{Weight Variation} = \frac{I_w - A_w}{A_w} \times 100\%$$

Where I_w = individual weight of tablets
A_w = average weight of tablets.

2.4 Disintegration test

The disintegration test for the fluoxetine capsules were carried out according to the method described in the BP.[7] A 700 ml of distilled water was placed into the beaker in the disintegration apparatus. The temperature of immersion fluid was maintained at 37°C. Six capsules were randomly selected from each brand of fluoxetine, one capsule was placed in each of the six tubes and the tubes were immersed into the fluid. The determination was done in triplicate. The disintegration time was recorded and average time and percentage deviation were calculated.

2.5 Preparation of 0.1N Hydrochloric Acid

A 0.1 N hydrochloric acid was prepared by dissolving 10 ml of concentrated hydrochloric acid in 500 ml of distilled water and made up to 1000ml with distilled water.[8]

2.6 Dissolution test

The dissolution test for the different brands of fluoxetine capsules was carried out according to British Pharmacopoeia using Erweka Dissolution Apparatus, Germany (paddle type).[7] The 0.1N hydrochloric acid (900 ml) was placed in each of the vessels of the dissolution apparatus and the medium maintained at 37°C. The paddles were rotated at a rotational speed of 50 rpm. A capsule from each brand was placed in the vessel containing 0.1 N hydrochloric acid and the dissolution apparatus was operated for 30 min. A 5 ml of dissolution medium was withdrawn using a pipette for each brand at 5, 10, 15, 20, 25 and 30 min intervals, and immediately replaced with 5 ml of 0.1N hydrochloric acid after each withdrawal. The withdrawn samples were filtered and assayed using UV-Visible spectrophotometer at 241 nm to determine the release of fluoxetine from the capsules.

2.7 Assay of active ingredient

The content of ten capsules from each brand of fluoxetine was weighed and its content emptied from their shells into a mortar. A 20 mg equivalent of fluoxetine was weighed, transferred into a volumetric flask and dissolved in 100 ml 0f 0.1 N hydrochloric acid. The solution was filtered through a Whatman® filter paper. A 2 ml volume of filtrate was withdrawn and diluted to 10 ml. The absorbance of the resulting solution was measured at 241 nm against a solvent blank. The mean percentage drug content was determined for each brand.[7]

2.8 Bioequivalence Determination using Dissolution profile

Similarity factor (f2) determination was carried out to compare the dissolution efficiency of the various brands. F2 is a logarithmic reciprocal square root transformation of the sum of square error and is a measurement of the similarity in the percentage dissolution between the two curves.[9] The similarity factor was calculated for the different brands of fluoxetine against the innovator brand Prozac® using the formular below.[10]

$$f_2 = 50\ log\left\{\left(1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right)^{-0.5} \times 100\right\}$$

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

3.0 RESULTS

Table 1: Result of the labelling and Inspection Test.

S/N	*Brand*	*Batch No*	*Label claim (mg)*	*Manufacturing date*	*Expiry date*	*Country of origin*
1	*F1*	*2788485*	*20*	*06/2016*	*05/2019*	*UK*
2	*F2*	*V618*	*20*	*05/2016*	*04/2019*	*India*
3	*F3*	*PJC7009*	*20*	*12/2017*	*01/2020*	*UK*
4	*R2*	*7230812*	*20*	*09/2017*	*08/2020*	*UK*

Table 2: Results of the general appearance for the tested brands of Amitriptyline.

Product code	Colour	Dosage form
F1	Green and White	Capsule
F2	Green and White	Capsule
F3	Green and White	Capsule
R2	Green and White	Capsule

Table 3: Results of weight variation, hardness, % friability, disintegration and % content tests.

Sample	*Weight variation mean (mg)± SEM*	*% Dissolution*	*Disintegration Mean (min)*	*% content*	*F2 (vs R1)*
F1	*302. ± 2.04*	*71.41*	*3.90*	*99.20*	*34.30*
F2	*314.0 ± 5.02*	*87.00*	*3.80*	*75.00*	*52.43*
F3	*312.5 ± 4.63*	*69.40*	*3.80*	*99.20*	*41.00*
R2	*311.5 ± 4.57*	84.41	*5.30*	*100*	-
Official Specification	*≤ 5-7.5 (USP)*	*4-8 (USP)*	*5-30 (USP)*	*95-105 (USP)*	*> 50 (FDA)*

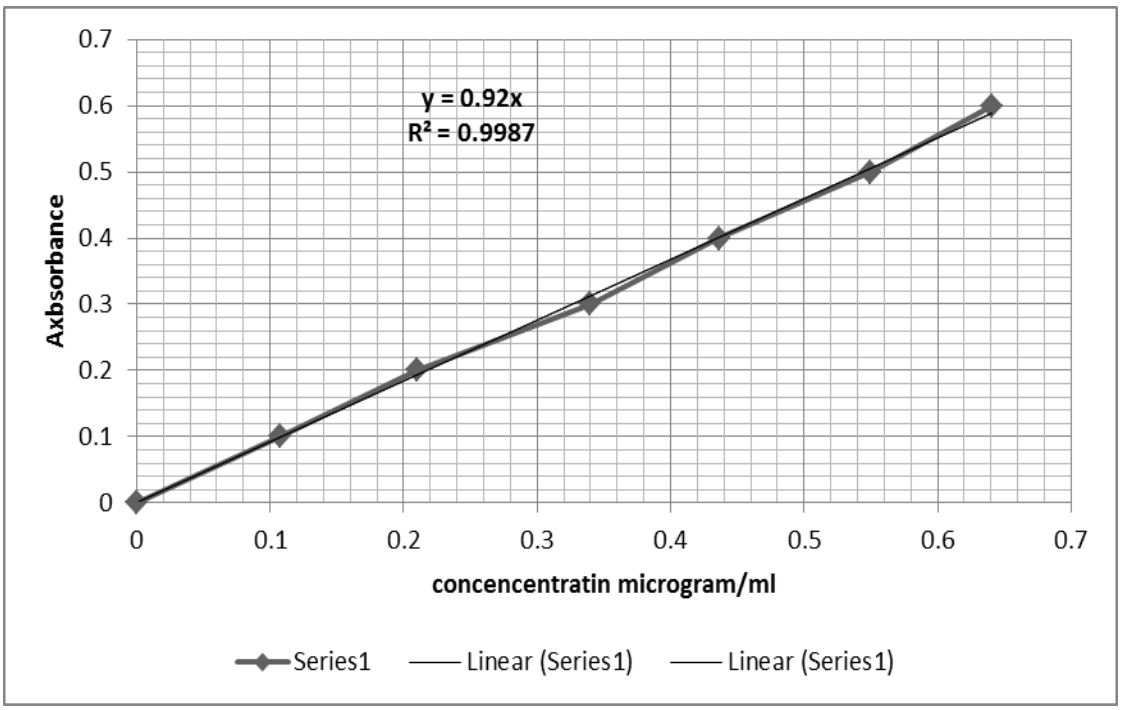

Fig 2: Standard Calibration Curve of fluoxetine hydrochloride.

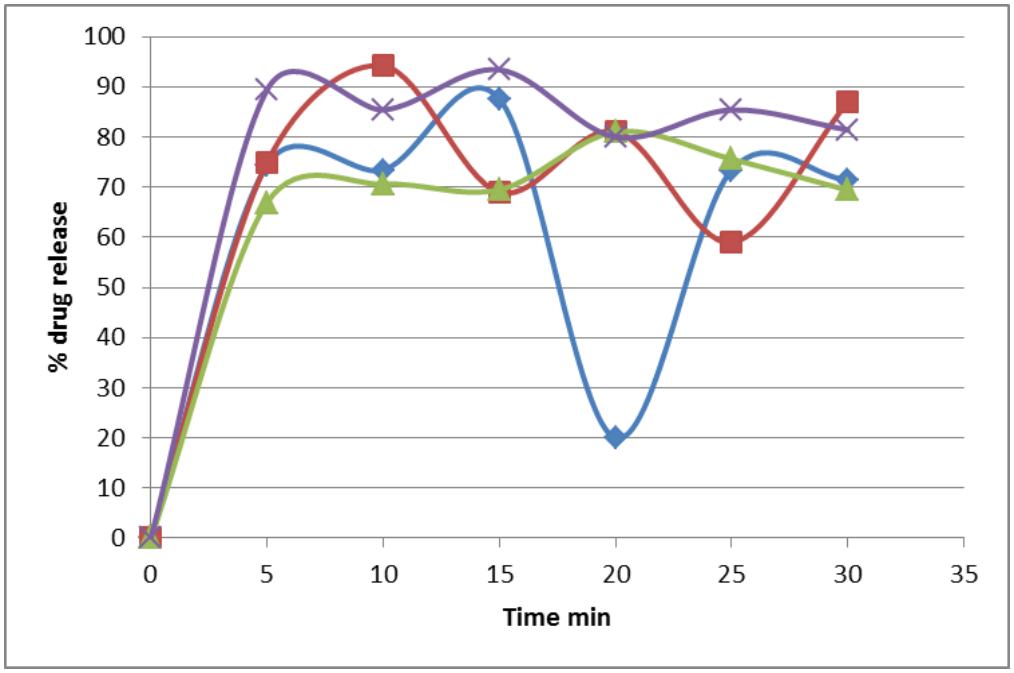

Fig 3: Graph of % drug release against Time (Fluoxetine).

4.0 DISCUSSION

The physical and organoleptic tests revealed that all the brands of fluoxetine (20 mg) capsules used in this study were within their shelf lives with batch numbers and country of manufacture clearly indicated (Table 1). They were capsules with a green and white shell colour contained in aluminium foils and well-sealed plastic containers. (Table 2).

Weight variation test was carried out to ensure that each of the capsules contained uniform amount of drug (Table 3). The sample with the least mean weight variation (302. ± 2.04) was brand F1 while brand F2 had the highest weight variation (314.0 ± 5.02). All the brands, however, complied with the BP official specifications, as none had a coefficient of variation greater than 10% of their average weight.[11]

Content uniformity test is a very important assessment for oral solid dosage forms. The label claim for fluoxetine in the samples were 20 mg. Sample F2 had the least percentage drug content (75.0%) while the other remaining samples had percentage drug content approximating 100 ±2 % of the labelled claim (Table 3). The BP specification for the assay is that the fluoxetine content should not be less than 98 % and not more than 102 %.[7] Therefore, the assay results ascertained the acceptable quality of fluoxetine in three of the tested brands.

Disintegration for capsules is the gradual released of drugs from the capsule shell and breakdown into smaller particles and is seen as the first step towards dissolution.[12] The USP requires that disintegration of uncoated tablets and hard gelatin capsules should occur within 15 minutes.[8] As shown in Table 3, the disintegration time for all the brands ranges from 3.8 (F2) to 5.3 min (R2), hence all samples complied with the official requirements. Thus, the result showed that all the samples are expected to release their active ingredients when administered within specified time limits, having given acceptable disintegration time values.

Dissolution test was carried out to determine the percentage amount of fluoxetine released from the capsules within 30 minutes when in contact with simulated body fluids (Fig. 3). Dissolution studies help to determine the amount of drug available for absorption after oral administration. Drugs with poor dissolution will not be available in the body system or target organ/tissues to elicit therapeutic effect [6]. Two brands (F1 and F3) failed the USP requirement that not less than 85% of fluoxetine hydrochloride should be released within 30 min.[8]

Similarity factor (f2) was done to determine the equivalence between the dissolution profiles of the brands, with the innovator brand serving as the reference with which other brands were compared. The specification by the FDA is that only similarity factor values from 50 to 100 indicate identical profiles, and such brands are interchangeable.[9] From the results shown in Table 3, only sample F2, with an f2 value of 52.43 could be said to be bio-pharmaceutically equivalent with the innovator brand, R2.[13]

5.0 CONCLUSION

The study revealed that only one generic brand of fluoxetine capsules marketed in parts of Nigeria was found to be interchangeable with the innovator brand. Therefore, the random therapeutic use of multisource fluoxetine in Nigeria could potentially affect therapeutic outcome and safety.

6.0 Conflict of Interests

The authors declare no conflict of interest in the course of this study.

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