ejpmr, 2021, 8(6), 27-31

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

A COMPARATIVE STUDY OF THE QUALITY OF MULTISOURCE RISPERIDONE TABLETS MARKETED IN NIGERIA

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Article Received on 27/03/2021 **Article Revised on 16/04/2021** **Article Accepted on 30/04/2021**

ABSTRACT

Recently, multisource psychotropic medications have become the mainstay of clinical management of psychotic and neurological disorders resulting in decreased treatment cost. The World Health Organization (WHO), however, had estimated that 30 % of the medicines in circulation in low- and middle-income countries, like Nigeria, are substandard and counterfeit, thus, posing serious public health challenge to patients. The objective of this study was to evaluate the degree of compliance of different brands of risperidone with pharmacopeia standards. Generic brands of risperidone were sourced from pharmacies in south-south states of Nigeria and analyzed for uniformity of weight, hardness, friability, disintegration, and dissolution profiles. The content of active ingredients and similarity factor (*F2*) of the dissolution profiles for the tablets were also determined. All the tests were done according to USP and BP specifications. Risperidone content was determined at a wavelength of 241 nm using UV-spectrophotometer. The innovator brand (R1) was applied as the reference standard. All the brands, passed the content of active ingredients assessment (> 95%), weight uniformity test (< 7.5 mg coefficient of variation), friability test (< 1.0%), disintegration test (< 10 min) and dissolution test (> 85% at 30 min). Only R1 and R2 passed the hardness test (> 4 kg/f)), while the comparison of their dissolution profiles via *F2* determination gave values greater than 50, suggesting good potential for interchangeability of the brands. The study therefore indicated that the brands of risperidone available in Nigerian market met most of the stringent quality and safety standards necessary to ensure efficacy and interchangeability, but, the slight variations in some of the assessment parameters must be taken into account when brands are switched to avoid inconsistency in treatment outcomes.

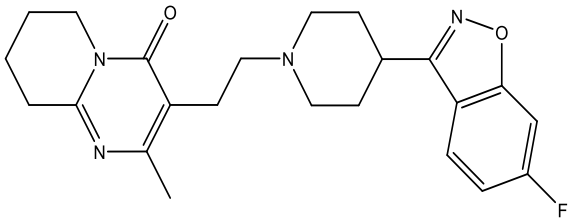
KEYWORDS: Risperidone, Substandard, Counterfeit, Pharmacopoeia, bioavailability, Similarity factor.

1.0 INTRODUCTION

Poor quality medicine, especially among multisource generics, has become a global issue as it has defied most existing international and national regulations. This, however, occurs more in developing countries like Nigeria.[1] The World Health Organization (WHO) estimated that 30% of the medicines in circulation in low- and middle- countries are substandard and counterfeit due to very weak policies, regulation and policy enforcement systems for medicine. Poor quality medicine poses serious public health challenge to end-users globally.[2] Antipsychotics, such as risperidone, have become one of the major targets for counterfeiters due to its increasing use in the relief of symptoms of mental health disorders.[3]

Risperidone is a selective blocker of dopamine (D2) and serotonin 5-HT2 receptors. It acts as an atypical antipsychotic agent which has been shown to improve both positive and negative symptoms in the treatment of schizophrenia.[3] It is used widely in the treatment of mania and schizophrenia, and its therapy is associated with serum amino transferase elevations, and in rare instances, has been linked to clinically apparent acute liver injury.[4]

Risperidone belongs to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ with molecular weight of 410.49.[5] The chemical structure is shown below (Fig. 1).



Chemical Formula: $C_{23}H_{27}FN_4O_2$
Molecular Weight: 410.49
m/z: 410.21 (100.0%), 411.22 (24.9%), 412.22 (2.7%),

411.21 (1.5%)
Elemental Analysis: C, 67.30; H, 6.63; F, 4.63; N, 13.65; O, 7.80

Fig 1: Structure of Risperidone.

Quality assurance of multi-source pharmaceutical products ensures that the manufacturing processes of the products comply with required specifications thereby assuring product efficacy when used interchangeably.[6] This study was aimed at investigating the *in-vitro* dissolution profiles and other physicochemical parameters of different generics of risperidone tablets that are available in some Nigerian markets to determine their biopharmaceutical equivalence and interchangeability.

2.0 MATERIALS AND METHOD

2.1 Sample Collection: Three brands of risperidone (2 mg) tablets (coded R1 – R3) used in this study were purchased from retail pharmacy outlets in south-south states of Nigeria in the first quarter of 2018. R1 was the innovator brand which served as the primary standard. These were stored under appropriate conditions and tested within their expiration dates.

2.2 Instruments/Reagents used in the study

Jenway 6405 UV/Vis Spectrophotometer, Acculab analytical weighing balance, Dissolution tester (DT 600 High head), Erweka disintegration tester (ZT122, serial No: 125397.Oa96; ZT x 20 series), Erweka Friabulator and Monsanto Hardness Tester were used in this study. Methanol, 5% NaOH, Distilled water, NaOH Pellets and Potassium dihydrogen phosphate were also used. All reagents were of analytical grade.

2.3 Preliminary test

2.3.1 General Appearance

Organoleptic analysis was performed on each sample. The shape, colour and coating type of the different brands of risperidone tablets were examined and recorded.

2.3.1 Packaging and Labeling Inspection: The labeling on the primary and secondary packages of the tablets was properly examined for the following details: name and strength of active ingredient, batch number, brand name, manufacture and expiry dates. The manufacturers' addresses were also noted.

2.4 *In Vitro* Official Tests

2.4.1 Uniformity of Weight

Twenty tablets from each brand of risperidone were selected and weighed with Acculab® analytical balance ALC210.4 (Germany) individually. The determinations were done in triplicates. The weights were recorded and the mean, standard deviation, and percentage standard deviation were calculated using the formula.

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

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

2.4.2 Disintegration Test

The disintegration test for the different brands of risperidone was 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 (Erweka disintegration machine, Germany). The temperature of immersion fluid was maintained at 37^{o}C. Six tablets were randomly selected from each brand of risperidone, one tablet was placed in each of the six tubes and the tubes were immersed into the fluid. The disintegration time was recorded and average time as well as percentage deviation was calculated.

2.4.3 Preparation of standard stock solution

A 10 ml volume of concentrated hydrochloric acid was dissolved in 500 ml of distilled water and made up to 1000 ml with distilled water to give 0.1 N HCl. A 10 mg powder equivalent of crushed risperidone tablet was dissolved in 10 ml of distilled water in a beaker and filtered. The filtrate obtained was used as stock solution to obtain concentrations of 0.1, 0.2, 0.3, 0.4, 0.5 and 0.6 µg/mL solutions.

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

An aliquot from the stock solution was scanned in the UV-Visible spectrophotometer at different wavelengths to determine the maximum wavelength of absorption. Maximum wavelength obtained was 241 nm.

2.4.5 Determination of standard calibration curve

The serial dilutions (0.1, 0.2, 0.3, 0.4, 0.5, 0.6 µg/ml) obtained from risperidone stock solution were passed through the UV-Visible spectrophotometer and their absorbance was read at 241 nm. A plot of concentration against absorbance was made and it's coefficient of determination (r^2) was calculated.

2.4.5 Assay of Content of Active Ingredients

Ten tablets from each brand of risperidone were weighed and crushed to powder in a mortar. An average weight of the tablets (2 mg) was weighed, transferred into a 100 ml volumetric flask and dissolved with 100 ml of 0.1 N hydrochloric Acid. A 0.05 ml of the solution was measured and transferred to 10 ml volumetric flask separately; 0.1 N HCl was added to make up to 10 ml volume. Aliquot volume of the solution was diluted to get a concentration of 20 µg/ml. The average absorbance of the sample solution after two determinations at 241 nm against a blank solvent obtained was recorded. The percentage drug content was calculated for each batch.

2.4.6 Disintegration test

The disintegration test for the different brands of risperidone was carried out according to the method described in the BP.[7] A 700ml of distilled water was placed into the beaker in the disintegration apparatus

(Erweka disintegration machine, Germany). The temperature of immersion fluid was maintained at 37 ^{o}C. Six tablets were randomly selected from each brand of risperidone. One tablet was placed in each of the six tubes and the tubes were immersed into the fluid. The disintegration time was recorded and average time and percentage deviation were calculated. This was repeated for all six tablets.

2.4.7 Dissolution Test

The dissolution test for the different brands of risperidone tablets were carried out according to United States Pharmacopoeia using Erweka dissolution apparatus Germany (paddle type).[8] The 0.1 N hydrochloric acid (900 ml) was placed in each of the vessels of the dissolution apparatus and the medium was maintained at 37^{o}C. The paddles were rotated at a rotational speed of 50 rpm. A tablet 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 replaced immediately 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 risperidone from the tablets.

2.5 *In Vitro* Unofficial Tests

2.5.1 Hardness/Crushing Strength Test

Ten tablets were randomly selected from each brand of risperidone. One tablet was placed between the jaws of a hardness tester and adjusted by pushing forward the movable jaw inside, turning the plunger clockwise. The value on the scale that coincides with the pointer was noted and pressure applied till the tablet breaks. The value on the scale was recorded. The procedure was repeated for all tablets.

2.5.2 Friability test

Ten tablets were selected at random. Each batch of ten tablets was weighed. The tablets were placed in the friabilator and rotated for 4 min at 25 revolutions per minute (rpm). The tablets were removed, de-dusted and reweighed.

2.5.3 Calculation of fit factor (F)

Similarity factor

The similarity factor (f2) 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 the curves. F2 acceptable range falls within 50 to 100.[9]

Fit factor was calculated using the formula; F2

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

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 labeling and Inspection Test.

S/N	Label Claim	Batch No	Manufacturing date	Expiry date	Company name/country of origin
R1	Risperidone 2mg tablets	010087	06/2016	05/2019	United Kingdom
R2	Risperidone 2mg tablets	BCR9D003	04/2017	05/2021	India
R3	Risperidone 2mg tablets	2240817	07/2016	08/2019	United Kingdom

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

Product code	Coating type	Colour	Dosage form
R1	Film coated	Peach	Tablet
R2	Film coated	Peach	Tablet
R3	Film coated	Peach	Tablet

Table 3: Results of weight variation, hardness, % friability, disintegration, % content and fit factor (F2) of risperidone brands.

Sample	*Weight variation mean (mg)± SEM*	*Hardness (Kg/f)*	*% friability*	*Disintegration time (min)*	*% content*	*F2 (vs R1)*
R1	204.10±2.97	5.10	0.15	*1.0*	*100.0*	-
R2	202.10±2.54	5.17	0.27	*2.2*	96.5	75.10
R3	208.60±4.24	2.21	0.17	*1.5*	95.5	78.12
Official Specification	*≤ 5-7.5 (USP)*	*4-8 (USP)*	*<1.0 (USP)*	*5-30 (USP)*	*95-105 (USP)*	*> 50 (FDA)*

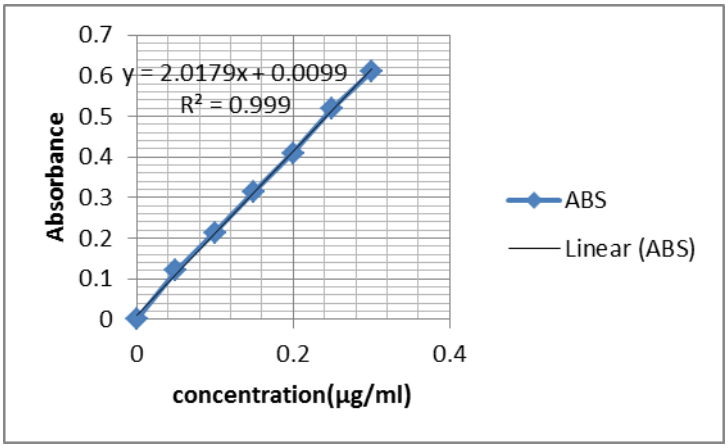


Fig 2: Standard Calibration Curve of Risperidone.

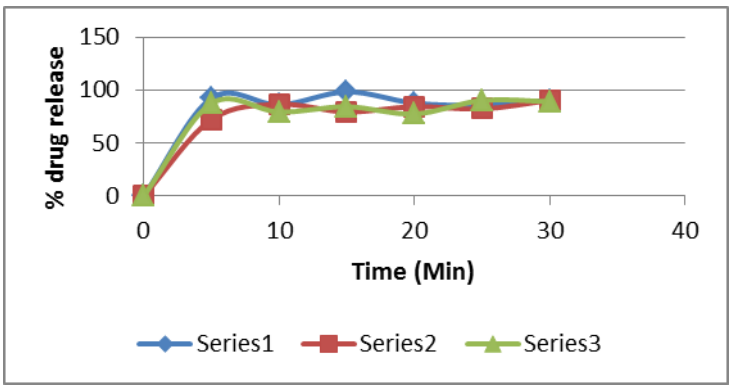


Fig 3: Graph of % drug release against time of Risperidone

4.0 DISCUSSION

The different brands of risperidone used in this study had suitable appearance, properly labelled and registered with NAFDAC. The samples were all within their expiry dates with batch numbers clearly indicated (Table 1). They were filmed coated and peach colored (Table 2). The overall appearance of tablets determines consumer acceptability and can affect the level of compliance to the dosage regimen by the patient.[10] Thus, the risperidone samples in this study complied with acceptable standards for organoleptic presentations and packaging of pharmaceutical dosage forms.

Hardness test is designed to determine the load required to crush the tablet when placed on its edge. All the brands of risperidone tablets in this study, except R3, failed the hardness test (Table 3). The USP specification for tablet hardness ranges from 4 to 8 kgf.[8] This showed that tablets in sample R3 might not be able to withstand rigorous treatment in the course of packaging and transportation. Factors affecting the hardness of tablets include compressive force applied during the compression process, the amount of binder and method of granulation.

Friability test is used to evaluate tablet resistance to abrasion. The USP states that the percentage friability permitted should be less than 1%. From the result carried out, all brands passed the friability test.[8] This implied that the tablet brands possess enough robustness to withstand packaging and handling pressures that would make the tablets to maintain the desired weight and content uniformity.

Weight uniformity was done to determine the consistency of the weight of the tablets. Determination of percentage standard deviation of tablets and capsules gives an idea of how tablets and capsules vary from each other in a batch. The BP specified that for drugs weighing 80 mg or less, the percentage standard deviation should not be more than 10%.[7] The different brands of tablets used for this study all passed the weight uniformity test. Factors such as the formulation and manufacturing processes influences the weight of tablets in the different brands of a generic drug.[11] This result showed that all the brands tested could contain similar quantities of active ingredients and excipients and thus reducing dosage fluctuations when the drugs are administered.

For content uniformity test, BP specifies that risperidone tablet should have an active ingredient content ranging from 90-110%.[7] All brands in this study passed this test (Table 3). The slight variation in the amount of active ingredients contained in these samples could, however, result in unpredictable treatment outcomes considering the little quantity (2 mg) of risperidone contained in each tablet.

The disintegration test was carried out to determine the release of the active ingredient from the tablets. Disintegration time is the time required for a dosage form to break up into granules under carefully specified conditions. For disintegration test the USP states that film coated tablets should disintegrate within 15 min.[8] This also applies to hard gelatin capsules. The risperidone tablets used for this research all passed the disintegration test with an average disintegration time ranging from 1.0 to 2.5 min showing quick disintegration time and possible quick onset of action (Table 3). For a drug to be absorbed into the systemic circulation it must first disintegrate to release its active ingredient. Thus, the result showed that all the samples are expected to release their active ingredients within specified time limits, having given acceptable disintegration time values.

The effectiveness of solid dosage forms relies on its ability to dissolve in the fluids of the gastrointestinal tract prior to absorption into systemic circulation. Dissolution is therefore a very important factor to consider because without such drugs would not be absorbed. According to the USP, not less than 85% of risperidone hydrochloride should be released within 30 min.[8] From the results obtained, all brands of risperidone tested passed the dissolution test (Fig 3). This implied that the samples could achieve the desired therapeutic goal when administered, including timely onset of action and attainment of adequate peak plasma concentrations. Factors that affect the dissolution rate of drug ranges from physiochemical properties of drug, drug product formulation factors, processing factors, factors relating to dissolution apparatus and factors related to the dissolution test parameters.[10]

Similarity factor (*F2*) was carried out to determine the bio-pharmaceutical equivalence between the reference brand and the other samples of risperidone using their drug release profiles.[11] The standard specification by the FDA for *F2* values ranges from 50 to 100.[9] Risperidone brand R2 and R3 gave values greater than 50 when compared with R1. Values above 50 indicate the possibility of interchangeability between the tested drug profile and that of the reference sample.[11]

5.0 CONCLUSION

The study indicated that the brands of risperidone tablets available in some Nigerian markets meet most of the stringent quality and safety standards necessary to ensure efficacy and safety of the patient, but, the slight variations in such parameters like percentage drug content and crushing strength must be taken into account when brands are being switched to avoid inconsistent therapeutic outcome in mental health management.

6.0 Conflict of Interests

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

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