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Comparative *in-vitro* quality assessment of Risperidone Tablets marketed in Kaduna State, Nigeria.

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ABSTRACT

Approximately 1% of the world population develops psychosis during their lifetime. Risperidone, a benzisoxazole derivative, has been found to be effective in the management of psychosis especially in refractory psychotic patients with minimal side effects. This has contributed to its widespread use, resulting in the emergence of numerous generic brands. A comparative *in-vitro* quality assessment was carried out on four generic brands (A, B, C and D) and the innovator brand (E) of 2 mg risperidone tablets. Tests on uniformity of weight, friability, disintegration, dissolution and assay were carried out on the five brands and the result of the generics was compared with that of the innovator. The innovator brand passed all the tests. The generic brands passed the uniformity of weight, friability and disintegration tests, not exceeding the acceptable limits (BP, 2009). Only brand A failed the assay with a percentage content of 46 %. Brands C and D were found to have dissolution differencefactors within the accepted range of 0-10 %, but their similarity factors fell outside the acceptable range of 50-100 %. Brands A and B failed the dissolution tests entirely. This suggests that some of the generics of risperidone tablets marketed in Kaduna fall below the acceptable specifications.

Keywords: Quality assessment, *in vitro*, risperidone

INTRODUCTION

Risperidone is a second generation atypical antipsychotic drug used for the acute and long- term treatment of patients with schizophrenia. It is a dopamine antagonist possessing anti-serotonergic, anti-adrenergic and anti-histaminergic properties (Hardman *et al.*, 2001). The absolute oral bioavailability of risperidone is 70 % and a half-life of 3 hours in extensive metabolizers and 20 hours in poor metabolizers. It is rapidly and well absorbed and food does not affect the rate or extent of absorption. It is rapidly distributed with a volume of distribution of 1-2 L/kg. It is 90 % protein bound to albumin and undergoes extensive hepatic metabolism (USP, 2006). Risperidone has lesser side effects compared to haloperidol at dosage of 6 mg/day or less. This coupled with its efficacy in the management of refractory psychosis, has made it a drug of choice in the management of psychosis (Hardman *et al.*, 2001). It was first developed by Jassen-Cilag and approved by the Food and Drug Administration (FDA) in 1994. However, Jassen-Cilag's patent expired in 2003 and this paved the way for the introduction of cheaper generics into the drug market. Therefore, it is important that routine quality assessment tests are carried out the different brands of risperidone available. Quality assessment of pharmaceuticals needs to be routinely carried in order to prevent the kind of product which is not suitable for the aims of which it has been prescribed (Birhanu, *et al.*, 2014). Drug quality is a source of great concern worldwide, especially in developing countries and the failure of an effective control mechanism has led to the presence of fake and substandard drugs in these countries. Surveys have shown that about 20 % of sampled drugs failed quality assessment tests (Birhanu *et al.*, 2014; Taylor *et al.*, 2000; Wondemagegnehu *et al.*, 1999). Widespread counterfeit of medicines in developing countries, excessive decomposition of active ingredient as a result of high temperature and humidity especially in tropical climates and poor quality assurance during the manufacture of pharmaceuticals are some of the reasons for poor quality (Benjamin *et al.*, 2005). Use of poor quality drugs can lead to treatment failure, adverse reactions, drug resistance, increased morbidity and mortality. It can also erode public confidence in a country's health program, waste scarce resources and severely affect the business of the manufacturer whose product is being copied through loss of confidence as well as revenue (Jim, 2005).

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Antipsychotics (risperidone inclusive) are used for long durations, which may result to tolerance and hence relapse especially if substandard brands are administered (Hoen, 2010). According to the British Pharmacopoeia, BP (2009), the official tests carried out to determine the quality of tablets include weight variation test (uniformity of weight), disintegration test, *in vitro* dissolution test and drug assay. Other tests include hardness and friability tests. The aim of this study is to carry out quality assessment tests on the different brands of 2 mg risperidone marketed in Kaduna, Nigeria using the above mentioned tests.

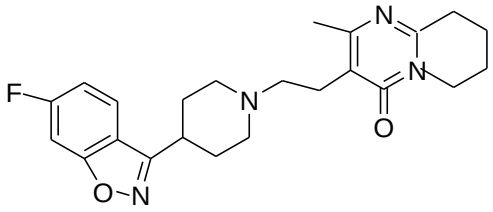

Fig. 1 Chemical structure of risperidone

MATERIALS AND METHODS

Materials

Equipment: UV spectrophotometer (SP8-100, Cambridge, England), fribilator (Erweka, TA3, Germany), dissolution apparatus (Erweka, Germany), disintergration apparatus (Erweka, Germany), analytical balance (Mettler Gallenkamp), manual tablet hardness tester, mortar and pestle.

Chemicals/Reagents: Risperidone reference standard (Sigma-Aldrich; R1000600), five brands of risperidone 2 mg tablets (Royale Risperidone 2®, Risperidone 2 mg (Teva), Risperidone 2 mg (Sandoz), Rispzen-2®, Risperdal®; coded as A, B, C, D, and E respectively), 0.1N HCl, methanol, ethyl acetate and bromocresol green.

Methods

Identification test of the risperidone standard powder

The standard powder was purchased from Sigma-Aldrich, Germany and was identified by melting point and infra-red (I.R) spectroscopy methods.

Preparation of standard stock solution of risperidone

A stock standard solution equivalent to 100µg/ml risperidone was prepared by dissolving 10mg of reference standard in 100 ml of 0.1 N HCl. Working solutions were prepared as required by serial dilution.

Determination of wavelength of maximum absorption of risperidone

An aliquot of 2 ml stock standard solution of risperidone was measured into a 10 ml beaker and made up to 10 ml with 0.1 N HCl. The solution was scanned on the spectrophotometer in the range 200 to 600 nm and the maximum absorption was determined.

Preparation of calibration curve

Calibration curve of risperidone in 0.1 N HCl was constructed by preparing a serial of dilution with different concentrations (4, 8, 12, 16, 20 µg/ml) from stock solution. The absorbance was then measured at the wavelength of maximum absorption of the drug. The measured absorbance was plotted against the respective concentrations.

Quality Control assessment of risperidone tablets (B.P. 2009)

Sampling of tablets

Five brands of risperidone were randomly purchased from pharmacies and information about the batch number, manufacturing date and expiry date for each brand was noted down. The four generic brands were coded brands A, B, C and D while the innovator brand was coded brand E.

Physical tests and identification

Physical assessment of the tablets was carried out, noting down the colour and shape of tablets of each brand. A manual tablet hardness tester was used to carry out the crushing strength test of the tablets of each brand. The diameter and thickness of each tablet was also measured for each brand (n=6). Identification of tablets of each brand of risperidone was also carried out by IR spectroscopy.

Uniformity of weight

Six tablets were individually weighed using the analytical balance and the weights were recorded and the average weight determined.

Friability test

Six tablets from each brand were initially weighed and placed in a friabilator, which was operated at 25 revolutions per minute. After four minutes (100 revolutions), the tablets were removed, dusted with a tissue paper, weighed and the difference in tablet weight was determined. The percentage loss was calculated as follows:

Friability (%) = $(W_1\text{-}W_2/W_1) \times 100$

Where W_1= Initial weight and W_2= Final weight

Disintegration test

The disintegration test was carried out using the Erweka disintegration apparatus as described in the B.P. (2009). 0.1 N HCl solution was used as the medium and it was maintained at 37 ± 10 ^{o}C. Six (6)

tablets were randomly selected from each brand and a tablet was placed in each of the six tubes/units of the disintegration apparatus. The time taken for each of the individual tablets to pass through the tube was recorded.

Dissolution test

The dissolution rate for risperidone tablet was determined using Erweka dissolution apparatus as described in the B.P. (2009). The medium, 500 ml 0.1 N HCl is placed into the vessel of the dissolution apparatus and a tablet of risperidone (n=6) was placed into the rotating basket and the apparatus was assembled and allowed to equilibrate at 37 ˚C and run at 50 rpm for 45 minutes. 5 ml of the medium was withdrawn from a zone midway between the surface of the dissolution medium and the top of the rotating basket at 5, 10, 15, 30 and 45 minutes. The absorbance of risperidone from the solution was determined using UV spectrophotometer at 275 nm. The absorbance was converted to concentration using the calibration curve earlier constructed and the percentage released was determined at each time interval.

Assay of risperidone tablets

Assay of the risperidone tablets were carried out by adopting the method described by Idris *et al*., (2015), for quantitative determination of risperidone in tablet dosage forms. Twenty tablets were grounded into fine powder and the quantity of powder equivalent to 10 mg of risperidone was weighed accurately into a 100 ml calibrated flask and 10 ml of ethyl acetate was added. The content was shaken for 30 minutes, made up to the 100 ml mark with ethyl acetate, mixed well and filtered using a Whatman No.41 filter paper. The filtrate containing risperidone was subjected to analysis by taking 1 ml of the filtrate and adding 0.5 ml of bromocresol green. The volume is made up to 5 ml with ethyl acetate and the absorbance is taken at 414 nm.

RESULTS AND DISCUSSION

The melting point range of the risperidone standard powder was gotten as 169- 172 ˚C and the IR spectra was obtained and compared with that of the standard spectrum of risperidone in B.P. (2009) and they were found to be super imposable. Identification of each brand of risperidone was also done using the IR method.The wavelength of maximum absorption of risperidone in 0.1 N HCl was determined to be 275 nm. A calibration curve for risperidone at this wavelength was generated (Fig. 1) and used for the dissolution test.

Table 1 Label information of five brands of risperidone tablets

Product code	Batch number	Manufacturing date	Expiry date
A	6168	June 2017	May 2020
B	69695-U	November 2017	November 2019
C	GH267	February 2017	February 2019
D	PZL-160610	June 2017	May 2019
E	014125	November 2016	November 2018

Table 2 Physical assessment and tests

Product code	Physical properties	Hardness (kg/cm^3)	Thickness (mm)	Diameter (mm)
A	Blue; round	3.40±0.10	2.91±0.01	6.49±0.01
B	Light orange; round	4.10±0.10	3.64±0.01	8.28±0.00
C	Light orange, oblong	3.40±0.10	3.51±0.00	5.77±0.01
D	Deep orange; round	4.20±0.12	3.24±0.01	8.18±0.01
E	Light orange; oblong	5.40±0.40	3.53±0.01	5.09±0.00
Acceptable range	NA	4-10	NA	NA

NA- Not applicable

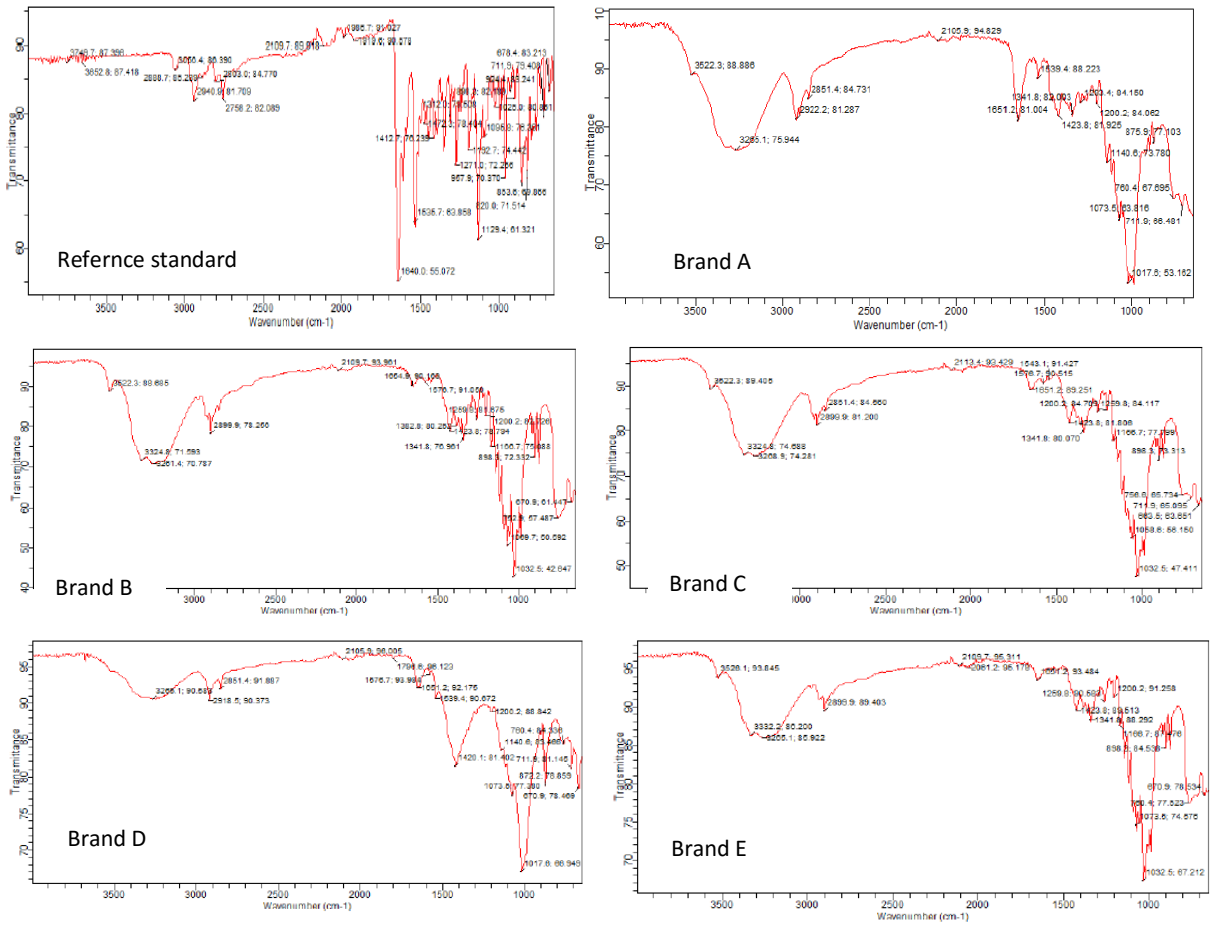

Fig. 1 Infrared spectra of risperidone reference standard and tablets

Table 3 Uniformity of weight, Disintegration test and assay of risperidone tablets

Product code	Friability (%)	Weight uniformity: Percentage weight deviation (%)	Disintegration test (min)	Assay (%)
A	0	2.59	4.08±0.90	46.0
B	0	2.15	2.13±0.05	91.0
C	0	0.00	5.50±0.56	96.0
D	0	2.18	0.93±0.18	96.0
E	0	2.15	2.33±0.22	97.0
Acceptable range	≤ 1 %	≤ 5 %	≤ 15 min	90-110 (USP 2006)

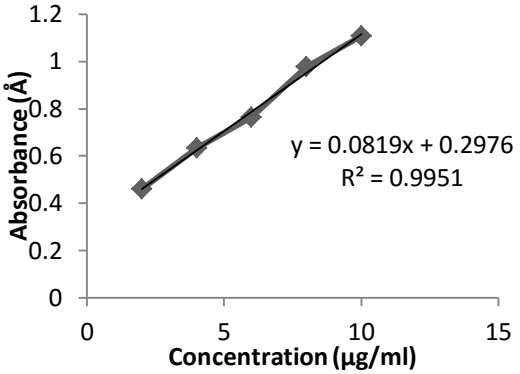

Fig. 1 Calibration curve of risperidone in 0.1 N HCl

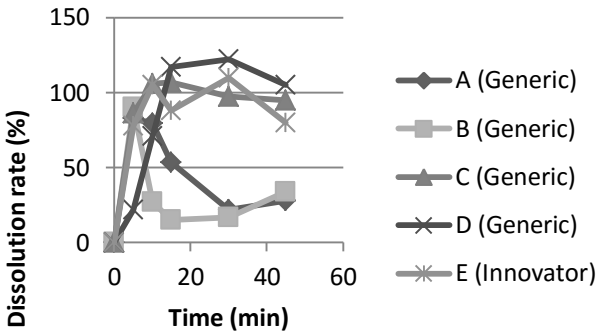

Fig. 2 Dissolution rate of five brands of risperidone

Table 4 Table showing the difference and similarity factors of four generic brands (A, B, C and D) of risperidone as against the innovator brand (E)

Product code	**Difference factor (%)** $f_1 = [\{\Sigma \lvert Rt - Tt \rvert\} / \Sigma Rt\}] \times 100$	**Similarity factor (%)** $f_2 = 50 \times \log \{ [1 + (1/n) \Sigma t=1^n (Rt - Tt)^2]^{-0.5} \times 100\}$
A	42.3	15.1
B	60.3	8.8
C	6.7	44.6
D	5.2	23.1
E	0	50
Acceptable range	0-15	50-100

The accepted range for the crushing strength test (hardness test) is 4-10 kg/cm^3. The hardness of brands A and C fell below (but not too far) the lower limit of the accepted range. This can be attributed to the compression force used in compression of the tablets. All brands of the tablets showed very little variation in thickness and diameter. This suggests that the tablets were filled uniformly into the tablet press. The five brands of risperidone tablets assessed were all film-coated and it was expected that the friability test will turn up as 0 % because coated tablets are not expected to be friable. This also suggests that the coating of the tablets were done properly.

The uniformity of weight test showed that there was not much weight variation among tablets of each brand, especially with brand C which showed no variation at all. All brands showed a percentage weight variation of $\leq$ 5 %, thus satisfying the specifications in BP (2009). Furthermore, all brands passed the disintegration test and not a single tablet disintegrated in more than 15 minutes. All brands passed the assay except for brand A with a percentage content of 46 %. According to Benjamin *et al.*, (2015), widespread counterfeiting of medicines in developing countries, excessive decomposition of active ingredient as a result of high temperature and humidity especially in tropical climates and poor quality assurance are reasons why a drug will fail an assay test.

The dissolution profile of the five brands was analysed using the difference and similarity factors by comparing the four generic brands (A, B, C and D) against the innovator brand E. Brands C and D have difference factors within the acceptable range which indicates that there is no difference in the dissolution profile of brands C or D and the innovator brand. No generic brand had a similarity factor within the acceptable range, with only brand C having a similarity factor near the lower limit of the acceptable range. This suggests that all the four generic brands have no similarity with the dissolution profile of the innovator brand. However, the difference that exists between the dissolution profile of the generics and the innovator is more with brands A and B than with brands C and D. According to Shah *et al.*, (1998), when the dissolution profile of a drug is being compared to another, and its f_2 values falls within the ranges of 50- 100 %, the performance (efficacy) of the two drugs is said to be equivalent, and one can be substituted for the other by the consumer.

CONCLUSION

The quality assessment of five brands of risperidone was conducted and the innovator brand passed all the tests while only two out of the four generic brands passed all the quality control tests. It is recommended that manufacturers conduct comparative *in vitro* quality assessment tests of their brands as against the innovator brand in order to validate their claims and ensure supply of only quality drugs.

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