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QUALITY CONTROL ASSESSMENT OF FIVE BRANDS OF KETOCONAZOLE TABLETS MARKETED IN NIGERIA

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Abstract
The qualities of five different brands of ketoconazole tablets commercially available in Nigeria were assessed. The weight uniformity, hardness, friability, disintegration time, absolute drug content and dissolution rate of the brands were determined using official or standard methods, as applicable. The five brands passed the uniformity of weight test with the range of 0.351 – 0.676 g, hardness test with a range of 4.00 – 7.70 kgF, friability test with a range of 0.146 – 0.268 % and absolute drug content with a range of 98.82 – 107.02 % and conformed to the pharmacopoeias specifications. However, all the tested brands had poor dissolution profiles. None of the brands was bioequivalent with the innovator brand.

Keywords: Ketoconazole tablets, quality control, interchangeability, Nigeria

INTRODUCTION

The production of generic drug equivalents of innovator products is aimed at improving availability and affordability of such drug products. However, in some developing countries, the qualities of such generics are compromised with the attendant untoward influence on therapeutic outcome and loss of confidence in the healthcare system.

Many developing and underdeveloped countries import a large proportion of their drug requirement due to lack of manufacturing facilities (Mikere and Mekonnen, 2006). Most of these countries also have few or lack well-equipped quality control laboratories which would routinely ascertain the quality of the imported or locally produced drugs before circulation. Consequently, substandard or counterfeit generic drug products abound.

The counterfeit drug products may include those that have correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging (Kenyon *et al*, 1999). Several factors which encourage counterfeit drug production include ineffective enforcement of existing laws, involvement of non-professionals in drug business, loose control system, high cost of drugs, greed, ignorance, corruption (Erhun *et al*, 2001). The overall effect is that a patient changing from one brand to another may not obtain the desired

effect at the required time (Bakare-Odunola *et al*, 2006).

The existence of substandard brands of any drug or drug product impairs interchangeability among its different brands (Okonkwo *et al*, 2006). Interchangeable drug products should essentially be bioequivalent and contain same amounts of active principles and exhibit similar bioavailability profile after administration of equimolar doses (Olaniyi, 2001; Nwodo *et al*, 2007).

Bioavailability of a drug and their consequent therapeutic efficacies are dependent on the formulation protocols or manufacturing process of the manufacturers (Bakare-Odunola *et al*, 2006). Thus the determination of such quality control/assurance parameters including tablet hardness, friability, weight uniformity, disintegration time, dissolution time, content uniformity of active ingredient, become imperative.

Ketoconazole (*cis*-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy] phenyl]piperazine) is an imidazole–dioxolane antimycotic agent which has a broad spectrum of activity against dermatophytes, yeasts and other systemic fungal infections including candidiasis, oral thrush, candiduria, blastomycosis as well as recalcitrant cutaneous dermatophytoses (Taketomo *et al.*, 2000; Sharma, 2004). Ketoconazole is used in the prevention and treatment of skin and fungal infections, especially in immune-compromised patients, such as those with HIV/AIDS. It is usually prescribed for topical infections such as athlete's feet (*Tinea pedis*), *Tinea corporis, Tinea cruris, Tinea versicolor*, ringworm, jock itch, and cutaneous candidiasis. The over-the-counter shampoo version can also be used as a body-wash and as anti-dandruff. Jang *et al*., 2005 also showed that ketoconazole may have a stimulatory effect on hair growth.

Ketoconazole, just like other azole antifungal agents, inhibits the activity of cytochrome P_{450}, 14 alpha-demethylase (P_{450} 14 DM) – an enzyme in the sterol biosynthesis pathway leading from lanosterol to ergosterol (Sheppard and Lampiris, 2001). It therefore blocks the fungal synthesis of ergosterol, which is essential for the integrity of the cell membranes of nearly all pathogenic fungi (Sharma, 2004). Hence, the drug alters the permeability of the fungal cell wall, inhibits fungal biosynthesis of triglycerides and phospholipids, and inhibits several fungal enzymes that result in a build-up of toxic concentration of hydrogen peroxide (Taketomo *et al.*, 2000).

Many brands of ketoconazole tablets are commercially available in Nigeria. Since malevolent dealings in counterfeit drugs are now very much a contemporary reality (Ogaji, 2006), the objective of this study is therefore to assess the quality of five different brands of ketoconazole tablets marketed in Nigeria.

MATERIALS AND METHODS

The five commercial brands of ketoconazole tablets (200 mg) used for the assay were purchased from local pharmacy shops in Enugu, Enugu State and Awka, Anambra State, Nigeria. All the drugs were stored in their packets and used for the study before their specified expiry dates. All reagents used for the analysis were of analytical grade.

The following equipment were used: Roche Friabilator (Model TAR 50234, W. Germany), Mosanto Hardness Tester (Manesty, England), Erweka Disintegration Apparatus (Multiple unit), VEEGO Tablet Dissolution Test Apparatus, UV-Spectrophotometer UNICO-2102,

Autoclave, Incubator and Hot Air Oven.

Uniformity of weight test

Ten tablets, selected randomly from each brand, were weighed individually and collectively using an analytical weighing balance. The mean weights, as well as the deviations (standard error of mean), of the individual tablets from the mean weight were calculated.

Hardness test (crushing strength)

Five tablets were randomly selected from each brand and their hardness determined using the Mosanto Stokes hardness tester. Each tablet was placed between the spindle and anvil and pressure applied by turning the knob sufficiently to hold the tablet in position. The pointer on the scale was adjusted to zero reading and pressure gradually and steadily increased until the tablet breaks. The pointer reading from the scale was taken as the pressure required to break the tablet. The above procedure was repeated for the five different brands of ketoconazole tablets.

Friability test

Five tablets from each brand of ketoconazole tablets were de-dusted, weighed and subjected to vibration and shock in a Roche Friabilator rotating at 25 rpm for 4 minutes. Thereafter, they were de-dusted, reweighed and the percentage loss in weight calculated using the equation:

Percentage friability = loss in weight/initial weight x 100

Disintegration time test

The Erweka multiple unit disintegration apparatus was used for the test. It consisted of a basket rack holding six plastic tubes, open at both ends. The bottoms of the tubes were covered with a 10-mesh screen. The basket was immersed in 900 ml of 0.1N hydrochloric acid contained in 1 liter capacity pyrex beaker and maintained at a temperature of 37 ± 1 °C in a water bath. One tablet from each brand of ketoconazole tablet was dropped into each of the tubes. The rack moved up and down in the dilute acid at the rate of fifty movements per minute. The time taken for all the tablets to break up and pass through the 10-mesh sieve was recorded as the disintegration time.

Absolute drug content

Five tablets of randomly selected ketoconazole brand were collectively weighed, crushed and the quantity equivalent to the brand´s mean weight dissolved with 0.1N HCl, and made up to 100 ml with the dilute acid. The filtrate was obtained and the absorbance read at 235 nm using an Unico-UV 2102 PC Spectrophotometer. The concentration of the active ingredient was determined from the Standard Beer- Lambert's plot obtained with pure sample of ketoconazole.

Dissolution profile studies

The VEEGO tablet dissolution apparatus was used. The tablet was placed in a wire-mesh basket suspended in a dissolution medium of 500 ml of 0.1N HCl maintained at 37 ± 1^{O} C in a water bath. The wire-mesh basket was rotated at a speed of 50 rpm and the experiment allowed to run for 60 minutes for each tablet tested. The stirrer was maintained at a constant speed. At predetermined time interval, 5 ml samples were withdrawn from the beaker and the volume immediately replaced with 5 ml of 0.1N HCl. The withdrawn samples were diluted in a 50-ml volumetric flask and analyzed for ketoconazole contents at 235 nm using a UV-Vis 2102 PC spectrophotometer. The concentration of the active ingredient was then

obtained from the standard Beer-Lambert's plot.

Melting point

Finely powdered dry sample of each tablet brand was introduced into a dry capillary melting-point tube, sealed at one end, so as to form a compact column, 4-6 mm in height. The melting point was then determined by gently heating with liquid paraffin (Atherden, 2006).

RESULTS AND DISCUSSION

The ketoconazole tablets were all circular in shape and had colours that varied between white and off-white colour. The identity profiles of the different brands of ketoconazole tablets marketed in Nigeria are presented in Table 1. While three of the brands (representing 60 %) were imported from Asia, the other two brands (representing 40 %) were imports from Europe. None of the brands was manufactured in Nigeria. This implies that the indigenous pharmaceutical industries in Nigeria are yet to meet up to the challenges of tableting some of the needed drug products.

The results of the quality control parameters of the different brands of ketoconazole tablets are shown in Table 2. The five brands of ketoconazole tablets passed the weight uniformity test since they all had low coefficient of variation in line with the specifications for compressed uncoated tablets (Lund, 1994). Tablet weight variations are attributed to various formulation factors which are dependent on the manufacturer.

The hardness and friability tests results revealed that the five brands complied with the crushing strength (2.0 - 7.9 kgF) and friability (0.8 – 1.0 % loss in weight) specifications (British Pharmacopoeia, 1998; Ofoefule, 2002; USP, 2005). According to Ofoefule, 2002, friability is a measure of the resistance of tablets and granules formulations of pharmaceutical products to abrasion. The results confirm that the ketoconazole brands could withstand the stress of handling and transportation.

The results of the disintegration time (DT) test showed that the five brands of ketoconazole tablets had disintegration times ranging between 0.49 and 8.51 minutes. The test tablets are considered to have satisfactory DT values since the obtained values are in agreement with the mean disintegration time specification for uncoated tablets which should not exceed 15 minutes (British Pharmacopoeia, 2004). In the context of tablet technology, disintegration implies penetration of the tablet by an aqueous liquid, disruption of internal bonds and subsequent breakdown of the tablet. Factors that can affect disintegration time of the tablets include the rate at which a liquid penetrates a tablet, the nature and method of incorporation of lubricants, the action of disintegrants, and the degree of compaction and reduction of inter-particle bond strength in the presence of water (Rawlins, 1970).

All the brands of ketoconazole tablets had active ingredient which fell within the USP, 2004 acceptable limit of 90 - 110 %. The chemical qualities of ketoconazole tablets marketed in Nigeria were assured and are independent of the drug´s country of origin.

The dissolution profile of the different brands of ketoconazole tablets (Figure 1) revealed poor drug release. *In vitro* dissolution studies help in predicting biological drug release pattern in terms of rate and extent of release. No universal dissolution tests has been designed that gives the same rank order for *in vitro* dissolution and *in vivo* bioavailability

Table 1: Identity profile of the brands of the ketoconazole (200 mg) tablets

S/N	Brand Code	Country of Origin	NAFDAC Reg. Number	Lot Number	Manufacture Date	Expiry Date
1	A	India	04-6093	VE-08	10/2006	10/2010
2	B	England	04-3217	MP-680	02/2008	02/2011
3	C	Malaysia	04-1023	HS-AJ07	07/2008	07/2011
4	D	India	04-9538	EL-0508	02/2009	07/2012
5	E	Belgium	04-1410	JF-04CQ	03/2007	03/2012

Table 2: Quality control parameters of the different brands of ketoconazole 200mg tablets

BRAND	Average weight ± SEM (mg)	Hardness ± SEM (kg/cm^2)	Friability (%)	Absolute drug content (%)	Disintegration (minutes)
A	0.358 ± 0.002	4.48 ± 0.42	0.146	107.02	0.81 ± 0.002
B	0.351 ± 0.007	4.62 ± 0.18	0.168	101.00	2.55 ± 0.003
C	0.367 ± 0.004	4.00 ± 0.10	0.181	98.82	2.87 ± 0.004
D	0.676 ± 0.002	4.48 ± 0.58	0.268	101.56	0.49 ± 0.005
E	0.415 ± 0.011	7.70 ± 0.80	0.198	104.40	8.51 ± 0.002

Table 3: Results of dissolution profile (mg%) of the different brands of ketoconazole 200 mg tablets

Brand	Time (minutes)							AUC_{60}	PAE
	5	10	20	30	40	50	60		
A	2.90	8.50	16.80	23.76	25.30	28.50	39.15	115.25	59.60
B	4.85	9.00	15.80	19.70	22.60	27.30	29.50	112.875	44.48
C	3.00	6.20	14.20	19.60	22.40	27.50	32.00	159.5	62.85
D	4.55	6.55	10.00	20.00	27.20	34.00	40.00	172.25	67.88
E	6.75	8.35	19.90	29.30	39.15	46.75	57.50	253.75	100.00

AUC_{60} = Area under curve for 60 minutes
PAE = Predicted availability equivalent

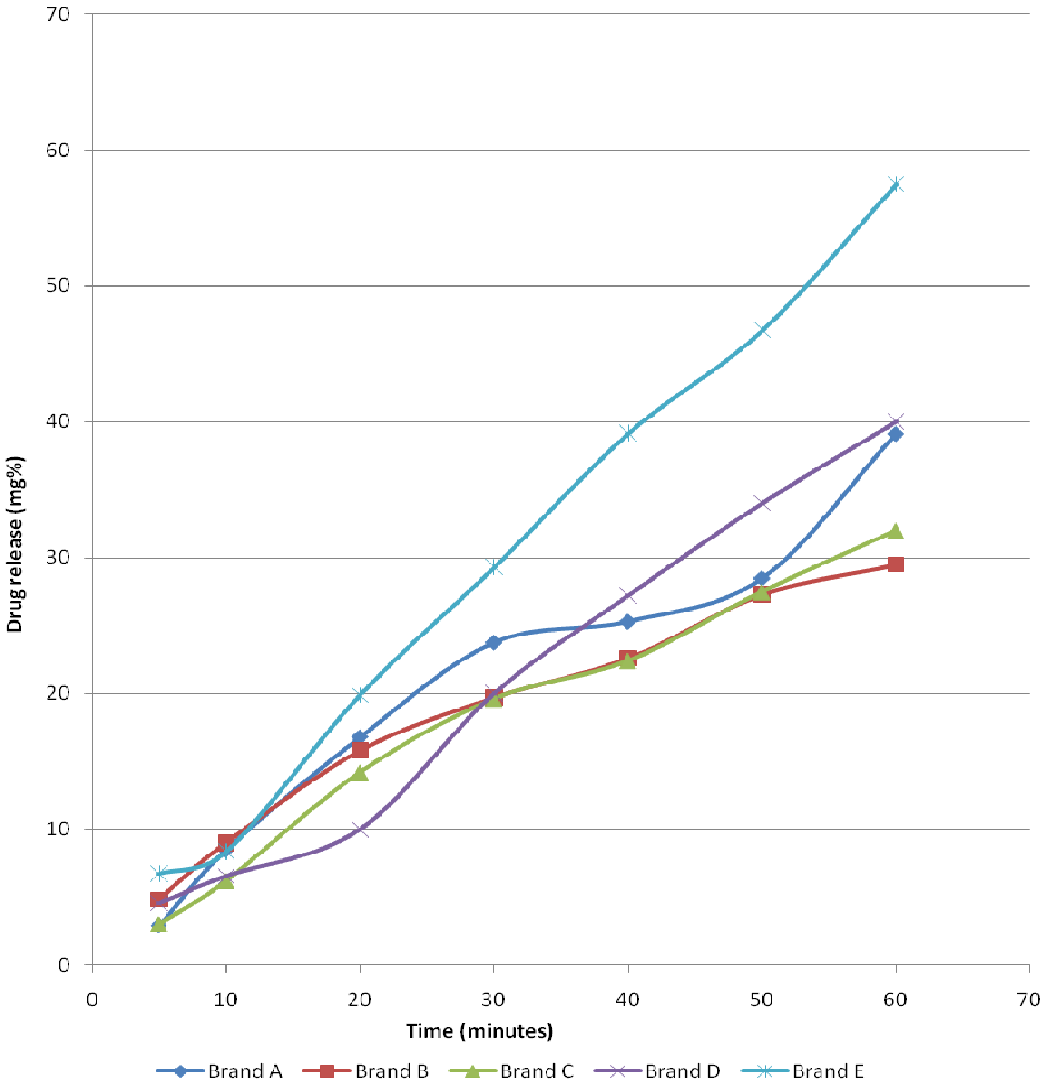

Figure 1: Dissolution profile (mg%) of five different brands of ketoconazole tablets

from different formulations and batches (Ford and Rajabi-Siahbooni, 2002). However, Tongiven and Bintin, (1998) posits that it is desirable that 75 % of a tablet sample should dissolve within 45 minutes. This was not attained by any of the tested brands of ketoconazole.

The dissolution studies showed that the innovator brand, brand E, had the highest dissolution rate of about 56 % at 60 minutes. In drug delivery systems, polymer type of binders is known to retard drug release due to an increase in tortuosity on gelling and this increases the path length available for the drug to diffuse out from the gel matrix (Tongiven and Bintin, 1998). However, the rate of release and the total amount released from each sample at any given time gives the pharmacological indication of the

performance of the drug when used. The authors suggest further product research by manufacturers in order to enhance ketoconazole release from tablet dosage forms.

In order to compare the different brands of ketoconazole tablets, we employed the area under curve (AUC) and predicted availability efficiency concepts (Khan, 1975; Osadebe and Akabogu, 2004). The AUC of the dissolution curves of the different ketoconazole brands for 60 minutes were calculated using the trapezoidal rule. The predicted availability efficiency (PAE) for a brand is the quotient of the brand´s AUC to the innovator brand´s AUC multiplied by 100. Brands whose PAE are significantly different ($P<0.2$) from the PAE of the innovation brand were considered bioinequivalent (Nwodo *et al.,* 2007). The results of the PAE shown in table 3 revealed the surprisingly bioinequivalence of the four brands of ketoconazole tablets to the innovator brand, E. Our study has reinforced the idea that chemical equivalence may not necessarily infer bioequivalence (Bakare-Odunola *et al.*, 2006).

CONCLUSION

The present study showed that there are variations in the physicochemical parameters of the multi-sourced tablets namely hardness and weight uniformity characteristics of the five selected ketoconazole brands of tablets marketed in Nigeria. All the brands passed the disintegration time, hardness test and friability tests. The studies proved that the absolute drug contents of all the ketoconazole brands conformed to the pharmacopoeia standard had poor dissolution profiles and were bioinequivalent to the innovator brand.

REFERENCES

Atherden, L.M. (2006) Melting point In: *Bentley and Driver's Textbook of Pharmaceutical Chemistry*, eighth edn., Oxford University Press, India. pp 9-12.

Bakare-Odunola, M.T. Garba, M and Balat, L. (2006) Quality control of some brands of chloroquine tablet available in Nigeria, *Nigerian Journal of Pharmaceutical Research* **5**(1): 22-26.

British Pharmacopoeia (1998) University Press, Cambridge, Vol I and II, p 828.

British Pharmacopoeia (2004) The Stationery Office Ltd., London Vol I and III pp 2283-2285; 482-485.

Erhun, W.O., Babalola O.O. and Erhun, M.O. (2001) Drug regulation and control in Nigeria: The challenge of counterfeit drugs, *J. Health and population in developing countries,* **4:** 23-24.

Ford, J. L. and Rajabi-Siahboomi, A. R. (2002) Dissolution and dissolution testing in encyclopedia of pharmaceutical technology, 2nd edition, vol 1 edited by James Swarbrick and James C. Boylan, Marcel Dekker Inc, Switzerland, p717.

Jang, J., Tsuboi. R., Kojima, Y. and Ogawa, H. (2005) Topical application of ketoconazole stimulates hair growth in C3H/HeN mice, *J. Dermatol*. **32**: 43-47.

Kenyon, T.A., Kenyon, A.S. and Kgarebe, B.V. (1999) Detection of substandard fixed-dose combination tuberculosis drugs using thin layer chromatography. *Int. J. Tuberc. Lung. Dis.* **3** (11): S347-S350.

Khan K. A. The concept of dissolution efficiency, *J. Pharm. Pharmacol.* 1975, 27, 48.

Lund, W. (1994) *The Pharmaceutical codex, principles and practice of Pharmaceutics*. The Pharmaceutical Press, London. pp. 835-838.

Mikre, W. and Mekonnen, N. (2006) Assessment on the quality and influence of tropical storage conditions on amoxicillin formulations marketed in Ethiopia. *Nigerian Journal of Pharmaceutical Research* **5**(1): 159-166.

Nwodo, N., Uzochukwu, I. and Omeje, E.O. (2007) Quality Control assessment and the

possibility of interchangeability between multisourced norfloxacin tablets marketed in Nigeria, *Scientific Research and Essay* **2** (8): 348-352.

Ofoefule, S.I. (2002). A Textbook of Pharmaceutical Technology and Industrial Pharmacy, Samakin (Nig.) Ent Lagos, pp 57-66.

Ogaji, I. (2006) Regulation and Registration of Pharmaceuticals in Nigeria, *Nigerian Journal of Pharmaceutical Research* **5** (1): 142-153.

Okonkwo, T. J., Afierobo, E. O., Odigwe, A. and Osadebe, P. O. (2006) Assessment of the quality control parameters of five brands of ciprofloxacin hydrochloride Caplets in Nigeria, *Journal of Pharmacy and Bioresources*, **3** (1):83-88

Olaniyi AA. (2001) *In vitro* testing in Bioavailability studies. In: *Towards Better Quality assurance of Drugs in the 3rd Millennium – Biopharmaceutical methods in drug quality assurance*, Olaniyi AA, Bababola CP, Oladeinde OF, Adegoke AO (eds). Omoade Printing Press: Nigeria, pp 58-78.

Rawlins, E.A. (1970) *Bentley's TextBook of Pharmaceutics*, eighth edn, Billiere Tindall London. pp 283-308.

Sharma, V. N. (2004) Antifungal agents. In: *Essentials of Pharmacology*. Second edn. CBS Publishers and Distributors, India, pp 342-347.

Sheppard, D. and Lampiris, H.W. (2001). Antifungal agents. In: *Basic and Clinical Pharmacology*, eighth edn; Bertram G. Katzung (ed), Lange Medical Books, New York, USA, pp 813-822.

Taketomo, C. K., Hodding, J. H. and Kraus, D. M. (2000) Ketoconazole. In*: Pediatric Dosage Handbook*, sixth edn Lexi-Comp Inc., Hudson, U.S.A., pp 508-509.

Tongiven, X and Bintin, H. (1998) Mechanism of sustained drug release in diffusion controlled polymer matrix-application of the percolation theory, *Int. J. Pharm*. **170**: 139-140.

United States Pharmacopocia (2004) The United States Pharmacopoeia Convention, Inc, Rockville, pp 454-405, 2302-2304, 2396-2394.

United States Pharmacopoeia (2005) 28th revision, United States Pharmacopoeia Convention Inc., Rockville, p 2504.