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Research Article

Comparative *in Vitro* Evaluation of Some Brands of Metformin Hydrochloride Tablets Marketed In Southern Nigeria

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Abstract: The issue of fake drugs has been on the increase in Nigeria and is of great concern to the entire populace. Due to the expiration of the patent right of the innovator metformin brand, several generic brands of metformin were introduced into the market and there is fear about the effectiveness of these brands. This study was conducted to authenticate the efficacy or otherwise, of some of the brands of metformin marketed in Southern part of Nigeria. Different brands of metformin hydrochloride tablets were purchased from pharmacies in some states in southern part of Nigeria. The physical properties of the tablets and their packs were assessed. The tablets were evaluated based on official and unofficial tests such as uniformity of weight, hardness, friability, disintegration time, *in vitro* dissolution and drug content.The results obtained showed that the tablets and their packs had acceptable physical appearance. Tablets from all the brands passed the uniformity of weight test (< 5%), hardness (6.28 ± 0.37 to 36.12 ± 3.24), friability (0.01 to 0.80), disintegration time (2.6 to 8.4 min) and drug content (95.03 to 104.75%). The percentage cumulative drug released from the tablets at 45 min was more than 75% for all the brands.This study showed that all the brands studied passed the various official and unofficial tests and were comparable to the innovator brand. Therefore, any of the brands could be used to substitute for the innovator brand.

Keywords: Metformin hydrochloride, tablets, fake drugs, innovator brand, generic brand.

INTRODUCTION

Metformin is an oral antihyperglycemic drug used in the management of non-insulin-dependent diabetes mellitus (NIDDM). It improves glucose tolerance in NIDDM subjects, lowering both basal and postprandial plasma glucose. It lowers hepatic glucose production, decreases intestinal absorption of glucose and enhances insulin sensitivity (increases peripheral glucose uptake and utilization). Unlike sulfonylureas, metformin does not produce hypoglycemia in either diabetic or nondiabetic subjects and does not cause hyperinsulinemia. The absolute bioavailability of 500 mg metformin given under fasting conditions is ≈ 50% to 60%. (Drug Facts and Comparisons, 1999)

The innovator brand, Glucophage(R) was the first metformin to be marketed in Nigeria. Prior to the expiration of its patent right, there was the challenge of parallel imported packs and availability of fake versions. The company addressed the issue by deploying "mobile authentication service" (MAS). 'MAS' involves attaching a scratch card that contains specific number to drug sachets or boxes that contains the tablets. The end user scratches the card and sends the specific number as a text message to the anchor company and receives a reply whether the product is genuine or not. As a result of MAS, presence of fake metformin reduced, however, upon the expiration of the patent right of the innovator brand, some brands were produced locally and there was massive influx of imported generic brands. The increase in the number of generic drug products from multiple sources has become a burden to healthcare providers with respect to having to select one from among several seemingly equivalent products (Elghnimi *et al.*, 2016; Xhafaj *et al.*, 2015).

The introduction of multisource products in form of non-proprietary (generic) drug products globally was meant to provide alternatives to specific brands in areas where they are limited in supply or too expensive due to low income level of the populace, however, this has resulted in increased prevalence of fake, sub-standard and counterfeit drug products. The fake products are often less expensive in order to attract higher market patronage (Eraga *et al.*, 2015; Nwodo *et al.*, 2007; Adegbolagun and Nwabuife, 2018). The myriads of market forces, the low per capita spending on pharmaceuticals by most of the population and the lack of adequate resources for controlling and monitoring the quality of drugs in the market have

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created an environment favorable for introduction of low quality drugs in developing countries like Nigeria. (odunfa *et al.,* 2009; Osonwa *et al.,* 2016)

The production of counterfeit drugs is a big but poorly reported problem that mainly affects poorer countries. This usually causes unnecessary mortality and morbidity, and loss of public confidence in medicines and health structures (Olusegun, 2013; Uzondu and Okafo, 2016).

The prevalent factors that promote the presence of counterfeit drugs in Nigeria include ineffective enforcement of existing laws, non-professionals in drug business, porous control systems, high cost of genuine drugs, greed, ignorance, corruption, illegal drug importation, chaotic drug distribution network, demand exceeding supply amongst many others (Chinwendu, 2008; Erhun *et al.,* 2001; Uzondu and Okafo, 2016). Akunyili (2005) noted that the problem of counterfeit drugs have embarrassed the Nigerian healthcare providers and denied the confidence of the public on the nation's healthcare delivery system. Also, it was noted that fake drug proliferation has caused treatment failures, organ dysfunction or damage, worsening of chronic disease conditions and death of many Nigerians. Even when patients are treated with genuine drugs, no response is seen due to resistance caused by previous intake of fake drugs (Akunyili, 2005).

Drug having more than three generic products require analysis for their biopharmaceutical and chemical equivalency. (Chandrasekaran *et al.,* 2011) FDA considers a drug product to be pharmaceutically equivalent to another if they contain the same active ingredient(s), of the same dosage form and route of administration and are identical in strength or concentration. Drug products are considered to be therapeutically equivalent only when they are pharmaceutically equivalents. (Walker *et al.,* 2007; Sheela and Tharani, 2015) Quality of pharmaceutical product is the most important factor that ensures its efficacy and safety. Quality control tests are conducted on tablets during production and on the final product batches. Generic drugs are chemically equivalent to their brand-name counterparts in terms of active ingredients but may vary in other areas like colour, shape, excipients employed and manufacturing process. (Elghnimi *et al.,* 2016) Dissolution testing of drug products plays a vital role as a quality control tool in assessing batch - to – batch consistency of drug release from a dosage form. It also functions as a qualitative and quantitative tool, which can provide important information about biological availability of a drug (Chandrasekaran *et al.,* 2011; Elghnimi *et al.,* 2016; Derkar *et al.,* 2016).

The quality control parameters that are usually assessed in tablet dosage forms include uniformity of weight, hardness, friability, disintegration time, in vitro dissolution and drug content.

The study was conducted to ascertain if the generic brands of metformin marketed in Southern part of Nigeria are genuine or fake and also if they could be interchanged with the innovator brand during therapy.

MATERIALS AND METHODS

Materials:

All the chemicals used were of analytical grades and they include, metformin (Kores Chemical Ltd, India), hydrochloric acid (JHD, Guangdang Guanghua Chemical Factory Co. Ltd., Shanfua, Guandang, China). The metformin brands were procured from pharmacies in Enugu and Anambra States in South east Nigeria; Rivers, Delta and Edo States in South south Nigeria and Lagos and Ondo States in South west Nigeria.

Physical appearance

The colour, shape, scoring and embossment on the tablets were noted. The batch number, manufacturing date, expiry date, MAS and embossment on sachets and packs were recorded.

Uniformity of weight

Twenty tablets were chosen at random and weighed individually using a Shimadzu model ATY224 analytical balance (Shimadzu Manufacturing Inc. Philippines). The average weight of the tablets was calculated. The percentage deviations of each tablet from the mean tablet weight were calculated.

Hardness

Five tablets were selected at random and one of the selected tablets placed at a time in the tablet chamber of a Veego digital tablet hardness apparatus (Veego Instruments, India). The hardness button was selected and the figures displayed on the screen were recorded.

Tablet thickness and diameter

Five tablets were selected at random and one of the selected tablets was placed in the tablet chamber of a Veego digital tablet hardness apparatus (Veego Instruments, India). The thickness and diameter button was selected respectively and the readings displayed on the screen were recorded. This was repeated for the remaining four tablets.

Friability

Ten tablets randomly selected were weighed together and placed in the drum of the Veego friabilator (Veego Instruments, India). The drum was rotated at a speed of 25 rpm for 4 min. The tablets were de-dusted and reweighed. Friability was calculated using equation 1

$$Friability = \frac{initial\ weight - final\ weight}{initial\ weight}\ X\ 100\% \quad . \quad . \quad . \quad . \quad . \quad 1$$

Drug content

Ten tablets selected at random were crushed to powder. Equivalent of 100 mg of the drug substance was weighed and transferred to a 50 ml beaker. Thirty milliliters (30 ml) of 0.1 N HCl was added and stirred properly It was transferred into a 100 ml volumetric flask and the volume was made up to 100 ml using 0.1 N HCl. It was filtered and 1 ml of the filtrate was diluted to 100 ml with 0.1 N HCl to obtain a 10 µg/ml solution. A sample from this solution was analyzed using a UV spectrophotometer (Agilent Technologies, Malaysia) at 233 nm.

Disintegration time

Six tablets were selected randomly and placed in the respective tubes of a tablet disintegration test apparatus (Manesty, Liverpool, England). The basket rack containing the tubes were raised up and down in a chamber that contained 0.1 N HCl as medium maintained at 37 ± 2^o C. The time taken for each of the 6 tablets to break up completely and pass through the sieve at the base of the tube was recorded. The average value was calculated as the disintegration time.

***In vitro* dissolution studies**

One tablet was selected at random and placed in the basket inserted in the flask containing 0.1 N HCl as dissolution medium in a single unit Copley dissolution test apparatus (Erweka Apparatebau GMBH, Heusengtamm, Germany). The medium was maintained at 37± 2^o C and rotated at 100 rpm. Five milliliters samples were collected at 10, 20, 30, 45 and 60 min and replaced with 5 ml preheated fresh medium. The samples were filtered, diluted appropriately and analyzed using a UV spectrophotometer (Agilent Technologies, Malaysia) at 233 nm.

RESULTS AND DISCUSSION

Physical appearance

The tablets from all the brands evaluated were white, round and film-coated. They were all registered with National Agency for Food and Drugs Administration and Control (NAFDAC). All the brands had shelf life of 3 years except the innovator brand (A) and two other brands (E and F from the same manufacturer) that had 5 years shelf life. Tables 1 and 2 contained vital information on the physical appearance of the different metformin products.

Table 1: Vital information on different brands of metformin hydrochloride 500 mg tablets evaluatedj

Code name	Batch No.	NAFDAC Reg. No.	Brand Name	Manufacturer	Marketer in Nigeria
A	E200885	04 – 6233	Glucophage	Merck S. L. Poligono Merck, 08100 Mollet Del Valles (Barcelona) Spain	Merck
B	0027	04 – 7963	Juformin	Juhel Nigeria Ltd. 35 Nkwubor Road, Emene, Enugu, Nigeria	Juhel Nigeria Ltd.
C	FPA 080218	04 – 6426	Gluformin	Nigerian – German Chemicals Plc. Km. 38, Abeokuta Expressway, Otta. Ogun State, Nigeria	Nigerian – German Chemicals PLC
D	BJ 05 681	04 – 0810	Diabetmin	Hovid Bhd. 121, Jala Tunku Abdul Rahman, 30010 Ipoh, Malaysia.	Pharmatex Nig. Ltd, Lagos
E	1905	A4 – 6319	Avrophage	SKG Pharma Ltd. 7/9 Sapara Street, Ikeja, Lagos, Nigeria	Avro Pharma Ltd. Lagos
F	1912	A4 – 6597	Biophage	SKG Pharma Ltd. 7/9 Sapara Street, Ikeja, Lagos, Nigeria	SKG Pharma Ltd
G		B4 – 2429	Tricophage	Baroque Pharmaceuticals Pvt. Ltd. Sokhada, Khambhat 388620 Gujarat, India.	Tricare Pharma Ltd. Lagos
H	7B002	A4 – 3332	Glumin 500	Osaka Pharmaceuticals Pvt Ltd. Old National Highway No. 8, Sankarda – 391 350, Dist. Vadodara, Gujarat, India.	Seagreen Pharmaceuticals Ltd. Lagos
I	GT 18009	B4 – 7368	Scrip - metformin	Globela Pharma Pvt. Ltd. 357, G.I.D.C, Sachin Surat – 394230. Gujarat. India	Scrip Pharmaceuticals Ltd. Lagos
J	180515	180515	Diacophage	Jiangsu Ruinian Qianjin Pharm. Co. Ltd. Chuanbu village, Dingshu Town, Yixing City, Jiangsu, China.	St. Luke's Pharm. Ltd. Onitsha.

NAFDAC – National Agency for Food and Drugs Administration and Control, **Reg. No** – Registration number

Table 2: Vital information on different brands of metformin hydrochloride 500 mg tablets evaluated (Continued)

Code Name	Mfg. Date	Expiry Date	MAS	Embossment on Tablet	Sachet Type
A	02/2018	01/2023	YES (Sachet)	1 side (GL 500)	Blister
B	03/2017	02/2020	No	2 sides (MET 500 /Juhel)	Blister
C	01/2018	12/2020	No	2 sides (MET 500 /NGC)	Alu – alu
D	05/2018	04/2021	No	1 side (HD)	Blister
E	05/2019	05/2024	Yes (Box)	2 sides (AVG 500/ AVRO)	Blister
F	04/2019	04/2024	Yes (Box)	2 sides (BG 500 / SKG)	Blister
G			No	No	Blister
H	02/2017	01/2020	No	1 side (GM 500)	Blister
I	01/2018	12/2020	No	No	Blister
J	05/2018	05/2021	No	1 side ((DCG)	Alu – alu

Mfg. Date – Manufacturing date

Uniformity of weight

Twenty tablets were evaluated per brand. As shown on Table 3, all the tablets had percentage deviation from the mean of less than 5% except for two tablets from brand B and one tablet each from brands C and E. The British pharmacopoeia (2014) specifies under uniformity of weight test, that for tablets weighing 250 mg and above (uncoated or film coated), a deviation of ± 5% from the mean tablet weight is allowed. For the batch to pass the test not more than 2 of the 20 tablets will be outside ± 5% and none will be outside ± 10%. This shows that all the brands evaluated passed the weight uniformity test and there may be no issue of variation in content uniformity and ultimately no sub-therapeutic dose or over dose.

Table 3: Uniformity of weight for different brands of metformin hydrochloride tablets (n = 20)

Code Name	Mean Weight (mg) ± Standard deviation	Number of tablets outside the BP range
A	539.8 ± 0.00	0
B	536.8 ± 0.02	2
C	547.2 ± 0.01	1
D	572.8 ± 0.01	0
E	571.2 ± 0.02	1
F	579.6 ± 0.01	0
G	627.9 ± 0.01	0
H	558.1 ± 0.01	0
I	557.4 ± 0.01	0
J	606.2 ± 0.01	0

Disintegration time test

As shown on Table 4, all the brands passed the disintegration time test. The BP (2014) specifies that uncoated tablets should disintegrate within 15 min while film coated tablets in 30 min. All the brands were within the limits for uncoated tablets.

Hardness

Hardness is a non-official test. It shows the ability of tablets to withstand stress and pressure encountered during handling, packaging and transportation. It shows tablet ability to resist permanent deformation. The hardness value for tablets from the evaluated brands ranged from 1.67 ± 0.69 to 9.98 ± 2.11 as shown on Table 4. The innovator brand, A had the least hardness value (1.67 ± 0.69) but interestingly it had a very low friability value. This may be due to the excipients used in formulating the tablets.

Friability

This is the ability of tablets to withstand abrasion during handling and transportation. All the evaluated brands passed the friability test as shown in Table 4. They showed friability values that ranged from 0.01 to 0.80% which was below the limit value of 1% (BP, 2014).

Drug content

According to BP 2014, the content of metformin hydrochloride in metformin hydrochloride tablet should be 95.0 to 105.0% of the stated amount. As shown on Table 4, the drug content of the assessed brands ranged from 95.03 to 104.75% and they were within the acceptable limits.

Table 4: Some physicochemical properties of metformin hydrochloride 500 mg tablets

Code Name	Disintegration Time (min) (n = 6)	Hardness (Kgf) (n = 5)	Friability (%) (n = 10)	Drug Content (%) (n = 10)
A	6.2	20.10 ± 1.20	0.07	103.38
B	4.6	20.07 ± 5.12	0.08	98.25
C	4.4	10.52 ± 4.45	0.80	101.56
D	3.4	36.12 ± 3.24	0.14	99.91
E	4.2	23.22 ± 6.90	0.09	95.59
F	6.2	27.42 ± 6.09	0.01	104.75
G	17.4	6.28 ± 0.37	0.07	104.31
H	8.4	9.62 ± 2.19	0.01	95.03
I	3.8	34.32 ± 10.26	0.01	97.91
J	6.6	10.91 ± 1.66	0.04	96.81

***In vitro* dissolution test**

The cumulative release of metformin from the different brands is shown on Fig. 1 and 2. All the brands released more than 75% of their metformin content (76.22% to 94.30%) within 45 min of the test and therefore passed the dissolution test.

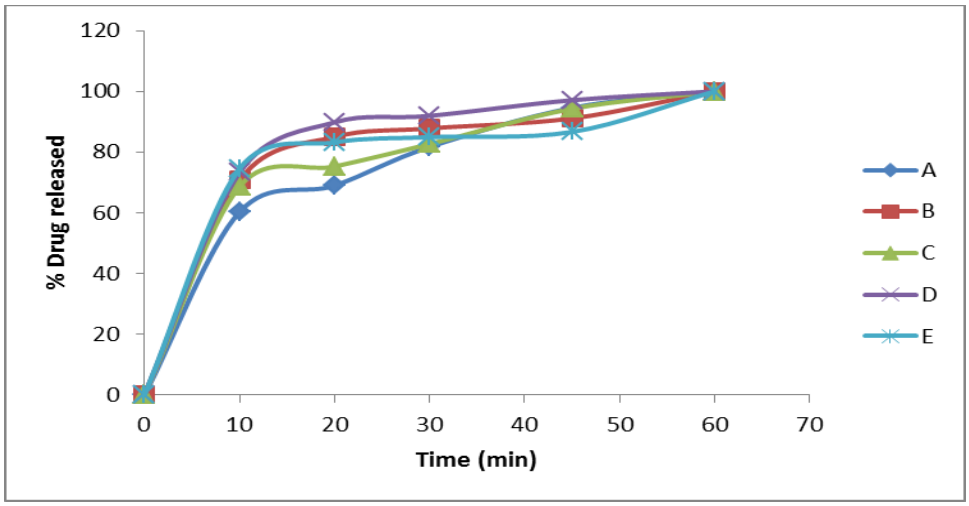

Fig. 1: Cumulative % drug of release of metformin from Brands A to E tablets

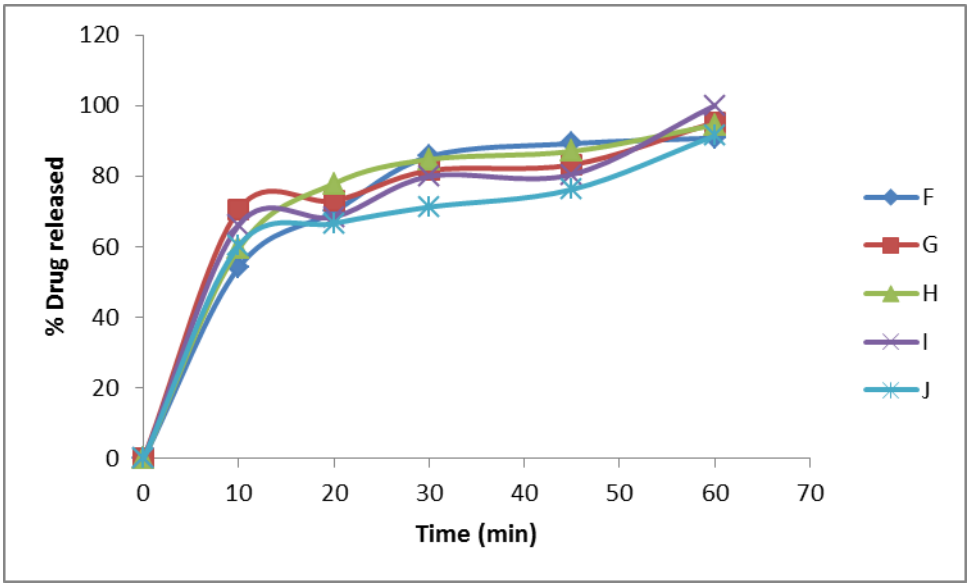

Fig. 2: Cumulative % drug of release of metformin from Brands F to J tablets

CONCLUSION

This study showed that all the brands studied complied with the official standards, were chemically equivalent and could be interchangeable with the innovator brand.

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