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Comparative Evaluation of Physicochemical Properties of Some Commercially Available Brands of Metformin Hcl Tablets in Lagos, Nigeria

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ABSTRACT

There are several generics of metformin hydrochloride tablets available within the drug delivery system globally. Availability of numerous brands of Metformin tablets in Nigerian drug market today places health practitioners in a dilemma of generic substitution. The objective of the study was to determine the biopharmaceutical and chemical equivalence of eight brands of Metformin tablets marketed in Nigeria using *in vitro* tests. The physicochemical equivalence of eight brands of Metformin hydrochloride tablets were assessed through the evaluation of both official and non-official standards such as uniformity of weight, friability, hardness, disintegration, Assay and dissolution rate. All the brands complied with the official specifications for uniformity of weight, disintegration and dissolution tests. Brand B and C had the highest and lowest crushing strength respectively. However, for the friability test, one of the eight brands failed to meet the British pharmacopoeia specification for friability. Seven brands had values within the range specified for assay in the BP while Brand G failed the test. Only brand F, G and H met the BCS biowaiver criteria for very rapidly or rapidly dissolving tablets. Of all the eight brands evaluated in this study, only four brands could be regarded as being biopharmaceutically and chemically equivalent and therefore can be interchanged in the clinical practice.

Keywords: Metformin hydrochloride, physicochemical equivalence, quality, dissolution test, Biowaver.

INTRODUCTION

World Health Organization has estimated that about 30% of the medicines on sale for consumption in many countries in Africa and parts of Asia and Latin America are counterfeit. In some developing markets the figure is thought to be as low as 10% (WHO, 2006). Counterfeiting can apply to both branded and generic products and could include products with the correct ingredients or with the wrong ingredients, without active ingredient, with insufficient active ingredient, or with fake packaging (WHO, 1999). While substandard drugs are genuine drug products that upon laboratory testing do not meet the quality specifications claimed by their manufacturers (Taylor *et al.*, 2009). The introduction of generic drug product from multiple sources into the health care delivery system of many developing countries is aimed at improving the overall health delivery systems in such countries (Adegbolagun *et al.*, 2007).

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However, this has been bedevilled with widespread distribution of fake and substandard drug products. Quality of medicinal drugs in many underdeveloped countries is inadequate. In some cases, use of poor-quality medicines has resulted in treatment failure (Petralanda, 1995).

The report on pharmacopoeial quality of drugs supplied by Nigerian pharmacies published in 2001 revealed that 48% of drug tested failed to comply to pharmacopoeial limits which is the benchmark for assessing quality of pharmaceutical preparations (Taylor *et al.*, 2009). Another survey carried out in Tanzania on the quality of antimalarials in retail outlets also returned 12.2% failure and were found to be of poor quality (Harparkash *et al.*, 2008). This revelation reiterates the importance of monitoring drug quality in order to safeguard the health delivery system of government authorities to her teeming population.

The first stage in establishing the therapeutic equivalence of any drug product involves ascertaining the chemical and biopharmaceutical equivalence of such drug products (Olaniyi *et al.*, 2001).

Drug products that are chemically and biopharmaceutically equivalent must be identical in strength, quality, purity (Adegbolagun *et al.*, 2007), active ingredient release profile and must be in the same dosage form, for the same route of administration. Any substantial variations in the dissolution rate among same generics indicate deficiency in the entire drug formulation and the delivery system. Dissolution testing of drug products plays an important role as a quality control tool to monitor batch to batch consistency of drug release (Awofisayo *et al.*, 2010) and also for prediction of *in-vivo* bioavailability in most oral preparations (Esiomone *et al.*, 2008; Osadebe and Akabogu, 2004; Pamula *et al.*, 2010). To this extent, manufacturing methods, coupled with excipients used in the production processes, could contribute to the overall quality and release proficiency of medicament. Therefore, in order to ensure the requisite quality, drug manufacturers are required to test their products during and after manufacturing and at various intervals during the shelf life of the product (Chow, 1997). As such the need to ensure that the generic and branded drugs products are pharmaceutically equivalent cannot be overemphasized and the necessity to select one product from several generic drug products of the same active ingredients during the course of therapy is always a cause for concern to healthcare practitioners (Adegbolagun *et al.*, 2007).

Metformin hydrochloride belongs to the class of drug called biguanide. It is the first line drug of choice for the treatment and management of various diabetes especially Type 2 diabetes particularly in overweight, obese people and polycystic ovary syndrome (International Diabetes Federation, 2005). There are several generics of metformin hydrochloride tablets available within the drug delivery system globally as well as in Nigeria after the expiration of patent on Glucophage, the innovator brand. The increasing level of use of metformin hydrochloride tablets in clinical practice creates the need to monitor and ascertain the quality of the various brands available in the drug market for quality control assessment and for purpose of generic substitution.

The objective of this study was to evaluate the physicochemical properties of eight brands of metformin tablets using both official and unofficial compendia method.

MATERIALS

Metformin hydrochloride, having a label strength of 500mg of eight different brands were purchased from registered pharmacies in Lagos, Nigeria. The products were coded as A (Auden Mckenzie Ltd, England); B (Sterling Lab, India); C (May & Baker, Nigeria); D (Hovid Bhd, Malaysia); E (Medopharm, India); F (VapiCare Pharma, India); G (NGC Plc, Nigeria) and H (Merck Sante, France) and the study was performed within product expiration dates.

The reagents used were sodium hydroxide (BDH Chemicals, UK) and potassium dihydro orthophosphate (BDH Chemicals, UK). Freshly distilled water was used throughout the work.

METHODS

Uniformity of Weight

Sample tablets (20) of each brand were weighed together and average weight was determined. Each tablet was weighed individually on mettler toledo analytical balance and the percentage (%) deviation was determined.

Hardness Test

Sample tablets (10) of each brand were taken, a tablet was placed between the spindle of the Erwerka hardness tester machine and pressure was applied by turning the knurled knot just sufficiently to hold the tablet in position. The pressure was then increased as uniformly as possible until the tablet breaks and the pressure required to break the tablet was then read off the machine and recorded.

Friability Test

Sample tablets (10) of each brand were taken and weighed, these tablet were then put in the automated Friabilator Distek DF-3 model and this test for the tendency to crumble by allowing it to roll and fall within the rotating apparatus, after 100 revolutions the tablets were weighed and recorded. The friability of the tablets were then calculated using the following expression

$$\% \text{ Friability} = \frac{[(\text{Initial weight} - \text{Final weight}) / \text{Initial weight}] \times 100}{1}$$

Disintegration Test

The disintegration time of randomly selected six tablet of each of the eight brands was determined at 37°C in distilled water using a Multi-unit disintegration tester (USP) Electrolab® apparatus. The disintegration time was taken to be the time no granule of any tablet was left on the mesh.

Dissolution studies

This was determined using a 7-compartment Veego dissolution test apparatus (basket type) containing 900ml of

phosphate buffer pH 6.8, maintained at $37 \pm 0.5^\circ\text{C}$ with a fixed speed of 100rpm. A tablet was put in each of the compartments and the machine operated at the intervals of 5, 10, 15, 30, 45 and 60minute. In all the experiments, 5ml of the sample was withdrawn at specified intervals and replaced with a fresh 5ml dissolution medium to maintain the sink conditions. Each of the withdrawn sample was filtered with syringe filter $0.45\mu\text{m}$, the filtrate diluted and its absorbance at 233nm was measured using UV-visible spectrophotometer. The concentration of Metformin hydrochloride in the samples was calculated According to metformin monograph in the BP.

Assay of the Tablets

The assay was done in line with the specifications of BP, 2007.

Data Analysis

The dissolution profiles were estimated by plotting the percent drug released versus time and were compared using a model independent approach, similarity factor f_2 as described by the US FDA and presented in the following equation:

$$F_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

where R_t and T_t are percent dissolved at each time point for reference (Innovator brand, brand H) and test products respectively. If the f_2 value is greater than or equal to 50 it shows sameness or equivalence of the two dissolution profiles. If f_2 is less than 50, that means the dissolution profile is different from the innovator product hence not interchangeable (Moore and Flanner, 1996).

RESULTS AND DISCUSSION

Table 1 shows the evaluated physicochemical parameters while figure 1 represents the dissolution profiles of all the eight brands. Table 2 shows the f_2 similarity factor comparing the dissolution curves of seven brands with the innovator brand. All the brands used were within their shelf life as at the time of study. Eight different brands of metformin hydrochloride tablets obtained from different retail pharmacy outlets within Lagos metropolis were subjected to a number of pharmacopoeial tests in order to assess their biopharmaceutical equivalence. The assessments involved the evaluation of uniformity of weight, friability, hardness, disintegration and dissolution tests as well as chemical content determination. The uniformity of weight determination for all the brands gave values which complied with official book specifications for weight uniformity as none of the brands deviated by up to $\pm 5\%$ from the mean value.

The result of tablet friability test showed that virtually all the brands (A, B, C, D, E, F & H) tested had impressive friability values ranging from 0.01% to 0.44%w/w except for brand G with friability value of 10.33%w/w. According to BP no batch should have a friability value greater than 1.0%w/w, therefore, only brand G failed the test.

Crushing strength test shows the ability of tablets to withstand pressure or stress during handling, packaging and

transportation. It is a property of a tablet that is measured to assess its resistance to permanent deformation. This result also indicates only three (C, E & G) brands passed the non-official test of crushing strength/hardness while remaining brands (A, B, D, F & H) failed. Brand B had the highest crushing strength of all the eight brands with hardness of 48.74kgf. Disintegration is a crucial step in release of drugs from immediate release dosage forms. The rate of disintegration is directly proportional to the rate of dissolution. The rate of disintegration is influenced by the rate of influx of water into the tablets which is also dependent on the porosity of the tablets. The results showed that all the brands passed the disintegration test according to British pharmacopeia (BP 2007) which specifies 30minutes for film coated tablets. According to the monographs in British Pharmacopoeia, for each of the tablets tested for dissolution, the amount of active ingredient in solution is not less than 70% of the prescribed or stated amount. The results obtained from the study revealed that all the brands passed the BP general specifications standard for dissolution rate test for conventional release tablets. The results obtained from the assessment of the percentage content of active ingredient in the eight brands of metformin tablets showed that seven out of eight brands gave values within the monograph specifications (95-105%), while only brand G failed the test with the value of 74.58%. Metformin hydrochloride is classified according to Biopharmaceutical Classification System (BCS) as a Class III drug therefore not qualifies for biowaiver. In all the brands tested only sample F, G and H met the BCS biowaiver criteria for very rapidly or rapidly dissolving tablets as others had less than 85% of the active released within 30minutes. Dissolution profile curves of all the brands were compared using similarity factor, f_2 statistical method. Based on this assessment only generic A, C, D and F had f_2 values greater than 50 and therefore can be interchanged with the innovator brand.

Table 2: f_2 Statistical values for the generics relative to innovator product.

Generic Products	A	B	C	D	E	F	G
f_2 Values	73	27	68	58	42	50	36

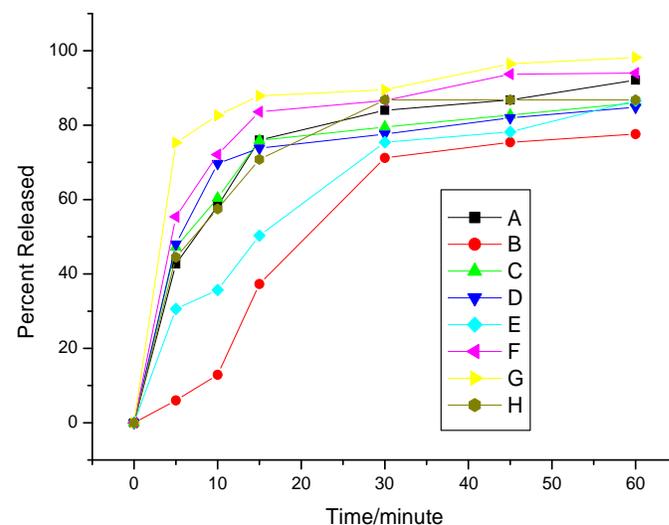


Fig. 1: Dissolution profile of all the 8 Brands.

Table. 1: The evaluated physicochemical characteristics of Metformin tablets.

Code	Code Weight uniformity Deviation (%) \pm SEM	Friability (%)	Hardness Kgf \pm SEM	Disintegration time (minute)	Drug Released (%)		Assay(%)
					30min	45min	
A	0.93 \pm 0.10	0.40	20.56 \pm 0.17	10.3	84.0 \pm 0.3	86.8 \pm 1.3	99.1
B	1.97 \pm 0.31	0.44	48.74 \pm 0.21	15.4	71.0 \pm 1.5	75.4 \pm 0.3	95.7
C	1.67 \pm 0.24	0.01	5.38 \pm 0.21	7.4	79.5 \pm 1.6	82.7 \pm 1.2	95.6
D	1.13 \pm 0.32	0.03	23.83 \pm 0.88	7.6	77.6 \pm 2.4	82.0 \pm 1.3	98.7
E	0.72 \pm 0.10	0.33	7.20 \pm 0.36	15.6	75.4 \pm 1.8	78.2 \pm 2.1	97.0
F	0.54 \pm 0.09	0.11	45.66 \pm 1.28	5.2	86.6 \pm 1.3	93.7 \pm 1.5	95.9
G	1.37 \pm 0.35	10.33	5.62 \pm 0.30	5.1	89.5 \pm 1.1	96.5 \pm 1.0	74.6
H	0.81 \pm 0.14	0.26	10.71 \pm 0.19	8.0	86.6 \pm 0.9	86.8 \pm 1.2	99.6

SEM = Standard Error of Mean

CONCLUSION

It can be concluded that of all the eight brands evaluated in this study, only four brands A, C, D and F passed both pharmacopoeial limit tests and their dissolution curves were similar thus could be considered biopharmaceutically and chemically equivalent and therefore they can be substituted with the innovator product in clinical practice.

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