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Full Length Research Paper

The Pharmaceutical Quality of Brands of Metformin Tablets in Ogun-State, Nigeria

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ABSTRACT

The pharmaceutical quality of randomly selected brands of metformin tablets used (prescribed or dispensed) by Community Pharmacists and Doctors in Ogun state, southwestern Nigeria, were evaluated. Eight brands were randomly procured from community pharmacies after administering a pre-tested semi-structured questionnaire to 100 Pharmacists and 15 Physicians across different local government areas in Ogun state, South Western part of Nigeria. The physicochemical properties of the different brands were analysed using the Pharmacopoeia standard. The results showed that Pharmacists' choice of stocking was based mainly on clients' demand and quality, while doctors prescribe what is made available by the hospital pharmacy. Out of the eight brands assessed, seven are pharmaceutically equivalent and can be substituted for one another. However, there were quality variations from brand to brand. The ranking of crushing strength for the metformin brands was H>>>G>E>F>D>B>C>A, while the trend for friability was D>>>E>C>H>A>G>F>B. The trend of disintegration time among the brands was D>G>C>E>A>F>B>H and ranking of CSFR/DT was H>>B>F>G>A>E>C>>D. Two brands (D and E) failed the friability test while brand D had significantly lower balance of mechanical and release properties as determined by CSFR/DT. There is therefore a continuous need for random assessment of the quality of metformin brands by regulatory bodies to ensure compliance to specifications.

Keywords*:* Metformin brands, community pharmacists, doctors, perception, pharmaceutical equivalence

INTRODUCTION

Generic substitution has become popular in order to reduce the cost of drugs and overall treatment. As prescriptions are being written and interpreted, both the Pharmacists and Physicians must decide to administer a branded product or a generic equivalent (Shakoor *et al*, 1997). The need to select one product from a wide range of drug products containing the same active ingredients (and seems to be equivalent) in the course of patient therapy pose a great concern to health providers (Adegbolagun *et al*, 2007). Moreover, variable clinical responses have been documented when using drugs from different sources (Oladimeji and Iranloye, 1990). Past researches have shown that various counterfeit drugs are available in the market worldwide (Euchie *et al*, 2009).

Treatment failure and drug resistance are reported frequently in developing countries due to the inability of such countries to ensure an effective means of monitoring the quality of generic drug products in their market (Ogwal-Okeng *et al*, 2003). In the study of counterfeit drugs in Myanmar and Vietnam, about 1.7% of anti-diabetic agents are being faked (WHO, 1988). This problem of drug faking made it necessary to routinely asses the pharmaceutical quality of drugs in the Nigerian market (Erhun *et al*, 2001). It was in view of this fact that the WHO issued guidelines for global standard and requirements for the registration,

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assessment, marketing, authorisation and quality control of generic pharmaceutical products (Nnamdi *et al*, 2009). It was to give technical guidelines to regulatory authorities' like NAFDAC which is responsible for drug administration and control in Nigeria and the quality of drug dosage form generally available in the market. Generic drugs are expected to satisfy the same standard of quality, efficacy, and safety as those applicable to the innovator products (WHO, 1996). Physicochemical assessment of drug products has been shown to be very important because *in vitro* dissolution and assay of content can be a valuable predictor of bioavailability and bioequivalence of oral dosage forms (Odeniyi *et al*, 2006).

Metformin is an anti-diabetic drug and was originally marketed as Glucophage®. It is the first line drug of choice for the treatment of type-2 diabetes, particularly in overweight and obese patients and those with normal kidney function. The use of metformin increases continually especially because it does not cause hypoglycaemia like the sulfonylureas. It is also used in the treatment of polycystic ovary syndrome (Eurich *et al*, 2007). There is a need to determine if the quality of metformin brands commercially offered for prescribing and dispensing is satisfactory and possibly interchangeable without compromising desired efficacy. In the present study, the pharmaceutical equivalence of eight brands of metformin from different registered community pharmacies in Ogun state was determined using *in vitro* analysis and the perception of Community Pharmacists (CPs) and Doctors (DRs).

MATERIALS AND METHODS

The study utilized both qualitative and quantitative research methods. The qualitative aspect was carried out by administering a pre-tested semi- structured questionnaire which was used to determine CPs/DRs perception of quality and select the brands of metformin stocked by Pharmacists in their pharmacies and prescribed by Doctors consulting in diabetic clinics in Ogun state. The quantitative aspect was carried out using physicochemical tests and content assay on randomly selected brands of metformin tablets using materials of analytical grade.

Sampling

A year 2010 document of pharmaceutical zones in Ogun state obtained from the Food and Drug section of the Ministry of Health was used as the sampling frame for community pharmacies. The document contains a list of all registered pharmacies by local government areas (LGAs). Out of the five zones, four (Egba, Ijebu, Remo and Ota) were randomly selected. The list of community pharmacies in each zone were also used to randomly select which to include in the survey. Table 1 shows the details of LGAs from which community pharmacies were surveyed. The percentage of premises sampled for the state is 82.44% derived from comparing the total number of registered community pharmacies (131) in the state to the total sampled (108). In addition, there were a total of ten (10) hospitals offering secondary to tertiary level care thus having diabetic clinics. All the doctors attending to diabetic patients were included in the survey. At the end, a total of fifteen (15) doctors were interviewed. Participation in all cases was made voluntary and respondents had to give their informed consent.

Table 1:
Details of sampling of Community Pharmacies

S/N	Name of LGA	No of registered Community Pharmacies	Number included in the survey	% per LGA
1	Abeokuta south	37	35	94.6
2	Abeokuta North	9	7	77.8
3	Odeda	3	3	100
4	Ijebu-ode	11	10	90.9
5	Sagamu	16	14	87.5
6	Ikenne	5	4	80
7	Ado-Odo /Ota	24	21	87.5
8	Ifo	11	9	81.8
9	Yewa-south	5	5	100
	Total	**121**	**108**	**100**

LGA= Local Government Area

RESULTS

All the brands of metformin tablets used for the study were within their shelf-life at the time of investigation and all the brands were registered by NAFDAC. Only one of the brands was manufactured in Nigeria, others were imported from other countries (Table 2). Tables 3 and 4 shows the determinant factors influencing the perception of metformin quality by Community Pharmacists (CPs) and Doctors (DRs). For CPs; Clients' demand ranked highest (41%) followed by drug quality (36%). The CPs were more influenced in their choice of brands for stocking by the clients' request showing their interest in providing prompt relief and subsequent satisfaction for clients. They might also have perceived that clients' request are due

to alleviation of symptoms by a particular brand. The cost of the brands (14%) was also given consideration but much less than the interest in drug quality. The pharmacists determined quality by experience in their practice, NAFDAC registration number and frequency of the brand name on doctor's prescription sheets.

Table 2:
The details of the brands of Metformin tablets

Brand code	Country	Batch number	NAFDAC number	Expiry date
A	France	102759	04-6233	12/2014
B	Malaysia	AK06558	04-0810	06/2013
C	India	HU34577	04-8864	11/2013
D	India	SRNH0002	04-7764	07/2014
E	Nigeria	S4303	04-7968	09/2013
F	India	7207548	04-4803	12/2012
G	India	MN5008039	04-7945	09/2013
H	India	FVU902	A4-2278	12/2012

For the doctors; availability in the hospital pharmacy ranked highest (82.1%) in their determinant factors for prescribing metformin brands. This may be due to the fact that they have to prescribe what is in stock in the hospital Pharmacies. The CPs and DRs with years of experience greater than 15 had more interest in quality than the younger professionals. It is possible that the more experienced professionals had a better understanding of the disease condition and the need for prompt and consistent control of the sugar level than the younger ones. Generally, the innovator brand was more stocked by Pharmacists and more prescribed by doctors showing that the brand must have maintained its integrity both with the clients and the health professionals. Majority (57.5% of CPs and 67.5% of DRs) of the professionals do not have confidence in the presence of NAFDAC registration number as a sign of metformin quality. This could be due to possible experience of therapeutic failure with any registered brand. The results of the in *vitro* analysis are presented in Table 5 and Figure 1 with a summary of all the analysis in Table 6. The uniformity of weight for seven of the brands showed compliance with the official specification as the deviation in weight was not greater than 5% (B.P 1994).

Table 3:
Factors affecting the perception of metformin quality by Community Pharmacists

Determinant of choice of brand for stocking		Years of experience of pharmacists and interest in quality		NAFDAC registration numbe a sign of quality		Presence on doctors' prescription sheet as a sign quality	
Factor	Percentage	Years	Percentage	Response	Percentage	Brand	Percentage
Demand	41	< 7	19.4	Yes	41.0	A	64.1
Quality	36	7-15	36.1	No	57.5	B	29.4
Cost	14	>15	44.4	Uncertain	1.5	C	3.9
Prescription	7					D	0
Availability	2					E	0
						F	1.3
						G	1.3
						H	0
Total	**100**		**100**		**100**		**100**

Table 4:
Factors affecting the perception of metformin quality by Doctors

Determinant of choice of brand for prescribing		Years of experience of doctors and interest in quality		NAFDAC registration numb as a sign of quality		Brands prescribed	
Factor	Percentage	Years	Percentage	Response	Percentage	Brand	Percentage
Demand	NA	< 7	21.3	Yes	28.0	A	89.1
Quality	17.0	7-15	30.9	No	67.5	B	8.2
Cost	0.9	>15	47.8	Uncertain	4.5	C	2.3
Availability						D	0
in the clinic	82.1					E	0
						F	0.4
						G	1.3
						H	0
Total	**100**		**100**		**100**		**100**

NA-Not available (patients do not demand for brands from the doctors interviewed)

Table 5:
The physicochemical properties of the brands of metformin tablets

S/N	Brand code	Weight uniformity (g)	Crushing strength (N)	Friability (FR) (%)	Crushing strength-Friability ratio (CSFR)	Disintegration time (Minutes)	CSFR/DT	Content Assay (%)
1	A	0.541±0.011	48.77±2.481	0.42	117.241	6.60±0.101	17.76	100.75±0.81
2	B	0.580±0.023	57.90± 4.370	0.17	340.592	3.80±0.402	89.63	100.42±2.91
3	C	0.619±.020	54.53± 8.372	0.83	65.703	9.12± 0.132	7.20	98.06±1.60
4	D	0.656± 0.021	103.80± 5.601	14.49	7.164	11.37± 0.223	0.63	96.76±2.01
5	E	0.566± 0.003	116.70±16.880	1.12	104.191	7.77±1.312	13.41	95.71±1.96
6	F	0.575±0.005	105.03± 3.851	0.30	350.102	6.10± 0.643	57.39	95.62±1.78
7	G	0.541±.020	119.33±16.013	0.32	372.911	10.21± 0.104	36.53	98.25±0.94
8	H	0.676±.010	234.53±17.901	0.63	372.272	2.64±0.073	141.01	92.02±2.11

Data expressed as mean± SD, CS=crushing strength, DT=disintegration time

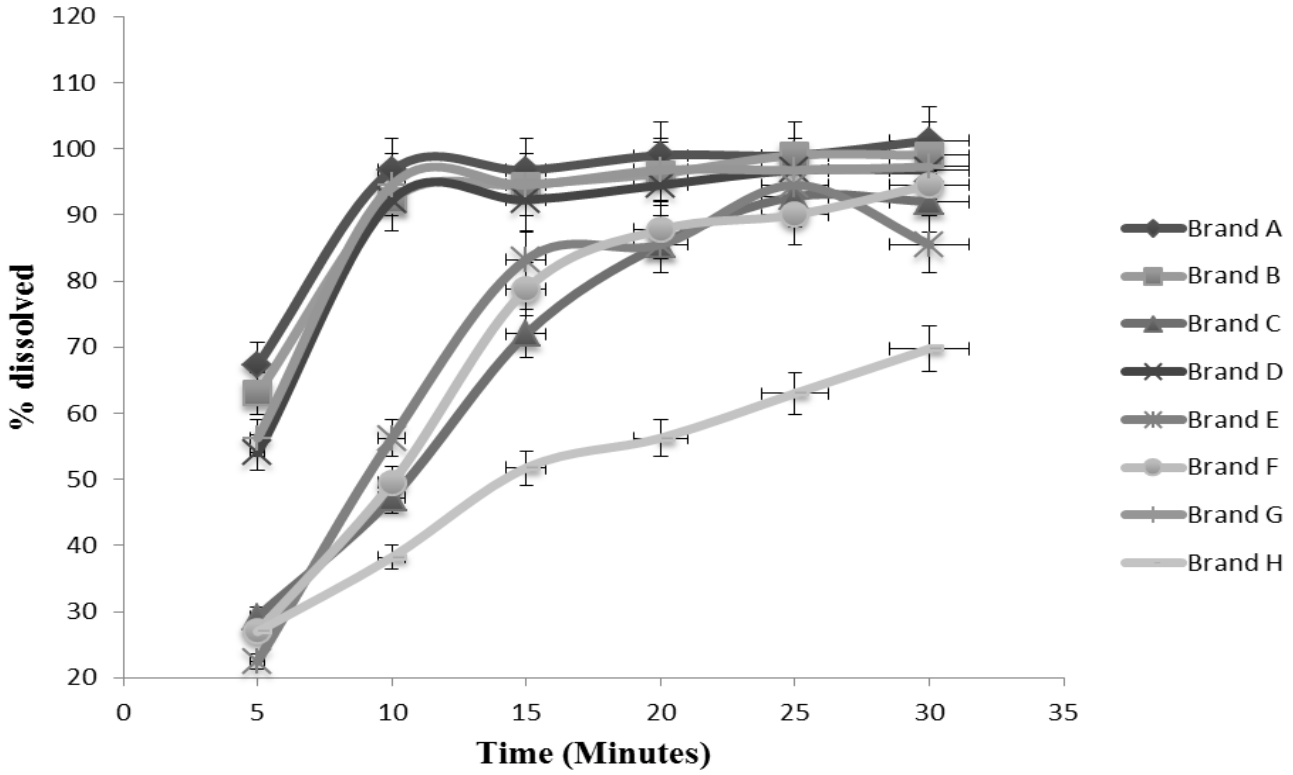

FIGURE 1: Dissolution profiles of brands of metformin tablets

DISCUSSION

The mechanical properties of pharmaceutical tablets are quantifiable by the crushing strength and the friability. Crushing strength provides a measure of tablet strength while friability is a measure of tablet weakness (Odeku and Itiola, 2003). Official requirements are now available for crushing strength and friability in the British Pharmacopoeia (Dires,2005), though the limits are not clear for acceptance or rejection of tablet batches. This may be because in the case of crushing strength, the desired requirement is largely dependent on the intended use of the tablet (Odeku and Itiola, 2003). For friability, conventional compressed tablets that lose less than 1% of their mass during friability test are generally considered acceptable (Riipi *et al*, 1998). Failure of friability test indicates that such tablets would not be able to withstand abrasion during packaging, shipping, handling and storage. This loss of drug due to high tablet weakness could lead to the delivery of insufficient drug dose to the patient which might cause inadequate sugar control.

Table 6:
Summary of results of tests carried out on the brands of Metformin tablets

Brand code	1	2	3	4	5	6
A	passed	passed	passed	passed	passed	passed
B	passed	passed	passed	passed	passed	passed
C	passed	passed	passed	passed	passed	passed
D	Failed*	passed	Failed*	passed	passed	passed
E	passed	passed	passed	passed	passed	passed
F	passed	passed	passed	passed	passed	passed
G	passed	passed	passed	passed	passed	passed
H	passed	Failed*	passed	passed	passed	Failed*

key: 1-Uniformity of weight 2-Crushing strength test 3-Friability 4-Disintegration 5-Dissolution 6-Assay

Brand H has significantly higher CS ($p<0.001$) than others but still passed FR and DT tests hence the CSFR and CSFR/DT values were high enough showing a good balance of mechanical and release properties. The higher the CSFR, the stronger the tablet and the higher the CSFR/DT, the better the balance of mechanical and release properties (Odeku and Itiola, 2003). The ranking of CS for the metformin brands was H>>>G>E>F>D>B>C>A, while the trend for FR was D>>>E>C>H>A>G>F>B. Brand D which had a significantly higher ($p<0.001$) FR and failed the test could not also demonstrate good overall mechanical and release properties since the CSFR and CSFR/DT were quite low (7.16 and 0.63 respectively). The failure of brands D and E in the FR tests may have been caused by insufficient binding agent, inadequate moisture content and lack of sufficient compression pressure or inadequate dwell time. A high CS may be attributed to a high compression pressure, high binder concentration or due to excessive addition of granulating fluid (Dires, 2005).

Tablet disintegration time (DT) is one of the very important physicochemical properties in solid dosage forms. It is the rate limiting step in the process of absorption. The BP (1998) stipulates that uncoated tablets should disintegrate within fifteen (15) minutes. As shown in Table 5, all the tablets disintegrated in not more than 15minutes hence passed the test. Brands D and G has the highest disintegration time. Brand H which has the highest CS also gave the lowest DT which implies that the DT was not affected by the high CS. This rapid disintegration could be due to the amount and type of disintegrant present in the tablet. The trend of DT among the brands was D>G>C>E>A>F>B>H and ranking of CSFR/DT was H>>B>F>G>A>E>C>>D. Furthermore, the result of the assay of the active ingredient to determine the amount of metformin hydrochloride present in each formulation is also presented in Table 5. All the brands except brand H passed the test with values within the USP (1980) specified limits of 95-105%. The failure of brand H could be due to poor granulation and poor flow of granules from hopper to die to produce the tablet. The flow of granulation is also affected by the presence of sufficient lubricating agent.

The dissolution profiles of the different brands of metformin are presented in Figure 1. Dissolution studies give an idea of the amount of drug available for absorption after oral administration. Drugs with poor dissolution profile will not be available in the systemic circulation to elicit its therapeutic action. The BP (1997) stipulates that 70% of metformin should be released within 40 minutes. All the brands released up to an approximate value of 70% drug in less than 40minutes and as such passed the BP standard. The ranking of percentage dissolved among the brands was A>B>G>D>F>C>E>>H. The slower release of brand H could be due to the high crushing strength observed in this particular brand and this may be due to excessive use of granulating agent or other processing factors like high compression pressure. Wells, (1980) reported that tablets containing soluble binders (hydrolysed gelatine and PVP) have rapid dissolution rate whereas slow and incomplete dissolution resulted with starch paste (Dires, 2005). The disintegrant used could also affect the rapid release of the drug into solution as the tablet must disintegrate quickly to liberate a large effective surface area of the drug in the dissolution medium.

Generally, the physicochemical properties of the brands of metformin showed significant differences ($p<0.05$) in their mechanical (crushing strength and friability) and release (disintegration and dissolution) parameters. This implies that the brands cannot be substituted for each other because they are not pharmaceutically equivalent and may therefore not be bioequivalent. This is in agreement with the report of Osadebe and Akabogu (2004) where not all the brands of metformin tablets evaluated had acceptable standard and interchangeable with the innovator brand. In all, 5(62.5%) of the brands passed all the tests hence considered to be of high quality while 3 (37.5%) were rated low quality having failed at least one test. There was also no significant difference ($p>0.05$) in the

perception of community pharmacists about the quality of the brands and the results of *in vitro* analysis showing that these health providers are utilizing appropriate professional judgement in exhibiting pharmaceutical care.

The study showed that metformin tablets in the community and hospital pharmacies were markedly different in their pharmaceutical quality. Community Pharmacists and Doctors were influenced in their stocking or prescribing of metformin by different factors. Majority (>50%) of both health professionals do not rely on NAFDAC registration number as a quality variable. The variation in brand quality observed from the *in vitro* analysis agrees with the perception of both CPs and DRs that the brands are different. Therefore in dispensing and prescribing, CPs and DRs should be cautious in their choice for alternative use and rely on their professional judgement. There is also the continual need for proper and stricter measures by regulatory bodies to ensure compliance and consistency.

In conclusion, the perception of quality by community pharmacists and medical doctors about the brands of metformin tablets used in this study was comparable to the results of the *in vitro* tests. The study also showed that in a multisource product range, while some are not equivalent, others will compete adequately with the innovator product and serve as substitutes.

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