African Journal of Pharmaceutical Research & Development

Vol. 12 No.3; pp. 333-341 (2020)

PHARMACEUTICAL QUALITY ASSESSMENT OF BRANDS OF METFORMIN HYDROCHLORIDE TABLETS AVAILABLE IN SOUTH-EAST NIGERIA

ERAGA SYLVESTER OKHUELEGBE[1,*], IDEMILI CHIDOZIE AUGUSTINE DENNIS[2], IWUAGWU MAGNUS AMARA[2]

1. Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, Benin City, 300001, Nigeria.
2. Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Madonna University, Elele, River State, Nigeria.

ABSTRACT

Nigerian pharmaceutical market is replicate with various imported brands of metformin tablets. The aim of the study was to assess the quality of different brands of metformin hydrochloride tablets available in the south-east zone of Nigeria. Fifteen (15) brands of metformin hydrochloride tablets were bought and evaluated for tablet weight, dimensions, friability, crushing strength, disintegration time and dissolution profiles. Content of active pharmaceutical ingredient (API) of the different brands was determined using spectrophotometric analysis. Twelve brands of the tablets were immediate release, two were slow release and one was an extended release dosage form. They were within their shelf lives, well labelled and packaged, and only two brands were not registered by the National Agency for Food and Drug Administration and Control (NAFDAC). There were significant variations ($p < 0.05$) in the weight, friability, hardness and disintegration times among the brands but not within the brands. The crushing strength and friability values of some brands were not within acceptable official limits. Three (3) immediate release brands released less than 70% of metformin within 45 min. All the brands met the official specifications of 95-105% drug content in the content assay results. The brands of metformin hydrochloride (500 mg tablets) exhibited variations in their tablet parameters. Three brands failed the dissolution test and all the brands had acceptable content of API. These results highlight the need to routinely carry out market surveillance of pharmaceutical drug products to ensure access to quality and efficacious drugs.

KEYWORDS: **Metformin hydrochloride; Tablets properties; Pharmaceutical quality; Assay.**

INTRODUCTION

The issue of substandard and falsified medicines remains a global concern. The scale of concern is even greater in developing countries where drug regulatory agencies are less equipped to enforce laws which ensures a reliable supply of good quality medicines [1]. Globally, every health sector is faced with the challenges of eradicating sub-standard medicines because of the health risks and treatment failures arising from their use. The need to maintain public confidence in the health care system has also been identified as one of the reasons for identifying and eradicating sub-standard medicines [2].

Diabetes mellitus is a chronic metabolic disorder that results from a failure of the body to produce the hormone insulin and/or an inability of the body to respond adequately to circulating insulin. It has become the third most common disease that heavily threatens human health in the world, following cardiovascular diseases and cancers [3]. According to the International Diabetes Federation (IDF), approximately 463 million persons worldwide suffer

***Corresponding author:** eragaso@uniben.edu; +2348030884928*

from various forms of diabetes and this is estimated to rise to 700 million by the year 2045 [4].
Metformin is an oral antidiabetic drug that works by suppressing glucose production by the liver and it is the first-line drug for the treatment of Type II Diabetes Mellitus [5,6]. It is one of only two oral antidiabetics in the World Health Organization Model List of Essential Medicines [7].
Treatment failures and even death has been reported in the use of substandard antidiabetic drug like glibenclamide in China and insulin in Nigeria [2]. Several bioequivalence studies of various brands of metformin tablets available in pharmacies across different cities in Nigeria have shown one or more brands failing to meet pharmacopeial standards [8-12]. Additionally, the number of brands been imported into the country or manufactured locally is increasing hence the need to routinely evaluate the pharmaceutical quality of those available brands in the market. .
The aim of this study was to assess the pharmaceutical quality of different brands of metformin hydrochloride tablets available in the Nigerian market. Specifically, the physical, chemical and pharmaceutical equivalence of fifteen (15) brands of metformin hydrochloride tablet marketed in the south-east region of Nigeria were investigated.

MATERIALS AND METHODS

Materials
Pure metformin powder (May and Baker, Lagos, Nigeria), fifteen brands of metformin hydrochloride (500 mg) tablets were purchased from different registered pharmacies in Akwa-Ibom, Bayelsa, Delta, Edo and Rivers States of Nigeria.

Sampling method
A minimum of ten registered pharmacies per state capital were visited. A sampling method of purchasing all available brands in a pharmacy without re-purchasing any brand already gotten from a previous pharmacy was adopted. Labelled information of the brands purchased are presented in Table 1.

Evaluation of tablets
The following evaluations were carried out on the metformin tablet samples using standard procedures: tablet dimensions, weight uniformity, hardness, friability, disintegration time, content of active pharmaceutical ingredient and dissolution studies [13].

Dimensions
The thickness and diameter of each of ten tablets per brand were measured using a digital vernier caliper (Mituloyo 500-196-30, Japan).

Uniformity of weight
Twenty (20) tablets were randomly selected from each brand and weighed individually using an analytical weighing balance (Tianfu - DT-1000, China).

Hardness test
Ten (10) tablets randomly selected from each brand were subjected to hardness test using a tablet hardness tester (Campbell Electronics, Mumbai, India). Each tablet was diametrically compressed until it fractured and the mean crushing strength was calculated.

Friability test
Ten (10) tablets randomly selected from each brand were weighed and placed in a friabilator (Erweka GmbH, Germany), which was set to rotate at 25 rpm for 4 min. The tablets were collected afterwards, dedusted and reweighed. The weight loss was obtained from the differences between the initial weight and the final weight. The percentage friability was calculated as the percentage weight loss.

Disintegration test
Six (6) tablets per brand were used for the determination. The tablets were placed in the tubes of a disintegration apparatus (Erweka DT-D, Germany) and constantly agitated in water maintained at 37 °C. The time taken for each tablet to completely pass through the mesh of the disintegration basket was noted and the mean disintegration time determined.

Content of active pharmaceutical ingredient (API)
Standard calibration curve
A standard stock solution of metformin hydrochloride was prepared by dissolving 100 mg of pure metformin powder with sufficient volume of 0.1 M HCl to get a 100 ml solution. Various standard concentrations ranging from 1.0 - 10 µg/ml obtained from further dilution of the stock solution with 0.1 M HCl were analysed spectrophotometrically at 232 nm (Cecil Instruments Ltd., UK). The mean absorbances of triplicate determinations were plotted against their corresponding concentrations to obtain a calibration curve.

Sample preparation

Twenty tablets randomly selected from each brand were weighed and crushed into powders. Powder quantity equivalent to 100 mg of metformin was weighed into a volumetric flask and dissolved in 0.1 M HCl to give a 100 ml solution. The solution was filtered using Whattman filter paper (No. 1) and 1.0 ml aliquot of the solution was further diluted to 100 ml to give a 10 µg/ml solution. The resulting solution was read at 232 nm and the average absorbance for triplicate measurement of each brand was extrapolated on the calibration curve derived from the pure metformin powder to get the equivalent concentration and the percentage content calculated [14].

Dissolution test

The dissolution was carried out using the British Pharmacopeia paddle method in 900 ml of 0.1 M HCl solution maintained at 37 ± 1 °C with a paddle revolution of 100 rpm (Erweka Apparatebau, Germany). Three tablets per brand was randomly selected and used in the determination. A 5.0 ml quantity of the dissolution medium was periodically withdrawn and replaced with an equal amount of fresh dissolution medium at 5, 10, 15, 20, 30, 45 and 60 min. Each of the samples withdrawn was filtered with a fresh filter paper and the filtrate diluted appropriately. The absorbance values of the diluted filtrate were read spectrophotometrically at λmax of 232 nm with 0.1 M HCl solution as blank. The concentration and the percentage of drug released at each time interval was determined using the equation from the standard calibration plot obtained from the pure metformin. A minimum of triplicate determinations were carried out for all brands and the results were recorded as mean ± standard deviation (SD).

Statistical analysis

Experiments were carried out in triplicates and mean values reported with standard deviation. Differences between means were subjected to one-way ANOVA with Dunnett multiple comparison test against the brand that met the BP standard for crushing strength (5.0 - 8.0 kp) at $p \leq 0.05$ using GraphPad InStat 3.10.

RESULTS

All the metformin tablets investigated had label strength of 500 mg (Table 1) and were within their shelf lives. Twelve brands were immediate release dosage forms while two brands were slow release formulations and one was an extended release dosage form. Eight out of the fifteen brands studied were formulated in India, four in Nigeria and one each in Cyprus, Yemen and Malaysia. All the brands had batch numbers and were all registered except two brands with the National Agency for Food and Drug Administration and Control (NAFDAC), the drug regulatory agency in Nigeria.

The tablets exhibited weights ranging from 510 - 850 mg with no significant variation within each brand but a significant difference among the brands. Also, the tablet dimensions showed no significant differences ($p > 0.05$) within each brand but some differences were evident amongst the brands especially in their tablet thickness which were also not significant (Table 2).

The mean crushing strength of the tablets ranged from 3.00 - 14.90 kp with seven brands having values lower than 5.0 kp. The BP recommends optimum crushing strength values ranging from 5.0 - 8.0 kp [13]. There were no significant differences in the crushing strength values within each brand but differences ($p \leq 0.05$) occurred amongst the brands with values of eight (8) brands not significantly different from BP specifications (Table 2). Tablets of seven brands (A, B, D, G, H, J and K) gave friability values below 1.0% while those of other brands gave values less than 2.0% except brand I with a friability value of 2.99%. The disintegration times of the tablets were within 9.0 min except brands A, E and M tablets which failed to disintegrate within 1 h of testing (Table 2).

The dissolution drug profiles (Figure 1a, b and c) of the different brands of tablets revealed variable drug release profiles with only nine brands (B-D, F-I, K and O) releasing up to 70% of their labeled contents within 45 min (Table 3). Tablets from brands A, E and M had the lowest drug release with a percentage drug release of 48.50, 45.88 and 43.25%, respectively, in the 60 min of dissolution testing. All the brands had drug content ranging from 95 - 102% with brand H tablets exhibiting the highest drug content of 102.20% and brand E tablets with the lowest drug content of 95.50% (Table 3).

DISCUSSION

In Nigeria, NAFDAC, the drug regulatory agency is empowered to inspect, register and permit the sales of drug products. Out of the total fifteen (15) brands studied, two of them (H and L) had no NAFDAC registration number. This suggests that the drug might have been smuggled into the country by the manufacturers or distributors of the product, by-passing the drug regulatory body [15]. This action already casts doubts as to the authenticity of these two brands and are therefore considered as substandard and falsified products [16].

Table 1: Label details on the different brands of metformin.

Sample code	Manufacturer/Country of origin	Brand name	Expiry date	Batch number	NAFDAC number
A	Lupin Laboratories Ltd, India	Gluconorm SR 500	May, 2021	HB 8001	Yes
B	Biopharm Pharm. Industry, Yemen	Biophage	Mar, 2024	1908	Yes
C	SKG Pharma Ltd, Nigeria	Avrophage	Feb, 2024	1902	Yes
D	May and Baker Nig Plc, Nigeria	Diamet	Mar, 2021	A190731	Yes
E	Nemel Pharmaceutical, Nigeria	Nelovix-XR	Oct, 2020	01K	Yes
F	Nigerian-German Chem. Plc, Nigeria	Gluformin	Feb, 2022	FPCO8019	Yes
G	Hovid Bhd, Malaysia	Diabetmin	Oct, 2021	BJ 11535	Yes
H	Sandoz Pharmaceuticals, India	Metformin Sandoz	Jul, 2021	JD1321	No
I	Vapi Care Pharma Pvt Ltd, India	Forbetic	Aug, 2020	FVU 1703	Yes
J	Fourtt Lab Pvt Ltd, India	Dibinorm	Sept, 2021	F1804	Yes
K	Baroque Pharm. Pvt Ltd, India	Tricophage-500	May, 2021	G038001	Yes
L	CFL Pharmaceuticals Ltd, India	Diaformin	May, 2021	MTE 01	No
M	Inventia Health Care, India	Panfor SR-500	Feb, 2022	PAF01463	Yes
N	Remedica Ltd, Cyprus	Glyformin	Aug, 2019	S4302	Yes
O	Rhydburg Pharmaceuticals Ltd, India	Sivophage	Dec, 2020	GT 18026	Yes

Table 2: Properties of the metformin tablets

Sample Code	Weight (g)	Dimensions (mm)		Crushing strength (kp)	Friability (%)	Disintegration time (min)
		Diameter	Thickness			
A	0.85 ± 0.01	10.0 ± 0.01	0.7 ± 0.01	*14.00 ± 0.16	0.06 ± 0.22	> 1 h
B	0.58 ± 0.10	10.0 ± 0.02	0.4 ± 0.03	4.40 ± 0.17	0.05 ± 0.16	5.23 ± 0.22
C	0.67 ± 0.01	10.0 ± 0.04	0.7 ± 0.01	3.50 ± 0.23	1.62 ± 0.06	5.55 ± 0.10
D	0.51 ± 0.01	10.0 ± 0.03	0.4 ± 0.03	4.10 ± 0.34	0.60 ± 0.02	8.56 ± 0.27
E	0.85 ± 0.03	10.0 ± 0.01	0.7 ± 0.01	*14.60 ± 0.20	1.82 ± 0.42	> 1 h
F	0.55 ± 0.00	10.0 ± 0.02	0.6 ± 0.02	*10.80 ± 0.16	1.72 ± 0.56	4.12 ± 0.03
G	0.56 ± 0.00	9.0 ± 0.04	0.6 ± 0.02	4.60 ± 0.38	0.02 ± 0.62	3.88 ± 0.02
H	0.52 ± 0.03	10.0 ± 0.01	0.4 ± 0.03	*9.40 ± 0.26	0.19 ± 0.40	8.08 ± 0.01
I	0.67 ± 0.00	10.0 ± 0.02	0.7 ± 0.01	*9.00 ± 0.18	2.99 ± 0.32	2.96 ± 0.04
J	0.69 ± 0.00	10.0 ± 0.01	0.7 ± 0.01	4.10 ± 2.90	0.04 ± 0.12	5.04 ± 0.03
K	0.62 ± 0.01	10.0 ± 0.03	0.7 ± 0.01	6.20 ± 2.58	0.30 ± 0.14	4.02 ± 0.03
L	0.65 ± 0.01	12.5 ± 0.01	0.4 ± 0.03	3.00 ± 2.60	1.35 ± 0.06	3.03 ± 0.02
M	0.83 ± 0.01	9.0 ± 0.03	0.6 ± 0.02	*14.90 ± 3.78	1.36 ± 0.04	> 1 h
N	0.55 ± 0.01	12.5 ± 0.01	0.4 ± 0.03	*10.90 ± 0.15	1.17 ± 0.10	4.22 ± 0.02
O	0.55 ± 0.01	10.0 ± 0.01	0.6 ± 0.02	4.40 ± 0.38	1.95 ± 0.02	5.71 ± 0.08

Samples A = Gluconorm SR 500, B = Biophage, C = Avrophage, D = Diamet, E = Nelovix-XR, F = Gluformin, G = Diabetmin, H = Metformin Sandoz, I = Forbetic, J = Dibinorm, K = Tricophage-500, L = Diaformin, M = Panfor SR-500, N = Glyformin and O = Sivophage

* $p \leq 0.05$.

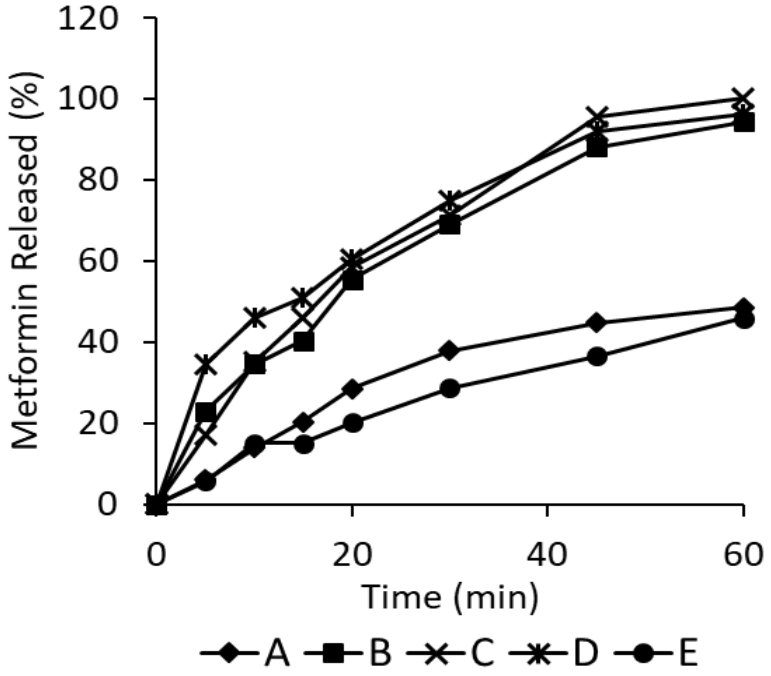

Figure 1a: Dissolution profiles of drug samples A-E
Samples A = Gluconorm SR 500, B = Biophage, C = Avrophage, D = Diamet and E = Nelovix-XR.

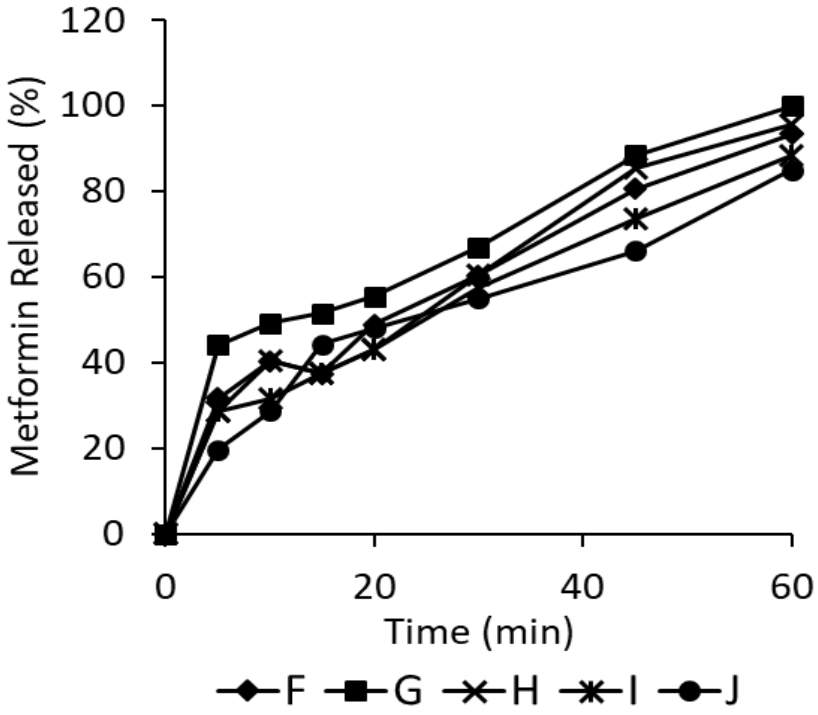

Figure 1b: Dissolution profiles of drug samples F-J
Samples F = Gluformin, G = Diabetmin, H = Metformin Sandoz, I = Forbetic and J = Dibinorm.

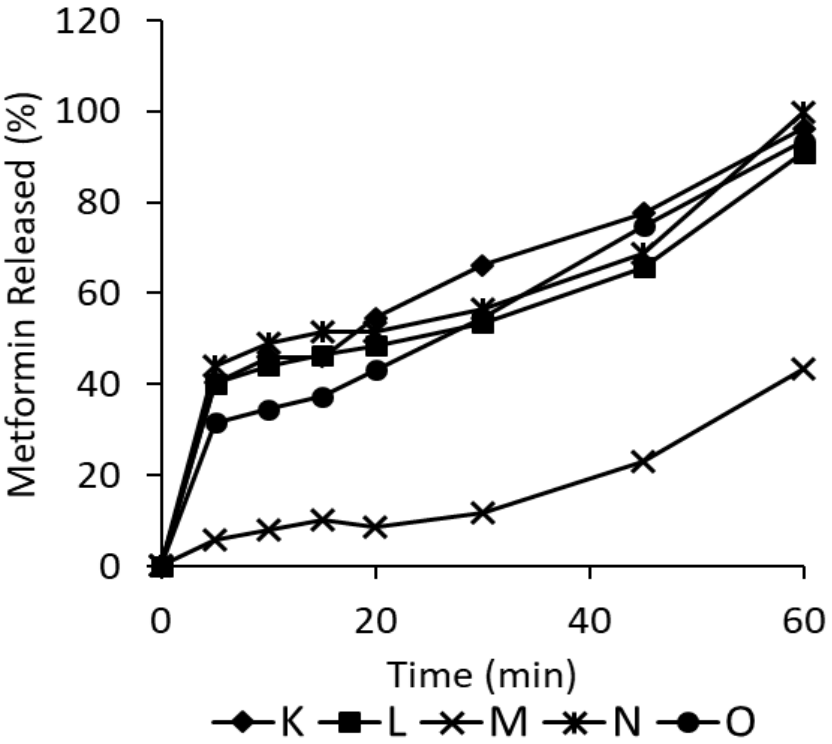

Figure 1c: Dissolution profiles of drug samples K-O
Samples K = Tricophage-500, L = Diaformin, M = Panfor SR-500, N = Glyformin and O = Sivophage.

Table 3: Some dissolution parameters and content of active

Sample code	Dissolution parameters		Content of active		
	$T_{50\%}$ (min)	$M_{45\ min}$ (%)	Labelled (mg)	Content (mg)	% Content
A	-	44.68	500	508.15	101.63
B	19.1	88.14	500	501.00	100.20
C	14.0	95.64	500	494.95	98.99
D	16.4	92.01	500	481.50	96.30
E	-	36.50	500	497.50	99.50
F	21.0	80.51	500	491.30	98.26
G	18.0	88.38	500	485.35	97.07
H	24.2	85.51	500	513.10	102.62
I	26.0	73.39	500	487.45	97.49
J	23.8	66.00	500	497.85	99.57
K	17.0	77.64	500	478.50	95.70
L	23.0	65.67	500	489.95	97.99
M	-	23.13	500	504.00	100.80
N	12.0	68.76	500	481.50	96.30
O	26.0	74.76	500	479.50	95.90

Key: $T_{50\%}$ = time taken to release 50% of drug, $M_{45\ min}$ = amount of drug released in 45 min
Samples A = Gluconorm SR 500, B = Biophage, C = Avrophage, D = Diamet, E = Nelovix-XR, F = Gluformin, G = Diabetmin, H = Metformin Sandoz, I = Forbetic, J = Dibinorm, K = Tricophage-500, L = Diaformin, M = Panfor SR-500, N = Glyformin and O = Sivophage.

Results from the tablet's weight uniformity test indicated that there were no significant differences ($p > 0.05$) in their weights within each brand and hence conformed to the British Pharmacopoeia specification [17]. Tablets weight uniformity has been shown to be a pointer to dosage uniformity or content uniformity [18,19]. Also, the differences in weight among the brands indicating tablets of different sizes, may lead to reservations among patients and prescribers on the bioequivalence of these brand when there is need to change brand. Even though the WHO Model Formulary [20] advises that patients should be placed on a single brand, this becomes difficult when such brand are no longer available in the market.

An unduly hard tablet would increase disintegration time significantly and in turn affect dissolution as exhibited by brands A, E and M. The high crushing strength values of three brands is expected since they are sustained release formulation and not expected to disintegrate. Although some authors have recommended an optimum tablet hardness value of 4.0 kp [21], the low crushing strength values of brands C and L could be due to errors in manufacturing. These errors emphasize the need for strict in-process control measures by manufacturers to check and correct such errors during the manufacturing process.

The friability values of the tablet showed that only seven brands met the BP recommendation of 0.8 - 1.0% loss in weight [13]. The hardness of the tablets did not correlate with their friability values, as harder tablets are expected to be less friable. Although up to 2.0% loss is permissible especially for large tablets prepared by direct compression [22]. The 2.99% value of brand I may be attributed to negligence on the part of the formulator in selecting proper excipients of known physicochemical properties and being able to predict the behaviour of these excipients in the tablet dosage form.

All the tablets disintegrated within 15 min as specified by BP for uncoated tablets [13] except brands A, E and M tablets. As sustained release formulation, these brands are not expected to disintegrate at all and if disintegration was to occur, it is not expected to be within the time limit for conventional tablets. There was no direct relationship between disintegration times and crushing strength values of the tablets among the conventional tablets as the less hard tablets did not necessary exhibit significantly lower disintegration times. This may be due to the different processes employed by different manufacturers to ensure good disintegration times for their drug products [23].

Most times, the *in vitro* dissolution profile of a drug is a reflection of drug release *in vivo*. A dosage form may meet all other compendial specifications but not be able to release sufficient amount of drug *in vivo* for optimum therapeutic response.

All the brands adhered to the British Pharmacopeia [16] stipulation of a 95 - 105% of active drug content. Though these results indicate that all the brands passed the content of active test, the sensitivity of the ultra-violet (UV) spectrophotometric test method in content assay still permits some reservations. A more sensitive method such as the reverse phase high-performance liquid chromatographic (HPLC) method would be recommended for further and future analysis as some comparative analyses studies that employed both methods in drug content assay obtained some differences in results [24-28].

CONCLUSION

All the brands of metformin hydrochloride 500 mg tablets assessed exhibited variations in tablet weight, crushing strength, friability and disintegration times. Two brands were not registered by the drug regulatory agency in the country. Three conventional tablet brands failed the dissolution test for not releasing up to 70% of its drug content in 45 min and all the brands met acceptable standards in their content of active. These results highlight the importance for manufacturers and drug regulatory bodies to routinely carry out market surveillance of pharmaceutical drug products to ensure access to quality and efficacious medicines at all times.

ACKNOWLEDGMENTS

The authors acknowledge the technical support received from the laboratory staff of the Department of Pharmaceutics and Pharmaceutical Technology, University of Benin, Benin City.

REFERENCES

1. Suleman S, Zeleke G, Deti H, Mekonnen Z, Duchateau L, Levecke B, Vercruysse J, D'Hondt M, Wynendaele E, De Spiegeleer B. Quality of medicines commonly used in the treatment of soil transmitted helminthes and giardia in Ethiopia: A nationwide survey. PLoS Neglected Tropical Diseases 8, 2014: e3345.
2. Clinical Guidelines Task Force. Glucose Control: Oral Therapy. In Global Guidelines for Type II Diabetes Mellitus. International Diabetes Federation, Brussels. 2005: pp. 35-38.

3. World Health Organization Global Report on Diabetes. Geneva, Switzerland, 2016.
4. International Diabetes Federation (IDF) Diabetes Atlas. Ninth Ed. International Diabetes Federation, Brussels, Belgium, 2019. [cited July 25, 2020]. Available from: https://www.diabetesatlas.org/en/sections/worldwide-toll-of-diabetes.html.
5. Hundal RS, Inzucchi SE. Metformin: New understandings, new uses. Drugs 63, 2003: 1879-1894.
6. Joint Formulary Committee. Chapter 6: Endocrine system. British National Formulary (BNF) 65th Ed. Pharmaceutical Press, London, UK. 2013: pp. 447-448.
7. Lacher M, Hermanns-Clausen M, Haeffner K, Brandis M, Pohl M. Severe metformin intoxication with lactic acidosis in an adolescent. European Journal of Pediatrics 164, 2005: 362-365.
8. Osadebe PO, Akabogu IC. Assessment of quality control parameters and interchangeability of multi-sourced metformin HCl tablets marketed in Nigeria. Bollettino Chimico Farmaceutico 143, 2004:170-173.
9. kinleye MO, Adelaja IA, Odulaja JO. Comparative evaluation of physicochemical properties of some commercially available brands of metformin HCl tablets in Lagos, Nigeria. Journal of Applied Pharmaceutical Science 2, 2012: 41-44.
10. Ajala TO, Adebona AC, Bamiro OA. The pharmaceutical quality of brands of metformin tablets in Ogun-State, Nigeria. African Journal of Biomedical Research 17, 2014: 43-48.
11. Eraga SO, Arhewoh MI, Oruh EP, Iwuagwu MA. A comparative evaluation of the pharmaceutical quality of different brands of metformin hydrochloride tablets available in Abuja, Nigeria. West African Journal of Pharmacy 28, 2017: 61-71.
12. Garba MA, Dauda NJ, Mohammed M, Bello SS. Comparative quality control studies on three brands of metformin hydrochloride tablets marketed in Kaduna, Nigeria. Journal of Pharmaceutical and Allied Sciences 16, 2019: 3086-3093.
13. British Pharmacopoeia. Volume III. British Pharmacopoeia Commission. The Stationery Office Limited, London, UK. 2009: pp. 6578-6585.
14. Patrick JS. Martin's Physical Pharmacy and Pharmaceutical Sciences, 5th Ed. Lippincott Williams and Wilkins, Philadelphia, PA. 2006: pp. 337-354.
15. Eraga SO, Uzochukwu OC, Iwuagwu MA. Pharmaceutical equivalence of some brands of 5.0 mg amlodipine besylate tablets available in southern Nigeria. West African Journal of Pharmacy 25, 2014: 38-45.
16. WHO Global Surveillance and Monitoring System for substandard and falsified medical product: Executive summary. Geneva, Switzerland, 2017.
17. British Pharmacopoeia. Volume I. British Pharmacopoeia Commission. The Stationery Office Limited, London, UK, 2011: p. 1110.
18. United States Pharmacopoeia/National Formulary (USP/NF). United States Pharmacopoeial Convention, Rockville, MD, 2003: p. 2227.
19. Alderborn G. Tablets and compaction. In: Aulton ME, Ed. Pharmaceutics: The Science of Dosage Form Design. Longman Group, London, UK, 2002: pp. 397-448.
20. WHO Model Formulary. Couper MR, Melhta DK, Eds. World Health Organization, Geneva, Switzerland, 2002: p. 236.
21. Rudnic EM, Schwartz JB. Oral solid dosage forms. In: Troy DB, Beringer P. Eds. Remington - The Science and Practice of Pharmacy. Lippincott Williams and Wilkins, Baltimore, 2006: pp. 889-928.
22. European Pharmacopoeia. Supplement 5.0. European Pharmacopoeia Commission, Council of Europe, Strasbourg, 2005: p. 234.
23. Eichie FE, Arhewoh MI, Isesele JE, Olatunji KT. *In vitro* evaluation of the pharmaceutical quality of some ibuprofen tablets dispensed in Nigeria. International Journal of Health Research 4, 2011: 57-61.
24. Samar AA, Shaimaa A. A comparative study for evaluation of different brands of metformin hydrochloride 500 mg tablets marketed in Saudi Arabia. Life Science Journal 9, 2012: 4260-4266.
25. Parmar VK, Desai SB, Vaja T. RP-HPLC and UV spectrophotometric methods for estimation of pirfenidone in pharmaceutical formulations. Indian Journal of Pharmaceutical Sciences 76, 2014: 225-229.
26. AlKhalidi BA, Shtaiwi M, AlKhatib HS, Mohammad M, Bustanji Y. A comparative study of first-derivative spectrophotometry and column high-performance liquid chromatography applied to the determination of repaglinide in tablets and for dissolution testing. Journal of AOAC International 91, 2008: 530-535.

27. Busaranon K, Suntornsuk W, Suntornsuk L. Comparison of UV spectrophotometric method and high-performance liquid chromatography for the analysis of flunarizine and its application for the dissolution test. Journal of Pharmaceutical and Biomedical Analysis 41, 2006: 158-164.
28. Saravanan VS, Revathi R. Comparative UV-spectroscopy and HPLC methods for content analysis of zolpidem tartrate in solid dosage forms. Turkish Journal of Pharmaceutical Sciences. 11, 2014: 127-136.