A comparative evaluation of the pharmaceutical quality of different brands of metformin hydrochloride tablets available in Abuja, Nigeria

Sylvester O. Eraga, Matthew I. Arhewoh, Enifome P. Oruh and Magnus A. Iwuagwu
Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, PMB 1154, Benin City, 300001, Nigeria.

Corresponding author: Sylvester Eraga
E-mail: eragaso@uniben.edu, Tel: +2348030884928

ABSTRACT

Background: Metformin hydrochloride tablets are the most commonly prescribed drug for the management of Type II Diabetes Mellitus. This has resulted in increased importation and manufacturing of various brands of the tablets in Nigeria.

Objective: To evaluate the pharmaceutical quality of different brands of metformin hydrochloride tablets available in Abuja, Nigeria.

Method: Ten brands of metformin hydrochloride tablets were purchased and subjected to pharmaceutical quality evaluations such as friability, hardness, disintegration and dissolution tests. Content of active pharmaceutical ingredient (API) was determined using spectrophotometric analysis as well as reverse phasehigh performance liquid chromatography (RP-HPLC).

Results: All the brands were elegantly labelled, packaged and within their shelf lives. With exception of one brand, they all had NAFDAC registration number. The weight uniformity, friability, hardness and disintegration time values for all the brands were within acceptable limits. Three brands of the products released less than 70 % of their API after 45 min and therefore failed the dissolution test. There was disparity between content assay results using UV spectrophotometry and HPLC. HPLC results showed that only brand failed the test by having 86 % of the API while with UV spectrophotometry; four brands failed the test.

Conclusion: This investigation suggest that four brands of metformin hydrochloride tablets available in Abuja, did not met official specifications even though only one brand was implicated by HPLC analysis. Consequently,

this research would recommend continuous sentinel surveillance of metformin tablets and the use of HPLC for product analysis for its high sensitivity and accuracy.

Keywords: Metformin, UV, RP-HPLC, assay, pharmaceutical quality, label claim

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Une évaluation comparée de la qualité pharmaceutique de différentes marques de comprimés de chlorhydrate de metformine disponibles à Abuja au Nigeria

Auteur de correspondance: Sylvester Eraga
E-mail: eragaso@uniben.edu, Téléphone: +2348030884928

RESUME

Contexte: Les comprimés de chlorhydrate de metformine sont le médicament le plus couramment prescrit pour la gestion du diabète sucré de type II. Cela a entraîné une augmentation de l'importation et la fabrication de diverses marques de ces comprimés au Nigeria.

Objectif: Évaluer la qualité pharmaceutique des différentes marques de comprimés de chlorhydrate de metformine disponibles à Abuja, au Nigeria.

Méthode: Dix marques de comprimés de chlorhydrate de metformine ont été achetées et soumises à des évaluations de la qualité pharmaceutique telles que la friabilité, la dureté, les tests de désintégration et de dissolution. La teneur en ingrédient pharmaceutique actif (IPA) a été déterminée en utilisant une analyse spectrophotométrique ainsi qu'une chromatographie liquide à haute performance en phase inverse (CLHP-PI).

Résultats: Toutes les marques étaient élégamment étiquetées, emballées et dans leur durée de vie. À l'exception d'une marque, ils avaient tous le numéro d'enregistrement NAFDAC. L'uniformité du poids, la friabilité, la dureté et les valeurs de temps de désintégration pour toutes les marques étaient dans des limites acceptables. Trois marques des produits ont libérés moins de 70% de leur IPA après 45 min et ont ainsi échoué au test de dissolution. Il y avait une disparité entre les résultats des essais de contenu en utilisant la spectrophotométrie UV et la CLHP. Les résultats de CLHP ont montré que seule la marque a échoué au test en ayant 86% de l'IPA alors qu'avec la spectrophotométrie UV, quatre marques ont échoué au test.

Conclusion: Cette enquête suggère que quatre marques de comprimés de chlorhydrate de metformine disponibles à Abuja n'ont pas satisfait pas aux spécifications officielles, même si une seule marque a été impliquée par l'analyse HPLC. Par conséquent, cette recherche recommanderait la surveillance sentinelle continue des comprimés de metformine et l'utilisation de la CLHP pour l'analyse du produit pour sa grande sensibilité et précision.

Mots-clés: Metformine, UV, RP-HPLC, essai, qualité pharmaceutique, libellé de l'étiquette

INTRODUCTION

Safety of medicines is a global responsibility. A reliable, good quality medicines supply is essential for health but it is often missing in developing countries with weak regulatory system.[1] The problem of spurious/falselylabelled/falsified/counterfeit (SFFC) medicines was first addressed in 1985 at an international conference in Nairobi on the rational use of drugs. The meeting recommended that World Health Organization (WHO) together with other international and nongovernmental organizations should study the feasibility of setting up a clearing house to collect data and to inform government about the extent of counterfeiting.[2] Identifying and eliminating SFFC medicines has been a considerable health challenge as their use can result in treatment failure or even death and public confidence in health care system can be eroded following their use or detection.[3]

Metformin is an oral antidiabetic drug in the biguanide class. It works by suppressing glucose production by the liver and it is the first-line drug of choice for the treatment of type 2 diabetes mellitus, in particular, in overweight and obese people and those with normal kidney function.[4-6] Its use in gestational diabetes has been limited by safety concerns. It is also used in the treatment of polycystic ovary syndrome, and has been investigated for other diseases where insulin resistance may be an important factor. Metformin is one of only two oral antidiabetics in the World Health Organization Model List of Essential Medicines.[7]

Metformin has an oral bioavailability of 50 - 60 % under fasting conditions and is absorbed slowly. Peak plasma concentrations (Cmax) are reached within one to three hours of taking immediate-release metformin and four to eight hours with extended-release formulations.[8] The plasma protein binding of metformin is negligible and a plasma steady state of the drug is usually reached in one or two days of commencement of therapy.[8] Treatment failures and even death has been reported in the use of substandard antidiabetic drug like glibenclamide in China and insulin in Nigeria.[3] Akinyele and his co-workers, in their study to evaluate the bioequivalence of eight brands of metformin tablets available in pharmacies in Lagos, Nigeria discovered that four brands failed one or more pharmacopeial tests.[9] With this growing concern, the number of brands of metformin been imported into the country or manufactured is also increasing hence the need for continuous sentinel surveillance of the available brands in the market in order to minimize the manufacture and importation of counterfeit, substandard and adulterated products.

The objective of this study was to investigate the different brands of metformin hydrochloride tablets commonly available in the Nigerian market.

Specifically, the physical, chemical and pharmaceutical equivalence of ten different brands of metformin hydrochloride tablet, marketed in Abuja, Nigeria were compared; whether there was any conformity with the official specifications.

MATERIALS AND METHOD Materials

Metformin powder (May and Baker, Nigeria), ten brands of metformin hydrochloride tablets were purchased from different registered pharmacies in Abuja, Nigeria.

Methods Sampling method

Convenience sampling method was employed; one of the researchers posing as a patient purchased the drugs from different pharmacies within the city until ten different brands were obtained. Labelled information of the drugs purchased are presented in Table 1.

Table 1: Labeling details of the different brands of metformin tablets

Sample Code	Country of Origin	Expiry Date	Batch Number	NAFDAC Number	Manufacturer
A	India	Nov. 2016	PAF0267	Yes	Inventia Health Care
B	France	Dec. 2018	102888	No	Merck Sante SAS
C	Nigeria	Feb. 2016	B0802	Yes	Nigerian-German Chemicals
D	Nigeria	Mar. 2018	1301	Yes	SKG Pharma
E	Bangladesh	Jun. 2016	SWF012	Yes	Beximco Pharmaceuticals
F	India	Oct. 2016	FT1259	Yes	Fredun Pharmaceuticals
G	Nigeria	Nov. 2015	TEL2-138	Yes	Lifeback Pharmacy
H	Nigeria	Jan. 2017	FT1008	Yes	Astranad Pharmaceuticals
I	Nigeria	Dec. 2015	A140026	Yes	May and Baker
J	Malaysia	Jun. 2015	BE06607	Yes	Hovid Bhd

Uniformity of weight

Twenty (20) tablets were randomly selected from each brand and weighed individually using the electronic weighing balance (College B154, Mettler Toledo, Switzerland). The mean weight was calculated as well as the standard deviation.

Hardness test

Ten (10) tablets randomly selected from each brand were subjected to hardness test using a motorized hardness tester (Campbell Electronics, Model HT30/50, Mumbai, India). Each tablet was diametrically compressed until it fractured and the mean crushing strength and the standard deviation was calculated.

Friability test

Ten tablets randomly selected from each brand were weighed and placed in a friabilator (Erweka GmbH, Heusenstamm, 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. Triplicate determinations were carried out for all brands and the results were recorded as mean ± SD.

Disintegration test

Six tablets per brand were used for the determination. The tablets were placed in the tubes of a British Pharmacopoeia (BP) disintegration apparatus (MK IV, Manesty Machines, UK) and constantly agitated in water maintained at 37 °C. The time taken for each tablet to break up and the primary particles to completely pass through the mesh of the disintegration basket was noted and the mean disintegration time and standard deviation determined.

Uniformity of content UV assay 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 to 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 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.[10]

HPLC assay Chromatographic conditions

Chromatographic separation was performed on an Agilent 1260 Infinity Series (Agilent Technologies Inc., USA) arranged with a gradient pump, auto injector, column oven and DAD detector. An Agilent ZORBAX ODS, 150 x 4.6 mm, 5-µ column was used as the stationary phase. The drug samples were separated isocratically with a mobile phase consisting of acetonitrile and 0.05 M potassium dihydrogen phosphate buffer (60:40) adjusted to pH of 3.0 ± 0.1 (HI 2215, Hanna Instruments, USA) at a flow rate of 2 mL/min. The analysis was carried out at 30 °C and the injection volume was 10 µL. The detector was set at 218 nm.

Mobile phase preparation

Potassium dihydrogen phosphate salt (8 g) was weighed into a 1 L beaker and dissolved with sufficient distilled water. Triethylamine (0.5 mL) was added and the pH was adjusted to 3.0 with ortho-phosphoric acid. The volume was then adjusted to 1 L. Four hundred millilitres of the solution was transferred into a beaker and 600 mL of HPLC grade acetonitrile was added to it. The premix mobile phase was filtered through a 0.45 µm nylon filter with the aid of a vacuum pump and then used in equilibrating the HPLC column and system.

Standard calibration curve

Various weights of metformin hydrochloride powder (10, 20, 40, 60, 80 and 100 mg) were diluted with 70 mL of methanol/distilled water mixture (50:50) in a 100 mL volumetric flask. The solutions were sonicated for about 20 min to ensure complete dissolution, allowed to settle and then made up to 100 mL with sufficient diluent. Further dilutions were carried out with the diluent to achieve a concentration of 1.0 - 10 µg/mL. Six injections of the final solutions were run on the HPLC system to determine system suitability and also calibrated to quantify the samples. The mean peak area (mPA) of the determinations for each concentration was plotted against the respective concentration to get the calibration curve.

Sample preparation

Twenty tablets of each brand of metformin HCl tablet were weighed and pulverized into powder. A quantity of the powder equivalent to 100 mg of metformin HCl was weighed into 100 mL volumetric flask and dissolved with about 70 mL of the diluent by sonicating for about 20 min. After sonication, the solution was allowed to settle and then made up to 100 mL with sufficient diluent. A 1 mL aliquot of the solution was further diluted to 100 mL and filtered before injection into the chromatographic system.[11] Three injections were run on each brand and the average peak area for the triplicate measurement was extrapolated on the calibration curve derived from the pure metformin powder to obtain the equivalent concentration and the percentage content calculated.[10] The mobile phase was also run as the blank.

Dissolution test

The dissolution was carried out using the BP paddle method in 900 mL of 0.1 M HCl solution maintained at 37 ± 1 °C with a paddle revolution of 100 rpm (Caleva ST7, UK). Three tablets per brand was randomly selected and used in the determination. A 5 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 max 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 ± SD.

Statistical analysis

Data obtained were computed and analyzed using GraphPad InStat software version 3.10. The statistical differences among brands were obtained using student's t-test at 5 % level of significance.

RESULTS

All the metformin tablets investigated were within their shelf lives and were immediate release dosage forms with label strength of 500 mg except brand A that was a sustained release formulation and with a label strength of 1000 mg (Table 1). Five out of the ten brands studied, were formulated in Nigeria, two in India and one each in France, Bangladesh and Malaysia. They were all registered with the National Agency for Food and Drug Administration and Control (NAFDAC) except one brand.

Some physicochemical parameters of the various brands of metformin tablets studied are presented in Table 2. The weight uniformity test on the tablets indicated that there were no significant differences ($p > 0.05$) in the weights of tablets from the different brands and hence conformed to the British Pharmacopoeia specification i.e., that not more than two of the individual weights should deviate from the average weight by more than 5 % and none should deviate by more than 10 %.[12] Table 2 also shows that the mean tablet crushing strength for the brands ranged from 1.70 to 20.06 kp. This result showed that only brands D, E, F, G and J conformed to BP (2009) The *in-vitro* drug release data shows that four of the brands (A, E, H and I) did not release up to 70 % of their labeled contents within 45 min (Figure 1a and b). The BP (2009) specified that at 45 min, at least 70 % of the labelled strength of the conventional metformin hydrochloride tablets should have been released.[13] Brands E, H and I failed the dissolution test as conventional tablets but the release data of brand A supports it as a sustained release formulation.

specifications for tablets hardness of between 5 to 8 kp.[13] All the brands gave friability values below 1.0 % except brand I with a friability value of 1.2 %. Although friability is a nonofficial test, it is related to the hardness of the tablet and

it is the tendency of tablets to powder, chip or fragment. It can negatively affect the elegance, appearance and consumer acceptance of the tablet. The disintegration times of the samples were within 15 min as specified by BP 2009 for uncoated tablets except brand G which failed the test with a slightly higher value of 16.76 min.[13] Brand A did not disintegrate within 1 h, which is expected as sustained release formulation. The results of the assay of chemical content using UV and HPLC analysis to determine the amount of metformin present in each brand are presented in Table 3. The British Pharmacopeia stipulates a 95 to 105 % of active drug content.[12] While brands D, E, G and H failed this requirement in the UV assay, all the brands except brand D met this requirement in the HPLC assay method. 6

Table 2 : Some physicochemical properties of the metformin tablets studied.

Sample	Weight* (g)	Crushing Strength* (kp)	Friability* (%)	Disintegration Time* (min)	Amount Released at 45 min (%)
1	1.37 ± 0.010	20.06 ± 1.42	0.19 ± 0.22	> 1 h	< 10
2	0.53 ± 0.008	4.00 ± 0.58	0.32 ± 0.16	8.15 ± 0.11	101
3	0.56 ± 0.015	11.11 ± 1.60	0.30 ± 0.06	3.07 ± 1.31	97.80
4	0.59 ± 0.011	5.77 ± 0.30	0.13 ± 0.02	9.72 ± 0.59	98.45
5	0.70 ± 0.007	5.84 ± 0.46	0.12 ± 0.42	13.65 ± 0.67	54.98
6	0.56 ± 0.008	5.78 ± 1.08	0.14 ± 0.56	7.79 ± 0.36	100.39
7	0.54 ± 0.014	8.49 ± 0.98	0.22 ± 0.62	16.76 ± 1.15	104.31
8	0.67 ± 0.017	18.16 ± 2.45	0.35 ± 0.40	13.77 ± 0.91	66.39
9	0.52 ± 0.010	1.79 ± 0.15	1.22 ± 0.32	12.06 ± 0.46	63.58
10	0.56 ± 0.008	7.82 ± 0.90	0.10 ± 0.12	8.55 ± 0.43	100.58

*All values are mean ± sd

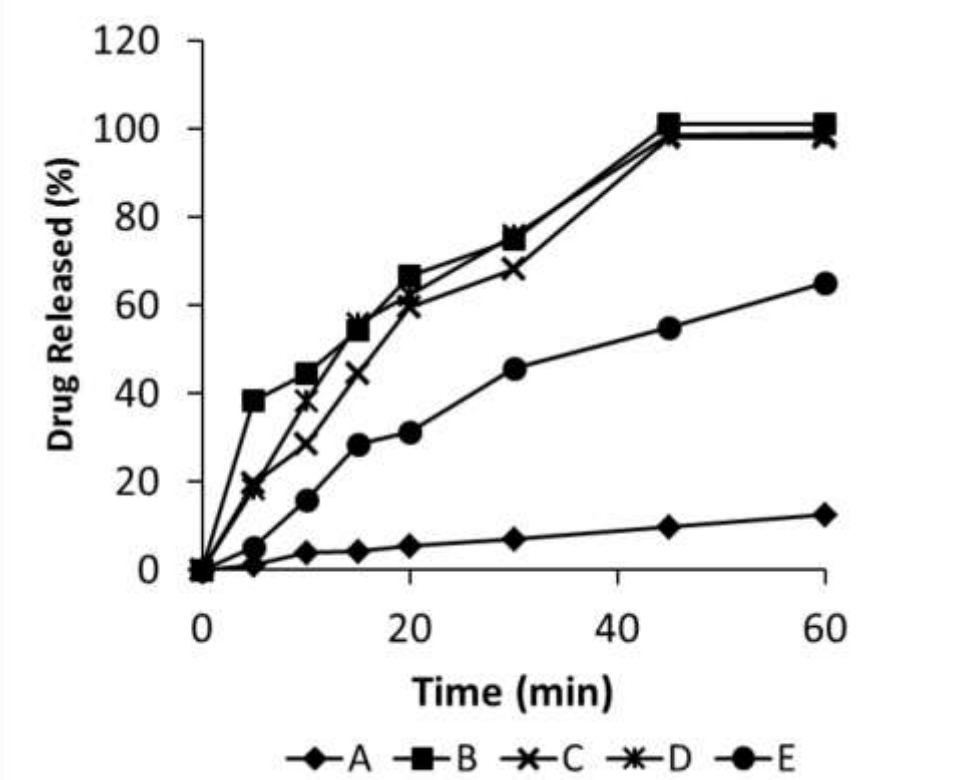

Figure 1a: Dissolution profiles of the metformin drug samples A-E

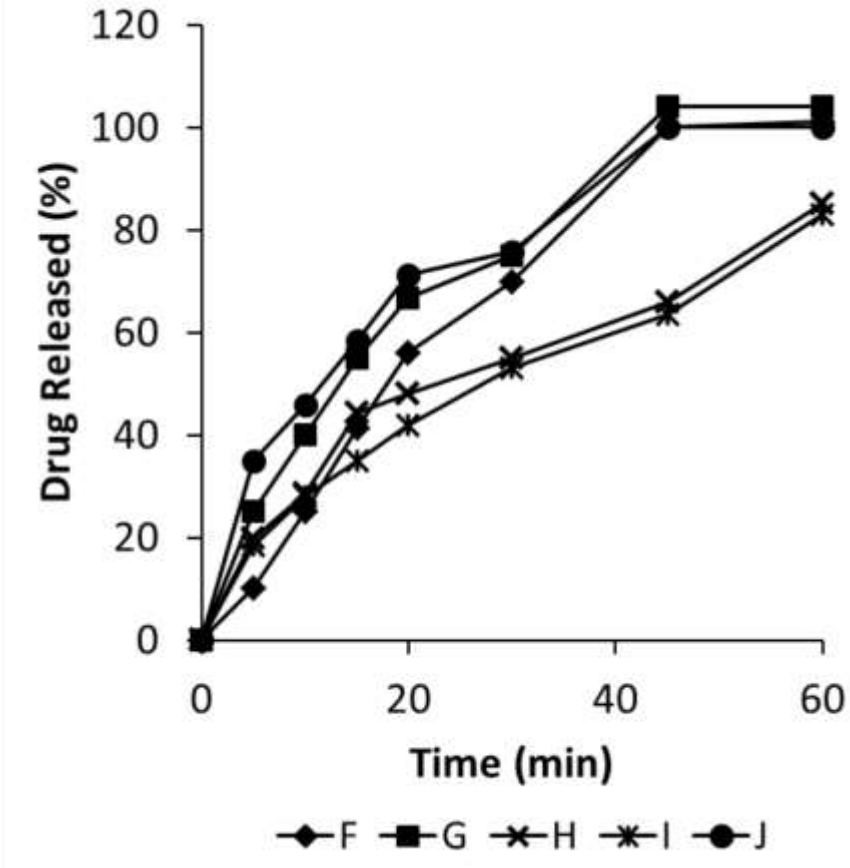

Figure 1b: Dissolution profiles of the metformin drug samples F-J

Table 3: Assay result obtained from UV and HPLC analysis

Sample	Amount (mg/tablet)			% Label Claim	
	Labelled	Amount Found		UV	HPLC
1	1000	950.1	946.0	95.01	95.63
2	500	500.3	504.0	100.05	100.80
3	500	494.9	490.0	98.97	97.99
		UV	**HPLC**		
4	500	472.2	431.5	94.43	86.30
5	500	411.5	476.6	82.30	95.49
6	500	511.3	491.3	102.26	98.26
7	500	448.3	484.2	89.65	97.07
8	500	462.0	513.1	92.40	102.62
9	500	490.0	487.5	98.00	97.49
10	500	507.8	496.4	101.56	99.57

DISCUSSION

Product registration suggests preliminary investigation by the regulatory authorities. In Nigeria, NAFDAC is empowered to investigate, register and authorize the sales of drug products. From the brands studied, brand B had no NAFDAC registration number which means that the drug may have undergone a process known as paralleling; where the distributors of the product bypassed the drug regulatory body by smuggling the drug into the country.[14] The uniformity of weight observed within each brand studied is an important index in correlating the uniformity of the dosage units as this uniformity in dosage can be shown by either weight variation or content uniformity study.[15] These either reflect indirectly or measure directly the amount of drug substance in the tablet.[16] Also, the weight disparity among the brands which also tells about the sizes of the tablet, can lead to doubt in the minds of patient and clinician on the bioequivalence of these various brand. Although the WHO Model Formulary advises that patients should be placed on a single brand, this becomes difficult when such brand becomes unavailable and there is need to change brand.[17] The crushing strength of a tablet is a measure of its hardness which is dependent on the manufacturing process, type and quality of binding agent used. Although BP 2009 recommends a crushing strength of 5 - 8 kp, as an overly hard tablet would increase disintegration time significantly and in turn affect dissolution.[13] The crushing strength value of brand A is expected since it is a sustained release formulation and it is not expected to disintegrate within the time limit for conventional tablets. But the very low crushing strength value of brand I could be attributable to manufacturing error even though it performed creditably well in the disintegration time test. This manufacturing error emphasizes the need for in-process control measures by manufacturers to check and correct such errors. The minimal friability values for all the tablet brands is an indication of the ability of the tablet to withstand stress due to abrasive forces, without crumbling during transportation, packaging, handling and dispensing. These values also reflect the hardness of the tablets. The disintegration of tablets is dependent on the type of formulation excipients and processes used by different manufacturers which consequently influence the bioavailability of the drug.[18] Therefore, it is one of the factors that affect the rate determining step in drug absorption. There was no direct relationship between disintegration times and crushing strength values of the tablets except for brand A. This may be as a result of different processes employed by different manufacturers to ensure good disintegration times for their drug products.[9,19,20] Brand A being a sustained release formulation is not expected to disintegrate within the limits of conventional tablets.

The establishment of the dissolution profile of a drug is probably the best available indication of *in vivo* drug release characteristics of the drug. Although a drug

may comply with the official requirement of disintegration time and yet, it may not be able to release sufficient amount of the active drug *in vivo* for optimum therapeutic response. This may be the case with brands (E, H and I) that did not meet the compendial specification in their dissolution profiles but gave good disintegration times. In the chemical content assay using the chromatographic method, only brand D failed and this underscores the need for HPLC assay for drug content because it is more specific and accurate. It removes interferences from excipients. It indicated that only sample D did not meet the content of active specification while UV showed four samples, D, E, G and H failed the content assay. Although other workers have maintained that results from the two methods for content assay are comparable most time, the HPLC analysis results have consistently shown high sensitivity and reproducibility.[21-24]

CONCLUSION

Nine out of ten brands of metformin hydrochloride tablets assessed were within the acceptable standards and of good quality based on the HPLC analysis. However, the variations in their physicochemical properties will to a large extent affect the bioavailability of the different brands and as such brand substitution should not be encouraged as expected therapeutic outcome may not be achieved.

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