British Journal of Pharmaceutical Research
9(1): 1-14, 2016, Article no.BJPR.21862
ISSN: 2231-2919, NLM ID: 101631759

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Evaluation of the Physicochemical and *in vitro* Dissolution Properties of Metformin Hydrochloride Tablet Brands Marketed in Five Cities in Ghana

Akwasi Sougi[1], Kwabena Ofori-Kwakye[1*], Noble Kuntworbe[1], Samuel Lugrie Kipo[1] and Mariam El Boakye-Gyasi[1]

[1]Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, College of Health Sciences, Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, Ghana.

Authors' contributions

This work was carried out in collaboration between all authors. Author AS performed the experimental work and wrote the first draft of the manuscript. Author KOK designed the study and reviewed the manuscript. Authors NK, SLK and MEBG were involved in data analysis and review of the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJPR/2016/21862
Editor(s):
(1) Mohamed Fathy, Assiut University, Assiut, Egypt.
Reviewers:
(1) Antonello Santini, University of Napoli Federico II, Italy.
(2) Panna Thapa, Kathmandu Unviersity, Nepal.
Complete Peer review History: http://sciencedomain.org/review-history/11792

Original Research Article

Received 6th September 2015
Accepted 30th September 2015
Published 16th October 2015

ABSTRACT

Aim: A comparative evaluation of the physicochemical and *in vitro* dissolution properties of metformin hydrochloride tablet brands sampled in five cities in Ghana was undertaken to assess their pharmaceutical equivalence.
Place and Duration of Study: Department of Pharmaceutics, KNUST, Kumasi, Ghana, between August 2012 and December 2012
Methodology: Fourteen brands of metformin tablets plus the innovator brand, Glucophage, purchased from retail pharmacies were studied. The genuineness of the samples was determined using Fourier transform infra-red (FTIR) spectroscopy and thin layer chromatography (TLC). Pharmacopoeia tests such as uniformity of weight, hardness, friability, disintegration and assay were used to assess the physicochemical equivalence of the tablet brands. *In vitro* dissolution testing was conducted and the dissolution data subjected to analysis involving dissolution

**Corresponding author: Email: koforikwakye@yahoo.com;*

efficiency (DE), similarity factor (f_2) and Biopharmaceutics classification system (BCS)-based biowaiver conditions, as a surrogate for bioequivalence studies.
Results: All the tablet brands complied with the official specifications for identification, uniformity of weight hardness and disintegration. Brand M9 failed the friability test while brands M5, M9 and M12 failed the assay test. Dissolution efficiency (DE) and similarity factor (f_2) of the brands varied with pH of dissolution media with M4 (in 0.1 M HCl) having the highest DE and M9 (in phosphate buffer pH 6.8) the lowest.
Conclusion: Eleven of the fifteen tablet brands passed all the official tests and could be regarded as pharmaceutically equivalent but f_2 analysis showed only six brands were similar to the reference brand (with f_2 values ≥50 in the three dissolution media used). None of the metformin brands satisfied the criteria for BCS-based biowaiver for rapidly dissolving tablets. The study has shown that not all the metformin tablet brands sampled in five cities in Ghana are pharmaceutically equivalent.

Keywords: Metformin hydrochloride; physicochemical properties; in vitro dissolution; bioequivalence; biowaiver.

1. INTRODUCTION

Diabetes mellitus is a metabolic disease with characteristic chronic hyperglycaemia and defective protein, fat and carbohydrate metabolism due to deficient insulin secretion and/or action [1,2]. There are two main types of diabetes mellitus (type 1 and type 2 diabetes mellitus) though there are other rare forms of diabetes mellitus. Globally, 347 million people have diabetes [3]. Data on the prevalence of diabetes in Ghana is scanty and unreliable. The incidence of diabetes in Ghana among an urban outpatient population in Accra was estimated at 0.5% in the late 1950's [4]. However, a recent study reported a significant prevalence rate of 6.3% [5].

Metformin is an oral hypoglycaemic agent which belongs to the class of drugs called biguanides. It is the first line drug for the management of Type 2 diabetes mellitus. Metformin functions as an antihyperglycaemic agent through reduced gluconeogenesis and by enhancing the action of insulin in skeletal muscles. There are many generics of metformin hydrochloride tablets available in community pharmacies and hospitals in Ghana and other developing countries. Generic products are generally readily available and less expensive compared to the innovator products. The high prevalence of generic products is the major means through which people from developing countries are able to access important life-saving medicines [6]. However, generics are more likely to be of spurious and substandard quality than their innovator products. Also many generic products have been found to be fake or counterfeit products [7-10].

In addition to the obvious advantages of availability and low cost, generics are expected to demonstrate comparable quality with the innovator products before they could be clinically interchangeable. Thus, generics must exhibit equivalent pharmaceutical and therapeutic properties with the innovator products to make them acceptable substitutes. An important step in determining the therapeutic equivalence of a product is to establish whether they are chemically and biopharmaceutically equivalent [11].

Dissolution testing is an important quality control and drug development procedure employed in the pharmaceutical industry to evaluate the *in vitro* drug release profiles of solid dosage forms. Dissolution testing is used to establish the pharmaceutical quality of a product and it is also used as a surrogate for in vivo drug dissolution. The drug release profiles of a product and drug quality as a whole could be affected by the type and amount of API and excipients used in the manufacturing process as well as the manufacturing techniques employed. Dissolution testing is an important tool used to evaluate the pharmaceutical quality of generics and innovator products and to determine their possible equivalence. Thus pharmaceutically equivalent products would exhibit similar or equivalent drug release profiles. It should therefore be possible to select from a myriad of generic products one or more products which are pharmaceutically and therapeutically equivalent to the innovator drug. This is to prevent the situation whereby different products of the same API (generics) would demonstrate distinct differences in their therapeutic effects [12].

The aim of the current study was to ascertain the quality and drug release proficiency of commercial metformin hydrochloride tablet brands marketed in five cities in Ghana. This will allow prescribers to select appropriate generic metformin tablet brands as substitutes for the innovator brand, Glucophage.

2. MATERIALS AND METHODS

Pure metformin hydrochloride (RS) was obtained from the Department of Pharmaceutics, KNUST, Ghana. Hydrochloric acid fuming GR (Merck, Germany), sodium hydroxide, absolute ethanol, sodium nitroprusside, acetonitrile, glacial acetic acid (BDH, PROLABO), potassium dihydrogen orthophosphate (Fisons Laboratory), butanol, potassium ferricyanide, potassium bromide (BDH, Poole, England), ortho-phosphoric acid (Phillip Harris, England). All other reagents used were of analytical grade and were obtained from the Chemical store of the Department of Pharmaceutical Chemistry, KNUST, Kumasi, Ghana. Fourteen generic brands of metformin hydrochloride tablets plus the innovator brand Glucophage, each having label strength of 500 mg were purchased from retail pharmacies in five cities in Ghana, namely: Kumasi, Accra, Sunyani, Sekondi-Takoradi and Koforidua. General information on the metformin tablet brands is reported in Table 1.

2.1 Extraction of Metformin Hydrochloride from Tablets

A quantity of the powdered tablet equivalent to 60 mg of metformin hydrochloride was shaken with 60 ml of ethanol and filtered with Whatman filter paper (No 5). The filtrate was evaporated to dryness on a water bath and the residue dried at 105ºC for one hour [13]. The procedure was repeated for the other tablet brands and the residue of each brand used for subsequent infra-red and thin layer chromatography analysis.

2.2 Identification of Extracted Metformin Hydrochloride Using TLC

TLC silica gel G plate was used and the solvent system consisted of a mixture of glacial acetic acid, butanol and water (10:40:50). Twenty milligram of the extracted residue of each metformin tablet brand as well as 20 mg of reference metformin hydrochloride powder was dissolved in distilled water and diluted to 5 ml with same solvent. The test solutions and the reference were spotted on the plate and immersed in the solvent system contained in the chromatank. The plate was removed when the solvent had moved three-fourths of the length of the plate. The solvent front was marked, allowed to evaporate from the plate and the spots detected by spraying with a mixture of equal volumes of sodium nitroprusside, potassium ferricyanide and sodium hydroxide solution all of 100 g/L. The Rf value of each spot was then determined [13].

2.3 Identification of Extracted Metformin Hydrochloride Using FTIR

Twenty milligram of the test sample (extracted residue) was triturated with 200 mg of dry, finely powdered KBr of spectroscopic grade using agate pestle and mortar. The mixture was ground thoroughly, spread uniformly in a suitable die and compressed into a disc using a pressure of 10 tons. A reference disc was similarly prepared with KBr alone. The resultant disc was mounted in a suitable holder in an Interspectrum Fourier Transform infra-red spectrophotometer and the IR spectrum was obtained at 600-4000 cm^{-1}. The infra-red spectrum of each brand of metformin tablet was then compared with the reference spectrum.

2.4 Thickness Test

A digital vernier caliper was used to measure the thickness of ten tablets from each brand and the mean (±S.D) determined.

2.5 Weight Uniformity Test

Twenty (20) tablets from a particular brand were randomly selected and weighed collectively to obtain a mean weight. The tablets were then weighed individually and the percentage deviation of each tablet from the mean was then calculated [13]. The procedure was repeated for the other brands.

2.6 Friability Test

Ten tablets were randomly selected from a particular brand, dusted and weighed together and then placed in the Erweka friabilator (Type TA 20, Germany) and operated for 4 minutes at 25 rpm. The tablets were dedusted and reweighed and the percentage weight loss calculated. The procedure was repeated for the other brands.

Table 1. Profile of metformin hydrochloride tablet brands studied

Sample code	Coating	Country of origin	Batch number	Mfg. date	Expiry date
M1	Film-coated	Ghana	2909m	*	09/16
M2	Film-coated	United kingdom	MEAG016	*	06/14
M3	Film-coated	Germany	81R	08/12	07/16
M4	Uncoated	Ghana	12018	05/12	05/16
M5	Film-coated	Germany	BS1579	05/12	05/16
M6	Film-coated	Malaysia	BC06712	06/12	06/15
M7	Film-coated	India	MH008	12/10	11/13
M8	Uncoated	India	NP11061	05/11	04/14
M9	Film-coated	Ghana	1012	-	11/14
M10	Film-coated	India	B344	12/11	12/14
M11	Film-coated	France	108007	04/12	03/17
M12	Film-coated	United Kingdom	BUH022139	*	11/16
M13	Film-coated	United Kingdom	RM1001	*	12/13
M14	Film-coated	United Kingdom	RM1286	*	07/14
M15	Uncoated	India	E07515	01/11	12/13

**, not provided*

2.7 Hardness Test

Ten tablets were selected at random from each brand to perform this test using a DBK hardness tester (India). A tablet was placed between the spindle and anvil of the tester and the calibrated scale adjusted to zero. Compression force was applied on the tablet and the position on the calibrated scale at which the tablet broke was recorded in Kgf units. A mean hardness (±S.D) was calculated for each brand.

2.8 Disintegration Test

Six tablets selected randomly from a brand were placed individually in each of the six cylindrical tubes of the basket rack of an Erweka disintegrating test apparatus (Type ZT 3/1, GmbH Heusenstamm, Germany) at 37±0.5ºC. The disintegration time was taken to be the time no tablet fragment with firm core was left on the mesh.

2.9 Assay of Metformin Hydrochloride Tablets by HPLC

The content of metformin in each of the fifteen tablet brands was determined with a reverse phase chromatographic technique developed and validated by Kar and Choudhury [14] with minor modifications. A 100 μg/ml stock solution of metformin hydrochloride was prepared in a mobile phase of acetonitrile and phosphate buffer (65:35, pH 5.75). A series of 10 ml volumetric flasks containing 0.25-2.5 ml of the stock solution were made up to volume with the mobile phase. Each solution was filtered with a sintered glass filter and loaded in the injector of a Shimadzu HPLC (LC-10A Shimadzu pump with programmable absorbance detector and Shimadzu CR50 Chromatopac. Column used was Agilent Zorbax SB C-18 4.6 x 250 nm) fitted with 20 µl fixed volume loop, injected by rheodyne at a flow rate of 1.0 ml/min and the chromatogram for each injection was recorded. The calibration curve was plotted between concentration of drug and peak area of metformin hydrochloride.

A quantity of powdered metformin tablets equivalent to 10 mg metformin hydrochloride was accurately weighed into a 100 ml volumetric flask containing about 75 ml of mobile phase. The powder mixture was dissolved in the mobile phase with the aid of sonication and then made up to the 100 ml mark with the mobile phase. The solution was filtered through Whatman filter paper (No 5) and 1 ml was taken and made up to 10 ml with the mobile phase and filtered using sintered glass filters. The sample solution was analysed with a Shimadzu HPLC consisting of LC-10A Shimadzu pump with programmable absorbance detector and Shimadzu CR50 Chromatopac. The column used was Agilent Zorbax SB C-18 (4.6 x 250 nm). Flow rate employed was 1.0 ml/min, an injection volume of 20 µl and the detection of eluent was carried out at 232 nm. The injection was repeated three times and the peak area of metformin hydrochloride was recorded. The average peak area and calibration curve were used to calculate the amount of drug present [14]. The experimental procedure was repeated for the other metformin tablet brands.

2.10 *In vitro* Dissolution Study

Nine hundred milliliters each of 0.1 M HCl, phosphate buffer pH 4.5 and phosphate buffer pH 6.8 were used based on the FDA Guidance for Industry and the need to meet the criteria for biowaiver [15]. Nine hundred millilitres of 0.1 M HCl was placed in each of the six vessels of an Erweka dissolution apparatus (Type DT6, GmbH Heusenstamm, Germany) (USP Apparatus 2) rotating at 50 rpm and equilibrated to 37±0.5℃. One tablet was placed in each of the dissolution vessels and at 10, 15, 20, 30, 45, and 60 min, 10 ml samples were withdrawn and replaced with 10 ml of fresh dissolution medium. The withdrawn samples were filtered with Whatman filter paper (No 5) and diluted appropriately with distilled water. The diluted filtrates were analysed by UV spectrophotometer at 232 nm. The amount of drug released was determined from regression data obtained from calibration plot of metformin in distilled water (0.2-0.9 mg/100 ml) and the percentage drug released calculated. A plot of mean cumulative percentage drug release against time was established. The experiments were repeated using phosphate buffer pH 4.5 and phosphate buffer pH 6.8 as dissolution media.

2.11 Dissolution Data Comparison

Dissolution data obtained from the dissolution studies were fitted into a model-independent equation to determine the similarity factor (f_2) of the various brands compared to the reference drug (Glucophage)

$$f_2 = 50 \text{x} \log \{[1+ (1/n) S\ t=1n\ (Rt-Tt)\ 2] – 0.5\text{x}100\}$$

where, f_2 = similarity factor, n = time points, Rt = cumulative percentage dissolved at time t for the reference, and Tt = cumulative percentage dissolved at time t for the test.

The similarity factor falls between 0 and 100. If $f_2 \geq 50$, it implies the two dissolution profiles are equivalent or similar therefore the two products could be interchanged. If $f_2 < 50$, it means the dissolution profiles are different or dissimilar hence the products cannot be interchanged.

The dissolution efficiency (DE) was estimated for each brand [16-18]. The dissolution efficiency was calculated using the equation:

$$DE = \{(0\int t\ Y.dt) / Y100.\ (t_2-t_1)\}\times 100$$

Where, $(0\int t\ Y.dt)$ = area under the dissolution curve (AUC), Y= the percentage dissolved at t_2, t_2= time for all active ingredient to dissolve, and t_1= time at which first sample was withdrawn.

The dissolution data of metformin tablets (BCS class 3 drug) in the three dissolution media were subjected to BCS-based biowaiver under WHO criteria (i.e. very rapidly dissolving). The percentage drug dissolved at 15 minutes in 0.1 M HCl (pH 1.2), phosphate buffer pH 4.5 and phosphate buffer pH 6.8 were estimated and compared to the specification of ≥85% drug release at 15 min in all the three dissolution media**.**

3. RESULTS

Each of the fifteen metformin hydrochloride tablet brands purchased had at least 6 months left on the shelf-life and all analytical procedures were carried out before product expiration dates. Twelve brands were imported while three were manufactured in Ghana and this suggests the high prevalence of foreign brands of metformin tablets in Ghana. Twelve of the fifteen metformin tablet samples studied were film coated while three were uncoated.

In identification test employing thin layer chromatography (TLC), the principal spot in the chromatogram obtained for each brand of metformin tablet was similar in position, colour and size to the principal spot in the chromatogram obtained with the pure metformin hydrochloride. A retention factor (Rf) of 0.24 was obtained for ten tablet brands, 0.25 for three brands and 0.23 for two brands. These values are similar to the Rf value of pure metformin hydrochloride (0.25) (Table 2). The IR spectrum obtained for metformin extracted from each metformin tablet brand showed absorption bands at 740, 935, 1075, 1063, 1620 and 1580 cm^{-1} similar to the reference spectrum of pure metformin hydrochloride [13]. Fig. 1 presents a sample IR spectrum of metformin for tablet brand M1.

The physicochemical properties of the metformin tablet brands are shown in Table 3. The metformin tablet brands generally possessed good physicochemical properties. The tablets passed the uniformity of weight test and friability test except brand M9 (1.24%, friable). All twelve film-coated tablet brands disintegrated in aqueous medium <30 min and passed the disintegration test but one uncoated tablet

brand (M8) disintegrated >15 min and hence failed the test. The drug content of the tablet brands was in the range 99.52-110.99%. Twelve metformin tablet brands passed the assay test while three (M5, M9, M12) were overdose hence failed the test. The amount of drug dissolved in 45 min (D_{45}), in all the tablet brands was >80%, thus passed the dissolution test for immediate release tablets.

Table 2. Rf values of various metformin hydrochloride tablet preparations

Sample code	Rf value
M1	0.24
M2	0.24
M3	0.24
M4	0.24
M5	0.24
M6	0.24
M7	0.23
M8	0.24
M9	0.24
M10	0.25
M11	0.23
M12	0.24
M13	0.24
M14	0.25
M15	0.25

Rf = Retention factor; Rf value of pure metformin hydrochloride powder (reference standard) = 0.25

The dissolution profiles of metformin hydrochloride tablet brands in 0.1 M HCl (pH 1.2), phosphate buffer pH 4.5 and phosphate buffer pH 6.8 are presented in Figs. 2, 3 and 4, respectively. The tablets showed similar dissolution profiles and achieved >80% drug release in 45 min in the three dissolution media. The dissolution efficiencies (DE) and similarity factors (f_2) of the various metformin tablet brands are presented in Table 4. Generally, both the DE and f_2 of the tablet brands varied with pH of the dissolution medium employed. Metformin tablets exhibited high dissolution efficiencies with 13 brands >90% DE in 0.1 M HCl, 14 brands > 90% DE in phosphate buffer pH 4.5, and 14 brands >90% DE in phosphate buffer pH 6.8. The f_2 values were ≥50 for ten brands in 0.1 M HCl, ten brands in phosphate buffer pH 4.5, and seven brands in phosphate buffer pH 6.8. Also, f_2 values were ≥50 for seven brands in both 0.1 M HCl and phosphate buffer pH 4.5, seven brands in 0.1 M HCl and phosphate buffer pH 6.8, and six brands in both phosphate buffer pH 4.5 and phosphate buffer pH 6.8. Six metformin tablet brands (M2, M5, M6, M12, M13 and M14) had f_2 values ≥50 in all the three dissolution media. All the tablet brands failed the BCS-based biowaver specifications for rapidly dissolving tablets as none of the brands achieved ≥85 % drug release in 15 minutes in the three dissolution media. However, eight tablet brands, M2, M3, M5, M6, M11, M12, M13 and M14 attained ≥85 % drug release in 30 min in the three media.

4. DISCUSSION

Fifteen metformin hydrochloride tablet brands were subjected to both FTIR and TLC analysis to ascertain the identity of the active pharmaceutical ingredient (API). Results from the identification tests indicated that all the metformin tablet brands contained metformin hydrochloride as API hence were not fake or counterfeit products. The capacity to identify fake and substandard pharmaceutical products on the market is a crucial component of a drug quality assurance system.

Metformin hydrochloride tablet brands sampled were subjected to pharmacopoeia and other tests to assess their quality and pharmaceutical equivalence. The assessment tests involved uniformity of weight, thickness, hardness, friability, disintegration, drug content and dissolution. These parameters are used to assess the consistency in quality among different batches of tablets and capsules during production. The nature of formulation of a drug product, the physicochemical properties of the API and excipients and the procedures used in manufacturing have marked effect on quality parameters of tablets [19]. The quality parameters are interrelated and have profound effect on drug absorption and bioavailability [20,21]. The tablet brands studied passed most of the quality evaluation tests undertaken. The thickness of a tablet can vary with no change in weight due to the difference in density of the granulation and the force of compression applied to the tablets. The uniformity of weight test is performed to assure constant dosing among tablets within a batch to prevent the incidence of overdosage or underdosage. The weight variation of a tablet directly affects the change in drug content of the tablet [22]. All the brands of metformin hydrochloride tablets weighed more than 350 mg, hence to pass the weight uniformity test, not more than two of the individual weight of the tablets should deviate from the average weight by more than ±5% and none of the tablets should deviate by more than twice the permissible percentage deviation [23]. All metformin tablet brands studied satisfied this

specification and therefore passed the uniformity of weight test. This could be attributed to good flow properties of the granules and even feeding of granules into the die.

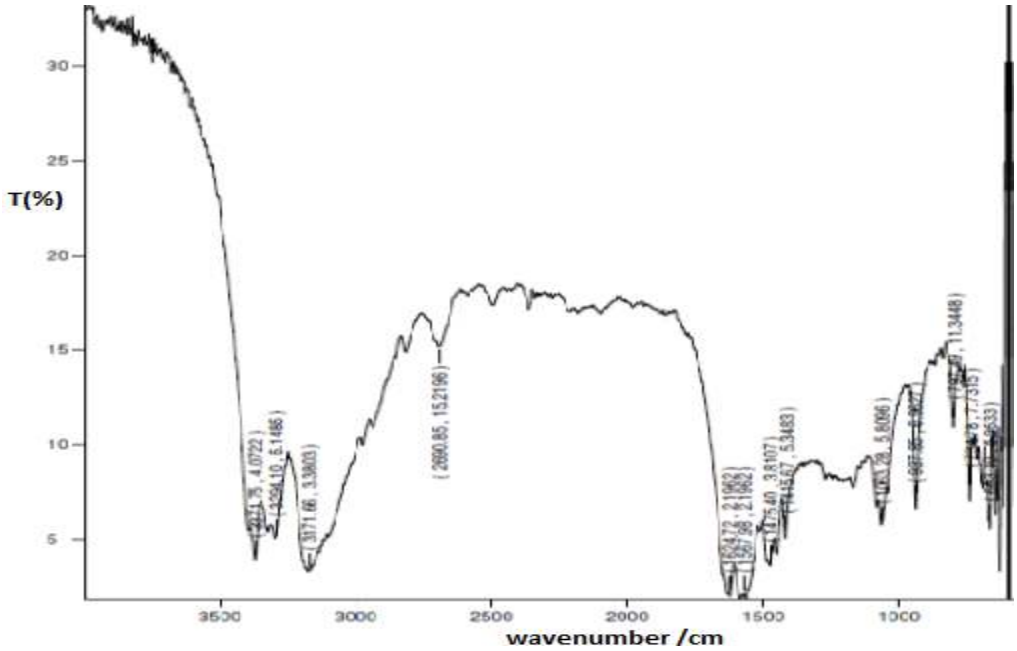

Fig. 1. Sample infra-red spectrum of one of the metformin tablet brands

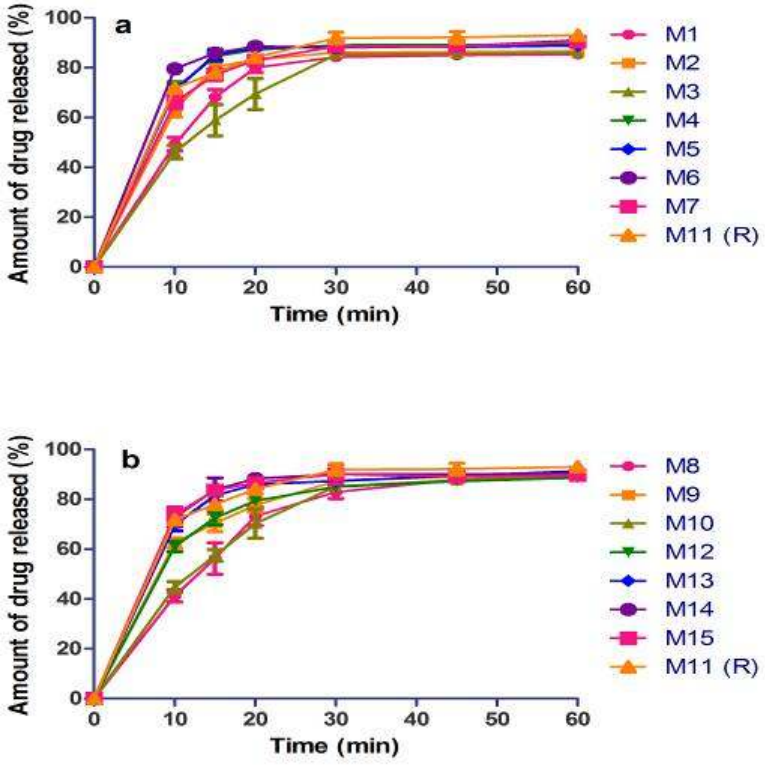

Fig. 2. Dissolution profiles of metformin hydrochloride tablet brands in 0.1 M HCl (pH 1.2), a) Brands M1-M7, M11 (R), b) Brands M8-M15, M11 (R) (mean ± S.D., *n* = 6)

Table 3. Evaluated physicochemical properties of metformin hydrochloride tablet samples

Sample code	Average weight g (S.D) n=20	Thickness mm (S.D) n=10	Hardness kg (S.D) n=10	Friability % n=10	Disintegration time (min)	Content of metformin	
						mg	*(%)
M1	0.6315(0.013)	5.80(0.02)	12.16(0.85)	0.63	13.12	498.7	99.74
M2	0.5916(0.008)	6.14(0.01)	18.76(0.04)	0.93	11.87	497.6	99.52
M3	0.6496(0.006)	6.08(0.02)	14.64(0.73)	0.15	17.14	521.1	104.21
M4	0.6117(0.015)	5.60(0.04)	8.24(0.97)	0.66	7.36	505.1	101.01
M5	0.6482(0.006)	5.88(0.01)	11.26(0.77)	0.15	9.22	539.2	107.84
M6	0.5679(0.008)	5.88(0.02)	18.78(0.05)	0.48	8.31	510.3	102.05
M7	0.6158(0.009)	5.67(0.02)	8.34(0.90)	0.16	16.74	512.0	102.39
M8	0.5949(0.006)	5.18(0.01)	15.52(1.44)	0.15	22.32	504.7	100.93
M9	0.6394(0.070)	5.25(0.01)	6.22(0.45)	1.24	21.09	554.9	110.99
M10	0.6366(0.009)	4.74(0.02)	14.62(0.79)	0.94	16.15	516.3	103.26
M11	0.5314(0.004)	5.62(0.02)	17.08(0.92)	0.94	7.81	517.4	103.47
M12	0.5986(0.007)	6.00(0.01)	13.64(0.52)	0.15	8.78	543.3	108.65
M13	0.5893(0.011)	5.93(0.01)	12.20(0.42)	0.16	8.82	502.5	100.49
M14	0.5810(0.010)	6.05(0.05)	10.62(0.47)	0.16	8.10	499.7	99.93
M15	0.6093(0.009)	5.33(0.01)	14.88(0.30)	0.66	9.30	494.9	98.99

**Percentage of the labelled amount*

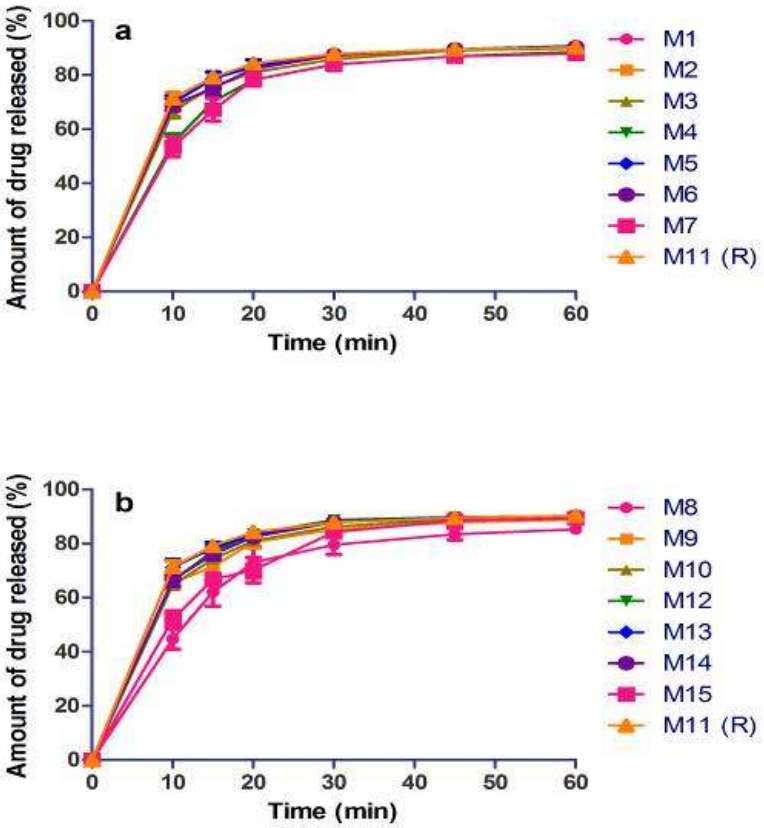

Fig. 3. Dissolution profiles of metformin hydrochloride tablet brands in phosphate buffer pH 4.5, a) Brands M1-M7, M11 (R), b) Brands M8-M15, M11 (R) (mean ± S.D., *n* = 6)

Friability test is used to assess the ability of a tablet to withstand abrasion associated with handling, packaging, transportation and shipping. This property of tablets is influenced by the nature and amount of binder used and the force of compression applied. A weight loss of not more than 1% of the weight of tablet being tested is generally considered acceptable for pharmaceutical products [13]. From the results, all the brands passed the friability test with the exception of M9 which had a percentage weight loss of 1.24%. The failure of M9 could be due to application of inappropriate compaction force and the use of insufficient binder. Tablet hardness determinations are made during tablet compression and are used to determine the need for pressure adjustment on tablet machines. A very hard tablet may fail to disintegrate in the required period in aqueous medium while a very soft tablet may not withstand handling processes such as coating, packaging and shipping operations. The hardness of a tablet depends on the force of compression and the nature and amount of the binder used. A 4 Kgf diametric crushing force is the minimum force for a satisfactory tablet. All the metformin hydrochloride tablet brands had optimal ability to withstand fracture as they exceeded the minimum 4 kgf.

Disintegration is an important step prior to drug release from immediate or conventional release dosage forms. The disintegration time of uncoated and coated tablets should not exceed 15 and 30 min, respectively [13]. From the results (Table 3), all the film coated and uncoated tablets, except M8 (uncoated) exhibited good disintegration properties. The poor disintegration properties of M8 could probably be due to the use of high amount of binder, inadequate amount of disintegrant and high compression force [24]. According to the British pharmacopoeia, metformin hydrochloride tablets should contain 95% - 105% of the label claim of

the drug upon assay [13]. Results obtained from the HPLC analysis (Table 3) showed that all the brands, except M5, M9 and M12, satisfied this pharmacopoeia specification. Brands M5, M9 and M12 had percentage drug content above the upper limit of 105% and can be considered as of substandard quality. The failure of the assay test of M5, M9 and M13 could be attributed to inaccuracy in weighing the API, poor mixing during granulation and the use of excess amount of API during tablet formulation. This particular problem has also been reported in a recent study in Nigeria in which one out of eight brands of metformin hydrochloride tablets tested showed unacceptable quantity of the drug against the label claims [25].

Oral solid dosage forms only become available for absorption following disintegration and dissolution. Dissolution testing is therefore employed to predict product behavior *in vivo* and also to establish the influence of manufacturing variables, including binder effect, mixing effect, granulation procedure and excipients type on solid dosage forms [26]. Dissolution testing is employed as an *in vitro* bioequivalence test to determine the equivalence/similarity or otherwise of solid dosage forms [27]. Conventional or immediate release tablets should release ≥70 % of the prescribed amount in 45 min [13]. Results from the study revealed that all the brands exhibited good dissolution profiles as immediate release tablets.

The comparison of therapeutic performance of two medicinal products containing the same API is a critical means of assessing the possibility of interchangeability of the products. In the US Food and Drug Administration (FDA) guidance on Immediate Release, the similarity factor (f_2) was adopted in comparing profiles of a Reference and a Test drug and f_2 comparison has been the focus in various regulatory policies [28]. When two profiles are identical, f_2 is equal to 100. Conventionally, a test brand is considered similar to a reference brand if the f_2 value of the two profiles is between 50 and 100 [29]. From the results (Table 4), brands M2, M5,

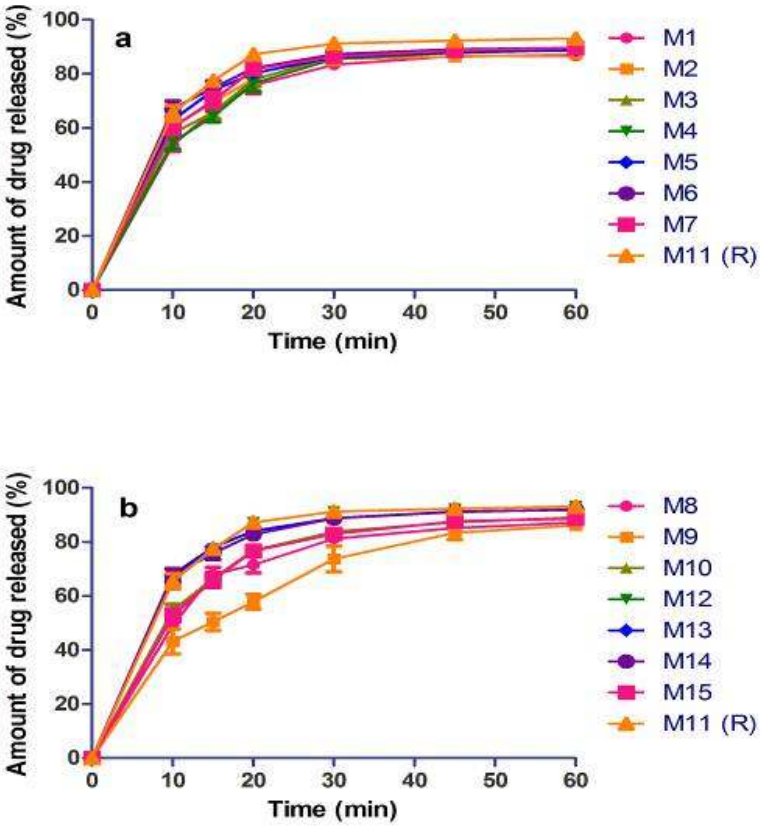

Fig. 4. Dissolution profiles of metformin hydrochloride tablet brands in phosphate buffer pH 6.8, a) Brands M1-M7, M11 (R), b) Brands M8-M15, M11 (R) (mean ± S.D., *n* = 6)

Table 4. Dissolution efficiencies (DE) and similarity factors (f_2) of metformin hydrochloride tablet samples in different dissolution media

Sample code	0.1 M HCl (pH 1.2)		Phosphate buffer pH 4.5		Phosphate buffer pH 6.8	
	DE (%)	f_2	DE (%)	f_2	DE (%)	f_2
M1	94.5	28	93.8	69	92.9	39
M2	97.1	55	95.1	86	94.1	51
M3	91.3	33	94.3	69	93.1	49
M4	98.1	63	92.5	42	91.8	45
M5	98.0	60	95.0	89	94.5	59
M6	96.8	56	94.3	75	95.0	65
M7	94.8	66	92.6	39	93.7	57
M8	88.7	27	90.4	30	90.6	35
M9	88.5	53	89.9	60	83.9	15
M10	93.5	33	94.0	64	91.4	41
M11	95.2	ND	95.8	ND	95.0	ND
M12	93.6	52	95.6	73	93.5	76
M13	95.2	69	95.8	94	93.7	70
M14	97.7	66	95.2	72	94.2	72
M15	97.8	66	90.5	36	91.5	40

ND= Not determined (reference sample)

M6, M12, M13 and M14 had f_2 values within the range specified by the FDA (50-100) in all the three dissolution media. These brands can therefore be considered to have the same drug release performance or bioequivalence with the reference brand, M11 in the three media. However, brands M1, M3, M4, M7, M8, M9, M10 and M15 had f_2 values outside the accepted range or within the accepted range in only one or two of the dissolution media used and therefore cannot be considered to be similar to the reference brand in terms of drug release performance in simulated gastrointestinal media. A study conducted by Akinleye and others found four out of seven brands of metformin hydrochloride tablets tested to have similar dissolution profiles as the innovator brand based on f_2 analysis [25].

The dissolution efficiency was determined for the tablet brands to ascertain their efficiency in releasing the drug to achieve their therapeutic activity. According to Anderson and others, the higher the dissolution efficiency, the more efficient the tablet is at releasing its embedded drug [18]. DE was generally higher in 0.1 M HCl (pH 1.2) than in phosphate buffers (pH 4.5 and 6.8). Brand M4 (in 0.1 M HCl) exhibited the highest dissolution efficiency of 98.1% while M9 (in phosphate buffer pH 6.8) had the least value of 83.8%. Based on this analysis, brand M4 could be considered the most efficient brand in the release of the API whereas M9 was the least efficient.

Two oral dosage forms are said to be bioequivalent if they demonstrate the same rate and extent of drug absorption. The bioequivalence of products are usually established through *in vivo* bioequivalence (human pharmacokinetic) studies. However, these *in vivo* bioequivalence studies are generally expensive and involve the use of invasive procedures [30]. *In vitro* dissolution studies have been shown to be as useful as and sometimes better than *in vivo* pharmacokinetic studies in demonstrating the bioequivalence of some products. Other advantages of *in vitro* dissolution studies in establishing product bioequivalence include low cost, better assessment of product performance and better ethical considerations [31].

Metformin hydrochloride is a Biopharmaceutics Classification System (BCS) class III drug which is characterized by high solubility and low permeability. The very rapid dissolution of metformin and other BCS class III drugs in aqueous media will facilitate their absorption *in vivo*. BCS class III drugs are therefore suitable for biowaiver under WHO criteria, thus exempt from *in vivo* bioequivalence studies, if a solid dosage form achieves ≥ 85% dissolution in 15 minutes using 0.1 M HCl (pH 1.2), phosphate buffer pH 4.5 and phosphate buffer pH 6.8) as dissolution media [32,33].

In the current study, none of the tablet brands met this biowaiver requirement of attaining ≥

85% dissolution in 15 minutes in all three dissolution media. Even though dissolution of metformin tablets was relatively slow in the three dissolution media used, a high *in vivo* drug absorption and bioavailability could still be achieved [34,35]. Thus, generic metformin tablets with different dissolution profiles could still exhibit similar therapeutic effect *in vivo* because of the relatively high dissolution of the drug in physiological media.

5. CONCLUSION

Fifteen metformin hydrochloride tablet brands sampled complied with the official specifications for identification, disintegration, uniformity of weight, hardness and dissolution rate test for immediate release tablets. One brand failed the friability test, while three failed the assay test. The dissolution efficiencies of the tablets were generally high (>83%) and varied with pH of dissolution media. Similarity factor, f_2 analysis, showed the dissolution profiles of M2, M5, M6, M12, M13 and M14 were similar to the reference brand (M11) in three physiological media. None of the brands satisfied the criteria for WHO BCS-based biowaiver for rapidly or very rapidly dissolving drugs. There is the need for drug regulatory authorities in Sub-Saharan Africa to intensity post-market inspection and surveillance on metformin and other life-saving medicines on the market to assure their quality and therapeutic efficacy.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the technical assistance of technicians in the Department of Pharmaceutics, KNUST, Kumasi, Ghana.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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