INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

COMPARATIVE EVALUATION OF PHYSICOCHEMICAL PROPERTIES OF SOME COMMERCIALLY AVAILABLE BRANDS OF METFORMIN HCL TABLETS MARKETED IN SUDAN

Zuheir Osman, Alaa Elmardi Osman, Aminah M. Abedelghayoum
Department of Pharmaceutics, Faculty of Pharmacy, University of Khartoum, Khartoum, Sudan.

ARTICLE INFO

Article history
Received 20/01/2017
Available online
31/01/2017

Keywords
Metformin Hydrochloride,
Physicochemical Equivalence,
Dissolution,
Similarity Factor,
Difference Factor.

ABSTRACT

The pharmaceutical equivalence of five different brands of metformin hydrochloride 500 mg tablets available in the Sudanese market was evaluated using a number of official and non-official pharmacopoeial tests; which included determination of assay of content, evaluation of uniformity of weight, friability, hardness, thickness, disintegration time and dissolution tests. The dissolution profiles of the generic brands and innovator were studies and compared using similarity factor f2 and difference factor f1. The results showed that all the five tested brands complied with the requirements of weight variation test, thickness test, friability, disintegration time test and dissolution test. However, the assay test showed that all brands complied with pharmacopeias specifications except for brand (B) which failed to pass the test. Also regarding the crushing stress (Hardness) test, four brands complied except brand (D) which failed to pass the non-official test. All brands showed good release profile with f2 values greater than 50 and difference factor f1 lower than 15 when compared with the innovator drug (A). It concluded that from all the tested brands of metformin hydrochloride tablets, only brands A, C, D and E could be considered biopharmaceutically and chemically equivalent and therefore can be used interchangeably in the clinical practice.

Corresponding author
Zuheir Osman
Department of Pharmaceutics,
Faculty of Pharmacy, University of Khartoum, Khartoum, Sudan.
00249122730707
azuheir@yahoo.com

*Please cite this article in press as **Zuheir Osman** et al. Comparative Evaluation of Physicochemical Properties of Some Commercially Available Brands of Metformin HCl Tablets Marketed In Sudan. Indo American Journal of Pharmaceutical Research.2017:7(01).*

INTRODUCTION

There is a great increase in the availability of generic drug products in recent years, the introduction of generic drug products from multiple sources into the health care delivery system of many developing countries aim at improving the access to life-saving drugs [1] as well as economic reasons.

Over the past 25 years it has become an evident that marketed products having the same amount of the drug chemical entity may exhibit marked differences between their therapeutic responses; It has been estimated that about 25% of the medicinal products on sale for consumption in developing countries are counterfeit and substandard, in some countries the figures thought to be as high as 50% according to World Health Organization (WHO) [2].

In Sudan in 2007, a post-marketing surveillance study conducted on drug product samples obtained from different pharmacy shops revealed that 35% of drug products related to public drug sources and 16% of those registered in association with the private sector companies or agencies were substandard products [3].

For drug products to be considered pharmaceutically equivalents, if they contain the same active ingredient (s), are of the same dosage form, route of administration and are identical in strength or concentration; they are formulated to contain the same amount of active ingredients in the same dosage form and to meet the same or compendial or other applicable standards i.e. strength, quality, purity, and identity [4]

Several in vitro tests are currently employed to assure drug product quality. These tests include: purity, potency, assay, content uniformity, and dissolution specifications [5]. Dissolution testing of drug product emerge as a most powerful and valuable tool to guide formulation development, monitor the manufacturing process, assess product quality, and in some cases to predict in vivo performance of solid oral dosage forms. Under certain conditions, the dissolution test can be used as a surrogate measure for bioequivalence (BE) and to provide biowaivers, assuring BE of the product [5].

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug products [6].

Tablets as a dosage form should meet certain specific requirements. The diameter, shape, thickness, uniformity of content and weight, hardness, disintegration time and dissolution of tablets all have to conform to certain parameters.

Metformin is one of the available biguanide. Indeed, it is one of the most widely used oral anti-diabetic drugs, which is the first drug of choice in obese patients whose diet control fails to control diabetes. It's also used in patients on sulfonylurea with inadequate control of diabetes according to United Kingdom Prospective Diabetes Study (UKPDS) [7].

Metformin is reviewed as an agent that improves the sensitivity of the liver and muscle to insulin, and it is demonstrated by the landmark UKPDS. This group established that metformin has favorable effects on body weight, lipid profile and fibrinolysis [8].

Selection of one product among different available generic drug products of the same active ingredients is always a cause of concern to healthcare practitioners [1]. A study on assessing the chemical and biopharmaceutical equivalency of eight metformin hydrochloride generics available in Nigerian market was conducted by Olusola *et al.*,[9]. The tested brands were evaluated using both official and non-official tests; friability test, weight uniformity, hardness, assay, disintegration time and dissolution rate. From the tested brands in that study, four out of eight were regarded as being biopharmaceutically equivalent and therefore they can be used interchangeblly in the clinical practice.

Five multisource products of metformin 500 mg tablets available in the Sudanese market were studied, all of them are formulated as immediate release oral dosage form.

The aim of this work was to assess the physicochemical parameters of the multisource products, to compare the dissolution profiles of the multisource products and the innovator to investigate the interchangeability of multisource products in the clinical practice.

MATERIALS AND METHODS

Materials

Five different brands of metformin hydrochloride 500 mg were randomly purchased from registered pharmacies in Khartoum state, Sudan. The products were coded for purposes of the research as A, B, C, D and E with A being the innovator. The study was performed within products expiration date. Metformin hydrochloride reference standard RS was a gift from Blue Nile Pharmaceuticals .The reagents used were all of analytical grades; Sodium hydroxide (Scharlab S.L, Spain), Sodium acetate anhydrous (Scharlab S.L, Spain), Hydrochloric acid (Scharlab S.L, Spain) and potassium dihydrogen orthophosphate (Scharlab S.L, Spain). Freshly distilled water was used throughout the work.

Methods

Assay of the tablets

Twenty tablets of metformin hydrochloride were weighed and then powdered using mortar and pestle. A quantity of the powder equivalent to 0.1 g of metformin hydrochloride was made into solution by adding distilled water, the resulting solution was then diluted with suitable dilution and the absorbance of the resulting solution was measured using UV- visible spectrophotometer at a wavelength 233 nm. The content of metformin hydrochloride was then calculated using calibration curve. The experimental procedure was then repeated for the other brands.

UV analysis-Calibration curve

A calibration curve of standard metformin hydrochloride tablets was made. The relationship between concentration and absorbance was plotted and the equation and correlation values of the curve were generated from the scatter plot.

Weight Variation Test

Ten tablets from each brand were weighed collectively and the average weight was calculated, after that each tablet weighed individually and the percentage deviation from the average weight was calculated according to United States Pharmacopeia(USP) [10].

Thickness test

A sample of ten tablets from each brand was selected, and the thickness of each tablet was calculated using Baker® thickness tester. The mean and standard deviation were then determined for all brands. Tablet thickness should be controlled within a ± 5 % variation of a standard. It is expressed in mm [11].

Friability test

From each brand ten tablets were selected, then weighed and placed in Electrolab® friabilator. The instrument was operated at 25 revolutions per minute for 4 minutes and the tablets were then dedusted and reweighed. The difference in weigh (weight loss) was then calculated as percentage lost using the formula:

% Friability = [(Initial weight – Final weight)/Initial weight] ×100

Hardness Test

The hardness (crushing strength) was determined using Electrolab® hardness tester. From each brand ten tablets were selected randomly and then the hardness values were recorded for each brand. The mean value for the hardness and standard deviation were then calculated.

Disintegration Test

The disintegration time was determined at 37^{o} C in distilled water using a Multi-unit disintegration tester USP Electrolab® apparatus. Six tablets from each brand were selected randomly and then the disintegration time was taken to be as the time that no granule or any residue of the tablet was left on the mesh.

Dissolution Test

This dissolution test was carried using Elctrolab® USP apparatus 1 (Basket type). A medium containing 900ml of phosphate buffer (pH 6.8), the basket rotated fixed speed of 100 rpm (rotation per minute), and the temperature maintained at 37 ±0.50 ^{o} C. Six tablets of each brand were selected randomly and then subjected for the test. In all the experiments and from each dissolution vessel, 5ml samples were withdrawn at specified time periods of 5, 10, 20, 15, 20, 30, 45 and 60 minutes. The withdrawn samples were replaced by a fresh dissolution medium (5ml) to maintain the sink conditions. Each sample was then filtered using filter paper, diluted and its absorbance was measured at λ_{max}233nm using UV-visible spectrophotometer. The concentration of the drug (metformin hydrochloride) in the samples was calculated according to metformin hydrochloride tablets monograph in British Pharmacopeia(BP) [12].

Dissolution data analysis

The mean percentage amounts of drug that released (dissolved) against their respective time points was plotted for each brand to obtain the release profiles and then it compared to that of the reference drug (A) using simple model independent approach; similarity factor f2 and difference factor f1 suggested by Food and Drug Administration (FDA) in 1995 [13], were calculated using the following equations

$$f2 = 50 \log \{[1 + (1/n) \sum_{t=1}^{n} (Rt-Tt)^2]^{-0.5} \times 100\}$$

$$f1 = \{[\sum_{t=1}^{n} |Rt-Tt|] / [\sum_{t=1}^{n} Rt]\} \times 100$$

Where, n is the number of dissolution sample times, Rt and Tt are the individual or mean percent dissolved at each time point, t, for the reference and test dissolution profiles, respectively.

RESULTS AND DISCUSSION

Five different brands of metformin hydrochloride tablets obtained from different retail pharmacy outlets within Khartoum state in Sudan were subjected to a number of pharmacopoeial tests in order to assess their biopharmaceutical equivalence. The tests include determination of content percent, evaluation of uniformity of weight, friability, hardness, thickness disintegration and dissolution tests. All brands were film-coated tablets except brand D which was uncoated tablet.

For determination of content percent of Metformin hydrochloride the assay was done using Ultra violet spectrophotometry. A stock solution of pure Metformin hydrochloride powder of concentration 0.1% w/v was prepared by dissolving 0.1g of pure metformin hydrochloride powder in distilled water., using simple dilutions then concentrations: 2, 4, 6, 8 and 10 mcg/ml were then prepared form the stock solution and the absorbance of these solutions was determined by ultraviolet spectrophotometry at a wavelength of 233 nm as shown in Table 1. A calibration curve showing the relationship between concentration of standard metformin and their respective absorbance was plotted in Figure 1 and the equation and correlation values of the curve were generated from the scatter plot. From the equation obtained the concentration of different brands was then calculated and then their content percent was estimated as shown in Table 2; four brands (A, C, D and E) fulfil the compendial specifications for assay of content of Metformin tablets (NLT 95% and NMT 105% according to BP[12],except for brand B which is (94.13%).

Table1: Standard Calibration data of metformin hydrochloride RS.

Concentration (mcg/ml)	Absorbance
2	0.157
4	0.297
6	0.445
8	0.566
10	0.734

Table 2:Content % of metformin hydrochloride in the tested brands.

Code	Absorbance.	Concentration	content %
A	0.762	10.58	96.13
B	0.75	10.42	94.13
C	0.762	10.58	96.25
D	0.781	10.85	99.0
E	0.784	10.89	98.5

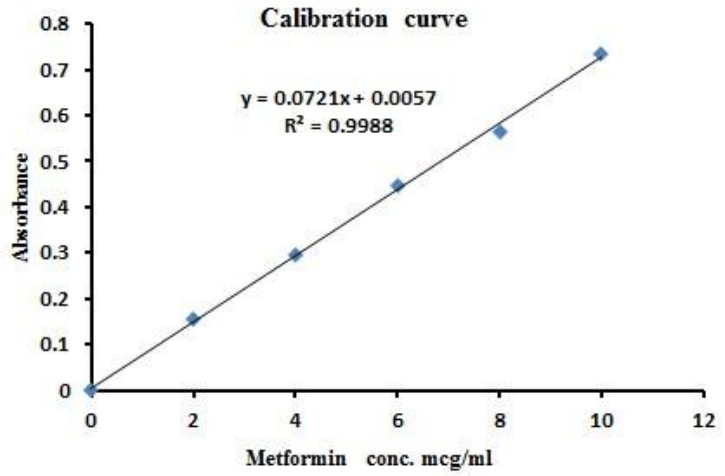

Figure1: Calibration curve of standard metformin hydrochloride.

Test results of uniformity of weight as shown in Table 3 illustrated that all brands studied fulfill the compendia specification which is; not more than 2 of the individual masses deviate from the average mass by more than 5% and none deviates by more than twice that percentage according to USP [10].

Table 3:Uniformity of weight of the different brands of metformin hydrochloride tablets.

Code	Total weight(g)	Mean weights ±SD*	Deviation %	No. of tablets deviating by ±5%	No. of tablets deviating by ±10%
A	5.32	0.532±0.006	0.011	Nil	Nil
B	5.71	0.571±0.005	0.008	Nil	Nil
C	6.54	0.654±0.006	0.009	Nil	Nil
D	5.30	0.53±0.005	0.009	Nil	Nil
E	6.37	0.637±0.005	0.008	Nil	Nil

*SD: Standard deviation

Thickness of tablets must be controlled to facilitate packaging and it should controlled within a ± 5 % variation [12].Table 4 shows that all brands tested had values ranged from 5.08-5.48 mm with the highest standard deviation equals 0.087 and hence complied with the test specifications.

Table 4: Results of thickness of the different brands of metformin hydrochloride tablets.

Code	Thickness (mm) ±SD
A	5.12±0.042
B	5.39±0.031
C	5.19±0.087
D	5.48±0.042
E	5.08±0.042

The results of tablet friability test showed in Table 5, indicated that all brands A, B, C, D and E had passed the test with values ranged from 0%-0.03%.

Table 5: Results of Friability test of the different brands of metformin hydrochloride tablets.

Code	Initial weight(g)	Final weight (g)	Friability% w/w
A	5.3266	5.3266	0
B	5.7136	5.7150	0.024
C	6.4880	6.4878	0.003
D	5.2915	5.2809	0.20
E	6.3665	6.3697	0.05

Hardness test results as illustrated in Table 6, showed that all brands except brand D complies with the non- official test, brand D with hardness value of 13.9 kgf, despite the fact that it was the only uncoated tablet in this study.

Table 6: Results of Hardness of metformin hydrochloride tables.

Code	Mean force applied (Kgf) ± SD
A	6.4±1.8
B	7.7±1.6
C	8.7±1.8
D	13.9±1.8
E	8.8±0.8

Table 7 showsthe disintegration test results of the tested brands, all the film coated brands A, B, C and E passed the disintegration test according to BP [12], which specifies 30minutes for film coated tablets and specifies 15 minutes for uncoated tablets and so also brand D also had passed the test of disintegration. Drug D tablets were the least to disintegrate this could be due to high crushing strength values.

Table 7:Results of disintegration time of different brands of metformin hydrochloride tablets.

Code	Disintegration time/min.
A (Film-coated)	8.36
B (Film-coated)	9.3
C (Film-coated)	7.55
D (Uncoated)	13.32
E (Film-coated)	6.07

Table 8 shows the dissolution test results for all brands. All brands dissolution results complied with the monographs in British Pharmacopoeia that is for each of the tablets tested for dissolution, the amount of active ingredient in solution is not less than 70% of the prescribed or stated amount.

According to WHO [14], Metformin hydrochloride is classified as BCS Class 3 drug. The dissolution data of metformin hydrochloride tablets were obtained and dissolution profile curves of all the four brands and the innovator (A) were plotted in Figure 2 and compared using similarity factor f2. Also difference factor (f1) was calculated as shown in Table 9.

Table 8:Percentage released of metformin hydrochloride from the tested tablets after dissolution at pH 6.8.

Time(min.)	A	B	C	D	E
0	0	0	0	0	0
5	32.9	26.8	46.66	25.87	55.35
10	64.32	89.5	92.23	45.78	90.28
15	86.43	91.0	92.31	60.33	92.31
20	95.6	91.79	93.45	74.11	92.72
30	97.3	92.37	96.07	87.77	93.05
45	97.52	93.03	96.28	88.55	93.81
60	98.99	94.01	97.2	92.77	94.4

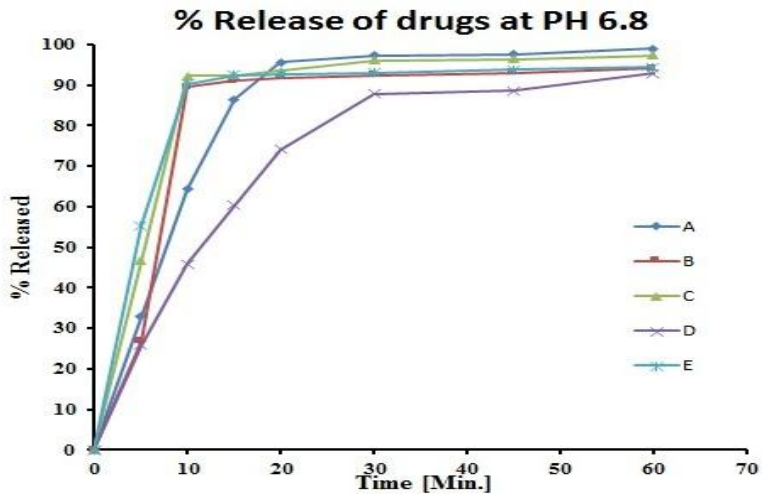

Figure 2: Dissolution profiles of the tested metformin hydrochloride tables.

Table 9: f2 and f1 Statistical values for the generics relative to innovator product (A).

Code	f2 values	f1 values
A	Innovator	Innovator
B	66	5
C	75	3
D	54	8
E	67	4

The calculated f2 values show that all brands had values > 50, which indicate the similarity of generics release profiles to that of the innovator according to FDA [13], also all results of f1 were < 15 indicating that there is no difference between generics release profiles and that of the innovator.

CONCLUSION

Based on the results obtained, it can be concluded that of all the five tested brands of metformin hydrochloride that evaluated in this study; four brands A, C, D and E were passed the pharmacopoeial limit tests and their dissolution profiles were found to be similar; thus could be considered biopharmaceutically and chemically equivalent and therefore they can be substituted with the innovator product in the clinical practice**.** Further ongoing post marketing surveillances are highly recommended for other generic brands available in the market to assure generics safety and substitution between the available generics and innovator.

ACKNOWLEDGEMENT

The authors is thankful to Blue Nile Pharmaceuticals for providing tools and equipments during the experimental phase of the study .

REFERENCES

1. Adegbolagun O, Olalade O, Osumah S. Comparative evaluation of the biopharmaceutical and chemical equivalence of some commercially available brands of ciprofloxacin hydrochloride tablets. Tropical journal of pharmaceutical research. 2007;6(3):737-45.
2. World HealthOrganization. Substandard and counterfeit medicines. Fact Sheet no. 275. Geneva: WHO. 2003.
3. Ali GK, Omer AM. Pharmaceuticals in Sudan: Development in regulations, governance and implementation of national drug policies. African Journal of Pharmacy and Pharmacology. 2012;6(1):1-12.
4. Leon S, Susanna Wu, Andrew B.C.2004. Applied pharmaceutics and pharmacokinetics. McGraw-Hills.
5. Dressman JB, Krämer J. Pharmaceutical dissolution testing: Taylor & Francis Boca Raton, FL:;2005.
6. Krishnaiah. Pharmaceutical technologies for enhancing oral bioavailability of poorly soluble drugs. Journal of Bioequivalence & Bioavailability. 2012;2010.
7. Group UPDS. UKPDS 28: a randomized trial of efficacy of early addition of metformin in sulfonylurea-treated type 2 diabetes. Diabetes Care. 1998;21(1):87-92.
8. Group UPDS. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). The Lancet. 1998;352(9131):854-65.
9. Olusola AM, Adekoya AI, Olanrewaju OJ. Comparative evaluation of physicochemical properties of some commercially available brands of metformin HCL tablets in Lagos, Nigeria. Journal of Applied Pharmaceutical Science.2012;2(2):41.
10. Unites States Pharmacopoeia Convention. United States Pharmacopoeia 38-National Formulary 33, Stationery Office, USA, 2010.
11. Lachman L, Lieberman HA, Kanig JL. The theory and practice of industrial pharmacy: Lea & Febiger; 1986.
12. British Pharmacopoeia. The stationery Office, London. 2013: Volume 1 & II
13. FDA, 1995, Center for Drug Evaluation and Research, Guidance for Industry: Immediate Release Solid Oral Dosage Forms. Scale-up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation [SUPAC-IR], November 1995.
14. World Health Organization. Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. Technical Report Series, 2006.