Physicochemical Quality of Metformin Hydrochloride tablet Brands available in Jimma Town, South west, Ethiopia

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Abstract

Introduction: Metformin hydrochloride, classified under the class of biguanide, is an oral anti-diabetic agent used in type 2 diabetes mellitus patients. According to the biopharmaceutical classification system, metformin is classified as a Class III drug. This study aims to compare the quality of metformin hydrochloride 500 mg tablets available in Jimma town.

Methods: The physical characteristic, packaging and labeling information of samples were evaluated according to the WHO guideline. *In-vitro* tests such as weight variation, friability, dissolution rate, and assay were performed on six brands of metformin hydrochloride tablets available in Jimma town following method outlined in USP. Experimental data were analyzed using SPSS- 20 and one-way ANOVA. To compare the dissolution profiles of the generic products with innovator product, a model-independent approach, similarity factor (f_2), difference factor (f_1) and dissolution efficiency (DE) were used.

Results: All the tested brands were in line with the WHO specifications for physical characteristics, packaging and labeling of pharmaceuticals. Insumet had percent weight deviation more than 5% and failed to comply with the USP specification for uniformity of weight. Statistically, all brands had significant difference in their mean weight variation ($P < 0.001$). The assay results range from 95.21% to 99.61% showing that all the brands met the USP requirement. Moreover, a single point dissolution test results of the brands ranged from 85.4% to 96.7% showing compliance to USP specification.

Conclusion: No brand showed any sign of counterfeit and only Insumet failed to comply with the USP specification for weight variation test. All brands complied with the United States Pharmacopeia specification for the friability, assay and single point dissolution test. Furthermore, the model-independent approach and dissolution efficiency revealed that all the brands were interchangeable with the comparator product.

Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by a persistently elevated blood glucose associated with absent or inadequate pancreatic insulin secretion, with or without concurrent impairment of insulin action.¹ There are two main types of diabetes, type 1 diabetes mellitus and type 2 diabetes mellitus. Type 2 diabetes mellitus is the most common form of diabetes and a rapidly growing health concern in both developed and developing nations.^{2,3} It accounts for 90–95% of all person with diabetes and is expected to increase to 439 million by 2030.^{4,5} Among the treatment options existing, Metformin hydrochloride is the most widely used oral medication to treat type 2 diabetes worldwide.³

Metformin hydrochloride, an oral anti-diabetic agent, acts by lowering both basal and postprandial plasma glucose. Other anti-diabetic agent such as sulfonylurea may induce hypoglycemia but metformin hydrochloride does not cause hypoglycemia at any reasonable dose and usually called anti-hyperglycemic agent. Metformin hydrochloride work as an insulin sensitizer; allowing the body in utilizing insulin and it's classified under biguanide class.^{6–8}

Metformin hydrochloride (N, N-dimethyl-imido-dicarbonimidic diamide hydrochloride) is small basic compound which has molecular weight of 129 Da and ionized at physiological PH.⁹ Even though metformin is hydrophilic base chemically, it's usually present in an oral dosage forms in its hydrochloride salt form (Fig. 1). This chemical property shows that metformin has low lipophilic property and therefore, the diffusion of metformin through cell membrane is low. After oral administration, metformin is largely absorbed from the upper small intestine, and it undergoes limited systemic absorption with a half-life of about 3 hours. Therefore, repeated administration of the conventional metformin hydrochloride tablets is mandatory for effective treatment.^{10–12}

According to Biopharmaceutical Classification System (BCS), metformin is classified under class III drugs.¹³ For such drugs, permeability is the rate-limiting step for drug absorption. Rapid dissolution is especially desirable to maximize the contact time between the dissolved drug and mucosal membrane. So that, the duration of dissolution should be strict. Hence, as drug permeation is rate-limiting, no *in-vitro in-vivo* correlation (IVIV) is expected.^{14, 15}

Pharmaceutical products containing the same active ingredient can be produced and marketed by many companies under different 'brand' name as a generic drug products once the patent for the innovator get expired. Generic and innovator products should be the same with respect to quality, safety, efficacy, strength, dosage form, route of administration and intended use.^{16–18} The introduction of generic drugs from multiple sources into the markets improved availability and access to life-saving drug especially in developing countries.¹⁹ In addition, these generic drugs are marketed with lower price and related with public health cost reduction.^{20, 21} Despite these benefits, generic products are also related with variety of problems which might place the customers' health at risk. The interchangeability of generic drugs with the originator might still be questionable.

Quality is one of the most important criteria in guarantying optimal treatment out come from medicines and is presently receiving increased attention in generic manufacturing.²² Circulation of poor quality drug products in the international market increased significantly as a result of ineffective regulation of manufacturing and trading of pharmaceutical products.²³ Therefore, the manufacturing, distribution, storage and use of drugs need to be regulated by authorized regulatory institutions.

Poor quality medicines are public health problems and affect both developing and developed countries.^{24, 25} The World Health Organization reported that 10% medical products in low and middle-income countries are either substandard or falsified²⁶ and Ethiopia is one of the low-income countries. Considering this, falsified or substandard medicines could be available in the drug market. Reasons for the supply of such drugs in low and middle income country could be attributed to weak regulatory enforcement, lack of informal market control, weak port control, poor cooperation between executive bodies and resource constraint.^{27, 28} The availability of such types of drugs on the market might leads to treatment failure, increased mortality and morbidity, drug resistance and economic loss.²⁹

For better health of the public, supplying good quality medicine is mandatory. But it is often missing in developing country like Ethiopia which has weak regulatory system for pharmaceuticals. World Health Organization (WHO) has estimated that about 30% of the medicines on sale in Africa countries and parts of Asia and Latin America are counterfeit, while other developing countries have < 10%; overall, a reasonable range is between 10–30%.³⁰ In 2013, the Public Health and Drug Testing Laboratory (PHDTL) tests 5000 drug samples from Bangladesh's mammoth Pharmaceutical industry and according to this study, 60% of drugs are either counterfeit or of very poor quality.³¹

Generally, medicines used in health care need certain types of standards to have quality, safety and efficacy. So, monitoring drug quality through *in-vitro* test is mandatory to safeguard the health of the public as a whole and to reduce morbidity and mortality associated with poor quality medicines.³² In Ethiopia, there are very few pharmaceutical manufacturing companies and the country is principally dependant on imported pharmaceuticals. There are many multisource metformin hydrochloride tablets that are legally registered by Ethiopian food and drug administration and available on market for public use. Hence, there should be a means to determine that generic pharmaceutical products are therapeutically equivalent and interchangeable with their innovator's as unpredictable clinical responses have been reported from similar drug products manufactured by different companies.^{33,34} Therefore, this study was conducted to assess the *in vitro* equivalency of different brands of Metformin hydrochloride 500 mg tablet which are commonly available in drug retail outlet and hospital pharmacies in Jimma town and indiscriminately used in the treatment of diabetic patients. Six different brands of metformin hydrochloride 500 mg tablets that are available in jimma town were tested and compared for different physicochemical quality parameters including weight variation, friability, dissolution and assay.

Material And Methods

Study setting and period

The study was conducted on six brands of metformin hydrochloride tablets available in Jimma town. Jimma town is located 357 km southwest of Addis Ababa, the capital of Ethiopia and had 17 kebeles with a population of 120,960 and 32,192 households.³⁵ The laboratory work was conducted in Jimma University Laboratory of Drug Quality (JuLaDQ). All the brands included in the study were within their shelf life at the time of the study. The laboratory work was done from April-June 2019.

Instruments

Analytical Balance (Mettler Toledo, Switzerland), RC-6D Dissolution Apparatus (Apparatus 2; Tian Jin Optical Instruments, China), UV–Vis Spectrophotometer (Cecil Instruments, United Kingdom), Friability Tester (Pharma Test), PH meter (AD 1020 PH /MV/ISE), and Water Purification System (Thermo Scientific, Model-7143, Waltham, MA, USA) were used for the study.

Chemical and reagents

Distilled water, sodium hydroxide (BDG Laboratory Supplies, Purity = 97.5%), potassium dihydrogen orthophosphate (Techno Pharm Chem, Bahadurgarh, Purity = 99–101%, India) were used. The working standard of metformin hydrochloride was donated by the Ethiopian Food and Drug Administration Authority (EFDA).

Sampling technique and sample collection

Before the actual sample collection, we conducted market surveillance and identified that five imported and one locally produced metformin hydrochloride 500 mg tablets are marketed in Jimma town. All available six brands were purchased from drug retail outlets and hospital pharmacies by mystery shoppers who were trained and blinded about the purpose of the study. The mystery shoppers were told to approach the pharmacist/druggist working in the retail outlets and hospital pharmacies by stating that they are travelers and who has been taking metformin for their diabetic condition and now running out of medication. Guidelines to Conduct Surveys of the Quality of Medicines by Newton were used for sampling strategy.³⁶ After collection, all samples were subjected to visual inspection and their manufacturing license number, batch number, manufacturing, and expiry dates, country of origin, batch/lot number were recorded immediately. The samples were kept in their original package, transported to Jimma University laboratory of drug quality (JuLaDQ), and stored under storage condition specified on the label of each product until the analysis. Detail information of the samples was presented in Table 1.

Table 1
Detail information of metformin hydrochloride tablet brands included in the study

Brands	Manufacturer	Country	Batch number	Man. Date	Exp. Date
Glucophage	Merck serono	France	F0582	10/2018	09/2023
Metformin denka	Denka pharma	Germany	9N6	07/2018	06/2023
Insumet	Cadila Pharmaceuticals PLC	Ethiopia	D18076T212	12/2018	09/2021
Brot	Medochemie Ltd;Limassol	Cyprus	A1H115	08/2018	08/2022
Etform	Lek SA,Styrykow;Sandoz anovartis company	Poland	JC2413	06/2018	06/2021
Metformin	Ningho Shuangwei Pharm.co.Ltd.	China	180719	07/2018	07/2021

Quality assessment

Physical characteristics, packaging and labeling

All samples were visually inspected for their Physical characteristics (shapes, color, breaks, cracks and splits), packaging and labeling information (name of the active pharmaceutical ingredient, the country of origin, manufacturing company, manufacturing date, expiry date, batch/lot number, number of units per strip/package and labeled dose (strength) of the active ingredient) using the modified World health organization (WHO) checklist designed to health professionals to carry out visual inspection of medicines for signs of counterfeiting and report to appropriate national authority or directly to WHO.³⁷

Weight variation

The weight variation test for metformin hydrochloride tablet brands was evaluated according to the method given in USP.³⁸ Randomly selected twenty tablets from each brand were weighed individually with calibrated analytical balance and the average weight for each brand was determined. The percentage deviation was calculated from the average weight of the tablets using Eq. 1 and compared against the USP limits for tablet weighing 250 mg or more (i.e.; No more than 2 individual tablet weight deviate by > 5% of the average tablet weight and none deviating by more than 10% of the average tablet weight).

$$\text{percentage deviation} = \frac{(\text{weight of individual tablet} - \text{Average weight of tablet}) \times 100}{\text{Average weight of tablet!}} \dots \dots \dots 1$$

Friability Test

Friability test for metformin hydrochloride tablet brands was evaluated according to the method outlined in USP.³⁸ Randomly selected twenty tablets from each brand were weighed and subjected to abrasion using the drum of friability tester at 100 revolutions for 4 min. Then, the tablets were removed from the drum, dedusted and weighed again. Then, percentage weight loss was calculated using Eq. 2, compared against USP criteria for compressed tablets and considered as friability. According to USP criteria, percentage weights lose not more than 1% is considered to be acceptable and if cracked, cleaved, or broken tablets are present within the tablet sample after tumbling, the tablet fails the test.

$$\% \text{ weight loss} = \frac{\text{initial weight} - \text{weight after abrasion}}{\text{initial weight}} \dots \dots \dots 2$$

Assay

The determination of metformin hydrochloride API in metformin hydrochloride tablet of each brand was evaluated following the method given in USP.³⁸

Standard solution preparation

One milligram USP Metformin Hydrochloride RS (Reference Standard) was weighed with calibrated balance (Mettler Toledo, Switzerland) and transferred to a 100 ml volumetric flask. Then 50 ml of water was added, shaken for five minutes and diluted to volume with the same solvent

Sample solution preparation: - The sample solution for metformin hydrochloride tablet brands was prepared by randomly selecting and powdering twenty tablets from each brand using mortar and pestle. Powder weight equivalent to 100 mg of metformin hydrochloride was weighed and transferred to 100 mL volumetric flask. Then, 70 mL of water was added, shaken by mechanical means for 15minutes, diluted with water to volume and filtered. Then, 20 mL of the first filtrate was discarded after which 10 mL of the filtrate was taken and diluted with water to 100 mL. Finally, 10 mL of the resulting solution was taken and further diluted with water to 100 mL and the absorbance of the resulting solution and standard preparation was measured using Ultraviolet visible spectrophotometer at wavelength of 232 nm using water as a blank. The quantity, in milligram, metformin hydrochloride in the portion of tablet taken for assay was calculated using Eq. 3 and compared with USP acceptance limit (%label claim: 95%- 105%).

$$\text{Quantity (mg)} = 10C \frac{Au}{As} \dots \dots \dots (3)$$

Where C is the concentration, in mg/mL, of USP Metformin hydrochloride RS in the standard preparation, *Au* and *As* are Metformin hydrochloride peak responses obtained from the assay preparation and the standard preparation respectively.

Dissolution test

Calibration curve construction

Hundred (100 mg) of USP metformin hydrochloride RS was dissolved in 100 mL of phosphate buffer to prepare stock solution having 1mg/ml concentration. From the stock solution, five concentration levels (6, 7, 8, 9 and 10 µg/mL) were prepared using the same phosphate buffer as a diluent. Then, absorbance of these concentrations was determined spectrophotometrically at a wavelength of 233 nm and plotted against the five concentration levels to obtain the calibration curve.

Dissolution profile

The dissolution profile for metformin hydrochloride tablet was evaluated following the method given in USP.³⁸ The dissolution study was carried out using the USP Apparatus II (paddle). The dissolution medium (1000 mL phosphate buffer) was transferred to vessels of dissolution apparatus and maintained at temperature of 37°C ± 0.5°C and paddle rotation of 100 rpm. Randomly selected metformin hydrochloride tablets (n = 6) from each brand were assigned to the six dissolution vessels. According to USP 2015 specification, at a single point time of 30 minutes, at least 80% of the drug needs to be released. However, to study the dissolution profile of the drug, 10 ml sample of dissolution medium containing metformin hydrochloride was withdrawn at predetermined time points (5, 15, 30, and 45 min) and replenished with an equal volume of fresh dissolution medium maintained at the same temperature. The withdrawn sample was filtered and diluted (100x). Then, their absorbance was measured by ultraviolet-visible spectrophotometer at a wavelength of 233 nm using phosphate

buffer as a blank. The concentration was calculated by using the calibration curve equation generated from a known concentration of Metformin hydrochloride RS and the percentage drug release was calculated at each time point.

Statistical analysis

For statistical analysis, Microsoft excels 2010 and statistical package for social science were used and $p < 0.05$ were used as a cut point for significance. Percentage label claim, weight variation and dissolution profile of different brands were compared by one way analysis of variance (ANOVA). The dissolution profiles of the brands were also compared by the model independent method of fit factors approach and dissolution efficiency (DE). The fit factor approach includes the difference factor (f_1) and the similarity factor (f_2).³⁹ DE is the area under the dissolution curve between defined time points.⁴⁰

Results

Among the six different brands of metformin hydrochloride tablets evaluated, one brand was locally produced in Ethiopia, while the remaining five brands were imported from abroad. Both official and non-official tests were done to evaluate the quality of the different brands of metformin hydrochloride tablets. Official tests like Weight variation, dissolution test and drug content analysis (assay) and the non-official test; friability test were evaluated according to the method outlined in USP. One of the non- official test hardness was not performed. This is because hardness test is mainly done to determine the need for pressure adjustment on the tableting machine during production and by itself it is not quality determinant.

Physical characteristics, packaging and labeling

The physical characteristics, packaging and labeling result showed that all the tested brands had a uniform white color, undamaged, and did not had any odor. Except for Insumet, all metformin hydrochloride tablets had a circular shape. But, Insumet had an oval shape. The packaging and labeling of all brands meet the minimum requirement required by the World Health Organization for packaging and labeling (The result for physical characteristics, packaging, and labeling was presented in the supplementary file 1.

Weight variation and friability

The weight variation and friability test result of metformin hydrochloride tablet were depicted in Table 2. Brot and Etform had the highest and lowest mean weight respectively. Except for insumet, all the brands passed the weight variation test as none of them had percentage deviation greater than 5% from the mean tablet weight as specified in USP. Statistical analysis using One-way ANOVA at 95% confidence interval (CI) showed significant differences ($p < 0.001$) among samples mean weight of all brands. Furthermore, Dennett multiple comparisons test performed to identify the source of difference between the test products and the comparator revealed that there was a mean tablet weight difference between the compactor and all tested products (Table 3). In this study, the percentage friability of the tested brands ranged from 0–7.37%. Metformin denk and Etform did not lose their content after the friability test. Except for Brot, all the brands passed the friability test according to the USP limit, which states percentage weight lose not more than 1% is considered to be acceptable.

Table 2
Physicochemical characteristics (weight variation, friability and assay test) of metformin hydrochloride tablets tested.

Brands	Weight variation (mean ± std. error)	UB	LB	P-value	Friability (%)	Assay % (mean ± SD; n = 3)	p-value
Glucophage*	532.08 ± 0.91	533.99	589.07	P < 0.001	0.014	96.46 ± 0.03	P < 0.001
Metformin denk	656.87 ± 1.19	659.35	654.39		-	95.21 ± 0.14	
Insumet	660.72 ± 1.36	663.58	657.86		0.0197	99.61 ± 0.03	
Brot	677.14 ± 0.87	678.97	675.30		7.37*10 ⁻⁴	95.41 ± 0.03	
Etform	524.51 ± 0.82	526.22	522.80		-	98.28 ± 0.02	
Metformin	554.26 ± 3.54	561.68	546.84		0.055	96.12 ± 0.02	

*Comparator; SD: - Standard Deviation; UB: - Upper Bound; LB: - Lower Bound

Table 3
-Dennett multiple comparisons test for uniformity of weight of metformin hydrochloride tablets tested with innovator

Tested brands	Innovator	Mean difference (tested-innovator)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Insumet	Glucophage	128.64	2.46	< 0.001	122.38	134.89
Metformin denk	Glucophage	124.79	2.46	< 0.001	118.53	131.04
Etform	Glucophage	-7.58	2.46	< 0.001	-13.83	-1.32
Metformin	Glucophage	22.18	2.46	< 0.001	15.92	28.43
Metformin	Glucophage	145.05	2.46	< 0.001	138.79	151.31
Brot	Glucophage	128.64	2.46	< 0.001	122.38	134.89

The result for the Ultraviolet visible spectrophotometer assay of the different brands of Metformin hydrochloride tablet is depicted in Table 2. With regard to the Metformin hydrochloride content in the tablet dosage forms analyzed, all the brands complied with the acceptance specification set in USP, (i.e. % label claim: 95% -105%). The Metformin hydrochloride content in Metformin hydrochloride tablet dosage forms ranged from 95.21–99.61%, with Insumet and metformin denk respectively. The statistical analysis using One-way ANOVA at 95% CI showed that there was significant difference in drug content among the different brands of metformin hydrochloride tablet (Table 2). Additionally, post hoc Dennett multiple comparisons test performed to spot out the source of difference between the test products and the comparator in terms of their drug content revealed that there was a drug content difference between the compactor and all tested products (Table 4).

Table 4
Dennett multiple comparisons test for assay of metformin hydrochloride tablets tested with innovator

Tested brands	Innovator	Mean Difference (tested-comparator)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Insumet	Glucophage	3.15	0.05	< 0.001	3.01	3.29
Metformin denk	Glucophage	-1.25	0.05	< 0.001	-1.39	-1.11
Etform	Glucophage	1.82	0.05	< 0.001	1.68	1.96
Metformin	Glucophage	-0.34	0.05	< 0.001	-0.48	-0.20
Brot	Glucophage	-1.05	0.05	< 0.001	-1.19	-0.91

Calibration curve for dissolution study

The calibration curve for the applied UV-visible spectroscopic method in the determination of amount of Metformin hydrochloride released is shown in **Fig. 2**. The result from the calibration curved revealed the presence of strong positive relationship ($r^2 = 0.9986$) between the concentration and absorbance over the concentration range of 6 to 10 µg/ml.

Dissolution Study

The dissolution profile of tested brands of metformin hydrochloride tablet is indicated in **Fig. 3** and a single point dissolution test result at pharmacopoeial specified time of 30 minute is shown in Table 5. The dissolution result indicates that all the tested brands released more than 80% of the labeled amount within the specified time point showing compliance to USP pharmacopoeial specification for dissolution of metformin hydrochloride table dosage form. The release rate of the drug ranged from 85.4% for Metformin denk to 96.7% for Etform. The result of one-way ANOVA statistical analysis conducted at 95% CI revealed that there was no s significant difference in the release of Metformin hydrochloride from the drug matrices among the tested brands and the comparator product (Table 5). In order to assess the interchangeability, the model independent method (f_1 and f_2) were done and the result showed that Metformin denk, Insumet, and Brot had a similarity factor (f_2) of greater than 50%, and all the brands had a difference factor (f_1) of less than 15 (Table 5). All the brands had a difference in dissolution efficiency of within $\pm 10\%$.

Table 5
Single point
(t = 30 min)
dissolution
test result for
metformin
hydrochloride
tablets tested

Brands	Dissolution at 30 minutes	p-value	tablets tested		DE (%)	Difference of dissolution efficiency (%)
			f ₁	f ₂		
Glucophage	94.7	0.91	-	-	72.65	-
Metformin denk	85.4		9.29	86.32	66.84	5.81
Insumet	87.4		7.33	53.80	65.22	7.43
Brot	87.1		7.58	57.45	71.83	0.82
Etform	96.7		1.96	3.83	75.54	-2.89
Metformin	89.1		5.77	33.29	75.99	-3.34
DE: Dissolution efficiency, f ₁ : Difference factor, f ₂ : Similarity factor, -: not calculated for the innovator.						

To augment the one-way ANOVA, the Dunnett multiple comparisons test were conducted at 95% CI with the comparator/innovator and the result indicates that there was no statistically significant difference in the release profile between comparator and tested brands (Table 6).

Table 6
Dunnett multiple comparisons test for dissolution study of metformin hydrochloride tablets tested with the innovator

Tested brands	Innovator	Mean Difference (tested-comparator)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Insumet	Glucophage	-5.13	21.73	.999	-65.14	54.8692
Metformin denk	Glucophage	-13.99	21.73	.948	-74.00	46.0061
Etform	Glucophage	-13.99	21.73	.948	-74.00	46.0061
Metformin	Glucophage	7.15	21.73	.997	-52.85	67.16
Brot	Glucophage	-2.14	21.73	1.000	-62.14	57.86

Discussion

According to the present study, all the tested brands had a uniform white color, undamaged, and did not have any odor. All the tested brands had a circular shape except Insumet which had an oval shape. The results for visual inspection of physical characteristics, packaging and labeling did not show any signs of spurious, falsely labeled, falsified or counterfeit products as defined by the WHO. No defect in physical characteristic of the tablets was observed and there was also no incorrect, inadequate or incomplete labeling of metformin hydrochloride tablet brands that leads to suspicion of the product for potential counterfeit.³⁷ weight variation test was used to check if the tablets have uniform content or not. So, batch/s has active pharmaceutical ingredient/s within a narrow range round the label claim.³⁸ Dosage unit was dosage form containing a unit dose or a part of a dose of drug substance in each unit.

According to this study, only Insumet has failed the weight variation test by having a percent mean deviation of more than 10. Weight variation test failure of Insumet may cause the unavailability of the necessary amount of active pharmaceutical ingredient required for therapeutic effect in the unit dose; this might intern leads to a reduction in the therapeutic activity of the drug and cause a reduced patient outcome. Furthermore, statistical analysis revealed that there were significant differences ($p < 0.001$) between the samples mean weights of all brands. This weight variation might be due to the difference in the types of excipients like diluent, disintegrant, lubricant, and glidants used during the manufacturing process. This difference might also associate to differences in manufacturing process. A study conducted in India on four different brands of metformin hydrochloride tablets showed that the entire tablets were passed the test for weight variation and friability.⁴¹ From eight metformin HCL tablet brands tested in Nigeria, all the brands were also passed the test for weight variation, and one of the brands was failed to pass the test for friability.⁴² A similar result was also reported from India in 2012 in which all the tested brands were passed the weight variation and friability test.⁴³ However, according to this study, Insumet failed the official test of weight variation. The discrepancy may be attributed to the types of brands included in the study, difference in personnel qualifications and the standard of laboratory.

The assay test is an important test used to quantify the amount of active ingredients present in the product. The amount of active ingredient present in one product affects the quality and will have an impact on the therapeutic effect. The drug which does not have the required active pharmaceutical ingredient cannot produce the necessary therapeutic outcome, and might leads to treatment failure, morbidity, and mortality to patients. According to this study, all metformin hydrochloride tablet brands were within their specifications and satisfied the assay requirement of USP 2015 (95–105% I_c). The finding was similar to the reports from Tigray.⁴⁴ Sri Lanka⁴⁵ and India⁴⁶, but, different from study done in Nigeria.⁴² This difference might be due to differences in the drug regulation system of different countries and differences in types of brands included in the study.

In vitro dissolution study from oral solid dosage forms is an important precondition for drug bioavailability and can be used as an alternative approach for bioequivalence studies that can forecast therapeutic equivalence between reference and test products which are pharmaceutical equivalent.⁴⁷ Dissolution test result of tablets may indicate the impact of ingredients included in the formulation on the in vivo performance of the drug. According to this study, all the brands passed a single-point dissolution study and complied with USP specification by releasing more than 80% in 30 minutes. However, metformin hydrochloride, a BCS class III drug fails to release more than 85% within 15 minutes and not eligible for biowaiver. This might be due to either the excipients used or due to the PH of the dissolution medium used. The dissolution result was similar to the report from India⁴³ and different from a study done in Addis Ababa, Ethiopia.⁴⁸ This difference in dissolution might be due to the inclusion of different brands for the study.

Statistically, there were no significant differences in the release of the drug substance from metformin hydrochloride tablet matrices of the brands ($p > 0.05$). To support the one-way ANOVA, Dunnett multiple comparisons test was also performed at 95% CI between the innovator and tested brands and revealed that there was no statistically significant difference in the release profile between comparator and tested brands. In addition, the interchangeability/equivalency of tested brands and innovator was evaluated by fit factors. Fit factors include similarity (f_2), and the difference (f_1) factors. For the test drugs to be used interchangeably with the innovator, the similarity factor (f_2) should be 50–100, and the difference factor (f_1) should be 1–15.³⁹ According to the above acceptance criteria, Insumet, Metformin denk, and Brot had f_2 value of > 50 and f_1 value of < 15 and were equivalent with the innovator drug Glucophage. On the other hand, Etform and Metformin had $f_2 < 50$ and failed to be bioequivalent with the innovator drug Glucophage. Furthermore, to ensure the interchangeability of such drugs with the innovator drug, the release profile was compared by calculating the dissolution efficiency for the different brands of metformin hydrochloride tablets included in the study. The test product is interchangeable/equivalent with the innovator if and only if the difference between their dissolution efficiency (innovator drug–test drug/vice versa) is within $\pm 10\%$.⁴⁰ Based on this requirement all brands of metformin hydrochloride tablets were equivalent to the innovator product as the difference in dissolution efficiency is $< 10\%$.

Conclusion

This study tried to analyze the quality as well as the physicochemical equivalency of six brands of metformin hydrochloride tablets available in Jimma town. All the tested brands were in line with the World Health Organization guideline for evaluation of packaging and labelling of pharmaceuticals for the sign of counterfeit. The physicochemical evaluation revealed that all brands met the USP quality specification for friability, dissolution and assay. However, one brand (Insumet) failed to comply with the United States Pharmacopeia specification for uniformity of weight. Statistically, all the brands had a significant difference in their mean weight and mean assay value from the innovator ($p < 0.05$). The dissolution profile comparison has established the interchangeability of the tested products with the comparator drug.

Declarations

Ethical approval:

Not applicable

Consent for publication

Not applicable

Data Availability

All necessary data are available within the manuscript and if required, raw data like chromatograms will be available from the corresponding author up on request

Competing interest

The authors declare that they have no competing interest.

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Authors' contribution

YM designed and coordinated the study, along with AB. BU collected the samples and drafted the manuscript. SS performed the data analysis. All authors read and approved the final manuscript.

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Figures

Figure 1

Chemical structure of metformin hydrochloride

Figure 2

Calibration curve of Metformin HCL reference standard in phosphate buffer at maximum wave length of 223nm.

Figure 3

Dissolution profile (mean $\pm$ SD, n = 6) of Metformin hydrochloride tablet brands in phosphate buffer medium (1000 mL) using USP apparatus II.

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