

Assessment of Physicochemical Properties and Comparison of Dissolution Profiles of Metformin Hydrochloride Tablets in Saudi Arabia

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ABSTRACT

Although prevalence of substandard or counterfeit drugs is a world-wide problem, poor and developing countries are affected the most. To be a quality product, drug formulation must comply with certain standards. Consequently, in this study, metformin hydrochloride (MH) tablets (500 mg) available in the Saudi Arabian market were assessed through various pharmacopeial quality control tests. Parameters including weight variation, hardness, friability, drug content, and disintegration time were evaluated. Results were within acceptable limits for all selected products (nine generic and an innovator). Fourier-transform infrared spectroscopy (FT-IR) spectra of MH for all tested products were completely superimposed with that of the pure drug, confirming the use of correct active ingredient in all tablet formulations. The products were also evaluated by comparing the dissolution profile of the generic products with the innovator brand in pH 6.8 phosphate buffer. The range of percent drug release in 30 min was 82.71–98.43%, in comparison to 91.86% for reference product, which complies with the USP-NF specification of at least 80% drug release in 30 min. The difference factor (f_1), similarity factor (f_2 , except product H), and dissolution efficiency revealed that the dissolution profiles of the tested products were comparable to that of the reference product. These results show that the tested generic products were biopharmaceutically similar (except product H) to the innovator formulation. Therefore, the consumer can select any one of these equivalent products as a substitute for innovator product in case of cost concern or unavailability.

KEYWORDS: Metformin hydrochloride, dissolution study, disintegration test, generic

INTRODUCTION

Metformin hydrochloride (MH) is biguanides class drug that is orally administered as a first-line medication used to control blood glucose in type-2 diabetes (1, 2). It is a prescription medication approved by the United States Food and Drug Administration (US FDA). The anti-hyperglycemic action is attributed to increase in insulin sensitivity, peripheral use of glucose, along with reduction in glucose production by the liver and intestinal glucose absorption (1, 3). Metformin lowers the risk of cardiovascular complications and heart attack by controlling the blood sugar level. Moreover, it improves endothelial function, hemostasis, oxidative stress, insulin resistance, lipid profile, and fat redistribution (1, 4-8).

Generic medicines are produced after the patent

protection of innovator product is over and made available in markets with different names, which are claimed to be chemically and biopharmaceutically equivalent to the innovator product (9). Generic drugs are significantly useful to decrease the cost of healthcare; however, sometimes the quality of medication has been compromised, mainly in products manufactured in poor and developing countries. There are certain cases of identification of counterfeit and substandard drugs, where the quality of these products does not meet the pharmaceutical standards; as a result, such products may be ineffective or even harmful for the consumers (10, 11). Counterfeit drugs may be a drug product with inadequate or without active ingredient, wrong ingredients, and correct active ingredient with fake packaging (12). As per the World Health Organization (WHO), the counterfeit

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drug's share in the global pharmaceutical market is approximately 10%, which is estimated to be increased to 25% in developing countries and may increase to 50% in certain poor countries. The FDA has reported that in poor countries, approximately 25% of drugs available for the consumers are either substandard or counterfeit drugs (10). Moreover, according to WHO, the annual trade from fake medicines are about 73 billion Euros (13). The FDA, WHO, and other concerned organizations such as the Saudi Food and Drug Authority in Saudi Arabia are making continuous efforts to control counterfeit medicines worldwide .

A pharmaceutical product must fulfill certain standards to qualify as a quality drug. To ensure the quality of the available generic products, there are various parameters that must be examined during the manufacturing processes as well as throughout the shelf-life of the product at regular intervals. Several tests are used to evaluate the physicochemical features of drug formulations, such as weight variation, friability, hardness, and content of the active ingredient, whereas the drug release pattern from tablet dosage forms is tested through disintegration and dissolution studies (14). It is well known that, prior to absorption into the systemic circulation, a drug must be in solution, which means a dosage form must efficiently release the drug in the gastrointestinal tract for effective absorption into the systemic circulation. Consequently, *in vitro* dissolution testing is one of the most crucial steps for understanding the rate and extent of drug release inside the body (15). To reduce the cost of health expenses, WHO favors the substitution of the innovator product with generic ones, provided there is enough evidence supporting that the products are bioequivalent and are of acceptable quality. Comparative *in vitro* bioequivalence between innovator and generic products is established through the above-mentioned quality tests, which are the prerequisites for the marketing authorization of generic formulations (16). Administration of non-bioequivalent generic products may result in alteration in the pharmacokinetic profile of the drug, leading to subtherapeutic drug concentration at the site of action and insignificant therapeutic action (17, 18). Dissolution testing has been considered as an indicator for identification of bioavailability-related problems (19). Recently, the application of *in vitro* dissolution testing has been significantly amplified, as it could replace the *in vivo* bioequivalence study for some active pharmaceutical ingredients (APIs) (20).

As an effort to minimize the prevalence of substandard and counterfeit medicines, the present study was aimed

to evaluate the quality of various brands of MH tablets (500 mg) that are commercially available in the Saudi Arabian market and compare the dissolution profiles in phosphate buffer (pH 6.8) with the innovator product. We hope that the present study will provide scientific basis for consumers to select an appropriate generic substitute for the innovator tablet formulation of MH, especially in case of non-availability or cost concern.

MATERIALS AND METHODS

The innovator tablet formulation (Glucophage, Merck Sante, Lyon, France), coded as Brand A, and nine generic products, coded as Brand B–J, each containing 500 mg MH were procured from community pharmacies of Jazan, Saudi Arabia. Generic tablet brands B–J included: Formit (SPIMACO, Buraydah, Saudi Arabia), Metfor (Tabuk Pharmaceuticals, Riyadh, Saudi Arabia), Dialon (Julphar, Ras Al Khaimah, UAE), Metaphage (Kuwait Saudi Pharmaceutical Industries Co., Kuwait City, Kuwait), Omformin (National Pharmaceutical Industries, Muscat, Oman), Dimetor (Oman Pharmaceutical Products, Muscat, Oman), Glucare (Jazeera Pharmaceutical Industries, Riyadh, Saudi Arabia), Glymet (Pharma International Co., Amman, Jordan), and Riyadhformin (Riyadh Pharma, Riyadh, Saudi Arabia), respectively. Pure MH was purchased from Med Chem Express (NJ, USA). Sodium hydroxide pellets, potassium dihydrogen phosphate, methanol, and hydrochloric acid were acquired from Sigma Aldrich (USA). Spectroscopic grade potassium bromide powder was purchased from Thermo Scientific (USA). The chemicals used in this experiment were of analytical grade and used without further purification. The ultra-pure water used in the experiment was produced in-house by using Millipore water purification system (Millipore, France). Microsoft Office 2010, Sigma plot 14.0 software, and Excel 2010 were used for determination of the following parameters: area under dissolution curve (AUC), mean dissolution time, dissolution efficiency (DE), difference factor (f_1), and similarity factor (f_2). The selected generic and innovator products were subjected to weight variation, friability, and hardness tests according to the methods described by the United States Pharmacopeia (10, 21).

Extraction and Identification of Active Ingredient

Five tablets of each product were finely crushed with mortar and pestle and transferred into a beaker. Methanol (50 mL) was added to the crushed powder and dispersed properly by mechanical shaking. The mixture was sonicated for 15 min at room temperature and filtered through a Whatman filter grade 1 (GE Healthcare Life Sciences, 150 mm). The filtrate was dried

under vacuum using a rotary evaporator (Stuart, UK). The extracted MH was identified by Fourier-transform infrared (FT-IR) spectroscopy using a compressed pellet technique. Dried sample (1 mg) was triturated with 100 mg of spectroscopic grade potassium bromide and compressed into a thin transparent pellet with a suitable disc using 10 tons hydraulic pressure. FT-IR spectra of the pellet was recorded by scanning over the transmittance range of 4000–500 cm^{-1} . The procedure was repeated for all tablet brands including the innovator product and pure MH. The spectra from all tablet formulations were compared with that obtained for pure drug.

Determination of Drug Content

Drug content in each of the selected tablet formulation was determined by performing the assay analysis using the ultraviolet-visible (UV-VIS) spectrophotometer. Pure MH (100 mg) was transferred to a 100 mL volumetric flask and dissolved in 10 mL of methanol by sonication, and the volume was made up with phosphate buffer (pH 6.8). The solution was further diluted to obtain calibration standards solutions having concentrations of 2, 4, 6, 8, and 10 $\mu\text{g}/\text{mL}$. The absorbance values of these solutions were measured at 233 nm, and a calibration plot was constructed using measured absorbance on y-axis against the concentration on x-axis. The mean weight of 10 tablets from each selected product was determined and crushed into powder. The powder equivalent to 100 mg of MH was transferred to a 100 mL volumetric flask and 10 mL of methanol was added. The mixture was sonicated for 10 min, and final volume was maintained with pH 6.8 phosphate buffer. The mixture was further sonicated for 5 min and diluted to achieve a target concentration. The solution was filtered with nylon filter (0.45 μm) and absorbance was measured at 233 nm. Phosphate buffer (pH 6.8) was used as blank. The procedure was repeated for all the selected tablet brands and drug content per tablet was calculated (22). A result of 100% \pm 5% was considered as acceptable limit.

Disintegration Test

The disintegration test was performed by using USP disintegration apparatus (basket-rack assembly, Copley Scientific, Nottingham, UK). The test was carried out for all brands included in this study by placing one tablet in each of the six tubes. The tablets were enclosed in a perforated plastic disc to avoid floating on the surface. Each assembly along with the test tablets was placed in 1000-mL vessels containing 900 mL water maintained at 37 \pm 2 $^{\circ}\text{C}$. The basket assembly was operated vertically on its axis at a speed of 30 cycle/min in such a way that

the tablets remained 2.5 cm beneath the surface of the water and 2.5 cm above the bottom of the vessel during the upward and downward movement of the shaft. Tubes were examined regularly to check for complete disintegration (23).

Dissolution Test

The dissolution test was performed for innovator tablets and all selected generic tablet brands using USP apparatus 2 (paddle) dissolution apparatus. One tablet was placed in each of the six vessels containing dissolution medium (phosphate buffer pH 6.8, 900 mL) maintained at 37 \pm 2 $^{\circ}\text{C}$. The apparatus was operated at a fixed rotational speed of 50 rpm. A sample of 5 mL from each vessel was withdrawn at fixed time intervals (10 min) for 60 min and was compensated by immediately replacing with fresh dissolution medium after withdrawal. The samples were filtered with a 0.45- μm nylon filter and further diluted 100 times with the buffer. The absorbance values of the diluted samples were recorded at 233 nm using a UV spectrophotometer. The drug released at each time of sampling was calculated from a standard calibration curve prepared by plotting the concentrations of pure MH in calibration standards against their respective absorbance values. Furthermore, the dissolution profile curve was prepared by plotting percentage release of drug versus time of sample withdrawal. As per USP, the tablets were considered to comply with the standards if at least 80% of the drug released in 30 min (14, 24). The difference factor (f_1) and similarity factor (f_2) for all generic products were determined with reference to the innovator product. The f_1 value is the variation between two drug release curves, whereas, f_2 represents the similarity in the percent drug release between the two dissolution curves at each time point. The values of f_1 and f_2 were used to analyze the dissolution profiles of the test products. A generic product with a value of f_1 between 0–15 and f_2 in the range of 50–100 is considered to have a similar drug release profile as the innovator product (25, 26).

The drug release is also characterized by DE. It is considered as a non-comparative parameter of dissolution kinetics. DE is defined as the area under the drug dissolution curve (AUC) up to time t (in minutes), expressed as a percentage of the area of the rectangle described by 100% dissolution of the product label value in the same amount of time (25). The DE for MH was determined as the ratio of $\text{AUC}_{0 \rightarrow t}$ ($t = 60$ min) and the total area of the rectangle (TR_{100}). The area of rectangle was obtained from the multiplication of abscissa ($t_{60} = T$) and ordinate (100% release = R_{100}) of release (%) versus time profile (25, 27).

RESULTS AND DISCUSSION

The results of weight variation, hardness, friability, and disintegration tests of innovator and generic products of MH tablets (500 mg) are presented in Table 1. Weight variation of the tablet formulation may be due to a variety of reasons and can directly affect the amount of active ingredient in the finished products, which results in poor content uniformity in the dosage forms. To ensure uniform dose, the weight variation among the tablets should be minimum. This may prevent the chance of receiving overdose or underdose tablets, which could result in unpredictable therapeutic effects. The products were considered to pass the weight variation test if the individual weights of not more than 2 tablets (out of 20) were deviated by $\pm 5\%$ of the average weight. All selected brands of MH tablets were found to comply with the acceptance criteria and hence, were within the USP-NF specifications.

Differences in tablet hardness among the brands may be due to different properties of the excipients used in the manufacturing processes. Hardness is a measure of the crushing strength of the tablets and may affect the rate of tablet disintegration and drug release. The mean hardness values of the tested generic formulations were in the range of 68.65–177.79 N. The lowest mean hardness (68.65 N) was recorded for product B, whereas

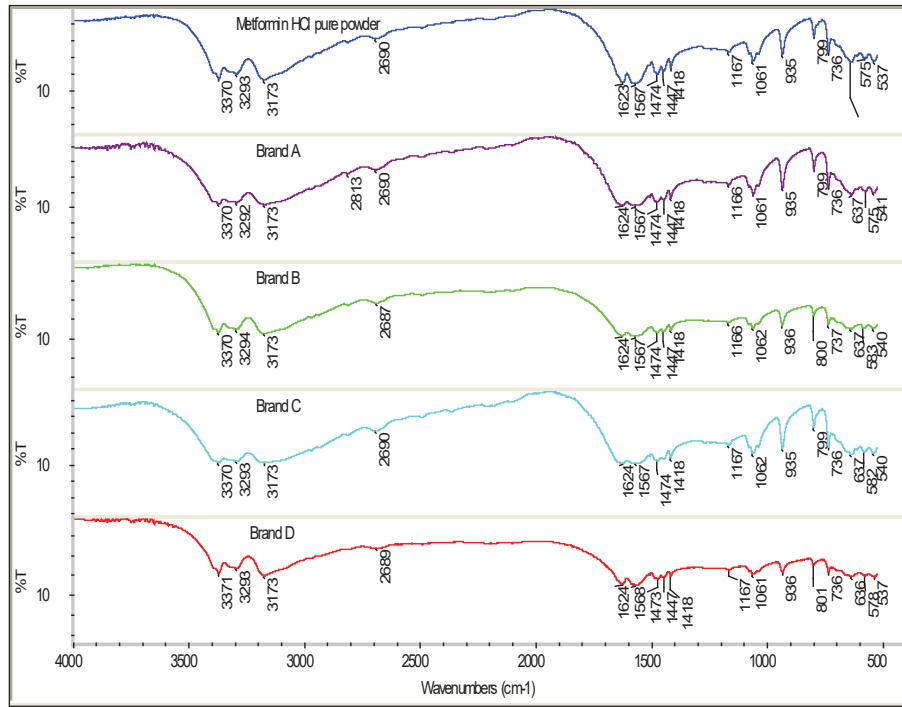
the product H was able to withstand the highest mechanical force (177.79 N) applied to crush the tablets. However, none of the products, except product B, could satisfy the in-house criteria of 39.23–68.65 N. Results revealed that all products could pass the lower limit, and only one product met the limit of maximum hardness. Friability testing was done to evaluate the capacity of a tablet to withstand abrasion during handling, packaging and transportation. Excess friability of a tablet formulation may result in weight loss, affecting the therapeutic response, in addition to general appearance and patient acceptability. Maximum friability was recorded for product B (0.363%), which is most likely to lose particles during handling, while the least friable product was found to be product D (0.030%). Overall, the weight loss recorded for all the tested products were below 1%, which complies with USP-NF specifications.

Identification of active ingredient in generic products was established by comparing the FT-IR spectrums with that of the pure MH. The spectra of all products were completely superimposed with that of the pure drug, which confirms the presence of MH as an active ingredient in all tested tablet formulations. FT-IR spectra of pure MH, the innovator product (brand A), and the selected generic products (brands B-J) are shown in Figure 1.

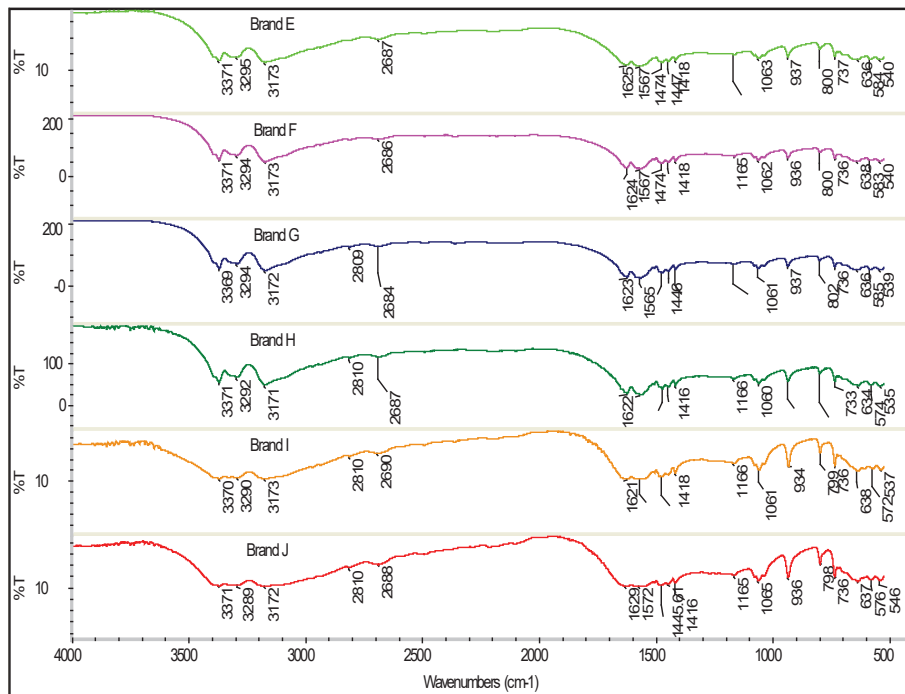
Table 1. Weight Variation, Hardness, Friability, and Disintegration Time of Tested Tablets Containing 500 mg MH

Product	Weight, mg (n = 20)	Hardness, N (n = 10)	Friability, % (n = 10)	Disintegration Time, min (n = 6)
A*	531.34 \pm 6.49	129.45 \pm 3.43	0.038 \pm 0.01	8.24 \pm 0.43
B	524.98 \pm 4.62	68.65 \pm 6.54	0.363 \pm 0.03	9.09 \pm 0.28
C	545.20 \pm 6.82	94.18 \pm 6.43	0.055 \pm 0.02	8.50 \pm 0.21
D	650.81 \pm 9.76	126.01 \pm 5.66	0.030 \pm 0.01	6.34 \pm 0.25
E	555.46 \pm 5.40	93.62 \pm 4.28	0.288 \pm 0.07	8.05 \pm 0.46
F	600.30 \pm 4.34	125.56 \pm 2.50	0.116 \pm 0.04	7.54 \pm 0.38
G	557.64 \pm 3.27	87.00 \pm 2.35	0.079 \pm 0.01	7.89 \pm 0.44
H	525.22 \pm 4.86	177.79 \pm 3.32	0.053 \pm 0.02	14.45 \pm 0.33
I	589.43 \pm 3.21	85.85 \pm 4.18	0.121 \pm 0.04	10.43 \pm 0.52
J	566.86 \pm 2.51	93.39 \pm 3.29	0.084 \pm 0.03	9.32 \pm 0.42

*Innovator brand product. Data are expressed as mean \pm SD. MH, metformin hydrochloride.



A



B

Figure 1. FT-IR spectra of pure MH and MH extracted from tablet dosage forms of innovator (brand A) and test generic brands (B–D) (A) and (E–J) (B). FT-IR: Fourier-transform infrared; MH: metformin hydrochloride.

The percentage of the drug content for the selected products is shown in Figure 2. The assay results for all products were in the range of 96.52%–103.37%, which meets USP-NF acceptance criteria of $100 \pm 5\%$ per tablet. The amount of drug content was estimated after comparing with calibration curve. The correlation coefficient (R^2) was 0.9999, and the regression equation was obtained as, $y = 0.0809x + 0.0056$. Disintegration time may directly influence the MH release from tablets and hence, MH bioavailability in tablet formulations. In this study, all the selected tablet brands passed the disintegration test according to the USP-NF specifications for film coated tablets, as all tablets were completely disintegrated within 30 min (Table 1). Among the tested products, the fastest disintegration was recorded for product D (6.34 min), and product H exhibited slowest disintegration rate (14.45 min).

Dissolution Profile

The dissolution profile of a drug product is of extreme importance in predicting the bioavailability and in vivo drug release pattern (28, 29). Metformin belongs to Class 3 as per Biopharmaceutics Classification System (BCS) and according to USP specifications, at least 80% of the drug should be released in 30 min at 50 rpm. The observed dissolution profiles of generic products were compared with the innovator product to examine the pharmaceutical similarity of these products. The percentage of metformin released from the innovator (A) and generic (B–J) formulations at the 30-min time point was: 91.86%, 89.37%, 91.09%, 96.65%, 93.91%, 98.43%, 82.71%, 85.37%, 85.89%, and 86.12%, respectively. The dissolution test results revealed that all tested products released more than 80% of drug at 30 min time point and complied with the USP-NF specifications. Therefore, these products may be considered as pharmaceutically equivalent on the basis of their in vitro drug release profiles. However, the small differences in the drug release from one product to another may be due to the differences in the amount and types of excipients used in the manufacturing process of these formulations (30). The dissolution profiles of all the generic and innovator products is shown in Figure 3. The mean drug content measured for product F was 96.52% of the label claim, which is significantly lower than other tested generic formulations (100.66–103.37%) in this study. However, the drug release of product H was close to 100% (98.43%) in 30 min. The possibility of differences between drug content and release of drug in dissolution test may be explained on the basis of the type of tablets selected for the test. In this study, the tablets were randomly selected for each test. Hence, there is a possibility that the tablets

selected for drug content analysis contained less drug than those selected for dissolution study. However, the results of both tests satisfied the acceptance criteria set by USP-NF.

The difference factors (f_1) for all the tested generic products were below 15 and the similarity factors (f_2) were in the range 50–100, except product H ($f_2 = 43.89$), as shown in Table 2. The f_1 and f_2 values were calculated using the dissolution profile of individual products. These values show that in vitro drug release profiles of the tested products are similar to the innovator product, except product H, which did not achieve the US-FDA recommendation of $f_2 \geq 50$ (31). Among the tested products, dissolution profiles of products B and E were the most similar to the reference product as these products have exhibited lowest f_1 (4.08 and 2.47, respectively) and highest f_2 values (67.83 and 77.68, respectively). On the other hand, product H had the highest f_1 (12.26) and lowest f_2 (43.89) values among the tested generic products. The low f_2 value of product H suggests that the dissolution profile was not similar to the innovator product; however, product H did comply with the USP criterion of $\geq 80\%$ drug release in 30 min.

Determination of the DE is another way to evaluate and compare the drug release pattern from several products. The DE of a product is directly related to the actual amount of active ingredient dissolved in the solution and it provides better prediction of in vivo drug release. Calculation of DE employs area under dissolution curve over a time period. The test products are considered to be similar when their DE values are close to that of reference product (within $\pm 10\%$ is often acceptable) (26). DE values of all generic products selected in this study ranged from 74.2% to 88.0%, which were within $\pm 10\%$ range of the innovator product (81.4%), as shown in Table 2. The highest DE value was recorded for product D (88.0%), and the lowest value (74.2%) was observed for product H. Moreover, mean dissolution time was also estimated to better understand the dissolution profile of the tested products. Mean dissolution time of all tested products was similar to that of innovator product (9.69 min). The product D showed highest value (10.38 min) and product H had the lowest value (8.55 min).

CONCLUSION

Commercially available immediate-release MH tablets (500 mg) in the Saudi Arabian market were subjected to several quality control tests. All selected products were found to comply with USP-NF specifications with respect to weight variation, friability, disintegration time, and

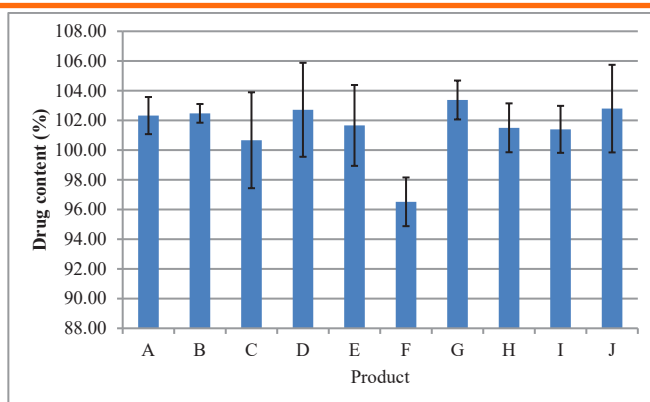


Figure 2. Drug content (mean ± SD) of different brands of metformin hydrochloride tablets. Brand A is the innovator product; brands B–J are generic products.

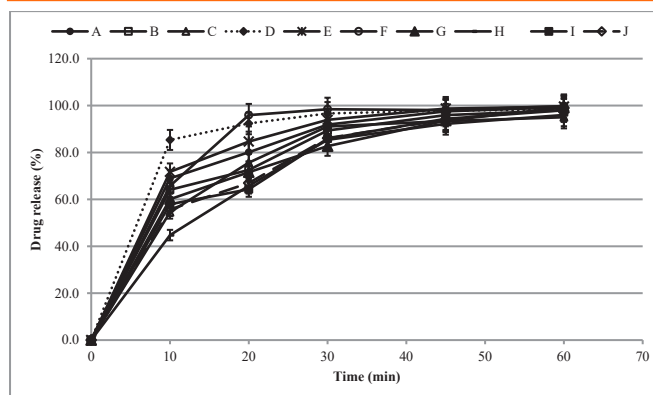


Figure 3. Dissolution profiles (mean ± SD) of metformin hydrochloride tablets in phosphate buffer pH 6.8. Brand A is the innovator product, brands B–J are generic products.

Table 2. Parameters for Drug Release Including of Tested Tablets Containing 500 mg MH

Product	AUC	MDT, min	DE, %	Difference factor (f_1)	Similarity factor (f_2)
A*	4846.7	9.69	81.4	0	100
B	4656.9	9.31	79.2	4.08	67.83
C	4553.9	9.10	79.9	6.41	56.71
D	5190.2	10.38	88.0	7.92	51.18
E	4965.4	9.93	83.1	2.47	77.68
F	5065.9	10.13	84.6	6.07	55.24
G	4498.5	8.99	75.6	6.98	57.28
H	4275.4	8.55	74.2	12.26	43.89
I	4446.4	8.89	75.6	8.51	51.80
J	4456.3	8.91	75.1	8.21	52.47

*Innovator product. Dissolution medium was phosphate buffer pH 6.8. MH, metformin hydrochloride; AUC, Area under the dissolution curve; MDT, Mean dissolution time; DE, dissolution efficiency.

drug content analysis. The dissolution profile for eight out of nine generic products was similar to that of innovator product and satisfied the USP-NF specifications. MH release from all tested products in phosphate buffer (pH-6.8) in 30 min was more than 80% of the labeled claim at 50 rpm paddle speed. Generic products B and E displayed the most similar dissolution profiles and DE values in comparison to the innovator product. These two products also had lowest f_1 and highest f_2 values. Although generic product H had an f_2 value < 50; it passed dissolution test specifications for USP and exhibited acceptable DE compared to the innovator product. Therefore, all generic products tested are considered to be acceptable substitutes for the innovator brand in case of unavailability and when the cost is a concern. However, in vivo bioequivalence study may be needed for final

comment on the similarity of efficacy of these generic formulations.

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CONFLICTS OF INTEREST

The authors disclosed no conflicts of interest related to this article.

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