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SHORT COMMUNICATION article

Evaluation of some metformin hydrochloride brands available in the Libyan market

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Abstract: Various quality control tests are employed for solid dosage forms such as uniformity, dissolution and drug contents to assess their pharmaceutical equivalence. The objective of the current study was to assess and contrast five distinct metformin hydrochloride brands that are offered for sale in the Libyan market. The physicochemical equivalence of the five brands of metformin hydrochloride tablets (500 mg) was determined through the evaluation of official and non-official standards according to the USP including uniformity of weight, friability, hardness, dissolution rate and drug content. All the examined brands available in the Libyan market passed the official weight variation, friability, dissolution and disintegration tests and were equivalent. The friability test was found within the specified limit. All the formulations were disintegrated within 09-15 min. The tested brands were non-equivalent to the innovator Glucophage® according to their dissolution evaluation. The percentage content of the active ingredient of five brands of metformin tablets showed values within the monograph specifications (95%-105%). In conclusion, all the five brands available in the Libyan market that were evaluated in this study cannot be substituted with the innovator product in clinical practice.

Introduction

Metformin is the first-choice oral anti-hyper-glycemic agent from the biguanide class for the treatment of type II diabetes with a low risk of hypoglycemia, especially in obese patients and those with normal kidney function [1, 2]. Metformin is also used in the treatment of polycystic ovary syndrome (PCOS). In addition, metformin is used as a second-line drug for infertility in those with PCOS [3]. Metformin works by decreasing the production of glucose by the liver, by increasing insulin sensitivity of the body tissues [1, 4]. Historically, metformin has been discovered in 1922 [5]. In the 1950s, French physician Jean Sterne began the study of metformin in humans. It was introduced as a medication in France in 1957 and the United States in 1995. It is on the World Health Organization's list of essential medicines [WHO-LEM]. In 2019, it was the fourth-most commonly prescribed medication in the United States, with more than 85 million prescriptions. The American Diabetes Association (ADA) and the American College of Physicians recommend metformin as a first-line agent to treat type II diabetes [6]. It is considered superior to sulphonylurea because it causes no weight gain and it has rarely been associated with hypoglycemia [7, 8]. Moreover, it is safer than thiazolinedidiones because it offers a cardio-protective effect instead of cardio-toxicity [9, 10]. Metformin is highly soluble in water (about 300 mg/ml) with poor permeability and as such it is classified as a BCS class 3 [11]. Metformin

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is provided as 500 mg, 850 mg and 1000 mg tablets, either as immediate release (IR) or extended-release (ER) formulations. Although Glucophage® is a cutting-edge product that continues to stand out in terms of quality and effectiveness over time, it can be expensive for some patients. In general, patients may choose generic products due to the high cost of some branded products. This pattern has lessened the increase in pharmaceutical waste, especially in low- to middle-income countries. However, generic substitution should take into account the overall cost-effectiveness of pharmacological treatment and the initial treatment cost. As a result, the standard for generic substitution was established. When the generic product exhibits bio-equivalence and therapeutic equivalence with the innovator, interchangeability is allowed [12]. To assess the physicochemical characteristics of drug's formulations, many tests are utilized 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 [13, 14]. Thus, the present study aims to evaluate and compare five different metformin tablet brands available in the Libyan market by applying official and unofficial compendia methods following the USP.

Materials and methods

Metformin hydrochloride tablets with a label strength of 500 mg were purchased from local pharmacy stores in Al Bayda City, East of Libya. All the tests were performed within product expiration dates. Metformin hydrochloride powder was purchased from CID company pharmaceuticals, Giza, Egypt. The reagents used were potassium dihydrogen orthophosphate and sodium hydroxide pellets as well as freshly prepared distilled water. All the reagents used were of analytical grade. Study samples were coded as shown in **Table 1**.

Table 1: Commercial metformin hydrochloride tablets available in Libyan market

Brand code	Brand name	Manufacturer, Country
A	Glucophage®	Merck Santé s.a.s, France
B	Metforal®	Laboratori GUIDOTTI S.p.A., Italy
C	Metformin®	BRISTOL, UK
D	Formit®	Dar Al-Dawa, Jordan
E	Glucophage®	MINAPHARM Merck, Egypt

Visual inspection: The diameter and thickness of the five tablets from each brand were measured and the average value was taken and the standard deviation was calculated.

Friability test: Twenty tablets of each brand were weighed and subjected to abrasion using a Roche Friabilator at 100 revolutions for four min. The tablets were deducted and weighed again then the percentage of weight loss was recorded. The friability of the tablets was then calculated using the following expression:

$$\text{Percentage of friability} = [(\text{Initial weight} - \text{Final weight}) / \text{Initial weight}] \times 100$$

Hardness test: The crushing strength of the tablets was determined using ERWEKA (Heusenstamm, Germany) hardness tester. Sample tablets of ten of each brand were taken. The tablet was placed between the spindle of the ERWEKA hardness tester machine until the tablet broke and the pressure required to break the tablet was then read off the machine and recorded.

Uniformity of weight: Twenty tablets of each brand were weighed individually using a digital analytical balance. The average weight was determined and the percentage of deviation of the individual tablet from the mean was determined.

Dissolution rate determination: Dissolution rates in the stimulated intestinal fluid pH 6.8 were determined using ERWEKA DT600 dissolution apparatus (Heusenstamm, Germany). The dissolution medium used was

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a 0.68% w/v solution of potassium dihydrogen phosphate, adjusted to pH 6.8 by the addition of 1.0 M sodium hydroxide. One tablet was put in each of the compartments of the apparatus using 900 ml of medium at 37 ± 0.5 °C. The paddle was rotated at 100 rpm. Ten milliliters of the sample were drawn at intervals of 5, 15, 30 and 45 min with 10 ml bulb pipette. A fresh a 10 ml dissolution medium was replaced after each sampling to maintain the sink conditions. Each withdrawn sample was filtered through the Whatman filter and analyzed for metformin after appropriate dilution by UV-visible spectrophotometer at λ_{max} 232 nm. The concentration was determined against a standard solution having a known concentration of metformin hydrochloride in the same medium. The percentage of drugs released is calculated using the given formula:

$$\text{Percentage of drug release} = \frac{Amount\ of\ drug\ released\ (mg/ml) \times 100}{500(drug\ content\ in\ a\ tablet)}$$

Assay of metformin hydrochloride tablet: This test is done to find out the actual amount of active ingredient present in the tablet and whether it is the same as the labeled amount. Twenty tablets from each brand were weighed and finely powdered then an accurately weighed portion of powder equivalent to 100 mg metformin hydrochloride was transferred to a 100 ml volumetric flask, 70 ml of distilled water then was added and shacked mechanically for 15 min then diluted to the volume and filtered. Ten ml of the filtrate was transferred to 100 ml volumetric flask and further diluted to a 100 ml with distilled water. Then, 10 ml was transferred to another 100 ml volumetric flask and the volume was completed with distilled water. The absorbance of assay preparation was determined at λ_{max} 232 nm with GENESYS 10S UV-visible spectrophotometer (Thermo Fisher Scientific, USA) using water as a blank. The quantity in mg of metformin hydrochloride in the portion of tablet taken was calculated by the formula: 10 C (Au/As), in which C is the concentration of metformin hydrochloride in µg per ml and Au and As is the absorbance obtained from assay preparation and standard preparation, respectively.

Statistical analysis: The dissolution profiles were estimated by plotting the percent drug released versus time and were compared using a model independent approach, similarity factor f2 as described by the US FDA and presented in the following equation: $F2 = 50 \log \{[1 + 1/n\sum^{n=1}(R_t - T_t)^2]^{-0.5} \times 100\}$. Where R_t and T_t are the percentage of dissolved at each time point for reference (Innovator brand, brand A) and test products, respectively. If the f2 value is greater than or equal to 50, it shows the sameness or equivalence of the two dissolution profiles. If f2 is less than 50 that means the dissolution profile is different from the innovator product and hence not interchangeable [14].

Results

The physicochemical properties of metformin hydrochloride tablets including weight variation, hardness and friability as well as thickness and diameter are shown in **Table 2**. All the five brands show very similar findings. However, the hardness test of the average of five tablets from each brand revealed that there is a three-time difference between the brands (brand code D is stronger than brand E by three times and brands A and E are equal in hardness test as brands B and C are also equal (32.92 and 31.89, respectively). The drug content findings are also shown in **Table 2** which shows almost within 100±5.0 (%) for the investigated brands. **Figure 1** illustrates the dissolution profile of the innovator and the four test metformin hydrochloride generics. The dissolution curve for each brand was the average of three tablets. The dissolution rate findings of the five brands revealed some variable releases, as the fastest release showed with brand A within 5 min., but, other brands (B & E) showed the slowest release. In contrast, others (C & D) were in between. The release of metformin from all tablets was immediate, and more than 70.0% of the drug had been released within 45 minutes.

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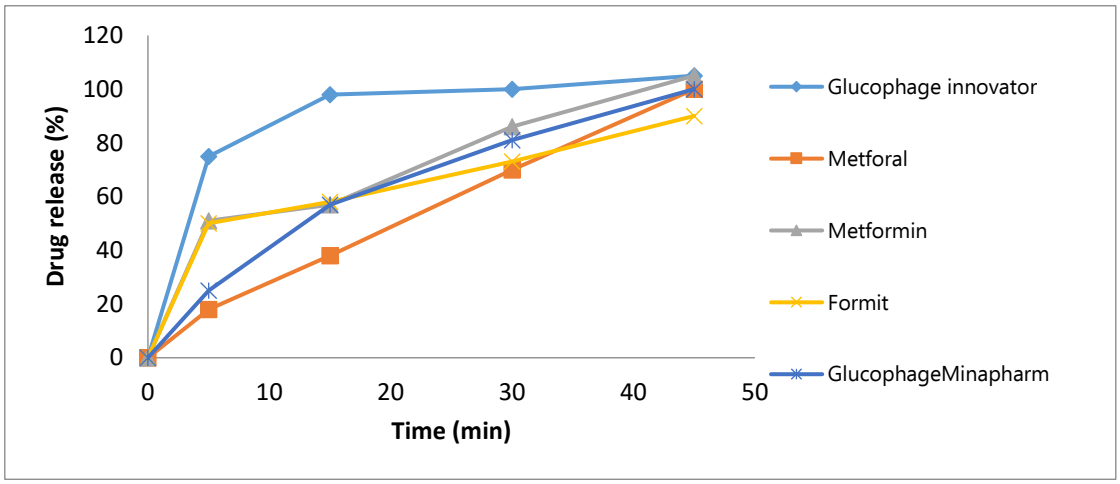
Table 2: Physicochemical properties of metformin hydrochloride tablet available in Libya

Brand code	Uniformity of weight (gm), mean ± SD	Hardness (kg/cm^2) ± SD	Assay (%)	Diameter (mm) mean ± SD	Thickness (mm) ± SD	Friability (%)
A	0.525 ± 0.005	16.00 ± 1.50	103	11.0 ± 0.20	03 ± 0.02	0.04
B	0.555 ± 0.107	32.92 ± 1.72	095	11.0 ± 0.05	03 ± 0.04	0.01
C	0.587 ± 0.006	31.89 ± 6.42	099	10.0 ± 0.10	05 ± 0.01	0.02
D	0.537 ± 0.005	49.72 ± 0.10	105	10.8 ± 0.08	03 ± 0.20	0.01
E	0.534 ± 0.010	14.24 ± 2.95	104	12.0 ± 0.30	03 ± 0.02	0.01

Figure 1: Dissolution profile of metformin hydrochloride tablet



Discussion

In this study, various pharmacopeial quality control tests, involving the evaluation of uniformity of weight, friability, hardness and dissolution tests as well as drug content determination, were employed for five brands of metformin hydrochloride tablets available in the Libyan market to assess their pharmaceutical equivalence. The weight uniformity for the five brands of metformin hydrochloride tablets gave values that comply with the USP specification with a deviation less than 5.0% from the mean value (maximum deviation value 0.107). The strength of tablets was evaluated using an ERWEKA hardness tester. All the tablets failed this non-official test in compliance with USP criteria (4-6 kg). Brand E had the minimum hardness and brand D had the maximum hardness. Hardness values of brands A, B and C were 16, 32 and 31, respectively. A previously published study on different metformin hydrochloride brands in Saudi Arabia showed that all brands failed to have a good crushing strength (7-25 kg) [14]. Another research showed that all tested brands failed too (15-26 kg). This outcome may be explained by the fact that all metformin tablets include a film coating to lessen their gastrointestinal side effects. The variation in hardness between the batches may also be explained by the various excipients included in each generic. The solubility of metformin tablets was unaffected by their hardness [15]. The friability test is a fundamental test designed to examine whether tablets have a good withstand strength for transportation, packaging, shipping and coating. For all the brands, the friability was less than 0.10%. Values below 1.0% are regarded as evaluation characteristics that are highly satisfactory (**Table 2**). Friability of Glucophage® was evaluated and found to be higher than other generics, recording 0.04%. The rest of the generics had lower friability percentages ranging from 0.01% to 0.02%. Our tested samples passed this test with a percentage friability <01.0%. The assay technique was employed to demonstrate that the product batch's level of active component is fairly near what the label claims. The assessment of the percentage of active components in five different brands of metformin hydrochloride tablets showed values within the monograph specification (95.0%-105.0%) of a stated amount of metformin as illustrated in this study. A comparative study in Libya evaluated five different Metformin hydrochloride

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brands that were commercially available in the Libyan drug market and it was found that all the available brands in the local market of Libya were, within the specified quality range and can be interchanged of found any non-compliance due to cost issue [17]. Thus, test methods must be properly established through studies during formulation and manufacturing process design and clinical development if one is to obtain meaningful results and interpret dissolution data. These conditions must be met to fully comprehend the biopharmaceutical and physical properties of the drug products.

These findings do not necessarily point to a failure on the part of the regulatory authority's control laboratories, but rather to the inadequacy of the BP 2007 dissolution standards for identifying variations in the performance of the different commercial tablets of metformin [18]. Dissolution was another studied important quality control parameter directly related to the absorption and bioavailability of drugs [18]. Since metformin is a class III medication, its dissolution is crucial for drug absorption. Metformin must be solubilized in the aqueous environment of the gastrointestinal tract to be absorbed [19]. Dissolution testing of solid oral dosage forms is among the most significant control tests for ensuring product uniformity and batch-to-batch equivalence [20]. According to the current study, the release of metformin from all tablets was immediate, and more than 70.0% of the drug had been released within 45 min as shown in this study. The study's findings showed that every brand of conventional release tablet passed the USP 32 general specifications criterion for dissolution rate. This study shows clearly that different products have different dissolution profiles. To judge whether these differences in dissolution profiles were significant, all dissolution profiles were compared to that of the innovator (Glucophage®) brand A using the similarity factor (f2) value. The obtained values of f2 were: 18, 27, 27 and 24 for brand B, brand C, brand D and brand E, respectively. Similarly, factor analysis between the four marketed tablets and the innovator brand A for the release of metformin showed f2 factor of less than 50 for all brands. The higher the f2 values, the more similar the dissolution profiles, so, f2 <50 represented non-similar profiles of four marketed brands B, C, D, E and the innovative brand A. So, all studied brands were found nonequivalent in their dissolution profile to the innovator (brand A). A previous study evaluated differences in eight brands of metformin hydrochloride marketed in the Nigerian market. The results revealed that the release of metformin from five generic brands was nonequivalent to the innovative brand. In all the brands tested only two brands met the BCS bio-waiver criteria. The values of their similarity factor revealed that only four brands have a similarity factor of more than 50. So, they are equivalent according to their dissolution profiles to innovators [16]. In a study of four generic brands of metformin tablets available in the Jordanian market, the results showed that all the tested brands were in accordance with the pharmacopeial specifications [18]. However, dissolution profile comparisons, which are not required by British Pharmacopoeia, revealed potentially serious differences in the performance of the studied products. According to similarity factor calculations, only one generic product was found to have a similar dissolution profile to the originator (f2 >50) [18]. Test methods must be properly established through studies during formulation and manufacturing process design and clinical development if one is to obtain meaningful results and interpret dissolution data. These conditions must be met to fully comprehend the pharmaceutical and physical properties of the drug products. These findings do not necessarily point to a failure on the part of the regulatory authority's control laboratories, but rather to the inadequacy of the BP 2007 dissolution standards for identifying variations in the performance of the different commercial tablets of metformin [18].

Conclusion: The interchangeability of the generic brands available in the Libyan market cannot be guaranteed due to variations in the way the drug is released from the tablet, which may result in differences in bioavailability. Thus, in-vivo bioavailability studies of the various brands of metformin are therefore recommended. This study supports the need for activation of the regulatory rules with an emphasis on post-marketing evaluation of pharmaceutical products.

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