A Comparative Study for Evaluation of Different Brands of Metformin Hydrochloride 500 Mg Tablets Marketed in Saudi Arabia

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Abstract: The aim of the present study was the evaluation and comparison between six different Metformin hydrochloride brands which are commercially available in the Saudi Arabia market. The physicochemical equivalence of six brands of Metformin hydrochloride tablets were determined through the evaluation of both official and non-official standards according to the USP pharmacopoeia including uniformity of weight, friability, hardness, disintegration, dissolution rate and drug content. A variation of the concept of dissolution efficiency (DE), known as predicted availability equivalent (PAE), was used to predict the likely in vivo bioavailability. All the tested six brands were bioequivalent and complying with the official tests for weight variation, friability, disintegration and dissolution tests. The friability test was within the specified limit. All formulations were disintegrated within 15-30 min. The tested brands were identical according to their dissolution evaluation. Only Glucare® was nonequivalent to the innovator Glucophage®. The percentage content of active ingredient of six brands of Metformin tablets showed values within the monograph specifications (95-105%). All the six brands evaluated in this study could be considered biopharmaceutically and chemically equivalent and therefore they can be substituted with the innovator product in clinical practice except Glucare®. Therefore, patients can safely switch from one brand to another.
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1. Introduction

Metformin HCl is an oral anti-diabetic drug from the biguanide class used mainly to treat type 2 diabetes mellitus. Metformin hydrochloride works by improving the body's sensitivity to insulin, allowing it to use glucose in the normal way. It is the first-line drug of choice for the treatment of type 2 diabetes, particularly in overweight and obese people and those with normal kidney function. Metformin hydrochloride is also being used increasingly in polycystic ovary syndrome (PCOS) which is a syndrome of ovarian dysfunction and hyperandrogenism [1]. Evidences suggest that insulin resistance and resulting hyper insulinaemia play a central role in the pathogenesis of the syndrome. Metformin, an insulin sensitizer, not only improves hyperandrogenism but also improves ovulation as well as pregnancy rates in patients with PCOS, non-alcoholic fatty liver disease (NAFLD) and premature puberty [2]. Metformin was first described in the scientific literature in 1922, by Emil Werner and James Bell, as a product in the synthesis of *N*, *N*-dimethyl-guanidine free user [3]. French physician Jean Sterne published the first clinical trial of Metformin as a treatment for diabetes. It was introduced to the United Kingdom in 1958, Canada in 1972, and the United States in 1995. Metformin hydrochloride is now believed to be the most widely prescribed anti-diabetic drug in the world; in the United States alone, more than 48 million prescriptions were filled in 2010 for its generic formulations [4, 5].

Drug products that are biopharmaceutically and chemically equivalent must be identical in their quality, strength, purity and active ingredient release profile. They must to be in the same dosage form and intended for the same route of administration [6]. Dissolution testing of drug product is an important criterion in assessing the quality control to monitor batch to batch consistency of drug release [7]. The variations in the drug release among some generics indicate deficiency in the entire drug formulation and the delivery system. Dissolution rate determination used also for prediction of in-vivo bioavailability in most oral preparations [8, 9].

Manufacturing methods and the excipients used in the production processes could contribute to the quality and release skillfulness of medicament. Therefore, to ensure the requisite quality, drug manufacturers are required to examine their products during and after manufacturing and at various intervals during the shelf life of the product [10]. Accordingly, to ensure that the generic and branded drugs products are pharmaceutically equivalent cannot be overemphasized. So, the selection of one product from several generic drug products of the

same active ingredients is concerned important for healthcare workers [6].

Metformin hydrochloride is the most popular anti-diabetic drug in the Saudi kingdom as well as all over the world. As reported by the annual statistical studies (MOH annual statistical book 2010) more than 25% of population is diabetic in Saudi Arabia. Accordingly, the use of Metformin hydrochloride tablets needs to monitor and ensure the quality of the various brands commercially available in the Saudi market in order to assess their quality control. Additionally, if these brands are interchangeable and patients can safely switch from one brand to another or not and which is the best economically. Numerous Metformin tablets brands in Saudia Arabia drug market today make a problem of alternative generic brands for physician and the pharmacist.

The present study aimed to evaluate and compare between different six Metformin tablets brands applying both official and unofficial compendia method following the USP pharmacopeia.

2. Experimental

2.1. Materials

Metformin hydrochloride brands having label strength of 500 mg (Table 1) were purchased from a retail pharmacy in Riyadh city, Saudi Arabia. All tests were performed within product expiration dates. Metformin HCL powder was a gift of (CID co. pharmaceuticals, Giza, Egypt). The reagents used were potassium dihydrogen orthophosphate (WINLAB chemicals, UK) and sodium hydroxide pellets (Poole BH15, UK). All reagents used were of analytical grade. Distilled water was used throughout the work.

Table 1: List of the tested commercial Metformin hydrochloride tablets available in Saudi market

Tablet	Brands	Manufacturer
A	Glucophage®	Merck santé s.a.s, France
B	Formit®	SPIMACO, Saudia Arabia
C	Glucare®	Jazeera Ph. Industries, Saudi Arabia
D	Dialon®	Julphar, U.A.E
E	Metaphage®	Kuwait Saudi ph.industries co., Kuwait
F	Metfor®	Tabuk ph. Manufacturing co., Saudi Arabia

2.2. Prepared reagents

Stimulated intestinal fluid pH 6.8 was prepared by dissolving 34 grams of potassium dihydrogen orthophosphate in distilled water in 2-Lvolumetric flask. The pH was adjusted by 1M sodium hydroxide which prepared by dissolving accurately weighted 40 grams of sodium hydroxide pellets in1000 ml distilled water in a volumetric flask. Then the mixture was diluted to volume in a 5-L volumetric flask [11, 12].

2.3. Visual Inspection

The shape, size, and color of the different brands of tablets were examined visually.

The diameter and thickness of 5 tablets from each brand were measured and the average was taken and standard deviation was calculated.

2.4. Friability Test

Twenty tablets of each brand were weighed and subjected to abrasion using a Roche friabilator at 100 revolutions for 4 min. The tablets were dedusted and weighed again then percent of weight loss was recorded. The friability of the tablets were then calculated using the following expression

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

2.5. Hardness Test

The crushing strength of the tablets was determined using ERWEKA (Heusenstamm, Germany) hardness tester. Sample tablets (10) of each brand were taken, a tablet was placed between the spindle of the ERWEKA hardness tester machine until the tablet breaks and the pressure required to break the tablet was then read off the machine and recorded.

2.6. Uniformity of Weight

Tablets (20) of each brand were weighed individually using a digital analytical balance. The average weight was determined and the percentage (%) deviation of the individual tablets from the mean was determined.

2.7. Disintegration Test

Tablet disintegration was determined at 37 °C using ERWAKA (Heusenstamm, Germany) disintegration apparatus. The disintegration time of randomly selected six tablets of each brand was determined in distilled water. The disintegration time was taken to be the time no granule of any tablet was left on the mesh.

2.8. Dissolution Rate Determination

Dissolution rates in the stimulated intestinal fluid pH 6.8 were determined using ERWEKA DT600 dissolution apparatus (Heusenstamm, Germany). One tablet was put in each of the compartments of the apparatus using 1000 mL of medium at 37 ± 0.5 °C. The basket was rotated at 100 rpm. Ten milliliters of sample was drawn at intervals of 10, 20, 30, 45 and 60 minute with 10 mL bulb pipette. A fresh 10 ml dissolution medium was replaced after each sampling to maintain the sink conditions.

Each of the withdrawn sample was filtered with syringe filter 0.45µm, the filtrate diluted. The absorbance was measured at λ max 233nm using UV-visible spectrophotometer. The concentration was determined against standard solution having a known concentration of Metformin hydrochloride RS in the same medium. The percentage of drug released is calculated using the given formula.

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

The difference factor (f1) and similarity factor (f2) was calculated for each local brand respect to the reference brand (Glucophage®) equation (1) and (2), respectively.

The percentage of drug released from Glucophage® as an innovative was compared with the percentage of drug released from each brand individually using the next formulas:

$$f_1 = \{[\sum_{t=1}^{n} |R_t - T_t|] / [\sum_{t=1}^{n} R_t]\} \times 100 \quad \ldots\ldots(1)$$

$$f_2 = 50 \times \log \{[1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100\} \quad \ldots\ldots(2)$$

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

The similarity factor should be between 0 and 100. It is 100 when two comparative groups of reference and test are identical and approaches 0 as the dissimilarity increases, factor of 50-100 ensures sameness of two products. Difference factor of 0-15 ensures minor difference between two products.

If the f2 value is greater than or equal to 50 it shows 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 hence not interchangeable [13].

2.9. Assay of Metformin hydrochloride tablets

The test for assay 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.

20 tablets from each brand weighed and finely powdered then an accurately weighed portion of powder equivalent to 100mg Metformin hydrochloride were transferred to a 100ml volumetric flask ,70ml of distilled water then added and shacked mechanically for 15minutes then diluted to the volume and filtered. 10ml of the filtrate was transferred to100ml volumetric flask and further diluted to 100mlwith distilled water. Then 10ml was transferred to another 100ml volumetric flask and the volume was completed with distilled water.

An accurately weighed 100mg from RS powder added to 1000ml volumetric flask then transfer 10ml by bulb pipette to 100ml volumetric flask and complete the volume with distilled water to get 10µg/ml concentration.

The absorbances of the standard preparation and assay preparation were concomitantly determined at λmax 232nm with UV-3300PC Spectrophotometer using water as a blank. The quantity in mg of Metformin hydrochloride in the portion of tablet taken calculated by the formula:

$$10C(Au/As)$$

In which C is the concentration of Metformin HCl RS in µg/ml and Au and As are the absorbances obtained from assay preparation and standard preparation, respectively.

3. Results

3.1. Physicochemical properties of Metformin hydrochloride tablets

Weight variation, hardness and friability and disintegration time as well as thickness and diameter are shown in Table 2. The drug content was assessed and also shown in Table 2.

Table 2: Disintegration time, hardness, uniformity of weight, friability, and chemical content of six brands of Metformin hydrochloride tablets

Brands	Uniformity of weight (g) ± SD	Hardness (kg/cm^2) ± SD	Disintegration time (min.)	Assay (%)	Diameter (mm)	Thickness (mm)	Friability %
A	0.525±0.008	16±1.6	9	102	11.6±0.3	3	0.04
B	0.522±0.004	10.2±0.5	8	101.6	11±1.8	3	0.02
C	0.521±0.012	25±0.7	6	98.9	10±1.2	4.4	0.05
D	0.636±0.009	12.5±1.6	10	100.9	12.4±0.005	4.63	0.09
E	0.552±0.005	7.2±0.9	9	100.1	10±0.75	4.5	0.07
F	0.543±0.004	12±1.6	16	99	11.5±0.04	3.1	0.04

Figure 1 illustrates the dissolution profile of the six tested Metformin hydrochloride different brands. The dissolution curve for each brand was the average of 6 tablets.

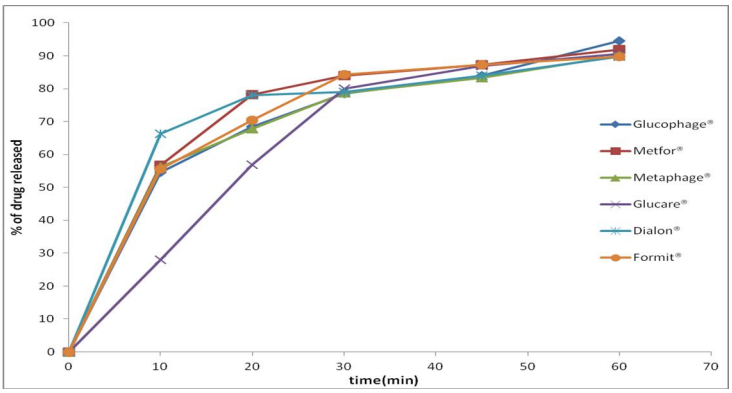

Figure 1: Dissolution profiles of the different brands of Metformin hydrochloride tablets. Each data point is the average of 6 determinations.

Dissolution efficiency (DE) was calculated according to the following equation and the result for each brand is cited in Table 3.

$$DE = \frac{\int_0^t y.dt}{y_{100}.t} x\,100\%$$

Dissolution efficiency is defined as the area under the dissolution curve up to the time, *t*, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. Where y is the percent drug release as the function of time, *t*. y_{100} is 100% drug release and *t* is the total time of drug release.

Table 3: Dissolution efficiency % for six brands of Metformin hydrochloride

Brand A	Brand B	Brand C	Brand D	Brand E	Brand F
100	102	87	105	99.4	105.3

The similarity factor f2 and the difference factor f1 method can be used to compare two dissolution profiles. The reference drug was used. The results of f2 and f1 are shown in Table 4 comparing the dissolution curves of five brands with the innovator brand.

Table 4: Values of f2 and f1 for all six brands of Metformin hydrochloride

Brand	A	B	C	D	E	F
f2	100	72	45	57	93	61
f1	0	4	11	7	1	6

Table 5 shows the percentages of the patients suffered from the common side effects of Metformin hydrochloride after the first three months treatment or as a result of switching between brands.

Table 5: The percentages of the patients suffering from the common side effects of Metformin hydrochloride after treatment

Side effect	Number of patients	% of patients
Nausea	139	38.7%
Emesis	89	24.8%
Chest pain	72	20%
Weight loss	97	27%
Diarrhea	69	19.22%
GIT disturbance	52	14.5%
Dehydration	36	10%
Drowsiness	57	15.88%

Figure 2 demonstrates the percentage of number of pharmacists and their opanion about if different Metformin hydrochloride brands can be interchangable in Saudi market.

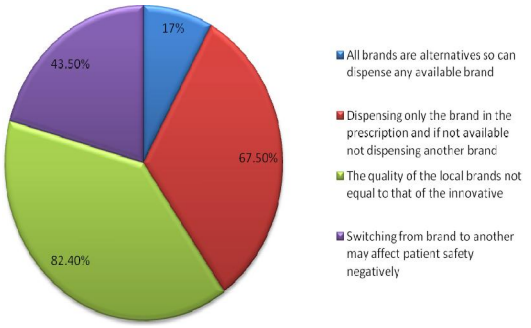

Figure 2: The point of view of some pharmacists about brands interchangeability in Riyadh

4. Discussion

Six different brands of Metformin hydrochloride tablets which are commercially available in Riyadh were subjected to a number of quality control tests in order to assess their biopharmaceutical equivalence. The assessments involved the evaluation of uniformity of weight, friability, hardness, disintegration and dissolution tests as well as chemical content determination. All the brands used were within their shelf life as at the time of study.

The weight uniformity for the six brands of Metformin hydrochloride tablets gave values that comply with the USP specification with a deviation less than 5% from the mean value (i.e., maximum deviation value 0.012) Table 2.

Using ERWEKA hardness tester, the strength of the tablets was tested. All the tablets failed this non-official test according to USP specifications (4-6 kg). Brand E had the minimum hardness and brand C had the maximum hardness. Hardness values of brand A, B, D and F were 16, 10.2, 12.5 and 12, respectively Table 2.

Previous study on different Metformin hydrochloride brands in Nigeria [15] showed that from eight brands three brands pass the hardness test (5-7 kg) and five brands failed to have good crushing strength (10-48 kg) [15]. Another research group [16] showed that all the tablets in four tested brands showed good strength (13-15 kg).

The friability test is mostly important criteria for uncoated tablets (during and after manufacture) to examine that the tablets have a good withstand strength for transportation, packaging, shipping and coating. All the tested brands in this study are film coated tablets. The friability was also tested for these coated tablets for all brands. The friability was less than 0.2% for all the brands. The values of <1% are considered to be highly satisfactory evaluation characteristics Table 2.

The results obtained from the assessment of the percentage content of active ingredient of six brands of Metformin hydrochloride tablets showed values within the monograph specification 95% to 105% of stated amount of Metformin HCL as demonstrated in Table 2.

The observed disintegration times for all the brands of Metformin hydrochloride investigated was less than the 30-min limit prescribed by the official compendium (Table 2). All tablets of the different generic brands passed the disintegration test. The fastest disintegrated tablets were of brand E while the slowest one was brand B. The various brands could have employed different disintegrants to improve the penetration of aqueous liquids.

Dissolution of drug from oral solid dosage forms is an important aspect for drug bioavailability (i.e., the drug must be solubilized in the aqueous

environment of the gastrointestinal tract to be absorbed). Accordingly, dissolution testing of solid oral drug products has emerged as one of the most important control tests for assuring product uniformity and batch-to-batch equivalence [13, 14].

In the present investigation, the release of Metformin hydrochloride from all tablets was immediate release and the percent of drug released at 45mins was more than 70% as shown in Figure 1. The results obtained from this study revealed that all the brands passed the USP 32 general specifications standard for dissolution rate test for conventional release tablets.

Dissolution efficiencies variation known as predicted availability equivalent (PAE) is used to predict the likely in vivo bioavailability. The implication of the PAE is to express the relative ease of release and predictive release pattern of the drugs in vivo [21].

It is obvious from Figure 1and Table 3 that various products exhibit different dissolution profiles. In order to judge whether these differences in dissolution profiles were significant, all dissolution profiles were compared to that of the originator (Glucophage®) brand A using the similarity factor (f2) value recommended by FDA[17] . The obtained values of f2 were: 72, 45, 57, 93, 61 for Formit®(B), Glucare®(C), Dialon®(D), Metaphage®(E) and Metfor®(F), respectively (Table 4).

Similarity factor analysis between five of the marketed tablets and the innovator brand A (Glucophage®) for the release of Metformin hydrochloride showed an f2 factor greater than 50 for all brands except brand C (Glucare®). The higher the f2 values, the more similar the dissolution profiles, so f2 < 50 represented non-similar profiles, while f2 > 50 denoted a similarity between profiles of four marketed brands B, D, E, F and the innovative brand A. So, Brand C was found nonequivalent in their dissolution profile to the originator (Glucophage®). The values cited in Table 4 shows that Metaphage® (brand E) is the most similar local product to the innovative product (Glucophage®) brand A. The similarity factor f2 was 93 and difference factor f1was only 1.

It was mentioned recently that there is a correlation between the difference in dissolution profiles of the tested brands and their bioavailability [18]. For this reason, Glucare® (brand C) might be recommended to be unused as alternative to Glucophage® (brand A). These findings support the need for activation of the regulatory rules with emphasis on postmarketing evaluation of pharmaceutical products. This difference could be also due to the various binders and disintegrate used by different companies.

Another previous study discussed and evaluated differences between five brands of Metformin hydrochloride marketed in Jordanian Market. The results revealed that the release of Metformin hydrochloride from three brands namely, Metforal®, Diaphage® and Formit® were nonequivalent to the innovative brand (Glucophage®). The values of their similarity factor (f2) were 24.5, 39.4 and 28.2 for Metforal®, Diaphage ® and Formit®, respectively. Only Glymet® has similarity factor more than 50. So Glymet® is equivalent according to its dissolution profile to originator [19].

In vitro dissolution methods are developed to assess the potential in vivo performance of a solid oral dosage form. The appropriate performance of drugs products is determined through the quality control tests. Recently, understanding of the physiological environment and processes of absorption, critical deconstruction of the mechanisms of release from formulations, and improved computational tools has led to a more sophisticated discussion of the role of dissolution testing in drug product design and control [20]. This previous study declared that meaningful results and interpretation of dissolution data can be achieved only when the biopharmaceutical and physical properties of the drug products are well understood, and that test methods are properly established through studies during formulation and manufacturing process design and clinical development.

The common side effects of Metformin hydrochloride were monitored through survey on a small sample of 359 patients treated with different brands, 211 of which are diabetic and 48 are not. The results obtained in Table 5 showed that the high percentage of patients can suffer from nausea and emesis especially at the first three months of the treatment or after change to another brand.

On the other side, a simple questionnaire forwarded to more than 80 pharmacists about their opinion if different brands of Metformin hydrochloride tablets are alternative to each other in Saudi market or not. Figure 2 illustrated that high percent 82% of the pharmacists believed that the quality of local brands is unequal to the innovative brand.

67% of the pharmacists don't dispense alternative brand if the prescribed brand is not available in the pharmacy.

5. Conclusion

Five generic brands of Metformin hydrochloride tablets, namely Formit® , Glucare®, Dialon®, Metaphage® and Metfor® together with the innovative (Glucophage®) have been subjected to analysis according to the monograph of USP 32 Pharmacopoeia. The results have shown that all the

tested brands satisfied the USP requirements in terms of identification, assay and dissolution. Dissolution profiles revealed differences between the different generics. Four generic products could be said to be equivalent to the originator (Glucophage®) while the Glucare® was nonequivalent. According to the present study patients can safely switch from one brand to another but with consulting them of the possibility of some minor GIT complications that may occur after the treatment with new alternative brand. Pharmacists have to be informed which Metformin hydrochloride brands in the Saudi market are alternative to each other.

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