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Research Article

COMPARATIVE STUDY BETWEEN FIVE BRANDS OF METFORMIN HYDROCHLORIDE AVAILABLE IN LIBYAN DRUG MARKET

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ABSTRACT

Objective : Metformin hydrochloride is a drug of choice in the treatment of diabetes mellitus type-2 especially in obese patients. It is normally given orally as tablets in doses of 500 mg two or three times daily or 850 mg once or twice daily during or after meals. The aim of the present study was the comparative study and evaluation between five different Metformin hydrochloride brands which are commercially available in the Libyan drug market (Metformin, Glymet, Metformin(STADA), Metforal & Dialon). Methods : To assess quality, all products were examined visually for their organoleptic properties. The physicochemical equivalence of five brands of Metformin hydrochloride tablets were determined through the evaluation of 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. **Results :** All the tested five brands were equivalent and complying with the official tests for weight variation, friability, hardness, 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. The percentage content of active ingredient of five brands of Metformin tablets showed values within the monograph specifications (95-105%). All the brands are within their expiry dates but there is major difference in price. The basic function groups of five metformin brands and metformin standard was identified by Infra-Red (IR) spectrophotometer. The spectroscopic investigations were revealed no any difference between Metformin five brands and showed identical peaks compared to the reference.**Conclusion :** All the available brands in local market of Libya are having, with in the specified quality range and can be interchange of found any non-compliance due to cost issue. The results have shown that all the tested brands satisfied the USP requirements.

Keywords: Metformin, IR, friability test, hardness, disintegration and dissolution tests.

INTRODUCTION

Metformin hydrochloride is used for the treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. Metformin may be used as initial treatment or in sulfonylurea failures either alone or in combination with a sulfonylurea and other oral agents. It is also used as an adjuvant therapy in insulin dependent diabetes especially if overweight [1]. Metformin hydrochloride has been used in the management of metabolic and reproductive abnormalities associated with polycystic ovary syndrome (1.5–2.25 g) of metformin is given daily in divided doses generally[2]. Metformin is contraindicated in the following conditions: dehydration, diabetic coma, ketoacidosis, marked renal impairment, chronic liver disease, cardiac failure, recent myocardial infarction, alcoholism (both acute and chronic), conditions associated with hypoxemia, states associated with lactic acidosis such as shock or pulmonary insufficiency in patients with a history of lactic acidosis and in the period around surgery. It is also contraindicated in case of hypersensitivity to metformin [3]. Evidences suggest that insulin resistance and resulting hyperinsulinism 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 [4].

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 [5, 6].

Results from the United Kingdom Prospective Diabetes Study show that long-term control of blood glucose with the aid of metformin decreases the potentially fatal risks linked to diabetes, such as myocardial infarction and coronary disease in overweight diabetic patients. Since metformin is not associated with weight gain, it is the hypoglycaemic agent of choice for the treatment for this kind of diabetic patients [7].

The metformin solution is bioequivalent to the immediate-release (IR) tablet which dissolves completely in 1h [8, 9] state that if a pharmaceutical form dissolves quickly, the bioavailability of the active ingredient will not be affected by dissolution and, in this case, there is the possibility of extending bio-waivers (relaxing the need for bioavailability tests) to Class III, on the basis of the in vitro dissolution profile.

Drug products that are bio-pharmaceutically 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 [10]. Dissolution testing of drug product is an important criterion in assessing the quality control to monitor batch to batch consistency of drug release [11]. 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 [12, 13]. 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 [14].

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 [10].

Metformin hydrochloride is the most popular anti-diabetic drug in the Libya as well as all over the world. Accordingly, the use of Metformin hydrochloride tablets needs to monitor and ensure the

quality of the various brands commercially available in the Libyan 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 Libyan 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 five Metformin tablets brands applying both official and unofficial compendia method following the USP pharmacopeia.

MATERIALS AND METHODS

Materials and Instruments

Brand name	Manufacturer	Batch No	Expiry date
(i) Metformin tablet	BRISTOL “United kingdom”	BUH106138	11-2020
(ii) Glymet tablet	Pharma International “Jordan”	17351	6-2021
(iii) Metformin STADA	STADA “Germany”	CHB44512	11-2019
(iv) METFORAL	Menarini International “Italy"	68003	12-2020
(v) Dialon	Julphar “U.A.E”	0747	11-2020

Instruments

For samples preparation an analytical balance Sensitive Balance "Sartorius" Germany, The Friability test was done by using Friabilator "Pharma Test" type: PTF E, Germany, The hardness test was determined using Hardness tester "Pharma Test" type: PTB E, Germany, Disintegration Tester Disintegration apparatus "Pharma Test" type: PTZ, Germany, and a Dissolution testing, Dissolution apparatus, basket-type, Germany was used. All UV spectroscopic measurements were performed using a UV spectrophotometer (Shimadzu UV-1700; Shimadzu). IR Spectroscopy was done by using Infra-red spectrophotometer.

The examined tablets were purchased from the local market in the same way the patient might have bought them from the pharmacy. A list of the tested products is shown in the above Table.

Methods

The study was carried out in October 2018 at Faculty of Pharmacy, department of Pharmaceutics, University of Tripoli, Libya.

We have subjected all five brands of Metformin tablets such as (i) Metformin tablet, (ii) Glymet tablet, (iii) Metformin STADA, (iv) METFORAL & (v) Dialon tablets for Fulfilment of the compendia specification for visual inspection, uniformity of weight, friability hardness, disintegration, Dissolution test as well as Infra-red spectroscopy .

Visual Inspection

The shape, size, and colour 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

Uniformity of Weight

Tablets (20) of each brand were weighed individually using a Sensitive Balance "Sartorius" Germany balance. The average weight was determined and the percentage (%) deviation of the individual tablets from the mean was determined. according to compendia requirements of the United States Pharmacopeia (USP) [15].

Friability Test.

A number of 10 tablets of each brand of Metformin hydrochloride were weighed and subjected to abrasion using Friabilator "Pharma Test" type: PTF E, Germany at 100 revolutions for 4 min. The tablets were deducted 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.

Hardness Test

The crushing strength of the tablets was determined using Hardness tester "Pharma Test" type: PTB E, Germany. Sample tablets (10) of each brand were taken, a tablet was placed between the spindle of the hardness tester machine until the tablet breaks and the pressure required to break the tablet was then read off the machine and recorded.

Disintegration Test

The disintegration test was carried out in accordance with USP [15]. specifications by using Disintegration apparatus "Pharma Test" type: PTZ, Germany Six tablets from each formulation were subjected to disintegration test. One tablet was placed in each of the six tubes of the basket. Then disks were added to each tube of the basket. The time taken for the last tablet to disintegrate completely was recorded in minutes. Film-coated tablets comply with the disintegration test prescribed above except that the apparatus is operated for 30 min.

Dissolution Rate Determination

Dissolution rates of five metformin hydrochloride five brands were determined using dissolution apparatus. One tablet was put in the basket which rotates in the vessel filled with 900 mL of phosphate buffer 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, 40, 50 and 60 minutes 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 0.45 μm, 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.

Infra-red spectroscopy

Infrared spectra were recorded for the obtained residue using KBr method. Triturate 1-2 mg of the substance to be examined with 300-400 mg of finely powdered and dried potassium bromide R . These quantities are usually sufficient to give a disc of 10-15 mm diameter and a spectrum of suitable intensity . Carefully grind the mixture, spread it uniformly in a suitable die, and submit it to a pressure of about 800 MPa (8 t•cm-2).

IR Spectroscopy is used for recording spectra in the region of 4000-650 cm-1 (2.5-15.4 μm) or in some cases down to 200 cm-1 (50 μm).

RESULTS

Table 1: Visual inspection of tested five brands of Metformin Hydrochloride tablets.

	Color	Clarity	Shape	Surface	Diameter (mm)	Thickness(mm)	Tablet Type
Metformin	White	Clear	Round Convex	Smooth	11.15 mm	5.9 mm	Film coated
Glymet	Pale orange	Clear	Round Convex	Smooth	15.0 mm	7.0 mm	Caplet
Metformin STADA	White	Clear	Round Convex	Smooth	12.19 mm	5.25 mm	Film coated
METFORAL	White	Clear	Round Flat	Smooth	12.03 mm	4.56 mm	Film- coated
Dialon	White	Clear	Round Convex	Smooth	12.83 mm	5.18 mm	Film coated

Table 2: Weight variation, Friability, hardness, Disintegration time, of five brands ofMetformin hydrochloride tablets

	%Weight variation test	% Friability test	Average Hardness test (kg/cm)	Average Disintegration test (min)
Metformin	4.83 to -2.76	(0.98)	18.7	(0:07:15)
	PASS	PASS	PASS	PASS
Glymet	1.63 to -2.64	(0.0318)	5.279	(0:07:59)
	PASS	PASS	PASS	PASS
Metformin STADA	1.48 to -2.16	(0.02874)	15.94	(0:13:12)
	PASS	PASS	PASS	PASS
METFORAL	0.96 to -1.04	(0.11)	8.68	(0:09:24)
	PASS	PASS	PASS	PASS
Dialon	2.29 to -4.48	(0.02042)	14.79	0:05:35)(
	PASS	PASS	PASS	PASS

Table 3: Content uniformity of five brands of Metformin hydrochloride tablets.

Brand Name	Absorbance	% Content uniformity	Remark
Metformin	**0.335**	**91%**	**Confirm**
GLYMET	**0.342**	**93%**	**Confirm**
Metformin STADA	**0.350**	**95%**	**Confirm**
METFORAL	**0.320**	**99%**	**Confirm**
Dialon	**0.369**	**102%**	**Confirm**

Table 4: Dissolution efficiency % for five brands of Metformin hydrochloride

Time (min)	% Metformin Release	% Glymet Release	% Metformin STADA Release	% METFORAL Release	% Dialon Release
10 min	84%	79%	30%	25%	50%
20 min	100%	105%	56%	42%	76%
30 min	100%	100%	77%	64%	98%
40 min	100%	100%	82%	90%	100%
50 min	100%	100%	90%	100%	100%
60 min	100%	100%	95%	100%	100%

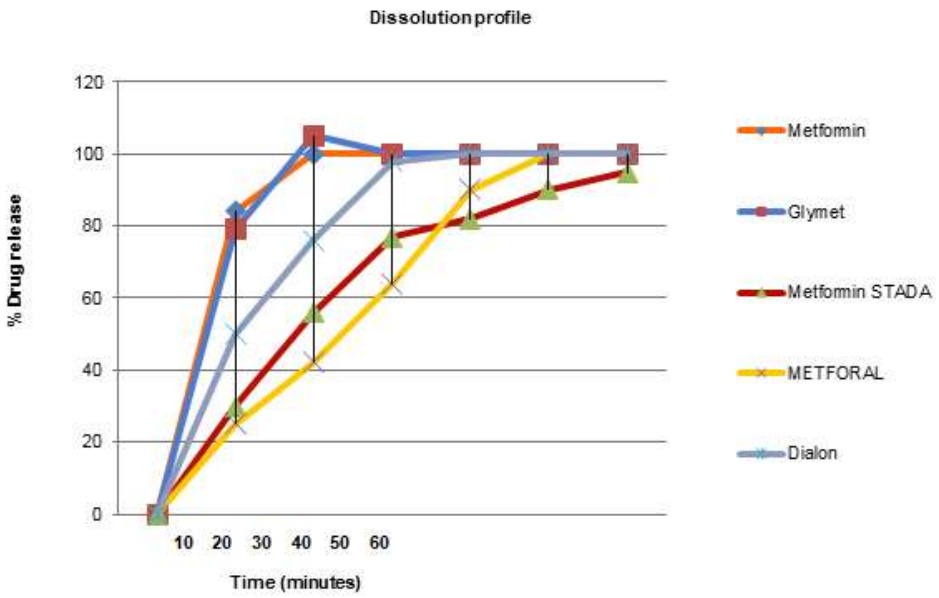

Fig. 1: Dissolution profiles of five commercial product of metformin 500 mg tablets, at 50 rpm (basket apparatus), with dissolution medium pH 6.8 phosphate buffer, at 37 ± 0.5°C

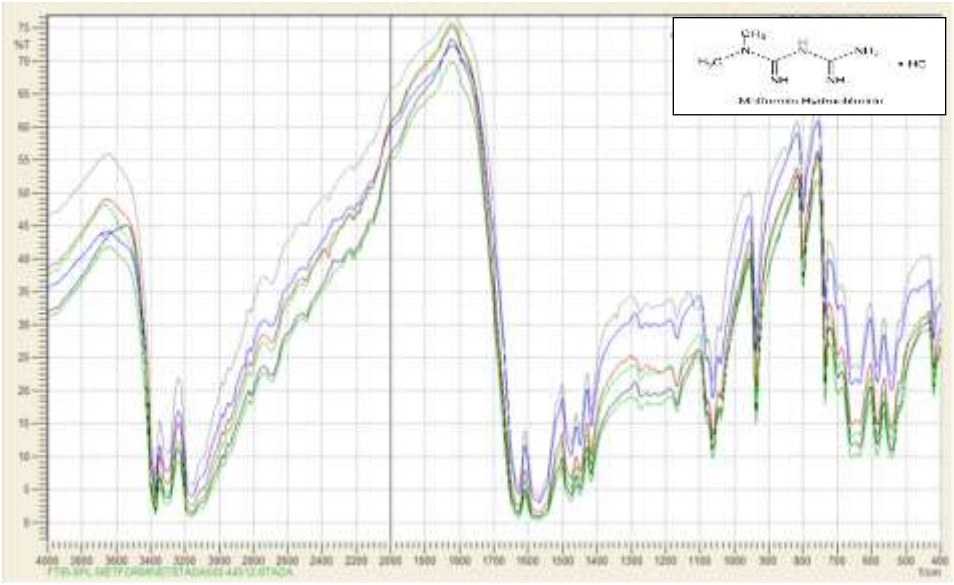

Fig. 2: Spectrum of Metformin hydrochloride provided by the active pharmaceutical ingredient and five brands tablets.

DISCUSSION

Metformin hydrochloride is a widely prescribed oral anti-diabetic drug. Several brands of Metformin tablets are available in the market leading to a confusion of their quality and prices. The objective of the present study is to make a comparative evaluation of five different brands of Metformin hydrochloride which are commercially available in Libyan market . They were subjected to number of quality control tests in order to assess their biopharmaceutical equivalence. The branded products of Metformin tablets evaluated for various physiochemical properties. The size of tablets was in the range of (11.15 to 15 mm) with all five brands. There is no significant difference between the batches of the brands as shown in Table 1. The uniformity of weight for the five brands of Metformin hydrochloride tablet gave values that compiled with USP specification and deviated less than 5 % from the mean value .The result of tablet friability test showed that all the brands tested had impressive friability values ranging 0.028% to 0.98% w/w According to USP. no batch should have a friability value greater than 1% w/w. Using hardness tester, the strength of the tablets was tested. Hardness of the tablets was in the range between 21.86 kg/cm to 1.09 kg/cm with all five brands. The observed disintegration times for all the brands of Metformin hydrochloride investigated was less than 30 min. The fastest disintegration tablets were of Dialon brand was 5,35 min, while the slowest one was Metformin STADA brand was 13.12 min. The various brands could have employed different disintegrates to improve the penetration of aqueous liquids as shown in Table 2. The result obtained from the assessment of the percentage drug content of five brands of Metformin hydrochloride tablets showed within the monograph specification 90 % to 110% of stated amount of Metformin hydrochloride as mentioned in Table 3. Dissolution of drug from oral solid dosage forms is an important aspect for drug bioavailability. The in-vitro drug release characteristics of the developed marketed tablets were studied. The dissolution of all five brand tablets indicated more than 70 % of the drug is released within 45 min, which complies with the USP specification as shown in Table 4 and Figure 1.

Furthermore, the dissolution rate results of these brands revealed some variable release, as the fastest release showed with Metformin and Glymet within 20 min but, Dialon within 40 min. In contrast, to Metforal and Metformin STADA within 50 & 60 min respectively.

The IR spectra revealed that there was no any difference between metformin hydrochloride five brands, It showed Identical peaks compared to the reference. The principal absorption peaks of metformin hydrochloride appear at 3169 cm−1 due to the N-H stretching of the primary amine group (-NH2) and at 1063 cm−1 due to C-N stretching. A peak at 1584 cm−1 occurs due to N-H bending vibrations of the primary amine group. The identical peaks (N-H stretching, C-N stretching, and N-H bending vibrations as shown in Figure 2.

CONCLUSION

It can be concluded from above discussion that all the available brands in local market of Libya are having, with in the specified quality range and can be interchange of found any non-compliance due to cost issue. The results have shown that all the tested brands satisfied the USP requirement in terms of uniformity of weight, friability, disintegration, assay and dissolution. According to the present study patients can be safely switch from one brand to another but with consulting them of the possibility of some minor GIT complication that occur after the treatment with new alternative drug.

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REFERENCES

1. Gong Li, Goswami S, Giacomini K.M Altman R.B Teri E. Metformin pathways: pharmacokinetics and pharmacodynamics. Pharmacogenet Genomics, 2012; 22: 820–827.
2. Akram M. Diabetes mellitus type II: treatment strategies and options: a review". Journal of Diabetes and Metabolism, 2013; 4,(9):2-9.
3. Akinboboye O, Idris O, Akinkugbe O. Trends in coronary artery disease and associated risk factors in Sub-Saharan Africans". Journal of Human Hypertension, 2003; 17:381-387.
4. Giovanna C, Francesca M, Marzia C, Naima Z, Poala M . Development and evaluation of an in vitro method for prediction of human drug absorption II demonstration of the method suitability. European 2006;27:354-362.
5. Bailey CJ, Day C. Metformin: its botanical background. Practical Diabetes International, 2004; 21(3):115–7.
6. [6] Alan D. The use of Medicines in the United States. IMS Institute for Healthcare Informatics .2011; 28.

7. Campbell IW. Metformin and the united kingdom prospective diabetes study: a commentary. Arq Bras Endocrinol Metabol 2000; 44(2):121-24.
8. Sambol NC, Brookes LG, Chiang J, Goodman AM, Lin ET, Liu CY, Benet LZ. Food intake and dosage level, but not tablet vs solution dosage form, affect the absorption of metformin HCl in man. Br J Clin Pharmacol 1996; 42:510-12.
9. Cheng CL, Yu LX, Lee HL, Yang CY, Lue CS, Chou CH. Biowaiwer extension potential to BCS Class III high solubility-low permeability drugs: bridging evidence for metformin immediate-release tablet. Eur J Pharm Sci 2004; 22(4):297-304.
10. Adegbolagun OA, Ololade OA, Osamah SE. Comparative evaluation of biopharmaceutical and chemical equivalence of some commercially evaluable brands of ciprofloxacin hydrochloride tablets. Tropical journal of pharmaceutical research 2007; 6:737-745.
11. Awofisayo OS, Oladoja AA, Nse E, Imo EU. Comparative Assessment of the quality control measurements of multisource ofloxacin tablets marketed in Nigeria. Dissolution Technologies 2010;6:20-25.
12. Esiomone CO, Okoye FBC, Onah BU, Nworu CS, Omeje EO. In-vitro bioequivalence study of nine brands of artesunate tablets marketed in Nigeria. J.Vector Borne Dis 2008; 45:60-65.
13. Pamula RB, Surender G, Reddy KVS, Ujwala P, Jyosthna G, Kumar RM. Comparative in vitro evaluation of commercial metformin HCL tablets. JITPS 2010; 1:152-157.
14. Chow SJ. Pharmaceutical Validation and process controls in drug development. J Drug development 1997;31:1195-1201.
15. United States Pharmacopeia and National Formulary USP 24–NF 19. Rockville, Maryland, United States Pharmacopeial Convention, Inc., 2000:1882–1883.