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Article *in* Journal of Chemical and Pharmaceutical Sciences · January 2016

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ISSN: 0974-2115
www.jchps.com Journal of Chemical and Pharmaceutical Sciences

Assessment of physicochemical properties of metformin hydrochloride (850mg) tablets marketed in Syria

Oussama Mansour*, Mostafa Isbera
Department of Pharmaceutical Chemistry and Quality Control, Faculty of Pharmacy, Al Andalus University, Tartous-Syria
***Corresponding Author: E-Mail: mansouroussama@yahoo.fr; phone number: 00963966391986**

ABSTRACT

There are several generics of metformin hydrochloride tablets available within the drug delivery system globally. Numerous brands of Metformin tablets (850mg) are available in the Syrian drug market. The objective of this study is to determine the biopharmaceutical and chemical equivalence of five brands of Metformin tablets marketed in Syria. The physicochemical equivalence of five brands of Metformin hydrochloride tablets were assessed through the evaluation of both official and non-official standards such as weight variation, friability, hardness, content uniformity, and dissolution rate. All the brands complied with the official specifications for weight variation and friability tests. The result indicates that only two (B & E) brands passed the non-official test of crushing strength/hardness while the remaining brands (A, C & D) failed. Three brands had values within the range specified (95-105%) for content uniformity in the USP while brands (A & D) failed the test. Three tested brands released more than 75% drug in 30 minutes except brand A and brand C; therefore, all formulations excluding formulation A, and C passed this acceptance pharmacopeia criterion (USP).

KEY WORDS: Metformin hydrochloride, hardness, friability, weight variation, content uniformity, dissolution test.

1. INTRODUCTION

Issues related to drugs and pharmaceutical services are gaining pace in the government agenda and society nowadays and increasingly safe and effective drugs for almost all diseases have been developed recently. This quality is not only a commercial attribute, but also a legal and moral issue since the non-compliance of quality specifications that are considered essential can have serious implications such as lack of effectiveness in the treatment due to therapeutic sub-doses, toxic effects caused by therapeutic over-doses and, consequently, lack of patient adherence to treatment (Kohler, 2009).

The evaluation of pharmaceutical equivalence for drugs in tablets form is very important since these are forms in which most problems can occur affecting the dissolution and undertaking bioequivalence (Prista, 1995). Hence, during drugs production, certain factors must be controlled to ensure the therapeutic efficacy (Ansel, 2000), guaranteeing the safety, efficacy, and quality of the product throughout the expiration date (Peixoto, 2005).

Metformin hydrochloride (MET) is chemically N, N-dimethyl imido dicarbonimidic diamide hydrochloride (1, 1-dimethylbiguanide hydrochloride) that acts by decreasing intestinal absorption of glucose, reducing hepatic glucose production, and increasing insulin sensitivity (Fig.1). Metformin is considered the first-line oral hypoglycemic agent in the treatment of type 2 diabetes mellitus. MET is the drug of choice in obese patients.1–3 Metformin activates adenosine monophosphate activated protein kinase (AMPK), a liver enzyme that plays an important role in insulin signaling, whole body energy balance, and metabolism of glucose and fats. Activation of AMPK is required for metformin's inhibitory effect on the production of glucose by liver cells.

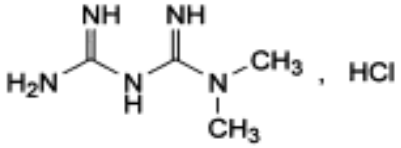

Figure.1. Structure of metformin hydrochloride

This study aims at evaluating the physicochemical properties of five brands of Metformin tablets marketed in Syria.

2. MATERIALS AND METHODS

Five commercial brands (A, B, C, D, E) of metformin hydrochloride were randomly selected. Metformin brands having label strength of 850 mg were purchased from registered pharmacies in Lattakia, Syria. All tests were performed within product expiration dates. The reagents used were sodium hydroxide (BDH Chemicals, UK) and potassium di hydro orthophosphate (BDH Chemicals, UK). Freshly distilled water was used throughout the work.

Hardness test: Sample tablets (10) of each brand were taken, a tablet was placed between the spindle of the Erwerka hardness tester machine and pressure was applied by turning the knurled knot just sufficiently to hold the tablet in position. The pressure was then increased as uniformly as possible until the tablet broke and the pressure required to break the tablet was then read off the machine and recorded.

Friability test: Sample tablets (20) of each brand were weighed together before transferring them to the Roche friabilator. The friabilator was adjusted to 25 rpm for 4 minutes. After that, the tablets were taken and cleaned from dust and weighed again. By using this formula % of Friability = [(Wi – Wf)/ Wi] x 100 was calculated. The loss should be less than 1% according to BP.

Weight variation: 20 tablets were taken from each brand. Each tablet was weighed individually. Then the average weight was calculated for every brand. The individual weight was compared with an average weight. Not more than two of the individual weights deviated from the official standard (limit ±5%).

Calibration curve of metformin hydrochloride in distilled water at 232 nm: A standard curve was created for metformin hydrochloride using pure drug powder diluted to 5 known concentrations (range between 0.21 and 0.84 mg/100ml). These standard curves were established to verify accurate analysis of the drug.

Uniformity of content: 10 tablets were taken from each brand. Each tablet was crushed and dissolved separately using a combination of manual agitation and sonication techniques in 100 ml of distilled water. Then the samples were mixed well before filtration through a membrane filter. The samples of each solution were assayed for drug concentration using spectrophotometer at 232 nm. The drug content was quantified by calculating the concentrations from the absorbance readings obtained through UV analysis.

Several measures were calculated in order to assess the amount and acceptability of variations in drug content. The measured drug content expressed as a percent of label claim was calculated for each tablet. Individual values for each tablet should be in the range of 95-105% metformin hydrochloride (proxy USP specification for drug content).

Calibration curve of metformin hydrochloride in phosphate buffer (pH 6.8) at 232 nm: A standard curve was created for metformin hydrochloride using pure drug powder diluted to 5 known concentrations (range between 0.33 and 0.91 mg/100ml).

Dissolution test: This was determined using a 7-compartment Veego dissolution test apparatus (paddle type) containing 900ml of phosphate buffer pH 6.8, maintained at 37 ±0.50C with a fixed speed of 75rpm. A tablet was put in each of the compartments and the machine operated at the intervals of 5, 10, 15, 30, 45 and 60 minute. In all the experiments, 5ml of the sample was withdrawn at specified intervals and replaced with a fresh 5ml dissolution medium to maintain the sink conditions. Each of the withdrawn samples was filtered with syringe filter 0.45µm, the filtrate diluted and its absorbance at 232 nm were measured using UV-visible spectrophotometer. The concentration of each sample was determined from a calibration curve in phosphate buffer. The main purpose of performing dissolution study for test and reference product was to compare the product's dissolution profiles. All drug products have dissolution specification, Q, stated in the USP, and for passing the test, all metformin immediate release tablets must release 75% of drug within 30 minutes.

3. RESULTS AND DISCUSSION

Hardness and friability tests: Crushing strength test shows the ability of tablets to withstand pressure or stress during handling, packaging and transportation. It is a property of a tablet that is measured to assess its resistance to permanent deformation. This result also indicates that only two (B & E) brands passed the non-official test of crushing strength/hardness while the remaining brands (A, C & D) failed. Brand C had the highest crushing strength of all the brands with hardness of 44.12KP (Table 1).

The result of tablet friability test shows that virtually all the tested brands had impressive friability values ranging from 0.01% to 0.76%w/w (Table 1). According to BP no batch should have a friability value greater than 1.0%w/w; therefore, all the brands passed the test.

Table.1. Hardness and friability of metformin tablets

Brand	Hardness (KP±SD); N=10	Friability (%); N=20
A	40 ±0.76	0.05
B	5.56 ±0.54	0.81
C	44.12 ±0.93	0.01
D	35.76 ±0.32	0.03
E	6.22 ±0.31	0.76

Weight variation: Uniformity of Dosage Form can be demonstrated by two methods, content uniformity and weight variation. All the individual weights deviated from the official standard less than±5%, so all the brands passed the test for weight uniformity (Table 2).

Table.2. Weight variation of metformin tablets

Brand	Measured weight mean (mg); N=20	Deviation range (%)	RSD (%)
A	1203	-2.31 – 2.54	2.41
B	1197	-3.21 – 2.21	3.11
C	1205	-1.78 – 2.12	1.56
D	1198	-3.11 – 2.96	2.01
E	1201	-2.55 –2.54	2.12

Calibration curve of metformin hydrochloride in distilled water at 232 nm: A linear relationship between the absorbance and the concentration of metformin hydrochloride in distilled water at 232 nm in the concentration range of 0.21-0.84mg/100ml is observed. The regression equation is Y= 0.9326X+0.039 and the correlation coefficients (r) of the linear regression of the calibration curves is 0.9974.

Content uniformity: The results obtained from the assessment of the percentage content of active ingredient in the eight brands of metformin tablets showed that three brands (B, C, E) gave values within the monograph specifications (95-105%), while brands (A, D) failed the test with values outside of proxy USP specification in all tablets for brand A and 7 tablets for brand D. Tablets of brand B have the largest content 844 mg and tablets of brand A have the lowest content 795 mg (see table 3).

Table.3. Content uniformity of metformin tablets

Brand	Measured drug content mean (mg); N=10	Percent of content range (%); N=10	RSD (%)	Outside of proxy USP specification
A	795	90.12 – 93.67	4.76	10
B	844	97.54 – 99.13	1.21	0
C	830	96.14 – 98.09	1.45	0
D	811	92.65 – 96.23	5.04	7
E	835	96.15 – 98.67	1.79	0

Calibration curve of metformin hydrochloride in phosphate buffer at 232 nm: A linear relationship between the absorbance and the concentration of metformin hydrochloride in phosphate buffer at 232 nm in the concentration range of 0.33-0.91mg/100ml is observed. The regression equation is Y= 1.0275X-0.1014 and the correlation coefficients (r) of the linear regression of the calibration curves is 0.9979.

Dissolution test: Oral dosage forms only become available for absorption following the process of disintegration and dissolution. Dissolution testing is employed to distinguish the influence of manufacturing variables such as binder effect, mixing effect, granulation procedure and excipients type and can be used as a tool to predict product behavior *in vivo* (Papadopoulou and Valsami, 2008). Consequently, dissolution test is currently used as an *in vitro* bioequivalence (BE) test, mainly for figuring out dissolution profile and profile comparison, establishing the similarity of pharmaceutical dosage forms (Amidon and Lennernas, 1995; Cheng and Yu, 2004; Esimone and Okoye, 2008). Five different brands of metformin (850 mg) tablets were studied. To evaluate the dissolution profiles, dissolution curve (based on mean percentages of drug released) of test products was combined and depicted in figure 2. In this study, as expected for highly soluble compound, metformin, it was observed that for all products, at least 75% release in 30 min took place except brand A and brand C. Therefore, all formulations excluding formulation A and C passed this acceptance pharmacopeia criterion.

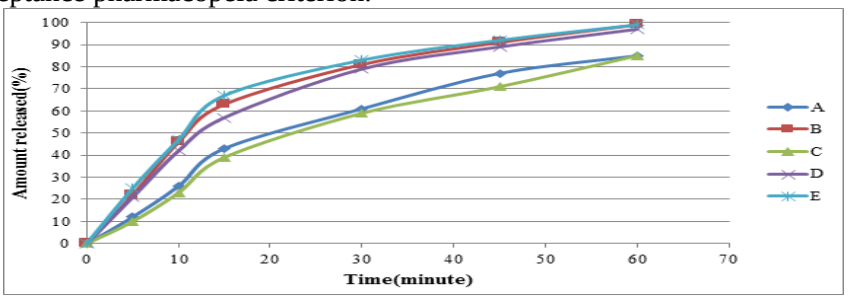

Fig.2. Dissolution profiles of metformin tablets

4. CONCLUSION

All in all, there was a wide variation in the results of the hardness test between the studied brands. All brands passed the tests for friability (less than 1%) and weight variation (deviation less than ±5%). Three brands (B, C, E) gave values within the monograph specifications (95-105%), while brands (A, D) failed the test with values outside of proxy USP specification. In this study, as expected for highly soluble compound, metformin, it was observed that for all products, at least 75% release in 30 min took place except brand A and brand C. This verifies serious need for constant post marketing monitoring of the marketed products with a view to bioequivalence and agreement with pharmacopoeia standards.

5. ACKNOWLEDGEMENT

I would like to thank Mr. Ayham Aljghami, for the language assistance provided during the writing process of this article.

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