IN VITRO EQUIVALENCE EVALUATION OF FIVE DIFFERENT METFORMIN TABLET PRODUCTS USING UV SPECTROMETER

Baraa Ramzi Abdulhameed *, Hazhar Ibrahim Karim *, Gulala Ibrahim Qader and Mohammed Omer Mohammed *

Submitted: 18/5/2016; Accepted 18/10/ 2016; Published: 1/12/2016

ABSTRACT

Background

Equivalence studies are needed to assess and confirm the safety and efficacy of generic formulations and are essential for the protection of patients from being treated by counterfeit medicines or from unwanted effects of medications. Two pharmaceutical products are considered to be bioequivalent when their bioavailability factors are similar and they show clinically comparable therapeutic effects.

Aim of the study

To compare the in vitro equivalence of five products of metformin tablets available in the markets of Kurdistan Region of Iraq.

Materials and Methods

This work involved studying of five products of metformin tablets available in the markets of Kurdistan Region of Iraq. The products were compared to investigate their contents, dissolution and friability profiles

Results

Results of content assay indicated that all five products stayed within the standard value ranges, which should not be less than 95% and not more than 105% of labeled amount. The dissolution profile study showed that all five brands of metformin released at least 80% of their contents in 30 minutes and passed the acceptance criteria for US Pharmacopeia 2015. The friability test demonstrated that the tablets manufactured by Bristol had maximum loss while tablets manufactured by Merck showed minimum friability, as compared to other brands in the study.

Conclusion

The study indicates that the five tested products of metformin tablets, which are available in Iraqi markets, Comply with the standards set by US Pharmacopeia and are considered to be equivalent to each other.

Keywords: *Metformin, In vitro equivalence, UV-Spectrometry.*

* Department of Pharmacology, College of Medicine, University of Sulaimani.
Correspondence: baraa.abdulhameed@univsul.edu.iq

https://doi.org/10.17656/jsmc.10100

INTRODUCTION

Metformin hydrochloride (dimethylbiguanide), is an oral glucose-lowering agent. Its origins traced to *Galega officinalis*, also known as French lilac or goatsrue [1].

Chemically 1, 1-dimethylbiguanide hydrochloride ($C_4H_{11}N_5$.HCl) is white crystalline powder, hygroscopic and freely soluble in water, acts by decreasing intestinal absorption of glucose reducing hepatic glucose production and increasing sensitivity to insulin [2]. Over the last 15 years, metformin has become the first line agent for the treatment of type 2 diabetes, as noted in several international guidelines, including the ADA-EASD guidelines [3].

Metformin hydrochloride is an antidiabetic drug from the biguanide class of oral hypoglycemic agent that has been widely used as a first line treatment of type II diabetes [4, 5], particularly in overweight people, when diet and exercise have failed to control.

In recent years, in many countries generic copies of the reference medicinal products containing identical amounts of the same active ingredient in the formulation and same route of administration were made and generic drug products have become very popular. Evidences point to the fact that different products with the same amount of active pharmaceutical ingredient have shown distinct differences in their therapeutic effects [6]. This may be due to the differences in rate and extent of absorption, possibly by the reason of difference between the purity of active ingredients, type of excipients, proportion between them and the manufacturing variables such as the influence of mixing method and granulation procedure as well as coating parameters [7]. Therefore there are serious concerns that various generic substitutions may have different bioavailability and couldn't be used interchangeably.

Two pharmaceutical products are considered to be equivalent when their bioavailability factors are so similar that they could show clinically comparable therapeutic effects. Bioequivalence (BE) studies focus on the drug release from the formulation and subsequent absorption into the systemic blood circulation, which consist of both in vivo and in vitro studies [8]. Until recent years, bioequivalence was determined only by in vivo tests. However, there are many reports that have been utilized in vitro bioequivalence studies instead of in vivo bioequivalence tests or immediate release solid oral dosage forms of highly soluble drugs. Therefore in vitro tests can be used solely to determine bioequivalence of products [9].

Several analytical methods have been reported for the determination of metformin in tablets such as: high performance liquid chromatography (10), Nuclear Magnetic Resonance [11] UV-VISspectrometer [12]. Most of these methods are tedious and time-consuming, involving complex sample preparation.UV spectroscopy is simple, precise, accurate and economical technique for estimation of drugs and amongst the wide variety of available techniques.Hence the present study was carried out to investigate the bioequivalence of different metformin tablet products made by national and international companies.

MATERIALS AND METHODS

This comparative study was carried out in the School of Pharmacy Faculty of Medical Sciences, University of Sulaimani between March 10th to May 7th 2016. It's ethically granted by the ethical committee of Faculty of Medical Sciences.

Chemicals and samples

The working standard of Metformin-HCl was provided by Abhilash Chemicals and Pharmaceuticals Private Ltd, India (batch No.MET/01/14010088). Five different products of Metformin tablets were investigated in this study, two local Iraqi Manufacturers and Three international manufacturers (table 1).

1. Content Assay

The methods described in this study are in line with United States Pharmacopeia (USP) [13].

Standard solution preparation

The standard solution was prepared by dissolving 2 mg of standard material (metformin hydrochloride RS) in distilled water until the concentration of 10 µg/mL was obtained, from which four different aliquots were prepared.

Sample preparation

The assay solution was prepared by weighing and powdering 20 tablets of metformin hydrochloride. A portion that was equivalent to100 mg of metformin hydrochloride was then transferred to a 100-mL volumetric flask to which 70 mL of water was added and shaken by mechanical means for 15 minutes. The resulting mixture was diluted with water to 100-ml volume and filtered, and then the first 20 mL of the filtrate was discarded. Furthermore, an aliquot of 10.0 mL of the filtrate was diluted with water to 100.0 mL, this step was repeated to come up with the final solution.

The absorbance of both standard and assay preparations was determined using 1-cm cells at the wavelength of maximum absorbance at about 232 nm using water as a blank. An ultraviolet-visible (UV-VIS) spectrometer (shimadzu UV-1800, Japan) was used to perform the content assay.

2. Dissolution Test

For the making of the standard curve, five solutions having different concentrations of 5, 10, 15, 20 and 25 mg/L were prepared. In a dissolution apparatus (CALEVA dissolution tester, UK) biological conditions are maintained by providing appropriate dissolution media and keeping the temperature at 37 °C throughout the test with the help of thermostat. The percentage of the released metformin was then assessed by using an UV-Vis spectrometer at the wavelength of maximum absorbance, which was 234 nm.

3. Friability Test

This test is performed to make sure that the edges of tablet do not break away. Roche friabilator was used to study the friability of the five different brands of metformin.

As a principle, for tablets weighing less than 650 mg, 10 tablets should be tested. The tablets were dedusted with a brush, weighed then placed in the drum. The drum was then rotated at 25 RPM for 4 minutes, which resulted in a total of 100 rotations.The tablets were cleaned with a brush then weighed, a weight loss of less than 1% was considered to be acceptable.

The assays were carried out by inserting one tablet of each brand in a basket and attach the rod using apparatus 1. The test was initiated by turning on the motor at a speed of 100 RPM and a syringe was employed to withdraw 10 ml at 5, 10, 15, 30, 45 and 60 min, respectively. The withdrawn aliquots were filtered and placed in plastic containers, then placed in 500 ml volumetric flasks and diluted to the mark.

The amount of metformin hydrochloride RS dissolved was determined by employing UV spectrometer at the wavelength of maximum absorbance at about 233 nm on filtered portions of the solution under test. Distilled water was used as blank.

Table 1. The five products of metformin tablets studied and their manufacturing information

Manufacturer	Country	Batch No.	Prod. Date	Exp. Date
Pioneer	Iraq	150064A	1/1/15	1/1/2018
Awamedica	Iraq	DN4014	1/7/14	1/6/2017
Macleods	India	HMK503A	1/10/15	1/9/2018
Bristol	UK	BUH065053	1/2/15	1/2/2019
Merck	France	281064	1/1/15	1/12/2019

RESULTS

Content Assay

The standard curve was linear over five different concentrations (Figure 1). The intercept and slope were, 0.00003 and 0.236, respectively.

As specified by US Pharmacopeia 2015, the content should not be less than 95% and not more than 105% of labeled amount. Results in figure 2 indicate that all five products stayed within the acceptable limits.

Dissolution profile

The standard curve for the dissolution test was linear over five different concentrations. The intercept and slope were, 0.001 and 0.1316, respectively (figure 3).

To compare the dissolution profiles, dissolution curve (based on mean percentages of drug released) of five different brands were compared in figure 5.

Comparison of the dissolution curves shows that all five brands, as expected for highly soluble compound, metformin, showed at least 80% release in 30 min. Therefore all formulations passed the acceptance pharmacopeia criteria (2015).

Friability

All the five brands underwent testing for friability showed less than 1% loss, which means that they were all within the normal range (figure 4). Tablets manufactured by Merck showed minimum loss after the friability test.

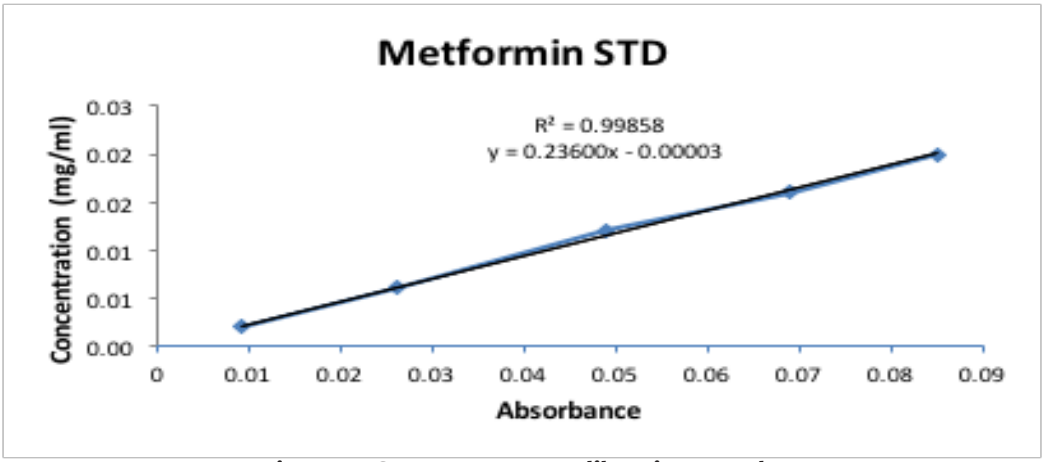

Figure 1. Content Assay calibration graph.

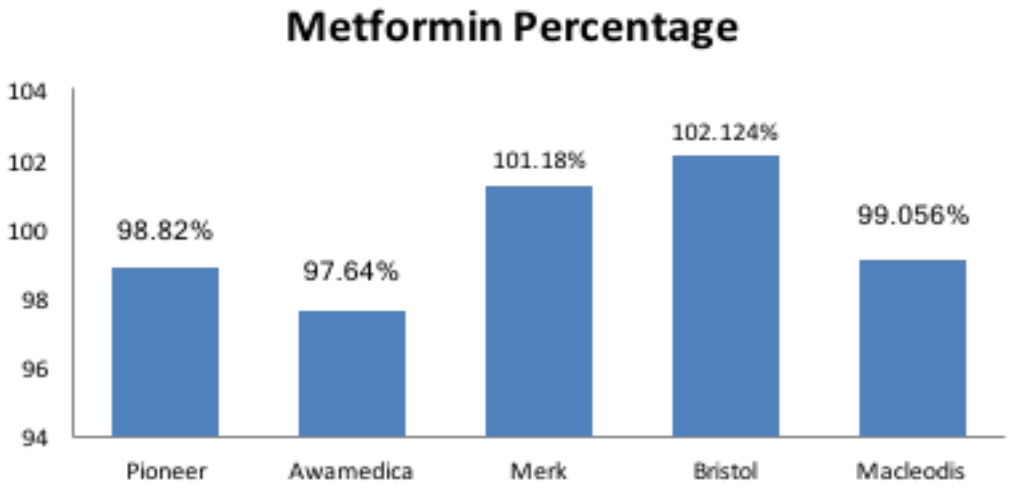

Figure 2. Content Assay recovery percentage.

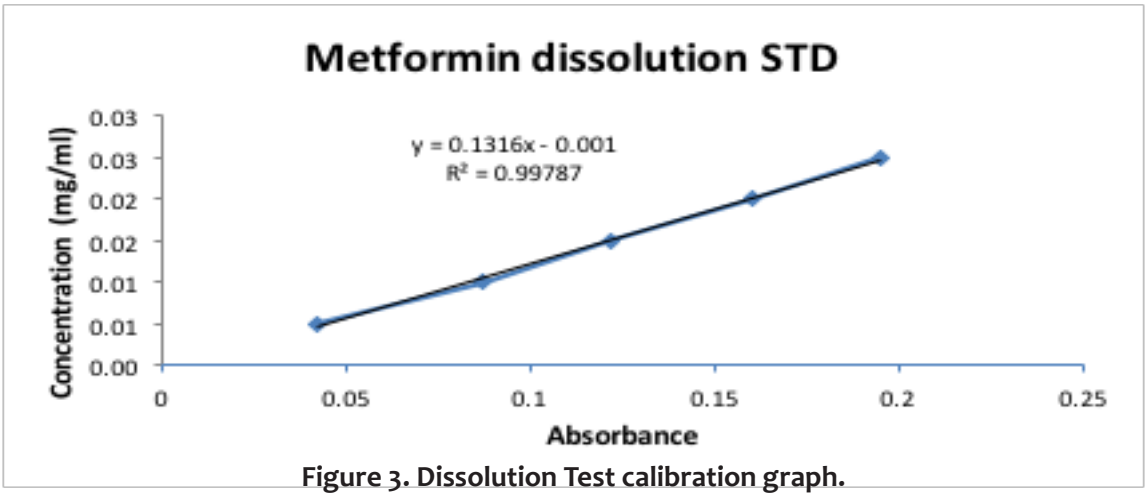

Figure 3. Dissolution Test calibration graph.

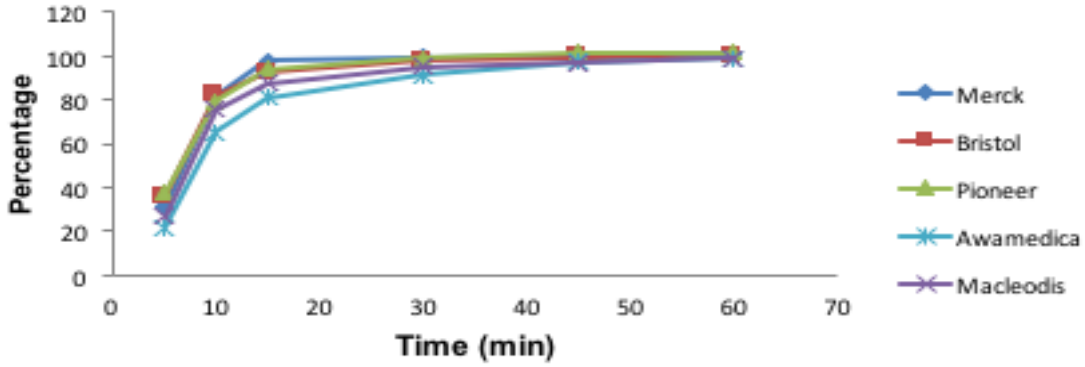

Figure 4. Dissolution profiles of the five metformin tablets.

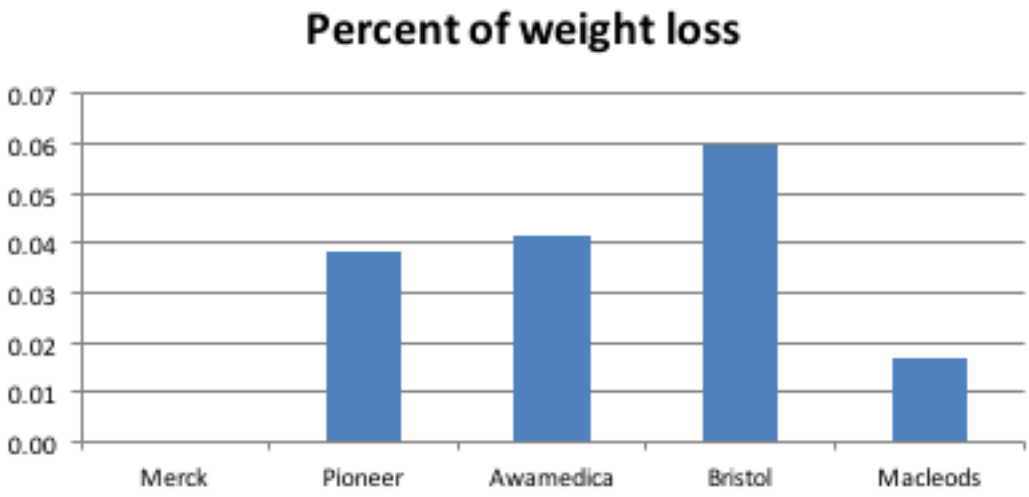

Figure 5. Percentage of weight loss after friability test.

DISCUSSION

Even though the use of generics is an important opportunity to reduce health care expenditure, there is a concern about the quality and clinical effectiveness of these medications, thus studying the equivalence of generic drugs is considered extremely important. In vitro equivalence is the study of different products of a same drug and its dosage forms. Two different formulations of a same drug are equivalent when their rate of dissolution and absorption is same.Generic copy should be therapeutically equivalent to the original drug.

In vitro equivalence studies evaluate the safety and efficacy of generic formulations. When 2 formulations of the same drug are equivalent in the rate and extent to which the active drug ingredient is absorbed, and becomes equally available at the site of drug action, they are equivalent and thus are assumed to be therapeutically equivalent.

In order to protect patients, these generic formulations must be demonstrated to be therapeutically equivalent to an innovator formulation.

The fundamental reason for performing bioequivalence testing is to ensure, as far as possible, that there are not any important differences in safety and efficacy between a generic and an innovator drug formulation and the formulations are therapeutically equivalent. Moreover, it has been shown that changes in pill colors and shapes increase the risk of non-adherence among patients.

In our study, The dissolution profiles showed that all five brands of metforminreleased at least 80% of their contents in 30 min. Therefore all formulations passed the acceptance US pharmacopeia criteria (2015).

It is worthy to mention that, metformin tablets produced by Pioneer showed faster dissolution rate, as compared to other manufacturers, both during the first five minutes and after sixty minutes, which can be related to its chemical composition.

Friability is a phenomenon where surface of tablet is damaged or shows a site of damage due to mechanical shock. We observed that tablets manufactured by Bristol showed maximum loss while tablets manufactured by Merck showed minimum friability,as compared to other brands, with 0% weight loss after the completion of the test.

In conclusion, the results of the study indicate that all five brands of metformin included in this paper, which are available in Iraqi markets, are equivalent to those produced by the mother company, as investigated by their content, dissolution and friability profiles.

The authors disclose that they have no conflict of interest in this study.

REFERENCES

1. Bailey CJ, Day C (1989) Traditional plant medicines as treatments for diabetes. Diabetes Care 12:553–564.

2. Budavari S, editor. The Merck Index. 13th ed. Whitehouse Station: Merck & Co Inc; 2001. p. 998.

3. Davidsen M B and Peters A L, Am J Med.,1997, 102, 99-110.

4. Inzucchi SI, Bergenstal RM, Buse JB et al (2015) Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centered approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 58:429–442

5. Kirpichnikov D, McFarlane S I and Sowers J R, Ann Intern Med.,2002, 137(1), 25-33.

6. DPP Research Group, N Engl J Med., 2002, 346, 393-403.

7. Pillay V. and Fassihi R. Evaluation and comparison of dissolution data derived from different modified release dosage forms: an alternative method. J Control Release. 1998; 55(1): 45-55.

8. Polli J. E. In vitro studies are sometimes better than conventional human pharmacokinetic in vivo studies in assessing bioequivalence of immediate-release solid oral dosage forms. AAPS J. 2008; 10(2): 289-299.

9. Anderson N. H., Bauer M., et al. An evaluation of fit factors and dissolution efficiency for the comparison of in vitro dissolution profiles. J Pharm Biomed Anal. 1998; 17(4-5): 811-822.

10. Arayne, M. et al. (2006). Development and validation of RP-HPLC method for analysis of metformin. Pak J Pharm Sci. 19 (1), p232.

11. Gadpe, H.H. and ParkishK.S.. (2011). Quantitative Determination and Validation of Metformin Hydrochloride in Pharmaceutical Using Quantitative Nuclear Magnetic Resonance Spectroscopy. E-Journal of Chemistry. 8 (2), 767.

12. Umapathi, P. et al. (2012). Quantitative Determination of Metformin Hydrochloride in Tablet Formulation Containing Croscarmellose Sodium as Disintegrant by HPLC and UV Spectrophotometry. TROP J PHARM RES. 11 (1), 107.

13. The United States Pharmacopeia 30: The National Formulary 25.2015 Rockville, the United States Pharmacopeial Convention, Inc,p433