



ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2018; 7(6): 05-08
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www.thepharmajournal.com
Received: 02-04-2018
Accepted: 04-05-2018

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Comparative *in vitro* dissolution test and other physicochemical parameters of some commercially available metformin HCl brands in Bangladesh

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Abstract

Metformin is an oral anti diabetic medicine that helps control blood sugar levels used together with diet and exercise in adults with type 2 diabetes mellitus. The aim of this work was to evaluate the quality parameters of three marketed brands of Metformin HCl 500 mg available in Bangladesh and to do a comparative study of these brands. In weight variation test highest positive and negative percent deviations were +2.491 and -3.361 which were within the limits. Average diameter, thickness, hardness and friability were found within the limits. Potency of brand A, B and C were 100.42%, 100.06% and 104.6%, respectively. All the samples had shown satisfactory percent drug release (>80%) within 30 minutes. Dissolution studies were performed using USP type II apparatus at a temperature of $37\pm 0.5^\circ\text{C}$, 100 RPM, 900 ml phosphate buffer (pH 6.8) and samples were estimated spectrophotometrically at 231 nm. After sixty minutes *in-vitro* dissolution study of sample A, B and C, an average % drug release of 98.96%, 100.165% and 100.77% were found, respectively. All the brands of Metformin HCl successfully met the quality parameters.

Keywords: Bangladesh, Bioavailability, Disintegration Test, Dissolution Test, Metformin HCl.

Introduction

Diabetes is one of the major causes of death and disability in the world. The latest, WHO estimate for the number of people with diabetes worldwide, in 2000, is 171 million, which is likely to be at least 366 million by 2030. The focus of medical community is on the prevention and treatment of the disease. Though there are so many route of administration but oral route is more convenient for the patients [1]. Metformin HCl is now a widely used oral medication to treat type 2 diabetes. This study was performed to compare the dissolution, potency, hardness, disintegration time of marketed brands of Metformin HCl available in Bangladesh. The use of oral anti-diabetic drugs for treatment of type 2 diabetes increases rapidly. It is widely used with the discovery and approval of several new types of oral anti-diabetic drugs with different mechanism of pharmacological action [2]. It is usually called an antihyperglycemic rather than a hypoglycemic drug [3]. Metformin act as an insulin sensitizer that improves hyperandrogenism and ovulation as well as pregnancy rates in patients with polycystic ovary syndrome (PCOS), nonalcoholic fatty liver disease (NAFLD) and premature puberty [4]. In order to achieve an optimal therapy, there are continued efforts to improve the pharmaceutical formulation of metformin hydrochloride. After its patent expiry in 2001, formulation development has accelerated [5].

At present time, it is believed that Metformin HCl is 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. In fact, in the major UKPDS (United Kingdom Prospective Diabetes Study), it was the only drug that reduced diabetes-related death rates, heart attacks, and strokes. Metformin has been also been shown to be effective in normal weight patients [6]. Alcoholic and people who have congestive heart failure, or have significant kidney, liver, lung diseases should avoid metformin. It does not cause weight gain, helps combat hyper-triglyceridemia, and has been ascribed some vaso-protective properties. In case of overweight noninsulin-dependent diabetes mellitus (NIDDM) patients Metformin provides convenient treatment [7].

During this study, three units from each brand of Metformin HCl 500 mg were tested for dissolution and potency was compared. Other physical quality parameters like diameter,

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thickness, hardness, disintegration time were measured. Every parameter was performed comparing with the standard protocols and was within the standard range.

Materials and Methods

Materials

Drug

Standard of Metformin HCl was supplied by University laboratory.

Dosage form

Metformin HCl 500mg of three different brands were purchased from local medicine shop at Green Road, Dhaka. The sample was purchased by checking their manufacturing license numbers, production batch numbers, manufacturing and expiry date. They were coded as brand A, B and C.

Solvents and Reagents

Potassium dihydrogen Phosphate was taken from DAEJUNG chemicals and metals (LOT NO: P21010D) and Sodium Hydroxide was taken from Merck Specialties Private Limited, Mumbai (LOT NO. OF30631279). Distilled water was used during preparation of the media.

Method

Diameter and Thickness

20 tablets were taken from each brand and their diameter and thickness was measured by digital slide caliper to calculate average diameter and thickness. Tablet thickness should be controlled within a range of $\pm 5\%$ [8].

Hardness Test

Tablet hardness is an important parameter for giving optimum effect in body. If the tablet is too hard it will not disintegrate at required time and fail to meet the dissolution specification, if it is too soft that will create difficulties in transporting the tablets [9]. The crushing strength (N) was determined with an Automatic Tablet Hardness Tester (DrSchleuniger Pharmatron, Switzerland). The force applied to the edge of the tablet was gradually increased until the tablet was broken. 3 tablets were randomly selected from each brand and the pressure at which each tablet crushed was recorded.

Friability Test

Seven tablets from each brand were weighed (W1) and subjected to abrasion by employing a Roche friabilator operated at 25 RPM for 4 minutes. The friabilator was divided into two plastic chambers. During each revolution the tablets were made to fall from a distance of six inches to undergo shock. After 100 revolutions the tablets were weighed (W2) again. The loss in weight indicated the friability [10].

Determination of Uniformity of Weight

Weight variation test was run by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average according to USP. If more than 2 tablets are outside the percentage limit then the tablets fails the USP test [11]. 20 tablets from each three brands were weighed individually with an electrical analytical weighing balance (OHAUS Pioneer, USA). The average weight for each brand was determined as well as the percentage deviation from the mean value were calculated.

Disintegration Test

Three tablets from each brand were employed for the test in distilled water at 37 °C using a Tablet Disintegration Tester (Model: VDT-2, Veego, India). The frequency of the movements of basket was 28-32 cycle per minute [12]. According to BP, the release of drug from the conventional tablet should be 75% in 5 min and 100% in 3-4min [13]. The drug release process from tablets often includes a step at which the tablet disintegrates into smaller fragments. The disintegration time (DT) was taken as the time when no particle remained in the basket of the system [14].

Dissolution Test

In-vitro dissolution study of Metformin hydrochloride tablets were performed by three tablets of each brand for sixty minutes under the standardized condition in 900 ml phosphate buffer (pH 6.8) medium; at the temperature of $37 \pm 0.5^\circ\text{C}$ using USP Apparatus II (paddle) and the rotation per minute (RPM) was set to 100. 231 nm wavelengths were used to detect the drug in UV-VIS spectrophotometer. During dissolution test, 10 ml of dissolution sample was withdrawn at 0, 5, 15, 30, 45 and 60 min and replaced with an equal volume to maintain an ideal sink condition. The concentration of each sample was determined from a eleven point calibration curve (Fig. 1), which was obtained from standard curve of Metformin HCl. Drug lost by per withdrawn from the vessel was considered during the determination of concentration.

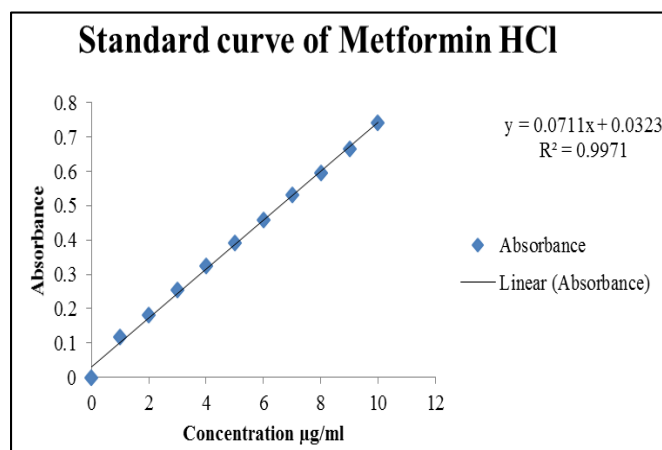


Fig 1: Standard calibration curve of Metformin HCl

Potency Analysis

For most larger-dose drugs in tablet form, the official potency range that is permitted is not less than 95% and not more than 105% of the labeled amount [15]. The potency was determined by crushing four tablets of each different brand. Equivalent to 10 mg of Metformin hydrochloride was taken and dissolved in 100 ml phosphate buffer (pH 6.8) medium and then filtered through 0.45-µm membrane filter paper. 10 ml of the filtrate was taken in another 100 ml volumetric flask and diluted up to 100 ml by using the same medium. Percent potency was assayed by using UV spectrophotometer at 231 nm. It was calculated by using following formula:

$$\% \text{ Potency} = \left\{ \frac{\text{Conc. (mg/ml)} \times \text{Dilution Factor} \times \text{Total Volume (ml)} \times \text{Average Weight} \times 100}{\text{Sample Taken (mg)} \times \text{Strength (mg)}} \right\}$$

Results and Discussions

Weight Variation Test

Weight variation is measured by taking weight of twenty tablets of each different brand and calculating the percent deviation for each tablet. The average weight of the tablets was more than 500 mg and so all branded of tablets are found within the USP limit of 5% deviation. Here we found maximum positive % deviation +2.491 and maximum negative % deviation -3.361 of brand C.

Table 1: Weight variation and percent deviation from average weight

Brand	Average Weight(mg)	Positive % deviation	Negative % deviation
A	697.9	1.447	-1.848
B	598.1	0.684	-1.174
C	591.95	2.491	-3.361

Diameter Determination

Average diameter was determined by measuring twenty tablets of each different brand using digital Vernier caliper. Shapes were determined by comparing them with FDA specifications.

Thickness Determination

Average thickness is determined by measuring twenty tablets of each different brand using digital Vernier caliper. With an increasing thickness, there is a decrease in hardness due to compression force and vice versa. The average thickness of brand A, B and C were 7.1405 mm, 3.70 mm and 5.6435 mm, respectively.

Table 2: A summary of quality control tests of three brands of Metformin HCl

Brand	Diameter (mm)	Thickness	Hardness	% Friability	DT (min)	% Potency
A	12.093	7.1405	117.67	0.143	4.49	100.42
B	L-17.6205 W- 6.6205	5.6435	233.33	0.048	4.31	100.06
C	13.1195	3.70	196.00	0.191	4.41	104.6

Potency Analysis

The percent potency was determined by crushing three tablets of each different brand. The percent potency of the tablets as shown in Table 2, were within the limits of USP i.e. not less than 95% and not more than 105% of the labeled amount of drug.

In-vitro Dissolution Study

In-vitro dissolution study is an alternative to bioequivalence studies and it can, therefore, provide evidence for similarities and differences between medicinal formulations. From the point of view of quality assurance, it is more effective using a discriminating dissolution method because that will indicate possible changes in the quality of the product before affecting the *in-vivo* performance of the drug [17]. *In-vitro* dissolution study was performed by three tablets of each brand for sixty minutes under the controlled condition of 900 ml phosphate buffer (pH 6.8) medium at the temperature of 37±0.5°C using USP Apparatus II (paddle), the RPM was set to 100 and wavelength was 231 nm. All the tablets have given satisfactory % drug release within 60 minutes. Not less than 80% (Q) of labeled amount of drug have released according to the USP specifications for Metformin Hydrochloride tablet assay. So, all the tablets comply with the specifications.

Hardness Test

Hardness has a correlation with tablet disintegration. If hardness is more disintegration time will be large, if hardness is lower disintegration time will be short. The hardness of tablets, which is the force required to break a tablet in a diametric compression force [16]. Average hardness was measured for three tablets of each brand. Maximum average hardness found for brand C (233.33N) and minimum average hardness was found for brand A which was 117.67N.

Friability Test

Friability assessment reveals good mechanical strength of tablets. Percent friability was calculated for seven tablets of each different brand using Roche Friabilator. It was within the limit of not more than 1.0% for each tablet which indicates good mechanical strength. Brand B had shown maximum % friability 0.191 and brand C had shown minimum % friability of 0.048.

Disintegration Test

Disintegration means the breakdown of tablets. It has an important connection with the dissolution rate. Disintegration time was determined by counting time required for breaking down three tablets of each different brand. The average time required for disintegration of tablets was within the limits of USP specification (not more than 30 minutes) for uncoated tablets. Average disintegration time of three brands was 4.49 min, 4.31 min and 4.41 min, respectively. Maximum standard deviation was found 0.0987 for brand A and minimum standard deviation was found 0.0331 for brand C.

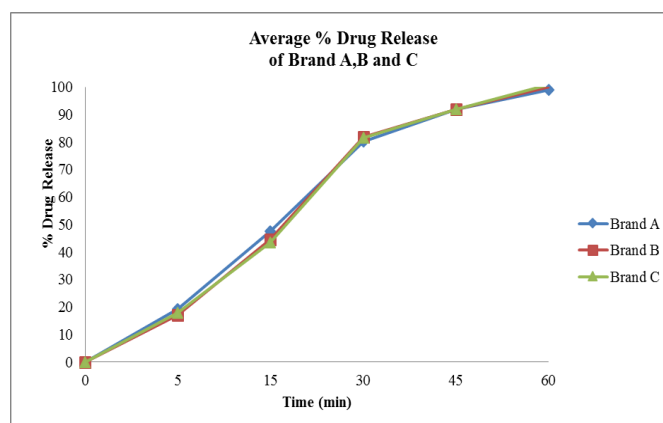


Fig 2: Graphical Presentation of Average % Drug Releases of Tablets of Brand A, B and C

Conclusion

In this competitive condition of pharmaceuticals every products have to give optimum result. For detecting the right product *in vitro* dissolution studies are very beneficial. This study shows the chemical equivalence of the products. The drugs from three brands comply with all specification. They

fulfill all the specification and no drug crossed the range in any criteria.

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