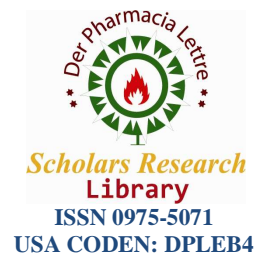




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Comparative *in-vitro* evaluation of four different brands of metformin HCl available in Kanpur district, India

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ABSTRACT

Metformin hydrochloride is an oral anti-diabetic drug used mainly to treat type II diabetes mellitus and available as several brands in the market which make it difficult to select the safe, effective and economic one. The aim of this research work was to check, compare and evaluate the quality standards of different brands of Metformin hydrochloride tablets available in local market of Kanpur, India. Four brands of Metformin tablets (500mg) were selected and evaluated comparatively for their physical and chemical parameters as per official method. The physiochemical equivalence of all the tablet brands were assessed through evaluation of both official and non-official standards such as uniformity of weight, friability, hardness, disintegration, assay and dissolution rate. Disintegration time for all brands was within 15 minutes prescribed by official compendium. All the four brands of Metformin hydrochloride tablets fulfilled the official *in-vitro* dissolution rate test specification more than 70% of the drug is released within 45 minutes. The present finding suggest that almost all brands of Metformin Hydrochloride that are available in Kanpur meet the I.P. specification for quality control analysis and interchangeable.

Key words: Metformin hydrochloride, physiochemical equivalence, *in-vitro*, dissolution rate.

INTRODUCTION

World health organization has estimated that about 30% of the medicines are counterfeit on sale for the consumption in many countries in Latin America, Africa and parts of Asia. The process of fraudulently manufacturing can apply to both generic and branded products and could include products with the wrong ingredients, without active ingredient, with insufficient active ingredient or fake packaging [1]. While the substandard drugs are genuine drug that do not meet with quality specifications claimed by their manufacturers during laboratory testing. The introduction of generic drug product from multiple sources into the health care delivery system of many developing countries for improving the overall health delivery system in such countries. Quality of medicinal drugs in many underdeveloped countries is inadequate. In some cases, use of poor quality medicines has resulted in treatment failure [2].

Metformin Hydrochloride is chemically N,N-dimethylimidodicarbionimidic diamide hydrochloride (1,1-dimethylbiguanide hydrochloride), belongs to the 'biguanide' class (figure 1) [3,4]. It is an oral anti-diabetic drug used mainly to treat type II diabetes mellitus. They act by decreasing intestinal absorbance of glucose, increasing insulin sensitivity and suppressing glucose production by the liver [5, 6, 7]. Many brands are available for

Metformin hydrochloride in the Indian market. The study was committed to evaluate the quality of the different brand of Metformin. The biological half life of Metformin HCl is 1.5-4.5hrs. So, conventional Metformin HCl tablets should be administered 2-3 times a day to maintain the therapeutic effect of the drug throughout the day [8].

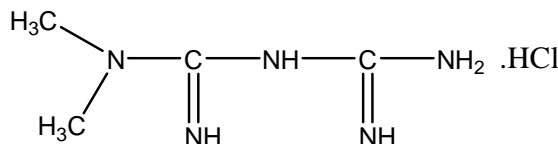


Figure 1: Chemical structure of Metformin hydrochloride

The aim of this research work was to check, compare and evaluate the quality standards of commercially available Metformin hydrochloride tablets as prescribed by I.P. used for the type II diabetes mellitus. Four brand of Metformin hydrochloride were evaluated comparatively for their physical and chemical parameters. The performed physical and chemical tests like in-vitro dissolution, disintegration, hardness, friability, percentage purity etc. were found to be varying for each tablets, but within the specified limits [9, 10].

In-vitro bioequivalence studies are commonly used to assess therapeutic equivalence, but these studies involve invasive procedure. The Biopharmaceutics classification system (BCS) can be used to reduce in-vivo bioequivalence requirement. In-vitro dissolution test based on BCS are acceptable for establishing the bioequivalence of generics with the innovator products [11]. Metformin hydrochloride is highly soluble and low permeability, it therefore a BCS class 3 drug and is eligible for bio-waiver based on the WHO criteria. Dissolution time is the time required for the tablet to go into solution in the suitable medium, dissolution rate is the rate of which a drug goes into solution, both these are determined in simulated gastric fluid at 37°C by the help of dissolution instrument. After oral administration, a tablet undergoes disintegration on and then the drug goes into the solution. The rate of absorption and bioavailability of the drug are directly related to the dissolution rate of the drug [12, 13].

MATERIALS AND METHODS

2.1 Sample

Metformin hydrochloride, having label strength of 500mg of four different brands was purchased from a Kanpur city, India. All the study was performed within product expiration dates. The different brands were listed in table 1.

Table 1: List of the tested commercial Metformin hydrochloride tablets

Brand	Batch No.	Expiry date	Manufacturer
Melmet [®]	MEAD0099	04/ 2017	Micro Labs Limited
Obimet [®]	AMA0232	04/ 2018	Acme-Formulation Pvt. Ltd.
Glycomet [®]	32001062	09/ 2019	USV Limited
Glyciphage [®]	MI5039	06/ 2018	FRANCO-INDIAN Remedies Pvt. Ltd.

2.2 Chemicals and Reagent

Metformin hydrochloride powder (Reference standard) was a gift from Novartis Pharmaceuticals Pvt. Ltd., Hyderabad.

The entire reagent used was of analytical grade. Freshly distilled water was used throughout the work.

2.3 Visual Inspection

The shape, size and color of the different brand of Metformin tablets were examined visually. The size and thickness of tablets from each brand was examined with the help of Vernier caliper.

2.4 Uniformity of Weights

Sample tablets (20) of each brand were weighed individually on a digital analytical balance. The average weight was determined and the percentage (%) deviation of the individual tablets from mean weight was determined. In order to pass weight variation test, the tablet should be within the limits of the percentage deviation allowed by I.P.

2.5 Hardness Test

The hardness of different brand of tablets was determined by Monsanto hardness tester and measured in terms of Kg/cm². Sample tablets (10) of each brand were taken, a tablet placed between the spindle of the hardness tester machine until the tablet breaks and the pressure required to break the tablet was recorded.

2.6 Friability Test

Ten tablets of each brand were taken and weight, these tablet subjected to abrasion using a Roche friabilator at 100 revolutions for 4 minutes. The tablets were dedusted carefully and weighed accurately again then percentage of weight loss recorded. The friability of the tablets was calculated using the formula.

$$\% \text{ Friability} = [(\text{Initial weight} - \text{Final weight}) / \text{Initial weight}] \times 100$$

2.7 Disintegration Test

Tablet disintegration time of randomly selected six tablets of each brand was determined at 37°C using disintegration apparatus employing distilled water as test fluid. The disintegration time was taken to be the time no granule of any tablet was left on the mesh.

2.8 Estimation of Metformin Hydrochloride

An U.V. spectrophotometric method based on the measurement of absorbance at λ_{max} 232nm in phosphate buffer of pH 6.8 was used for estimation of Metformin hydrochloride. Before performing dissolution test, ten serially diluted solution of reference standard (Metformin hydrochloride) and a standard solution curve drawn. The curve was linear between concentration range 1-10 µg/ml. Mean peak absorbance was plotted against the concentration to form the calibration curve. The regression equation was established.

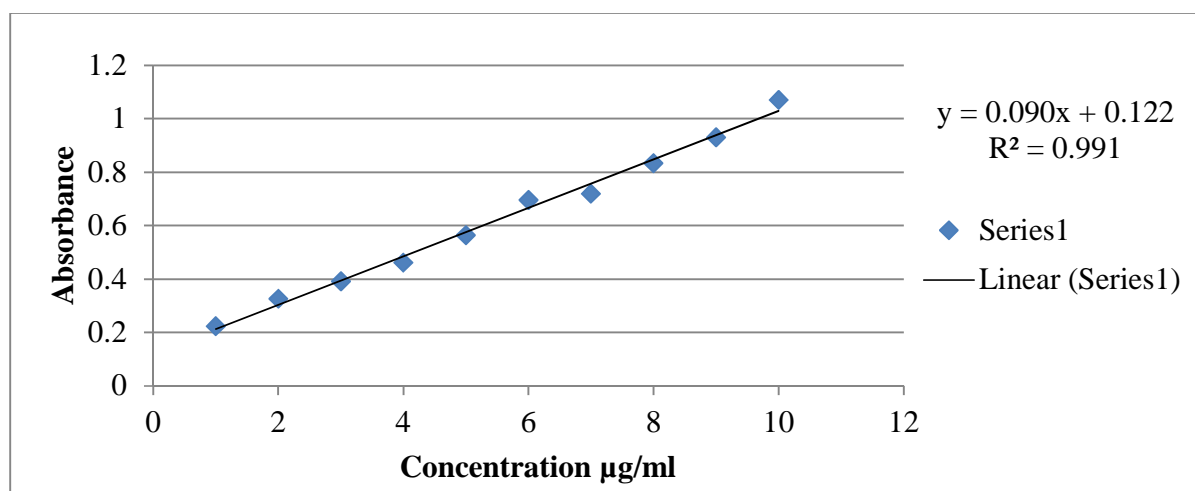


Figure 2: Calibration curve of Metformin Hydrochloride

2.9 Dissolution rate determination

Dissolution rate of the each brand of tablets was determined using an 8-compartment Veego dissolution test apparatus using paddle stirrer at 100 rpm and at temperature of 37±0.5°C. Phosphate buffer pH 6.8 (900 ml) was used as dissolution fluid. One tablet (500 mg) was used in each test. Sample of dissolution fluid (10ml) was withdrawn at intervals of 5, 10, 15, 30, 45 and 60 minute. A fresh 10 ml dissolution medium was replaced after each sampling to maintain sink condition.

Each of the withdrawn samples was filtered and the filtrate diluted. The absorbance was measured at λ_{max} 232nm using U.V. Visible double beam spectrophotometer (Systronic 2201). The concentration was determined against standard solution of Metformin hydrochloride drug in the same medium. From the concentration, percentage (%) drug release was determined at specified time interval. Each dissolution experiment was run in triplicate (n=3). The percentage of drug released is calculated using formula.

Percentage of drug release (%) = [Amount of drug released (mg/ml)/ drug content in label (mg)] × 100

2.10 Assay of Metformin Hydrochloride tablet

The assay was done to find out the % purity of the given four brand of metformin tablet. The test for assay was carried out using U.V. spectrophotometer method at specific absorbance (232nm) as per Indian pharmacopoeia [14].

RESULTS

3.1 Physicochemical properties of Metformin hydrochloride tablets

Uniformity of weight, hardness, friability, disintegration time and drug content as well as size and thickness are shown in Table 2. The in-vitro percentage drug release of Metformin hydrochloride tablets are shown in Table 3. Figure 2 illustrates the dissolution profile of the all tested Metformin hydrochloride tablets of different brands.

Table 2: The evaluated physicochemical parameters of the different brands of Metformin hydrochloride tablets

Brand	Size (cm)	Thickness (cm)	Uniformity of weight (gm)± SD	Hardness (kg/cm ²)	% Friability	% purity	Disintegration time (min.)
Melmet®	1.60	0.30	0.628±0.006	7.45±0.21	0.462	97.71	7 min 52 sec
Obimet®	1.65	0.35	0.590±0.009	6.74±0.11	0.821	95.11	5 min 30 sec
Glycomet®	1.30	0.35	0.602±0.008	7.98±0.18	0.168	96.56	5 min 15 sec
Glyciphage®	1.60	0.30	0.552±0.006	5.60±0.13	0.110	102.37	5 min 21 sec

SD= standard deviation

Table 3: In vitro percentage drug released of different brands of Metformin hydrochloride tablets

Brand	Drug released (%)± SD					
	5 min	10 min	15 min	30 min	45 min	60 min
Melmet®	28.72±0.7	41.40±0.8	61.20±1.2	84.60±0.9	91.16±1.9	96.92±0.4
Obimet®	33.84±1.2	39.96±0.4	55.98±0.5	73.94±1.4	84.30±1.6	91.20±0.8
Glycomet®	30.14±0.7	49.06±1.3	68.02±1.1	85.07±1.7	92.12±2.1	97.05±0.7
Glyciphage®	32.15±1.1	44.92±0.9	67.04±1.3	82.16±2.1	86.05±1.5	93.92±1.1

SD= standard deviation

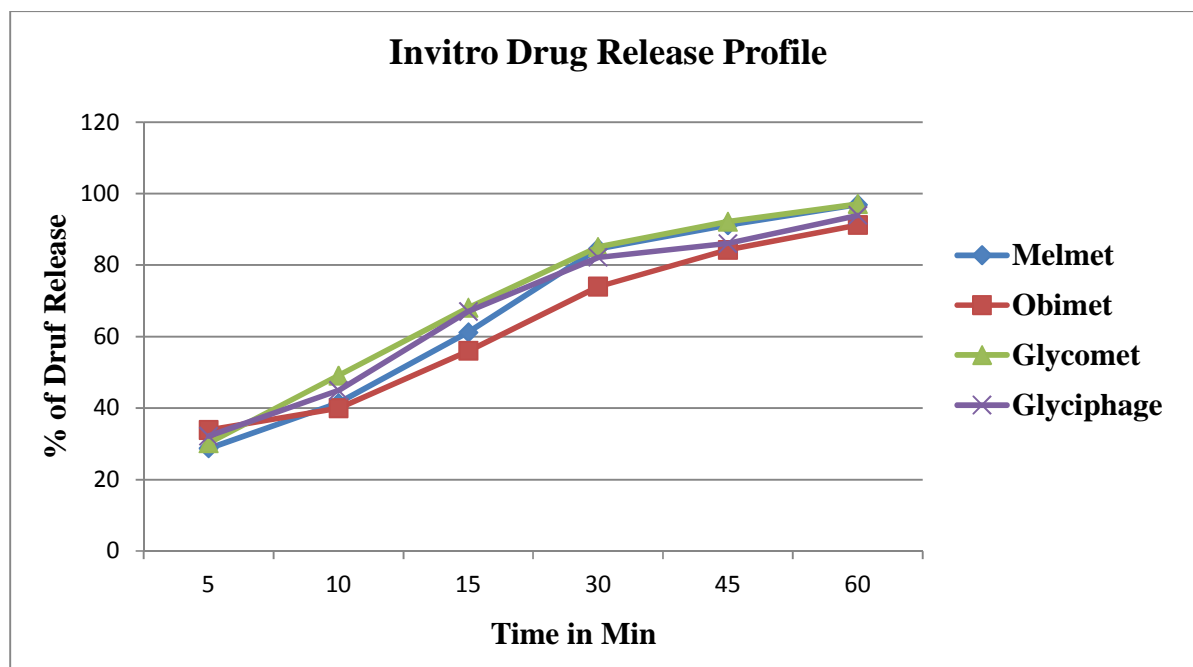


Figure 2: Dissolution profile of the different brands of Metformin hydrochloride tablets

DISCUSSION

Metformin hydrochloride is a widely prescribed oral anti-diabetic drug and its official in I.P. 2007. 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 four different brands of Metformin hydrochloride which are commercially available in Kanpur, India. 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 (Table-2). The size of tablets was in the range of 1.30–1.65cm with all four brands. There is no significant difference between the batches of the brands. The uniformity of weight for the four brands of Metformin hydrochloride tablet gave values that compiled with I.P specification and deviated less than 5% from the mean value. Using hardness tester, the strength of the tablets was tested. Hardness of the tablets was in the range of 5.60 ± 0.13 - $7.98 \pm 0.18 \text{ kg/cm}^2$ with all four brands.

The result of tablet friability test showed that all the brands tested had impressive friability values ranging 0.110% to 0.821% w/w in Table-2. According to I.P. no batch should have a friability value greater than 1%w/w.

The observed disintegration times for all the brands of Metformin hydrochloride investigated was less than 15 min limit prescribed by official compendium (Table-2). The fastest disintegration tablets were of Glycomet[®] brand while the slowest one was Melmet[®] brand. The various brands could have employed different disintegrates to improve the penetration of aqueous liquids.

The result obtained from the assessment of the percentage drug content of four brands of Metformin hydrochloride tablets showed within the monograph specification 95% to 105% of stated amount of Metformin HCl as demonstrated in Table 2.

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. Dissolution data for all the experiments were highly reproducible and hence only the average values were plotted. The dissolution of all four brand tablets indicated the more than 70% of the drug is released within 45 min, which complies with the I.P. (2007) specification (Table 2) [13, 14].

CONCLUSION

It can be concluded from above discussion that all the available brands in local market of Kanpur, India 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 I.P 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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