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A Comparative *In-Vitro* study for Evaluation of different Marketed brands of Metformin Hydrochloride (500 mg) Tablets

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Abstract

Metformin hydrochloride is an first line anti-diabetic drug used for the treatment of type II diabetes mellitus especially in obese patients. Various brands of metformin are available in the market which makes it challenging to select, effective and economic one. The aim of the present research work was designed to examine, compare and evaluate the different marketed brands of metformin tablets for their performance. Four brands of metformin tablets (500 mg) were selected and evaluated comparatively for their physical and chemical parameters as per official method. The physicochemical equivalence of all brands of metformin hydrochloride tablets were determined through the evaluation of official standards according to the USP, IP including uniformity of weight, friability, hardness, disintegration time, dissolution profile and drug content. Weight variation and friability test of all brands was within the specified limit.

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 80 % of the drug is released within 30 minutes. UV analysis of different sample shows that the percentage content of active ingredients of four brands of metformin hydrochloride tablets was within the monograph specification (95 – 105 %). All the four brands of metformin hydrochloride tablets taken for comparative evaluation gives different result from each other but meet the pharmacopoeial specification for quality control analysis. The result indicated that all the selected brand fulfilled the required official specification and thus if one brand is not available in the marketthenany of the other brands can be used freely as a substitute of that unavailable brand.

Keywords: Metformin hydrochloride, In–vitro study, Physicochemical equivalency, Dissolution rate, Comparative evaluation

Introduction

Oral drug delivery is the fastest and more preferred route for the drug administration is also the largest and oldest segment of the total drug delivery market.[1] Metformin is the drug approved by USFDA as prescription medication to treat diabetes.[2]Metformin HCl is an oral anti-diabetic drug from the biguanide class of oral hypoglycemic agents**.** Metformin is the first-linedrug of choice for the treatment of non-insulin dependent diabetes mellitus (type II diabetes)particularly in overweight and obesepeople and those with normal kidney function.[3]

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Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia, altered metabolism of carbohydrates, fats and proteins with an increased risk of complication of vascular diseases. Type II diabetes mellitus is a clinical syndrome due to relative orabsolute deficiency of insulin (defects in insulin secretion)or resistance to the action of insulin atthe cellular level as a result hyperglycemia and glycosuria occurs.Type II diabetes mellitus is associated with disturbances in learning, memory, and cognitive skills in the diabetic patients.Metformin was first described in the scientific literature in 1922, by Emil Werner and James Bell, as a product in the synthesis of *N*, *N*dimethyl- guanidine free user. French physician Jean Sterne published the first clinical trial of Metformin as a treatment for diabetes. It was introduced to the United Kingdom in 1958, Canada in 1972, and the United States in 1995. 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.

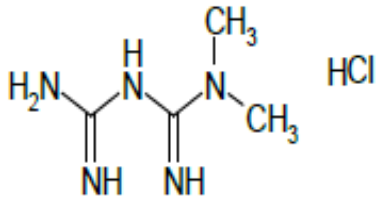

Fig. 1: Structure of Metformin HCl

Metformin hydrochloride is also being used increasingly in polycystic ovary syndrome (PCOS) which is a syndrome of ovarian dysfunction and hyperandrogenism. Metformin, an insulin sensitizer, not only improves hyperandrogenism but also improves ovulation as well as pregnancy rates in patients with PCOS, nonalcoholic fatty liver disease (NAFLD) and prematurepuberty.

Chemical name of metformin hydrochloride is 1,1-Dimethylbiguanide hydrochloride($C_4H_{11}N5$, HCl) with a molecular weight of 165.6 g/mol. Metformin hydrochloride acts by decreasing intestinal absorption of glucose, increasing insulin sensitivity,suppresses glucose production, especially hepatic gluconeogenesis andimproves peripheral tissue insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin hydrochloride works by improving the body's sensitivity to insulin, allowing it to use glucose in the normal wav. 4.5.6

Metformin helps to control the amount of glucose (sugar) in your blood. It decreases the amount of glucose you absorb from your food and the amount of glucose made by your liver. Metformin also increases your body's response to insulin, a natural substance that controls the amount of glucose in the blood. Metformin is not used to treat type 1 diabetes (condition in which the body does not produce insulin and therefore cannot control the amount of sugar in the blood).[7]

The quality of pharmaceuticals is a global concern, counterfeit medicines are increasingly detected worldwide. Drug products that are chemically and biopharmaceutically equivalent must be identical in strength, quality, purity, active ingredient release profile and should be in the same dosage form, for the same route of administration. In order to ensure the requisite quality, drug manufacturers are required to test their products during and after manufacturing and at various intervals during the shelf life of the product. As such the need to ensure that the generic and branded drugs products are pharmaceutically equivalent cannot be overemphasized and the necessity to select one product from several generic drug products of the same active ingredients is the cause for concern. When there is shortage in market of the multinational brand and some life saving drugs, the patients are always reluctant to take the alternate local brands of same generic. If the patient does so, he would not psychologically satisfy & ultimately results in poor patient compliance. Some multinational brands are out of reach from buying due to high prices and comparatively local brands of same generic are available at much lower prices.[8]The quality of marketed drugs determines the quality of treatment patients receive, which in turn ensures their well-being. Constant screening of marketed drugs by the drug regulatory authority or a consumer organization, using pharmacopoeial methods, therefore enables consumers to be aware of the quality of drugs available to them.[9]It is therefore very mandatory to lay quality assurance mechanism to ensure the authenticity of pharmaceutical products. *In vitro* quality

parameters such as drug content and dissolution tests are important quality indicators of solid oral dosage forms such as tablets.[10]

As per pharmaceutical standards, the parameters like weight variation, hardness, friability, disintegration, dissolution and content uniformity should be checked to assure the effectiveness of any drug. The prediction of the in-vivo bioavailability of most oral drugs depends on the in-vitro dissolution studies. Dissolution testing of drug products plays an important role as quality control tool to monitor batch to batch consistency of drug release from a dosage form. It is a vital tool used to evaluate the pharmaceutical quality of different brand of drugs and to determine their possible equivalence.Various brands of metformin are available in the market so the quality of the various brands commercially available should be ensured in order to assess their quality control which helps in the selection of brand of the drug.[11,12]

Evaluation and comparative study of quality control parameters is important because standard quality parameters are essential for better quality of medicine. The study aim was to analyse the four different brands of Metformin 500mg tablets for its quality by performing weight variation, Hardness, friability, disintegration, pharmacopoeial assay and dissolution test methods as prescribed by the US pharmacopeia and Indian pharmacopeia.

Material and Methods

Chemicals and reagent

Metformin hydrochloride, having a label strength of 500mg of four different brands were purchased from registered pharmacy shop of rural area of Nagpur and were coded as A,B,C,D. All the study was performed within product expiration dates. All the used reagents like potassium-di-hydrogen phosphate, Sodium hydroxide were of analytical grade. Freshly prepared distilled water was used throughout the work. Finally the following four different brands were taken for evaluation.

Code	Brand	Manufacturer
A	Glycomet	USV Ltd.
B	Glyciphase	Franco Indian pharmaceuticals Ltd
C	Okamet 500	Cipla Ltd.
D	Glycirite 500	MHS pharmaceuticals Pvt. Ltd

Apparatus and Equipments

Double beam UV-Visible Spectrophotometer (Systronic's Model no: 2201), Analytical balance (Electric precision balance, Model no.:3003), Hardness Tester (Monsanto, Mht-20), Tablet Friability Tester (Roche, FTV-2), Disintegration apparatus (ED-2L), Dissolution test apparatus (EDT-08LX) and Ultrasonicator (Toshcon, SW 4) and pH meter (EI) were used.

Methods

Visual Inspection[13]

The shape,colour and texture of the different brands of metformin tablets were examined visually.

Thickness and Diameter[14]

The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter. The thickness and diameter of the tablets were determined by using vernier callipers. Ten tablets were randomly selected and thickness was determined using a vernier calipers and the result was expressed in mean and unit in millimeters.

Weight variation test[15]

The purpose of this test is to verify the uniformity of each batch which ultimately reflect thedrug content uniformity in all the formulation batches. The test was performed as per the official procedure, 20 tablets were randomly selected and weighed individually and also average weight, standard deviation and percentdeviation was calculated.

$$\% \text{ Deviation} = \frac{W_{avg} - W_{ind}}{W_{avg}}$$

Where,

W_{avg}= Average weight of tablets ,W_{ind} = Individual weight of tablet

Friability test

This test is usually performed to check possible wear and tear loss in the tablet during the transportation and this is closely related to tablet hardness. It is usually performed by the Roche Friabilator. Randomly five tablets were selected and their initial weight (W1) was recorded and after that these weighed 05 tablets were placed in

the friabilator and the friabilator was operated for 4 minutes at 25 rpm speed and 100 revolutions, the tablets were weighed again (W2) and the percent loss (Friability) was then calculated by using following formula.

% Friability = [(Initial weight – Final weight)/Initial weight] × 100

The official permissible limit for friability is 1%.

Hardness Test[16]

The hardness of different brand of tablets was determined by Monsanto hardness tester and measured in terms ofKg/cm2. Five sample tablets of each brand were taken, a tablet placed between the spindle of the hardness testermachine until the tablet breaks and the pressure required to break the tablet was recorded. The result was expressed in mean and unit in millimeters.

Tablet Disintegration Test

Tablet disintegration time of randomly selected six tablets of each brand was determined using disintegration apparatus employing distilled water as test fluidat 37 ± 0.2 °C. The disintegration time was taken to be the time no granule of any tablet was left on the mesh.The time taken for tablets to disintegrate was noted down.

Tablet Dissolution[17]

Dissolution test of four brands of metformin hydrochloride was carried out using single flask dissolution apparatus. Dissolution medium used was 0.68 % w/v solution of potassium dihydrogen phosphate, adjusted to pH 6.8 by the addition of 1 M sodium hydroxide. One tablet (500 mg)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 for 45 minutes. A volume of 10 ml of sample was drawn at intervals of 5,10, 15, 20, 30,45 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 and the filtrate diluted. The absorbance of the resulting solutionwas measured at λmax 233nm using UV visible double beam spectrophotometer (Systronic 2201).The % drug release of each brand of metformin hydrochloride tablet was calculated by using standard calibration curve method.

Pharmacopoeial Assay[18]

The assay was done to find out the % purity of the given four brand of metformin tablet. Initially 20 tablets from each brand of metformin hydrochloride were weighed using analytical balance and average weight was taken. Tablets were then powdered using mortar and pestle. Powder equivalent to 0.1g of Metformin hydrochloride was then stirred with 70 ml of distilled water for 15 minutes using a magnetic stirrer. Weighed quantity of powder equivalent to 0.1 g of metformin hydrochloride was transferred to 100 ml of volumetric flask , to it 70 ml of distilled water was added, stirred for 15 minutes and it was diluted to 100 ml with distilled water and filtered. 10 ml of this filtrate was diluted to 100 ml with distilled water. Further diluted the 10 ml portion to 100 ml with distilled water and the absorbance of the resulting solution was taken at the maximum at about 232 nm, the drug content was calculated by taking 798 as the value of taking A (1%, 1cm) at the maximum at about 232 nm.

Results and Discussion

General appearance

The shape, colour and texture were examined visually and result are shown in Table 1.

Thickness and Diameter

The thickness and diameter of all brands of Metformin hydrochloride tablets was measured by using verniercalliper. 5 tablets of each brand were used and average values were calculated. The results are shown in Table 1.

Table 1: Data of shape, colour, texture, thickness and diameter of Metformin HCl tablets

Brand Code	Shape	Colour	Surface texture	Thickness (mm)	Diameter (mm)
A	Rounded	White	Smooth	4.1	13.1
B	Cylindrical	White	Smooth	4.2	11.1
C	Cylindrical	White	Smooth	4.1	12.2
D	Cylindrical	White	Smooth	5.1	14.1

Weight Variation

Tablets were taken, weighed and their average weight was calculated. The test stated that all the four brands of metformin hydrochloride have

passed the weight variation uniformity testwhich complied with the USP specifications for weight uniformity as none of the brands deviated by upto ±5% from the mean value.The results are shown in Table 2.

Friability

Five tablets of all selected brand were weighed and placed in Roche friability apparatus. The % friability of the tablets meet the specification of USP which specifies that the friability study must not lose 1% of their initial weight. The results are shown in Table 2.

Hardness

Hardness of the tablet was determined using the Monsanto hardness tester.The observed results showed that all the selectedbrands of metformin havean acceptable crushing strength or hardness. The results are shown in Table 2.

Disintegration

Disintegration is essential for better bioavailability which results in better absorption and consequently better therapeutic action. The results of disintegration test shows that the disintegration time of all four different brands of metformin tablet is less than 10 minutes which is less than the standard disintegration time proves that all these brands of metformin tablet passes the quality control limits as per the pharmacopoeia. The time taken for disintegration of tablet are shown in Table 2.

Pharmacopoeial Assay

The test for assay is done to find out the actual amount of active ingredient present in the tablet and whether it is the same as the labeled amount. The percentage of drug release of all brands of tablets wasfound within the range as per IP, USP and BP specification. The percent drug content are shown in Table 2.

Table 2: Comparative data of different quality control parameters of four brands of Metformin HCl tablets

Brand Code	Weight variation Mean weight ± SD	Friability %	Hardness Kg/cm^2	Disintegration Time Min.sec	% Drug Content
A	0.930 ± 0.011	0.085	3.3	6.16	98.49
B	0.871 ± 0.007	0.091	4.1	5.24	99.08
C	0.825±0.005	0.099	3.8	5.42	96.33
D	0.985±0.014	0.048	5.0	4.10	97.08

Standard Calibration Curve

For standard calibration curve different solution of increasing concentration of standard Metformin were prepared. The solution concentration of 5, 10, 15, 20, 25, 30,35, 40 µg/ml were prepared by proper dilution. The results are shown in Table 3.

Table 3: Data for standard calibration curve of Metformin HCl

S/No.	Concentration (µg/ml)	Absorbance
1.	5	0.439
2.	10	0.576
3.	15	0.723
4.	20	0.822
5.	25	0.972

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6.	30	1.108
7.	35	1.288
8.	40	1.418
Slope		0.027
Intercept		0.290
Correlation Coefficient		0.997

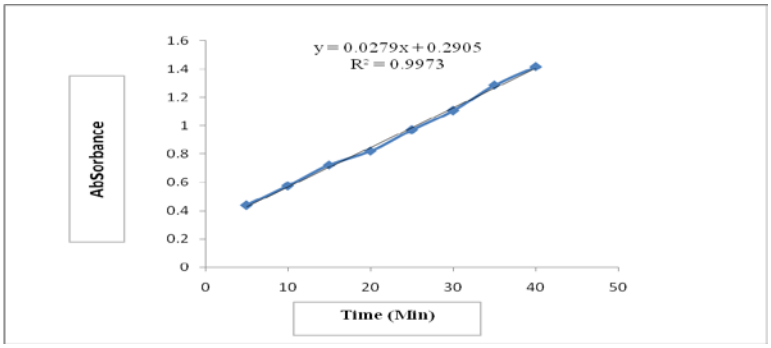

Fig. 2: Standard Calibration curve of Metformin Hydrochloride

Dissolution

Dissolution was another studied important quality control parameters directly related to the absorption and bioavailability of drug.Dissolution of the all the selected brands of metformin hydrochloride tablets was found to be within the specified limits of not less than 80 % in 30 min (USP). The results are shown in Table 4.

Table 4: Comparative study of dissolution of four brands of Metformin HCl tablets

Sr. No.	Time (min)	% drug release			
		A	B	C	D
1.	5	20.78	26.21	21.50	20.06
2.	10	34.70	39.97	30.91	33.39
3.	15	44.60	50.06	51.06	51.46
4.	20	59.25	73.68	64.85	60.07
5.	30	86.30	85.79	84.43	90.56
6.	45	99.34	98.49	99.98	98.71

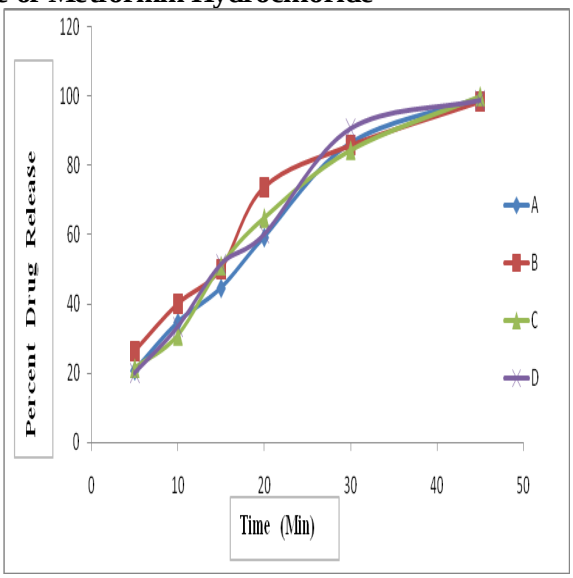

Fig 3.Comparative dissolution profile of four different brands of Metformin HCl

Conclusion

This study was aimed to assess quality as well as physicochemical equivalence of four different marketed brands of metformin hydrochloride.The study confirmed that all brands of metformin hydrochloride tablets complied with the official specification for weight variation, hardness,

friability, disintegration, assay and dissolution. All the evaluated brands of metformin tablet showed the released of about 80% of metformin hydrochloride within 30 min as stipulated in the pharmacopoeia, there exist variations in their release profiles. The percent drug content of all brands ofmetformin hydrochloride tablets are within thepharmacopoeial limit. From the obtained result we were conclude that the selected brands of metformin hydrochloride tablet taken for comparative evaluation of their quality assessment to assure its efficacy and potency gives different results from each other but not a single brand crosses the limits given in official books. The result indicated that the entire selected brand fulfilled the required official specification and thus assures that these brands although manufactured by different pharmaceutical companies it can be used interchangeably. If one of the selected brand is not available in the market then any of the other three brands can be used freely as a substitute for that unavailable brand.

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