

Pharmaceutical equivalent dissertation of Metformin hydrochloride brands

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Abstract: The aim of study is to establish pharmaceutical equivalence of different brands of Metformin tablets available in Karachi, Pakistan. The quality control parameters which are studied are weight variation test, hardness test, thickness, friability, disintegration and dissolution specified by BP/USP (British and United State Pharmacopoeia). Weight variation and hardness value requirement was complied by all brands. Disintegration time for all brands was within range i.e. 15 minutes and also complies with the BP/USP recommendation. All brands showed more than 90% drug release within forty five minutes. The present conclusion suggests that almost all the brands of Metformin that are available in Karachi meet the specification for quality control analysis. Assay performed by HPLC by keeping flow rate of 1.0 ml/min of the mobile phase and the quantitative evaluation at 225 nm was performed. The retention time of Metformin was found to be 2.5min. Method suitability for the quantitative determination of the drugs was proved by validation according to the International Conference on Harmonization (ICH) guidelines.

Keywords: Metformin, analysis and HPLC.

INTRODUCTION

Metformin HCl belongs to drug category Oral Anti-Diabetics of class Biguanides. Its chemical name is *N,N*-Dimethyl-imido-dicarbonimidicdiamide with molecular formula of C₄H₁₁N₅. Its chemical structure is:

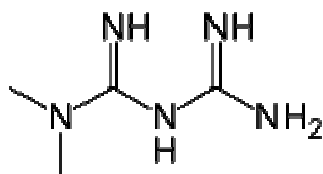


Fig. 1: Structure of Metformin

These tablets are being used as hypoglycemic agents to treat non-insulin dependent diabetes mellitus (type-2) which is also sometimes termed as maturity-onset diabetes as it develops in later life in which insulin secretion appears normal or excessive. Metformin tablets are the first line drug therapy to control high glucose levels in blood in type-2 diabetes mellitus patients (Jones *et al.*, 2009). Metformin tablets work by lowering the amount of sugar in the blood by the following mechanisms (Akinleye *et al.*, 2012):

- It activates a liver enzyme called AMP-activated protein kinase (AMPK), thereby inhibits the production of glucose by liver cells i.e. hepatic gluconeogenesis and thus improves hyperglycemia.

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- It increases the removal of glucose from the blood by muscle and fat tissues. As a result of increased peripheral glucose uptake due to increased insulin sensitivity that results in improved binding of insulin to insulin receptors, it lowers the level of sugar in the blood.
- Initially a dose of 500mg is given 12-hourly with meal to lessen the gastrointestinal side effects and a maximum dose of 3g daily is given in divided doses (Parvin *et al.*, 2012).
- Side effects with these tablets include:
- Gastrointestinal side effects like nausea, anorexia, vomiting, diarrhea
- Lactic acidosis in renal failure patients and
- Hypoxia in cardiac failure patients (Danish 2012).

The bioavailability is 50-60% under fasting conditions. The duration of action is 8-12 hours. The half-life of drug is 6.2 hours. It is not metabolized and excreted unchanged in urine by tubular secretion (Bristol-Myers Squibb 2008).

MATERIALS AND METHODS

The increasing level of use of Metformin HCl develops a need to monitor the quality for the assessment of its quality control parameters of the various brands of Metformin tablets that are available in the market. The objective of this study was to determine the physical and chemical properties of four different Metformin tablets brands marketed in Karachi. These tablets were evaluated by official and non-official standards like weight

variation, the thickness, the diameter, the disintegration and the dissolution with the specifications of British Pharmacopoeia.

Metformin HCl, the film coated tablets, having label strength of 500mg. Different brands were purchased from market in Karachi and the study was performed within product expiration dates.

Uniformity of weight

The sample of the tablets of each brand were weighed together and by using weighing balance (Electronic Balance, Model No.FX-400), average weight was determined. The weight variation of the 20 tablets was conducted for each brand as per specification and the results were recorded.

Thickness

The thickness from individual brand on 10 tablets was measured and also average thickness of tablets of each brand by using Vernier Caliper and the results were recorded.

Diameter

Diameter was determined of 10 tablets of each brand by using Vernier Caliper and also the results of average diameter of tablets of each brand were recorded.

Disintegration test

The disintegration test was performed on 6 tablets from individual brand as per procedure and specification. The disintegration time of 6 tablets of individual brand was determined at 37°C in distilled water using Tablet Disintegrator of Curio Apparatus. The time of disintegration was taken to be the time when any of the granules of tablet was left on the mesh.

Dissolution test

The dissolution test was conducted by the use of basket apparatus as per procedure specified in British Pharmacopoeia on tablets from individual brand. This was determined by using a Tablet Dissolution Apparatus i.e. Basket Type (GDT-7L from Galvano Scientific) containing 900 ml of distilled water maintained at 37°C with a speed of 100rpm. All tablets were put from each brand in each of the compartments and the machine was fixed operated at the intervals of 0, 15, 30 and 45 minutes. In all the experiments, at specified intervals, 10ml of the sample was taken. Absorbance of each of the withdrawn sample at 233nm was determined by using UV-visible spectrophotometer. The concentrations of Metformin tablets present in the samples were determined according to the specified monograph of Metformin in the B.P.

Assay by HPLC

For assay of all formulation solutions were prepared in water, the final concentration of drug injected 200 ppm.

High pressure liquid chromatography system model Shimadzu LC-20 AT, with a UV-visible detector (model SPD-10A (V-vp), connected with CBM-102 communication Bus Module Shimadzu to Intel Pentium 4 with Shimadzu Class LC-20. HPLC Column was used i.e. MEDITERRANEA SEA 18 of dimension 150 mm 4.6 mm i.e. 5 µm.

RESULTS

The results of the physicochemical parameters of four brands of Metformin HCl film coated 500mg tablets were discussed. The three local brands i.e. MET-02, MET-03 and MET-04 compared with the multi-national brand used as standard brand which is shown by having a * sign i.e. MET-01*. The assessments involved evaluation of weight variation, thickness, diameter, disintegration and dissolution studies.

Table 1 of weight variation shows the different brands averages and standard deviation. We use standard deviation against weight of tablet for comparison and more accuracy. The tablets of brand 3 i.e. MET-03 have high values of standard deviation while the tablets of brand 2 i.e., MET-02 have values of standard deviation in range. The results of weight variation in table 1 for all the brands gave values which complied with B.P. Specifications for weight uniformity as none of the brands deviated from the mean value by up to ±5%.

Diameter and Thickness was measured and evaluated of 10 tablets of each brand and the average diameter and thickness with their standard deviation values were recorded in table 2 of diameter and table 3 of thickness that shows that the brand that is used as a standard i.e. MET-01* have lower standard deviation values of diameter and brand 2 i.e. MET-02 have lower values of standard deviation of thickness while brand 3 i.e. MET-03 have high values of standard deviation of both diameter and thickness. The disintegration results of table 4 showed that all the brands passed the disintegration test as per British Pharmacopoeia (BP 2007) that specifies 30 minutes for film coated tablets. According to the monographs of B.P. for each of the tablets tested for dissolution, the active ingredient amount in solution is not less than 80% of the stated amount. Disintegration test is an important step in drugs release from immediate release dosage forms. The rate of disintegration is directly related to the rate of dissolution. The results obtained from the dissolution studies stated in table 5 of Dissolution revealed that all the brands passed with the standards of B.P. for conventional release tablets.

DISCUSSIONS

Rezk *et al.* (2013) developed the two simple and rapid methods for simultaneous determination of two anti-

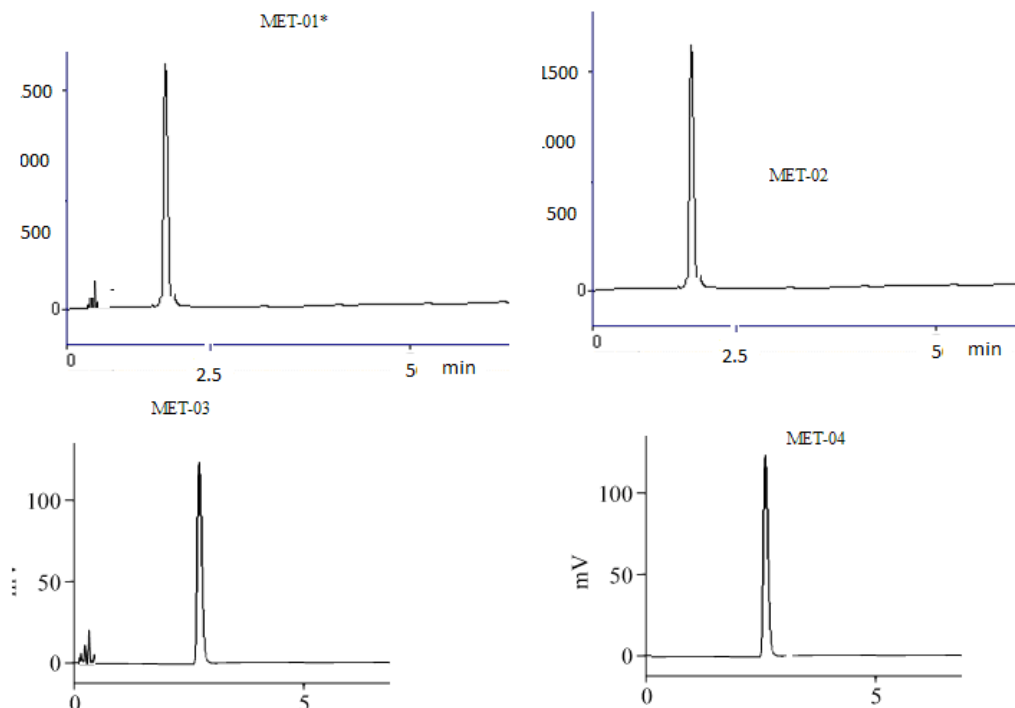


Fig. 2: Assay of different brands by HPLC

diabetic drugs i.e. sitagliptin phosphate and Metformin HCl in their pharmaceutical formulation. The first is a TLC method and the second is an HPLC method in which a C18 column is used. In both methods, the bulk form of Metformin HCl is measured and analyzed in their pharmaceutical formulation without any other interference from other additives.

Potur *et al.* (2010) prepared an immediate release formulation of two anti-diabetic drugs i.e. Metformin HCl and glibenclamide by design of experiments and optimized the delivery of these two different antidiabetic agents within a single-tablet combination. In order to attain the dose uniformity, a wet granulation manufacturing process was used for Metformin HCl due to its poor flow properties and the prepared tablets were evaluated for the release of Metformin HCl using validated HPLC methods. The desired drug release can be achieved by using a proper percent of super disintegrate, reducing the filler or by the presence of extra granular added binder that shows the investigation is reproducible.

Osadebe *et al.* (2004) assessed the quality control parameters and interchangeability of five different brands of Metformin tablets of Nigeria and the study was carried out in which the disintegration time, dissolution rate and absolute content of the drug were evaluated. The uniformity of weight and hardness tests according to the specified official methods was also performed. The results proved that all the brands passed the weight uniformity

and disintegration tests and four out of five brands were bioequivalent that showed that brands of Metformin hydrochloride that are marketed in Nigeria are of acceptable standards therefore interchangeable with Glucophage R (Merck) i.e. innovator drug.

Nyback-Nakell *et al.* (2014) conducted a controlled cross-over study and the effect on glycemic control was measured by adding an anti-diabetic drug i.e. glimepiride to on-going treatment with metformin and insulin with type-2 diabetes patients of more than 10 years. No severe hypoglycemic event was observed and a more pronounced decrease in HbA_{1c} was associated with the magnitude of the increment in C-peptide/glucose. The patients with old age were associated with a smaller response. Therefore it can be concluded that after long duration of diabetes, addition of anti-diabetic drug glimepiride to insulin and metformin can be effective in lowering HbA_{1c} and reducing the need for exogenous insulin.

McAdam-Marx C *et al.* (2014) evaluated the relationship between weight change and glycemic control after initiation of anti-diabetic therapy in patients with type-2 diabetes. This study evaluates the relationship between HbA_{1c} and weight change outcomes by anti-diabetic weight-effect properties in patients newly treated for type 2 diabetes; a relationship that was not previously characterized. Thus it can be concluded that weight loss of $\geq 3\%$ was associated with better achievement of

Table 1: Weight variation of different Brands

No.	Serial No.	Batch No.	Average weight	S.D	Upper limit (UCL)(X+3S)	Lower limit (LCL) (X-3S)	Results in gm	BP Specs.	Deviation from BP
1.	MET-01*	29046XV	528.76	9.43	557	500.5	0.52876	±5%	Within limit
2.	MET-02	WL165	537.09	4.02	549.14	525.02	0.53708	±5%	Within limit
3.	MET-03	4206	529.18	13.28	569	489.37	0.52918	±5%	Within limit
4.	MET-04	BF573	530.96	8.43	556.25	505.67	0.53096	±5%	Within limit

Met-01* = Standard brand (Multi-National)

Table 2: Diameter of different Brands

SERIAL No.	Average Diameter	S.D	Upper Limit(UCL)(X+3S)	Lower Limit (LCL)(X-3S)
MET-01*	10.953	0.0094	10.98	10.92
MET-02	11.089	0.012	11.12	11.05
MET-03	11	0.017	11.05	10.94
MET-04	11.031	0.0099	11.06	11

Table 3: Thickness of different Brands

SERIAL No.	Average Thickness	S.D	Upper Limit (UCL)(X+3S)	Lower Limit (LCL)(X-3S)
MET-01*	5.821	0.07	6.01	5.62
MET-02	5.492	0.02	5.57	5.40
MET-03	5.663	0.16	6.13	5.18
MET-04	5.558	0.03	5.64	5.46

Table 4: Disintegration of different Brands

SERIAL No.	Code No.	Batch No.	Disintegration Time	Official Limits	Comments
MET-01*	025526	29046XV	11mint 20sec	Not more than 30min	Within specified limit
MET-02	021783	WL165	13mint 58sec	Not more than 30min	Within specified limit
MET-03	000552	4206	10mint 50sec	Not more than 30min	Within specified limit
MET-04	005310	BF573	12mint 47sec	Not more than 30min	Within specified limit

Table 5: Dissolution of different Brands

Serial No.	0min	15min	30min	45min	% Dissolution at 45min	BP Specs.	Deviation from BP
MET-01*	0.023	2.575	2.543	2.533	98%	Not less than 80%	Within specified limit
MET-02	0.139	2.515	2.51	2.5	98.70%	Not less than 80%	Within specified limit
MET-03	0.188	2.507	2.525	2.494	98.46%	Not less than 80%	Within specified limit
MET-04	0.095	2.397	2.391	2.398	94.67%	Not less than 80%	Within specified limit

glycemic control in patients newly treated for type 2 diabetes. Therefore anti-diabetics associated with weight-loss were associated with greater weight loss and HbA1c goal attainment.

Ekeruo *et al.* (2013) conducted a study on the use of Metformin as safe and effective treatment in diabetic patients with also heart failure. As management of diabetic patients which have also heart failure is a complex task. In this study, it is proposed that an increase of substrate uptake by the insulin resistant heart is not good because the heart is already flooded with fuel. In light of this evidence, it is observe that metformin offers a

unique safety profile in the patient with diabetes and heart failure as Metformin targets both the source as well as heart of excess fuel.

The results of HPLC indicate that all drugs show good peak using simple methanol water mobile phase and all brands assay results are in range when using C-18 column.

CONCLUSION

It can be occulted that all of the four brands determined in this study have shown good results and all are in range of

the physicochemical comparison of different brands of the generic i.e. Metformin HCl

REFERENCES

- Ekeruo IA, Solhpour A and Taegtmeier H (2013). Metformin in diabetic patients with heart failure: Safe and effective. *Curr. Cardiovasc. Risk Rep.*, **7**(6): 417-22.
- Jones MR, Mudaliar S, Hernandez-Triana E, Unnikrishnan AG, Lai YL, Abby SL, Misir S, Jin X and Nagendran S (2009). Rationale and design of a clinical trial to evaluate metformin and colesevelam HCl as first-line therapy in type 2 diabetes and colesevelam HCl in prediabetes. *Curr. Med. Res. Opin.*, **25**(9): 2239-2249.
- McAdam-Marx C, Mukherjee J, Bellows BK, Unni S, Ye X, Iloje U and Brixner DI (2014). Evaluation of the relationship between weight change and glycemic control after initiation of antidiabetic therapy in patients with type 2 diabetes using electronic medical record data. *Diabetes Res. Clin. Pract.*, **103**(3): 402-411.
- Mohammad Inam Danish (2012). Short Textbook of Medical Diagnosis and Management, International Edition 2012.
- Nyback-Nakell A, Adamson U, Lins PE L and stedt-Hallin L (2014). Adding glimepiride to insulin plus metformin in type 2 diabetes of more than 10 years duration-A randomised, double-blind, placebo-controlled, cross-over study. *Diabetes Res. Clin. Pract.* S0168-8227(14)00023-0.
- Olusola AM, Adekoya AI and Olanrewaju OJ (2012). Comparative evaluation of physicochemical properties of some commercially available brands of metformin HCl tablets in Lagos, Nigeria. *J. Pharm. Sci.*, **2**(2): 41.
- Osadebe PO and Akabogu IC (2004). Assessment of quality control parameters and interchangeability of multisourced metformin HCl tablets marketed in Nigeria. *Bollettino Chimico Farmaceutico*, **143**(4): 170-173.
- Potur RG and Gafițanu E (2004). Formulation by design of experiments of immediate release tablets with metformin hydrochloride and glibenclamide. *Revista medico-chirurgicala a Societati de Medici si Naturalisti din Iasi.*, **114**(4): 1219-1226.
- Rezk MR, Riad SA, Mahmoud GY, Aleem A, El Bayoumi AA (2013). Simultaneous determination of sitagliptin and metformin in their pharmaceutical formulation. *J. AOAC Int.*, **96**(2): 301-306.
- Squibb BM, US Food and Drug Administration. Glucophage (metformin hydrochloride tablets) Label Information.
- Zakeri-Milani P, Nayyeri-Maleki P, Ghanbarzadeh S, Nemati M, Valizadeh H. In-vitro bioequivalence study of 8 brands of metformin tablets in Iran market. *J. Pharm. Sci.*, **2**(8): 194.