Research Article

Formulation Development of Metformin Tablet and its Comparative *In-Vitro* study with Different Brands in Pakistan

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Accepted on: 18-02-2013; **Finalized on:** 31-03-2013.

ABSTRACT

The objective of this study was to develop formulation of metformin HCl 500 mg film coated tablets, compare in-vitro evaluation of self designed formulation with four different brands of metformin HCl 500 mg film coated tablets and to compare the physicochemical equivalency of the four brands. The tables were prepared by using wet granulation method. All the coated tablets passed weight variation test as the percentage of weight variation was within USP limits of ± 5% of the average weight. The chemical assay test of all the tablets showed that none had potency less than the required specifications of USP. The in vitro dissolution test results were found within the USP recommended limits for metformin HCl 500 mg film coated tablets. The comparative in-vitro study of $F_{Met\text{-}HCl}$ with four different brands showed that $F_{Met\text{-}HCl}$ has almost comparable characteristics with these brands. This study also proved the physicochemical equivalency of the four different brands. So if one brand is not available in the market then any of the other three brands can be taken in place of that unavailable brand.

Keywords: Metformin HCl, *In-vitro* study, Dissolution, Physicochemical equivalency.

INTRODUCTION

Metformin HCl is an orally administered anti-diabetic drug from the Biguanide class. It is recommended as the first-line drug of choice for the treatment of non-insulin-dependent diabetes mellitus (NIDDM) or type 2 diabetes mellitus[1]. Metformin therapy has significantly improved ovulation rates and pregnancy rates, especially in patients with clomifene-resistant polycystic ovary syndrome[2]. After metformin treatment, a reduction in mean systolic and diastolic blood pressure in PCOS patients has been reported [3]. The cardiovascular protective effects of metformin therapy include decreases hyperglycemia, improves diastolic function, decreases total cholesterol levels, decreases low-density lipoprotein (LDL) cholesterol levels, decreases very low-density lipoprotein (LDL) cholesterol levels, increases high-density lipoprotein (HDL) cholesterol levels and improves vascular relaxation[4]. Tablets are the most frequently administered oral solid dosage form. The wet granulation method is a process of size enlargement, sticking particles of drug and excipients together by using a liquid granulating agent to produce a granular product with improved free-properties and an increased ability to cohere under pressure[5]. It is used to improve the flow properties of the powder blend as well as to decrease the dust problems in the handling of the powder blends [6]. The introduction of generic drug product from multiple sources into the health care delivery system of many developing countries was aimed at improving the overall healthcare delivery systems in such countries. However, this has been accompanied by a variety of problems of which the most critical is the widespread distribution of fake and substandard drug products. Drug products that are chemically and bio pharmaceutically equivalent must be identical in strength, quality, purity as well as content uniformity, disintegration and dissolution rates. The need to ensure that the generic and branded drug products are pharmaceutically and therapeutically equivalent cannot be over emphasized[7]. Therefore the present study was designed to formulate metformin tablet and its in vitro study with other different available brands.

MATERIALS AND METHODS

Materials

Metformin HCl powder was received as a gift from Valor Pharmaceutical Islamabad. Poly vinyl pyrrolidone - PVP K30 (Yuking Chemtech Co. Ltd., China), Microcrystalline cellulose (Avicel PH 102; Mingtai Chemical Co Ltd., Taiwan), Sodium starch glycolate (Yung Zip Chemical Industries, Taiwan), Magnesium stearate (Coin Chemical Industrial Co. Ltd., Taiwan), Talcum (Micron, Pakistan), Colloidal silicon dioxide (Cab-O-Sil; Cabot Corporation, Germany), Hypromellose (Methocel E5; Colorcon, UK.),Titanium dioxide (Shanghai Hychem Co., Ltd, China) , Isopropyl alcohol (Lee Chang Yung Chemical Industry Corporation, Taiwan), Methylene chloride (ICI, UK.), Monobasic potassium phosphate, Sodium hydroxide and Orthophosphoric acid (Merck, Germany) was received as a gift from Amson Vaccines & Pharma (PVT) Ltd.

Different brands of Metformin HCl

Four different brands of Metformin HCl 500 mg film coated tablets as shown in Table 1 were evaluated.

Table 1: Four different brands of Metformin HCl (500 mg) film coated tablets.

Brand name	Manufacturer	Batch No.	Manufacturing date	Expiry date	Price/50 units Rs.
Glucophage	Merck	3313	10/2010	09/2013	75.00
Metphage	Efroze	J – 022	02/ 2010	01/2013	65.78
Neodipar	Sanofi Aventis	WH116	08/2010	07/2013	65.80
Neophage	Abbott	86331XV	06/2010	06/2013	55.64

Methods

Formulation of Metformin HCl tablets

Metformin HCl 500mg tablets were prepared by wet granulation method according to the formulation given in Table 2. The self designed formulation was coded as $F_{Met\text{-}HCl}$.

Table 2: Formulation ($F_{Met\text{-}HCl}$) of Metformin HCl 500 mg tablets

Ingredients	Quantity/tablet (mg)	% age
Metformin HCl	500	79.36
PVP K30	15	2.38
Avicel PH 102	93	14.76
Sodium starch glycolate	8	1.26
Magnesium stearate	10	1.58
Talcum	2	0.31
Cab-O-Sil	2	0.31
Isopropyl alcohol	Q.S.	–
Total weight of tablet	630	99.96

Preparation of granules

The active pharmaceutical ingredient (API) and all the excipients were weighed accurately. Metformin Hcl powder was passed through oscillating granulator having stainless steel mesh # 16. PVP K30 was used as a binder solution for granulation and dissolved in sufficient quantity of isopropyl alcohol. Metformin HCl powder was granulated by using PVP K30 binder solution. The wet mass obtained from granulation was passed through rotary granulator having mesh # 8. The resulting granular material was spread on trays and placed in humidity controlled area for overnight. These granules were then dried in a hot air circulation oven at about 50^0C. The dried granules were passed through oscillating granulator having mesh # 12. These granules were mixed with sodium starch glycolate passed through mesh # 40 and avicel PH 102 passed through mesh # 16 and finally lubricated with magnesium stearate, talcum, and cab-o-sil passed through mesh # 40. The powder blend was mixed well for about 15 minutes.

Evaluation of powder blend

The prepared powder blend was evaluated for following different parameters.

Angle of repose

The angle of repose (θ) is used to measure the friction forces in the powder blend or granules. It indicates the maximum angle which is possible between the surface of the pile of powder blend or granules and the horizontal plane. It was determined by using method described by Wells, 2002 [8].

Angle of repose was calculated by the formula given below.

$\tan \theta = h/r$

$\theta = \tan^{-1} (h/r)$

Bulk density

Bulk density (ρb) indicates the ratio of total mass of powder to the bulk volume of powder. It was determined by pouring the accurately weighed amount (M) of the powder blend into graduated cylinder and the initial volume of packing also called as bulk volume (Vb) was measured. The bulk density was then calculated by the following formula [9].

$\rho b = M/ Vb$

Tapped density

Tapped density (ρt) indicates the ratio of total mass of the powder to the tapped volume of powder. It was determined by using method described by [9] Levis et al., 2001. The tapped density was calculated by the following formula.

$\rho t = M/ Vt$

Carr's compressibility index

Carr's compressibility index is used to indicate the compressibility of a power. It was calculated by the formula given below.

Carr's Index = $[(\rho t – \rho b) / \rho t] \times 100$

Hausner's ratio

Hausner's ratio (H) indirectly expresses an ease of flow of powder blend. It was calculated by the formula given below.

Hausner's ratio (H) = $\rho t / \rho b$

Carr's compressibility index and Hausner's ratio were determined by using standard method [10].

Moisture content

The moisture content of the powder blend was determined by placing a specific quantity (5 gm) of the powder blend in the moisture analyzer (MA-45, Sartorius) at 105°C.

Compression of granules

The granules were compressed on rotary press machine ZP-19 (Model No. ZBC92005, China) having 12 mm concave punches. Round biconvex shaped core tablets were produced with an average hardness of 15 kg/cm^2, friability 0.4% and disintegration time 5 minutes.

Film coating of core tablets

Metformin HCl core tablets were film coated according to the formulation given in Table 3.

Table 3: Formulation of film coating material

Ingredients	Unit	Quantity/tablet
Methocel E5	Mg	25.2
Talcum	Mg	2.54
Titanium dioxide	Mg	2.50
Isopropyl alcohol	Ml	0.472
Methylene chloride	Ml	0.157

Procedure of film coating

Methocel E5 and talcum were added to isopropyl alcohol under constant stirring and mixed for about 15 minutes. Titanium dioxide was dissolved in small quantity of isopropyl alcohol and filtered into solution containing the coating material. Finally Methylene chloride was added to this solution and mixed well. The core tablets of metformin HCl were put into the conventional coating pan and heating was started with hot air. Coating was done by spraying the coating solution on core tablets with continuous heating.

Evaluation of Metformin HCl film coated tablets

The film coated tablets of formulation $F_{Met\text{-}HCl}$ and the selected brands were evaluated according to specifications of U.S.P.

Thickness and diameter test

Ten tablets from $F_{Met\text{-}HCl}$ and each brand were selected randomly to determine thickness and diameter by using digital Vernier Caliper (Model No. CD – 6$^{//}$ CS, Mitutoyo, Japan).

Hardness test / crushing strength

Ten tablets from $F_{Met\text{-}HCl}$ and each brand were selected randomly and subjected to hardness test by using Monsanto hardness tester.

Weight variation test

Twenty tablets from $F_{Met\text{-}HCl}$ and each brand were weighed on electronic balance (Model No. JS-110, YMC Co.Ltd., Japan) and the average weight was calculated. Each tablet was then weighed individually and maximum and minimum values for weight of the tablet were noted.

Disintegration test

The disintegration test was carried out in accordance to USP 30 specifications by using Disintegration Tester (Model No.DT-122, Galvano Scientific, Pakistan). Six tablets from $F_{Met\text{-}HCl}$ and each brand were subjected to disintegration test. One tablet was placed in each of the six tubes of the basket. Then disks were added to each tube of the basket. The time taken for the last tablet to disintegrate completely was recorded in minutes.

Chemical assay

The chemical assay of film coated tablets of $F_{Met\text{-}HCl}$ and each brand was carried out according to USP 30 by using UV-Visible Spectrophotometer (Model No. 1800, Shimadzu, Japan). The assay was performed in triplicate.

Standard preparation

About 100 mg of reference working standard of metformin HCl was weighed accurately on electronic balance and transferred into a 100 ml volumetric flask. About 70 ml of distilled water was added to it and sonicated to dissolve. The volume was made up to the mark and mixed.10 ml of the first dilution was taken into another 100 ml volumetric flask and volume was made up to the mark. Again 10 ml of the second dilution was taken into a third 100 ml volumetric flask and the volume was made up to the mark to achieve final concentration of 0.01 mg/ml.

Sample preparation

20 tablets were weighed on electronic balance and average weight of the tablet was calculated. Tablets were grinded to a fine powder. Powder equivalent to about 100 mg of metformin HCl was weighed accurately and transferred into a 100 ml volumetric flask. About 70 ml of distilled water was added to it and sonicated for about 10 minutes. The volume was made up to the mark with distilled water, mixed and filtered through Whatman filter paper. 10 ml of the filtrate was taken into another 100 ml volumetric flask and volume was made up to the mark. Again 10 ml of the second dilution was taken into a third 100 ml volumetric flask and volume was made up to the mark to achieve final concentration of 0.01 mg/ml.

Procedure of assay

Both standard preparation and sample preparation were scanned between 190 – 400 nm and the absorbance was taken at the maximum wavelength (λ_{max}) at 232 nm using distilled water as blank solution.

% of metformin HCl = (Absorbance of sample/ Absorbance of standard) x 100

***In-vitro* dissolution test**

The *in vitro* dissolution test of film coated tablets of $F_{Met\text{-}HCl}$ and each brand was carried out according to USP 30 by

using Tablet Dissolution Tester (Model No. GDT-7Tv3, Galvano Scientific, Pakistan)

Parameters of dissolution test

Medium: Phosphate buffer pH 6.8 maintained at 37±0.5°C

Volume: 1000 ml

Apparatus: 2 (Paddle type)

Speed: 50 rpm

Time: 30 minutes

Limits: Not less than 80% (Q) of the labeled amount of metformin HCl is dissolved in 30 minutes.

Preparation of phosphate buffer pH 6.8

Phosphate buffer pH 6.8 was prepared according to USP 30.

Potassium phosphate, monobasic 0.2M

27.22 gm of monobasic potassium phosphate (KH_2PO_4) were dissolved in distilled water and diluted with distilled water to 1000 ml.

0.2M NaOH

8 gm of NaOH pellets were dissolved in distilled water and diluted with distilled water to 1000 ml.

Method of Preparation of phosphate buffer pH 6.8

250 ml of 0.2M monobasic potassium phosphate solution were transferred into a 1000 ml volumetric flask and 112 ml of 0.2M NaOH solution were added to it. The volume was made up to the mark with distilled water and mixed well. The pH of the dissolution medium was adjusted to 6.8, if necessary, with 1M NaOH or orthophosphoric acid solution.

Procedure of dissolution test

Six tablets were taken and one tablet was placed in each of the six baskets. Dissolution test was carried out according to above mentioned parameters. After completion of 30 minutes, the dissolved amount of metformin HCl was determined by employing UV absorption at the wavelength of maximum absorbance (λ_{max}) at about 233 nm on filtered portion of solution under test suitably diluted with the dissolution medium to concentration of 0.01 mg/ml in comparison with reference working standard solution having a concentration of 0.01 mg/ml in the same medium using phosphate buffer pH 6.8 as blank solution. % of metformin HCl = (Absorbance of sample/Absorbance of standard) x 100

Statistical analysis

The data of dissolution test was evaluated statistically by analysis of variance (ANOVA) and comparison among mean dissolution data was made by Least significant difference (LSD) test.

RESULTS AND DISCUSSION

The tablets of metformin HCl 500 mg which is an oral anti-diabetic drug used in the management of type 2 diabetes were prepared by using wet granulation method. The self designed formulation was coded as $F_{Met-HCl}$. The prepared powder blend was evaluated for different parameters before compression. Table 4 shows the results of evaluation parameters of powder blend of $F_{Met-HCl}$.

Table 4: Evaluation of powder blend of $F_{Met-HCl}$.

Angle of repose (°)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio	Moisture content (%)
29.24	0.666	0.769	13.39	1.15	2.4

The angle of repose < 30^0 indicates good flow properties while an angle of > 40^0 shows poor or absent flow [11].The result of angle of repose (29.24^0) indicated good flow properties of the powder blend. There is no large difference in the values of bulk density and tapped density of the powder blend. The data of both bulk and tapped densities was used to calculate Carr's compressibility index and Hausner's ratio. Lower Carr's index (<20%) indicates better flow properties of the powder blend than higher ones (>20%) [12]. Lower Hausner's ratio (<1.25) indicates better flow properties of the powder blend than higher ones (>1.25) [13]. The compressibility – flow ability correlation data indicated good flow of the powder blend with less moisture content.

The lubricated powder blend was compressed on compression machine. The core tablets were film coated. The film coated tablets of $F_{Met-HCl}$ and four different brands were evaluated for various parameters according to USP. All the tablets of $F_{Met-HCl}$ and different brands were found within the acceptable range of USP for different quality control tests. The tablets of $F_{Met-HCl}$ and different brands did not show any significant difference in thickness and diameter ranging between 5.4-5.95 mm and 11.02-11.99 mm respectively as shown in Table V.

The average hardness of tablets was determined by using Monsanto hardness tester. The tablets of $F_{Met-HCl}$ and different brands possessed good mechanical strength with sufficient hardness. The maximum hardness (15.4 Kg/cm^2) was observed for Glucophage while minimum hardness (7.7 Kg/cm^2) was shown by Neophage as in Table 5.

Disintegration test was carried out under USP specifications. The tablets of formulation $F_{Met-HCl}$ and different brands showed small difference in disintegration time and no correlation was found between hardness and disintegration time because metformin HCl is freely soluble in water. The tablets of $F_{Met-HCl}$ had minimum disintegration time (6 minutes) which is due to the presence of sodium starch glycolate which acts as a good

disintegrant and avicel PH 102 which is very dispersible in water leaving the effect on disintegration time (Tab. 5). Disintegration could be directly related to dissolution and subsequent bioavailability of a drug. The drug which is incorporated in a tablet is rapidly released when the tablet disintegrates. It is an important step for immediate release dosage forms because the rate of disintegration affects the dissolution and subsequently the therapeutic efficacy of the medicine.

Table 5: Evaluation of tablets

Parameters	$F_{Met-HCl}$	Glucophage	Metphage	Neodipar	Neophage
Thickness (mm)	5.4	5.7	5.95	5.66	5.93
Diameter (mm)	11.99	11.03	12.09	11.06	11.02
Weight variation (± %)	630±5	527±5	623±5	544±5	530±5
Hardness (Kg/cm^2)	15	15.4	11.1	14.2	7.7
Disintegration time (min.)	6	14	10	12	15
Chemical assay (%)	99.74	99.22	100.38	100.12	100.64
Dissolution data (**%**)	96.27	97.93	99.72	95.64	97.47

The average tablet weights of $F_{Met-HCl}$ and four different brands were found in the range of 527-630 mg as in (tab.5). All the film coated tablets passed weight variation test as the percentage of weight variation was within USP limits of ± 5% of the average weight.

Similarly the chemical assay of tablets was carried out in accordance to USP 30. There was no considerable difference in chemical assay of $F_{Met-HCl}$ and the four brands. The results of chemical assay were in the range of 99.22% (Glucophage) to 100.64% (Neophage) (Tab.5).

The in vitro dissolution test was carried out in accordance to USP 30. There was no considerable difference in dissolution data of $F_{Met-HCl}$ and different brands. The maximum average dissolution (99.72%) was observed for Metphage while the minimum average dissolution (95.64%) was shown by Neodipar (Tab.5). It has been reported that dissolution rate has a direct effect on the bioavailability profile of tablet dosage forms because it can be used to determine the pattern of drug release *in vivo*.

CONCLUSION

The present study showed that wet granulation is a suitable method for the preparation of metformin HCl 500 mg tablets. The comparative in-vitro study of the self designed formulation $F_{Met-HCl}$ with four different brands showed that $F_{Met-HCl}$ has almost comparable characteristics with these brands. The study also proved the physicochemical equivalency of the four different brands. So if one brand is not available in the market then any of the other three brands can be taken in place of that unavailable brand.

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Source of Support: Nil, **Conflict of Interest:** None.