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A SHORT PREFORMULATION STUDY OF PURE METFORMIN HCL

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ABSTRACT

Metformin HCl is a first line drug of choice for the treatment of type II diabetes which acts by decreasing hepatic glucose output and peripheral insulin resistance. It can be given to obese patients with overweight having normal kidney function. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms, to determine kinetics and stability of drug and to establish drug excipients compatibility. Preformulation study was done and allresults were in the range of prescribed in Indian Pharmacopoeia, so the drug was found to be of standard prescribed purity and quality Infrared spectra of the drug reveal that there is no significant interaction between drug polymers. The primary objective of this DSC study was to identify a stable storage condition for Metformin HCL in solid state and identification of compatible. A solution of 10µg/mL of Metformin HCl was scanned in the range of 200 to 400 nm. The drug exhibited the λmax at 234 nm in distilled water has good reproducibility graph. UV method was used for Estimation of Metformin HCl and absorbance values were measured using an ultraviolet–visible (UV-VIS) spectrophotometer at λmax 234 nm.[1]

KEYWORDS: MetforminHCl, Preformulation and Type II diabetes.

INTRODUCTION

Diabetes is a chronic health problem with devastating, yet preventable consequences. It is characterized by high blood glucose levels resulting from defects in insulin production, insulin action, or both. Globally, rates of type II diabetes were 15.1 million in 2000, the number of people with diabetes worldwide is projected to increase to 36.6 million by

2030.Out of these, 90-95% of the cases were adults with type II diabetes. Type II diabetes impacts men and women proportionately; there are over 12 million men with diabetes and 11.5 women with diabetes. Metformin HCl is a first line drug of choice for the treatment of type II diabetes which acts by decreasing hepatic glucose output and peripheral insulin résistance. It can be given to obese patients with overweight having normal kidney function. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms, to determine kinetics and stability of drug and to establish drug excipients compatibility. Preformualtion studies have a significant impaction manufacturing, storage, and performance of the drug production. Preformulation studies well-built then the scientific foundation of the guidance, provide regulatory relief and conserve resources in the drug development and evaluation process, improve public safety standards, enhance product quality facilitate the implementation of new technologies, and facilitate policy development and regulatory decision making. It also gives directions for development of formulation in choice ofdrug form, excipients, composition, physical structure, helps in adjustment of pharmacokinetic and biopharmaceutical properties, support for process development of drug substancesupport for process analytical technology, produce necessary and useful data for development of analytical methods. It not only helps to guide dosage form selection, but also provides insights into how drug products should be processed and stored to ensure their superiority.[1]

MATERIAL AND METHODS

Pure Metformin HCl is obtained from Goodman pharmaceuticalsas a gift sample.

Methods

1. **Organoleptic properties:** The organoleptic studies of Metformin HCl like general appearance like nature, colour, odour etc. were performed and observed.[2]

2. **Detection of melting point range:** For determination of melting point USP method was followed. Small quantity of Metformin HCl was placed into a sealed capillary tube. The tube was placed in the melting point apparatus. The temperature in the apparatus was gradually increased and the observation of temperature was noted at which Metformin HClstarted to melt and the temperature when the entire drug gets melted. This method is also known as open capillary method.[1]

3. Differential Scanning Colorimetry (DSC) studies

DSC Thermogram of pure metformin

Differential Scanning Calorimetry and Differential Thermal Analysis Earlier methods areas adaptable as either differential thermal analysis (DTA) or differential scanning calorimetry (DSC). An additional advantage is that the sample size required for these are only 1-2 mg. Differential thermal analysis instrument the temperature difference between the sample and a reference as a function of temperature or time when heating at a constant rate.

Thermograms of the pure drug and physical admixtures of drug with various excipients were obtained by Differential Scanning Calorimetry and analysed for interaction. Each sample was sealed in standard aluminum pans with lids and purged with air at a flow rateof 40 ml/min. A temperature ramp speed was set at 20°c /min, and the heat flow was recorded in the range of 30–300°C under inert nitrogen atmosphere.

Differential Scanning Colorimetry (DSC) studies The DSC spectrum of the pure Metformin was compared. The thermograms showed that there were no incompatibility problems between the drug. When no physical or chemical change occurs within the sample then there is either a temperature change or input energy to maintain as isotherm however, when phase changes occur then latent heat suppresses a temperature change and the isothermal energy required registers as an electrical signal generated by thermocouples. Crystalline transitions, fusion, evaporation and sublimation are changes in state which can be deliberated.

4. FT-IR Spectrum of pure drug

FTIR spectroscopy was performed on Fourier trans formed infrared spectrophotometer. The pellets of drug and potassium bromide were prepared by compressing the powders at 20 psi for 10 min on KBr-press and the spectra were scanned in the wave number range of 4000-600 cm1.Fourier Transform Infrared Spectrophotometry was used for structure analysis of drug (Metformin HCl).[3]

5. UV Spectrum Analysis of Metformin HCl: The solution was scanned in the range of 200 to 400 nm to fix the maximum wave length and UV spectrum was obtained.

Preparation of stock solution in water: Metformin hydrochloride were accurately weighed 10mg and transferred to 10ml volumetric flask. Drug was dissolved in 5mlof water shaken manually for 10 minute and volume was made up to the mark with the same solvent. This was the standard mother solution containing 1mg/ml (1000µg/ml). 1ml of this prepared

solution was pipette out and transferred to the 10mlvolumetric flask, and volume made up to 10ml with same solvent to obtained final concentration 0.1mg/ml(100µg/ml i.e. stock solution).2.5ml solution is pipette out from stock solution and transferred to 25ml volumetric flask. This concentration found to 10µg/ml solution.

Spectrophotometric scanning of metformin hydrochloride in water: An appropriate portion of 1, 2, 3, 4, and 5ml of metformin hydrochloride stock solution in water was pipette out and transferred to separate 10ml volumetric flask and then volume made up to 10ml with water to obtain concentration 1, 2, 3, 4 and 5µg/ml. the solution were scanned separately between 200nm to 400nm. The spectrum of drug was recorded. Wavelength 234nm was selected for further study.

Preparation of calibration curve of metformin hydrochloride in water: Taken a series of concentration of ranging between 1-5µg/ml. Absorbance was measured using spectrophotometerat234nmagainstwater as blank. Standard calibration curve was plottedas absorbance against concentration.

Preparation of saline pH 7.4 phosphate buffer: Dissolve 2.38 g of disodium hydrogen phosphate, 0.19g of potassium dihydrogen phosphate and 8.0 g of sodium chloride in sufficient water to produce 1000ml.

Preparation of stock solution in phosphate buffer pH 7.4: Metformin hydrochloride was accurately weighed 10mg and transferred to 10ml volumetric flask. Drug was dissolved in 5 ml of phosphate buffer pH 7.4, shaken manually for 10 minute and volume was made up to the mark with the same solvent. This was the standard mother solution containing 1mg/ml (1000µg/ml). 1ml of this prepared solution was pipette out and transferred to the 10 ml volumetric flask, and volume made up to 10ml with same solvent: to obtained final concentration 0.1mg/ml (100µg/ml i.e. stock solution). 2.5 ml solution is pipette out from stock solution and transferred to 25 ml volumetric flask. This concentration found to 10µg/ml solution.

Spectrophotometric scanning of metformin hydrochloride in phosphate bufferpH7.4: Wavelength 234nm was selected for further study. Anappropriateportionof1,2, 3, 4, and 5ml of metformin hydrochloride stock solution in phosphate buffer pH 7.4was pipette out and transferred to separate 10ml volumetric flask and then volume made up to 10ml with

phosphate buffer pH7.4 to obtain concentration 1, 2, 3, 4 and 5µg/ml. The scanning of solution was separately done between 200nm to 400nm. This spectrum of drug was recorded.

Preparation of calibration curve of metformin hydrochloride in phosphate buffer pH 7.4: Taken a series of concentration of ranging between 1-5µg/ml. absorbance was measured using spectrophotometer at 234nm against phosphate buffer as blank. Standard calibration curve was plotted as absorbance against concentration.[3]

6. **Bulk density:** The bulk density was determined by transferring the accurately weighed sample of powder to the graduated cylinders calculated by using the following formula.

Db= M/Vb

Where M (mass of powdered drug), Vb (bulk volume of the powdered drug).[4]

7. **Tapped density:** Weighed powder sample was transferred to a graduated cylinder and was placed on the tap density apparatus, was operated for fixed number of taps (500). The tapped density was determined by the following formula.

Dt= M/Vt

Where, M (mass of powdered drug), Vt (tapped volume of the powdered drug).[5]

8. **Carr's Index:** Based on the apparent bulk density and the tapped density, thepercentage Compressibility of the bulk drug was determined by the following formula.[6-7]

$$\text{Carr's compressibility index} = \frac{[\text{aest-ukest}]}{\text{aest}} \times 100$$

9. **Hausner's ratio:** It indicates the flow properties of powder and is measured by the ratio of tap density to bulk density.[8-10]

$$\text{Hauser's ratio} = \frac{\text{aest}}{\text{ukest}}$$

RESULTS AND DISCUSSION

1. Spectrophotometric methods for estimationofmetforminhydrochlorideby UV

The solutions containing Metformin hydrochloride (µg/ml) were prepared in water and phosphate buffer pH 7.4 and prepared solutions were scanned for absorption maxima in range

of 200-400nm. The λ max obtained was recorded. **Calibration curve for the estimation of Metformin hydrochloride in water** Calibration curves of Metformin hydrochloride were prepared according to the method described in section methodology. The absorbance values of the dilutions, in the concentration range of 1-5 µg/ml in water. The data were plotted without standard deviation andthe calibration curves obtained followed Beer's- lambert law.

Table 1: Calibration data of Metformin HCL at 234nm in water.

Concentration (µg/ml)	*Absorbance at 234nm*
1	0.110 ± 0.012
2	0.303±0.008
3	0.507± 0.011
4	0.740± 0.012
5	0.951± 0.009

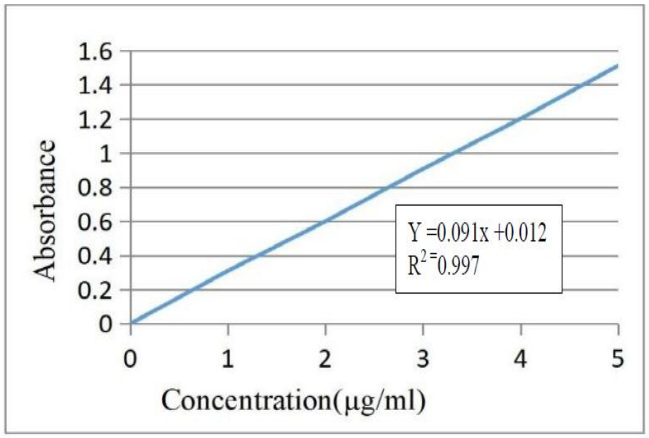

Figure 1: Calibration curve of metformin HCL in water.

Calibration curve for the estimation of metformin hydrochloride in phosphate buffer pH 7.4

Calibration curve of Metformin hydrochloride were prepared according to the method described in section methodology. The absorbance values of the dilutions, in the concentration range of 1- 5µg/mlinphosphatebuffer pH7.4.Thedata were plotted without standard deviation and the calibration curves obtained followed Beer's- Lambert law.

Table 2: Calibration data of Metformin HCL at 234nm in **phosphate buffer pH 7.4.**

Concentration(µg/ml)	*Absorbance at234nm*
1	0.214±0.054
2	0.410±0.032
3	0.591±0.022
4	0.735±0.012

5	0.850±0.031

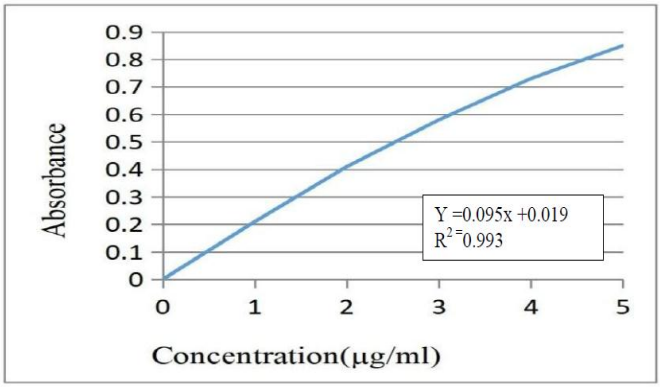

Figure 2: Calibration curve of Metformin HCL at 234nm in phosphate buffer pH7.4.

1. **Organoleptic properties:** Inorganoleptic evaluation, Metformin HCl was found to be WhiteCrystalline odourless powder.

2. **Detection of melting point range:** Melting point of Metformin HCl was found to be in the range of 222ºC to 226ºC which was in the range as prescribed in Indian Pharmacopoeia, so the drugwas found to be of standard prescribed purity and quality.

3. **Differential Scanning Colorimetry (DSC) studies:** The DSC spectrum of the pure Metformin was compared. The thermograms showed that there were no incompatibility problems between the drug.. When no physical or chemical change occurs within the sample then there is either a temperature change or input energy to maintain as isotherm however, when phase changes occur then latent heat suppresses a temperature change and the isothermal energy required registers as an electrical signal generated by thermocouples.

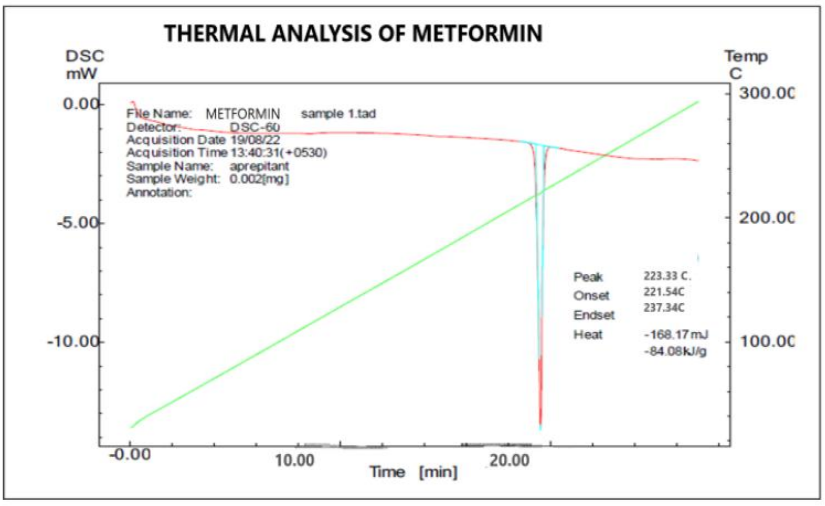

Figure 3: DSC Thermogram of Pure Metformin HCL.

4. **FTIR** Crystalline transitions, fusion, evaporation and sublimation are changes in state which can be deliberated.

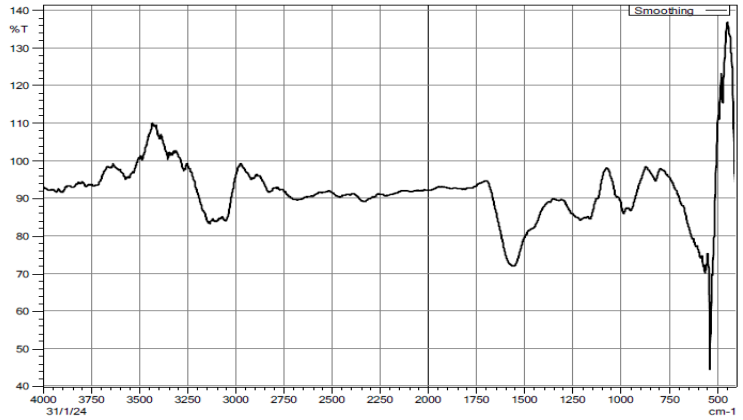

Figure 4: FT IR of Pure Metformin.

Table 4: Interpretations of IR Spectra of Pure Metformin HCL.

S. NO.	Functionalgroup	Wave number Range
1	C-HStretching	3500-3000cm^{-1}
2	N-HStretching	3600-3200cm^{-1}
3	C–HStretching	3200-3000cm^{-1}
4	O–HStretching	3000-2500cm^{-1}
5	C≡CStretching	2500-2000cm^{-1}
6	N–Oasymmetricstretching	2000-1500cm^{-1}
7	C–NStretching	1500-1000cm^{-1}
8	=C–Hbending	1000-500cm^{-1}

5. **Bulk density**

Bulk density of powdered drug was found to be 0.550g/cm3.

6. **Tapped density**

Tapped density of powder was found to be 0.646g/cm3.

7. **Carr's index % Compressibility**

The compressibility index was found to be 14.86%.Hence the type of flow of powderis good.

8. **Hausner's ratio**

Hasuner's ratio was found to be 1.17%, therefore it indicates good flow

CONCLUSION

Diabetes mellitus is a chronic health problem with demoralizing, up till now preventable fine. It is characterized by high glucose levels resulting from defects in insulin production, insulin action or both. The Global diabetes prevalence in 2019 is estimated to be 9.3%(463 million people), rising to 10.2% (578million) by 2030 and 10.9 % (700 million) by 2045. Out of these above date expressed in future 90-95% of these cases were adults with type II diabetes. Metformin HCL is a first line drug of choice for the treatment of type II diabetic which act by decreasing hepatic glucose output and peripheral insulin resistance. Currently 90% of adults with diabetes type II are overweight or obese. People with severe obesity are at greater risk of type II diabetes then obese persons with lower BMI along with usual renal function. Deprivation is closely linked to the risk of both obesity and type II diabetes. Pharmacopoeia, hence the drug was found to be standard prescribed purity and quality. DSC and FT IR spectra of the drug reveal that respectively. A solution of 5(µg/ml) of MetforminHCL was scanned in the range of 200-400 nm.The drug exhibited the λ max at 234nm in distilled water has good reproducibility graph. UV method was used for estimation of Metformin HCL and absorbance values were measured using an ultraviolet-visible (UV- VIS) Spectrophotometer at λ max 234nm.Linearity was observed over a concentration range of 1 to 5 (µg/ml).

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