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Assessment of Thermal Stability of Metformin Hydrochloride

VIPIN K. SHARMA*, VINOD NAUTIYAL, KAPIL K. GOEL and ASTHA SHARMA†
Department of Pharmaceutical Sciences, Gurukul Kangri University, Haridwar-249 404, India
E-mail: sharma_dibru@yahoo.co.in

Metformin hydrochloride is a drug of choice of biguanide category in the management of diabetes mellitus. The drug sample was scanned for λ_{max} by spectrophotometer and also by HPLC. The FTIR spectrum of the sample drug was compared with reference for genuinety. The thermal stability of the drug was studied at 30, 40, 50 and 70 ºC in aqueous medium as it is freely soluble in water. The data obtained was treated by Arrhenius, zero order and first order kinetics. Metformin followed zero order kinetics in thermal degradation and covered 208 h to be decomposed up to 10 %.

Key Words: Metformin hydrochloride, Thermal stability, Arrhenius plot.

INTRODUCTION

Diabetes mellitus is a heterogenous endocrine disorder in which hyperglycemia is the unifying feature. Type I diabetes is an autoimmune disorder that results in an absolute insulin deficiency while type II diabetes has a more complex pathophysiologic basis that is not yet completely understood. Seven types of medications are commonly used to treat diabetes: insulin, biguanide (*i.e.*, repaglinide), phenylalanine derivatives (*i.e.*, glyburide, glipizide), meglitinides (*i.e.*, repaglinide), phenylalanine derivatives (*i.e.*, nateglinide), α-glucose inhibitors (*i.e.*, acarbose, miglitol) and thiazolidinediones (*i.e.*, pioglitazone and rosiglitazone)[1]. A typical treatment schedule requires metformin to be taken with meals and a total daily dose of three to four 500 mg tablet or two to three 850 mg tablets[2]. Although metformin's exact mechanism of action is not completely understood, its main blood glucose-lowering activity appears to be primarily through suppression of hepatic glucose output. Its therapeutic blood glucose-normalizing action is dependent on the presence of circulating insulin. It may also act in the liver by activation of adenosine monophosphate-activated protein kinase, resulting in inhibition of the genes that regulate lipid genesis and enhancement of lipolysis in hepatocytes. It has an absolute oral bioavailability of 40-60 %. Gastrointestinal absorption occurs mainly in the upper intestine and is complete at 6 h, with plasma concentrations (C_{max}) reached after 2-3 h and the plasma elimination half-life ($t_{1/2}$) of 2-6 h and a terminal elimination $t_{1/2}$ of 8-20 h[3].

†Department of Pharmacy, Lloyd Institute of Management and Technology, Greater Noida-201 308, India.

Metformin hydrochloride is 1,1- dimethyl biguanide hydrochloride. It is freely soluble in water, slightly soluble in ethanol (95 %), practically insoluble in acetone, chloroform, dichloromethane and in ether[4]. In present study, the stability of metformin hydrochloride at various temperatures *i.e*., 30, 40, 50 and 70 ºC was evaluated.

EXPERIMENTAL

Metformin hydrochloride was procured as gift sample from Alkem Laboratories Ltd. (Mumbai). Disodium hydrogen phosphate, acetonitrile and methanol purchased were of Rankem Laboratories, New Delhi. All other chemical and reagents were used without further modification.

Characteization of metfromin hydrochloride for purity: The purity of gift sample was analyzed by FTIR, UV-visible scanning and HPLC.

Fourier transform infrared spectroscopy: The spectrum was recorded for pure metformin hydrochloride identification (Perkin-Elmer). Samples were prepared in KBr discs (2 mg drug in 8 mg KBr) with a hydrostatic press at a force of 8 ton cm^{-2} for 2 min. The scanning range was 2000-400 cm^{-1} and resolution was 2 cm^{-1}.

Scanning of metformin hydrochloride by UV-visible spectrophotometery: The drug, *ca.* 50 mg, accurately weighed on electronic balance (Mettler Toledo 303, Netherland) was solubilized in distilled water. The drug solution was diluted up to the appropriate dilution in different concentrations. The absorbance was determined spectrophotometrically (Hitachi, U-2001, Japan) and also scanned for the λ_{max}, characteristics feature of the drug. The observed λ_{max} was compared with reference value for the drug[4].

Calibration curve for metformin hydrochloride: The standard solution of metformin hydrochloride was prepared in different concentrations. The absorbance of different samples was determined spectrophtometrically on scanned λ_{max} and calculated by using linear regression equation.

Scanning of drug by HPLC: The drug was scanned by a Shimadzu HPLC (Shimadzu, Japan, AT-10VP) with C_{18} column. The drug solution was prepared in HPLC grade water in concentration of 1 µg/mL. It was passed through membrane filter (Pall Life Science, 0.22 µm) to find out the homogenous solution and for degassing kept in ultrasonicator. The mobile phase used in analysis was 0.01 M Na_2HPO_4 solution (pH = 6.5), methanol and acetonitrile (20:3:6 v/v)[5]. The component of mobile phase were also filtered through vacuum filter by using 0.22 µm membrane filter. The drug solution was injected and the peak position was analyzed.

Effect of different temperature on drug stability: Different drug solutions were prepared in distilled water in appropriate concentration (70 mg/mL). These solutions in volumetric flasks were kept at different temperatures *i.e.*, 30, 40, 50 and 70 ºC. The samples were withdrawn from each flask at preset time interval. The samples were diluted up to appropriate concentration and absorbance was determined spectrophotometrically. After finding concentrations in different temperatures at different times, the dissociation constants for zero order and first order kinetics

were analyzed. From the data of different kinetics, $t_{10\,\%}$ (time required to decompose the 10 % drug) was determined[6].

RESULTS AND DISCUSSION

The infrared spectrum of the reference and the sample has been shown in the Fig. 1. It was observed that both the spectrum were similar. The wave numbers observed in sample drug IR were in the range of 1500-1300, 3400-3300, 1700-1500 and 3000-2700 cm^{-1}. These were the bands of CH_3^-, =N-, =C=NH and C-H aliphatic group.

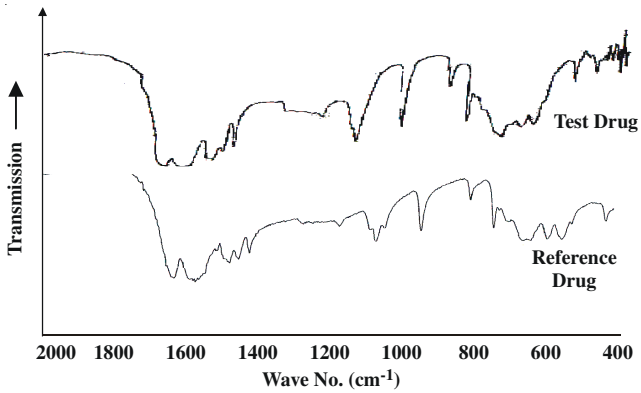


Fig. 1. FTIR spectra of reference and test drug, metformin hydrochloride

The standard spectrum of the drug from the reference (Indian Pharmacopoeia)[4] also showed the bands in 1500-1300 and 1700-1500 cm^{-1} and in the range of 2000-400 cm^{-1}. This investigation confirmed the identity and purity of the drug sample used.

UV-Visible wavelength scanning: The UV-visible scanning of pure drug in distilled water has been summarized in the Fig. 2. The λ_{max} value of the drug was at 233 nm which is similar to standard value for metformin chloride (233 nm)[4]. Moreover, 233 nm was selected for absorbance in drug analysis.

Analysis of drug by high performance liquid chromatography: The drug solution in HPLC grade water after appropriate dilution was analyzed by HPLC (Shimadzu, Japan, AT-10VP series) at 233 nm. The drug showed a single sharp peak as shown in Fig. 3. The single peak also confirmed the identity and purity of metformin hydrochloride.

Calibration curve of metformin hydrochloride: Different concentration of the drug solution were taken and after appropriate dilution the absorbance was determined by UV-visible spectrophotometer (Hitachi, Japan, U-2001) at 233 nm. The absorbance *versus* concentration curve has been shown in the Fig. 4. The linear regression equation obtained after regression was used for calculation of drug concentration.

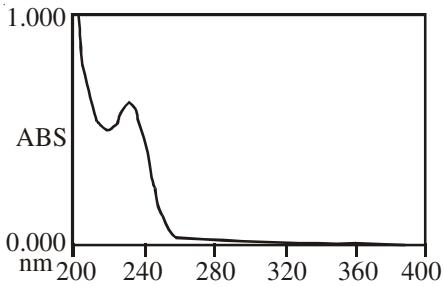


Fig. 2. Scanning of metformin by UV-visible spectrophotometer

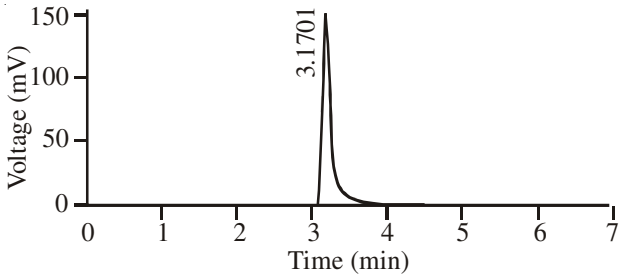
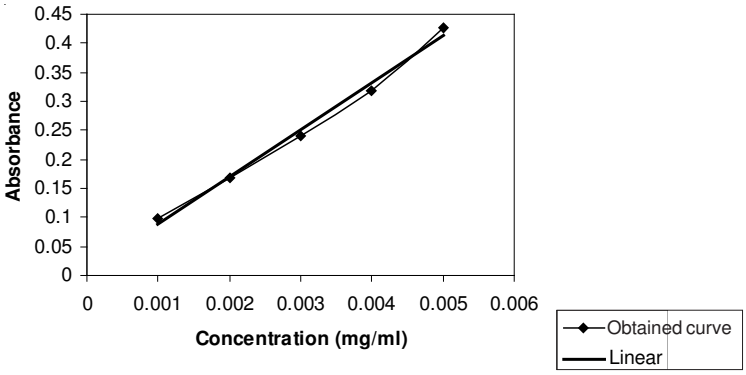


Fig. 3. HPLC spectrogram of metformin hydrochloride



Y = 81.3X + 0.0067; R^2 = 0.9916 where Y = absorbance,
X = concentration of drug R = Linear regression coefficient

Fig. 4. Calibration curve of metformin hydrochloride between absorbance *versus* concentration in aqueous medium

Thermal stability of metformin hydrochloride: It was observed that the initial amount of metformin taken was decreased at every temperature which indicated the decomposition of drug which might be due to different chemical pathways. The graphs of degradation by first order and zero order have been shown in Fig. 5. Decomposition constants at different temperature for different kinetics have been summarized in Table-1. Arrhenius plot[7] has been shown in Fig. 6. Different kinetics

constants are shown in Table-2. From the plot, it is clear that the log value of the K values at different temperatures (*e.g.,* 30, 40, 50 and 70 ºC) provided straight line which may indicate that drug may follow zero order kinetic at the temperatures mentioned above[7]. It was also observed that at different temperatures, there was no statistically significant difference in degradation of the drug ($F_{3.35} = 2.297$, $P_{(0.096)} > 0.05$). The slope or decomposition constant by the Arrhenius plot was 5×10^{-4} mg/ $^0K \times 10^6$. It was calculated that the time required for 10 % decomposition would be 208 h.

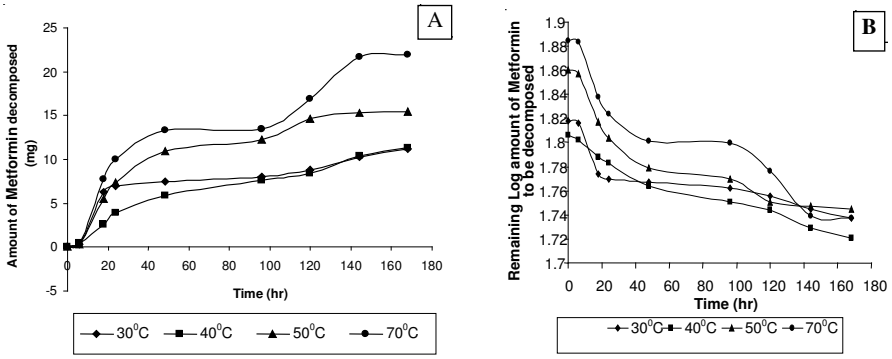


Fig. 5. Kinetics curves of drug degradation at different temperatures; Zero order (A) and first order (B)

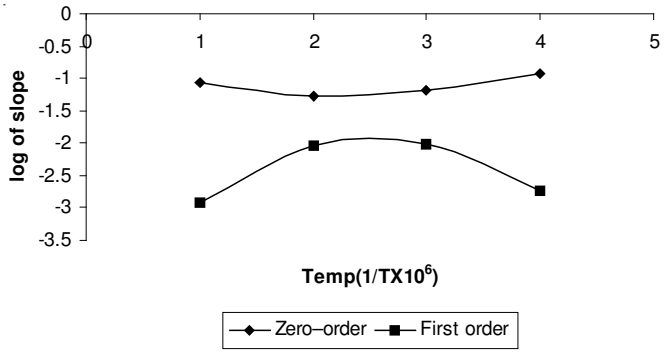


Fig. 6. Arrhenius plot for drug stability

TABLE-1
DECOMPOSITION CONSTANT (k), INTERCEPT AND REGRESSION COEFFICIENT (R) OF DIFFERENT KINETICS

S. No.	Temp. (ºC)	Zero-order kinetics			First order kinetics		
		k-Value	r^2	Intercept	k-Value	r^2	Intercept
1	30	0.0526	0.7200	2.9418	9.2120×10^{-3}	0.7421	1.7981
2	40	0.0634	0.9448	1.2178	9.1515×10^{-3}	0.9654	1.7986
3	50	0.0881	0.8445	2.9613	1.2181×10^{-3}	0.8404	1.8370
4	70	0.1184	0.8689	3.4828	1.8424×10^{-3}	0.8940	1.8800

TABLE-2
LOG OF DECOMPOSITION CONSTANT (k) AND THERMAL DEGRADATION TEMPERATURE (K) FOR DIFFERENT KINETICS

S. No.	Temp.	$(1/T) \times 10^6$ K	Slope		Log slope	
			Zero order	First order	Zero order	First order
1	30 ºC	(3300 K)	0.0526	9.2120×10^{-3}	-1.28	-2.04
2	40 ºC	(3194 K)	0.0634	9.1515×10^{-3}	-1.20	-1.04
3	50 ºC	(3095 K)	0.0881	1.2181×10^{-3}	-1.06	-2.91
4	70 ºC	(2915 K)	0.1184	1.8424×10^{-3}	-0.93	-2.73

Conclusion

The metformin hydrochloride was pure and genuine as per official compendia as shown by FTIR, spectrophotometric and HPLC study. It was observed that 10 % of the drug will decompose within 208 h on 30 ºC. As the dug is freely soluble in water, it may provide a clue about the storage condition and the effect of temperature in fabrication of pharmaceutical formulations of metformin hydrochloride *e.g.*, during the compression cycle of tablet, sustained release dosage forms alone and in combination with other antidiabetic drugs *etc*.

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