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Research Article

SOLUBILITY AND DISSOLUTION PROFILE STUDIES OF GLICLAZIDE IN PHARMACEUTICAL FORMULATIONS BY RP-HPLC

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ABSTRACT
This study describes the solubility and dissolution profile of Gliclazide. The solubility study was evaluated by using the shake flask method. The dissolution study has been carried out in different buffers for Gliclazide solid dosage form and estimated by using the RP-HPLC technique. In the present study a dissolution medium was developed and selected on the basis of solubility data of Gliclazide at 37 °C. The solubility data revealed that pH 7.4 phosphate buffer (0.6375 mg/ml) shall be suitable dissolution medium. The discriminating power of the selected dissolution medium relative to the other dissolution medium was evaluated. The described method can be successfully applied for the analysis of tablets, active pharmaceutical ingredient and drug dissolution studies.
KEY WORDS: Gliclazide; RP-HPLC; Solubility study.

INTRODUCTION

Gliclazide, 1-(1-azabicyclo-[3,3,0]-oct-3-yl)-3-(p-tolylsulfonyl) urea (Fig. 1), is a potential oral hypoglycemic drug which is useful for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). Prior reports show that the drug shows good general tolerability, low incidence of hypo-glycemia, and a low rate of secondary failure. In addition, it has potential for slowing the progression of diabetic retinopathy. For these reasons, Gliclazide appears to be a drug of choice in long-term sulfonylurea therapy for the control of NIDDM.

The low water solubility of Gliclazide leads to a low dissolution rate. The solubility study of Gliclazide has been evaluated in few buffer and followed by dissolution profiles in the selected dissolution media. Gliclazide drug is belongs to Class II of the biopharmaceutical classification system (BCS) that means it has low solubility and high permeability (Fug.2).

The literature survey revealed that a number of analytical methods have been developed for the quantitative determination of Gliclazide in pharmaceutical dosage forms[1-12] and also one of the analytical method has been reported for solubility and dissolution properties of Gliclazide[13].

The aim of present work was to study the solubility of Gliclazide (0.1 N HCl, pH 4.5 sodium acetate, pH 6.8 phosphate buffer, pH 7.4 phosphate buffer and pH 5.8 FeSSIF buffers) and its dissolution profile in different mediums by using the RP-HPLC technique. The procedure based on the use of reverse phase high performance liquid chromatography is simple, rapid and provides accurate and precise results.

MATERIALS AND REAGENTS

All the reagents were of analytical reagents grade unless state otherwise. Glass-distilled and de-ionized water (Nanopure Barnsted, USA), HPLC grade acetonitrile, Hydrochoric acid, sodium acetate, potassium dihydrogen phosphate, glacial acetic acid, sodium hydroxide (Merck, India) were used in the separation technique. Gliclazide tablets and working standards were manufactured by Dr.Reddy's Laboratories Ltd (Hyderabad, India) Placebo mixtures were prepared in the laboratory using United States Pharmacopoeia (USP) grade excipients.

Equipment

The dissolution test carried out by using DISSO2000 model of LABINDIA dissolution apparatus. Agilent 1200 series integrated high performance liquid chromatographic system was used for this experiment. Agilent 1200 series system equipped with Agilent 1200 series binary pump, Agilent 1200 series auto sampler, Agilent 1200 series variable wavelength detector, Agilent 1200 series Column thermostat and controlled by Empower 2 software.

Preparation of dissolution media buffer

The solubility of Gliclazide has been performed in the following dissolution media.

a) **0.1N Hydrochloric acid:** Transferred 8.5 ml of Conc. HCl (35%) into a 1000 ml volumetric flask and made upto volume with water.
b) **pH 4.5 Sodium acetate buffer:** Weighed and transferred 2.99 g of sodium acetate ($NaC_2H_3O_2 \cdot 3H_2O$) in a 1000ml volumetric flask, added 14.0 ml of 2 N acetic acid (CH_3COOH) and made up to volume with water.
c) **pH 6.8 phosphate buffer:** Transferred 250 ml of 0.2 M monobasic potassium phosphate solution, 112 ml of 0.2 M NaOH into 1000 ml volumetric flask and made up to volume with water.
d) **pH 7.4 phosphate buffer**: Transferred 250 ml of 0.2 M monobasic potassium phosphate solution, 195.5 ml of 0.2 M NaOH into 1000 ml volumetric flask and made up to volume with water.
e) **pH 5.8 FeSSIF Bio-relevant buffer:**

Preparation procedure

i.Lecithin Solution: Dissolved 20 g of Soya bean Lecithin in 200 ml of Dichloromethane

ii.Glyceryl Mono Oleate (GMO) solution: Dissolved 25 g of GMO in 500 ml of DCM

iii.Blank Solution Preparation: Dissolved 52 g of sodium chloride, 63 g maleic acid and 32g sodium hydroxide in 10000 ml.Adjusted pH to 5.8 with sodium hydroxide.

iv.Sodium Taurocholate solution: Dissolved 53 g of sodium taurocholate in 500 ml of blank, added 157 ml of Lecithin solution and mix. Evaporated at 40 °C under vacuum to remove DCM with Rota evaporator. Added 357 ml of GMO solution and evaporated DCM. Dissolve 2.4 g of sodium oleate in this solution and mixed it

REVERSE PHASE HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

Chromatographic conditions

The analysis carried out on LichroSphere 100 RP-18e, 150 mm × 4.6 mm, 5µm. A HPLC column using the mobile phase was a mixture of a HPLC grade water, acetonitrile and triethylamine and tryfluoroacetic acid in the ratio of 60: 40: 0.1: 0.1, (v/v/v/v) respectively. The mobile phase was filtered through 0.45 µm Nylon 66 filter paper using the vacuum pressure and degassed. The injection volume was 10µl and the detection was performed at 235 nm using a Agilent 1200 series binary HPLC system with UV detector. The separation has been achieved by using flow rate with 1.5 ml/min and with 25 °C column oven temperature. The retention time of Gliclazide was 8.0 and the total run time was 15 min.

Solubility study

The dissolution was applied to the in vitro solubility studies of Gliclazide. The saturation solubility of the compound was determined at five different pH values (1.2, 4.5, 5.4, 6.8, and 7.4) according to biopharmaceutical classification system (BCS). Solubility studies were repeated three times at each pH conditions. Five different pH mediums (Table.1) were prepared according to USP 32.

The determination of solubility of Gliclazide drug substance in respective dissolution media [0.1N hydrochloric acid (pH 1.2), pH 4.5 sodium acetate buffer, pH 6.8 phosphate buffer, pH 7.4 phosphate buffer, pH 5.4 FESSIF Bio-relevant buffer] by shake flask method.

Shake flask method:

An accurately weighed Gliclazide drug substance was transferred (or/ active pharmaceutical ingredient) in to a 250 ml conical flask containing 100 ml of dissolution media. The solubility study has been performed at a temperature of 25 °C. The shaking process was happed for 24 hours by keeping conical flasks on rotary shaker at 200 rpm. A portion of drug substance dissolved buffer solutions were filtered through 0.45 µm Nylon 66 filter and injected into reverse phase high performance liquid chromatographic system. The determined, the amount of drug substance added (wt) in mg, the quantity (L) of drug substance dissolved in percentage (wt/v), the actual amount (N) of drug substance dissolved in mg and the solubility of drug substance in mg/ml in dissolution medium tested (S) were calculated and reported. The tests were prepared in triplicate in the selected buffers of dissolution medium (0.1 N Hydrochloric acid, pH 4.5 Sodium acetate buffer, pH 6.8 phosphate buffer, pH 7.4 phosphate buffer, pH 5.4 FESSIF Bio-relevant buffer), respectively. (Where, A1 = Response of Gliclazide in test preparation; A2 = Response of Gliclazide in standard preparation; Sc = Concentration of standard in mg/ml; Tc = Concentration of standard in mg/ml).The results are shown in Table.1.

$$L = \frac{A1 \times Sc \times 100}{A2 \times Tc} \quad \ldots\ldots\ldots\ldots\ldots\ldots \textit{(i)}$$

$$N = \frac{L \times Wt}{100} \quad \ldots\ldots\ldots\ldots\ldots\ldots \textit{(ii)}$$

$$S = \frac{N}{100} \quad \ldots\ldots\ldots\ldots\ldots\ldots \textit{(iii)}$$

Preparation of standard solution

A stock solution of Gliclazide working standard (0.33 mg/ml) was prepared by dissolving an appropriate amount in dissolution medium and along with addition of 10 ml of methanol. Final working standard (0.033 mg/ml) was prepared from above stock solution in dissolution medium for dissolution test of Gliclazide tablets 30 mg.

Dissolution test of tablets and sample preparation

The dissolution study has been performed by using 900 ml of dissolution medium, USP-II Apparatus (paddle), 75 rpm of paddle speed and 37 ± 0.5 °C of bath temperature, respectively. Accurately weighed tablets containing the equivalent of 30 mg of Gliclazide were placed in the dissolution medium and samples were collected at 2, 8, 12, 16, 22 hours. Equal volumes (10 µl) of these test solutions (0.033 mg/ml) were injected into the liquid chromatographic system with auto sampler and peak areas were measured (Tab.2).

RESULTS AND DISCUSSION

The objective of this study was to estimate solubility of Gliclazide drug substance and to study Gliclazide tablets dissolution profile in selected media by using the RP-HPLC system in a simple isocratic mode of elution and could be faced problems during the preparation of FeSSIF bio-relevant medium. Gliclazide was unstable at low pH rage, due to this reason Gliclazide drug substance has been degraded in 0.1N HCl. The dissolution profile of Gliclazide tablets was not given satisfactory results and also, the stabilization processes were not given successful result (Fig.3).

CONCLUSIONS

According to shake flask solubility studies, the solubility of Gliclazide drug substance has been found satisfactory in 7.4 phosphate buffer (0.6475mg/ml) compared to all other buffers. Gliclazide drug was completely release within the 24hrours. The rate of dissolution was found in the increasing order at the time interval of last. The simple isocratic mode reverse phase high performance liquid chromatographic method was developed for determination of solubility and study of dissolution profile of Gliclazide. Thus the developed method can be used for quantitative determination of Gliclazide in raw materials and solid dosage forms of pharmaceuticals. Thus from above results it was concluded that 7.4 phosphate buffer is considered as suitable dissolution medium for routine in-vitro dissolution testing of conventional Gliclazide formulations (Internal Reference No.: PUB 00153-12).

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Table. 1: Results table of solubility profile of Gliclazide

Sr.No.	Name of the buffer solution	Solubility in mg/ml
1.	pH 4.5 Sodium acetate buffer	0.0576
2.	pH 6.8 Phosphate buffer	0.2954
3.	pH 7.4 Phosphate buffer	0.6375
4.	pH 5.4 FESSIF	0.0742

Table. 2: Dissolution profiles of Gliclazide

S.No.	Name of the buffer solution	% Drug release (Mean of six units)				
		2 Hrs	6 Hrs	12Hrs	16Hrs	24Hrs
1	pH 4.5 Sodium acetate	5	25	50	65	73
2	pH 6.8 Phosphate	19	49	72	79	89
3	pH 7.4 Phosphate	13	39	79	92	99

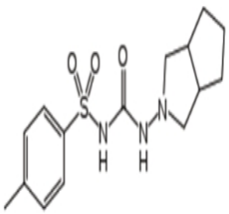

Figure.1a: The chemical structure of Gliclazide

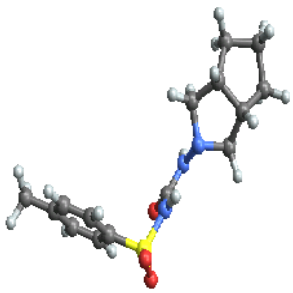

Figure.1b: The 3D-chemical structure of Gliclazide

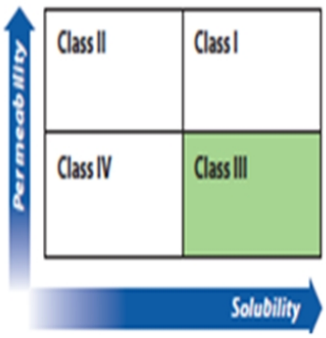

Figure.2: BCS Classification system

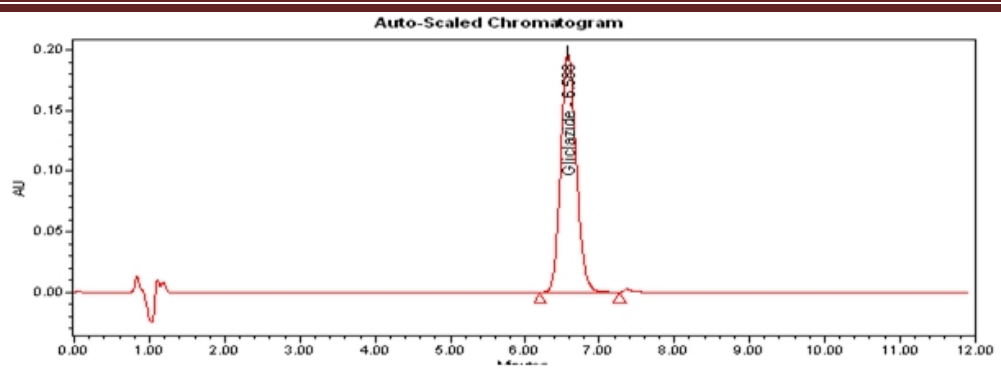

Figure.3a: A typical chromatogram of Gliclazide standard in 7.4 phosphate buffer

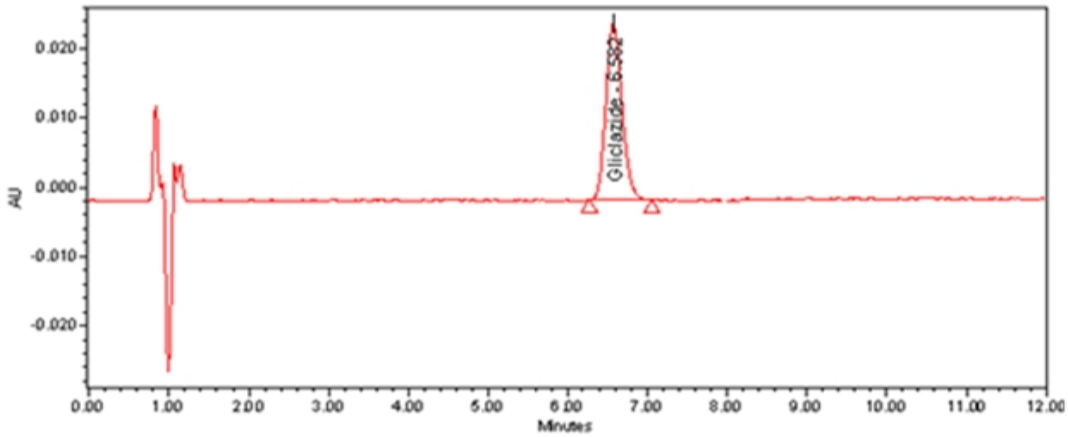

Figure.3a: A typical chromatogram of Gliclazide test in 7.4 phosphate buffer

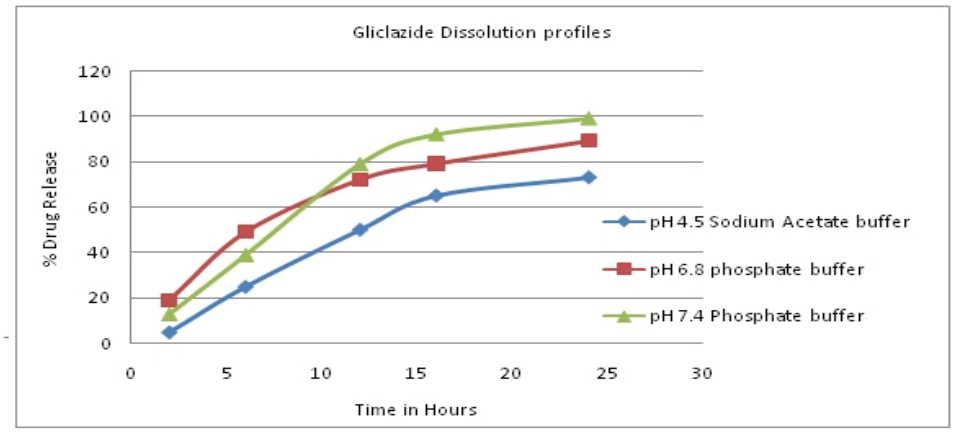

Figure.3c: A typical plot of Gliclazide DPDM

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