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DEVELOPMENT AND CHARACTERISATION OF GLICLAZIDE COCRYSTALS

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ABSTRACT

Pharmaceutical co-crystallisation is a reliable method to modify physical and technical properties of drugs such as solubility, dissolution rate, stability, hygroscopicity, and compressibility without alternating their pharmacological behaviour. Gliclazide cocrystals are prepared by using tartaric acid and succinic acid as co-formers and chloroform, methanol as the solvent mixture. Various ratios of drug and co-formers were taken to prepare co-crystals by using solvent evaporation method and undergone studies like dissolution study, FTIR, differential scanning calorimetry, X-Ray diffraction study. The results are compared with standard drug. The gliclazide-tartaric acid co-crystals have shown good dissolution and melting point results, so further studies like XRD and DSC were done. So, it is concluded that dissolution rate of gliclazide drug was increased.

KEY WORDS

Pharmaceutical co-crystallisation; co-former; solubility; melting point; solvent evaporation

INTRODUCTION:

Poor dissolution rate, solubility, chemical stability and moisture uptake influence therapeutic efficacy of many pharmaceuticals, and significantly lower the market value of a drug. A solid can exist in two forms viz. either amorphous or crystalline[1]. Solid dosage forms are by far the preferred drug delivery systems. In crystalline form a solid can exist as polymorph, hydrate, solvate, or co-crystal[2,11]. Chemists and engineers in the pharmaceutical industry prefer to deliver crystalline forms of their active compounds, mainly due to the inherent stability of crystalline materials and the well-established impact of crystallization processes on purification and isolation of chemical substance[7]. New opportunities for producing a larger diversity of solid forms of drug substances exhibiting the proper balance of important properties for development into a viable and effective drug product may be met by co-crystals[10].

Cocrystals are the most dynamically developing group of solid substances. The definition of the term "pharmaceutical cocrystal" is still under discussion, but essentially it is multi component compound that is formed between a molecular or ionic API and a co-former under ambient conditions[3,13].

The physical and chemical property improvements through pharmaceutical cocrystals draw closer the fields of crystal engineering and pharmaceutical sciences. A pharmaceutical cocrystal is a single crystalline solid that incorporates two neutral molecules, ne being an API and other a co-crystal former[13].

Co-crystal former may be an excipient or another drug. Pharmaceutical co-crystal technology is used to identify and develop new proprietary forms of widely prescribed drugs and offer a chance to increase the number of forms of an API[34]. Scientists showed that modifying the physical properties of a pharmaceutical compound through pharmaceutical co-crystal formation improved

the performance of a drug known to have poor solubility. Pharmaceutical co-crystallisation is a reliable method to modify physical and technical properties of drugs such as solubility, dissolution rate, stability, hygroscopicity, and compressibility without alternating their pharmacological behavior[27]. The expanding scope of crystal form selection, emergence of crystal engineering in pharmaceutical sciences and pharmaceutical cocrystals are reviewed. Some common aspects of cocrystal formation, screening strategies and outline methodologies for co-crystal functionality were reported. The use of cocrystals in drug design and delivery and as functional materials with potential applications as pharmaceuticals has recently attracted considerable interest. Pharmaceutical co-crystals have been described for many drugs such as acetaminophen, aspirin, ibuprofen, flurbiprofen etc. Co-crystals of antitubercular drugs with dicarboxylic acids were reported using acid-pyridine synthon as a reliable tool[10].

Mechanism for cocrystal synthesis:

Amorphous phases generated by pharmaceutical processes lead to co-crystal formation during co grinding and storage. The mechanisms underlying moisture uptake generated co-crystals of carbamazepine- nicotinamide, carbamazepine-saccharin, and caffeine or theophylline with dicarboxylic acid ligands (oxalic acid, maleic acid, glutaric acid, and malonic acid) when solid mixtures with co-crystal reactants were exposed to deliquescent conditions involve

(i)moisture uptake

(ii)co-crystal aqueous solubility

(iii)solubility and dissolution of co-crystal reactants, and

(iv)transition concentration [26].

Cocrystal Design:

Cocrystal design is based on crystal engineering principles. By understanding supramolecular chemistry of the functional group present in a drug and coformer. Hydrogen bonding can be easily formed between the drug and coformer if it contains functional groups like carboxylic acids, amides and alcohols[28]. Etter and co-workers proposed guidelines to promote design of hydrogen-bonded solids along with graph set descriptors and classification of packing. The rules of hydrogen bonding are: 1. All good proton acceptors and donors are only used in hydrogen bonding. 2. Six-membered ring with intramolecular hydrogen bonds form are preferred for intermolecular hydrogen bonds. 3. The best proton acceptor and donor remained after intramolecular hydrogen bond formation it will form intermolecular hydrogen bonds to one another. Statistical analysis of hydrogen bonding motifs in the Cambridge Structural Database help to the identification of molecular properties and their role in cocrystal formation. The observed data from CSD will help to provide qualitative guidelines for the designing cocrystals[16].

MATERIALS AND METHODS:

Material	Source	Rationale
Gliclazide	Bal pharma Ltd	Active pharmaceutical ingredient
Tartaric acid	Ashwini chemical Ltd	Conformer
Succinic acid	Triveni interchem Ltd	Conformer

Equipment name	Manufacturer	Model no.
Digital weighing balance	Shimadzu	AY 220
Rotary flash evaporator	IKA-Werke	RV 10
UV-Visible spectrophotometer	Labindia	UV 3000
Fourier transformer infrared spectroscopy	Bruker	Alpha
Differential scanning calorimetry	TA Instruments	DSC Q200
X-ray diffractometer	BRUKER AXS	D8

METHODOLOGY:

COMPOSITION OF BUFFER SOLUTIONS:

Potassium dihydrogen phosphate 0.2M:

27.218gm of potassium dihydrogen phosphate was dissolved in distilled water and made upto 1000ml with the distilled water.

Sodium hydroxide 0.2M:

8gm of sodium hydroxide was dissolved in distilled water and made upto 1000ml with distilled water.

Phosphate buffer pH 7.4:

250ml of 0.2M potassium dihydrogen phosphate was placed in a 1000ml volumetric flask;and to it 195.5ml of 0.2M sodium hydroxide was added and rest of the volume was made up by distilled water.

Spectrophotometric method for estimation of Gliclazide:

Determination of Gliclazide λmax in pH 7.4 phosphate buffer:

Stock solution:

Accurately weighed quantity of 100mg Gliclazide was taken in 100ml volumetric flask and dissolved by using 5ml methanol, finally the volume was made up with pH 7.4 phosphate buffer up to 100ml to produce 1mg/ml of solution.

Scanning:

A series of concentrations i.e. 10, 15, 20 mcg/ml were prepared by using above stock solution and scanned between 200-400nm. The absorption maxima of 226nm was selected and used for further studies.

Preparation of calibration curve in pH 7.4 phosphate buffer:

Accurately weighed amount of equivalent to 100mg Gliclazide was dissolved in small volume of methanol, in 100ml volumetric flask and the volume was adjusted to 100ml with pH7.4 phosphate buffer. A series of standard solution containing concentration range from 2 to 14 µg/ml of Gliclazide were prepared and absorbencies were measured at 226nm against blank reagent.

PREPARATION OF COCRYSTALS

The cocrystals were prepared by solvent evaporation method. Drug and selected conformers were dissolved in suitable solvents. The required quantities of drug and conformers in different ratios like 1:1,1:2,1:3 were taken and dissolved in suitable solvent of specific volume. The solutions are then poured into the rotary evaporator's jar. The temperature of water bath is maintained at room temperature. The rpm was settled, and the vacuum was put to on. Now, rotary jar starts to rotate and then crystals were formed. The formed cocrystals were taken out from the jar and characterized for different studies.

Composition of various cocrystals:

Drug: coformer	API(mg) Gliclazide	Coformer(mg)
1:1	647mg	300
1:2	647	600
1:3	647	900

PREFORMULATION STUDIES:

Preformulation is an exploratory activity that begins early in drug development. These studies are designed to determine the compatibility of intial excipient with the active substance for a biopharmaceutical, physicochemical and analytical investigation in support of promising experimental formulations. Data from preformulation studies provide the necessary ground work for formulation attempts.

API CHARACTERISTICS:

It is the first preliminary study carried out during the preformulation studies. The following parameters were evaluated by observation.

1.Colour

2.Odour

3.Texture

Solubility studies:

Solubility of Gliclazide in various solvents was determined. The vehicles in which solubility are to be determined were taken separately in a cap vial containing excess of the drug solubility is determined.

Melting point:

MP was determined using MP apparatus. The sample was placed in apparatus and observed for the temperature at which drug melts.

CHARACTERISATION OF COCRYSTALS

Solubility Studies:

Solubility studies were carried out according to the method reported by Higuchi and Connors. An excess of Gliclazide was added to 10 ml portions of distilled water and was shaken in rotary shaker for 24 hours. After shaking, the solution was filtered, and their absorbance was noted at 226 nm.

Dissolution studies for Gliclazide cocrystals:

In-vitro dissolution of gliclazide solid dispersions was studied in USP dissolution apparatus (Electrolab) employing a basket stirrer. 900 ml of phosphate buffer of pH 7.4 was used as dissolution medium at 50 rpm. The temperature of 37±0.5 °C was maintained throughout the experiment. Cocrystals equivalent to 100 mg of gliclazide was used in each test. 5 ml of sample of dissolution medium were withdrawn by means of syringe fitted with pre-filter

at known intervals of time and analysed for drug release by measuring the absorbance at 226nm.After suitable dilution with phosphate buffer. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. The amount of gliclazide released was calculated and plotted against time and compared with pure drug.

Fourier Transform infrared (FTIR) Spectroscopy:

In order to investigate the potential interactions between the ingredients used, FTIR spectroscopy was performed using FTIR spectroscope. Samples analyzed were gliclazide,tartaricacid,succinicacid,and cocrystals of gliclazide and tartaric acid cocrystals.A small amount of sample was analyzed from

Differential Scanning Calorimetry (DSC):

The molecular state and thermochemical properties of the drug in cocrystals was evaluated by performing DSC analysis of pure drug, Tartaric Acid, and cocrystals. The thermogram curves of the samples were obtained by differential scanning calorimeter (DSC Q200, TA INSTRUMENTS, USA). About 2mg of a test sample was weighed using a microbalance (Satorius), the sample was placed in an aluminium pan with a lid and the pan was sealed. An empty aluminium pan with its lid was used as a control. The samples were purged with pure dry nitrogen at a flow rate of 70ml/min. The temperature ramp was set at 10^0c/min and the heat flow was recorded. the temperature scale was calibrated with high purity standards.

Powder X-ray diffraction analysis:

The physical states of Gliclazide, tartaric acid, succinic acid, and co-crystals were obtained using a BRUKER D8 FOCUS High Resolution Powder Diffractometer (BRUKER AXS, Germany) equipped with a scintillation counter detector with a divergent beam. This beam employed a Cu.Kα radiation source with a wavelength of λ=1.5418 containing 2mm slits over a range of 0-60^0 2θ. X-Ray diffraction data were collected at room temperature and scanned with a step size of 5^0 2θ and a dwell time of 12 min at each step.

RESULTS AND DISCUSSION:

Preformulation studies:

Preformulation is defined as the phase of the research and development process where physical, chemical and mechanical properties of a new drug substance are characterized alone and when combined with excipients, in order to develop stable, safe and effective dosage form.

Preformulation studies of gliclazide were performed before formulating cocrystals.After formulation they were evaluated for drug content, percentage encapsulation efficiency, vesicle size analysis and in-vitro drug release.

API characterization:

Organoleptic evaluation:

Colour : white
Odour : odourless
Texture : soft

Solubility profile:

Solubility of gliclazide was determined in various dissolution media and organic solvents by shake flask method and the results of the solubility studies were given in the table no.

From the solubility studies it was concluded that gliclazide has solubility in chloroform, acetone and methanol.

Table.No.5: Solubility of Gliclazide in organic solvents:

Organic solvents	Drug solubility
Chloroform	Soluble
Acetone	Soluble
Methanol	Slightly soluble

Table.No.6 : Solubility of gliclazide in water:

Water	Insoluble

Table.No.7: Solubility of gliclazide in various phosphate buffer:

Phosphate buffer(ph)	Drug solubility
6.8	Insoluble
7.2	Insoluble
7.4	Insoluble

b. **Melting point determination**: The melting point of obtained sample(gliclazide) was found to be 180° c, which compiled with the reported melting point of standard gliclazide thus indicates the purity of the obtained sample.

Calibration curve of gliclazide in phosphate buffer pH 7.4:

a standard graph was plotted for the analysis of gliclazide in phosphate buffer pH7.4 at a wavelength 226 nm and was found that, within the concentration range of 1-10 mcg/ml obeyed beer's law. A calibration curve was constructed at an absorption maximum of 226nm, which had a regression co-efficient of 0.9984.

Table.no.8 Data for the construction of calibration curve of gliclazide in phosphate buffer7.4:

Concentration(mcg/ml)	Absorbance(nm)
0.5	**0.224**
1	**0.5283**
1.5	**0.8079**
2	**1.1387**
2.5	**1.4083**

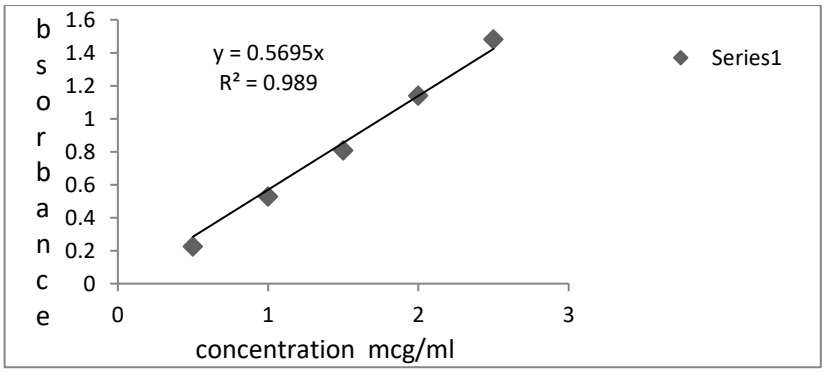


Fig.no.1. calibration curve of gliclazide

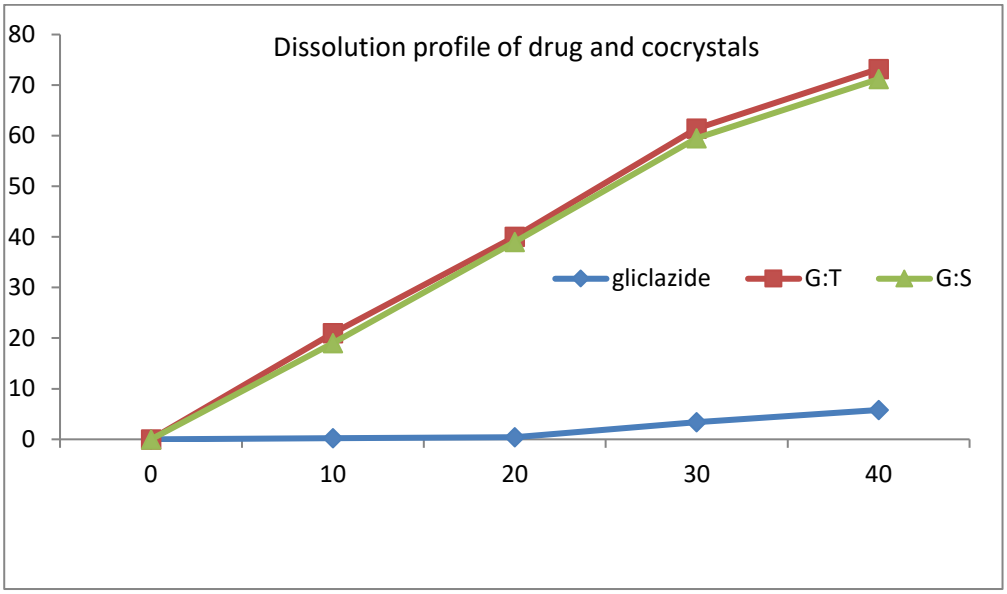
Dissolution profile of gliclazide:

Gliclazide dissolution profile was estimated in 7.4 phosphate buffer media by U.V Visible spectrophotometer at 226nm.

Tableno.9. dissolution profile of gliclazide

Cocrystals and conformer	% of drug
Gliclazide drug	5.8%
Gliclazide:tartaric acid(1:1)	72%
Gliclazide:tartaric acid(1:2)	78%
Gliclazide:tartaric acid(1:3)	78.8%
Gliclazide:succinic acid(1:1)	71%
Gliclazide:succinic acid(1:2)	73.4%
Gliclazide:succinicacid (1:3)	75%

Drug and cocrystals	% of drug
Gliclazide	5.8%
Gliclazide:tartaricacid cocrystals (1:1)	72%
Gliclazide:tartaricacid cocrystals (1:2)	78%



Fourier transform infrared (FTIR) spectroscopy:

Fourier transform IR spectra were recorded on FT/IR-Alpha type A. The spectra were recorded for gliclazide cocrystals. Samples were prepared in KBr disc (2 mg sample in 200 mg KBr). The scanning range was 400-4000 cm-1.

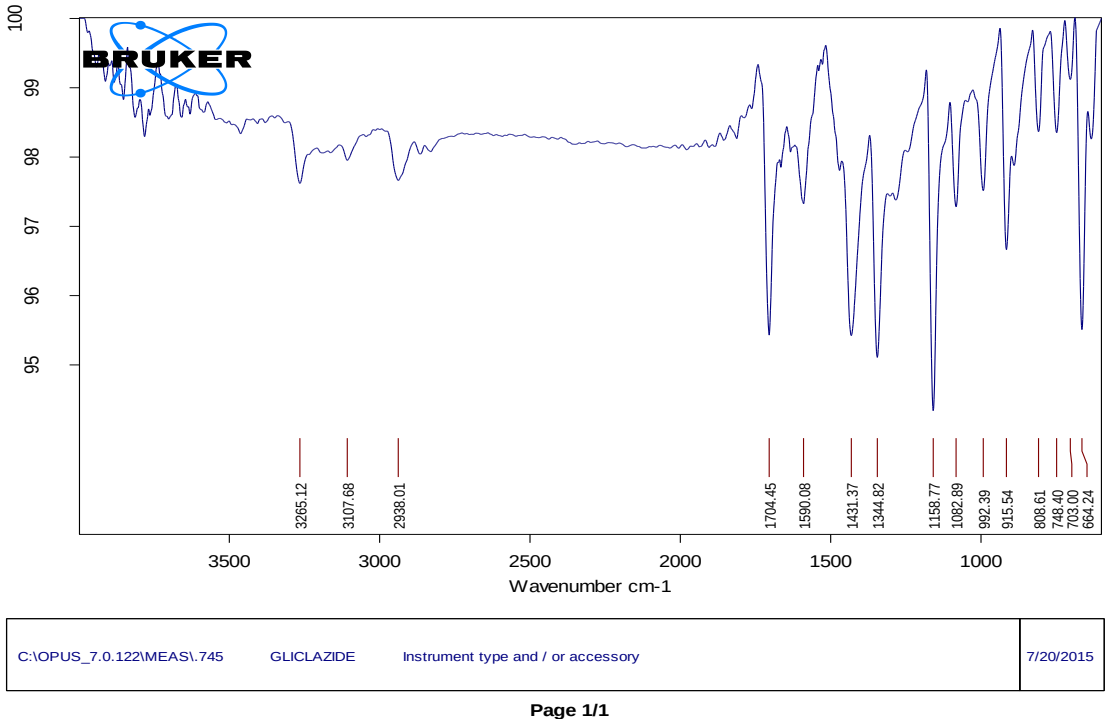


Fig.no.3. FTIR characteristic peaks of Gliclazide

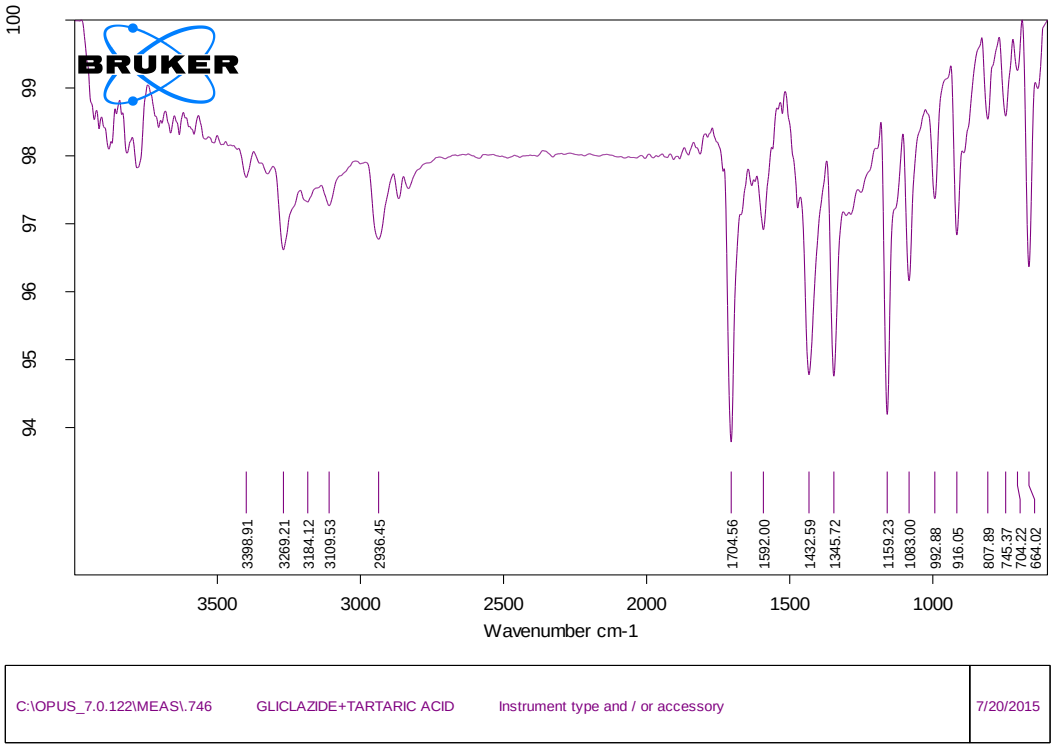
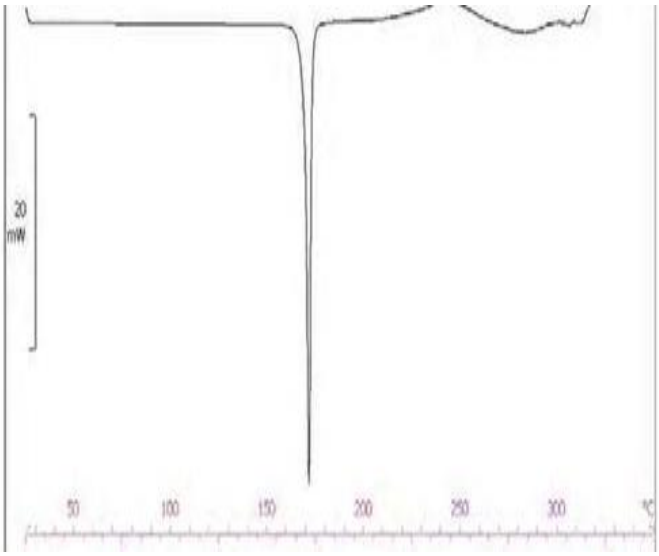


Fig No.4 FTIR characteristic peaks of gliclazide and tartaric acid cocrystals

Differential Scanning Calorimetric analysis (DSC):

The DSC technique can provide qualitative and quantitative information about the physicochemical status of drug in cocrystal, which is reported to be involved in the endothermic or exothermic process. The DSC thermograms shown in figure indicates melting peak of gliclazide was-in DSC thermograms of cocrystals containing gliclazide, reveals that there is decrease in the melting point of gliclazide.so, there is increase in solubility of gliclazide drug.



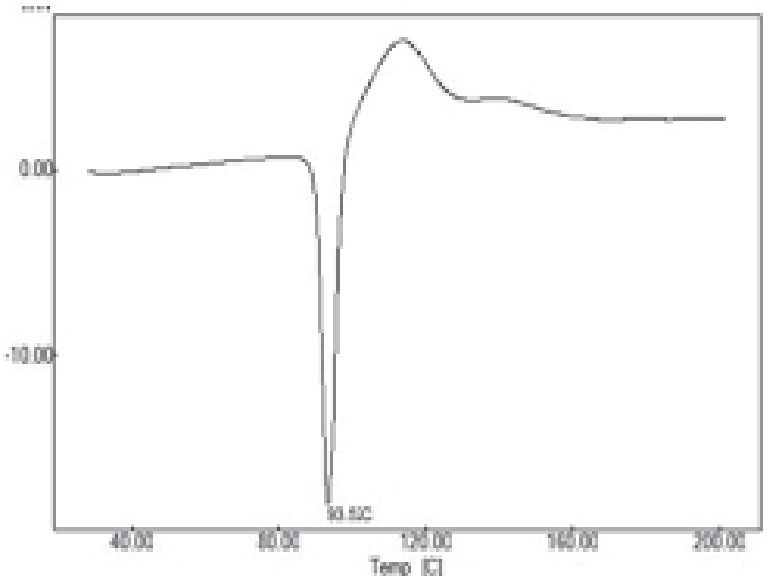


Fig no.6 Differential scanning calorimetry of tartaric acid

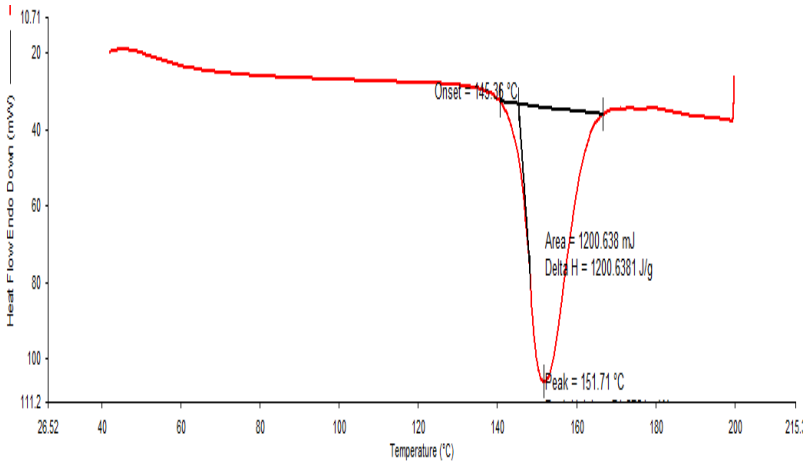


Fig.No.7 DSC thermogram of gliclazide and tartaricacid cocrystals

Powder X-ray diffraction analysis:

XRD is a powerful technique for identification of crystalline solid phase, but there are numerous sources of error in quantitative XRD. X-ray lines are affected by preferred orientation of the particle in the sample. Variation in particle size can have a significant influence on the peak shape. Pure Gliclazide, Tartaric acid, cocrystal 1:2 ratio were characterized by prominent diffraction peaks. The drug peak did not appear in formulation and only carrier peak was observed, which revealed that may be in amorphous state in formulations.

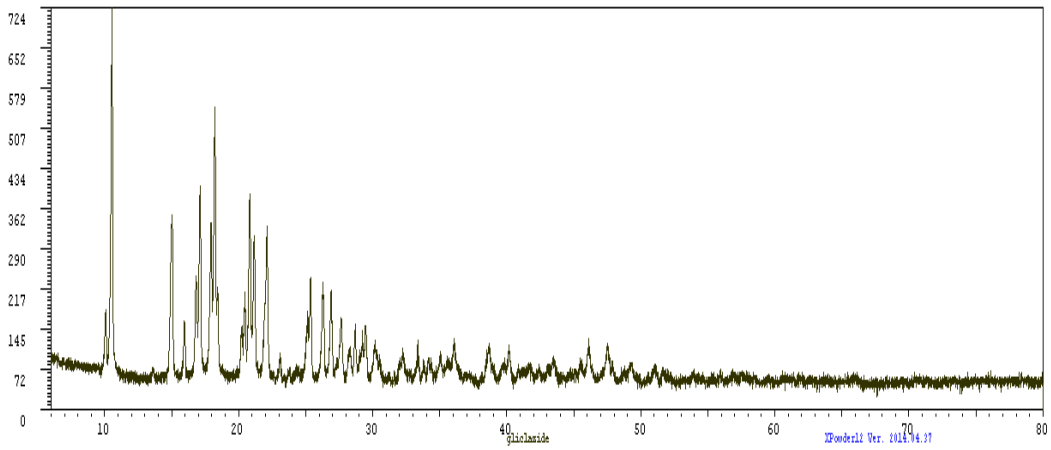


Fig No. 8: Powder X-ray diffraction of pure drug

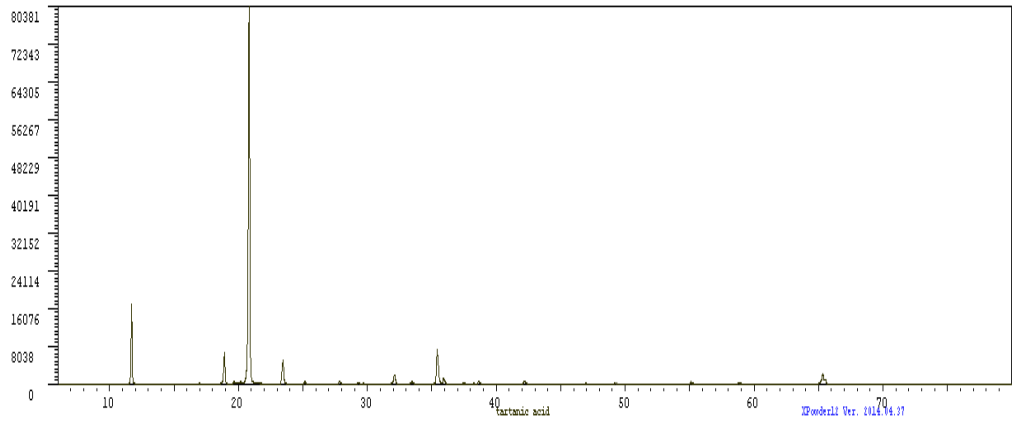


Fig No.9 Powder X-ray diffraction of Tartaric acid

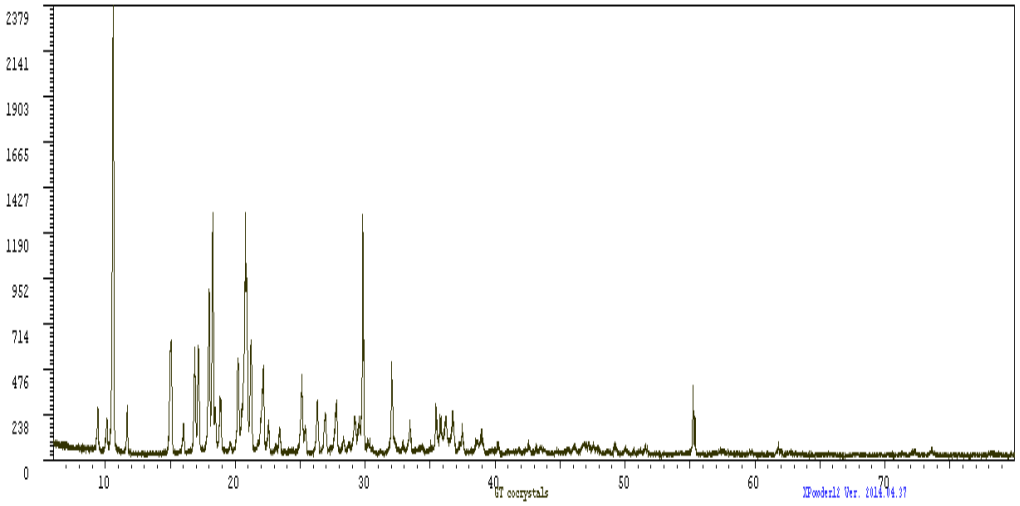


Fig No.10 Powder X-ray diffraction of gliclazide and Tartaric acid cocrystals

SUMMARY:

In the present study an attempt was made to develop cocrystals of gliclazide, an antidiabetic drug. The main objective of the study is to increase solubility of gliclazide by using coformers and conducting invitro studies.

The conventional dosage forms face the problem of low solubility in water. These problems are associated with increased frequency of dosing and patient

incompliance. Hence to overcome such problems drug can be prepared as cocrystals by using coformers.

The scheme work has been divided into various parts. The collections of technical and theoretical data by literature survey, review articles.

The cocrystals were prepared by solvent evaporation method using different coformers. the drug and coformers were taken in different ratios. Tartaric acid and succinic acids are used as coformers. The solvent mixture was chloroform and methanol.

The prepared cocrystals were evaluated for solubility, solid state characterization (DSC, FT-IR and PXRD studies).

Among all the cocrystals prepared, cocrystals containing drug and Tartaric acid in 1:3 ratio was found to have high dissolution rate.

As gliclazide and Tartaric Acid cocrystals were got good increase in dissolution profile, cocrystals containing Tartaric Acid as co former were studied for DSC, XRD studies. In DSC studies it is seen that there is decrease in melting point, so there is increase in solubility.

CONCLUSION:

From the conducted study, we can conclude that cocrystals with Tartaric Acid prepared by the use of co-crystallization technique i.e solvent evaporation method showed an improvement in the dissolution rate as compared with pure drug. Solid state characterization of drug and cocrystals showed satisfactory results such as FTIR proves compatibility; while DSC showed thermal evaluation. On the basis of these results, it could be concluded that, cocrystals of gliclazide with tartaricacid could be possible. The highest of dissolution rate is cocrystal gliclazide-tartaric acid in ratio 1:3. An emerging approach to improve properties of pharmaceutical solids.

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