

PHYSICOCHEMICAL CHARACTERIZATION AND IN-VITRO DISSOLUTION BEHAVIOR OF GLICLAZIDE –SOLUPLUS SOLID DISPERSIONS

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ABSTRACT

For a quality formulation, various formulation parameters that play a crucial role are aqueous solubility; stability at ambient temperature and humidity, photo-stability, compatibility with solvents etc. Among all these, Solubility is the most important property for developing formulations. The present study is an attempt to improve the solubility and dissolution rate using solid dispersion of a poorly soluble drug Gliclazide by using Soluplus as carrier material to enhance the solubility as well as dissolution rate. Four different formulations were prepared using hot melt extrusion technique in different ratios i.e., 1:1, 1:2, 1:3 and 1:4 were further characterized by FTIR, DSC, and XRD analysis. The results of FTIR revealed that no chemical interaction between the drug and the polymer exist. DSC studies showed that the drug was in amorphous state completely entrapped by the polymer. XRD studies showed decrease in the peak intensity or absence of peaks which indicated the amorphous nature of gliclazide in solid dispersions. All the formulations showed a marked increase in drug release with the increase in the concentration of soluplus when tested for their in vitro studies. Formulation SD4 showed the desired release with a cumulative release of 95% in 50 mins when compared to the pure drug, Physical mixture. Hence, soluplus look to be a promising carrier to improve the solubility of poorly soluble drugs

Keywords: Gliclazide, Soluplus, Hot melt extrusion, Solid dispersion, In-vitro dissolution

INTRODUCTION

With the introduction of combinatorial chemistry and high throughput screening, the properties of new chemical entities shifted towards higher molecular weight and increasing lipophilicity that results in decreasing aqueous solubility. Thus the drug solubility, absorption, and reproducible bioavailability are recognized today as few of the major challenges in oral delivery of new drug substances. Drug substances, for which solubility enhancement can improve the oral bioavailability, are substances that are classified in class II (poor soluble/permeable) and class IV (poor soluble/poor permeable). Specially for class II substances, solubility enhancement is part of the strategies to improve the oral bioavailability [1,2]. Solubility of a drug plays a very important role in determining the dose of the drug to be taken since it has a major impact on the bioavailability. Formulating poorly water soluble drug into a dosage form is always a challenging task because of the less solubility and dissolution [3,4]. Solid dispersions in water-soluble carriers have shown promising results as a means of enhancing the dissolution rate, thus improving bioavailability for most of hydrophobic drugs [5]. To enhance the solubility of those drugs scientists over the world are inventing various approaches. Formulation approaches such as micronization, modification of crystal habits, complexation, using surfactants and co-solvents, solid dispersions, etc have been extensively studied. Chemical modifications such as prodrugs, salt formation, and polar group incorporation were also studied. Solid dispersion is an attractive approach to improve solubility of hydrophobic drugs. Solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier matrix at solid state prepared by melting (fusion), solvent or melting solvent method, super critical fluid technology, lyophilization, hot melt extrusion etc [6,7] Many of the said approaches were proved to be beneficial and produced good results but in few cases it lack commerciality because of various problems [8].

Hot Melt extrusion technology (HME) is the novel technology with an aim to produce solid dispersions with lower cost and is commercially feasible [9]. HME involves passing the physical mixture of the drug-polymer blend through a series of heat zones through screw blend. This process softens the mass and help in efficient mixing of the drug and polymers giving a uniform dispersion of drug in the polymer [10,11]. The screw extruder provides high shear stress and intense mixing and can therefore handle high drug loads thus proving advantageous in pharmaceutical industry [12,13]

In this study, solid dispersions were prepared by hot melt extrusion method. This method is suitable for thermostable drugs and for the polymers that possess high melting points or Tg values [14], soluplus is a polyvinyl caprolactum (57%)-polyvinyl acetate (30%)-poly ethylene glycol (PEG 6000-13%) graft co-polymer. It is a polymeric solubilizer with an amphiphilic chemical structure and due to its bi functional characters it is able to act as a matrix polymer for solid solutions on one hand and on the other it is capable of solubilizing poorly soluble drugs in aqueous media [15]. Solid dispersions bear most common disadvantage like instability of solid dispersion. This is because the drug tends to convert amorphous form of solid dispersion into crystalline form which leads to poor solubility and stability [16,17]. The stability of the drug can be maintained by impregnating drug into the polymeric matrix. As soluplus aides in stabilizing the active ingredient in amorphous form, solubility is improved.

Gliclazide is a hypoglycemic agent used in the treatment of non-insulin dependent diabetes mellitus (NIDDM). It acts by stimulating insulin secretion from pancreatic beta cells. Prior research work revealed that it has good general tolerability, low incidence of hypoglycemia and low rate of secondary failure [18]. In addition; it has the potential for slowing the progression of diabetic retinopathy. For these reasons, it appears to be a drug of choice in prolonged therapy for the control of NIDDM. In the long-term, it reduces hepatic gluconeogenesis and increases insulin effects by acting at receptor or post-receptor sites. It also inhibits platelet aggregation and increases fibrinolysis. However, the drawback of this potentially useful hypoglycemic agent is that it belongs to BCS class 2 and therefore is highly hydrophobic and practically insoluble in water. In general, rapid gastrointestinal (GI) absorption is required for oral hypoglycemic drugs, in order to prevent a sudden increase in blood glucose level after food intake in patients with diabetes mellitus. However, the GI absorption rate of Gliclazide in conventional dosage form appears to be rather slow. Several studies using healthy volunteers or patients revealed that the time to reach peak serum concentration ranged from 2 to 8 hr following oral administration of a conventional tablet. Slow absorption of a drug usually originates from either its poor dissolution from the formulation or poor permeability across the GI membrane. This eventually limits its oral bioavailability and therapeutic efficacy [19]

MATERIALS AND METHODS

Gliclazide were generously gifted by Matrix Laboratories Ltd, Hyderabad. Soluplus was obtained from BASF Chemical, Mumbai.

Physical mixtures of gliclazide with three different mass ratios (1:1, 1:2 and 1:3 as PM 1, PM 2 and PM3) of soluplus were prepared in a glass mortar by light trituration for 5 minutes. Solid dispersion of Gliclazide was prepared with soluplus with various drug-polymer ratios (1:1, 1:2, 1:3, 1:4,). Hot melt extrusion method was used to prepare the solid dispersion. Hot melt extrusion approach represent the advantageous mean of preparation of solid dispersion by using the twin screw hot melt extruder where only thermostable components are relevant. The extruder consists of a hopper, barrel, a die, a kneading screw and heaters. The physical mixture is introduced into the hopper that is forwarded by feed screw and finally is extruded from the die. Melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. When compared to melting in a vessel, the product stability and dissolution are similar, but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms.

Drug Content

Solid dispersions equivalent to 80 mg of drug were taken and dissolved in methanol and filtered. Then the filtrate was suitably diluted with 6.8 phosphate buffer and drug content was analyzed against blank by UV spectrophotometer at 226 nm. The concentration of drug present in solid dispersion is compared with that of standard solution containing 80 mg of pure drug. The percentage of drug present in the solid dispersions was calculated with respect to standard concentration.

Solubility studies

Solubility studies were performed by taking solid dispersions equivalent to 80 mg of drug in 250 ml of buffer solution and subjected to incubated shaking at 100 rpm for 5hrs at 36°C. The resultant suspensions were collected and filtered through 0.45 µ membrane filters and the concentration of drug was determined spectrophotometrically at a λ max of 226 nm. The solubility of solid dispersions at different pH conditions.

In-vitro Dissolution study

Dissolution of drug powder, gliclazide (80 mg), its physical mixtures (Drug: Soluplus ratio 1:1, 1:2 and 1:3 as PM 1, PM 2 and PM 3) and solid dispersions (Drug: Soluplus ratio 1:1, 1:2, 1:3 and 1:4 as SD 1, SD 2, SD 3 and SD4) (equivalent to 80 mg), was carried out using USP dissolution test apparatus (Type II) at a temperature of 37 ± 0.5 °C, at 100 rpm using 900 ml of dissolution medium. The dissolution study was carried out separately for two hours in 2 different dissolution mediums viz. 4.5 acetate buffers and 6.8 phosphates buffer (USP, 2000). Samples (5 ml) were withdrawn at predetermined time intervals (10, 15, 30, 45, 60, 90 and 120 minutes), filtered through what man filter paper No. 41, suitably diluted and analysed at 226 nm. Sink conditions were maintained by replenishing the medium with equal amounts (5 ml) of dissolution medium. The percentage of gliclazide dissolved was calculated from the regression equation generated from standard data. Based up on the data from the dissolution studies the *in vitro* kinetic modeling parameters such as T 50, T 90 was obtained from % drug release versus time profile.

Characterization of gliclazide and its solid dispersion

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) has been one of the commonly used calorimetric methods to characterize the solid state property of the drug in the solid dispersions. Samples of gliclazide, soluplus, physical mixtures and solid dispersion were taken in a flat round bottomed aluminum pans and heated in a temperature range of 50 to 250 °C at a rate of 10 °C per minute with purging of nitrogen (10 ml/min). Indium was used as reference standard in a differential scanning calorimeter (Mettler Toledo, DSC822e, and Greifensee, Switzerland)

Powder X-ray diffraction

Powder X-ray diffraction studies have been used along with DSC to characterize the physical state of the drug in the solid dispersions. X-ray powder diffraction profiles were recorded on x-ray

diffractometer (BrukerD8 advance, Germany). The measurement conditions were as follows: Cu Kα radiation; voltage, 20 kV; current, 20 mA; receiving slit, 0.1 mm; time constant, 1 second; 2θ range, 3 - 40°; scanning speed 4° 2θ/ min.

Fourier Transform Infrared Spectroscopy (FTIR)

The interaction between Gliclazide and the carrier in solid dispersions were studied by using Bruker FTIR spectrophotometer. The spectra were recorded by KBr pellet method.

Stability Studies

The solid dispersion was further subjected to accelerated stability studies upto 3 month at 40 °C with 75% RH. The samples were withdrawn after 3 month and analyzed by DSC.

RESULTS AND DISCUSSION

In the present investigation an attempt was made to improve the solubility and dissolution rate of gliclazide. Gliclazide is a white crystalline powder, relatively insoluble in water. The pKa value of gliclazide is 5.8. Gliclazide exhibits slow GI absorption rate and inter individual variations of its bioavailability, the absorption rate of gliclazide was increased from upper part to lower part of GIT and from jejunum to descending colon which has pH-dependent solubility. Gliclazide solubility was increased by preparing solid dispersion with composition of Table 1.

Table 1: Compositions of Gliclazide physical Mixture and Solid Dispersion

Formulation code	Carrier	Ratios
PM1	Drug :Soluplus	1:1
PM2	Drug :Soluplus	1:2
PM3	Drug :Soluplus	1:3
SD1	Drug :Soluplus	1:1
SD2	Drug :Soluplus	1:2
SD3	Drug :Soluplus	1:3
SD4	Drug :Soluplus	1:4

Solid dispersions were prepared by hot melt extrusion method using soluplus as carriers. All the solid dispersions prepared by this method were found to be stable with good flow characteristics. The drug content in various solid dispersions prepared was estimated spectrophotometrically by measuring the absorbance at 226 nm. All the solid dispersions were found to have excellent entrapment of drug in to them. The gliclazide drug content in all the dispersions were found to be in the range of 95.00 to 99.8 %. The results are given the Table 2.

Table 2: Percentage of Drug content in Physical mixture and Gliclazide Solid dispersion

Formulation	% Drug content
PM1	98±0.09
PM2	97±0.83
PM3	99± 0.78
SD1	98±0.09
SD2	95±0.83
SD3	96± 0.78
SD4	97± 0.78

Initially saturated solubility studies were performed for the gliclazide pure drug and also for the solid dispersions by using different buffer media. Gliclazide having the good solubility in basic side and less solubility in acidic region. The solubility studies indicated that, the phosphate buffer having pH 6.8 was found to be ideal dissolution media. Because of pH dependent solubility, dissolution was choosed to perform in two media that is 4.5 acetate buffer and 6.8 phosphate buffer of gliclazide. The results are given the Table 3

Drug dissolved at specific time periods was plotted as cumulative percent release versus time (minutes) curves. In the dissolution

study carried out in 4.5 acetate buffer of pure drug, physical mixtures of drug with soluplus at three different mass ratios showed 38.89%, 43.89%, and 42.78% of drug release, while solid dispersions showed 67.89%, 85.67% and 94.56% during the first

one hour of study. The percentage drug release from solid dispersions was initially slow but at the end of 120 min was 94.89%, 97.65% and 100.67%. The dissolution profile of 4.5 acetate buffer was shown in the [Figure 1 and 2]

Table 3: Solubility studies of Pure Drug, Physical mixture and Gliclazide Solid dispersion

Solubility in Multi Medium	Solubility of Pure Drug($\mu\text{g/ml}$)	PM1	PM2	PM3	SD1	SD2	SD3	SD4
pH 1.2	156.00	167.00	180.00	180.00	190.00	210.00	240.00	280.00
pH 4.5	56.00	57.00	65.00	67.00	95.00	130.00	160.00	190.00
pH 6.8	430.00	470.00	500.00	510.00	510.00	540.00	570.00	600.00

Similar dissolution studies were carried out in phosphate buffer. In the first 30 min, cumulative % drug release from physical mixtures was 65.87%, 72.26% and 73.89, respectively, while solid dispersions showed 83.56%, 85.78%, 90.76% and 91.67%. At the end of the study, solid dispersions showed 98.89%, 99.89%, 99.78% and 99.99% drug release and physical mixtures showed 87.89%, 93.90% and 96.89% of drug release. The dissolution profile of 6.8 phosphate buffer was shown in the [Figure 3 and 4]. The dissolution rate of all the solid dispersions was found to be rapid when compared to

physical mixture. The T50, T90 values of the dispersions indicates their rapid drug dissolution that pure drug. Drug release studies of physical mixture and solid dispersion results are in the Table 4. Solid dispersions prepared by hot melt extrusion method were found to be suitable in increasing the dissolution rate of poorly soluble drug. Increase in solubility in media with different pH and dissolution rate of solid dispersion when compared to physical mixtures indicates efficient entrapment of drug in polymeric carrier.

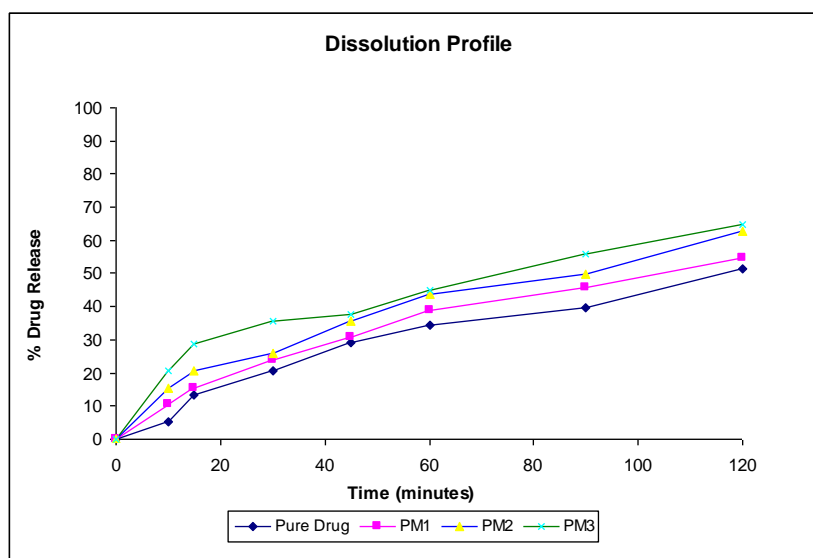


Fig. 1: % drug release in 4.5 acetate buffer Pure drug, PM 1, PM 2 and PM 3 indicates physical mixtures of drug: Soluplus at 1:1, 1:2 and 1:3 ratios.

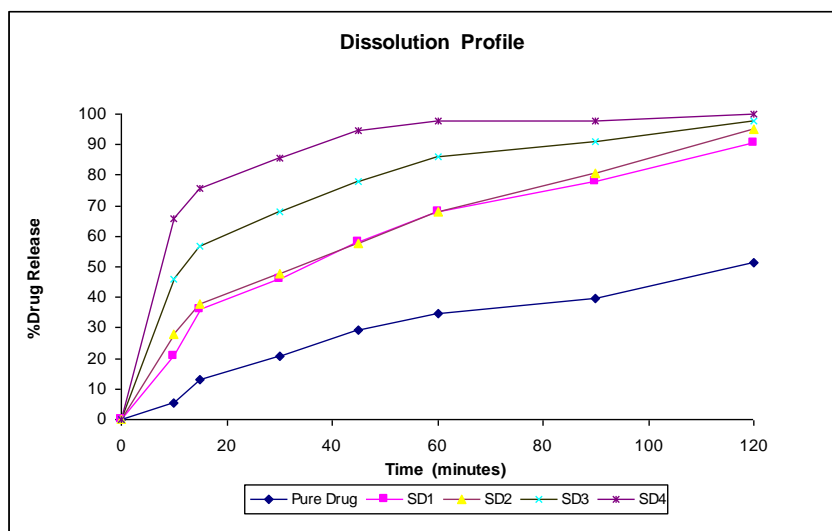


Fig. 2: % drug release in 4.5 acetate buffer. Pure drug, SD 1, SD 2, SD 3 and SD4 indicate solid dispersions of drug: Soluplus at 1:1, 1:2, 1:3 and 1:4 ratio

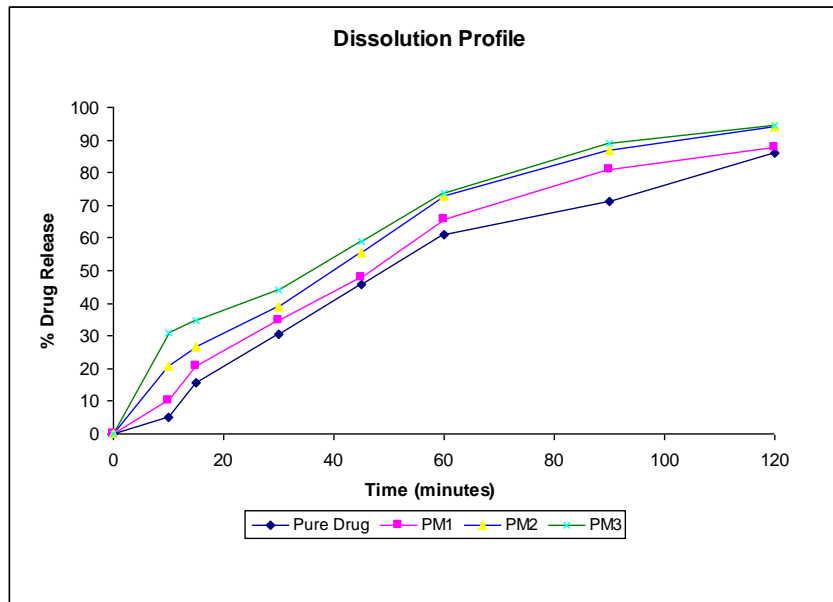


Fig. 3: % drug release in 6.8 phosphate buffer, pure drug, PM 1, PM 2 and PM 3 indicates physical mixtures of drug: Soluplus at 1:1, 1:2 and 1:3 ratios

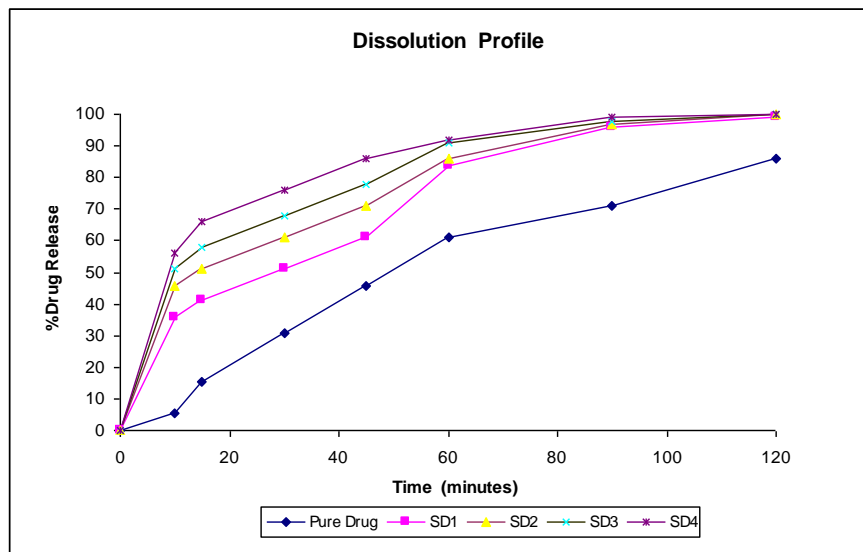


Fig. 4: % drug release in 6.8 phosphate buffer pure drug, SD 1, SD 2, SD 3 and SD4 indicate solid dispersions of drug: Soluplus at 1:1, 1:2, 1:3 and 1:4 ratios

Solid dispersions prepared by hot melt extrusion method were found to be suitable in increasing the dissolution rate of poorly soluble drug. The results indicated that, as the concentration of polymer in the dispersed system increases, dissolution of poorly soluble drug also increases. In all cases, solid dispersions exhibited faster and almost complete dissolution compared to the pure drug and its corresponding

physical mixtures. The possible mechanisms responsible for increased dissolution could be reduction of crystallite size, a solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersibility of a drug from the dispersion, dissolution of the drug in the hydrophilic carrier, and conversion of the drug to an amorphous state.

Table 4: Drug release studies of Physical Mixture and solid dispersion

S. No.	SD	%Drug released on 120minutes	T50(minutes)	T90(minutes)
1	Drug	85.89	54	-
2	PM1	87.89	50	-
3	PM2	93.90	45	120
4	PM3	96.89	45	110
5	SD1	98.89	30	65
6	SD2	99.89	15	60
7	SD3	99.78	10	55
8	SD4	99.99	7	45

The DSC thermograms of gliclazide alone showed endothermic peak at 167-172°C, corresponding to its melting point. The DSC thermograms of soluplus have shown endothermic peak at 52 °C. The complete disappearance of gliclazide melting peak in solid dispersion could be attributable to the complete miscibility of the

drug in the melted carrier. But melting peak was observed in physical mixture. The thermograms were recorded and were shown in the [Figures 5 and 6] Based on the solubility, dissolution and DSC study, SD4 was selected as optimized formulation for further solid state characterization study. This was further supported by XRD.

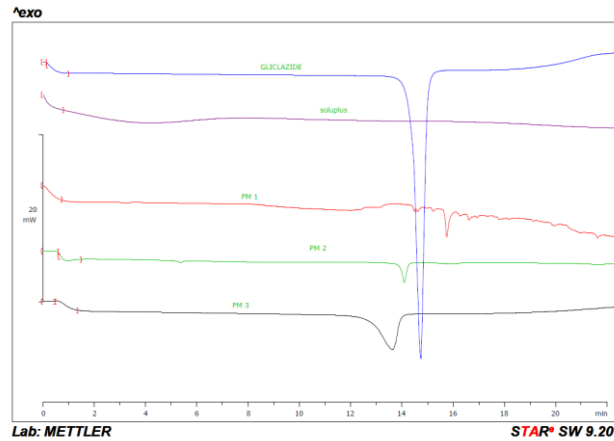


Fig. 5: DSC Thermogram of pure drug and physical Mixture (Drug: Soluplus)

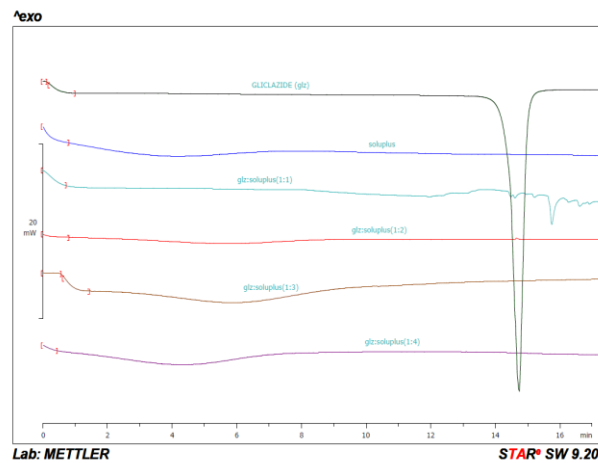


Fig. 6: DSC Thermogram of pure drug and solid dispersion (SD1, SD2, SD3, SD4)

[Figure 7] Showed the XRD pattern of pure Gliclazide with number of peaks that were intense and sharp, indicating its crystalline nature. The spectrum of soluplus was characterized by complete absence of any diffraction peak. The diffraction patterns of solid dispersion (i.e.with Soluplus) showed decrease in the peak intensity or absence of peaks which indicated the amorphous nature of Gliclazide in solid dispersion

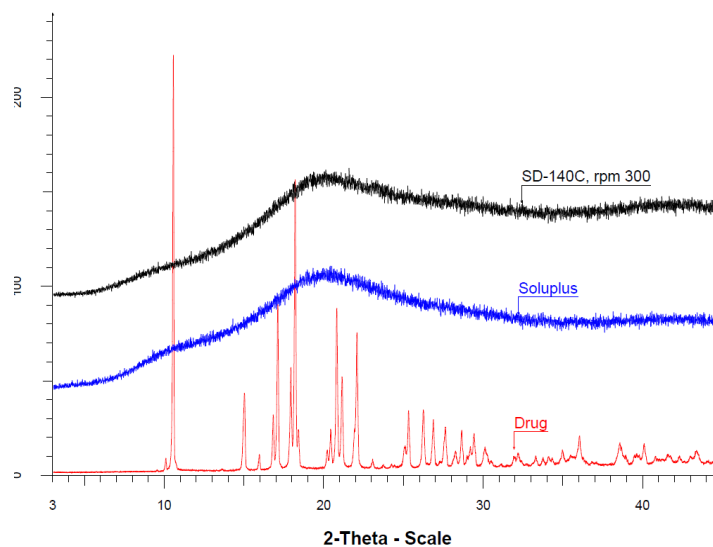
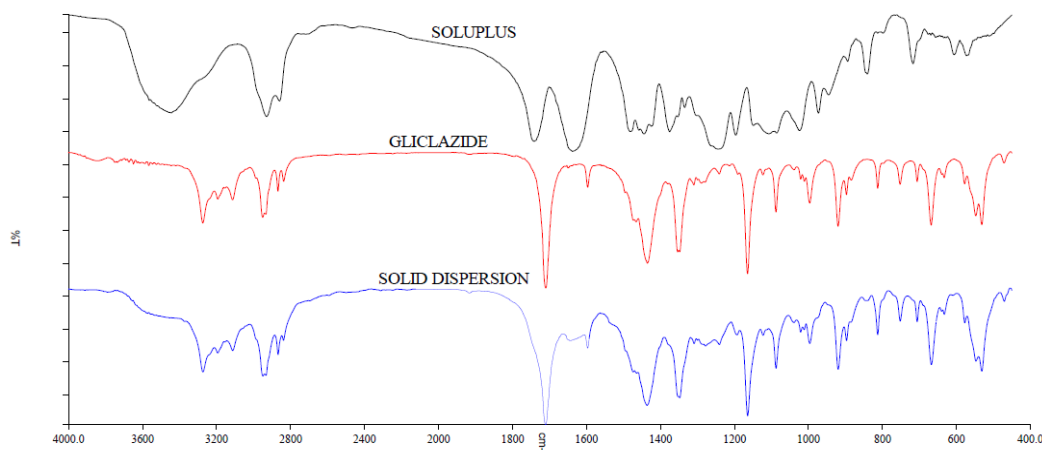
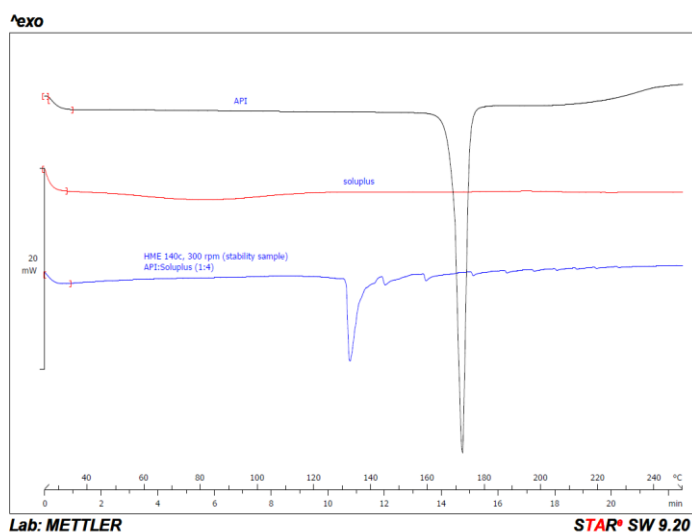


Fig. 7: XRD pattern of Gliclazide, soluplus and solid dispersion (SD4)

FTIR Spectrum of pure gliclazide, demonstrated the FTIR peaks at 1710.46 cm⁻¹(Carbonyl sulfonyl urea group), 3274.34cm⁻¹(-NH group), 1349 and 1162cm⁻¹(Sulfonyl group bands). The same peaks were observed in the drug substance, solid dispersion indicates that there are no chemical changes in the drug substance during the

preparation of solid dispersion with soluplus. Thus these studies indicated that there were no major interactions between the functional moieties of drug molecule with the excipients incorporated in the formulation of solid dispersions. The FTIR spectra of various dispersions were shown as [Figure 8]

**Fig. 8: FT-IR spectrum of Gliclazide, soluplus, solid dispersion (SD4).****Fig. 9: DSC Thermograms of SD4. After 3 months stability study**

The solid dispersions SD4 were further evaluated for accelerated stability studies at 40°C/75% RH for a period of three months. Gliclazide found to be present in amorphous form in SD4 formulations which was observed in the DSC thermograms. The thermograms were recorded and were shown in the [Figures 9]

CONCLUSIONS

The approach of the present work was to characterize the solid dispersion of a Class II drug (Biopharmaceutical Classification System) and study its effect on dissolution. Infra-red spectroscopy studies indicated no interaction between drug and carrier. The drug was completely miscible in water-soluble carrier. The enthalpy of melting of the drug in solid dispersion was gradually decreased compared to pure drug, as revealed by DSC thermograms. The XRD study showed that the drug was present in amorphous form. The study showed increased dissolution rate with the formation of solid dispersion. Solid dispersion performed better than the corresponding physical mixture while physical mixture performed better than the pure drug. The mechanisms responsible for this improvement could be a solubilization effect of the carrier,

miscibility of the drug in melted carrier, and conversion of the drug from crystalline to amorphous form.

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