

SOLUBILITY ENHANCEMENT OF GLICLAZIDE BY SOLID DISPERSION METHOD

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ABSTRACT

In the present research work, an attempt was made to improve the solubility and dissolution rate of a poorly soluble drug, Gliclazide by solid dispersion method using soluplus and kollidon VA64 as a carrier and PEG 4000, sorbitol, cremophor EL as a plasticizer. Evaluation of solid dispersion i.e. in vitro- dissolution, differential scanning calorimetry (DSC), Fourier transform infrared (FTIR), X-ray diffraction (XRD) was performed. The solid dispersion of KollidonVA64 and PEG 4000(1:1) showed the best cumulative drug release (72.16±2.01). The solid dispersions were then formulated as tablets and were subjected to various preformulation and post formulations studies. The evaluation of tablet batches i.e. hardness, friability, drug content, *in vitro* release, and stability parameters have been studied. After the evaluation of all batches, the F₄ batch shows the best cumulative release (95.57±1.25%). From this study, it can be concluded that dissolution rate of gliclazide could be enhanced by tablets containing solid dispersion by direct compression technique.

Keywords: Gliclazide, Solid Dispersion, Fusion Method, Plasticizer.

INTRODUCTION

40 percent of new chemical entities discovered by the pharmaceutical industry today are poorly soluble or lipophilic compounds. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs.[1] The enhancement of oral bioavailability of such drugs, whose solubility is poor, remains one of the most challenging aspects of drug development.[2]

Solubility: The term 'solubility' is defined as maximum amount of solute that can be dissolved in a given amount of solvent. Quantitatively it is defined as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion[3].

Gliclazide N-(hexahydrocyclopenta[c]pyrrol-2(1H)-ylcarbamoyl)-4 methyl benzene sulfonamide is an antidiabetic agent used for control of hyperglycemia in GLZ-responsive diabetes mellitus of stable, mild, non-ketosis prone, type 2 diabetes.

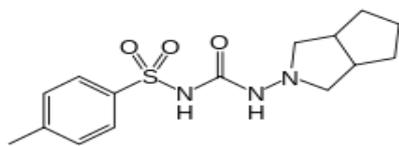


Figure 1: It shows the structure of Gliclazide

GLZ is a BCS class II drug with low solubility and high permeability characteristics. It is practically insoluble in water having a molecular weight of 323.412 g/mol and shows good permeability with log P of 2.6. It also exhibits pH dependant solubility and 94% plasma protein binding.[4,5,6] But the aqueous solubility and poor dissolution of the drug remains a problem for the required therapeutic effect. This solubility benefit can be further enhanced by preparing solid dispersion.

Solid Dispersion: Chiou and Reigelman first by defined solid dispersion in 1971 as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by fusion, solvent or melting solvent method.[7]

Solid dispersions have attracted considerable interest as a mean of improving the dissolution rate, hence possibly bioavailability of a range of hydrophobic drugs.

OBJECTIVES OF THE STUDY:

The objectives of the present study include:

- In the present work attempts will be made to improve the bioavailability of poorly water soluble antidiabetic drug by solid dispersion method.
- Determine the effect of change in polymer and plasticizer composition and drug-polymer ratio on solubility.
- Study of in vitro dissolution kinetics of the drug from the formulated solid dispersion systems in a tablet form.
- To compare the release profile with the existing marketed products.

MATERIALS AND METHODS**Materials**

Gliclazide was procured from Gen Pharma Pvt. Ltd., Bhosari, Pune. The polymers Soluplus, KollidonVA64, Cremophor EL From BASF India Ltd, Mumbai and all the other ingredients used were procured from college source.

Methods**Determination of solubility**

10ml of the distilled water was taken in conical flasks and an excess quantity of GLZ was added to these and shaken for 24 hrs by using mechanical shakers. At the end of 24 hrs period, the solution was filtered through whatman filter paper and the filtrate was suitably diluted with distilled water and the aqueous solubility was estimated spectrophotometrically at λ max of 226nm.[8]

Preparation of Physical Mixtures (PM)

Physical mixtures of GLZ at different mass ratios (1:1, 1:2) were prepared in a glass mortar by light trituration for 5 minutes. The mixtures were passed through a sieve. The prepared mixtures were then filled in glass bottles and stored in a dessicator until further use.[9]

Preparation of the Solid Dispersions (SD) using Fusion Method

Solid dispersions (SD) were prepared by melting the accurately weighed amounts of polymer and plasticizer on heating mantle and the drug was dispersed in the molten solution. The mixtures were stirred repeatedly, after 10 min cooled by placing the petridish for 15 min in an ice bath. Solid mass obtained was passed through the # 80 and stored in vacuum desiccator until use.[10,11,12,13]

Table 1: It shows the formula for the preparation of GLZ Solid Dispersion

Batches	SD-1	SD-2	SD-3	SD-4	SD-5	SD-6
Drug	80	80	80	80	80	80
	mg	mg	mg	mg	mg	mg
Soluplus	80	80	80	-	-	-
	mg	mg	mg			
KollidonVA64	-	-	-	80	80	80
				mg	mg	mg
PEG 4000	8 mg	-	-	8 mg	-	-
Sorbitol	-	8 mg	-	-	8 mg	-
Cremophor	-	-	8 mg	-	-	8 mg
EL						

Table 2: It shows the formula for the preparation of GLZ tablets

Ingredients	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆
SD equivalent to 80 mg GLZ	168mg	168mg	168mg	168mg	168mg	168mg
Magnesium stearate	1.7 mg					
Aerosil	0.3mg	0.3mg	0.3mg	0.3mg	0.3mg	0.3mg
Total Weight	170mg	170mg	170mg	170mg	170mg	170mg

In-vitro Dissolution Studies

Dissolution studies on GLZ pure drug as well as the SDs were performed using the USP tablet dissolution test apparatus II with the paddle rotating at 100 rpm in 900 ml phosphate buffer (pH 7.4) at 37±0.5°C. SDs equivalent to 80 mg of GLZ were taken for the dissolution test. At 5 min intervals, 5 ml samples were withdrawn, filtered through a whatman filter paper and assayed for cumulative drug release by measuring the absorbance at 226 nm using UV-Visible spectrophotometer. Fresh medium (5 ml) was added to the dissolution medium after each sampling to maintain a constant volume throughout the test.[18]

Drug Content

A quantity of solid dispersion equivalent to 80 mg of GLZ was accurately weighed and dissolved in phosphate buffer (pH 7.4) in a 100 ml volumetric flask. Then the volume was made up to 100ml with phosphate buffer (pH 7.4). From this serial dilution were made with pH 7.4. The absorbance of the resulting solution was measured.[19]

Determination of % practical yield

Determination of practical yield is useful to determine the efficiency of a preparation technique. The practical yield is calculated by using following equation.[20]

$$\% \text{ Practical yield} = \frac{\text{Weight of prepared solid dispersions}}{\text{Theoretical yield}} \times 100$$

Stability Study

After determining the drug content and release studies, the optimized formulation was charged for the accelerated stability studies according to ICH guidelines (40 ± 2°C and 75 ± 5% RH) for a period of 1 month in a stability chamber. The optimized formulations were placed in amber colored bottles. The samples

Preparation of Gliclazide tablets

GLZ tablets were prepared by direct compression. SD and the excipients required were passed through 60 mesh sieve. Quantity of solid dispersion and excipients were weighed accurately as mentioned in Table 8. The solid dispersion was mixed with the excipients and then it was blended for 10 minutes to get the blend uniformity. The tablets of 170 mg were compressed using 9 mm concave punch and with 8 station tablet machine.[14,15]

Evaluation of Solid Dispersion

Solubility Studies of Solid Dispersions

Solubility determinations were performed in triplicate according to the method of Higuchi and Connors (Higuchi and Connors, 1965). In brief, an excess amount of solid dispersion was taken into the conical flask to which 10 ml of distilled water were added. The samples were shaken at room temperature for 24 hr on the rotary shake and filtered through a whatman filter paper. The filtrate was suitably diluted and analyzed spectrophotometrically at the wavelength of 226 nm using a UV-VIS spectrophotometer.[16,17]

were withdrawn at 15, 30 days and evaluated for the drug content and in vitro drug release.[21]

Fourier-transform infrared (FTIR) spectroscopy

FT-IR spectra were recorded using an FT-IR spectrophotometer.[22,23] The samples were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powder. Scans were obtained at resolution of 4cm⁻¹ from 400 to 4000cm⁻¹.

Powder X-ray diffraction spectroscopy

The crystalline state of different samples was evaluated with X-ray powder diffraction. Powder X-ray diffraction patterns of pure drug, carriers, solid dispersions and corresponding physical mixtures were recorded using a powder x-ray diffractometer.[24] The scanned range was 0- 50°

DSC Analysis

The DSC thermograms were recorded for pure drug, carriers and corresponding solid dispersions using a differential scanning calorimeter. Approximately 2-5mg of each sample was heated in an open aluminum pan from 10-350°C at a scanning rate of 10°C/min under steam of nitrogen.[25]

Evaluation of Tablets

In-vitro dissolution studies

The drug release profile of the formulated tablets was studied using USP dissolution apparatus II. The paddle speed of 100 rpm was used for dissolution testing for selected tablets. The media used was pH 7.4 phosphate buffer, 900 mL. Sample aliquots were withdrawn at predetermined time points at 5, 10, 15, 20, 30, 45, 60, 90, 120 min, filtered through whatman filter paper and were suitably diluted. The GLZ content was estimated using a UV spectrophotometer at 226nm. The amount of the drug released was then estimated and it was then compared with the marketed tablet RECLIDE 80mg.[26]

Determination of Drug Content

Ten tablets were weighed and taken in mortar and crushed to make powder. A quantity of powder weighing equivalent to 80 mg GLZ of was taken in 100 ml volumetric flask and phosphate buffer pH 7.4 was added. Then the solution was filtered using whatman filter paper and then the solution was diluted up to 10 μ g and absorbance was measured. Then the amount of drug present was calculated.[27]

Weight variation

Twenty tablets were selected randomly and the average weight was determined. Then the individual tablets were compared with the average weight. The limit for weight variation was kept at $\pm 3\%$.[28]

Friability

The friability test was done with a Friabilator. Ten tablets were weighed and subjected to the combined effect of attrition and shock by utilizing a plastic chamber that revolved at 25 rpm and dropped the tablets from a distance of 6 inches with each revolution. After 100 revolutions, the tablets were dusted and reweighed. The percentage friability was calculated from the loss in weight of intact tablets.[29]

Hardness

The hardness of the tablets was checked using Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning the threaded bolt until the tablet fractured. As a spring was compressed a pointer rides along a gauge in the barrel to indicate the force required to break the tablet. The average weight of 5 tablets was recorded.[30]

Thickness

Twenty tablets were randomly selected from formulations and thickness was measured individually by Screw gauge. It was expressed in millimeter.[31]

Disintegration time

The disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

Stability study

GLZ tablets were packed in aluminum foil and subjected to the stability studies as per the ICH guidelines 40°C/75% RH. The tablets were analyzed for the drug release and were tested after 15, 30 days of storage time points.

Drug release kinetics

In order to understand the mechanism and kinetics of drug release, the results of the in vitro drug release study were fitted with various kinetic equations like zero order (cumulative percent drug released vs. Time), first order (Log cumulative percent drug retained vs. Time), Higuchi (cumulative percent released vs. \sqrt{T}), Peppas (log of cumulative percent drug released Vs. log Time) and Hixson- Crowell's cube root model ((Percentage Retained) $1/3$ Vs. Time). The kinetic model that best fits the dissolution data was evaluated by comparing the regression coefficient (r) values obtained in various models. Peppas model used 'n' value to characterize different release mechanisms. The values of n = 0.5 for Fickian diffusion, between 0.5 to 1.0 for non-Fickian diffusion and n = 1 for zero order.[32, 33]

RESULT AND DISCUSSION

Calibration curve in phosphate buffer pH 7.4

Calibration curve of GLZ in phosphate buffer (pH 7.4) was carried out. Table 3 shows the concentrations of GLZ in phosphate buffer (pH 7.4) and the respective absorbance. Figure 2 shows the standard graph of GLZ in phosphate buffer (pH 7.4)

Table 3: It shows the standard Calibration Curve Data of GLZ in 7.4 Phosphate Buffers

Sr. No.	Concentration(μ g/ml)	Absorbance \pm Standard deviation
1.	0	0000
2.	2	0.1417 \pm 0.012
3.	4	0.2669 \pm 0.029
4.	6	0.3906 \pm 0.017
5.	8	0.5281 \pm 0.019
6.	10	0.674 \pm 0.037
7.	12	0.7673 \pm 0.014
8.	14	0.9005 \pm 0.020

(n=3)

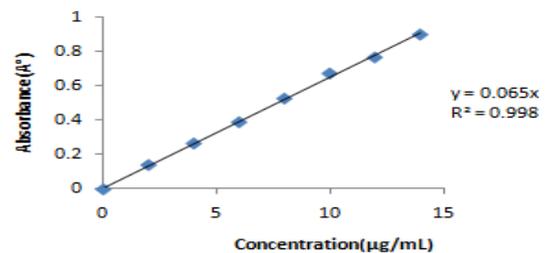


Figure 2: It shows the standard calibration curve for GLZ in phosphate buffer

Evaluation of solid dispersion

Phase Solubility study

The phase-solubility diagram for the GLZ solid dispersion was shown in Figure 3. The solubility and drug content data was given in table 4. The solubility of SD-1 was 34.21 \pm 0.59 μ g/ml and that of SD-4 was 37.77 \pm 0.96 μ g/ml. The solubility of pure GLZ was found to be 16.51 \pm 0.26 μ g/ml which was less than that of SD.

Table 4: It shows the phase solubility studies data Solubility of GLZ (μ g/ml)

Sr. No.	Formulation Code	Solubility (μ g/ml)
1.	Pure drug	16.51 \pm 0.26
2.	SD-1	34.21 \pm 0.59
3.	SD-2	26.18 \pm 1.25
4.	SD-3	27.64 \pm 1.85
5.	SD-4	37.77 \pm 0.96
6.	SD-5	21.26 \pm 1.02
7.	SD-6	29.56 \pm 0.47

(n=3)

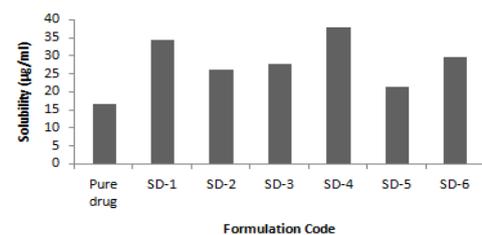


Figure 3: It shows the phase-solubility diagram for the GLZ solid dispersion

Drug Content

The drug content of solid dispersion containing kollidonVA64 and PEG 4000 as a carrier was found to be in the range of 99.74±0.08.

Table No.5: It shows the drug Content of solid dispersion

Batches	Drug Content (%)
SD-1	99.81±0.35
SD-2	98.34±0.84
SD-3	98.14± 0.76
SD-4	99.74±0.08
SD-5	97.64±1.06
SD-6	99.71±0.06

Dissolution Studies

The dissolution profiles of pure GLZ and SD are shown in following figures. The dissolution profile of the pure GLZ showed 60.83±1.92 release in 120 min. Solid dispersion of soluplus and PEG 4000 (SD-1) showed 70.58±0.94 release in 120 min and that of kollidonVA64 and PEG 4000(SD-4) showed 72.16±2.01 release in 120 min. Cumulative drug release was found to be highest for SD of kollidonVA64 and PEG 4000 (SD-4) than the pure drug and other SD under investigation.

Table 6: It shows the in- Vitro dissolution data for GLZ: Soluplus solid dispersion

Time (min)	%Cumulative Drug Release			
	GLZ	SD1	SD2	SD3
5	22.3±0.18	35.66±1.23	22.95±0.92	28.61±0.58
10	31.52±0.62	40.59±0.89	23.18±0.42	31.26±0.46
15	39.27±0.86	45.92±0.46	25.45±0.84	35.71±0.16
20	44.88±0.46	50.26±0.94	31.29±0.38	42.29±0.73
30	45.26±0.59	54.39±0.38	49.91±0.64	56.97±1.76
45	48.95±0.94	63.18±0.56	55.99±0.56	59.5±1.58
60	50.28±0.61	65.47±0.84	61.84±1.09	59.66±0.21
90	54.26±1.03	69.45±0.16	65.14±0.78	61.85±0.52
120	60.83±1.92	70.58±0.94	66.45±0.48	67.91±0.31

(n=3)

Table 7: It shows the in- Vitro dissolution data for GLZ: KollidonVA64 solid dispersion

Time (min)	%Cumulative Drug Release			
	GLZ	SD4	SD5	SD6
5	22.3±0.18	32.56±0.47	31.63±20.85	21.75±0.41
10	31.52±0.62	42.59±0.16	32.28±0.85	24.68±1.25
15	39.27±0.86	55.35±0.24	35.15±0.40	25.15±1.13
20	44.88±0.46	64.53±1.64	49.2±0.35	36.1±1.45
30	45.26±0.59	65.65±1.26	59.6±0.17	49.16±0.24
45	48.95±0.94	67.48±0.17	59.9±0.67	52.4±0.42
60	50.28±0.61	69.27±0.56	60.91±0.94	55.22±0.81
90	54.26±1.03	70.43±0.58	62.45±1.03	66.86±0.73
120	60.83±1.92	72.16±2.01	62.96±2.16	69.61±1.02

(n=3)

Table 8: It shows stability study data of solid dispersion

Batches	% Cumulative Drug Release		Drug Content (%)	
	15 days	30 days	15 days	30 days
	SD1	70.58±0.21	70.58±0.15	99.81±0.84
SD2	67.45±0.55	67.44±1.53	98.34±0.25	98.34±1.06
SD3	67.91±0.47	67.90±1.06	98.14±0.35	98.13±0.65
SD4	71.64±0.85	71.64±0.85	99.74±0.19	99.73±0.46
SD5	62.96±0.23	62.95±0.84	97.64±0.28	97.64±0.19
SD6	69.61±10.52	69.60±0.15	99.71±0.74	99.70±0.58

(n=3)

X-Ray Diffraction

The diffraction spectrum of pure GLZ showed that the drug is of crystalline nature as demonstrated by numerous peaks observed at 2θ of 10.7, 15.2, 17.1, 18.2, 21.1 and 22.4 in finger print region. Some peaks shown by pure GLZ were also found to be absent in formulation peak and the intensity of peaks

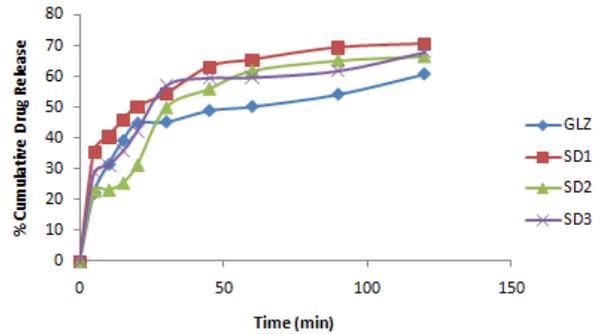


Figure 4: It shows the dissolution profile of GLZ: Soluplus formulations in phosphate buffer pH 7.4

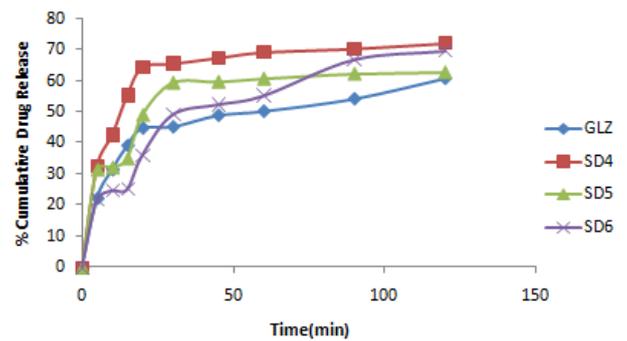


Figure 5: It shows the dissolution profile of GLZ: KollidonVA64 formulations in phosphate buffer pH 7.4

Stability study

The optimized formulation (SD-4) did not show any significant change in the drug content during stability study.

observed was markedly reduced in the XRD spectrum of the solid dispersion. The prominent peaks for pure GLZ were clearly seen at the same positions in PMs and SDs but with decreased intensities. Soluplus solid dispersion shows peak at 2θ of 10.7, 15.2, 17.1, 18.2, 21.1 22.3 and the physical mixture at 10.8, 15.2, 17.1, 18.2, 21.4, 22.4. Kollidon solid dispersion shows peak at 2θ

of 10.7, 18.2, 21.1 22.3 and the physical mixture at 10.8, 15.2, 17, 18.1, 21.1, 22.4. The results indicated that the drug in solid dispersion was present in an amorphous state.

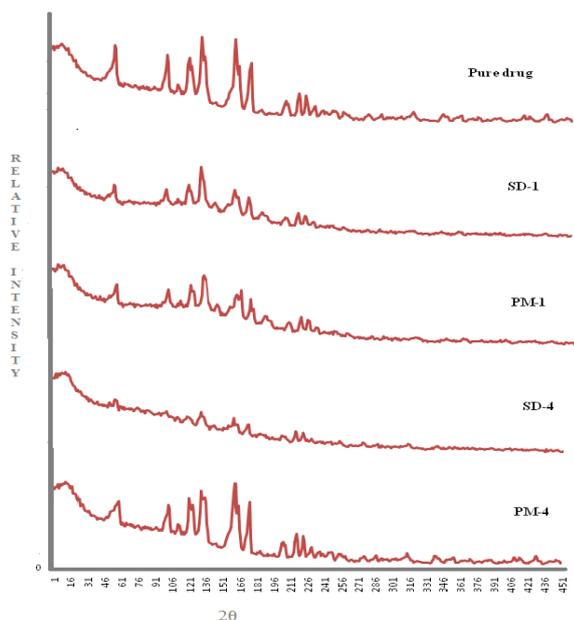


Figure 6: It shows the X-ray diffraction pattern of GLZ, solid dispersion and physical mixture

FTIR spectroscopy

Fourier-transform infrared (FT-IR) spectroscopy was used to characterize possible interactions between the drug and the carrier in solid state. The IR spectra of SDs and PMs are compared with the standard spectrum of GLZ. The IR spectrum of GLZ was characterized by the absorption of carbonyl (C=O) sulphonyl urea group and NH group at 1706 cm^{-1} and 3265 cm^{-1} , respectively. For the sulphonyl group bands, the spectrum showed stretching peak at 1164 cm^{-1} and 1350 cm^{-1} (Table 9). The shift in the peaks associated with the GLZ indicates an increase in bond strength, possibly due to the stabilizing effect of the hydrogen atoms of PEG. This may be attributed to the intermolecular hydrogen bonding between GLZ and PEG in the solid state.

Table 9: It shows the stretching vibrations of solid dispersion and physical mixture

Stretching	SD-1	PM-1	SD-4	PM-4
N-H	3188 cm^{-1}	3188 cm^{-1}	3188 cm^{-1}	3188 cm^{-1}
C=O	1709 cm^{-1}	1709 cm^{-1}	1709 cm^{-1}	1709 cm^{-1}
S=O	1350 cm^{-1}	1350 cm^{-1}	1349 cm^{-1}	1349 cm^{-1}
C-H	2943 cm^{-1}	2946 cm^{-1}	2943 cm^{-1}	2943 cm^{-1}
C=C	1646 cm^{-1}	1645 cm^{-1}	1644 cm^{-1}	1644 cm^{-1}

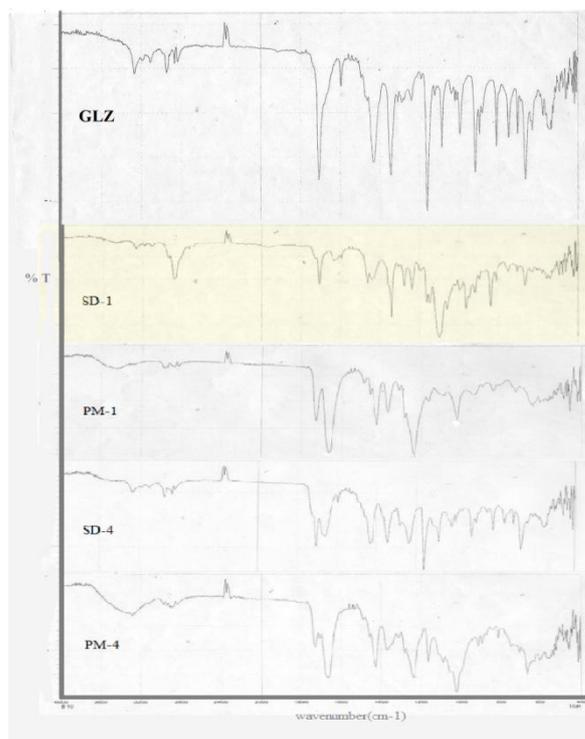


Figure 7: It shows the infrared spectrum of solid dispersion and physical mixture

DSC Analysis

The DSC curve of pure GLZ exhibits a single endotherm corresponding to the melting of the drug. The onset of melting was observed at 173.77 $^{\circ}\text{C}$, and the corresponding heat of fusion (H) is 284.4750 J/g. A slight difference was evident in the thermograms of the physical mixture and solid dispersion. The complete disappearance of GLZ melting peak observed in both PM and SD was attributable to the complete miscibility of the drug in the melted carrier. The enthalpy of melting of drug in solid dispersion was gradually decreased compared to the drug (ΔHf : 284.4750 J/g). This phenomenon could be attributed to the amorphous form of the drug in solid dispersion. It suggesting that GLZ is completely soluble in the liquid phase of the polymer or that the crystalline nature of GLZ is absent.

Table 10: It shows DSC data of GLZ, solid dispersion and physical mixture

Formulation code	Peak ($^{\circ}\text{C}$)	ΔH (J/g)
GLZ	173.77	284.47
SD-1	89.86	30.91
PM-1	140.54	26.95
SD-4	130.89	79.73
PM-4	124.67	113.98

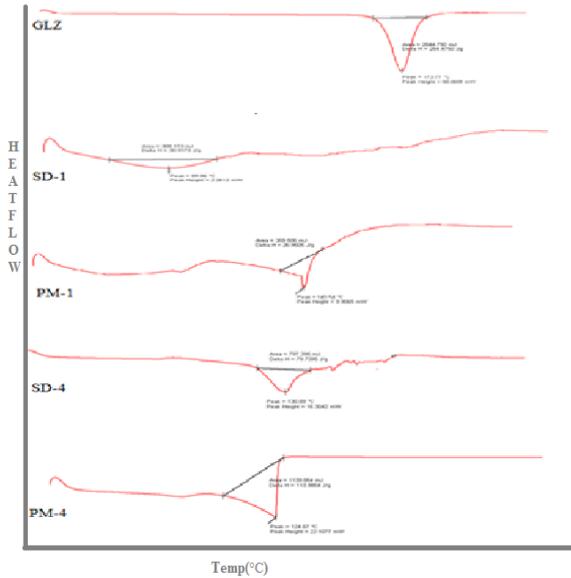


Figure 8: It shows the DSC thermogram of GLZ, solid dispersion and physical mixture

Evaluation of Tablets

Pre-compression parameteres

The Pre-compression parameteres of GLZ tablets were given in the table 10. The thickness of the tablet was found to be 3.5 mm. The average weight of the prepared tablet was between 168 to 172 mg. So, it was predicted that all the tablets exhibited uniform weight with low standard deviation values within the acceptable variation as per IP. The hardness of the prepared tablet varied from 5.0 to 6.9 kg/cm², which has satisfactory strength to withstand the applied mechanical shocks. The friability of all the formulations was found to be less than 1.0%, which shows the durability of the prepared tablets; resistance to loss of weight indicates the tablets ability to withstand abrasion in handling.

In-vitro dissolution studies

The dissolution profiles of GLZ tablets as compared to marketed tablet. Dissolution studies were carried out in phosphate buffer pH 7.4. In 120 min, cumulative % drug release from F₁, F₂, F₃ batches of tablet was 42.29±0.99, 25.88±0.68, 33.45±0.94 respectively, while F₄, F₅, F₆ batches of tablets showed 95.57±1.25, 81.94±0.89, 86.49 ±1.22 respectively. The marketed tablet shows release of 98.98±0.62 in 120 min. Drug dissolved at specific time periods was plotted on cumulative percent release versus time (min) curves.

Table 10: It shows the pre-compression parameteres of GLZ tablets

Parameters	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆
Thickness(mm)	3.5±0.85	3.5±0.16	3.5±0.48	3.5±0.67	3.5±0.28	3.5±0.16
Weight variation (%)	2.15±0.26	2.91±0.84	1.88±0.57	2.44±0.14	2.47±0.55	3.81±0.84
Hardness(kg/cm ²)	6.2±0.15	5.1±0.56	5.6±0.54	6.3±0.15	5.4±0.48	5.8±0.55
Friability (%)	0.72±0.06	0.60±0.04	0.65±0.01	0.79±0.03	0.61±0.02	0.69±0.05
Disintegration time (sec)	281±4.2	126±1.4	195±1.32	258±2.51	135±0.84	175±0.51
Drug Content (%)	98.43±1.56	97.12±0.42	97.61±1.0	98.74±1.0	96.25±0.4	97.81±1.8

Table 11: It shows the in- Vitro dissolution data for GLZ: Soluplus tablets with the marketed tablet

%Cumulative Drug Release			
F ₁	F ₂	F ₃	Marketed
15.23±0.34	6.69±0.37	12±0.55	25.83±1.68
17.39±0.86	9.02±0.69	20.6±0.63	28.52±1.61
18.64±0.94	12.53±0.56	21.41±0.49	46.68±1.28
18.85±1.48	13.58±0.43	21.45±0.51	48.51±1.51
19.9±0.81	18.45±0.75	21.7±0.63	53.16±1.08
20.12±0.93	20.45±1.91	21.76±0.18	59.63±0.96
29.93±0.76	21.48±1.78	23.72±0.34	79.57±0.81
36.78±0.64	22.99±0.75	25.7±0.92	92.7±0.46
42.29±0.99	25.88±0.68	33.45±0.94	98.98±0.62

(n=3)

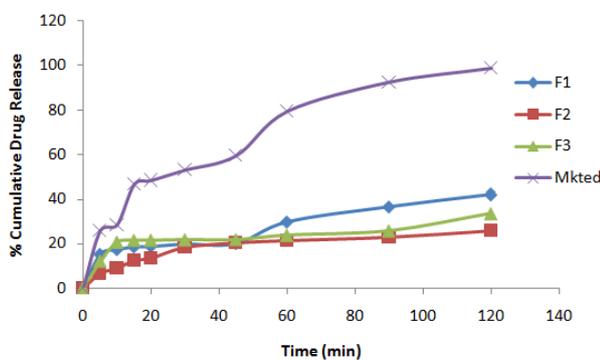


Figure 21: It shows the dissolution profile of GLZ: soluplus tablets

Table 12: It shows the in- Vitro dissolution data for GLZ: KollidonVA64 tablets with the marketed tablet

%Cumulative Drug Release				
Time (min)	F ₄	F ₅	F ₆	Marketed
5	23.06±0.28	22.15±0.73	19.6±1.45	25.83±1.68
10	29.89±0.31	24.35±0.29	34.72±1.86	28.52±1.61
15	36.98±0.63	31.64±0.23	41.38±0.25	46.68±1.28
20	44.15±0.84	33.42±0.43	43.68±1.64	48.51±1.51
30	47.23±0.15	39.35±0.27	45.22±0.37	53.16±1.08
45	51.49±0.71	45.84±0.53	49±0.95	59.63±0.96
60	77.39±1.46	51.35±0.36	61.9±0.46	79.57±0.81
90	85.43±1.94	68.25±0.79	77.07±1.68	92.7±0.46
120	95.57±1.25	81.94±0.89	86.49±1.22	98.98±0.62

(n=3)

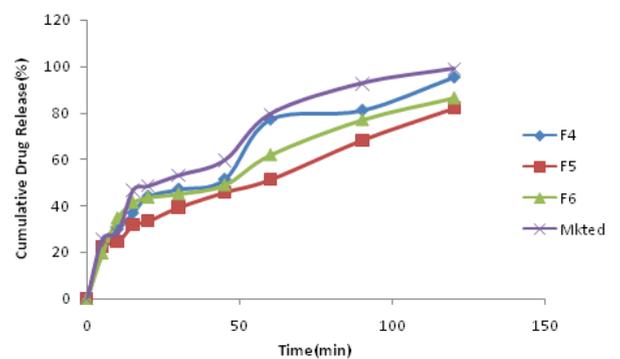


Figure 22: It shows the dissolution profile of GLZ: KollidonVA64 tablets

Drug release kinetics

When the data were fit into various kinetic models, it was found that the matrix model is the best fit model for all. Table 13 shows the kinetic model fitting for the drug release data. The F₁ fits in to Hixson-Crowell release kinetic model and the F₄ fits in to the Korsmeyer- Peepas kinetic model.

Table 13: It shows the kinetics of in vitro Release of GLZ tablets

Formulation Code	R ² value					'n' value
	Zero order	First order	Higuchi	Higson-Crowell	Peepas	
F ₁	0.857	0.393	0.929	0.956	0.834	0.3634
F ₂	0.762	0.438	0.945	0.411	0.988	0.3968
F ₃	0.592	0.634	0.788	0.686	0.767	0.1495
F ₄	0.883	0.391	0.976	0.888	0.978	0.4534
F ₅	0.918	0.401	0.984	0.958	0.97	0.4583
F ₆	0.852	0.36	0.967	0.849	0.945	0.351

Table 14: It shows the stability data of GLZ tablets

Batches	% Cumulative Drug Release		Drug Content (%)	
	15 days	30 days	15 days	30 days
F ₁	42.20±1.22	41.15±0.25	98.43±1.65	98.41±1.23
F ₂	24.82±1.67	23.76±0.51	97.12±1.56	96.05±0.14
F ₃	33.16±1.46	32.11±0.45	97.61±1.25	95.54±0.64
F ₄	95.19±1.30	95.10±0.94	98.74±1.84	98.70±0.84
F ₅	81.59±1.12	80.45±0.47	96.25±1.69	94.15±0.55
F ₆	86.34±1.31	85.21±1.02	97.81±2.01	96.55±0.47

CONCLUSION

Gliclazide is a poorly water soluble drug. Among the various approaches to improve the dissolution of poorly water soluble drugs, the preparation of physical mixing and fusion method have been proven to be very successful. In this study, soluplus, kollidonVA64, PEG 4000, sorbitol, cremophor EL was used in the preparation of solid dispersion of GLZ to increase its dissolution. The formulations were prepared at different ratios of drug and polymers and plasticizers. In vitro dissolution studies have shown significant increase in the dissolution of GLZ when PEG 4000 was used as a plasticizer in the preparation of solid dispersion. Sorbitol and cremophor EL also enhanced the solubility of GLZ as compared to the pure drug. The SD-4 was found to be the optimized formulation out of all the SD. On the contrary, the present study has shown that dissolution rate of the solid dispersion by fusion method was highest than by physical mixing method.

When solid dispersion was administered to rats orally, the maximum plasma concentration of GLZ significantly increased compared to pure drug. This suggested that solid dispersion could improve both the dissolution rate and bioavailability of a poorly water soluble drug GLZ.

IR spectra indicated no well-defined interaction between the drug and polymer. DSC thermograms of physical mixture and solid dispersion indicated complete miscibility of the drug in melted carrier. Amorphous nature of the drug in solid dispersion was confirmed by a decrease in enthalpy of drug melting in solid dispersion compared to the pure drug. XRD analysis indicated a reduction in drug crystalline nature in solid dispersion.

The tablets were successfully prepared by direct compression method. The tablets prepared by drug and kollidonVA64 in combination with PEG4000 (SD-4) was found to be the optimized, shows higher dissolution rate compared with the other tablets.

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Stability study

The formulation did not show any significant change in the drug release and drug content during stability study.

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