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Studies on the Solid Dispersion Systems of Glipizide

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Solid dispersions of glipizide were prepared using water-soluble carriers such as polyvinylpyrrolidone and polyethylene glycol by common solvent method in an attempt to increase the dissolution rate of glipizide, a practically insoluble drug in water. Differential scanning calorimetry, x-ray difiractometry and *in vitro* dissolution studies were used to characterize the solid dispersions. No chemical interaction was found between glipizide and polyvinylpyrrolidone/polyethylene glycol. The results from Differential scanning calorimetry and x-ray diffractometry studies show that polyvinylpyrrolidone/polyethylene glycol inhibits the crystallization of glipizide. The solid dispersions prepared in this study were found to have higher dissolution rates compared to intact glipizide and physical mixtures of polyvinylpyrrolidone/polyethylene glycol and glipizide. It was found that the optimum weight ratio for glipizide:carrier is 1:5 for polyvinylpyrrolidone and 1:7 for polyethylene glycol.

Glipizide is an oral hypoglycemic agent, 100 times more potent than tolbutamide in evoking pancreatic secretion of insulin[1,2]. As per the BP[3], it is practically insoluble in water. Because of its poor aqueous solubility, conventional glipizide dosage forms show absorption problems[4]. It has been reported that glipizide from rapid release soft gelatin capsules showed complete drug absorption and a greater reduction of postprandial glucose levels compared to conventional tablet dosage form[4,5]. The aim of the present study was the preparation of solid dispersions of glipizide using water-soluble carriers like polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG).

The solid dispersion approach has been widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly water-soluble drugs[6]. This system provides the possibility of reducing the particle size of drugs to nearly a molecular level, to transform the drug from the crystalline to the partial amorphous state and/or to locally increase the saturation solubility. A number of freely water soluble materials such as citric acid, succinic acid, bile acids, sterols and related compounds and polymers like PVP and PEG are used as carriers for solid dispersions[7,8].

In the present investigation, an attempt was made to improve the dissolution rate of glipizide through the preparation of solid dispersions of glipizide and water-soluble carriers like PVP (K-90) and PEG 6000 by common solvent method.

MATERIALS AND METHODS

Glipizide was obtained as a gift sample from Wallace Pharmaceuticals Ltd, Mumbai. Polyvinylpyrrolidone (K-90) and polyethylene glycol 6000 were gift samples provided by BASF, Ludwigshafen, Germany. All other chemicals used were of analytical grade.

Preparation of solid dispersions and physical mixtures:

Accurately weighed quantity of carriers (PVP or PEG) in various 1:1, 1:3, 1:5, 1:7, 1:9 (drug:carrier) proportions

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were carefully transferred into test tubes and dissolved in chloroform. To these solutions, accurately weighed quantities of glipizide were added and allowed to dissolve. Then solvent was removed by evaporation at 40° under reduced pressure by using vaccum evaporator (Super fit India ltd.). The mass obtained in each tube was scraped, crushed, pulverized and sifted through mesh No. 100. The physical mixtures of glipizide with PVP (K-90) or PEG 6000 were prepared by mixing accurately weighed quantities of drug and carrier in above stated proportions in a glass mortar and sifted through mesh No. 100.

Differential scanning calorimetry (DSC) curves and powder x-ray diffraction (XRD) patterns of solid dispersions and physical mixtures were obtained using a differential scanning calorimeter (DSC 220, SEIKO, JAPAN) and Philips diffractometer (PW 1140), respectively.

Estimation of drug content:

An accurately weighed quantity of solid dispersion equivalent to 50 mg of drug was taken into a 100 ml volumetric flask and dissolved in minimum amount of methanol and the volume was made up to the mark with phosphate buffer (pH 7.4), and assayed for drug content using UV double beam spectrophotometer at 274 nm. Four replicates were prepared and the average drug contents were estimated in the prepared solid dispersions.

***In vitro* dissolution study:**

Dissolution test was carried out using USP paddle method (Apparatus 2) for 3 h. The stirring rate was 100 rpm. Phosphate buffer (pH 7.4) was used as dissolution medium (900 ml) and was maintained at 37±1°. Sample equivalent to 5 mg of glipizide was used for dissolution studies. Samples were collected at regular time intervals and assayed for drug content spectrophotometrically at 274 nm. Each dissolution rate test was repeated thrice and average values were reported. T_{50} values were calculated directly from dissolution data.

RESULTS AND DISCUSSION

Low values of standard deviation in respect of drug content as given in Table 1 indicated uniform drug distribution in all the solid dispersions. ANOVA test indicated that there is no significant difference between the percent of drug content at 5% level of significance in all the prepared batches of solid dispersions. Hence the technique used was found to be reproducible.

The DSC scans of pure drug, PEG, PVP, physical mixtures and solid dispersions are presented in figs. 1 and 2. The melting endotherms of pure glipizide and PEG alone gave peaks at 211.6° and 59.6° respectively corresponding to their melting points, where as PVP showed broad peak at 89.1° may be due to dehydration. Physical mixtures of glipizide and PEG/PVP showed same peaks at temperatures corresponding to the pure compounds indicating no interaction of the carrier with the drug in the physical state. The intensity of the peaks of the 1:1 weight ratio of glipizide and PEG/PVP solid dispersions were smaller than those of the physical mixtures at same weight ratio. These results suggested that glipizide became partially amorphous during dispersion into PEG/PVP matrix.

TABLE 1: ESTIMATED DRUG CONTENTS OF GLIPIZIDE AND PEG OR PVP PREPARATIONS.

Drug: PEG/PVP ratio	Glipizide Content (%)			
	PEG preparations		PVP preparations	
	PM	SD	PM	SD
1:1	49.21±2.12	48.23±2.06	49.96±2.37	49.63±2.51
1:2	32.19±1.97	33.16±2.98	34.01±2.96	33.01±1.83
1:5	15.12±2.31	16.13±1.99	15.37±2.04	14.97±2.15
1:7	11.91±2.11	12.21±2.39	12.03±2.19	12.33±2.76
1:9	10.23±2.16	10.07±2.71	9.93±1.03	9.57±3.11

Drug contents of preparations were estimated by dissolving weighed quantity of physical mixture (PM) or solid dispersion (SD) in minimum amount of methanol, then, the volume was made up with phosphate buffer (pH 7.4), and assayed for drug at 274 nm.

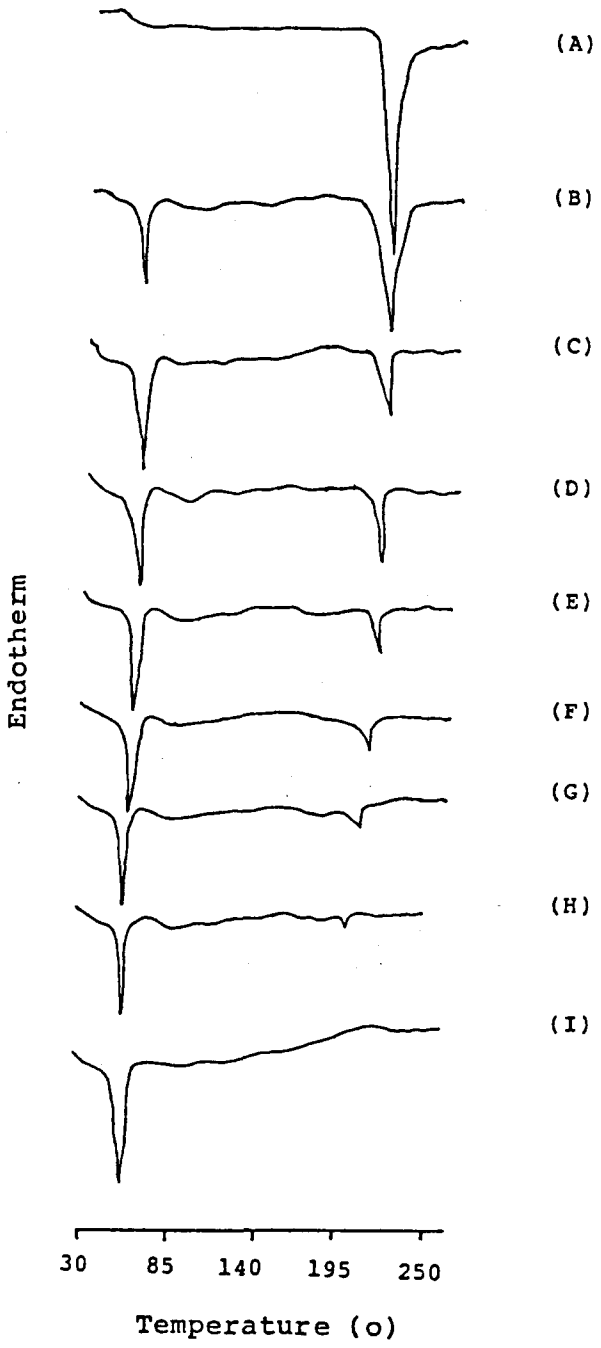

Fig. 1: DSC thermograms of physical mixtures and solid dispersions of glipizide and PEG.

Differential scanning calorimetric thermograms of A) pure glipizide, B) physical mixture (1:1) (drug:PEG), C) physical mixture (1:9), D) solid dispersion (1:1) (drug:PEG), E) solid dispersion (1:3), F) solid dispersion (I:5), G) solid dispersion (1:7), H) solid dispersion (1:9) and I) PEG.

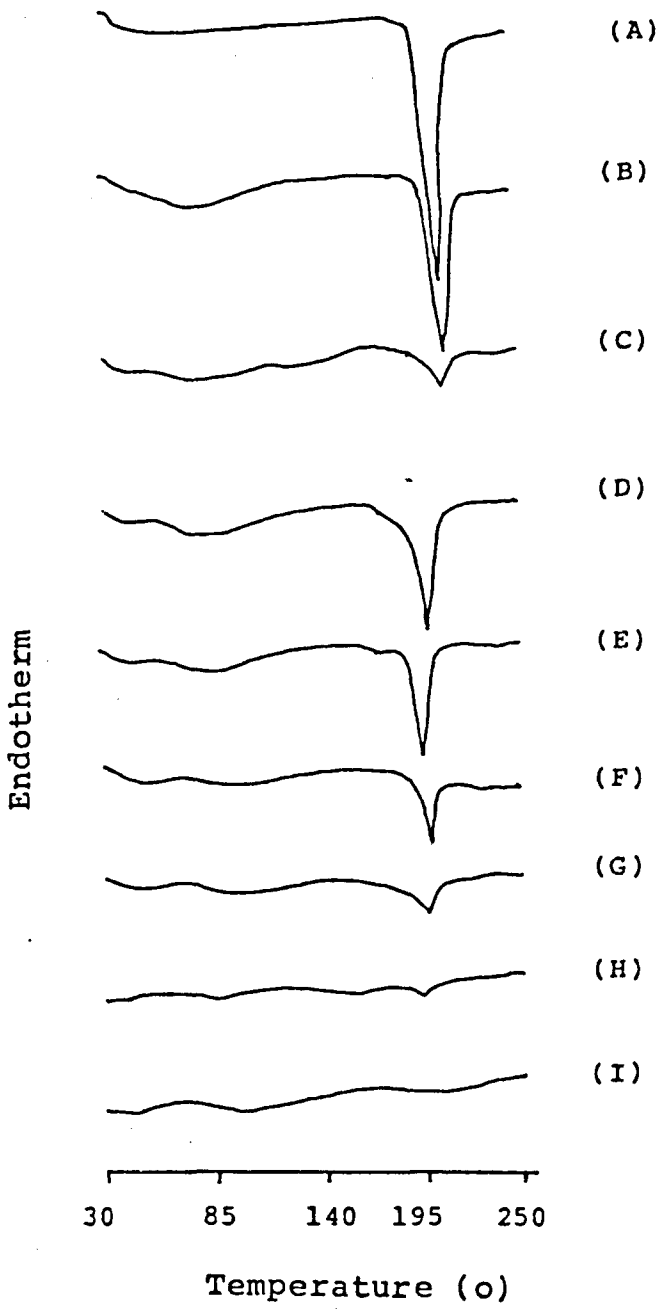

Fig. 2: DSC thermograms of physical mixtures and solid dispersions of glipizide and PVP.

Differential scanning calorimetric thermograms of A) pure glipizide B) physical mixture (1:1) (drug:PVP), C) physical mixture (1:9), D) solid dispersion (1:1) (drng:PVP), E) solid dispersion (1:3), F) solid dispersion (1:5), G) solid dispersion (1:7), H) solid dispersion (1:9) and I) PVP.

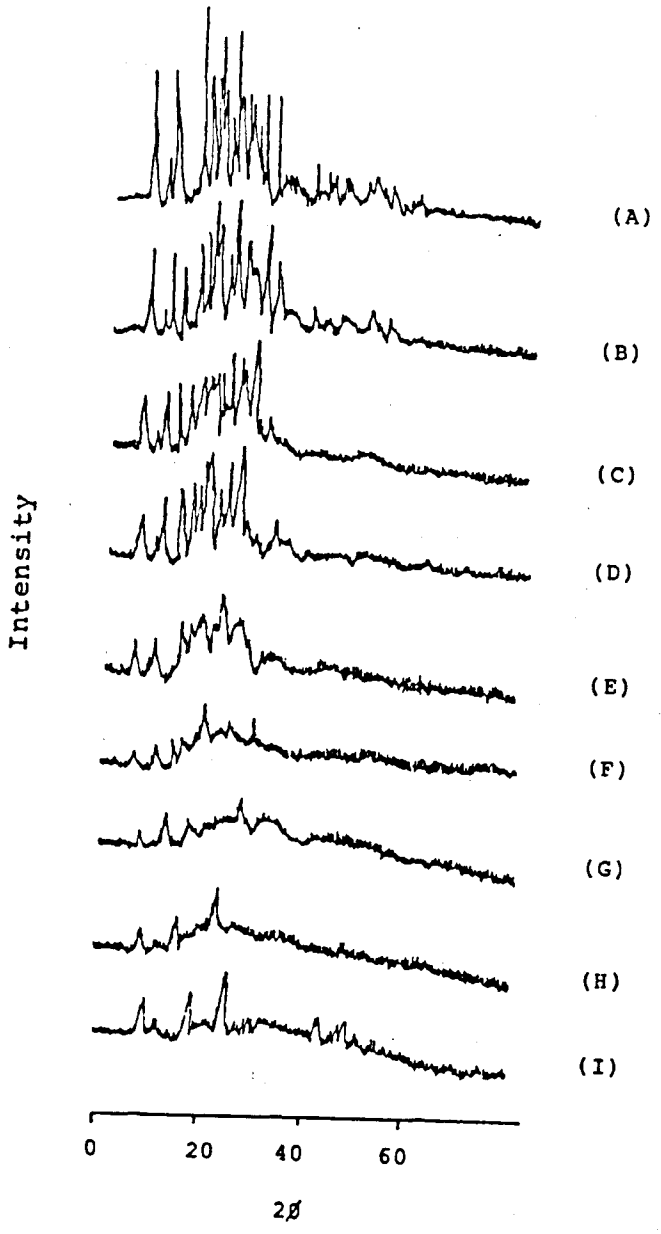

Fig. 3: XRD patterns of physical mixtures and solid dispersions of glipizide and PEG.

Powder x-ray diffraction patterns of A) pure glipizide, B) physical mixture (1:1) (drug:PEG), C) physical mixture (1:9), D) solid dispersion (1:1) (drug:PEG), E) solid dispersion (1:3), F) solid dispersion (1:5), G) solid dispersion (1:7) H) solid dispersion (1:9), and I) PEG.

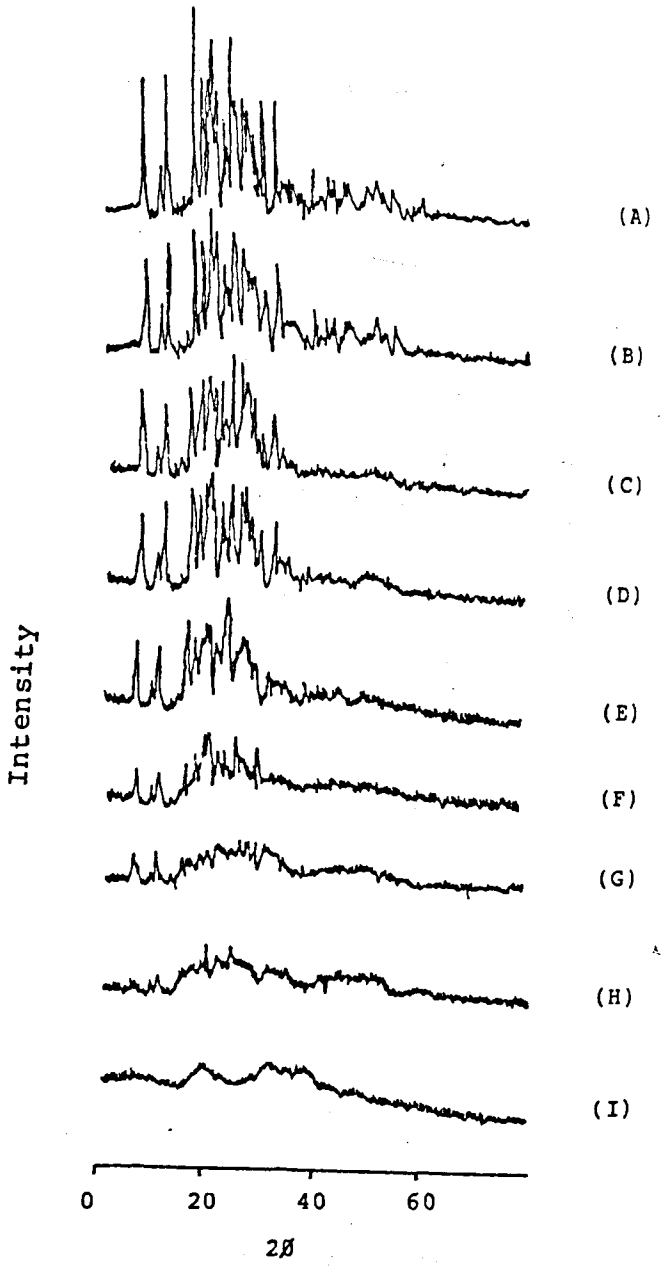

Fig. 4: XRD patterns of physical mixtures and solid dispersions of glipizide and PVP.

Powder x-ray diffraction patterns of A) pure glipizide, B) physical mixture (1:1) (drug:PVP), C) physical mixture (1:9), D) solid dispersion (1:1) (drug:PVP), E) solid dispersion (1:3), F) solid dispersion (1:5), G) solid dispersion (1:7), H) solid dispersion (1:9) and I) PVP.

As the carrier level increased in the glipizide and PEG solid dispersions, the intensity of peak corresponding to glipizide was decreased though the thermogram showed two peaks corresponding to the melting points of pure compounds. This phenomenon was observed with drug:carrier ratio up to 1:7. The DSC curve of 1:9 ratio of glipizide:PEG showed only one endothermic peak corresponding to the melting of PEG. This may be due to low drug level in the dispersion or complete miscibility of the drug within the carrier polymer.

DSC thermograms of glipizide and PVP solid dispersions (fig. 2) showed only one broad peak in the range of 200-220°, which decreased when polymer content increased. The widening of the endothermic melting peak can explain the highly dispersed form of the drug in the dispersion. The similarities between the DSC data for the solid dispersions and physical mixtures as shown in figs. I and 2 indicated the absence of a well-defined chemical interaction between glipizide and PEG/PVP.

Figs. 3 and 4 illustrate the XRD patterns of glipizide,

TABLE 2: DISSOLUTION PROFILES OF PHYSICAL MIXTURES AND SOLID DISPERSIONS OF GLIPIZIDE AND PEG OR PVP.

Time	Pure	Glipizide-PEG preparations									
(min)	drug	1:1		1:3		1:5		1:7		1:9	
0	0	0	0	0	0	0	0	0	0	0	0
15	0.81	2.10	13.28	2.80	15.40	3.25	17.50	4.10	20.50	5.55	20.10
30	0.95	4.80	15.70	5.20	18.10	6.28	20.75	7.25	24.50	7.85	23.20
45	1.25	7.92	17.50	8.38	21.20	9.45	25.82	10.25	28.70	10.55	29.20
60	5.72	10.20	20.55	11.25	24.50	11.75	28.50	12.55	34.80	13.75	32.50
90	10.52	12.80	25.20	14.85	30.50	15.20	33.52	16.10	47.70	16.85	48.20
120	17.85	20.50	30.50	21.25	47.25	22.25	50.72	24.50	55.50	25.50	54.78
150	21.43	25.75	35.72	26.70	54.25	27.50	58.40	30.50	67.25	32.50	65.25
180	23.04	33.50	38.25	35.25	55.50	37.10	64.50	39.10	69.98	40.25	70.00
Time	Pure	Glipizide-PEG preparations									
(min)	drug	1:1		1:3		1:5		1:7		1:9	
0	0	0	0	0	0	0	0	0	0	0	0
15	0.81	3.25	16.75	3.95	20.50	4.78	32.50	5.25	80.50	5.45	80.25
30	.95	5.60	20.25	5.70	22.70	6.85	41.75	7.70	89.00	7.55	89.00
45	1.25	8.52	25.80	9.75	27.50	10.92	52.80	9.25	89.00	10.27	89.00
60	5.72	11.11	28.72	12.22	34.25	12.32	60.75	13.34	89.00	13.45	89.00
90	10.52	13.25	30.82	15.75	41.70	16.82	72.80	17.28	89.00	18.50	89.00
120	17.85	22.25	36.52	25.25	52.50	28.50	80.25	28.25	89.00	27.82	89.00
150	21.43	26.85	45.75	33.50	58.70	34.52	85.25	35.52	89.00	37.50	89.00
180	23.04	35.25	52.50	37.25	65.00	38.25	87.00	38.50	89.00	39.20	89.00

In vitro dissolution profiles of glipizide from physical mixtures (PM) and solid dispersions (SD) of glipizide and PEG or PVP were studied in phosphate buffer (pH 7.4), samples drawn at regular time intervals and glipizide content was measured spectrophotometrically at 274 nm.

PEG, PVP, physical mixtures and solid dispersions. The diffraction pattern of glipizide showed that glipizide has high crystallinity because of the presence of numerous peaks. PEG and PVP are found to be amorphous powders having no crystalline structures. The XRD peaks of crystalline glipizide in all the physical mixtures of both drug:PEG and drug:PVP were similar to those in the pure drug, indicating that the crystallinity of glipizide did not change in the physical mixtures.

The crystalline structure of glipizide in all the solid dispersions were different from that of pure drug and corresponding physical mixture as indicated from the differences in their XRD patterns. All the glipizide and PEG/PVP solid dispersions, except the 1:1 solid dispersion, did not show the characteristic peaks of glipizide. The peaks of diffraction patterns of the 1:1 solid dispersion were smaller than those of the its 1:1 physical mixture. The number of peaks and peak height was reduced in all the solid dispersions as the polymer concentration increased. These findings suggest that the glipizide crystals get converted to amorphous form in the polymer matrix in solid dispersions with higher weight ratios of polymer. This finding is also in good agreement with the enhanced rate of dissolution of dispersions with increase in polymer concentration.

Only 23% of pure glipizide is found to be released in 180 min as shown in Table 2. Dissolution profiles of solid dispersions with PEG/PVP showed increase of dissolution rate with respect to the corresponding physical mixtures and the pure drug as indicated by the T_{50} values given in Table 3. The increase in the dissolution of drug when it is physically mixed with PEG/PVP is probably due to wettability improvement and local solubilization effect of the carrier at diffusion layer. In addition to these factors, enhancement of dissolution of drug from PEG/PVP solid dispersions could be attributed to the amorphous state of the drug in solid dispersions, absence of aggregation and particle size reduction[9]. It is observed that PEG and PVP solid dispersions showed 15 fold increase in dissolution rate in comparison with that of pure drug at 1:7 and 1:5 (drug:carrier) ratios, respectively.

TABLE 3: T_{50} VALUES OF PREPARATIONS OF GLIPIZIDE AND PEG OR PVP.

Drug: PEG/PVP ratio	T_{50} values (min)			
	PEG preparations		PVP preparations	
	PM	SD	PM	SD
1:1	177	123	178	112
1:2	172	78	174	43
1:5	171	26	166	10
1:7	163	11	162	47
1:9	159	29	156	69

Where, T_{50} is the time at which 50% of the drug release occurs, PM_{50} represents the physical mixture of glipizide and PEG or PVP and SD represents the solid dispersion of glipizide and PEG or PVP.

As indicated in Table 2 and 3, the dissolution rate of glipizide was strongly dependent on the relative concentration of the drug to PEG/PVP ratio. The dissolution rate of glipizide from PEG solid dispersions was increased with increment in PEG concentration up to the drug:carrier ratio of 1:7, where as for PVP solid dispersions maximum dissolution rate was obtained from the drug:carrier ratio of 1:5. The further increase in amount of PEG/PVP in solid dispersions decreased the dissolution rate. The decrease in dissolution rate of the solid dispersions containing higher polymer proportions might be caused by leaching out of the carrier during dissolution which could form a concentrated layer of solution around the drug particles thereby reducing the migration of the release drug particles to the bulk of the dissolution[10].

In conclusion, a maximum increase in dissolution rate was obtained with glipizide-PEG solid dispersion with a weight ratio of 1:7 (drug:PEG) and glipizide:PVP solid dispersion with a weight ratio of 1:5 (drug:PVP). Though, PVP dispersions showed faster dissolution at low polymer level in comparison with that of PEG dispersions, PEG dispersions are more suitable for formulation development as PVP is more hygroscopic.

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