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DESIGN AND EVALUATION OF SOLID DISPERSED GLICLAZIDE TABLETS

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ABSTRACT

Gliclazide (GZ), an oral hypoglycemic agent, belongs to BCS class II. It is poorly soluble in water (5.23 µg/mL) and requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. In the present investigation, solid dispersed systems of GZ were prepared using polyethylene glycol (PEG-6000) and poly vinyl pyrrolidine (PVP k_{25}). The feasibility of employing solid dispersion technique for enhancing the solubility and dissolution rate was investigated. The aqueous solubility of GZ was increased linearly as a function of the concentration of polymers used in the study. PVP gave higher enhancement in the solubility and dissolution rate when compared to PEG tested. Characterization of co-evaporates was studied by DSC thermograms. Solid dispersions of gliclazide-PVP prepared by co-evaporation were developed into tablet dosage forms by wet granulation method. The solid dispersion tablets were evaluated and compared with some of the gliclazide conventional tablets, which are commercially available. Solid dispersion tablets of co-evaporation method showed better correlation with marketed formulations.

Key words : Gliclazide, Evaluation, Co-evaporation.

INTRODUCTION

Solid dispersion techniques can be used to increase dissolution and absorption of several insoluble drugs[1-2]. To date a number of drugs are not showing complete therapeutic effect because of their poor solubility and dissolution, which in turn leads to poor bioavailability of the drug[3-4]. So in the modern days, top most importance is given for increasing the dissolution rate of poorly soluble drugs, which enhances their bioavailability.

A number of poorly soluble drugs have been shown to improve their dissolution

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characteristics, when converted to solid dispersions. Gliclazide (GZ) is widely used in the treatment of diabetes mellitus, which stimulates insulin secretion from functional pancreatic β-cells and increases the sensitivity of the β-cells to a glucose stimulus. GZ is a white or almost white powder and it is poorly soluble in water. Since the dissolution rate of a drug from a surface is affected by the carrier in solid dispersion, the carrier has an ultimate influence on the dissolution of the dispersed drug. Therefore, highly soluble PEG and PVP were used as carriers for converting GZ into solid dispersions in this study.

EXPERIMENTAL

Materials and methods

Gliclazide was obtained as gift sample from Dr. Reddy's Labs, Hyderabad, A. P, PVP k_{25} and PEG-6000 from Loba Chemie, Mumbai, methanol and dichloromethane from Finar Chemicals, Ahmedabad, sodium benzoate from Qualigens Fine Chemicals, Mumbai, starch from Hi-Pure Fine Chem Industries and Magnesium stearate from s. d fine – chem., Mumbai. All other materials used are pharmacopoeial grade.

Estimation of gliclazide

An UV spectrophotometric method based on the measurement of absorbance at 228 nm in water was used in the estimation of GZ. The method obeyed Beer's law in the concentration range of 0-10 μg/mL. Low RSD values ensured reproducibility of the method. Thus, the method was found to be suitable for the estimation of GZ content in various products and *in vitro* dissolution studies.

Phase solubility studies

Phase solubility studies were performed according to the method reported by Higuchi and Connors[5]. Excess of drug was added to 15 mL of distilled water containing various concentrations of polymer (PEG and PVP in percentages) taken in a series of 25 mL stoppered conical flask and the mixtures were shaken for 72 hrs at room temperature on a rotary flask shaker. After 72 hrs of shaking to achieve equilibrium, 2 mL aliquots were withdrawn at 1 hr interval and filtered immediately using 0.45μ nylon disc filter. The filtered samples were diluted suitably and drug content was assessed by U. V. spectrophotometer method at 228 nm. The solubility experiments are conducted in triplicate. The results of phase solubility studies are shown in the Table 2 and depicted graphically in Fig. 1.

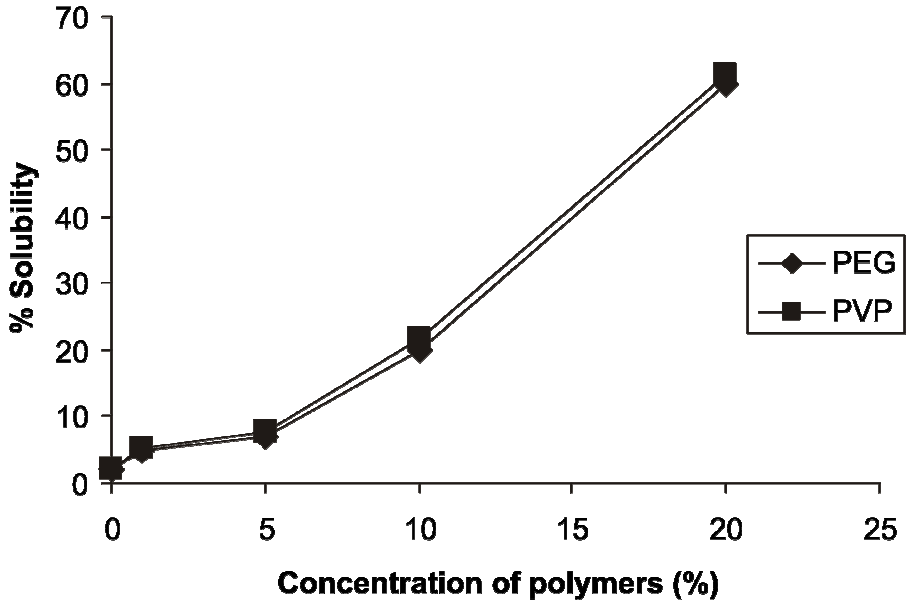

Fig. 1 : Effect of PEG and PVP on the solubility of GZ

Preparation of solid dispersions of gliclazide

Solid dispersions containing gliclazide- PEG and PVP in the proportions of 1 : 1, 1 : 2 and 1 : 3 were prepared by physical mixing and co-evaporation methods.

Preparation of physical mixtures (PM) of gliclazide

Physical mixtures of the drug gliclazide with the excipients (PEG and PVP) in various ratios such as 1 : 1, 1 : 2 and 1 : 3 were prepared by physical mixing thoroughly for 5 min in a mortar until a homogenous mixture was obtained. Then, it was passed through mesh No #100 and stored in a desiccated environment.

Preparation of co-evaporates of gliclazide

Co-evaporates of GZ were prepared by using the solvent evaporation technique. Gliclazide was dissolved in a solvent blend of methanol and dichloromethane (1 : 1) to get a clear solution in a 100 mL round bottom flask. The excipient was then added and dispersed. The solvent in the mixture was removed by evaporation at 50ºC under pressure while mixing the contents. The mass obtained was pulverized, mixed and passed through mesh No #100. Co-evaporates were prepared in various ratios of drug : excipient such as 1

: 1, 1 : 2 and 1 : 3.

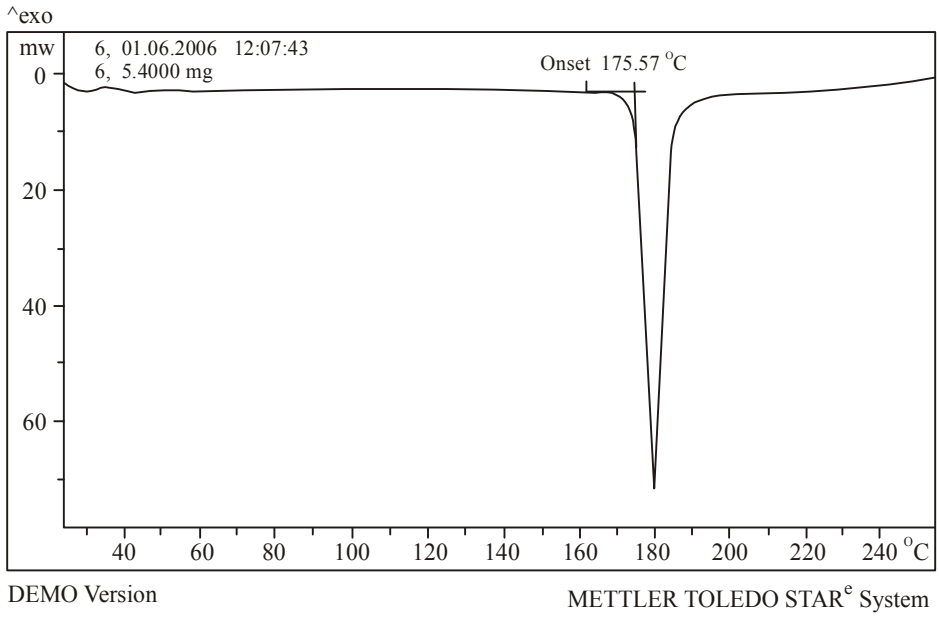

Fig. 2 : DSC thermogram of GZ

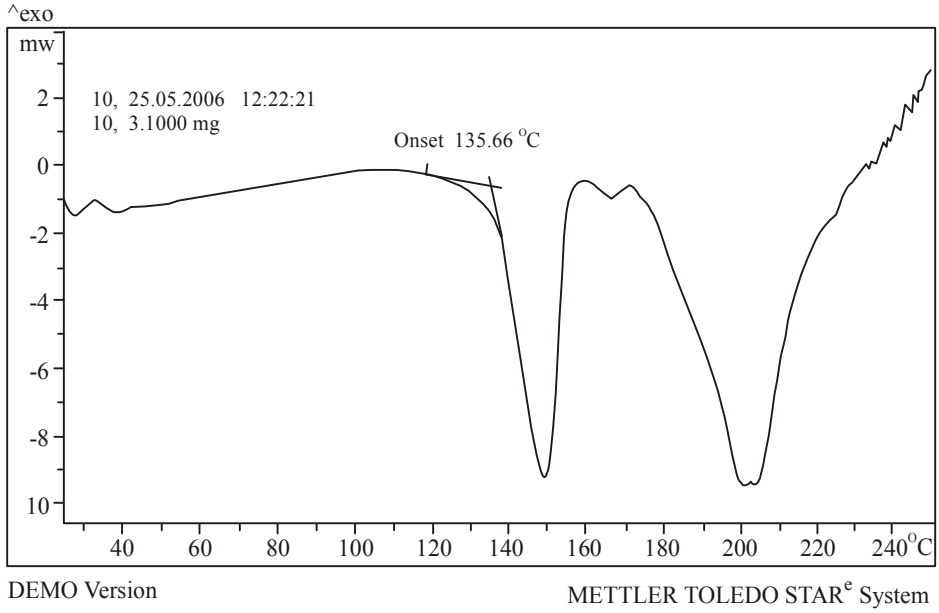

Fig. 3 : DSC thermogram of GZ-PVP (1 : 3)

Estimation of drug content in physical mixtures and co-evaporates

The powder form of physical mixtures/ co-evaporates equivalent to 50 mg of drug GZ was taken in 50 mL volumetric flask. About 40 mL of methanol was added and mixed thoroughly. The solution was made upto volume with methanol. The solution was then suitably diluted with water and assayed for the drug content by UV spectrophotometric method. The results are given in Table 3.

Dissolution rate studies on gliclazide solid dispersions

Dissolution rate of gliclazide as such and from solid dispersions was studied using Lab India DISSO 2000, an 8 stage dissolution rate testing apparatus, with a paddle stirrer. The dissolution fluid was 900 mL of distilled water. Dissolution studies were carried out by taking solid dispersion equivalent to 50 mg of GZ, a speed of 50 rpm and a temperature at 37 ± 1.0ºC were used in each test. Samples of dissolution medium (5 mL) were withdrawn through a filter of 0.45µm at different time intervals, suitably diluted and assayed for GZ by measuring absorbance at 228 nm. The dissolution experiments were conducted in triplicate and the results are shown in the Figs. 4 and 5 and dissolution parameters are given in Tables 4 and 5.

Physico-chemical compatibility between gliclazide and solid dispersions of PVP using differential scanning calorimetry

To know the physico-differential compatibility between gliclazide and the polymer PVP Sieko, Japan DSC 220C Model Differential scanning calorimeter was used. Samples (1-4mg) in weight were sealed hermetically in flat bottomed aluminium cells (pans). These samples were then heated over a temperature of 35-300ºC in an atmosphere on nitrogen (50 mL/min) at a constant rate of 10ºC per minute using alumina as reference standard. The results are shown in Figs. 2 and 3.

Formulation of gliclazide tablets

Tablets each containing 80 mg of gliclazide were formulated employing GZ as such and GZ co-evaporates of PVP (1 : 1 and 1 : 3) along with the usual tablet excipients. The formula of gliclazide tablets are given in Table 1. Gliclazide tablets were prepared by conventional wet granulation method as per formula given in Table 1. Gliclazide or its solid dispersion, lactose and half the amount of sodium starch glycolate were blended thoroughly in a dry mortar. To the blend of powders, starch mucilage (5%) was added and mixed thoroughly to form dough mass. The wet mass was passed through mesh No. 12 to

produce granules. The granules were dried at 65ºC for 2 hrs. The dried granules were sieved through mesh No. 14 and blended with sodium benzoate, magnesium stearate and the remaining amount of sodium starch glycolate. The granules were then compressed into 300 mg tablets on a Cadmach single punch tablet machine (M/S Cadmach Machinery Co, Pvt. Ltd., Ahmedabad.)

Table 1 : Formula of gliclazide tablets

Ingredients (mg/tablet)	F1	F2	F3
Gliclazide	80	-	-
GZ : PVP (1 : 1)	-	160	-
GZ : PVP (1 : 3)	-	-	240
Lactose	200	120	50
Sodium starch glycolate	6	6	6
Starch mucilage	q. s	q. s	q. s
Sodium benzoate	3	3	3
Magnesium stearate	6	6	6
Total weight of tablet (mg).	300	300	300

Evaluation of gliclazide tablets

Compressed tablets were then evaluated for hardness, disintegration, friability and drug content. Hardness was measured by Monsanto type hardness tester. One tablet was placed in each tube of disintegration apparatus (thermonic model) and the test was carried out using distilled water as disintegrating media at 25ºC. Friability was determined in 'Roche friabilator' by taking ten tablets. For drug content analysis, twenty tablets were accurately weighed and finely powdered. The quantity of powder, equivalent to 80 mg of gliclazide was taken in a 50 mL volumetric flask and dissolved in methanol. Five millilitres of the filtrate was diluted to 100 mL with water and assayed for drug content at 228nm, using UV/Vis spectrophotometer.

In vitro dissolution study of tablets

In vitro dissolution study of tablets was conducted using USP dissolution apparatus II (Lab India DISSO 2000) at 50 rpm, using distilled water maintained at 37±0.5ºC. Samples were withdrawn at various intervals, filtered through a 0.45 micron membrane filtered, diluted and assayed at 228 nm, using a UV/Vis spectrophotometer. The results are

given in Fig. 6.

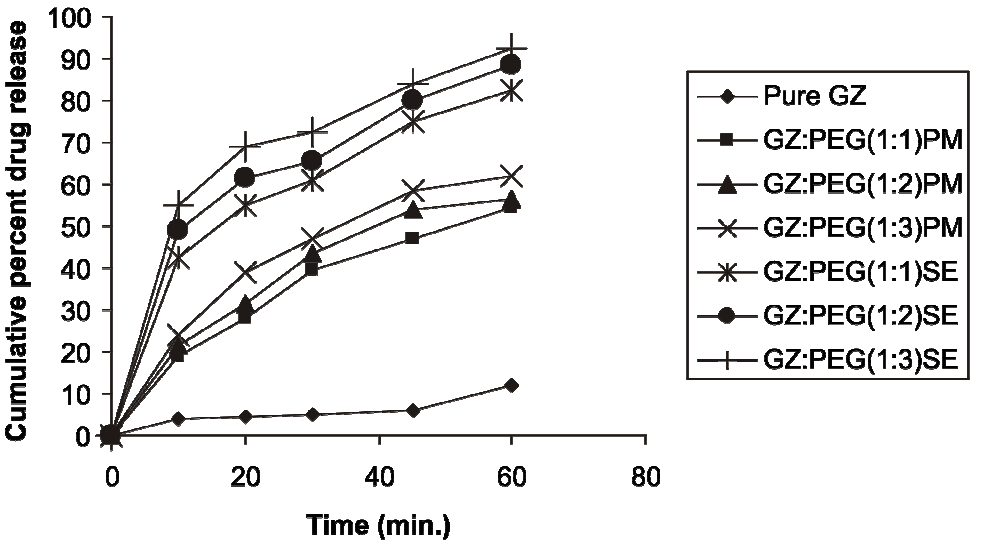

Fig. 4 : Dissolution profiles of GZ as such and from GZ-PEG solid dispersions prepared by physical mixing and solvent evaporation

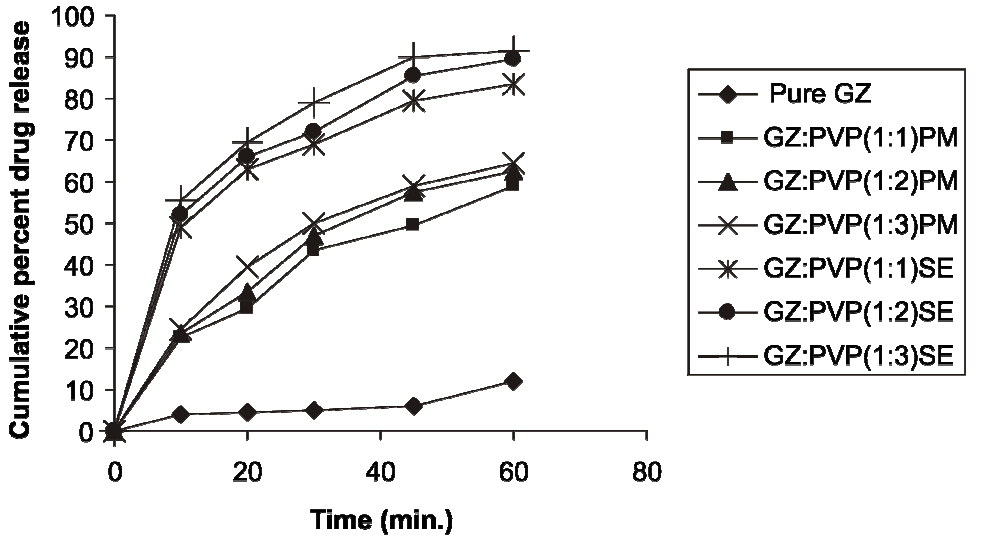

Fig. 5 : Dissolution profiles of GZ as such and from GZ-PVP solid dispersions prepared by physical mixing and solvent evaporation

RESULTS AND DISCUSSION

The solubility increased linearly as a function of carrier concentration and the solubility curve can be classified as Higuchi's type A_L.

Table 2 : Saturation Solubility Studies

Concentration of polymer (%w/v)	Saturation solubility (µg/mL)(mean ± S. D., n = 3)	
	PEG	PVP
0	2.23 ± 0.23	2.23 ± 0.23
1	4.89 ± 0.76	5.20 ± 0.32
5	6.89 ± 0.49	7.61 ± 0.34
10	19.87 ± 0.56	21.53 ± 0.69
20	59.98 ± 0.63	61.38 ± 0.86

All the mixtures were found to be fine powders. Low SD in % drug content values indicated uniformity of drug content in each batch of physical mixtures / co-evaporates. The results are given in Table 3.

Table 3 : Drug content of solid dispersions of GZ

Solid dispersion systems	Percent GZ content (mean ± S. D, n = 3)	
	Physical mixtures	Co-evaporates
GZ : PEG (1 : 1)	96.86 ± 0.127	97.11 ± 0.018
GZ : PEG (1 : 2)	97.06 ± 0.192	97.56 ± 0.196
GZ : PEG(1 : 3)	97.22 ± 0.154	98.85 ± 0.097
GZ : PVP (1 : 1)	98.15 ± 0.186	98.78 ± 0.385
GZ : PVP (1 : 2)	98.78 ± 0.195	99.04 ± 0.196
GZ : PVP (1 : 3)	98.89 ± 0.199	99.97 ± 0.194

DSC thermograms of GZ and its solid dispersion in PVP are shown in Figs. 2 and 3. DSC thermogram of GZ exhibited a sharp endothermic peak at 180ºC corresponding to its melting point. In the DSC thermograms of solid dispersion, the endothermic melting point peak was shifted to a lower temperature i. e., 150ºC in the case GZ : PVP (1 : 3) solid dispersion. The intensity of peak also gradually reduces, as the concentration of PVP was increased. The DSC patterns thus suggest an interaction between GZ and the carrier (PVP) and physical conversion of GZ into solution form (solid solution) at higher concentration of carrier. The rapid dissolution and higher dissolution efficiency values observed with solid dispersion is due to this interaction and physical conversion of GZ to solid solution form.

Table 4 : Dissolution parameters of GZ and its solid dispersions (GZ : PEG) prepared by physical mixing (PM) and solvent evaporation (SE) method.

Solid dispersion	T_{50} (min)	DE_{30}%	$K_1(min^{-1})$	R^1 value
Pure drug	200	10	0.0016	0.9737
GZ : PEG (1 : 1)PM	60	23.30	0.0079	0.9960
GZ : PEG (1 : 2)PM	43	26.85	0.0088	0.9975
GZ : PEG(1 : 3)PM	30	30.00	0.0095	0.9980
GZ : PEG (1 : 1)SE	17	51.17	0.0209	0.9983
GZ : PEG (1 : 2)SE	6	62.35	0.0237	0.9989
GZ : PEG (1 : 3)SE	5	72.60	0.0260	0.9999

Table 5 : Dissolution parameters of GZ and its solid dispersions (GZ : PVP) prepared by physical mixing (PM) and solvent evaporation (SE) method

Solid dispersion	T_{50} (min)	DE_{30}%	$K_1(min^{-1})$	R^1 value
Pure drug	200	10	0.0016	0.9656
GZ : PVP (1 : 1)PM	58	28	0.0089	0.9961

Cont…

Solid dispersion	T_{50} (min)	DE_{30}%	K_1(min^{-1})	R^1 value
GZ : PVP (1 : 2)PM	43	31.21	0.0098	0.9973
GZ : PVP (1 : 3)PM	38	33.3	0.011	0.9985
GZ : PVP (1 : 1)SE	6	53.3	0.0221	0.9975
GZ : PVP (1 : 2)SE	5	65.64	0.0248	0.9989
GZ : PVP (1 : 3)SE	4	73	0.0287	0.9999

From the dissolution profiles and dissolution parameters, it is clear that there is greater increase in the dissolution rate (K_1) and DE_{30} values of GZ : PVP solid dispersions when compared to GZ : PEG solid dispersions and pure GZ. The dissolution of GZ has improved to a greater extent considerably from GZ : PVP solid dispersions prepared by solvent evaporation, when compared to physical mixing method. So GZ : PVP solid dispersions prepared by solvent evaporation were formulated into cost effective tablet formulations, with improved dissolution.

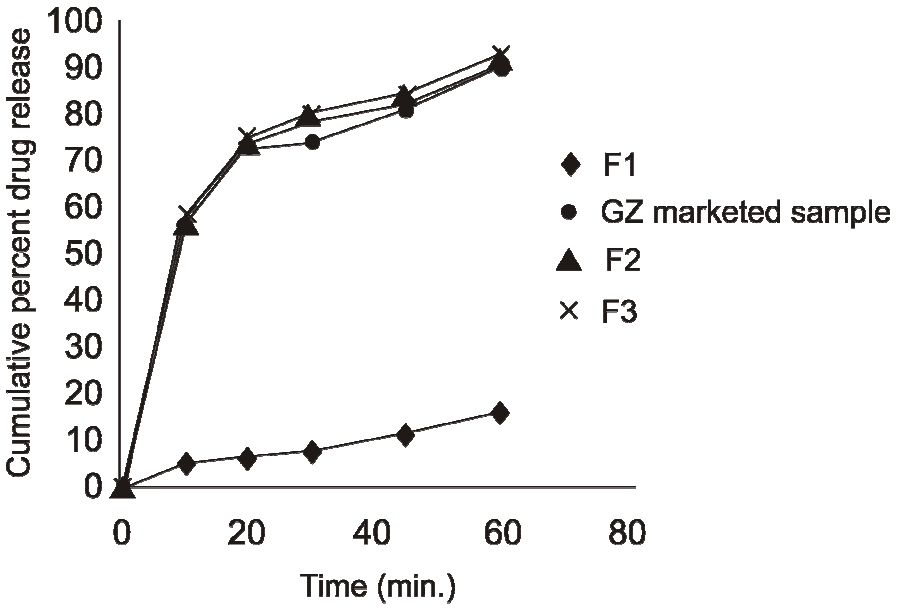

Fig : 6 : Dissolution profiles of GZ tablets

Table 6 : Evaluation of tablets

Tablet formulation	Hardness (kg/sq. cm)	Disintegration time (min.)	Friability (%)	Drug content(%)
F1	3.8	5	0.55	99.21
F2	3.9	4	0.41	99.54
F3	4.0	2	0.34	99.87

From the physico-mechanical parameters of the formulated tablets, it is clear that all the tablets fulfilled the official requirements of the compressed tablets. The results of the disintegration test revealed that F3 has faster disintegration and it disintegrates within two min (120 sec).

Table 7 : Dissolution parameters of GZ tablets

Formulations	Dissolution parameters		
	T_{50}(min)	DE_{30}%	K_1(min^{-1})
F1	200	10	0.0016
F2	7	65	0.0440
F3	6	66	0.0442
GZ Marketed Sample	8	65	0.0441

From the dissolution profiles and dissolution parameters, it is clear that among all in-house formulations, F3 showed maximum dissolution and a 27.66 fold and 6.6 fold increase in the dissolution rate (K_1) and DE_{30} were observed with the F3 tablets. F3 tablets are also on par with marketed tablets.

CONCLUSION

It was found that dissolution rate of poorly soluble drug GZ can be increased by

forming into solid dispersions. Solid dispersions demonstrated a higher dissolution rate than pure drug. The GZ : PVP (1 : 3) solid dispersion made by solvent evaporation method showed highest dissolution rate than the other formulations. GZ : PVP solid dispersions (1 : 1 and 1 : 3) formulated into tablets (F2 andF3). F3 showed maximum dissolution when compared to pure drug with a 27.66 fold and 6.6 fold increase in the dissolution rate (K_1) and DE_{30} and it is on par with marketed formulation. Thus, both solubility and dissolution rate of GZ were markedly enhanced by solid dispersion technique.

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