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Formulation and characterization of Glipizide solid dispersions using the Poly vinyl pyrrolidine k-30 polymer

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ABSTRACT

Glipizide is oral hypoglycemic agent, used for treatment of type II diabetes mellitus. Glipizide is insoluble in water. To increase the solubility, dissolution rate and bioavailability of glipizide it must be made its a suitable formulation by incorporating with suitable hydrophilic carriers. Such formulation provides a means of reducing particle size to nearly a molecular level. solid dispersion technique was adapted to enhance the solubility and dissolution rate of glipizide by incorporating hydrophilic carrier such as Polyvinylpyrrolidone K30 (PVP-K30) in different ratios were used . The formulation of the solid dispersion were carried our by preparing the physical mixtures of glipizide using the Polyvinylpyrrolidone K30 (PVP-K30) in four different ratios.(1:2, 1:4, 1:6 and 1:8).Characterization of solid dispersions and physical mixtures were confirmed by Determination of Drug content, Solubility study, Thermal study, I R Spectral Analysis, Differential Thermal Analysis (DSC) and Powder x-ray Diffraction Analysis (XRD).From the results it was concluded that the Glipizide : polyvinylpyrrolidone K30 The dissolution study showed that a maximum increase in dissolution rate was obtained with glipizide: PVP K-30 solid dispersions with a higher ratio of (1:8).

Keywords: Glipizide, PVPK-30, DSC, XRD, Solid dispersions.

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INTRODUCTION

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid state in order to achieve increased dissolution rate, altered solid state properties, enhanced release of drugs from ointment, suppository bases, improved solubility and stability. Most of the drugs are passively absorbed and their rates of absorption depend upon the gradients in each case. By increasing the dissolution rate in the gastro intestinal tract, the rate of absorption is increasing. Many water soluble carriers such as mannitol, citric acid, Beta cyclodextrin, succinic acid, polyvinyl pyrrolidone and PEG have been used in the formation of solid dispersion, which can be facilitate in improving the dissolution rate of poorly soluble drugs to improve bioavailability[1,2]

It is a unique approach to present a poorly soluble drug in an extremely fluids. This dispersion consists of a microcrystalline dispersion of a poorly soluble drug in a matrix consisting of physiologically inert, readily carrier[3]

The aim of the present research work is to increase the solubility, dissolution rate and bioavailability of glipizide solid dispersion by incorporating with polyvinylpyrrolidone K30 (PVP-K30) in different ratios.

MATERIALS AND METHOD

The instruments and chemicals that are AR grade or the best possible pharma grade available were used for the experimental studies. The solid dispersion of glipizide using hydrophilic carrier polyvinylpyrrolidone K30 (PVP-K30) in different ratios. The formulated solid dispersions were characterized by the determination of Drug content, Solubility study, Thermal study, I R Spectral Analysis, Differential Thermal Analysis (DSC), Powder x-ray Diffraction Analysis (XRD), Dissolution studies and Stability studies.

Calibration Curve of Glipizide

A slight modified spectrophotometric method was developed for the quantitative estimation of glipizide[4] A stock solution of Glipizide was prepared by dissolving 100mg of Glipizide in sufficient quantity of methanol and make upto the mark with methanol. From this, 10ml was pipette out to 100ml standard flask and make upto the mark with phosphate buffer pH 7.4 solution. From this, aliquots of 2ml, 4ml, 6ml, 8ml, 10ml, 12ml, and 14ml (2,4,6,8,10,12,and 14mcg/ml) were pipette out to 100ml standard flask separately and make up to 100ml with phosphate buffer pH 7.4 solution. The absorbance of the solution was determined in UV-Visible spectrophotometer at 274 nm using phosphate buffer pH 7.4 as blank. A standard curve was drawn by relating

concentration (µg/ml) on X-axis and absorbance on Y-axis. The standard curve was used to estimate the concentration of the drug released from the solid dispersion of Glipizide.

Preparation of Solid Dispersion

Preparation of Solid Dispersions by Kneading method[5]

Solid dispersion of glipizide with PVP in four different ratios 1:2,1:4,1:6 and 1:8 were prepared by kneading method. Glipizide and PVP were weighed accurately according to these weighed ratios. These four formulations were wetted separately with water and kneaded for 30 minutes in a glass mortar and then dried at 40^0C in an oven for 24 hours. The dried mass was then pulverized, passed through sieve no:30. The resulting products were stored in vacuum desiccator for 24 hours and then passed through sieve no:60. These final products were stored in air tight containers and stored in a desiccators until further use.

Preparation of Physical Mixture[6]

The physical mixture having the same weight ratio as solid dispersions were prepared by mixing thouroghly the required amount of Glipizide and PVP (different ratios) for 10mts in a mortar. The resulting mixtures were sieved through a 100-mesh sieve. The physical mixtures were stored in air tight containers and kept in a desiccator until further use.

Characterization of Solid Dispersions[7]

Any interaction between the drug and carriers were studied the identity, any interference in drug release and to know the stability of the drug in the presence of carriers.

The above formulations were evaluated by the following studies:

1. Estimation of drug content.
2. Solubility studies.
3. Thermal Analysis.
4. Infrared (IR) spectroscopic analysis.
5. Powder X-ray Diffraction (XRD) analysis.
6. Differential Scanning Calorimetry (DSC) Analysis.
7. Dissolution studies.
8. Stability studies.

Estimation of Drug Content[8]

The drug content in all solid dispersion were estimated as per the method described by Murthy and Reddy. From all the formulation (Both in SD and PM), the amount equivalent to 100mg of glipizide was weighed accurately and transferred to a 100ml standard flask, dissolved in minimum quantity of methanol and made up to 100ml. The solution was diluted suitably with buffer solution

(pH 7.4) and the absorbance was measured at 274nm spectrophotometrically. The amount of Glipizide was calculated.

Solubility Studies[9]

Solubility determination was performed according to the method of Higuchi and Connors. The effect of different concentrations of various polymers on the solubility of Glipizide in Phosphate buffer pH 7.4 at room temperature. An excess amount of solid dispersion and physical mixture formulations were suspended in 50ml of phosphate buffer in a stoppered conical flask. The flasks are placed in a rotary flask shaker for 8 hours. 10ml aliquots were withdrawn and filtered through whatman filter paper No:41. The filtrate was collected and diluted suitably and drug content was determined spectrophotometrically at 274nm.

Thermal Analysis[10]

The thermal analysis studies were carried out to ascertain the effect of heating on the stability of drug. In this method a sample of the drug is placed in a capillary melting point tube and heated gradually until the drug is melted. The melting point of Glipizide is 208-209^{0}C. The pure Glipizide was melted to above the melting point and allowed to solidify rapidly. The solidified mass was again melted to find out the effect of heating process on the stability of the drug.

IR Spectral Analysis[11]

It is used to study the interactions between the drug and polymers. The drug and polymers must be compatible with one another to produce a product stable, efficacious and safe. IR spectral analysis of pure drug and highest proportion of polymers (Drug: polymer ratio is 1:8) was carried out. The peaks and spectrum produced by the pure drug were compared with the peaks and spectrum of the combination of drug and polymers.

Powder x-Ray Diffraction[12]

The X-ray powder diffraction spectrum were obtained at room temperature using a PW 1710 X-ray diffractometer (Philips, Holland) with Cu as anode material and graphite monochromatic, operated at a voltage of 40kV, current 35 mA. The samples were analyzed in the 2θ angle range of 5^0-70^0 and the process parameters were set as scan step size of 0.02^0 (2θ), scan step time of 29.5s.

Deferential Scanning Calorimetry Analysis (DSC)[13]

The DSC thermograms were recorded using differential scanning calorimetry (DSC) (Shimadzu DSC-60 Japan). The experiment was done in non-hermetically sealed aluminium pans; the heating rate was 10^0/min and using nitrogen as purge gas (20ml/min). Samples of approximately 5mg were weighed into aluminium pans. The temperature range was 25-300^0.

DISSOLUTION RATE STUDIES[14]

In vitro drug release

In vitro drug release of all the formulations were carried out using USP type II dissolution apparatus (paddle type). The dissolution medium, 900 ml pH 7.4, was placed in to the dissolution jar maintaining the temperature of 37 ± 0.5^0 C and rpm of 50. The solid dispersions and physical mixtures equivalent to 5mg of glipizide was filled in capsule and placed in jar of dissolution apparatus. The apparatus was allowed to run for 3 hours. 5 ml sample was withdrawn after every 15 mts interval upto 3 hours using 5 ml pipette. The fresh dissolution medium (37^0C) was replaced every time with the same quantity of dissolution medium. Collected samples were suitably diluted to 100 ml with pH 7.4 in 100 ml standard flasks and analyzed at 274 nm using pH 7.4 as blank. The percentage of drug release was calculated.

Stability Studies[15]

The stability study aims at determining the result of aging and storage under various conditions and the effect on the release characteristics and chemical stabilities of the solid dispersions. Stability studies were carried out to evaluate the stability of glipizide, the solid dispersion and physical mixture formulations after storing at 45^0 ± 2^0Cfor 60 days. About 1 gm of pure Glipizide and all SD formulations with highest ratio (1:8) were taken in well closed containers and stored at 45^0C±2^0C for 60 days. Samples equivalent to 5mg of Glipizide were removed from all the stored preparations after 60 days and analyzed the drug content and percentage of drug release.

RESULTS AND DISCUSSION

Estimation of Drug Content

The entire formulation equivalent to 100mg of Glipizide was dissolved in sufficient quantity of methanol and made up to 100ml with methanol. The solution was suitably diluted with buffer pH 7.4 and drug content was estimated spectrophotometrically at 274 nm. The results are presented in Table-1.

Table-1 Estimation of Drug Content

Drug :carrier ratio	PVP K-30 Preparations	
	PM	SD
1:2	95.71±0.13	95.35±0.12
1:4	96.78±0.10	96.78±0.17
1:6	95.71±0.14	95.71±0.13
1:8	97.85±0.14	97.78±0.11

The results showed that the percentage of glipizide was ranging from 93.9% to 98.2% in all formulations. This revealed that the drug is uniformly dispersed in all the formulations and

confirms the homogeneous mixing of drug and carriers. However a slight variations of the percentage of glipizide in the carriers may be due to physical loss of the drug during preparation.

Solubility Studies

Maximum solubility enhancement was found in 1:8 ratios. PVP K-30 gave maximum enhancement solubility. It may be due to reduction in particle size and retarding the crystallisation of poorly water soluble drugs. The results were Tabulated in Table 2.

Table-2 Solubility of Glipizide In the Presence of Carriers

S.No	Drug: Carrier Ratios	Pure drug (µg/ml)	With PVP K-30	
			PM	SD
1.		8.12±1.08		
2.	1:2		24.12±1.62	31.78±1.42
3.	1:4		28.11±1.08	35.0±0.86
4.	1:6		31.27±1.25	38.21±0.91
5.	1:8		33.54±1.60	41.34±1.26
			33.54±1.60	41.34±.26

Thermal Analysis

From the results it was observed that the melting point of Glipizide does not change after thermal studies. It was proved that Glipizide was thermally stable.

IR spectral analysis

IR studies of pure glipizide, PVP K-30 and solid dispersions and physical mixtures containing higher proportion of carriers (1:8) were carried out to study the interaction between the drug and carriers used. The results are presented in Table 3& 4 and Figures 1&2.

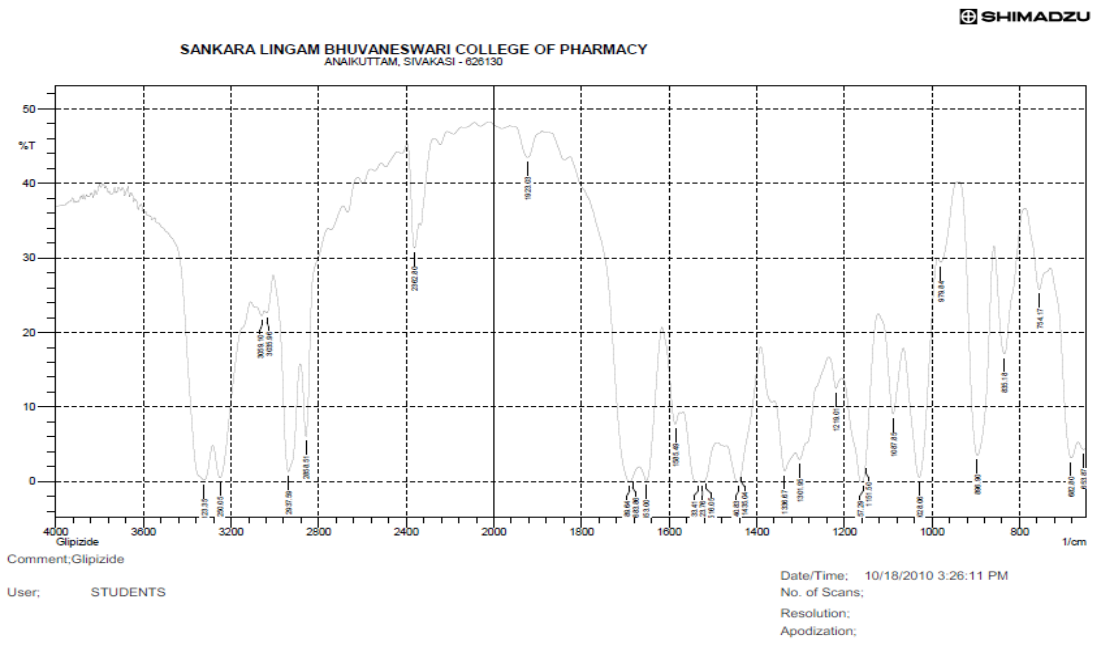

Figure:1: IR Spectrum of Glipizide

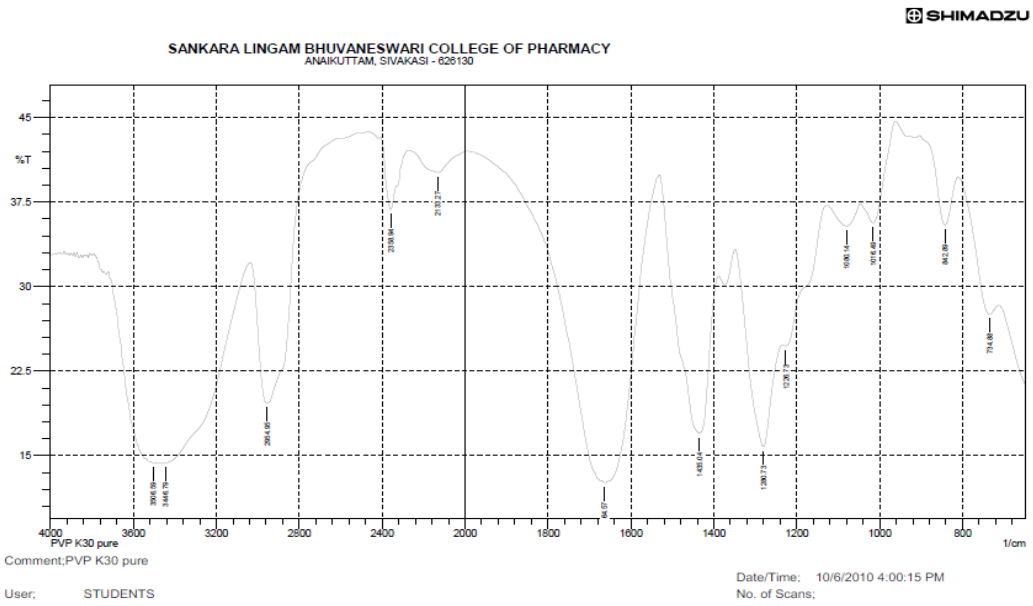

Figure:2 IR spectrum of pure PVP K-30

Table-3 IR Spectrum of Pure Glipizide

S.NO	Wave number (CM^{-1})	Functional Groups Present
1.	3323.35-3250.05	NH Doublet/ Secondary amine
2.	3059.10	Aromatic CH
3.	2937.59	Aliphatic C-H
4.	2858.51	CH_2 Asymmetric stretching
5.	1689.64-1653	C = O Diketone
6.	1533.41	C = C
7.	1028.06	S = O
8.	896.90	C-N Stretching

Table-4 IR Spectrum of Pure PVP K-30

S.NO	Wave Number (CM^{-1})	Functional Groups Present
1.	3056.59	O – H stretching
2.	2954.95	CH Aliphatic stretching
3.	1664.57	C=O Stretching
4.	1435.04	CH bending
5.	1280.73	C-N Stretching
6.	1080.14	C-O Stretching
7.	1016.49	Bending vibration

The results of IR spectral analysis showed the peaks and spectrum of the spectra were similar in all cases. This indicates that there was no chemical interaction or bonding decomposition of glipizide prepared in the form of solid dispersions and physical mixtures.

X-ray Diffraction Studies

XRD spectrum indicated that glipizide was present as a crystalline material with major characteristic, intense diffraction peaks appearing at a diffraction angle of 2θ at 3.73, 7.33,10.92,

15.54, 16.81, 17.90, 18.54, 19.11, 21.68, 22.06, 23.44, 25.18. in the range of intensities of 20.1% - 100%

Solid dispersions using PVP K-30, the characteristic peaks are less and the intensity was found between 0.5% to 51.7%. When the drug : polymer ratio was increased, the crystalline peaks are widened and less number of peaks also appeared. It was in the following order 1:8 > 1:6 > 1:4 > 1:2. The result shown that the maximum change of amorphous form from crystalline form was in the highest ratio 1:8 of PVP K-30. (Figures 3,4 & 5 and Table 5,&6).

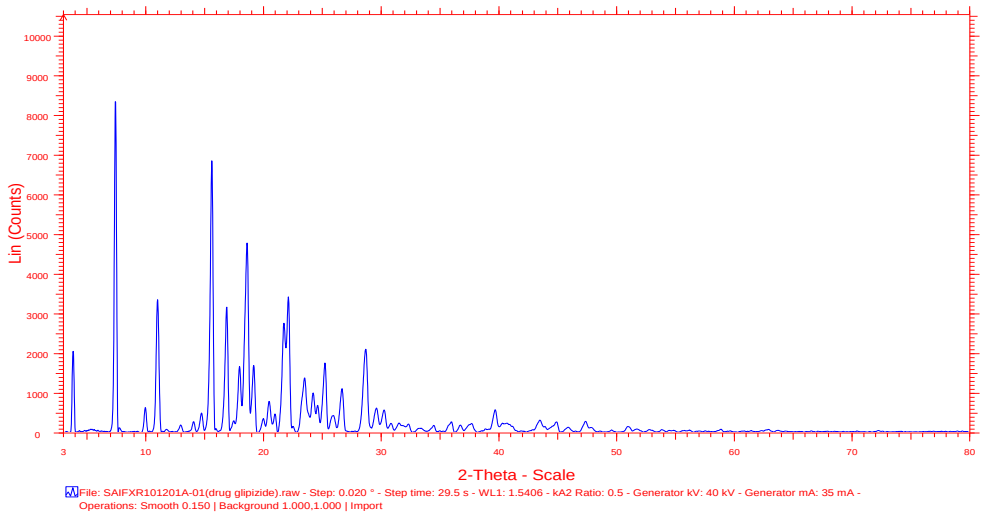

Figure:3 XRD Spectrum of Pure Glipizide

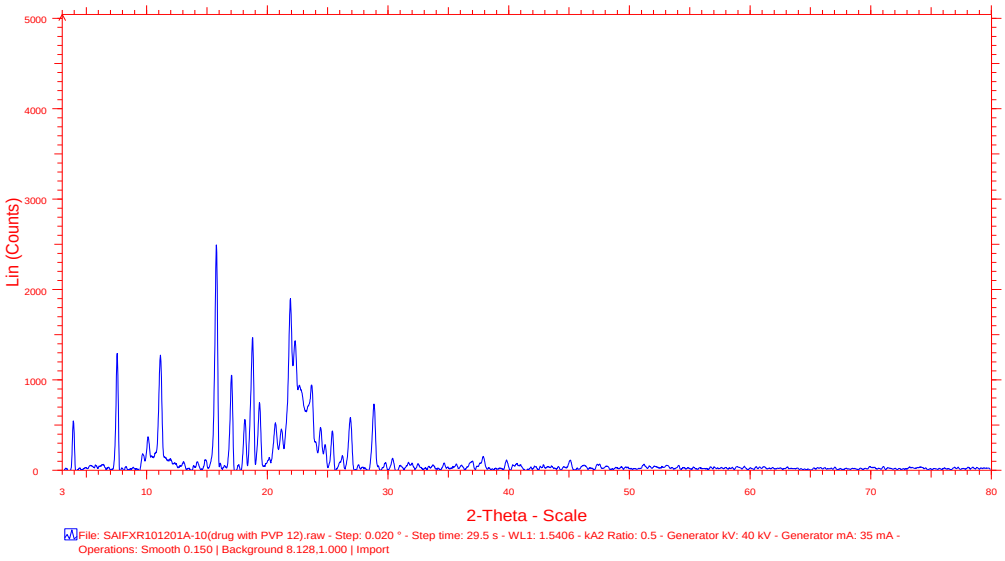

Figure:4 XRD Spectrum of Pure Glipizide+PVP k 30

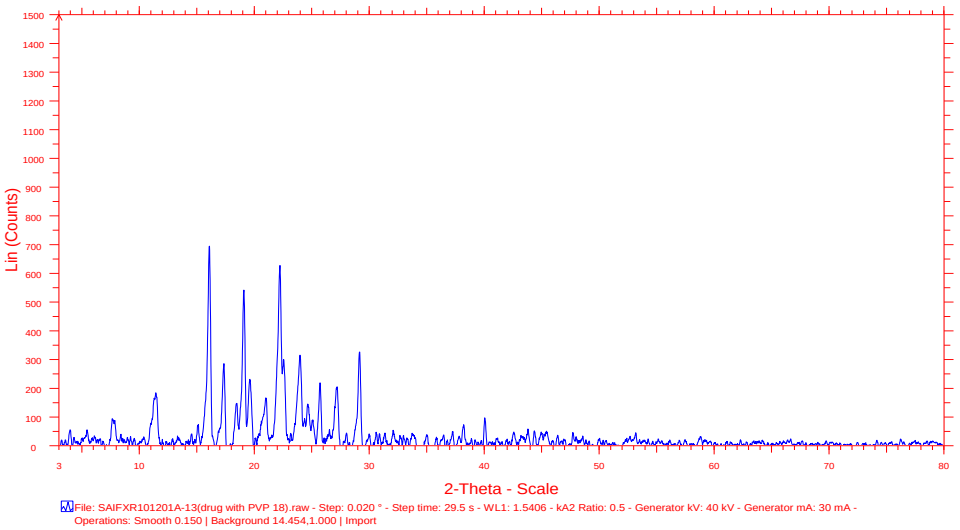

Figure:5 XRD Spectrum of Solid Dispersion of Glipizide With PVP (1:8)

Table-5 XRD Pattern of Pure Glipizide

Angle 2-Theta	Intensity % %
3.723	24.4
7.327	100
10.919	40
15.541	82.1
16.807	37.8
17.902	19.8
18.543	57.2
19.11	20.1
21.684	32.9
22.059	40.9
23.443	16.3
25.176	20.9

Table-6 XRD Pattern of Pure Glipizide With PVP k-30

S.No.	Angle $2\theta^0$	Intensity (%) 1:2	1:4	1:6	1:8
1.	3.82	21.5	31.2	21	6.0
2.	7.46	51.6	45.2	15.7	2.7
3.	10.605	7.2	4.5	51.3	10.9
4.	15.215	3.3	0.9	32.3	14.4
5.	16.961	41.8	42.2	12	6.9
6.	17.642	0.8	2.3	3.1	0.5
7.	18.067	22.1	32.3	46.2	20.8
8.	19.283	29.7	33.9	30.1	32.9
9.	21.471	19.4	10.1	51.7	10.7
10.	22.597	37.5	34.5	8.5	34.0
11.	23.327	28.2	34.1	21.7	17.4
12.	25.082	3.0	21.7	6.6	8.8

The results proved that the crystalline nature of glipizide has been changed from crystalline form to amorphous form in all solid dispersion preparations using PVP K-30.

Differential Scanning Calorimetry (DSC) Studies

For confirmation of change of crystallinity into amorphous form of glipizide, DSC study was applied. The thermograms of pure glipizide and solid dispersions with different proportions of carrier were also presented for comparison.

Solid dispersions prepared with PVP K-30 in all four ratios, two endothermic peaks were observed in the range of 177.20^0-186.46^0C (widening peak) and 49.05^0-57.05^0C (broad peak). The widening and broad peaks may be due to highly dispersed form of drug in the solid dispersion preparations. The intensity of the peaks were also smaller. These results proved that the crystalline form of drug became amorphous in solid dispersion preparations. The results were represented in figure 6 & 7.

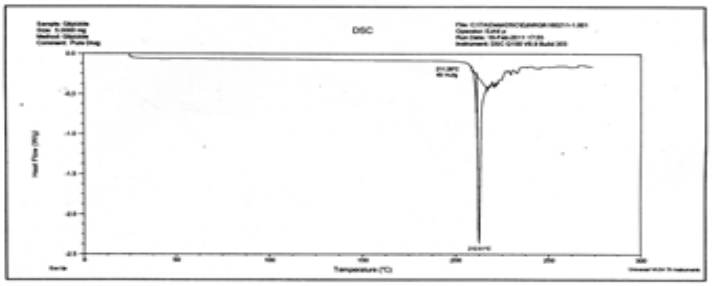

Figure:6 DSC Thermogram of Pure Glipizide

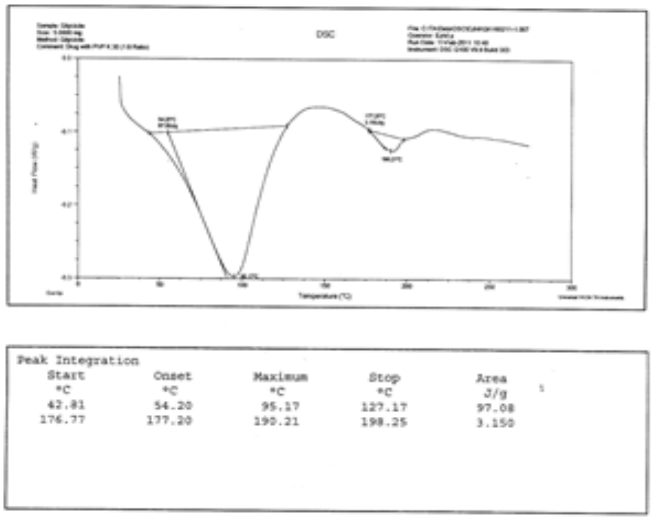

Figure: 7 DSC Thermogram of Pure Glipizide with PVP K-30 (1:8)

Dissolution Studies

The dissolution rate studies were performed to evaluate the dissolution character of glipizide from solid dispersion (SD) and physical mixture (PM) the result was compared with pure drug and marketed sample of glipizide (Glynase). The percentage of drug release from all these formulations, marketed sample and pure drug is presented in Table 7.

The percentage release of glipizide from pure drug (GLZ), marketed sample (MS) and from SD formulations and PM formulations using carrier PVP K-30. It was found that 25.74% in pure Glipizide, 31.94% in Marketed sample and 52.61% (PM) and 73.12% (SD) in PVP K-30 formulations at 180 minutes. The result showed that the percentage release of glipizide was more in PVP K-30 than Marketed Sample and pure GLZ.

Table-7 Dissolution profiles of pure Glipizide, marketed sample of Glipizide (Glynase5mg), physical mixture (PM) and solid dispersion (SD) using PVP K-30

Time (min)	Pure Glipizide	Marketed sample of Glipizide	Percentage drug release							
			1:2		1:4		1:6		1:8	
			PM	SD	PM	SD	PM	SD	PM	SD
0	0	0	0	0	0	0	0	0	**0**	**0**
15	2.88±0.17	9.00±0.11	3.62±0.10	40.12±0.10	10.20±0.10	54.86±0.10	15.68±0.09	55.12±0.12	21.64±0.12	57.14±0.11
30	6.28±0.10	11.26±0.10	8.76±0.10	43.17±0.10	14.22±0.07	57.14±0.09	21.16±0.12	59.18±0.09	27.81±0.14	61.27±0.10
45	9.72±0.07	16.24± 0.11	14.62±0.08	48.59±0.09	19.16±0.08	60.38±0.09	25.80±0.09	62.10±0.13	32.68±0.12	62.91±0.11
60	12.06±0.08	19.50±0.12	16.14±0.08	54.16±0.08	26.81±0.11	62.58±0.07	29.48±0.12	63.58±0.11	34.02±0.12	66.72±0.10
90	15.78±0.10	21.74± 0.11	20.52±0.08	58.18±0.11	27.54±0.10	63.21±0.12	34.96±0.08	64.17±0.09	41.41±0.12	67.15±0.10
120	18.8±0.34	24.72±0.11	23.90±0.11	59.65±0.10	31.79±0.09	66.13±0.09	36.47±0.11	67.40±0.12	44.08±0.09	67.58±0.09
150	21.96±0.08	29.18±0.09	27.61±0.11	61.75±0.12	36.04±0.09	68.20±0.06	41.96±0.09	68.12±0.12	48.69±0.09	70.46±0.10
180	25.74±0.08	31.94±0.09	34.74±0.09	68.16±0.10	40.78±0.11	69.72±0.10	46.16±0.12	70.79±0.09	52.61±0.12	73.12±0.12

Table-9 Stability Studies of Glipizide Solid Dispersions Stored

Days	Formulations Drug: Carrier Ratio	Percentage of drug release (%) Time in minutes*							
		15	**30**	**45**	**60**	**90**	**120**	**150**	**180**
	PUREDRUG	2.33±0.11	5.23±0.12	8.67±0.21	10.32±0.16	13.25±0.09	16.52±0.19	19.69±0.08	22.30±0.14
60	PVP K-301:8	53.31±0.05	59.64±0.11	59.46±0.10	61.87±0.13	64.89±0.18	64.98±0.11	64.65±0.10	68.71±0.16

AT 45^{0}C – Percentage of Drug Release After 60 Days Interval

Stability studies

The stability study of the developed formulations (all SD formulation with 1:8 ratios) was carried out at 45^0C for a period of 2 months to investigate the influence of temperature. After 2 months, the drug content analysis and drug release studies were carried out and the results are presented in Table 8&9.

Table 8 Stability Studies of Glipizide Solid Dispersions Drug Content Estimation At Temperature (45^0c)

Temperature 45^0c	Formulations Drug: Carrier (1:8 Ratios)	Percentage of Glipizide* Number of Days			
		0	20	40	60
	Pure drug	100±0.13	100±0.11	99.68±0.19	99.31±0.09
	Glipizide: PVP K-30	97.21±0.09	96.94±0.13	96.16±0.15	97.37±0.11

Solid Dispersion of Glipizide was prepared by using the carrier PVP K 30 in different ratios. This revealed that the drug is uniformly dispersed in all the formulations and confirms the homogeneous mixing of drug and carriers. The improvement in solubility was observed in all physical mixtures and solid dispersions. However increase in the proportion of hydrophilic carriers resulted in an increase in the solubility of glipizide in all solid dispersion than in physical mixture formulations.

Thermal study was carried out to find out the decomposition of the drug. From the results it was observed that the melting point of Glipizide does not change after thermal studies. From the IR study indicates that there was no chemical interaction or bonding decomposition of glipizide prepared in the form of solid dispersions and physical mixtures. From the DSC studies all solid dispersion preparations with PVP k-30 using four different ratios, the major characteristic crystalline peaks are disappeared and the intensity of peaks was also significantly less.

Dissolution profile of all solid dispersions with PVP k-30 showed increase of dissolution rate than pure drug and marketed sample . This increase in all solid dispersion preparations may be due to wettability improvement and local solubilization effect of the carrier at the diffusion layer.

In addition to these factor, enhancement of dissolution of drug from PEG 6000 and PVP K-30 SD preparations could be attributed to the amorphous state of the drug in solid dispersion, absence of aggregation and particle size reduction.

There was no significant change in drug content and dissolution of glipizide from three solid dispersions prepared with PVP K-30 (1:8 ratio) after 2 months at 45^0C. The improved stability of SD preparations could be due to the hydrogen bonding in between the drug and hydrophilic

carriers. It was indicated that hydrophilic carriers contributed towards protecting the dispersion state of the drug. [16]

CONCLUSION

From these observations, glipizide may be tried for the formulation development of liquid dosage form using PVP K-30 carrier over conventional marketed formulation in order to maximize the bioavailability and therapeutic efficacy.

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