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Preparation and Evaluation of Fast Disintegrating Tablet with Gliclazide Solid Dispersions

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ABSTRACT

The main objective of the present study was to enhance the solubility of BCS Class-II drug, gliclazide, and formulate it into a fast-disintegrating tablet to give faster dissolution and improve systemic bioavailability. Solid dispersions of gliclazide were prepared using PVP-K30 by a solvent evaporation method, β-cyclodextrin by kneading method, and physical mixtures using PEG-600 and poloxamer with varying ratios of drug and polymer. Solubility studies of solid dispersions was obtained in water and 0.1N HCl at 37°C. The solubility of gliclazide was highly increased in P1 formulation developed by using Drug: PVP K-30 in 1:0.5 ratio by the solvent evaporation method. Further, it was selected for fast-disintegrating tablet formulation using Sodium Croscarmellose and microcrystalline cellulose as super disintegrants. The higher the concentration of super disintegrant resulted in reduction of disintegration time and higher % drug release within a short time. F3 formulation containing the highest concentration of Croscarmellose showed 99.59% drug release at 20 mins in 0.1N HCl as dissolution medium. FTIR spectra showed stability of gliclazide in presence of all other excipients and polymers. XRD studies indicated the reduced intensity of distinct peaks of gliclazide in solid dispersion probably the reason for the reduced crystallinity of drug and increase in its solubility.

INTRODUCTION

Oral route is the most convenient and commonly used route of drug delivery due to the convenience in administration, high patient compliance, cost-effectiveness, unit dosage form and flexibility in formulation.[1]However, the major challenge in formulating the oral dosage form is its poor bioavailability. Solubility is the main constrain to attaining desired therapeutic concentration in the bloodstream. The BCS Class-2 drugs have poor solubility but high permeability thus increasing their solubility can result in improved therapeutic efficiency. The drug solubility can be increased by many ways out of which the most widely used and convenient is solid dispersions method. Solid dispersions when formulated as fast disintegrating tablet significantly increase the dissolution rates of the drug.

Solid dispersion: The term solid dispersion implies the dispersion of one or more active pharmaceutical ingredients in an inert carrier or matrix (hydrophilic) at solid-state which can be prepared by various methods like melting, solvent evaporation, fusion process, hot-melt extrusion, dropping methods or other techniques of solid dispersion.[2]Various polymers like PVP K-30, PEG, Poloxamer are used in formulating the solid dispersions due to their strong hydrophilic properties and their capability to form molecular abducts with many compounds.

Fast Disintegrating Tablet: A fast-disintegrating tablet is intended to disintegrate within a short time interval as soon as it meets the solvent and provides quick onset of action. Various methods for formulating the Fast-Disintegrating Tablets are direct compression, wet granulation, mass extrusion, melt granulation and others. Super disintegrants like Sodium Croscarmellose, microcrystalline cellulose, cross povidone, and sodium starch glycolate are used.[3]

BCS Class-II drugs are highly permeable but the rate-limiting step is its solubility in the solvent. One of the most common drugs of BCS class II is Gliclazide. It is used in the treatment of the most common type of diabetes, type 2 (DM2) diabetes mellitus.[4]Gliclazide being a weak acid (pKa 5.8) has a lower solubility in acid medium and this could be a problem in formulating an immediate release oral dosage form as the dose should be instantly released in the upper part of GIT (predominantly in stomach). Thus, enhancing the solubility of Gliclazide and then formulating its fast-disintegrating tablet will result in enhancing its bioavailability and therapeutic efficacy.

MATERIAL AND METHODS:

MATERIALS:

Gliclazide (API), PVP-K30, β-cyclodextrin, Poloxamer, PEG 6000, Croscarmellose sodium, and micro-crystalline cellulose were the main polymers used for research work. All other ingredients and solvents used were of laboratory grade.

METHODS:

Pre-formulation Studies:

It included organoleptic studies like appearance, colour, solubility analysis and melting point determination, estimation of λ max and plot of Calibration Curve by UV-VIS spectroscopy.

Preparation of Solid Dispersion: Solid Dispersions of Gliclazide (GLZ) and polymers were prepared in different Drug: Polymer ratios by following three methods: -

1. Physical mixture
2. Kneading method
3. Solvent evaporation method

Physical mixture: Physical mixture was prepared by blending the drug and polymer in a mortar for ten minutes to obtain a homogeneous mixture. The resulting mixture was sieved through 60 mesh sieve and stored in an airtight container and placed in desiccators for further evaluation.[5]

Kneading method: A mixture of Gliclazide (GLC) and β-cyclodextrin (CD) was wetted with a mixture of acetone and water (1:1) and kneaded thoroughly for 3 min in a glass mortar. The paste formed was scrapped through sieve no 100, dried and stored in desiccators for further study.[6]

Solvent evaporation: Accurately weighed quantities of Gliclazide and PVP K-30 were homogeneously dissolved in a minimum amount of methanol and acetone solution mixture. The solvent solution was rapidly evaporated with the aid of mild heat and continued stirring to form a uniform solid mass. The solid mass was then crushed and stored in desiccators for further studies.[7]

Table No. 1: Formulation Code for Solid Dispersion.

Sr.No.	Method	Polymer	Ratio	Code
1	Physical Mixture	Poloxomer 407	1:5	PM1
		PEG 6000	1:5	PM2
2	Kneading Method	β-cyclodextrin	1:5	KM1
			1:10	KM2
			1:15	KM3
3	Solvent Evaporation Method	PVP-K30	1:0.5	P1
			1:1	P2
			1:1.5	P3

Evaluation of solid dispersion batches [8]

Fourier transforms infrared spectroscopy: FTIR spectra of GLZ and solid dispersion were recorded by applying samples to FTIR Spectrophotometer.

Samples were prepared using KBr pellets and were scanned from 4000 to 400 cm^{-1}.

X-ray diffraction (XRD): The degree of crystallinity is one among the factors influencing the solubility and dissolution rate. Hence, the crystalline nature of drugs and extend of its conversion to amorphous form was studied by X-Ray Diffractometry. XRD patterns were studied using an X-Ray diffractometer.

Solubility studies: To evaluate the rise in solubility of Gliclazide from solid dispersions, saturation solubility measurements were conducted and compared with that of pure drug. The known quantity of solid dispersions was added to the solvents of distilled water and 0.1N HCL to obtain a saturated solution. This saturated solution was then filtered, suitably diluted, and analyzed by UV-VIS spectrophotometer at 225.2nm and 228.2nm, respectively.

Determination of drug content: The solid dispersion corresponding to 10mg of Gliclazide was weighed accurately and dissolved in 50 ml of methanol and volume was makeup up to 100ml. The drug content was noted at 228 nm by UV spectrophotometric analysis after suitable dilutions.

Determination of percentage yield: Percentage practical yield were calculated to understand the percent yield or efficiency of any method; thus, it helps in the selection of appropriate

method production. Solid dispersion was collected and weighs to determine percentage yield from the subsequent equation.

$$\text{Percent yield} = \frac{\text{Wt. of prepared solid dispersion}}{\text{Wt. of drug} + \text{Wt. of carriers}} \text{ X } 10$$

Preparation of Immediate Release Drug Delivery System (Fast Disintegrating Tablet) [9-12]: The fast-disintegrating tablet of Gliclazide solid dispersion showing the highest improved solubility was selected for preparing the fast-disintegrating tablet. It had been prepared by using super disintegrants- cross carmellose sodium and microcrystalline cellulose by direct compression method. All materials were accurately weighed and passed through 60# screen before mixing and transferred to glass mortar and triturated until mixed uniformly. The mixture was then evaluated for pre-compression parameters. Then the powder mixture was compressed into tablets by using a rotary tablet punching machine using the punch size of 6mm. (Table 2)

Table No. 2: Formulation Table of Fast disintegrating tablet.

Sr.No	Drug/ Ingredient	P1 Batch		
		F1	F2	F3
1	**Solid dispersions (mg)**	45	45	45
2	**Cross carmellose sodium(mg)**	1.5	4.5	7.5
3	**MCC (mg)**	22.5	22.5	22.5
4	**Mannitol (mg)**	15	15	15
5	**Mg stearate (mg)**	3	3	3
6	**Talc(mg)**	3	3	3
7	**Dicalcium phosphate (mg)**	60	57	54
8	**Total (mg)**	150	150	150

Pre-compression evaluation of powder [13]

The powder blend was evaluated for the flow properties by calculating Carr's Compressibility Index, Hausner's Ratio and Angle of Repose.

Table No. 3: Formulae for Pre-Compression Evaluation

Sr.No.	Property	Formula
1	Bulk Density	$\text{Bulk density (BD)} = \frac{\text{weight of powder(M)}}{\text{bulk volume (Vb)}}$
2	Tapped Density	$\text{Tapped density (TD)} = \frac{\text{weight of powder (M)}}{\text{Tapped volume(Tb)}}$
3	Carr's Compressibility Index	$\text{Carr's index (I)} = \frac{\text{tapped density(TD)-bulk density(BD)}}{\text{tapped density(TD)} \times 100}$
4	Hausner's Ratio	$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{bulk density}}$
5	Angle of Repose	$\text{Angle of repose } (\theta) = tan^{-1}\frac{h}{r}$

Evaluation of fast disintegrating tablet: [14-17]

Weight Variation: The total weight of 20 tablets from each formulation was noted and the average weight was calculated. The individual weights of the tablets were also determined accurately, and the weight variation was calculated.

Hardness: It is a measure of the force required to break the tablet. The force is measured in kg. The hardness of about 3-5 kg/cm^2 is satisfactory for uncoated tablets. The hardness of 10 tablets from each formulation was determined by Monsanto hardness tester.

Friability Test: Digital Programmable Friability Apparatuswas employed for finding the friability of the tablets. 20 tablets from each formulation were weighed and placed in Apparatus that rotated at 25 rpm for 4 minutes. The tablets were dedusted and weighed again. The percentage of weight loss was calculated.

Disintegration Time: The six-glass tube disintegration apparatus each containing 1 tablet was placed in 1 litre beaker of distilled water, such that the tablets remain below the surface of liquid on their upward movement and descend not closer than 2.5 cm from the bottom of the beaker and the time for the tablet to start to disintegrate was noted down.

***In-vitro* Dissolution Study** [18]**:** The dissolution test was performed in the USP Type II dissolution testing apparatus (LABINDIA). 900 ml of 0.1 N HCl was taken as the dissolution medium at 50 rpm and 37 ºC ± 0.5 ºC. Five milliliters of aliquots were periodically withdrawn, and the sample volume was replaced with an equal volume of fresh dissolution

medium. The samples were analyzed spectrophotometrically at 228.2 nm, and percent drug release was calculated.

RESULTS AND DISCUSSIONS

Preformulation Studies:

Organoleptic Analysis: The Gliclazide was white crystalline powder with no odour. The Melting Point was determined by the Capillary Tube Method which was found in the range of 180-182^{0}C. The Solubility of Pure drugs in water and 0.1N HCl was found to be 0.4275mg/ml and 0.0272mg/ml respectively.

UV Spectroscopy: A standard solution of gliclazide was prepared in water, 0.1NHCl and methanol separately. This solution was scanned in the range of 400-200 nm. Maximum absorbance and Standard calibration curve were determined for the same.

Table No.4: Lambda Max Values

Sr.No.	Solvent	λ_{max}
1	Water	225.2nm
2	0.1N HCl	228.2nm
3	Methanol	228.0nm

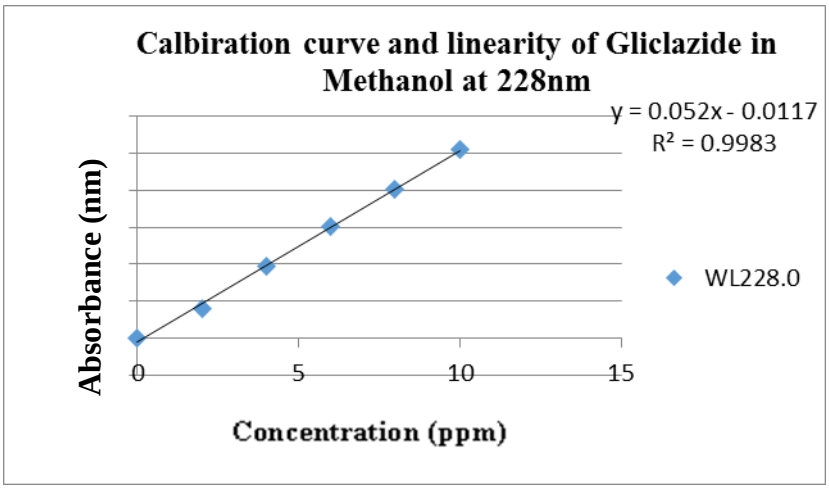

Figure No.1: Calibration curve of Gliclazide in Methanol

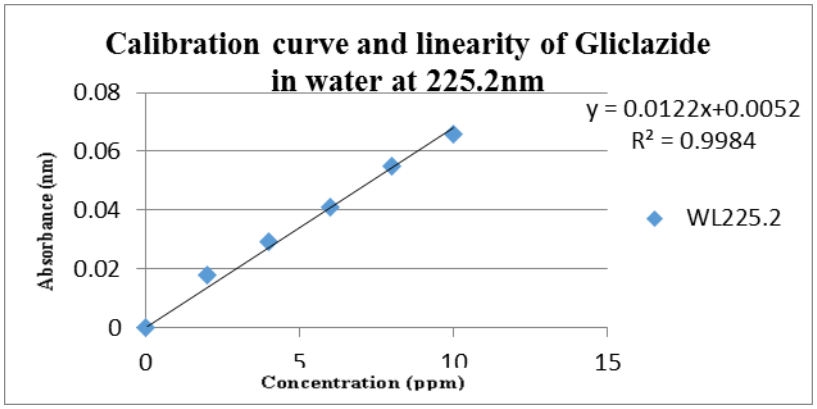

Figure No.2: Calibration Curve of Gliclazide in Water

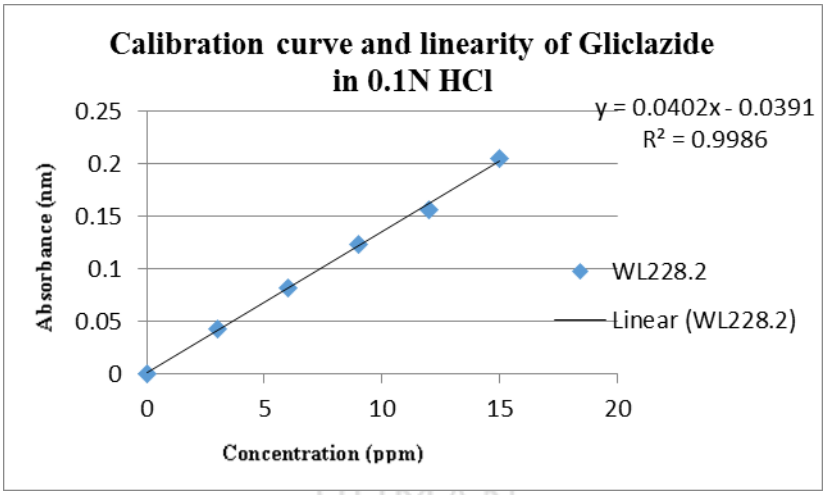

Figure No. 3: Calibration Curve of Gliclazide in 0.1N HCl

Fourier Transforms Infra-Red Spectroscopy:

The Gliclazide spectrum exhibit characteristics peak was shown in Table 6. The FTIR spectrum of GLZ and Batch P1 spectra gave peak intensity for the free carbonyl group stretching mode at 1703.14 cm^{-1} and 1714.2 cm^{-1}respectively. For C-H stretching vibration, GLZ showed the characteristic peak at 2941 cm-1 that slightly shifted in batch P1 at 2926 cm-1. For –C=C– Aromatic ring 1595.13 was for Gliclazide and 1569.34 for P1 batch. The FTIR spectrum of GLZ obtained a characteristic peak which was slightly shifted in P1 batch spectra. These results indicated that GLZ and P1 interact via strong hydrogen bonds then shifting formulation from crystalline to amorphous. This indicated that there was no change in the internal structures and conformation of these samples and no interaction between the drug and the polymer.

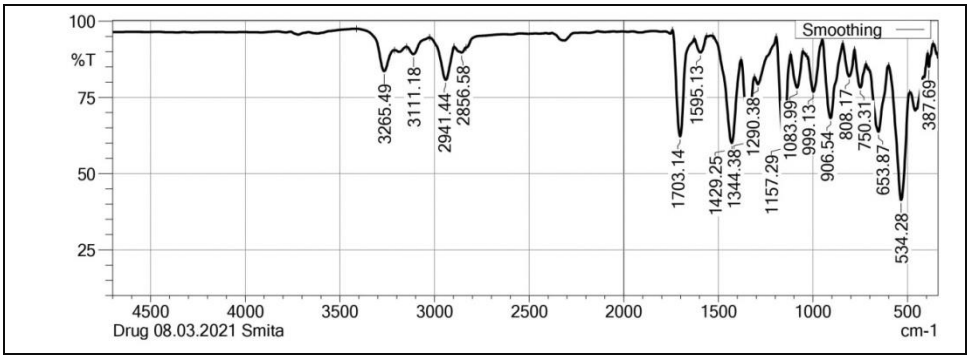

Figure No.4: FTIR Spectra of Gliclazide

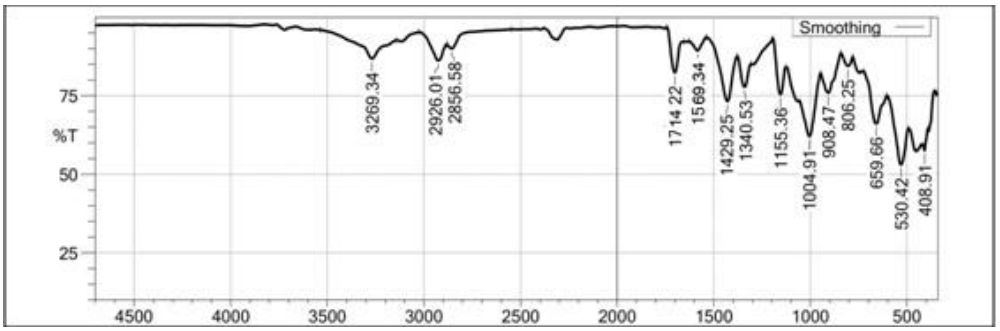

Figure No. 5: FTIR Spectra of P1 batch

X-Ray Diffraction (XRD):. In the XRD patterns, highly intense and less diffused peaks show the crystalline nature of the drug. The XRD patterns of pure gliclazide and batch P1 were similar just the peak height for batch P1 was small than that of pure gliclazide drug. The peak height is affected by crystal size and crystallinity. The smaller peak heights of batch P1 indicated reduced crystal size and crystallinity as compared to gliclazide.

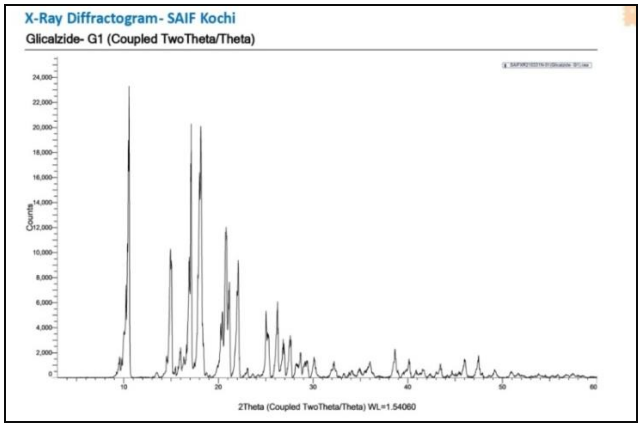

Figure No.6: X-Ray Diffractogram of Gliclazide

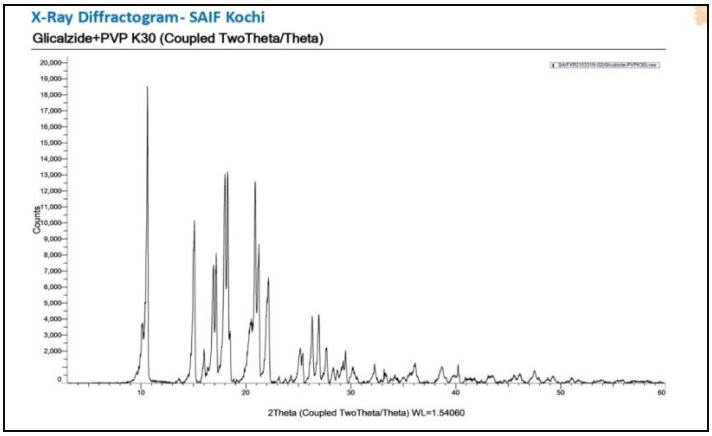

Figure No.7: X-Ray Diffractogram of Batch P1

Solid Dispersion Evaluation Results: The solubility of all solid dispersions was found to be increased when compared with the pure drug. Out of the entire formulations, the P1 batch showed the highest solubility increase and thus it was considered for further tablet preparation.

Table No. 5: Saturated Solubility of drug & solid dispersion batches

BATCHES	Pure Drug	PM1	PM2	P1	P2	P3	KM1	KM2	KM3
Solubility in water (mg/ml)	0.4275	0.90	1.375	36.83	28.66	21.50	3.175	2.341	3.583
Solubility in 0.1N HCl (mg/ml)	0.0272	0.45	0.357	31.25	25.14	20.85	0.740	0.395	0.452

Drug Content and Percentage Yield.

The drug content study was carried out to determine the percent amount of drug incorporated in the solid dispersions. The drug content for all formulations was within 95-98%.

The percent practical yield was found in the range of 91-95% which was within the limit.

Table No. 6: Drug content & percentage yield of all batches

	PM1	PM2	P1	P2	P3	KM1	KM2	KM3
Drug content (%)	95.75	96.08	98.58	98.43	97.82	96.52	97.62	98.83
Percentage yield (%)	95.22	93.12	92.96	91.51	92.86	91.58	93.12	93.44

Evaluation of Tablets

Pre-Compression Evaluation Results: The results for pre-compression evaluation are shown in table no-6. The angle of repose was in the range of 26-31^{o} which shows good flow properties. Hausner's ratio was in the range of 1.13-1.20 which shows good flowability. Carr's compressibility index was found in the range of 11-17. Thus, the powder blend possessed good flow properties.

Table No. 7: Pre-Compression Results

	Bulk Density	Tapped Density	Carr's Compressibility Index	Hausner's Ratio	Angle Of Repose
F1	0.4285	0.5172	17.15	1.20	31.16
F2	0.5	0.5660	11.66	1.13	26.71
F3	0.375	0.4347	13.75	1.15	26.18

Post Compression Evaluation Results

The hardness and friability were found within the range of 2.5-5 kg/cm2 and less than 1% respectively which shows good mechanical resistance of tablets. Uniformity of weight was found as in the specifications of Indian Pharmacopeia. The lowest disintegration time was seen by the F3 formulation with 42 secs. Maximum drug release was observed for all three formulations within 20 mins among which F3 showed the highest % drug release i.e., 99.59% in 20 mins.

Table No.8: Post compression results

PARAMETERS	F1	F2	F3	RANGE
Hardness (Kg/Cm^2)	3.5	3.4	3.2	2.5-5.0
Friability (%)	0.29	0.33	0.22	0.5-1.0
Weight variation (mg)	150.34	150.36	150.46	-
Disintegration Time (Secs)	53	47	42	-
Drug Release At 20 Mins (%)	92.54	98.63	99.59	-

Table No.9: %Drug release for P1 Batch

Time (mins)	% Drug Release for P1 Batch		
	F1	F2	F3
0	0	0	0
5	64.41	72.72	77.25
10	78.95	84.32	88.88
15	86.10	93.74	95.34
20	92.54	97.24	99.59
25	94.54	99.26	99.39
30	97.29	99.06	98.43

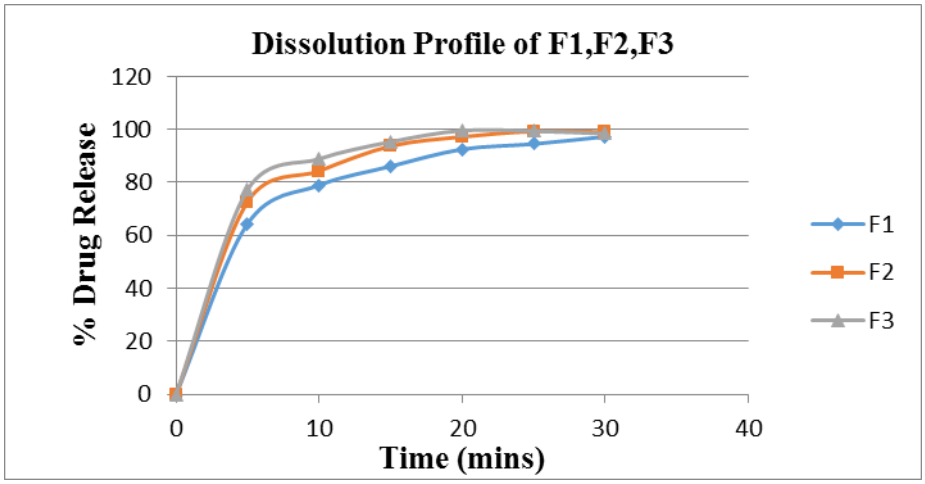

Figure No. 8: Dissolution profile of F1,F2 & F3

CONCLUSION:

The results of solubility studies revealed that gliclazide is practically insoluble in water as well as in 0.1N HCl. But the preparation of its solid dispersions using water-soluble carriers showed a drastic increase in its solubility. Hence developing solid dispersion of the drug and then an immediate-release tablet could be an industrially feasible solution for resolving the drug-related poor bioavailability issue. Amongst all the solid dispersions formulated, the highest dissolution was observed with P1 (Gliclazide: PVP-K30; 1:0.5).

The micromeritic parameters of the pre-compression powder blend indicated excellent flow properties. The tablets were found to be mechanically stable as indicated by hardness and friability tests. The tablet disintegration time was reduced on increasing the concentration of cross carmellose sodium, a super disintegrant used for the formulation of the fast disintegrating tablet. As a result of faster disintegration, the drug.

Thus, it can be concluded that the solubility and dissolution rate of gliclazide can be enhanced by formulating solid dispersions of gliclazide with all the polymers and methods but the significant increase can be obtained by using PVP K-30 and solvent evaporation method. The solvent evaporation may have formed hydrogen bonds between the sulfonyl group of gliclazide with a hydrogen atom in PVP-K30. From XRD patterns it can be assumed that the drug remains crystalline, but its intensity has been decreased which can be also the reason for its increase in solubility and eventually dissolution rates. From the FTIR spectroscopy, it was concluded that there were no well-defined chemical interactions between gliclazide and PVP-K30 in solid dispersions as no important new peaks could be observed. Thus, preparation of solid dispersions by solvent evaporation method with PVP K-30 as a water-soluble polymer proves to be an effective way in enhancing the oral bioavailability of poorly soluble drugs like gliclazide.

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