

SOLUBILITY AND DISSOLUTION ENHANCEMENT OF POORLY WATER SOLUBLE GLIMEPIRIDE BY USING SOLID DISPERSION TECHNIQUE

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ABSTRACT

Glimepiride is one of the third generation sulfonylurea used for treatment of type 2 diabetes. Poor aqueous solubility and slow dissolution rate of the glimepiride lead to irreproducible clinical response or therapeutic failure in some cases due to subtherapeutic plasma drug levels. Consequently, the rationale of this study was to improve the solubility, dissolution rate and biological performance of the drug. Solid dispersion of glimepiride in polyvinylpyrrolidone (PVP K30) with water soluble polymers were prepared by the solvent evaporation method, and then formulating solid dispersion (SDs) tablets of the best formulation of SDs. Tablet formulations were prepared by direct compression technique using superdisintegrant crospovidone in different concentrations. SDs was evaluated for FTIR, XRD, SEM, *in vitro* dissolution profiles. Among different formulations of SDs, SD prepared by solvent evaporation method containing drug to PVP K30 polymer in the ratio of 1:5 gives best dissolution profile, and among tablet formulations, formulations containing 5% crospovidone gives best disintegration and dissolution profiles compared with other formulations. Results showed that polyvinylpyrrolidone is a promising polymer for enhancing the solubility of glimepiride. Prepared tablets were evaluated for routine Pharmacopoeial tests. Stability studies and FT-IR studies clearly indicated that there is no drug-polymer interaction.

Keywords: Glimepiride, Polyvinyl pyrrolidone (PVP K30), Solid dispersions, Solvent evaporation method, Solid dispersion tablets.

INTRODUCTION

The use of oral antidiabetic drugs for treatment of type 2 diabetes increases rapidly. It is widely used with the discovery and approval of several new types of oral antidiabetic drugs with different mechanism of pharmacological action. Many of the drugs belong to class II of the biopharmaceutical classification system showing poor solubility and high permeability. Glimepiride shows low, pH dependent solubility. In acidic and neutral aqueous media, glimepiride exhibits very poor solubility at 37°C (<0.004 mg/ml). In media pH>7, solubility of drug is slightly increased to 0.02 mg/ml. These poorly water soluble drugs provide challenges to deliver them in an active and absorbable form to the desired absorption site using physiologically safe excipients^{1, 2}. Therefore, one of the most important steps in the development of dosage forms for these drugs is to improve their solubility and/or dissolution rate. Chiou and Rigelman and Serajuadin *et al.* have used the solid dispersion (SD) technique for dissolution enhancement of poorly water-soluble drugs^{3, 4}. Among the various approaches, the SD technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble active pharmaceutical ingredients because it is simple, economic, and advantageous⁵. Sekiguchi and Obi were the first to propose the SD method using water-soluble carriers to improve the dissolution characteristics of poorly water-soluble drugs⁶. Many water-soluble carriers have been employed for preparation of SD of poorly soluble drugs. The most common are polyethylene glycols^{7, 8}, polyvinyl pyrrolidone⁹, mannitol¹⁰ and hydroxypropyl methylcellulose¹¹. Due to poor solubility in GI fluids, it results in low and erratic oral bioavailability¹². Glimepiride was selected as a model drug for dissolution enhancement studies in the present investigation. Attempts were made to enhance the dissolution of GMP using a SD technique. SDs of GMP with PVP K 30 was prepared in different ratios using solvent evaporation method and then tablets of best formulation of SD were formulated by using direct compression method. Tablet formulations were prepared by direct compression technique using super disintegrants crospovidone in different concentrations. SDs were evaluated for FTIR, XRD, SEM, *in vitro* dissolution profiles, and developed tablet formulations were evaluated for various pharmaceutical characteristics viz. hardness, % friability, weight variation, drug content, disintegration time, *in vitro* dissolution profiles.

MATERIALS AND METHODS

GMP was obtained from Zim Laboratories Pvt Ltd, Nagpur India as a gift sample; Poly vinyl pyrrolidone K 30, Crospovidone, and Avicel PH 102, Magnesium stearate and talc were obtained from were

obtained from Loba chem, Mumbai, India. All other chemicals/reagents used were of analytical grade, except for those used in high performance liquid chromatography (HPLC) analysis, which were of HPLC grade.

Preparation of Solid Dispersion

Solvent evaporation method was used for the preparation of SDs. Five different drug: carrier ratios (1:1, 1:2, 1:3, 1:4, and 1:5) were used in Table 1. GMP and PVP K 30 were weighed according to these weighed ratios.

Table 1: Composition of glimepiride-PVP K 30 solid dispersions

Formulation Number	Drug: Carrier Ratio
SD1	1:1
SD2	1:2
SD3	1:3
SD4	1:4
SD5	1:5

Solvent Evaporation Method

For preparation of solid dispersions, firstly drug was dissolved in insolvent (methanol). Then a polymer (PVP K30) was dissolved in that solvent with continuous stirring using mechanical stirrer. The solvent was allowed to evaporate on hot plate with stirring at 45±5°C. The process of evaporation was continued till constant weight was obtained. The solid dispersions were kept in desiccator for 24 h, then pulverized and passed through 100 # sieve. The resultant powders were stored in a desiccator until further investigation.

Preparation of Physical Mixture

Physical mixture of drug and polymers PVP K30 in 1: 5 ratio (PM) was prepared by thoroughly mixing the accurately weighed quantity of drug and carrier for 5 minutes in glass mortar, which was then passed through mesh number 40 and stored in a desiccator respectively.

Fourier-transform infrared spectroscopy (FTIR)

The infrared (IR) spectra were recorded using an FTIR spectrophotometer (Shimadzu IR affinity 1) and spectra were recorded in the wavelength region between 4000 and 400cm⁻¹ by using KBr. The FTIR spectra obtained for pure drug (GLM), polymers (PVP K30) and physical mixtures of drug with excipients are compared.

Differential Scanning Calorimetry (DSC)

DSC studies of pure drug, pure polymer and solid dispersions were performed to access what changes had actually occurred when SD were prepared. Analysis of samples was carried out on Differential Scanning Calorimeters (DSC 60, Shimadzu, Japan) instruments at heating rate of 10°C/min. The measurements were performed at a heating range of 0 to 300 °C under nitrogen atmosphere.

X-Ray Diffraction studies (XRD)

XRD study of drug, pure polymers, physical mixture of drug and polymer and solid dispersions were carried out to access the changes in the crystallinity when drug was mixed with polymer. X-ray diffraction patterns of samples were obtained using Philips diffractometer (PW1140) and Cu-K α line as a source of radiation which was operated at the voltage 40 kV and the current 30 mA. Diffractograms were run at a scanning speed of 2 $^\circ$ /mm and a chart speed of 2 $^\circ$ /2 cm per 2 $^\circ$.

Scanning Electron Microscopy (SEM)

The morphology of samples were determined using scanning electron microscope (SEM) (Make Jeol model 6390 LV) operated at an accelerating voltage of 3 kV. Samples were prepared by mounting powder on to a brass stub using graphite glue and coated with gold under vacuum before use.

Dissolution study of SDs

Accurately weighed preparations equivalent to 10 mg of GMP were added to 900 ml of dissolution media (6.8 phosphate buffer) in a USP dissolution apparatus II (Paddle type) and stirred at a speed of 50 rpm at 37 \pm 0.5°C. Five millilitre aliquots were withdrawn at 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60 minutes and replaced by 5 ml of fresh dissolution media (37°C). The collected samples were analyzed after suitable dilution (if required) at λ max 226.6 nm using UV-visible spectrophotometer against the blank. Drug release studies were carried out in triplicate. The dissolution of pure GMP was done similarly. The release profile data were analyzed for cumulative percent dissolved at different time intervals and for dissolution efficiency at 6 and 10 minutes (UV 1700, Shimadzu).

Preparation of glimepiride Solid Dispersion tablet

Tablets weighing about 100 mg were prepared by using Glimepiride-PVP K30 solid dispersions (M5) equivalent to 04 mg glimepiride, crospovidone, magnesium stearate, avicel pH 101 and talc. The SDs of glimepiride and PVP K30 were used for the preparation of glimepiride tablets. Superdisintegrant was utilized for formulating glimepiride tablets. The composition of tablets was as per Table 2. All the components of the tablet were sieved through sieve #60, weighed, mixed and compressed into tablets using 6 mm punch on rotary tablet minipress (Rimek, Ahmedabad, India).

Table 2: Composition of glimepiride solid dispersion tablets

Ingredients	Formulation code (mg)			
	F1	F2	F3	F4
SD5	24.8	24.8	24.8	24.8
Crospovidone	1.0	2.5	3.5	5.0
Avicel PH 101	71.7	70.2	69.2	67.7
Talc	1.5	1.5	1.5	1.5
Mg-Stearate	1.0	1.0	1.0	1.0

Evaluation of glimepiride solid dispersion tablets^{13, 14, 15}

Tablet Weight Variation

Twenty tablets were selected at random and the average weight of the tablets was determined. The weight of individual tablets was compared with the average weight.

Tablet thickness

Ten tablets were randomly selected to determine thickness by using Vernier caliper.

Tablet hardness

The crushing strength of tablet was determined by Monsanto hardness tester.

Tablet friability

The friability test was carried out using Roche friabilator (Erection instrument & engineering, Ahmadabad, India). Ten tablets were weighed and subjected to the combined effect of attrition and shock by utilizing a plastic chamber. The friabilator was operated for 100 revolutions (4 min, 25 rpm). The tablets were dedusted and re-weighed to calculate the percentage of friability.

Invitro disintegration test

The *in vitro* disintegration time was determined using Disintegration Test Apparatus. This device uses six glass tubes that are three inches long, open at the top, and held against a 10-mesh screen at the bottom end of the basket rack assembly. To test for disintegration, one tablet was placed in each of the six tubes of apparatus and one disc was added to each tube. The basket rack assembly was positioned in 1 l of pH 6.8 phosphate buffer at 37 \pm 2°C. The time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in minutes.

In-vitro dissolution test for tablet formulations

In vitro dissolution studies for all the fabricated tablets were carried out using USP paddle method in 900 ml of phosphate buffer (pH 6.8) as dissolution media, maintained at 37 \pm 0.5°C at 50 rpm. Five milliliter aliquots were withdrawn at 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 90, 105, 120 minutes and replaced by 5 ml of fresh dissolution media (37°C). The collected samples were analyzed after suitable dilution (if required) at 226.6 nm using UV-visible spectrophotometer against phosphate buffer (pH 6.8) as the blank. The release profile data were analyzed for cumulative percent dissolved at different time intervals.

RESULTS AND DISCUSSION

GMP assay in all SDs was almost more than 99% and also the low values of standard deviation indicate that the drug was uniformly distributed in SDs. Hence, the method used to prepare SDs was found to be reproducible.

Fourier-transform infrared spectroscopy (FTIR)

The IR spectra indicates that the characteristic absorption peaks of GLM was found at 3367 cm⁻¹ (N-H stretch), shows strong absorption peak at 1707 cm⁻¹ (C=O) and 1346cm⁻¹ (S=O). These characteristic peaks also found in the drug-polymer mixture, which indicates no drug-excipient interaction.

Differential Scanning Calorimetry (DSC)

The DSC thermograms of GLM, polymer (PVP K30), physical mixture of drug and polymer (PM), solid dispersion prepared by solvent evaporation method are in Figure 2. GLM was characterized by sharp melting endothermic peak at 213°C during DSC analysis. The DSC thermograms of physical mixture as well as solid dispersion showed slightly increase in broadness and decrease in intensity of peaks. Further, the decrease in intensity and increase in broadness of GLM endothermic peak in both the solid mixture may be due to low amount of drug in the dispersions and decrease in crystallinity of GLM. IR and DSC studies support same hypothesis, which is confirmed by X-ray diffractometry.

X-Ray Diffraction studies (XRD)

The X-ray diffractograms (Figure 3) of pure GMP and pure PVP K30 show that both are crystalline in nature. The XRD of SD (SD5 formulation) shows peaks corresponding to GMP and also the peaks related to PVP K30 persist. But, the GMP peaks with reduced peak height and area was observed, suggesting reduced crystallinity of GMP in SD5 formulation.

Scanning Electron Microscopy

In scanning electron microscopy (Figure 4) GMP appeared in a crystal form and PVP K30 as smooth-surfaced spherical particles. In SD, the crystals of GMP were dispersed between the carriers (PVP K30) in the SD5 formulation, which demonstrated that the drug was thoroughly mixed in the carriers with the loss of little crystallinity.

Dissolution Studies of solid dispersions

In vitro release of Glimepiride from different solid dispersions was determined by *in vitro* dissolution study. From the result shown in table solid dispersions (prepared by solvent evaporation method) gives 89.56 % release within 30 minutes. From the dissolution profile of solid dispersion it was evident that there is a remarkable improvement in the dissolution rates of solid dispersion than that of pure drug.

Characteristics of Powder Blend

Preformulation studies such as angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio were determined for their micromeritic properties. The pre-compression parameter values of

all formulation were evaluated and indicated good free flowing property (Table 3).

Physicochemical Properties of glimepiride Tablets

The physicochemical properties of the tablets are summarized in Table 4. The thickness of all tablet batches ranged from 3.75 ± 0.05 to 3.81 ± 0.06mm. The friability parameters of all tablet batches ranged from 0.51 to 0.63. The hardness of glimepiride tablets was between the range 3.5 to 4.0 kg/cm². The drug content of all tablets ranges from 97.2 ± 1.3% to 99.45 ± 0.7 % which is within acceptable limits. The tablet weight all tablets range from 98 ± 0.6 to 102 ± 1.9. The disintegration time all tablets range from 28 ± 1.5 to 45 ± 1.34. The wetting time of all tablets ranges from 545 ± 4.2 to 655 ± 6.2.

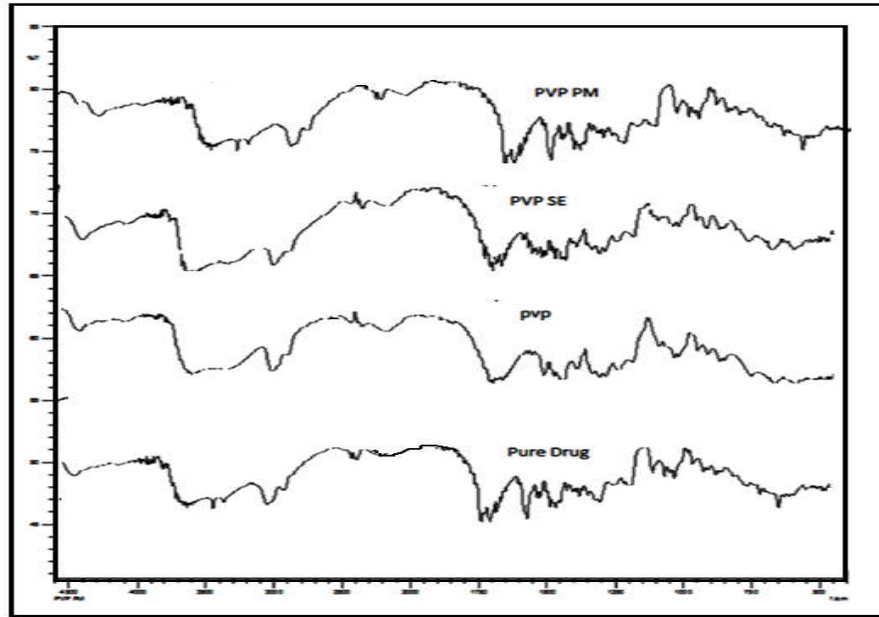


Fig. 1: FTIR spectra of Glimepiride (GLM), PVP K30 polymer, SDS by solvent evaporation method (GSESDS), Physical mixture of Glimepiride and PVP K30 (PM)

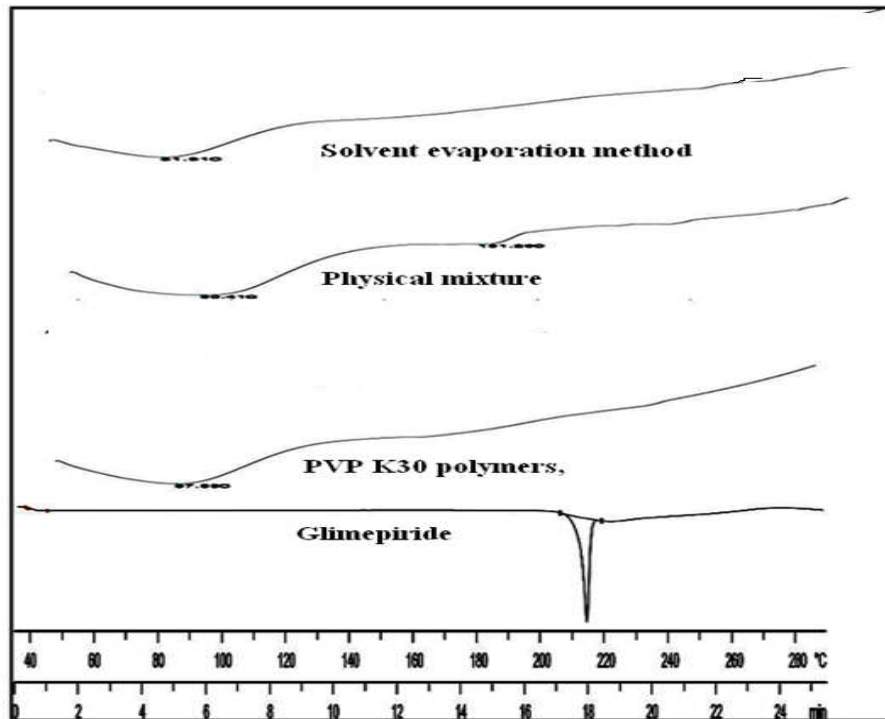


Fig. 2: DSC thermograms of Glimepiride (GLM), Pure PVP K30 polymers, Physical mixture Glimepiride PVP K 30(PM), and SDS by Solvent evaporation method (GSED)

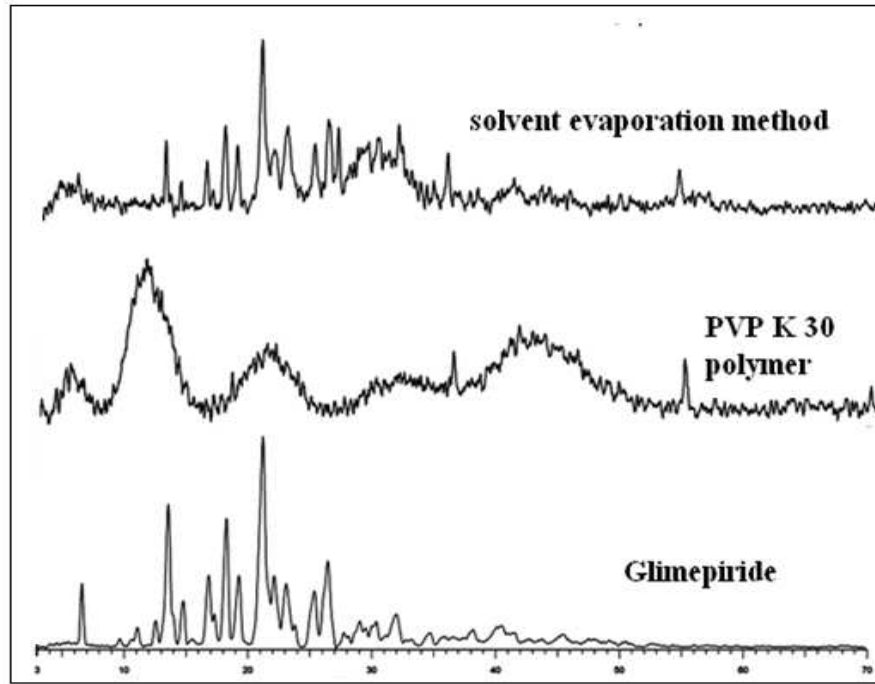


Fig. 3: X-ray Diffraction patterns of Glimepiride (GLM), PVP polymer, SD by solvent evaporation method (GSED)

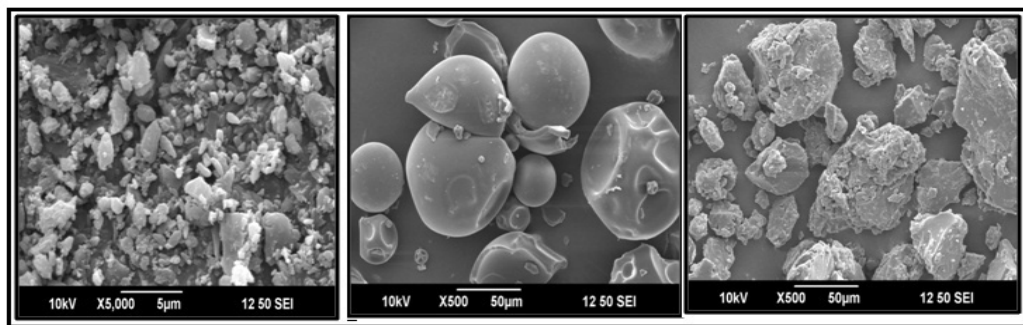


Fig. 4: Scanning electron micrographs: (a) glimepiride, (b) PVP K30 and (c) 1:5 solid dispersions

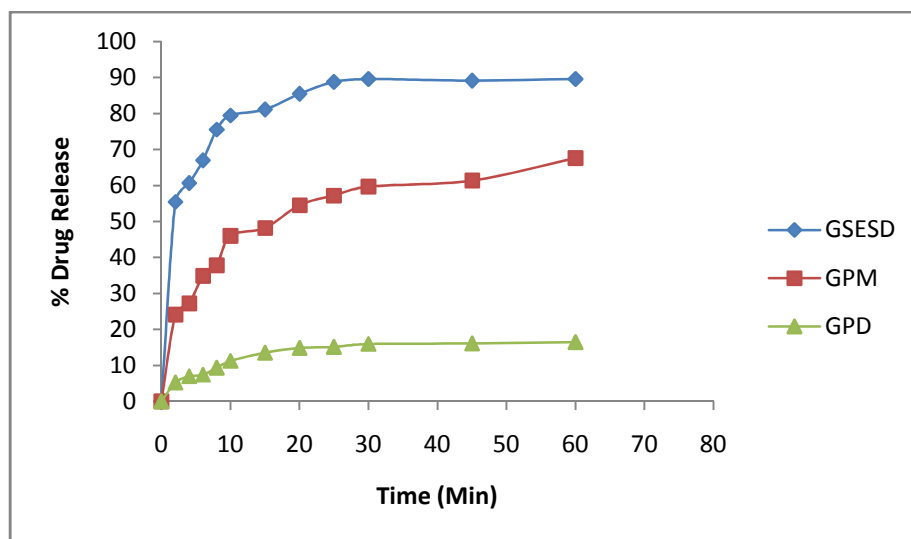


Fig. 5: Dissolution Profile of glimepiride SDS

Table 3: Evaluation of powder blend of formulation

Batch	Angle of Repose	LBD (gm/ml)	TBD (gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	31.87	0.48	0.54	15.33	1.22
F2	33.58	0.54	0.59	17.76	1.28
F3	31.71	0.55	0.57	14.13	1.16
F4	32.78	0.47	0.51	11.23	1.17

Table 4: Evaluation of GLM- PVP K30 Conventional Tablets

Properties	F1	F2	F3	F4
Weight (mg)	98 ± 0.6	102 ± 1.9	99 ± 0.5	99.5 ± 0.5
Hardness (kg/cm ²)	3.5	3.7	3.9	4.0
Thickness (mm)	3.76 ± 0.07	3.75 ± 0.05	3.78 ± 0.06	3.81 ± 0.06
Friability (%)	0.51	0.59	0.63	0.63
Drug content (%)	97.2 ± 1.3	98.4 ± 1.4	98.74 ± 0.7	99.45 ± 0.7
Disintegration time (min)	45 ± 1.34	38 ± 2.3	32 ± 1.5	28 ± 1.5
Wetting time (seconds)	655 ± 6.2	545 ± 4.2	582 ± 4.8	578 ± 4.8

All results were calculated as mean ± 3 SDS,*Value indicate P<0.001

In-Vitro Release Profile of Formulated Tablets

The following theoretical drug release profile of formulation F4, i.e., 31.12 % in 5 min, 49.95 % in 10 min, 71.65 ± 2.51 in 15 min, 81.96 ± 1.52 in 30 min, 99.81 ± 1.73 in 60 min, 98.48 ± 2.64 in 90 min, 98.72 ± 2.30 in 120 min (Fig. 6). Hence it was observed that Crospovidone showed better results. The cumulative % released of the glimepiride tablet is achieving 99.81% drug release in within 60 min by using crospovidone in 5%. Hence F4 formulation is optimized batch.

In Vitro Release Profile of Marketed tablets and Optimized Batch

The following theoretical drug release profile of Optimized Batch and Marketed tablets formulation are shown in figure 7. The

cumulative % released of the glimepiride tablet is achieving 99.81% drug release in within 60 min by using crospovidone in 5%. Hence F4 formulation shows better release as compared to marketed formulation.

Stability studies

Stability studies of the formulated Solid dispersion tablet were carried out as per ICH guidelines. Various parameters such as drug content and *in vitro* release were determined during study. There was no color change observed after stability study. From the results of stability studies it was found that, solid dispersion tablets were stable at 40 °C/ 75% RH.

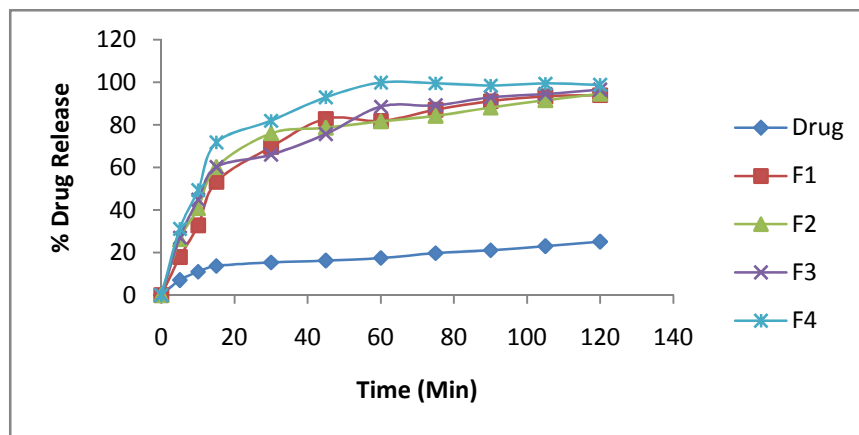


Fig. 6: Dissolution Profile of Glimepiride Tablets (Glimepiride-PVP)

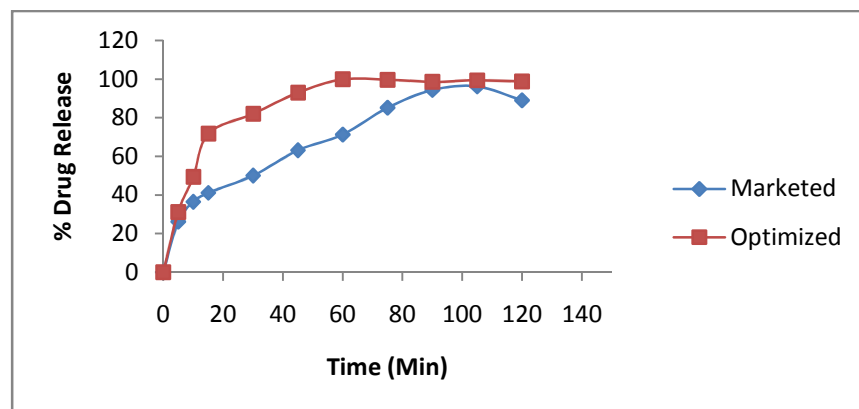


Fig. 7: Dissolution Profile of Marketed Glimepiride Tablets and optimized batch

Table 5: Physicochemical evaluation of solid dispersion after stability studies

Time (days)	Hardness(kg/cm ²)	Drug content (%)	In vitro drug release (%)
0	3-4	99.45±0.14	99.81±0.18
30	3-4	99.09±0.23	99.57±0.27
60	3-4	98.56±0.09	99.43±0.22
90	3-3.5	98.12±0.12	99.13±0.13

All results were calculated as mean ± 3 SDS,*Value indicate P<0.001

CONCLUSION

Solid dispersion with polymer having high Tg value (PVP K30) by solvent evaporation technique having both advantage, generation of amorphous system and formation of solid dispersion simultaneously. In this study, solvent evaporation method was applied for the preparation of solid dispersion. In particular, it was proved that the solvent evaporation technique increased the solubility of binary systems. This activated system prepared with PVP K 30 as carrier, was able to remarkably increase the dissolution profile and solubility of the poorly soluble Glimperide as compared to other solid dispersion techniques.

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