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Research Article

SOLVENT EVAPORATION METHOD FOR AMORPHOUS SOLID DISPERSIONS: PREDICTIVE TOOLS FOR IMPROVE THE DISSOLUTION RATE OF PIOGLITAZONE HYDROCHLORIDE

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ABSTRACT

The present study was aimed to improve the solubility of Poorly water soluble drug (pioglitazone HCl), by the solvent evaporation method in order to achieve increased dissolution rate, improved solubility, bioavailability and stability. The main purpose of this investigation was to increase the solubility and dissolution rate of Pioglitazone HCl by the preparation of its solid dispersion with polyvinyl pyrrolidone K30 using solvent evaporation methods. FT- IR spectra revealed no chemical incompatibility between drug and polyvinyl pyrrolidone K30. Drug-polymer interactions were investigated using differential scanning calorimetry (DSC), Powder X-Ray Diffraction (PXRD).

Keywords: polyvinyl pyrrolidone K30, solid dispersion, solvent evaporation methods, Pioglitazone HCl.

1. INTRODUCTION

The formulation of poorly water-soluble drugs has always been a challenging problem faced by pharmaceutical scientists and it is expected to increase because approximately 40% or more of the new chemical entities being generated through drug discovery programs are poorly water-soluble.

Pioglitazone is a Thiazolidinedione antidiabetic agent that depends on the presence of insulin for its mechanism of action[1, 2]. Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPARg)[3]. Pioglitazone decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Pioglitazone HCl is a poor water soluble drug, it is necessary to improve the solubility and bioavailability. There are many techniques that have commonly been used to improve dissolution and bioavailability of poorly water-soluble drugs, which includes the surfactants, micronization, and the formation of solid dispersion.

The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion),[4] solvent or the melting-solvent method. Chiou and Riegelmen outlined 6 types of drug carrier[5] interactions in solid state dispersions: simple eutectic mixtures, solid solutions,[6] glass solutions of suspension,[7, 8] compound or complex formations between the drug and the carrier,[8] amorphous precipitations of a drug in a crystalline carrier.[9] Polyvinyl pyrrolidone K30 is most commonly used as a carrier in the solid dispersion system.[10]

2. MATERIALS AND METHODS

2.1 Materials

Pioglitazone HCl sample from Ontop Pharmaceuticals LTD (Bangalore, India), Polyvinyl pyrrolidone K30 was purchase in the market; all the chemicals were A.R. Grade.

2.2 Preparation of physical mixture and solid dispersions

Physical mixtures were prepared by mixing the appropriate amount of Pioglitazone HCl and Polyvinyl pyrrolidone K30 (PVP K30) and Polyethylene glycol 6000 (PEG 6000) in pestle and mortar separately and passed through sieve # 60. Solid dispersions were prepared by solvent evaporation method. The carrier (PVP K30 and PEG 6000) and adding amounts of Pioglitazone HCl corresponding to ratio 1:1, 2:1, 3: 1 and 5:1 was accurately weighed and mixed properly. This physical mixture was solubilized in a common solvent that is in ethanol (25 ml). The solvent was allowed to evaporate in hot air oven at 45°C ± 10°C. The process of evaporation was opted until the constant weight was obtained. This formulation was kept in dessicator for 24 h under vacuum. Then, solid dispersion formulation was pulverized using a porcelain mortar and pestle. The pulverized powder was classified using the sieves (size 60 # and 120 # mesh) and the particle size fraction of 100-250 mm was used for the study (Table 1).

Table 1: Composition of solid dispersions (SD) and physical mixtures (PM) of Pioglitazone Hydrochloride

S. No.	Name of Carrier	Product Name	Drug (mg)	Carrier (mg)	Drug carrier Ratio	Description of product	Preparation of method
1.	Polyvinyl pyrrolidone K30	A11	1500	1500	1:1	Solid Dispersion	Solvent Evaporation
2.	Polyvinyl pyrrolidone K30	A12	1000	2000	1:2	Solid Dispersion	Solvent Evaporation
3.	Polyvinyl pyrrolidone K30	A13	750	2250	1:3	Solid Dispersion	Solvent Evaporation
4.	Polyvinyl pyrrolidone K30	A15	500	2500	1:5	Solid Dispersion	Solvent Evaporation
5.	Polyvinyl pyrrolidone K30	PMA15	500	1500	1:3	Physical Mixture	----------
6.	Polyethylene Glycol 6000	B11	1500	1500	1:1	Solid Dispersion	Solvent Evaporation
7.	Polyethylene Glycol 6000	B12	1000	2000	1:2	Solid Dispersion	Solvent Evaporation
8.	Polyethylene Glycol 6000	B13	750	2250	1:3	Solid Dispersion	Solvent Evaporation
9.	Polyethylene Glycol 6000	B15	500	2500	1:5	Solid Dispersion	Solvent Evaporation
10.	Polyethylene Glycol 6000	PMB13	500	1500	1:3	Physical Mixture	.....

2. 3 Pre-formulation Studies

2. 3.1 Estimation of Drug

Pioglitazone was estimated by UV spectrophotometric (Shimadzu UV-1700 UV/Vis double beam spectrophotometer) method. Aqueous solutions of pioglitazone were prepared in phosphate buffer (pH 7.4) and absorbances were measured on UV spectrophotometer at 269 nm. The method was validated for linearity, accuracy and precision. The method obeys Beer's Law in the concentration range of 1-10 µg/ml. The standard curve of pioglitazone is shown in (Fig. 1 & 2).[12, 13]

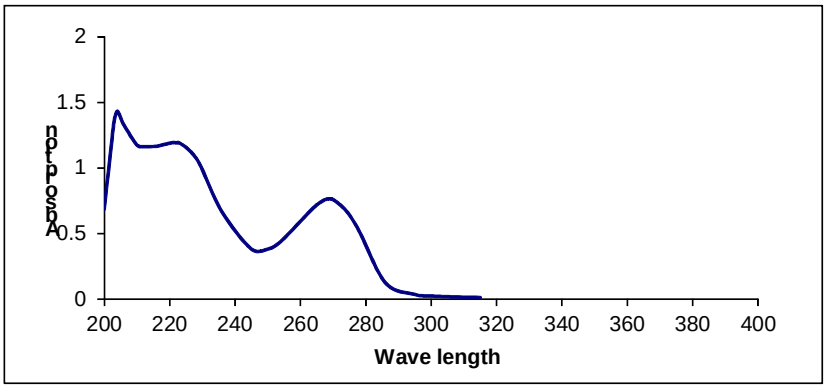

Fig. 1: Spectrum of Pioglitazne in Phosphate buffer (pH 7.4)

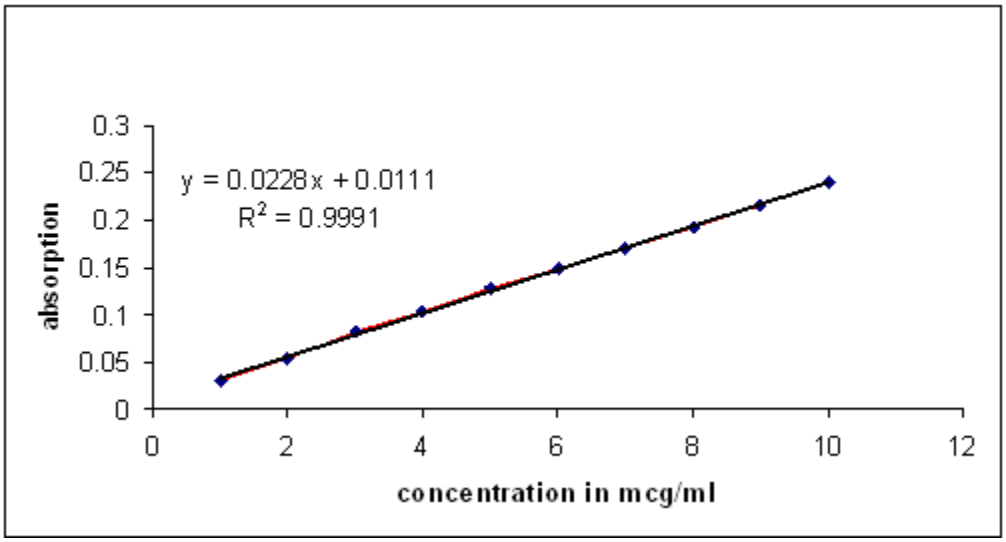

Fig. 2: Standard curve of Pioglitazone Hydrochloride in Phosphate buffer (pH 7.4)

2.3.2 Phase solubility study

Solubility studies were performed according to the Higuchi[11] and Connors method. An excess amount of Pioglitazone hydrochloride was placed in to 50 ml flask containing different concentration of polyvinyl pyrrolidone K30 and poly ethylene glycol 6000 separately in 25 ml distilled water. All flasks were closed with stopper and covered with cellophane membrane to avoid solvent lose. The flasks were kept in the incubator shaker for 72 h. After 72 h the content of each flask was then filtered through Whatman filter paper; the filtrate was diluted and assayed spectrophotometrically (Shimadzu 1700 UV spectrophotometer) for Pioglitazone HCl content at 269 nm. All solubility measurements were performed in triplicate (Figure 3).

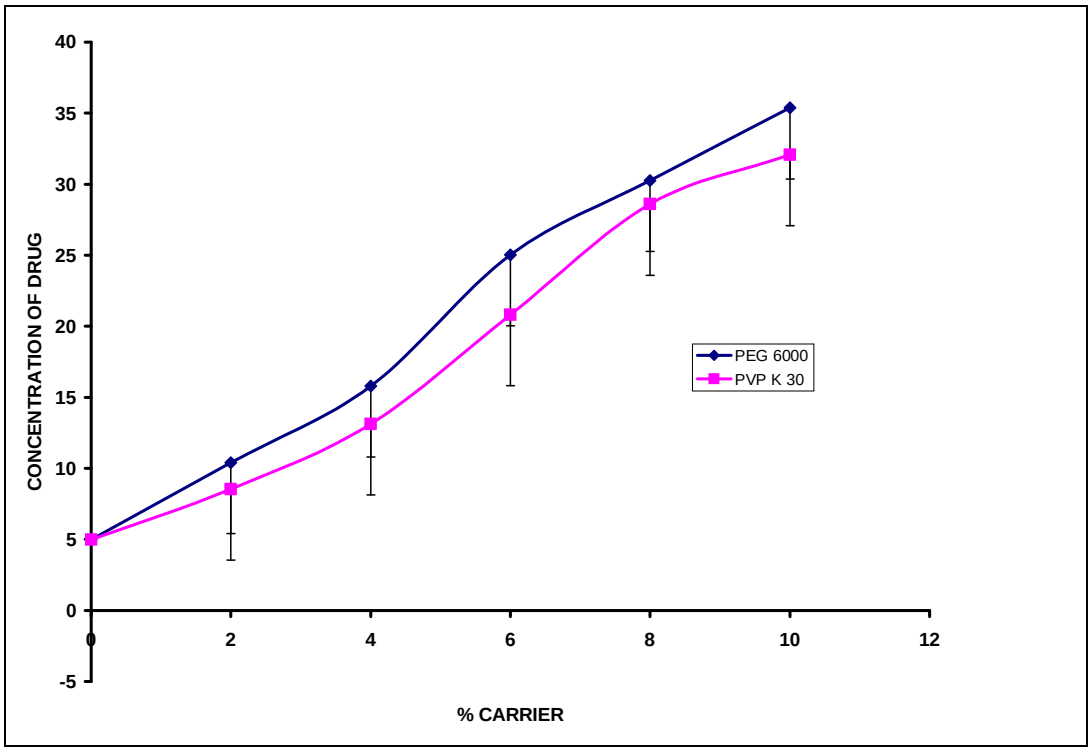

Fig. 3: Phase solubility diagram of Pioglitazone hydrochloride in different carrier

2.3.3 Characterization of solid dispersion

2.3.3.1 Physical characterization

The surface and internal structure of solid dispersion was observed through the Scanning Electron microscopy (SEM), by using the scanning electron microscope (SEM- LEICA S430, London, UK). (Fig-4).

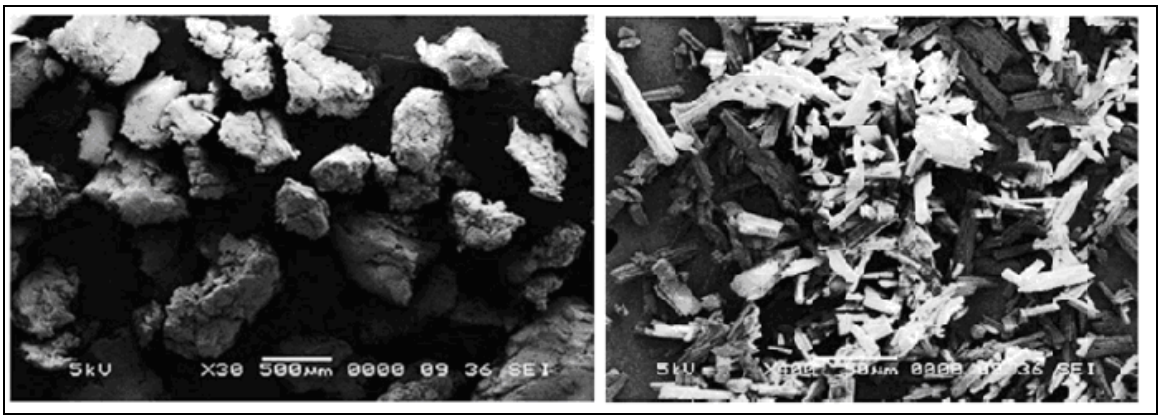

Fig. 4: Internal structure of solid dispersion of sample B13 show the amorphous and A13 show the crystalline stage

2.3.3.2 Practical yield

The percentage yield of Pioglitazone in the microencapsulated product is determined by using the formula:

$$\% \text{ Yield} = \frac{\text{Weight of Microcapsules}}{\text{Theortical Weight of drug and polymer}} \times 100$$

2.3.3.3 Percentage drug content

The dispersion system equivalent to 25 mg of Pioglitazone hydrochloride was taken in 25 ml volumetric flask and dissolved in phosphate buffer (pH 7.4). The volume was made up to the mark with phosphate buffer (pH 7.4) and filtered. One ml of filtrate was further diluted to 10 ml with phosphate buffer (pH 7.4) and absorbance was recorded at 269 nm. The amount of drug in each dispersion system was determined spectrophotometrically (Table 2).

$$\% \text{ Drug content} = \frac{\text{Actual drug content of microcapsules}}{\text{Theoretical weight of drug in microcapsules}} \times 100$$

Table 2: Drug Content of solid dispersion system

S. No.	Product Name	% yield	% Drug content
1	A11	84.91	97.54
2	A12	87.55	92.22
3	A13	82.98	95.14
4	A15	88.67	89.07
5	PMB13	87.90	97.54
6	B11	81.37	98.02
7	B12	86.56	91.17
8	B13	89.39	86.52
9	B15	82.99	83.37
10	PMB13	85.81	96.02

2.4 In vitro drug release

2.4.1 Release in pH 7.4-phosphate buffer

In vitro release rate of Pioglitazone HCl alone and Pioglitazone HCl from solid dispersion of different samples was determined using single station USP dissolution test apparatus. The dissolution medium consisted of phosphate buffer (pH 7.4) was used. Samples of drug, solid dispersion equivalent with 100 mg of drug were spread onto the surface of 900 ml of preheated dissolution medium at 37°C. Aliquots of 2 ml were withdrawn at regular intervals of time i.e. (5, 10, 15, 20, up to 120 min) and the same is replaced with fresh dissolution medium each time. The samples obtained were filtered through Whatman filter paper no. 1. The filtrate was diluted up to 6 ml with citrate buffer (pH = 3.0). Then the absorbance was measured at 269 nm.

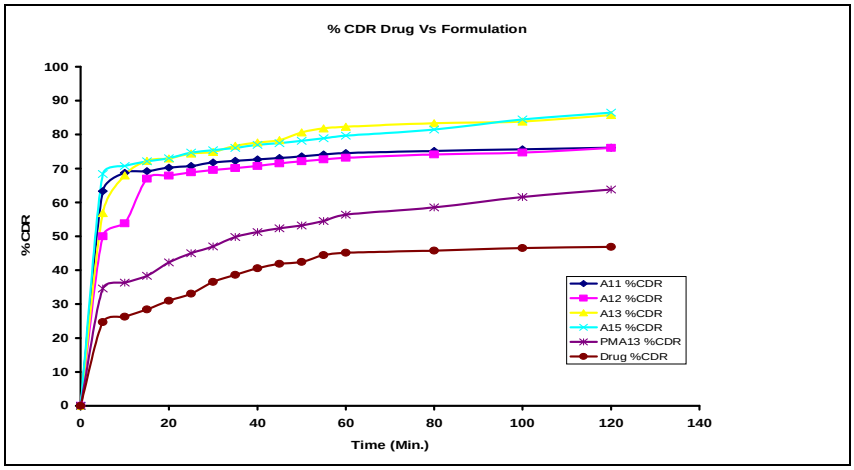

Fig. 5: Comparative % release of pure drug and different formulations containing PVP K30 as carrier

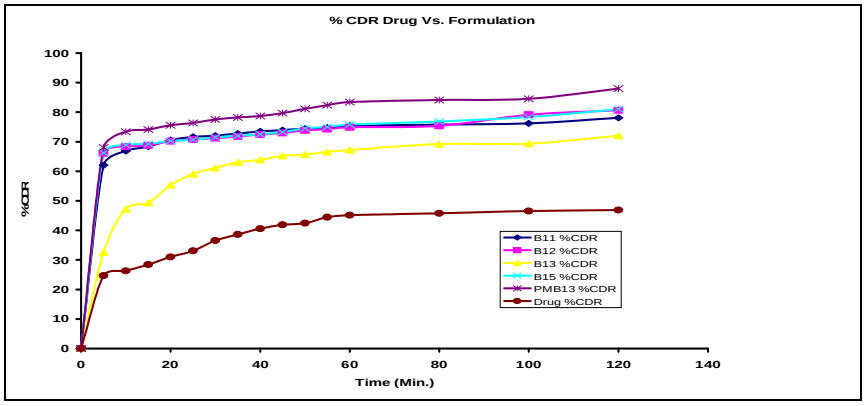

Fig. 6: Comparative % release of pure drug and different formulations containing PEG 6000 as carrier

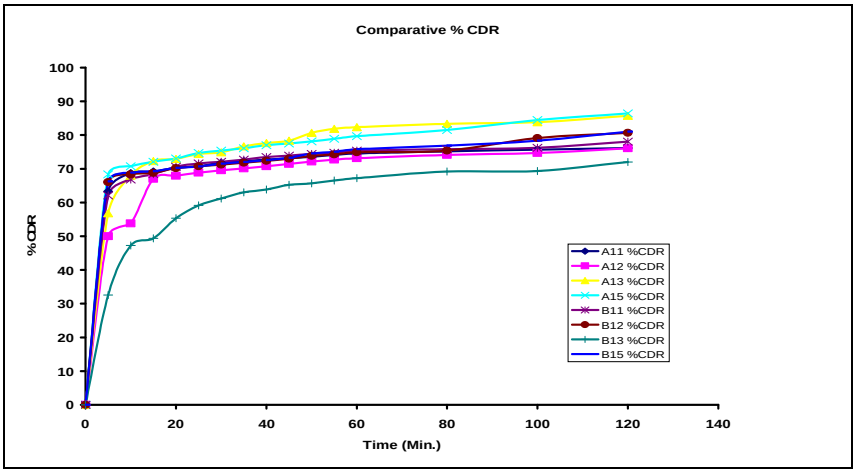

Fig. 7: Comparative % CDR of different formulations

2.4.2 Drug release kinetics studies

In order to understand the kinetics and mechanism of drug release, the results of the *in vitro* drug release study were fitted with various kinetic equations like zero order, first order, Weibull model, Korsmeyer -peppas model, Hill equation, Michaelis- Menten model. The kinetic model that best fits the dissolution data was evaluated by comparing the regression coefficient (r) values obtained in various models.

Table 3: Drug release kinetics data

Formulation code	Regression Coefficient (r) value					
	Zero order	First order	Weibull	Korsmeyer-peppas	Hill equation	Michaelis-menten
A11	0.2239	0.1183	0.9873	0.9859	0.9892	1.0000
A12	0.3320	0.1223	0.9901	0.9897	0.9927	1.0000
A13	0.3499	0.1223	0.9907	0.9876	0.9945	1.0000
A15	0.3023	0.1203	0.9888	0.9864	0.9920	1.0000
PMA13	0.6156	0.1309	0.9922	0.9903	0.9943	1.0000
B11	0.2520	0.1192	0.9880	0.9863	0.9903	1.0000
B12	0.2689	0.1194	0.9877	0.9861	0.9900	1.0000
B13	0.2943	0.1202	0.9892	0.9865	0.9927	1.0000
B15	0.2686	0.1194	0.9878	0.9861	0.9901	1.0000
PMB13	0.4870	0.1287	0.9928	0.9904	0.9955	1.0000

2.5. Analytical testing of solid dispersion

2.5.1 Fourier transforms infrared spectroscopy

FT-IR spectra (500-4000 cm^{-1}) were obtained on a Nicolet Avatar 37- DTGS FT-IR spectrophotometer (Nicolet) with a resolution of 4 cm^{-1}. KBr pellets were prepared by gently mixing 1 mg sample with 200 mg potassium bromide.

Table 4: Characteristic IR peaks of drug, carriers and their physical mixture

S. No.	Description	Characteristic peaks (Cm-1)
1	Pioglitazone Hydrochloride	3416.9, 3084.9, 2741.2, 2616.1, 1885.8, 1743.1, 1689.8, 1551.6, 1510.1, 1314.5, 1241.3, 1150, 930.9, 849.3, 739.9, 713.0, 660.1, 584.3, 549.4, 516.5
2	Polyethylene glycol 6000	1413.18, 1280.97, 1060.13 and 3445.20 (broad band)
3	Polyvinylpyrrolidone K30	2955.39, 1662.12 and 3433.66(broad band)
4	Pioglitazone Hydrochloride and Polyethylene glycol 6000	**1413.18, 1280.97, 1060.13 and 3446.20,** 3416.9, 3084.9, 2741.2, 2616.1, 1885.8, 1743.1, 1689.8, 1551.6, 1510.1, 1314.5, 1241.3, 1150, 930.9, 849.3, 739.9, 713.0, 660.1, 584.3, 549.4, 516.5
5	Pioglitazone Hydrochloride and Polyvinylpyrrolidone K30	**2955.39, 1662.12 and 3433.66,** 3416.9, 3084.9, 2741.2, 2616.1, 1885.8, 1743.1, 1689.8, 1551.6, 1510.1, 1314.5, 1241.3, 1150, 930.9, 849.3, 739.9, 713.0, 660.1, 584.3, 549.4, 516.5

2.5.2 X-ray diffraction

Diffraction patterns were obtained at room temperature on a Philips PW 1710 Diffractrometer (Philips, Holland). Samples were exposed to Cu Ka radiation, wavelength 1.54060 Å through 1 x slits from 5.025 to 59.685 2q with a step size of 0.60° 2q and a count time of 1 sec. per step; the generator was set to 40 kV and 30 mA.

3. RESULTS AND DISCUSSIONS

3.1 Solubility studies of pioglitazone

The Solubility of Pioglitazone HCl in distilled water at 27°C was found to be 5.32µg/mL. The influence of polyvinyl pyrrolidone K30 and polyethylene glycol 6000 upon the solubility of Pioglitazone HCl is presented in Figure 3 and shows the solubility of Pioglitazone HCl increases with increase the concentration of both carriers. PVP K30 has the better solubility enhancing capacity than PEG 6000.

3.2 Characterization of solid dispersion

3.2.1 Physical characterization

The solid dispersion of pioglitazone prepared by solvent evaporation method were found to be discrete and free flowing. The SEM photographs indicated that internal structure of solid dispersion of sample B13 show the amorphous and A13 show the crystalline stage. (Figure 4)

3.2.2 Practical yield

The percentage practical yield was found to be in the range of 81.37to 89.39 %. The maximum percentage practical yield was found to be 89.39% for B13. (Table-2)

3.2.3 Percentage drug content

The actual drug content of all formulations are given in Table .the percentage drug content ranges from 83.37% to 98.02% for formulation B15 to B11. The maximum percentage drug content was found to be 98.02% IN B11. (Table-2)

3.3 In Vitro release study

3.3.1 In vitro dissolution studies pioglitazone HCl solid dispersion

Pioglitazone HCl release from the solid dispersion and alone was studied in phosphate buffer (pH 7.4) up to 2 hours. The average percentage release of the pure Pioglitazone HCL was found to be 46% in 2 hours. In the solid dispersion formulation using polyvinyl pyrrolidone K30 and polyethylene glycol 6000 as carriers, the dissolution rate increased with increased amount of carriers. The best results among solid dispersions with Polyvinyl pyrrolidone K30 were obtained from the formulation A13 (Figure 3). The increased dissolution rate may be due to the higher solubility of PVP K30 in dissolution medium and better wettability of Pioglitazone hydrochloride in the formulation. The regression coefficient (r) values for formulations A11 to B15 are tabulated in Table 3. The model that gave higher 'r' value was considered as best fit model.

3.3.2 Drug release kinetics studies

The regression coefficient 'r' values were found to be higher in the Korsmeyer-peppas models, Hill equation model, Michaelis menten model and Weibull model respectively, indicating that the dissolution of pioglitazone from all formulations followed following above model.(Table 3)

3.4 Analytical testing of solid dispersion

3.4.1 Fourier transforms infrared spectroscopy

FT-IR studies were done to detect the possible interactions between the Pioglitazone hydrochloride and carriers (polyvinyl pyrrolidone K30 and polyethylene glycol 6000). The characteristic peaks of Pioglitazone hydrochloride, polyvinyl pyrrolidone K30, polyethylene glycol 6000, physical mixtures and their formulations are given in figure 8. Comparing the spectra of physical mixtures with those of solid dispersions prepared by using different methods revealed that there were no differences in the positions of the absorption bands, hence providing evidence for the absence of hydrogen bonding interactions in the solid state between Polyvinyl pyrrolidone K30 with Pioglitazone HCl under investigation (Table 4). The absence of any significant change in the IR spectral pattern of drug-polymer physical mixture indicated the absence of any interaction between the drug and the polymer.

3.4.2 Powder X-ray diffraction study

The diffraction spectra of Pioglitazone HCl and polyethylene glycol 6000 show numerous distinct peaks indicating that both are present in a highly crystalline state (Figure 9A, C) and the broad peaks of Polyvinyl pyrrolidone K30 indicating a amorphous state. The PXRD pattern of solid dispersion of sample A13 (Figure 9F) exhibits the characteristic broad peaks of polyvinyl pyrrolidone K30 and crystalline pioglitazone HCl, represent the amorphous state of sample A13. B13 represent the numerous distinct peaks indicating that sample B13 is present in a highly crystalline state (Figure 9G).

4. CONCLUSION

The study clearly shows that addition of polyvinyl pyrrolidone K30 to Pioglitazone HCl improved its dissolution rate. Mechanisms involved are solubilization and improved wetting of the drug in the polyvinyl pyrrolidone K30 rich micro-environment formed at the surface of drug crystals after dissolution rate compared with physical mixtures. No solid solution formation and no hydrogen bonding interaction between polyvinyl pyrrolidone K30 with pioglitazone HCl could be detected. The crystallinity of the drug was reduced in solid dispersion formulation with polymers i.e. polyvinyl pyrrolidone K30.

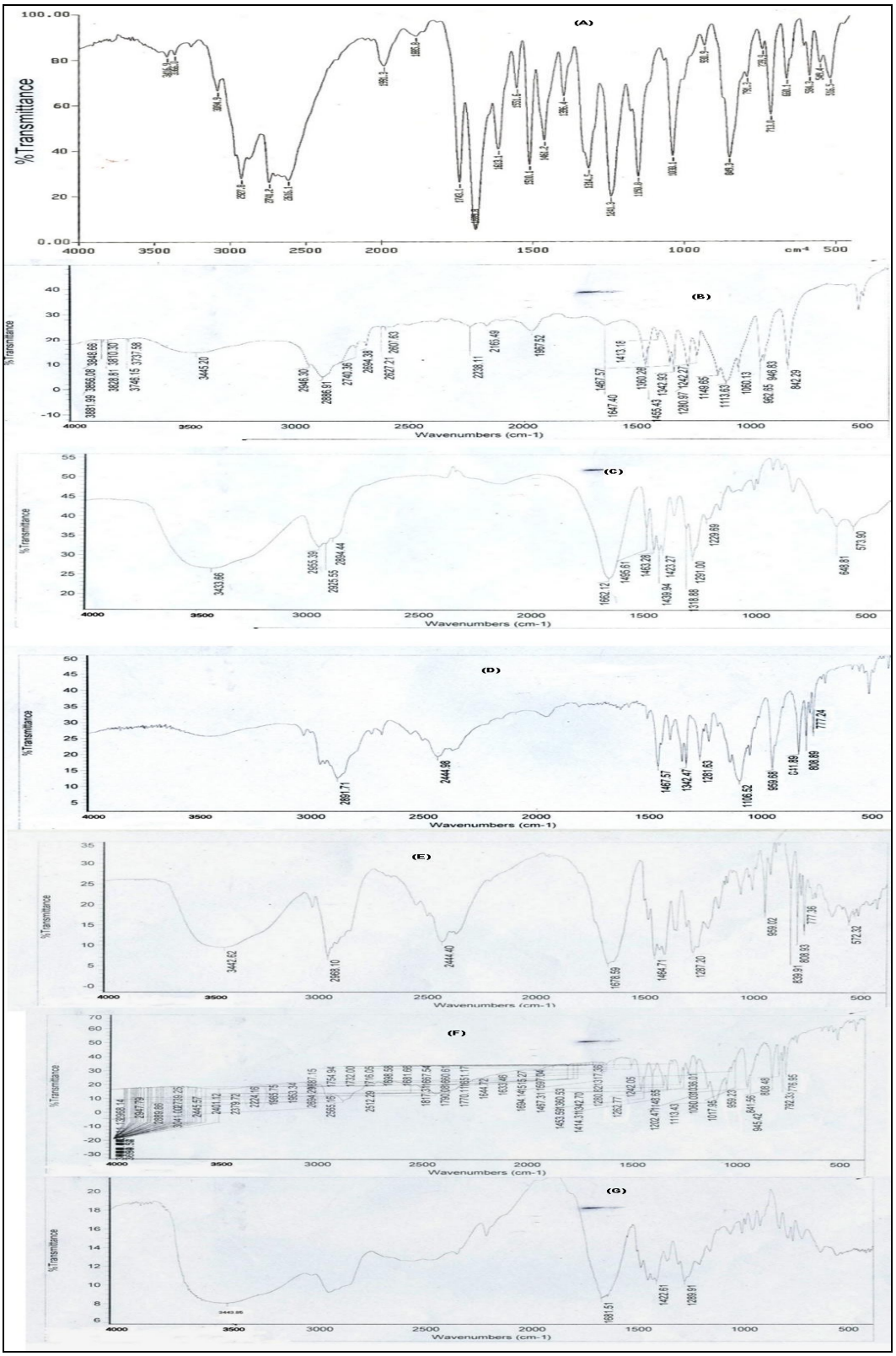

Fig. 8: FTIR Spectra of (a). Pioglitazone HCL, (B). PVP K30, (C). PEG 6000, (D). PMA13, (E). PMB13, (F). A13, (G). B13

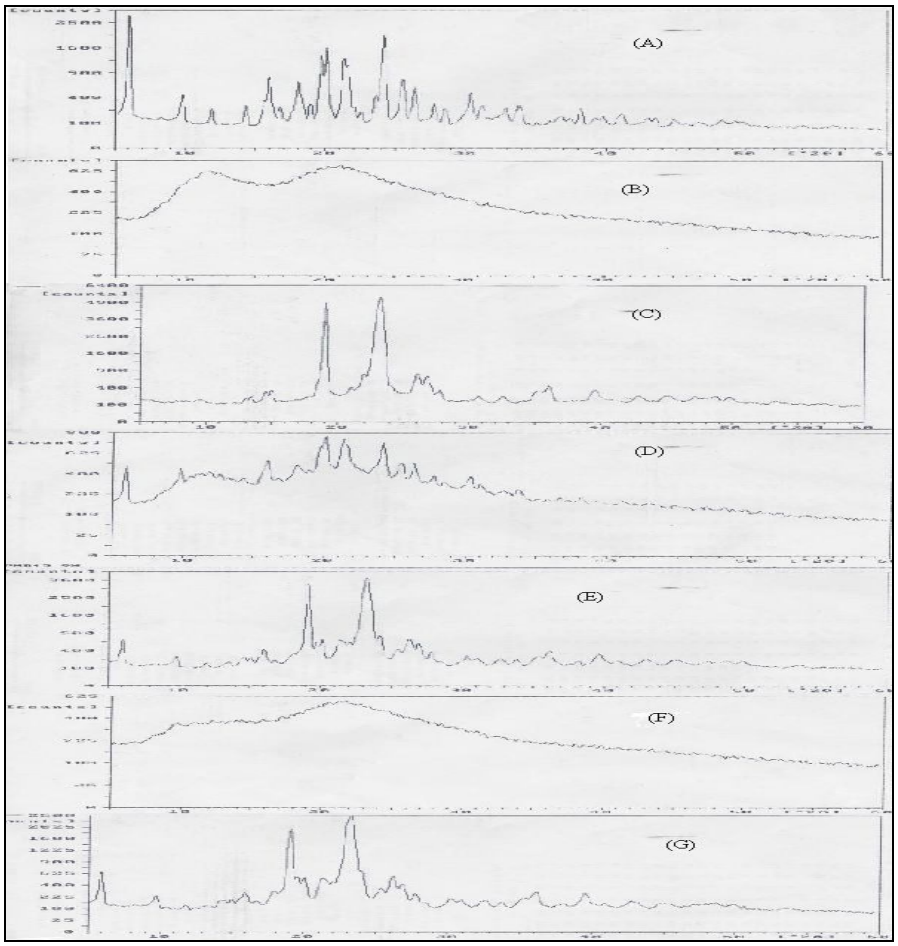

Fig. 9: XRD Spectra of (a) Pioglitazone HCL, (B) PVP K30, (C) PEG 6000, (D) PMA13, (E) PMB13, (F) A13, (G) B13

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