

Research Article

FORMULATION AND OPTIMIZATION OF PIOGLITAZONE SOLID DISPERSIONS PREPARED BY HOT MELT EXTRUSION TECHNIQUE

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ABSTRACT

The main objective of the present study was to develop a novel and stable pioglitazone loaded solid dispersions with enhanced solubility and dissolution rate. Different drug-to-carrier ratios were prepared by employing hot melt extrusion technique. These formulations were characterized for solid state properties by differential scanning calorimetry, X-ray powder diffraction and FT-IR spectral studies. Formulations were further evaluated for dissolution and stability studies. The aqueous solubility of pioglitazone, in present formulation was improved by the presence of both the polymers. Solid-state characterization indicated pioglitazone was present as amorphous material in formulation with Soluplus and polyethylene glycol, due to efficient entrapment in polymer matrix. The diffraction patterns of solid dispersion indicated the amorphous nature of pioglitazone in solid dispersions. The dissolution rate of all the solid dispersions was found to be rapid when compared to pure pioglitazone. Pioglitazone in pure form has very slow dissolution rate, when compared with the solid dispersions. Thus the solid dispersion prepared with Soluplus and polyethylene glycol would be useful for delivering poorly soluble pioglitazone with enhanced solubility and dissolution rate.

Key words: pioglitazone, soluplus, solid dispersions, melt extrusion technique.

INTRODUCTION

With the introduction of combinatorial chemistry and high throughput screening, the properties of new chemical entities shifted towards higher molecular weight and increasing lipophilicity that results in decreasing aqueous solubility. Thus the drug solubility, absorption, sufficient and reproducible bioavailability are recognized today as one of the major challenges in oral delivery of new drug substances. Especially for class II substances, solubility enhancement is part of the strategies to improve the oral bioavailability (Stegemanna *et al* 2007; Naveen *et al* 2007). Formulating poorly water soluble drug into a dosage form is always a challenging task because of the less solubility and dissolution concern (Dehghan *et al* 2006; Christian *et al* 2000). A well-established method for increasing the solubility and bioavailability of poorly water soluble drugs is the solid dispersion technique. Drugs in solid

dispersion systems can exist in an amorphous form in polymeric carriers and such a system improves the solubility and dissolution rate of the drug compared to the crystalline material (Srinivasa Babu *et al* 2007). Solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier matrix at solid state prepared melting (fusion), solvent evaporation, solvent wetting, super critical fluid technology, lyophilization, melt extrusion etc. (Venkatesh *et al* 2010; Leuner *et al* 2000). Many of the said approaches were proved to be beneficial and produced good results but in few cases it lack commerciality because of various problems (Abu 1999).

Hot Melt extrusion technology (HME) is the novel technology with an aim to produce solid dispersions with lower cost and is commercially feasible (Gavin *et al* 2009; Singhal *et al* 2011; Breitenbach 2002; Dong *et al* 2008; Mooter *et al* 2008).

In this study, solid dispersions were prepared by hot melt extrusion method using Soluplus as carrier. This method is suitable for thermostable drugs and for the polymers that possess high melting points or T_g values (Bell 1995). Soluplus is a polyvinyl caprolactum (57%)-polyvinyl acetate (30%)-poly ethylene glycol (PEG 6000-13%) graft co-polymer (Linn, *et al.*, 2011). Soluplus shows superior performance in forming solid solutions, especially in hot melt extrusion processes. PEG 1500 is used as carrier, solubilizer, absorption improvers for active substances usually processed in the form of a melt extrusion and plasticizer to decrease the processing temperature in extruder (Khan *et al* 1998; Verheyen *et al* 2002). Pioglitazone is a BCS class II drug with hypoglycemic action to treat diabetes mellitus type 2 (Shahzad *et al* 2011).

MATERIALS AND METHODS

Pioglitazone, Soluplus, PEG 1500 were obtained as gift samples from Mylan Laboratories Ltd, Hyderabad. All other chemicals and reagents used were of analytical reagent grade.

Preparation of solid dispersion

The solid dispersions of pioglitazone were prepared by hot melt extrusion technique using Soluplus and PEG 1500 as carriers. The pioglitazone, soluplus and PEG 1500 were weighed accurately in different ratios and passed through sieve #40 and blended in double cone blender for 10 minutes. These blends are then processed in the hot melt extruder instrument. The temperatures of the heating zones are adjusted in such a manner that the drug and the polymer mix well and melt well to give a uniform solid dispersion. The compositions of various solid dispersions were given in table I.

The melting point of the pioglitazone (183-192°C) and the T_g of the Soluplus (70°C) were taken into consideration while setting the temperatures of the heating zones. Temperatures of 60-100-135-150°C ($\pm 5-10^\circ\text{C}$) across the four heating zones and an rpm of 100(± 5) was maintained for intense mixing in order to obtain uniform and efficient solid dispersion. The torque was maintained by

regulating the feed rate of the blend into the screw feeder. The obtained mass is milled by using Quadra-co mill and passed through sieve No # 60 to obtain uniform fine particles of solid dispersions. The obtained solid dispersions were subjected to DSC, XRD to confirm the conversion of crystalline drug into amorphous form and FT IR for drug – carrier interaction studies. The drug content, solubility studies, dissolution and stability studies were carried out for solid dispersion.

Solubility studies

These studies were performed by taking the pioglitazone pure drug and pioglitazone solid dispersion equivalent to 30mg of pioglitazone and added to 10mL each of distilled water and buffer solutions. The samples were then subjected to incubated shaking at 100rpm for 24h at 36°C. The resultant solutions were collected and filtered through 0.45 μ membrane filters and analyzed spectrophotometrically at 269nm after suitable dilutions.

Characterization of pioglitazone solid dispersions

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry measurements were performed on pioglitazone, Soluplus, PEG 1500 and solid dispersion formulations using differential scanning calorimeter (METTLER TOLEDO with eSTAR software). The samples were placed in a sealed aluminium crucible and evaluated with a heating rate of 20°C/min at a temperature range of 25-250°C. The thermograms were recorded and were shown in the figures 1 and 2.

X-Ray Powder Diffraction (XRD)

The powder crystallinity of the pioglitazone and the pioglitazone solid dispersions were determined using Bruker D8 Advance XRD with copper target instrument. The conditions were maintained at 40 Kv voltages, with 40MA current at room temperature. The scanning rate employed was 0.1°/sec over a range of 2 θ values from 3° to 45°. The diffractograms were shown as figures 3 and 4.

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra of pioglitazone, Soluplus, PEG 1500 and solid dispersion formulations were obtained by using Bruker

FTIR spectrophotometer to study the interaction between drug and carrier in solid dispersions. The samples were prepared in KBr discs (2mg sample in 200mg KBr) and the sampling range was 400-4000 cm^{-1} and the resolution was 4 cm^{-1} . The FTIR spectra were shown in 5.

Drug content

Solid dispersions equivalent to 30mg of drug were taken and dissolved in methanol and filtered using 0.45 μ membrane filters. Then the filtrate was suitably diluted with buffer and drug content was analyzed against blank by UV spectrophotometer at 269nm. The concentration of drug present in solid dispersion is compared with that of standard solution containing 30mg of pure drug. The percentage of drug present in the solid dispersions was calculated with respect to standard concentration.

In vitro dissolution studies

Dissolution rate studies of pure pioglitazone and pioglitazone solid dispersions were performed in ELECTROLAB 8 stage dissolution apparatus with rotating paddles at 75rpm employing 900mL of pH 2.0 hydrochloric acid buffer (Marcel Dekker 2004) and the temperature was maintained at 37 \pm 0.5 $^{\circ}\text{C}$ throughout the experiment. 5mL of the samples were withdrawn at various time intervals. The absorbance of the samples was measured at 269nm for determining the amount of drug release at various intervals. Each time the equal volume of buffer was added for maintaining the constant volume of dissolution medium. The dissolution studies were carried out in triplicate. Based up on the data obtained from the dissolution studies the *in vitro* kinetic modeling parameters such as T 50, T 90, zero order and first order rate constants for solid dispersions were determined. The dissolution parameters were given in table II.

Data analysis

Data are expressed as mean \pm standard deviation, correlation coefficients (R^2) and were processed using Microsoft Office Excel 2007

software. The dissolution profiles of all the selected formulations for pioglitazone (SD8) were compared with the marketed formulation of pioglitazone by using a model independent approach of similarity factor, f_2 , with all time points included in the *in vitro* dissolution studies (19). The equation for calculating similarity factor is

N

$$f_2 = 50 \times \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum |R_t - T_t|^2 \right]^{-0.5} \times 100 \right\}$$

$J = 1$

Where 'n' is the number of dissolution time and R_t and T_t are the reference (theoretical) and test dissolution values at time 't'. Dissolution profile was considered satisfactory if f_2 value lies more than 50. The dissolution profiles are considered similar when the f_2 value is 50 to 100.

Stability studies

The prepared solid dispersions were further subjected to accelerated stability studies upto one month at 40 $^{\circ}\text{C}$ with 75% RH. The samples were withdrawn after one month and analyzed by PXRD and FTIR.

RESULTS AND DISCUSSION

In the present investigation an attempt was made to improve the solubility and dissolution rate of pioglitazone. The solid dispersions of pioglitazone were prepared by melt extrusion method using hot melt extruder with soluplus alone and in combination with PEG 1500 (10%) as carriers.

Solubility measurement

Initially saturated solubility studies were performed for the pioglitazone pure drug and also for the solid dispersion by using different buffer media. The solubility of pure drug and solid dispersions decreased gradually with increase in pH which indicated pH dependent solubility of the drug. The solubility studies also indicated that, the solubility of solid dispersion was increased by 16-18 folds at lower pH (1.2 and 2.0 pH) and 2-8 folds at higher pH (4.5, 6.8, 7.4 pH) when compared to that of pure drug.

Table I. Compositions of pioglitazone Solid Dispersions (SD)

Formulation code	Carrier	Ratios	Quantity (g)
SD1	Drug: Soluplus	1:2	10: 20
SD2	Drug : Soluplus	1:3	10: 30
SD3	Drug: Soluplus	1:4	10: 40
SD4	Drug: Soluplus	1:5	10: 50
SD5	Drug: Soluplus +PEG 1500(10%)	1:2	10: 18+2
SD6	Drug: Soluplus +PEG 1500(10%)	1:3	10: 27+3
SD7	Drug: Soluplus +PEG 1500(10%)	1:4	10: 36+4
SD8	Drug: Soluplus +PEG 1500(10%)	1:5	10: 45+5

Table II. Drug release studies of pioglitazone and SD 8

S. No	SD	% Drug released at 90 min	T ₅₀ (min)	T ₉₀ (min)	First Order Rate Constant K(min ⁻¹)	R ² (First order curve)
1	PD	61.36 ± 0.12	30	>90	0.042	0.920
2	SD1	70.24± 0.17	28	>90	0.094	0.977
3	SD 2	76.54± 0.30	24	>90	0.098	0.982
4	SD 3	80.63± 0.17	18	>90	0.167	0.987
5	SD 4	100.24± 0.22	16	45	0.181	0.992
6	SD 5	100.00± 0.24	14	55	0.194	0.987
7	SD 6	100.00± 0.27	9	35	0.173	0.994
8	SD 7	100.00± 0.11	8	28	0.183	0.996
9	SD 8	100.03± 0.13	6	20	0.173	0.997

The pure drug pioglitazone and its respective solid dispersions have exhibited very high solubility in pH 2.0 buffer than the other buffer media. The drug content in various solid dispersions prepared was estimated spectrophotometrically by measuring the absorbance at 269 nm. All the solid dispersions were found to have excellent entrapment of drug in the carrier. The pioglitazone drug content in all the dispersions were found to be in the range of 97 ± 1.1 to 99.89 ± 1.3 %.

Characterization of Solid Dispersions.

The physical state of pioglitazone in the solid dispersions was characterized by DSC, XRD and FTIR spectral studies. The DSC thermograms of pioglitazone alone showed endothermic peak at 192-199°C, corresponding to its melting point. The DSC thermogram of soluplus and PEG1500 (10%) have shown endothermic peak at 52°C indicating the melting point of PEG1500. Slight endothermic peak of drug was observed in solid dispersions

prepared with soluplus alone indicating the crystalline nature of drug. No sharp endothermic peak of pioglitazone was observed in solid dispersions prepared with combination of soluplus and PEG1500 (10%) indicating that pioglitazone was efficiently dispersed at molecular level. However, the peak of PEG 1500 in those solid dispersions was found to be shifted to lower values, indicated the solid-solid phase transition. This was further supported by XRD. The DSC thermograms of pioglitazone and other solid dispersions were given as figures 1 and 2.

The XRD patterns of pioglitazone, soluplus, PEG 1500 and solid dispersions were shown in figures 3 and 4. The powder diffraction patterns of pure pioglitazone showed characteristic high diffraction peaks. The diffraction patterns of Soluplus showed only few peaks with very weak intensities indicating the amorphous nature. On the other hand the diffraction patterns of solid dispersions showed decrease in the peak

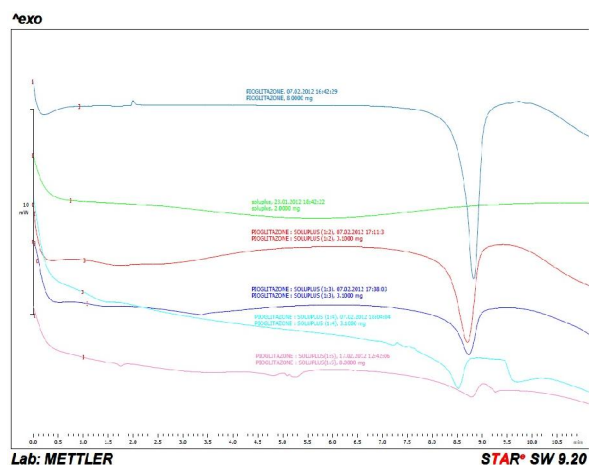


Figure 1. DSC Thermograms of Pioglitazone, SD1, SD2, SD3, SD4

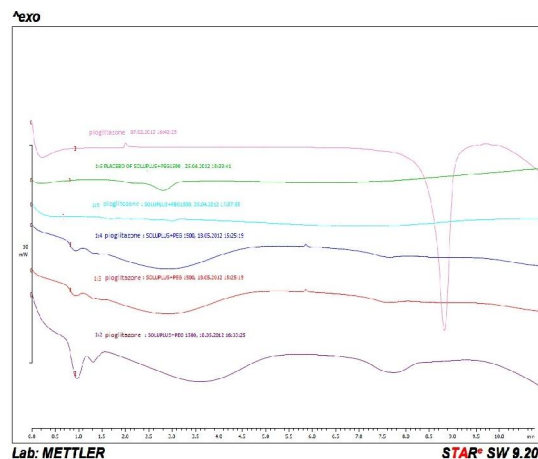


Figure 2. DSC Thermograms of Placebo, Pioglitazone, PLACEBO, SD5, SD6, SD

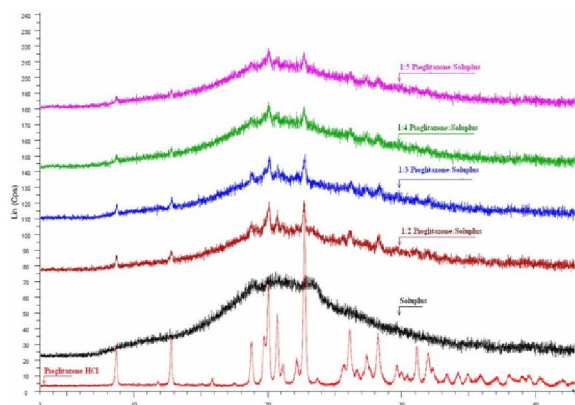


Figure 3. PXRD data of Drug, Placebo, SD1, SD2, Placebo, SD5, SD3, SD4.

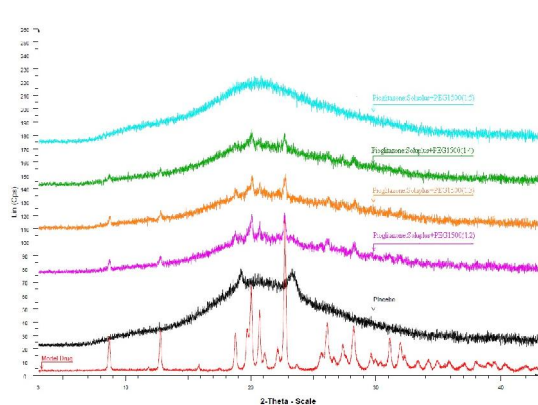


Figure 4. PXRD data of Drug, SD6, SD7, SD8

intensity and finally absence of peaks was observed in solid dispersions which indicated the amorphous nature of pioglitazone in solid dispersions and are considered to be the reason for the dissolution and solubility enhancement.

In order to investigate the possible interaction of the drug with carrier FTIR analysis was performed. Figure 5 shows the FTIR spectra of pure pioglitazone, soluplus and pioglitazone solid dispersion (SD8). FTIR spectra of pioglitazone showed characteristic absorption peaks at 3364 cm^{-1} (N-H stretching amide), 3084 cm^{-1} (aromatic C-H stretching), 2928 cm^{-1} (aliphatic C-H stretching asymmetric), 1743 cm^{-1} (amide C=O stretching), 1616 cm^{-1} (C=C), 1460 cm^{-1} (ring

C-N stretching), 1242 cm^{-1} (C-S stretching), 1084 cm^{-1} (aliphatic C-O-C) and 850 cm^{-1} (para disubstituted aromatic ring). A very broad band was observed at 2900 cm^{-1} that in solid dispersion which was due to the presence of water molecule. Along with the broad peaks from soluplus and PEG 1500 at 3600 cm^{-1} and 2900 cm^{-1} the FTIR spectra of solid dispersion still showed the peaks at same position of the drug. Hence the FTIR spectrum of the solid dispersion is seemed to be only a summation of drug and soluplus and PEG 1500. This indicates that there were no major interactions between the functional moieties of drug molecule with the excipients incorporated in the formulation of solid dispersions.

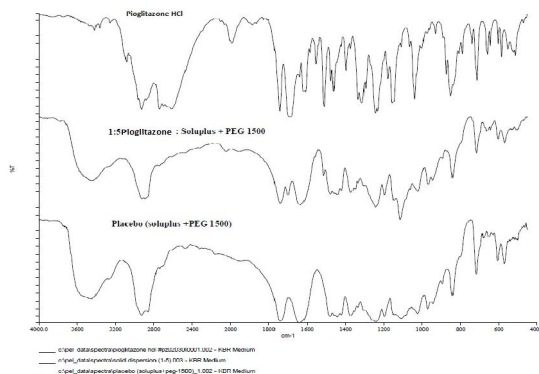
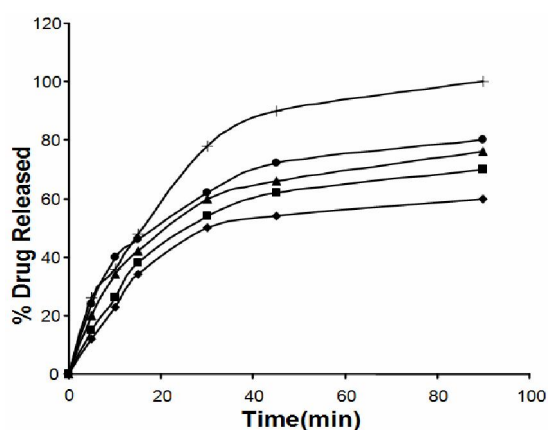
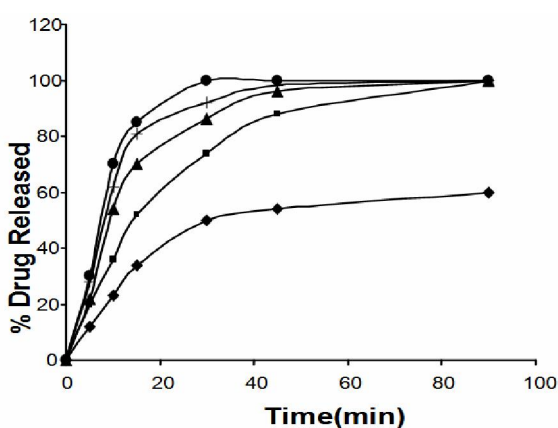


Figure 5: FTIR data of Drug, Placebo, SD8.

Fig 6: *In vitro* dissolution profiles of SD1, SD5, SD2, SD3, SD4 & Pioglitazone pure drug. Key: ♦ = Pure Drug, ■ = SD1, ▲ = SD2, ● = SD3, + = SD4Fig 7: *In vitro* dissolution profiles of SD6, SD7, SD8 and Pioglitazone Key: ♦ = Pure Drug, ■ = SD5, ▲ = SD6, + = SD7, ● = SD8

Dissolution Studies

The dissolution studies of pioglitazone as pure drug and its solid dispersions were performed in pH 2.0 hydrochloric acid buffer by using USP-II paddle method. Based upon the data obtained from the dissolution studies, various parameters such as T₅₀, T₉₀, DE30% and first order and zero order release rate constants were estimated. The dissolution parameters such as T₅₀ and T₉₀ were measured directly from the dissolution profile curves and DE30% was estimated by employing trapezoidal rule to the dissolution profiles. The first order release rate constant was calculated by multiplying the slope value obtained from log per cent drug undissolved *versus* time plot with 2.303. The dissolution rate of all the solid dispersions was found to be

rapid when compared to pure pioglitazone (Figure 6 and 7). The T₅₀, T₉₀ and rate constants (K) values of the dispersions indicated their rapid drug dissolution than that of pure drug. The kinetics of drug release from all the solid dispersions follows first order. The dissolution profiles of pioglitazone solid dispersions were compared with marketed tablet formulation of pioglitazone. The similarity factors were calculated for these formulations. The similarity factor *f*₂ values were in the 48 for the solid dispersion. All results were calculated as mean ± 3 S.D.

Solid dispersions prepared by melt extrusion method were found to be suitable in increasing the dissolution rate of poorly soluble drug pioglitazone. The rapid dissolution of

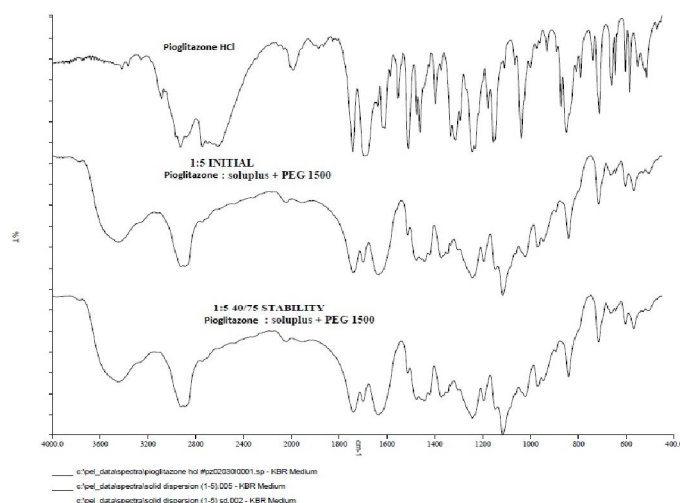


Figure 8. FTIR Stability data of Drug, Placebo, SD8.

pioglitazone from solid dispersions may be attributed to decrease in crystallinity of drug and its molecular and colloidal dispersions in hydrophilic carrier. As soluble carrier dissolves, the insoluble drug gets exposed to dissolution medium in the form of fine particles for quick and faster dissolution. It was found that solid dispersions containing drug and Soluplus plus PEG 1500 in the ratios of 1:5 prepared by melt extrusion method has shown faster dissolution rates than other dispersions.

Stability Studies

The solid dispersions (SD8) were further evaluated for accelerated stability studies at 40°C/75% RH for a period of 1 month. Pioglitazone found to be present in amorphous form in all the three formulations which was observed in the FT IR spectra given in figure 8 were recorded after 1 month.

Hot melt extrusion process was selected to prepare the solid dispersions of pioglitazone. Soluplus and PEG 1500 are used as carriers in preparing solid dispersions. The purpose of the study was to prepare solubility enhanced stable solid dispersions of pioglitazone and examines the solid-state properties of pioglitazone solid dispersions prepared using Soluplus and PEG 1500 at varying ratios. The solubility studies, DSC, XRD and FT IR characterization studies revealed that pioglitazone solubility was enhanced and it was in an amorphous state and uniformly distributed throughout matrix. The

spectral studies of pioglitazone solid dispersions exhibited no changes in the principle peaks and all the peaks were observed at specific wave numbers as that of their respective pure drug. Thus these studies indicated that there were no major interactions between the functional moieties of drug molecule with the excipients incorporated in the formulation of solid dispersions.

The XRD patterns of pioglitazone showed sharp peaks indicating the crystalline nature of pioglitazone. The diffraction patterns of solid dispersion showed decrease in the peak intensity or absence of peaks which indicated the amorphous nature of pioglitazone in solid dispersions. The dissolution studies of pioglitazone as pure drug and its solid dispersions were performed in pH 2.0 hydrochloric acid buffer by using paddle method. The dissolution rate of all the solid dispersions was found to be rapid when compared to pure pioglitazone. The T50, T90 and K values of the dispersions indicated their rapid drug dissolution that pure drug. The kinetics of drug release from all the solid dispersions follows first order. The release characteristics of poorly water soluble drug, pioglitazone from solid dispersion containing Soluplus and PEG 1500 was found to give rapid dissolution profiles than their respective counterpart. The solubility and dissolution rate of pioglitazone in its dispersions form was increased due to formation of a matrix with

Soluplus as a polymer. Soluplus is a polymeric solubilizer having amphiphilic chemical structure which is widely used for the development of solid solutions. Pioglitazone solid solutions prepared by Soluplus are capable of acting as matrix dispersions with enhanced dissolution rate.

CONCLUSION

The present research showed the suitability of Soluplus and PEG 1500 as carriers for the preparation of pioglitazone solid dispersions by hot melt extrusion process. The release characteristics of poorly water soluble drug, pioglitazone from solid dispersion containing Soluplus and PEG 1500 was found to give rapid dissolution profiles than their respective counterpart. Based on the above results solid dispersions prepared by hot melt extrusion process were found to be ideal for improving the dissolution rate and bioavailability of poorly soluble drug pioglitazone.

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