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Research Article

Enhancement of dissolution of Fenofibrate by Solid dispersion Technique

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ABSTRACT

Fenofibrate is a lipid lowering drug used in the treatment of hyperlipidemia, which is not soluble in water and lower absorption in gastric fluid. In order to improve the solubility and oral absorption of the drug in gastric fluid and to enhance its dissolution rate solid dispersions and Lyophilization of dispersion is designed and evaluated. Solid dispersions of Fenofibrate were prepared using PEG 6000, Poloxamer 407 and a mixture of PEG 6000 and Poloxamer 407(1:1 mixture). The effect of melt and solvent methods of preparation of solid dispersion on dissolution behavior was also investigated. Dissolution studies indicated a significant increase in dissolution of Fenofibrate when dispersed in PEG6000 and Poloxamer 407. Physical mixtures containing PEG and Poloxamer 407 also showed improved dissolution of Fenofibrate as compared with that of pure drug, indicating the solubilizing effect of PEG6000 and Poloxamer 407. Solid dispersions containing Fenofibrate /Poloxamer 407, 1: 8, showed a 14-fold increase in dissolution after 60 min (D60) and another dispersion containing Fenofibrate /PEG 6000, 1:10, showed an 8-fold increase in the 0.1 N HCl systems. The dispersion containing six parts of the PEG 6000: Poloxamer 407 mixture (PEG 4000/PEG 6000, 1:1 mixture) showed a 12-fold increase in D60 as compared with pure drug. When multi-carrier solid dispersion containing six parts of mixture was prepared by the solvent method, the D60 value was about 2-fold that of the same dispersion prepared by the melt method. The dissolution of lyophilized solid dispersions further increased the dissolution of Fenofibrate significantly.

Keywords: Fenofibrate; Poloxamer 407; Physical Mixture; Solid dispersion; Lyophilization; Solubility; Enhancement in dissolution.

1. INTRODUCTION

Poorly water-soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Improvement in the extent and rate of dissolution is highly desirable for such compounds, as this can lead to an increased and more reproducible oral bioavailability and subsequently to clinically relevant dose reduction and more reliable therapy. Nowadays, pharmaceutical technology provides many approaches to enhance the dissolution rate of poorly soluble drugs. Physical modifications often aim to increase the surface area, solubility and/or wettability of the powder particles and are therefore focused on particle size reduction or generation of amorphous states [Hancock, 1997 & Grau, 2000]. Several methods have been employed to improve the solubility of poorly water soluble drugs. A solid dispersion technique has been used by various researchers who have reported encouraging results with different drugs The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi (Sekiguchi, 1961). Technique for the preparation of solid dispersions, Lyophilization has also been thought of as a molecular mixing technique where the drug and carrier were co-dissolved in cyclohexanol, frozen and then sublimed under vacuum to obtain a lyophilized molecular dispersion (Lin, 1980). In conclusion, physical mixtures, solid dispersions and lyophilized solid dispersions increase dissolution of Fenofibrate. Lyophilized solid dispersions of Poloxamer 407 had the maximum effect on the rate and extent of dissolution of Fenofibrate. The results of this study clearly suggest that Lyophilization of solid dispersions is ideal for poorly water soluble drugs and aging has an adverse effect on the dissolution.

Fenofibrate has been used for many years to lower cholesterol levels and its pharmacokinetic profile is well understood (Martindale, 1989 & Munoz, 1994). Originally launched in 1975, it is currently on the compound is practically insoluble in water (Adkins, 1994 & Guichard, 2000) and has high lipophilicity (log P = 5.24) (Martindale, 1989). Thus the dissolution rate of fenofibrate is expected to limit its absorption from the gastrointestinal tract. Attempts to increase the oral bioavailability of the drug have therefore chiefly centered on particle size reduction. Increasing the rate and ex-

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tent of dissolution of fenofibrate by micronization has been shown to lead directly to an increased oral bioavailability, which in turn enables dosage reduction (Martindale, 1989). Recently, ''suprabioavailable'' tablets have been developed combining the classic micronization process with a specific microcoating technology, through which micronized drug particles are coated onto hydrophilic polyvinylpyrrolidone (PVP) cores (Guichard, 2000).

In this study, Freeze drying is used to develop solid dispersion of drug. There are various methods like physical mixing, fusion method and solvent evaporation is employed for the formulation of solid dispersion but freeze drying method has advantage that in this technique porous and amorphous microparticle of solid dispersion is forms and this will helps in the reduction of dose of the drug. Fenofibrate was chosen as a water-insoluble model drug and PEG 6000, Poloxamer 407 as a hydrophilic polymer and surfactant. Poloxamer 407 and PEG 6000 were employed as a carrier material for formulation of solid dispersion with model drug. Differential scanning calorimetry (DSC), X-ray powder diffraction and scanning electron microscopic (SEM) analysis were performed to determine the physicochemical properties of the solid dispersions in comparison with the plain drug.

2. EXPERIMENTAL METHODS

2.1 Apparatus and chemicals

Fenofibrate (99% purity) was obtained from Cadila Pharmaceuticals Ltd, India. Poloxamer 407 (Pluronic F127) was obtained from BASF (Mount Olive, NJ, USA). PEG 6000 was purchased from Sigma (UK). Other excipients used were of analytical grade. All chemicals were used as received.

2.2 Composition of Solid dispersion

Single component solid dispersions contained 2, 4, 6, 8 or 10 parts by weight of Poloxamer 407 or PEG 6000 and 1 part of Fenofibrate. Multi component solid dispersions contained 2, 4, 6, 8 or 10 parts by weight of a Poloxamer 407 and PEG 6000 (1:1, by weight) mixture and 1 part of Fenofibrate. Physical mixtures containing either Poloxamer 407 or PEG 6000 contained equal amounts of carrier and Fenofibrate. Table 1 lists the solid dispersion preparations used and gives their code numbers.

2.3 Preparation of solid dispersions

2.3.1 The fusion (melt) method

Accurately weighed amounts of carrier(s) were placed in an aluminum pan on a hot plate and melted, with constant stirring, at a temperature of about 60°C. An accurately weighed amount of Fenofibrate was incorporated into the melted carrier(s) with stirring to ensure homogeneity. The mixture was heated until a clear homogeneous melt was obtained. The pan was then removed from the hot plate and allowed to cool at room temperature.

Table 1: Composition of Solid dispersion

Carrier	Drug: Carrier	Method	Formulation code
Poloxamer 407	1:2	Fusion	FPL-2
	1:2	Solvent	SPL-2
	1:4	Fusion	FPL-4
	1:4	Solvent	SPL-4
	1:6	Fusion	FPL-6
	1:6	Solvent	SPL-6
	1:8	Fusion	FPL-8
	1:8	Solvent	SPL-8
	1:10	Fusion	FPL-10
	1:10	Solvent	SPL-10
PEG 6000	1:2	Fusion	FPE-2
	1:2	Solvent	SPE-2
	1:4	Fusion	FPE-4
	1:4	Solvent	SPE-4
	1:6	Fusion	FPE-6
	1:6	Solvent	SPE-6
	1:8	Fusion	FPE-8
	1:8	Solvent	SPE-8
	1:10	Fusion	FPE-10
	1:10	Solvent	SPE-10
Poloxamer 407-PEG 6000 (1:1)	1:2	Fusion	FX-2
	1:2	Solvent	SX-2
	1:4	Fusion	FX-4
	1:4	Solvent	SX-4
	1:6	Fusion	FX-6
	1:6	Solvent	SX-6
	1:8	Fusion	FX-8
	1:8	Solvent	SX-8
	1:10	Fusion	FX-10
	1:10	Solvent	SX-10

2.3.2 The solvent method

Accurately weighed amounts of Fenofibrate and carrier(s) were dissolved in minimum quantities of chloroform in a round-bottom flask. The solvent was removed using a rotary evaporator. The resultant solid dispersion was transferred to an aluminum pan and allowed to dry at room temperature.

2.4 Lyophilization of solid dispersions

The selected solid dispersions were dissolved in a minimum amount of Chloroform. This solution was rapidly solidified by transferring small portions with a Pasteur pipette onto the inner surface of a cold flask rotating in a -50°C methanol bath. After a certain layer thickness was obtained, the flask was attached to the vacuum adapter of the lyophilizer. The solvent was sublimed under a pressure of 8-10 mmHg and condensed onto a -60°C condenser. After the solvent was completely removed, the powder residue appeared as a porous,

light and fluffy mass. The lyophilized preparations were stored in a desiccator at room temperature.

2.5 Dissolution rate determination

An ELECTROLAB dissolution test apparatus type II (Paddle) at rotation speed of 50 rpm was used for the study. Dissolution of the drug and solid dispersion was carried out on an equivalent of 100 mg of the Fenofibrate in 0.1 M SLS as dissolution media. The volume and temperature of the dissolution media were 900 ml and 37 ± 0.2 0C, respectively. After fixed time intervals, 5 ml of samples were withdrawn and replace the same fresh dissolution media so as to maintain sink condition. The samples were filters through 0.2µm filters and diluted with HPLC mobile phase and these samples were assayed HPLC at 286 nm. To increase the reliability of the observations, the dissolution studies were performed in triplicate.

2.6 Statistical analysis

A cumulative correction factor was applied to compensate for the previously withdrawn samples in the dissolution studies. The following equation (Wurster and Taylor, 1965) was used:

$$C_n = C_{nobs} + (5/450)C_n - 1$$

Where C_{nobs} is the observed concentration of the n^{th} sample, C_n- 1 is the concentration of n- 1 sample and C_n is the corrected concentration of the nth sample. One way analysis of variance and the Student t-test were used to determine the presence of any significant differences ($P < 0.05$) among the test groups. (5) Differential scanning calorimetry studies

Thermal properties of the untreated drug and the prepared solid dispersion were analyzed by DSC (TA Instruments, USA, and Model: SDT 2960). The samples were heated in a hermetically sealed aluminum pans. Heat runs for each sample were set from 30 to 350°C at a heating rate of 10°C/ min, using nitrogen as blanket gas.

2.7 FT-IR Studies

FT-IR spectra of prepared Lyophilized solid dispersion were recorded on Shimadzu FT IR – 8400 spectrophotometer (Shimadzu Corporation, Kyoto, Japan). Potassium bromide pellet method was employed and background spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region 400 – 4000 cm^{-1} at spectral resolution of 2 cm^{-2} and ratio against background interferogram. Spectra were analyzed by software supplied by Shimadzu.

2.8 X-ray powder diffraction analysis

Crystallinity of the drug and the samples was determined using the Philips Analytical XRD (Model: PW 3710, Holland) with copper target. The conditions were: 40 kV voltages; 30 mA current; at room temperature. The samples were loaded on to the diffractometer and scanned over a range of 2° values form 10 to 80° at a scan rate of 0.05° /min.

3. RESULTS AND DISCUSSION

3.1 In Vitro Dissolution Study of Solid Dispersion

The dissolution of Fenofibrate from physical mixtures (Fenofibrate/Poloxamer 407 1:1) is shown in Fig. 1. The dissolution rate of Fenofibrate from all the physical mixtures was significantly higher than Fenofibrate alone. This demonstrates the solubilizing effects of the Poloxamer 407. The dissolution profiles of solid dispersions prepared using Poloxamer 407 exhibited significant increase in rate of dissolution in the 0.1 N HCl.

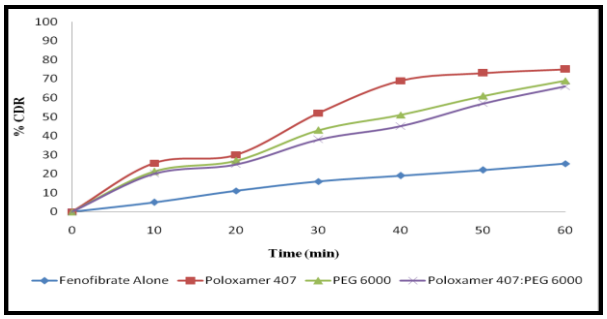


Figure 1: In vitro dissolution profile of Fenofibrate alone and Physical Mixtures (1:1) with Poloxamer 407 and PEG 6000

Dissolution for all the dispersions was significantly greater than those for Fenofibrate alone. Rate of dissolution was higher with the dispersions prepared by the fusion method. The dispersions prepared by the solvent method also shows the higher dissolution rate of drug then drug alone but it was lower than the dispersion prepared by the solvent method. The dispersion prepared with 10 parts of PEG 6000 had the highest dissolution at 60 min (D60) of 95%, which is significantly greater than the other dispersions. In both methods, the D60 values exhibited a direct proportionality with the amount of Poloxamer 407 & PEG 6000 contained in the solid dispersions. The dissolution profiles of solid dispersions containing Poloxamer 407 show identical dissolution for dispersions containing 1 part of Fenofibrate and 2, 4, 6, 8 and 10 parts of Poloxamer 407. Dispersions containing 8 parts of Poloxamer 407 appear to be the best preparation, showing a D30 value of 55.2% and a D60 value of 99.6%, which is about a 17- and 18-fold increase, respectively, compared with Fenofibrate alone. Dissolution profiles of solid dispersions prepared using a Poloxamer 407 and PEG 6000 mixture (1:1) were significantly higher than that of pure Fenofibrate. The dispersion containing 1 part of Fenofibrate and 6 parts of Poloxamer 407 mixture has the highest D30 and D60 values. The dissolution profiles of these preparations show identical dissolution for dispersions containing 1 part of Fenofibrate and 2, 4, 6, 8 and 10 parts of Poloxamer 407 mixture. Solid dispersions prepared with 10 parts of PEG 6000, 8

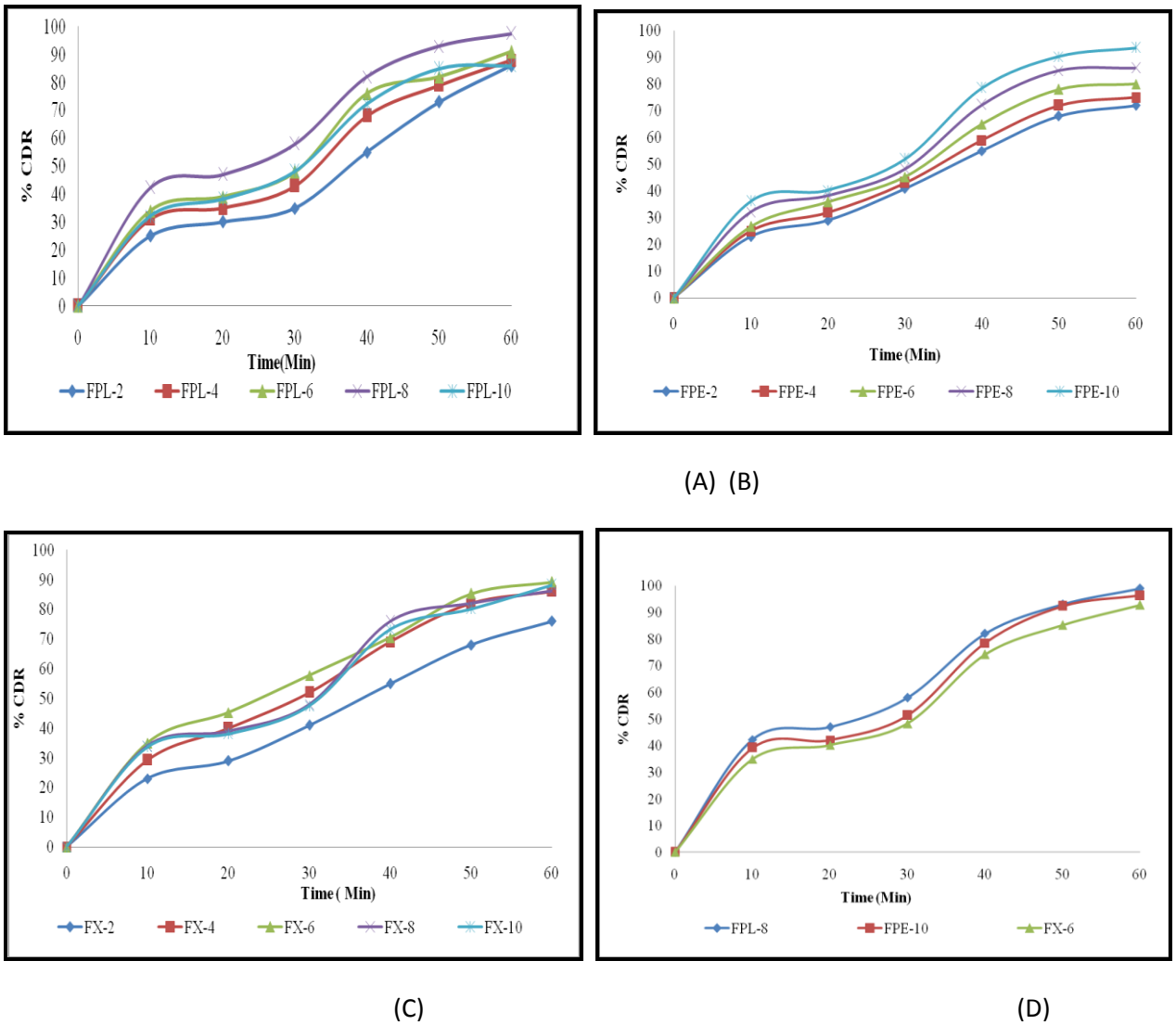


Figure 2: In vitro dissolution of solid dispersions at 60 mins (A) Ploxamer 407 (B) PEG 6000 (C) Poloxamer 407 : PEG 6000 Mixture (1:1) (D) Layophillised Solid dispersion

parts of Poloxamer 407 and 6 parts of mixtures of Poloxamer 407 and PEG 6000 were chosen for lyophilization because these dispersions provided the best dissolution profiles. The rate and extent of dissolution increased with all the lyophilized solid dispersions. However, the extent of dissolution was maximum with the dispersions prepared using Poloxamer 407 and Poloxamer 407 mixture. Dissolution of Fenofibrate, physical mixtures, solid dispersions and lyophilized solid dispersions at 60 min (D60) are shown in Figure. 2.

All the lyophilized solid dispersions show a significant increase in D60 values compared with their respective plain solid dispersions. Lyophilized solid dispersion prepared with 6 parts of Poloxamer 407 mixtures showed the steepest increase, with D60 almost doubling upon lyophilization. The non-equilibrium solubility studies with powdered materials give a good indication of the dissolution profiles of solid dispersions of different drugs. The dissolution of the drug from the solid dispersion is also affected by the method of preparation of the solid dispersion. It also depends on the proportion and properties of the polymer carrier used in the composition of solid dispersion (Corrigan, 1985).

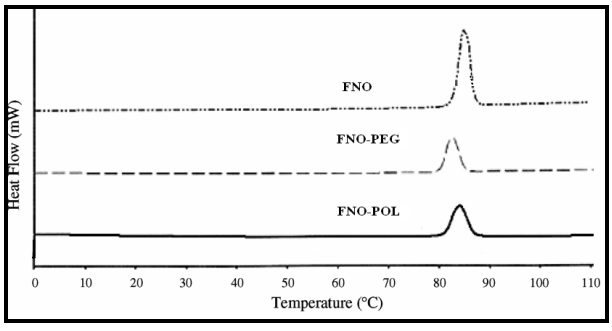


Figure 3: DSC of Fenofibrate alone, Lyophilized Solid dispersion with PEG 6000 and Poloxamer 407

Solid dispersions containing Poloxamer 407, PEG 6000 and a mixture of the Poloxamer 407 & PEG 6000 all showed higher dissolution rates compared with Fenofibrate alone. Physical mixtures also exhibited higher

dissolution rates as compared with Fenofibrate alone, demonstrating the solubilizing properties of Poloxamer 407. However, dissolution rates of solid dispersions were significantly higher than their corresponding physical mixtures. The process of lyophilization occurs in three stages: freezing, primary drying (ice sublimation) and secondary drying (water desorption) (Pikal, 1983).

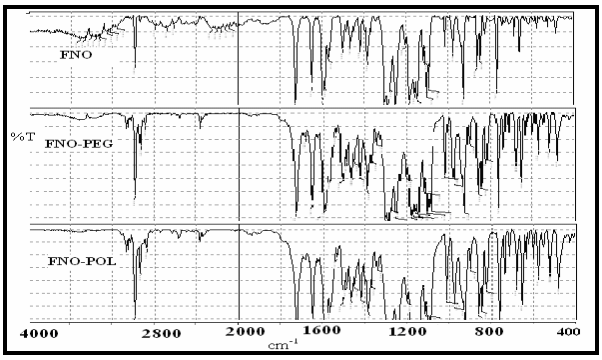
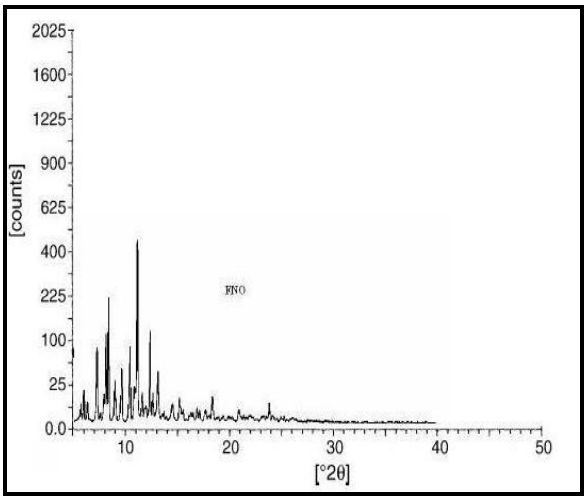
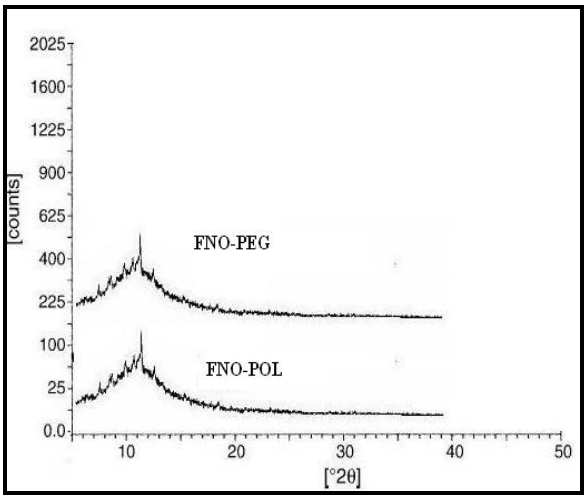


Figure 4: FT-IR of Fenofibrate alone, Lyophilized Solid dispersion with PEG 6000 and Poloxamer 407

The freezing process largely determines the physical traits of the dried solid product (MacKenzie, 1976). Primary drying represents the initial onset of the drying process from the top. Secondary drying process begins when the ice has been completely removed from that area. Thus, primary and secondary drying could occur simultaneously. The resultant dry mixture is porous and fluffy and the original starting volume is maintained. This increases the surface area and hence, the surface free energy is also higher, resulting in an increase in the dissolution rate. The initial rapid dissolution of Fenofibrate could be due to finely divided particles of Fenofibrate in a lyophilized solid dispersion surrounded intimately in the matrix by the Poloxamer 407 particles. Two theories have been proposed to explain the higher dissolution rates of solid dispersions. One theory proposes that higher energy metastable states of the components are formed as a function of the carrier system being used and the proportion of carriers present (Simonelli, 1969). This could explain the fact that solid dispersions exhibit higher dissolution rates than physical mixtures. The method of preparation of solid dispersions could also determine the solid phase energy states. The second theory states that the dissolution is affected because of the formation of a solid solution of the drug. The particle size is reduced to molecular size when the carrier brings the drug into the dissolution medium. Thus, the faster dissolution rate can be explained based merely on the particle size without anything to do with energy changes. The presence of carrier may also prevent aggregation of fine drug particles, thereby providing a larger surface area for dissolution. The wetting properties are also greatly increased due to the surfactant property of the polymer, resulting in decreased interfacial tension between the medium and the drug and, hence, higher dissolution rates. The presence of carrier polymers also inhibits crystal growth of the drug which facilitates faster dissolution (Sekikawa, 1979).



(A)



(B)

Figure 5: (A) Powder XRD of Fenofibrate alone, (B) Lyophilized solid dispersions with PEG 6000 and Poloxamer 407

3.2 DSC Study

Figure 3 represents the DSC study of Fenofibrate and Fenofibrate solid dispersions. The corresponding melting point depressions, enthalpy of fusion and degree of crystallinity are shown in figure. A depression in melting point of fenofibrate was found in solid dispersions, which indicates an interaction of fenofibrate with carrier molecule Poloxamer 407 and PEG 6000. The DSC thermograph of Fenofibrate lyophilized formulation shows only endothermic peak; the absence of exothermic re-crystallization peak may be attributed to interaction between drug and polymers.

3.3 FT-IR Study

State of drug molecule with the different hydrophilic polymers and surfactants was determined using FT-IR.

Figure 4 shows IR spectra of Fenofibrate and prepared solid dispersion. IR-spectra of Fenofibrate and solid dispersion are exactly same, and there is no shift of peaks after adsorption of drug onto polymer and surfactants surface; indicating that there is no change in chemical structure of drug after preparing it into melt granules. Specific Fenofibrate peaks are observed at 2990, 1740, 1660, and 1600cm $^{-1}$ and observed same in prepared solid dispersion formulation.

3.4 Powder X-RAY Diffraction Study

Fenofibrate crystals show various diffraction peaks (figure 5) due to its crystalline structure. However, the solid dispersion shows a loss of drug crystallinity due to drug loading onto polymers and surfactants surface. In optimized solid dispersion, a few less intense and wide diffraction peaks of fenofibrate are observed, which may be attributed to the adsorption process in which some of amorphous drug may have crystallized due to higher temperature.

4. CONCLUSION

In conclusion, physical mixtures, solid dispersions and lyophilized solid dispersions increase dissolution of Fenofibrate. Lyophilized solid dispersions of Poloxamer 407 had the maximum effect on the rate and extent of dissolution of Fenofibrate. The results of this study clearly suggest that lyophilization of solid dispersions is ideal for poorly water soluble drugs. The adsorption of Fenofibrate does not leave any residual solvent in the final formulation because of elimination of use of solvent from the preparation of solid dispersion. Crystallinity of the solid dispersion are reduced due to drug–excipients interaction in formulation obtained using lyophilization technique without any chemical interaction and slightly reducing the melting point.

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