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Research Article

BINARY AND TERNARY SOLID DISPERSIONS OF FENOFIBRATE FOR SOLUBILITY ENHANCEMENT

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ABSTRACT

Fenofibrate is a class II BCS drug, having poor solubility and high permeability. It is widely prescribed as an anti-hyperlipidemic drug. Since fenofibrate shows dissolution-rate limited bioavailability, the aim of the present study was to improve its solubility and dissolution rate by preparing various binary and ternary solid dispersions comprising polyethylene glycols of different molecular weights along with anionic and non-ionic surfactants. Melt method was used to prepare the solid dispersions, which were characterized by DSC, FT-IR and XRPD. Solubility studies indicated that ternary solid dispersions comprising fenofibrate, PEG 10000 and TPGS showed significant increase in the solubility of the drug as compared to binary solid dispersions prepared with PEGs of any molecular weight. Solubility of drug was enhanced from 4.14µg/ml to 63.67µg/ml, thus an increase of 15 folds was evident. The percent release of the drug from ternary solid dispersions was above 95% in both distilled water and in 0.1N HCl. At lower molecular weights of PEG, increase in saturation solubility was evident with increase in molecular weight. At higher molecular weights, though saturation solubility was much greater than with lower molecular weight PEGs, no significant difference was seen between saturation solubilities with PEG 8000 and 10000.

Keywords: Fenofibrate, Polyethylene glycols, TPGS, Solubility enhancement

INTRODUCTION

Together with permeability, the solubility of a drug is a key determinant of its oral bioavailability. With the advent of high throughput screening and combinatorial chemistry, the number of poorly soluble drugs has dramatically increased[1].

These 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.

Fenofibrate(FEN) is ahypolipidemic drug that is practically insoluble in water and has very high lipophilicity(log P = 5.24). Hence, the dissolution profile of FEN is expected to limit its absorption from the GIT[2]. It is therefore critical to improve the dissolution rate of FEN to enhance the bioavailability due to its low solubility. For improving the dissolution rate, the dissolution medium used must provide sink conditions (i.e. saturation solubility must be at least three times more than the drug concentration in the dissolution medium as outlined in USP)[3].For obtaining good results, the drug concentration in the dissolution medium should not exceed15% to 20% of saturation solubility of the drug so as to achieve sink conditions[4,5,6].

Various strategies for solubility enhancement can be broadly classified as formulation based and structure based approach. The former involves inclusion of various solubility enhancers and the second approach involves modification of either the physical or chemical structure. Based on these strategies, several techniques that have been reported in literature for enhancing drug solubility include complexation with βcyclodextrins, preparation of high energy drug states related to polymorphic or amorphic transformations, use of particle size manipulation via micronization and nanonization[7-11]and the use of co-solvents, micellar solutions and lipid based systems for lipophilic drugs[12,13].

The solid dispersion (SD) technique for poorly water soluble drugs developed by Chiou and Reigelman14 provides an efficient method to improve the dissolution profile of a drug. In a SD, the drug may exist as an amorphous form in polymeric carriers; which may lead to its increased solubility when compared with its crystalline form15,16. Drug solubility and wettability may be enhanced by these surrounding hydrophilic carriers17.The aim of the present study was to improve the solubility and dissolution rate of a poorly water-soluble drug FEN using binary and ternary SDs prepared using polyethylene glycols (PEGs) of different molecular weights and surfactants like to copherol polyethylene glycol succinate (TPGS) and sodium lauryl sulphate (SLS). Melt method was used to prepare the SDs.

MATERIALS AND METHODS

Materials

FEN was obtained as a gift sample from Smruthi Organics, India. Tocopherol polyethylene glycol succinate (TPGS), PEG 8000 and PEG 10000 were obtained as a gift samples from Isochem Group SNPE, France and S.D. Fine Chemicals Ltd., Mumbai respectively. PEG 2000, PEG 4000, PEG 6000, sodium lauryl sulphate (SLS) and other ingredients were purchased locally. All the chemicals and reagents used were of analytical (AR) grade.

Methods

Preparation of physical mixtures (PM)

PMs were prepared in 1:1 ratio (drug: polymer) by mixing FEN and the polymers in a mortar for 5 min and then sieving through 44 mesh screen.

Preparation of solid dispersions (SDs)

Binary SDs of FEN with PEGs as carriers and ternary SDs additionally comprising TPGS or SLS as surfactants were prepared in 1:1:0.25 ratios by melt method[18].

For preparation of binary SDs, FEN (M.P=80.5°C) and PEGs were melted separately in an evaporating dishand mixed and cooled to room temperature till the mass solidified.

In case of ternary SDs, 0.25 g of TPGS or SLS were dispersed in the melt, mixed and cooled to room temperature till the mass solidified. The SDs thus prepared were then passed through sieve no. 44 and stored in glass vials till further evaluation. The details of the solid dispersions prepared have been listed in Table 1.

Drug Content (Assay)

SDs(10 mg)were accurately weighed and dissolved in 10 ml of ethanol and filtered through the Whatmanfilter paper no 1.Filtrate (1 ml) was diluted with ethanolup to 10 ml and absorbance was measured by UV spectrophotometryat λmax of 290 nm(Jasco,V-530,Japan).

Table 1: Table shows Scheme for binary and ternary solid dispersions

S. No.	Solid dispersions	Ratios	Codes
1.	Drug+PEG 8000 (Physical Mixture)	1:1	PM1
2.	Drug+PEG 10000 (Physical Mixture)	1:1	PM2
3.	Drug+PEG 8000	1:1	SD1
4.	Drug+PEG 10000	1:1	SD2
5.	Drug+PEG 8000+TPGS	1:1:0.25	SD3
6.	Drug+PEG 8000+SLS	1:1:0.25	SD4
7.	Drug+PEG 10000+SLS	1:1:0.25	SD5
8.	Drug+PEG 10000+TPGS	1:1:0.25	SD6
9.	Drug+PEG 2000	1:1	SD7
10.	Drug+PEG 4000	1:1	SD8
11.	Drug+PEG 6000	1:1	SD9
12.	Drug+PEG 2000+TPGS	1:1:0.25	SD10
13.	Drug+PEG 4000+TPGS	1:1:0.25	SD11
14.	Drug+PEG 6000+TPGS	1:1:0.25	SD12
15.	Drug+PEG 2000+SLS	1:1:0.25	SD13
16.	Drug+PEG 4000+SLS	1:1:0.25	SD14
17.	Drug+PEG 6000+SLS	1:1:0.25	SD15

Saturation solubility studies

The saturation solubility of FEN was determined in distilled water (DW) using shake flask method at 37ºC for 24 h using rotary orbital shaker (REMI INSTRUMENTS Ltd., CHM 6S). The samples were filtered through Whatman filter paper No. 1and the filtrate was assayed by UV spectrophotometry.

***In vitro* dissolution studies**

The dissolution of the samples was studied using USP dissolution apparatus II (paddle method). The studies were carried out in 900 ml of DW maintained at 37□0.5°C at 100 rpm. Accurately weighed SDs equivalent to 160 mg of FEN were placed in the dissolution medium and 5 ml aliquots were withdrawn at appropriate time intervals over period of 2 h and filtered through 0.45 µm membrane filter. An equal volume of fresh dissolution medium was immediately replaced. The concentration of FEN at each sampling time was analyzed spectrophotometrically at 290 nm and cumulative percent release was plotted against time.

X Ray Powder Diffraction (XRPD) studies

The crystallinity of samples was investigatedby XRPD using Brukerdiffractometer (WI 1140, Japan) and Cu-Kα radiation. Thediffractograms were run at 2.5 °C min^{-1} and chart speed of 2°/2 cm per 2θ angle.Degree of crystallinity (DC) of the product was calculated usingthe following equation[19,20]

$$DC = \frac{S_{cr}}{S_{cr} + S_{am}} \times 100$$

Where, 'S_{cr}' is the total area of peaks of the crystalline phase and 'S_{am}' is the area of halo from the amorphous phase.

FT-IR studies

Structural changes and lack of a crystal structure can lead to changes in bonding between the functional groups which can be detected by infrared spectroscopy. The FT-IR spectra of the samples (pure drug, PMs and SDs) was determined by grinding and mixing the samples with potassium bromide in a ratio of 1:100(sample:KBr). Samples were subjected to FTIR studies on FTIR-4100Type with TGS Detector, over a spectral range of 4000 to 400 cm^{-1}.

DSC analysis

The thermal characteristics of the pure drug, PMs and SDs were determined by differential scanning calorimetry (DSC Q2000 V24.2 Build 107). The scanning rate was 10°/min, and the scanning temperature range was between 30° and 300°.Samples of about 5 mg were sealed into aluminum pans.

Stability studies

SDs were put into glass vials and subjected to stability studies at 40°/75% RH for period of 6 months. Samples were kept in stability chambers (REMI INSTRUMENTS Ltd., CHM 6S) and samples were withdrawn at specified intervals for analysis of its drug content.

RESULTS AND DISCUSSION

Saturation Solubility Studies

The solubility of FEN in water at 37°C was found to be 4.14µg/ml. Therefore, FEN can be considered as practically insoluble drug in water. When saturation solubility values of SDs prepared by melt method were compared, an enhancement in the solubility of the drug was evident. Binary SDs with PEGs of different molecular weights (2000, 4000, 6000, 8000 and 10,000) produced a marginal increase in saturation solubility of FEN. Binary SDs with PEG 8000 and 10000 produced a 2.3-2.5 fold increase in saturation solubility. Ternary SDs with the PEGs were prepared which comprised an anionic and non-ionic surfactant. The SDs containing SLS as surfactant produced a significant enhancement in solubility in the range of 14-30 µg/ml. The higher molecular weight PEGs exhibited a greater enhancement in the range of 7.5 times that of plain drug. In case of ternary SDs with TPGS, the increase was significantly greater for PEGs of all molecular weights as compared to SDs prepared with SLS as surfactant. The ternary SDs with PEG 2000, 4000 and 6000 containing either SLS or TPGS displayed an increase which was proportional to their molecular weights. However at higher molecular weights of 8000 and 10000 the increase in saturation solubility was almost similar. The ternary SD comprising FEN, PEG 10000 and TPGS showed maximum solubility enhancement as compared to the other SDs. Solubility of FEN was enhanced from 4.14µg/ml to 63.67µg/ml (Fig.1).Thus, we may conclude that non-ionic surfactant (TPGS) plays a synergistic role along with the hydrophilic polymers in enhancing the saturation solubility of FEN. The effect of SLS on saturation solubility of FEN was not as dramatic as that of TPGS. However it did produce an increase of 3.5-7.5 times that of pure drug. For all ternary dispersions, molecular weight was found to be an important parameter influencing solubility only at the lower end of the spectrum (PEG 2000, 4000 and 6000). At higher molecular weights of PEGs namely, PEG 8000 and PEG 10000, the increase in saturation solubility was higher than lower molecular weight PEGs but the respective solubility of FEN in SDs of PEG 8000 and 10000 was almost similar. Solid dispersions with hydrophilic polymers are known to increase the saturation solubility of poorly water soluble drugs by one or more of the following mechanisms, viz., a) disrupted crystal lattice, b) reduced particle size *in vivo* as the polymer dissolves in the biological fluids, c) improved wettability and d) prevention of agglomeration[1]. FEN is reported to have a high log P of 5.24 which is indicative of its high lipophilicity. It was

observed that the binary SDs did not significantly impact the saturation solubility whereas the ternary SDs produced a comparatively dramatic increase. We may infer from this that the surfactants reduce the interfacial tension between the hydrophobic FEN particles which have precipitated in vivo and the biological fluids. This appears to improve the wettability of the particles thereby allowing access to the aqueous fluids. Hydrophobic particles tend to agglomerate in unfavorable surroundings i.e. aqueous surroundings in an attempt to reduce the interfacial area of contact. Presence of surfactants appeared to prevent this tendency by forming an interfacial barrier film on the particles. The cumulative effect of all this is improvement in saturation solubility. In case of sodium lauryl sulphate due to the presence of a negative charge, formation of an effective barrier may be precluded, thus accounting for the comparatively less dramatic increase in solubility than TPGS.

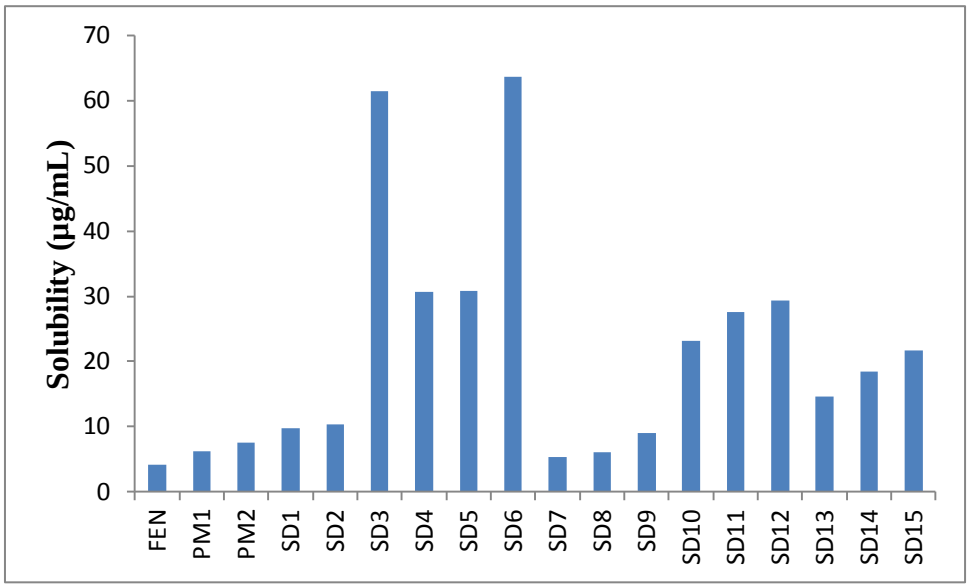

Fig. 1: It shows Solubility profiles of binary and ternary SDs

DSC studies

Differential Scanning Calorimetry (DSC) is a useful method that enables the quantitative detection of all processes in which energy is required or produced (i.e. endothermic and exothermic transformations). Since binary and ternary SDs with PEG 8000 and 10000 were found to have a greater influence on saturation solubility of FEN than the other PEGs, their physical mixtures and SDs were subjected to thermal analysis. The DSC thermograms for pure drug, SDs and their corresponding physical mixtures are displayed in Fig.2.FEN and PEG 8000 displayed sharp melting endotherms at ~80 and 60°C whereas a broad endotherm was seen in the thermogram of PEG 10000 with an onset of about 55°C. This can be attributed to impurities of lower molecular PEGs in the raw material. Reduction in sharp melting peak of drug in SDs may be due to dilution effect of polymers or to amorphization of drug. The intensity of melting endotherm of FEN was found to be reduced and the peak had shifted to lower temperature. So, shift of melting peak and reduction in intensity of the peak are indicative of the fact that FEN may be present in amorphous state in the SD or may have formed solid solution. The enthalpy of melting (Table 2) for plain drug was found to be 84 J/g and for the SDs it was found to be in the range of 94-99 J/g. When a solute goes into solution, it is present in the liquid state and hence the enthalpy of melting is a critical physical property affecting its solubility. A higher enthalpy is indicative of stronger crystals lattice energy and hence of poor solubility. For SDs of FEN the enthalpy of melting was found to increase nominally to the extent of 18%. This could be attributed to presence of the PEGs which themselves have a relatively higher enthalpy. However this factor did not appear to have an impact on saturation solubility of FEN as SDs.

XRPD studies

The XRPD of FEN shows sharp peaks at a diffraction angle of 2θ at 5.6 º, 10.2º and 22.7º as shown in Fig.3.This suggests that the drug is present as a crystalline material. The XRPD of SD showed a decrease in the number of peaks and the peak intensity. This indicates the decrease in the crystallinity of the drug i.e. amorphization which might have led to improved solubility of FEN. The degree of crystallinity for the SDs was found to be in the range of 72-80% of that of plain drug.

Table 2: Table shows Thermal analysis data for SDs

S. No.	Batch code	Peak temperature (°C)	Enthalpy (J/g)
1.	FEN	80.55	84.82
2.	PEG8000	59.89	190.7
3.	PEG10000	60.31	182.51
4.	PM1	78.13	57.88
5.	PM2	76.64	58.03
6.	SD1	57.34	99.96
7.	SD2	58.09	94.28
8.	SD3	56.59	94.06
9.	SD4	53.09	93.27
10.	SD5	56.95	99.60
11.	SD6	56.91	99.99

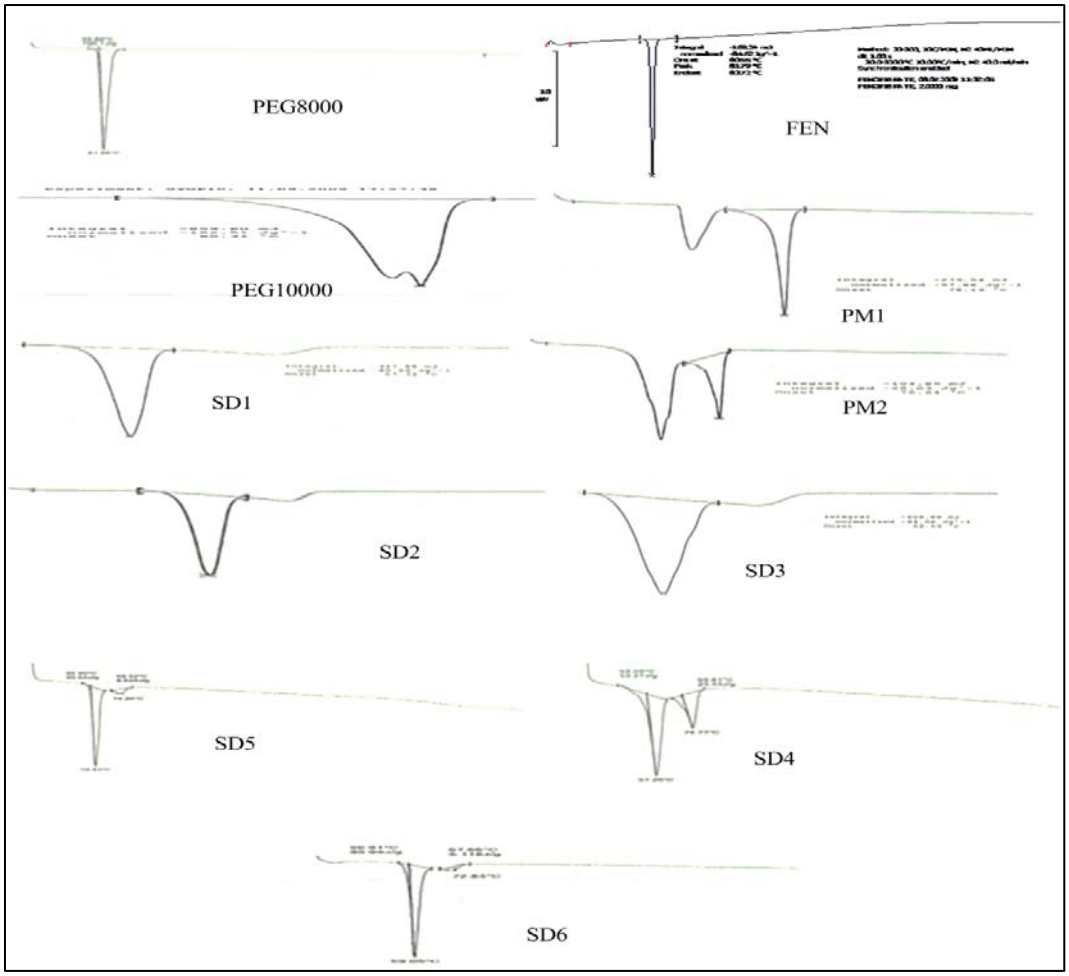

Fig. 2: It shows DSC thermograms of various SDs

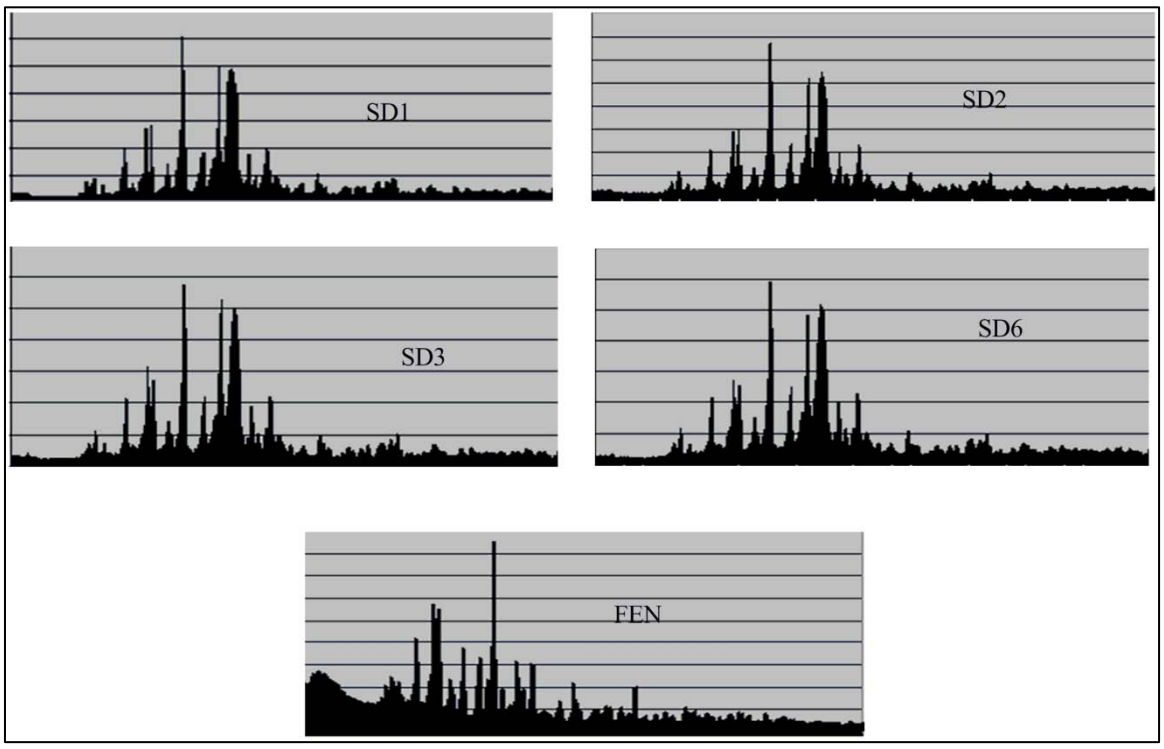

Fig. 3: It shows XRPD of various SDs

FTIR studies

FTIR spectra of the pure drug and SDs have been depicted in Fig.4.The spectrum of pure drug shows characteristic sharp peaks at 3039cm^{-1} due to alkyl groups, at 3439cm^{-1} due to phenol and at 1625cm^{-1} due to carbonyl group. Whereas, the spectra of SDs showed broadening of the peaks which indicate that the drug may be present in the molecular state that may have led to its increased solubility. The absence of any gross changes in the IR spectra is indicative of the stability of FEN in the SDs.

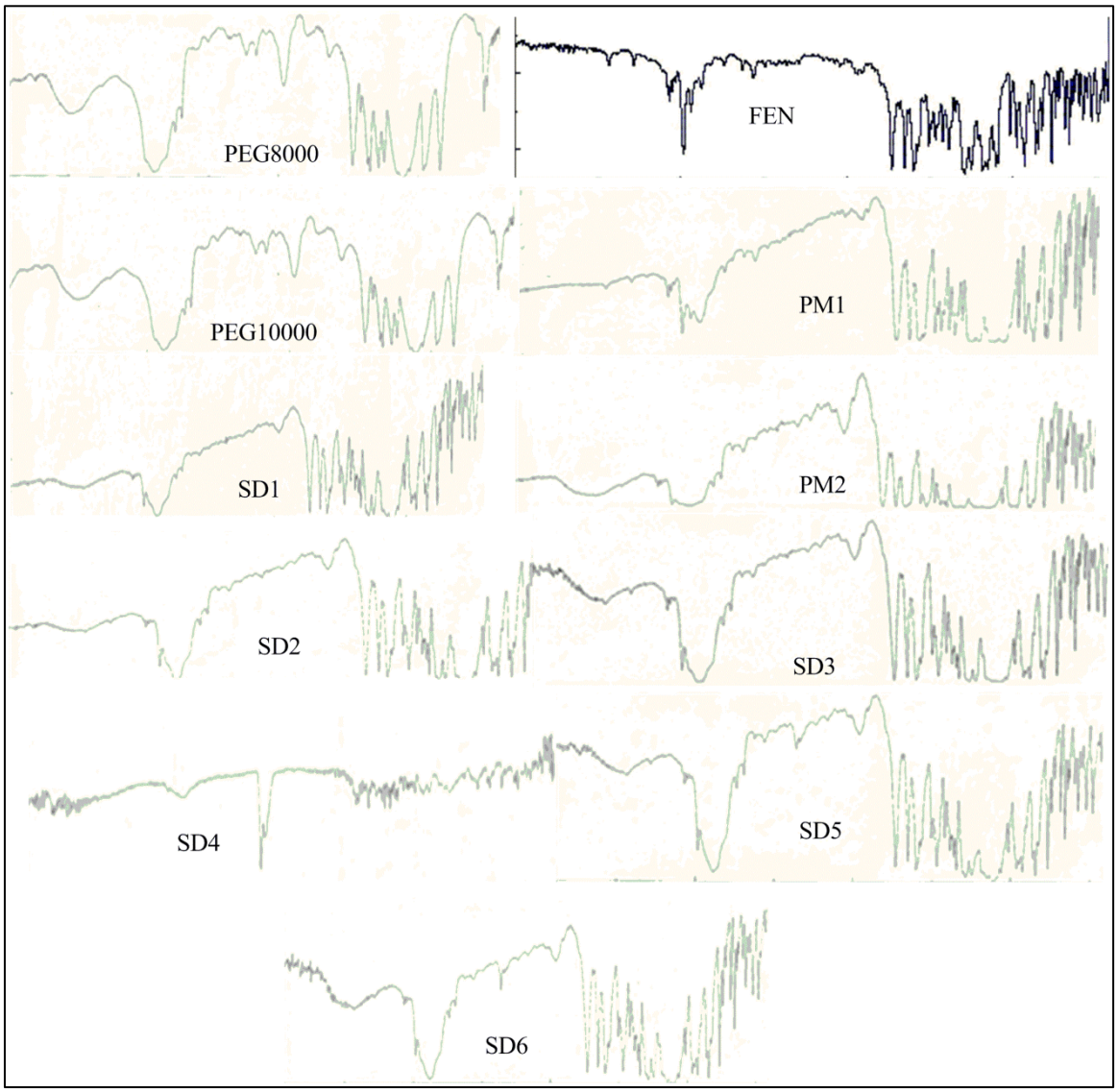

Fig. 4:It shows FTIR graphs of SDs

***In vitro* dissolution studies**

In vitro dissolution test is used as an indirect measurement of the drug bioavailability. Dissolution rates of the solid dispersions were found significantly higher than the pure drug. The dissolution media used were DW and 0.1NHCl respectively. Fig.5A&Fig. 5B depicts the dissolution rate profile for the solid dispersions prepared by melt method in DW and 0.1N HCl respectively. A release of 7% and 12 % was seen for FEN in DW and 0.1 N HCl. In fact the release was found to reach a plateau at these values. This could be due to the agglomeration of FEN particles which is highly hydrophobic in nature. Binary SDs with PEG 8000 and 10000 released 38-45% drug in a span of 120 min. Ternary SDs with PEG 8000 and TPGS (SD3) released 95% drug in 120 min while with SLS (SD4) the release was to the tune of 78%. Similarly ternary SDs with PEG 10000 and TPGS (SD6) released more than 98% drug in 2h while ternary dispersions with PEG 10000 and SLS (SD5) were found to release 89% drug in the same duration. Since similar dissolution patterns were observed in 0.1N HCl for all the SDs, we may infer that pH did not have any effect on the release profile of FEN from the SDs. Thus it was observed that an enhancement in dissolution rate is also evident and a similar trend in observations as saturation solubility is observed.

Stability studies

The protocol of stability studies were in compliance with the guidelines in the WHO document for stability testing of protocol intended for the global market. Samples were withdrawn at intervals of 0,15,30,90,150 and 180 days and retested for their drug content. The results for drug content are depicted in Table 3.The drug was found to be stable at the end of testing period and we may conclude that the heat employed during processing of the SDs does not have an adverse impact on the drug stability.

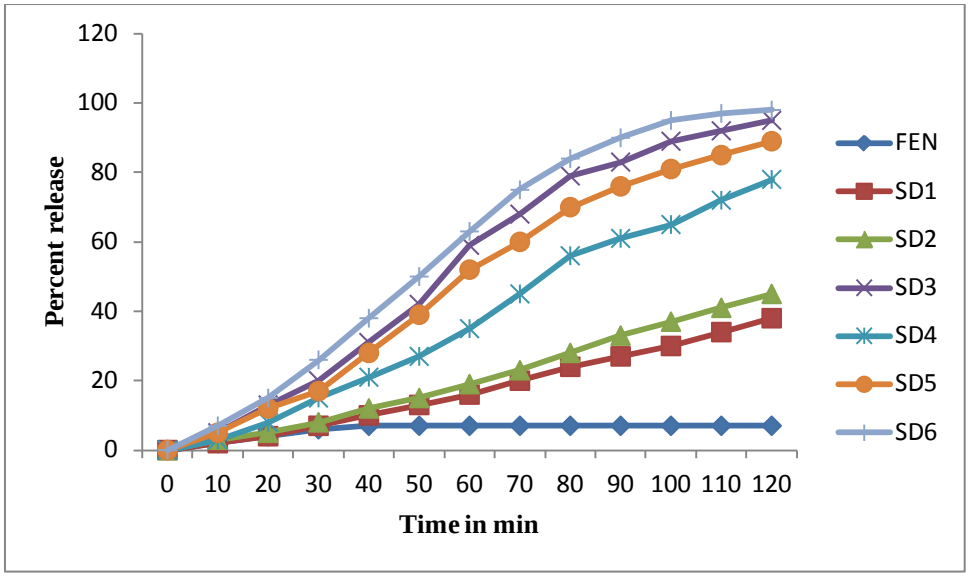

Fig. 5.A: It shows Dissolution profile of SDs in DW

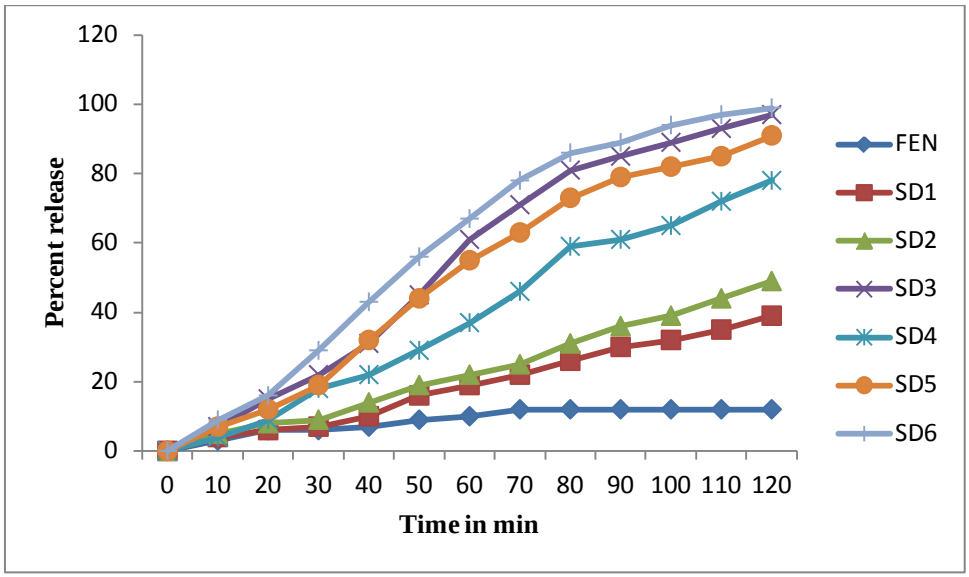

Fig. 5.B: It shows Dissolution profile of SDs in 0.1N HCl

Table 3: Table shows Percent drug content for stability samples

Polymer	Surfactant	0days	15days	30days	90days	150days	180days
PEG 8000	Nil	98.86	98.78	98.64	98.27	97.96	97.14
PEG 8000	SLS	98.82	98.77	98.72	98.62	98.13	97.68
PEG 8000	TPGS	99.14	99.06	98.83	98.66	98.52	8.21
PEG 10000	Nil	98.88	98.76	98.70	98.14	97.73	97.24
PEG 10000	SLS	98.80	98.60	98.45	98.18	97.69	97.32
PEG 10000	TPGS	99.16	99.08	98.85	98.71	98.67	98.42

CONCLUSION

Solid dispersion with PEGs of different molecular weights was found to be an effective and simple technique to enhance the solubility and dissolution rate of fenofibrate. The fusion method employed for preparing the SDs also did not adversely impact the stability of the drug. At lower molecular weights of PEG, increase in saturation solubility was evident with increase in molecular weight. At higher molecular weights, though saturation solubility was much greater than with lower molecular weight PEGs, no significant difference was seen between saturation solubilities with PEG 8000 and 10000.

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