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Der Pharmacia Lettre, 2015, 7 (3):162-173
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Enhancement of dissolution and bioavailability of fenofibrate by Solid Dispersion with sodium citrate, HPMC and sugar derivatives

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ABSTRACT

In this study, a significant effect of sodium citrate increasing fenofibrate dissolution has been demonstrated. This effect was dependent on the polymer: drug mixing weight ratio, the sodium citrate type and the method used to disperse the drug with in the polymer. The greater the sodium citrate content the higher the drug dissolution was, up to a maximum corresponding to a polymer: drug ratio of 6:1. Significant differences within the various tested polymers were observed. The various sodium citrate: fenofibrate solid mixtures were ordered, according to the efficiency of improving the drug dissolution, as follows: solid dispersion\kneaded mixture\solvent evaporation. The drug dissolution enhancement was attributed to the decreased drug crystallinity and size and polymer wetting effect. Solvent evaporation of sodium citrate along with fenofibrate in a 6:1 ratio, which leads to solid mixtures exhibiting a significantly improved dissolution profile without requiring the addition of organic solvents or high temperatures for its preparation, appears to be the more simple and convenient method.

Keywords: Sodium Citrate; Kneading methods; Dissolution enhancement; Fenofibrate; Bioavailability

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INTRODUCTION

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 [1]. Fenofibrate has been used for many years to lower cholesterol levels and its pharmacokinetic profile is well understood [2]. Originally launched in 1975, it is currently on the compound is practically insoluble in water (Adkins, 1997) and has high lipophilicity (log P = 5.24) [2]. Fenofibrate (2-[4-(4-cholrobenzyol) phenoxy]-2-methylpropanoic acid, 1-methylsethyl ester) is hydrophobic/lipophilic (MW= 360.831 g/mol, log *P* = 5.575; [3] drug with negligible solubility in water [4]. Bioavailability of fenofibrate solely depends on dissolution rate in the gastrointestinal tract [5]. In the present research work our aims to enhance the bioavailability by improve the solubility and dissolution rate. We are used the solvent evaporation and kneading methods [6]. In the solvent based process used the ethanol to dissolve the drug and carriers (HPMC, PEG-4000, sucrose, mannitol and sodium citrate) in the ratio of 1:2, 1:4 and 1:6 followed by evaporation of solvents. The main advantage of the solvent method is that thermal decomposition of drug and carriers can be prevented because low temperature is required for the solvent evaporation of organic solvents. In the kneading method for preparation of such binary systems by direct mixing of the fenofibrate and the carriers (HPMC, PEG-4000, Sucrose, mannitol and sodium citrate) in the ratio of 1:2, 1:4 and 1:6 and kneading the mixture in the pastel mortar by using the ethanol. The dried formulations of both the processes are to be evaluated by solubility and *In-Vitro* dissolution study, the differential scanning calorimetry (DSC), Crystal structure determination by the powder X-ray diffraction studies (XRD) at the different angles [7]. Mean plasma concentration–time profiles of fenofibrate and its formulations were evaluated in rats after an oral administration of pure fenofibrate and its formulations [7].

MATERIALS AND METHODS

2.1 Materials: Fenofibrate (FEN) was obtained as gift sample from De Novo Biotech. Pvt. Ltd., India. , Hydroxypropylmethylcellulose (HPMC), Sucrose, Mannitol, Sidum Citrate and Poly Ethylene Glycol (PEG-4000) were purchased from Qualigens Fine Chemicals (Mumbai, India). All other chemicals were of extra-pure reagent grade and used as and when received.

2.2.1. Methods: Preparation of solid dispersions with kneading methods: HPMC, sucrose, mannitol, sodium citrate and PEG-4000 of fenofibrate in the ratio of (1:2, 1:4 and 1:6): Kneading formulations of solid dispersions were obtained by mixing fenofibrate, HPMC, PEG-4000, sucrose, mannitol and sodium citrate using spatula and pestle in a mortar. The weight ratios of drug to each carrier were 1:2, 1:4, and 1:6 for kneading method. A mixture of polymers (HPMC, PEG-4000, Sucrose, mannitol and sodium citrate) and fenofibrate in the ratio of 1:2, 1:4 and 1:6 was wetted with water and kneaded thoroughly for 30 minutes in a glass mortar. The paste formed was dried under vacuum for 24 hours. Dried powder was passed through sieve no 80 and stored in desiccators until further evaluation [8]. A total of 15 samples FEN-01 to FEN-15 **(Table No 1)**.

2.2.2 Preparation of solid dispersion by solvent evaporation technique: HPMC, sucrose, mannitol, sodium citrate and PEG-4000 of fenofibrate in the ratio of (1:2, 1:4 and 1:6): In this technique the proper volume of two solutions were to be taken the drug (5%wt/v) and polymer HPMC/PEG-4000/Sucrose/Mannitol/Sodium citrate (5%wt/v), in ethanol were mixed and the mixtures were stirred for 10 minutes at rpm. The final solutions were poured onto Petri dish and the solvent was left to evaporate in open air for 2 days. After complete removal of the solvent the solid dispersions were stored at 25°C in desiccators [9]. A total of 15 samples FEN-01 to FEN-15 **(Table No 1)**

3. EVALUATION AND CHARACTERIZATION

3.1. Drug Content Studies

The individual formulations equivalent to 10mg of drug were weighed accurately and mixed with 100 ml of methanol. The solutions were filtered through 22µm nylon disc filter and after further dilution (10 times with methanol) the drug content was determined at 287nm using UV spectrophotometer [9], (Perkin Elmer EZ301, USA).

3.2. Solubility Studies

Solubility study of the drug and its formulations was carried by shaking 10 mg of Std. drug and its formulations (equivalent to 10 mg drug) with 40ml of distilled water in 100ml volumetric flask for 72 hours on BOD shaker. And then make up the volume up to 100ml. After 10 times dilution then filtering and determining the amount of drug dissolved spectrophotometrically at 287nm against suitable blank [10].

3.3. *In Vitro* Dissolution Study

The *in-vitro* dissolution study was carried out with 10 mg of Std. drug and its formulations (equivalent to 10 mg drug). Formulations (10mg) of fenofibrate were placed in hard gelatine(00 size) capsule with 200 mg sprayed dried lactose in a rotating basket dissolution apparatus (USP XXII) and then placed in 900 ml 0.1% SLS solution and stirred at a speed of 50 rpm with temperature maintained at 37 ± 1ºc. Aliquots of 10ml were withdrawn at appropriate time intervals and an equal volume of replaced in the vessel. 0.1%SLS was used to explore the dissolution of drug replaced in the vessel. Fenofibrate in the aliquot was assayed spectrophotometically by measuring absorbance at 287 nm against suitable blank [7].

3.4. Differential Scanning Calorimetry

DSC studies of the prepared samples were conducted immediately after preparation as well as after storage for 6 months. A (Q-10, TA) Instrument equipped with an intraocular 2p cooling accessory was used. Samples of 10mg to 5mg were placed in saturated aluminium pans and sealed with a lid. Heating scans by 10ºC /min applied with a purge of 50ml/min. Fast heating rates are preferred to prevent changes during scanning [10].

3.5. X-Ray Powder Diffractometry

X-ray powder diffraction patterns were recorded on a XPERTO-PRO x-ray diffractometer using Ni filtered, using a voltage of 45kV, and a 40mA current. The scanning employed was 1 min- 1 over the 6 to 90 diffraction angle (2θ) range. The relationship used for the calculation of crystallinity was presented by relative degree of crystallinity**.**

$$\text{Relative degree of crystallinity (RDC)} = \frac{I_{sam}}{I_{ref}}$$

Where,

I_{sam} = Peak height of the sample under investigation

I_{ref} = Peak height at the same angle for the reference with the highest intensity [9].

3.6. Pharmacokinetic Study in rats

The pharmacokinetics of drug (FEN-16) and test (FEN-01(K.M.) and FEN-15(S.E.) was evaluated following oral administration. The study was conducted in accordance with the regulation specified by the Institutional Animal Ethics Committee and Committee for the Purpose of Control and Supervision of Experiments on Animals (CPSEA). In total 04 groups (6 per group) Wistar rats (6-7weeks old) weighing between 180-240 g were used for the study. The rats were housed in a cage and maintained on a 12h light/dark at room temperature (21ºC to 24ºC) and relative humidity of 50 to 70% and acclimatized to study area conditions for at least 5 days before dosing. General and environmental conditions were strictly monitored. Each group was orally administered 1ml of 0.2%w/v methylcellulose aqueous suspension containing the drug and formulations of fenofibrate (equivalents to fenofibrate 50mg/kg body weight) respectively. Blood samples were collected from the retro-orbital vein from inner canthus of eyes using micro heamatocrit capillaries. Blood samples were collected at 0, 1, 2, 3, 4, 8, 12, 24 and 48 h post-dose in EDTA vials then centrifuged at 4000 rpm for 10 minutes to obtain plasma and stored at - 80ºC until bioanalysis [11].

3.7. Bioanalysis

The samples were analyzed using High performance liquid chromatography (HPLC Model Water) equipped with reverse phase column (Hypersil BDS C18 150×4.6mm) and UV detector at 287nm using 40:40:20 methanol: acetonitrile: water. The calibration curve was also drawn for analysis which was found to be linear from 125ng/ml to 2000ng/ml [12].

3.8. Pharmacokinetic data analysis

The area under the drug concentration-time curve from zero to 48h (AUC) was utilized for pharmacokinetic drug analysis. The maximal plasma concentration of drug (Cmax) and the time to reach maximal plasma concentration (Tmax) were directly obtained from data and area under the curve (AUC) [11].

RESULTS AND DISCUSSION

4.1. Drug content study

The drug content of the prepared formulations of fenofibrate was observed to be varying from **12.08 % to 83.81%** and it was maximum with formulation (FEN-13, K.M) and minimum in formulation (FEN-01, K.M.) as shown in **Table 2**. This studies shows that formulations with HPMC show the maximum drug content.

4.2. Solubility studies

The saturation solubility studies were to be carried out of pure fenofibrate and newly prepared fenofibrate solid dispersions using HPMC, PEG-4000, sucrose, mannitol and sodium citrate. All formulations with different ratios showed higher increase in saturation solubility as compared with pure fenofibrate, again formulations FEN-01(K.M.), FEN-07(K.M.), FEN-12(S.E.), FEN-13(K.M.), FEN-14(S.E.) and FEN-15(S.E.), show the maximum saturation solubility with hydroxyl propyl methyl cellulose (1:2), polyethylene glycol (1:4), mannitol (1:6), sucrose (1:6) and sodium citrate with kneading and solvent evaporation method. This might be attributable to an improvement of wetting of drug particles and localized solubilisation by the water soluble hydrotropic agents. In case of solid dispersions the order of carriers for increasing saturation solubility polymer (**Figure 01 and 02**, **Table No, 03)**

4.3. *In-Vitro* Dissolution studies

In all the formulation, the drug content was taken as 10 mg per capsule in 900 ml dissolution medium, 37˚C containing SLS (0.1 % w/v) and at different time intervals, 10ml of the solution was withdrawn until 4 hr. *In Vitro* dissolution study of the different formulations of fenofibrate prepared by solid dispersions technique, it was observed that the formulation FEN-01(K.M.), FEN-07(K.M.), FEN-12(S.E.), FEN-13(K.M.), FEN-14(S.E.) and FEN-15(S.E.), show the maximum increase in the %release of the drug from the HPMC (1:2), PEG-4000 (1:4 and 1:6), sucrose(1:6), mannitol (1:6) and Sodium citrate(1:6) formulations. The formulation FEN-04, FEN-06, and FEN-11, Show the lesser % release of the drug in the dissolution medium with the HPMC (1:4) and 1:6) and mannitol (1:2) polymer. The formulations which are to be kept in the capsule as compared to the std. drug profile.

The formulations show the % release of the drug in the dissolution medium as compared to the std. drug release profile as shown in (**Figure 03 and 04, Table No, 03)**

4.4. Differential scanning calorimetric (DSC) study

DSC analysis was done for pure fenofibrate and solid dispersions of fenofibrate using carriers (HPMC, PEG-4000, sucrose, mannitol and sodium citrate) of different ratios. The DSC thermogram of pure fenofibrate showed a sharp endothermic peak at **84.75ºC**, which was ascribe to drug melting. The DSC curves of kneading method were FEN-01, FEN-07 and FEN-14 for HPMC (1:2), PEG-4000 (1:4) and Mannitol (1:6) respectively. These formulations showed the maximum amorphous character. The DSC curves of solvent evaporation method were FEN-01, FEN-13 and FEN-15 for HPMC (1:2), Sucrose (1:6) and sodium citrate (1:6) respectively (**figure 05 and 06)**.

4.5. X-ray Diffraction Study

X-ray diffracometry (XRD) spectra of pure fenofibrate and binary systems with various carriers are presented in figure. The x-ray diffractogram of pure fenofibrate has sharp peaks at diffraction angles (2θ) 16.13, 16.60 and 22.16°. The relative drug crystallinity (RDC) values of FEN-01, FEN-07, FEN-13 and FEN-15 were **0.5199, 0.4614, 0.3243** and **0.6077** respectively. It is showing a typical crystalline pattern. However, all major characteristic crystalline peaks appear in the diffractogram of all the formulations of kneading method in the three different ratios like FEN-01(1:2), FEN-07(1:4) and FEN-14(1:6). Pure drug peak at 22.16° (2θ) was used for calculating RDC of formulations of fenofibrate. Moreover, the relative intensity and 2θ angle of these peaks remains practically unchanged. The XRD pattern of fenofibrate solid dispersions using hydroxyl propyl methyl cellulose, poly ethylene glycol-4000, sucrose, mannitol and sodium citrate showed various characteristic peaks of pure fenofibrate with/without very small shifting. It was also observed that the intensity of peaks of these fenofibrate solid dispersions were found to be markedly reduced when compared to that of the pure fenofibrate. The observation indicates that the drug in solid dispersion was amorphous as compared to the pure drug **(figure 07 and 08).**

4.7. Pharmacokinetic studies

As FEN-01(K.M.) and FEN-15(S.E.) formulations significantly improved the solubility and the dissolution rate of fenofibrate, the effect of formulation on the oral exposure of fenofibrate was examined in rats. Mean plasma concentration–time profiles of fenofibrate and its formulations were evaluated in rats after an oral administration (10 mg/kg) of pure fenofibrate and its formulations summarized in **Fig. 6**. The pharmacokinetic parameters were also determined and summarized in **Table 3**. The *In-Vivo* pharmacokinetic studies of formulation with the FEN-01 (HPMC, 1:2, K.M.) and FEN-15 (Sodium citrate, 1:6, S.E.) were carried out. The results indicated as, (AUC =7417.39, Cmax =1575.29 ng/ml and Tmax =8hours) and (AUC =7217.8, Cmax =1563.26 ng/ml and Tmax =8hours) respectively. It can be concluded that bioavailability of formulations has significantly increased as compared to the pure drug (AUC =3163.34, Cmax =616.51 ng/ml and Tmax =8hours). The Cmax of FEN-01(K.M.) and FEN-15(S.E.) were significantly higher than that of pure fenofibrate (approximately 2.6 and 2.5 folds higher for FEN-01(K.M.) and FEN-15(S.E.), respectively). In addition, the area under the plasma concentration–time curve (AUC) of itraconazole tends to be increased via the solid dispersions. Particularly, the AUC of FEN-01(K.M.) was enhanced significantly ($p < 0.05$, approximately 2.6 folds) compared to the pure fenofibrate. Those results indicated that the enhanced solubility and dissolution of fenofibrate via the solid dispersions formulations could lead to the improved oral bioavailability of fenofibrate. Given that the disconnect between in vitro and in vivo results of fenofibrate in inhibition could be due to the low bioavailability of fenofibrate the enhanced oral exposure of fenofibrate via the SDs preparation may lead to the improved in vivo performance of fenofibrate **(figure 09 and Table No,04).**

4.6. Effect of different carriers on the dissolution of fenofibrate

Solid dispersion techniques were employed for improving the solubility of fenofibrate. There are two processes kneading and solvent evaporation of solid dispersions was used with different carriers like polymer (HPMC and PEG-4000), Sugar derivatives' (Sucrose and mannitol) and hydrotropic agent (Sodium citrate). Incorporation of polymer/sugars/hydrotropic (HPMC, PEG-4000/sucrose, mannitol /sodium citrate) solid dispersion significantly enhanced the dissolution rate of fenofibrate. The enhancement of dissolution of drug from drug carrier systems can be ascribed to several factors. The mechanism of dissolution rate improvement from solid dispersion is lack of crystalinity and particle size reduction considered to be important factors for dissolution rate enhancement. Mixing of drug with a hydrophilic carrier results in greater wetting and increase surface available for dissolution by reducing interfacial tension between the hydrophilic drug and dissolution media. It was noted that drug carrier system sink immediately, while pure drug keeps floating on the surface for a longer time interval**.** The Solid dispersions formulated with the drug carriers exhibited significant improvement in the dissolution of drug. The dissolution enhancement with various binary systems was found to be in the order of FEN-07>FEN-13>FEN-15>FEN-14->FEN-16. The increase in the dissolution rate of the solid mixtures is due to size reduction and increase in the wettability of the drug molecules in presence of the polymers and sugar carriers.

Table No: 01 Formulations of solid dispersions by kneading and S.E. methods

Formulations	Drug+ Polymer	Kneading method	Solvent Evaporation
FEN-01	FEN+ HPMC	1:2	1:2
FEN-02	FEN+ PEG-4000	1:2	1:2
FEN-03	FEN+SUCROSE	1:2	1:2
FEN-04	FEN+MANNITOL	1:2	1:2
FEN-05	FEN+SOD CITRATE	1:2	1:2
FEN-06	FEN+ HPMC	1:4	1:4
FEN-07	FEN+ PEG-4000	1:4	1:4
FEN-08	FEN+SUCROSE	1:4	1:4
FEN-09	FEN+MANNITOL	1:4	1:4
FEN-10	FEN+SOD CITRATE	1:4	1:4
FEN-11	FEN+ HPMC	1:6	1:6
FEN-12	FEN+ PEG-4000	1:6	1:6
FEN-13	FEN+SUCROSE	1:6	1:6
FEN-14	FEN+MANNITOL	1:6	1:6
FEN-15	FEN+SOD CITRATE	1:6	1:6

Table No: 02 Drug Content Study of the formulations (FEN-01 to FEN-15)

Formulations	Drug+ Polymer	Weight Equi. To 10mg (K.M.)	Weight Equi. To 10mg (S.E.)
FEN-01	FEN+ HPMC	**12.08**	**17.99**
FEN-02	FEN+ PEG-4000	43.38	25.72
FEN-03	FEN+SUCROSE	27.07	24.38
FEN-04	FEN+MANNITOL	13.23	33.03
FEN-05	FEN+SOD.CITRATE	44.03	26.81
FEN-06	FEN+ HPMC	40.03	27.25
FEN-07	FEN+ PEG-4000	29.53	25.57
FEN-08	FEN+SUCROSE	32.15	30.93
FEN-09	FEN+MANNITOL	36.91	21.74
FEN-10	FEN+SOD.CITRATE	36.75	18.61
FEN-11	FEN+ HPMC	53.06	45.92
FEN-12	FEN+ PEG-4000	66.51	54.76
FEN-13	FEN+SUCROSE	63.81	51.71
FEN-14	FEN+MANNITOL	63.25	50.16
FEN-15	FEN+SOD.CITRATE	65.53	56.98
FEN-16	FENOFIBRATE	10	10

Table No. 03. Saturation Solubility Study and *In-Vitro* Dissolution Studies

Formulations	Kneading Method (ug/ml)	Kneading Method (%release)	Solvent Evaporation (ug/ml)	Solvent Evaporation (%release)
FEN-01	**5.80±0.14**	80.1%	**5.45±0.35**	75.6
FEN-02	**4.65±0.07**	66.6%	**3.85±0.07**	72.9
FEN-03	**5.15±0.06**	71.1%	**3.60±0.14**	68.9
FEN-04	**4.05±0.21**	63.9%	**4.01±0.14**	76.5
FEN-05	**5.25±0.07**	58.8%	**4.65±0.07**	71.1
FEN-06	**4.80±0.14**	63.9%	**4.15±0.07**	64.9
FEN-07	**5.75±0.07**	84.6%	**4.25±0.03**	74.6
FEN-08	**5.85±0.28**	57.6%	**4.85±0.04**	63.6
FEN-09	**4.40±0.07**	61.2%	**3.68±0.02**	78.3
FEN-10	**5.20±0.14**	78.3%	**4.10±0.08**	75.6
FEN-11	**5.35±0.07**	59.4%	**3.65±0.07**	59.2
FEN-12	**4.60±0.02**	69.0%	**4.60±0.01**	76.5
FEN-13	**5.75±0.07**	82.8%	**5.15±0.07**	77.4
FEN-14	**6.15±0.03**	72.9%	**5.10±0.01**	79.2
FEN-15	**6.05±0.07**	72.9%	**6.15±0.01**	82.3
FEN-16	**3.35±0.05**	52.1%	**3.35±0.05**	52.1

Table No. 04 Pharmacokinetic Study

Parameters	(FEN-16)	(FEN-01)KM	(FEN-15)SE
AUC	3163.34	7417.39	7217.80
Cmax(ng/ml)	616.51	1575.29	1563.26
Tmax (h)	8	8	8

Figure: 01 Solubility Study of the solid dispersions by kneading method (FEN-01 to FEN-15) and pure fenofibrate (FEN-16)

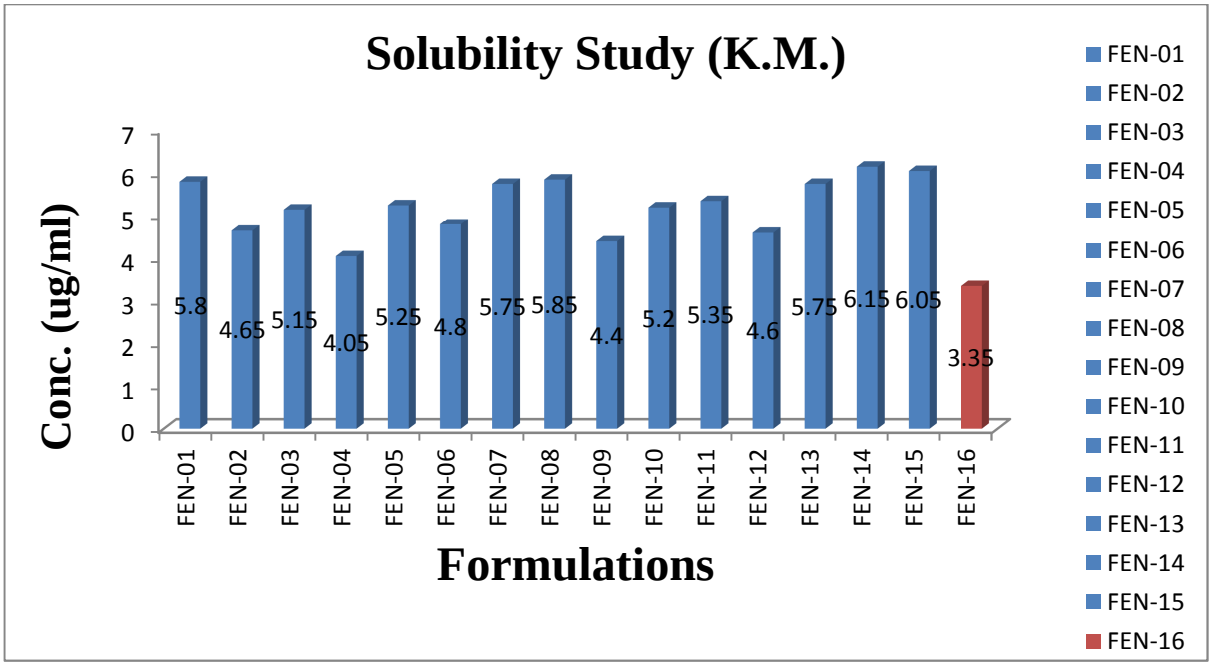


Figure: 02 Solubility Study of the solid dispersions by solvent evaporation method(FEN-01 to FEN-15) and pure fenofibrate (FEN-16)

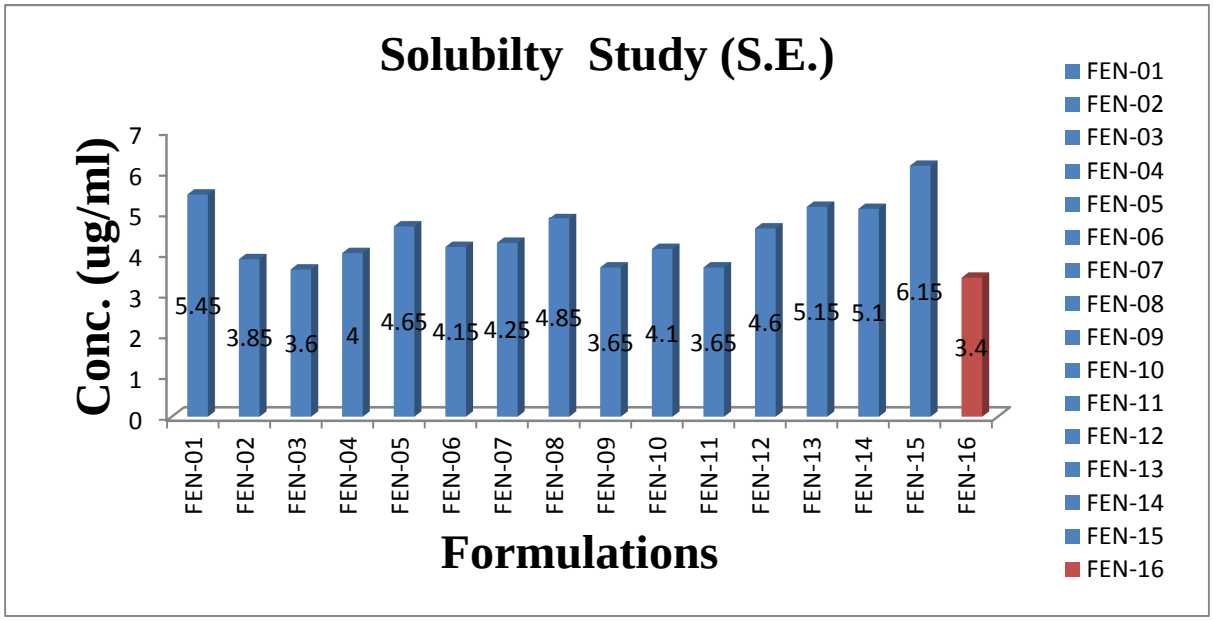
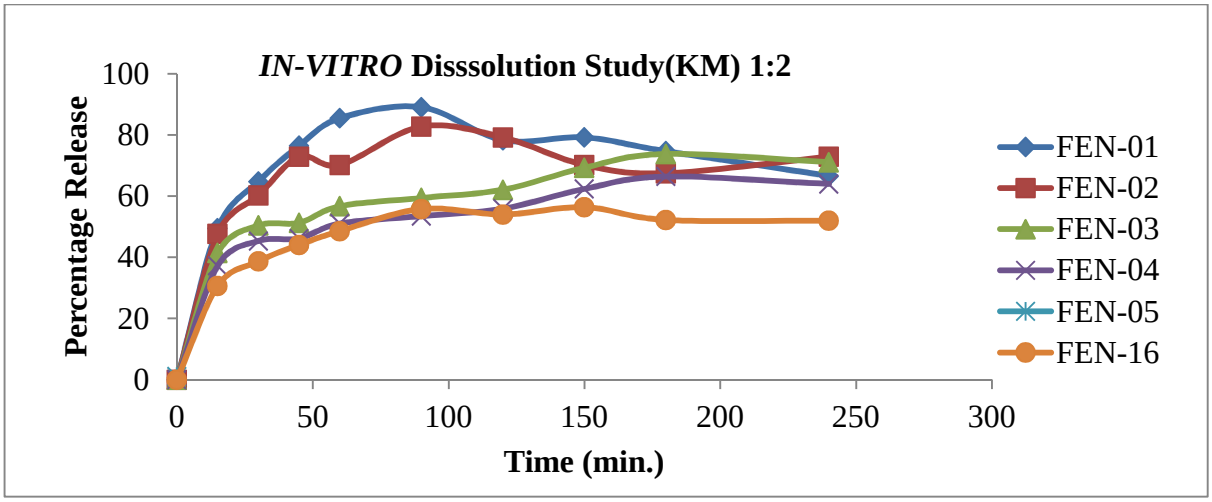
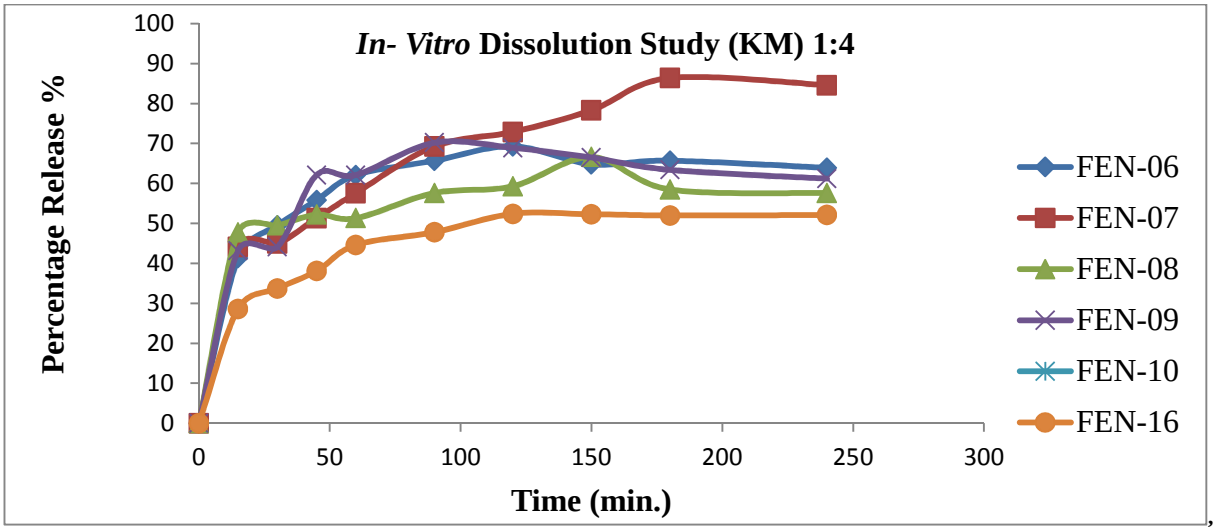


Figure: 03 *In-Vitro* dissolution study of the solid dispersions by kneading method (FEN-01 to FEN-15) and pure fenofibrate (FEN-16)





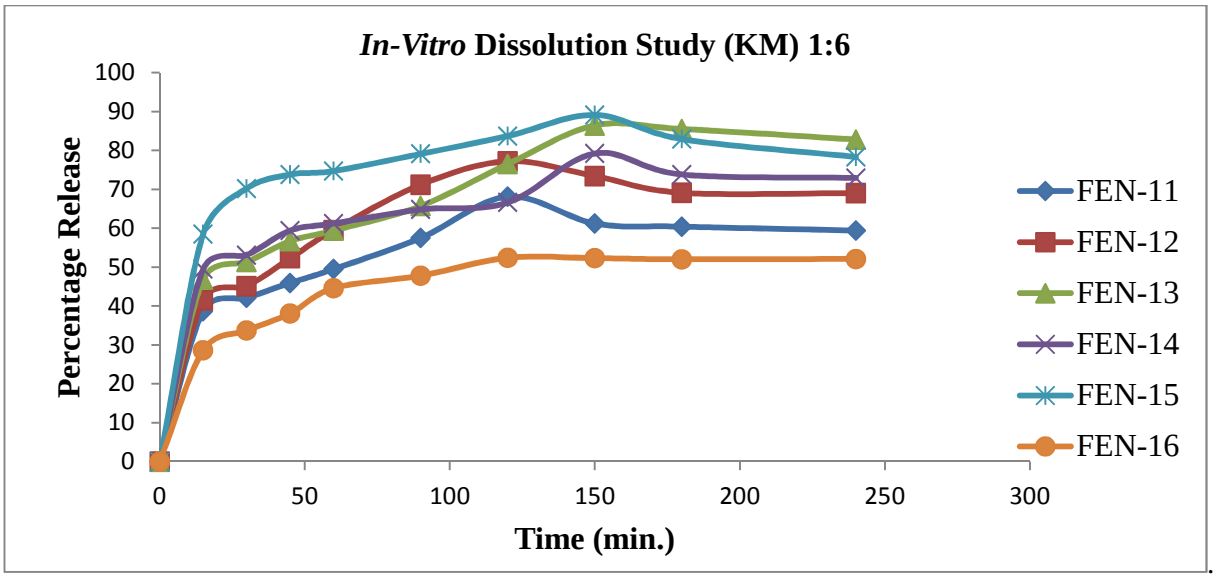
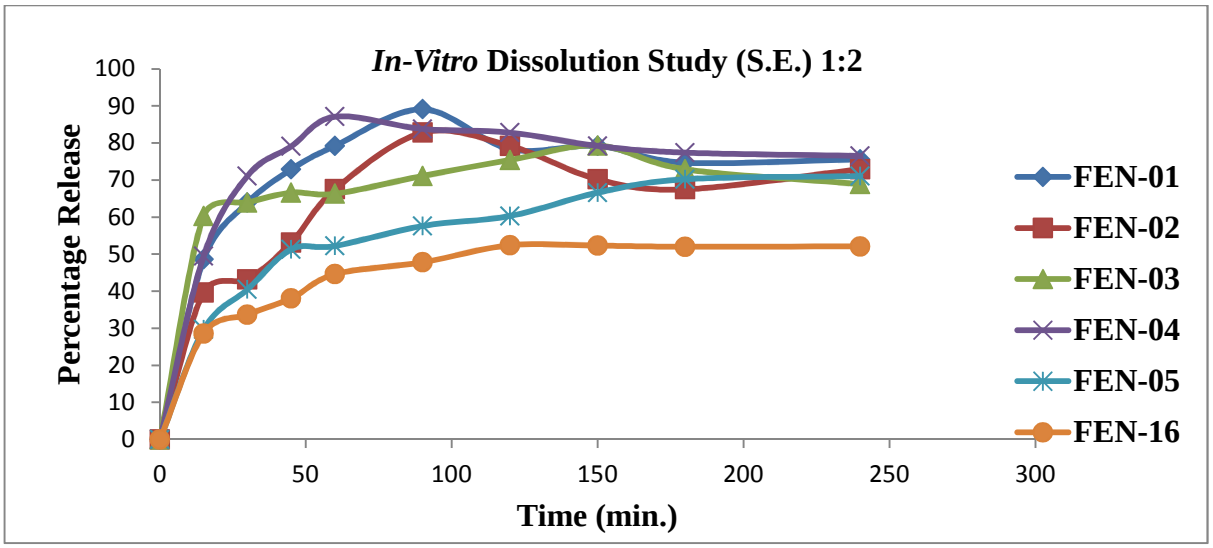
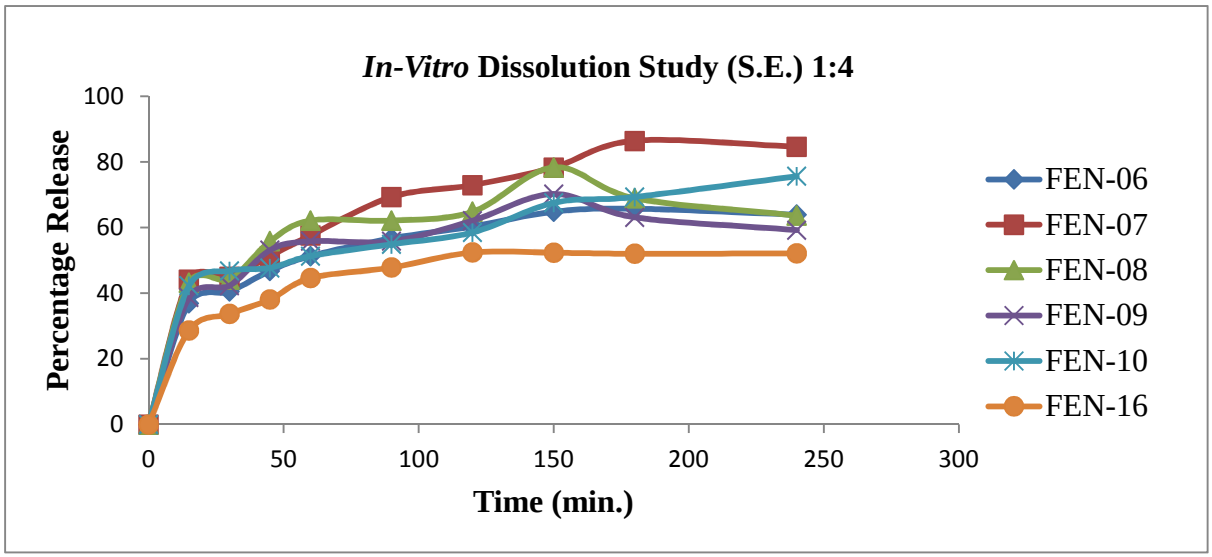


Figure: 04 *In-Vitro* dissolution study of the solid dispersions by solvent evaporation method (FEN-01 to FEN-15) and pure fenofibrate (FEN-16)





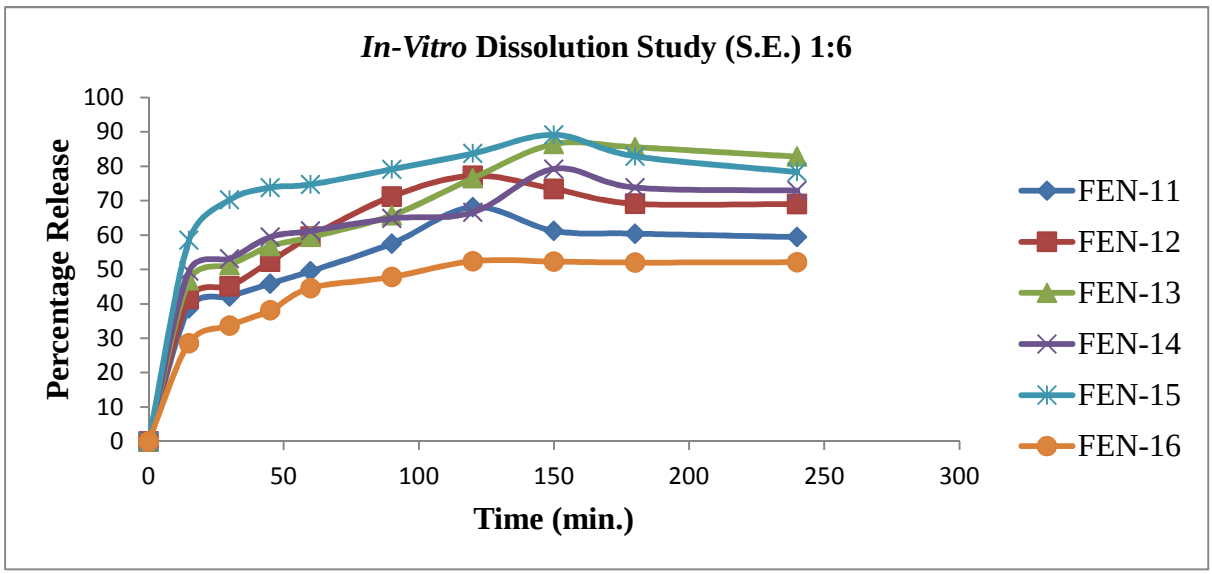


Figure: 05 DSC studies of the solid dispersions by kneading method of formulations and pure fenofibrate (FEN-01, FEN-07, FEN-14 and FEN-16)

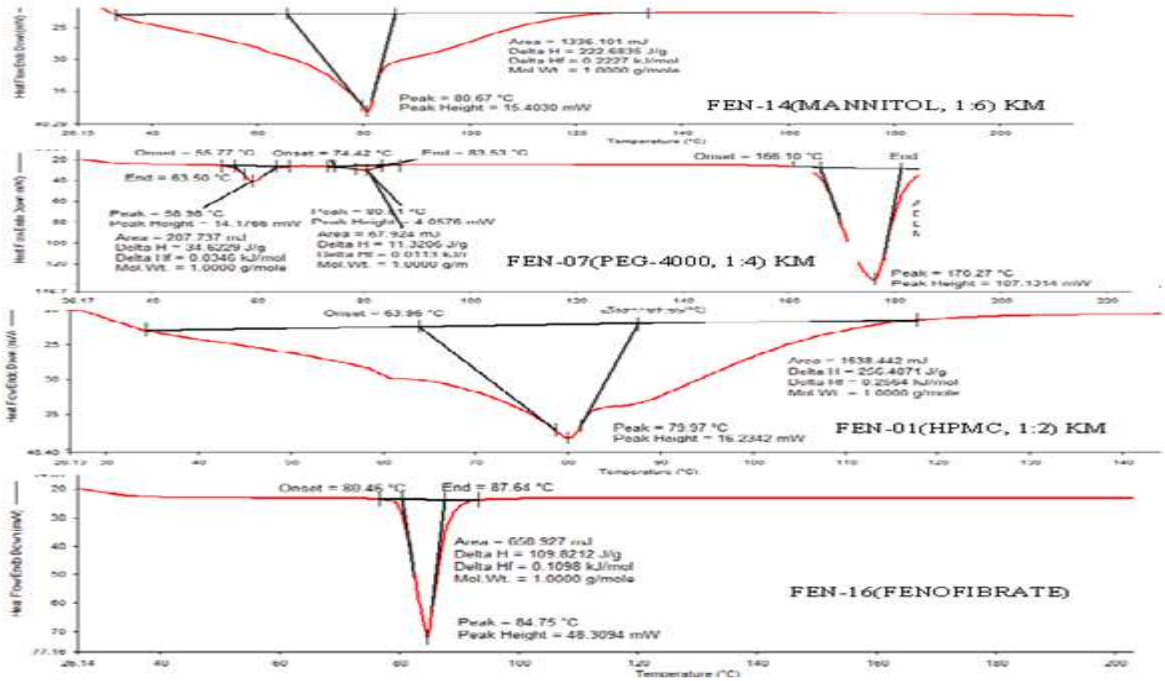


Figure: 06 DSC studies of the solid dispersions by solvent evaporation method of formulations and pure fenofibrate (FEN-01, FEN-13, FEN-15 and FEN-16)

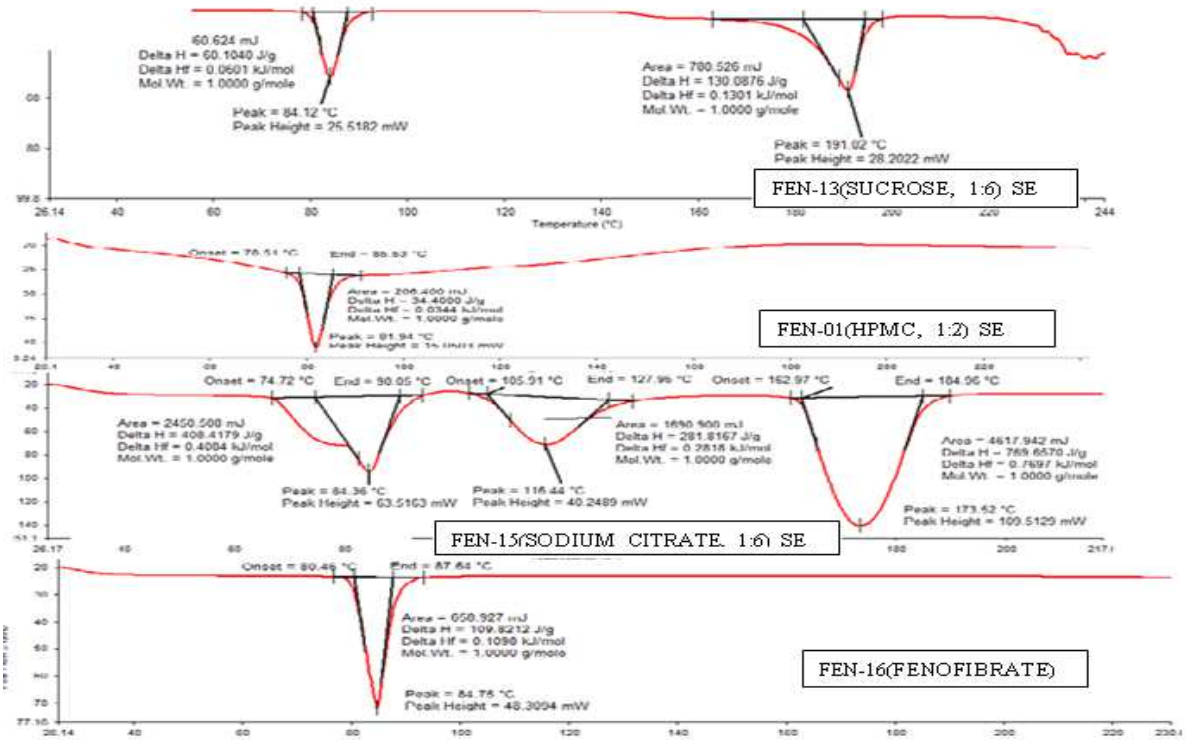


Figure: 07 XRD studies of the solid dispersions by kneading method of formulations (FEN-01, FEN-07, FEN-14 and FEN-16)

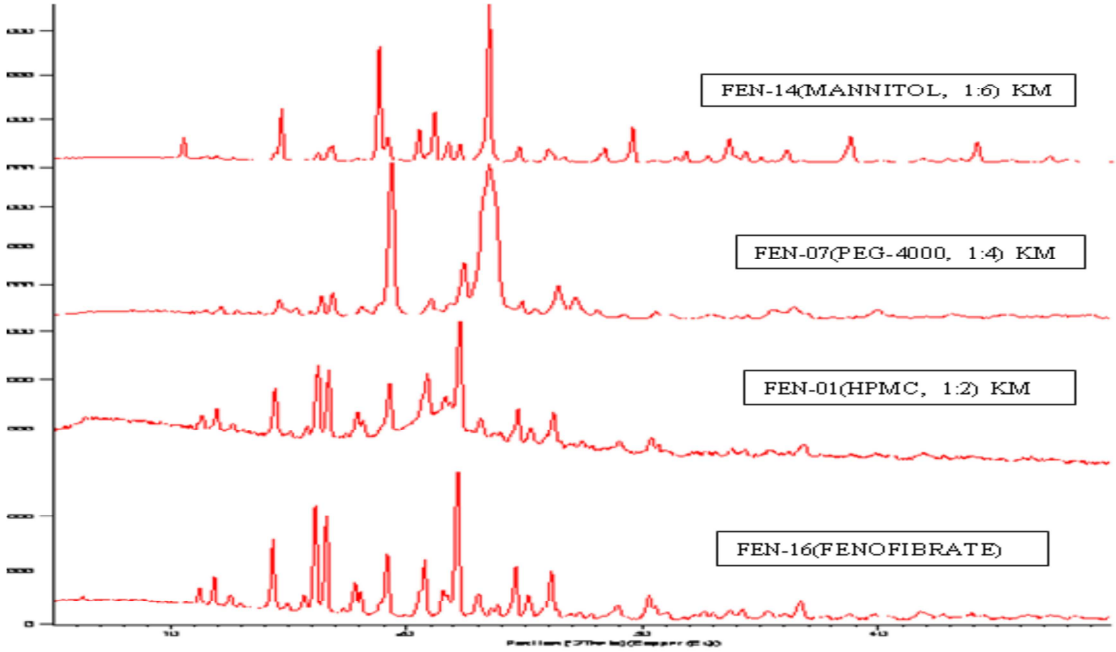


Figure: 08 XRD studies of the solid dispersions by solvent evaporation method of formulations (FEN-01, FEN-07, FEN-14 and FEN-16)

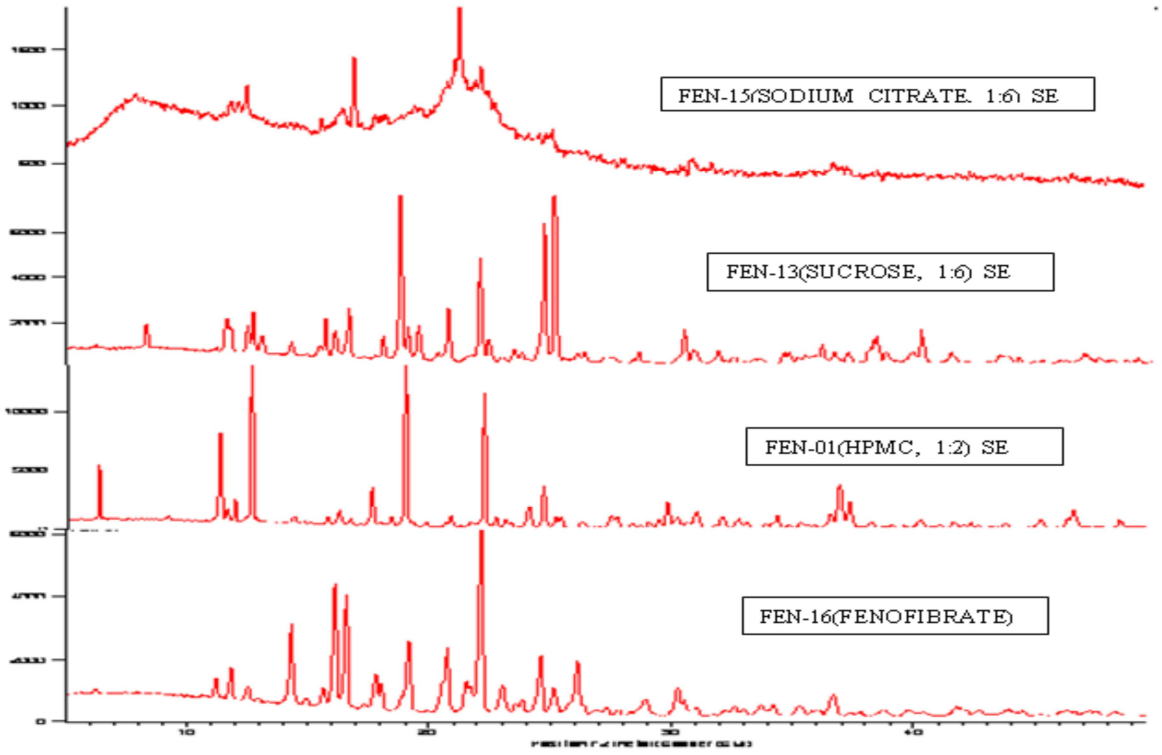
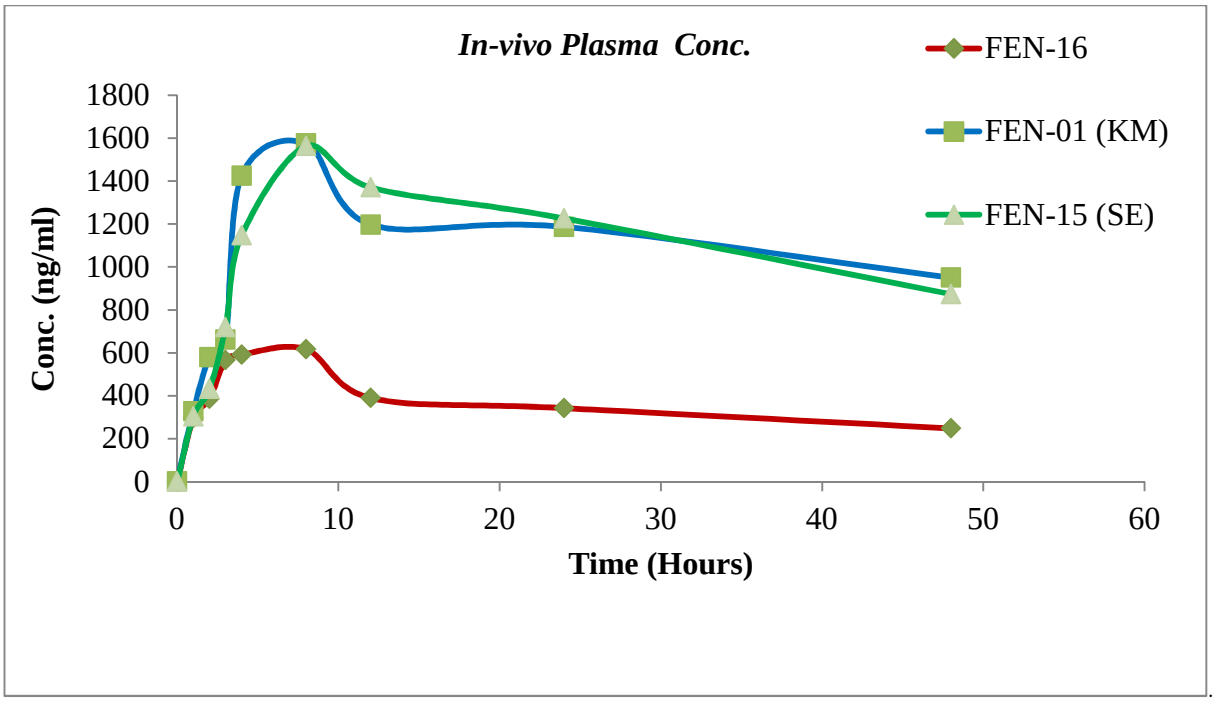


Figure: 09 Pharmacokinetic studies of the formulations (FEN-01, K.M.), (FEN-15, S.E.) and (FEN-16)



CONCLUSION

The Solid Dispersion of fenofibrate with HPMC, PEG 4000 and sodium citrate resulted in better dissolution **(~80% in 4 hrs)**. It also yielded almost **2.3** times higher bioavailability with the HPMC and 2.1 times with the sodium citrate as compare to the pure drug. The enhanced bioavailability may be attributed to amorphous nature of drug as evidenced by DSC and XRD of the formulations. The solvent based process uses organic solvent to dissolve and intimately disperse the drug and carrier molecule. These findings suggest that the above-mentioned technique can be employed successfully for improvement and stability of solid dispersions of poorly water soluble drugs. The main advantage of the solvent method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of organic solvents. A solid dispersion system is extremely useful method in improving the solubility and dissolution properties of poorly water-soluble drugs. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. Carriers with or without any surface activity, when used, can significantly increase the wettability properties of drugs. The increase in porosity also depends on the carrier properties, for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate and increases the solubility of poorly water soluble drug.

Acknowledgement
The authors express their thanks to the University Grant Commission, New Delhi for funding the research work under fellowship JRF/SRF vide letter no:**F.No.10-01/2008 (SA-I)**

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