Physicochemical and Micromeritic Studies on Fenofibrate Co-Crystals

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Abstract

The pharmaceutical co-crystals of poorly water soluble anti-hyperlipidemic fenofibrate were successfully prepared with different crystal forming agents (coformers); p-amino benzoic acid, benzoic acid and salicylic acid in equimolar ratios by solvent evaporation technique. The pure drug and co-crystals were characterized by physicochemical properties such as thermal analysis, infrared spectroscopy (IR), X-ray powder diffractometry (XRPD), scanning electron microscopy (SEM), drug content uniformity, saturation solubility and dissolution studies. The micromeritic (flow) properties of pure drug and co-crystals were also assessed in terms of Angle of repose, Hausnar's ratio and Carr's Index. The co-crystals of fenofibrate with p-amino benzoic acid showed marked increase in solubility and flow properties whereas the co-crystals of fenofibrate with benzoic acid improved flow properties significantly as compared to pure drug. The optimum flow properties and solubility were noted for the co-crystals of fenofibrate with salicylic acid.

Keywords: Hydrogen Bonding, Coformer, p-Amino benzoic acid, Salicylic acid, Benzoic acid.

Introduction

In pharmaceutical industry, the physico-chemical properties of API's such as aqueous solubility, melting point, temperature, chemical stability are the key factors for the formulators in the formulation design[1]. The crystal engineering is the technique useful to modify these properties. Crystal engineering is the exploitation of non-covalent interactions between molecular or ionic components for the rational design of solid state structures that might exhibit interesting electrical, magnetic and optical properties [2]. The crystal engineering technique involves number of approaches such as particle size reduction, salt formation, co-crystallization etc. The particle size reduction has major disadvantage of forming larger agglomerates or crystal growth by reducing their energy state. The salt formation is only applicable for ionizable compounds while co-crystallization is applicable for any API regardless of acidic basic or ionizable groups. A co-crystal is a molecular complex that contains two or more different molecules in the same crystal lattice [1, 3]. Cocrystals can be divided into: co-crystal anhydrates, co-crystal hydrates (solvates), co-crystals of salts (unsolvated, unhydrated or solvated, hydrated) [4].

Co-crystals enhance pharmaceutical properties by modification of chemical stability, physical stability, melting point, moisture uptake, compressibility, flowability, crystallinity, mechanical behavior, solubility, dissolution rate and bioavailability and also may reduce an API's susceptibility to polymorphism [3,5,6]. The API and co-former in a co-crystal exist in a definite stoichiometric ratio, and held together

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by non-covalent interactions such as hydrogen bonds, ionic bonds, π-π or van der Waals interactions [7]. The design of co-crystals depends on the pka, Hydrogen bond rule that is hydrogen bond donor and acceptor count and solubilities of an API and co-formers [3,8]. The co-crystals are prepared by various methods such as slow evaporation of solvent from a solution that contains stoichiometric amounts of the components (co-crystal formers), solution crystallization, sublimation, growth from the melt, slurry conversion, antisolvent addition, supercritical fluid technology and solvent assisted or heat assisted grinding of two solid co-crystal formers [5,9,10]. The co-crystals are generally characterized by Raman spectroscopy, IR Spectroscopy, NMR spectroscopy, XRPD, DSC, etc. Single crystal X-ray diffraction is preferred technique for characterization of co-crystals [3].

Fenofibrate is the drug selected for this experimental work. Fenofibrate is an antihyperlipidemic drug from class of fibrates. Chemically it is a 2-[4-(4-chlorobenzoyl) phenoxy] 2-methyl propanoic acid 1-methyl ethyl ester. Fenofibrate is poorly water soluble. The bioavailability of fenofibrate is 60- 81%. Bioavailability of fenofibrate can be improved by improving solubility. An attempt was made to improve the solubility of fenofibrate by nano-crystallization[1], melting inclusion in mesoporous silica[11], self emulsifying drug delivery system[12], spray drying technique[13], HPβCD inclusion complexation [14] and solid dispersion techniques[15], ternary solid dispersion with poloxamer 188 and TPGS technique[16] and drug loaded lipospheres technique [17].

The main objective of the present work was to improve the solubility and physicochemical properties of fenofibrate by using co-crystallization technique. The pharmaceutical co-crystals of fenofibrate were prepared by solvent evaporation technique. p-amino benzoic acid, salicylic acid and benzoic acid were used as co-former in 1:1 stoichiometric ratio with fenofibrate for the synthesis of co-crystals. The flow properties, saturation solubility, drug content and dissolution profile of pure fenofibrate and co-crystals were determined. The pure fenofibrate and co-crystals were further characterized by Melting point, DSC, IR, XRPD and SEM.

Materials and methods

Fenofibrate was obtained as gift sample from Piramal Healthcare, Mumbai, India. The coformers p-amino benzoic acid, salicylic acid and benzoic acid (extra pure grade) were purchased from Loba Chemie, Mumbai, India. All other reagents used were of analytical grade. Double distilled water was used throughout the experiment.

Preparation of co-crystals

The cocrystals of fenofibrate with coformers were prepared by slow solvent evaporation method. Acetone and absolute ethanol (1:1) was used as solvent for fenofibrate and p-amino benzoic acid cocrystals. For preparation of cocrystals of fenofibrate with salicylic acid and benzoic acid, pure acetone was used. The clear solution of fenofibrate and coformer in 1:1 stoichiometric ratio was allowed to evaporate at room temperature with occasional stirring. After complete evaporation for one day the crystals were dried at about 40˚C in hot air oven and then stored in a desiccator until further analysis.

Melting point determination

The melting points of pure fenofibrate, coformers and cocrystals were determined using the open capillary tube method. The substance was filled in capillary tube and tied with thermometer by using thread. The thermometer along with capillary containing substance was placed in Thiele's tube containing liquid paraffin. The side arm of the Thiele's tube was heated by using gas burner. The progress in temperature was monitored. The temperature at

which substance starts melting was noted and the experiment was repeated three times for each substance.

Thermal characterization

The thermal properties of pure drug and co-crystals were recorded using a differential scanning calorimeter (SDT Q600 V 20.9 Build 20, USA). Approximately 2-5 mg of sample was heated in pierced aluminum pan from 30 to 300˚C at a heating rate of 10˚C/min under a stream of Nitrogen at a flow rate of 40mL/min[18].

IR characterization

IR (Bruker, Germany) was used in attenuated total reflectance (ATR) mode for collecting the IR spectra of the samples. The spectra were collected over the range of 4000–600 cm−1 in 32 scans, with a resolution of 4 cm−1 for each sample[19].

XRPD characterization

The XRPD data of Fenofibrate and co-crystals were recorded on a Bruker-AXS(D8) X-ray diffractometer (Karlsruhe Germany, Madison Wisconsin) with tube anode Cu over the interval 10–50°/2θ under the following set of conditions: the Generator tension (voltage): 40 kV and Generator current: 25 Ma[20].

SEM analysis

The surface morphological properties of pure drug and co-crystals were investigated by scanning electron microscopy (SEM-Jeol Instruments, JSM-6360. Japan). Samples were mounted on a double-faced adhesive tape, sputtered with gold. Scanning electron photographs were taken at an accelerating voltage of 5-20 kV and obtained micrographs were examined at ×500 and ×2000 magnifications [20].

Evaluation of flow property

The flow properties of pure drug and co-crystals were determined in terms of angle of repose, bulk density, tapped density, Carr's compressibility index and Hausnar's ratio. Angle of repose was determined by fixed funnel method. Carr's compressibility index and Hausnar's ratio were calculated from bulk density and tapped density by using following equations [20].

$$Carr's\ index = \left[\frac{Tapped\ density - Bulk\ density}{Tapped\ density}\right] \times 100$$

$$Hausnar's\ ratio = \frac{Tapped\ density}{Bulk\ density}$$

The flowability data was statistically validated (n=6).

Determination of drug content

Drug content was determined by dissolving samples of co-crystals equivalent to 5 mg of Fenofibrate in 20 ml of methanol and the volume was adjusted to 50 ml with distilled water. The solution was filtered through Whatman filter paper No. 41, suitably diluted and absorbance was measured at 286.7 nm using double beam UV spectrophotometer (Shimadzu 1800, Japan)[20].

Determination of saturation solubility

Saturation solubility studies were performed with distilled water in triplicate according to the method reported by Higuchi and Connors. [16] Excess of pure drug and co-crystals were added to 20 ml of distilled water taken in a screw cap tube and shaken for 24 hours in a rotary flask shaker at a room temperature to achieve the equilibrium. Appropriate aliquots were then withdrawn and filtered through Whatman filter paper no. 41 and analyzed spectro-photometrically at 290.1 nm. The results obtained from saturation solubility studies were statistically validated [20].

Dissolution studies

The dissolution rate studies were conducted in 900 ml of 0.75% Sodium lauryl sulfate solution in distilled water at 75 rpm maintained at 37±0.5 °C in a dissolution test apparatus (Disso 2000 tablet dissolution test apparatus, Lab India, India) using paddle method. 40 mg of fenofibrate or its equivalent amount of co-crystals were added to dissolution medium and samples were withdrawn at time interval of 5, 10, 20, 30, 45 and 60 minutes. The volume of dissolution medium was adjusted to 900 ml by replacing it with fresh medium. The samples were immediately filtered through Whatman filter paper no. 41. Filtrates were appropriately diluted and analyzed spectrophotometrically at 290.5 nm. The data obtained from dissolution studies were statistically validated (n=3).

Results and discussion

Melting point determination

The melting point of a compound is a fundamental physical property determined for the purpose of characterization or to check purity or identification of compound [3]. Change in melting points of co-crystals as compared to pure API and crystal forming agent might be due to different packing arrangement and change in the crystal habit of molecules in the co-crystals [20]. The melting point of pure fenofibrate was found to be 78-82˚C. The melting points of pure p-amino benzoic acid, Salicylic acid and benzoic acid were found to be 184-186˚C, 158-160˚C and 122-124˚C respectively. The melting points of FPABA, FSA and FBA cocrystals were found to be 76-78˚C, 74-76˚C and 70-72˚C. It was observed that the melting points of cocrystals were significantly decreased than pure fenofibrate and individual coformers.

Thermal characterization

DSC technique is useful to observe fusion and crystallization events as well as glass transition temperatures3. The DSC thermogram of pure fenofibrate showed sharp melting endotherm at 83.02°C indicating crystalline nature of drug. Similarly, the thermogram of p-amino benzoic acid, salicylic acid and benzoic acid showed sharp endothermic peaks at 186.11°C, 160.48°C and 124.54°C respectively, indicating their characteristic crystalline nature. It was observed that the FPABA, FSA and FBA co-crystals showed sharp melting endothermic peak at 78.62°C, 75.15°C and 72.96°C respectively which is lower than the pure fenofibrate and respective co-former. The comparative DSC thermograms are shown in figure 1. This assures the formation of cocrystals.

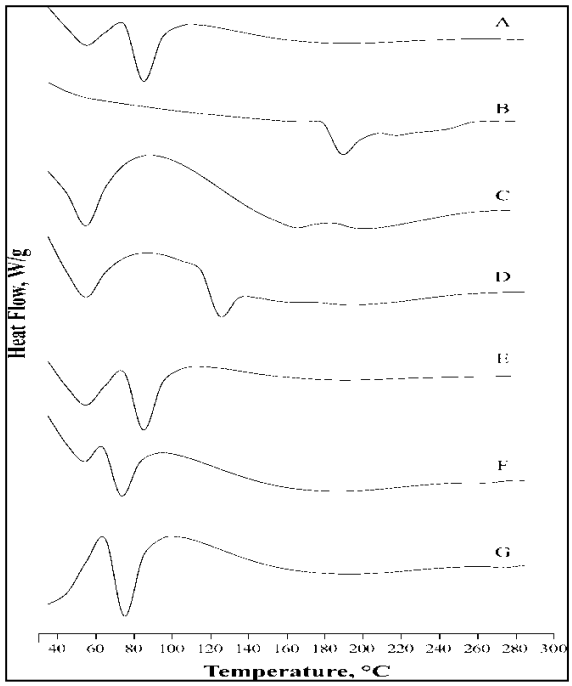

Figure 1. Comparative DSC Thermograms; A: Fenofibrate, B: p-Amino benzoic acid, C: Salicylic acid, D: Benzoic acid, E: FPABA cocrystal, F: FSA cocrystal, G: FBA cocrystal.

IR characterization

The cocrystals were further characterized by IR spectroscopy. IR spectra of pure fenofibrate, coformers and cocrystals were determined by Attenuated total refluctance mode of IR spectroscopy. Analysis by IR spectroscopy was carried out to access any possible interaction between drug and co-former. An IR spectrum of fenofibrate is characterized by principle peaks at

2982.26 cm−1 (Aliphatic C–H stretch of CH3), 1725.76 cm−1 (C=O Stretch of Ketone), 1648.71 cm−1 (C=O Stretch of Ester), 1596 cm−1 (ring skeletal vibration band), 1464.15 cm−1 (C=C stretch of aromatic ring), 1383.57 cm−1 (C–H deformation in CH3), 1246.94 cm−1 (C-O Stretch in ester), 858.63 cm−1 (C–Cl stretch), and 821.90 cm−1 (ring vibration due to para-di-substituted benzene).

Table 1. Frequency peaks of IR spectra

Functional Groups	Wave number (cm-1)			
	Fenofibrate	FPABA	FSA	FBA
Ketonic C=O stretch	1725.76	1723.82	1723.93	1723.04
C=O stretch of Ester	1648.71	1647.95	1647.60	1647.23
C-O stretch of ester	1246.94	1244.88	1244.07	1245.01
C-Cl stretch	858.63	841.76	843.60	843.00

The possible hydrogen bonding sites of fenofibrate are considered to correlate the results of IR. In the hydrogen bond formation the ketonic oxygen, ester oxygen, ether oxygen and chlorine of fenofibrate may involve. In the cocrystals, as shown in Table 1, wave number decreases than fenofibrate at respective functional groups. The decrease in frequency implies that the functional groups participate in strong Hydrogen bond. An increase in frequency implies that the functional groups participate in weak hydrogen bond [21].

As shown comparative IR spectra in figure 2, the frequency of functional groups in cocrystals increases (and wave number decreases) than in fenofibrate, therefore the functional groups participates in weak hydrogen bonds. The peaks at 3300-2500 cm-1 in cocrystals are not prominent. This may be due to the involvement of hydroxyl groups of coformers in hydrogen bonding. Hence all the coformers used shown the formation of cocrystals.

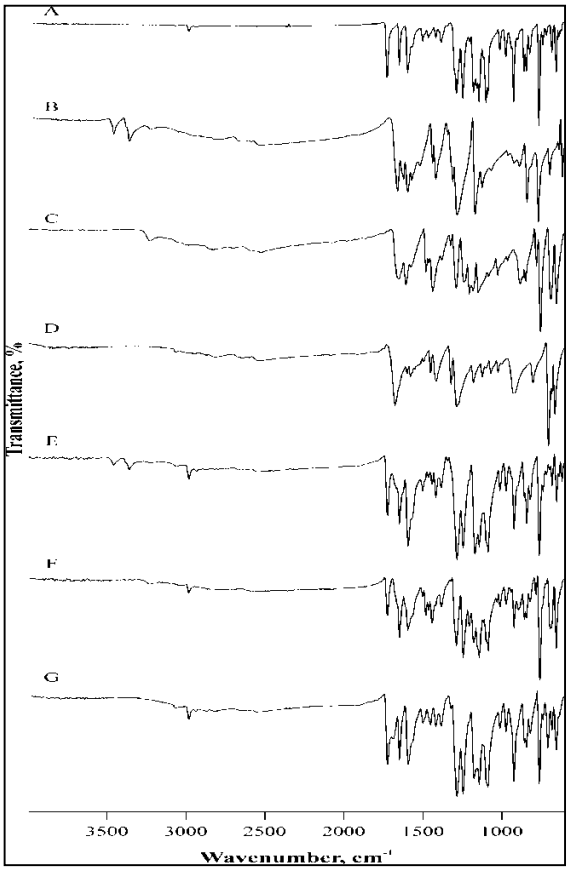

Figure 2. Comparative FTIR spectra; A: Fenofibrate, B: p-Amino benzoic acid, C: Salicylic acid, D: Benzoic acid, E: FPABA cocrystal, F: FSA cocrystal, G: FBA cocrystal.

XRPD characterization

The formation of co-crystal has been also confirmed on the basis of XRPD studies which indicated completely different diffractogram of newly formed co-crystals from pure drug and co-formers. XRPD is a powerful technique for determining the presence of polymorphs, crystal habit modifications in drug crystals and/or generation of a new crystal form during co-crystallization process20. Table 2 shows highest peak intensities of pure drug, co-former and co-crystals and their respective diffraction angles

(2θ°).

As shown in figure 3, the diffraction pattern of co-crystals is completely different from the fenofibrate and respective co-formers. It can be seen that the cocrystals exhibited spectra with different peak positions from the fenofibrate and respective conformers. Crystals possesses different internal structures with significant habit modification. The relative intensities of their XRPD peaks were modified which might be attributed to the different crystal habits and arrangement of molecules indicating formation of new crystal forms.

Table 2. XRPD results showing 2θ values with high peak intensity

Sample	2 Theta (2θ)	Intensity
Fenofibrate	14.48	1880
	16.32	2591
	16.76	2285
	22.32	3551
PABA	14.12	11050
	15.58	26523
	22.14	5224
SA	10.89	12253
	17.18	6496
	25.00	4368
BA	16.12	5230
	17.06	10835
	23.56	4183
FPABA Co-crystals	14.29	1837
	16.08	2416
	22.16	1834
	24.59	1800
FSA Co-crystals	14.25	1713
	16.08	1976
	22.08	3612
	25.10	2240
FBA Co-crystals	16.10	2161
	19.10	1256
	22.14	2635
	24.53	1261

SEM analysis

The Scanning electron microscopy images as shown in figure 4 show the surface morphological properties of the pure fenofibrate and co-crystals. The SEM images show that the fenofibrate exists in small smooth white crystalline particles with aggregation, FPABA cocrystals are rod shaped with round edges, FSA cocrystals are in the form of flakes and FBA cocrystals exist in cube like structures with large size.

Evaluation of flow property

The flowability of co-crystals compared to the pure drug was determined. It shows that the flowability of co-crystals was improved significantly compared to that of the original drug powder. The parameters of flowability such as angle of repose, Hausnar's ratio and Carr's compressibility index are shown in table 3. Flowability data was statistically validated (n=6).

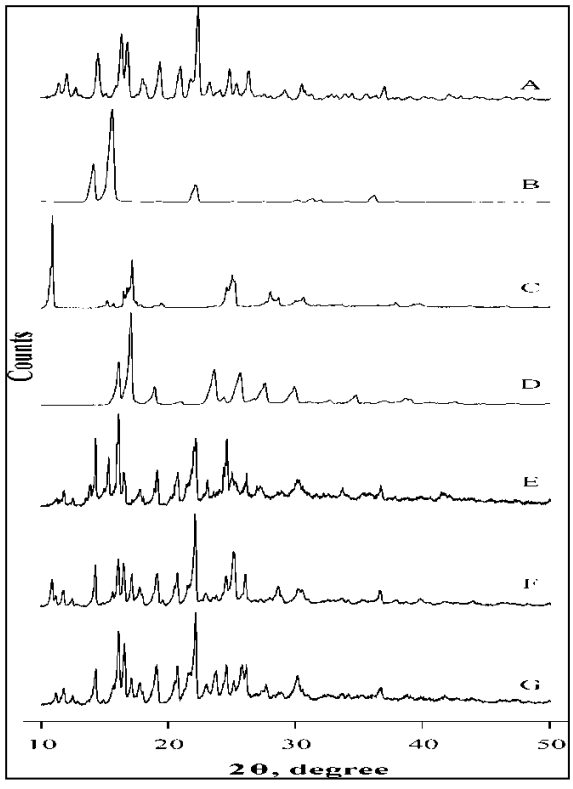

Figure 3. Comparative XRPD pattern; A: Fenofibrate, B: p-Amino benzoic acid, C: Salicylic acid, D: Benzoic acid, E: FPABA cocrystal, F: FSA cocrystal, G: FBA cocrystal

The angle of repose, Hausnar's ratio and Carr's compressibility index for all the co-crystals were reduced significantly in comparison with the original drug crystals. This indicates the flowability of co-crystals is improved significantly. The flowability of fenofibrate is lower due to smaller particle size and aggregation of crystals. The rod shaped crystals are having low flowability but due to round edges the flowability of FPABA cocrystals is improved. The flow properties of the FPABA cocrystals are more than the fenofibrate and lower than the FSA and FBA cocrystals. Due to the large and thick flat sheets or flakes the flowability of FSA is more than fenofibrate and FPABA but less than FBA cocrystals. The flowability of FBA cocrystals is significantly greater than the other cocrystals and fenofibrate. The co-crystals of fenofibrate exhibited larger particle size with significant reduction in the cohesive forces between them. This could be one of the possible reasons for the excellent flowability of the co-crystals.

Determination of drug content

Percentage drug contents of co-crystals FPABA, FSA and FBA were found to be 99.83±3.91w/w, 101.54±4.03w/w, and 98.74±7.65w/w respectively.

Determination of saturation solubility

The saturation solubility of pure drug and co-crystals are given in table 4. Prepared co-crystals have shown increased solubility in comparison to the pure drug. The saturation solubility of FPABA co-crystals was increased by 3146 folds than that of fenofibrate. The difference in saturation solubility of FPABA co-crystal and fenofibrate is highly significant. The saturation solubility of FSA co-crystal and FBA co-crystal was improved by 354 fold and 68 fold respectively. The difference in saturation solubility of FSA co-crystal and fenofibrate is significant. The difference in saturation solubility of FBA co-crystal and fenofibrate is not much significant.

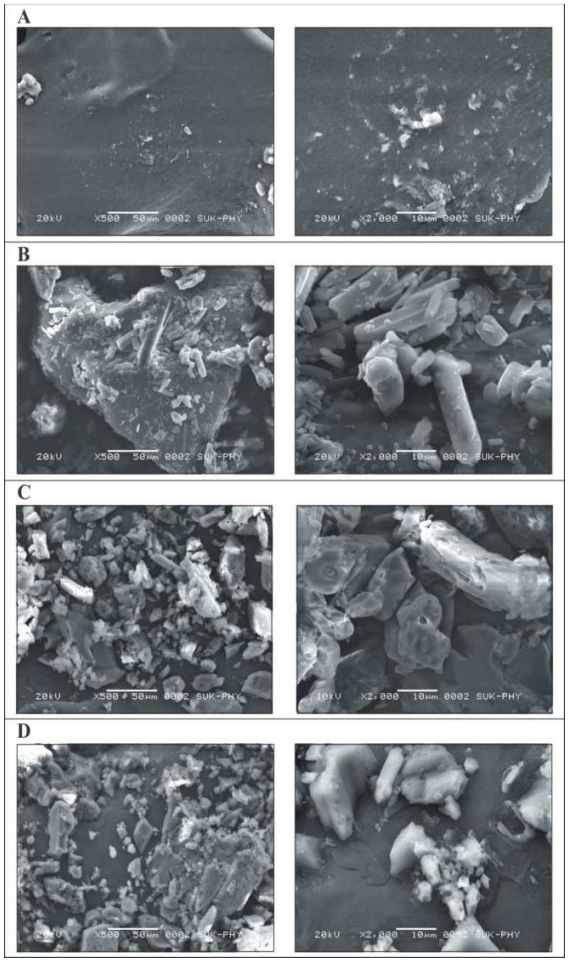

Figure 4. SEM photographs of- A: Fenofibrate, B: FPABA cocrystal, C: FSA cocrystal, D: FBA cocrystal.

Dissolution studies

The dissolution rate of pure fenofibrate and co-crystals in 0.75% SLS in Distilled water is shown in figure 5. The FPABA co-crystals showed highly improved dissolution profile than pure fenofibrate, FSA and FBA co-crystals.

The increase in saturation solubility and dissolution of FPABA cocrystals is due to the hydrophilic surface of FPABA cocrystals exerted by the free amino group in 1:1 stoichiometry. In case of FSA cocrystals of 1:1 stoichiometry, saturation solubility and

dissolution is not improved significantly because of intramolecular hydrogen bonding. In case of FBA cocrystals of 1:1 stoichiometry, the surface of cocrystal becomes hydrophobic and hence the saturation solubility and dissolution decreased.

Table 3. Flow properties of pure fenofibrate and co-crystals

System	Angle of repose[a] (θ°)	Hausnar's ratio[a]	Carr's compressibility index[a] (%)
Fenofibrate	49.26±3.57	2.058±0.0837	50.37±2.003
FPABA cocrystals	38.81±1.67 [b]	1.593±0.0956 [b]	37.21±3.646[b]
FSA cocrystals	28.95±4.03 [b,c]	1.344±0.0301[b,c]	25.88±1.661[b,c]
FBA cocrystals	32.42±2.77 [b,d,e]	1.265±0.0234 [b,c,e]	20.86±1.487 [b,c,f]

a indicates mean ± S.D.(n=6); S.D.: Standard deviation; FPABA: Co-crystals of fenofibrate with p-amino benzoic acid.; FSA: Co-crystals of fenofibrate with salicylic acid.; FBA: Co-crystals of fenofibrate with benzoic acid.

b significant difference compared to pure fenofibrate i.e. significant ($p<0.001$).

c significant difference compared to FPABA co-crystals i.e. significant ($p<0.001$).

d significant difference compared to FPABA co-crystals i.e. significant ($p<0.05$).

e significant difference compared to FSA co-crystals i.e. not significant ($p>0.05$).

f significant difference compared to FSA co-crystals i.e. significant ($p<0.01$).

Table 4. Saturation solubility of pure fenofibrate and co-crystals

System	Saturation solubility (mg/mL)[a]
Fenofibrate	0.032 ± 0.0072
FPABA co-crystals	100.66 ± 4.580 [b]
FSA co-crystals	11.35 ±0.7821[c,e]
FBA co-crystals	2.18 ± 0.060 [d,e]

a indicates mean ± S.D.(n=3); S.D.: Standard deviation; FPABA: Co-crystals of fenofibrate with p-amino benzoic acid.; FSA: Co-crystals of fenofibrate with salicylic acid.; FBA: Co-crystals of fenofibrate with benzoic acid.

b significant difference compared to pure fenofibrate i.e. significant ($p<0.001$).

c significant difference compared to pure fenofibrate i.e. significant ($p<0.01$).

d significant difference compared to pure fenofibrate i.e. not significant ($p>0.05$).

e significant difference compared to FPABA co-crystals i.e. significant ($p<0.001$).

Conclusion

The present study reveals that the solvent evaporation method is the reliable technique for synthesis of cocrystals of fenofibrate. The p-amino benzoic acid, salicylic acid and benzoic acid are good co-formers for synthesis of co-crystals. The co-crystals of fenofibrate with p-amino benzoic acid shows marked increase in solubility and flow properties also. The co-crystals of fenofibrate with benzoic acid shows marked increase in flow properties. The co-crystals of fenofibrate with salicylic acid shows optimum flow properties and solubility. For

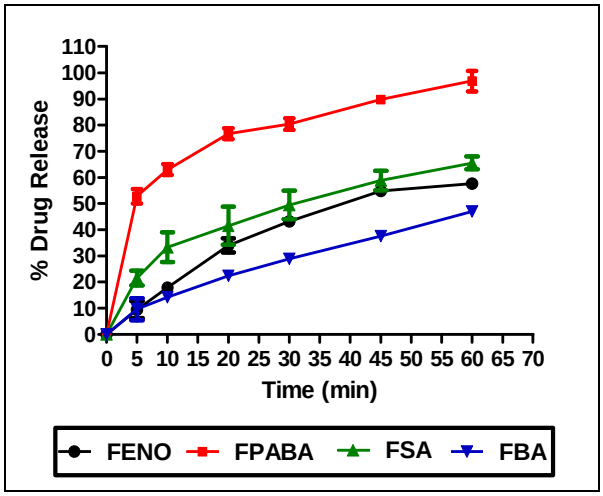

Figure 5. Dissolution profile of pure fenofibrate and cocrystals

greater advantage, the synthesis of co-crystals of fenofibrate with p-amino benzoic acid is desirable. As a result of the study, the co-crystals of the fenofibrate can be prepared according to the need of formulator by using the p-amino benzoic acid, salicylic acid and benzoic acid as co-formers.

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