RESEARCH ARTICLE

Preparation and Characterization of Molecular Complexes of Fenofibrate Cocrystal

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Abstract

Aim: The objective of this study was to investigate whether the miscibility of a drug and coformer, as predicted by Hansen solubility parameter (HSP), can indicate cocrystal formulation. It was also our aim to evaluate various HSP-based approaches in miscibility predication. HSP for fenofibrate drug over 20 coformers was calculated according to the group contribution method. **Materials and Methods:** The selection of coformer was based on hydrogen bond present in structure which clearly shows the importance of hydrogen bonding in forming cocrystals. Solubility parameters for solutes are obtained by group contribution method. **Result and Discussion:** In the present investigation, these methods were employed to arrive at the solubility parameter values. The basic steps in Fedor's method are to open the rings and treat the resultant structure as an open-chain compound. These were sum-up, and the solubility parameter was calculated as square root of the sum of energy of mixing substituent constants divided by the sum of molar volume substituent constants. Hoy's procedure expressed in the ratio of molar attraction constant to molar volume. The resultant δ values of drug and coformers are compared, and their solid state miscibility is expressed. Possibility of cocrystal formulation by Krevelen's is $\Delta\delta < 5$ MP and Greenhalgh $\Delta\delta < 7$ MP. The present investigation deals with the formulation of coformer (saccharin, succinic acid, and sucrose) based on cocrystals fenofibrate by different methods and solid-state characterization of prepared cocrystals. Fenofibrate and coformers in molar ratio were used to formulate molecular complexes by solution evaporation, slow evaporation, antisolvent addition, net grinding method, and solvent-drop grinding methods. The prepared molecular complexes were characterized by powder X-ray diffraction, differential scanning calorimetry, Fourier-transform infrared spectroscopy, and *in vitro* dissolution study. **Conclusion:** Considerable improvement in the dissolution rate of fenofibrate from optimized cocrystal formulation was due to an increased solubility that is attributed to the supersaturation from the fine cocrystals which is faster due to large specific surface area of small particles and prevention of phase transformation to pure fenofibrate.

Key words: Cocrystal formation, Hansen solubility parameters, group contribution methods (Fedor's substituent constants, Hoy's molar attraction constants, and Van Krevelen constants)

INTRODUCTION

The poor solubility and dissolution rate of active pharmaceutical ingredient (API) is one of the main challenges in pharmaceutical development and is becoming more common among new drug candidates over the past due to the use of high throughput and combinatorial screening tools during the drug discovery and selection phase. The improvement of solubility and dissolution profiles of these lipophilic drug molecules without altering the molecular structure is particular change for the successful development of pharmaceutical product.[1] According to the biopharmaceutical classification system, the compounds mostly belong to class II which are poorly soluble and highly permeable according to the pH of gastrointestinal fluid and tend to present dissolution-limited absorption. Despite their high permeability, these drugs often have low oral

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bioavailability because of their slow and limited release of drug in gastrointestinal fluid. Therefore, one of the major challenges of the pharmaceutical industry is to apply strategies that improve the dissolution and/or apparent solubility of poorly soluble drugs to develop such problematic compounds into orally bioavailable and therapeutic effective drug.[2]

Many approaches have been adopted for improving the aqueous solubility of drug such as micronization, salt formation, emulsification, solublization using cosolvent, and use of coformer drug vehicles for delivery of poorly soluble drugs. Although these techniques have been shown to be effective at enhancing oral bioavailability, success of these approaches is dependent on the specific physicochemical nature of the molecules being studied. Over the past decade, there has been growing interest in the design of pharmaceutical cocrystal, which emerges as a potential approach to enhance the solubility of the drug.[3] Cocrystallization as a method of obtaining new forms of APIs with improved physicochemical properties (e.g., solubility, stability, and melting point) has gained much attention in the recent year and is a promising alternative to so far employed preparation of salt, hydrates, solvates, and other forms. Cocrystal design for a specific APIs is based on evaluating possible heteromolecular synthons, which are reliable hydrogen bonding motifs sustaining crystal structures.[3,4]

"Cocrystals are homogeneous solid phases containing two or more neutral molecular components in a crystal lattice with defined stoichiometry, which are solids at room temperature and are held together by weak interactions, mainly hydrogen bonding." Cocrystals can be constructed through several types of interaction, including hydrogen bonding, p stacking, and van der Waals forces. Solvates and hydrates of the API are not considered to be cocrystals by this definition. However, cocrystals may include one or more solvent/water molecules in the crystal lattice. Cocrystals often rely on hydrogen-bonded assemblies between neutral molecules of API and other components. For non-ionizable compounds, cocrystals enhance pharmaceutical properties by modification of chemical stability, moisture uptake, mechanical behavior, solubility, dissolution rate, and bioavailability.[5]

A pharmaceutical cocrystal can be designed by crystal engineering with the intention to improve the solid-state properties of an API without affecting its intrinsic structure. Cocrystals can be considered as molecular complexes which differ from solid solutions or mixed crystals. Cocrystals are divided into cocrystal anhydrates and cocrystal hydrates. Salts can be differentiated from cocrystals, in that, the former mainly improve solubility and stability of a compound, while the latter is an alternative to salt when salts do not have solid properties due to the absence of ionizable salts in API. Structural properties of a cocrystal are based on the structure of cocrystal former. Examples of cocrystal former include ascorbic acid, gallic acid, nicotinamide, citric acid, aglutamic acid, histidine, urea, saccharine, glycine, succinic acid, sucrose, and alpha ketoglutaric acid.[6,7]

Solubility parameter

Solubility of drug molecule is the one of the important parameters where the solubility plays an important role in pharmaceutical formulation with optimized physical properties for effective absorption of drug. In general, solubility parameters are termed as cohesion energy parameters and derive from the energy needed to convert a liquid phase to a gas phase. The energy of vaporization is direct measures of the total (cohesive) energy present in the liquid's molecules together. All types of bonds present in the liquid together are broken by evaporation, and this has led to the concepts described in more detail later. The term cohesion energy parameter is more appropriately used when referred to surface phenomena.[8]

$$c = \frac{\Delta H - RT}{V_m} \quad (1)$$

Where
c=Cohesive energy density,
H=Heat of vaporization,
R=Gas constant,
T=Temperature,
V_m=Molar volume.

The cohesive energy density (CED) of a liquid phase is a numerical value, indicating the energy of vaporization in calories per cubic centimeter, and is a directly reflecting to degree of van der Waals forces holding the molecules of the liquid together. Such correlation between vaporization and van der Waals forces also transforms into a correlation between vaporization and solubility behavior. This is because the same intermolecular attractive forces have to be overcome to vaporize a liquid as to dissolve it. The solubility of two materials is only possible when intermolecular attractive forces are quite similar, and one might also expect that materials with similar CED values would be miscible.[9]

Hildebrand parameters and polymer solution thermodynamics

The Hildebrand solubility parameter is defined as the square root of the CED.[10]

$$\delta = \sqrt{c} = \left[\frac{\Delta H - RT}{V_m}\right] 1/2 \text{ or } \delta = (E/V)1/2 \quad (2)$$

V is the molar volume of the pure solvent, and E is its (measurable) energy of vaporization. The numerical value of the solubility parameter in $MPa^{½}$ is 2.0455 times larger than that in $(cal/cm^3)^{½}$. The solubility parameter is an important quantity for predicting solubility relations.

Hansen solubility parameters (HSP)

The concept of a solubility parameter (δ) was introduced by Hildebrand and Scott, who proposed that materials with

similar δ values would be miscible (Hildebrand and Scott, 1964). The HSP model in 1967, which was developed later, is based on the concept of dividing the total cohesive energy into individual components, i.e., dispersion and polar and hydrogen bonding. HSPs have been widely used to predict liquid-liquid miscibility, miscibility of polymer blends, surface wettability, and the adsorption of pigments to surfaces (Hansen, 2007). In pharmaceutical sciences, HSPs have been used to predict the miscibility of a drug with excipients/carriers in solid dispersions. Further, it has been suggested that HSPs could predict the compatibility of pharmaceutical materials, and their use is recommended as a tool in the pre-formulation and formulation development of tablets. This study investigated whether the miscibility of a drug and its coformer components, as predicted by theoretical miscibility tools, could be used to predict the formation of cocrystal. Fenofibrate was selected as the model API.[11-14] The HSPs of the coformers and fenofibrate were calculated using group contribution methods. The miscibility of fenofibrate with a coformer was predicted using three established miscibility tools. Based on the prediction of miscibility, laboratory screening for cocrystals was conducted using thermal methods and liquid-assisted grinding. The preliminarily characterization of cocrystal was performed using high-performance liquid chromatography, thermal methods, and powder X-ray diffraction (PXRD).

$$\Delta H = V_T \left(\sqrt{Ev_1 / Vm_1} - \sqrt{DEv_2 / V_m}\right)^2 Ø1.Ø2 \quad (3)$$

ΔH is the heat of mixing, V_T is the total volume, ΔE_V is the energy of vaporization, V_m is the molar volume, ϕ is the volume fraction, and 1 and 2 stands for the solute and solvent. Hildebrand *et al.* named the energy of vaporization per unit volume as the CED.

$$\delta=(CED)^{0.5}=(\Delta E/V)^{0.5} \quad (4)$$

Where V is the molar volume.

Hansen assumed that total cohesion energy is the sum of dispersion E_D, polar E_P, and hydrogen bond energy E_H.

$$ET=ED + EP + EH \quad (5)$$

And by dividing both sides of the equation by molar volume V, we will have the total Hansen solubility parameter or Hildebrand solubility parameter δ_T:

$$\delta^2_T=\delta^2_D\delta^2_P\delta^2_H$$

Where
δ=Total solubility parameter
δ=Dispersion interactive (London) force
δ=Permanent dipoles in interacting molecules, called dipole-dipole interactive forces
δ=Hydrogen-bonding force

If δ_T of both solute and solvent is alike, this will allow predicting solubility according to Equation (1). The common used units for δ in literatures are (J/m³) 0.5, MPa 0.5, or (cal/cm³) 0.5, where one (cal/cm³) 0.5 is equivalent to 2.0421 MPa 0.5 or (J/m³) 0.5.[2] δ calculation methods were varied between practical and theoretical ones according to either direct or indirect measuring of intrinsic properties of material as evaporation temperature, viscosity, and solubility in predetermined solvents.

Theoretical screening/prediction of fenofibrate for cocrystallization

Solubility parameters for dry solutes may be obtained by group contribution methods. Calculations using Hoy's molar attraction constants, Fedor's substituent constants, and Van Krevelen constants are the currently used methods. In the present investigation, these methods were employed to arrive at the solubility parameter values. The basic steps in Fedor's method are to open the rings and treat the resultant structure as an open-chain compound. Then, the approximate substituent constants are applied.[15] These are summed, and the solubility parameter calculated as square root of the sum of energy of mixing substituent constants divided by the sum of molar volume substituent constants. Hoy's procedure expressed the ratio of molar attraction constant to molar volume. The resultant Δ values of drug and conformers are compared, and their solid state miscibility is expressed.[16]

The group contribution method is used for theoretical calculation which helps for the selection of coformer which is compatible with drug. The HSP predicts whether drug and coformer are compatible and form the molecular complex with drug and coformer. The group contribution reduces practical work by predicting whether the molecular complex is formed or not. The Fedor's method, Hoy's method, and Van Krevelen's method calculation is based on the attachment of atom or molecules from the structure. These methods are used for theoretical calculation of solubility. The theoretical prediction or possibility of cocrystal formulation by krevelens and Greenhalgh methods mainly confers, based on delta(Δ) value $\leq$ 5MP and $\leq$ 7 MP respectively.[17,18]

MATERIALS AND METHODS

Materials

Fenofirate was purchased from Unic biological and chemical Ltd. (Kolhapur, India). All the other chemicals and solvents were analytical grade procured from Merck (India) and Molychem, Mumbai (India).

Theoretical prediction of solubility

Fedor's method/Fedor's substituent constants

$$\delta = \sqrt{\frac{\sum \Delta\Delta U}{\sum \Delta V}} \quad (6)$$

Where
*ΔΔU is constant for energy mixing
**ΔV is constant for molar volume

Hoy's method/Hoy's Molar attractions

According to ([cal cc] 1/2 mol^{-1}) unit,

$$\delta = \frac{\sum \text{molar attraction}}{V} \quad (7)$$

Van Krevele's solubility parameters

The calculation of solubility parameter and molar volume van Krevelen's method, which is based on experimental molar volume measured cm^3/Mol, is as follows:

$$\delta d = \sum Fd/V \quad (8)$$

$$\delta p = \sqrt{\sum Fp2 / V} \quad (9)$$

$$\delta h = \sqrt{\sum Uh / V} \quad (10)$$

$$\delta^2 T = \sqrt{\delta d^2 + \delta p^2 + \delta h^2} \quad (11)$$

Preparation of cocrystals

Neat grinding method

The accurately weighed quantity of drug and coformer in 1:1 molar ratio was grounded in mortar and pestle for 30 min, the powder obtained was collected and stored in desiccator till further use.[19]

Solvent-drop grinding

In the solvent-drop grinding method, drug and coformer were weighted in 1:1 molar ratio and ground together with addition of 3–4 drops of ethanol. The mixture was ground for 30 min at room temperature.[20]

Slow evaporation method

The accurate weight of drug and coformer in 1:1 molar ratio was separately dissolved in ethanol. After stirring, it was mixed with each other store for 48 h at room temperature. The crystal obtained was collected and stored in a tight container and stored in desiccators for further use.[16]

Antisolvent addition method

FNO (drug) and coformer weight in 1:1 molar ratios were dissolved in 20 ml ethanol using moderate stirring. The solution was then filtered through a Whatman filter paper to remove any undissolved material. Distilled water was then added dropwise to the above solution with constant stirring to induce cocrystal precipitation. The cocrystals were allowed to dry overnight in desiccators.[21]

Solution cocrystallization method

FNO (drug) and coformer in 1:1 molar ratio were dissolved in 20 ml ethanol with sonication, the saturation solution was kept overnight to evaporate solvent, and the crystal obtained after evaporation of ethanol was allowed to dry in the air.[22]

Slurry method

FNO (drug) and coformer were carefully weighted in 1:1 molar ratio, respectively. Both powders were mixed homogeneously in mortar, 15 ml of water was added to mixture to form slurry sample solution. The formed cocrystal was dried at temperature of 40°C for 48 h. The solid crystal was collected and stored in desiccators.[14,23-25]

Evaluation of cocrystals of FNO

Flow properties of FNO and FNO cocrystals

The prepared cocrystal were evaluated for flow properties thesuch as angle of repose, flow rate (g/s), bulkiness, loose bulk density, porosity (%), and compressibility (%).[26]

Saturation solubility of cocrystals

Saturation solubility studies were carried out using ethanol as a solvent. Each excessive quantity (10 mg) of FNO and equivalent prepared cocrystals were taken in screws capped test tubes with fixed volume (10 ml) of ethanol. The resultant suspension was treated at 37°C with 100 rpm in incubator shaker. After 24 h, samples were withdrawn and filtered through 0.2 µ filter. The filtrate was suitably diluted with ethanol and analyzed at 290 nm by UV visible spectrophotometer.[27]

Drug content

The prepared cocrystals were weighed, and process yield was calculated. From prepared cocrystals, powder equivalent to 10 mg FNO was weighed and dissolved in 100 ml ethanol, then filtered through a Whatman filter paper and volume was adjusted to 100 ml. After sufficient dilutions with ethanol, samples were analyzed spectrophotometrically at 290 nm, and FNO content was calculated.[28]

In vitro dissolution studies of co-crystals

In vitro dissolution studies of solid-state forms of fenofibrate were performed using eight-station USP type II dissolution rate test apparatus. The accurately weighed samples equivalent of 100 mg of drug was used. The dissolution profiles of fenofibrate and cocrystals were determined in 900 ml of simulated gastric fluid 1.2 pH. Dissolution medium was kept in a thermostatically controlled water bath, maintained at 37°C ± 0.5°C at

rotation speed of 100 rpm. Samples were withdrawn periodically, and fresh equal volume of dissolution media was introduced in vessels to maintain the sink condition. Samples were filtered through whatman filter paper, diluted and analyzed at 290 nm using Shimadzu UV-1800 Japan Spec, spectrophotometer.[29,30]

Analysis of molecular complexation by solubility

Complex compounds are defined as those molecules in which most of the bonding structures can be described by classical theories of valency of atoms or molecules, but one of these bonds is somewhat anomalous.[31-33]

FNO stock solution (0.1M)

The molecular weight FNO is 360.83 mg/ml. Accurately weighed 3.6083 g of anhydrous FNO transferred into 100 ml of volumetric flask and volume was adjusted with ethanol to make up the final volume.

Saccharine solution

The amount of saccharine to be added for FNO sample is constant. The molecular weight of saccharine is 250.16 weights accurately the required number of sample of saccharine each containing 100 mg.

Solid-state characterizations of cocrystals of FNO

Fourier-transform infrared (FTIR) spectroscopy

The FTIR spectra of FNO and its cocrystals were determined using FT-IR (Cary-60 ATR), and the spectra were recorded on a Cary-60 ATR. FTIR spectrometer is in the range of 4000–400/cm, the study was carried out to detect any changes on chemical constitution of the FNO and its coformers.[34]

Differential scanning calorimetry (DSC)

DSC was performed using DSC-60A (Shimadzu, Tokyo, Japan) calorimeter to study the thermal behavior of drug alone and prepared cocrystals. The samples were heated in hermetically sealed aluminum pans under nitrogen flow (30 ml/min) at a scanning rate of 100°C/min from 500°C to 3000°C.[35]

PXRD studies

The X-ray diffraction patterns of pure drug and the optimized crystals formulation were recorded using Philips analytical X-ray diffractometer (Model: PW 3710) (Philips, Almelo, The Netherlands) with a copper target over the interval of 5–70° 2θ−1. The conditions were as follows: Voltage 40 kV; current 30 mA; scanning speed 20/min; temperature of acquisition: Room temperature; detector: Scintillation counter detector; and sample holder: Non-rotating holder.[36]

Scanning electron microscopy of FNO and FNO cocrystals

Scanning electron microscopy

The outer macroscopic structure of the FNO and FNO cocrystals was investigated by scanning electron microscopy (SEM) with a FEI Sirion-200 scanning electron microscope (FEI, the Netherlands), operating at 10 kV. The sample was fixed on a SEM-stub using double-sided adhesive tape and then coated with a thin layer of gold.[37,38]

Proposed structures of cocrystals

The proposed structures of cocrystals were developed using Chemsketch software. The thorough understanding of the structure of API and cocrystal formers is required to correctly locate the hydrogen bonding sites.[39]

RESULTS AND DISCUSSION

Theoretical prediction of solubility

Fedor's substitution constants

Fedor's proposed a method of determining solubility parameter without using the density value of the compound. This method is supposed to be better than Small's method for two reasons: The contributions of much larger number of functional groups have been evaluated, and the method requires only the knowledge of structural formula of the compound [Table 1].[40] The following equation is used for directly determining cf:

$$\delta 2 = \sqrt{\frac{\sum \Delta\Delta U}{\Delta V}} \quad (12)$$

Where ΔΔU and ΔV are the constant for energy mixing and constant for molar volume for the energy of vaporizations and molar volume, respectively [Table 2].

Calculation of solubility parameter.

Based on Fedor's Substitution constants,

$$\delta 2 = \sqrt{\frac{\sum \Delta\Delta U}{\Delta V}} \quad (13)$$

$$= 10.37H$$

Hoy's method

Small's scheme has offered a convenient method for estimating the SP value for many solvents and polymers. However, the list of the constants is incomplete. Hoy published more group molar attraction constants derived from measurement of the vapor pressure of a wide variety of groups[41] [Table 3]. Solubility parameter (δ) is calculated from the following equation:

cf−density ×$\sum F_i$/molecular weight

Where is the ∑F sum of the group molar attraction constants of the compound. Hoftyzer and Van Krevelen published a series of group molar attraction constants similar to small and Hoy [Table 4].

According to Equation 12

$$\delta_{2=} \frac{\sum \text{molar attraction}}{V_2} \quad (14)$$

=9.78 H

Table 1: Calculation of *∂* value of Fenofibrate by F, G, and C method

Fragments/groups	Number of groups	ΔΔU* for each (cal.mol^{-1})	Total ΔΔU	ΔV** for each (m^{-1} mol^{-1})	Total ΔV
-Cl	1	2760	2760	24	24
-CH3	4	125	4500	33.5	134
-CH2	2	1180	2360	16.1	32.2
-CH=	9	1030	9270	13.5	121.5
-CH-	1	820	820	−1.0	−1.0
-C-	2	350	700	−19.2	−19.2
-C=O	2	4150	8300	10.8	21.6
-O-	2	00	1600	3.8	7.6
Ring closer	2	250	500	16	32
Conjugated bond	8	400	3200	−2.2	−17.6
			∑=34010		∑=315.9

*ΔΔU is constant for energy mixing. **ΔV is constant for molar volume

Table 2: Theoretical prediction of cocrystal formation by Fedor's method

Compound	δ value	Difference δ1–δ2	Δδ	Possibility of cocrystal formation	
				Krevelen's Δδ≤5MP	Greenhalgh Δδ≤7MP
Fenofibrate	10.37 H			-	
Sucrose	14.52 H	10.37–14.52	4.15	Yes	
Saccharine	13.07 H	10.37–13.07	2.7	Yes	
Succinic acid	15.13 H	10.37–15.13	4.28	Yes	

Table 3: Calculation of solubility parameter of fenofibrate based on Hoy's molar attractions

Fragments/groups	Number of groups	ΔΔU* for each (cal/mol)	Total ΔΔU	ΔV** for each (m^{-1} mol^{-1})	Total ΔV
-Cl	1	161	161	19.504	19.504
-CH=	9	117.12	1054.08	13.417	120.753
-CH_2	2	131.5	263	15.553	31.106
-CH_3	4	148.36	593.44	21.548	86.192
C=O	2	262.96	525.92	17.265	34.53
-CH-	1	85.99	85.99	9.557	9.557
-O-	2	114.98	229.96	6.46	12.92
-C-	2	32.03	64.06	3.562	7.124
Six-membered ring	2	−23.44	−46.88	0	0
Conjugated bond	8	23.26	186.08	0	0
Ortho	2	9.69	19.38	0	0
Meta	1	6.6	6.6	0	0
Base value	0	0	0	0	0
			∑=3142.63		∑=321.686

Van Krevelen's method

Van Krevelen derived Fi values for the contributions of atoms, i.e., C, H, N, 0, halogens, and constitutional effects [Table 5] [27] (such as double or tribal bonds). Solubility parameter (δ) can be calculated using the following equation:

$$\delta = \frac{\sum F_i}{V_m} \quad (15)$$

Where $\sum=F_i$ is the sum of the atomic contribution and V_m is molar volume [Table 6].

Based on experimental molar volume 334.2 cm^3/mol,

$$\delta^2 T = \sqrt{\delta d^2 + \delta p^2 + \delta h^2} \quad (16)$$

$$=7.71 \text{ H}$$

Preparation and evaluation of FNO cocrystal

The angle of repose for all preparation fell within the range of 25–300 indicates good flow properties. The angle of repose is a characteristic of internal frication or cohesion of the particles. If the value of the angle of repose is high, crystals are cohesive, and if it is low, crystals are non cohesive. There is a relationship between the angle of repose and the ability of crystals to flow.[42,43] The angle of repose should be in between 25 and 300 for good flow properties of crystals. The bulk density of a crystal depends primarily on particle size distribution, particle shape, and the tendency of particle to adhere together. Tables 7-9 present the bulk density values of all preparations, which were in the range of 0.13–0.18 g/cm^3, indicating good packing capacity.

Flow properties of FNO and FNO cocrystal

The fenofibrate showed good flow properties while the prepared cocrystals showed excellent flow properties. This indicates that the cocrystals improved the flow properties of fenofibrate [Tables 7-9].

Table 4: Theoretical prediction of cocrystal formation by Hoy's Method

Compound	δ value	Difference δ1–δ2	Δδ	Possibility of cocrystal formation	
				Krevelen's Δδ ≤ 5MP	Greenhalgh Δδ ≤ 7MP
Fenofibrate	9.78 H				
Sucrose	15.31 H	15.31–9.78	5.53	Yes	
Saccharine	15.53 H	15.53–9.78	5.37	Yes	
Succinic acid	15.13 H	15.13–9.78	5.37	Yes	

Table 5: Calculation of solubility parameter and molar volume of fenofibrate by Van Krevelen's solubility parameter

Fragments/groups	Number of groups	Fd	Total Fd	Fp	Total Fp	Fp^2	Uh	Total Uh
-Cl	1	450	450	550	550	302500	400	400
CH2	2	270	540	0	0	0	0	0
-CH3	4	420	1680	0	0	0	0	0
-CH=	9	200	1800	0	0	0	0	0
-CH-	1	80	80	0	0	0	0	0
-C-	1	–70	–70	0	0	0	0	0
C=O	2	0	0	0	0	0	0	0
-O-	2	100	200	410	820	672400	3000	6000
6/5 membered ring	2	190	380	0	0	0	0	0
			Σ=5060			Σ=974900		Σ=6400

Table 6: Theoretical prediction of cocrystal formation by van Krevelen method

Compound	δ value	Difference δ1–δ2	Δδ	Possibility of cocrystal formation	
				Krevelen's Δδ ≤ 5MP	Greenhalgh Δδ ≤ 7MP
Fenofibrate	7.71 H				
Sucrose	6.40 H	7.71–6.40	0.65	Yes	
Saccharine	2.00 H	7.71–2.00	5.05	Yes	
Succinic acid	7.18 H	7.71–7.18	0.12	Yes	

Saturation solubility study of FNO and FNO-coformer cocrystals

Figure 1-3 summarizes the experimentally determined solubility of fenofibrate in ethanol solution. The prepared cocrystals with coformers such as sucrose, succinic acid, and saccharine were show significantly higher solubility compared to their cocrystals and drug alone. It is to be expected that fenofibrate would be solubilized well in cocrystal form due to a reduction in crystallinity of drug and hydrogen-bond formation between drug and conformer.[44] The cocrystals prepared by antisolvent addition method and slow evaporations method show higher solubility than that of the fenofibrate and other cocrystals because addition of an antisolvent which reduces the solute solubility in the resultant system or changing the solute by chemical reaction producing another substance with much lower solubility [Figures 1-3].

Drug content

Cocrystals are prepared by various methods; it involves inclusion of solvent. However, drug content analysis was done on cocrystals prepared by all methods in triplicate.[45] The fenofibrate content in the prepared cocrystals showed in range of 60–94% as mentioned in Table 10.

In vitro dissolution studies

The *in vitro* dissolution profiles of the cocrystals prepared by various methods were compared with that of pure FNO. The *in vitro* dissolution rate of all prepared cocrystal was increased compared to the drug. Pure drug shows 48.34% drug release after 60 min, whereas cocrystals prepared by solution evaporation and slow cocrystallization method show 92.9% and 91.14% after 60 min, respectively [Figures 4-6]. The high dissolution rate of prepared cocrystals can be attributed to decrease in crystallinity of fenofibrate due to interaction with coformer. The antisolvent addition method produces small, uniform, and stable FNO cocrystal with markedly enhanced dissolution rate due to an increased solubility that is attributed to partial amorphization of drug with increased surface area and improved wettability.

Table 7: Flow properties of FNO and sucrose cocrystal

Method of preparation	Angle of repose	Bulk density	Tapped density	Hausner's ratio	Carr's index
FNO	38.65±0.6	0.133±0.0005	0.166±0.0005	1.24±0.01	19.87±0.6
Slow evaporation	41.98±0.6	0.106±0.0005	0.118±0.0010	1.11±0.01	10.16±0.5
Solution cocrystallization	40.69±0.6	0.119±0.0005	0.125±0.0005	1.09±0.01	8.33±0.6
Net grinding	19.56±0.6	114±0.00057	0.13±0.00057	1.14±0.01	12.3±0.5
Solvent grinding	46.39±0.6	0.117±0.0005	0.14±0.00057	1.19±0.01	16.42±0.5
Antisolvent grinding	58.93±0.6	0.102±0.0005	0.113±0.0005	1.1±0.050	9.73±0.5
Slurry method	35.37±0.6	0.107±0.0005	0.115±0.0057	1.07±0.01	9.09±0.7

Table 8: Flow properties of FNO and succinic acid cocrystal

Method preparation	Angle of repose	Bulk density	Tapped density	Hausner's ratio	Carr's index
FNO	38.65±0.6	0.133±0.005	0.166±0.0005	1.24±0.0005	19.87±0.6
Slow evaporation	28.81±0.6	0.121±0.005	0.131±0.0005	1.08±0.0005	7.63±0.5
Solution cocrystallization	35.37±0.5	0.116±0.005	0.125±0.0005	1.09±0.005	8.33±0.6
Net grinding	39.69±0.6	0.134±0.005	0.145±0.0006	1.08±0.0069	7.58±0.6
Solvent grinding	43.51±0.6	0.13±0.0005	0.141±0.0005	1.08±0.0107	7.8±0.6
Antisolvent grinding	40.69±0.7	0.163±0.005	0.184±0.0005	1.12±0.0005	11.41±0.4
Slurry method	30.11±0.5	0.18±0.0005	0.21±0.00057	1.16±0.005	14.28±0.5

Table 9: Flow properties of FNO and saccharine cocrystal

Method of preparation	Angle of repose	Bulk density	Tapped density	Hausner's ratio	Carr's index
FNO	38.65±0.6	0.133±0.0005	0.166±0.0005	1.24±0.0005	19.87±0.5
Slow evaporation	28.81±0.6	0.153±0.0005	0.175±0.0006	1.14±0.0005	12.57±0.6
Solution cocrystallization	27.47±0.6	0.153±0.001	0.176±0.0005	1.15±0.0005	13.06±0.5
Net grinding	34.21±0.5	0.162±0.0005	0.174±0.0010	1.07±0.0005	6.89±0.6
Solvent grinding	32.61±0.6	0.16±0.00057	0.187±0.0006	1.16±0.0005	14.43±0.6
Antisolvent grinding	29.68±0.7	0.146±0.0005	0.167±0.0011	1.14±0.0005	12.57±0.6
Slurry method	30.11±0.5	0.155±0.0005	0.181±0.0005	1.16±0.0005	14.36±0.5

Analysis of molecular complexation solubility method[46]

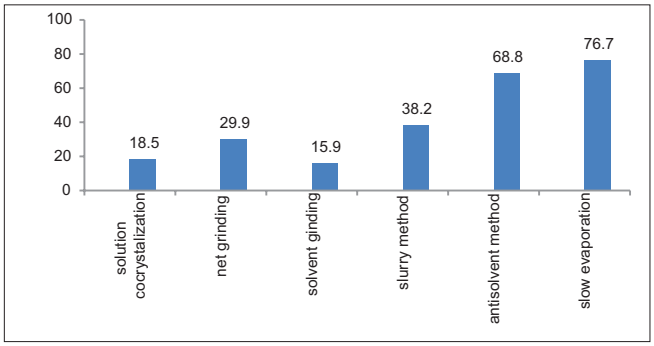

Figure 1: Solubility of FNO-sucrose cocrystals prepared by different methods

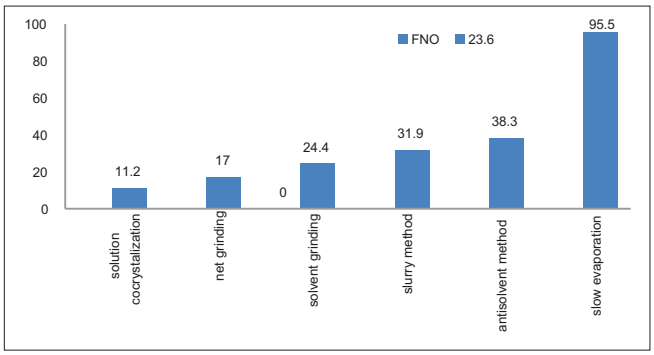

Figure 2: Solubility of FNO-succinic acid cocrystals prepared by different methods

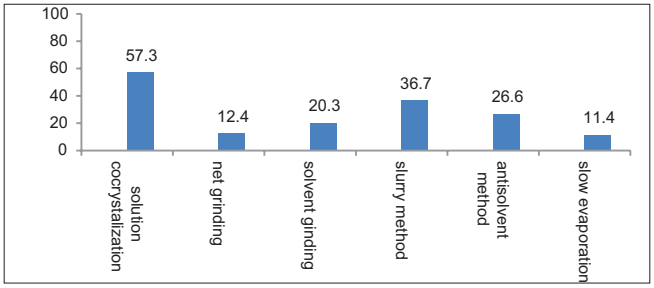

Figure 3: Solubility of FNO-saccharine cocrystals prepared by different methods

Estimation of parameter of complex

$$\text{Stoichiometric ratio} = \frac{\text{Fenofibrate complex}}{\text{Saccharine complex}}$$

Considering the concentration of FNO and saccharine entering the complexation [Figure 7].

$$\text{Stoichiometric ratio} = \frac{\text{Fenofibrate entering into complex}}{\text{saccharine entering into complex}}$$

FNO entering into complex = [FNO] at point C–[FNO] at point B

=2 mol/L

Saccharine entering into complex = [saccharine] total taken−[saccharine] at point B or C

= 0.06 mol/L

$$\text{Ratio} = \frac{\text{Fenofibrate complex}}{\text{Saccharine complex}}$$

=33.33

Therefore, donor or accepter = 1:33

$$\text{Stability constant K} = \frac{\text{Saccharine - FNO}}{[\text{Saccharine}][\text{FNO}]}$$

Saccharine−FNO complex = $(0.60\times10^{-2})-(0.54\times10^{-2})$

$=0.06\times10^{-2}$ mol/L

FNO complexed=(saccharine-FNO)$=0.06\times10^{-2}$ mol/L

Based on equi-molar relationship,

[Saccharine] uncomplexed = [saccharine] at solubility

$=0.60\times10^{-2}$ mol/L

FNO = $(2\times10^{-2})-(0.06)$

Table 10: The percentage FNO content in cocrystals using different of preparation

S. No.	Method of cocrystal preparation	% FNO content in Coformer		
		Sucrose	Succinic acid	Saccharine
F1	Slow evaporation	84±0.57	91.38±0.43	92.53±0.52
F2	Solution cocrystallization	92.44±0.60	92.4±0.64	68.9±0.79
F3	Net grinding	93.16±0.36	93.88±0.83	96.09±0.59
F4	Solvent grinding	81.48±0.57	89.25±0.57	53.12±0.58
F5	Antisolvent grinding	93.51±0.60	80.84±0.63	96.87±0.62
F6	Slurry method	68.35±0.56	67.31±0.48	72.68±0.68

*All values are mean±SD (n=3). SD: Standard deviation

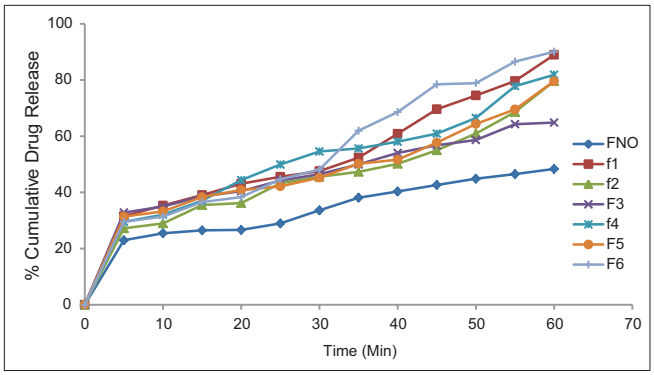

Figure 4: *In vitro* dissolution of FNO and succinic acid cocrystals prepared by different methods

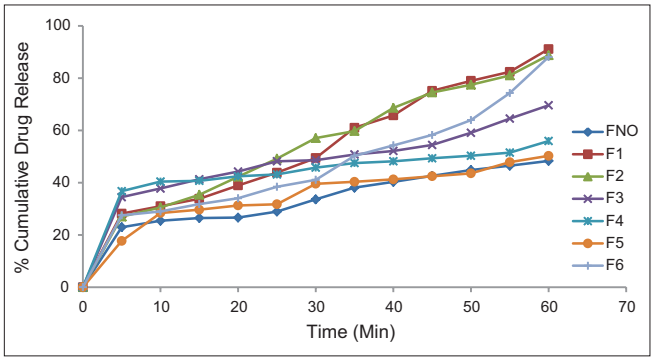

Figure 5: *In vitro* dissolution of FNO and saccharine acid cocrystals prepared by different methods

$$=1.94\times10^{-2}$$

$$\text{Stability constant K} = \frac{\text{Saccharine - FNO}}{[\text{Saccharine}][\text{FNO}]}$$

$$=5.15 \text{ l/mol}$$

Equilibrium stability constant for the complex of FNO and saccharine is 5.15 L/mol.

Solid-state characterizations of FNO cocrystals

FTIR spectroscopy

The possible interaction between the drug and the cocrystal formers was studied by FTIR spectroscopy. From the results of FTIR, it was observed that all the important peaks due to functional groups of drug were present in the cocrystals along with some new peaks. The result revealed considerable changes in the IR peaks of fenofibrate in prepared cocrystals when compared to pure drug, thereby indicating the presence of hydrogen bonding had occurred in the cocrystals [Figure 8].

Specific FNO peaks are observed. The peak at 2982/cm indicates aromatic C-H stretching, peak at 1588/cm indicates C=O stretching, whereas peaks at 1285/cm and 1087/cm indicate aralkyl and dialkyl ether C-O stretching, respectively. Furthermore, peak at 764/cm indicates the presence of

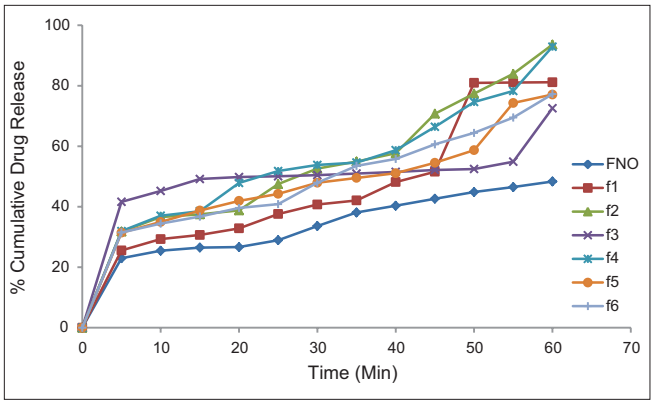

Figure 6: *In vitro* dissolution of FNO and sucrose cocrystals prepared by different methods

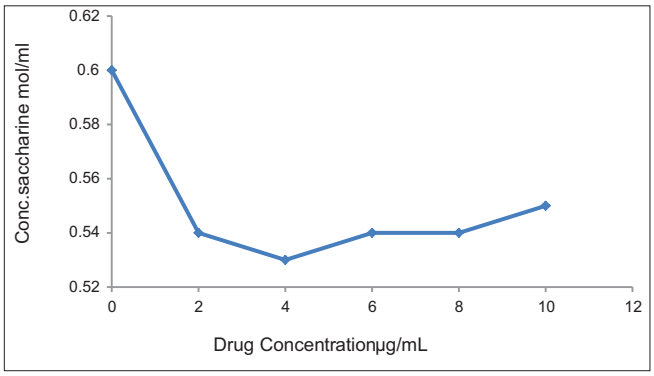

Figure 7: Molecular complex of FNO-saccharine cocrystals

halogen-hydrogen interaction.[47]

DSC

DSC was conducted to indicate the molecular dispersion of fenofibrate into coformer. DSC thermograms are obtained for FNO, succinic acid, and sucrose and saccharine. DSC curves of pure drug and formulations were compared [Figure 9]. DSC revealed complex structure of solid crystals. DSC thermograms are obtained for FNO and different coformers. DSC curves of pure drug and formulations were compared. Pure fenofibrate has showed well-defined endothermic peak (Tm) at 83.98°C corresponding to the melting point of crystalline drug. The prepared cocrystals showed crystal in melting point, in prepared SA solvent grinding, SA solution cocrystallization, saccharine AG, saccharine slurry conversion, and sucrose neat grinding showed endothermic peaks at 86.40°C, 86°C, 84.39°C, 84.79°C, and 87.71°C, respectively.[8,48]

Crystalline state evaluation: PXRD analysis

The XRD patterns of the pure drug and cocrystals are shown in Figure 7. The XRD scan of Pure fenofibrate showed intense peaks of crystallinity at 13.71°, 17.380, 19.400, 21.310, 23.400, and 26.220 (2θ) with peak intensities of 700, 1000, 1200, 1500, 2300, and 2800, respectively,

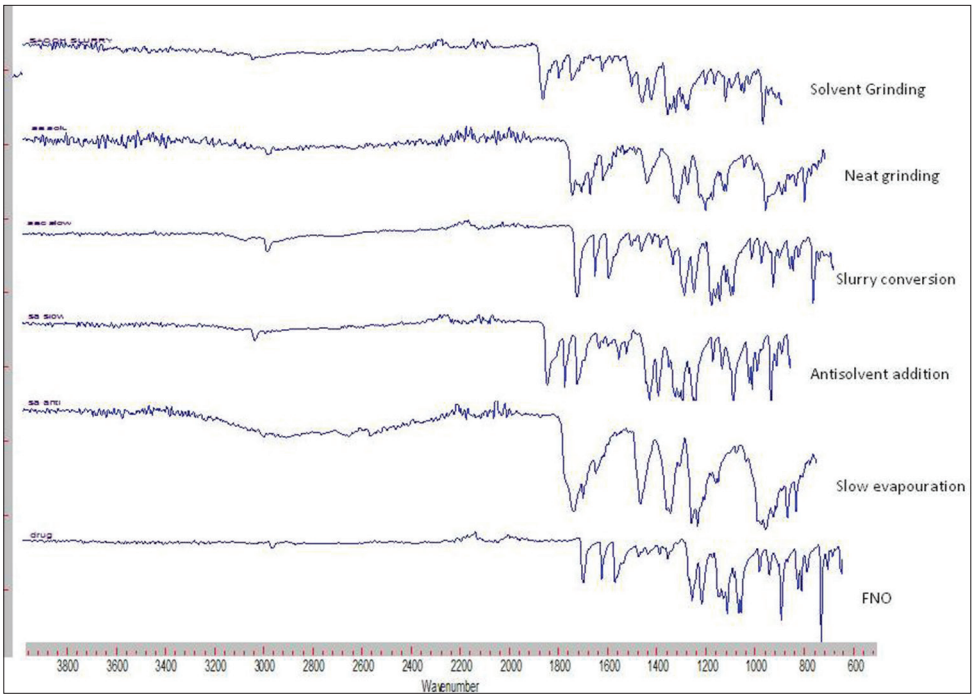

Figure 8: Comparative Fourier-transform infrared pattern of FNO and cocrystals using three different coformer and by various methods. (a) pure FNO, (b) slow evaporation, (c) solution crystallization, (d) neat grinding, (e) solvent grinding, (f) antisolvent addition method, and (g) slurry method

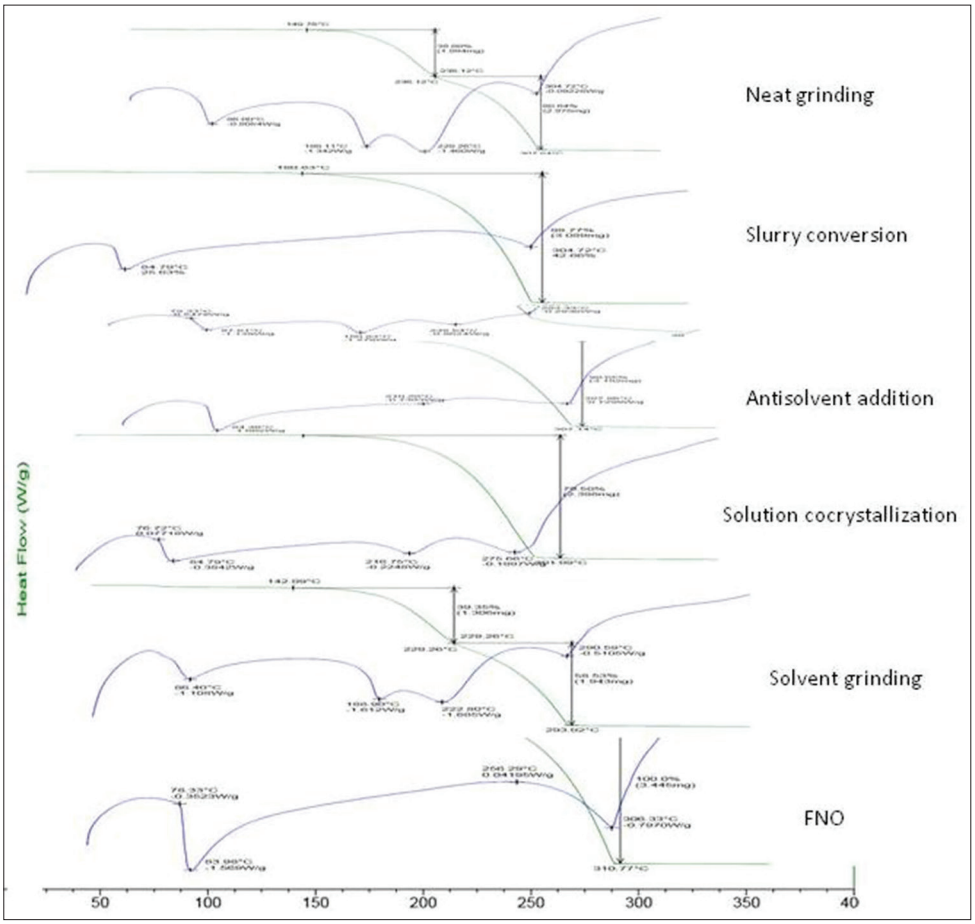

Figure 9: Differential scanning calorimetry thermograms of FNO and cocrystals using three different coformer and by various methods. (a) Pure FNO, (b) slow evaporation, (c) solution crystallization, (d) neat grinding, (e) solvent grinding, (f) antisolvent addition method, and (g) Slurry method

indicating its crystalline nature [Figure 10]. Crystallinity was determined by comparing representative peak heights in the diffraction patterns of the cocrystals with those of reference. The relative degree of crystallinity (RDC) of fenofibrate in cocrystals was calculated according to the equation RDC = Isam/Iref, whereas Isam is the peak height of the sample under investigation and Iref is the peak height at the same angle for the reference with the highest intensity.[49,50] The newly formed cocrystals showed the same 2θ but with lower intensities, also the presence of some new peak for coformer.

SEM

Crystals of bigger size and regular shape with an apparently smooth surface characterized the pure drug. Figure 11 shows microphotographs of fenofibrate and prepared cocrystals, from that it was observed that fenofibrate showed large crystals while cocrystals of antisolvent addition method showed small, uniform crystals.[50] Cocrystals of other methods showed reduced crystallinity as compared to pure fenofibrate. It was also confirmed by PXRD study.

Proposed structure with copolymer

The characterization results of drug and all cocrystals enable one to determine the possible structures of newly formed cocrystals using concept of hydrogen bonding [Figure 12]. The chloride ion is one of the most preferred anions for salts of cationic APIs. It has been estimated that approximately half of the salts of cationic drugs are marketed as hydrochloride salts. The exceptional ability of the chloride ion to act as hydrogen bond acceptor is the key to the approach. In addition, chloride ions may form hydrogen bonds to weaker, neutral hydrogen bond donors available in the system. These neutral donors play a role in the chloride coordination sphere.[42] For example, when a stronger donor is not available, the ubiquitous C-H donors will often occupy available acceptor sites on the chloride ion. In systems with only a few strong hydrogen bond donors, the hydrogen bond accepting ability of the chloride ion will often be underutilized, and the addition of another strong hydrogen bond donor guest molecule can be accommodated, often by displacing one of the weaker C-H...Cl^- interactions. The possible structure of fenofibrate with conformer, i.e., succinic acid, sucrose, and saccharine was shown in Figure 12.

CONCLUSION

The present investigation shows that the miscibility of drug and coformers as predicated by HSP can indicate cocrystal formulation. HSP for fenofibrate drug over twenty coformers was calculated according to the group contribution method. The selection of coformer was based on hydrogen bond present in a structure which clearly shows the importance of hydrogen bonding in forming cocrystals. Using Fedor's substitution constants, Hoy's molar attraction constants

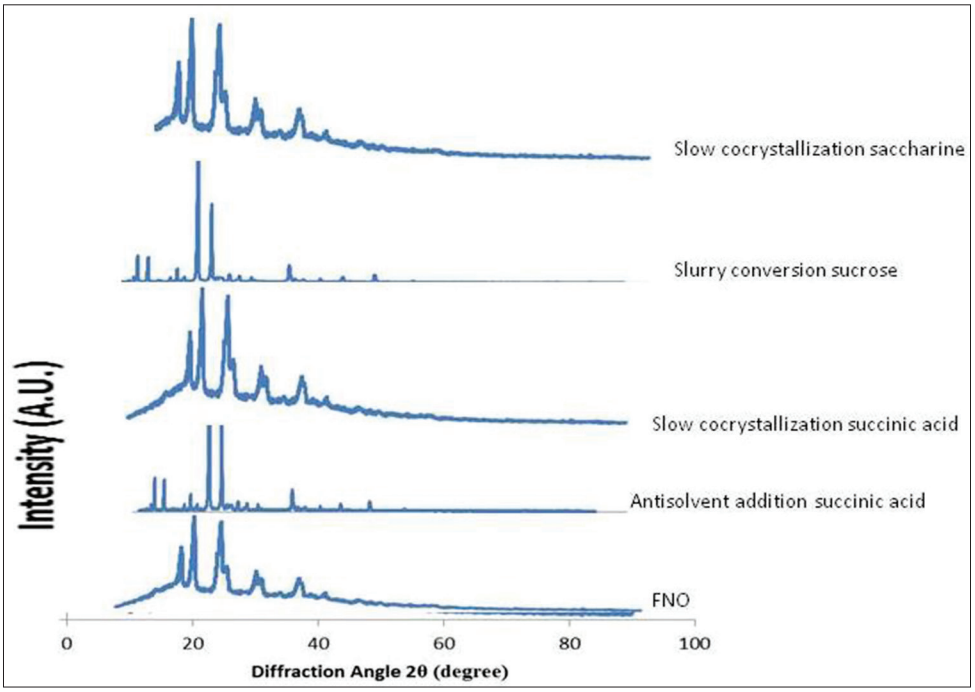

Figure 10: Overlay of comparative powder X-ray diffractograms of FNO and cocrystals using three different coformer and by various methods. (a) Pure FNO, (b) slow evaporation, (c) solution crystallization, (d) neat grinding, (e) solvent grinding, (f) antisolvent addition method, and (g) slurry method

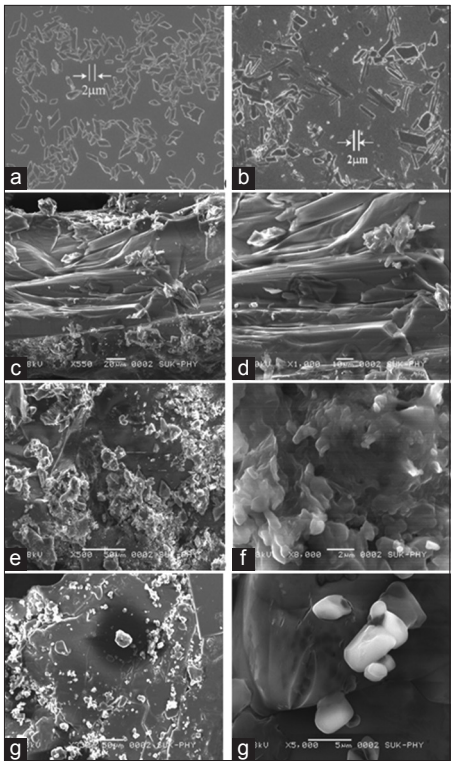

Figure 11: The scanning electron microscopy images of FNO and cocrystals using three different coformers, by methods. (a and b) Pure FNO, (c and d) (×550; ×1000) solvent grinding method Neat grinding, (e and f) (× 500; ×8000) solvent grinding method, and (g and h) (×330; ×5000) slurry method

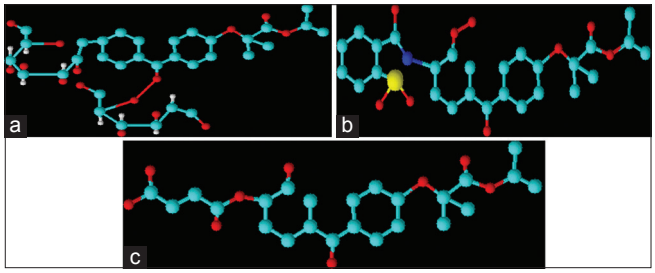

Figure 12: The proposed 3D structure of FNO with coformer (a) sucrose; (b) saccharine; and (c) succinic acid

and Van Krevelen's constant were calculated and currently used method. The resultant δ values of drug and coformers are compared, and their solid-state miscibility is expressed. The possibility of cocrystal formulation by Krevelen's is $\Delta\delta < 5$ MP and Greenhalgh $\Delta\delta < 7$ MP. We have developed fenofibrate cocrystals with succinic acid, sucrose, and saccharine. Dissolution rate was determined for the obtained solid-state forms and characterized for FTIR, DSC, and PXRD and compared with the pure fenofibrate. The results revealed that the new solid-state form of fenofibrate with succinic acid, sucrose, and saccharine shows higher dissolution rate and is stable. Calculations of solubility parameters for theoretical prediction of cocrystal formation were successfully employed which determines the possibility of cocrystal formation by the use of miscibility models. Succinic acid, sucrose, and saccharine form stable cocrystals with fenofibrate, theoretically and practically. Antisolvent addition method, slow evaporation method, and solution cocrystallization method are best because it produces small, uniform. and stable FNO cocrystals with markedly enhanced dissolution rate and solubility of fenofibrate. There was a significant improvement in solubility and dissolution rate of the drug in all co-crystal formulations due to the alternation of surface properties of drug. The results revealed that the new solid-state form of fenofibrate with coformer shows higher dissolution rate and are stable. By considering overall results, the cocrystal should be useful approach to improve poor solubility and dissolution rate.

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