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Research Article

CRYSTAL ENGINEERING OF ANTIVIRAL AGENT EFAVIRENZ FOR SOLUBILITY ENHANCEMENT

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ABSTRACT

In the current study, we attempted to improve the physicochemical properties of antiviral drug efavirenz through the cocrystal synthesis. The neat grinding performed to study the effect of coformer-fumaric acid (FA) on solubility and dissolution of efavirenz, which can serve as the green cocrystal synthesis approach. The prepared cocrystals were characterized for characteristics like powder flow properties, aqueous saturation solubility, *in vitro* powder dissolution study. The synthesized cocrystals were characterized by Fourier transform infrared spectroscopy, differential scanning calorimetry, powder X-ray diffraction. The formation of a cocrystal of efavirenz and caffeine was confirmed by the characterization techniques which suggests the interactions between efavirenz and coformer-fumaric acid leads to cocrystal formation. The powder flow properties, solubility, and dissolution profile of efavirenz are significantly improved by its cocrystallization.

Keywords: Efavirenz; cocrystal; solubility; dissolution; crystal engineering.

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1. INTRODUCTION

Crystal engineering or solid state supramolecular synthesis deals with the understanding of intermolecular interactions in the context of crystal packing and in applying this understanding to the design of pre-desired crystal structures with specific physical or chemical properties^{1,2}. Co-crystals are solids that are crystalline materials composed of two or more molecules in the same crystal lattice. Given the association of two or more molecules in the co-crystal lattice, it is useful to consider the association of components more generally².

Neat grinding method without utilizing any solvents^{3,4} or by solvent drop grinding⁵, where the small or acceptable amount of solvent is utilized which ultimately evaporate during synthetic process^{6,7} can be used to cocrystals green synthesis method. It is outcome

of non-covalent interactions which include hydrogen bonding, dipole interactions, π - π interactions, ion- π interactions, halogen bonding, closed shell interactions or van der Waals interactions. The selection of the second component in cocrystal synthesis i.e. coformer is crucial in the development of multicomponent systems. The properties of cofomers decide the fate of cocrystal system; it has implications on physicochemical properties as well as the pharmacokinetic behaviour of cocrystals⁸.

Efavirenz, (4S)-6-chloro-4-(cyclopropylethynyl)-4-(trifluoromethyl)-1,4-dihydro-2H-3,1-benzoxazine-2-one, is a HIV-1 specific, non-nucleoside reverse transcriptase inhibitor⁹. It was approved for the treatment of human immunodeficiency virus type-1 infection (HIV-1). Efavirenz (EFV) belongs to Biopharmaceutical Classification System (BCS) class II.

Being poorly water soluble drug, significant differences in bioavailability can be observed in the various polymorphic forms of EFV¹⁰. Previous studies reported attempts to improve solubility and dissolution of EFV by solid dispersion and drug milling^{11,12}. It was also revealed that EFV shows improved pharmaceutical properties by cocrystallization with adipic acid¹³, lactic acid¹⁴, glutaric acid¹⁵.

In this work we attempted to prepare cocrystals of EFV with fumaric acid (FA) for enhancement of pharmaceutically physicochemical properties of EFV, and to characterize the cocrystals using powder Fourier transform infrared (FTIR), differential scanning calorimetry (DSC), powder X-ray powder diffraction (PXRD), saturation solubility and dissolutions.

2. MATERIAL AND METHODS

EFV was obtained as gift sample from Mylan Laboratories, Hyderabad. FA was procured from Research Fine Lab, Mumbai. All other chemicals and solvents employed in present work were of analytical grade and procured from Research Fine Lab, Mumbai.

2.1 Miscibility of the components

Hansen solubility parameters of EFV and FA were computed by using the group contribution method following the collective utilization models of Fedors and Van Krevelen-Hoftyzer. The solubility parameter components were computed from group contributions (F) and molar volume (Vm), using the following equations where δ_d represent dispersion forces energy, δ_p represents polar forces energy and δ_h represents hydrogen bonding energy^{16,17}.

$$\delta_d = (\sum F_{di} / \sum V_m) \quad (1)$$

$$\delta_p = ([\sum F_{pi}]^{0.5} / \sum V_m) \quad (2)$$

$$\delta_h = (\sum F_{hi} / \sum V_m)^{0.5} \quad (3)$$

$$\delta_t = (\delta^2_d + \delta^2_p + \delta^2_h)^{0.5} \quad (4)$$

Miscibility of components can be predicted according to predictive principle that if $\Delta\delta_t < 7 \text{ MPa}^{0.5}$ of the components they may be miscible and forms multicomponent system and hence, if this criterion is fulfilled the cocrystal may be formed.

2.2 Preparation of cocrystals

Cocrystals of EFV with coformers were prepared by the neat grinding method. A stoichiometric mixture of EFV and coformer-FA (1:1 M) was ground in an agate mortar with a pestle for about 20 mins by neat grinding method (NG). The obtained cocrystals were used for characterization¹⁸.

2.3 Micromeritic properties

The active pharmaceutical ingredient-EFV and its cocrystals with FA was evaluated for various micromeritic flow properties that is bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose¹⁹.

2.4 ATR-Fourier transform infrared spectroscopy (FTIR)

Fourier transform infrared spectroscopy (FTIR) was employed for the vibrational spectroscopic analysis of the active pharmaceutical ingredient (API)-EFV and its cocrystals with a coformer-FA obtained by NG method¹⁸. The FTIR spectrums were recorded with the FTIR spectrophotometer with ATR attachment (Bruker; ALPHA-T) and the scanning range was in between 4000-660 cm^{-1} .

2.5 Thermal Analysis

Differential scanning calorimetry (DSC) studies were performed using Shimadzu TA-60WS Module to understand the thermal characteristics of an EFV alone and its cocrystal with FA. Weighed samples were heated in aluminum pans at a rate of 20°C/min, from 50 to 300°C temperature range, under a nitrogen atmosphere and empty aluminum pan were used as a reference^{20,21}.

2.6 Powder X-ray diffraction (PXRD)

PXRD patterns were obtained using a Bruker D8 Advance X-ray diffractometer (Cu K α radiation). A continuous scanning method was used for recording with a fixed tube current (32 mA) and a 40 kV voltage. The scanning range of 5-50° (2 θ) was used to measure the diffraction intensities of powder samples of API and cocrystals²².

2.7 Saturation Solubility Study

Solubility studies EFV and its cocrystal with FA was performed in accordance method reported by Higuchi and Connors²³. For saturation solubility, an excess quantity of cocrystal powder was added to distilled water. The vials were then subjected to rotary shaking for 24 hours and filtrate obtained after filtration through the 0.2 μm pore size membrane filter (Whatman[®]) was analyzed by UV spectrophotometer at 247.6 nm.

2.8 Powder Dissolution Study and Intrinsic dissolution rate study (IDR)

Powder dissolution study of EFV and its cocrystal with FA was performed using 2% aqueous sodium lauryl sulphate as dissolution medium at 37 \pm 0.5°C. An aliquot of dissolution medium was withdrawn at 10, 15, 30, 45, and 60 min intervals and concentration of API was determined at 247.6 nm spectro-photometrically.

The intrinsic dissolution rate of EFV and EFV-FA cocrystals was evaluated to study dissolution of API per unit area and time. The tablets of EFV and EFV-FA cocrystals with hardness 8 kg/cm^2 were compressed. The tablet compacts were coated using paraffin wax, leaving only the surface under investigation free for dissolution and affixed to the paddle of USP dissolution apparatus. The IDR studies were performed in 2% SLS at 37°C for 120 mins. The intrinsic dissolution rate (IDR) was determined from the slope of the dissolution time profiles²⁴.

3. RESULTS AND DISCUSSION

3.1 Miscibility of the components

Solubility parameters (δt) for EFV and FA were computed using the group contribution method following the collective utilization models of Fedors and Van Krevelen–Hoftyzer and reported in the table 1.

Table 1: Solubility parameters (HSP) for EFV and FA

Particulars	δd^*	δp^*	δh^*	δt^*
EFV	28.56	7.16	7.55	30.40
FA	17.38	7.07	15.43	24.29

*(MJ/m³)^{1/2}

Table 1: Micromeritic properties of EFV and its cocrystal

Material	Bulk Density (g/cm ³)	Tapped density(g/cm ³)	Carr's Index	Hausner Ratio	Angle of repose
EFV*	0.2535±0.0015	0.3288±0.0045	22.89±1.15%	1.30±0.019	43.99°± 2.39°
Cocrystal*	0.3521± 0.0049	0.4145±0.0104	17.93±0.99%	1.17±0.013	36.94°±1.66°

*(n=3)

3.3 Vibrational spectroscopic study

The assignments to the major vibrational peaks in the FTIR spectral studies ²⁷ (Fig.1) were as elucidated in table 3. The additional new peaks were observed in spectrum of EFV-FA cocrystal at 1681.48 cm⁻¹ and 3742.82 cm⁻¹ which can assigned to aliphatic alkene and hydroxyl functions in the fumaric acid respectively. The peak of tri-fluoro-alkane function in the EFV was shifted from 1325.00 cm⁻¹ to 1317.52 cm⁻¹ suggesting its participation in intermolecular interactions. These peaks may be assigned to halogen bonding interaction between fluorine functions of EFV with cyclic amine function of FA due to cocrystal formation. The additional peaks observed are marked in spectrum which suggests the formation cocrystal.

The resulting $\Delta\delta$ value for EFV and FA is 6.11 (MJ/m³)^{1/2} which indicates the miscibility of an API with the coformer-FA¹⁶) as $\Delta\delta$ value <7. It indicates that the components are miscible consequently may result in formation of cocrystal ^{19,25}.

3.2 Micromeritic properties

Carr's index and Hausner's ratio were derived from bulk density and tapped density of materials (Table 2). Carr's Index and Hausner's ratio for unprocessed EFV were fits into passable scale while these properties for EFV-FA cocrystal can be scaled into good to fair flow property on the scale of flowability²⁶. It shows improved flow properties of later against unprocessed EFV.

Table 2: Assignment of vibrational frequencies to EFV and its cocrystal

EFV (cm ⁻¹)		EFV FA Cocrystal (cm ⁻¹)	
Group	FTIR	Group	FTIR
NH	3311.97, 806.95	NH	3312.23, 807.32
CH	1495.28	CH3	3087.72
Alkyne	2247.52	Alkyne	2247.62
C=O	1745.67	C=O	1746.49
-Ar-C=C	1601.35	-Ar-C=C	1601.82
		C=C	1681.48
-CF3	1325.00	-CF3	1317.52
-C-O-C	1188.50	-C-O-C	1188.15
-C-Cl	1074.87	-C-Cl	1074.33
-OH	--	-OH	3742.82

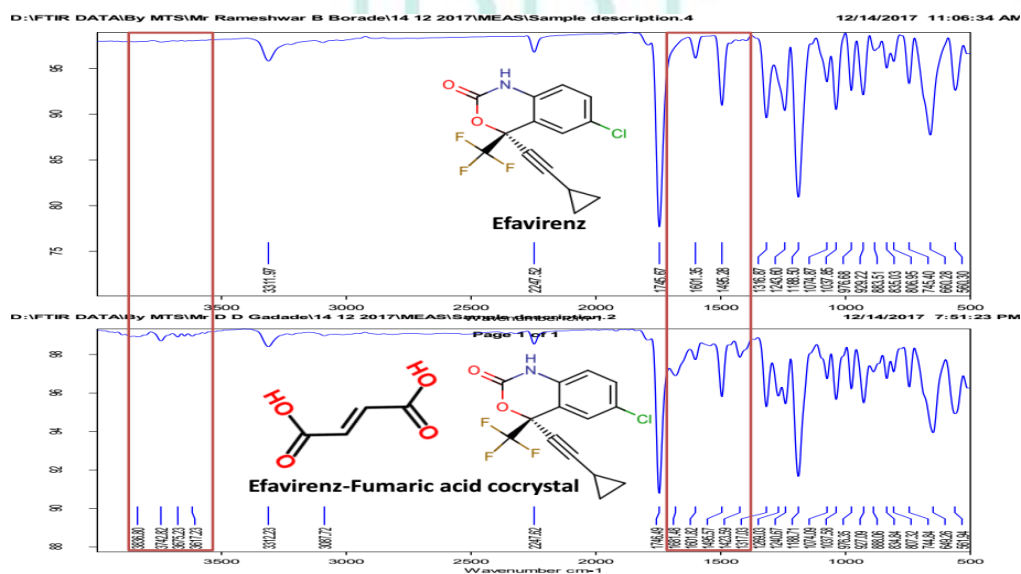


Figure 1 FTIR spectra of EFV and EFV-FA cocrystal

3.4 Thermal Analysis

EFV shows melting at 140.15 °C with heat 48.61 J/g which was confirmed to be its form I from reported literature^{9,10}. EFV-FA cocrystal shows melting at 208.76

°C and an additional peak at 266.76°C were observed in DSC thermogram (Fig. 2). It indicates formation of new phase which altered melting behaviour and which supports to assumption of EFV-FA cocrystal formation.

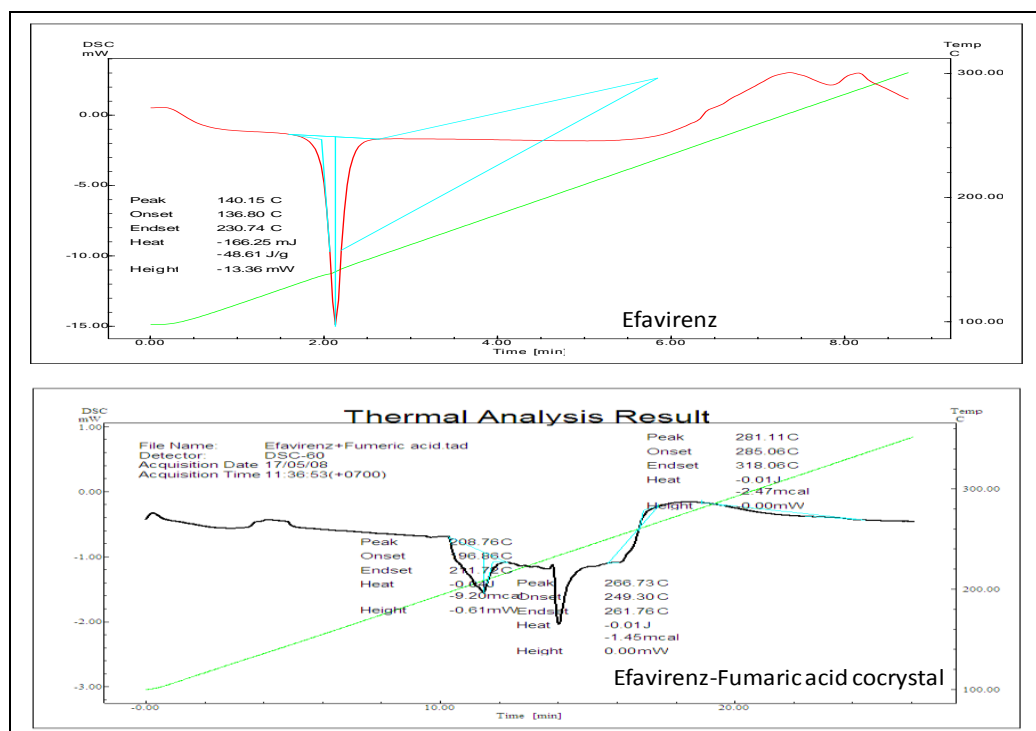


Figure 2 DSC thermogram of EFV and EFV-FA cocrystal

3.5 Powder X-ray diffraction (PXRD)

PXRD study was employed to assess transformations in the crystallographic nature of an API and coformer subsequent to the cocrystallization (Fig. 3). In correlation with the reported data²⁸ for EFV, a very intense peak was observed around 2θ of 6.26 along with 10.80, 11.26, 12.1, 13.6, 14.54, 15.56, 17.1, 19.18, 20.3,

21.4 and 25.04. In contrast to PXRD pattern of EFV, additional characteristic distinct multiple sharp peaks were observed at 2θ of 28.79, 29.41, 38.62 in the diffractogram of cocrystal which can be assigned to the formation of new crystalline phases in cocrystal of EFV-FA²⁹.

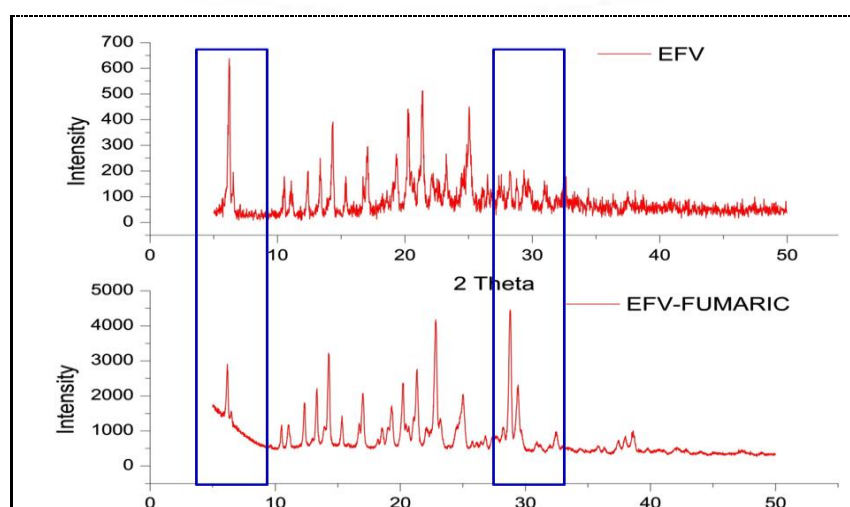


Figure 3 PXRD diffractograms of EFV, FA and their cocrystal

3.6 Saturation Solubility Study

Saturated solubility of EFV was found to be 8.39 (± 0.10) $\mu\text{g/ml}$ in distilled water and it was improved in cocrystal form with FA to 223.6 (± 11.88) $\mu\text{g/ml}$. It clearly indicates solubility advantage of cocrystal formation of EFV-FA. It demonstrates that solubility of cocrystal form is as result of molecular transformation by non-covalent interaction in the crystalline material.

3.7 Powder Dissolution Study

Powder dissolution study of API-EFV and Cocrystal of EFV with FA shows a clear improvement of cocrystal formation.

4. CONCLUSIONS

Cocrystals of EFV-FA were obtained by neat grinding approach of green synthesis. The new cocrystal of EFV with FA shows improved pharmaceutical characteristics particularly, micromeritic flow properties, solubility and dissolution against unprocessed EFV. The prepared cocrystals were confirmed by FTIR spectroscopy, DSC and PXRD. The vibrational spectroscopy-FTIR, revealed the possible halogen bonding interactions between EFV and EFV-FA cocrystals could be formulated in an immediate release dosage form to attain a rapid and complete release of the API available for absorption overcoming problem of low solubility of drug which can be explored to industrial scale.

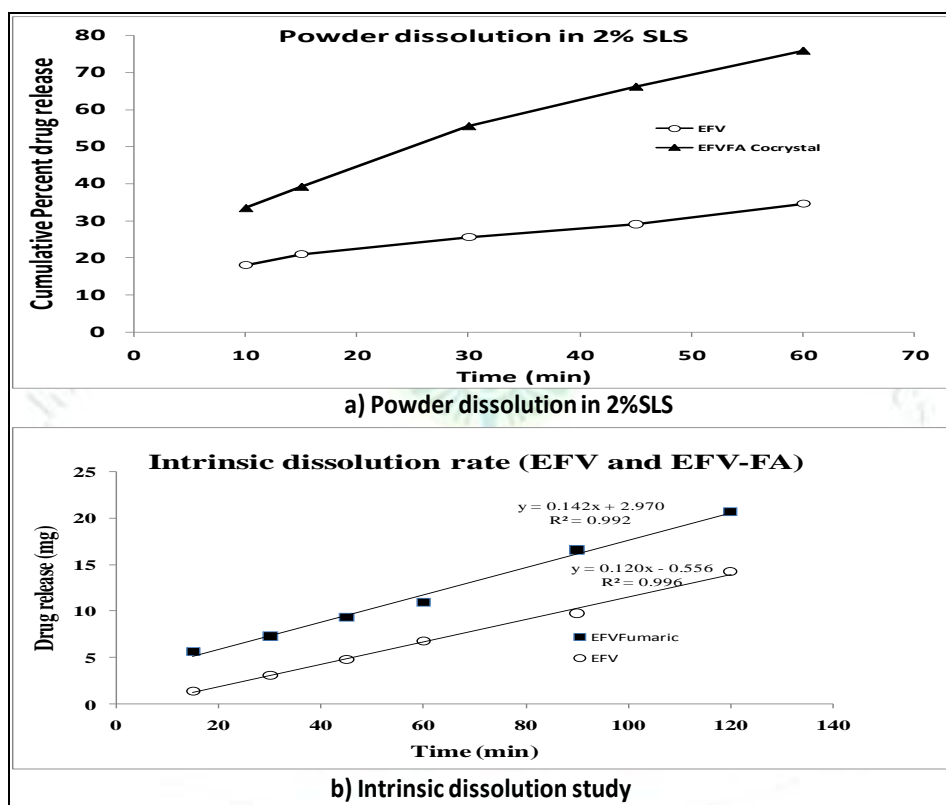


Figure 4 a) Powder dissolution study in 2% SLS b) intrinsic dissolution study of EFV and EFV-FA cocrystals

Only 34.52 ($\pm 1.22\%$) EFV was released from API powder in comparison with 75.70 ($\pm 0.66\%$) from cocrystal powder at the end of 60 min in powder dissolution study (Fig.4a). The obvious improvement in dissolution characteristics of cocrystal can be correlated to intermolecular interactions between EFV and FA.

The IDR of EFV was $126.38 \pm 18.51 \mu\text{g}/\text{min}/\text{cm}^2$ while that EFV-FA cocrystal was $148.78 \pm 10.58 \mu\text{g}/\text{min}/\text{cm}^2$ as determined from the slope of dissolution curve (Fig. 4b). EFV dissolved more rapidly from the cocrystal tablet formulation than API tablets, consistent with the solubility studies outcomes.

Conflict of Interest

The authors declare that they have no conflict of interest.

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