Research Paper

A Study on Solubility Enhancement of Etravirine by Crystal Engineering Method

SAYANI BHATTACHARYYA*, H. ADHIKARI, D. REGMI AND R. R. V. HOSURU

Department of Pharmaceutics, Krupanidhi College of Pharmacy, Chikka Bellandur, Varthur, Bangalore 560035, India

Etravirine, an antiretroviral agent, used in the treatment of human immunodeficiency virus belongs to biopharmaceutical classification system classification IV. The reported solubility of the drug is 0.0169 mg/ml. In the present study, an attempt was made to enhance the solubility of etravirine by crystal engineering technique. The cocrystallization method was carried out using 12 different coformers and each coformer was studied in two different stoichiometric ratios. A preliminary screening of all the cocrystals was done by determination of melting point and solubility. A statistical evaluation of all the cocrystals on solubility was carried out at a significance level of $p<0.05$. The best cocrystals were subjected to drug content, *in vitro* drug release, solid-state study (fourier transform infrared spectroscopy, differential scanning calorimetry, powder x-ray diffraction) and stability study for 3 mo. Coformer benzoic acid showed a significant improvement in etravirine solubility in the drug:coformer ratio of 1:1 and 1:2. The drug:benzoic acid ratio of 1:2 was found to have more solubility and showed enhanced dissolution compared to pure drug. The *in vitro* dissolution rate of the drug:benzoic acid ratio of 1:2 was found to be more than 90 % in 60 min. Therefore, it can be concluded that the cocrystallization method with benzoic acid as coformer can be a promising approach for solubility improvement of etravirine.

Key words: Etravirine, cocrystal, crystal engineering, solubility enhancement, dissolution

The crucial factors that determine the oral bioavailability of drugs are solubility and permeability. Among the biopharmaceutical factors, solubility of the drug is the key factor for the successful delivery of drugs, as it determines the systemic exposure in terms of dissolution particularly when administered orally. At the time of development and formulation, the pharmaceutical industries face major challenges in improving the bioavailability of the drugs having poor solubility. There are various methods available to improve the bioavailability of the drugs including micronization, nanonization, salt formation, micellar solubilizations and complexation, etc[1]. The modification of crystal habit of the Active Pharmaceutical Ingredient (API) either in amorphous form, anhydrous form or polymorphism suffers from many drawbacks in preserving the stability of the component, balancing hygroscopicity and removal of toxic solvents used in the crystallization process. Therefore, to fine-tune the API properties like solubility, stability and micromeritics, the co-crystallization process is found to be beneficial for the pharmaceutical industry[2]. Cocrystals are homogeneous crystalline materials comprised of at least two different components incorporated in the same crystal lattice with a defined stoichiometry[3]. Cocrystal structures are made up of noncovalent interactions between the API and the coformers which lead to the formation of supramolecular synthons[4]. The supramolecular assembly not only fine-tunes the physical properties like solubility, hygroscopicity and stability of the API in its crystal structure but also helps to address the flow property, compressibility and manufacturability.

Etravirine is an antiretroviral agent used in the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection. It is classified as a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI). It belongs to Biopharmaceutical Classification System (BCS) class IV molecule. The problems associated with class

***Address for correspondence**
E-mail: sayanibh@gmail.com

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IV include low aqueous solubility, poor permeability, significant food effect which lead to low and variable bioavailability. The reported solubility of etravirine is 0.0169 mg/ml[5]. Reported literature showed that the improvement of solubility of etravirine was studied by solid dispersion and spray drying methods[6,7]. The present study focuses on the development of cocrystals of etravirine using different coformers in different molar ratios and evaluating their effects on melting point, solubility, and percentage (%) drug release.

MATERIALS AND METHODS

Etravirine was obtained as a gift sample from Apotex Pharmachem India Pvt. Ltd. Bangalore Karnataka. All other conformers and chemicals were of analytical grade, obtained from SD fine chemicals, Bangalore.

Method of preparation of etravirine cocrystal:

Etravirine cocrystals were prepared using twelve different coformers. The twelve different coformers used are mannitol, sodium saccharin, salicylic acid, tartaric acid, benzoic acid, urea, succinic acid, citric acid, ascorbic acid, caffeine, oxalic acid and magnesium stearate. The drug was mixed stoichiometrically with the coformers in a ratio of 1:1 and 1:2 in a mortar and pestle for 30 min. Few drops of 20 % w/v ethanol-water mixture were added during grinding[8]. The mixture was dried overnight at ambient temperature and stored in a desiccator[9]. The mixture was passed through sieve number 60 and stored in a glass vial for further studies.

Determination of melting point:

The melting point of the pure drug and its co crystals was determined by the capillary method. In this method, the powder sample was introduced into the capillary tube by gently tapping. The capillary tube was tied with a thermometer and was placed in the heated thiele tube containing liquid paraffin. The temperature was raised slowly until the transition happened to the liquid state. The temperature at which the sample started melting was recorded.

Determination of drug content:

The sample equivalent to 5 mg was dissolved in 25 ml of methanol. A quantity of 5 mg of drug was dissolved in 25 ml of methanol in a separate volumetric flask. The solutions were diluted suitably with methanol and the absorbance was estimated spectrophotometrically using methanol as blank at 311 nm. The % drug content was determined using the following formula. All findings were carried out in triplicates.

% Drug content=Absorbance×100/Standard absorbance

Determination of solubility:

The solubility of etravirine was determined by dissolving 25 mg equivalent of etravirine cocrystal in a flask containing 50 ml of distilled water. The solutions were vortexed for 2 min and placed afterward to a rotary shaker at 100 rpm for 48 h at room temperature. After that 0.5 ml slurry was withdrawn from each sample and filtered through 0.22 µm AST works disposable syringe filter. After suitable dilution with methanol, the concentration was measured spectrophotometrically at 311 nm. The solubility study was performed in triplicates for each sample to minimize the error[10].

Selection of dissolution media by estimation of Gibbs free energy:

The best cocrystals of etravirine were taken for solubility study in different dissolution media like 0.01 M hydrochloric acid solution, 1 % w/v Sodium Lauryl Sulfate (SLS) solution and phosphate buffer pH 7.4. Cocrystal equivalent to 100 mg was dispersed in 250 ml of the selected medium and placed in a rotary shaker for 48 h at room temperature. The solubility of the samples in different media was determined after suitable dilution. From the solubility data of the cocrystals in different media, Gibbs free energy was calculated using the following equation where RT=Ideal gas constant, S_0=Solubility of coformers in the selected media and S_S=Solubility of etravirine in the selected media[11].

$$\Delta G = -2.303\ RT \log S_0/S_S$$

Drug release study:

The dissolution study was carried out for the best cocrystals of etravirine in 900 ml of 1 % SLS in United States Pharmacopeia (USP) paddle-type II apparatus. An equivalent of 100 mg etravirine was used to study the release from the cocrystals. The stirring speed was maintained at 50 rpm and the bath temperature was kept at 37°±1°. The dissolution was carried out for 60 min. The sample was withdrawn from time to time and replaced with a fresh solution of media. The samples after dilution with methanol were analyzed spectrophotometrically at 311 nm. The analysis for each study point was performed in triplicates[7].

Particle size determination:

The particle size determination of the best cocrystals

was carried out in Malvern zeta sizer at a detection angle of 173° at 25°. A specific amount of sample was dispersed in millipore water (2 mg/ml) and sonicated for 10 min. The sample was further diluted with water and scanned to determine the particle size.

Fourier Transform Infrared (FTIR) spectroscopy study:

The cocrystals of etravirine were taken for interaction study. The sample was analyzed using FTIR 8400S device Shimadzu, Japan using the Potassium Bromide (KBr) pellet technique from a range of 4000 cm^{-1} to 400 cm^{-1}. The spectra were generated for the pure drug with the best coformer in both the ratio of 1:1 and 1:2[12].

Differential Scanning Calorimetry (DSC) study:

The thermal analysis of the samples was carried out using DSC 60 (Shimadzu) for the pure drug and the best cocrystals in both ratios. Around 5 mg sample was placed in the aluminum pan under a nitrogen flow rate of 20 ml/min, with a gradual increase in temperature by 10° per min from 30° to 300°. An empty aluminum pan was used as a reference standard. The thermograms and the phase transition behavior were recorded for further analysis[13].

Powder X-Ray Diffraction (PXRD):

PXRD diffraction pattern of the pure drug and the different ratios of the best cocrystal were studied in the Bruker D8 diffractometer instrument. A Copper K-alpha 1 (Cu K-α 1) tube was used as the source and the instrument was set at 40 kV and 30 mA. A scan was carried out from 5° to 59.98° 2θ at 2θ scan step of 0.03° at a scan step time of 0.8 s. The diffraction patterns were recorded for further analysis of the reflection angle and peak intensity[8].

Stability studies:

The best cocrystals were stored in sealed glass vials and kept at 40°±2° at a relative humidity of 75 %±5 % for 3 mo. The samples were analyzed for solubility, drug content and *in vitro* drug release every 30 d[9].

RESULTS AND DISCUSSION

Crystal engineering of poorly soluble drug etravirine was carried out by screening of different coformers. The solvent drop grinding method was used to prepare different cocrystals of etravirine. The melting point of each formulation was determined to estimate the entropy of the crystal lattice of the cocrystals. The melting point of the cocrystals of etravirine with various coformers in 1:1 and 1:2 ratios is listed in Table 1. The pure drug showed a melting point of 265°. It was found that all the coformers in the stoichiometric ratio could bring down the melting point of the cocrystals. Among them, the coformer benzoic acid showed the least melting point of the cocrystal of etravirine in both the stoichiometric ratios. This lowering of melting point is an indication of the asymmetric molecular structure of the cocrystals. The drug content for all the cocrystals was found to be within the range of 88 % to 91 % as shown in Table 1.

TABLE 1: MELTING POINT AND SOLUBILITY OF ETRAVIRINE WITH DIFFERENT COFORMERS

Coformer	Code for ratio 1:1	Melting point of cocrystal (1:1) (°)	Solubility of cocrystal (1:1) (mg/ml)	Drug content (%)	Code for ratio 1:2	Melting point of cocrystal (1:2) (°)	Solubility of cocrystal (1:2) (mg/ml)	Drug content (%)
D-Mannitol	ETM1	249±0.05	0.221±0.004	90.01±4.50	ETM2	251±0.02	0.031±0.001	88.23±1.76
Sodium saccharin	ETSS1	257±0.03	0.23±0.015	89.21±1.09	ETSS2	283±0.06	0.076±0.001	89.27±2.08
Salicylic acid	ETSA1	212±0.05	0.231±0.016	89.53±2.13	ETSA2	187±0.03	0.181±0.011	88.52±3.60
Tartaric acid	ETTA1	209±0.02	0.398±0.011	90.45±5.01	ETTA2	191±0.03	0.255±0.020	90.97±2.34
Benzoic acid	ETBA1	169±0.03	0.920±0.017	90.61±3.52	ETBA2	176±0.06	1.011±0.013	89.93±2.06
Citric acid	ETCA1	177±0.07	0.066±0.005	89.45±2.66	ETCA2	187±0.06	0.034±0.001	88.66±4.27
Urea	ETU1	183±0.04	0.022±0.001	89.88±2.90	ETU2	167±0.08	0.018±0.001	89.10±2.54
Succinic acid	ETSU1	176±0.05	0.078±0.001	91.03±5.12	ETSU2	184±0.06	0.075±0.004	88.54±2.98
Ascorbic acid	ETAA1	197±0.02	0.117±0.016	90.78±1.45	ETAA2	196±0.02	0.123±0.007	88.44±1.38
Caffeine	ETC1	182±0.06	0.029±0.015	90.09±3.06	ETC2	213±0.04	0.083±0.002	90.67±2.71
Oxalic acid	ETOA1	196±0.06	0.046±0.001	89.11±3.22	ETOA2	190±0.06	0.084±0.002	90.40±2.13
Magnesium stearate	ETMS1	249±0.04	0.070±0.008	89.31±4.12	ETMS2	269±0.06	0.019±0.001	89.54±2.04

Note: *All the values are mean±Standard Deviation (SD) (n=3)

The solubility study of the cocrystals revealed that the solubility of etravirine was increased with all the coformers compared to the pure drug. The solubility data of the different cocrystals were compared using Dunnett's test at a significant level $p<0.05$ using GraphPad Prism 5 software. It was found that the effect of different coformers on etravirine solubility was statistically significant in 1:1 ratio of drug and coformer except for urea and caffeine as mentioned in Table 2. The solubility was not found statistically significant for mannitol, citric acid and urea at a drug and coformer ratio 1:2. These differences in observation might be attributed to the mismatch of structural fit between the drug and coformers[14]. The solubility study revealed that among the 12 different coformers, benzoic acid was found to increase the solubility of the drug in water significantly as represented in fig. 1. The drug and benzoic acid at a stoichiometric ratio of 1:1 and 1:2 showed a drastic increase in the solubility of the drug. An approximately 54-folds and 60-folds increase in aqueous solubility was observed in cocrystals (ETBA1 and ETBA2) respectively. Therefore, the cocrystals ETBA1 and ETBA2 were taken for further evaluation.

To establish the solubility in different dissolution media, a 100 mg dose equivalent of ETBA1 and ETBA2 were tested for solubility in 0.01 M hydrochloric acid, 1 % w/v SLS solution and phosphate buffer 7.4. The study revealed that the solubility of both the cocrystals was high in 1 % w/v SLS solution and resulted in minimum Gibbs free energy, presented in Table 3. Therefore the dissolution study of the cocrystals was carried out in 1 % w/v SLS solution.

The release study of etravirine from the selected cocrystals of benzoic acid was compared with the equivalent amount of pure drug of etravirine in the same dissolution condition. The % cumulative drug release *vs.* time graph is presented in fig. 2. The pure drug showed a release of 10 % in 10 min and 41 % over 60 min. But both the cocrystals ETBA1 and ETBA2 showed an improved drug release in 10 min, and finally and approximately 86 % and 93 % of drug release for 60 min was observed for ETBA1 and ETBA2 respectively. The cocrystal ETBA2 showed higher release compared to ETBA1. The high release may be due to the formation of a weaker crystalline structure with the stoichiometric proportion of the coformer. The greater dissolution of the cocrystals over pure etravirine proved the enhancement of solubility of etravirine in presence of coformer.

TABLE 2: DUNNETT'S TEST

Dunnett's multiple comparison test	Drug:Coformer=1:1			Drug:Coformer=1:2		
	Mean difference	q	Significant, p<0.05	Mean difference	q	Significant, p<0.05
Pure drug *vs.* mannitol	-0.2044	25.1	Yes	-0.01528	2.384	No
Pure drug *vs.* sodium saccharin	-0.2119	26.03	Yes	-0.05899	9.207	Yes
Pure drug *vs.* salicylic acid	-0.2163	26.56	Yes	-0.1651	25.76	Yes
Pure drug *vs.* tartaric acid	-0.382	46.91	Yes	-0.2384	37.2	Yes
Pure drug *vs.* benzoic acid	-0.9031	110.9	Yes	-0.9873	154.1	Yes
Pure drug *vs.* citric acid	-0.04996	6.136	Yes	-0.01689	2.635	No
Pure drug *vs.* urea	-0.005013	0.6157	No	-0.00157	0.2455	No
Pure drug *vs.* succinic acid	-0.0621	7.627	Yes	-0.05855	9.138	Yes
Pure drug *vs.* ascorbic acid	-0.1001	12.3	Yes	-0.1061	16.56	Yes
Pure drug *vs.* caffeine	-0.01223	1.502	No	-0.0666	10.39	Yes
Pure drug *vs.* oxalic acid	-0.02904	3.566	Yes	-0.06673	10.41	Yes

Note: *q is the difference between the two means (D) divided by the standard error of that difference

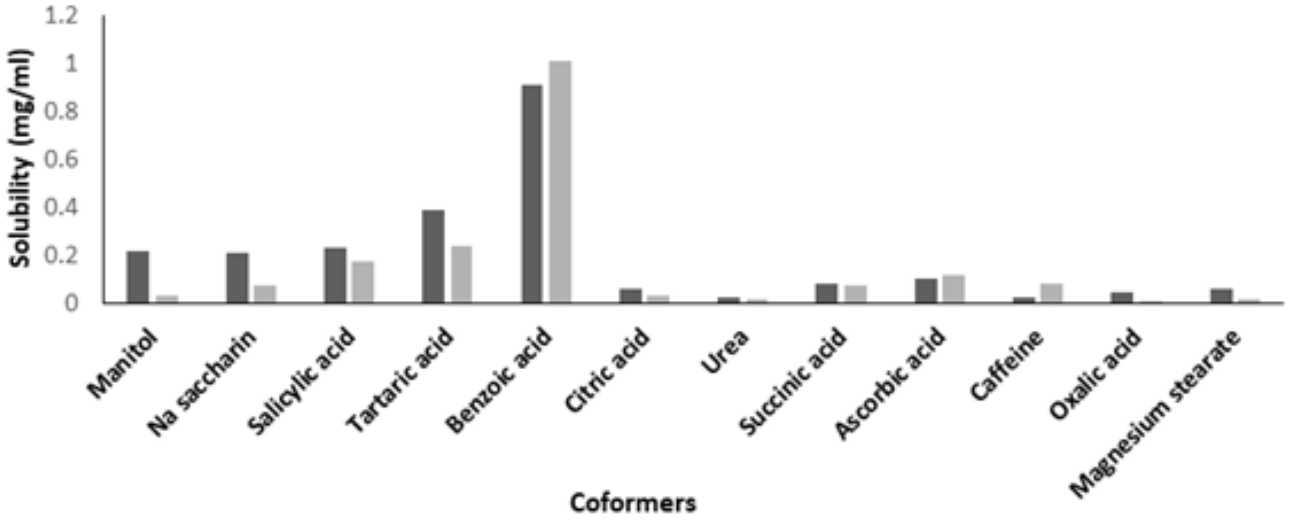


Fig. 1: Solubility of cocrystals of etravirine with different coformers in different stoichiometric ratios, (■) 01:01 and (■) 01:02

TABLE 3: SELECTION OF DISSOLUTION MEDIUM

Medium	Solubility (mg/ml)	ETBA1 ΔG (kJ/mol)	Solubility (mg/ml)	ETBA2 ΔG (kJ/mol)
0.01 M hydrochloric acid	0.396±0.12	-7.81±0.01	0.413±0.14	-7.92±0.04
1 % w/v SLS solution	1.98±0.25	-11.80±0.05	2.478±0.18	-12.35±0.03
Phosphate buffer pH 7.4	0.594±0.11	-8.82±0.02	0.619±0.43	-8.92±0.04

Note: *All the values are mean±SD (n=3)

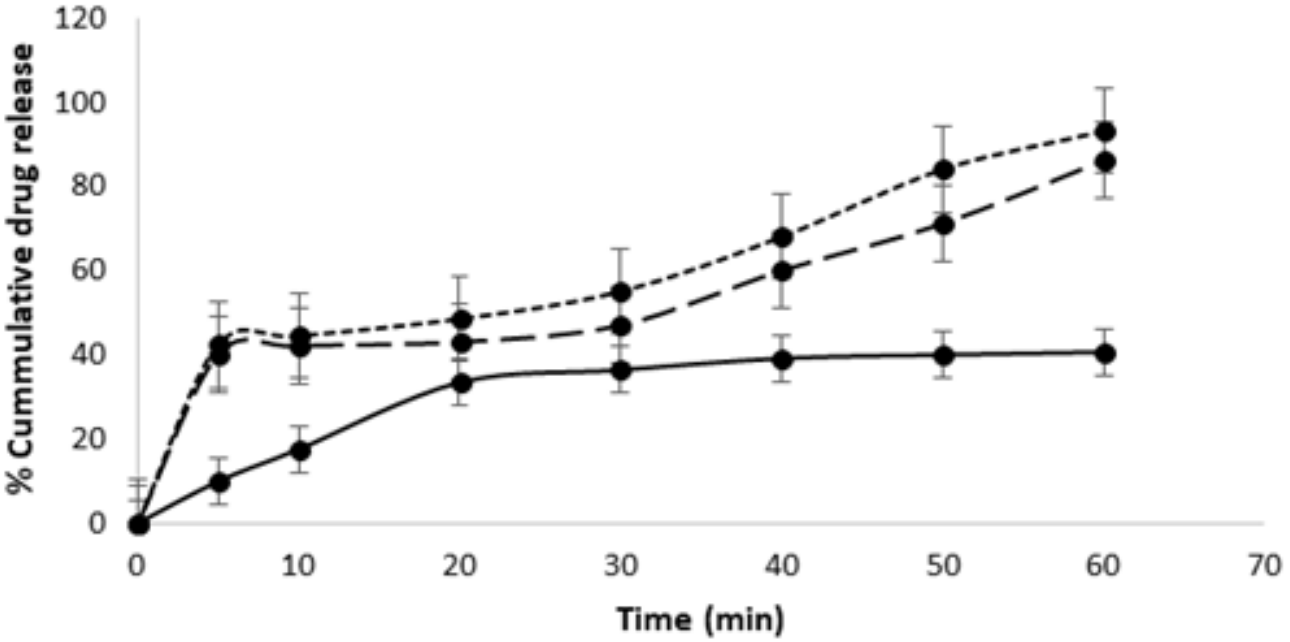
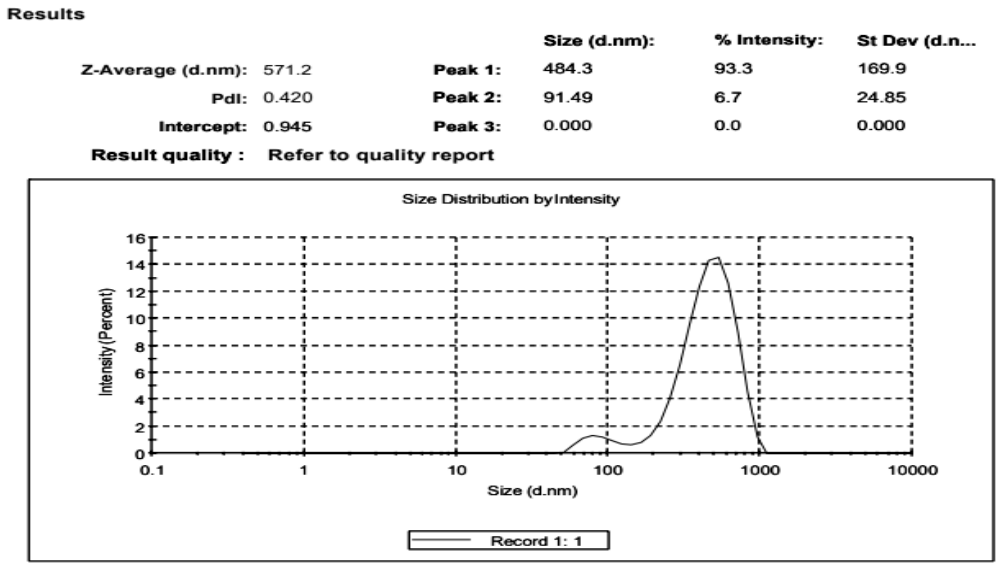


Fig. 2: Comparative release study of pure drug with cocrystals of benzoic acid, (—●—) Pure drug; (—●—) ETBA1 and (- -●- -) ETBA2

The particle size of the formulation ETBA1 and ETBA2 was found to be 571.2 and 550.6 nm respectively as shown in fig. 3. The nano-size range of the cocrystal also confirms the high rate of dissolution.

The FTIR spectra of pure drug and cocrystals of benzoic acid in different ratios are shown in fig. 4. The pure drug showed the characteristic peaks at 2220 cm-1 for the presence of aromatic -C≡N group, at 1305 cm-1 for the presence of C-O stretching, at 1238 cm^{-1} for the C-N stretching and a C-Br stretching at 684 cm^{-1}[15]. All the characteristic peaks are well preserved in the formulations ETBA1 and ETBA2. The spectra revealed neither appearance nor disappearance of any characteristic peaks of etravirine in the cocrystals. Therefore, it indicates that there is no incompatibility or interaction between the drug and benzoic acid. The stretching of -C≡N group in ETBA1 and ETBA2 indicated the formation of H bonding between etravirine and benzoic acid and the formation of an amorphous form[16].

The DSC thermograms are presented in fig. 5. Thermograms revealed that the phase transition of the pure drug occurred in the range of 263.75°. The DSC thermograms showed a shift of peak to 174° and 178° for the formulations ETBA1 and ETBA2 respectively. This shift might be due to the strong non-covalent interaction between etravirine and benzoic acid. Therefore, a new crystalline arrangement might have formed which had altered the physiochemical property of the drug inside the cocrystal that resulted in reduced melting point and improved solubility.



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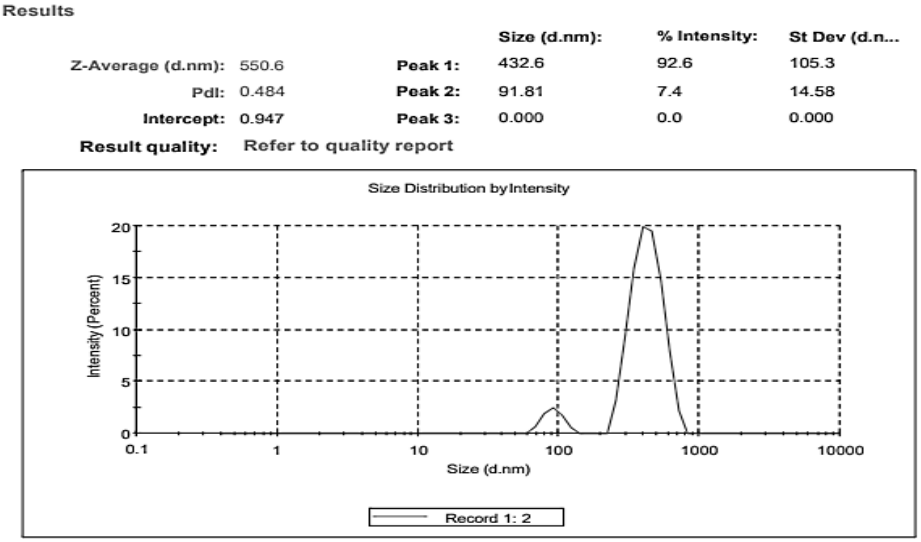
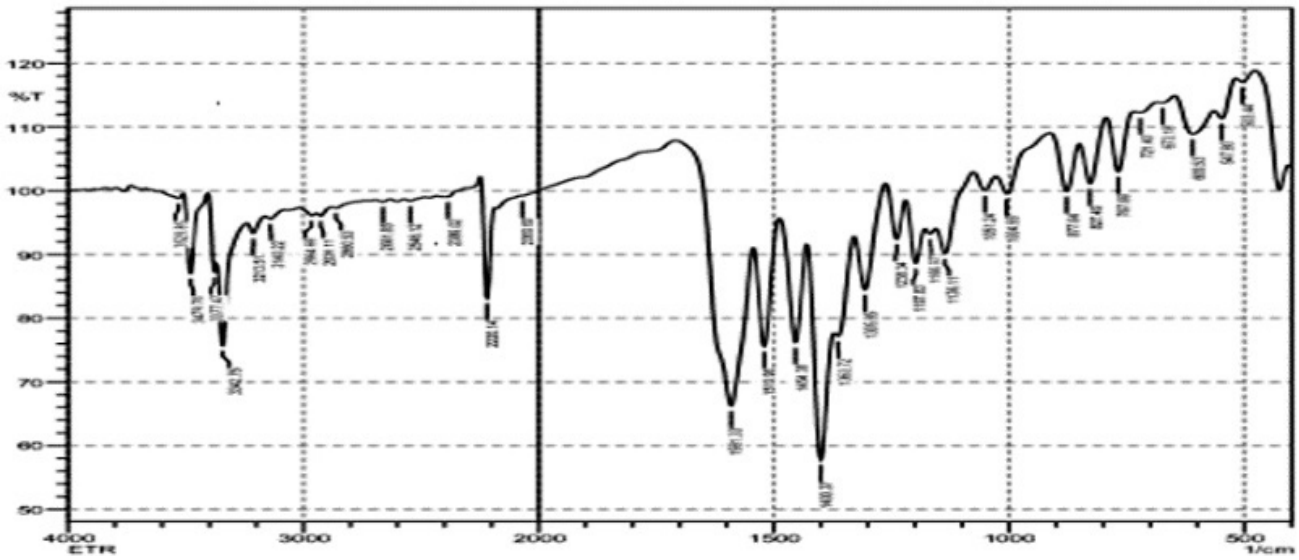


(B)

Fig. 3: Particle size of (A) ETBA1 and (B) ETBA2



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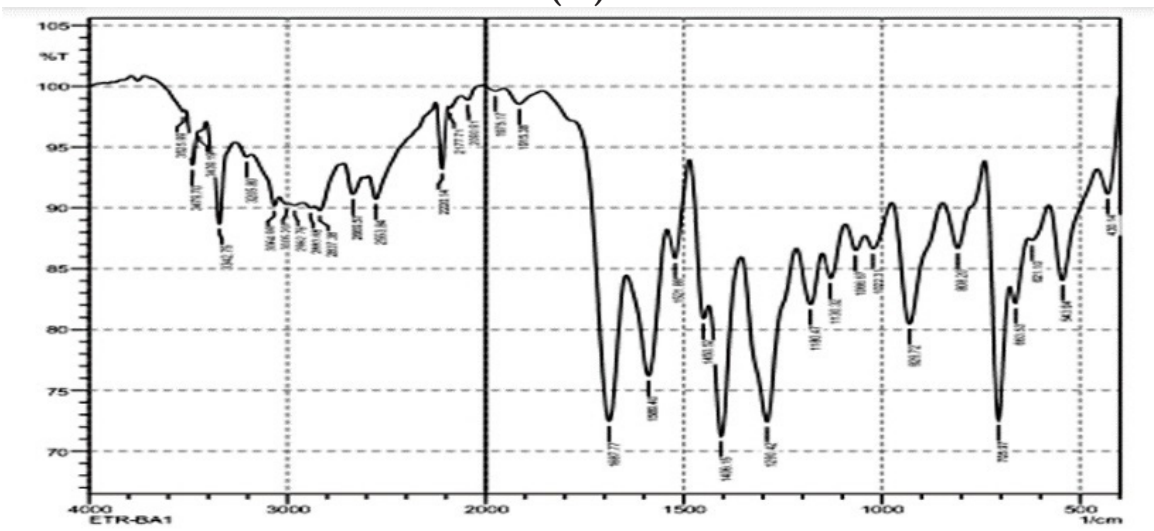

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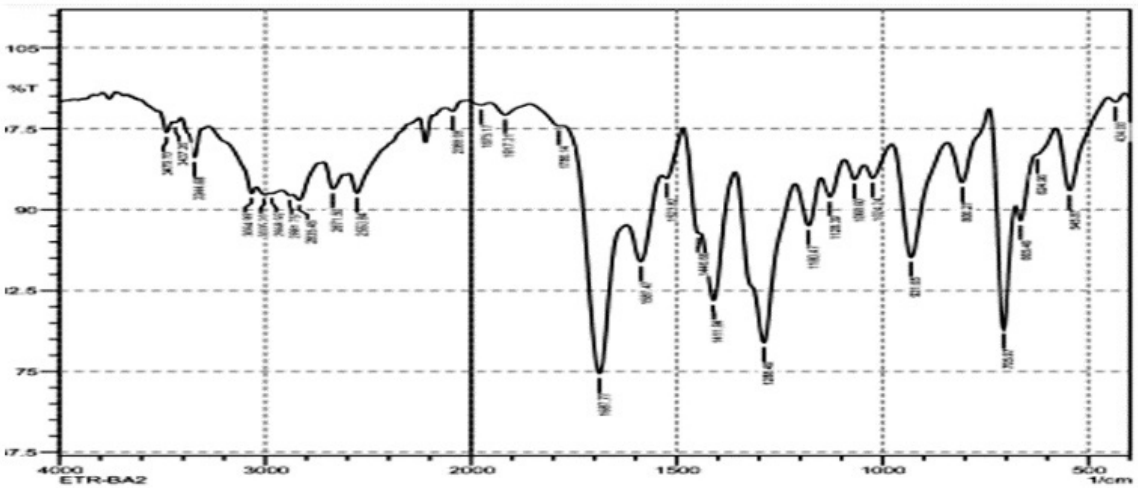

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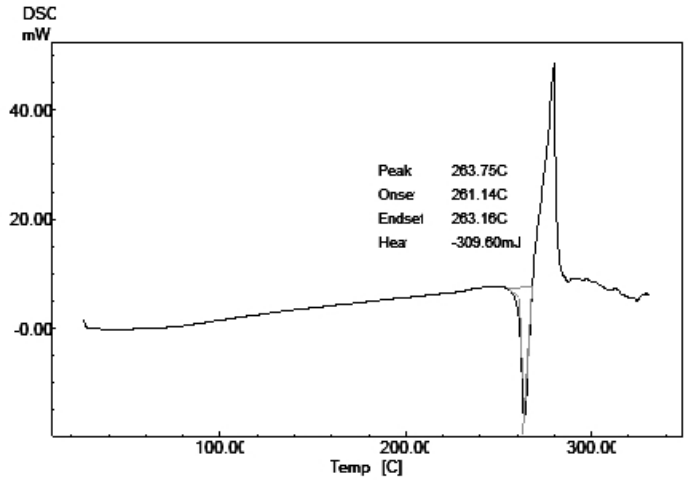
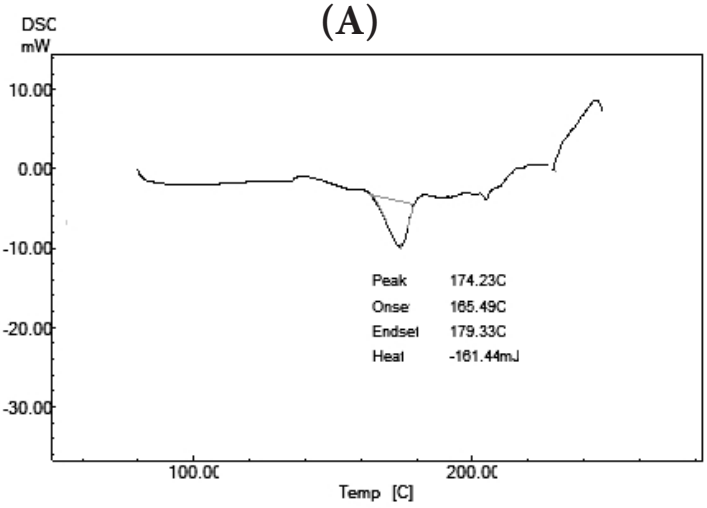
Fig. 4: FTIR spectra of (A) Pure drug and its cocrystals (B) ETBA1 and (C) ETBA2



(A)



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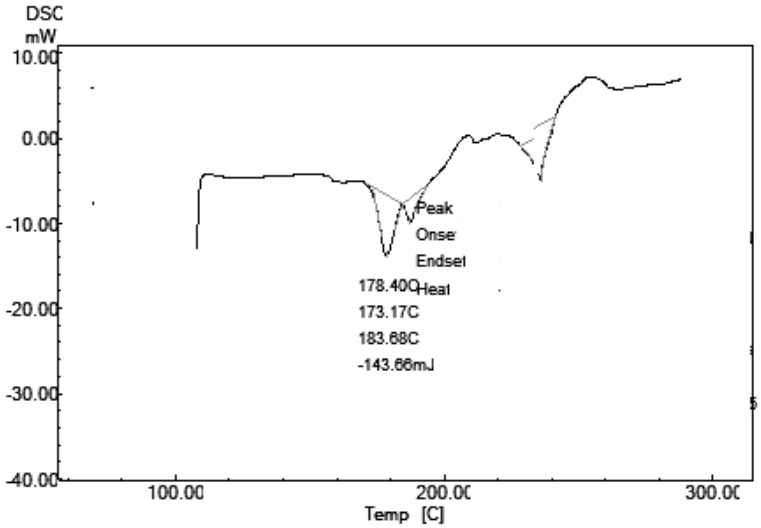


(C)

Fig. 5: DSC thermograms of (A) Pure drug etravirine and its cocrystals (B) ETBA1 and (C) ETBA2

The peak intensities of pure drug and the cocrystals of benzoic acid at various diffraction angles are represented in Table 4 and fig. 6. The diffraction pattern of the pure drug exhibited peaks of high intensities and indicated the crystalline form of the drug which was in confirmation with the DSC results. The PXRD pattern of the cocrystals also revealed that all the major peaks of the pure drug were preserved and confirmed the observations of compatibility study with FTIR[15]. The PXRD pattern of the physical mixture of the cocrystals showed the appearance of broader peaks with low intensities compared to the pure drug. The low intensities of the peaks were attributable to the effect of coformer in altering the physicochemical properties of etravirine. The lowest intensities of the peaks in the formulation ETBA2 indicated a strong transformation of the crystallinity of the pure drug and that might have led to the increase in solubility and improved dissolution.

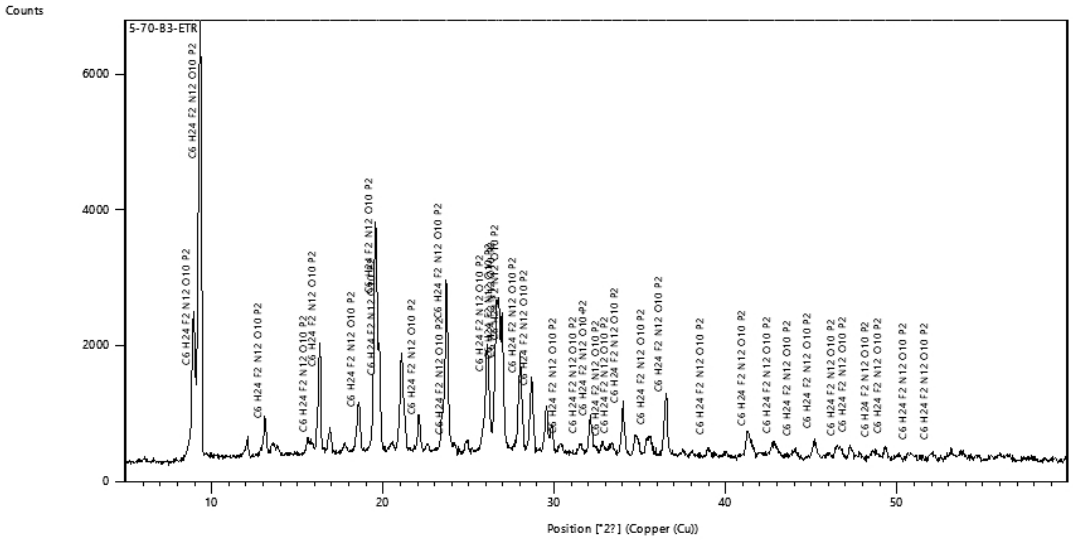
The above characterizations of the cocrystals of etravirine and its improved solubility can be further supported by the acid dissociation constant (ΔpKa) of the drug and the coformer. The Food and Drug Administration (FDA) guidance for the industry also says that the difference in pKa between drug and coformer should be <1, to be classified as cocrystal[17]. In the present study, the ΔpKa of the drug and coformer benzoic acid was found to be less than 1.

The 3 mo stability study of the cocrystals indicated that there were no major changes in the solubility, drug content and release of drug as indicated in Table 5. Both the cocrystals were found to be stable at the storage condition of 40°±2° at a relative humidity of 75 %.

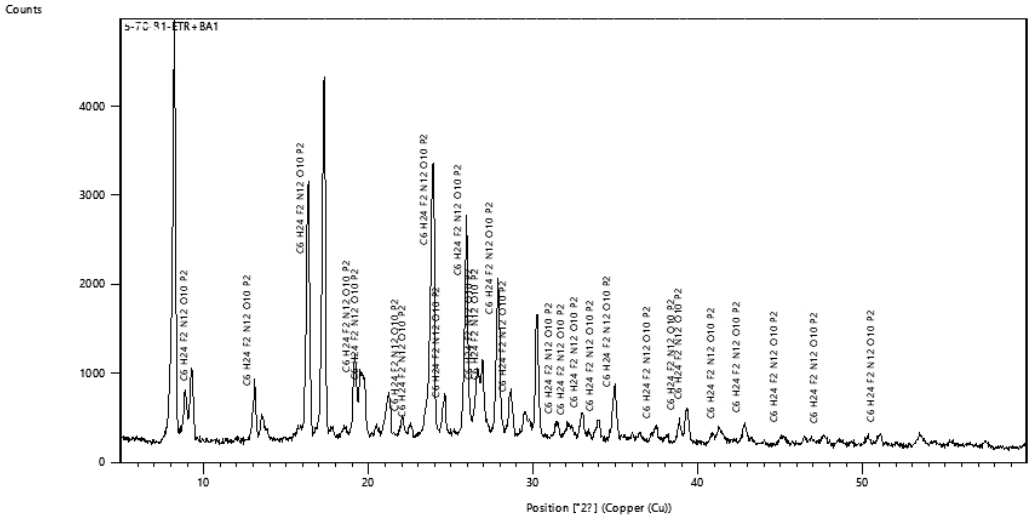
In conclusion, the crystal engineering of etravirine with coformers can be regarded as an effective method in improving solubility and dissolution of etravirine. In the present research, a screening of twelve different coformers was carried out. Among them, benzoic acid was found to be the most promising coformer based on the solubility study. The amount of benzoic acid in the cocrystals was also kept within the Generally Recognized As Safe (GRAS) limit[18]. The observation from the compatibility, thermal and surface characteristics study supported the formation of cocrystal of etravirine with benzoic acid. The improvement in solubility and dissolution of etravirine was attributed to the altered solid-state characteristics of the drug in the coformer. The significant improvement in the water solubility resulted in high drug release in the dissolution medium of 1 % w/v SLS solution. The results from the stability study indicated the firmness of the products. Therefore, it can be concluded that the co-crystallization approach and use of benzoic acid as a coformer can be suitably employed to improve the

TABLE 4: PEAK INTENSITIES OF PURE DRUG AND THE COCRYSTALS OF BENZOIC ACID

Etravirine (2θ)	% Intensities	ETBA1 (2θ)	% Intensities	ETBA2 (2θ)	% Intensities
9.35	100	9.3	16.46	9.32	7.99
19.59	51.6	19.65	16.65	19.58	10.05
22.1	9.14	22.07	5.3	22.07	2.52
23.7	42.68	23.89	3.03	23.57	1.43
26.06	24.29	26.61	16.66	26.62	7.06
28.66	19.28	28.62	12.2	28.65	4.64
29.53	12.04	29.54	6.06	29.59	2.55
32.11	8.59	32.96	6.47	32.17	1.82
36.49	17.13	37.4	3.09	36.1	0.83
45.19	4.71	45.09	2.07	45.14	1.15
47.27	3.51	47.58	1.92	48.63	1.09
9.35	100	9.3	16.46	9.32	7.99
19.59	51.6	19.65	16.65	19.58	10.05



(A)



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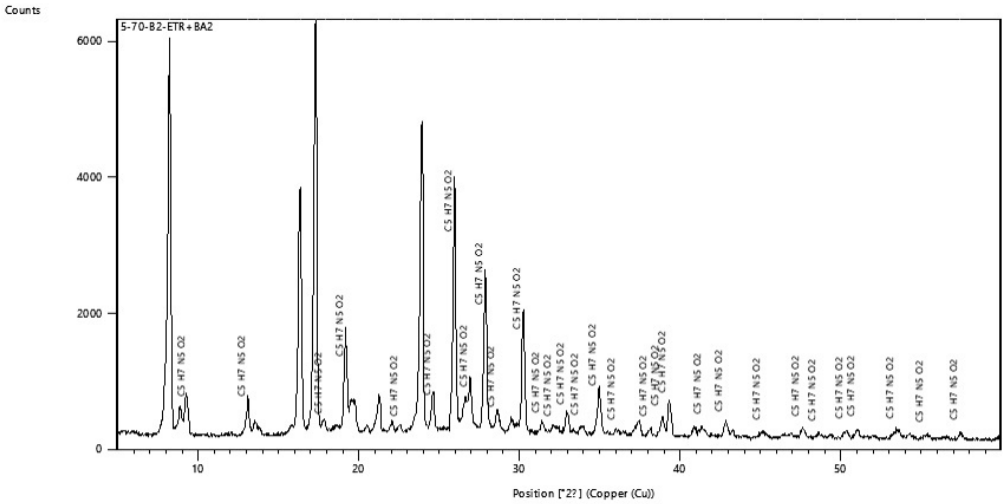

(C)

Fig. 6: PXRD of (A) Pure drug etravirine and its cocrystals (B) ETBA1 and (C) ETBA2

TABLE 5: STABILITY STUDY OF ETBA1 AND ETBA2

Days	ETBA1			ETBA2		
	Solubility (mg/ml)	% Drug content	% Drug release	Solubility (mg/ml)	% Drug content	% Drug release
30	0.91±0.012	88.0±2.13	85.87±1.10	0.989±0.015	90.02±1.05	92.89±2.11
60	0.90±0.02l	87.67±1.16	85.6±1.15	0.975±0.01	89.95±0.90	92.65±1.25
90	0.89±0.011	87.60±1.01	85.34±1.21	0.97±0.016	89.9±1.12	92.43±1.16

Note: *All the values are mean±SD (n=3)

solubility of etravirine.

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