

Tablet Formulation and Enhancement of Aqueous Solubility of Efavirenz by Solvent Evaporation Co-Crystal Technique

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Abstract

Improvement in the aqueous solubility, physicochemical and micromeritics property of insoluble and slightly soluble drugs is of major concern in pharmaceutical formulations. It is commonly observed in the drug industry that on average more than 35% of newly discovered drugs are poorly water-soluble. Poor "drug like" properties of lead compounds led to ineffective absorption from the site of administration, less bioavailability which has been designated as an important part of the high clinical failure. In the present work, Efavirenz, nonnucleoside reverse transcriptase inhibitors (NNRTIs) in first-line antiretroviral therapy (ART) belongs to BCS class II drug (highly permeable and low soluble). A simultaneous DSC, FT-IR, SEM, XRPD micro spectroscopy, dissolution study and micromeritics properties studies was used to quickly investigate the co-crystal. Tablet formulation was developed by direct compression method and there evaluation was performed.

Keywords: Efavirenz; Co crystal; DSC; SEM; XRPD; FT-IR; Tablet

Introduction

Efavirenz is one of the most widely used nonnucleoside reverse transcriptase inhibitors (NNRTIs) in first-line antiretroviral therapy (ART) and is recommended as a preferred option in adult treatment guidelines [1]. It is chemically (4S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3, 1-benzoxazin-2-one (Figure 1). The bioavailability of orally administered drugs depends on their absorption from the gastrointestinal (GI) tract; Efavirenz is a poor water soluble BCS class-II drug, with low aqueous solubility of 6.2 µg/mL. Due to its high lipophilicity (log P=5.4) and consequently poor aqueous solubility, the drug shows relatively low oral absorption and bioavailability (40-45%) and high inter-subject variability [2]. Efavirenz inhibits the reverse transcriptase enzyme, an essential viral enzyme which transcribes viral RNA into DNA; it acts allosterically by binding to a distinct site away from the active site known as the NNRTI (Non nucleocidal reverse transcriptase inhibitor) pocket [3]. In oral route of administration, poor water soluble drugs present low bioavailability because of their low solubility in GI media. The rate limiting step in the absorption of these drugs is the dissolution rate in the GI fluids rather than their diffusion through the GI membrane [4]. Various methods are available for enhancement of solubility like complexation, co solvents, micro emulsions, micelles, polymeric micelles, liposomes, pharmaceutical salts, pro-drugs, particle size reduction and cocrystalization. The term "crystal engineering" was introduced by R. Pepinsky in 1951. Further G.M.J. Schmidt in the 1960's implemented in the context of topochemical reactions on cinnamic acid. Co crystals

are multiple component crystals or crystalline complexes stabilized by types of interaction, including hydrogen bonding, p stacking, and Vander Waals forces. Different techniques are used for the preparation of co crystals they are as follows: Traditional Techniques 1.Solvent evaporation technique, 2.Solid state grinding or mechanical milling technique and 3.Solvent reduced technique A. Slurring technique and Solvent evaporation technique is commonly used for the preparation of co crystals. In this technique both drug substance and cofomers are dissolved in a common solvent and allowed to slow evaporation of a solvent. The technique works on the principle of formation of hydrogen bond in favorable drug substance and complementary cofomers [5,6]. This process can affect the physical and physicochemical properties. Variation in crystalline habit is one of the proceeding trends in order to increase the solubility, dissolution rate and bioavailability of the poorly soluble drugs. This process could potentially be utilized to a wide range of drugs with different crystalline forms. Different crystals show different dissolution rates and then different biological responses. Pharmaceutical co crystals can improve drug physiochemical and mechanical properties as well as *in vivo* performance and, hence, are a potential new alternative in the selection of optimal solid dosage forms in product development [7-11]. Coformer's Lactic acid has 2.32% and Adipic acid have high water solubility.

The present work oriented to improve physicochemical properties of Efavirenz using various conformers i.e., mainly solubility, dissolution and micromeritics properties. Co crystals of Efavirenz with Lactic acid and Adipic acid were prepared in different ratios by solvent evaporation method. The prepared co crystals were subjected to different evaluation tests like solubility analysis, *in vitro* dissolution study, evaluation of micromeritics properties, particle size determination, XRPD, DSC and SEM. Tablet formulation of Efavirenz co crystals were tried with direct compression method and evaluated.

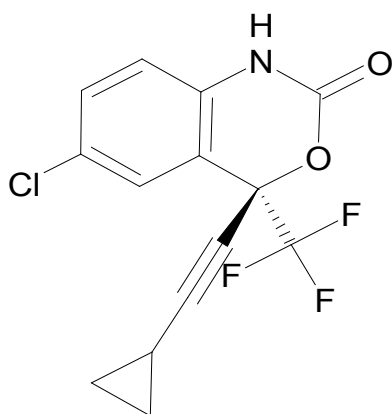


Figure 1: Chemical structure of Efavirenz.

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Materials and Methods

Synthesis of co-crystals

Method like solvent evaporation co-crystallization was employed for the synthesis of co crystals of Lactic acid and Adipic acid with Efavirenz. Solvent evaporation method was found to be the suitable for the synthesis of co-crystals in the present study.

Methods of synthesis

Solvent evaporation method

Co-crystals of Efavirenz with Lactic acid and Adipic acid: The co-crystals of Efavirenz were prepared by co-former method. Equimolar or different molar quantities of Efavirenz and different co-formers such as Lactic and Adipic acid were dissolved in 20 ml ethanol by keeping in water bath maintained at a temperature at 80°C to obtain clear solution. The solution was allowed to cool in ice bath for about 5 hr for thorough crystallization to occur. The crystals were collected by filtration through a Whatmann filter paper, dried in air for 24 hr and finally stored in desiccators until further investigated by microscopic, melting point, SEM, XRPD and DSC study [12,13].

Characterization

The prepared co-crystals and its tablets were investigated by different techniques and analysis which include:

1. Melting Point (Veego, Mumbai)
2. Solubility of Efavirenz and co crystals with Lactic acid and Adipic acid
3. Microscopic evaluation (Motic, BA-210, Hong Kong)
4. Differential Scanning Calorimetry (Detector 60, Mettler-Toledo DSC 821e, USA)
5. X-ray Powder Diffraction (PW 1729, Philips, Netherland)
6. SEM (JSM 6360 LV, Joel, Japan)
7. FT-IR (Alpha-E Bruker, Germany)
8. Weight Variation
9. Friability Test Data
10. Hardness and Thickness Test
11. Disintegration and
12. Dissolution study

Microscopic evaluation

Microscopic evaluation was observed under Motic BA 210 microscope, which was used as a primary investigation tool to confirm the formation of co-crystals visually and to observe the crystal habit of the prepared co-crystals, compared the shape of co-crystals was with the pure drug. Crystallization of the pure drug was also carried out in the same solvent which was used for the synthesis of co-crystals to investigate differences in crystal habit of co-crystals with that of pure drugs.

Solubility of Efavirenz and its Co crystals with Lactic acid and Adipic acid

The solubility study was carried out first in distill water at 27°C; excess amount of Efavirenz or its co crystals was added in 10 mL distill water and the bottle was screw capped with stopper. The bottle was kept shaking for about 24 hr and then centrifuge for 15 min; filtered;

filtrate 1.2 mL diluted up to 10 mL with aqueous ethanol i.e., ethanol and water (6:4) ratio; finally the absorbance of sample was taken at 247.8 nm (Table 1)[14].

Differential Scanning Calorimetric (DSC)

DSC analysis is a thermo analytical technique used to identify the difference in the amount of heat required to increase the temperature of a sample and reference as a function of temperature. The samples were analyzed by Differential Scanning Calorimeter (Detector 60, Mettler-Toledo DSC 821e) over the range of 0-200°C at the rate of 10°C per minute. DSC, thermo analysis gave characteristic and comparable results for the APIs and the synthesized co-crystals as shown in Figure 2A and 2B [15].

X-ray Powder Diffraction (XRPD)

X-ray Powder Diffraction was done for the prepared co-crystals; it reveals the information about the crystal structure, chemical composition, and physical properties of the material and also helps in structural characterization. XRPD spectra on a sample stage PW 1729, Philips, Netherland were performed on samples of 05-10 mg in the range of -100 to 200°C at a heating rate of 10°C/min (N₂-atmosphere: 80 l/min) at the minimum step size 02 Theta: 0.001 and minimum step size Omega: 0.001 (Figure 3A-3C).

Scanning Electron Microscopy (SEM)

The surface characteristic of prepared crystal was studied by SEM (JSM 6360 LV, Joel, Japan). Powder samples was mounted onto aluminum stub using double sided adhesive tape and sputter coated with a thin layer of gold at 10 Torr vacuum before examination. The specimens were scanned with an electron beam of acceleration potential of 20 kV and the images were collected as secondary electron mode. SEM analysis has been performed for the pure drug and co-crystals (Figure 4A-4C).

Fourier Transform Infrared (FT-IR)

Fourier Transform Infrared (FT-IR) spectra were recorded for the Efavirenz, co-former (Lactic acid and Adipic acid) and co-crystals. The spectra were recorded in an Alpha-E Bruker FT-IR spectrophotometer. Potassium bromide pellet method was employed and background spectrum was collected under identical conditions. Each spectrum was derived from 16 single average scans collected in the range of 400-4000 cm⁻¹ at the spectral resolution of 02 cm⁻¹; (Figure 5A and 5B) [16-18].

Study of micromeritics properties of Efavirenz and its co-crystals

Angle of repose of Efavirenz, its co-crystal with Lactic acid and Adipic acid: The frictional force in powder can be measured by the angle of repose. It is the maximum angle possible between the surface

Compound	Solubility
Efavirenz	5.46 µg/mL
Efavirenz co-crystal with Lactic acid (1:1)	9.25 µg/mL
Efavirenz co-crystal with Lactic acid (1:2)	11.91 µg/mL
Efavirenz co-crystal with Lactic acid (1:3)	12.94 µg/mL
Efavirenz co-crystal with Lactic acid (1:4)	14.04 µg/mL
Efavirenz co-crystal with Lactic acid (1:5)	15.01 µg/mL
Efavirenz co-crystal with Adipic acid (1:1)	7.84 µg/mL
Efavirenz co-crystal with Adipic acid (1:2)	11.19 µg/mL
Efavirenz co-crystal with Adipic acid (1:3)	11.48 µg/mL
Efavirenz co-crystal with Adipic acid (1:4)	15.74 µg/mL
Efavirenz co-crystal with Adipic acid (1:5)	18.31 µg/mL

Table 1: Solubility of Efavirenz and its Co crystals with Lactic acid and Adipic acid.

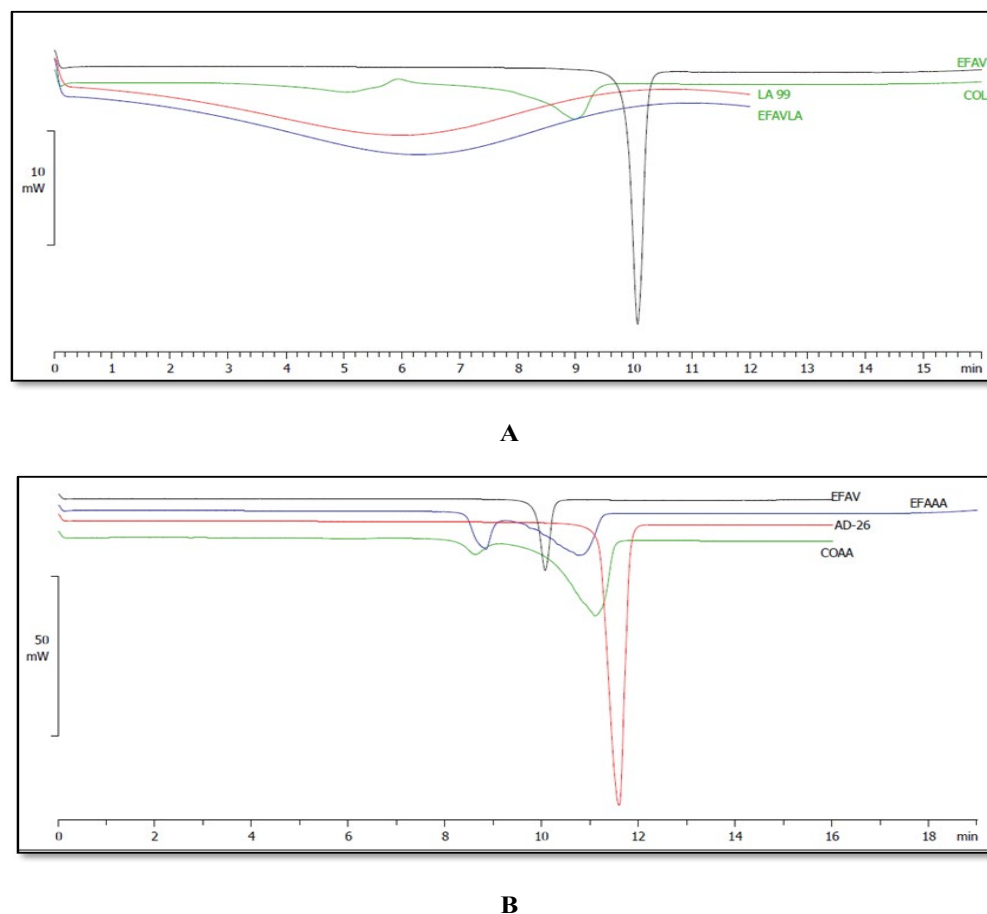


Figure 2: (A) DSC overlay spectra of Efavirenz-EFAV, Lactic acid-LA 99, physical mixture of Lactic acid and formulation of Efavirenz co-crystal with Lactic acid co-former-COLA (1:5). (B) DSC overlay spectra of Efavirenz-EFAV, Adipic acid-AD 26, physical mixture of Adipic acid and Efavirenz-EFAAA and formulation of Efavirenz co-crystal with Adipic acid co-former-COAA (1:5).

of pile of powder and the horizontal plane. The blend that has angle of repose in between 20° - 30° is best for compression as it has good flow property. Angle of repose was calculated by fixed funnel method, in which funnel was fixed to a stand in such a way that the lower tip of funnel was 2.5 cm above the surface. A graph paper was placed on the flat surface. The blend was allowed to fall freely on the graph paper through the funnel, till the tip of heap formed just touched the funnel. The radius of heap was noted and from this angle of repose was determined using following (Table 2).

$$\theta = \tan^{-1}(h/r) \text{ ----- 01}$$

Where, h=height of pile; r=radius of pile

Bulk density and Tapped density

Bulk density was determined by pouring preweighed and presieved bulk drug into a graduated cylinder via a large funnel and the volume was measured and recorded as bulk volume. The cylinder was tapped until powder bed volume reached a minimum volume and the volume was recorded as tapped volume. The bulk density and tapped density were calculated using following.

Bulk density=Mass/Bulk volume; Tapped density=Mass/Tapped volume ---- 02

Hausner's Ratio

Hausner's found that the ratio of tapped density/bulk density

was related to inter particle friction as such, and could be used to predict powder flow properties. He showed that the powder with low inter particle friction had ratio of approximately 1.2, whereas more cohesive less free flowing powders have Hausner's ratio greater than 1.6. Hausner's ratio less than 1.25 indicates good flow. It is the ratio of tapped density to the bulk density.

$$\text{Hausner's ratio} = \text{Tapped density/Bulk density} \text{ ----- 03}$$

Carr's index

This property is also known as percent compressibility, indirectly related to the flow rate, cohesiveness and particle size. Compressibility is the ability of powder to decrease in volume under pressure, is obtained from density determinations. The compressibility index of the powder was determined by Carr's compressibility index. It is simple, fast and accurate method of predicting powder flow characteristics (Table 3).

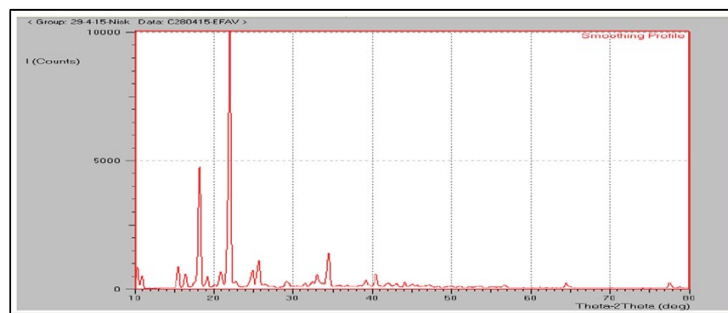
Carr's Index of Efavirenz

$$\text{Carr's Index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Bulk Density}} \times 100 \text{ ----- 04}$$

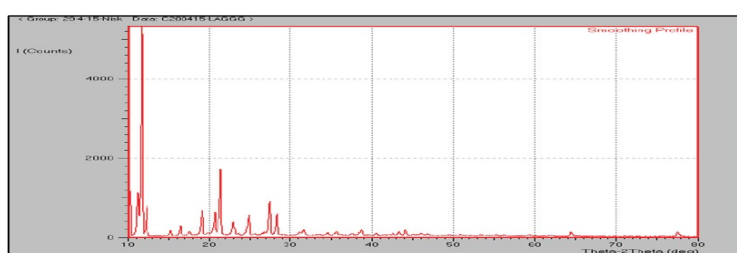
Carr's index is the measure of the potential strength that the powder could build up in its arch in a hopper and also the ease with which such an arch could be broken.

Preparation of Tablet by Direct Compression

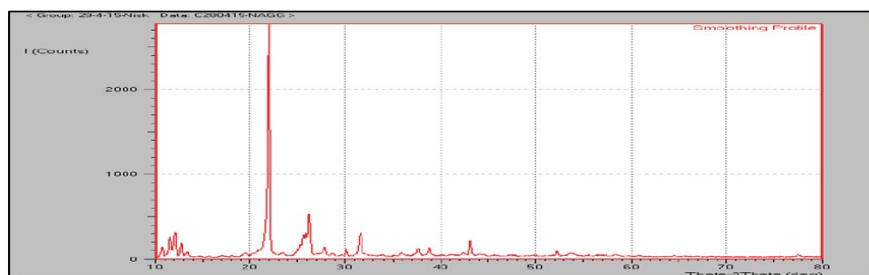
Accurately measured quantities of drug and excipients were



A

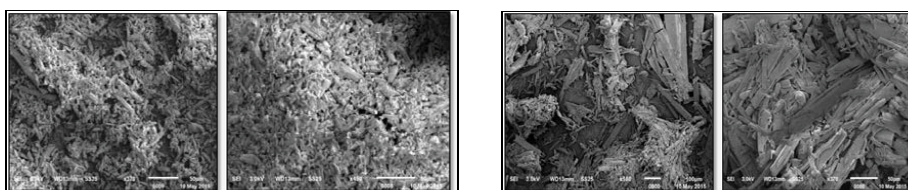


B



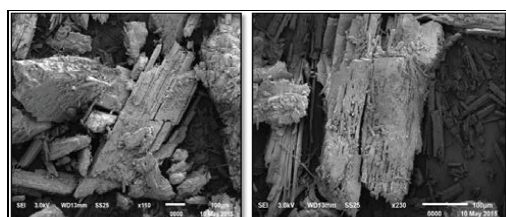
C

Figure 3: XRPD spectra of (A) Efavirenz, (B) Co-crystals of Efavirenz with Lactic acid and (C) Co-crystals of Efavirenz with Adipic acid.



A

B



C

Figure 4: SEM images for (A) Efavirenz, (B) Co-crystals of Efavirenz with Lactic acid and (C) Efavirenz with Adipic acid.

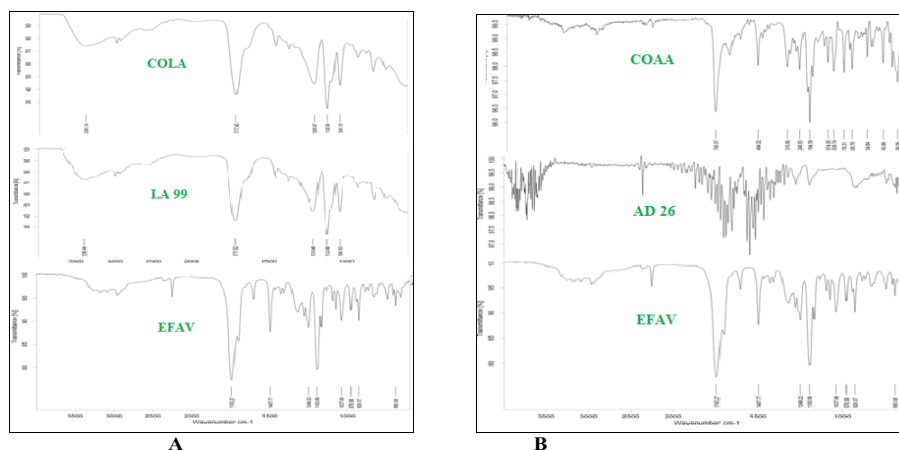


Figure 5: FT-IR spectra for (A) Efavirenz-EFAV, Lactic acid-LA 99 and formulation of Efavirenz co-crystal with Lactic acid co-former-COLA (1:5), (B) Efavirenz-EFAV, Adipic acid-AD 26 and formulation of Efavirenz co-crystal with Adipic acid co-former-COAA (1:5).

Parameter	Efavirenz	Co crystal with	
		Lactic acid (1:5)	Adipic acid (1:5)
h	2.3 cm	1.3 cm	1.9 cm
r	2.9 cm	4.9 cm	3.6 cm
tan Ø ⁻¹	38.41	14.85	27.82
Type of flow	Very Poor	Good	Good

Angle of flow <25: Excellent; 25-30: Good; 30-40: Passable and >40: Very Poor

Table 2: Angle of repose of Efavirenz, its co-crystal with Lactic acid and Adipic acid.

Parameter	Efavirenz	Efavirenz Co crystal with	
		Lactic acid (1:5)	Adipic acid (1:5)
Mass	10 g	4.17 g	4.17 g
Bulk volume	38 cc	12 cc	13 cc
Bulk density	0.26 g/cc	0.34 g/cc	0.32 g/cc
Tapped volume	20 cc	10 cc	11 cc
Tapped density	0.50 g/cc	0.41 g/cc	0.37 g/cc
Hausner's Ratio	1.92	1.2	1.15
Carr's index	24%	7%	5%

% Compressibility 5 to 15: Excellent; 12 to 16: Good; 18 to 21: Fair; 23 to 28: Poor; 35 to 38: Very poor and >40: Extremely poor

Table 3: Bulk density, Tapped density, Carr's index and Hausner's ratio of Efavirenz, its co-crystal with Lactic acid and Adipic acid.

taken as shown in Table 4. In this method involves simple blending of active pharmaceutical ingredient (API) with other Ingredients and direct compaction of the resultant mixture passed through 40# and were taken in to 'v' cone blender and blend for 15 min and taken for compression. The tablets were punched using rotary compression machine (Cadmac) of 12 mm punch. These compressed tablets were transferred in to packing area and these tablets were packed in paper-Aluminum packing with LDP coating.

Evaluation of Tablets

All the tablets were evaluated for different parameters as thickness, hardness, friability, uniformity of weight, disintegration time, *in vitro* dissolution and drug content study [19].

Dimensional analysis

The thickness and diameter of tablets was determined using vernier caliper. Twenty tablets from each batch were used and average values were calculated (Table 5).

Hardness

The Monsanto hardness tester was used to determine the tablet

hardness. The tablet was held between affixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of the hardness of the tablet. It is expressed in kg/cm². For each formulation, the hardness of six tablets was determined and average value was calculated (Table 5).

Weight variation

Randomly selected twenty tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablets pass the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double percentage limit (Table 5). IP limit for weight variation in case of tablets weighting up to 120 mg is $\pm 10\%$, 120 mg to 300 mg is $\pm 7.5\%$ and more than 300 mg is $\pm 5\%$.

$$PD = [(W_{avg} - W_{initial}) / (W_{avg})] \times 100$$

Where, PD=Percentage deviation; W_{avg} =Average weight of tablet,

$W_{initial}$ =Individual weight of tablet.

Friability

Twenty tablets samples were weighed accurately and placed in

Ingredient	Quantity/Tablet	
Co- crystal of Lactic acid	522.37 mg	-----
Co- crystal of Adipic acid	-----	516.79 mg
Sucrose	07 mg	125 mg
Polyvinyl alcohol	4.22 mg	26.81 mg

Table 4: Formula for Efavirenz Co-crystal Tablet (With Lactic Acid Co-former (1:5) and Adipic acid co-former (1:5)).

Test	Efavirenz Co crystal with		Observation
	Lactic acid (1:5)	Adipic acid (1:5)	
Thickness	3.05 ± 0.03 mm	3.07 ± 0.02mm	Complies with I.P
Hardness	3.3 ± 0.01 kg	4.05 ± 0.03 kg	Complies with I.P
Wt. Variation	510.1-545.7 mg	690.5-652.4 mg	Complies with I.P
Friability	0.79 ± 0.09%	0.63 ± 0.04%	Complies with I.P
Disintegration	7 ± 0.16 min	8 ± 0.08 min	Complies with I.P

Table 5: Evaluation of post direct compressed Efavirenz co crystal tablets.

friabilator (Roche friabilator). After the given specification (4 min at 25 rpm), loose dust was removed from the tablets. Finally tablets were weighed. The loss in weight indicates the ability of the tablets to withstand this type of wear (Table 5).

% friability was then calculated by
$$= \frac{(W_{\text{avg}} - W_{\text{initial}})}{(W_{\text{avg}})} \times 100$$

Disintegration test

Disintegration is evaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. Disintegration test was carried out using tablet disintegration test apparatus (Electro lab, India) using distilled water without disk at room temperature (37 ± 2°C) (Table 5).

In vitro dissolution study

UV-VIS measurement: The samples were analyzed UV spectrophotometer and the absorbance was recorded at 252 nm using UV spectrophotometer against a dissolution medium as a blank. *In vitro* dissolution study of co-crystal offers a convenient and inexpensive means of predicting absorption and bioavailability of formulations of the same drug. The release profile of co crystal of Efavirenz with Lactic Acid or Adipic acid or tablet of co crystal of Efavirenz with Lactic Acid or Adipic acid predicts how a delivery system might function and gives valuable insight into its *in vivo* behavior. *In vitro* release profile for co crystals or tablet as well as pure drug was performed using USP XXIV type II (paddle) dissolution apparatus. Took co crystal sample equivalent to 200 mg of Efavirenz or 200 mg equivalent Efavirenz co crystal tablet was added to 1000 ml phosphate buffer pH 7.2 at 37 ± 0.5°C and stirred at 75 rpm. Aliquot of 5 ml was withdrawn at time intervals of 5, 10, 15, 30 and 45 min. The withdrawn volume was replaced with the same volume of dissolution medium in order to keep the total volume constant [14-20]. The absorbance of the samples was measured at λ max 252 nm (Tables 6 and 7; Figures 6 and 7).

Drug Content

Co-crystals of Efavirenz with Lactic acid or Adipic acid 10 mg was accurately weighed and transferred to volumetric flask (10 mL). It was dissolved properly in ethanol and diluted up to the mark with ethanol to obtain final concentration of 1000 µg/mL and used as a stock solution (Stock Solution I). One ml of stock solution I was withdrawn and further diluted by ethanol to give 10 µg/mL. This solution was scanned in the UV region of 400-190 nm. The spectrum was obtained to determine the maximum absorbance (λ max). They were analyzed by UV Visible spectrophotometer by measuring the absorbance at 247.8 nm (Table 8).

$$y=mx+c$$

Where, y=Absorbance, m=Slope, c=Intercept

Results and Discussion

Synthesis of co-crystals of Efavirenz with Lactic acid or Adipic acid was carried out by solvent evaporation method and its tablet were produced by direct compression method. Ethanol employed as solvents for the synthesis of co-crystals was proved to be the suitable for formation of co crystals. Other solvents were used but they were failed to produce the crystal pattern of co-crystals different from the crystals pattern of pure drugs when observed using microscopy. Microscopic analysis of prepared co-crystals revealed visual difference between the co-crystals and pure drug Efavirenz. In aqueous solubility study of Efavirenz and its co crystals result reveal that Efavirenz 5.46 µg/mL, Efavirenz co-crystal with Lactic acid (1:5) 15.01 µg/mL and Efavirenz co-crystal with Adipic acid (1:5): 18.31 µg/mL, which suggest 3-3.5 fold improvement in solubility of co crystals than pure drug as shown in Table 1. The Differential Scanning Calorimetry (DSC) data of synthesized co crystals A (Efavirenz with Lactic acid) and B (Efavirenz with Adipic acid) showed difference of melting point which confirms the formation of stable co-crystals. The DSC of synthesized co crystals A (Efavirenz with Lactic acid) shows the single prominent endothermic peak at 129.67°C as shown in Figure 2A, which is neither the melting point of Efavirenz nor boiling point of Lactic acid. This supports the formation of co-crystals of Efavirenz with Lactic acid. Similarly, DSC result of B shows the prominent endothermic peak at 149.76°C as shown in Figure 2B, which is substantially different from the melting point of Efavirenz and Adipic acid. These results suggested the complete formation of co-crystals of Efavirenz with Lactic acid and Adipic acid and not simple physical mixtures. The co-crystals described here showed large variation in melting temperature from that of Efavirenz, suggesting that the cohesive energy of co crystals A and B is decreased and increased from that of pure drug Efavirenz.

In analysis of the X-ray Powder Diffraction data of the polycrystalline materials arising from solvent evaporation experiments revealed that for critical co-crystal formation of Efavirenz with Lactic acid or Adipic acid, reflections arising from the starting materials are absent, indicating the presence of new phase when they were taken in proportion of 1:5 for co-crystals of Efavirenz with Lactic acid and co-crystals of Efavirenz with Adipic acid. XRPD analysis supports the formation of co crystals of Efavirenz with Lactic acid or Adipic acid as showing different patterns in diffractogram with that of pure Efavirenz (Figure 3A-3C). In SEM results reveals that a pure drug Efavirenz

S. No.	Time (min)	% Cumulative drug release										
		Efavirenz	Lactic acid (1:5)					Adipic acid (1:5)				
			1:1	1:2	1:3	1:4	1:5	1:1	1:2	1:3	1:4	1:5
1	00	00	00	00	00	00	00	00	00	00	00	00
2	05	26.37	04.11	05.84	06.82	10.44	35.17	10.92	13.96	18.31	18.34	24.83
3	10	27.86	07.68	08.81	10.29	14.48	45.37	14.37	17.48	21.11	23.98	25.30
4	15	38.94	11.10	12.11	12.92	24.63	50.13	24.74	21.00	26.48	27.42	39.41
5	30	58.66	13.70	14.85	17.81	35.28	65.41	28.33	31.62	42.18	46.26	50.16
6	45	62.50	24.07	25.21	35.22	51.67	83.66	35.25	38.05	47.02	56.00	79.41

Table 6: Dissolution studies of Efavirenz co-crystal with Lactic acid or Adipic acid.

Time in min	Efavirenz Co crystal tablet with	
	Lactic acid (1:5)	Adipic acid (1:5)
05	34.70	25.20
10	44.90	27.41
15	49.95	40.97
30	66.10	51.50
45	84.35	81.60

Table 7: *In Vitro* drug release of Efavirenz co-crystal tablet (Lactic acid or Adipic acid).

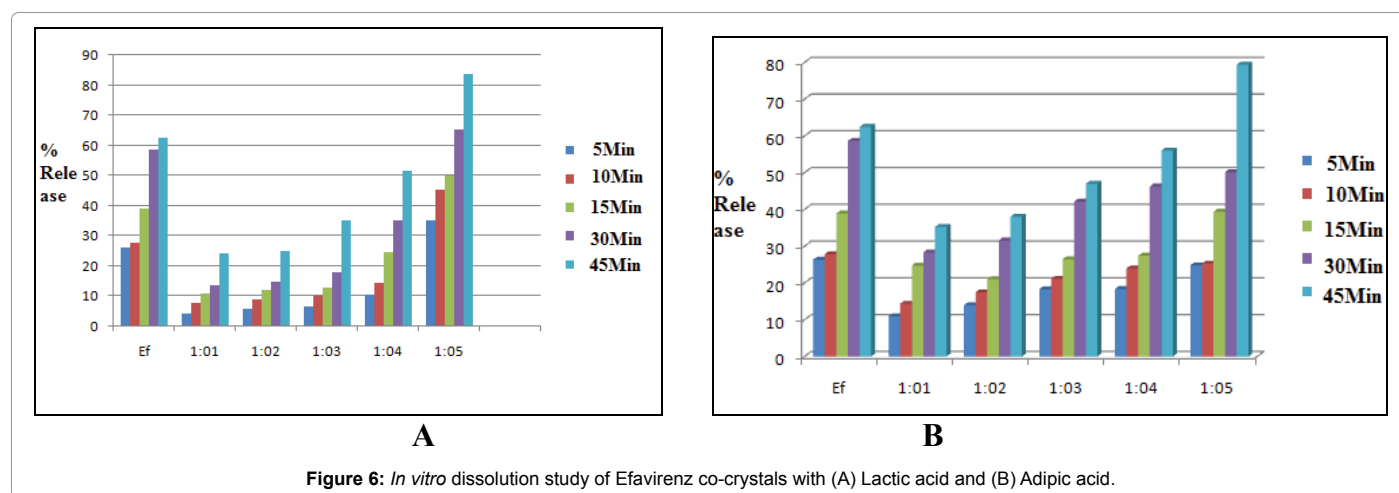
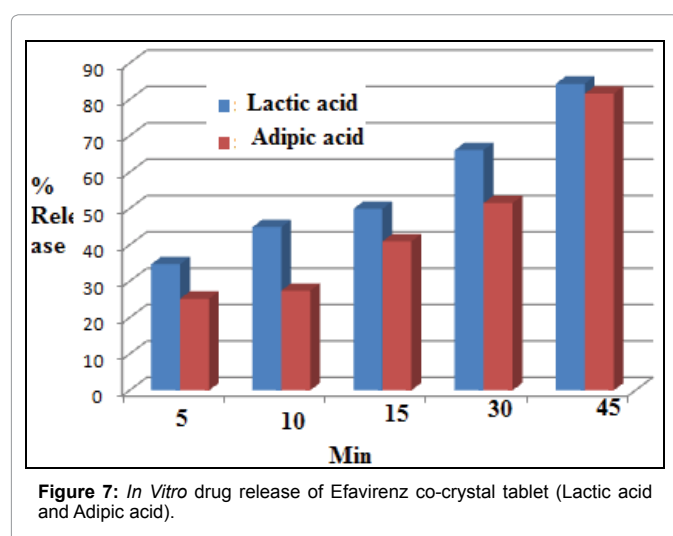


Figure 6: *In vitro* dissolution study of Efavirenz co-crystals with (A) Lactic acid and (B) Adipic acid.



exhibited irregular shape with smooth surface and the co-crystals of Efavirenz with Lactic acid or Adipic acid also exhibited irregular shape but the shape was different with those of the pure drug as shown in Figure 4A-4C. In FT-IR spectroscopy for Efavirenz and its co crystals

Co-crystal	Efficiency	Drug content
Lactic acid (1:5)	3.84 mg	97.66%
Adipic acid (1:5)	3.87 mg	98.29%

Table 8: Efficiency of Efavirenz co-crystals with Lactic acid and Adipic acid.

shows various FT-IR frequency bands are present in spectra's, In Efavirenz co crystals with Lactic acid shows shift in O-H bond of Lactic acid to low frequency at 3391 cm^{-1} from 3395 cm^{-1} and in case Efavirenz co crystals with Adipic acid shows shift in O-H bond of Lactic acid to low frequency at 3390 cm^{-1} from 3350 cm^{-1} of which reveals that drug is compatible with co formers as well as formation of co crystals as shown in Figure 5A and 5B. The dissolution curves of pure Efavirenz and its co-crystals with Lactic acid and Adipic acid and there prepared tablet formulation in phosphate buffer pH 7.2 reveals that improvement in release profile in 45 minutes by 33.85 and 27.05% respectively when compared with pure Efavirenz pure drug (Tables 6 and 7; Figures 6 and 7).

The micromeritics properties like bulk density, tapped density, angle of repose and Carr's index were determined and shown in Tables 2 and 3. The tapped density of the co-crystals of the Efavirenz with Lactic acid and Adipic acid are lower than the corresponding value of the Efavirenz pure drug. The lower density is likely to be related to the intraparticle porosity and almost retained bulk density of the treated samples indicates a greater porosity within the co-crystals of

Efavirenz with Lactic acid and Adipic acid particles. Carr's index of the co-crystals of Efavirenz with Lactic acid and Adipic acid was found to be lower when compared to Efavirenz pure drug. Fine particles having high surface to mass ratios are more cohesive than coarser particles, hence more influenced by gravitational force. Decreased values of Carr's index for co-crystals of Efavirenz with Lactic acid and Adipic acid indicate better pack ability, and that they might be suitable for direct tableting. Flow properties of the co-crystals of Efavirenz with Lactic acid and Adipic acid were reflected by angle of repose. It was found that angle of repose of the co-crystals of Efavirenz with Lactic acid and Adipic acids were decreased when compared to Efavirenz pure drug. Such decreased value indicates improvement in flow ability. Lower densities of the Efavirenz with Lactic acid and Adipic acid than the Efavirenz pure drug indicate better crystallinity and porosity. Lower Carr's index of the co-crystals of the Efavirenz with Lactic acid and Adipic acid makes their pack ability better, and suitable for direct tableting.

Conclusions

Synthesis of Efavirenz Co crystals with Lactic acid and Adipic acid were successfully prepared by solvent evaporation method ; aqueous solubility also enhanced by 33.85% and 27.05% respectively. Upon formulation and development of co crystals; micromeritics properties are found improved for development of tablet formulation.

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