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SOLUBILITY ENHANCEMENT AND CO CRYSTAL TABLET FORMULATION OF EFAVIRENZ BY CO-CRYSTALLIZATION TECHNIQUE

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ABSTRACT

More than 60% drugs coming from synthesis and 40% drugs in the development are poorly soluble and create problem of poor water solubility in the pharmaceutical industry. So various techniques are tried to overcome this problem like solid dispersion, Co-Solvent, Co-amorphous Co-crystallization. Most promising one is Co-crystallization. In the present work Efavirenz co-crystallize with suitable Co-former such as Saccharine and Caffeine by solvent evaporation technique in 1:1 ratio. The prepared Co Crystal was characterized by DSC, IR, XRPD & other pharmaceutical properties like melting point, Solubility etc. Prepared Efavirenz Co-crystals exhibited excellent physicochemical properties when compared with pure drug. In FTIR analysis, there were no new peaks observed, indicating that no chemical reaction occurred during cocrystal preparation. DSC, SEM study confirms that the third product which was form after co-crystallization, they are co-crystal with change in Shape, Size, habit, Melting point. The X-Ray Powder Diffraction pattern shows peak reduced and confirm that the third product Co-crystal was formed. XRD shows that different peaks height in drug & more sharp peaks at 22.96,27.From solubility studies it was found that the co-

crystal of Efavirenz with Saccharine in 1:1 stoichiometric ratio enhances the solubility up to 17 fold. So the Immediate release plain tablet of Efavirenz and its Saccharine co-crystal was prepared & evaluated for various post compression parameters such as thickness, hardness, friability, weight variation, drug content, disintegration. Faster disintegration and greater dissolution rate release 90.26% was observed with Cocrsytal compare to plain tablet of Efavirenz. Finally we concluded that Solubility enhancement & formulation development of Efavirenz successfully completed.

Keyword: Solubility, Cocrystal, Efavirenz, Saccharin, Caffine, Solvant Evaporation, Tablet

INTRODUCTION

Solubility is one of the biggest problems in pharmaceutical industries. Various techniques are used to enhance the solubility of poorly water soluble drugs. More than 60% drugs coming from synthesis and 40% drugs in the development are poorly soluble and create problem of poor water solubility in the pharmaceutical industry **[1]**. Poor water soluble drug is slowly released, slowly dissolved and poor bioavailability that leads to required large dose for produce desirable pharmacological effect so new techniques are tried to overcome this problem. Like solid dispersion, co-solvent, co-amorphous, co-crystallization. Most promising one is Co-crystallization **[2]**. Pharmaceutical co-crystal is a budding tool to modify solubility, dissolution rate and physical and chemical stability of drug substances while keeping the pharmacological effect of drug unchanged **[3, 4]**. Co-crystal can be defined as stoichiometric multi-component system connected by non-covalent interactions in which two distinct components are solid under ambient conditions **[5]**.

Pharmaceutical co crystals provide an alternative to chemical modification of the drug substance as well as established salt, amorphous, solvate, polymorphic drug forms and inclusion complexes, all of which have limitations in their utility **[6, 7]**.

Efavirenz is one of the most widely used nonnucleoside reverse transcriptase inhibitors in first-line antiretroviral therapy **[8]**.

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 inhibitor **[9]**. Efavirenz belongs to Biopharmaceutical Classification System class II having Low solubility High permeability so there is need to enhance solubility & dissolution of Efavirenz for effective management of diseases **[10]**.

Aim & objectives of our research project is to enhance solubility of Efavirenz by preparing co crystals of it with Sachhrine,

Caffine, characterize the cocrystals using powder Fourier transform infrared, Differential scanning calorimetry, Powder X-ray powder diffraction, Saturation solubility etc & formulation development of Efavirenz tablets, with effective Conformer.

MATERIALS AND METHODS

Efavirenz was gift sample from Mylan Laboratories, Hyderabad. (India). All other chemicals & solvent were obtained from the Research fine Lab. Mumbai

Method

Preparation of Co Crystals

Solvent evaporation method technique was used to prepare Co Crystals. Solvent evaporation co crystallization of Efavirenz in the stoichiometric ratio of 1:1 with saccharin and caffeine was performed in simple apparatus and kept it for several hours for complete evaporation of solvent, after complete evaporation dry it and then collected. For Crystallization methanol is used as a solvent **[8-10]**.

Characterization of Co crystal [12-17]

Melting Point Determination

The melting point of Efavirenz, Co-formers and co crystals was determined by the capillary method. Capillary filled with powder was placed in melting point apparatus separately containing liquid paraffin, and melting point was noted.

Saturation Solubility Determination

Saturation Solubility of Efavirenz and its co-crystal with saccharine and caffeine was carried out in distilled water, Phosphate buffer 6.8, Acetate buffer 4.5. Excess of Efavirenz and its co-crystal was added in bottles containing 10ml of media and bottle was capped with stopper.

Then it was kept for shaking for 24hours and after 24hours centrifuges it for 10minutes, filter it and take 1ml from it and diluted up to 10ml with methanol, finally the absorbance was taken at 247nm.

Infrared spectrum

The Efavirenz, Co-former Saccharine and co crystals samples and potassium bromide powder was mixed. The baseline of FTIR was carried out using dried Kbr and then spectrum of dried mixture of drug and Kbr were recorded by placing the powder in the light path and scanning the sample over the range of 400-4000/cm.

Differential Scanning Calorimetry

Thermal analysis by differential scanning calorimetry of Efavirenz, Co-former Saccharine and co crystal was performed .the samples 7-10mg were placed in aluminium pans, sealed hermentically and these sealed pans were heated at scanning rate of 20C◦/min from 50C◦ to 350°C under constant purging dry nitrogen flow (20mL/min),and empty aluminium pans used as a reference.

X-Ray Diffraction Method

In this , a Efavirenz and co crystal powder samples is exposed to a beam of monochromatic X-ray radiation, which is diffracted and recorded by an X-ray detector then diffracted data is processed and a X-ray powder pattern is plotted.

Scanning Electron Microscopy (SEM)

The surface characteristic of prepared crystal was studied by SEM in this technique, thevacuum dried formulations were mounted on Aluminium stubs and coated with platinum in electron microscopic sciences (EmS) 550 sputter coater the co crystals samples were coated under argon atmosphere at room temperature for 120 sec and were examined using Hitachi S-530 SEM. Pictures were taken t an accelerating voltage of 20/15 k V and working distance of 15mm.

Formulation of Plain and Co-crystal Tablet [18]

The immediate release plain and co-crystal tablet of Efavirenz prepared by direct compression method, and the composition of single tablet is given below in **Table 1**. An accurately weight quantity of Efavirenz in case of Plain tablet & an accurately weighed quantity of Cocrystal equivalent to drug Efavirenz dose (100 mg) was taken and all other ingredients was mixed. The mixture was directly compressed into tablets using flat round punch of 8 mm sizes on a Rotary tablet compression machine.

Evaluation of of plain and co-crystal Tablet [19-24]

A) Evaluation of Pre compression parameters

Angle of Repose:- It is maximum angle possible between the surface of pile and the horizontal plane. Angle of repose was calculated by Fixed funnel method.

Bulk Density:- It is determined by pouring preserved powder into funnel or graduated cylinder and volume was record as bulk volume.

Tapped Density:- It was tapped until powder bed volume reached a minimum volume and it is recorded as tapped volume.

Hausner's Ratio:- It is the ratio of tapped density and bulk density.

Carr's index:- It is related to flow rate, particle size, cohesiveness. The compressibility index of the powder was determined Carr's compressibility index.

B) Evaluation of Post compression parameters

Hardness:- The Monsanto hardness tester was used to determine hardness of Tablet. The tablet was held in between the moving jaw, Scale was adjusted to zero, load was increase gradually until the tablet break or fracture. It is expressed in Kg/cm.

Thickness:- The diameter and thickness of tablet was determined using vernier caliper.

Weight variation:-Selected twenty tablets are selected weight individually and together. The average weight was noted and standard deviation was calculated.

Friability:- Twenty tablets weight individually and placed in friabilator. After the given rpm, dust was removed from tablet, and finally tablets were weighted. The loss in weight of tablets indicates the power to withstand the wear. It was determined by formula.

Disintegration test:- Test was carried out using tablet disintegration apparatus using distilled water at room temperature 37±2 ^{o}C.

Drug Content

Drug content uniformly determined by randomly selecting 5 tablets were powdered. The quantity equivalent to single dose of the drug was dissolved in HCl buffer solution, pH0.1N HCl for 5 Hours with occasional shaking and diluted to 50ml with buffer. After filtrations to remove insoluble residue, 1ml of the filtrate was diluted to 10ml with the buffer, the absorbance was measured at the required wavelength maxima using UV.

In Vitro Dissolution Study of Plain/Co Crystal Tablet

The in–vitro release of plain Efavirenz and co-crystal tablet of Efavirenz was performed in SLS 2% in water. Using USP type II apparatus. Plain tablet wt. of 200 mg and Co-crystal tablet wt. of 200 mg was added in 900ml of SLS2% in water maintained at 37 °C and stirred at 50 rpm, an aliquot of 5ml was withdrawn at the time intervals of 5, 10, 15, 20,30, 45 and up to 150 minutes. The withdrawn volume was replaced with the same volume of dissolution media. The absorbance of the samples was measured by UV Spectrophotometer at 247nm.

Table 1: Compoition of Plain and Co-crystal Tablet

Sr. No	Ingredients (Plain Tablet)	Quantity (mg)	Ingredients (CoCrystal Tablet)	Quantity(mg)
1	Efavirenz	100	Cocrystal equivalent to drug dose	Cocrystal containing 100 mg Efavirenz
2	MCC	40	Sucrose	QS
3	Lactose	40	PVA	10
4	Sodium starch glycol ate	16	Sod. Starchglycol ate	16
5	Magnesium stearate	2	Mg. Stearate	2
6	Talc	2	Talc	2

RESULTS AND DISCUSSION

Melting Point Determination

Melting point of Efavirenz, Saccharine and Caffeine were determined by open capillary method and compare with the standard literature values as shown in table below the result indicates that the drug and co formers used were of pure quality.Melting

points of cocrystals were lesser than the efavirenz. The depression of melting points revealed multi component system and designated formation of cocrystals **(Table 2)**.

Saturation Solubility

From solubility studies it was found that the co-crystal of Efavirenz with Saccharine in 1:1 stoichiometric ratio by solvent evaporation method enhances the solubility up to 17 fold so the further studies continued with the formulation & evaluation of Cocerystal tablets. From the solubility study, it was confirmed that the efavirenz is poorly water soluble drug and fits in the criteria of solubility enhancement using co crystallization technique. From this result it was concluded that solubility of Efavirenz was enhanced in Efavirenz: saccharine co-crystal by solvent evaporation method in Acetate buffer 4.5 **(Table 3)**.

IR Study

The IR spectrum for pure drug, conformer and co crystal was recorded and shown in **Figure 1-3**. The principle bands were identified and associated changes were recorded. In FTIR analysis, there were no new peaks observed, indicating that no chemical reaction occurred during co crystal preparation.

Differential Scanning Calorimetry Study

DSC studies are performed to observe the solid-state interaction of two compounds or more by giving heat energy to the co-crystals to evaluate thermodynamic changes (endothermic or exothermicpeaks). The DSC thermogram of Efavirenz, Saccharin and Caffeine were recorded by using a differential scanning calorimeter equipped with computerized data system.

The sharp endothermic peak at 140.7°C that corresponds to the melting point of Efavirenz that confirm the crystalline nature of efavirenz.

The sharp endothermic peak at 232°C that corresponds to the melting point of saccharine that confirm the crystalline nature of saccharine.

The sharp peak at 102.21°C and 284.90°C confirm that the melting point of co- crystal is significantly different from the melting point of Efavirenz and co-crystal clearly indicates the formation of cocrystals **(Figure 4-6)**.

X-Ray Powder Diffraction Study

PXRD was performed to verify the formation of the cocrystal of Efavirenz. All crystal forms of a compound show the characteristic on diffractogram pattern of drug. The PXRD patterns for Efavirenz, saccharine and cocrystal. X-ray powder diffraction pattern of Efavirenz was clearly indicates its crystalline state as a showed sharp and intense peaks which are characteristics of crystalline materials. The crystalline nature of the drug was demonstrated by the characteristics PXRD

pattern as shown the sharp peaks at 15.2, 17.6, 19.88.

The XRD Pattern of co-crystal of Efavirenz and saccharine is different than the pattern of Efavirenz. So that it was concluded that peak reduced and confirm that the third product Co-crystal was formed. XRD shows that different peaks height in drug. And more sharp peaks at 22.96,27. The formation of cocrystals based on the PXRD pattern had been well documented, which showed new peaks that differ from the peaks corresponding to its input components **(Figure 5-8)**.

SEM Study

SEM study confirms that the third product which was form after co-crystallization, they are co-crystal with change in shape, size **(Figure 9 a, b)**.

Evaluation of formulated Efavirenz plain tablet & Cocrystal Tablets

Pre compression parameters

Both Efavirenz tablet were subjected to various pre-compression parameters such as angle of repose, bulk and tapped density, compressibility index and Hausners ratio. Results of all pre compression parameters are shown in table below which indicates good flow properties of prepared powder blends of co crystals as compared to pure drug **(Table 3)**.

Post compression parameters

Plain Efavirenz and co crystal tablet formulation were evaluated for various post compression parameters like thickness, hardness, friability, weight variation, drug content, disintegration Results of all as shown in **Table 4**.

Comparative % Drug release of Co-Crystal Tablet and Plain Tablet

It was found that plain made tablet release 90% in 2hr 30minutes and co crystal tablet release 90.26% in 1hr 30 minutes **(Figure 10)**.

Table 2: Melting Point Determination

Compounds	Melting point std value	Observed values
Efavirenz	139-141°C	130-135°C
Saccharine	228.8°C	220-225°C
Caffeine	235°C	220-227°C
Efavirenz: saccharine Co Crystal	-	102-110°C

Table 3: Saturation solubility of co crystals

Blend	*Solvent*	*Solubility(µg/ml)*	*Enhancement ratio*
Efavirenz	Water	0.665	
	Phosphate buffer6.8	3.070	-
	Acetate buffer4.5	0.552	-
Solvent Evaporation Method			-
Efavirenz:Saccharine	Water	4.82	*7.30*
Co-crystal 1:1 ratio			
	Phosphate buffer6.8	3.66	1.19
	Acetate buffer4.5	9.64	17.52
Efavirenz:caffeine Co-crystal 1:1ratio	Water	1.64	2.48
	Phosphate buffer6.8	1.50	0.48
	Acetate buffer4.5	0.51	0.927

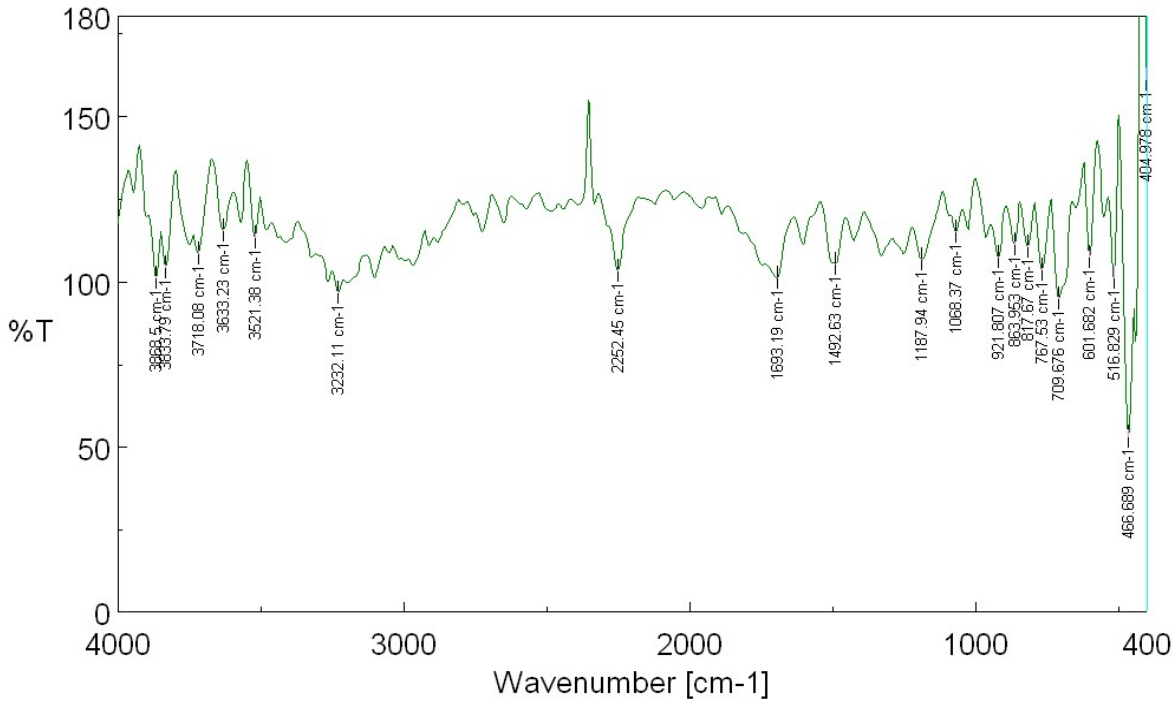

Figure 1: Infrared Spectrum of Efavirenz

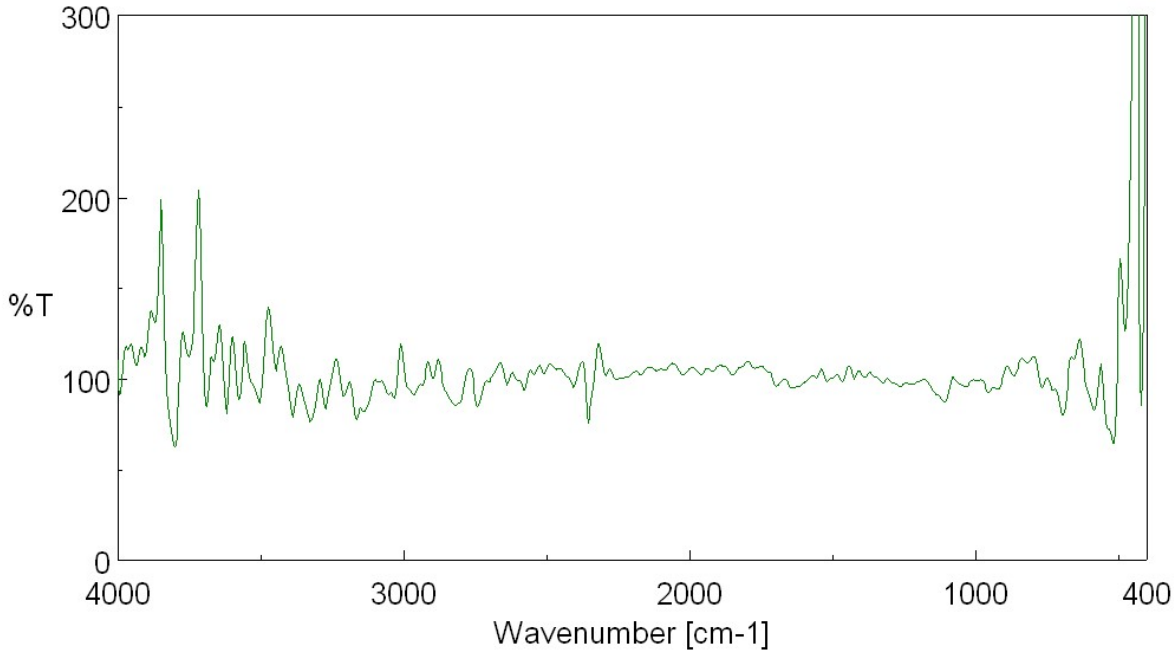

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Figure 2: Infrared Spectrum of Saccharine

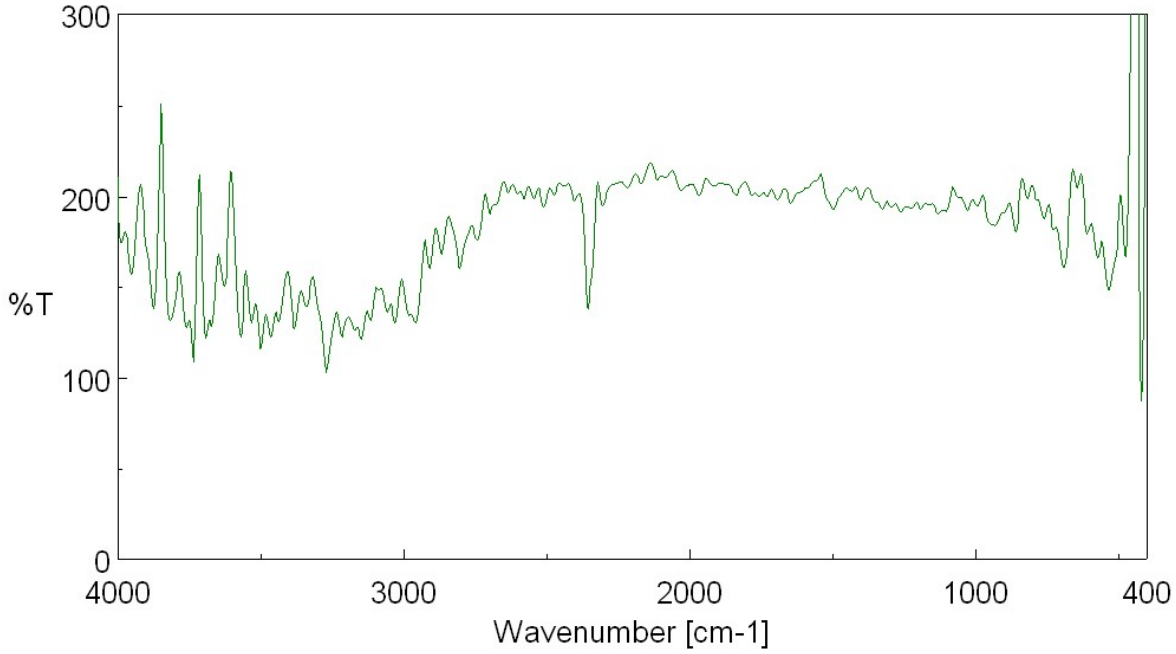

Figure 3: Efavirenz: Saccharine Cocrystal in 1:1 Ratio

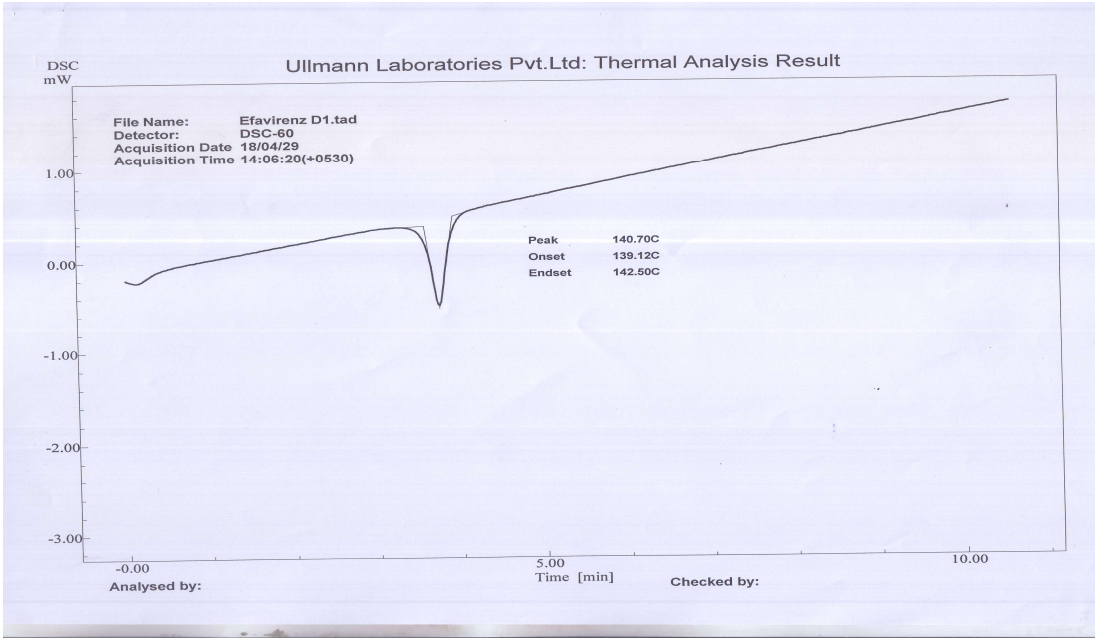

Figure: 4 DSC of Efavirenz

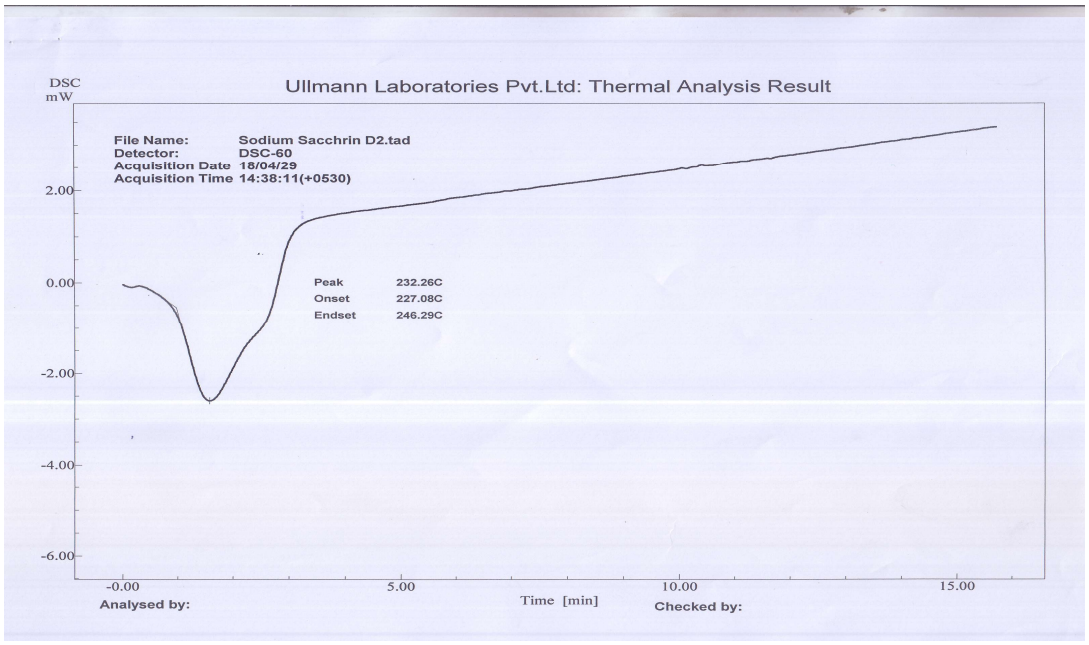

Figure: 5 DSC of saccharine

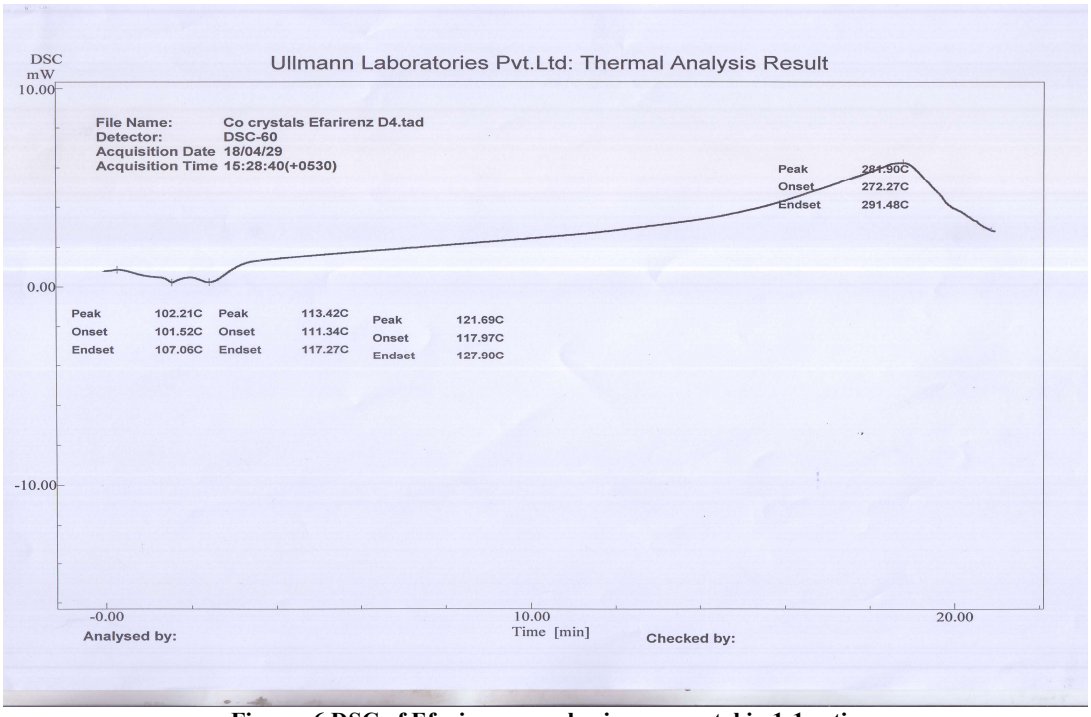

Figure: 6 DSC of Efavirenz: saccharine co-crystal in 1:1 ratio

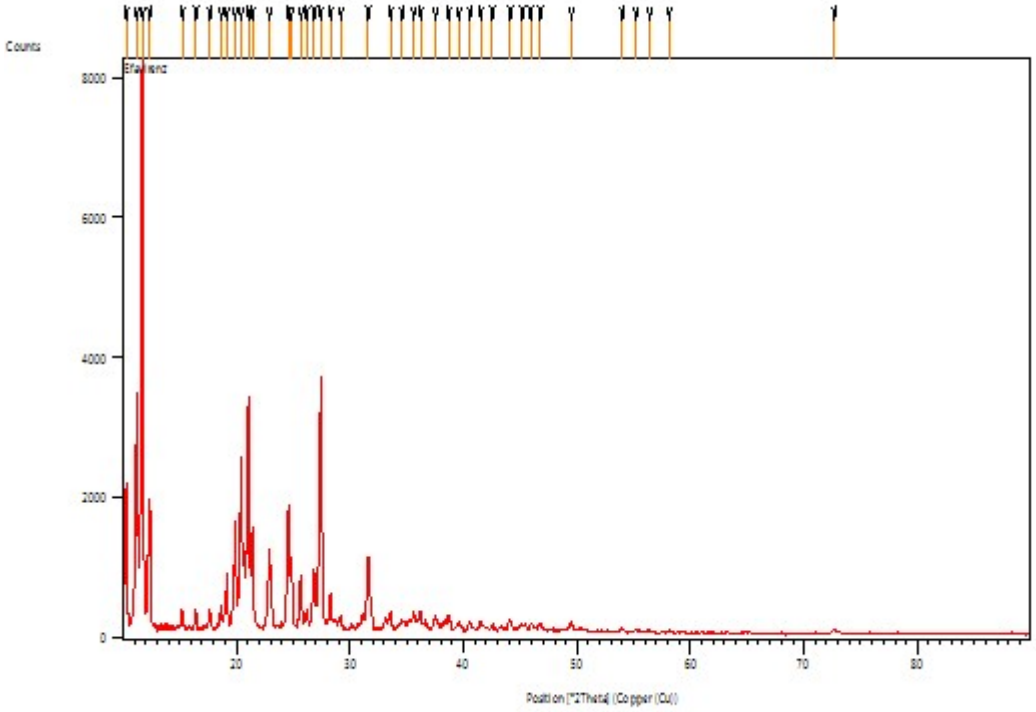

Figure: 7 XRD of Efavirenz

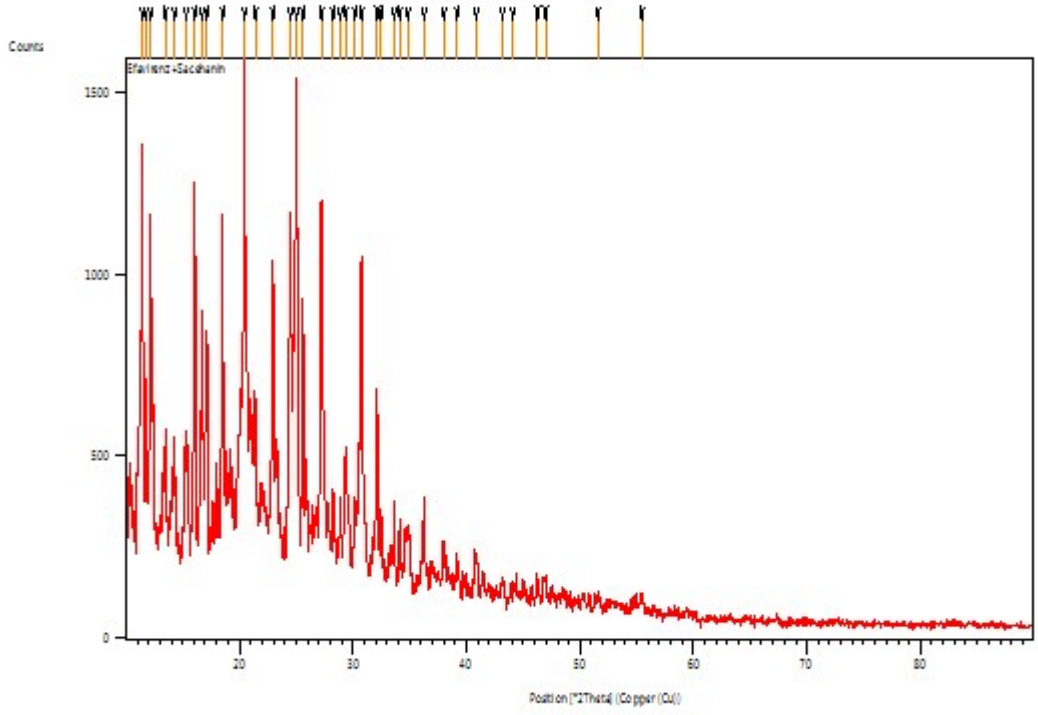

Figure: 8 XRD of Efavirenz: saccharine co-crystal in 1:1 ratio

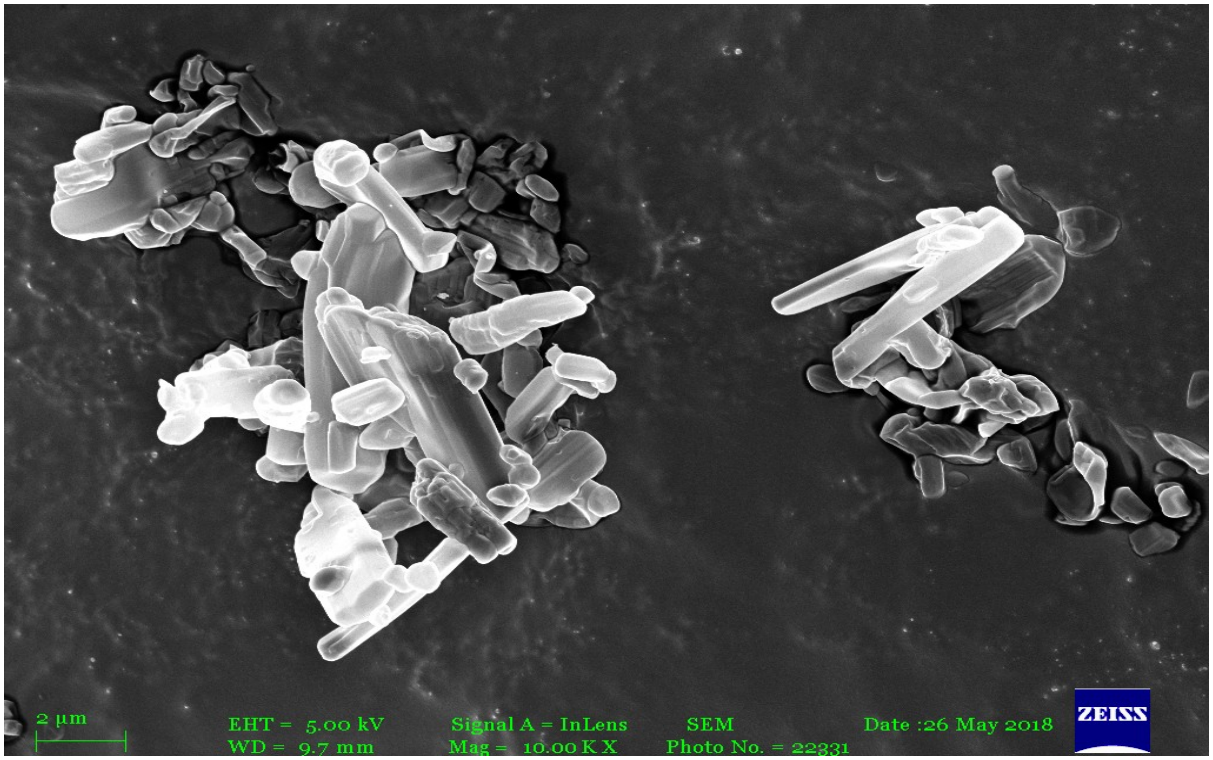

Figure: 9a: SEM study of co-crystal of Efavirenz (Bulk drug)

Figure 9b: SEM study of co-crystal of Efavirenz: saccharine

Table 3: Results of Pre compression parameters Determination

Method	System	Code	Physical properties					Inference
			Density(gm/cc)		Hausner´s ratio	Carr´s index	Angle of repose	
			Bulk	Tapped				
---------	Plain tablet powder	F0	0.39±0.001	0.63±0.02	15.51±1.6	31.9±1.7	40.3±1.05	Poor
Solvent Evaporation	Co crystal tablet	F1	0.49±0.015	0.61±0.030	1.3±0.031	15.51±1.60	30.2±0.35	Good

Table 4: Results of Post compression parameters Determination

Formulation code	Weight variation(mg)	Thickness(mm)	Friability (%)	Disintegration time(sec)	Hardness(Kg /cm²)	Drug content(%)
F0	199.7±0.02	2.6±0.05	0.32±0.01	15min	3.6±0.20	98.31±1.55
F1	201.5±0.74	2.8±0.12	0.34±0.03	11min	3.7±0.12	98.47±0.15

Table 5: % Drug release of Plain tablet & optimized co-crystal tablet

Time in minutes	% cumulative release ± S.D	
	Plain tablet.	Efavirenz: saccharine co crystal (S.E 1:10) tablet.
10	-0.35±0.03	4.41±1.21
20	0.23±0.27	9.51±1.7
30	0.70±0.48	13.6±2.1
40	3.29±1.03	26. 3±2.9
50	9.2±1.75	49.13±4.0
60	11.9±1.99	61.93±4.5
70	12.6±2.04	75.2±5.00
80	26.9±2.9	83.5±5.2
90	46.7±3.9	90.4±5.4
100	59.4±4.44	-
110	66.6±4.6	-
120	79.6±5.1	-
130	84.7±5.2	-
140	86.4±5.2	-
150	90.1 ±5.4	-

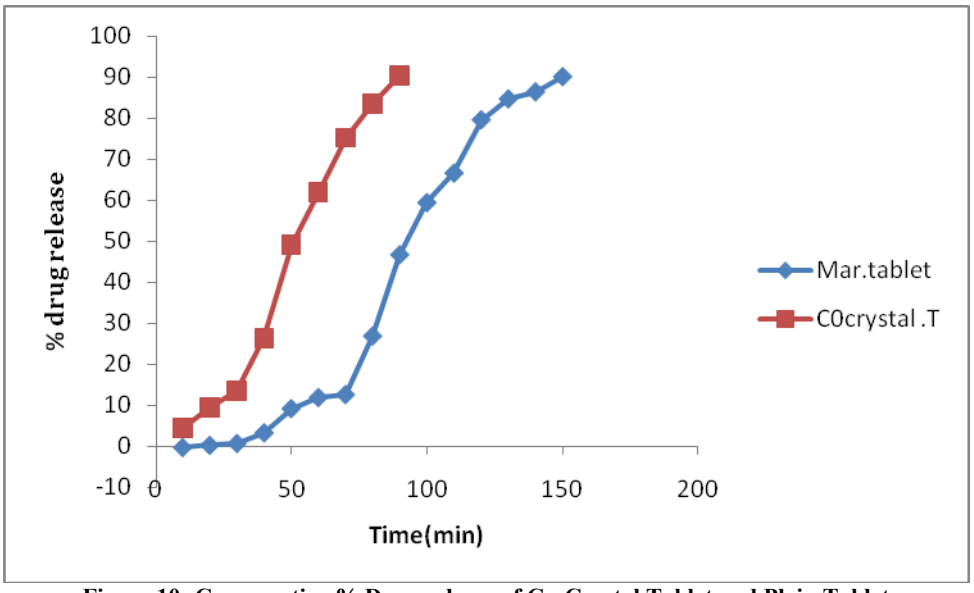

Figure 10: Comparative % Drug release of Co-Crystal Tablet and Plain Tablet

CONCLUSION

Aim & objectives of our research project is to enhance solubility of Efavirenz by preparing co crystals & formulation development of Efavirenz tablets, with effective Conformer Efavirenz co-crystallize with suitable Co-former such as Saccharine and Caffeine by solvent evaporation technique in 1:1 ratio. The prepared Co Crystal was characterized by DSC, IR, XRPD & other pharmaceutical properties like melting point, solubility etc. Prepared Efavirenz Co-crystals exhibited excellent physicochemical properties when compared with pure drug. Based on the FTIR analysis, it showed the shifting of characteristic bands of Efavirenz in the spectrum and there was no chemical reaction in Efavirenz co crystal. DSC, SEM study confirms that the third product which was form after co-crystallization, they are co-crystal with change in shape, size, habit, melting point. The X-Ray Powder Diffraction pattern shows peak reduced and confirm that the third product Co-crystal was formed. The co-crystal of Efavirenz with Saccharine in 1:1 stoichiometric ratio enhances the solubility up to 17 fold. So The Immediate release plain tablet of Efavirenz and its Saccharine co-crystal was prepared & evaluated for various post compression parameters. The tablets of Efavirenz-Saccharine cocrystal were successfully prepared by direct compression method which rapidly disintegrated and has higher quick 90.26% dissolution compared plain tablet of Efavirenz. Finally we concluded that solubility enhancement & formulation development of Efavirenz successfully completed

Conflict of Interest

The authors declare that they have no conflict of interest.

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