

Enhancement of Dissolution Properties of Efavirenz by Solid Dispersion Technique using Sylysia

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ABSTRACT

The objective of present study was to enhance the dissolution rate of Efavirenz(EFV) by using solid dispersion technique. Solid dispersions in water soluble carriers have attracted considerable interest as a means of improving the dissolution rate, and hence possibly bioavailability of a range of hydrophobic drugs. The poor solubility of Efavirenz leads to poor dissolution and hence variation in bioavailability. Efavirenz (EFV) is an antihuman immunodeficiency virus (antiHIV) drug that works by inhibiting the non-nucleoside reverse transcriptase of HIV and is used as a part of the highly active antiretroviral therapy. In the present investigation solid dispersions(SD) were prepared by employing different grades of silica gel(Sylysia). They were prepared by solvent evaporation and kneading method in two different mass ratios 1:1 and 1:2. Comparison of both methods was also investigated. Physicochemical characterisation of disperse systems was carried out using differential scanning calorimetry(DSC), X-ray diffraction(XRD), FTIR. Dissolution tests were conducted and evaluated on the basis of cumulative percentage drug release. The prepared solid dispersions were also evaluated for precompression parameters like angle of repose, bulk & tapped density, drug content, Carr's index and Hausner's ratio. Improved dissolution was observed in 1:1 ratio disperse system of kneading method compared to solvent evaporation method. Physicochemical characterisation results suggested that EFV existed in amorphous form in all dispersion systems which show that dissolution can be enhanced.

Keywords: Dissolution, efavirenz, kneading method, solvent evaporation, solid dispersions, sylysia

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INTRODUCTION

Oral route of drug administration is the most common method of drug delivery. For oral administration the drug must possess good solubility, however most of orally administered drugs have a reduced bioavailability due to poor solubility. In British Classification System (BCS) drugs with low aqueous solubility, slow dissolution rate, high dose and high permeability are categorised as Class-II drugs [1]. To overcome the low bioavailability solubility of drug can be enhanced either by particle size reduction, floating granules, cryogenic technology solid dispersions, nano suspension, micronization [2] etc.,

Solid dispersion is widely used technique to improve the bioavailability of poorly water soluble drugs [3]. In SD systems, a drug may exist as an amorphous form in polymeric carrier and this may result in improved dissolution rates and solubility compared with crystalline material. In SD's the hydrophobic drug is dispersed in a carrier matrix which is generally hydrophilic. It enhances solubility by reducing particle aggregation, eliminating crystallinity, increasing wettability, dispersability and altering the surface properties [4] of drug particles.

When SD is exposed to aqueous media the carrier dissolves and drug releases as fine

colloidal particles, the resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water soluble drugs.

In order to prepare solid dispersions, solvent evaporation [5-9] or kneading method is commonly adopted. Each method has its advantages and disadvantages. Solid method can be used for thermolabile drugs as minimal heat is required in the process.

In the present study the solid dispersion of EFV was prepared by employing Sylysia as carrier. Sylysia is an amorphous silica gel characterised by high purity and hygroscopicity which is used in pharmaceutical, nutraceutical, food and cosmetic industry. It is available in different grades. The nature of carriers used to prepare SD's typically influence the type of method employed.

Efavirenz (EFV) is an antihuman immunodeficiency virus (antiHIV) drug that works by inhibiting the non-nucleoside reverse transcriptase of HIV and is used as a part of the highly active antiretroviral therapy. EFV is freely soluble in methanol, but it is practically insoluble in water (4 µg/ml) and has a bioavailability of 40 to 45%, which makes it a suitable candidate for solid dispersion formulation [10,11].

In the present study SD's of EFV were prepared using solvent and kneading method with different grades of Sylysia as carrier. In order to characterize the physicochemical properties of solid dispersions the formulation were tested using DSC, XRD, FTIR.

MATERIALS & METHODS

Efavirenz(EFV) is a gift sample from Heterolabs, Hyd., India. Sylysia was procured from Fuji chemicals, Japan.

All other materials and reagents were of analytical grade.

Preparation of Solid Dispersions:

They were prepared with two different mass ratios 1:1 and 1:2 by solvent and kneading method.

Solvent Method: Solvent evaporation of drug (EFV): Carriers were prepared at two different mass ratios (1:1 and 1:2). EFV was dissolved in methanol to get clear solution. After that carrier (passed through sieve no. #80) was then added to clear drug solution and stirring. The solvent (methanol) was removed by evaporation technique (or) dried properly using Heating mantle at 45°C for 60min. The mass obtained was further dried at 50°C for 24hrs in an Hot air oven. The product was crushed, pulverized and passed through a sieve number # 80. The prepared/obtained product was then filled in glass bottles, sealed and stored in a desiccator until further use.

Kneading method: In Kneading method the drug (Efavirenz) and surface active carriers SYL 350 FCP, SYL 430, SYL 550 in the ratio of i.e. 1:1 and 1:2 were weighed accurately and triturated in a mortar and pestle by adding drop by drop of methanol for size reduction of the particles. This method was continued for nearly 45 min and made into dough like mass. The Kneaded dispersion was dried at 50°C for 24hrs in an Hot air oven. The product was crushed, pulverized and passed through a sieve number # 80. The prepared/obtained product was then filled in glass bottles, sealed and stored in a desiccator until further use. The data for composition of solid dispersions was given in (Table 1).

Table 1: Composition of EFV solid Dispersions

Solid dispersion composition	Method	Drug-carrier ratio	Formulation code
EFV:SYL 350 Fcp	Solvent evaporation method	1:1	SE I(1:1)
		1:2	SE I(1:2)
	Kneading method	1:1	KM I(1:1)
		1:2	KM I(1:2)
EFV:SYL 430	Solvent evaporation method	1:1	SE II(1:1)
		1:2	SE II(1:2)
	Kneading method	1:1	KM II(1:1)
		1:2	KM II(1:2)
EFV:SYL 550	Solvent evaporation	1:1	SE III(1:1)

method	1:2	SE III(1:2)
Kneading method	1:1	KM III(1:1)
	1:2	KM III(1:2)

Estimation of Efavirenz:

10 mg of Efavirenz was accurately weighed and transferred into 10 mL volumetric flask, dissolved in few ml of methanol and the final volume was made upto 10 mL with methanol to get a stock solution of concentration 1mg/ml. From stock solution further dilutions were made with SLS (2%w/v) medium to get the solution

ranging from 2 µg/mL to 10 µg/mL. The absorbances of these solutions were measured at 246 nm in UV-Visible Spectrophotometer (Elico SL 150). The absorbance was plotted against concentration of EFV as shown in (Table 2) and (Figure 1). The method obeyed Beer's law in the concentration of 2-10 µg/ml.

Table 2: Calibration curve data for the estimation of Efavirenz

S. No.	Concentration (µg/mL)	Absorbance (at 246 nm)
1	2	0.091
2	4	0.171
3	6	0.254
4	8	0.341
5	10	0.425

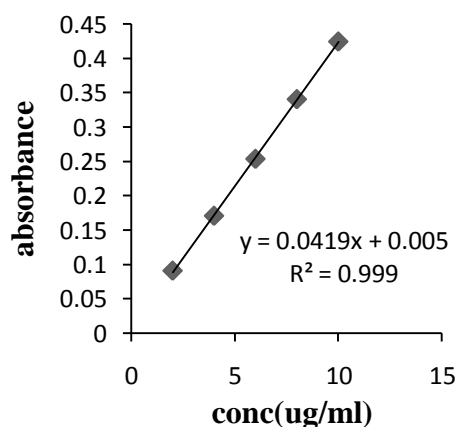


Figure 1: Standard Plot of Efavirenz

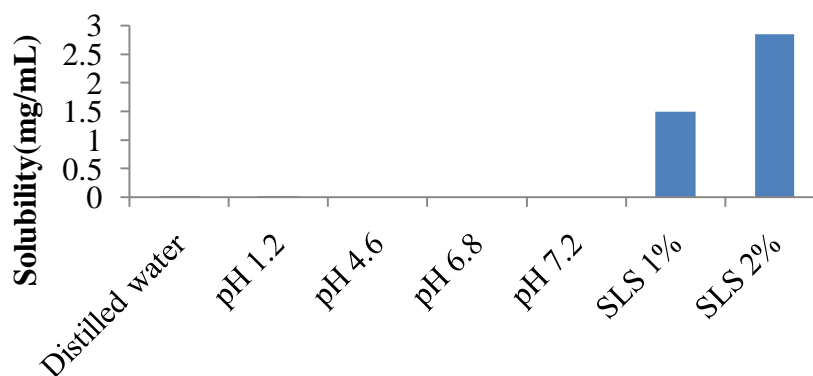
Solubility determination

Solubility studies were performed according to the method described by Higuchi and Connors [12]. An excess of Efavirenz was added to 5mL of each fluid in a 25 mL stoppered conical flasks and the mixture were shaken for 48 hrs at room temperature ($25 \pm 1^\circ\text{C}$) on a rotary flask shaker. After 48 hrs of shaking 1 mL

aliquots were withdrawn and filtered immediately using a 0.45μ nylon disc filter. The filtered samples were diluted suitably and assayed for drug measuring absorbance at 246 nm. Shaking was continued until three constructive estimations were same. The solubility experiments were run in triplicate. The results are given in (Table 3) and (Fig. 2).

Table 3: Solubility Analysis Data of EFV in Various Buffers

S no	Solution	Concentration (mg/mL)
1	Distilled water	.015
2	Ph 1.2 Buffer	.019
3	Ph 4.6 Buffer	.009
4	Ph 6.8 Buffer	.009
5	Ph 7.2 Buffer	.009
6	1% SLS Solution	1.50
7	2% SLS Solution	2.85

**Figure 2: Solubility Analysis Plot of EFV in various Solutions****Dissolution studies:**

The quantity of Solid Dispersion equivalent to 200 mg of EFV was placed in dissolution medium. The dissolution study of dispersion was conducted using dissolution testing apparatus II (paddle method) in 900 ml of 2%W/V SLS solution at $37 \pm 0.5^\circ\text{C}$ and at speed of 50 rpm. Aliquots of 5 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain volume after each sampling and analyzed Spectrophotometrically at 246 nm against suitable blank using UV-visible Spectrophotometer (Elico SL150).

Differential Scanning Calorimetry (DSC): Approximately 2 mg of EFV Solid Dispersion samples were taken in aluminium pan, sealed with aluminium cap and kept under nitrogen purging [13] (atmosphere). The samples were scanned from $30.0-300.0^\circ\text{C}$ with the scanning rate of 10.00°C rise/min using differential scanning calorimeter (DSC).

Powder X-Ray Diffraction studies (XRD):

The powder XRD of the Pure EFV and Solid Dispersions (EFV with SYL 430) was recorded using an X-ray Diffractometer using Cu radiation generated at 45 Kv and

40 mA and scanning rate was $2^\circ/\text{min}$ over a 2θ range of 10-40.

Fourier Transform Infrared spectroscopy (FT-IR):

Samples were analyzed using an ATR-FTIR spectrometer (Bruker, Germany). ATR spectra were measured over the wave number range of $4000-500\text{ cm}^{-1}$ at a resolution of 1.0 cm^{-1} . The powder or film sample is simply placed onto the ATR crystal and the sample spectrum is collected. The sample is then cleaned from the crystal surface and the accessory is ready to collect additional spectra.

Evaluation of Solid Dispersions:**Angle of Repose:**

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and horizontal plane.

The angle of repose was determined by funnel method suggested by Newman. Angle of repose is determined by following formula:

$$\tan \theta = \frac{h}{r}, \quad \theta = \tan^{-1} \frac{h}{r}$$

Where, θ = angle of repose,

h = height of the cone,

A funnel was fixed at a height of approximately of 2-4 cm over the platform. The sample was slowly passed along the wall of funnel, till the cone of the powder formed. Angle of repose was determined by measuring the height of the cone of powder and radius of the heap of the powder.

Bulk density (D_b):

It is the ration of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/mL and is given by

$$D_t = M/V_0$$

Where, M is the mass of powder

V_0 is the Bulk volume of the powder.

Tapped density (D_t):

Tapped density was determined by using graduated cylinder. An accurately weighed sample was carefully added to the graduated cylinder with the aid of funnel. The initial volume was noted and the sample was tapped on a horizontal base. Tapping was continued until no further reduction in sample volume was observed. Volume was noted and tapped density is calculated by using the following formula.

$$D_t = M/V_0$$

Where, M is the mass of powder

V_0 is the Bulk volume of the powder.

Carr's Index (I):

It indicates the ease with which a material can be induced to flow and powder compressibility. It is expressed in percentage and is given by

$$I = (D_t - D_b) / D_t \times 100$$

Where, D_t is the tapped density of the powder

D_b is the bulk density of the powder.

Where, D_t is the tapped density of the powder

D_b is the bulk density of the powder.

Compressibility Index and Hausner's ratio (H):

In recent years the compressibility index and the closely related Hausner's ratio have become the simple, fast, and popular

methods of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of the bulk density, size, shape, surface area, moisture content and cohesiveness of the materials. Both the compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of the powder.

$$\text{Compressibility Index} = (1 - V/V_0) \times 100$$

Where,

V = volume of powder blend before tap

V_0 = volume of powder blend after 100 tappings.

Hausner's ratio (H) is a number that is correlated to the flowability of a powder. The Hausner's ratio is related to the Carr's Index by the formula

$$H = 100 / (100 - C)$$

Hausner's ratio also expressed as,

$$H = D_t / D_b \text{ (or) Hausner's ratio} = \text{tapped density} / \text{bulk density}$$

Drug content:

An accurately weighed quantity of Solid Dispersions equivalent to 10mg of EFV, was taken into a 10 mL volumetric flask and dissolved in methanol and filtered through a Whatman No.1 filter paper (0.45 μ). The filtrates were diluted suitably with 2%W/V SLS solution. The content of EFV was determined Spectrophotometrically at 246 nm against suitable blank using UV-visible Spectrophotometer (Elico SL150).

RESULTS AND DISCUSSION

Dissolution data were evaluated on the basis of cumulative percent drug release which was plotted against time.

In Solvent Evaporation (SE II) dissolution study of EFV with SYL 430 in 1:1 ratio, the data showed that 85.41 \pm 2.25 % of drug was released within 20 minutes. The drug release in 1:2 ratio was found to be 69.72 \pm 3.24 % within 20 min. For initial periods of time for 5min, the drug release in 1:1 and 1:2 ratios was found to be 50.12 \pm 4.89 % and 43.39 \pm 4.21 % respectively this indicates that as the ratio of carrier is increased the dissolution is

decreased. 1:1 ratio attained complete dissolution within 30 min where as for 1:2 ratio it has taken 45min. The data is given in

(Table 4) dissolution profile in (Fig. 3 a), First order plot (Fig. 3b).

Table 4: Dissolution profiles of Efavirenz Solid Dispersion prepared by Solvent Evaporation method using SYL 430

TIME (min)	Mean % EFAVIRENZ released (x ± SD n=3)		
	PD	SE II (1:1)	SE II (1:2)
0	0	0	0
5	37.39±4.26	50.12±4.89	43.39±4.21
10	49.94±3.75	67.36±3.54	51.32±4.56
15	57.72±2.82	77.38±2.73	61.81±3.68
20	65.41±3.27	85.41±2.25	69.72±3.24
30	77.62±2.58	99.97±0.71	81.83±2.45
45	86.75±2.29		99.99±1.22
60	99.94±1.10		

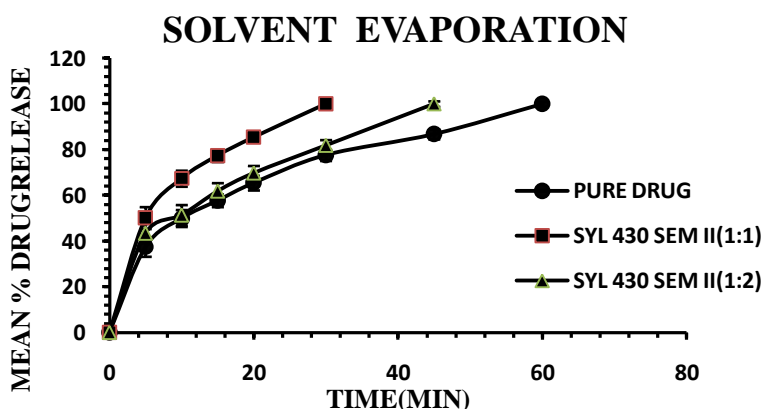


Figure 3 (a): Comparative *in-vivo* solution profiles of Efavirenz Solid Dispersions by Solvent Evaporation method using SYL 430 [SE-II (1:1), SE-II (1:2)] and Pure Drug (PD) (Mean ± SD., n=3)

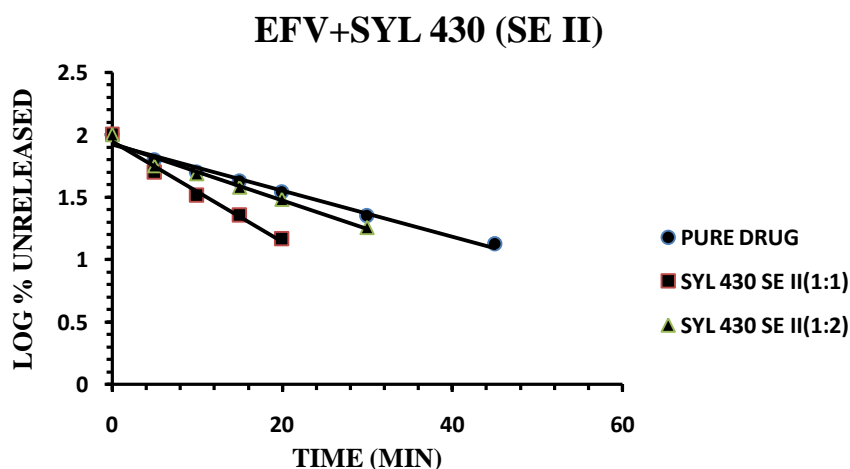


Figure: 3 (b): First order plot of Efavirenz dispersion by Solvent evaporation method using SYL 430 [SE- II (1:1), SE- II (1:2)] and Pure Drug (PD)

Kneading method (KM II) containing 1:1 molar ratios of drug and SYL 430 showed faster dissolution rate, about 100.10±1.25 % drug release was observed within 10 min. In 1:2 ratio only 45.46±2.72 of drug was released within 10 min, also in 1:2 ratio

100.12±0.95 % dissolution was obtained 60 min which indicates as the ratio of carrier is increased dissolution of drug is decreased. The dissolution data given in (Table 5), and shown dissolution profile in (Fig. 4 a), First order plot in (Fig. 4b).

Table 5: Dissolution profiles of Efavirenz Solid Dispersion prepared by Kneading method using SYL 430

TIME (min)	Mean % EFAVIRENZ released (x ± SD n=3)		
	PD	KM II (1:1)	KM II (1:2)
0	0	0	0
5	37.39±4.26	89.91±3.58	37.43±3.76
10	49.94±3.75	100.10±1.24	45.46±2.72
15	57.72±2.82		51.15±3.26
20	65.41±3.27		66.57±2.48
30	77.62±2.58		78.68±2.23
45	86.75±2.29		89.52±1.84
60	99.94±1.10		100.12±0.95

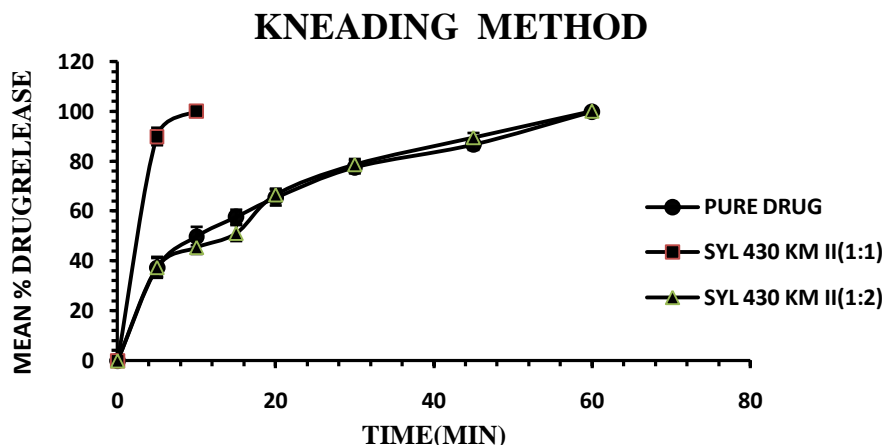


Figure 4 (a): Comparative *in-vitro* dissolution profiles of Efavirenz Solid Dispersions by Kneading method using SYL 430 [KM-II (1:1), KM-II (1:2)] and Pure Drug (PD) (Mean ± SD., n=3)

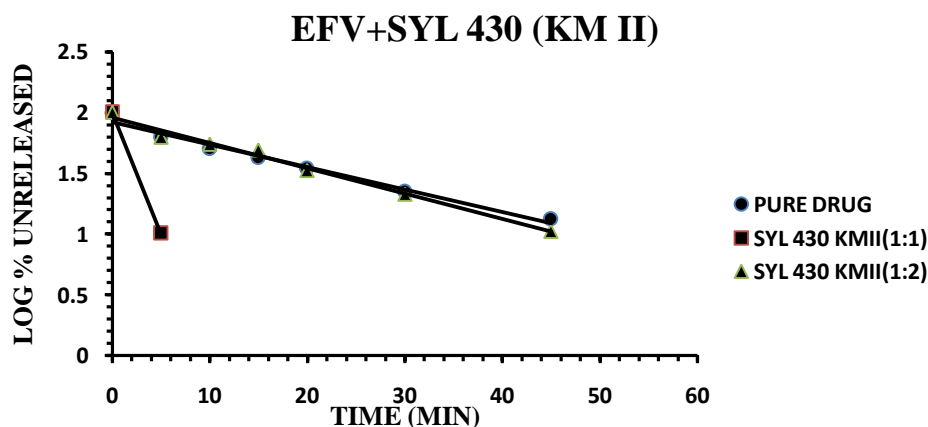


Figure 4(b): First order plot of Efavirenz dispersion by Kneading method using SYL 430 [KM-II (1:1), KM-II (1:2)] and Pure Drug (PD).

Solid dispersions prepared by 1:1 molar ratio by kneading method with different carriers showed increased drug release

compared to solvent method. The data was given in (Table 6) and (Figure 5).

Table 6: Dissolution profiles of Efavirenz Solid Dispersion prepared by Kneading method using SYL 430

TIME (min)	Mean % EFAVIRENZ released (x ± SD n=3)		
	PD	KM II (1:1)	KM II (1:2)
0	0	0	0
5	37.39±4.26	89.91±3.58	37.43±3.76
10	49.94±3.75	100.10±1.24	45.46±2.72
15	57.72±2.82		51.15±3.26
20	65.41±3.27		66.57±2.48
30	77.62±2.58		78.68±2.23
45	86.75±2.29		89.52±1.84
60	99.94±1.10		100.12±0.95

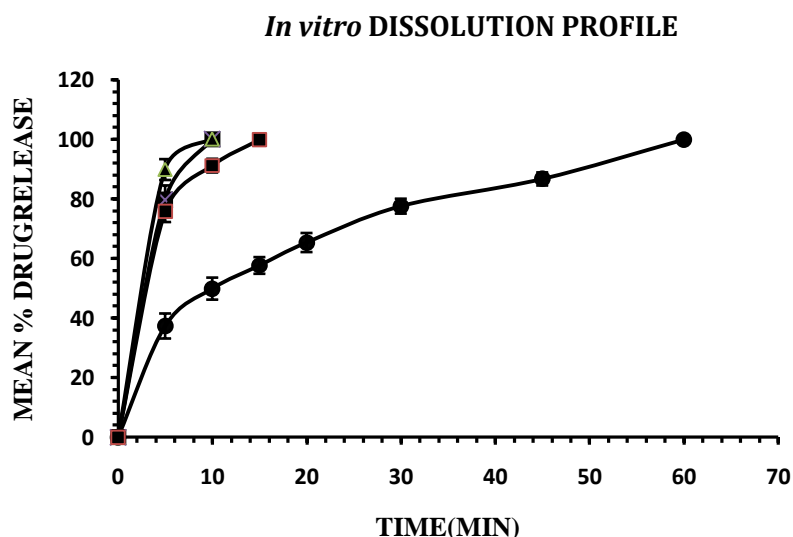


Figure 5: Comparative in-vitro dissolution profiles of Efavirenz Solid Dispersions (KM), SYL 430 KMI (1:1), SYL 430 KMII (1:1), SYL 430 KMIII (1:1)

In vitro dissolution studies were also carried for SD's prepared with two other carriers SYL350FCP and SYL550 but the release of drug slower compared to dispersions with SYL430.

The thermogram of Solid Dispersions showed a shift in the endothermic peaks of

both drug as well as polymer. This data suggests the complete amorphization of drug in the polymer. Moreover some degree of interaction was reported which was dictated by the shift in the endotherms to a lower value. The endothermic peak as shown in (Table 7) and (Fig. 6 a & b).

Table 7: Data for Differential Scanning calorimeter (DSC)

DSC	Pure Drug (FEV)	EFV:SYL 430 (KM 1:1)
Peak	140.0°C	137.8°C

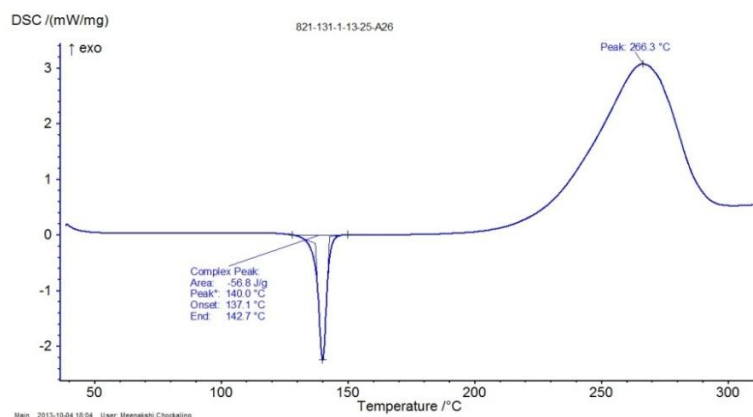


Figure 6 a: Differential Scanning Calorimetry (DSC) of Pure EFV

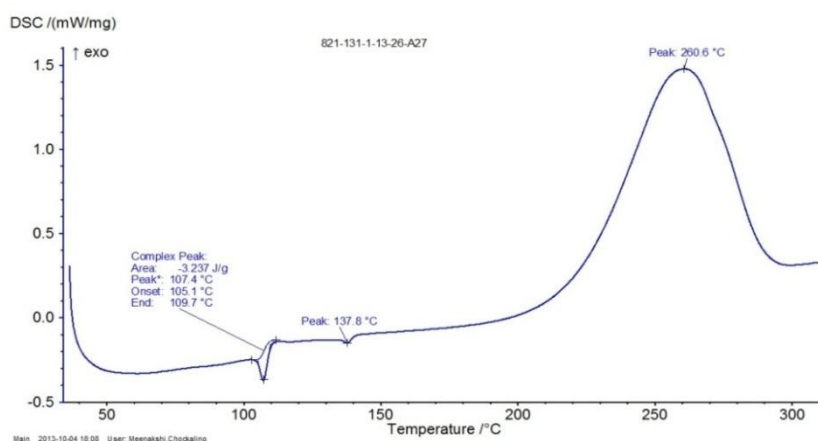


Figure 6 b: Differential Scanning Calorimetry (DSC) of EFV: SYL 430(1:1) Solid dispersion prepared by Kneading method

The diffraction spectrum of EFV showed that the drug was crystalline in nature as demonstrated by numerous peaks. The prominent peaks for Pure EFV were clearly seen at the same positions in Solid Dispersions but with decreased intensities. It has been observed that the diffraction

patterns of the Solid Dispersions are somewhat diffused compared to diffraction patterns of EFV. It also indicates that the crystallinity of the Solid Dispersions are less than that of the EFV. The XRD patterns of the Solid Dispersions prepared by EFV and EFV:SYL 430 are shown in (Fig. 7a & b).

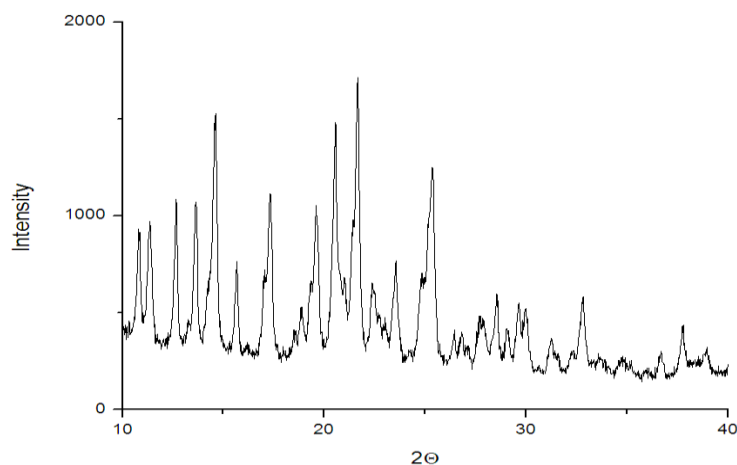


Figure 7 a: XRD pattern of Pure EFV

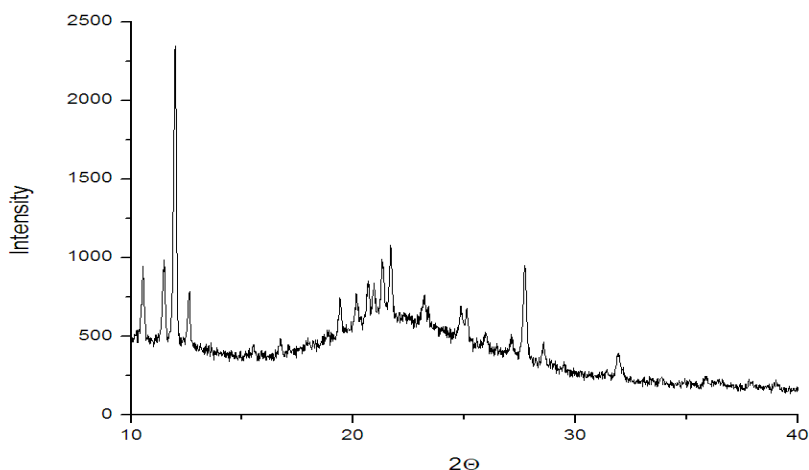


Figure 7 b: XRD pattern of EFV:SYL 430(1:1) SD Prepared by kneading method

Important vibrations detected in FT-IR spectra of pure EFV and drug with different carriers were due to bond stretching of

different functional groups like C=O,C-N,C-Cl&C-F and results were given in (Table 8) and shown in (Fig. 8 a-g).

Table 8: Compatibility studies for Solid Dispersions by FT-IR

2100-2250	Typical Exocyclic Triple bond Stretching	2249.41	2250.89	2251.08	2251.30
1700-1750	C=OStretching	1745.99	1745.84	1744.43	1741.90
1590-1660	C-N Stretching	1601.14	1602.47	1602.07	1601.93
1000-1400	C-F Stretching	1185.12	1184.59	1184.83	1184.77
600-800	C-CL Stretching	658.30	655.07	653.82	654.79

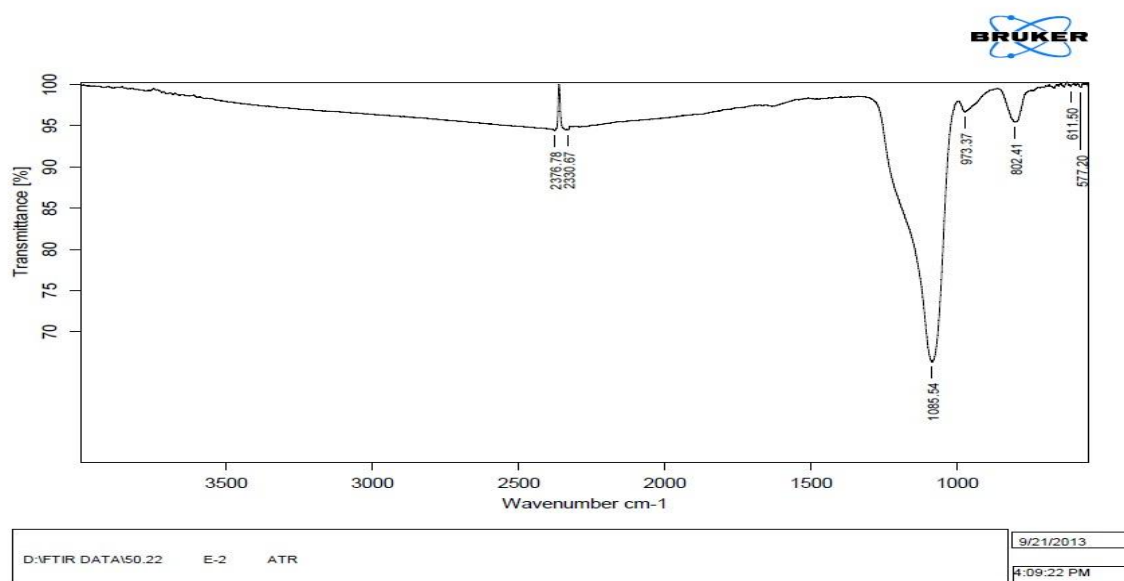


Figure 8 a: FT-IR spectra of Pure EFV (E-1)

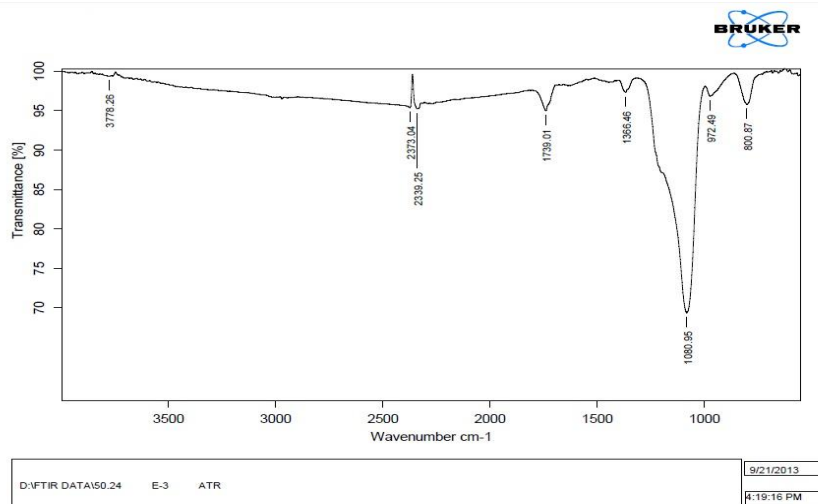


Figure 8 b: FT-IR spectra of Pure SYL 350 FCP (E-2)

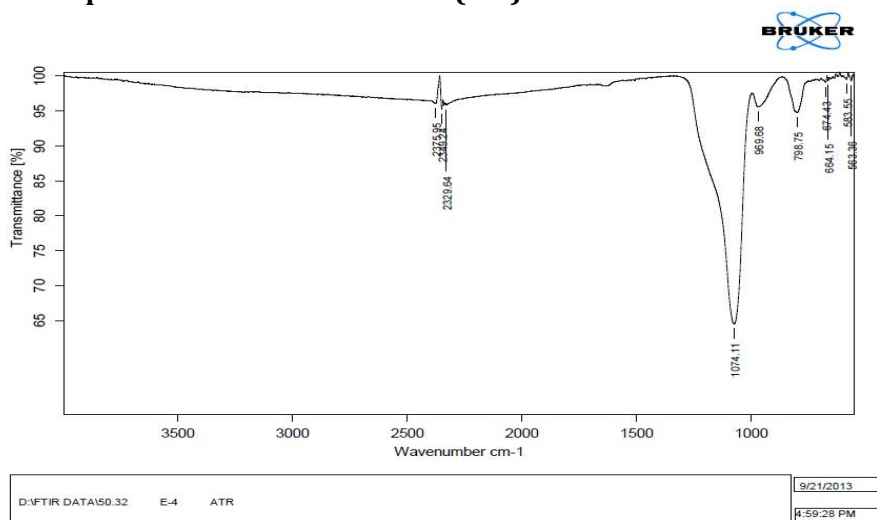


Figure 8 c: FT-IR spectra of Pure SYL 430 (E-3)

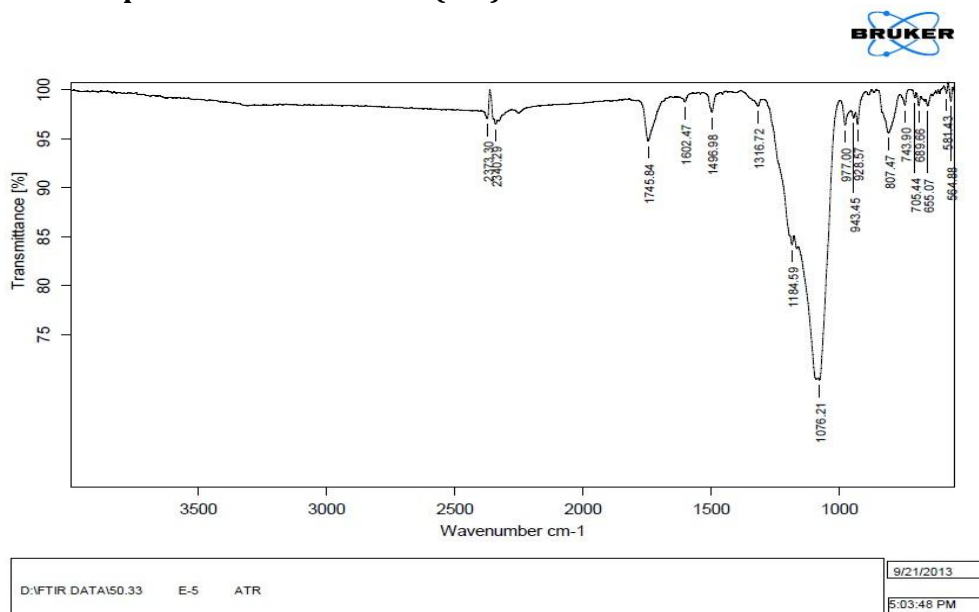


Figure 8 d: FT-IR spectra of Pure SYL 550 (E-4)

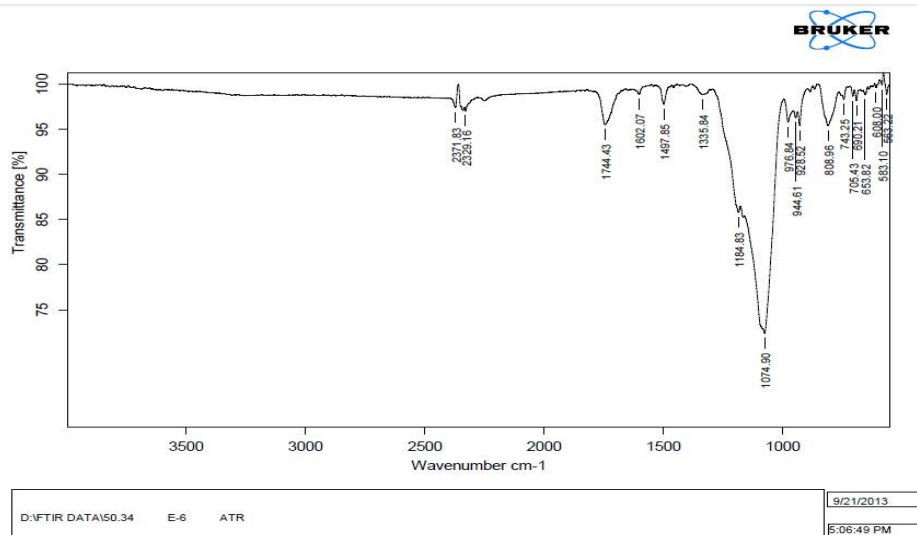


Figure 8 e: FT-IR spectra of Pure EFV with SYL 350 FCP (E-5)

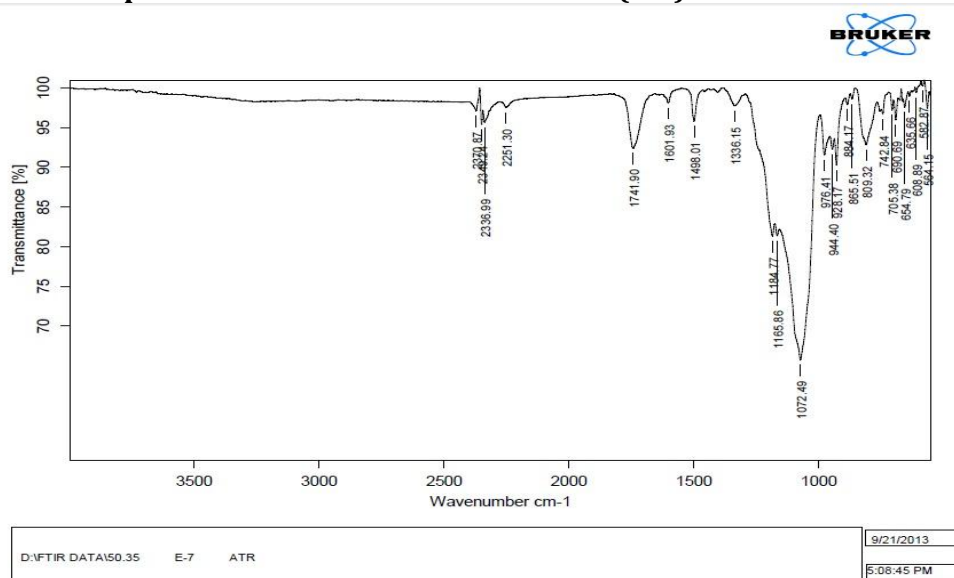


Figure 8 f: FT-IR spectra of Pure EFV with SYL 430 (E-6)

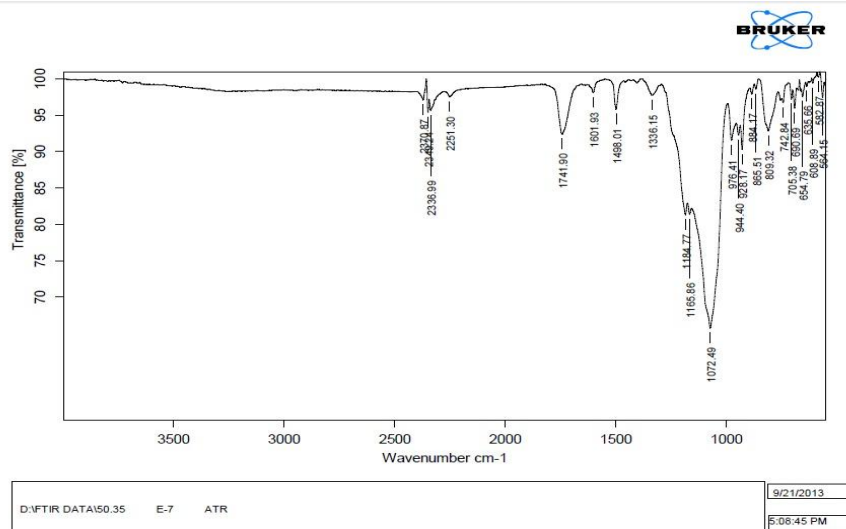


Figure 8 g: FT-IR spectra of Pure EFV with SYL 550 (E-7)

The solid dispersions were evaluated for physical properties like angle of repose,

bulk & tapped density, carr's index, hausner ratio and data was given in (Table 9-11).

Table 9: Physical Evaluation of Solid Dispersions EFV with SYL 350 FCP

PARAMETERS	Solvent Evaporation (SE)		Kneading Method (KM)	
	SE 1:1	SE 1:2	KM 1:1	KM 1:2
Angle of Repose (degrees)	22.66 ±0.16	21.45 ±0.33	26.02 ±0.02	26.28 ±0.31
Bulk density (g/cc)	0.78 ±0.32	0.77 ±0.24	0.93 ±0.44	0.92 ±0.67
Tapped density(g/cc)	0.96 ±0.21	0.95 ±0.54	1.01 ±0.05	0.99 ±0.21
Carr's Index (%)	18.64	15.25	9.72	8.65
Hausner's ratio	1.336	1.346	1.098	1.085
Flow comment	Good	Good	Excellent	Excellent
Drug content (%)	95.21±.058	95.36±.71	98.84±0.55	99.05±0.45

Table10: Physical Evaluation of Solid Dispersions EFV with SYL 430

PARAMETERS	Solvent Evaporation (SE)		Kneading method (KM)	
	SE 1:1	SE 1:2	KM 1:1	KM 1:2
Angle of Repose (degrees)	21.84 ±0.54	22.18 ±0.47	25.15 ±0.02	26.06 ±0.31
Bulk density (g/cc)	0.72 ±0.57	0.75 ±0.34	0.84 ±0.64	0.86 ±0.37
Tapped density(g/cc)	0.92 ±0.02	0.91 ±0.21	0.96 ±0.53	0.99 ±0.04
Carr's Index (%)	17.54	17.87	9.78	9.54
Hausner"s ratio	1.25	1.254	1.103	1.105
Flow comment	Good	Good	Excellent	Excellent
Drug content (%)	93.41±0.15	94.44±0.53	98.32±0.0.14	98.82±0.36

Table 11: Physical Evaluation of Solid Dispersions EFV with SYL 550

PARAMETERS	Solvent Evaporation (SE)		Kneading method (KM)	
	SE 1:1	SE 1:2	KM 1:1	KM 1:2
Angle of Repose (degrees)	20.74 ±0.12	20.86 ±0.48	26.22 ±0.92	25.50 ±0.42
Bulk density (g/cc)	0.72 ±0.84	0.74 ±0.24	0.83 ±0.56	0.85 ±0.24
Tapped density (g/cc)	0.92 ±0.10	0.92 ±0.52	0.95 ±0.21	0.96 ±0.05
Carr's Index (%)	18.54	18.09	9.42	9.45
Hausner"s ratio	1.156	1.21	1.042	1.021
Flow comment	Good	Good	Excellent	Excellent
Drug content (%)	92.45±0.55	94.01±0.76	97.74±0.26	98.34 ±0.56

CONCLUSION

From the above results it can be concluded that solid dispersions improved the dissolution rate of poorly soluble drug Efavirenz(EFV). 1:1 ratio kneaded systems showed better drug release compared to dispersions of solvent evaporation method. The DSC thermograms of solid dispersions showed a shift in endothermic peak compared to pure drug which indicates complete amorphization of drug in polymer. From the FTIR data it has been observed that there is no reaction between drug and the carrier when compared to pure drug.

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