

Formulation and Evaluation of Solid Dispersions of Efavirenz

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ABSTRACT

Efavirenz is an antiretroviral drug, a non-nucleoside reverse transcriptase inhibitor (NNRTI). It is employed in the management of HIV-1 infections. As efavirenz is poorly soluble it has low solubility and bioavailability to encounter and to enhance the drug's solubility and bioavailability solid dispersion technique is employed. The solubility is improved by solid dispersion and bioavailability of drugs that are poorly soluble, improves dissolution rates, stabilizes unstable compounds and enables controlled release formulations.

The goal of current investigation is to formulate and evaluate solid dispersion of efavirenz in different carrier combinations using PEG4000, Soluplus and HPMC E15 with ratios 1:1, 1:5 and 1:10 by employing the solvent evaporation method and fusion methods.

The formulated solid dispersions were subjected to pre formulation investigations, such as melting point, FT-IR and were assessed for in vitro drug release and characterized using DSC, XRD and SEM. The FT-IR showed no notable interactions between the pure efavirenz and carriers used. The in vitro drug release of all solid dispersions indicates improved dissolving rate when compared with efavirenz, the solid dispersion formulated by fusion method using PEG4000 and Soluplus as carriers (1:6:4 ratio) depicted higher dissolution rate of 70.8% in 90 mins and selected as optimized formulation. Physicochemical characterization results suggested that efavirenz existed in amorphous form providing evidence for improved dissolution.

KEYWORDS: Efavirenz, solid dispersions, solubility, PEG, HPMC E15, Soluplus, solvent evaporation method and fusion method.

I. INTRODUCTION

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) widely used in first-line antiretroviral therapy for the treatment of HIV-1 infection. It is a BCS Class II drug,

exhibiting low aqueous solubility and high permeability, where dissolution is the rate-limiting step for oral absorption^[1,2]. Efavirenz is commercially available as conventional tablets and capsules (200 mg and 600 mg); however, these marketed formulations show poor and variable dissolution profiles due to the drug's low intrinsic solubility (~9 µg/mL)^[3]. The poor solubility of efavirenz leads to inconsistent bioavailability and significant inter-patient variability. To achieve therapeutic plasma concentrations, higher doses are often required, which may result in dose-dependent adverse effects, particularly central nervous system-related side effects such as dizziness and insomnia^[4]. In addition, the absorption of efavirenz from conventional dosage forms is influenced by gastrointestinal factors such as food intake and pH, further limiting predictable drug release^[5].

Solid dispersion technology has been widely investigated as an effective approach to enhance the solubility and dissolution rate of poorly water-soluble drugs. By dispersing efavirenz in hydrophilic carriers, solid dispersions can reduce crystallinity, improve wettability, and enhance dissolution behavior, thereby improving oral bioavailability^[6,7]. Hence, the formulation of efavirenz as solid dispersions represents a promising strategy to overcome the limitations of marketed formulations.

The present study focuses on the formulation and evaluation of efavirenz solid dispersions with an objective to enhance the solubility and dissolution rate of efavirenz. Polymers PEG 4000, HPMC E15, and Soluplus were incorporated in varying combinations and ratios adopting solvent evaporation and fusion techniques. This approach facilitates comparison of the performance of different carrier systems and preparation methods.

II. MATERIALS AND METHODS

MATERIALS

Efavirenz was a gift sample from MYLAN Laboratories Ltd (Hyderabad), Soluplus was procured from BASF SE India Limited (Navi Mumbai, Thane, Maharashtra), HPMC E15 was procured from SPAN Chemie SC™, (Sky Industrial Estate, Waliv, Mumbai, Maharashtra), PEG 4000 was procured from SD Fine-Chem Limited, (Lower Parel, Mumbai, Maharashtra). All other materials and reagents used were of analytical grade.

ANALYSIS OF EFAVIRENZ

10 µg/ml of efavirenz in pH 6.8 phosphate buffer containing 0.2% SLS yielding a sample of concentration was scanned in UV double beam spectrophotometer in 200-400 nm wavelength range to determine its absorbance maxima. The absorbance of 8, 10, 12, 14, and 16 µg/mL concentrations was measured at determined wavelength and a graph was plotted taking concentrations on the x-axis and the respective absorbances on the y-axis to obtain linear equation $y = mx + c$.

PREFORMULATION STUDIES

a) Melting point of Efavirenz^[8]

The melting point of a sample was determined by using capillary tube method.

b) Fourier Transform Infrared spectrometry (FTIR)^[9]

IR interpretation was done to elucidate molecular interactions as well as the stability of drugs using Shimadzu FTIR AA-6300 Spectrometer. The Fourier spectrum of pure drug was compared with the reference spectra of efavirenz within the range of 4000cm^{-1} to 400cm^{-1} .

PREPARATION OF SOLID DISPERSIONS OF EFAVIRENZ

i. SOLVENT EVAPORATION METHOD

Efavirenz together with polymeric carriers were dissolved in ethanol. The resulting solution was allowed to solidify by keeping it at room temperature ($37^\circ\text{C} \pm 0.5$) for 24 hrs. The solid residue thus obtained was ground, sieved and stored in desiccator for future use^[10].

ii. FUSION METHOD

Efavirenz was added to molten mixture of carriers and then rapidly cooled on an ice bath for 2 hrs. The resulting solid mixture was ground, sieved and stored in desiccator for future use^[11].

Table 1: Composition of solid dispersions of Efavirenz by solvent evaporation and fusion methods.

INGREDIENTS (mg)	#SD1/ *FD10 (1:1)	#SD2/ *FD11 (1:1)	#SD3/ *FD12 (1:1)	#SD4/ *FD13 (1:5)	#SD5/ *FD14 (1:5)	#SD6/ *FD15 (1:5)	#SD7/ *FD16 (1:10)	#SD8/ *FD17 (1:10)	#SD9/ *FD18 (1:10)
EFAVIRENZ	200	200	200	200	200	200	200	200	200
SOLUPLUS	100	100	-	600	600	-	1200	1200	-
PEG 4000	100	-	100	400	-	400	800	-	800
HPMC E15	-	100	100	-	400	600	-	800	1200

#SD: dispersions prepared by solvent evaporation method; *FD: dispersions prepared by fusion method

III. EVALUATION OF SOLID DISPERSIONS OF EFAVIRENZ

a. Drug content^[12]

Accurately weighed solid dispersion equivalent to 10 mg of efavirenz was transferred into a 10 ml volumetric flask containing an appropriate quantity of methanol. The mixture was sonicated for 15–20 min to ensure complete extraction of the drug from the polymeric matrix and the volume

was made up to the mark with methanol. The resulting solution was filtered through Whatman filter paper No. 1, and suitable dilutions were prepared. The absorbance of the diluted solution was measured at 247 nm using a UV-visible spectrophotometer against methanol as blank and percentage drug content calculated using the formula

$$\% \text{ Drug content} = \frac{\text{Amount of drug estimated}}{\text{Theoretical amount of drug}} \times 100$$

b. in vitro dissolution study^[13]

Solid dispersions were evaluated for in vitro cumulative percent drug release. The study was conducted using USP Type II (paddle) dissolution apparatus containing 900 mL of pH 6.8 phosphate buffer with 0.2% (w/v) SLS, maintained at $37 \pm 0.5^\circ\text{C}$, stirred at 50 rpm. At each 15 minute time intervals, 5 mL aliquots were withdrawn and same volume was replaced to maintain sink conditions. The absorbance of the aliquots was measured at 282 nm.

IV. CHARACTERIZATION OF SOLID DISPERSIONS OF EFAVIRENZ

1. Powder X-ray Diffraction (PXRD)^[14]

PXRD investigations were conducted using a Shimadzu X-ray diffractometer to determine the crystalline characteristics of the prepared solid dispersions. In this technique, X-rays were focused on the sample, and the resulting diffraction patterns were recorded. The position and intensity of the diffracted peaks provide information regarding the degree of crystallinity and atomic arrangement within the crystal lattice.

2. Scanning electron microscopy (SEM)^[15]

The surface morphology of the solid dispersions was analysed using SEM. The samples were affixed onto brass stubs with double-sided adhesive tape and coated with a thin layer of gold under vacuum using a sputter coater. The surface features of the samples were then examined at magnification of 100x.

3. Differential Scanning Calorimetry (DSC)^[16]

DSC study was conducted to evaluate thermal behaviour of efavirenz and prepared solid dispersions. Accurately weighed samples (5-10 mg) were placed in aluminium pans, hermetically sealed and an empty sealed pan served as the reference. The samples were heated at a constant rate of 10°C per minute under a nitrogen atmosphere. The resulting thermograms were interpreted to determine the melting points, enthalpy changes, and possible interactions, providing insights into the degree of crystallinity or amorphous transformation.

V. RESULTS AND DISCUSSION

Absorbance maxima of efavirenz

The UV spectrum obtained on scanning the sample solution using a double beam uv spectrophotometer is indicated in figure:1

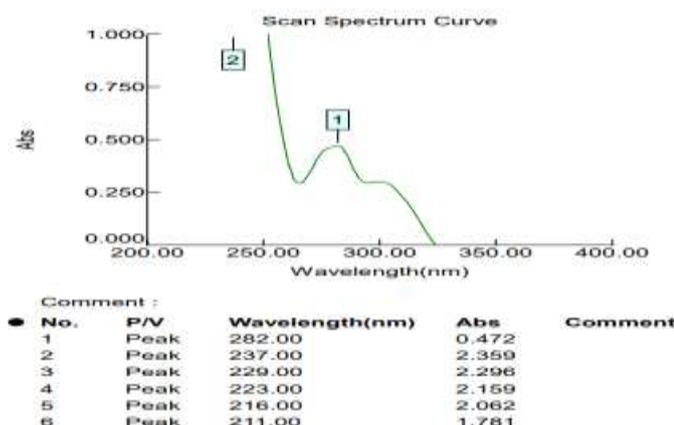


Figure:1 UV Spectrum of efavirenz

Absorption maxima of efavirenz in pH 6.8 phosphate buffer with 0.2% SLS is 282nm.

Calibration curve of efavirenz

Absorbance of 8, 10, 12, 14, and 16 µg/mL dilutions prepared in pH 6.8 phosphate buffer with

0.2% SLS was examined at 282 nm. Regression value of 0.9927 obtained indicated a linear relationship between concentration and absorbance. Figure: 2 is the calibration curve plotted taking concentration on x-axis and corresponding absorbance values on y-axis.

calibration curve of EFV in pH 6.8 phosphate buffer with 0.2% SLS

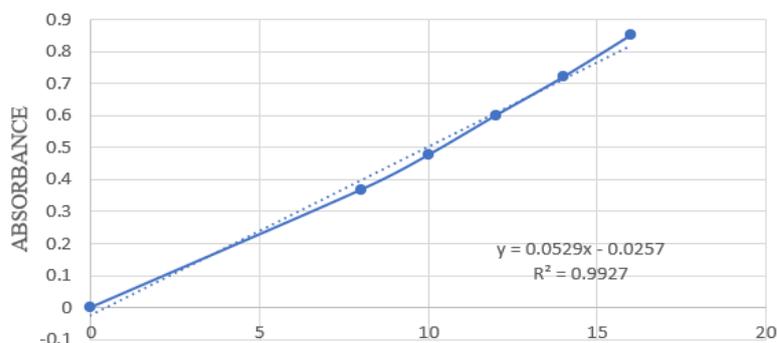


Figure:2 calibration curve of efavirenz in pH 6.8 phosphate buffer with 0.2% SLS

Linear equation obtained $y=0.0529x-0.0257$ is used to calculate drug release profile of the prepared dispersions.

PREFORMULATION STUDIES

a) Melting point of efavirenz

Melting point determined by capillary tube method was found to be 140°C which complied with the reference data.

b) Fourier Transform Infrared spectrometry (FT-IR)

The stability of efavirenz and the presence of any intermolecular interactions were determined using Fourier transform infrared spectroscopy. The FTIR spectrum of **pure efavirenz** was recorded in the range of **4000–400 cm⁻¹** to identify its characteristic functional groups and confirm drug purity.

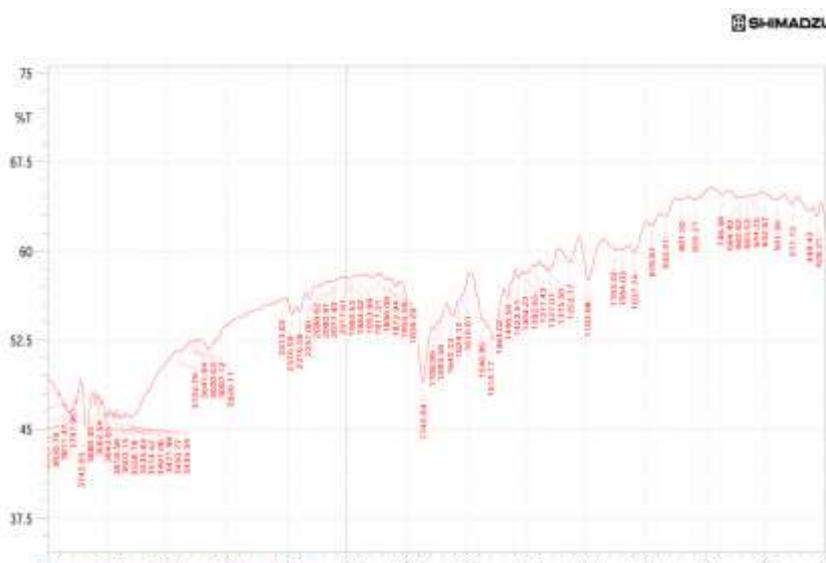


Figure:3FTIR spectra of Efavirenz

The FTIR spectrum of pure efavirenz exhibited characteristic peaks at 2250 cm⁻¹ (C≡C stretching), 1748 cm⁻¹ (C=O stretching), 1645 cm⁻¹ (C=C stretching), and 1111 cm⁻¹ (C–F/C–C

vibrations). These bands confirm the presence of major functional groups of efavirenz. The absence of additional or shifted peaks indicates the purity and chemical integrity of the drug.

EVALUATION OF SOLID DISPERSIONS OF EFAVIRENZ

a. Drug content

Formulation code	Drug content (%)	Formulation code	Drug content (%)
SD1	81.26	FD10	84.99
SD2	89.71	FD11	90.23
SD3	86.68	FD12	89.78
SD4	84.97	FD13	91.96
SD5	87.54	FD14	93.36
SD6	88.28	FD15	92.87
SD7	91.47	FD16	99.75
SD8	96.36	FD17	98.21
SD9	94.19	FD18	95.81

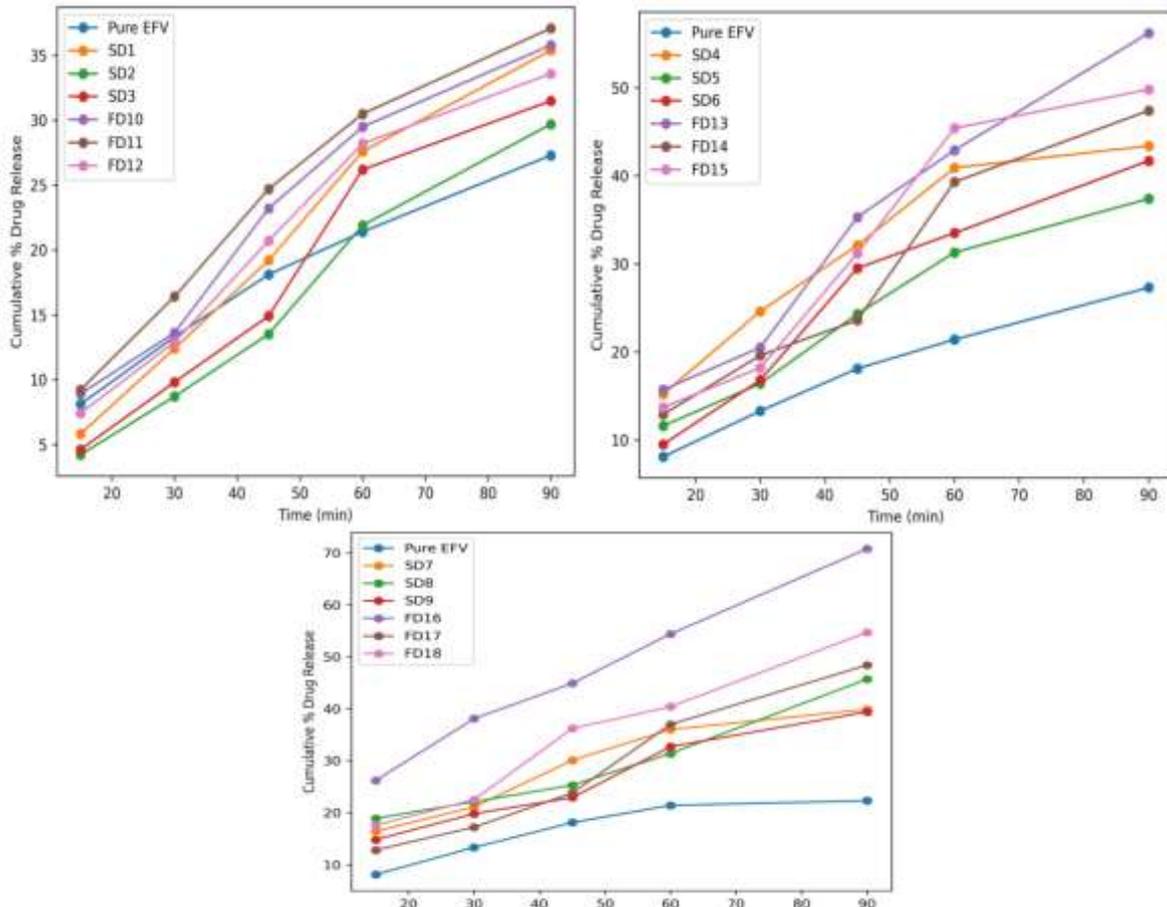
Table:2 percentage drug content of solid dispersions prepared by solvent evaporation and fusion method

The percentage drug content of solid dispersions prepared by solvent evaporation method demonstrated to be in the range of 81.26%(SD1) to 96.36%(SD8) while the solid dispersions prepared by fusion method demonstrated to be in the range of 84.99%(FD10) to 99.75%(FD16). The solid dispersions prepared by fusion method were superior when compared with solid dispersions prepared by solvent evaporation

method, the formulation FD16 had highest drug content of 99.75% confirming uniform dispersion of drug in polymeric inert carrier matrix.

b. In vitro dissolution studies

The % Cumulative Drug release of efavirenz and solid dispersions prepared using solvent evaporation method and fusion method are demonstrated below.



The in-vitro dissolution data from the above graphs demonstrated that all efavirenz solid dispersions exhibited significantly higher cumulative drug release compared to pure efavirenz, indicating successful enhancement of dissolution characteristics. In solid dispersions prepared by the **solvent evaporation method**, an increase in drug release was observed with increasing carrier concentration. Among these, formulations with a **1:10 drug-to-carrier ratio (SD7–SD9)** showed superior performance, with **SD8** achieving the highest cumulative drug release of **45.7% in 90 min**, which may be attributed to improved wettability and partial reduction in drug crystallinity.

Solid dispersions prepared by the **fusion method** showed a comparatively greater enhancement in drug release than those prepared by

solvent evaporation. The **1:10 formulation FD16** exhibited the maximum cumulative drug release (**70.8% in 90 min**), suggesting more efficient drug dispersion and possible conversion of efavirenz into an amorphous form during the fusion process. Overall, the results confirm that **higher carrier ratios and the fusion technique** play a crucial role in enhancing the dissolution profile of efavirenz.

VI. CHARACTERIZATION OF SOLID DISPERSIONS OF EFAVIRENZ

1. Powder X-Ray diffraction (PXRD)

XRD was used to validate the crystalline state of solid dispersions. Pure efavirenz and solid dispersion of optimized formulation are the samples utilized for measurement.

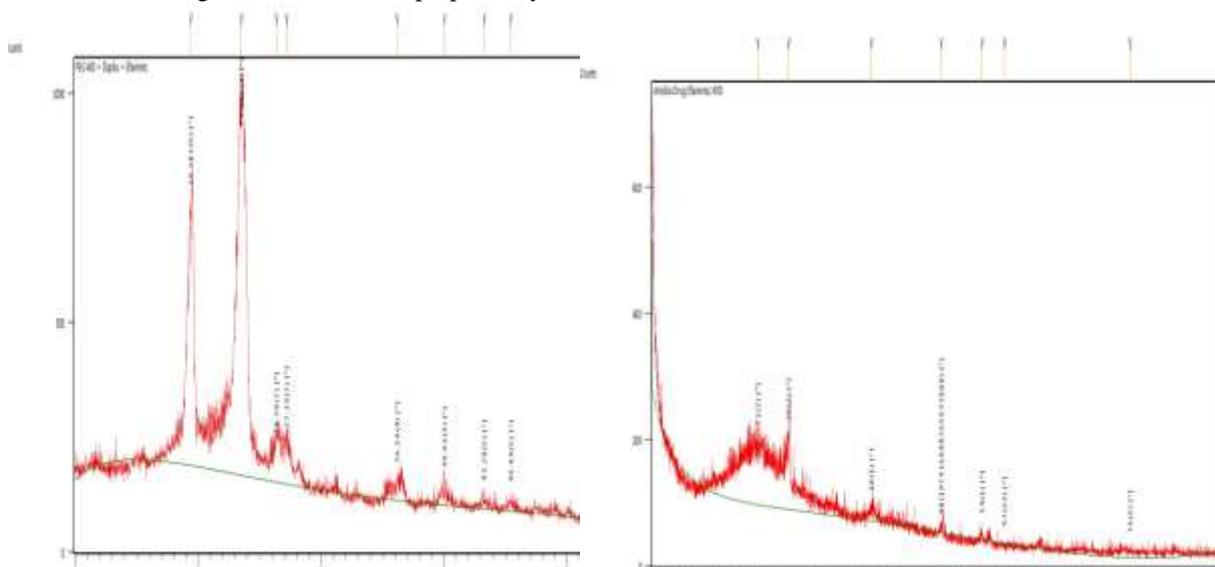


Figure:5(a) X-Ray diffraction patterns of pure EFV, 5(b) X-Ray diffraction patterns of Solid dispersion

The pure efavirenz exhibits distinct sharp peaks, confirming its crystalline form. In contrast, the solid dispersion of Efavirenz with PEG 4000 and Soluplus shows a marked reduction or disappearance of these peaks, indicating transformation from crystalline to an amorphous form.

2. Scanning electron microscopy (SEM)

SEM images of the efavirenz solid dispersion prepared with PEG 4000 and Soluplus showed irregular, rough-surfaced particles with agglomerated structures. The absence of well-defined crystalline drug particles indicates reduced crystallinity and uniform dispersion of efavirenz within the polymeric matrix.

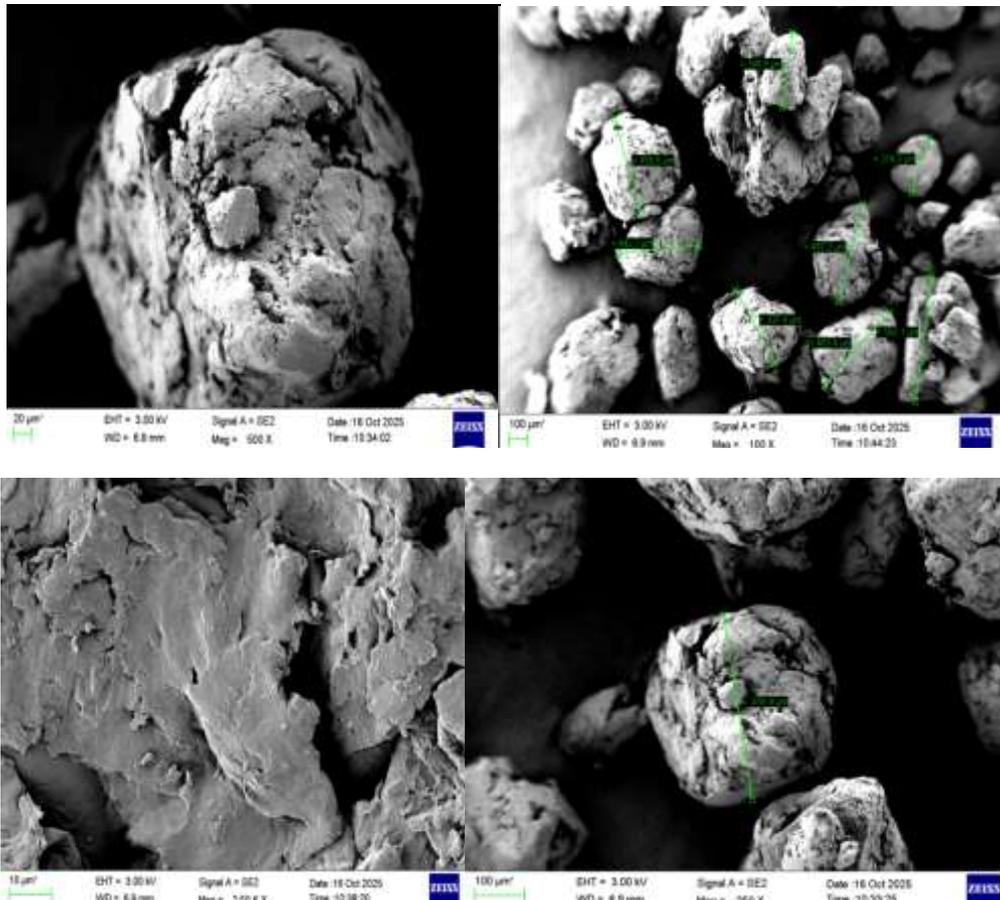


Figure6:SEM images of solid dispersion of Efavirenz with PEG4000 and Soluplus

3. Differential Scanning Calorimetry (DSC)

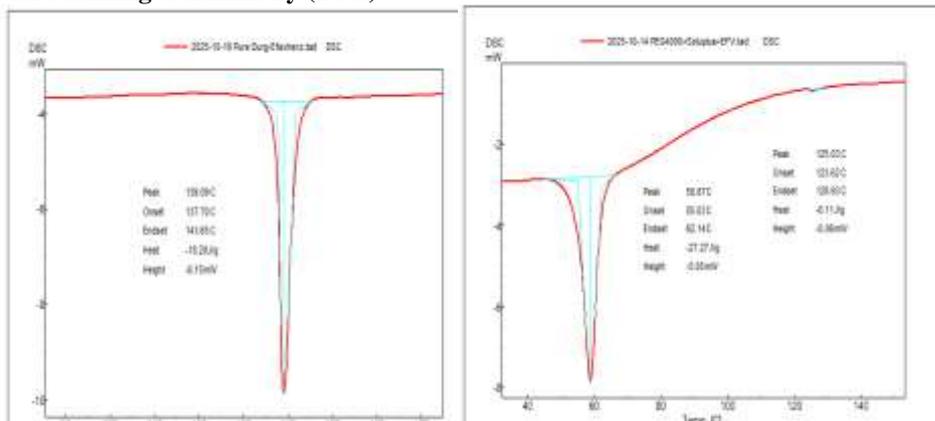


Figure:7(a) DSC thermogram of pure efavirenz, 7(b) DSC thermogram of solid dispersion

Differential scanning calorimetry was carried out to evaluate the thermal behaviour and physical state of efavirenz in its pure form and in the prepared solid dispersion. The DSC thermogram of pure efavirenz showed a sharp endothermic peak at approximately **139 °C**,

corresponding to its melting point, which confirms the crystalline nature of the drug. In contrast, the solid dispersion of efavirenz prepared with PEG 4000 and Soluplus exhibited a broadened and less intense endothermic peak with a noticeable reduction in enthalpy of fusion. The attenuation and

shift of the drug melting endotherm indicate a significant reduction in crystallinity and suggest the transformation of efavirenz into an amorphous or molecularly dispersed form within the polymeric

matrix. These results support the enhanced dissolution characteristics observed for the solid dispersion formulations.

4. Fourier Transform Infrared spectrometry (FT-IR)

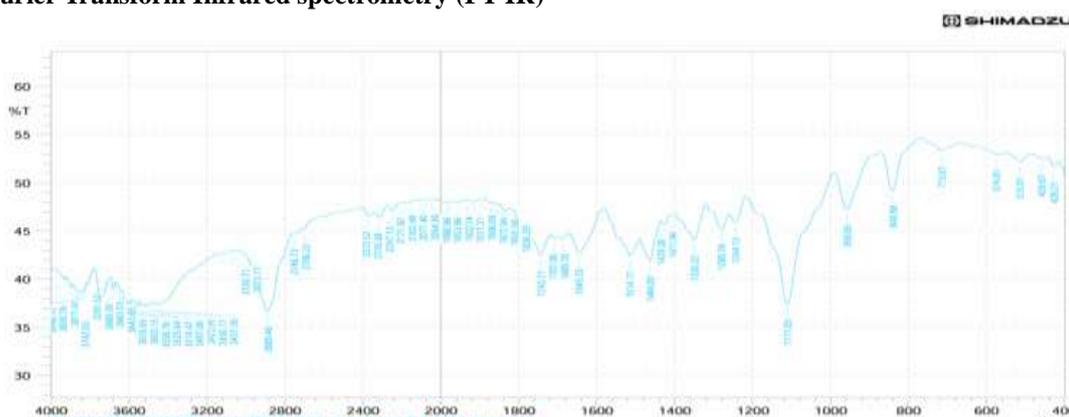


Figure 8: FTIR spectra of solid dispersion of EFV with PEG 4000 and Soluplus (1:10ratio).

S.NO	Wave number (cm-1) of Pure drug	Wave number (cm-1) of solid dispersion	Functional group
1.	2251.00	2247.15	C≡C stretching
2.	1743.71	1743.71	C=O stretching
3.	1645.33	1645.33	C=C stretching
4.	1111.03	1111.03	C-F & C=C vibration

Table 3: data of wave number and functional groups of pure drug and solid dispersion of EFV with PEG 4000 and Soluplus (1:10 ratio).

The FTIR spectra of **pure efavirenz** and its **solid dispersion with PEG 4000 and Soluplus (1:10 ratio)** were compared to evaluate possible drug–excipient interactions and to confirm the chemical stability of the drug after formulation. Pure efavirenz exhibited characteristic absorption bands as described in the above table, these peaks confirm the presence of the major functional groups of efavirenz and are consistent with reported literature values. In the **solid dispersion**, the characteristic peaks of efavirenz were retained. Only minor shifts in peak positions and changes in peak intensity were observed. These variations can be attributed to physical interactions such as hydrogen bonding between efavirenz and the polymeric carriers (PEG 4000 and Soluplus), rather than chemical incompatibility. Importantly, no new peaks, disappearance of characteristic peaks, or significant band broadening were detected in the solid dispersion spectrum. This indicates the absence of chemical interaction between efavirenz and the excipients.

The FTIR study confirms that efavirenz remains **chemically intact** in the solid dispersion system. The observed spectral similarity between pure drug and solid dispersion suggests **good compatibility** with PEG 4000 and Soluplus, supporting the suitability of these carriers for solid dispersion formulation aimed at improving solubility and dissolution behavior.

VII. SUMMARY AND CONCLUSION

Efavirenz, a BCS class II antiretroviral drug having poor aqueous solubility, was successfully formulated as solid dispersions using PEG 4000, Soluplus, and HPMC E15 by solvent evaporation and fusion methods. The dissolution enhancement observed for efavirenz solid dispersions in the present study is in good agreement with previously reported literature. Several experimental studies have demonstrated that efavirenz solid dispersions prepared using hydrophilic carriers such as PEGs and Soluplus significantly improve drug solubility and dissolution behaviour compared with the

crystallinedrug^[17,18]. Spray-dried amorphous solid dispersions of efavirenz with Soluplus at higher drug-to-polymer ratios (1:10–1:15) have been reported to achieve dissolution exceeding 90%, which has been attributed to complete amorphization, reduced particle size, and enhanced drug–polymer miscibility^[19,20]. In contrast, PEG-based solid dispersions prepared by fusion or solvent-evaporation techniques generally exhibit dissolution enhancement in the range of 70–95%, depending on PEG grade, polymer concentration, and processing conditions^[21,22]. The maximum drug release of 70.8% obtained in the present study using a PEG 4000–Soluplus binary carrier system is comparable to similar solvent-evaporated and melt-processed formulations reported earlier. Furthermore, reduced crystallinity confirmed by XRD and DSC, along with the rough and irregular surface morphology observed by SEM, supports the dissolution enhancement mechanisms described in earlier efavirenz solid dispersion studies^(23,24).

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