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SOLUBILITY ENHANCEMENT OF PROMINENT DRUG EFAVIRENZ BY PEG

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Abstract: In the case of BSC Class-II drugs, solubility is always a problem because of their lipophilic nature. To solve this pharmaceutical problem there are several ways but solid dispersion is the most promising one. Here Efavirenz was taken for increasing solubility. For this, we used PEG 4000, PEG8000 and PEG 20000 hydrophilic polymers in a 1: 0.5, 1: 1, 1: 1.5, 1: 2 and 1: 2.5 ratio by two techniques. The first technique was hot melt extrusion. Whereas the second one was lyophilization. The result came from dissolution and the result of DSC and FTIR also shows the same result.

Keywords: Efavirenz, PEG, BSC, hot melt extrusion, lyophilization.

INTRODUCTION

In the case of lipophilic drugs solubility is always a problem.[1] To solve this problem there are several ways. But finding the best one is very difficult. Because numerous factors influence API like required dose, shelf life, and manufacturability[2]. According to recent researches 75% of important drug candidates had poor solubility, and simultaneously, about 40% of marketed drugs are poorly soluble3. From this, it is quite clear that solubility enhancement is a major problem in the path of drug development[5].

BCS means Biopharmaceutics Classification System. Which is a basic method to identify the solubility and permeability of a drug. According to FDA, the Biopharmaceutics Classification system is a tool to know intestinal drug absorption. which was given by Dr. Gordon Amidon. Who was presented with a Distinguished Science Award in August 2006 by FIP.[1] In the BCS system drug can be classified into 4 groups BCS Class-I, BCS Class II, BCS Class III, and BCS Class IV drugs. BCS Class-I drugs are highly soluble and highly permeable. Like that BCS Class II drugs are low soluble and highly permeable. BCS Class III drugs are highly soluble but low permeable. While BCS Class-IV drugs are both low soluble and low permeable.[6]

All these approaches are based on the aqueous solubility of the drug and the permeation of the drug through the gastrointestinal tract and the classification system is based on Fick's first law.[7]

Here we increased the bioavailability of Efavirenz by PEG. Which is a BCS class II drug used to treat HIV infection. In the case of class II substances, the bioavailability of a poorly soluble drug may be enhanced by increasing its solubility and dissolution rate in the gastrointestinal fluids[8].

There are numerous methods for enhancement of solubility but Solid dispersion is the most promising method. Solid dispersion means dispersing the API or APIs in water-soluble carriers.

a) Preparation of Solid Dispersions by Physical Mixing:

The solid dispersions (SDs) of efavirenz with various hydrophilic polymers (PEG 4000, 8000, 20000) were meticulously formulated through the physical mixing method. Precise amounts of the drug and hydrophilic polymers were combined in a glass mortar and pestle, subjected to mixing for 5-10 minutes. To ensure a thorough and homogeneous blend, the mixtures underwent three cycles of passing through a 40-mesh sieve, following initial triturating in the glass mortar. Subsequently, the resulting formulations were carefully stored in screw-cap vials at room temperature for subsequent investigations.[9,11]

b) Preparation of Solid Dispersions by Melt/Fusion Method:

Solid dispersions of efavirenz with hydrophilic polymers (PEG 4000, 8000, 20000) at various weight ratios were created using the melt/fusion method. In this process, predetermined quantities of the drug and polymers were melted in a beaker using a heating mantle. Rapid cooling was achieved by placing the beaker in an ice bath for 5-10 minutes, leading to solidification. The dried mixture was then left undisturbed for 48 hours in a desiccator containing anhydrous CaCl2 for moisture removal. After sieving through a 40-mesh sieve, the formulations were securely stored in screw-cap vials at room temperature for further analysis.[10]

c) Preparation of Solid Dispersions by Solvent Evaporation Method:

Solid dispersions of efavirenz with hydrophilic polymers (PEG 4000, 8000, 20000) at different weight ratios were prepared using the solvent evaporation technique. In this method, the drug and hydrophilic carriers were dissolved in ethanol in a beaker. The solvent was allowed to evaporate, and the resulting dried mixture was kept in a desiccator with anhydrous CaCl2 for 48 hours to ensure complete removal of solvent and moisture. Following sieving through a 40-mesh sieve, the formulations were stored in screw-cap vials at room temperature for subsequent investigations.Evaluation of prepared drug-carrier solid dispersions:[10]

a) Drug content study (assay) of the solid dispersions: By UV- Vis spectroscopy at 248 nm all the prepared solid dispersions were evaluated

b) In vitro drug release studies: The dissolution studies for both the drug and drug-carrier formulations were conducted using an 8-station dissolution test apparatus (USP Type 2) equipped with a paddle rotating at a speed of 50 rpm. The dissolution medium, consisting of 900 ml of 0.5% SLS (Sodium Lauryl Sulfate) solution, was maintained at a temperature of 37 ± 0.5 ºC to mimic physiological conditions.

Throughout the study, at predetermined time intervals, an aliquot of the dissolution medium was withdrawn, and an equivalent volume of fresh medium was added to maintain sink conditions. The withdrawn samples were then assayed for the amount of drug using a UV-Visible spectrophotometer at a wavelength of 248 nm, with 0.5% SLS serving as the blank. [11]

All experiments were conducted in triplicate to ensure reliability, and the average readings were recorded. This comprehensive dissolution study provides valuable insights into the release kinetics and performance of both the drug and its carrier formulations under simulated physiological conditions, facilitating a thorough understanding of their dissolution behavior.

c) Fourier transform infrared spectroscopy (FTIR): The drug-carrier binary mixtures of efavirenz were meticulously prepared and transformed into KBr discs for Fourier Transform Infrared (FTIR) spectroscopy analysis. These discs were subjected to scanning across a spectral range from 4000 cm^{-1} to 400 cm^{-1} using an FTIR spectrophotometer. The FTIR analysis allowed for the examination of the molecular interactions and functional groups present in the binary mixtures. This comprehensive spectroscopic assessment provides valuable insights into the compatibility and potential chemical interactions between efavirenz and the respective carriers in the solid-state. The obtained FTIR spectra contribute to a better understanding of the formulation's structural characteristics, aiding in the optimization and assessment of its pharmaceutical properties.[12,16]

d) Differential scanning calorimetry (DSC): Approximately 2 mg of either the drug or the drug-carrier binary mixture was accurately weighed and placed in an aluminum pan. The pan was then sealed with an aluminum cap to prevent any external influences, and the entire setup was placed under a nitrogen purging atmosphere. Subsequently, both samples underwent scanning using a Differential Scanning Calorimeter (DSC) analyzer.[13,15]

The DSC analysis involved a temperature range from 40 to 240 °C, with a scanning rate set at 10 °C rise per minute. This controlled heating process allowed for the precise observation of thermal events such as melting points, crystallization, or any other phase transitions that might occur within the samples. The use of a nitrogen-purged atmosphere helped to eliminate the influence of oxygen and moisture on the thermal behavior of the substances under investigation. The collected DSC data provides valuable information about the thermal characteristics of both the drug and the drug-carrier binary mixture, aiding in the characterization and optimization of the formulation.[14,17]

RESULTS AND DISCUSSION

Spectrophotometric characterization of efavirenz

Table 1: Linear plot of efavirenz

Concentration (µg/ml)	Absorbance (at 248 nm)
5	0.233±0.001
10	0.448±0.002
15	0.676±0.003
20	0.887±0.002
25	1.089±0.002
30	1.296±0.001
35	1.476±0.001
40	1.69±0.002

The value represents mean ± SD (n=3)

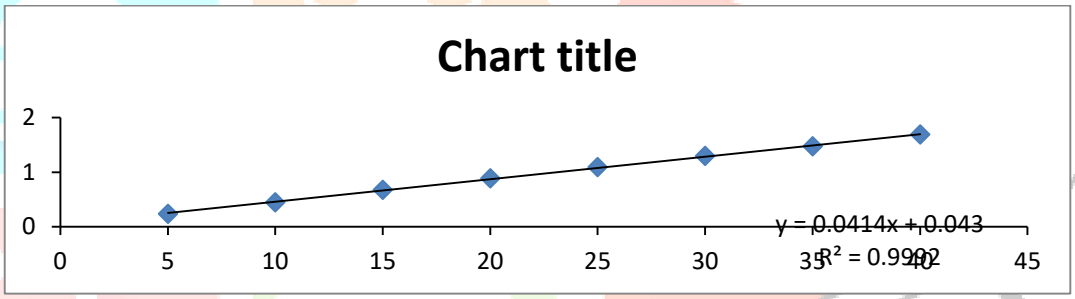

Figure 1 : Linear plot of efavirenz

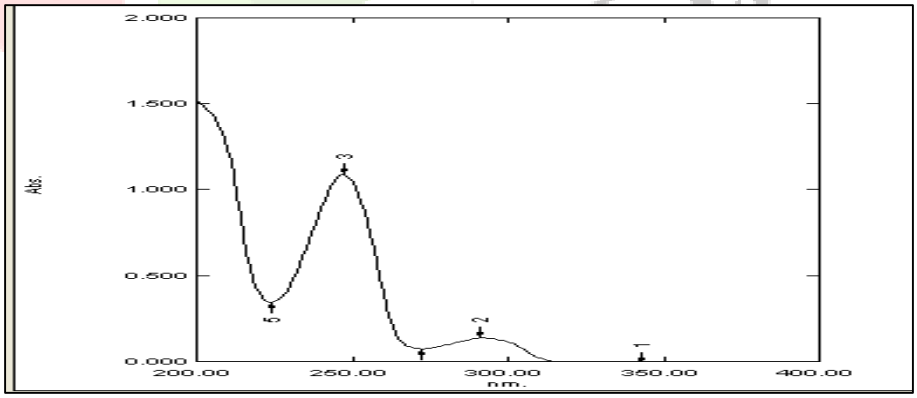

Figure 2 : UV spectrum of efavirenz

Dissolution studies of pure efavirenz

Table 2: Dissolution studies of pure drug (efavirenz)

The value represents mean ± SD (n=3)

Time (min)	% Drug Dissolved
0	0
10	21.29±1.44
15	28.97±1.76
30	33.75±0.99
45	37.41±2.03
60	41.19±0.26

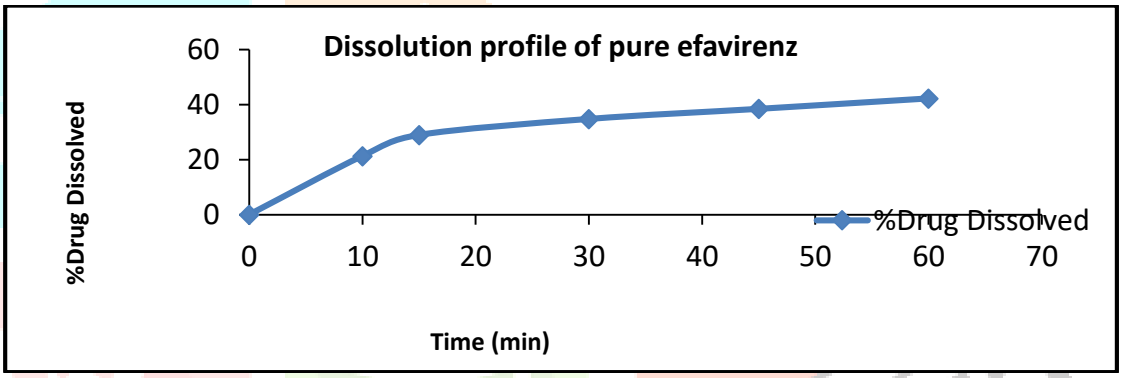

Figure 3: In vitro dissolution of pure efavirenz

Dissolution studies of efavirenz with PEG 4000

Table 4: Dissolution studies of efavirenz-PEG 4000 solid dispersions prepared by physical mixing

PEG 8000	% Drug dissolved					
Time (min)	Pure drug	1:0.5	1:1	1:1.5	1:2	1:2.5
0	0	0	0	0	0	0
10	20.31±1.34	22.14±0.94	23.92±2.88	24.71±3.01	25.16±0.77	27.73±1.77
15	27.95±1.45	29.56±2.21	31.66±1.22	32.51±1.45	33.1±1.87	32.85±2.18
30	33.76±2.89	35.71±1.94	37.43±3.01	38.42±2.77	39.2±2.76	37.92±3.08
45	37.42±2.84	38.93±2.57	40.75±2.33	41.16±2.78	41.89±2.44	42.93±1.99
60	41.21±2.86	41.25±3.17	42.16±1.85	42.26±1.82	42.91±1.80	46.83±2.75

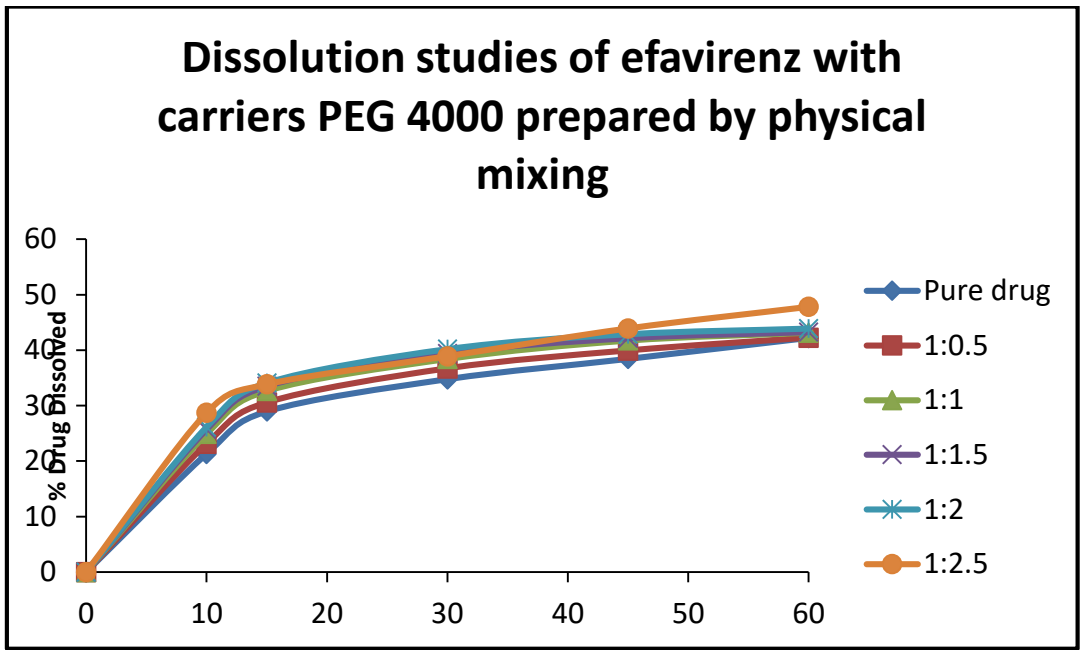

Figure 4: Dissolution studies of efavirenz-PEG 4000 solid dispersions prepared by physical mixing

Table 5: Dissolution studies of efavirenz-PEG 4000 solid dispersions prepared by melt/fusion method

PEG 8000	**% Drug dissolved**					
Time (min)	**Pure drug**	**1:0.5**	**1:1**	**1:1.5**	**1:2**	**1:2.5**
0	0	0	0	0	0	0
10	20.31±1.98	28.02±1.82	30.32±1.34	32.44±2.83	33.23±2.84	34.1±2.91
15	27.95±2.86	32.92±2.85	35.9±2.83	38.13±1.87	40.54±1.86	41.23±1.64
30	33.76±3.08	43.61±2.16	46.81±1.92	47.91±0.91	49.23±2.33	50.55±2.77
45	37.42±1.95	46.93±1.17	52.22±2.77	54.72±1.33	57.52±2.24	58.44±3.13
60	41.21±0.92	50.68±0.91	53.82±2.94	57.22±2.56	60.25±1.99	62.12±2.12

The value represents mean ± SD (n=3)

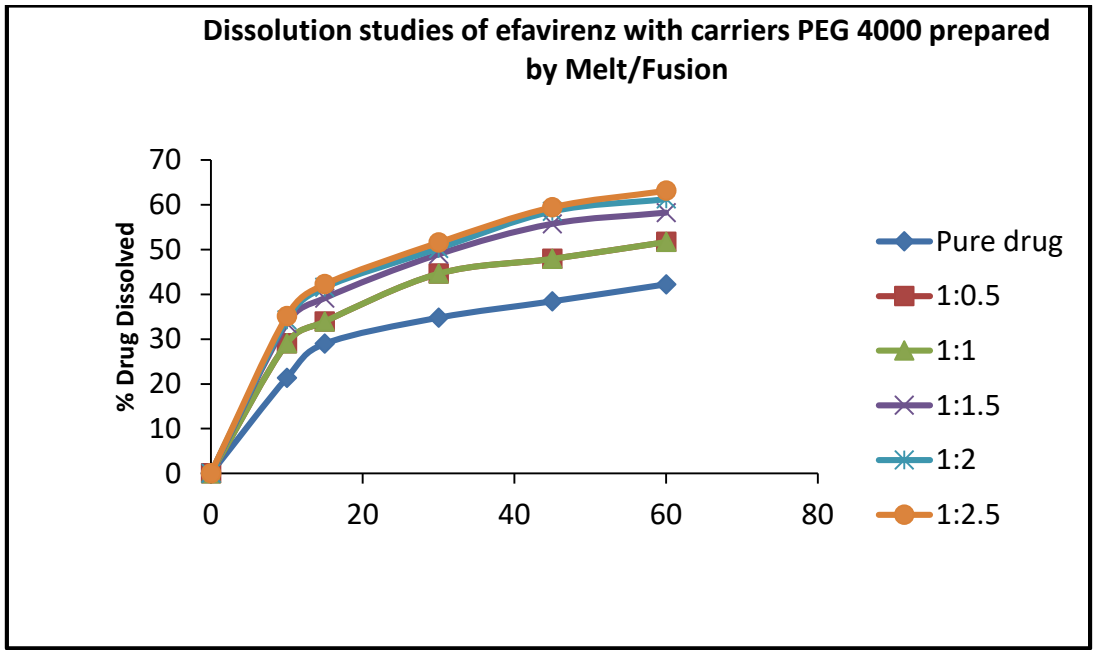

Figure 5: Dissolution studies of efavirenz-PEG 4000 solid dispersions prepared by melt/fusion method.

Table 6: Dissolution studies of efavirenz-PEG 4000 solid dispersions prepared by solvent evaporation technique

PEG 4000	**% Drug dissolved**					
Time (min)	**Pure drug**	**1:0.5**	**1:1**	**1:1.5**	**1:2**	**1:2.5**
0	0	0	0	0	0	0
10	20.31±1.92	27.23±2.21	29.91±1.78	32.92±2.89	33.11±2.81	34.22±2.71
15	27.95±2.65	33.82±2.83	34.66±3.15	37.55±1.34	39.31±1.83	39.40±1.85
30	33.76±3.14	42.93±0.82	45.93±0.69	46.88±1.85	47.12±2.91	48.56±2.36
45	37.42±1.96	46.25±1.46	50.99±1.48	53.63±2.95	55.66±2.78	56.16±3.72
60	41.21±2.81	49.66±3.35	52.22±2.53	56.91±2.51	59.22±1.95	60.58±1.43

The value represents mean ± SD (n=3)

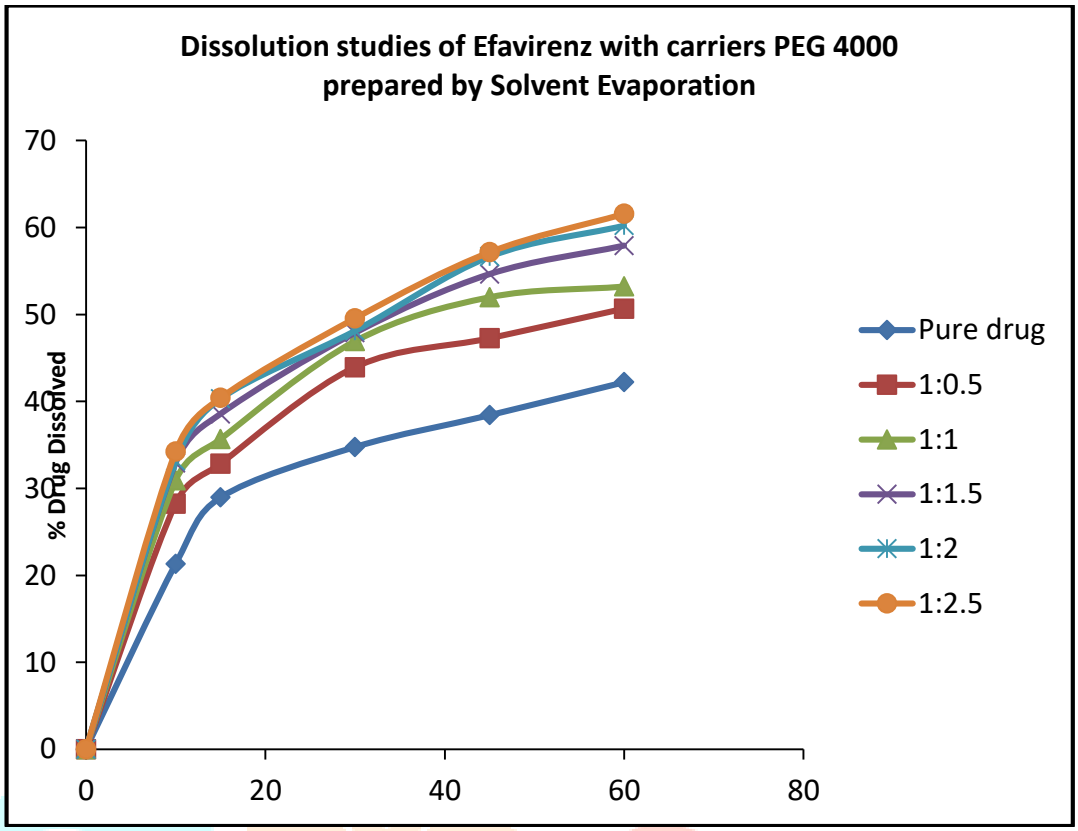

Figure 6 : Dissolution studies of efavirenz-PEG 4000 solid dispersions prepared by solvent evaporation

Dissolution studies of efavirenz with PEG 8000

Table 7 Dissolution studies of efavirenz-PEG 8000 solid dispersions prepared by physical mixing

PEG 8000	**% Drug dissolved**					
Time (min)	**Pure drug**	**1:0.5**	**1:1**	**1:1.5**	**1:2**	**1:2.5**
0	0	0	0	0	0	0
10	21.31±1.49	23.82±1.33	23.96±1.22	25.22±2.88	27.2±2.36	28.16±2.72
15	28.95±2.84	30.12±2.35	31.86±3.05	34.46±1.83	33.24±1.88	33.11±1.82
30	34.76±3.12	35.23±1.97	38.1±0.97	40.11±1.56	40.22±2.66	38.99±2.53
45	38.42±2.66	38.13±2.66	41.92±1.99	43.23±2.84	43.13±3.02	43.56±2.55
60	42.21±0.87	41.82±1.92	43.33±1.86	44.51±2.76	44.16±1.26	46.12±1.98

The value represents mean ± SD (n=3)

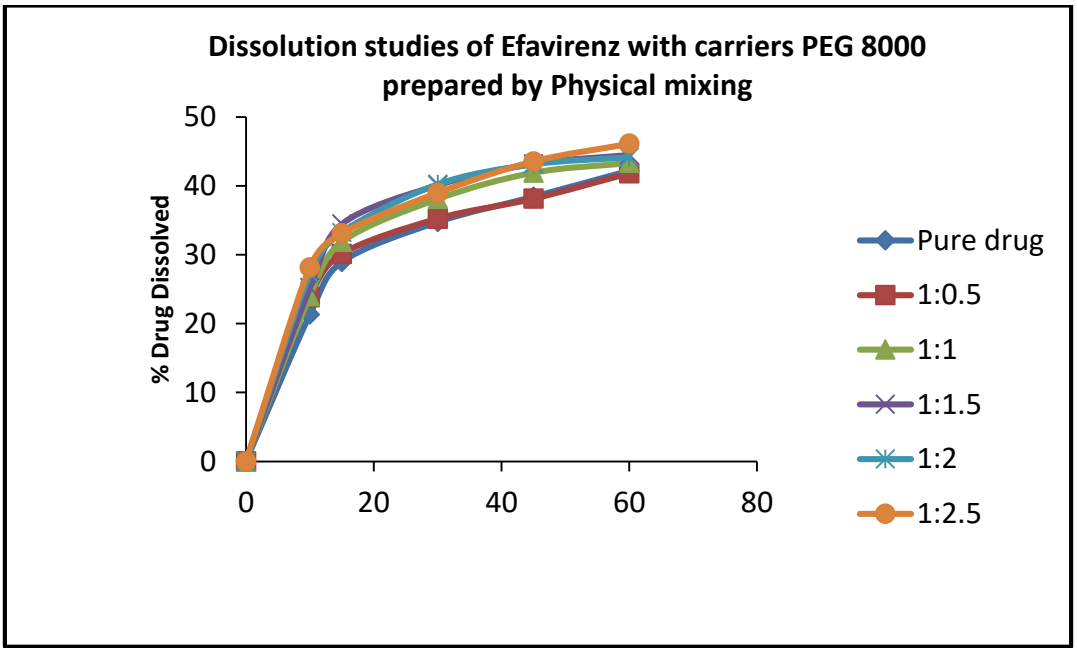

Figure 7: Dissolution studies of efavirenz-PEG 8000 solid dispersions prepared by physical mixing

Table 8: Dissolution studies of efavirenz-PEG 8000 solid dispersions prepared by melt/fusion method

PEG 8000	**% Drug dissolved**					
Time (min)	**Pure drug**	**1:0.5**	**1:1**	**1:1.5**	**1:2**	**1:2.5**
0	0	0	0	0	0	0
10	20.31±2.71	27.23±2.33	29.92±2.34	33.16±2.81	34.24±2.83	33.82±2.71
15	27.95±1.94	33.2±3.06	35.26±1.86	37.32±2.07	39.46±1.84	40.12±2.03
30	33.76±2.55	41.67±2.44	44.81±2.55	47.51±1.03	48.54±2.88	51.54±3.08
45	37.42±1.68	45.18±2.32	51.64±1.82	54.84±1.52	56.16±3.07	58.22±1.91
60	41.21±2.91	49.28±2.92	52.72±2.03	56.46±0.75	61.11±1.91	60.87±2.43

The value represents mean ± SD (n=3)

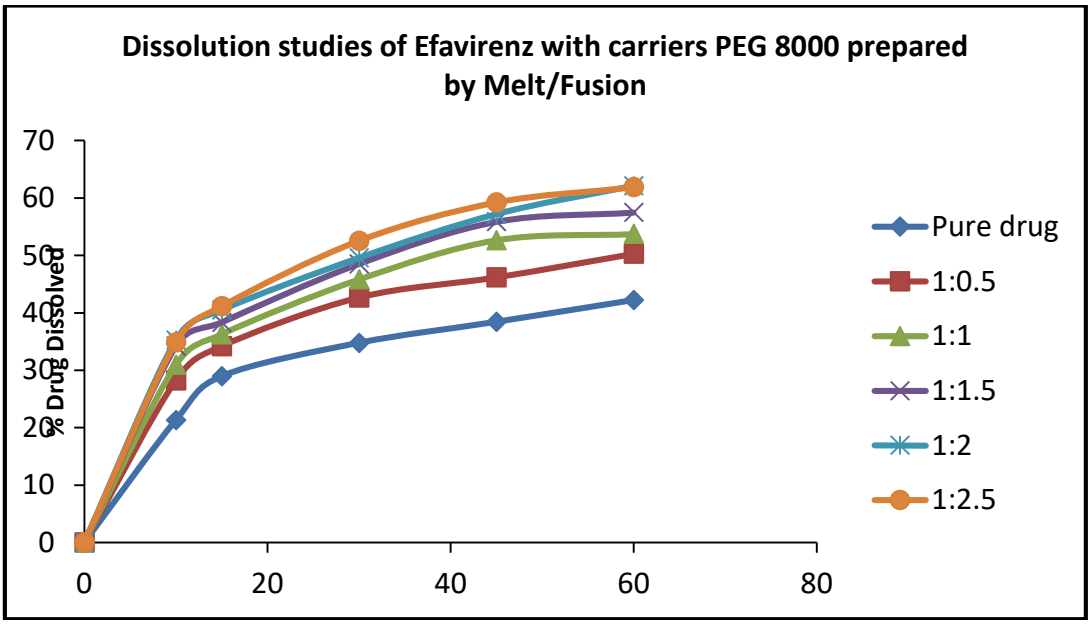

Figure 8: Dissolution studies of efavirenz-PEG 8000 solid dispersions prepared by melt/fusion method.

Table 9: Dissolution studies of efavirenz-PEG 8000 solid dispersions prepared by solvent evaporation method

PEG 8000	**% Drug dissolved**					
Time (min)	**Pure drug**	**1:0.5**	**1:1**	**1:1.5**	**1:2**	**1:2.5**
0	0	0	0	0	0	0
10	20.31±1.91	25.23±2.76	28.86±2.35	31.82±1.27	33.46±1.44	33.49±2.07
15	27.95±2.75	31.16±1.90	33.45±1.37	35.33±3.03	38.81±2.02	41.11±1.35
30	33.76±3.03	39.44±2.88	43.44±2.83	45.14±2.83	44.56±1.05	50.56±2.86
45	37.42±2.76	44.24±2.64	49.74±2.17	52.36±2.86	55.22±2.54	57.44±2.44
60	41.21±0.92	48.22±1.55	51.80±3.06	54.88±1.99	59.58±1.96	59.52±3.05

The value represents mean ± SD (n=3)

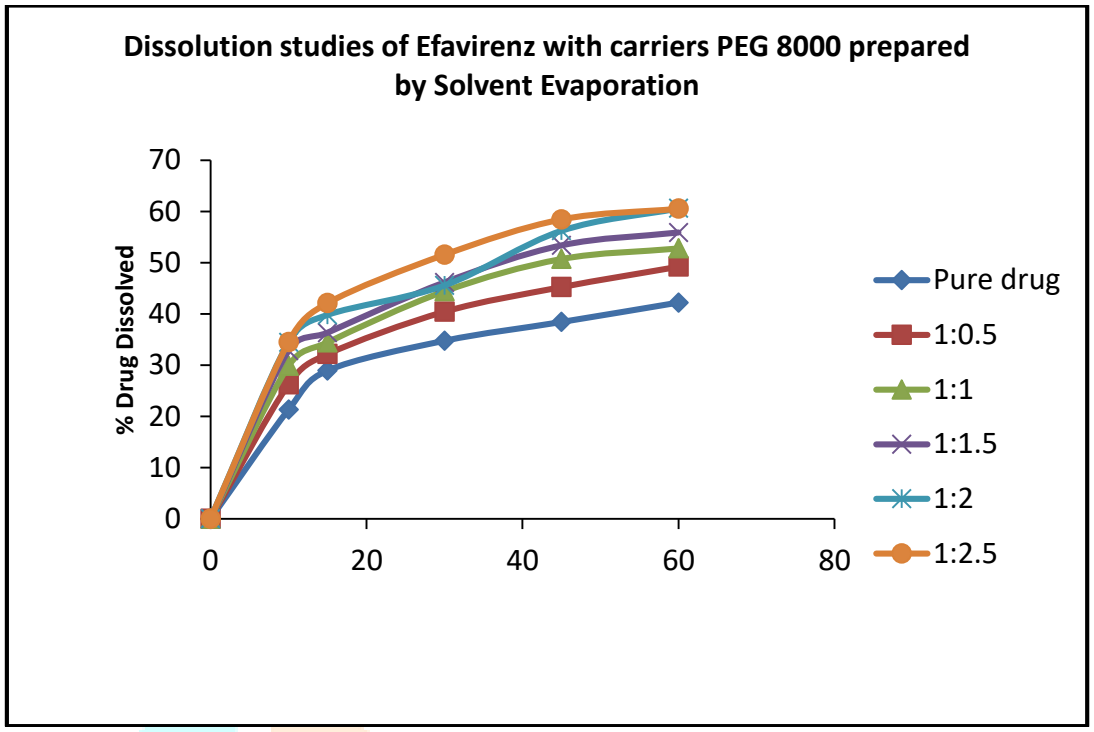

Figure 9: Dissolution studies of efavirenz-PEG 8000 solid dispersions prepared by solvent evaporation method

Dissolution studies of efavirenz with PEG 20000

Table 10 : Dissolution studies of efavirenz-PEG 20000 solid dispersions prepared by physical mixing method

PEG 20000	**% Drug dissolved**				
Time (min)	**1:0.5**	**1:1**	**1:1.5**	**1:2**	**1:2.5**
0	0	0	0	0	0
10	22.81±2.88	23.86±3.01	23.9±1.27	26.57±1.38	27.56±2.18
15	29.22±1.92	30.12±2.82	32.12±0.89	31.46±2.87	31.44±2.87
30	33.46±2.62	36.66±1.37	38.33±2.87	37.34±1.39	36.55±1.48
45	37.11±1.37	39.89±2.25	41.43±1.39	40.55±2.45	40.54±1.81
60	40.46±0.83	42.48±2.86	43.25±3.03	42.89±1.92	44.43±2.99

The value represents mean ± SD (n=3)

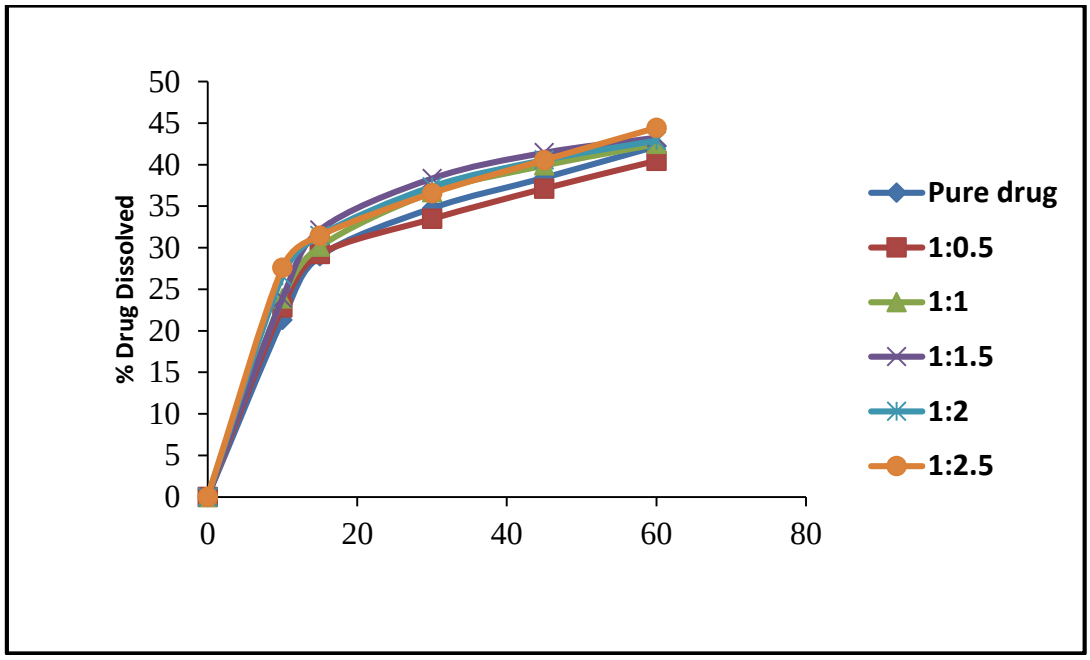

Figure 10: Dissolution studies of efavirenz-PEG 20000 solid dispersions prepared by physical mixing method

PEG 20000	**% Drug dissolved**				
Time (min)	**1:0.5**	**1:1**	**1:1.5**	1:2	**1:2.5**
0	0	0	0	0	0
10	26.66±1.89	31.12±2.31	32.66±2.13	34.55±2.11	32.67±2.07
15	32.43±2.67	34.46±1.22	36.16±1.15	38.82±1.05	37.23±1.32
30	39.68±2.91	43.87±2.68	44.92±2.88	46.36±2.06	44.11±2.03
45	43.84±1.33	48.94±1.99	52.55±2.65	55.63±2.45	52.87±1.46
60	48.34±2.78	51.87±2.46	57.12±0.89	60.87±1.67	58.84±2.89

The value represents mean ± SD (n=3)

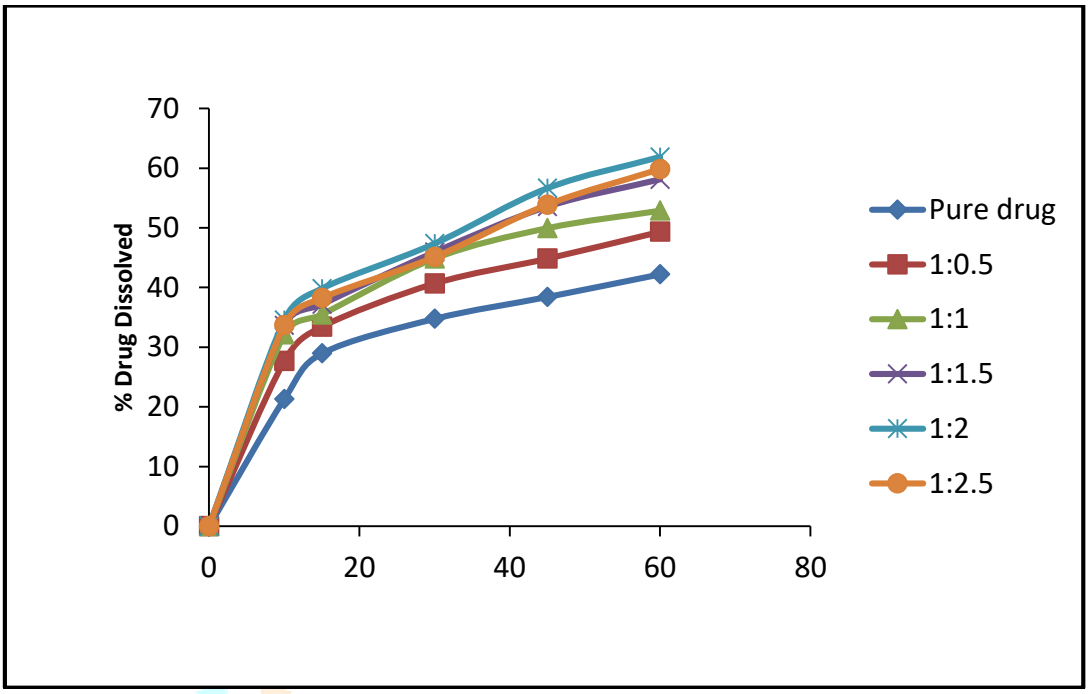

Figure 11: Dissolution studies of efavirenz-PEG 20000 solid dispersions prepared by melt/fusion method

Table 12: Dissolution studies of efavirenz-PEG 20000 solid dispersions prepared by solvent evaporation

PEG 20000 SE	**% Drug dissolved**				
Time (m)	**1:0.5**	**1:1**	**1:1.5**	**1:2**	**1:2.5**
0	0	0	0	0	0
10	25.76±2.54	29.34±1.33	31.45±2.33	32.12±2.03	31.43±2.39
15	31.41±1.65	33.51±2.45	35.84±1.55	36.44±1.08	36.29±1.44
30	37.66±1.93	40.45±1.68	42.55±2.96	45.84±1.01	43.36±2.07
45	43.33±2.87	46.63±2.02	50.89±2.08	54.54±2.99	51.88±3.02
60	45.86±2.37	49.88±1.67	56.63±0.99	59.68±1.04	56.54±1.77

The value represents mean ± SD (n=3)

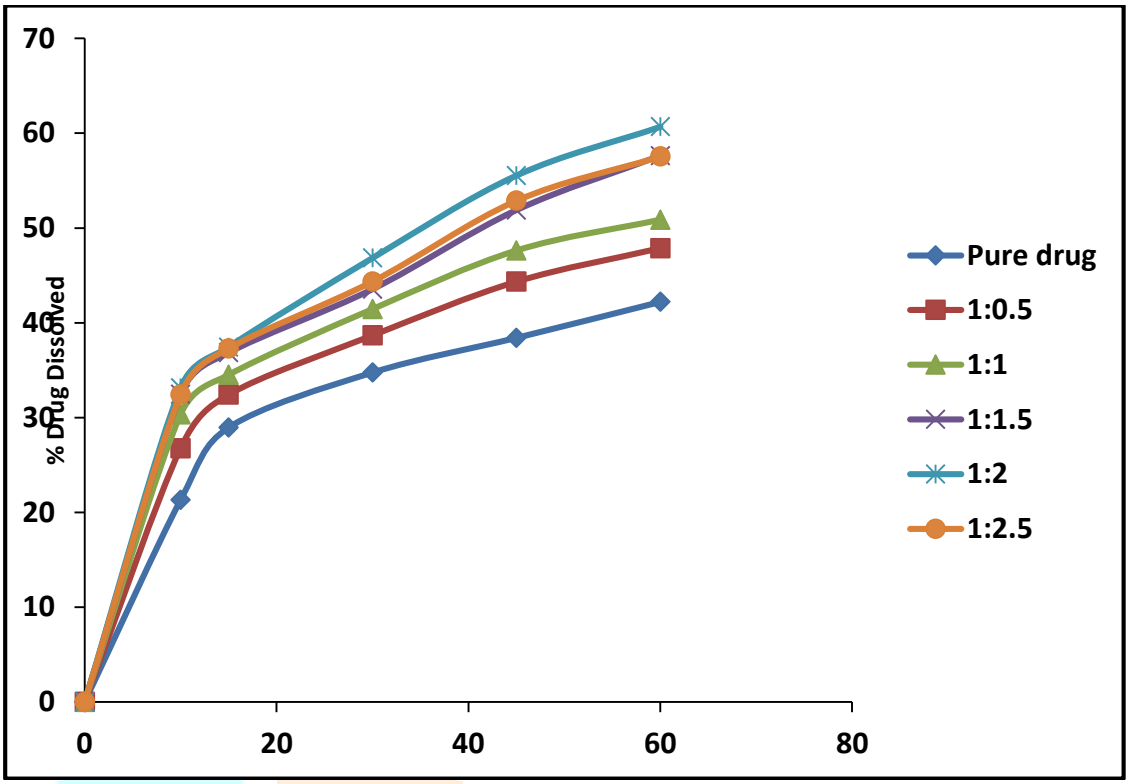

Figure 12: Dissolution studies of efavirenz-PEG 8000 solid dispersions prepared by solvent evaporation method

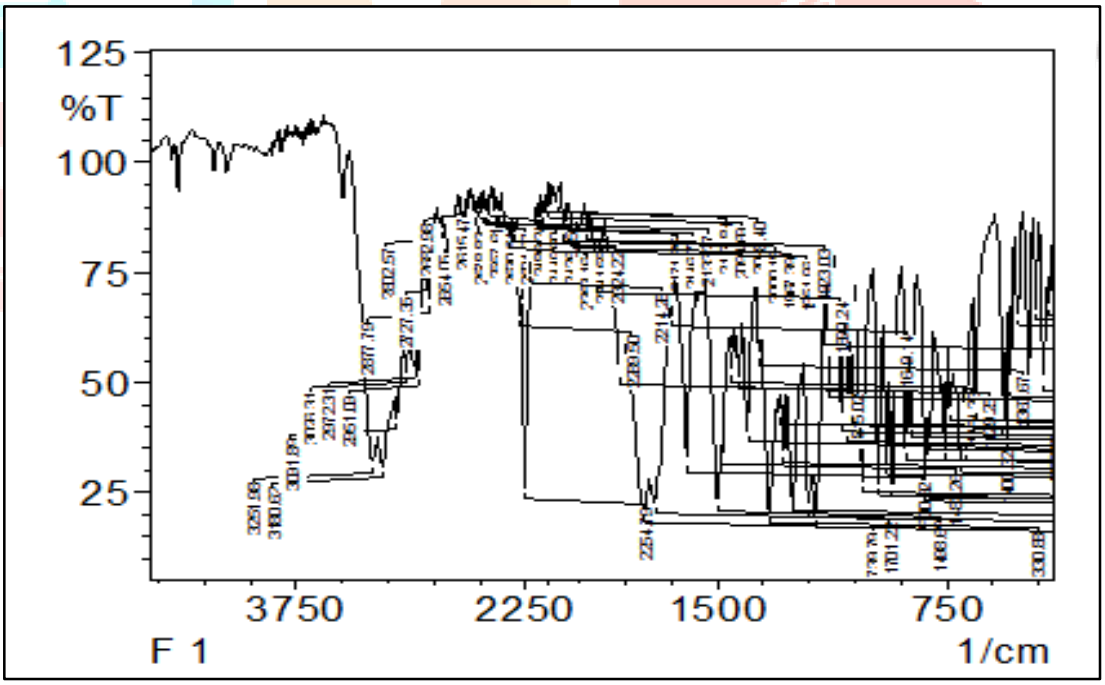

Figure 14: FTIR spectrum of efavirenz-PEG 4000 solid dispersions prepared by melt/fusion method

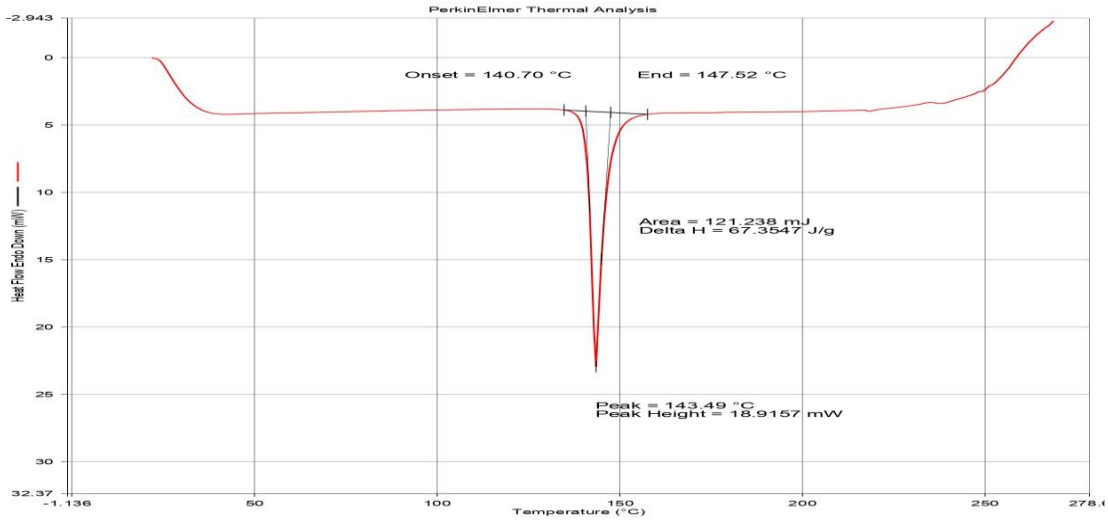

Figure 15: DSC thermogram of efavirenz pure drug

IR spectroscopic Analysis of Efavirenz

The infrared (IR) absorption spectrum of the bulk drug, efavirenz, was obtained using the KBr disc method in the spectral range of 4000-400 cm^{-1}. The major peaks identified in the FT-IR spectrum served as key indicators for the evaluation of the drug's purity.

The FT-IR spectrum of efavirenz exhibited distinctive peaks, confirming its identity and purity. Notable peaks included a strong N-H stretching peak at 3317 cm^{-1}, an aromatic C-H stretching peak around 3094 cm^{-1}, sp3 C-H stretching observed at 2926 cm^{-1}(s) and 2941 cm^{-1}(As), a robust C=O stretching peak at 1750 cm^{-1}, and a C-O stretching peak around 1050 cm^{-1}. These characteristic peaks are crucial in confirming the molecular identity and high purity of efavirenz.

The presence of these specific peaks in the FT-IR spectrum aligns with the expected molecular structure of efavirenz, validating the integrity of the bulk drug sample and providing confidence in its use for further pharmaceutical applications.

DSC Analysis of Efavirenz

The identity and purity of efavirenz were additionally confirmed using the differential scanning calorimetric (DSC) method. A critical parameter, the reported melting point, was compared with the observed melting peak of the test sample.

In the DSC analysis, the melting peak of efavirenz was found to be at 138 °C, which closely matched the reported melting point. This agreement between the reported and observed melting points provides strong evidence supporting the accurate identification and high purity of the efavirenz sample under investigation.

DSC Data analysis:

In the prelude to developing any dosage form, whether involving a new or established drug candidate, it is imperative to thoroughly ascertain the fundamental physical and chemical properties of the drug molecule and its powder characteristics. This foundational information serves as a guiding principle for subsequent events and approaches in the formulation development process. Notably, hydrophilic polymers and other excipients harbor reactive functional groups that may potentially lead to chemical and physical transformations. Consequently, the study of pharmaceutical formulations must include a careful examination of the likelihood of incompatibilities between their components.

The investigation of interactions between drugs and a distinct mixture [1:1] was conducted using Differential Scanning Calorimetry (DSC). The analysis relied on observing changes in thermal events, such as the elimination or appearance of endothermic or exothermic peaks, to deduce possible interactions. While some broadening of peaks may occur due to simple mixing without indicating significant interaction, the persistence of thermal features suggests compatibility.

In this study, it was observed that the position and shape of the endothermic peak for efavirenz, located at 138 °C, remained largely unchanged. The DSC thermogram of the formulation samples revealed the presence of both drug and excipient endothermic peaks, and these peaks exhibited no significant alterations in their shape or position. Consequently, it can be reasonably concluded that there are no substantial interactions between the drug and excipients in the formulated mixture. This information is pivotal for ensuring the compatibility of components and facilitating the development of a stable and effective pharmaceutical dosage form.

SUMMARY AND CONCLUSIONS

Among all the formulations tested, PEG 8000 at a ratio of 1:2 showed the highest percentage of drug release, reaching 61.11% in the melt/fusion method. This result indicates that this specific formulation is the most effective in increasing the solubility of the poorly soluble drug efavirenz. The success of this formulation highlights the potential of the melt/fusion method with PEG 8000 as a promising approach for solubility enhancement, paving the way for the development of improved pharmaceutical formulations for efavirenz.

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