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Formulation and Evaluation of Efaverinz Solid Dispersion

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ABSTRACT: The new drug entity is mostly poorly water-soluble; their oral bioavailability and solubility remain the major criteria for pharmaceutical formulations. Solid dispersion techniques have attracted much interest in improving the dissolution rate of highly lipophilic drugs. Efavirenz is a (NNRTI)non-nucleoside reverse transcriptase inhinbitor it is used in the treatment of HIV(human immunodeficiency virus) type I. Soluble in methanol,ethanol and dichloromethane, practically insoluble in water. Efavirenz belongs to BCS class II.

Purpose of present work is to improve the solubility of Efaverinz by preparing its solid dispersion with polymer PVP and HPMC by using solvent evaporation technique and characters are checked by using different parameters. Results shows that drug with PVP as a polymer enhances the rate of dissolution as compared with Drug with HPMC.

KEYWORDS: Efavirenz, Solid dispersion, BCS class, PVP, HPMC.

I. INTRODUCTION:

Nearly about 40% of drug suffers from poor aqueous solubility due[1] to which a high dose is required to meet the therapeutic level and it also effects its absorption[2]. After oral administration drug reaches to the systemic circulation, as poor solubility , the drug is not completely dissolves in GIT resulting in poor bioavailability and high intra and inter cellular pharmacokinetic variability.[3] The oral bioavailability is dependent[2] on many factors like solubility and permeability of the component, first pass metabolism, dissolution rate.[4]Drug with poor solubility exhibits dissolution rate limited absorption while with poor permeation are permeability rate limited absorption.[3] The BCS(biopharmaceutical classification system) classified the drug under 4 categories on the basics of their solubility and permeation.[5]Mostly the drug with poor oral bioavailability is due to its low solubility in aqueous medium and they belongs to the BCS Class II. In the BCS Class II and IV solubility and drug release was the rate limiting step nor its absorption.

A solid dispersion is the technique used to enhance the solubility of poorly soluble drug.

sulphathiazole [6] was the first drug whose solid dispersion was prepared.

The solid dispersion contains two components one is hydrophilic carrier and other is
hydrophobic drug. The process of dispersion of two these two components is known as **SOLID DISPERSION**.

Or

in other terms we can say that a drug is dispersed in water soluble carrier by
different techniques then it is known as solid dispersion[7].The carrier may be amorphous or crystalline.

This technique is also used to convert the component from crystalline form to amorphous form.[8,9]

DRUG PROFILE

EFAVERINZ

Pharmacopoeial Description: Pink to White coarse powder.

Melting Point : 1390C -1410C

Solubility: Freely Soluble in methanol,ethanol and dichloromethane, practically insoluble in water .

Chemical Formula: C14H9ClF3NO2 .

IUPAC Name:

S)-6-chloro-4-(Cyclopropylethynyl)-1,4-dihydro-(S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one4-(trifluoromethyl)-2H-3,1-benzoxazin-2- one

Chemical Structure:

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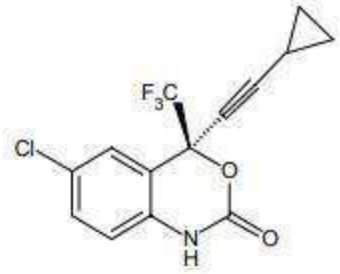

MECHANISM OF ACTION :

As solid dispersion comes in contact with water , the drug starts releasing and dissolution enhances.

Reduction in particle size of drug: As a particle size of drug is reduced then the wettability and dispersion of drug leads to enhanced dissolution. As the particle reduced the chance of agglomeration also reduced.[10]

The drug converts into crystalline form to amorphous state and improves wettability and dissolution of poorly water-soluble drugs. For better dissolution rate, purpose surfactant has been included. Surfactants are useful for better dissolution rate purpose. Surfactants are also helpful to avoid recrystallization and enhances potentiality of their solubility.

II. MATERIALS AND METHODS

Preparation of Standard Curve of EFAVIRENZ in 0.1N NaOH:

➢Accurately 10mg of EFAVIRENZ was weighed by using electronic balance.

➢ Then the drug was transferred into 10ml volumetric flask and the volume was made up to 10ml by methanol for getting the concentration of 1000 µg/ml.(STOCK I)

➢ Then the STOCK I was further diluted with distilled water for getting the concentration of 10µg/ml (STOCK II).

➢Then STOCK II was further diluted to get the concentration of 1 -15 µg/ ml by using O.1N NaOH.

➢Absorbance was measured at λmax of 246.08nm using UV-Visible spectrophotometer

METHOD OF PREPARATION :SOLVENT EVAPORATION METHOD:

➢EFAVIRENZ and hydrophillic carrier (PVP K-30 and HPMC 5cps) were accurately weighed according to their ratios .

➢Both the components were mixed in ethanol.

➢Then the resultant solution was kept on magnetic stirrer for 30minutes.

➢Then the solvent was completely evaporated .

➢The powdered solid dispersion was collected and sieved. [11,12, 13].

Instruments Used : Electronic balance , Magnetic stirrer , UV- Spectrophotometer, FT-IR , Dissolution apparatus , SEM , DSC

III. CHARACTERIZATION:

FTIR(Fourier Transform Infrared Spectroscopy):

➢ FTIR spectra is used for the disclosure of chemical interaction that take place between pure drug , polymer and drug and polymer mixtures(1:1).

➢ The range of interactions 4000 cm-1to 400 cm-1.

➢ IR spectra of pure drug and drug-polymer blend were determined by KBr disks method.

➢ The blend was triturated into fine particles.

➢ In KBr disks the samples were prepared by applying pressure of 5 for 5 min in hydrostatic press and spectra were obtained.

➢ The specific peaks of spectra of drug , polymer , drug polymer blend and final formulation were recorded.

DSC(Differential Scanning Calorimetry):

➢ Analysis of EFAVIRENZ , PVP K-30, HPMC5 cps, physical mixture and final formulation was determined by DSC instrument.

➢ It is also used for the determination of chemical interaction between components.

➢ The dried sample about 1-5mg was loaded on tray and sealed into DSC pan with the help of loading puncher.

➢ Sample was heated in an pan at a rate of 5 - 10ºC/min under the nitrogen atmosphere at temperature of 40-400°C.

➢ DSC thermo gram of individual sample were recorded.

SEM(Scanning Electron Microscopy):

➢ Surface of prepared solid dispersion were analysed by scanning electron microscopy.

➢ Solid dispersion were gold coated before subjected to electron scanning. The formulation were examined under 10,000 resolution.

➢ The beam of electron was passed at 10 KV.

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IV. RESULTS :

Calibration curve in 0.1N NaOH:

Table 1:Showing reading of calibration curve in O.1N NaOH

S.No.	Concentration (µg/ml)	Absorbance
1	0.5	0.045
2	1	0.073
3	2	0.116
4	3	0.167
5	4	0.205
6	5	0.265
7	6	0.299
8	7	0.374
9	8	0.426
10	9	0.502
11	10	0.560
12	11	0.616
13	12	0.669
14	13	0.719
15	14	0.765
16	15	0.812
17	16	0.869
18	17	0.925

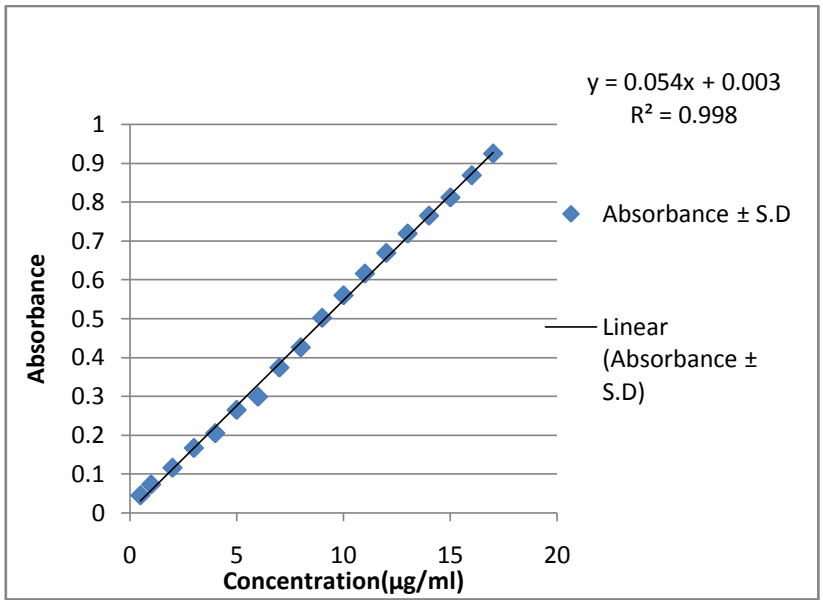

Fig. 1: Calibration curve of EFAVIRENZ with 0.1N NaOH.

Drug Polymer Interaction/ Compatibility Studies

FTIR Study

The FT-IR spectra of EFAVIRENZ, PVP K-30 ,HPMC 5cps was analysed. IR Spectra of blend was carried out for checking the compatibility between drug and polymer.

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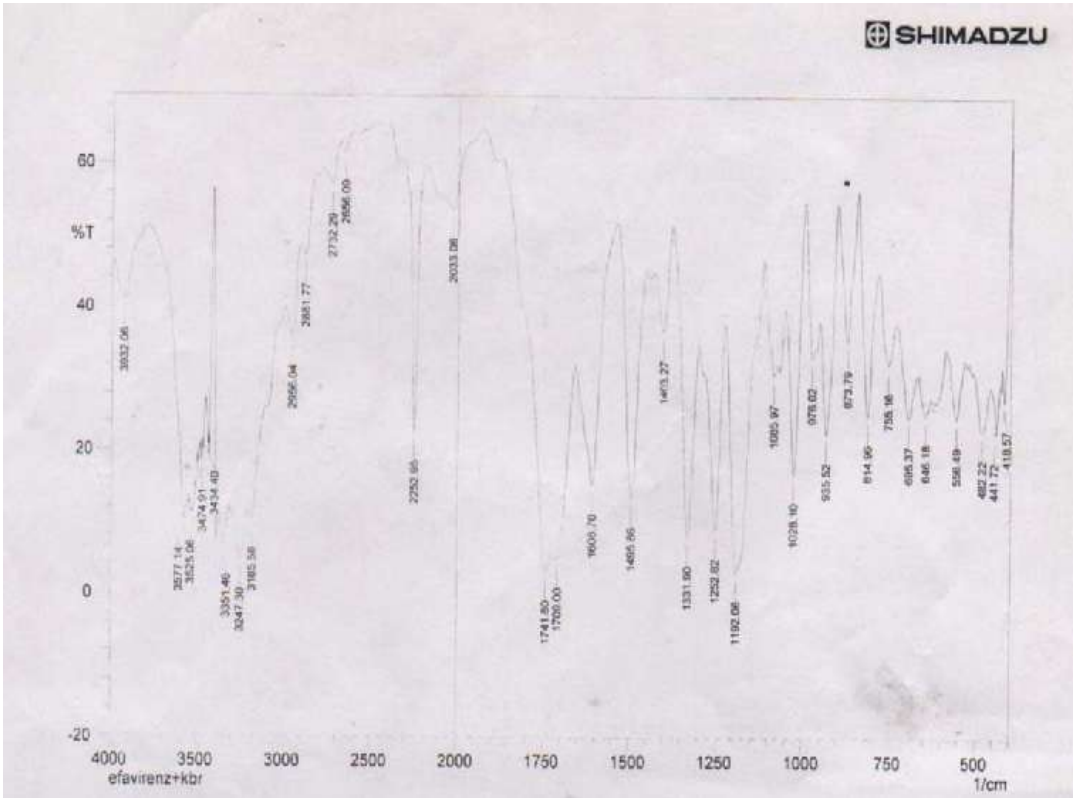

Fig.2 : FTIR of Efaverinz

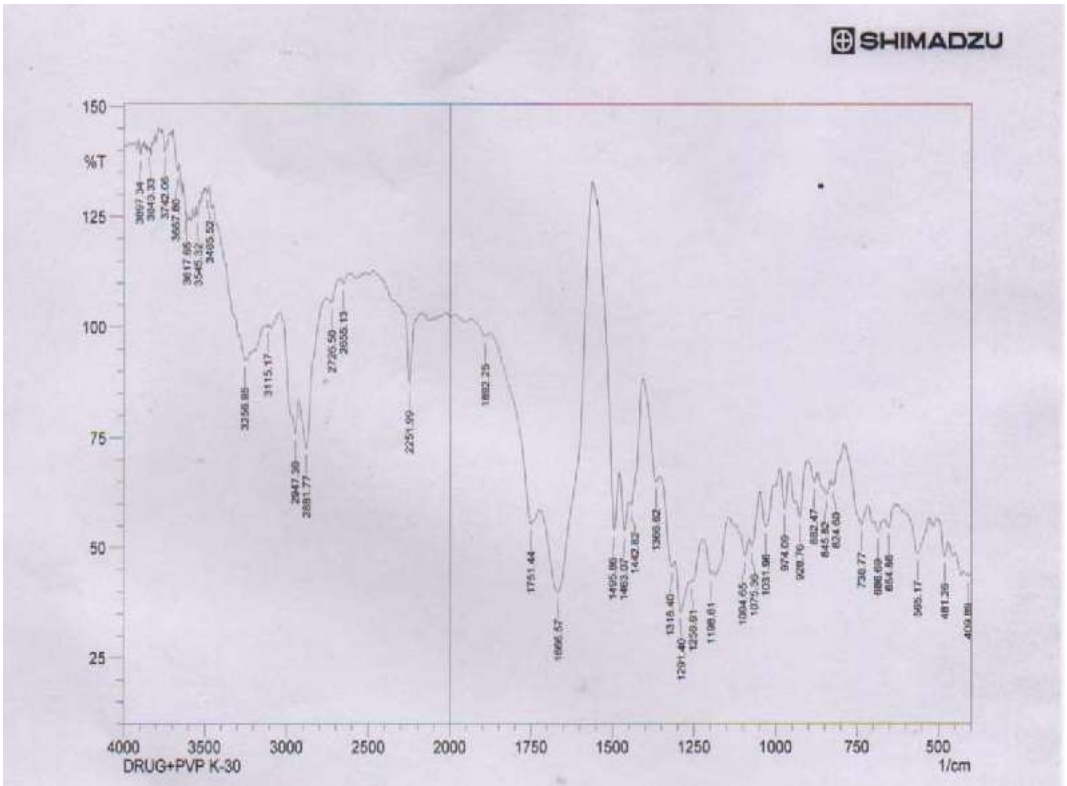

Fig.3 :FTIR of drug and PVP K-30

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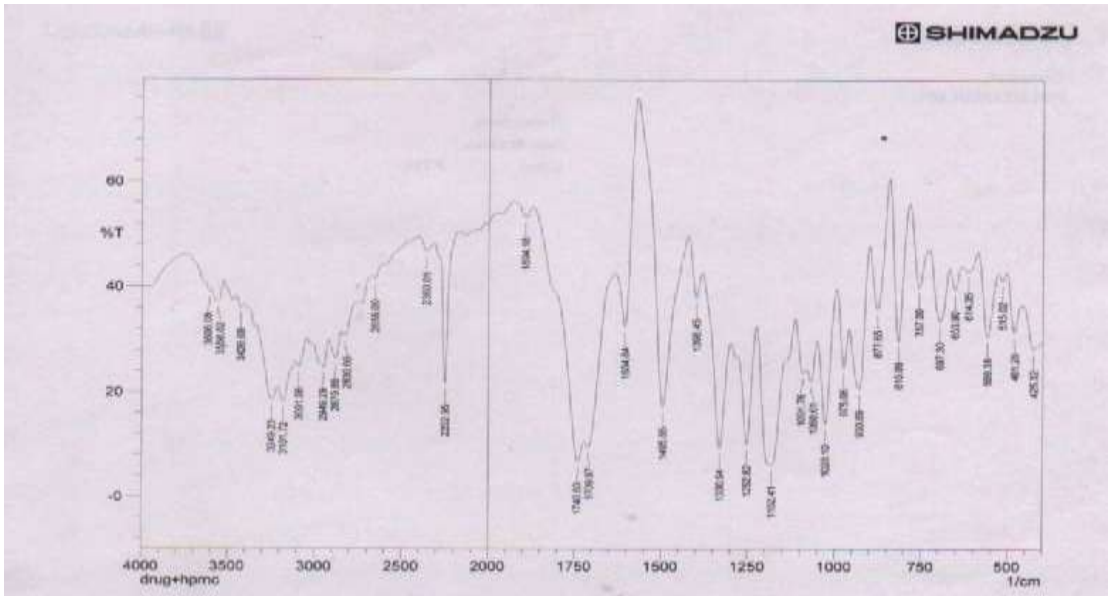

Fig.4 : FTIR of drug and HPMC

DSC (Differential scanning calorimetry):

The analysis of EFAVIRENZ , PVP K-30 , and HPMC 5cps was done. The analysis of blend was also done for checking the compatability between drug and polymer. The curves overlaps which indicates the possibility of interactions between them.

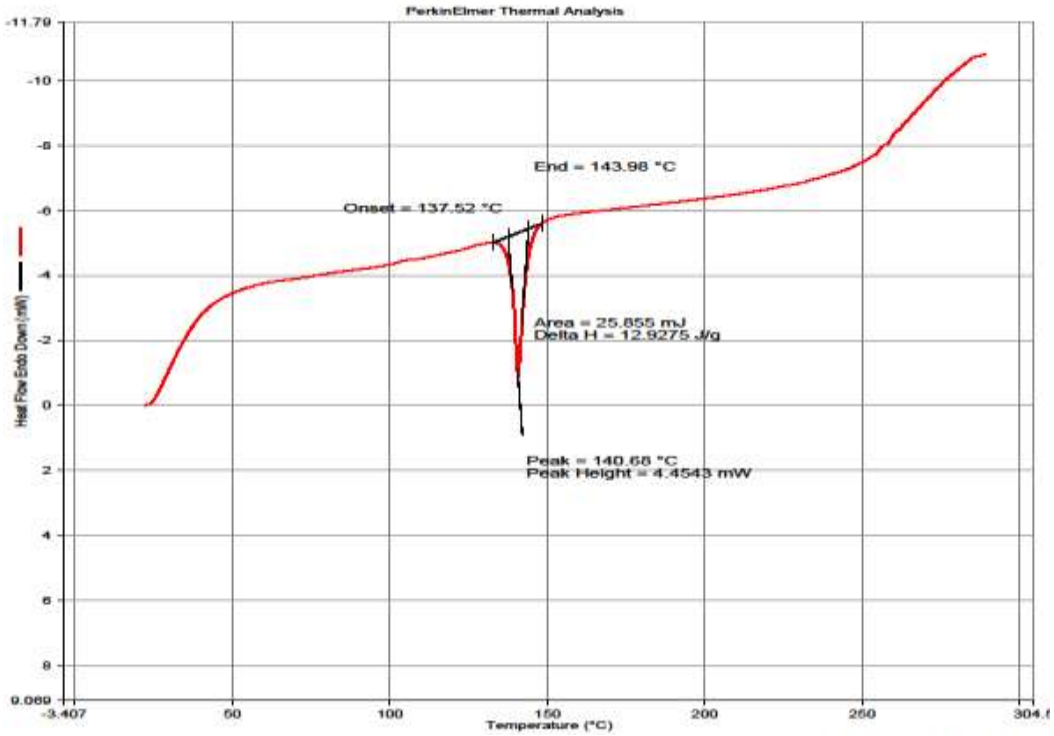

Fig. 5: DSC of Efavirenz

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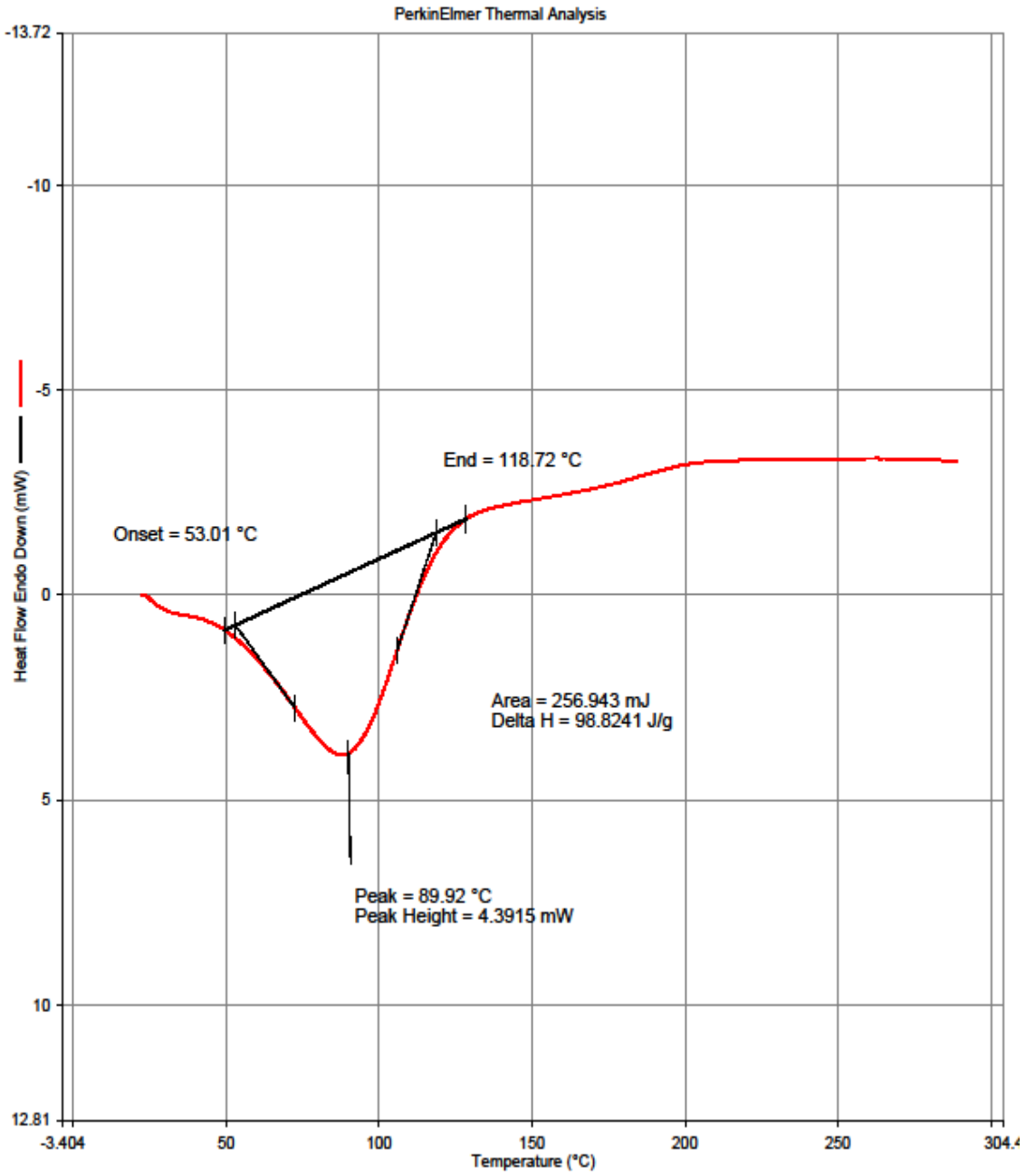

Fig. 6: DSC OF Efaverinz And HPMC

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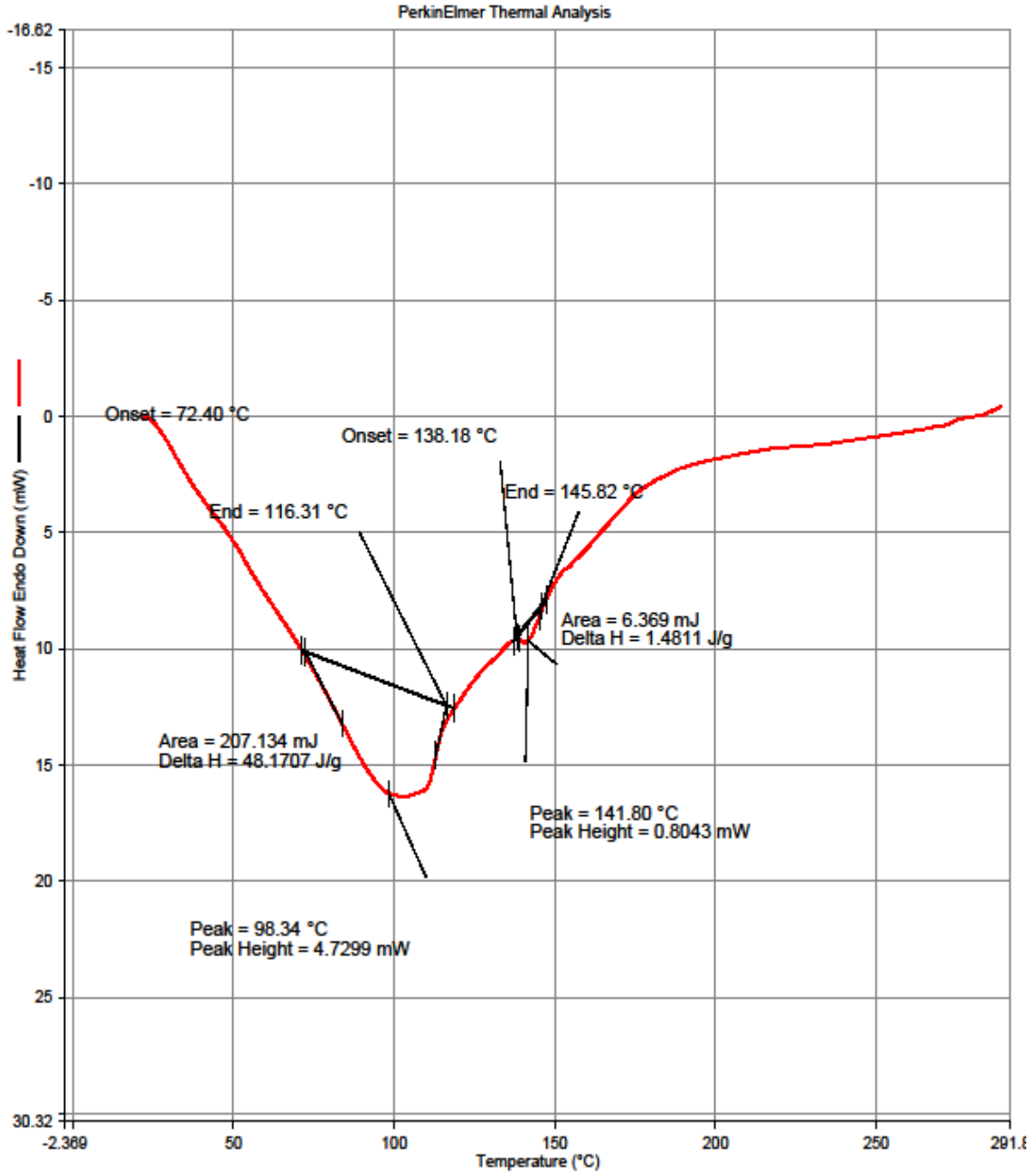

Fig.7: DSC OF Efavirenz and **PVP K30**

FORMULATION STUDIES

The solid dispersions of Efavirenz were successfully prepared bysolvent evaporation method using PVP((Polyvinylpyrrolidone) K-30 and HPMC (hydroxyl propyl methylcellulose) in different ratios.

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Table 2: Formulation Table

Formulation Code	EFAVIRENZ HPMC 5cps	EFAVIRENZ : PVP K-30
EH I	1:1	--
EH II	1:3	--
EH III	1:5	--
EH IV	1:7	--
EH V	1:9	--
EP I	--	1:1
EP II	--	1:3
EP III	--	1:5
EP IV	--	1:7
EP V	--	1:9

Percentage yield:
The percentage yield in all batch code was found to be between 88.65% to 96.98%.

Table 3: Showing Percentage yield of Drug with PVP and HPMC.

Formulation code	Percentage yield
EH I	89.45%
EH II	91.67%
EH III	96.98%
EH IV	94.45%
EH V	95%
EP I	88.65%
EP II	91.25%
EP III	94.50%
EP IV	96.23%
EP V	96.12%

Drug Entrapment Efficiency:
The drug entrapment efficiency was carried out for all formulation batches

Table 4: Showing Drug entrapment Efficiency

Formulation Code	Percentage Of Drug Entrapment Efficiency
EH I	75%
EH II	79%
EH III	82.8%
EH IV	84.5%
EH V	87%
EP I	80.4%
EP II	83.4%
EP III	86%
EP IV	87.5%
EP V	89.9%

SEM (Scanning Electron Microscopy)
SEM of EFAVIRENZ and final formulation (EH V)was done to know the surface topology of them. The SEM photographys were shown below:

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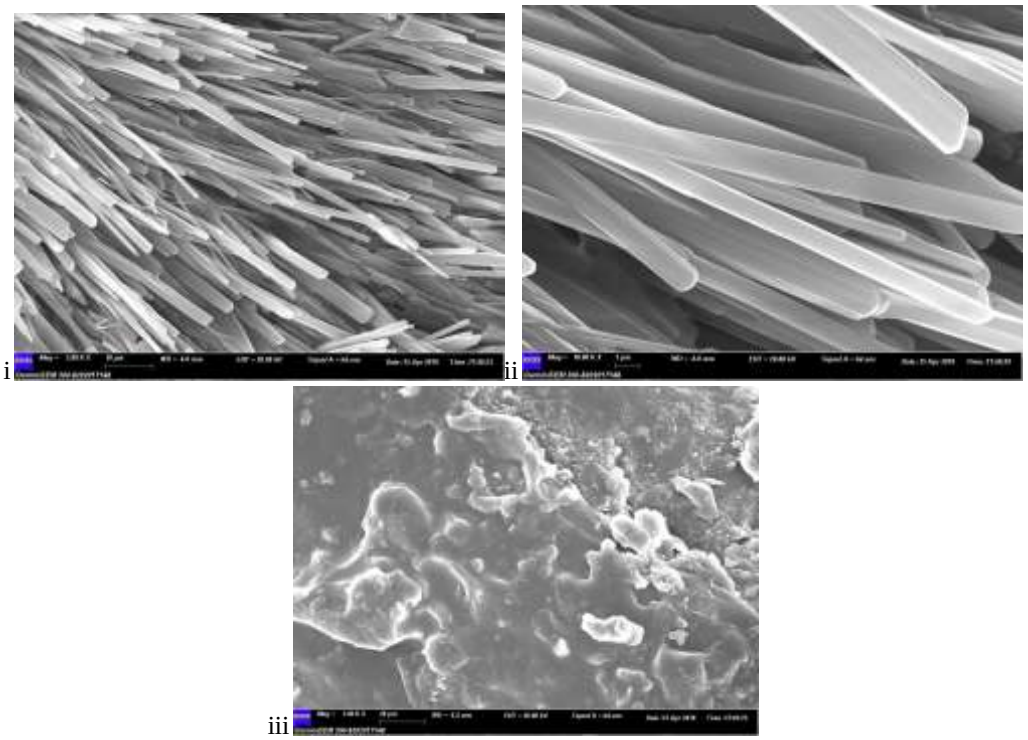

Fig. 8 : i- SEM of drug, ii- SEM of Drug: HPMC, iii- SEM Drug: PVP

In - Vitro Drug Release Study

The drug release pattern has been shown:

Table 5: Showing combined release of Drug with PVP (EP code) and Drug with HPMC (EH Code).

TIME	PD	EP I	EP II	EP III	EP IV	EP V	EH I	EH II	EH III	EH IV	EH V
5	0	2.67	3.25	3.75	4.15	4.3	2.25	3.08	3.5	3.8	3.9
10	2.42	6.75	8.35	10.00	12.17	12.5	5.92	7.58	8.67	10.00	11.8
15	5.92	13.00	16.25	20.08	23.42	24.3	11.08	15.50	18.00	19.75	23.6
20	10.42	20.92	27.25	34.67	37.67	39.0	18.08	25.50	29.83	32.33	38.8
30	15.83	30.75	41.83	51.00	53.92	57.5	26.75	36.50	44.42	48.58	56.3
45	23.42	42.58	58.25	68.50	71.25	78.5	37.35	49.83	61.50	66.42	76.8
60	32.75	57.83	75.92	88.5	91.25	**99.8**	51.67	66.17	80.83	87.50	94.0
90	44.33	65.45	85	96.5	98		61.23	76.8	89.9	95.8	**99.2**
120		77.3		92.5			69.9	89.0	94.6		

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RESULT

Efaverinz solid dispersion were prepared by solvent evaporation technique. The effect of variables like EFAVIRENZ: Carrier ratio, their yield and its characteristics were studied.

Drug Entrapment Efficiency(DEE)

The DEE was obtained from 75 – 89.9% showing in (Table no.). More the amount of carrier more will be its DEE, but upto a certain limit. Further increase in carrier amount may results in agglomeration or coning during dissolution.

Differtial Scanning Calorimetry Study

DSC of EFAVIRENZ is shown in figure 16, HPMC in figure 17,EH V 19 in figure , EP V in figure 18. The thermograph of efavirenz showed a sharp peak at 140.680C. HPMC has thermograph peak was at 89.920C. EP V shows a thermograph at 141.800C and EH V shows sharp peak at 143.12 0C.

In-Vitro Study

Release profile of solid dispersion of efavirenz demonstrated that the drug was released faster from the solid dispersion as compared with alone. Solid dispersion was prepared with using different hydrophilic polymer and have been enhanced the solubility and dissolution rate of efavirenz. Drug release from EP V was faster as compared with other EH and EP formulations over the entire duration of action. The dissolution profiles further reveals that the drug release was slower from the formulation containing low amount of polymer. As the amount of polymer increases the rate also increases because it produce better wettability resulting. According to study EP V shows maximum results in 60 minutes only.

FT-IR

FT-IR was done to check the interaction present between EFAVIRENZ and polymers. IR spectra of drug, polymers and optimized formulation were recorded in the range from 4000- 400 cm-1. EFAVIRENZ showed prominent and characteristics peaks at 3351.46, 2956.96, 1741.80, 1400.56, 755.00 cm-1 contributed to –NH stretching of the sec amines, -CH stretch of aldehyde, - C=O stretching of ketone,-C-F strecting, -C-Cl strecting. The final formulation (EH-V)

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showsaal the bands EFAVIRENZ without affecting its peak position and trends, which indicates that there was no interaction between the drug and polymer.

SEM (Scanning Electron Microscopy):

The topography of solid dispersion was obtained by SEM. The photographs reveals that the drug is in amorphous form when carrier was added to it.

➢SEM photographs of pure drug.

➢SEM photographs of Optimized formulation(EP V) .

V. CONCLUSION

The objective of this study was to prepare Efavirenz solid dispersion with an aim of enhancing the solubility and dissolution rate by using different carriers. EFAVIRENZ is antiretro viral agent belongs to BCS Class II. It is insoluble in water available in pink to white powder. Solid dispersion prepared by solvent evaporation method by using two different carriers in different ratios.

Characterization of prepared solid dispersion was done by SEM. FTIR and DSC was done for checking the possible interactions that can be take place between EFAVIRENZ , PVP K-30 and HPMC 5cps, no interaction were identified through results.

Solid dispersions prepared by solvent evaporation method using different carriers at 1:9 ratio and they showed enhanced solubility as compared to API. Carriers, PVP K-30,HPMC 5 cps have showed enhanced dissolution rate. Based on the dissolution profiles of solid dispersions and the solubility of efavirenz is enhanced using PVP as carrier. In future prospect it can be used in the treatment of Covid and other retroviral disease.

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