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A Comparative Study of Etravirine Solid Dispersions Using Hot-Melt Extrusion and Spray Drying Technique

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ABSTRACT

Etravirine is a non-nucleoside reverse transcriptase inhibitor(NNRTI) used in the treatment of HIV. One of the major problems with the Etravirine is its low solubility, which results into poor bioavailability after oral administration. Therefore, solid dispersions (SDs) of Etravirine were prepared by two methods, Hot-melt extrusion and Spray drying technique using various carriers like Polyvinyl Caprolactam-Polyvinyl Acetate-Polyethylene Glycol Graft Copolymer **(**Soluplus), Hypromellose 2.5 cPs, PEG 6000, Amino Methacrylate Copolymer (Eudragit EPO) &Copovidone (Kollidon VA64) and Povidone (Kollidon 30) to increase its aqueous solubility. Faster and high drug release was found in the SDs prepared by hot melt extrusion (HME) with soluplus in the ratio of 1:3 as compared with spray drying technique (SDT) using drug substance, Soluplus and Microcrystalline cellulose (Avicel PH105) in the ratio of 1:2:0.5. There is 4 folds increases in the solubility of Etravirine prepared by HME & SDT compared with plain drug substance. EHT3 and ESD4 are finalized as optimized formulations prepared by HME & SDT based on their solubility, drug substance content and *in vitro* drug dissolution studies. FT-IR, DSC and XRD of SDs by HME & SDT showed a change in crystal structure toward an amorphous form of Etravirine. The obtained results suggested that developed Etravirine SDs by HMT & SDT has potential for oral delivery and might be an efficacious approach for enhancing the therapeutic potential of Etravirine.

Keywords: Etravirine, HIV, Hot-melt extrusion, Spray drying, Soluplus.

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INTRODUCTION

About 40% of recently discovered drug candidates are poorly water soluble and therefore have limited bioavailability[1]. Researchers try to overcome this problem by converting the low energy and low solubility crystal forms to their corresponding highest energy states, i.e, amorphous state[2]**.** Solubility enhancement of such compounds is a major challenge to formulation scientists. Various approaches have been adopted to address this including preparation of solid dispersions and solid solutions[3] Solid dispersion (SD) is defined as a dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method[4]. The most relevant technologies for the manufacture of solid dispersions are melting of excipients or fusion method, embedding of drug by means of spray drying, co- evaporation, co-precipitation, freeze-drying and roll-mixing or co-milling[5] HME (Hot melt extrusion) has the unique property to maintain the amorphous state of the drug after the formation of solid dispersion[6] Spray drying technique (SDT) method consists of dissolving or suspending the drug and polymer in a common solvent or solvent mixture and then drying it into a stream of heated air flow to Remove the solvent[7]. Etravirine is anon-nucleoside reverse transcriptase inhibitor(NNRTI) used in the treatment of HIV. It works by reducing the amount of HIV and increasing the number of CD_4 or T cells in the blood[8]**.** The aim of the present study was to prepare the solid dispersions of Etravirine and polymers like Soluplus a novel polymer with amphiphilic properties, Hypromellose 2.5 cPs, Amino methacrylate copolymer (Eudragit EPO), Copovidone (Kollidon VA 64) and Polyethylene glycol (PEG 6000) etc. Soluplus has been especially developed for hot melt extrusion[9] **.**In this study, HME and Spray drying techniques (SDT) are used to obtain Etravirine solid dispersions, polymeric carriers are generally chosen depending on criteria such as hydrophilicity, solubility parameter and hygroscopicity.

MATERIALS AND METHOD

INTELENCE® (Etravirine) 200 mg tablets were obtained from Tibotec Pharmaceuticals Ltd, manufactured by Janssen CilagS.p.A., Latina, IT (which were being procured for Hetero Labs Ltd, Unit-III, Hyderabad, India), Etravirine drug substance was gifted by Hetero Drugs Ltd, Hyderabad, India. Microcrystalline cellulose, grade Avicel PH105 &Avicel PH 102 was gifted by FMC biopolymer, USA. Hypromellose 2.5 cPs was gifted by DOW chemical, USA. Amino methacrylate copolymer, grade Eudragit EPO & Colloidal silicon dioxide (Aerosil 200) was gifted by Evonik, Germany. Polyethylene glycol (PEG 6000) was purchased from SDFCL, Mumbai. Polyvinyl Caprolactam-Polyvinyl Acetate-Polyethylene Glycol Graft Copolymer, grade Soluplus,

Copovidone, grade Kollidon VA64 &Povidone, grade Kollidon 30 was gifted by BASF, USA; Lactose monohydrate (Super Tab 11 SD) &Croscarmellose sodium was gifted by DFE Pharma, Germany. Magnesium stearate was gifted by Peter Greven, Netherlands. Hard gelatine capsules were gifted by ACG associated Capsules, Mumbai. All other Polymers and solvents used were of analytical grade.

Hot Melt Extrusion

Preparation of etravirine solid dispersions by HME:

Etravirine solid dispersions were prepared by using different carriers like Soluplus, Hypromellose 2.5 cPs, Hypromellose 2.5 cPs with PEG 6000, Eudragit EPO &Kollidon VA64. Thermo Fischer, HME Parma 24 - Twin Screw Model was used for the preparation of solid dispersions with the feed rate of 1 to 1.25 Kg/hour, Torque**:** 4 Barr and 8 different zones of temperature as from 40˚± 2˚C to 180˚± 2˚C with cooling/chillers zone maintained at 2 - 5^0C (where melt will be converted into the pieces of flakes) shown in Table 1.

Table 1: Temperature ranges to be monitored during processing of Holt melt extrusion (HME)

Name of the zone	Temperature
Barrel Conveying Unit (BCU)	40˚± 2˚C
Zone – I	60˚C˚± 2˚C
Zone – II	80˚C˚± 2˚C
Zone – III	100˚C˚± 2˚C
Zone – IV	120˚C˚± 2˚C
Zone – V	140˚C˚± 2˚C
Zone – VI	160˚C˚± 2˚C
Zone – VII	180˚C˚± 2˚C
Die Zone	180˚C˚± 2˚C
Cooling / Chillers zone	Maintained at 2 - 5˚C (where melt will be converted into pieces of flakes)

Trials with Soluplus

Table 2: Formulation plan of Etravirine solid dispersions

S. No	HME trials→ Ingredients (Units)↓	HM1	HM2	HM3	HM4	HM5
Drug: Carrier ratio (Etravirine: Soluplus) →		1:1	1:2	1:3	1:4	1:5
1.	Etravirine (gm)	75.0	50.0	37.5	30.0	25.0
2.	Soluplus (gm)	75.0	100.0	112.5	120.0	125.0
Total qty of binary mixture for HME process (gm)		150.0	150.0	150.0	150.0	150.0

Etravirine and Soluplus were taken in the above mentioned ratios (Table 2), sifted together through ASTM #40 mesh and were mixed well in a poly bag for 5 minutes. The above binary mixture was

hot melt extruded with keeping above mentioned temperature at different zones. The pieces of flakes were transparent in HM3, HM4 & HM3, where as opaque in HM1 & HM2, crushed into powder using mortar and pestle. The powder was in granular nature and was sifted through # 30 mesh. The flow properties of blend were found to be satisfactory.

Trials with Hypromellose (Methocel 2.5 cPs)

Table 3: Formulation plan of Etravirine solid dispersions

S. No	HME trials→ Ingredients (Units)↓	HM6	HM7
Drug: Carrier ratio (Etravirine: Hypromellose 2.5 cPs) →		1:3	1:5
1.	Etravirine (gm)	25.0	20.0
2.	Hypromellose 2.5 cPs (gm)	75.0	100.00
Total qty of binary mixture for HME process (gm)		100.0	120.0

Etravirine and Hypromellose 2.5 cPs were taken in the ratios of 1:3 & 1:5 mentioned in the Table 3, then sifted together through ASTM #40 mesh and were mixed well in a poly bag for 5 minutes. The above binary mixture was hot melt extruded with keeping above mentioned temperature at different zones in Table 1. Since the polymer is degrading at the temperature above 170°C, it was concluded that Hypromellose 2.5 cPs is not suitable polymer for hot melt extrusion of Etravirine having melting point more than 200°C. In order to lower the glass transition temperature (Tg) of Hypromellose and smooth running of hot melt extrusion process at lower temperature below 170°C, it was decided to add plasticizer, Polyethylene glycol (PEG 6000) at 10% w/w of polymer.

Trials with Hypromellose (Methocel 2.5 cPs) with Polyethylene glycol 6000

In this trial, Etravirine, Hypromellose (Methocel 2.5 cps) and Polyethylene glycol 6000 were taken in 1:5:0.5 ratios with at 10.0% w/w of Polymer.

Table 4: Formulation plan of Etravirine solid dispersions

S. No	HME trials→ Ingredients (Units)↓	HM8
Drug: Carrier ratio (Etravirine: Hypromellose 2.5 cPs and Polyethylene glycol 6000) →		1:5:0.5
1.	Etravirine (gm)	20.0
2.	Hypromellose 2.5 cPs (gm)	100.0
3.	Polyethylene glycol (PEG 6000) (gm)	10.0
Total qty of tertiary mixture for HME process (gm)		130.0

Etravirine, Hypromellose 2.5 cPs and Polyethylene glycol (PEG 6000) were taken in the Above mentioned ratios (Table 4), sifted together through ASTM #40 mesh and were mixed well in a poly bag for 5 minutes. The above tertiary mixture was hot melt with keeping above mentioned temperatures at different zones shown in Table 1. There was no much improvement in the process

with the addition of Plasticizer, the polymer was get degrading at temperature of 160 ºC, and more over the formed flakes were not transparent, plastic in nature, very hard, off-white to brownish yellow with black spots. Since the polymer has been degraded, the batch was not processed further.

Trials with Etravirine and Eudragit EPO

In this trial, Etravirine was hot melt extruded with Amino methacrylate copolymer (Eudragit EPO) in 1:5 ratio, which is suitable polymer for hot melt extrusion for solubility improvement purpose taken in 1: 5 ratio and proceeded as per below procedure.

Table 5: Formulation plan of Etravirine solid dispersions

S. No	HME trials→ Ingredients (Units)↓	HM9
Drug: Carrier ratio (Etravirine: Eudragit EPO) →		1:5
1	Etravirine (gm)	20.0
2	Amino methacrylate copolymer (Eudragit EPO) (gm)	100.0
Total qty of binary mixture for HME process (gm)		120.0

Etravirine and Amino methacrylate copolymer (Eudragit EPO) were taken in the above mentioned ratio (Table 5), sifted together through ASTM #40 mesh and were mixed well in a poly bag for 5 minutes. The above binary mixture was hot melt extruded with keeping the temperature at different zones shown in Table 1. Since the flakes were opaque, plastic in nature and very hard, it is very difficult to break into powder, the batch was not processed further.

Trials with Etravirine and Copovidone (Kollidon VA 64)

In the next set of trials, Etravirine was hot melt extruded with the most commonly employed polymer for Hot melt extrusion, i.e., Copovidone (Kollidon VA 64) in 1:3 and 1:5 ratios.

Table 6: Formulation plan of Etravirine solid dispersions

S. No	HME trials→ Ingredients (Units)↓	HM10	HM11
Drug: Carrier ratio (Etravirine: Copovidone (Kollidon VA64) →		1:3	1:5
1	Etravirine (gm)	30.0	20.0
2	Copovidone (Kollidon VA64) (gm)	90.0	100.0
Total qty of binary mixture for HME process (gm)		120.0	120.0

Etravirine and Copovidone (Kollidon VA64) were taken in the ratios of 1:3 & 1:5 (**Table 6**), were sifted together through ASTM #40 mesh and were mixed well in a poly bag for 5 minutes. The above binary mixture was hot melt extruded with keeping above mentioned temperature at different zones shown in Table 1. The resulting flakes were transparent and were were crushed into powder using mortar and pestle. The powder was in granular nature and was sifted through # 30 mesh. The flow properties of blend were found to be satisfactory. Among the 11 trials, the hot melt

extrusion process was found to be satisfactory in terms of no degradation of polymer, brittleness of flakes in trial batches of Etravirine hot melt extruded with Soluplus in 1:3 (HM3), 1:4 (HM4) & 1:5 (HM5) and Etravirine hot melt extruded with Copovidone (Kollidon VA 64) in 1:3 (HM10) & 1:5 (HM11). These 5 batches were proceeded further for compression (along with some other raw materials like diluent, disintegrant, flow aids and lubricant,,etc), evaluation of compression parameters and dissolution profiles.

Table 7: Composition of Etravirine solid dispersion tablets

S.No	Raw materials	Function	Qty (mg / unit)				
Hot melt extrusion			EHT3	EHT4	EHT5	EHT10	EHT11
1.	Etravirine	API	200.0	200.00	200.0	200.0	200.0
2.	Polyvinyl Caprolactam-Polyvinyl Acetate-Polyethylene Glycol Graft Copolymer (Soluplus)	Polymer (for solubility enhancing)	600.0	800.00	1000.0	---	---
3.	Copovidone, US-NF (Kollidon VA64)		---	---	---	600.0	1000.0
Total quantity of Hot melt extruded granules			800.0	1000.00	1200.0	800.0	1200.00
Extra granular materials							
4.	Lactose monohydrate, US-NF (SuperTab 11SD)	Diluent	474.0	274.00	74.0	474.0	74.0
5.	Microcrystalline cellulose, US-NF (Avicel PH 102)	Disintegrant	35.0	35.00	35.0	35.0	35.0
6.	Croscarmellose sodium, US-NF (Ac-di-sol)	Disintegrant	70.0	70.00	70.0	70.0	70.0
7.	Colloidal silicon dioxide, US-NF (Aerol 200)	Glidant	7.0	7.00	7.0	7.0	7.0
8.	Magnesium stearate,US-NF	Lubricant	14.0	14.00	14.0	14.0	14.0
Total weight of Tablet			1400.0	1400.0	1400.0	1400.0	1400.0

Manufacturing process

Step – 1: The hot melt extruded binary mixture (#30 mesh passed) of Etravirine with Soluplus (HM1 -HM5) / with Kollidon VA64 (HM10 & HM11), Lactose monohydrate, Microcrystalline cellulose, Croscarmellose sodium and Colloidal silicon dioxide were sifted together through # 30 mesh and manually mixed well in a poly bag for 10 minutes.

Step – 2: Magnesium stearate was sifted through #40 mesh, added to blend of step-1 and manually mixed in a poly bag for 5 minutes.

Step – 3: The above lubricated blend was compressed into Etravirine Tablets 200 mg using compression machine with 22.0 x 11.0 mm, standard concave oval shape punches, upper punch

embossed with "109" and lower punch embossed with "J" at below given hardness ranges. The composition of Etravirine tablets was shown in Table7.

Characterization

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra for plain drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Affinity 1 Spectrophotometer. The IR spectrum of the samples was prepared using KBr (spectroscopic grade) disks by means of hydraulic pellet press at pressure of seven to ten tons.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. Accurately weighed samples were placed on aluminium plate, sealed with aluminium lids and heated at a constant rate of 5ºC/min, over a temperature range of 0 to 250ºC[10].

Powder X-ray diffraction:

A Bruker D8 diffractometer was used to perform powder X-ray diffraction (PXRD) of all samples. A Cu K-α 1 tube was the source, set at 40 KV and 50mA. A scan from 2 to 60^0 2 θ was carried out at a rate of 0.01220^0 2θ/s. The diffractometer was calibrated using powdered α-alumina. Hot-melt extruded samples were ground before analysis[11].

Evaluation of Etravirine solid dispersions

Solubility studies of Etravirine solid dispersion by Hot melt extrusion method

Solubility measurements of Etravirine were performed according to a published method (Higuchi and Connors 1965). Samples were shaken for the 48 hours at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no 1. Filtered solutions were analyzed for the Etravirine in UV 235 nm.

Drug content

Solid dispersions equivalent to 200mg of Etravirine was weighed accurately and dissolved in 100 ml of Methanol. The solution was filtered, diluted suitable and drug content was analyzed at λ_{max} 235 nm against blank by UV spectrometer. The actual drug content was calculated using the following equation as follows:

$$\% \text{ Drug content} = \frac{\text{Actual amount of drug in solid dispersion}}{\text{Theoretical amount of drug in solid dispersion}} \times 100$$

***In vitro* drug release studies**

The *in vitro* drug release profiles of Etravirine plain drug substance, 200 mg tablets of solid dispersion containing Etravirine with Soluplus in 1:3, 1:4 and 1:5 and corresponding Innovator product was performed using USP type 2 dissolution apparatus.

The samples were drawn at specified time intervals and the obtained samples were analyzed by using UV/Visible spectrophotometer at 235nm. The different dissolution parameters are summarised in Table 8. The cumulative percentage drug release was calculated.

Table 8: *In Vitro* dissolution studies test parameters:

Instrument	**Electro lab- USP type 2 dissolution test apparatus.**
Dissolution medium	% Sodium lauryl sulfate (SLS) in 0.01 M HCl in two phases:
Apparatus	USP type – II (Paddle type)
Temperature	$37\pm0.5^{0}C$
RPM	50
Volume of medium	900 ml.
Sampling intervals	5, 10, 15, 30,45,60 and 90minutes
Sample volume	10 ml withdrawn and replaced with 10 ml of dissolution medium.

RESULTS AND DISCUSSION

Preparation of Etravirine solid dispersions

Solid dispersions of Etravirine were prepared by usingSoluplus / Hypromellose 2.5 cPs / Hypromellose 2.5 cPs with PEG 6000 / Eudragit EPO / Kollidon VA 64 in different ratios. Based on the HME process feasibility, among the 11 formulation trials by HME process, it was concluded that both Soluplus and Kollidon VA64 were suitable for hot melt extrusion of Etravirine at temperature range of 160°C to 180°C (below 160°C, the transparent flakes were not formed and running the HME process above 190°C would not be advisable in point of Hot melt extruder efficiency and degradation of polymer.Based on the similar disintegration pattern as well as lower disintegration time, the batches with Soluplus in 1:3, 1:4 and 1:5 were evaluated for dissolution profiles and compared against dissolution profiles of plain drug substance and to that of Innovator product profiles.In the present investigation 5 formulations were prepared and their complete composition is shown in Table 7. All the solid dispersions prepared were found to be fine / granular in nature and found to be free flowing (Figure 1).

Figure 1: Etravirine solid dispersions (with Soluplus in 1:3 ratio)

Characterization

FT-IR studies

The prominent peaks of Etravirine was observed (Figure 2) the region of 3410.26 cm^{-1} due to the (Aromatic primary amine stretching), a peak at 2368.86 cm^{-1} due to aryl C=N stretching and a peak at 2978.19 cm^{-1} due to Aromatic C-H stretching. At the lower frequencies 650 cm^{1} (C-Br), 1365.65 cm^{-1} (primary & tertiary amine), 1188.19 cm^{-1} (ether C-O-C stretching) observed. Soluplus(Figure 3) shows the prominent peak at 3410.26 cm^{-1} due to polymeric OH stretching, a peak at 2978.19 cm^{-1} due to the (aliphatic CH_3 stretching). Physical mixture (Figure 4) of the drug and Soluplus shows summation of the spectra of the drug and Soluplus equivalent to the addition of the spectrum of polymer and drug. This indicates that interaction has occurred with simple physical mixture of drug and polymer. In case of solid dispersion (Figure 5)of the drug and Soluplus shows overlapping of O-H and N-H group and broadening of peak was observed. However other peaks related to C-O-C, C-H stretching remains unchanged. This indicates that overall symmetry of the molecule might not be significantly changed.

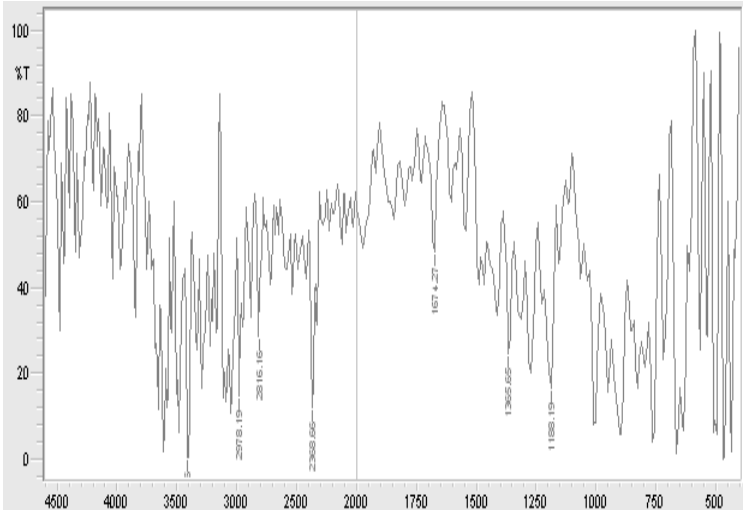


Figure 2: FTIR spectra of plain drug

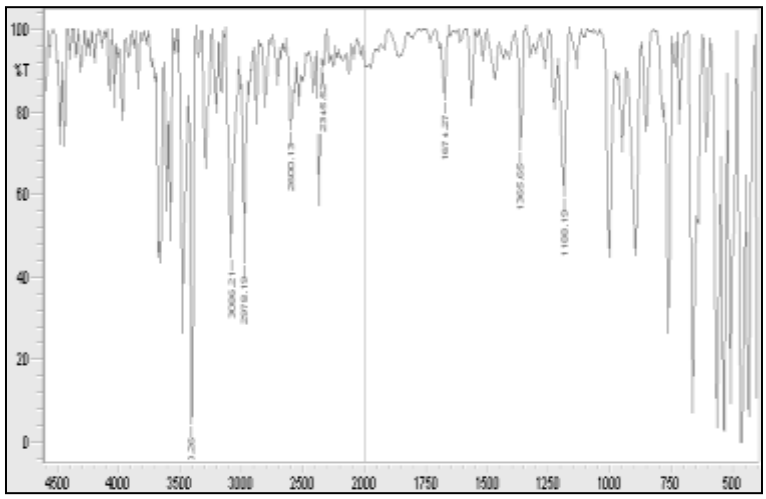


Figure 3: FTIR spectra of Soluplus

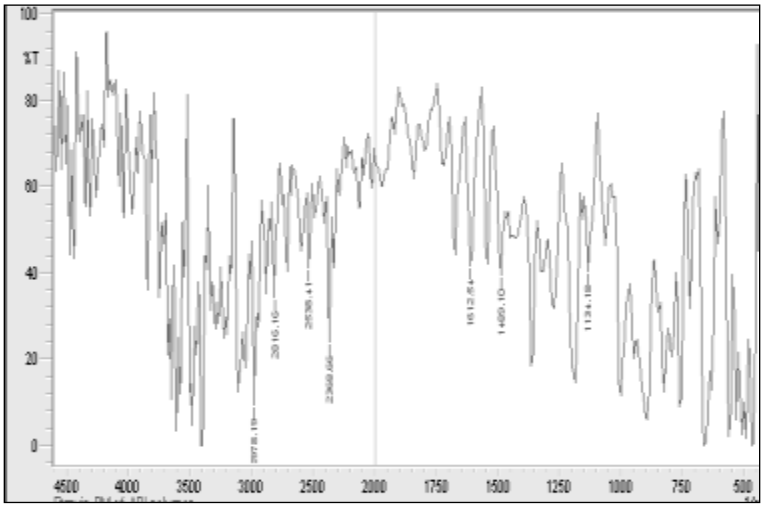


Figure 4: FTIR spectra of Physical mixture of Etravirine: Soluplus

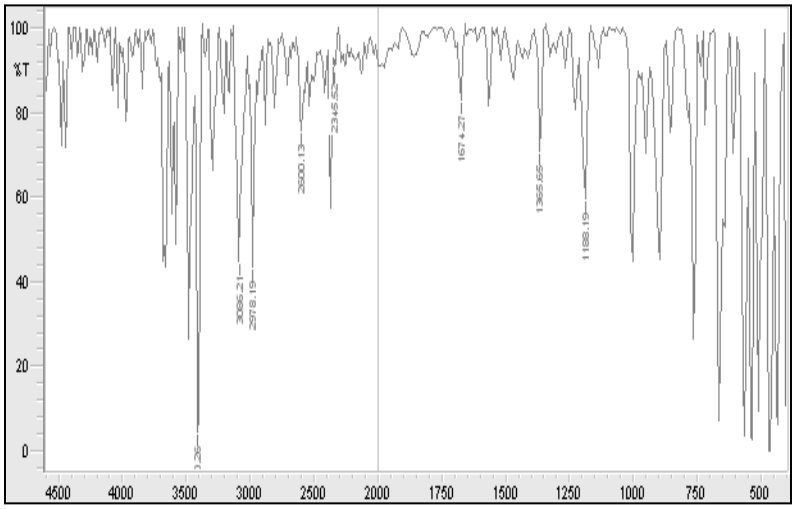


Figure 5: FTIR spectra of formulation HM3 solid dispersion prepared by hot melt extrusion

Differential scanning calorimetry

The DSC thermo grams of Plain Etravirine showed in Figure 6, sharp endothermic peak at melting point (265 ^{0}C), indicating that the drug is highly crystalline. The absence of drug peak in the solid dispersion formulation (HM3 (Etravirine&Soluplus (1:3)) indicating the drug was in amorphous form.

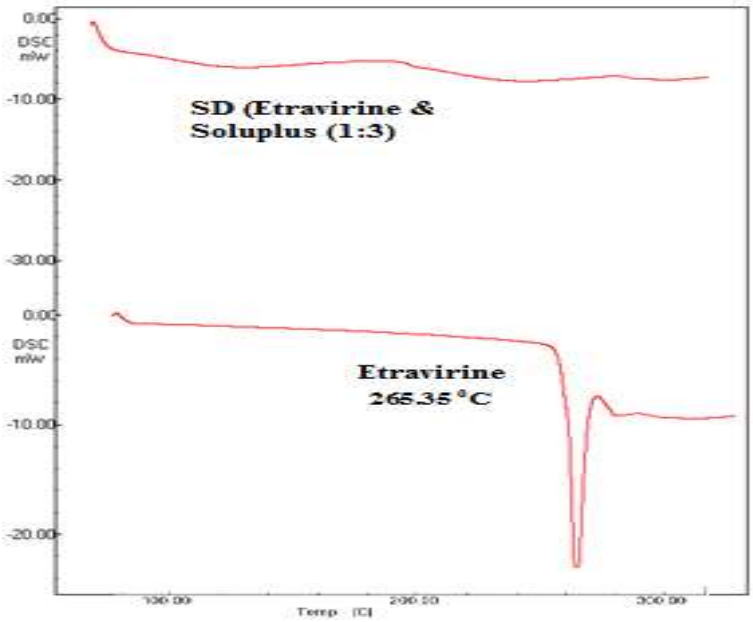
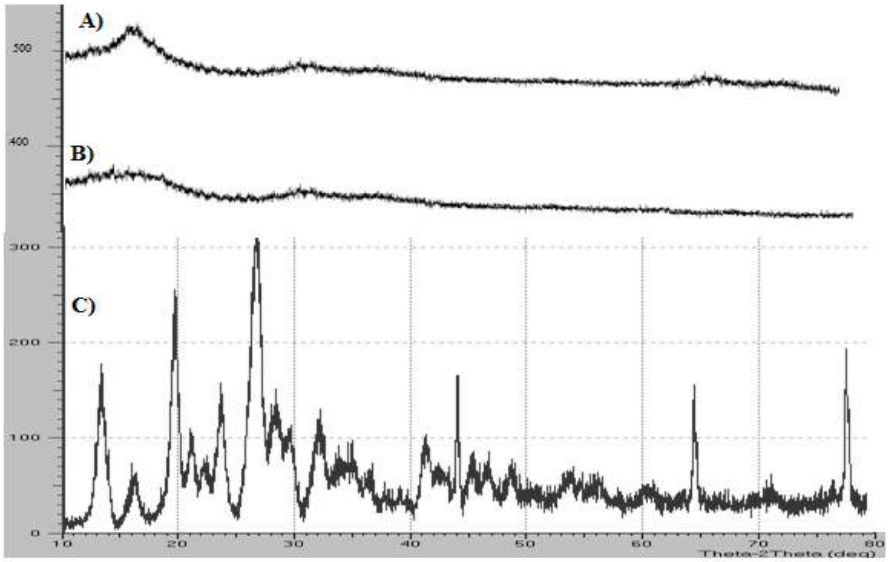


Figure 6: DSC thermograms of plain drug and optimized formulation HM3.

XRD Analysis

The XRD of Etravirine consist of sharp multiple peaks, indicating the crystalline nature of the drug. In case of SD (Etravirine with Soluplus (1:3)) when exposed to X-ray beam, disappearance of all crystalline endothermic peaks and characteristic intensities of Etravirine. This indicates complete transformation of crystalline Etravirine into amorphous form during HME process. From the XRD studies, it is confirmed that the drug substance in hot melt extruded granules (HM3) has been converted into amorphous form (Figure 7).



A) Optimized Formulation HM3 B) Placebo C) Etravirine plain drug

Figure 7: Powder X-ray diffraction patterns of plain drug, placebo and formulation

Evaluation parameters

Solubility studies & Drug content of Etravirine solid dispersions

Based on the HME process feasibility, among the 11 formulation trials by HME process, it was concluded that both Soluplus and Kollidon VA64 were suitable for hot melt extrusion of Etravirine at temperature range of 160°C to 180°C, the solubility of 7 formulations of solid dispersions (HM1 to HM5 and HM10 to HM11) were analysed for solubility of drug substance and were compared with plain drug itself. The formulation with Soluplus in the ratio of 1:3 (drug to carrier) which has shown increased the solubility almost 4 fold compared to that of the plain drug (Plain drug solubility is 0.07).The drug content of the prepared solid dispersions was found to be in the range of 92.2 – 98.5%. Maximum % drug content i.e. 98.5% was found in the formulation HM11. The results are tabulated in Table 9.

Table 9: Solubility studies & Drug content of solid dispersions prepared by hot melt extrusion method

S. No.	Formulation code	Solubility (mg/ml)	(%) Drug content
1	Plain drug	0.07	-------
2	HM1	0.23	92.2%
3	HM2	0.25	93.4%
4	HM3	0.30	96.3%
5	HM4	0.28	97.2%
6	HM5	0.27	98.3%
7	HM10	0.25	96.8%
8	HM11	0.26	98.5%

Table 10: Physico-chemical characteristics of Etravirine solid dispersion tablets

Batch No→ Parameters↓	**Intelence®** (Etravirine) 200 mg Tablets	**EHT3**	**EHT4**	**EHT5**	**EHT10**	**EHT11**
Description	Off-white coloured, Elliptical / Oval shaped, biconvex tablets debossed with 'T 200' on one side and plan surface on the other side.	Light brown coloured, oval shaped biconvex tablets debossed with '109' on one side 'J' on the other side			Off-white to light brown coloured, oval shaped biconvex tablets debossed with '109' on one side 'J' on the other side	
Weight of Tablets (mg)	1390 - 1408	1392 – 1405	1397 - 1406	1394 - 1408	1395 - 1405	1392 – 1406
Thickness (mm)	8.2 – 8.3 mm	8.3 – 8.5 mm			8.25 – 8.40 mm	
Hardness (kp)	15 – 18	15.5 – 17.5	15 - 17	15 – 16.5	13 - 15	13 - 15
Disintegration time (sec / minutes)	50 sec – 1 min 30 sec	50 sec - 1 min 45 sec	1 min 15 sec - 2 min	1 min 45 sec - 2 min 30 sec	25 – 27 minutes	35 – 38 minutes
DT pattern	Immediate bursting, some of the portion floating	Immediate bursting, some of the portion floating	Slow dispersion, some of the portion floating	Slow dispersion, some of the portion floating	Slowly eroding	Slowly eroding
% Friability	-	0.35%	0.28%	0.25%	0.25%	0.20%

The disintegration time (DT) of tablets of EHT3 (Etravirine and Soluplus in 1:3 ratios) was found to be similar to that of Innovator product and disintegrated by slow dispersion pattern, portion of tablets were floating on water and disintegration time was found to be 50 sec - 1 min 45 sec, where as DT of Innovator tablets was found to be 50 sec – 1 min 30 sec. Where as in EHT10 & EHT11 tablets were disintegrated by slow erosion pattern, and disintegration time was found to be 25 – 27 minutes and 35 - 38, respectively. The disintegration pattern of Tablets of hot melt extruded with Copovidone (Kollidon VA 64) was completely different from that of Innovator Tablets and more over there was a significant difference in the disintegration time. Among the 11 formulation trials by HME process, it was concluded that both Soluplus and Kollidon VA64 were suitable for hot melt extrusion of Etravirine at temperature range of 160°C to 180°C (below 160°C, the transparent flakes were not formed and running the HME process above 190°C would not be advisable in point of Hot melt extruder efficiency and degradation of polymer).Based on the similar

disintegration pattern as well as lower disintegration time, the batches with Soluplus in 1:1, 1:2, 1:3, 1:4 and 1:5 and in addition trials with Kollidon VA64 in 1:3 & 1:5 were evaluated for dissolution profiles and compared against dissolution profiles of plain drug substance and to that of Innovator product profiles. The results are depicted in Table 11.

***In vitro* dissolution studies**

Table 11: *In vitro* dissolution profiles of plain drug and different formulations of Etravirine solid dispersions (EHT1-EHT5; EHT10&EHT11)

Time in Min	Cumulative % drug release								
	Plain drug	INTELENCE® 200mg	EHT1	EHT2	EHT3	EHT4	EHT5	EHT10	EHT11
0	0	0	0	0	0	0	0	0	0
5	14.9	22.4	29.1	26.3	36.4	36.1	28.1	27.2	26.5
10	20.0	29.4	37.5	39.2	48.1	45.2	37.8	37.1	36.4
20	27.4	42.8	48.2	47.1	56.5	59.4	48.5	45.2	46.8
30	29.2	52	56.3	54.5	70.3	65.3	50.4	56.2	54.2
45	30.3	66.8	66.1	65.4	80.1	71.1	70.8	64.1	65.4
60	34.9	78.2	70.2	75.7	88.2	82.5	78.2	72.1	71.2
90	38.9	92.8	75.1	79.9	95.1	89.2	85.5	78.2	77.1

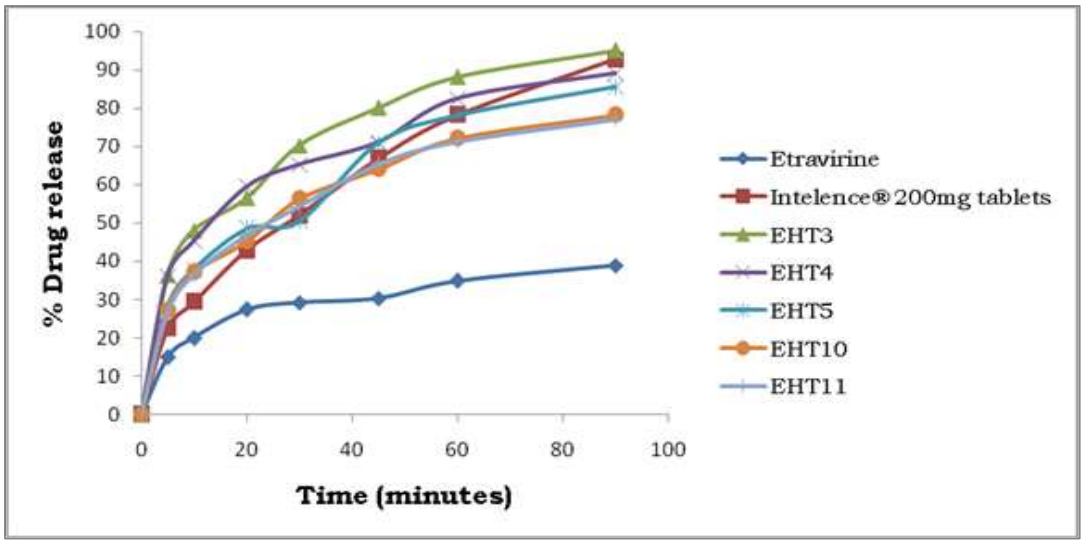


Figure 8: *In vitro* dissolution profiles of plain drug and solid dispersion of Etravirine solid dispersions EHT3-EHT5 & EHT10&EHT11.

The Table 11shows the cumulative percent drug released as a function of time for all formulations. Cumulative percent drug released after 90 min was 75.1%, 79.9%, 95.1%, 89.2%, 85.5%, 78.2% and 77.1% for EHT1-EHT5 & EHT10& EHT11respectively and was 38.9 %in 90 min for plain drug and was 92.8% for Innovator product. *In vitro* studies reveal that there is marked increase in the dissolution rate of Etravirine from all the solid dispersions when compared to plain Etravirine.

From the *in vitro* drug release profile, it can be seen that formulation EHT3 was best formulation containing Soluplus (1:3 ratio of drug: Soluplus) shown higher dissolution rate i.e. 95.1% in 90 minutes as compared with other formulations. This may be attributed to the increase in drug wettability, solubilization of the drug due to hydrophilic carrier. The graphical representation of solid dispersions of EHT3 to EHT5, EHT10 & EHT11 was depicted in Figure 8.

Spray Drying

Preparation of etravirine solid dispersions by spray drying

Etravirine was added slowly to 6:4 solvent mixtures ofDichloromethane and Acetone under continuous stirring and stirred well till to get a clear solution. In one set of trials Polyvinylpyrrolidone (Kollidon 30) / in other set of trials Polyvinyl Caprolactam-Polyvinyl Acetate-Polyethylene Glycol Graft Copolymer **(**Soluplus) was addedto the above drug solution and stirred well till to get a clear solution. Microcrystalline cellulose, grade Avicel PH105 was dispersed in the above solution. The above dispersion was subjected to spray drying using BUCHI spray dryer (Inlet air temperature 60 – 70°C, Aspiration 90 - 100%; Nozzle tip: 0.2 mm; Nitrogen gas cylinder). The composition is shown in Table 13. The particle size of MCC is selected such that when mixed into the solution of active drug substance and water soluble / hydrophilic polymer should not block / clog the atomizer, should be easily atomizable. With the addition of Microcrystalline cellulose, the density of the resulting solid pharmaceutical composition will be increased, it also helps in improvement of flow properties of resulting spray dried mixture, may also function to increase the properties compressibility, disintegration and dissolution of the spray-dried solid dispersion of Etravirine.The majority of the spray dried powder was collected in the drying chamber cylinder with aspiration below 90% and it was found to be coarser powder as compared to spray dried powder, which was collected in Extraction cyclone cylinder where aspiration above 90% to 100%. Spray dried powder was found to be coarser with nozzle size more than 0.4 mm, coarser grade powder was collected in drying chamber cylinder.The parameters are depicted in Table 12 and composition is shown in Table 13.

Table 12: Parameters considered during spray drying

Atomizer Qualifications:		**Spray drying parameters**	
Nozzle tip:	0.2 mm	Inlet temperature	60 - 70°C
Nozzle diameter:	0.4 mm	Pump rate for spraying Solution / dispersion	25 – 35%
Cap diameter:	1.4 mm	Nitrogen gas pressure	30mm Hg

Table 13: Composition of Etravirine solid dispersions by Spray drying technique (SDT)

S.No	Ingredients (Units)	ESD1	ESD2	ESD3	ESD4
1.	Etravirine (mg)	200	200	200	200
2.	Polyvinyl pyrrolidone (Kollidon 30)(mg)	400	100	-	-
3.	Soluplus	-	-	100	400
4.	Microcrystalline cellulose (Avicel PH 105)(mg)	100	100	100	100
5.	Dichloromethane (6 parts) (mg)	7,200	7,200	7,200	7,200
6.	Acetone (4 parts) (mg)	4,800	4,800	4,800	4,800

The resulting spray dried mixture was screened for drug substance solubility. The solid dispersion by spray dried mixture showing good solubility and were further studied for the % Practical yield, drug content and *in-vitro* release studies (spray dried powder was blended with 30 mg of Avicel PH102 and filled in empty hard gelatin capsule shells).

Solubility studies of Etravirine solid dispersions

Solubility measurements of Etravirine were performed according to a published method (Higuchi and Connors 1965).Etravirine with carriers were shaken for the 48 hours at room temperature. Subsequently, the suspensions were filtered through a whatman filter paper no 1. Filtered solutions were analyzed for the etravirine in UV 235 nm.

Evaluation of Etravirine solid dispersions

Solid dispersions of Etravirine with Kollidon 30 (in one set of trials) / and Soluplus (in another set of trials) with Microcrystalline cellulose (Avicel PH105) were prepared by Spray drying process.

Drug content

Solid dispersions equivalent to 200mg of Etravirine were weighed accurately and dissolved in 100 ml of Methanol. The solution was filtered, diluted suitable and drug content was analyzed at λ_{max} 235 nm against blank by UV spectrometer. The actual drug content was calculated using the following equation as follows:

$$\% \text{ Drug content} = \frac{\text{Actual amount of drug in solid dispersion}}{\text{Theoretical amount of drug in solid dispersion}} \times 100$$

***In vitro* drug release studies**

The *in vitro* drug release profile for each solid dispersion as well as plain drug was performed using USP type 2 dissolution apparatus. The sample equivalent to 200 mg of Etravirine was added and the conditions maintained were shown in the table 14 as follows:

The samples were drawn at specified time intervals and the obtained samples were analyzed by using UV/Visible spectrophotometer at 235nm. The cumulative percentage release was calculated.

Table 14:*In Vitro* dissolution studies test parameters

Instrument	**Electro lab- USP type II dissolution test apparatus.**
Dissolution medium	1.0 % Sodium lauryl sulfate (SLS) in 0.01 M HCl in two phases:
Apparatus	USP apparatus – II (Paddle type)
Temperature	37 ± 0.5^0C
RPM	50
Volume of medium	900 ml.
Sampling intervals	5, 10, 15, 30,45,60 and 90 minutes
Sample volume	10 ml withdrawn and replaced with 10 ml of dissolution medium.

RESULTS ANDDISCUSSION

Preparation of Etravirine solid dispersions

In first set of trials Solid dispersions of Etravirine were prepared with Kollidon 30 and Microcrystalline cellulose in 1:2:0.5 and 2:1:1 (Drug substance to Microcrystalline cellulose is in 2:1 ratio) and in second set of trials Solid dispersions of Etravirine were prepared with Soluplus and Microcrystalline cellulose in 2:1:1 and 1:2:0.5 (Drug substance to Microcrystalline cellulose is in 2:1 ratio) done by Spray drying process. In the present investigation 4 formulations were prepared and their complete composition is shown in Table 14. The resulting spray dried powder (Figure 12 & Figure 13) was filled in hard gelatine capsules and evaluated for dissolution profiles.

Characterization

FT – IR studies:

FT-IR spectrums are mainly used to determine if there is any interaction between the drug and any of the excipient used.The optimized formulation ESD4 (Figure 15) displayed the characteristic peaks at wave numbers nearer to that of plain Etravirine (Figure 14). Overall there was no alteration in the characteristic peaks of in the optimized formulation suggesting that there was no interaction between the drug and polymers.

Figure 12: Etravirine solid dispersion (ESD2)Figure 13:Etravirine solid dispersion (ESD4)

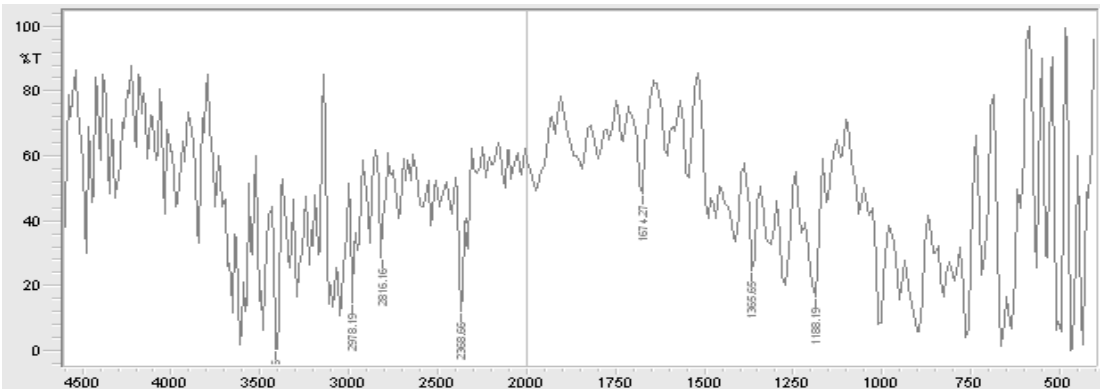


Figure 14: FTIR spectra of plain drug

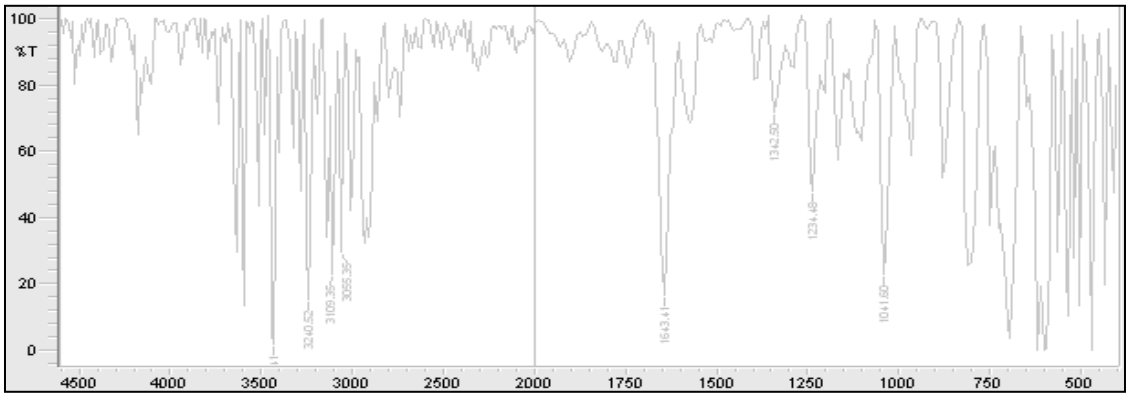


Figure 15: FTIR spectra of formulation ESD4 solid dispersion prepared by spray drying method

Differential scanning calorimetry

The DSC thermo grams of Plain Etravirineshowed in Figure 16, sharp endothermic peak at melting point (265^{0}C), indicating that the drug is highly crystalline. The absence of drug peak in the solid dispersion formulation ESD4 (Etravirine: Soluplus: MCC(1:2:0.5)) indicating the drug was in amorphous form.

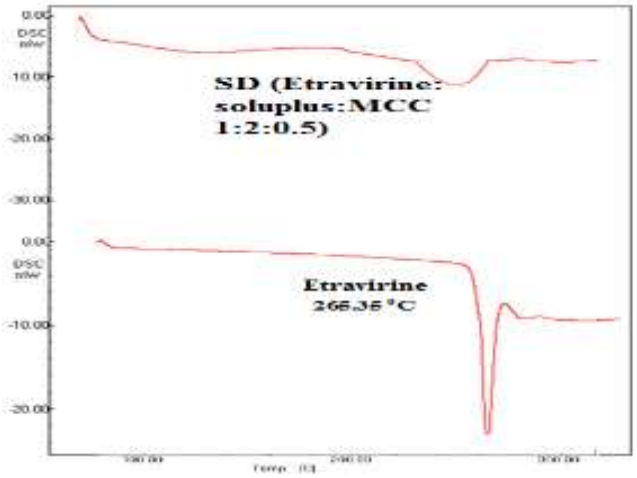
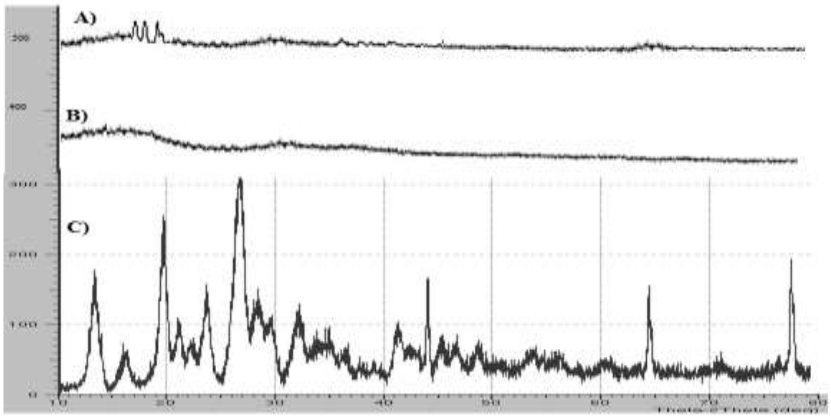


Figure 16: DSC thermo grams of plain drug and optimized formulation ESD4.

XRD Analysis

The XRD of Etravirine consist of sharp multiple peaks, indicating the crystalline nature of the drug. In case of SD optimized formulation ESD4 (Etravirine: Soluplus: MCC (1:2:0.5)) when exposed to X-ray beam, disappearance of all crystalline endothermic peaks and characteristic intensities of Etravirine (Figure 17). This indicates complete transformation of crystalline Etravirine into amorphous form during Spray drying process. From the XRD studies, it is clearly confirmed that the drug substance in spray dried powder (ESD4) has been converted into amorphous form.

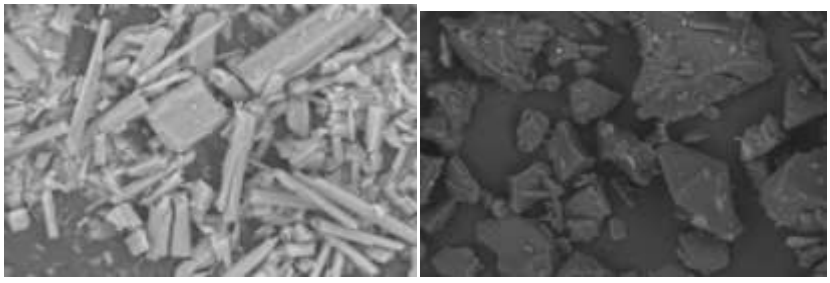


A) Optimized Formulation ESD4 B) Placebo C) Etravirine plain drug

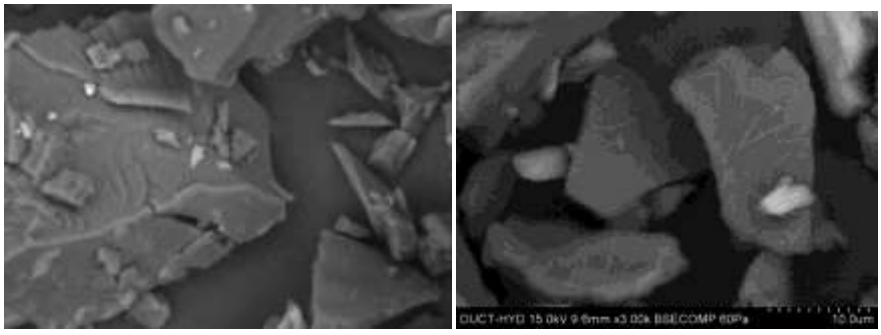
Figure 17: Powder X-ray diffraction patterns of plain drug, placebo and formulation

Scanning electron microscopy

Surface micrographs of prepared spray dried powder (ESD4) and plain Etravirine were determined using SEM technique. The SEM micrograph of plain Etravirine (Figure 18A) was observed with large crystalline forms of drug agglomerates with ordered shape and size (Figure 18A). The surface characteristics of SD of optimized formulation ESD4 (Figure 18 B, C & D) show rough disordered and intact structures, which subsequently help to dissolve drug when comes in contact with aqueous fluid.



A **B**



C **D**

Figure 18: SEM images of Etravirine plain drug (A), SD optimized formulation ESD4 (B, C & D)

Evaluation parameters:

Solubility studies of Etravirine solid dispersions:

Four formulations of solid dispersions were prepared by spray drying method / technique with their respective carriers with microcrystalline cellulose. After preparation of solid dispersion by spray drying process, the resulting spray dried mixture was analyzed for solubility of drug substance and were compared with plain drug substance itself. The formulation with Soluplus in the ratio of 1:2 (drug to carrier) which had shown increased solubility almost 4 fold as compared to that of the plain drug (Plain drug solubility is 0.07). The results are tabulated in Table 15. The drug content of the prepared solid dispersions was found to be in the range of 92.5 - 95.4 %. Maximum % drug content i.e. 98.47% was found in the formulation ESD4.

Table 15: Solubility studies and Drug content of solid dispersions prepared by spray drying method

S. No.	Formulation	Solubility (mg/ml)	% Drug content
1	Plain drug	0.07	---------
2	ESD1	0.22	90.5%
3	ESD2	0.24	92.4%
4	ESD3	0.26	95.4%
5	ESD4	0.28	95.2%

***In vitro* dissolution studies**

The drug release data obtained for formulations ESD1 to ESD4 are tabulated in Table 16. The Table shows the cumulative percent drug released as a function of time for all formulations. Cumulative percent drug released after 90 min was 76.8%, 79.8%, 82.2% and 94.1% for ESD1 to ESD4 respectively and was 38.9 %in 90 min for plain drug. *In vitro* studies reveal that there is marked increase in the dissolution rate of Etravirine from all the solid dispersions when compared to plain etravirine itself. From the *in vitro* drug release profiles, formulation ESD4 containing

Soluplus (1:2 ratio of drug: Soluplus) was best formulation which shows higher dissolution rate i.e. 93.0 % compared with other formulations. This may be attributed to the increase in drug wettability, conversion to amorphous form and solubilization of the drug due to hydrophilic carrier.

Table 16: *In vitro* dissolution profile of plain drug and different formulations of Etravirine solid dispersions (ESD1-ESD4).

Time in Min	Cumulative % drug release					
	Plain drug	INTELENCE® 200mg	ESD1	ESD2	ESD3	ESD4
0	0	0	0	0	0	0
5	14.9	23.6	26.2	28.2	25.4	30.2
10	20.0	30.2	37.3	37.1	35.1	42.1
20	27.4	43.4	48.1	48.5	42.2	53.3
30	29.2	53.2	55.5	50.3	58.5	68.2
45	30.3	69.4	66.3	69.4	63.3	79.4
60	34.9	80.6	71.4	77.1	75.5	88.2
90	38.9	93.2	76.8	79.8	82.2	93.0

The dissolution profiles of Etravirine solid dispersions prepared by HME (EHT3) and spray drying technique (ESD4) shown that the drug release was slightly on higher side at initial time points from Etravirine solid dispersion by HME when compared with Spray drying technique. The solid dispersion formulations by HME & SDT shown highest drug release i.e. 95.1% and 93.0% respectively after 90 minutes, where plain drug release was only 38.9% and Innovator product release was 93.2% (with basket at 100 rpm). The results are depicted in Table 17.

Table 17: *In vitro* dissolution profile of plain drug substance optimized Etravirine solid dispersions (EHT3 & ESD4) and Innovator product.

Time in Min	Cumulative % drug release				
	Plain drug	INTELENCE® 200mg		EHT3	ESD4
		Paddle at 50 rpm*	Basket at 100 rpm*		
0	0	0	0	0	0
5	14.9	22.4	23.6	36.4	30.2
10	20.0	29.4	30.2	48.1	42.1
20	27.4	42.8	43.4	56.5	53.3
30	29.2	52.0	53.2	70.3	68.2
45	30.3	66.8	69.4	80.1	79.4
60	34.9	78.2	80.6	88.2	88.2
90	38.9	92.8	93.2	95.1	94.1

*There was was no appreciable difference in the dissolution profiles of Innovator product with Paddle at 50 rpmm and with basket at 100 rpm in the same dissolution media.

CONCLUSION

In the present study the solid dispersions of the water insoluble drug substance Etravirine was successfully prepared by Hot-melt extrustion and Spray drying technique. The *in-vitro* dissolution test showed a significant increase in the dissolution rate of solid dispersions prepared by HME (95.1%) & SDT(93%) as compared with plain Etravirine (38.9%) within 90 minutes. The drug release was slightly on higher side at initial time points from Etravirine solid dispersion by HME when compared with Spray drying technique. The drug release from the innovator product was found to be 92.8% (Intelence 200 mg tablet). The increase in the dissolution rate of Etraviring is in the order of solid dispersions of HMT>SDT>Innovator product (Intelence® 200mg tablet) > Plain drug substance. The mechanism involved are solubilization and improved wetting of the drug substance with hydrophilic carriers rich microenvironment formed at the surface of the drug substance crystals after dissolution rate. The crystallinity of the drug substance was reduced in solid dispersion formulation with polymers. Results from FT-IR concluded that there was no well defined interaction between Etravirine and carriers.DSC and XRD showed a change in crystal structure toward an amorphous form of Etravirine. Finally it could be concluded that solid dispersion of Etravirine using hydrophilic polymers by HMT & SDT would improved the aqueous solubility, dissolution rate and thereby enhancing its systemic availability.

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