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Dissolution Enhancement of Poorly Water Soluble Efavirenz by Hot Melt Extrusion Technique

Smita Kolhe*[1], Dr. Praveen Chaudhari[2], Dhananjay More[3]
[1] P.E.S's, Modern College Of Pharmacy (For Ladies), Moshi, Pune, Ms, India
[2] P.E.S's, Modern College Of Pharmacy, Nigdi, Pune, Ms, India
[3] Emcure Pharmaceuticals Limited, Bhosari, Pune, Ms, India

Abstract

Large number of drugs; including new chemical entity (NCE), are facing the solubility problem [classified as biopharmaceutical classification system (BCS) Class II or IV]. Hence extensive development in solubility enhancement is required.

Hot melt extrusion (HME) is the most widely applied processing techniques useful for preparing granules, pellets, sustained release tablets, implants, transdermal and transmucosal drug delivery systems ,while its major advantages include enhancement of the dissolution rate and bioavailability, controlling or modifying drug release, taste masking, stabilizing the active pharmaceutical ingredient (API). Hot melt extruded dosage forms are generally complex mixtures of API, plastisizers and polymer carriers which are passed through single or twin-screw extruders at high temperature and stress, molten thermoplastic polymers during the extrusion process can function as thermal binders and/or release retardants.

Present investigation deals with enhancement of dissolution rate and hence solubility of Efavirenz (Efv), which belongs to BCS class II. Efv is non neucleotide reverse transcriptase inhibitor (NNRTI) for first line antiretroviral treatment type 1 with long half life of 52-56 hrs. Solubility enhancement techniques are available in wide range but HME was the preferred technique due to its several advantages. Copovidone (Kollidon VA64) as polymer and polyethylene glycol (PEG 4000), polyoxy 35 castor oil (Cremophor EL) and sorbiton monolaurate (Montane 20 PHA) as plasticizers were studied and optimized.

Evaluation techniques like saturation solubility, effect of temperature on preparation of complexes, differential scanning calorimetry (DSC), x-ray diffraction (XRD), Infra red (IR), dissolution and in vitro permeability studies were carried out. XRD data concluded that HME process demolished the sharp peaks of Efv which indicate the complete conversion of crystal form of Efv to amorphous form. Dissolution and solubility studies also showed enhancement in release rate of HME complex. Stability studies at 40 ° C/75 % RH (relative humidity) were studied and it shows that the sample is stable even after 3 months study.

HME is simple and efficient method to improve dissolution and permeability of poorly water soluble Efv.

*Corresponding author, Mailing address:
Smita Kolhe
C-302, Waghere Empire, Near City International School, Morwadi,
Pimpri, Pune.
EMAIL: smile1221@rediffmail.com

Key words:
Melt extrusion, solubility, glass transition temperature, plasticizers, BCS class II.

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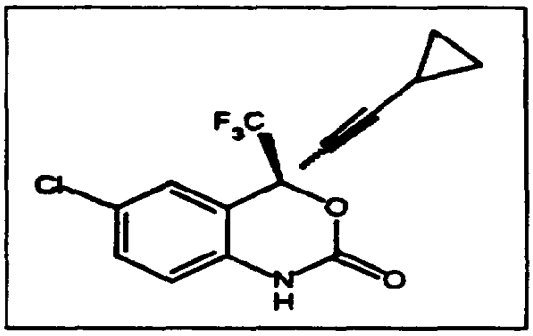
INTRODUCTION:

Millions of people are infected with human immunodeficiency virus type -1(HIV-1) worldwide. Efv[1-6], is non competitive inhibitor of reverse transcriptase enzyme in HIV-1, so it is effective against HIV-1[1,5,6,7,8,9], but has no efficacy on HIV -2

and human cellular DNA polymerase α, β, δ and γ. Reverse transcriptase enzyme transcribes viral RNA into DNA. Non- nucleotide reverse transcriptase inhibitor (NNRTI) binds within pocket, termed as NNRTI pocket. Efv is not effective against HIV-2 as pocket of HIV-2 reverse transcriptase has different structure which confers intrinsic resistance to NNRTI class.



Biopharmaceutical classification system (BCS), based on solubility and permeability of drug is divided into four classes. Efv shows low aqueous solubility and high membrane permeability (class II) [1, 10] as per the BCS classification given below:

BCS class I	**BCS class II**
High solubility	Low Solubility
High permeability	High permeability
BCS class III	**BCS class IV**
High solubility	Low Solubility
Low permeability	Low permeability

Increasing dissolution rate of poorly water soluble drug is major challenge in dosage form development. Bioavailability of orally administered drug mainly depends on its solubility and permeability. Drug discovery shows that compounds are often high molecular weight and highly lipophilic hence exhibits poor solubility.

Dissolution of various drugs can be improved by [11]

- Increasing the surface area available for dissolution.
- Optimizing wetting characteristics of compound surface.
- Decreasing boundary layer thickness.
- Ensuring sink conditions for dissolution.
- Improve apparent solubility.

Various solubility enhancement strategies in solid dispersion are fusion (melting), solvent evaporation, lyophilization (freeze drying), melt agglomeration process, extruding method, spray drying technique, use of surfactant, electrostatic spinning method and super critical fluid technology. One approach is formation of solid dispersion of drug with hydrophilic excipients. Ideal type of solid dispersion for increasing dissolution requires glass solution in which amorphous drug has low thermodynamic barrier to dissolve together with maximally reduced particle size. Also presence of hydrophilic excipients may lead to increase wetting leading to super saturation in the diffusion layer.

Glass solution is formed when two or more components are entirely miscible in molten state and cooled to form amorphous one phase system. For glass solution, melt extrusion studies were preferred due to several applications and advantages as given below:

Applications include: [12]

- Improving dissolution rate and bioavailability of drug.
- Controlling/modifying release of drug.
- Masking bitter taste of drug.

Advantages include: [12]

- Small equipment
- Economic and continuous process and scale up flexibility
- Solvent free manufacturing
- High mixing efficiency
- Closed process unit to prevent cross contamination
- Short processing time
- Easily controlled process parameters
- Possibility of online analytics for process control

Disadvantage includes: [12]

- Thermal process(drug/polymer stability)
- Flow properties of polymers are essential to processing
- Limited number of available polymers
- Require high energy input
- Melt technique process cannot be applied to heat sensitive materials due to high temperature involved.

HME can be simply defined as the process of forming a new material (the extrudate) by forcing it through an orifice or die under controlled conditions, such as temperature, mixing, feed-rate and pressure. [13]

A variety of carrier systems have been studied or used in HME dosage forms. Such carrier systems include polyvinylpyrrolidone (PVP) or its co-polymer such as polyvinylpyrrolidone-vinyl acetate, copovidone (Kollidon VA64), poly (ethylene-co-vinyl acetate), various grades of polyethylene glycols, cellulose ethers and acrylates, various molecular weight of polyethylene oxides, poly methacrylate derivatives and poloxamers. Amongst the different classes of biodegradable polymers, the thermoplastic aliphatic poly (esters) such as poly (lactide) (PLA), poly (glycolide) (PGA) and copolymer of lactide and glycolide, poly (lactide-co-glycolide) (PLGA) have been used in extrusion. Starch and starch derivatives have been applied along with low molecular weight excipients like sugars, sugar alcohols and waxes.

Plasticizers are added to HME formulations to facilitate the extrusion of the material and to increase the flexibility of the extrudate. The choice of suitable plasticizer depends on many factors, such as plasticizer-polymer compatibility and plasticizer stability. Polyethylene glycol (PEG 4000), polyoxy 35 castor oil (Cremophor EL) and sorbiton monolaurate (Montane 20 PHA), triacetin, citrate esters and low molecular weight polyethylene glycols have been investigated as plasticizers in hot-melt extruded systems.[14-21]

Basic requirements for polymers used in HME:

Thermoplastic behaviour	deformability is essential
Suitable Tg	50 – 180 °C
High thermal stability	50 – 180 °C
Low hygroscopicity	prevents crystallization
No toxicity	application of large amounts possible
High or no solubilization	thermodynamically stable capability formulation

MATERIALS AND METHODS:

Efv was received as gift sample from Emcure pharmaceuticals limited, Pune, India. Copovidone (Kollidon VA64), polyoxyl 35 castor oil (Cremophor EL), PEG 4000, sorbiton monolaurate and all other reagents and chemicals used were of analytical grade.

METHODS:

1. Characterisation of Efv:

Efv was characterized by following test:

A. Description:[1,4,6]

Efv was studied for its color and physical appearance.

B. Saturation Solubility:[1,13]

Solubility of Efv was measured in distilled water. An excess amount of drug was added to 50 ml conical flask and was kept under shaking for 72 hrs (Rotary shaker, Biomedica). Saturated solution was filtered through 0.45 µ membrane filter, absorbance of filtered solutions was determined and amount of drug solubilised was calculated.

C. Melting Point: [3,4]

Efv melting point was determined by both the capillary method and instrumental method. Capillary method was done by taking capillary in which drug was inserted and then attached to thermometer. Both capillary along with thermometer was inserted into the parrafin bath which was heated and the melting temperature was recorded.

Instrumental method involves insertion of capillary in the paraffin bath and the melting temperature was recorded electronically (Melting point apparatus VEEGO). This method proved to be more accurate than the former method.

D. XRD:[13]

Efv was subjected to XRD (P.W. 1729, X-ray generator, Philips, Nether land). To study XRD pattern, the drug sample was placed into aluminum holder and the instrument was operated between initial and final 2θ angle of 5-50° respectively in an increment of 0.4°2θ.

E. IR:[13]

Efv, was subjected to Fourier Transform Infra Red (FTIR 8400s spectrophotometer Shimadzu) studies to check the characteristic sharp peaks of drug and its functional groups. The Pottasium bromide (KBr) disk method was used for preparation of sample. The samples were ground gently with anhydrous KBr and compressed to form pellet. The scanning range was 400-4000cm^{-1}.

F. DSC:[13]

Efv was subjected to DSC study using (Mettler TA 4000) DSC apparatus. First 5-10 mg of sample was weighed into aluminum crucible. This powder was analyzed by heating at scanning rate of 10°C / minute over a temperature range 50 to 200° C with nitrogen flow of 50mL/min.

2. Preparation of Calibration Curve:[1, 13]

100µg/ml stock solution of Efv was prepared in 2% Sodium Lauryl Sulphate (SLS) by first dissolving 100mg of drug in 100mL of 2%w/v SLS. Further dilutions were made to obtain solutions of 1, 2, 3.....10 µg/mL. Respective absorbance values were measured at fixed λmax.

3. Determination of Drug :Polymer Ratio:[14,15]

Solubility of Efv was checked in different solvents such as methanol, ethanol and water. Both drug and polymer were soluble in ethanol and hence selected for optimization of ratio. Drug and polymer (1:1 to 1:5) were solubilised in ethanol. The obtained solution was then poured in petri plates and films were cast by solvent evaporation method and were observed after 24 hrs at room temperature for their appearance.

4. Effect of Temperature on Decomposition of Polymers:[14,15]

Polymer was subjected to different temperatures at 120, 130, 140, 150 °C, using heating mantle (Lab Hosp. Corp., ELCON) and the molten polymer was cooled at room temperature and then milled using hammer mill(Lab Hosp).The obtained granules of different processing temperature were then compared for their appearance and discoloration .

5. Preparation of Non HME (NHME) Formulation [As control sample]:

Table 1: NHME FORMULATION

Ingredient	Applications	Quantity per tablet (mg)
Efv	Drug	600
Lactose monohydrate	Diluent	200
Microcrystalline Cellulose	Diluent and binder	200
Crospovidone	Disintegrant	45
Magnesium Stearate	Lubricant	5
Total		1050

Efv (as such), lactose monohydrate, microcrystalline cellulose and crospovidone as in table 1 were (sifted through #40 sieve) mixed well for 5 min. Prepared dry mix lubricated by magnesium stearate (sifted through # 60 sieve) for 3 min. Lubricated granules were evaluated for flow properties and compressed into tablets.

6. Effect of type and concentration of plasticizer on solubility and dissolution:

Table 2: HME FORMULATION

	Applications	E1	E2	E3	E4	E5	E6	E7	E8	E9
Dry mix for HME		**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**
Efv	Drug	600	600	600	600	600	600	600	600	600
Kollidon VA64	Thermal binder	600	600	600	600	600	600	600	600	600
PEG 4000	Plasticizer	60*	-	-	120**	180#	-	-	-	-
Cremophor EL	Plasticizer	-	60*	-	-	-	120**	180#	-	-
Montane 20 PHA	Plasticizer	-	-	60*	-	-	-	-	120**	180#
HME Granules		1260	1260	1260	1320	1380	1320	1380	1320	1380
Lubricants										
Colloidal Silicon Dioxide	Lubricant	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
Sodium Stearyl Fumarate	Lubricant	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7
Total		1264	1264	1264	1324	1384	1324	1384	1324	1384

*10% w/w of polymer (Kollidon VA 64)
**20% w/w of polymer (Kollidon VA 64)
#30% w/w of polymer (Kollidon VA 64)

Efv, polymer and plasticizer as in table 2 were mixed well and taken in porcelain dish. This dry mix was subjected to melt at 140 ^{0}C using heating mantle (Lab Hosp. Corp., ELCON) with mixing to get clear molten mass. Curing of molten mass was done by keeping it at room temperature for 12 hrs.

a. Size Reduction of HME Flakes:

Solid dispersion prepared by HME was then passed through 3mm screen of hammer mill, milled granules were sifted through #40 sieve. Granules retained on #40 sieve then passed through 1mm screen of hammer mill, milled granules were sifted through #40 sieve. Obtained granules were mixed well for 5min.

b. Lubrication of HME Granules:

HME granules were then lubricated by sodium stearyl fumarate and colloidal silicon dioxide (sifted through #60 sieve) for 5 min. Lubricated granules were evaluated for flow properties and compressed into tablets. Compression parameters were recorded.

c. Characterization of drug , HME Granules And NHME Dry Mix:

i. DSC:

The drug, HME and NHME were subjected to DSC study using (Mettler TA 4000) DSC apparatus. First 5-10 mg of sample was weighed into aluminum crucible. These powders/granules were analyzed by heating at scanning rate of 10^{0}C / minute over a temperature range 50 to 200^0 C with nitrogen flow of 50mL/min.

ii. XRD:

The drug, HME complex and NHME formulated powder were subjected to XRD (using P.W. 1729, X-Ray Generator, Philips, Nether land). To study XRD pattern, the sample was placed into aluminum holder and the instrument was operated between initial and final 2θ angle of 5-50^0 respectively in an increment of 0.4^{0}2θ.

iii. IR:

The drug, HME complex and NHME formulated powder were subjected to FTIR (8400s spectrophotometer Shimadzu) studies to check the characteristic sharp peaks of drug and its functional groups. The KBr disk method was used for preparation of sample.

Prepared tablets (table 2) of formulation E1 –E9 were subjected to solubility and dissolution study.

5. In Vitro Permeability of HME and NHME Formulation:

The prepared tablets were subjected to In vitro permeability test using dialysis membrane LA401.

6. Stability Studies:[13,16]

Stability studies of tablets were performed as per International Conference on Harmonisation (ICH) guidelines. The tablets from the optimized batch were subjected for stability study at 40°C/75% RH for 3 months.

RESULT AND DISCUSSION

1. Characterisation of Efv:

A. Description:

White to slightly pinkish coloured powder. Hence confirms the description as per the certificate of analysis (COA).

B. **Saturation Solubility**:

As per literature the solutbility of Efv in water is less than 10µg/mL. Experimentally it was found to be 9.19µg/mL.

C. Melting point:

Melting point by capillary method and instrumental method observed was 136°C and 140°C respectively. (as per the literature 139-141°C)

D. XRD:

Sharp peaks were observed from 5 to 30° of 2θ scale, which reveals the crystalline nature of drug.

E. IR:

IR spectra reveal characteristic functional groups same as reference standard.

F. DSC:

DSC studies show the peak value at 138.77°C corresponds to standard melting point (139-141°C).

All the characteristic test of pure drug confirms the purity of Efv.

2. Preparation of Standard Curve:

Efv is soluble in 2% SLS in distilled water, so this medium was used for preparation of standard curve. λ max, correlation coefficient R and calibration curve equation are as given below.

Using absorbance and concentration data Beer lamberts plot was prepared which is shown in figure 1 and table 3. Calibration curve equation has shown linear relationship and high degree of correlation in the range of 1-10 µg/mL at 247nm. This curve was utilized in Efv estimation as and when required.

Table 3: Calibration Curve For Efv (Using 2% SLS)

Concentration (µg/mL)	Average Absorbance
1	0.0124±0.022
2	0.0732±0.134
3	0.1218±0.675
4	0.1795±0.400
5	0.2333±0.942
6	0.3042±0.0321
7	0.3506±0.001
8	0.3998±0.024
9	0.4604±0.768
10	0.5272±0.004

n=3

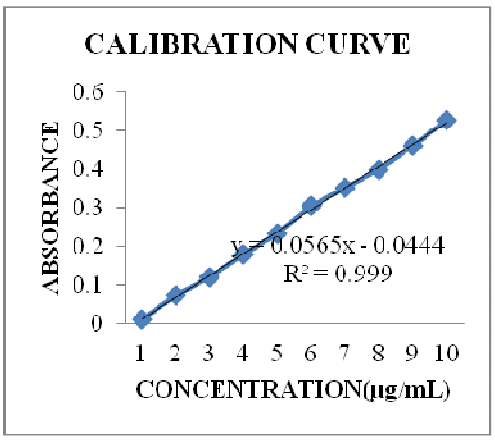


Figure 1: Calibration curve for EFV (using 2% sls in water)

3. Determination of Drug :Polymer Ratio

Initially all the prepared films were transparent as in table 4. Appearance of these films even after storage at room temperature for 24hrs remained transparent except film of pure drug which on storage shows the recrystallization of drug. In all other ratios of drug: polymer (1:1 to 1:5) Efv remain in solubilised state throughout the storage period as in figure 2. So 1:1 ratio was selected for further study as Efv remains in solubilised state in this ratio.

Table 4: Optimisation of Drug: Polymer Ratio

	Sample	Solvent	Ratio	Solubility	Appearence	Appearance after 24 hrs
A	Drug	Ethanol	-	Clear solution	Clear, transparent	White clusters were seen
B	Polymer	Ethanol	-	Clear solution	Clear, transparent	Clear, transparent
C	Drug:Polymer(1:1)	Ethanol	1:1	Clear solution	Clear, transparent	Clear, transparent
D	Drug:Polymer(1:2)	Ethanol	1:2	Clear solution	Clear, transparent	Clear, transparent
E	Drug:Polymer(1:3)	Ethanol	1:3	Clear solution	Clear, transparent	Clear, transparent
F	Drug:Polymer(1:4)	Ethanol	1:4	Clear solution	Clear, transparent	Clear, transparent
G	Drug:Polymer(1:5)	Ethanol	1:5	Clear solution	Clear, transparent	Clear, transparent

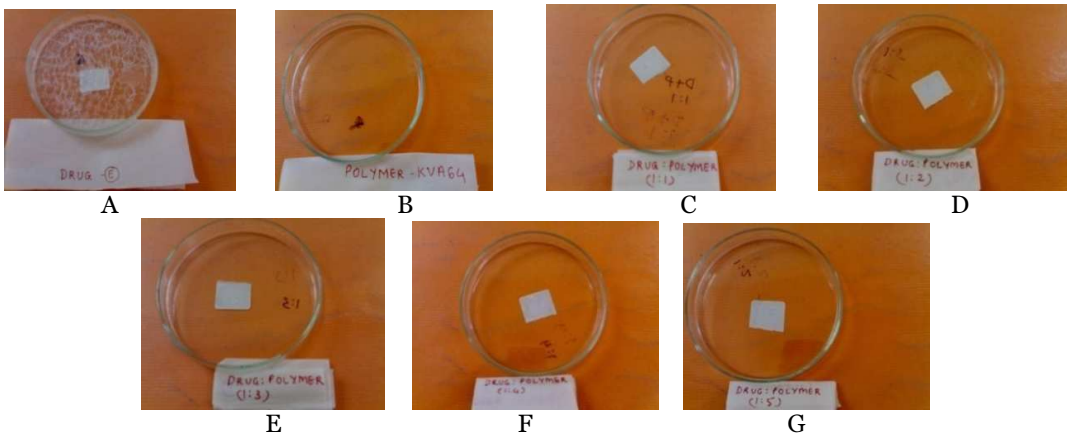


FIGURE 2: APPEARANCE OF FILMS AFTER 24 hrs (AT ROOM TEMPERATURE AND IN DESICATOR), A: PURE DRUG, B: POLYMER, C: DRUG: POLYMER (1:1), D: DRUG: POLYMER (1:2), E:DRUG: POLYMER (1:3), F: DRUG: POLYMER (1:4), G: DRUG: POLYMER (1:5)

4. Effect of Temperature on Decomposition of Polymer

Extrudates of Kollidon VA64 look clear and glassy, with increasing temperature the colour turns yellowish and brownish. The actual discolouration of polymer was observed above 120^0 C processing temperature. Above 200^{0}C melting temperature extrusion becomes difficult.

5. Preparation of Non HME Formulation

Lubricated granules characterization and compression parameters are as given below in table 5.

Table 5: Evaluation of Lubricated Granules and Tablets

Parameters for granules	**Observations**
Bulk Density(g/mL)	0.48±0.034
Tapped density(g/mL)	0.59±0.006
Hausner's Ratio	1.23±0.011
Carr's Index (%)	18.64±0.067
Angle of repose (⁰)	28±0.098
Parameters for tablets	**Observations**
Machine	Lab Hosp
Punch	19 x 9.5,Capsule shape
Weight of tablet(mg)	1050±0.024
Hardness(kg)	12-15±0.061
Disintegration Time(mins)	9±0.151
Friability (%)	0.2±0.101

n=3

6. Effect of type and concentration of plasticizer on solubility and dissolution:

Glass transition temperature (Tg) (figure 3) of Kollidon VA64 is 101⁰C, which may be reduced after addition of plastisizers. As a general rule, melt extrusion process should be run at temperature 20-40⁰C above the Tg. Temperature range for melt extursion of pure polymer is 155-200⁰C where as for polymer plastisizer combination it is 120-200⁰C

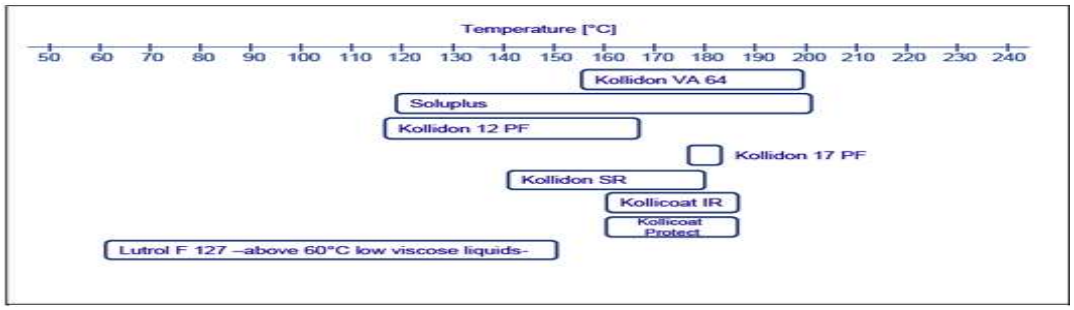


Figure 3: Temperature range for extrusion of pure polymers

In melt extrusion process drug can be either dissolved or dispersed in an amorphous or crystalline state. To obtain thermodynamically stable formulation drug must get completely dissolved below its saturation solubility in the polymer which is known as solid solution .When the main objective of melt extrusion technology is enhancement of

a. **Size Reduction and**
b. **Lubrication of Granules**

solubility, the processing temperature should be equivalent or slightly higher than melting point of drug to get solid solution system.Melting point of Efv is approximately 138⁰C (by DSC method), so the 140⁰C temperature was selected for melt extrusion processing to get solid solution.

Table 6: Evaluation of Lubricated Granules and Tablets

Parameters for granules	**Observations**		
	E1	**E2**	**E3**
Bulk Density(g/mL)	0.54±0.05	0.524±0.48	0.518±0.062
Tapped density(g/mL)	0.69±0.054	0.674±0.001	0.657±0.029
Hausner's Ratio	1.28±0.151	1.29±0.033	1.27±0.0364
Carr's Index (%)	21.74±0.011	22.25±0.0561	21.15±0.227
Angle of repose(⁰)	28±0.001	27±0.0723	29±0.0325
Parameters for tablets	**E1**	**E2**	**E3**
Machine	Lab. Hosp.		
Punch	19 x 9.5,Capsule shape		
Weight of tablet(mg)	1264 mg	1264 mg	1264 mg
Hardness(kg)	12-15 kg±0.076	12-15 kg±0.044	12-15 kg±0.071
Disintegration Time(min)	25mins±0.021	27mins±0.066	26mins±0.029
Friability(%)	0.28%±0.001	0.31%±0.008	0.26%±0.037

n=3

As compared to NHME granules, dense granules were obtained by HME process. Increased bulk and tapped density values confirmed the presence of dense granules. Hausner's ratio, carr's index and angle of repose values reveals the good flow characteristics of granules (table 6). Disintegration time of tablets prepared by HME technology was three times higher than those prepared by NHME technology (table 6). Disintegration pattern was bursting and erosion in tablets prepared by NHME and HME technology respectively.

c. Characterization of drug , HME Granules And NHME Dry Mix

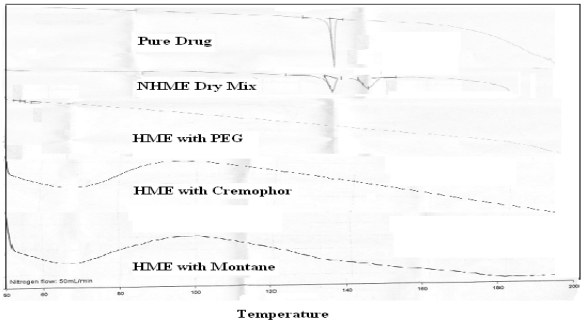


FIGURE 4 I: DSC OF A) PURE DRUG B) NHME C) HME PEG D) HME CHREMOPHOR E) HME MONTANE 20 PHA

Absence of sharp peak was observed in DSC of HME granules as compared to DSC of pure drug. This indicates the presence of amorphous drug in molten carrier, but in case of NHME the sharp peak was observed indicating the crystalline nature of drug. DSC thermograms of Efv in NHME and Efv HME granules represented in the figure 4I. The DSC thermograms of pure Efv shows sharp endotherm at 138.77°C attributed to the melting of Efv. This sharp melting endotherm indicates the crystalline nature of drug. The DSC thermogram of NHME shows melting at 135.24 and 144.03°C of the drug and polymer respectively. The DSC thermogram of HME PEG, HME Chremophor and HME Montane 20PHA shows absence of characteristic melting endotherm of efv indicating the perfect miscibility of drug and polymer in the solid dispersion. As single Tg is characteristic of the thermoplastic system, the DSC thermogram of solid dispersion shows complete amorphization of drug.

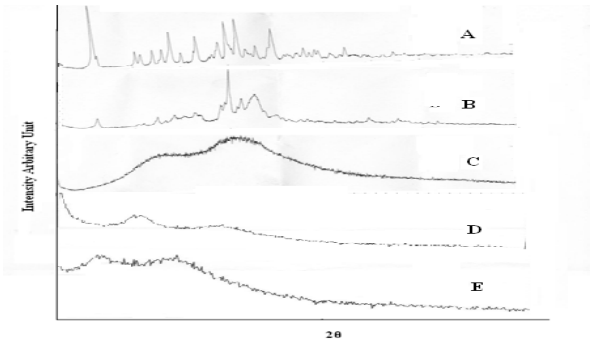


FIGURE 4 II: XRD OF A) PURE DRUG B) NHME C) HME PEG D) HME CHREMOPHOR E) HME MONTANE 20 PHA

The XRD pattern of pure drug, NHME, HME PEG, HME Chremophor and HME Montane PHA were recorded between 0-50 2θ scale and represented in the following figure 4II. The XRD pattern of pure drug shows several diffraction peaks indicating the crystalline nature of the drug. Peaks for crystallinity were observed in pure drug (Figure No. 4II a). The XRD pattern of NHME showed the presence of peaks with a significant decrease in intensity or absence of some major efv crystalline peaks (Figure No. 4II c). Generally this partial loss of crystallinity may be observed due to physical presence of amorphous excipients and their higher concentration. The drug was still in the crystalline state in this system. The XRD patterns of HME PEG, HME Sorbiton and HME montane 20 PHA showed complete absence of peaks of crystallinity as observed in pure Efv indicated complete amorphization of efv in the melt. The presence of hump in all the samples indicates the amorphous nature of drug in the HME granules (Figure 4II c, d, e).

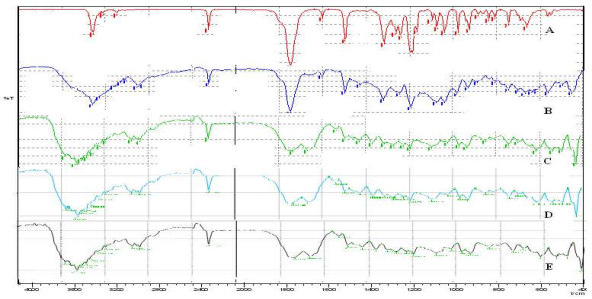


FIGURE 4 III: FOURIER TRANSFORM INFRARED OF A) PURE DRUG B) NHME C) HME PEG D) HME CHREMOPHOR E) HME MONTANE PHA

From the FTIR study it is clear that there is no interaction between drug PEG, drug chremophor, drug montane 20 PHA. All the peaks were responsible for active functional groups which were even present in HME granules of different types. In NHME similar peaks were observed as that of pure drug indicating no complex formation between drug and polymer

7. Dissolution and saturation solubility

In all the formulations prepared by HME technology the average dissolution at 120 min is as given below in table 7:

Table 7: DISSOLUTION STUDIES OF VARIOUS FORMULATIONS

Type of formulation	% Drug release
HME (10% PEG 4000)	85.20±0.035
HME (10% Chremophor)	88.00±0.044
HME (10% Montane20 PHA)	86.67±0.075
NHME	97.32±0.259
Marketed	98.44±0.067

n=3

The disintegration time of tablets prepared by HME process was three times more than DT of NHME and marketed formulations. This will reflect the incomplete dissolution of HME tablets in 120 min. For marketed products [Norvir (ritonavir) tablet] prepared by HME technology the dissolution time is 180 min. So, it was decided to do dissolution at 180min to achieve complete drug release.

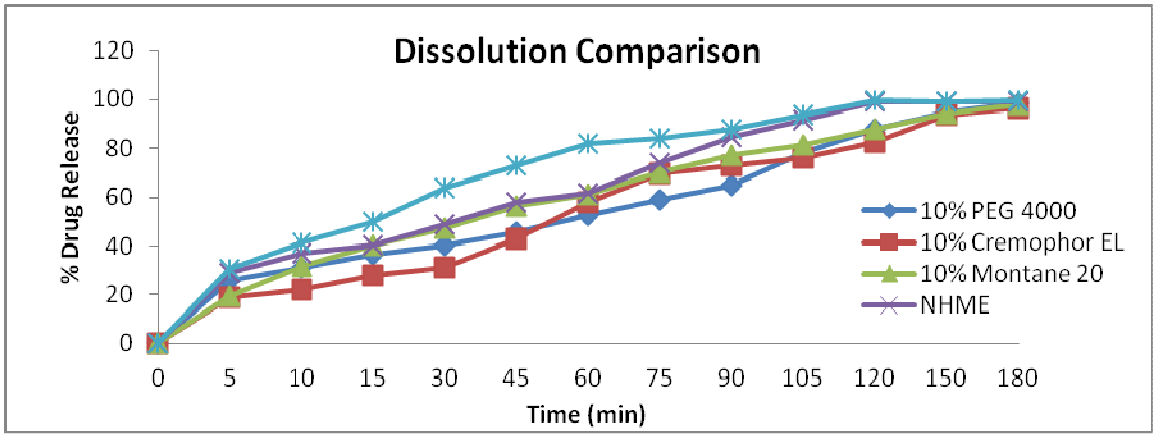


FIGURE 5I: DISSOLUTION STUDIES OF VARIOUS FORMULATIONS WITH SIMILARITY FACTOR (F2): FOR 10% PEG 4000 = 38, 10% CHREMOPHOR EL = 36, 10% MONTANE 20PHA = 46

Even though the complete release was observed during dissolution of Efv HME tablets in 180min, the dissolution rate is quite slower than NHME and marketed product. All formulations show less similarity in dissolution which is confirmed by similarity factor (F2).Comparatively, the Efv HME tablet prepared by using 10%w/w concentration of montane 20 PHA shows more similarity than other formulations.

Table 8: Saturation solubility of formulation (with 10%, 20%, 30% Plasticizer) in water

Solubility / Plasticizer concentration	Pure Drug (µg/mL)	Drug in 10%w/w aq. Solution of polymer (µg/mL)	Drug in Non HME Dry Mix (µg/mL)	Drug in HME granule with PEG 4000 (µg/ml)	Drug in HME granule with Chremophor EL (µg/mL)	Drug in HME granule with Montane 20PHA (µg/mL)
10%	9.19±0.034	237.68±0.001	18.39±0.27	38.59±0.012	234.19±0.044	683±0.007
20%	9.19±0.012	237.68±0.46	18.39±0.086	40.22±0.064	242.38±0.001	698.75±0.055
30%	9.19±0.065	237.68±0.11	18.39±0.034	39.50±0.021	245.10±0.62	695.04±0.092

n=3

Saturation solubility data (table 8) indicates that the hot melt process improved the solubility of Efv by 4 times, 25 times and 74 times of its original solubility by using PEG 4000, Cremophor EL and Montane 20 PHA respectively. As compared to encouraging results of saturation solubility, dissolution data didn't showed any noticeable discrimination in different plasticizers. So, it was decided to do the further study by using 20% w/w and 30%w/w concentrations of plasticizers. Increased concentration of plasticizers didn't show any noticeable improvement in saturation solubility (table8).

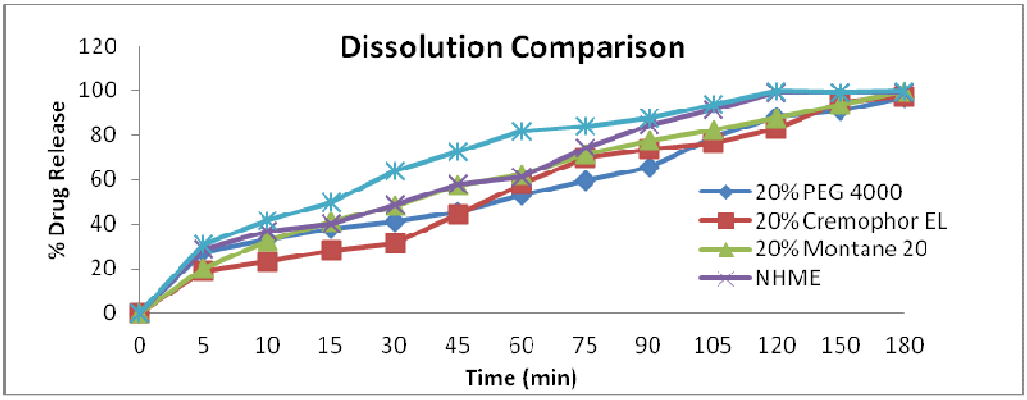


FIGURE 5II: DISSOLUTION STUDIES OF VARIOUS FORMULATIONS WITH SIMILARITY FACTOR (F2): FOR 20% PEG 4000 = 38, 20% CHREMOPHOR EL = 37, 20 % MONTANE 20PHA = 47

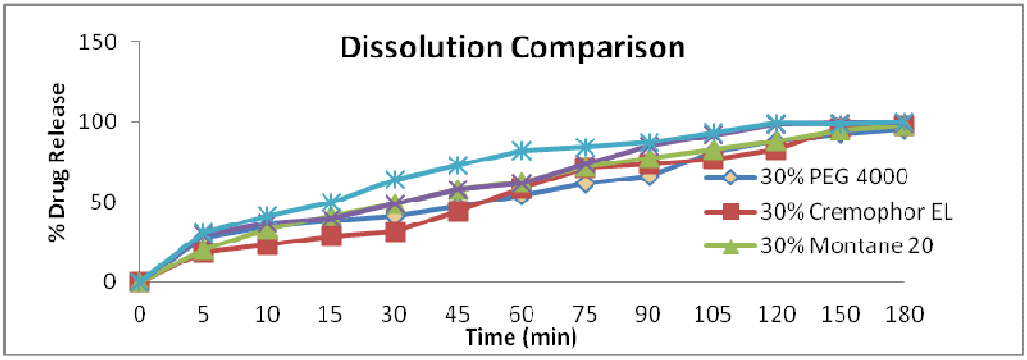


FIGURE 5III: DISSOLUTION STUDIES OF VARIOUS FORMULATIONS WITH SIMILARITY FACTOR (F2): FOR 30% PEG 4000 = 38, 30% CHREMOPHOR EL = 36, 30% MONTANE 20PHA = 46

Increased concentration of plasticizer did not show any improvement in dissolution rate (figure 5II and 5III). Increased concentration of plasticizer did not increase the solubility and dissolution of drug. So, as a discriminative method to determine the dissolution enhancement by HME technique the in vitro permeability of formulations containing 10% plasticizer (using dialysis membrane in disso apparatus) was performed.

8. In vitro permeability of HME and NHME formulation

In vitro permeability study shows (Figure 10) that the Efv HME tablets prepared by 10% Montane have highest permeability as compared to other Efv HME tablets. NHME tablets shows lowest in vitro permeability compared to all Efv HME formulations, even though have higher dissolution rate.

Increase in, in vitro solubility and permeability may increase the in vivo solubility and permeability which leads to reduction in some fold of Efv dose and cost of dosage form.

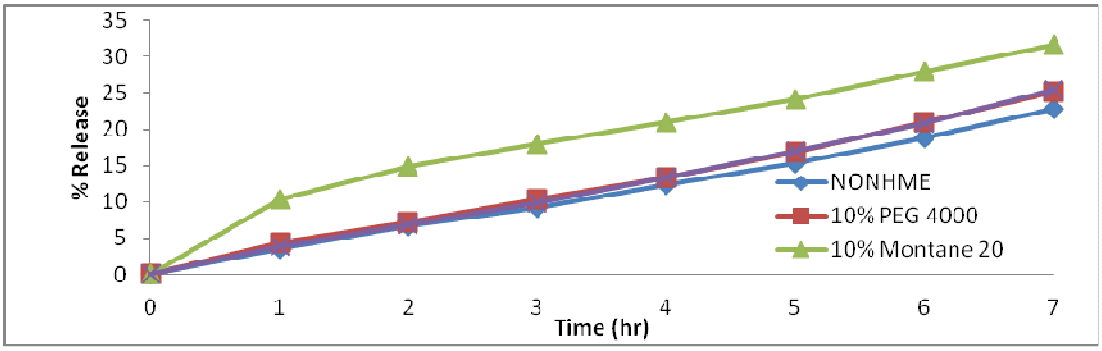


FIGURE 6: PERMEABILTIY STUDIES

9. **Stability Study**

Stability study (table 9) was carried out to determine the physical stability of the formulation carried out as per ICH guidelines at 40° C and 75 % RH for 1, 2 and 3 months. Various tests such as the drug content, moisture content and dissolution were carried out at the end of 1, 2 and 3 months and compared with the day 0 results.

TABLE 9: STABILITY STUDIES (FORMULATIONS CONTAINING 10% PLASTICIZER)

Formulation	E1				E2				E3			
Storage Condition	40°±2°C/75%±5%RH											
Storage Period	Initial	1M	2M	3M	Initial	1M	2M	3M	Initial	1M	2M	3M
Physical Appearance	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Moisture Content (%)	1.3±0.12	1.3±0.75	1.4±0.34	1.4±0.04	1.5±0.02	2.0±0.75	2.2±0.05	2.8±0.03	2.8±0.31	2.9±0.51	3.6±0.024	3.7±0.24
Drug Content (%)	99.2±0.06	99.11±0.01	98.97±0.07	98.7±0.017	99.00±0.08	98.88±0.28	98.12±0.33	97.11±0.85	98.2±0.85	98.01±0.50	97.99±0.32	97.12±0.64
Dissolution (%) at 150min	95.02±0.22	94.11±0.89	93.93±0.36	93.2±0.09	93.57±0.21	93.10±0.01	92.90±0.85	91.81±0.36	94.17±0.28	93.88±0.01	93.2±0.85	92.01±0.92

CONCLUSION:

Solubility of Efv can be increased by HME technology which is one of the method of solid dispersion. The XRD pattern shows amorphous nature of Efv in HME granules. The DSC thermogram of HME granules shows absence of characteristic melting endotherm of Efv indicating the perfect miscibility of drug and polymer in the HME granules. Dissolution rate of Efv HME tablets is not similar to that of NHME and marketed formulations, but the saturation solubility and in vitro permeability of Efv HME formulations is higher than NHME and marketed formulations. In

all HME formulations HME with Montane 20 PHA shows better enhancement in, in vitro permeability and saturation solubility. All optimized HME formulations shows good stability over the period of 3 month at 40°±2°C/75%±5%RH.

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