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Solubility Enhancement of Efavirenz Hydrochloride by Hot Melt Technique.

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Abstract

The present investigation is aimed to formulate & characterize the immediate release tablet of Efavirenz by using Soluplus as a polymer. The proposed formulation of the immediate release tablet of Efavirenz are prepared by using solid dispersion by hot melt technique to improve solubility and dissolution rate of poorly water soluble Efavirenz . The drug to polymer ratio in optimized batch (TABSD13) was 1:3. The obtained batch was characterized for its percent drug contenet, thermal analysis (DSC), crystallinity (PXRD), FTIR and *in vitro* drug release. There were no compatibility issues and the crystallinity of drug was found to be reduced in prepared tablet which were confirmed by DSC and PXRD studies. The average dissolution rate of six Efavirenz tablet & marketed formulation in 0.5 % SLS in distilled water in 45 min were 72.77 % & 69.37 % respectively while in 120 min they were about 90.08 % & 88.24 % respectively & the standard deviations were also within the limits. It shows that the dissolution profiles of hot melt Efavirenz tablet & Marketed formulation were comparable in 0.5 % SLS in distilled water. This may be because of the SLS which act as good surfactant. Further investigations are required to reduce the amount of polymer in tablet that can provide maximum drug loading and acceptable dosage form.

Key Words

Efavirenz, Soluplus, solid dispersion, hot melt technique, dissolution enhancement.

Introduction

Almost 60% of drug molecule available in market possesses either solubility or permeability related pharmacokinetic problems. The most important and common problem associated with the oral dosage form is low aqueous solubility of drug not only in dissolution media but also in gastrointestinal fluid. It is hence most important for budding formulation scientist to understand BCS classification, technology to improve bioavailability & analytical methods to study the bioavailability. In this project we have carried out reference work on solubility, BCS classification, technique to improve solubility, co-relation between solubility & bioavailability. By taking one example i.e. Efavirenz we have studied hot melt technique & compared the results with the marketed formulation. Melt extrusion is essentially the same as the fusion method except that the extruder induces intense mixing of the components. When compared to melting in a vessel, the product stability and dissolution are similar, but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. Solubility parameters are investigated to predict the solid-state miscibility and to select matrices suitable for melt extrusion. High shear forces resulting in high local temperatures in the extruder be a problem for heat sensitive materials. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding. As compare to other techniques of preparation of solid dispersion, hot melt extrusion process offers advantage of being Continuous, Reproducible, Fairly high throughput, Dust reduction, On-line monitoring of process. It is a striking example of a technology transfer establishing a new technology life cycle curve .The melt extrusion process is capable of handling active agents of different particle sizes as well as amorphous solids or other polymorphic forms

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leading to the same product. The use of melts in order to obtain solid molecular dispersions, e.g. glass or solid solutions, is well known to the expert and the essential advantage of a melt process in this domain is its solvent-free formation of such dispersions **.**Since with solvent processes there are various problems relating to their use (environmental pollution, explosion-proofing and residual organic solvent) and measures to counteract these problems are desirable. Starting from the plastic industry, today melt extrusion has found its place in the array of pharmaceutical manufacturing operations. Melt extrusion processes are currently applied in the pharmaceutical field for the manufacture of a variety of dosage forms and formulations such as granules, pellets, tablets, suppositories, implants, stents, transdermal systems and ophthalmic inserts. As a specific area melt extrusion process used to the manufacture of solid dispersions, in particular, solid molecular dispersions. Melt extrusion is considered to be an efficient technology in this field with particular advantages over solvent processes like co-precipitation. Potential drawbacks like the influence of heat stress and shear forces on the drug active have been overcome in a number of examples with drugs of different chemical structure. Improved bioavailability was achieved again demonstrating the value of the technology as a drug delivery tool. The various types of extruders have a common feature of forcing the extrudate from a wider cross-section through the restriction of the die. The most important application of extrusion in the pharmaceutical industry is in the preparation of granules or pellets of uniform size, shape, and density, containing one or more Drugs. Melt extrusion for the manufacture of pellets had revealed the potential for controlled release of polymer embedded drugs. The use of melts in order to obtain solid molecular dispersions, e.g. glass or solid solutions, is well known to the expert and the essential advantage of a melt process in this domain is its Solvent-free formation of such dispersions which can be formulated by hot melt extrusion technology. This process can be used for formulation of pharmaceutical implants, oral dosage forms, bioadhesive ophthalmic inserts, topical films, and effervescent tablets etc. Melt extrusion technology today represents an efficient pathway for the manufacture of drug delivery systems. Resulting products are mainly found amongst semi-solid and solid preparations. The potential of the technology is reflected in the wide scope of different dosage forms covering oral, parenteral and topical applications. In addition, the physical state of the drug in the melt extruded formulations reaches from simple crystalline embeddings, mainly in the field of sustained release applications, to amorphous or molecularly dissolved stages. Compared to solvent processes aiming at solid molecular dispersions melt extrusion offers a promising alternative. The possible use of a broad selection of excipients from high molecular weight polymers to low molecular weight additives like sugar alcohols, waxes or surfactants opens a field of numerous combinations for formulation research. Present investigation is attempt for improvement in solubility and dissolution rate of poorly water soluble Efavirenz by solid dispersions with the use of Soluplus as polymer with aim to improve the bioavailability, the pharmacokinetic properties and the patient compliance.

Materials and Methods

Commercial Efavirenz was gift sample from Emcure Pharma Ltd., Pune, Batch no. EFA 680001,

Soluplus (As gift sample from BASF Ltd; Mumbai), All other chemicals and excipient like Cremophor EL , Avicel PH102, Kollidon CL ,Magnesium stearate, Carbosil 200 are of analytical grade.

Instruments

- . Tap density tester (USP) (ETD-1020, Electro lab, India).
- Tablet compression machine (Rimek Tabletting Machine, MINIPRESS-I (Karnavati Eng., Ltd.), India).
- Rochi frabilator USP.(EF-2, Electro lab, India)
- . Disintegration tester USP (model ED2L, ELECTROLAB,).
- . Dissolution Test apparatus (USP type II TDL-08L ELECTROLAB).
- . UV/VIS Spectrophotometer (UV1800, SHIMADZU, Japan).
- . Infrared Spectrophotometer: (Jasco FT/IR-4100, Japan).
- . Differential Scanning Calorimeter (DSC Q100, TA instruments).
- . Powder X-ray diffractometer (Miniflex II, Rigaku).
- . KBr press (model M-15, techno search instruments)

- Hardness tester (Monsanto).
- Ultracentrifuge (Eppendorf, centrifuge 5810R, Hamburg, Germany).
- Walk in stability chamber (Newtronic Ltd.).
- Incubator shaker (C24KC, Refrigerated incubator shaker, New Brunswick scientific co., Inc. Edision, New jersey USA).
- Hot plate (Meta-lab scientific industries Mumbai-10).
- Distillation assembly (Lab hosp, water still, Lab hosp corporation, Mumbai).

Pharmaceutical characterization

Drug Content

The percent drug content in the solid dispersion were estimated by dissolving quantities equivalent to 10 mg of Efavirenz in 10 ml methanol and filtered through 0.45µm membrane filter, appropriately diluted with distilled water and the UV absorbance were recorded at 248 nm. The percent drug content was recorded by slope method.

Saturation Solubility

The saturation solubility of physical mixture & solid dispersion prepared by hot melt method were determined by equilibrating excess powder in distilled water as well as in 1% SLS in distilled water. The suspensions were stirred for 48 hours on an incubator shaker bath (C24KC, Refrigerated incubator shaker) at 120 rpm at the temperature of 37±0.50C. The solutions were then centrifuged (Eppendorf, centrifuge 5810R, Hamburg, Germany) at 7000 rpm for 10 mins supernatant was filtered through 0.45µm membrane filter, appropriately diluted and analyzed for Efavirenz spectrophotometrically at 248 nm.

Infrared Spectroscopy

All the physical mixtures and solid dispersions prepared by hot melt method were analyzed by FTIR (Jasco FT/IR-4100, Japan). The mixtures were mixed with KBr in mortar and pestle. The resulting mixture was then analyzed in FTIR and the range from 4000 to 400 nm.

Crystallographic Investigation

Differential Scanning Calorimetry (DSC*)*

The DSC measurements were performed using Differential Scanning Calorimeter (DSC Q100, TA instruments). The samples of about 5-10 mg were hermetically sealed in aluminum pans and heated at a constant rate of 10 °C/min over a temperature range of25–200 °C. An inert atmosphere was maintained by purging with nitrogen gas at a flow rate of 100 ml/min. An empty aluminum pan was used as reference.

Powder x-ray diffraction (XRPD)

The XRPD patterns were recorded on an X-ray diffractometer (Miniflex II, Rigaku). The samples were irradiated with monochromatized CuKα radiation (1.542 Å) and analyzed between 2 and 60° 2θ. The voltage and current used were 30 kV and 30 mA, respectively. The range and the chart speed were 1×104 CPS and 10 mm/°2θ, respectively.

Granules properties

Flow properties

The flow properties of granules were carried out in terms of angle of repose (θ), Hausner's ratio and Carr's Index. A weighed quantity of the sample was poured into a graduated cylinder and volume was calculated. Then mechanically tap the cylinder containing the sample by raising the cylinder & allowing it to drop under its own weight using the suitable mechanical tapped density tester (Electro lab ETD-1020, Mumbai India) that provide a fixed drop of 14 2 mm at a nominal rate of 300 drops per min . Unless otherwise specified, tap the cylinder 500 times initially & measure the tapped volume, V, to a nearest graduated unit. Repeat the tapping additional 750 times &measure the tapped volume V, to a nearest graduated unit. If the difference between the two tapped volume is less than 2%, V, is the final tapped volume. Repeat in increments of 1250 taps, as needed, until the difference between two successive measurements is less than 2 %.calculate the tapped density by using the formula (3). The packing properties of powders were determined using following equations.

Bulk density (σb) = Mass / Bulk volume……. (2)
Tapped density (σt) = Mass/Tapped volume… (3)

Carr's compressibility Index= [(Tapped density (σt) - Bulk density (σb)) / Tapped density (σt)] x 100 = [(σt – σb) / σt] x 100 …….....(4)

Hausner's Ratio = Tapped density (σt) / Bulk density (σb) ……..... (5)

Bulkiness = 1/bulk density ……..... (6)

Void volume: The volume of spaces is known as the void volume.

Void volume (V) =V bulk (untapped) – V true (tapped) …….....(7)

Angle of repose

For determination of angle of repose (θ), the powder were poured through the wall of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The powders were poured till the tip of the pile surface touched the lower tip of the funnel & the radius of the base of pile was measured. Angle of repose calculated by

tan–1 θ = Height of the pile / Radius of its base …….....(8)

Evaluation of Tablets

Prepared tablets were evaluated for the following parameters:

Thickness

The thickness of the tablets was determined using Vernier caliper. 5 tablets from batch were used and average values were calculated.

Hardness

The hardness of 6 tablets was determined using Monsanto hardness tester & average value of 6 tablets was calculated.

Weight Variation

20 tablets were selected randomly and weighed individually. The total weight of 20 tablets was calculated and average weight was determined. Not more than 2 of the individual weights deviate from the average weight by more than 10%.

Friability

The friability of 10 tablets was measured using a Roche Friabilator (EF-2, Electro lab, India). Tablets were rotated at 25 rpm for 4 minutes. The tablets were then re-weighed after dedusting and the % friability was calculated using formula no. 9 .The maximum weight loss should not be more than 1%. **% Friability** = Tablet weight before test – tablet weight after test × 100……..... (9)

Assay

The assay of the tablet was determined by the procedure given in the IP as follows.

Test Solution

Weigh & powder 20 tablets. Weigh accurately a quantity of tablets powder containing about 100 mg of Efavirenz & shake with sufficient methanol to obtain a mixture containing 6 mg of Efavirenz per ml. Sonicate the solution using bath sonicator for 20 min to ensure complete solubilization of drug in solution. Filter the solution through a membrane filter disc with an average pore diameter of 1.0 µm. Rejecting first few ml of filtrate and dilute 10.0 ml of the filtrate to 50.0ml with methanol. The absorbance of the above solution is taken on UV spectrophotometer (UV1800, SHIMADZU, Japan) at 248 nm.

Reference solution

A 0.12 % w/v solution of Efavirenz in methanol. The % of the Efavirenz in tablet is calculated from the slope of calibration curve of Efavirenz in methanol.

IP Limit

The Efavirenz tablet should contains not less than 90% and not more than 110 % of the stated amount of C14H9Cl F3NO2.

Measurement of Disintegration time:

The disintegration test was carried out using an Electrolab disintegration test apparatus (model ED2L, Electro lab.) The volume of disintegration medium (distilled water) used was 1000 ml; 1 tablet in each of 6 tubes of basket was carefully placed and if prescribed add a disk. Operate the apparatus using water or the specified medium as immersion fluid, maintained at 37o 2oC. At the end of the time specified basket was lifted from the fluid & observes the tablets. All of the tablets have disintegrate completely, if one or two tablets failed to disintegrate completely, then repeat the test on additional 12 tablets. The requirement is met if not more than 16 of total 18 tablets are disintegrated

Dissolution studies

Dissolution study was conducted using the USP type II apparatus (USP type II TDL-08L Electro lab) at 50 rpm in 900 ml of 1% sodium lauryl sulphate in distilled water and at 37±0.50 c. The drug was analyzed spectrophotometrically at 248 nm

The tablets containing 100mg of Efavirenz were placed in dissolution medium and apparatus was run maintaining above stated test conditions. 5 ml aliquot was withdrawn at time points of 5 min., 10 min., 15 min., 30 min., 45 min., 60 min., 90 min., and 120 min. and was replenished with fresh dissolution medium. The samples were estimated for Efavirenz content spectrophotometrically at 248nm. Percentage drug release was calculated

Dissolution studies in Discriminating Medias

1) 0.5 % SLS in distilled water
2) 0.1N HCl

Calculation of Similarity Factor

The similarity factor was calculated by following formula. This approach uses a similarity factor (f2) to compare dissolution profiles. The similarity factor f2 is a logarithmic reciprocal square root transformation of the sum of squared error and is measurement of the similarity in the percent dissolution between the two curves.

f2 = 50* log {[1+1/n Rt −Tt 2nt=1] 0.5* 100}

Where n is the number of time points, Rt is the dissolution value of the reference batch at time t, and Tt is the dissolution value of the test batch at time t.

Stability Studies

Stability studies of tablets were performed as per ICH guidelines. The tablets from the optimized batch (TABSD13) were stability tested by using following protocol

Results and Discussion

Characterization of Efavirenz

Melting point of Efavirenz

The melting point of Efavirenz was found to be 137.440C. This is within the accepted range as specified in Merck Index.

FTIR spectroscopy

Structure of Efavirenz

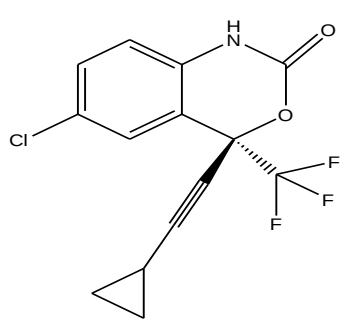

Fig. No. 8.1: Structure of Efavirenz.

The FTIR spectra of the pure Efavirenz were recorded in the wavelength range of 4000 to 400 nm. It shows characteristic peak at 3363 cm-1 , 3052 cm-1 , 2944 cm-1, 2300 cm-1, 1691 cm-1,1602 cm-1, 1217 cm-1 & 1326 cm-1 attributed to N-H stretching vibrations, aromatic C-H stretching vibration, aliphatic C-H stretching vibration, C≡C cm-1 stretching vibration, C=O stretching vibration , C=C stretching vibration, C-F stretching vibration , C-O-C stretching vibration respectively. The spectrum matches reference as given in Flory series.

8.1.3 Calibration curves of Efavirenz

Calibration curve of Efavirenz in 1 % SLS in water, 0.1NHCl & in distilled water was carried out. The resulting graphs &equation are represented in the following figure No. 3.

8.1.4 Saturation solubility of drug

The saturation solubility of Efavirenz in distilled water, in 0.1 N HCl & in 1 % SLS in distilled water at room temperature was found to be 6.5µg/ml, 0.4036µg/ml & 17.5 µg/ml respectively.

Intrinsic dissolution rate (IDR)

The intrinsic dissolution rate testing of the pure Efavirenz & the granules of Efavirenz along with Soluplus & Cremophor EL prepared by the hot melt technique was carried out using type II apparatus at 50 rpm in 1% SLS dissolution medium. The IDR of the pure drug in the dissolution medium was found to be 0.058 ± 0.0068 mg /min/cm2 while the IDR of the Efavirenz granules prepared with Soluplus & Cremophor EL was found 0.1166 ± 0.007 mg /min/cm2. As the intrinsic dissolution rate of drug was found to be 0.058 mg /min/cm2 which suggests dissolution rate-limited absorption problems for this drug because drugs having the dissolution rate less than 0.1 mg /min/cm2 have the dissolution rate limited absorption problems36. There was about two fold increase in the IDR of the Efavirenz granules as compare to the pure Efavirenz. This was attributed to increased wetting of the drug particles by the polymer as well as solublization of drug in hydrophilic polymer and formation of polymer coat around the drug particles. Hence we can conclude that the increase in IDR indicates that hot melt technique is capable of increasing the dissolution rate of Efavirenz.

Characterization of solid dispersion

Drug Content

The percentage drug content of physical mixtures and solid dispersions of Efavirenz summarized in table no.8.1. The drug content observed for the physical mixtures and solid dispersions prepared with Soluplus & Cremophor EL did not show any significant degradation as all the samples showed drug content of more than 98%.

8.2.2 Saturation solubility study of physical mixture & solid dispersion

Saturation solubility of pure drug, physical mixtures and solid dispersions by hot melt technique in distilled water & in 1% SLS summarized in table no. 8.2. Saturation solubility of pure Efavirenz was found to be 6.5 ± 0.4 µg/mL & 17.5± 3.5 µg/mL in distilled water & 1 % SLS in distilled water at room temperature. A significant improvement in the saturation solubility was observed with all physical mixtures and solid dispersions (Table 8.2). Physical mixtures with Soluplus in 1:2, 1:3 and 1:4 drug: polymer ratio showed 78 ± 0.7 µg/mL, 104 ±0.2 µg/mL, 117 ±0.6 µg/mL enhanced saturation solubility. Increases in weight fraction of the hydrophilic polymer resulted in improved saturation solubility. Solid dispersion with Soluplus in 1:2, 1:3 and 1:4 drug: Soluplus ratio showed 184 ± 0.5 µg/mL, 339 ±0.7 µg/mL, and 355 ± 1.3 µg/mL saturation solubility which were significantly high as compared to pure drug and physical mixtures. There was about 12 to 18 fold increase in saturation solubility in case of physical mixture and 28 to 55 fold increases in sold dispersion in distilled water. A 52 fold (339 ±0.7µg/ml) solubility enhancement was observed in 1:3 drug:Soluplus solid dispersion prepared by hot melt method. Significant improvement in saturation solubility was observed compared to physical mixtures. This can be attributed to coating of drug particles and formation of polymer coat around the drug particles. Solid dispersion in 1:4 drug : polymer weight ratio showed saturation solubility of 355 ± 1.3 µg/ml.Saturation solubility of pure Efavirenz was found to be 17.5± 3.5 µg/ml in 1 % SLS in distilled water at room temperature. A significant improvement in the saturation solubility was observed with all physical mixtures and solid dispersions (Table 8.2). Physical mixtures with Soluplus in 1:2, 1:3 and 1:4 drug: polymer ratio showed 227.5 ± 6.7µg/ml, 315±5.6 µg/ml, 367.5±4.2 µg/ml enhanced saturation solubility. Increases in weight fraction of the hydrophilic polymer resulted in improved saturation solubility. Solid dispersion with Soluplus in 1:2, 1:3 and 1:4 drug: Soluplus ratio showed525 ± 6.3 µg/ml, 945± 5.9µg/ml, and 1015±4.8 µg/ml saturation solubility which were significantly high as compared to pure drug and physical mixtures. There was about13 to 21 fold increase in saturation solubility in case of physical mixture and 30 to 58 fold increases in sold dispersion in distilled water. A 54 fold (945± 5.9µg/ml) Solubility enhancement was observed in 1:3 drug: Soluplus solid dispersion prepared by hot melt method. Significant improvement in saturation solubility was observed compared to physical mixtures. This can be attributed to coating of drug particles and formation of polymer coat around the drug particles. Solid dispersion in 1:4 drug: polymer weight ratio showed saturation solubility of 1015± 4.8 µg/ml the increase in saturation solubility of Efavirenz with increase in polymer amount was less in Solid dispersion in 1:4 drug: polymer weight ratio as compare to Solid dispersion in 1:3 drug: polymer weight ratio. The same behaviour was observed with the dissolution study of these two formulations hence we selected Solid dispersion in 1:3 drugs: polymer weight ratio as optimized batch (TABSD13)

8.2.3 FTIR spectroscopy

The FTIR spectra of the pure drug, polymer, physical mixture, solid dispersion & tablet were recorded in the wavelength range of 4000 to 400 nm & represented in the following Figure No 8.6 Efavirenz shows characteristic peak at 3363 cm-1 , 3052 cm-1 , 2944 cm-1, 2300 cm-1, 1691 cm-1,1602 cm-1, 1217 cm-1 & 1326 cm-1 attributed to N-H stretching vibrations, aromatic C-H stretching vibration, aliphatic C-H stretching vibration, C≡C cm-1 stretching vibration, C=O stretching vibration , C=C stretching vibration. C-F stretching vibration, C-O-C stretching vibration respectively. (Figure 8.8 a). Soluplus shows characteristic peak at 2991 cm-1 , at 1751 & 1652 cm-1 , at 1486 cm-1 attributed to aliphatic C-H stretching, due to C=O stretching, due to C-O-C stretching (Figure 8.8 b). Physical mixture of Efavirenz & Soluplus along with Cremophor EL shows all the characteristic peak of Efavirenz indicating that there may not be any interaction between the Efavirenz & Soluplus. (Figure 8.8 c). The IR spectrum of solid solution & tablet shows absence of characteristic peak of Efavirenz i.e. doublet peak of N-H stretching vibrations at 3363

cm-1 .This may attributed to possible interaction between the N-H group of Efavirenz & C=O group of the Soluplus leading to formation of amide group (Figure 8.8 d & e).

8.2.4 Powder x-ray diffraction (XRPD)

The X-ray diffraction pattern of pure drug, polymer, physical mixture, solid dispersion & tablet were recorded with 2θ angle between 2 to 600 & represented in the following figure No. 8.9. The XRPD pattern of pure drug presented several diffraction peaks indicating the crystalline nature of the drug. Peaks for crystallinity were observed in pure drug at 2θ values of 6, 10.9, 14.12, 16.84, 19.14, 20.08, 21.18, and 24.86. (Figure No. 8.9 a). The polymer was amorphous as it showed a hump & absence of characteristic peak. (Figure No.. 8.9 b) The XRPD pattern of physical mixtures showed the presence of peaks with a significant decrease in intensity or absence of some major Efavirenz crystalline peaks (Figure No. 8.9 c). Generally this partial loss of crystallinity may be observed due to physical presence of amorphous excipients and higher polymer concentration although the drug was still in the crystalline state in this system. The X-ray diffraction patterns of Efavirenz solid dispersions by hot melt technique & Efavirenz tablet showed complete absence of peaks of crystallinity of pure Efavirenz indicated complete amorphization of Efavirenz in solid dispersions. The presence of hump in both the samples indicates the amorphous nature of drug in the solid dispersion and tablet (Figure8.9d&e).

8.2.5 Differential Scanning Calorimetry (DSC)

The DSC measurements were performed over the temperature range of 25 to 2000C at a scanning rate of 100C/min under nitrogen flow rate of 100.0 ml/min. & The DSC thermograms for Efavirenz alone and its physical mixtures, solid dispersions obtained by hot melt technique represented in the following figure no 8.10. The DSC thermograms of pure Efavirenz shows sharp endotherm at 137.440C attributed to the melting of Efavirenz. This sharp melting endotherm indicates the crystalline nature of drug. (Figure No. 8.10 a) The DSC thermogram of Soluplus shows change in the heat capacity at 700C indicating the glass transition temperature (Tg) of the Soluplus. (Figure No. 8.10 b) The DSC thermogram of physical mixture in 1:3 drug to polymer proportion shows melting endotherm at around 135.67 0C which may be attributed to the melting of Efavirenz. This decrease in the melting of the Efavirenz may attributed to the partial amorphization of drug. (Figure No. 8.10 c). The DSC thermogram of solid dispersion shows absence of characteristic melting endotherm of Efavirenz as well as change in the heat capacity around 45 0C attributed to the single Tg of solid dispersion 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 No. 8.10d). The average dissolution rate of six Efavirenz tablets with drug to polymer ratio of 1:2, 1:3, 1:4 showed that the cumulative % drug releases of tablets batches TABSD13 & TABSD14 were almost similar both of which were significantly greater than batch TABSD12. Hence we selected the TABSD13 as optimized batch as it is always feasible to use low polymer concentration as compare to higher one. The average dissolution rate of six hot melt Efavirenz tablet by hot melt technique with 1:3 drug: polymer ratio showed 78.90 % cumulative % drug release in 45 min which complies with IP limit of NLT 70 % of Efavirenz in 45 min. & it shows 99.14 cumulative % drug release in 120 min. & the standard deviations were also within the limits. It indicates that the dissolution profiles of hot melt Efavirenz tablet & Marketed formulation were comparable. Hence we decided to carry out dissolution in discriminating medias i.e. 0.5 % SLS in dist. water & in 0.1 N HCl. Similarity factor for optimized batch (TABSD13) with marketed formulation was found to be 70.94 which highly insignificant

8.3.2 Dissolution study in Discriminating Medias

The average dissolution rate of six Efavirenz tablet & marketed formulation in 0.5 % SLS in distilled water in 45 min were 72.77 % & 69.37 % respectively while in 120 min they were about 90.08 % & 88.24 % respectively & the standard deviations were also within the limits. It shows that the dissolution profiles of hot melt Efavirenz tablet & Marketed formulation were comparable in 0.5 % SLS in distilled water. This may be because of the SLS which act as good surfactant. The avg. dissolution rate of six hot melt Efavirenz tablet & marketed formulation in 45 min were 26.56 % & 15.01 % respectively while in 120 min they were about 60.94 % & 48.61 % respectively & the

standard deviations were also within the limits which shows that there was significant differences 10-15% in dissolution behaviour of hot melt Efavirenz tablet & marketed formulation in 0.1 N HCl. This shows that Efavirenz formulation by hot melt method was more soluble in acidic condition than marketed formulation.

8.4 Stability Studies

Stability studies were carried out to determine the physical stability of the formulation and were carried out as per ICH guidelines by exposing them to 250 C at 60 %RH and 400 C at 75 % RH for 30 days. Various tests such as the drug content, moisture content and dissolution rate were carried out at the end of 15 days & 30 days and compared with the day 0 results. The average dissolution rate of six Efavirenz tablets stored at 250C/60 % RH for 15 days shows 80.01 % drug release in 45 min & 97.96 % drug release in 120 min. The average dissolution rate of six Efavirenz tablets stored at 400C/75% RH for 15 days shows 81.52 % drug release in 45 min & 98.79 % drug release in 120 min. There were no changes in initial dissolution profile of Efavirenz tablets & tablets stored at 250C/60 % RH & 400C/75% RH for 15 days which indicates that the tablets were stable for 15 days. The avg. dissolution rate of six hot melt Efavirenz tablets stored at 250C/60 % RH for 30 days shows 80.06 % drug release in 45 min & 97.56% drug release in 120 min. The avg. dissolution rate of six hot melt Efavirenz tablets stored at 400C/75% RH for 15 days shows 79.07% drug release in 45 min & 96.65% drug release in 120 min. There were no changes in initial dissolution profile of hot melt Efavirenz tablets & tablets stored at 250C/60 % RH & 400C/75% RH for 30 days which indicates that the tablets were stable for 30 days. The results of assay & moisture content showed in table No. 8.15 & 8.16. It was observed that assay of Efavirenz tablets stored at 250C/ 60% RH & 400C/ 75% RH were in the specified IP limits as well as there were no significant gain in moisture contents which indicates that tablets stored at 250C/ 60% RH & 400C/ 75% RH were stable for the period of 1 month.

Conclusion

Saturation solubility studies showed significant enhancement in solubility of all the physical mixtures and solid dispersions prepared by hot melt method. Solid dispersion obtained by hot melt method with drug: Soluplus ratio of 1: 3 showed a 52 fold increase in saturation solubility of the drug in distilled water.& 58 fold increase in saturation solubility of the drug in 1 % SLS distilled water. Intrinsic dissolution rate testing of pure Efavirenz & Efavirenz granules with Soluplus & Cremophor EL by hot melt method showed significant increase (two fold) in IDR of Efavirenz granules. IR spectra showed presence of all the characteristic peaks for Efavirenz in the physical mixture indicating no drug polymer interaction and while in case of solid dispersions the characteristic peak of Efavirenz at 3363 cm-1 due to N-H stretching a vibration was absent indicating drug: polymer interaction at N-H functional group of Efavirenz. The XRPD pattern shows partial loss of crystallinity due to physical presence of amorphous excipients and higher polymer concentration. This studies showed amorphous nature of the solid dispersion.The Dsc thermogram of solid dispersion shows absence of characteristic melting endotherm of Efavirenz as well as change in the heat capacity around 45 0C attributed to the single Tg of solid dispersion indicating the perfect miscibility of drug and polymer in the solid dispersion. In the in vitro dissolution studies of tablet of solid dispersion of Efavirenz with Soluplus by hot melt technique with 1:3 drug: polymer ratio showed 78.90 cumulative % drug release in 45 min which complies with IP limit of NLT 70 % of Efavirenz in 45 min. & it shows 99.14 cumulative % drug release in 120 min. Comparison of dissolution profile of hot melt Efavirenz tablet with marketed formulation showed comparable dissolution profile. Similarity factor for optimized batch (TABSD13) with marketed formulation was found to be 70.94 which highly significant. Comparison of dissolution profile of hot melt Efavirenz tablet with marketed formulation showed higher dissolution rate in 0.1N HCl. There is a 10-15 % difference in the dissolution profile. This signifies that hot melt products are more soluble in acidic condition as compared to marketed formulation. Thus, in conclusion ‘hot melt ’technique can be used to manufacture an Efavirenz tablets. Based on the dissolution studies in acidic condition these tablets can be better bioavailable than current formulation in market .Further studies are required to correlate the hypothesis.

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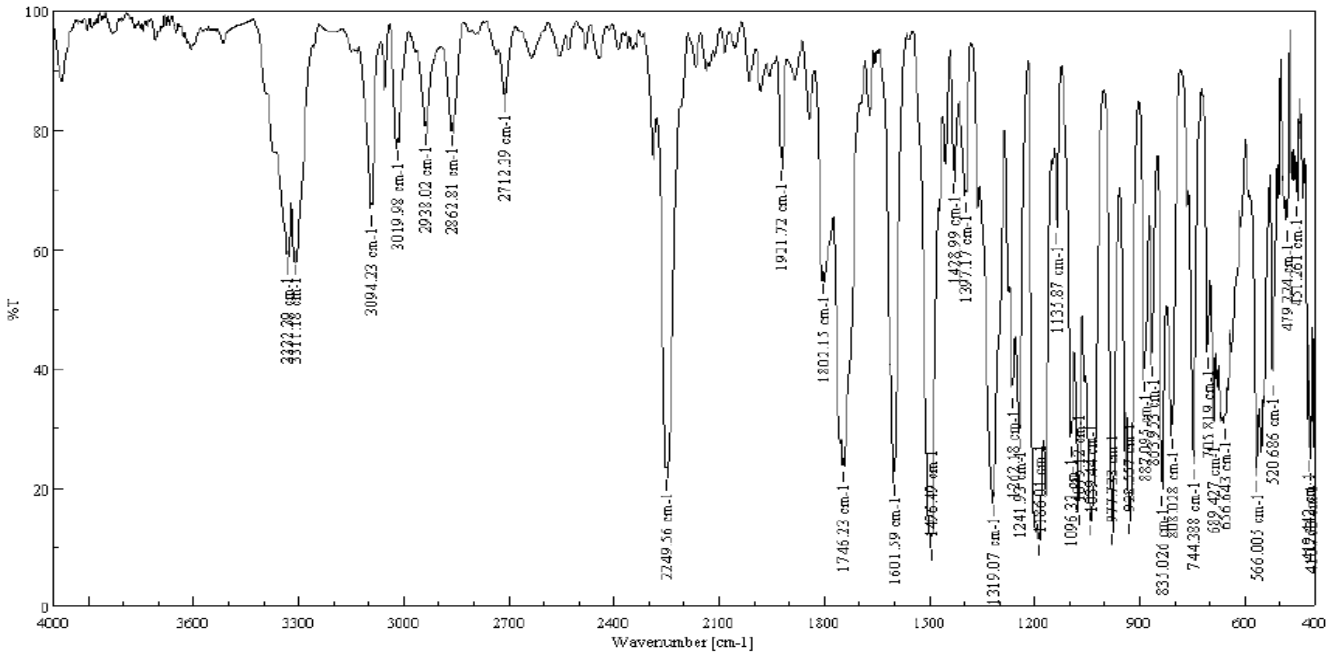

Fig. No. 8.2: IR spectrum of the Efavirenz.

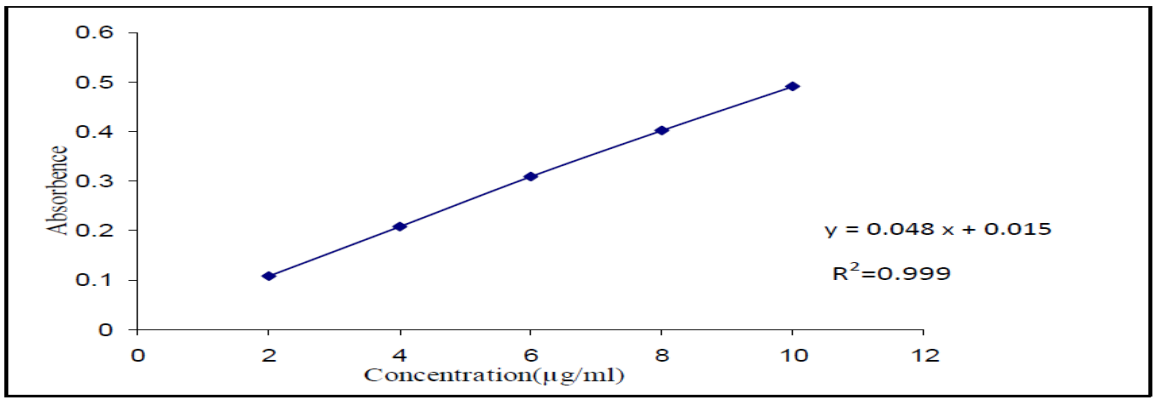

Fig. No. 8. 3: Calibration curve of Efavirenz in 1% SLS in water.

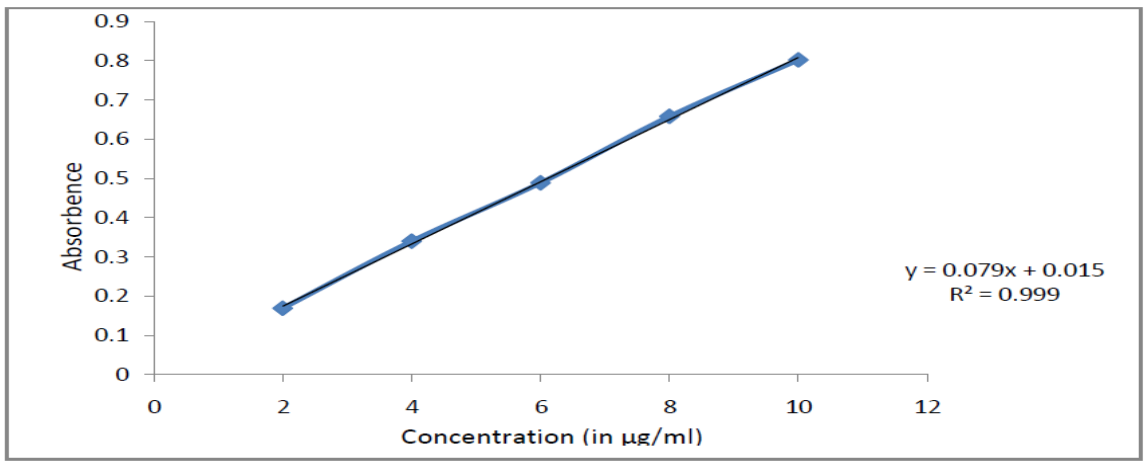

Fig. No 8. 4: Calibration curve of Efavirenz in distilled water.

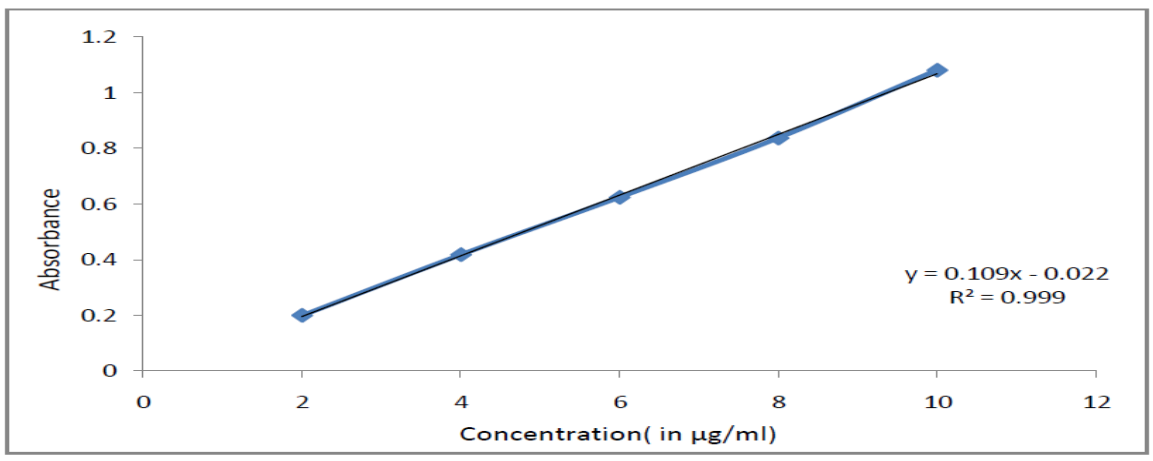

Fig. No. 8.5: Calibration curve of Efavirenz in 0.1N HCl.

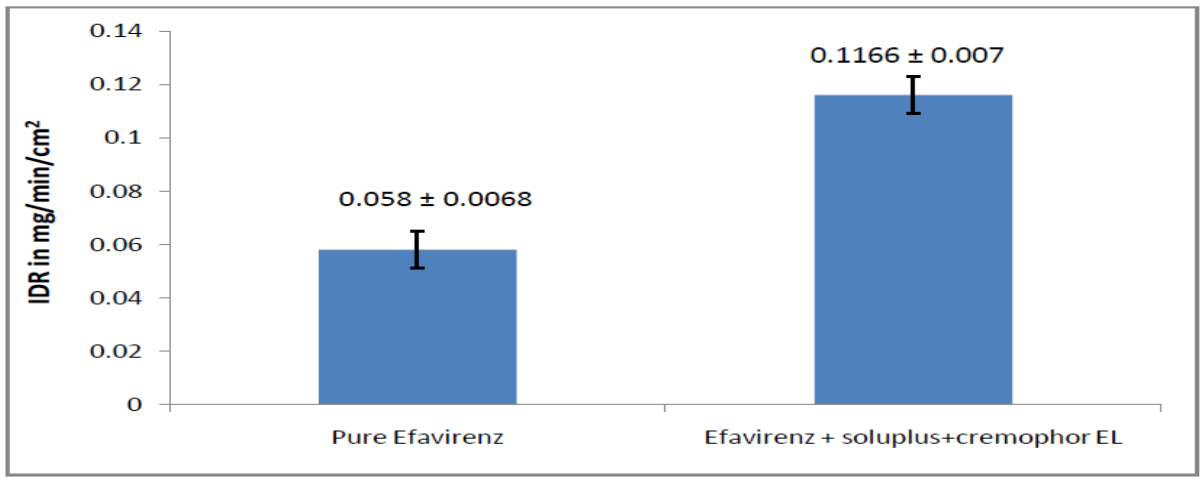

Fig. No.8.6: IDR of Pure Efavirenz & Efavirenz granules with Soluplus and Cremophor EL.

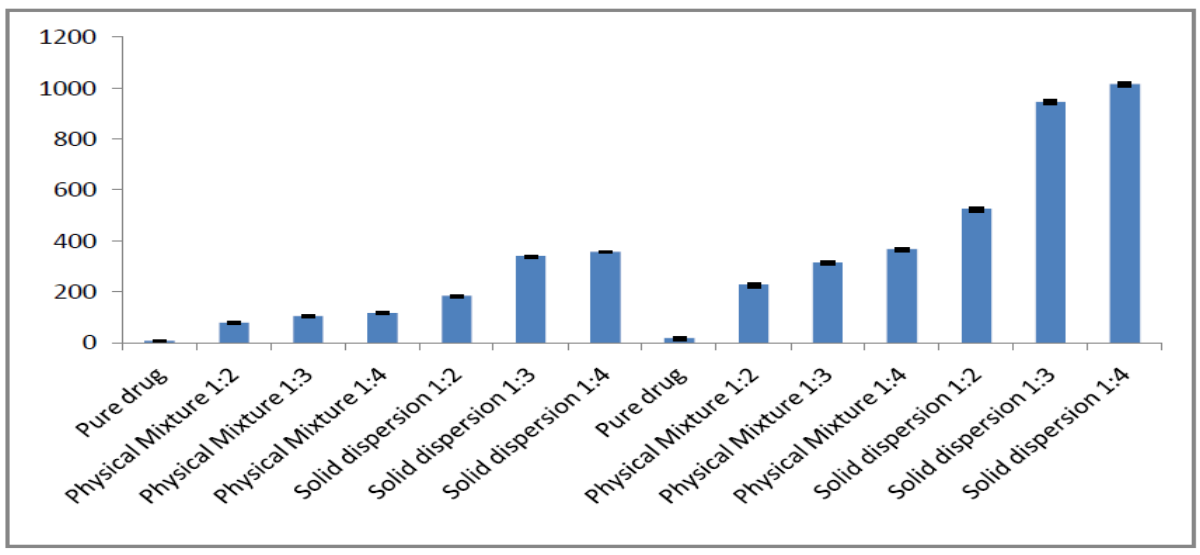

Fig. No. 8.7: Saturation solubility of pure drug, Physical mixtures & Solid dispersions in distilled water & in 1% SLS in distilled water.

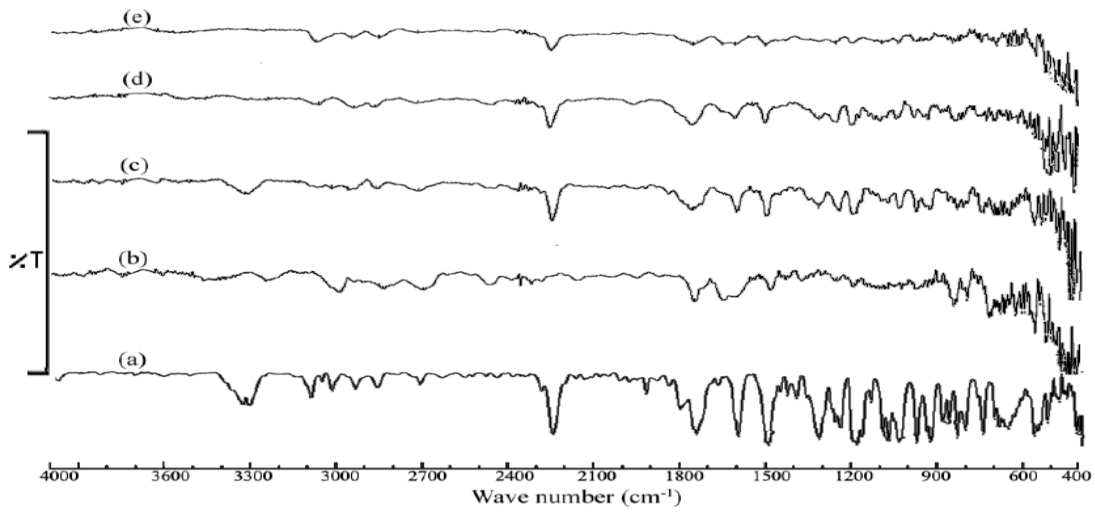

Fig. No 8.8: IR spectrums of (a) = Pure Efavirenz, (b) = Soluplus, (c) = Physical mixture, d) solid solution e) Efavirenz tablet.

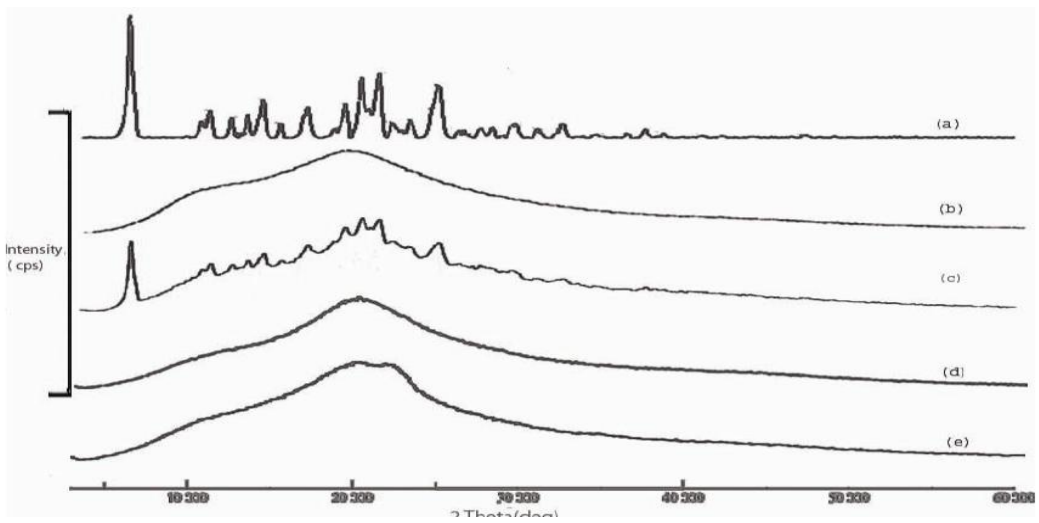

Fig. No. 8.9: X- Ray Diffraction Patterns of (a) = Pure Efavirenz, (b) = Soluplus, (c) = Physical mixture, d) solid solution e) Efavirenz tablet.

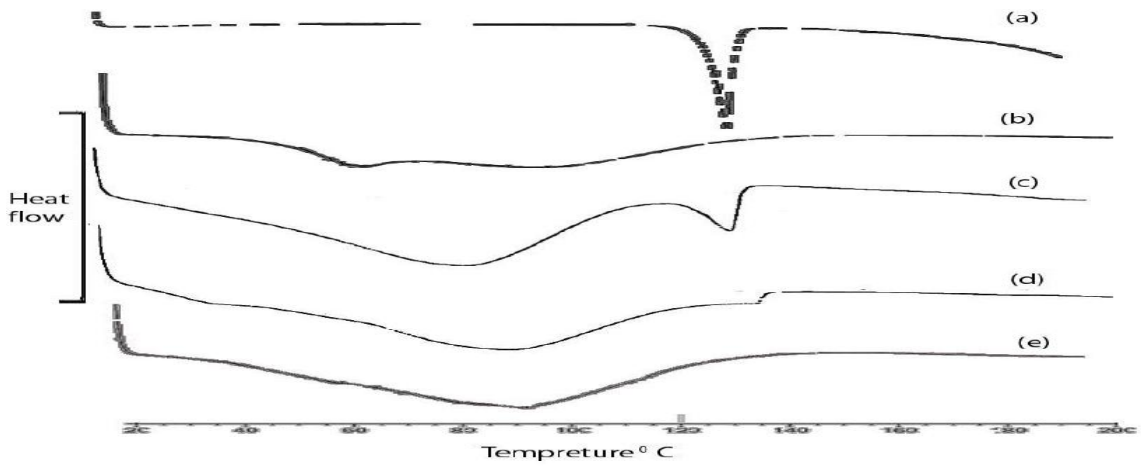

Fig. 8.10: DSC thermograms of (a) = Pure Efavirenz, (b) =Soluplus (c) = Physical mixture, d) solid solution e) Efavirenz tablet.

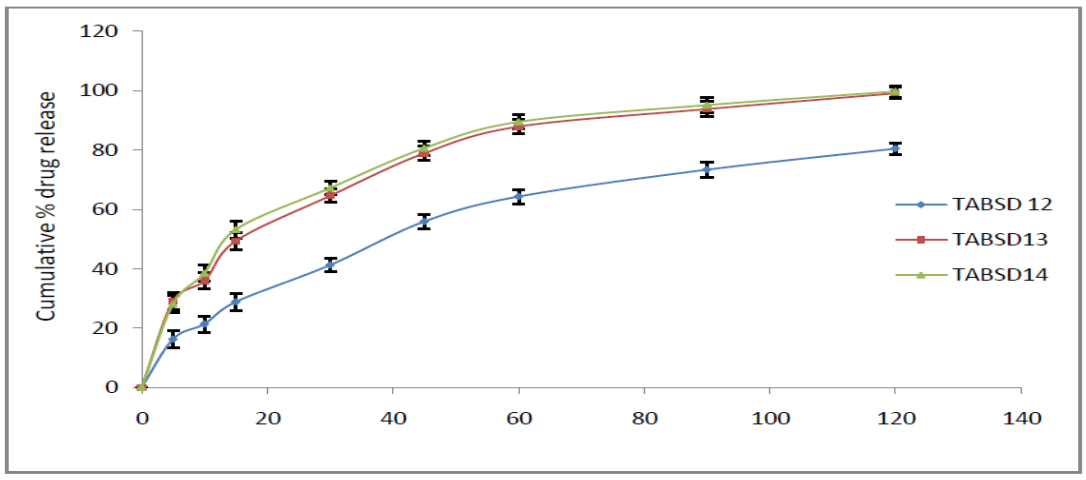

Fig. No 8.11: Dissolution study of three batches of tablets prepared with solid dispersion in drug to polymer ratio of 1:2(TABSD12), 1:3(TABSD13), 1:4(TABSD14).

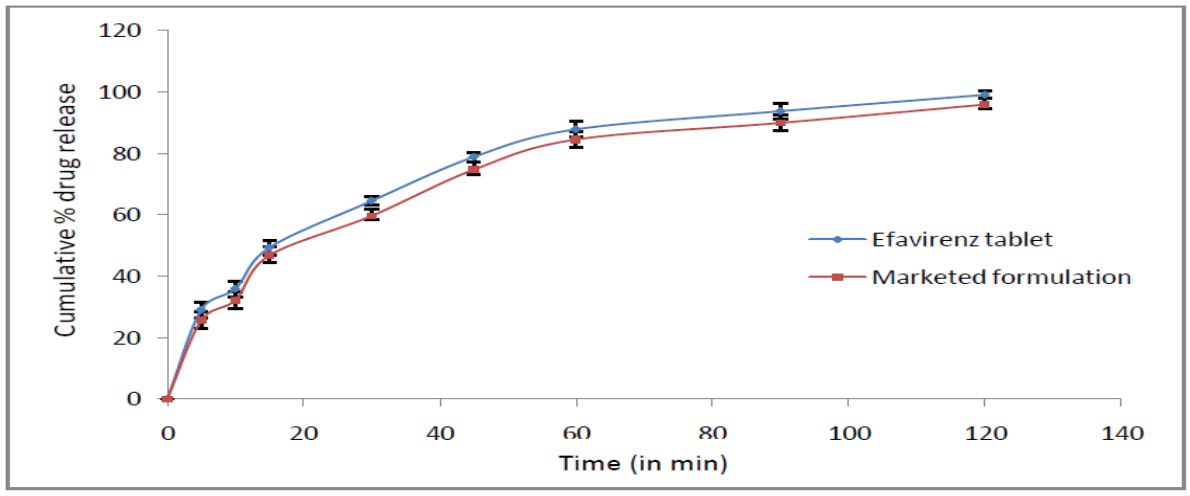

Figure No. 8.12: Comparison of dissolution profile of Efavirenz tablet with Marketed tablet in 1% SLS in water (IP dissolution medium).

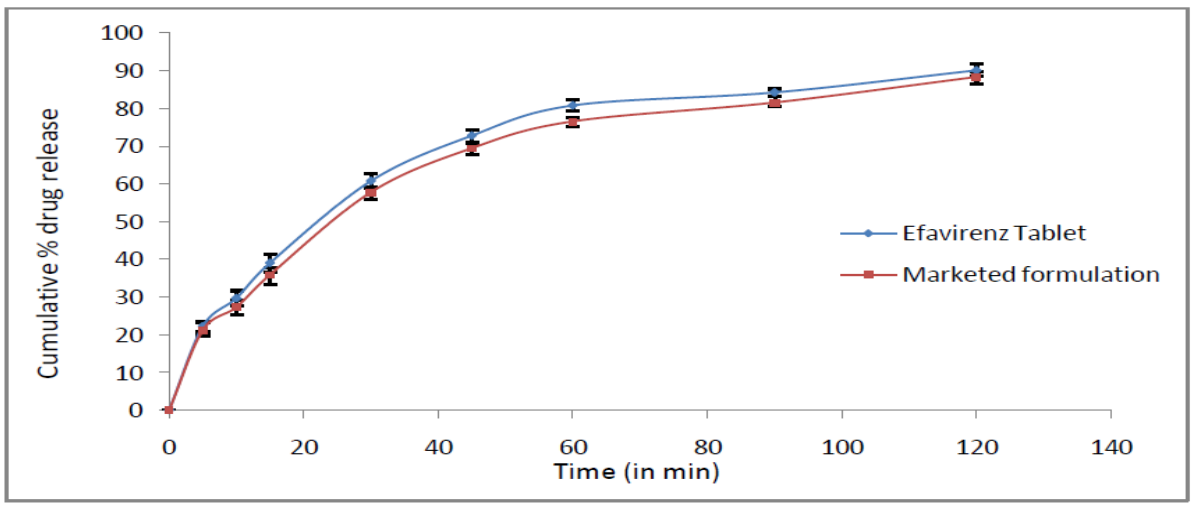

Fig. No. 8.13: Comparison of dissolution profile of Efavirenz tablet & Marketed formulation in 0.5 % SLS in distilled water.

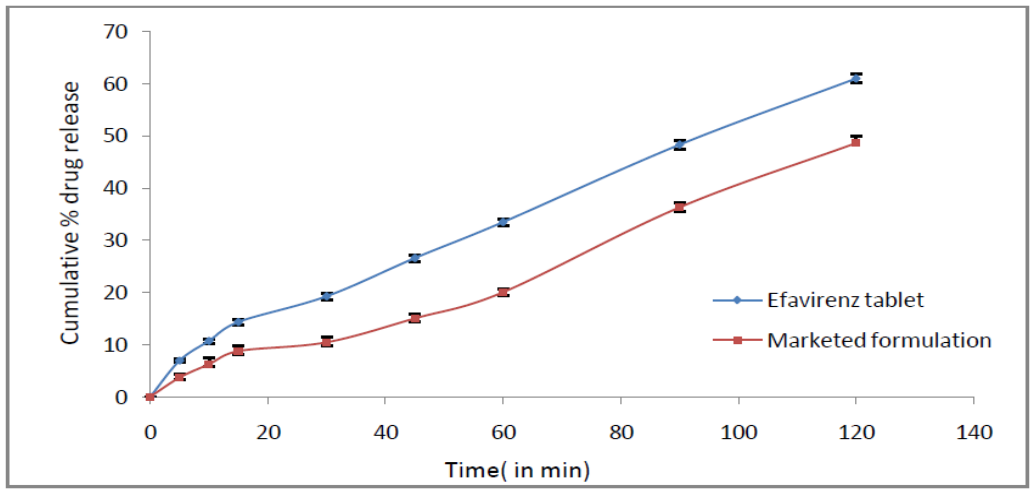

Fig. No. 8.14: Comparison of dissolution profile of Efavirenz tablet & Marketed formulation in 0.1 N HCl.

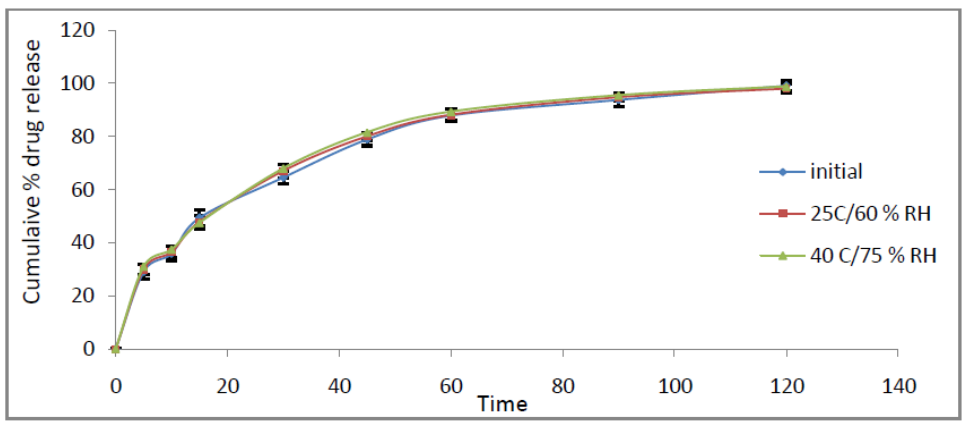

Fig. No. 8.15: Comparison of dissolution profile of Efavirenz tablet stored at 25 0C/60 %RH & 400C/75% RH for 15 days.

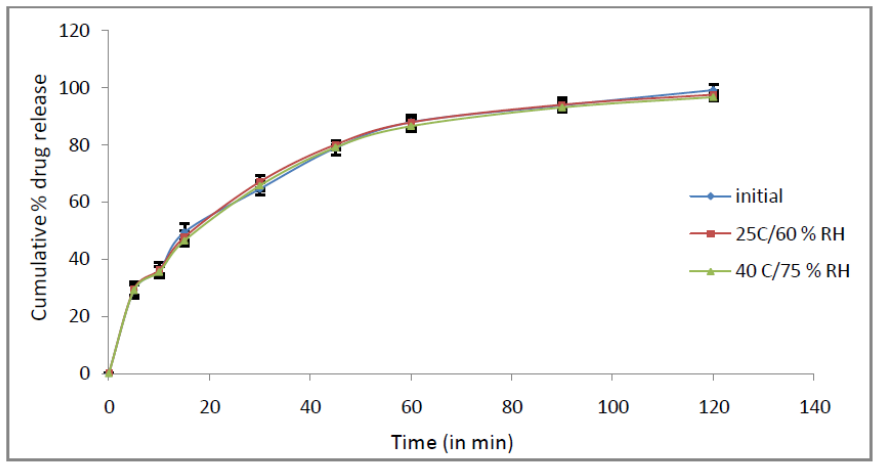

Fig. No .8.16: Comparison of dissolution profile of Efavirenz tablet stored at 25 0C/60 %RH & 400C/75% RH for 30 days.

Table No. 8.1: Drug content of Physical mixtures & solid dispersion of Efavirenz prepared with Soluplus & Cremophor EL.

Sr. no.	Batch code	Physical mixtures and Solid dispersion	Ratio of Drug:Carrier	Drug content (% ± SD)
1	PMEFZ12	Efavirenz : Soluplus: Cremophor EL	1:2	99.14 ± 0.08
2	PMEFZ13	Efavirenz :Soluplus : Cremophor EL	1: 3	98.67± 0.06
3	PMEFZ14	Efavirenz :Soluplus : Cremophor EL	1:4	98.29± 0.14
4	SD12	Efavirenz :Soluplus : Cremophor EL	1:2	99.57±0.28
5	SD13	Efavirenz :Soluplus : Cremophor EL	1: 3	98.15±0.04
6	SD14	Efavirenz :Soluplus : Cremophor EL	1:4	99.11±0.16

Table No.8.2: Saturation solubility of physical mixtures & solid dispersions in distilled water & 1 % SLS in distilled water.

Sr.No.	Batch code	System	Saturation solubility ±SD (µg/mL) in distilled water	Saturation solubility ±SD (µg/mL) in 1 % SLS in distilled water
1	-	Pure drug	6.5 ± 1.2	17.5± 3.5
2	PMEFZ12	Physical Mixture 1:2	78 ± 2.7	227.5± 6.7
3	PMEFZ13	Physical Mixture 1:3	104 ± 1.9	315±5.6
4	PMEFZ14	Physical Mixture 1:4	117 ± 1.6	367.5±4.2
5	SD12	Solid dispersion 1:2	184 ± 2.5	525± 6.3
6	SD13	Solid dispersion 1:3	339 ± 1.7	945 ± 5.9
7	SD14	Solid dispersion 1:4	356 ± 1.3	1015 ±4.8

Table No 8.3: Flow properties of granules of optimized batch (SD13).

Sr. No	Property of granules	unit	Result	Remark
1	Bulk density	g/ml	0.4347	-
2	Tap density	g/ml	0.5	-
3	Carr's Compressibility Index	%	13.06	Excellent
4	Hausner's ratio	-	1.15	Excellent
5	Bulkiness	ml/g	2.3004	-
6	Void volume	Ml	1.2	-

Table No 8.4: Tablet properties of optimized batch (TABSD13).

Test	IP Specification	Observation	Remarks
Thickness	-	4.3 mm	-
Hardness	-	13.2 kg/cm2	-
Weight Variation	**Wt. of tablet % variation** a) less than 80mg ± 10 % b) 80-250 mg ± 7.5 % c) more than 250 mg ± 5 %	2.7 %	Passes as per IP
Friability	Not more than 1% of total Weight of tab.	0.42%	Passes as per IP
Assay	The Efavirenz tablet should contains not less than 90% and not more than 110 % of the stated amount of C14H9Cl F3NO2	98.62 %	Passes as per IP
Disintegration time	Not more than 15 min	78 Sec	Passes as per IP

Table No. 8.5: Dissolution study of optimized batch (TABSD13) of Efavirenz tablet in 1% SLS in water (IP dissolution medium).

TIME	RUN1	RUN2	RUN3	RUN 4	RUN 5	RUN 6	AVG	SD	MIN	MAX
0	0	0	0	0	0	0	0	0	0	0
5	32.16	31.46	26.57	24.99	30.94	28.32	29.07	2.91	24.99	31.46
10	40.02	36.35	33.56	32.34	36.18	37.05	35.92	2.72	32.34	40.02
15	53.65	51.37	47.18	45.78	48.93	49.28	49.36	2.83	45.78	53.66
30	66.58	67.80	64.48	62.38	63.78	62.38	64.57	2.22	62.38	66.59
45	80.56	82.13	79.51	76.019	76.19	78.99	78.90	2.41	76.01	80.56
60	89.47	91.39	87.90	84.58	86.15	87.90	87.90	2.39	84.58	89.47
90	97.16	94.54	93.84	90	91.92	95.41	93.81	2.54	90	97.16
120	100.13	100.31	99.26	95.59	98.56	101.01	99.14	1.93	95.59	101.31
IP Limit- NLT 70% of stated amt. of Efavirenz in 45 min, dissolution medium: 1% SLS in H20										

Table No. 8.6: Dissolution study of Marketed tablet in 1% SLS in water (IP dissolution medium).

TIME	RUN1	RUN2	RUN 3	RUN4	RUN5	RUN6	AVG	SD	MIN	MAX
0	0	0	0	0	0	0	0	0	0	0
5	28.13	26.38	22.89	22.54	28.89	25.51	25.60	2.45	22.54	28.89
10	36.17	31.98	29.36	29.35	33.55	33.20	32.27	2.63	29.35	36.17
15	49.80	46.66	42.46	45.78	46.42	46.19	46.81	2.35	42.46	49.80
30	60.46	61.86	58.89	59.06	59.94	58.01	59.70	1.35	58.89	61.86
45	73.92	77.76	74.097	75.97	73.77	74.97	74.76	1.52	74.97	77.76
60	83.18	88.60	85.10	81.08	84.23	85.28	84.58	2.49	81.08	88.60
90	93.32	89.82	89.25	86.85	87.90	92.27	90	2.47	89.82	93.32
120	96.29	96.64	95.41	93.84	96.29	97.33	95.97	1.21	93.84	97.33
IP Limit- NLT 70% of stated amt. of Efavirenz in 45 min, dissolution medium: 1% SLS in H20										

TableNo 8.7: Dissolution study of Efavirenz tablet in 0.5 % SLS in Water.

TIME	RUN1	RUN2	RUN3	RUN4	RUN5	RUN6	AVG	SD	MIN	MAX
0	0	0	0	0	0	0	0	0	0	0
5	21.79	20.29	23.82	19.61	22.50	25.18	22.20	2.10	20.29	25.18
10	29.21	28.54	31.42	27.45	28.62	32.77	29.67	2.01	27.45	32.77
15	40.53	39.06	39.63	38.43	35.72	40.75	39.02	1.83	35.72	40.75
30	61.27	60.53	62.53	58.48	60.07	61.63	60.75	1.40	58.48	62.53
45	72.11	73.18	74.13	70.63	74.23	72.33	72.77	1.36	70.63	74.23
60	80.98	79.76	81.95	79.28	81.79	80.85	80.77	1.06	79.76	81.79
90	84.41	82.68	83.84	82.54	86.94	84.89	84.22	1.62	82.68	86.94
120	90.78	88.61	91.39	87.83	91.12	90.73	90.08	1.48	87.83	91.39

Table No.8.8: Dissolution study of Marketed tablet in 0.5 % SLS in Water.

TIME	RUN1	RUN2	RUN3	RUN4	RUN5	RUN6	AVG	SD	MIN	MAX
0	0	0	0	0	0	0	0	0	0	0
5	20.79	19.91	22.25	21.19	19.4	23.4	21.18	1.47	19.48	23.44
10	27.21	26.54	30.27	28.57	24.21	26.6	27.24	2.04	24.21	30.27
15	36.5	37.67	37.63	35.36	31.28	36.57	35.84	2.39	31.28	37.67
30	57.27	58.39	60.33	56.85	54.76	58.63	57.71	1.88	54.76	60.33
45	68.11	66.84	71.35	70.63	69.30	69.98	69.37	1.66	68.11	71.35
60	76.98	75.76	78.45	75.28	74.79	77.54	76.47	1.41	74.79	78.45
90	81.1	80.89	82.84	80.43	81.17	82.32	81.47	0.91	80.89	82.84
120	87.78	86.61	88.80	86.34	89.12	90.78	88.24	1.67	86.34	90.78

Table No. 8.9: Dissolution of Efavirenz tablet in 0.1N HCl.

Parameters	Details
Dissolution media	0.1N HCl solution
Volume	900 ml
RPM	50
Temperature	37±0.50C
Sampling volume	5ml, replacement of 5ml of dissolution media
Sampling interval	5,10,15,30,45,60,90,120 min

Table No.8.10: Dissolution of Efavirenz tablet in 0.1N HCl.

TIME	RUN1	RUN2	RUN3	RUN4	RUN5	RUN6	AVG	SD	MIN	MAX
0	0	0	0	0	0	0	0	0	0	0
5	6.77	7.51	6.44	7.79	6.16	6.91	6.93	0.62	6.16	7.51
10	10.75	11.65	9.26	12.16	9.20	11.25	10.71	1.23	9.20	12.16
15	14.56	15.60	13.13	15.38	12.99	14.29	14.32	1.09	12.99	15.38
30	19.30	20.19	17.73	20.49	17.97	19.74	19.24	1.14	17.73	20.49
45	26.71	27.26	25.21	27.71	26.08	26.41	26.56	0.88	25.21	27.71
60	33.48	34.07	32.82	34.35	32.49	33.55	33.45	0.69	32.49	34.35
90	48.46	49.16	47.35	49.28	47.51	47.78	48.26	0.83	47.51	49.28
120	61.10	61.75	59.46	62.75	59.58	61.01	60.94	1.26	59.46	62.75

Table No.8.11 Dissolution study of Marketed tablet in 0.1N HCl

TIME	RUN1	RUN2	RUN3	RUN4	RUN5	RUN6	AVG	SD	MIN	MAX
0	0	0	0	0	0	0	0	0	0	0
5	3.63	3.27	4.09	3.39	4.16	3.57	3.68	0.36	3.27	4.16
10	6.32	5.86	6.71	5.95	6.70	5.85	6.23	0.40	5.85	6.71
15	8.84	8.08	9.25	8.26	9.49	8.61	8.75	0.54	8.08	9.49
30	10.60	9.60	10.93	10.13	11.25	10.06	10.43	0.60	9.60	11.25
45	15.38	14.57	14.23	15.04	16.02	14.83	15.01	0.62	14.23	16.02
60	20.44	19.3	19.28	20.12	21.01	20.01	20.03	0.66	19.28	21.01
90	36.44	36.08	35.04	36.54	37.63	36.11	36.29	0.84	35.04	37.6
120	48.76	47.98	47.78	48.85	50.03	48.27	48.61	0.81	47.78	50.03

Table No. 8.12: Dissolution of Efavirenz tablets stored at 400C/75 % RH for 15 days.

TIME	RUN1	RUN2	RUN3	RUN4	RUN5	RUN6	AVG	SD	MIN	MAX
0	0	0	0	0	0	0	0	0	0	0
5	32.67	33.02	30.05	28.66	32.50	29.18	31.01	1.77	28.66	33.02
10	38.62	40.54	36.52	35.47	38.62	34.77	37.42	2.00	34.77	40.54
15	50.15	49.10	39.63	45.43	51.72	48.75	47.46	3.98	39.63	51.72
30	70.42	69.55	65.53	64.48	70.07	67.63	67.95	2.27	64.48	70.42
45	81.61	83.18	80.21	80.56	84.23	79.33	81.52	1.70	79.33	84.23
60	91.39	88.07	88.95	87.72	92.79	86.85	89.30	2.10	86.85	92.79
90	95.94	97.68	93.84	94.54	95.94	94.89	95.47	1.23	93.84	95.94
120	99.78	99.61	97.33	98.38	98.91	98.73	98.79	0.81	97.33	99.78
IP Limit- NLT 70% of stated amt. of Efavirenz in 45 min, dissolution medium:1% SLS in H20										

Table No. 8.13: Dissolution of Efavirenz tablets stored at 250C/60% RH for 30 days.

TIME	RUN1	RUN2	RUN3	RUN4	RUN5	RUN6	AVG	SD	MIN	MAX
0	0	0	0	0	0	0	0	0	0	0
5	31.98	31.63	27.61	29.18	30.05	25.94	29.40	2.33	25.94	31.98
10	36.87	37.92	34.25	36.52	35.65	35.82	36.17	1.24	34.25	37.92
15	47.88	49.45	44.38	45.96	48.23	49.98	47.65	2.12	44.38	49.98
30	67.63	67.98	63.78	65.53	67.98	69.55	67.07	2.06	63.78	69.55
45	79.68	79.16	78.46	80.73	80.91	81.43	80.06	1.14	78.46	81.43
60	87.90	85.45	85.98	88.95	90.52	88.42	87.87	1.89	85.45	88.42
90	93.32	95.59	91.39	94.89	93.49	95.59	94.04	1.63	91.39	95.59
120	97.16	98.38	95.53	97.68	97.16	99.43	97.56	1.31	95.53	99.43
IP Limit- NLT 70% of stated amt. of Efavirenz in 45 min, dissolution medium: 1% SLS H20										

Table No. 8.14: Dissolution of Efavirenz tablets stored at 400C/75 % RH for 30days.

TIME	RUN1	RUN2	RUN3	RUN4	RUN5	RUN6	AVG	SD	MIN	MAX
0	0	0	0	0	0	0	0	0	0	0
5	31.45	30.75	25.51	28.66	29.18	29.18	29.12	1.88	25.51	31.45
10	36.17	39.14	33.02	35.47	34.60	34.77	35.53	1.87	33.02	39.14
15	46.83	48.05	43.33	45.43	46.13	48.75	46.42	1.77	43.33	48.75
30	66.23	66.93	62.38	64.48	66.58	67.63	65.70	1.76	62.38	67.63
45	78.29	78.46	77.76	80.56	80.03	79.33	79.07	0.99	77.76	80.56
60	85.98	83.35	85.45	87.728	89.65	86.85	86.50	1.94	83.35	89.65
90	92.09	94.01	90.34	94.54	92.44	94.89	93.05	1.58	92.09	94.89
120	95.94	98.038	94.61	96.64	95.94	98.73	96.65	1.38	94.61	98.73
IP Limit- NLT 70% of stated amt. of Efavirenz in 45 min, dissolution medium: 1% SLS in H20										

Table No. 8.15: Assay & moisture content of tablet stored at 250C/ 60% RH.

Sr.no.	Time in days	Assay	Moisture content
1	initial	98.62 %	3. 248 %
2	15	98.13%	3.613%
3	30	99.62%	3.756%
IP Limit: The Efavirenz tablet should contains not less than 90% and not more than 110 % of the stated amount of C14H9Cl F3NO2.			

Table No. 8.16: Assay & moisture content of tablet stored at 400C/ 75% RH.

Sr.no.	Time in days	Assay	Moisture content
1	initial	98.62 %	3. 248 %
2	15	97.67 %	3.534 %
3	30	98.97 %	3.739 %
IP Limit: The Efavirenz tablet should contains not less than 90% and not more than 110 % of the stated amount of C14H9Cl F3NO2.			