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Research Article

Amorphous -state Characterization and Dissolution Behaviour of Efavirenz- Tocopheryl Polyethylene Glycol Succinate (TPGS)-1000 Solid Dispersions

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ABSTRACT
The aim of the present investigation was to enhance the aqueous solubility and dissolution rate of a poorly soluble drug, efavirenz, by preparation of solid dispersions with tocopheryl polyethylene glycol succinate (TPGS)-1000, a non - ionic surfactant. Phase solubility studies suggested that the solubility of efavirenz increased with the increase in TPGS concentration.1 absorption. Gibbs free energy (ΔG) were negative, indicatingthe spontaneous nature of efavirenz solubilization. Dispersions in different ratios were prepared using the fusion method and their physicochemical characteristics were investigated using Fourier Transform Infrared Spectroscopy(FTIR), X-ray Powder Diffraction studies(XRPD) and Scanning Electron Microscopy(SEM).A drug: carrier ratio of 1:1.5 w/w prepared by cooling the fused mixtures at 5°C showed the highest drug release of 33.27%.It was demonstrated that decrease in crystallinity of the drug and H-bonding between efavirenz and TPGS-1000 might be responsible for the enhanced dissolution rate. Analysis of dissolution data showed the best fitting with Higuchi model.

Keywords: Efavirenz; solid dispersion; TPGS-1000; Dissolution studies; Gibbs free energy; fusion method

INTRODUCTION

Efavirenz [(S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one] (molecular weight 315.68) , a HIV – type I specific non-nucleoside reverse transcriptase inhibitor (NNRTI) (Balani et al.,1999) ,is used in the treatment of HIV-1 infections at a usual adult dose of 600 mg once a daily (Csajka et al.,2003).It is a crystalline lipophilic solid with a low aqueous solubility of 0.01 mg/ml and a low intrinsic dissolution rate of 0.037mg/ cm^2/min^3 . An intrinsic dissolution rate less than 0.1 mg/ cm^2/min (Parvin et al.,2009) is a rate limiting factor for oral drug absorption(Kaplan,1972) It is classified under BCS class II according to the biopharmaceutical classification system by FDA (Kasim et al.,2004).Futhermore, It has very poor and variable absorption (40-45%) due to extremely low aqueous solubility. Efavirenz is currently administered in higher dose in oral dosage for, hence there is need to alleviate its dissolution rate limited absorption problem by enhancing its dissolution rate and thus achieve dosage reduction to achieve desired therapeutic effect.

TPGS, a D-alpha vitamin E ester derived from natural vitamin E, consists of mixture of monoester, certain diester and residual free PEG -1000.A non-ionic surfactant with HLB value of 13.2, it is used as a emulsifier, stabilizer, absorption enhancer and a controlled release agent in pharmaceutical formulations. It improves the solubility of lipophilic compounds through micelle solubilization above its critical micelle concentration (CMC) of 0.1 mM (Eastman chemical publication,1998).TPGS-1000 has been successfully used as solubility enhancer for furosemide (Shin and Kim,2003); to improve the bioavailability of cyclosporin and amprenavir substantially by enhancing their solubility and permeability (Yu et al.,1999) (Ismailos et al.,1994) ; to enhance oral absorption of cyclosporin A by improved solubilization through micellization in liver transplant patients (Sokol et al.,1991) and to enhance the aqueous solubility and absorption of paclitaxel (Varma and

Panchagnula,2005)

In the previous studies, the dissolution rate of efavirenz was enhanced using carriers like PEG 6000, poloxamer 407, carrageenan and by cyclodextrin complexation.

In the present investigation, solid dispersions of efavirenz with TPGS-1000 as a carrier were prepared using the fusion method. The objective of the current work was to evaluate the feasibility of formulating a solid dispersion of efavirenz with enhanced solubility/dissolution rate. The joint influence of 'drug to carrier ratio' and 'temperature to which drug-carrier fused mixture was cooled' was studied on the drug release. Fourier transform infrared spectroscopy (FTIR), X-ray powder diffraction (XRPD), scanning electron microscopy (SEM) and dissolution tests were employed to characterize the prepared solid dispersions.

MATERIALS AND METHODS

Materials

Efavirenz was obtained as a gift sample from Ranbaxy Laboratories Pvt. Ltd., Paonta Sahib.TPGS-1000 was obtained from Sigma Aldrich, Mumbai, India. All other reagents and solvents (Rions, India) used were of analytical grade. Double distilled water and triple distilled water were used throughout the studies.

Methods

Saturation solubility studies

Solubility determinations were performed in triplicate according to the method reported by Higuchi and Connors (Higuchi and Conners,1965).An excess amount of drug was added to each of 5 ml of aqueous solutions containing different concentrations of TPGS-1000 (i.e.0.001,0.005,0.01,0.05,0.1,1,2 and 4% w/v).in conical flasks and sealed with parafilm. The suspensions were stirred continously in a water- bath shaker (RSB-12, REMI) at 100 rpm at a temperature of 37± 0.5° C for 48 hours. The equilibrated solutions were filtered through 0.22 µm pore size Millipore membrane filter and analyzed by UV-VIS spectrophotometer at 248 nm (Deshmukh et al.,2011) (AU-2701, Blue Star).

Calculation of thermodynamic parameter (ΔG)

The thermodynamic parameter, change in Gibbs free energy (ΔG), indicates the spontaneity of given process at given conditions. It was calculated for the process of dissolution of efavirenz in TPGS aqueous solutions at physiological temperature (37˚C) using the following relationship (Chengsheng et al.,2005).:

$\Delta G = -2.303\ RT \log N/N_{\circ}$

Where $N/N_{\circ}$ is the ratio of molar solubility of the drug in aqueous solution of TPGS to that of the pure water, R is the gas constant (8.3143 J/K/mol) and T is the absolute temperature (K).

Preparation of Solid binary systems

Binary Physical Mixtures

Physical mixtures of efavirenz and TPGS were prepared in 1:0.5,1:1 and 1:1.5 w/w ratios by uniformly mixing the accurately weighed quantities at cold room temperature (as TPGS tends to melt during mixing) and the resultant mass was passed through a 44 mesh sieve (nominal mesh aperture size 355 µm), collected and stored in an amber colored vial away from light and humidity until use in a desicator (Sathigari et al.,2009)

Binary solid dispersions

The solid dispersions containing different ratios (1:0.5,1:1 and 1:1.5 w/w) of efavirenz and TPGS were prepared by the fusion method (Chio and Riegelman,1971)and cooled at three different temperatures (5°C,15°Cand 25°C) there of nine combinations (SD1 to SD9), were prepared

Efavirenz and TPGS-1000 were weighed accurately in required quantities. TPGS was melted at a temperature above its melting point (37°C) and the drug was dispersed into the molten carrier. The molten mass was stirred for 10-15 minutes on a magnetic stirrer until it becomes homogeneous. The resultant mixture was immediately cooled to the desired temperature using ice-water mixture and maintained for a period of 2 hours at the specified temperature. After solidification, the fused mixtures were removed from ice-water mixture and stored at room temperature (25-30°C) for 24 hours. The dried solid dispersions were pulverized, passed through a 44 mesh sieve, transferred to amber colored vials and stored in a glass dessicator over fused calcium chloride. The percentage yield was found using the formula:

% Yield = (a/b + c) x100

where a is the weight of solid dispersion obtained after sieving through sieve no. 44, b is the weight of carrier used for solid dispersion preparation, and c is the weight of drug taken for the solid dispersion preparation.

In-vitro Dissolution rate studies

In-vitro dissolution studies of pure drug, physical mixtures and solid dispersions equivalent to 50 mg of efavirenz were carried out using a USP II(Paddle type) dissolution apparatus (Lab India

Dissolution Test Apparatus, DISSO 2000,India) in 900 ml of distilled water maintained at 37 ±0.5°C and 75 rpm .Sampling(5 ml) was done at fixed intervals An equal amount of dissolution medium was replaced immediately after each withdrawal of the test sample to maintain the sink conditions .The withdrawn samples were filtered through 0.2 µm membrane filter and directly assayed without any further dilution for drug content spectrophotometrically at 248 nm.
The percentage cumulative drug release for each formulation was compared and the formulation exhibiting highest drug release was further characterized using the below mentioned techniques.

XRPD studies
Powder X-ray diffraction patterns for pure drug, carrier ,physical mixture and solid dispersion were recorded using X-ray diffractrometer (D8 Focus, Bruker) using CuKα radiation. It was operated at 40 KV, 40 mA at ambient temperature and the scanning rate used was 2°/min over the 2θ range of 20°-80°.XRD patterns were plotted using origin 8.5 software (Sathigari et al.,2012).

FTIR spectroscopic studies
FTIR spectra of efavirenz, TPGS-1000, physical mixture and solid dispersion were obtained using a FTIR spectrophotometer (C92035, Perkin Elmer).FT-IR study was done using KBr pellets as blank by using completely dried KBr powder and then samples were recorded in transmission mode from 4000 to 400cm^{-1}.

Scanning electron microscopy (SEM) analysis
The samples of pure drug efavirenz, physical mixture and solid dispersion were examined using scanning electron microscope (EVO LS10,Carl Zeiss) operated at an acceleration voltage of 10.00 KV and working distance of 6-7 mm. The samples were mounted onto the stubs using double-sided adhesive tape and analysed. The photographs were obtained at a selected magnification factor of × 500.

Analysis of mechanism of dissolution
The mechanism of drug release from the solid dispersion showing maximum drug release was studied by fitting the in-vitro drug release data to various kinetic models i.e. zero order, first order, Higuchi and Korsemeyer- Peppas model using the following equations (Ahuja et al.,2007).:
Zero order model:
$Q_o - Q_t = K_o t$
First order model:
$InQ_t = InQ_o - K_1 t$
Higuchi model:
$Q_t = K_H t^{1/2}$
Korsmeyer- Peppas model:
$Q_t/Q_\infty = K_k t^n$
The value of n in this model characterizes the release mechanism of drug from the given polymeric system.
where Q_o ,Q_t and Q_∞ are the amount of drug taken at time zero, amount of drug dissolved at a time t and amount of drug released at infinite time respectively. Various other terms like K_o ,K_1, K_H and K_k refer to the respective release constants of zero order, first order, Higuchi and Korsemeyer-Peppas models (Madhavi et al.,2011).

RESULTS AND DISCUSSION
Saturation solubility studies
The saturation solubility of efavirenz in distilled water at 37 °C was found to be 8.5 µg/ml. The determined solubility of efavirenz is in agreement with the previously published value by Madhavi et al, 2011. The solubility studies of efavirenz in aqueous TPGS solutions (ranging in concentration from 0.01mM – 26.4 mM) were performed at 37± 0.5°C. From the solubility studies, the CMC of TPGS at 37° C was found to be approximately 0.1 mM which is same as reported by Ismailos et al,1994. It was found that drug solubility increases as the TPGS concentration increases with the highest of about 10.97 µg/ml at the CMC (0.02 % w/v) of TPGS in water(Fig.1). It shows that at the CMC, the entrapment of drug molecules into micelles leads to enhanced aqueous solubility (Shin and Kim,2003).Further above CMC, the solubility of drug decreases which may be attributed to the fact that as more drug gets entrapped in the micelles structure above the CMC and fails to partition in water. Further above 1%TPGS concentration, the drug solubility increased linearily from 6.68±0.3 to 10.42±0.7µg/ml showing the characteristics of typical A_L -type system.

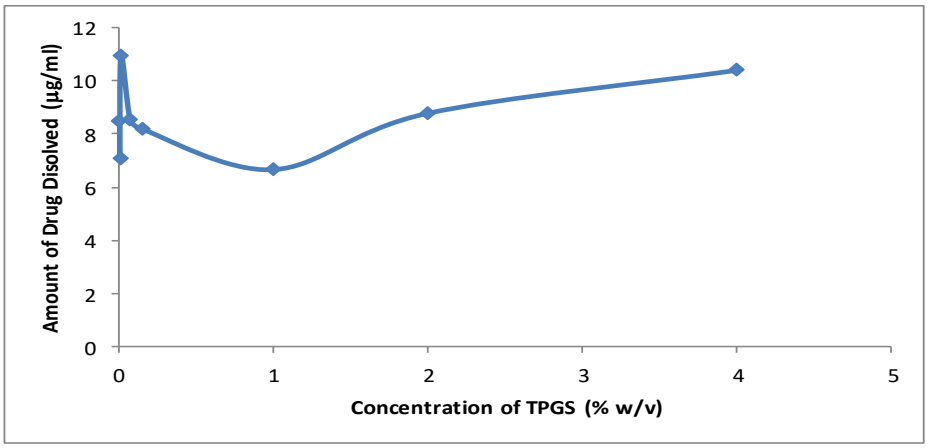


Fig.1 Phase solubility curve of efavirenz with TPGS (0.001-4% range) aqueous solutions

The total efavirenz concentration (S_{total}) above the CMC of TPGS is the sum of free (S_{free}) and micelle-bound (S_{bound}) efavirenz.

$S_{total} = S_{free} + S_{bound}$

The equilibrium between free and micelle bound solute exists as (Costa et al.,2001):

$$K_a = \frac{Sbound}{Sfree.(SAA)m}$$

Where K_a is the equilibrium-distribution coefficient and$(SAA)_m$ is the concentration of TPGS in micelle form which is equal to the difference between total TPGS concentration and the CMC.

From above equations:

$S_{total} = S_{free} [1 + K_a (SAA)_m]$

Fitting this equation to the efavirenz solubility and TPGS micellar concentration gives a straight line, the slope of which gives an equilibrium coefficient, K_a, of $0.2mM^{-1}$. As the aqueous solubility of efavirenz and K_a is very small, it shows that appreciable micellar solubilization of efavirenz can occur only at large TPGS concentrations (Amidon et al.,1982).

The negative nature of the ΔG values show the spontaneity of the dissolution process of efavirenz in TPGS aqueous solutions. Further, the magnitude of ΔG increases on increasing TPGS concentration reflecting the positive effect of TPGS on efavirenz solubility (see Table 1). As the values of ΔG reported in the present study are outside the range of values of ΔG for complexation i.e. 8.4-20.9 KJ/mol, this rule out the possibility of complexation mechanism between the drug and carrier for the enhanced solubility.

Table 1: Thermodynamic parameter (ΔG) for the dissolution of efavirenz in TPGS aqueous solutions

Sr. No.	Conc. of TPGS -1000 (wt %)	Amount of drug dissolved (µg/ml)	ΔG (J/mol)
1.	1	6.68	-801.901
2.	2	8.80	-1512.988
3.	4	10.42	-1947.475

Dissolution rate studies

The dissolution profiles of efavirenz and its binary systems are shown in Fig (2&3). The pure drug exhibited very low dissolution rate with only 10(±0.6) % of drug released at the end of 3 hours. Its dissolution profile was very erratic throughout the period of the study. This strongly emphasized the need to enhance the aqueous solubility of this drug. The dissolution rate of efavirenz from the physical mixtures increased rapidly as compared to the pure drug with a significantly higher cumulative percentage release of 23.36% of drug from the physical mixture (PM3). This can be attributed to the wetting, emulsifying and surfactant properties of the TPGS-1000 on the hydrophobic efavirenz particles in the physical mixtures (Yu et al.,1999).Further the TPGS melts at the temperature of the dissolution media (37°C) and dissolve quickly in it acting as a surfactant for the hydrophobic drug particles(Feldman and Gibaldi,1967). Moreover, the pure drug particles being hydrophobic and less dense, float on the surface of dissolution media during the whole period of study as compared to the physical mixture. The percentage cumulative release from the 1.0:1.5 ratio (PM3) was found to be 23.36% at the end of 180 minutes.

The dissolution rate from solid dispersions was also higher as compared to the pure drug. It was comparable to the physical mixtures but solid dispersions exhibited higher dissolution at the end of 3 hours. This increase over the physical mixtures may be ascribed to the partial reduction of crystallinity of the drug and existence of drug in more amorphous state in the fused drug-carrier mixtures. These results confirm the possibility of interaction between drug and carrier as evident from the physicochemical characterization.

The percentage cumulative drug release was found to be highest (33.27%) for solid dispersion SD3 containing the highest drug: carrier ratio (1.0:1.5) and prepared by cooling the fused mixture at the lowest temperature(5°C). This shows that as the drug: carrier ratio was increased and the temperature to which fused mixtures were cooled during preparation was decreased, the amount of drug released increases. This can be attributed to the existence of drug in amorphous state (higher energy state) at low temperature (Shah et al.,2007). Also as the weight fraction of TPGS increases, the proportion of the amorphous form of efavirenz may increase resulting in dissolution enhancement (Mu and Feng, 2002).

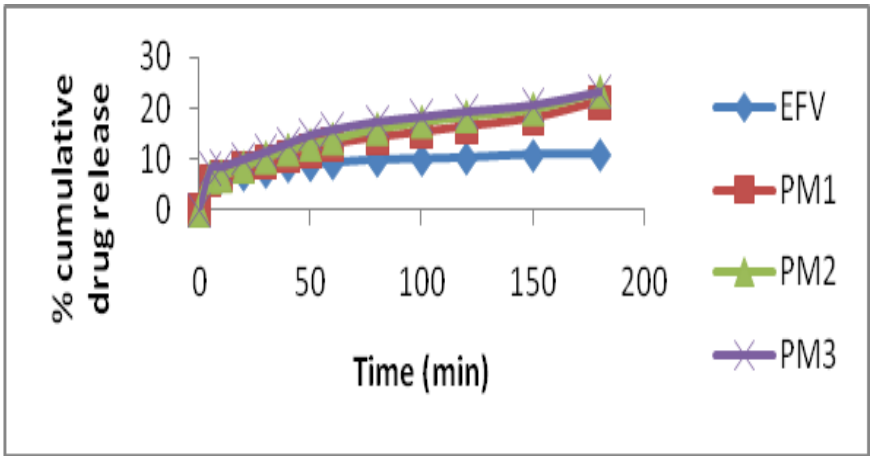


Fig 2: in vitrodrug release profile of drug, PM1-PM3

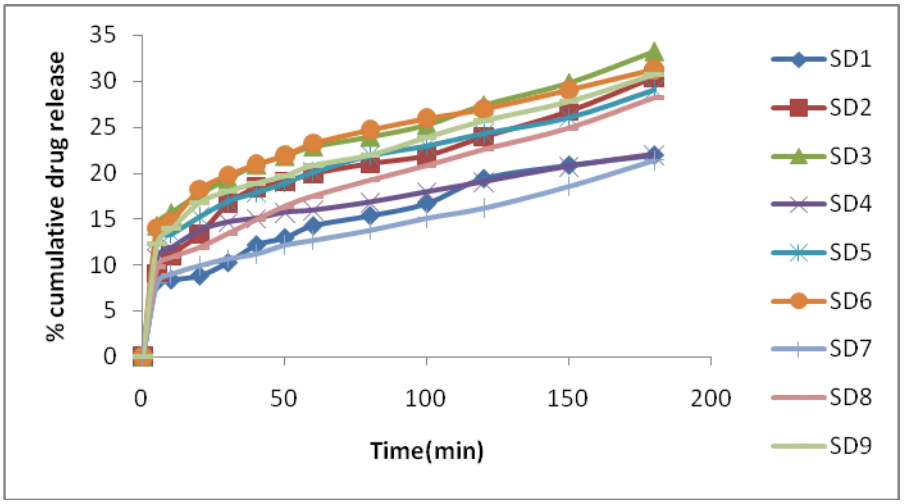


Fig 3: in vitro drug release profile of solid dispersions (SD1-SD9)

The percentage yield of all the solid dispersion batches was also determined. It was found that the % yield of solid dispersions decreases as the carrier content increases showing the increase in the stickiness of dispersion with the increase in carrier content , owing to its waxy nature which leads to the consolidation of the particles and difficult sieving (Table 2).The yield of SD3 (exhibiting highest drug release) was more than 60 %,hence it may be considered as a promising formulation for dissolution enhancement of efavirenz.

Table 2: Percent yield of Solid Dispersions

Sr. No.	Batch code	Drug-carrier ratio(w/w)	Temperature to which drug-carrier fused mixtures cooled(°C)	Percentage yield
1	**SD1**	1.0:0.5	5	71±1.03
2	**SD2**	1.0:1.0	5	66.5±1.45
3	**SD3**	1.0:1.5	5	62.4±2.32
4	**SD4**	1.0:0.5	15	64.6±0.74
5	**SD5**	1.0:1.0	15	65.5±0.98
6	**SD6**	1.0:1.5	15	55.2±1.23
7	**SD7**	1.0:0.5	25	64.6±1.73
8	**SD8**	1.0:1.0	25	58.2±2.01
9	**SD9**	1.0:1.5	25	49.2±1.29

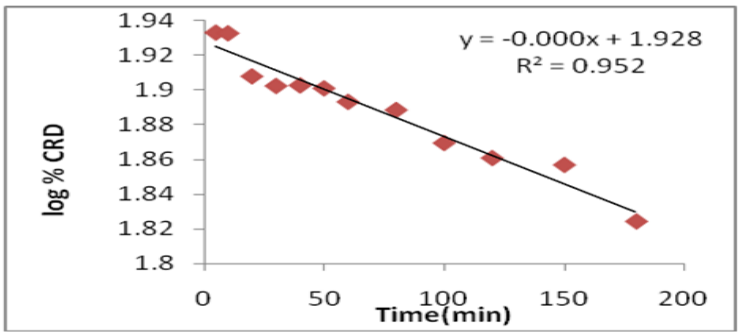
Mechanism of drug release

The mechanism of drug release kinetics from solid dispersion(SD3) was analyzed using various mathematical models. Table 3 lists the values of R^2 and slope of the various models. The release data as shown in Fig 4 shows the best fit with the Higuchi model with R^2 value of 0.954 indicating the release of drug from matrix as a square root of time dependent process. The goodness of fit was in the order of Higuchi >first-order>Korsemeyer-peppas >Zero-order. This shows that the drug gets entrapped in the hydrophilic matrix formed by the carrier through which the drug was released as the matrix depleted.

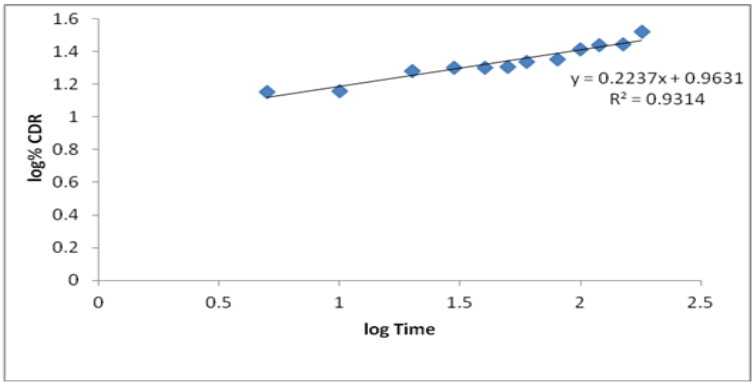
The value of n for the Korsemeyer-peppas model was found to be 0.2237 which lie beyond the limits of this model but indicate that the solid dispersion tended to exhibit the Fickian kinetics of diffusion release mechanism.

Table 3: Slope and r^2 values of various kinetic models for drug release from solid dispersion (SD3)

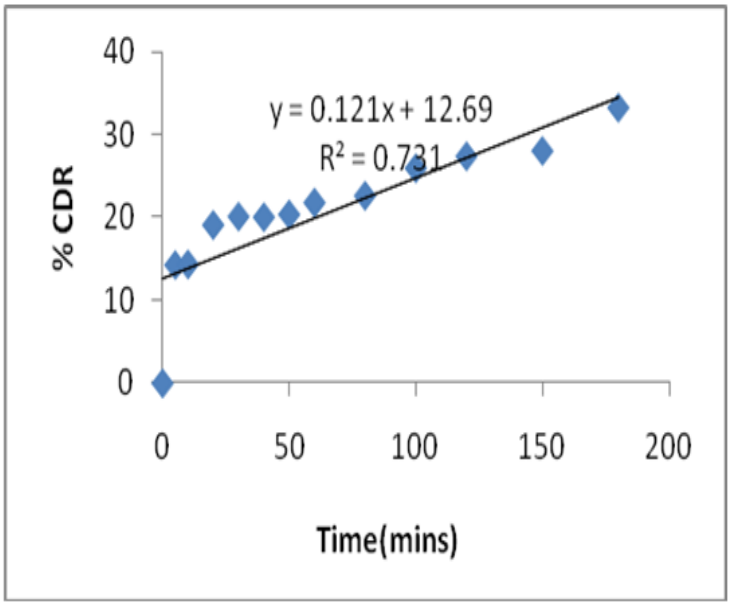
Zero-order		First-order		Higuchi		Korsemeyer-peppas	
Slope	**r^2**	**Slope**	**R^2**	**Slope**	**r^2**	**Slope**	**r^2**
0.1213	0.7312	-0.0005	0.9523	1.538	0.954	0.223	0.931



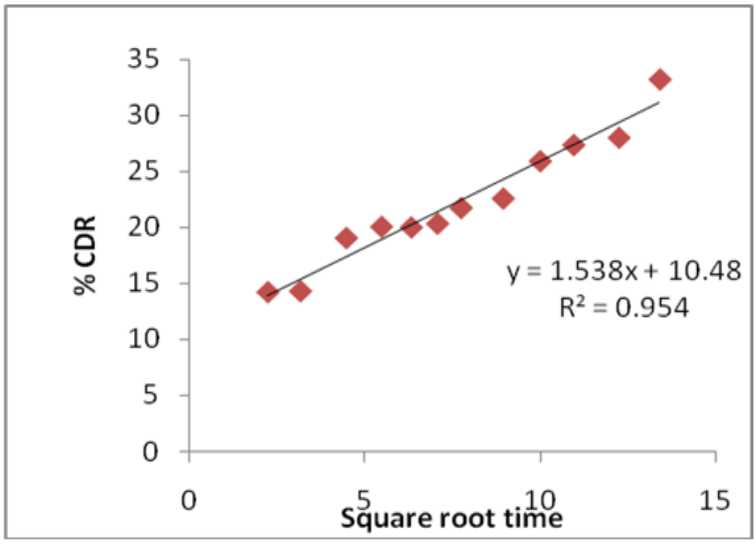
A: First order release model of SD3



B: Korsemeyer-Peppas model of SD3



C: Zero order model of SD3



D: Higuch model of SD3

Fig. 4 Release kinetic plots of SD3

X-Ray Diffraction studies

Figure 5 shows the XRD patterns of efavirenz, TPGS, physical mixture (PM 3) and solid dispersion (SD3). The XRD pattern of efavirenz exhibited large number of diffraction peaks indicating the crystalline nature of the drug. The peaks are reduced both in number and intensity in the XRD pattern of physical mixture as compared to the pure drug. Similarly, the diffraction pattern of solid dispersion also showed decrease in the number and intensity of peaks as compared to that of drug. These results confimed the reduction of crystallanity of drug as well as the carrier in the solid dispersion which is responsible for the enhanced aqueous solubility (Xie et al.,2009).

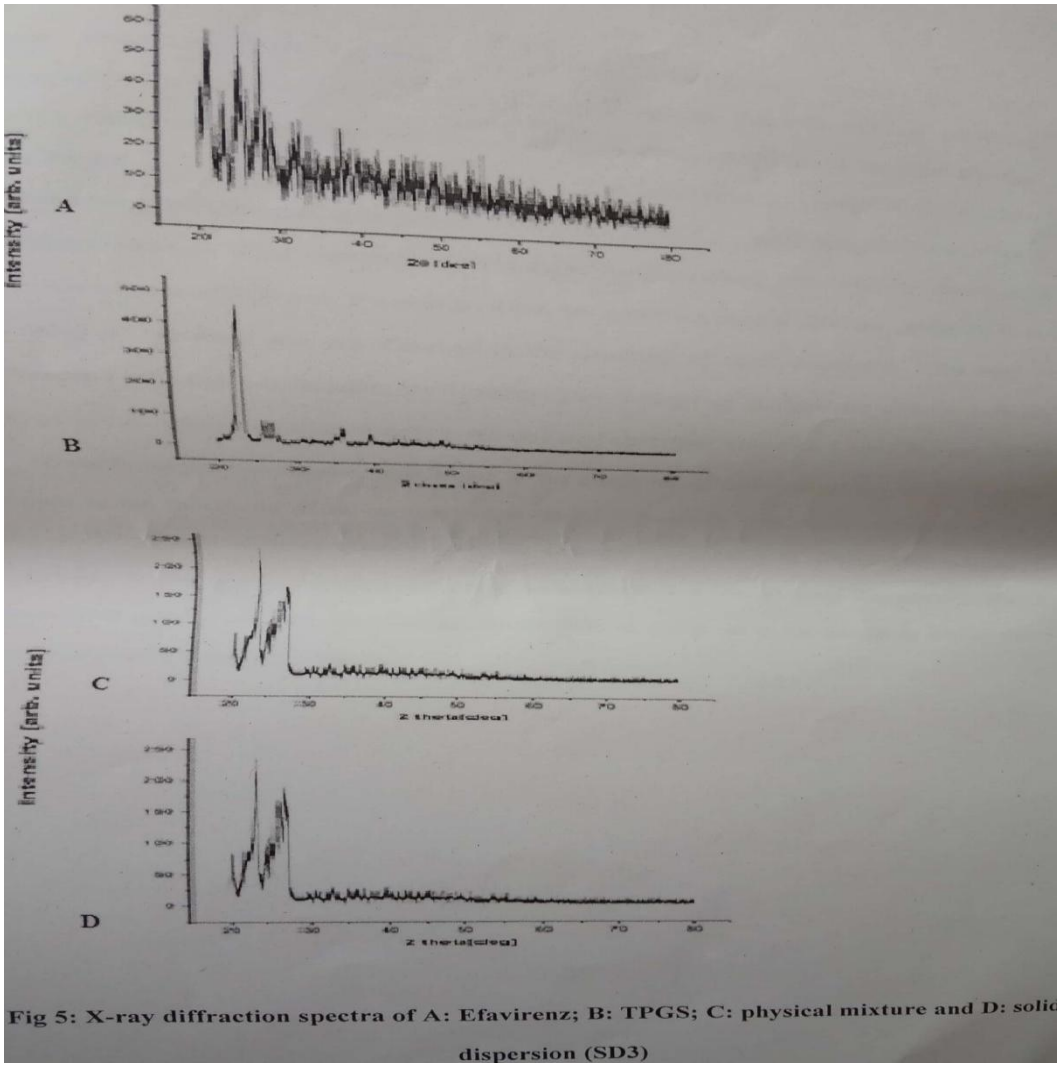
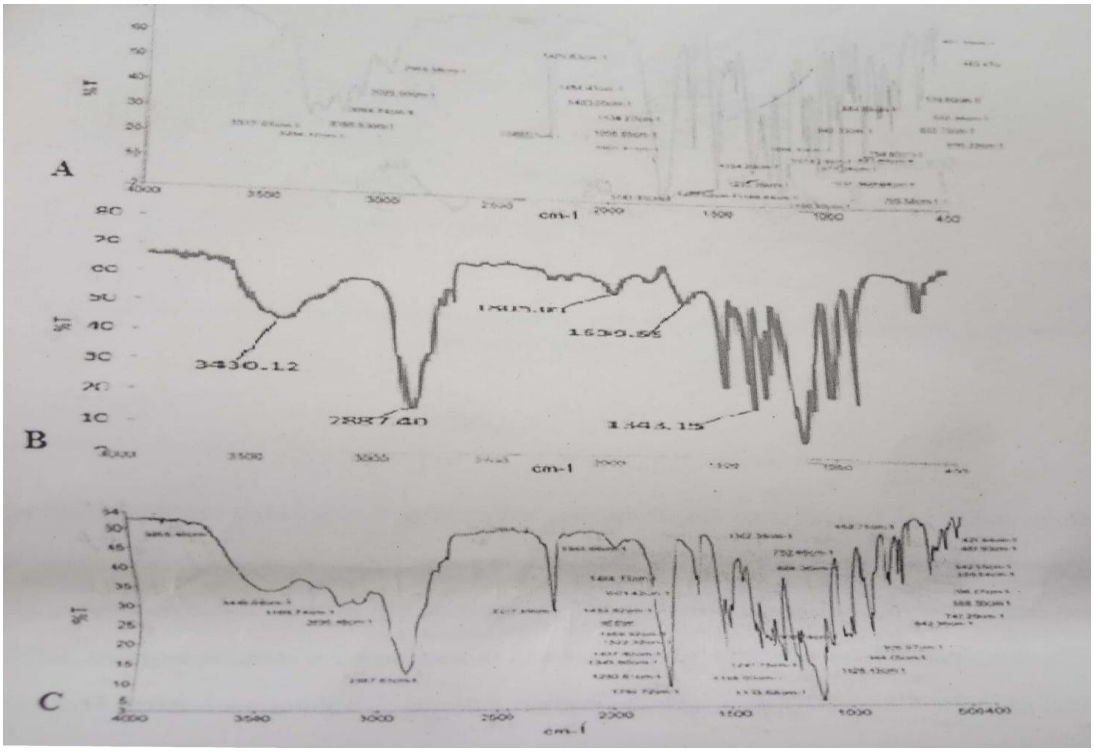


Fig 5: X-ray diffraction spectra of A: Efavirenz; B: TPGS; C: physical mixture and D: solid dispersion (SD3)

3.5 FTIR Analysis

Figure 6 shows the FTIR spectrum of efavirenz ,TPGS,physical mixture and solid dispersion(SD).The spectrum of efavirenz shows characteristic peaks at 3317.01 cm^{-1} (N-H streching vibrations),3020cm^{-1} and 2965.58cm^{-1} (C-H streching vibrations) in the 3500-2500cm^{-1} region. Further it shows peaks at 2249.37cm^{-1}(-C≡C stretching),1741.01cm^{-1}(C=O stretching),1601.99cm^{-1} (C=C stretching),1334.20cm^{-1}(C-O streching),1255.36cm^{-1} (C-F stretching),1166.65cm^{-1} (C-N stretching) and 754.80cm^{-1} (C-Cl streching vibrations).The spectrum of TPGS show peak at 3430.12 cm^{-1}due to the terminal hydroxyl group. It was noticed that the stretching band at 3317 cm^{-1} assigned to the N-H group of efavirenz was not observed in the spectrum of solid dispersion (SD).This may be attributed to the probable H- bonding involvement of the N-H group of efavirenz with the carbonyl group of TPGS. Also, a significant shift in the carbonyl stretching vibration from 1741 cm^{-1}-1756 cm^{-1} (towards longer wavenumber) was noted in the spectrum of solid dispersion which can be assigned to the shortening of the carbonyl bond- length through H- bonding involvement of the adjacent N-H functionality of efavirenz with the carbonyl functionality of TPGS. This may be responsible for the higher solubility of the drug molecules in water in the solid dispersion. The spectrum of physical mixture also exhibited similar shifts as compared to the pure drug which can also be attributed to the same reasons.



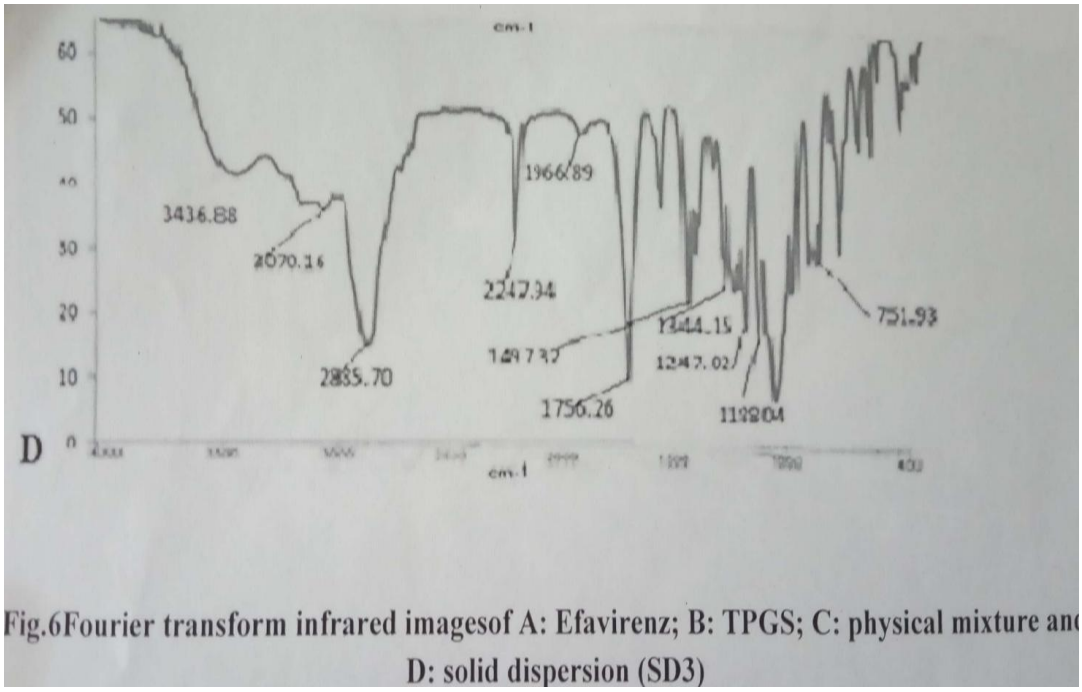


Fig.6Fourier transform infrared imagesof A: Efavirenz; B: TPGS; C: physical mixture and D: solid dispersion (SD3)

3.6 SEM Analysis

The SEM images of efavirenz and its binary systems are shown in Figure 7. The pure drug efavirenz is found to be in form of agglomerate of individual particles hence the exact morphology of the drug particles is not clear in the photograph. The particles of physical mixture of efavirenz with TPGS are more uniform in appearance as compared to the drug. The solid dispersion(SD3) particles also have uniform appearance confirming the loss of original morphology of the drug. This indicate the formation of new single phase consisting of drug and carrier which exhibits reduction of crystallinity of the drug in the solid dispersion particles (Ruan et al.,2005).

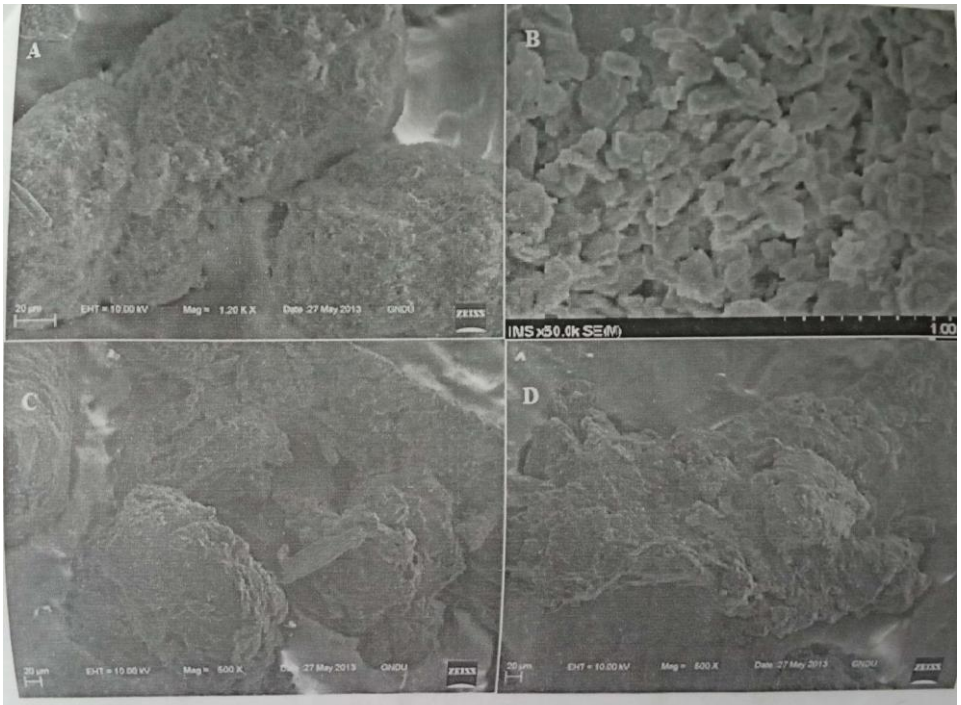


Fig. 7Scanning electron microscopy images of A: Efavirenz; B: TPGS; C: physical mixture and D: solid dispersion (SD3)

CONCLUSION

The present works shows that the dissolution rate of drug is improved by the addition of TPGS-1000 through physical mixture and solid dispersion methods.The mechanisms involved may be the enhanced wetting of the drug ,emulsifying effects of the carrier and reduction of crystallinity of the drug in the solid dispersion.The physicochemical characterization also confirmed the reduction of crystallinity of drug and interaction between the drug and carrier at the molecular state leading to improved solubility and dissolution rate. To further enhance the solubility and dissolution rate, investigations are required to study the drug release from solid dispersions of efavirenz and TPGS prepared by various other methods like solvent evaporation, spray drying, lyophilization etc.

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Conflict of Interest

None

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