



FORMULATION DEVELOPMENT AND *IN VIVO* EVALUATION OF EFAVIRENZ SOLID DISPERSIONS

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ABSTRACT

The applicability of the solid dispersion technique as a method for enhancing the GI absorption of a drug has been explored in order to achieve better dissolution characteristics and better bioavailability for poorly soluble drugs. Efavirenz is an antiretroviral agent often demonstrates poor gastrointestinal absorption due to inadequate drug solubility in GI fluids. The objective of the present study is to formulate and characterize free flowing efavirenz solid dispersions by short term heating and rapid drying (solvent-melt method) with polyvinyl pyrrolidone and adsorbent Neusilin as anti sticking agent. The release rate of Efavirenz from the resulting complexes was determined from dissolution studies and dissolution characteristics were carried out for solid dispersion formulations, pure drug and physical mixtures. The results indicated that dissolution of optimized formulation (FSD2) showed significantly higher than pure drug and physical mixtures. X-ray diffraction studies of optimized formulation showed no physicochemical interaction. DSC studies revealed that absence of drug peak in the free flowing solid dispersion formulation indicating the drug was in amorphous form. The comparison of *in vivo* bioavailability studies of optimized formulation and that of a pure drug as reference standard in Wistar rats confirmed that the higher amount of drug concentration in blood indicated better systemic absorption and bioavailability also found to be increased with optimized formulation.

Keywords: Efavirenz, Solid dispersions, Neusilin, Solubility.

INTRODUCTION

The enhancement of the bioavailability of poorly water-soluble drugs is one of the greatest challenges of drug development¹. Oral bioavailability of a poorly water-soluble drug was greatly enhanced by using its solid dispersion in a surface-active carrier². Solid dispersions have been explored as potential delivery systems for many poorly water soluble drugs³. Solid dispersion systems have been realized as extremely useful tool in improving the dissolution properties of poorly water-soluble drugs⁴. The use of solid dispersions to increase the dissolution rate and the bioavailability of poorly water-soluble drugs is now well established. Solid dispersions represent a useful pharmaceutical technique for increasing the dissolution, absorption and therapeutic efficacy of drugs in dosage forms⁵.

Efavirenz is a novel non-nucleoside reverse transcriptase inhibitor for the treatment of HIV-1-infected individuals⁶. Efavirenz is a class II drug according to the biopharmaceutical classification system. It often demonstrates poor gastrointestinal absorption due to inadequate drug solubility in GI fluids. Efavirenz is a hydrophobic drug with low density and high flow resistance⁷.

The concept of solid dispersions dates back to 1961 when Sekiguchi & Obi found that the administration of a fused mixture of the poorly water-soluble drug sulphathiazole and the water-soluble carrier urea produced an enhanced absorption of the drug in rabbit⁸. Subsequently, hundreds of papers have been published detailing the physico-

chemical properties phase equilibrium and pharmacological activity of solid dispersion-based drug carrier systems (Ford and Timmins, 1989). However, only few drug products based on solid dispersions have reached the market, because of physico-chemical instability and scale-up problems^{9,10}.

Solid dispersions are generally prepared by either a solvent method, whereby the drug and carrier are dissolved in a mutual solvent followed by solvent removal, or by a melting method, whereby drug-carrier mixtures are prepared by co-melting/cooling. The disadvantage of the solvent method is the use of organic solvents with issues of toxicity, safety hazards and solvent residuals and also the possible precipitation of the drug into various polymorphic forms, which have different solubilities and bioavailability. Therefore, melting is often the method of choice for the preparation of solid dispersions despite the potential problem of heat-induced degradation of drugs and carriers. In general, for solid dispersion formulations contains high amount of polymers and all polymers are very sticky in nature which creates problems like practical yield and flow problems during scale up. Polyvinyl pyrrolidone, hydroxy propyl cellulose and hydroxy propyl methyl cellulose commonly used in solid dispersion formulations.

The aim of the present study was, therefore, to investigate the physical state of model compound (efavirenz) in solid dispersions with PVP k-30, HPC and HPMC in order to contribute to the understanding of the factors that determine the stability of the amorphous state in solid dispersions using solvent heat method. The



amorphous presentation of the efavirenz was preferred as the highly disordered form has a lower energy barrier to overcome for dissolution than the structured crystalline form. Accordingly, excessively high temperatures and high amount of solvents were not required to produce the solid dispersion using solvent heat method. Additionally, neusilin acts as anti sticking agent which reduces the processing problems like less practical yield and flow problems normally occur in solid dispersion formulations.

MATERIALS AND METHODS

Materials

Efavirenz was obtained from Matrix laboratories (Hyderabad, India), as a gift sample. Hydroxy propyl methyl cellulose and Hydroxy propyl cellulose was obtained from Signet (Mumbai, India), Polyvinyl pyrrolidone (kollidon 30) was obtained from BASF (India), Neusilin US2 (magnesium aluminium silicate) obtained from Fuji chemicals (Japan). Dichloromethane, Ethanol, Sodium lauryl sulfate from Stepan company, USA. All other reagents were used of analytical grade.

Animals

Male Wistar rats (weighing approximately 250±25 g) were procured from institutional animal house. The animals were maintained at a temperature of 25°C and humidity 60% and were supplied with food and water. The study protocol was approved by the institutional animal ethics committee (IAEC), University College of Pharmaceutical Sciences, Kakatiya University, Warangal, India.

Preliminary solubility studies of Efavirenz

Solubility measurements of efavirenz were performed according to a published method¹¹. An excess amount of efavirenz was added to 25ml of aqueous solution of water soluble carriers like poly vinyl pyrrolidone and hydroxy propyl cellulose and hydroxy propyl methyl cellulose in the various ratios in screw capped bottles. Samples were shaken for the 24 hours at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no 1. Filtered solution analyzed for the efavirenz using HPLC method.

Preparation of Physical mixtures and solid dispersion formulation using Kollidon 30 & HPC

For physical mixtures, efavirenz was mixed with the kollidon 30 in a mortar for 5 minutes. The resulting mixture was the sieved # 30 (100 -200 microns). The weight ratio of the drug to kollidon 30 was 1:1 & 1:2. The powders were stored in screw cap bottles at room temperature until further analysis.

For solid dispersion, the sample was prepared by dissolving efavirenz in small volume of ethanol in 250ml round bottom flask. The flask was vortexed and then placed in a water bath maintained at 40°C. The kollidon 30 was added to the hot solution with continuous swirling until the kollidon 30 melted. The flask was then attached

to a buchi rotary evaporator, immersed in the water bath under vacuum for 15 minutes to remove the ethanol. After the majority of solvent had evaporated, the flask was then immersed in an ice bath for 15 minutes. The contents of the flask were transferred in to vacuum tray drier and dried at 40°C temperature under vacuum for 2 hours to remove residual solvent. After drying, the mass was pulverized and was sifted through # 30 (ASTM). The weight ratio of the drug to kollidon 30 was 1:1 and 1:2. The powders were stored in triple laminated bag at room temperature until further analysis. Same procedure was repeated with HPC.

% Practical Yield

Percentage practical yield was calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. SDs were collected and weighed to determine practical yield (PY) from the following equation. And the results are tabulated in table no.

Preliminary solubility studies of Efavirenz with anti-sticking agent

Solubility measurements of efavirenz were performed according to a published method¹². An excess amount of Efavirenz was added to 25ml of aqueous solution of water soluble carriers like polyvinyl pyrrolidone, hydroxy propyl cellulose and hydroxy propyl methyl cellulose using Neusilin in various ratios in screw capped bottles. Samples were shaken for the 24 hours at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no 1. Filtered solution analyzed for the Efavirenz using HPLC method.

Preparation of physical mixtures and solid dispersion formulation using polyvinyl pyrrolidone and HPC with anti sticking agent

To prepare physical mixtures and solid dispersion formulation using polyvinyl pyrrolidone and HPC using anti sticking agent neusilin US2, same method was adopted as mentioned for preparation of physical mixtures and solid dispersion formulation using Kollidon & HPC.

Solubility studies for physical mixtures and free flowing Solid dispersion by solvent heat method

50 mg of drug, and all solid dispersions, (i.e 50mg drug equivalent) were kept in 100ml volumetric flasks and containing 50ml of purified water for 24hrs on shaking. After 24hrs, the samples were withdrawn, filtered and analyzed by HPLC method. Solubility was calculated using the absorbance values obtained after analysis.

Flow properties and filling into capsules

The flow properties of physical mixtures and SDs formulations with and without anti sticking agent were characterized in terms of angle of repose, Carr index and Hausner ratio. For determination of angle of repose (θ), the sample was poured through the walls of a funnel,



which was fixed at a position such that its lower tip was at a height of exactly 2.0cm above hard surface. The sample was poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The \tan^{-1} of the (height of the pile / radius of its base) gave the angle of repose. Sample was poured gently through a glass funnel into a graduated cylinder cut exactly to 10 ml mark. Excess sample was removed using a spatula and the weight of the cylinder with powder required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0 cm until the time when there was no more decrease in the volume. Bulk density (ρ_b) and tapped density (ρ_t) were calculated. Hausner ratio (HR) and Carr index (IC) were calculated according to the two equations given as per following equation and results are tabulated in table no. All the compositions, as such efavirenz, physical mixtures and solid dispersion compositions were filled in '0' size hard gelatin capsules separately.

HPLC Analysis of Efavirenz

The HPLC analysis was carried out using high performance liquid chromatography system (Shimadzu, USA). The chromatograph column was Hypersil BDS, 250 x 4.0 mm 5- μ stainless steel. The Mobile phase is mixed Acetonitrile and Ammonium acetate solution (0.8mg/ml and pH adjusted to 7.5 with ammonium hydroxide solution) in 3:2 ratios at flow rate 1ml/min and run time was about 10 min. A 5- μ L volume was injected into the system and the eluent was monitored at 252 nm. Column temperature and sample temperature was maintained at 25°C and 10°C respectively.

Drug content

The amount of drug present in 50 mg equivalent amount of solid dispersion was determined by using HPLC method and drug concentration was determined from standard graph.

In vitro release studies

In vitro dissolution studies were performed for filled capsules of pure drug, physical mixtures and free flowing solid dispersion formulations by using Electro lab-USP paddle type dissolution test apparatus, 1% sodium lauryl sulfate in water as dissolution medium, temperature was maintained at 37 \pm 0.10°C and RPM adjusted to 50.

DSC studies

Based on invitro dissolution studies, DSC thermograms of pure efavirenz and selected free flowing solid dispersions were shown in Fig. Differential scanning calorimetry was conducted using Mettler Toledo Star system, Metallurgy department, Indian Institute of Science, Bangalore, India. Sample were weighed (5.00-8.00 \pm 0.5 mg) and placed in sealed aluminium pans. The coolant was liquid nitrogen. The samples were scanned at 100°C/ min from 200°C to 3000°C.

XRD (X-Ray diffraction) studies

Based on invitro dissolution studies, XRD studies performed on pure efavirenz and selected free flowing solid dispersions and results were shown in Fig. XRPD diffractograms of drug, and free flowing solid dispersion were recorded using a Bruker D8 advanced Diffractometer with a Cu line as the source of radiation. Standard runs using a 40-kv voltage, a 40-mA current, and a scanning rate of 0.02° min⁻¹ over a 2 θ range of 3-40° were used. DSC thermograms of pure Efavirenz and selected free flowing solid dispersions were recorded.

Pharmacokinetic study

The pharmacokinetic characteristics for pure drug suspension, and free flowing solid dispersion of efavirenz were evaluated using eight healthy Wistar rats weighing 250 \pm 10 g were used in the study. All rats were dosed following an overnight fast; food was returned after 4 h after dosing. Rats were divided in to two groups at random. First group was administered Efavirenz (as such) suspension was prepared in 0.5% methocel, and second group was administered free flowing solid dispersion suspension was prepared in 0.5% Methocel. All the case Efavirenz as such, and free flowing solid dispersion, 0.5% methocel used because efavirenz was virtually insoluble in water and each animal received dose equivalent to 50mg/kg of Efavirenz. Blood samples (approximately 0.5ml) were obtained with syringes pre dose and at 0.25, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 7.00, 24.00, 52.00 hrs post dose. During collection, blood sample has been mixed thoroughly with heparin in order to prevent blood clotting. Plasma was separated by centrifugation of the blood at 5000 rpm in cooling centrifuge for 5min to 10 minutes and stored frozen at -20°C until analysis. The concentration of Efavirenz in wistar rat plasma was determined by validated liquid chromatography–mass spectrometry (LC-MS) method.

Pharmacokinetic Data Analysis for free flowing solid dispersion formulation and pure drug suspension

The area under the drug concentration-time curve from zero to 52h (AUC) was calculated using the trapezoidal rule. The maximum plasma concentration of the drug (C_{max} and the time to reach C_{max} (T_{max}) were obtained directly from the plasma profiles. The relative bioavailability (BA) of the free flowing solid dispersion to the reference (pure drug suspension) was calculated as follows:

$$\text{Relative Bio Availability (\%)} = \frac{\text{AUC}_{\text{test}}}{\text{AUC}_{\text{reference}}} \times \frac{\text{Dose}_{\text{reference}}}{\text{Dose}_{\text{test}}}$$

Where, AUC_{test} and AUC_{reference} are AUCs obtained after the oral administration of the free flowing solid dispersion formulation and the reference (pure drug suspension), respectively. Dose_{test} and Dose_{reference} are the doses of the two products.

The pharmacokinetic parameters were performed by a non compartmental analysis using Win Nonlin 3.3®



pharmacokinetic software (Pharsight Mountain View, CA USA). All values are expressed as the mean±SD. Statistical analysis was performed with Graph Pad InStat software (version 3.00, Graph Pad Software, San Diego, CA, USA) using one-way analysis of variance (ANOVA) followed by Tukey–Kramer multiple comparison test. Difference with $p < 0.05$ was considered statistically significant.

The bioavailability of the free flowing solid dispersion containing efavirenz was evaluated using rats. Fig shows the plasma profiles of efavirenz in rats after the oral administration of the reference (pure drug suspension) and prepared free flowing solid dispersion formulation containing efavirenz at a dose of 50 mg/kg.

RESULTS AND DISCUSSION

Preliminary solubility studies of Efavirenz

Efavirenz was found increase in solubility with PVP, HPC and HPMC. Table 1 shows the solubility of efavirenz in various polymers in water at 25°C. The enhancement of the absolute amounts of the dissolved drug was approximately increased with increase in concentration of polymer. These results are in accordance with the well established formation of soluble complexes between water soluble polymeric carriers and efavirenz. However, in comparison with hydroxy propyl methyl cellulose, efavirenz was more soluble in polyvinyl pyrrolidone and hydroxy propyl cellulose.

Table 1: Solubility studies of efavirenz in different polymers

Sample (Physical mixtures)	Drug & Polymer ratios	Solubility (mg/ml)
Drug	-	2.56
Drug: PVP	1:1	3.62
Drug: PVP	1:2	3.92
Drug: HPC	1:1	3.12
Drug: HPC	1:2	3.45
Drug :HPMC	1:1	2.77
Drug :HPMC	1:2	2.91

% Practical Yield with and without anti sticking agent

Practical yield of solid dispersions were very low because of sticky nature of material. Almost all polymers were very sticky in nature which influences the stickiness of solid dispersion. When polymers dissolved in solvents, after drying the particle size of polymers were decreased and surface of particle size increases and which increases the sticky nature. The solid dispersion formulations were stucked to the bottom of vessel and which decreased the practical yield of formulation. In solid dispersion formulation using anti sticking agent like Neusilin US 2, it is insoluble in nature and settled at the bottom of the vessel and which prevented the polymers to stick to the vessel and which increased in practical yield of formulation. The results were shown in table 2. Practical yield of solid dispersion using anti sticking agent was more in comparison with solid dispersion without anti sticking agent.

Table 2: Practical yield of Physical mixtures and Solid dispersions using anti sticking agent

Sample (ratio)	% Yield
Physical mixture of drug, Kollidon and Neusilin US2 (1:1:1)	96%
Solid dispersion of drug, Kollidon and Neusilin US2 (1:1:1)	95%
Physical mixture of drug, Kollidon and Neusilin US2 (1:2:2)	95%
Solid dispersion of drug, Kollidon and Neusilin US2 (1:2:2)	93%
Physical mixture of drug, HPC and Neusilin US2 (1:1:1)	97%
Solid dispersion of drug, HPC and Neusilin US2 (1:1:1)	96%
Physical mixture of drug, HPC and Neusilin US2 (1:2:1)	96%
Solid dispersion of drug, HPC and Neusilin US2 (1:2:1)	94%

Solubility studies for solid dispersions with anti sticking agent

The solubility of efavirenz was increased with solid dispersions. Moreover, an increased solubility of efavirenz in solid dispersion formulation using anti sticking agent was observed in table 3, because this anti sticking agent prevents the agglomeration of drug and polymer complex.

Table 3: Solubility studies of solid dispersion containing efavirenz in different polymers

Sample (physical mixtures)	Ratio	Solubility (mg/ml)
Drug	-	2.56
Drug: PVP: Neusilin US2	1:1:1	3.62
Drug: PVP: Neusilin US2	1:2:2	4.21
Drug: HPC: Neusilin US2	1:1:1	3.01
Drug: HPC: Neusilin US2	1:2:2	3.52

Flow properties

The formulations were evaluated for their flow properties and results were summarized in table 4. Angle of repose was in the range of Around 48 for physical mixtures. Carr index was found to be around 28 and Hausner ratio around 1.37 for physical mixtures and angle of repose was around 30, Carr index was around 16 and Hausner ratio around 1.1 for solid dispersion prepared by using anti sticking agent. These values indicate that the solid dispersions prepared by using Neusilin having the good flow properties, which suggest neusilin increases the flow properties of solid dispersion by reducing the stickiness of mixture.

Drug content

The drug content was found in the range around 100%, indicating the acceptability of solvent heat method for preparation of solid dispersions table 5. Low values of standard deviation in drug content of physical mixtures and solid dispersions indicated uniform drug distribution in all the prepared batches.



Table 4: Flow properties of physical mixtures and solid dispersions with and without anti sticking agent

Sample (ratio)	Angle of repose	Carr Index (IC)	Hausner Ratio (HR)
Physical mixture of drug and Kollidon (1:1)	48	28	1.37
Solid dispersion of drug and Kollidon(1:1)	57	33	1.48
Physical mixture of drug and Kollidon(1:2)	47	28	1.39
Solid dispersion of drug and Kollidon(1:2)	56	32	1.49
Physical mixture of drug and HPC(1:1)	49	30	1.35
Solid dispersion of drug and HPC(1:1)	46	27	1.39
Physical mixture of drug and HPC(1:2)	51	31	1.38
Solid dispersion of drug and HPC(1:2)	50	29	1.41
Physical mixture of drug, Kollidon and Neusilin US2 (1:1:1)	40	19	1.24
Solid dispersion of drug, Kollidon and Neusilin US2 (1:1:1)	34	14	1.16
Physical mixture of drug, Kollidon and Neusilin US2 (1:2:2)	39	18	1.23
Solid dispersion of drug, Kollidon and Neusilin US2 (1:2:2)	31	16	1.16
Physical mixture of drug, HPC and Neusilin US2 (1:1:1)	39	17	1.22
Solid dispersion of drug, HPC and Neusilin US2 (1:1:1)	33	15	1.15
Physical mixture of drug, HPC and Neusilin US2 (1:2:1)	40	14	1.19
Solid dispersion of drug, HPC and Neusilin US2 (1:2:1)	30	15	1.15

Table 5: Assay of physical mixture and solid dispersions with different polymers

Codes	Sample	Assay (%)
PM1	Physical mixture of Drug: PVP: Neusilin (1:1:1)	97 ±0.52
FSD1	Free flowing Solid dispersion of Drug: PVP: Neusilin (1:1:1)	98 ±0.62
PM2	Physical mixture of drug: PVP: Neusilin (1:2:2)	98 ±0.47
FSD2	Free flowing Solid dispersion of drug: PVP: Neusilin (1:2:2)	99 ±0.19
PM3	Physical mixture of Drug: HPC: Neusilin (1:1:1)	96 ±0.61
FSD3	Free flowing Solid dispersion of Drug: HPC: Neusilin (1:1:1)	97 ±0.56
PM4	Physical mixture of Drug: HPC: Neusilin (1:2:2)	99 ±0.48
FSD4	Free flowing Solid dispersion of Drug: HPC: Neusilin (1:2:2)	99 ±0.45

Note: All the values are Mean ± SD.

Table 6: *In vitro* dissolution profile

Time in Min	Pure Drug	PM1	FSD1	PM2	FSD2	PM3	FSD3	PM4	FSD4
0	0	0	0	0	0	0	0	0	0
5	6	12	37	14	56	9	22	14	29
10	9	19	52	22	66	12	41	19	44
15	10	24	64	29	73	16	49	21	59
30	14	26	80	31	89	19	59	24	71
45	19	29	94	34	99	21	71	28	80

Table 7: Pharmacokinetic Parameters of Efavirenz Free flowing solid dispersion formulation and pure drug

Pharmacokinetic parameters	Efavirenz	Efavirenz-SD	Ratio (Free flowing solid dispersion/Suspension)
Dose (mg/kg)	50	50	1.00
C max (µg/ml)	0.52	1.16	2.24
AUC 0-t (µg.hr/ml)	2.62	7.94	3.04
AUC 0-inf (µg.hr/ml)	2.65	8.05	3.04
T max (hr)	1.50	1.88	1.25
t 1/2 (hr)	4.22	8.72	2.07
K el (hr ⁻¹)	0.164	0.081	0.49

***In vitro* release studies**

The dissolution data showed, faster dissolution rate observed for free flowing solid dispersion formulation using anti sticking agent in comparison with pure drug table 6. The enhanced dissolution rate of Efavirenz from the free flowing solid dispersions formulation might be due to the increase in the drug wettability and the efavirenz, PVP interactions. Our experimental approach has taken into account that the data from our previous physico-chemical investigations demonstrating that efavirenz exists as crystalline in nature and in solid

dispersion formulation shows amorphous and particle size of particles are very small. The improvement of dissolution of solid dispersion must be due to the increased surface area of the smaller particles.

DSC (Differential Scanning calorimetry) studies

The DSC thermograms of Pure Efavirenz showed in figure 2, sharp endothermic peaks at melting point, indicating that the drug is highly crystalline. The absence of drug peak in the free flowing solid dispersion formulation (FSD2) indicating the drug was in amorphous form.



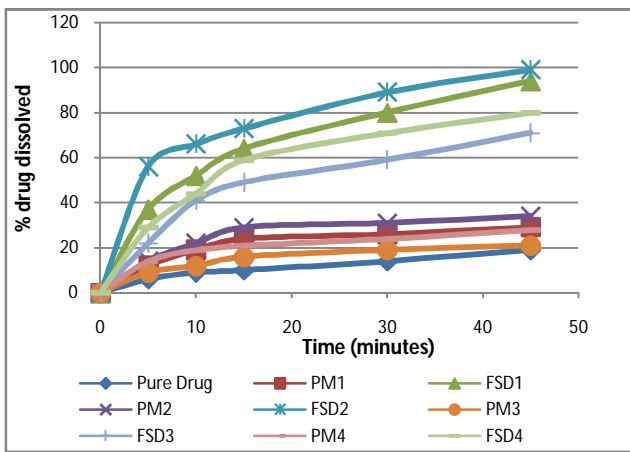
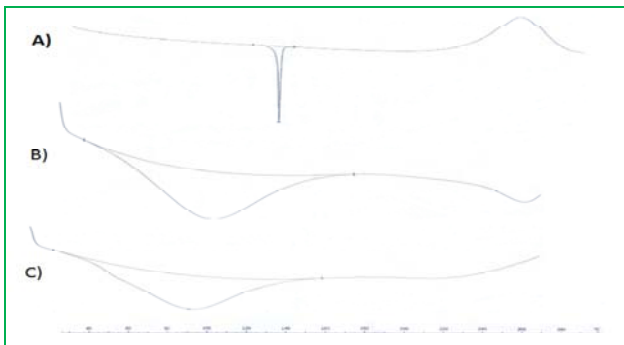


Figure 1: Comparative dissolution graphs of as such API, Physical mixtures and free flowing solid Dispersions



A) Efavirenz, B) Solid dispersion formulation and C) Placebo

Figure 2: DSC thermograms of pure drug, formulation and placebo.

XRD (X-Ray diffraction) studies

In x-ray diffraction study, the absence of drug peak in the free flowing solid dispersion formulation (FSD2) indicating that the drug was in amorphous state showed in figure 3.

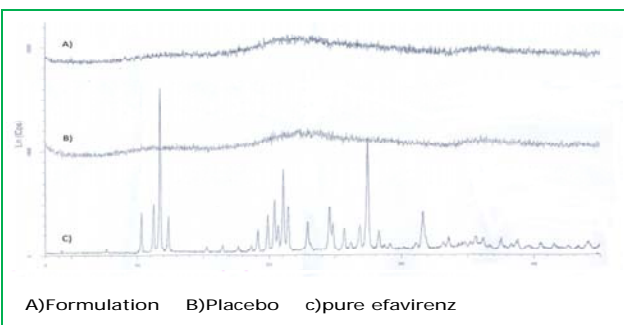


Figure 3: Powder X-ray diffraction patterns of pure drug, placebo and formulation

Pharmacokinetic parameters comparison for pure drug suspension and free flowing solid dispersion formulation

Figure 4 shows the plasma concentration–time curve in Wistar rats after a single oral dose of Efavirenz free flowing solid dispersion formulation as compared to efavirenz pure suspension. At all the indicated time points, the efavirenz plasma concentrations in rats treated with free flowing solid dispersion formulation were significantly higher than those treated with pure drug suspension. Plasma pharmacokinetic parameters of efavirenz after oral administration of the two formulations to Wistar rats are shown in table 7.

As can be seen from the above table, the test preparation shows the increased AUC and Cmax values, which are about 3.04 and 1.25 times, respectively, as high as those in the reference formulation. Accordingly, it can be identified that the efavirenz of the free flowing formulation is significantly increased in comparison with that of the pure drug (efavirenz suspension). Cmax of the free flowing solid dispersion formulation 1.16 µg mL⁻¹ was significant (p<0.05) as compared to the pure drug suspension formulation 0.52 µg mL⁻¹. Tmax of both free flowing solid dispersion formulation and pure drug suspension was 1.88 and 1.50 h, respectively. AUC is an important parameter in evaluating bioavailability of drug from dosage form, as it represents the total integrated area under the blood concentration time profile and represents the total amount of drug reaching the systemic circulation after oral administration. AUC_{0-∞}inf for free flowing solid dispersion formulation was higher (8.05 µg h mL⁻¹) than the pure drug suspension formulation 2.65 µg h mL⁻¹. Statistically, AUC_{0-∞}t of the free flowing solid dispersion formulation was significantly higher (p<0.05) as compared to pure drug suspension formulation. Higher amount of drug concentration in blood indicated better systemic absorption of efavirenz from free flowing solid dispersion formulation as compared to the pure drug suspension formulation. Figure 5 and figure 6 showed the difference of LC-MS chromatograms between pure drug suspension and solid dispersion formulations of Efavirenz at maximum concentrations. Calculated concentration was found to be more for solid dispersion formulations compared with pure drug of Efavirenz.

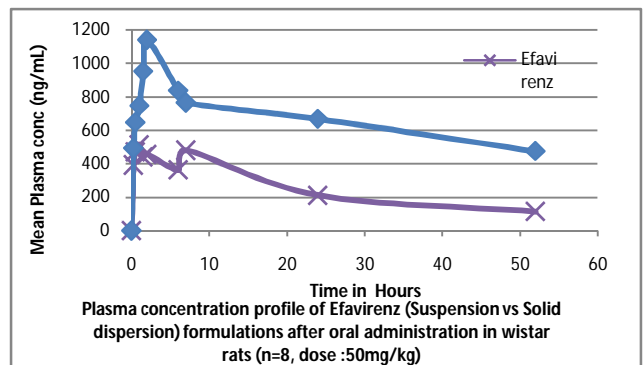


Figure 4: Plasma concentrations of efavirenz (suspension vs solid dispersion) formulations after oral administration in Wistar rats (n=8, Dose:50mg/kg)

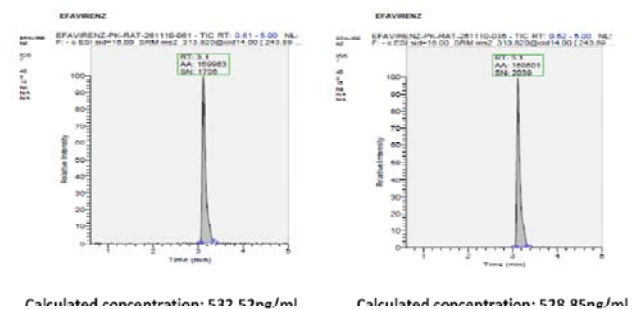
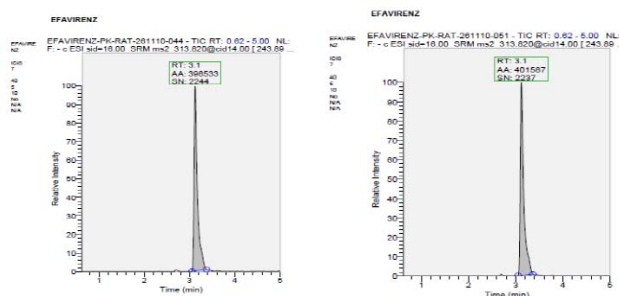


Figure 5: Reference LC-MS Chromatograms for Pure drug suspension at maximum concentration



Calculated concentration: 1002.17ng/ml

Calculated concentration: 1225.68ng/ml

Figure 6: Reference LC-MS Chromatograms for Free flowing solid dispersion formulation at maximum concentration

CONCLUSION

The rate of dissolution of Efavirenz from free flowing solid dispersion optimized formulation (FSD2) was found to be significantly higher than drug alone. Thus, a free flowing solid dispersion formulation of Efavirenz with increased dissolution efficiency was successfully developed using kollidon30 and Neusilin.

After oral administration of efavirenz (50 mg kg⁻¹) to either sex Wistar rats, these formulations (free flowing solid dispersion) showed superior absorption profile than the suspension of pure drug. The relative bioavailability of free flowing solid dispersion formulations were enhanced in comparison with pure drug suspension. It can be concluded that the present study successfully illustrates the potential utility of free flowing solid dispersion formulation for the delivery of poor water-soluble compounds such as efavirenz.

REFERENCES

1. Karavas E, Georgarakis E, Sigalas P, Avgoustakis K, Bikiaris K. Investigation of the release mechanism of a sparingly water-soluble drug from solid dispersions in hydrophilic carriers based on physical state of drug, particle size distribution and drug-polymer interaction. *E jour of phar and biophar.*, 66, 2007, 334-347.
2. Joshi H, Tejwani R, Davidovich M, Sahasrabudhe V, Mohammed Jemal. Bioavailability enhancement of a poorly water-soluble drug by solid dispersion in polyethylene glycol-polysorbate 80 mixture. *Int. J of phar.*, 269, 2004, 251-258.
3. Khoo S M, Porter C J H, Charman W N. The formulation of Halofantrine as either non-solubilising PEG 6000 or solubilising lipid based solid dispersions: Physical stability and absolute bioavailability assessment. *Int. J of phar.*, 205, 2000, 65-78
4. Dhirendra K. Solid dispersions: A review, *Pak. J. Pharm. Sci.*, 22, 2009, 234-246.
5. Ozkan Y, Doganay N, Dikmen N, Isimer A, Enhanced release of Solid dispersions of etodolac in polyethylene glycol, *IL FARMACO.*, 55, 2000, 433-438.
6. Veldkamp A I. Quantitative determination of Efavirenz, a novel non-nucleoside reverse transcriptase inhibitor, in human plasma using isocratic reversed-phase high-performance liquid chromatography with ultraviolet detection. *Journal of Chromatography B.*, 734, 1999, 55-61.
7. Sathigari S K. Physicochemical characterization of Efavirenz-Cyclodextrin inclusion complexes. *AAPS Pharm SciTech.*, 10, 2009, 81-87.
8. Sekiguchi K, Obi N. "Studies on absorption of eutectic mixture. I.A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man". *Chem Pharm Bull.*, 9, 1961, 866-872.
9. Serajuddin AT. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. *J Pharm Sci.*, 88, 1999, 1058-1066.
10. Craig DQ. The mechanisms of drug release from solid dispersions in water-soluble polymers. *Int. J Pharm.*, 14, 2002, 131-144.
11. Parakh S R, Gothoskar AV. A review of mouth dissolving tablet technologies. *Pharma Tech.*, 27, 2003, 92-100.
12. Higuchi T, Connors KA. Phase solubility diagram. *Adv. Anal. Chem. Instrum.*, 4, 1965, 17-21.

