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Research Article

Solubility Enhancement of Efavirenz by Solid Dispersion Techniques using Soluplus as Hydrophilic Carrier

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ABSTRACT

Low water solubility is an industry wide issue. Low bioavailability and irregular oral absorption are common problems in low water-soluble drugs. Efavirenz is an oral non- nucleoside reverse transcriptase inhibitor (NNRTI). It is a synthetic purine derivative and, similar to zidovudine, zalcitabine, and stavudine. Efavirenz was originally approved specifically for the treatment of HIV infections in patients who failed therapy with zidovudine. It comes under BCS class II drugs. Its water Solubility is 0.00855 mg/mL, practically insoluble in water. Although numerous methods are available to improve the solubility and/or dissolution rate of low soluble drugs, the most promising method for promoting dissolution is with preparation of solid dispersions. To enhance the solubility of low soluble drug efavirenz, solvent evaporation and lyophilization technique was followed, which can improve the solubility and dissolution rate of the drug. Among all the formulation soluplus (1:1.5) shows highest % of drug release i.e., 95.11 % in solvent evaporation process.

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INTRODUCTION

Worldwide 36 million people are infected with HIV-type-1(1). Only after the introduction of highly active antiretroviral therapy, the mortality rate gets reduced, even with chronic stage (2). Efavirenz is the drug among. It is a nonnucleoside reverse transcriptase inhibitor commonly used for HIV (3). But it shows aqueous solubility of 9.0 µg/mL with a low intrinsic dissolution rate (IDR) of 0.037 mg/cm^2/min (4). The drugs with less than 0.1 mg/cm^2/min of IDR indicates poor solubility (5). According to a recent analysis up to 75 % of potential drug candidates had poor solubility like efavirenz and simultaneously, about 40 % of marketed drugs are poorly soluble (6).

Solubility is defined in quantitative terms as the concentration of solute in a saturated solution at a certain temperature, and qualitatively, it can be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion (7). The following table indicates the meaning of the terms utilized in statements of approximate solubilities.

Table 1: Descriptive terms of solubility

Descriptive Term	Parts of solvent perone part of solute
Very Soluble	Less than 1 part
Freely Soluble	1 to 10 parts
Soluble	10 to 30 parts
Sparingly soluble	30 to 100 parts
Very insoluble	1000 to 10,000 parts
Insoluble	More than 10,000 parts.

Due to low aqueous solubility and high membrane permeability, efavirenz, are comes under BCS Class II drugs (8). Beside that it has its absorption window in the upper small intestine, that means like most of new discovered drug this one also highly absorbed through upper intestine mostly. Due to which it shows low bioavailability. Production of low bioavailability drugs coast more. It is quite clear that the poor solubility of the drug is the major obstacle (9).

Lots of methods are there to enhance the solubility and/or dissolution rate of low soluble drugs, the foremost promising method for promoting dissolution is that the formation of solid dispersions (10). It can be defined as “a dispersion of one or more active ingredients in an inert carrier or matrix of solid state prepared by melting (fusion),

solvent or melting solvent method" (11). In this process by the distribution of the drug in the carrier, some time at the molecular level, together with the enhanced wettability and microenvironment created by the carrier may increase both the solubility and dissolution rate (12).

METERIAL AND METHODS

There are several methods for preparation of solid dispersion e.g., Solvent evaporation method, lyophilization technique, melting or fusion method, spray drying, melt agglomeration process, extruding method, use of surfactant, electro spinning, super critical fluid technology, kneading, wet milling, cyclodextrin complexation, microwave irradiation, electrospinning, nanoparticles. But first two methods were selected for the experimental work.

(a) Solvent evaporation method

This method has been used for a long time in the preparation of solid solutions or mixed crystals of organic or inorganic compounds. They are prepared by dissolving a physical mixture of two solid components in a common solvent, followed by evaporation of the solvent (13).

(b) Lyophilization technique

Lyophilization is a dehydration process typically used to preserve a perishable material or make the material more convenient for transport. Freeze-drying works by freezing the material and then reducing the surrounding pressure and adding enough heat to allow the frozen water in the material to sublime directly from the solid phase to gas (14).

Just like different dispersion techniques, different polymer may be used for solubility enhancement of efavirenz but soluplus was selected, because it is a novel polymer unique in many ways. It is mixture of polyvinyl pyruvate and polyvinyl acetate. Developed specifically for solid solutions. Due to its high flowability and excellent extrudability, soluplus shows superior performance in forming solid solutions, especially in hot melt extrusion processes.

EXPERIMENTAL WORK

Linear plot for efavirenz

To prepare linear plot for efavirenz, 50 mg of drug was taken in 50 ml of volumetric flask. Then 2-3 mL of ethanol was added to it. After that volume was made up to with 0.5 % of SLS solution. Series of standard solution from 5-50 µg/mL were prepared with suitable dilutions. Linear plot was obtained from the absorbance values obtained using Shimadzu 1800 model UV spectrometer.

Pure Drug Dissolution

0.5 % SLS solution was used as dissolution media for dissolution studies. The temperature was maintained at 37.5

ºC, depth was 25mm and rpm was maintained at 50 rpm. Finally, 100 mg of drug was added to 6 flasks of LABINDIA DISSO 2000 dissolution test apparatus. After that, the samples are collected at intervals of 10, 15, 30, 45 and 60 m intervals (15).

Phase Solubility Study

In phase solubility study 12 glass vials of 20 mL were taken with water. In which 0%, 2%, 4%, 6% polymer was taken respectively and 25 mg of drug was also taken to each vial. After that, the REMI Water bath shaker was run at 37°C for 72h.

Methods

(a) Solvent Evaporation

In solvent evaporation technique the drug and soluplus were taken in 1:0.5, 1:1 and 1:1.5 ratios. First polymer was taken in a beaker with a drug and mixed with a minimum amount of ethanol vigorously. After that, the solvent was removed with help of heat. Then cooled and kept for 24 h. Finally, the mixture powder and collected (16).

(b) Lyophilization

In the Lyophilization Process drug and polymer were mixed with a minimum amount of water. After that, all were kept in a sonicator for 15m. Then all were kept in YORCO freeze dryer. After freeze drying powders were collected from vials.

Fourier-Transform Infrared Spectroscopy (FTIR)

The FTIR spectra were obtained by using an FTIR spectrometer (Shimadzu). The samples were previously ground and mixed thoroughly with potassium bromide pellets (KBR), an infrared transparent matrix. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 m in a hydraulic press. Scans were obtained at a resolution of 2 cm^{-1}, from 4000 to 400 cm^{-1}. It is used to detect the interaction between drug and polymer used for solid dispersion.

Differential Scanning Calorimetric (DSC)

Measurements were performed on a DSC analyzer with a thermal analyzer. All accurately weighed samples (about 25 micrograms) were placed in sealed aluminum pans, before heating under nitrogen flow (20 mL/min) at a scanning rate of 10 ºC min^{-1} from 50 to 300 ºC. An empty aluminum pan was used as a reference (17).

RESULTS AND DISCUSSION

Calibration Curve Preparation

From this experiment λmax was found to be 248nm, R^2 value was found to be 0.999

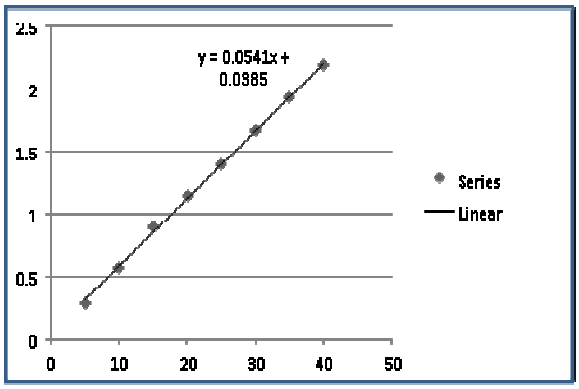

Figure 1: Calibration curve of efavirenz Pure drug dissolution.

Table 2: Pure drug dissolution of efavirenz

Time (min)	%
10	20.58
15	21.58
30	24.79
45	26.80
60	28.99

From Pure Drug Dissolution the solubility was found to be 28.99% at 60 min

Phase solubility study

In phase solubility it was found that

Table 3: Phase solubility study

Carrier	ΔG°_{tr}
Soluplus 2%	-11811.91
Soluplus 4%	-12325.47
Soluplus 6%	-12724.91

Table 4: Solvent evaporation by soluplus

Time (min)	Amount of drug release (mg/mL)			% Drug release		
	1:0.5	1:1	1:1.5	1:0.5	1:1	1:1.5
10	63.553	64.441	66.543	63.55	64.44	67.54
15	68.264	69.678	71.995	68.26	69.67	73.99
30	75.788	76.897	82.377	75.78	76.89	84.37
45	81.569	83.454	89.246	81.56	83.45	91.24
60	86.452	88.792	94.114	86.45	88.79	95.11

In solvent evaporation by soluplus (1:1.5)the solubility was found to be 95.11 % at 60 m

Table 5: Lyophilization by soluplus

In lyophilization by soluplus (1:1.5) the solubility was found to be 92.4 % at 60 m.

Time (min)	Amount of drug (mg/ml)			% Drug release		
	1:0.5	**1:1**	**1:1.5**	**1:0.5**	**1:1**	**1:1.5**
10	61.5	63.3	64.4	61.5	63.3	64.4
15	66.6	69.2	71.2	66.6	69.2	71.2
30	75.7	78.6	80.6	75.7	78.6	80.6
45	81.9	84.4	87.2	81.9	84.4	87.2
60	85.6	87.3	92.4	85.6	87.3	92.4

Fourier-Transform Infrared Spectroscopy (FTIR)

IR spectrum of efavirenz was characterized by presence of absorption bands at 3320 cm^{-1} (N- H stretch), 2924 cm^{-1} (C-H stretch), 1632 cm^{-1} (C=O stretch), 1416 cm^{-1} (O-C-O stretch). All the solid dispersions showed characteristic

peaks of efavirenz and the carriers. No significant shift in the characteristic peaks for the drug and carrier indicated less significant.

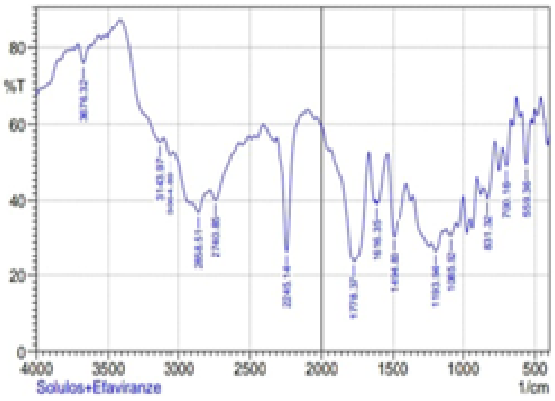

Figure 2: FTIR of physical mixture drug and soluplus

Differential Scanning Calorimetric (DSC)

The DSC thermogram of efavirenz showed presence of a sharp endothermic peak at 143.49 °C indicating melting point of the drug. The onset of melting was observed at 140.70 °C and end at 143.49 °C.

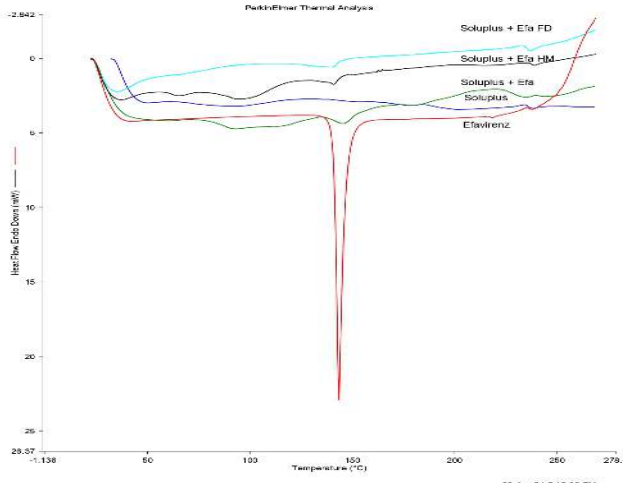

Figure 3: DSC of overlay spectra

SUMMARY AND CONCLUSIONS

Low solubility is an industry wide issue. Although numerous methods are available to improve the solubility and/or dissolution rate of poorly soluble drugs, the most promising method for promoting dissolution is the formation of solid dispersions.

The negative values of the Gibbs free energy of transfer from water to an aqueous solution of hydrophilic carriers indicated the spontaneity of drug solubilization. Increased solubility was also observed with all types of hydrophilic carriers used in the preparation of solid dispersions.

Among all the formulation Soluplus (1:1.5) shows highest % of drug release, that is 95.11% in solvent evaporation process. Which means this is the best formulation to increase the solubility of poorly soluble drug efavirenz.

From FTIR spectroscopy and DSC studies, it was concluded that there were no well-defined chemical interactions between the drugs and the carriers studied. Thus, the polymers and the methods described above can be successfully employed for enhancement of solubility of efavirenz.

Experience with solid dispersions indicates that this is a very loyal approach to improve the release rate and oral bioavailability of poorly soluble drugs.

The most important aims with solid dispersions have been the ability to scale-up the manufacturing method, the physical stability of the dispersion and the amount of carrier needed to facilitate the required increase in the release rate.

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