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Enhancement of dissolution rate of Efavirenz by solid dispersion technique

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ABSTRACT

Efavirenz is an HIV-1 specific, non-nucleoside reverse transcriptase inhibitor (NNRTI).It is an antiretroviral agent indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection, which is not soluble in water and lower absorption in gastric fluid. In order to improve the solubility and oral absorption of the drug in gastric fluid and to enhance its dissolution rate, solid dispersion method is designed and evaluated. Solid dispersions of Efavirenz were prepared using PEG 6000. The effect of fusion-solvent methods of preparation of solid dispersion on dissolution behavior was also investigated. Dissolution studies indicated a significant increase in dissolution of Efavirenz when dispersed in PEG6000. Solid dispersions containing Efavirenz / PEG 6000, 1: 8, showed a 2-fold increase in dissolution after 180 min in the 0.1 N HCL systems.

Key words: Efavirenz, PEG 6000, Solid dispersion, Enhancement in dissolution.

INTRODUCTION

Poorly water-soluble drugs[1] often requires high doses in order to reach therapeutic plasma concentrations after oral administration. Improvement in the extent and rate of dissolution[2] is highly desirable for such com-pounds, as this can lead to an increased and more re-producible oral bioavailability[3] and subsequently to clinically relevant dose reduction and more reliable therapy. Nowadays, pharmaceutical technology provides many approaches to enhance the dissolution rate of poorly soluble drugs[4]. Physical modifications often aim to increase the surface area, solubility and/or wettability of the powder particles and are therefore focused on particle size reduction or generation of amorphous states [Hancock, 1997 & Grau, 2000]. Several methods have been employed to improve the solubility of poorly water soluble drugs. A solid dispersion technique[5] has been used by various researchers who have reported encouraging results with different drugs .The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi (Sekiguchi, 1961).Technique for the preparation of solid dispersions[6] and Lyophilization has also been thought of as a molecular mixing technique where the drug and carrier were co-dissolved in cyclohexanol, frozen and then sublimed under vacuum to obtain a lyophilized molecular dispersion (Lin, 1980). In conclusion, solid dispersion increases the rate and extent of dissolution of Efavirenz[7].

There are various methods like freeze drying, physical mixing, fusion (melt) method and solvent evaporation are employed for the formulation of solid dispersion and this will helps in the reduction of dose of the drug. Efavirenz was chosen as a water-insoluble model drug and PEG 6000, as a hydrophilic polymer and surfactant. PEG 6000 was employed as a carrier material for formulation of solid dispersion with model drug.

MATERIALS AND METHODS

Apparatus and chemicals:

Efavirenz (99% purity) was obtained from Hetero drugs Ltd, Hyderabad, India. PEG 6000 was procured from Hetero drugs, Hyderabad. Other excipients used were of analytical grade. All chemicals used were purchased from Merck, Mumbai, India.

Dissolution testing of Efavirenz marketed tablets in different dissolution media:

Conducted dissolution testing of Efavirenz tablets 200 mg in various dissolution medias like distilled water, acetate buffer, Phosphate buffer, 2% sodium lauryl sulfate(SLS) and 0.1 N HCL to know the release pattern of the Efavirenz from the tablet dosage form.

Table 1: The dissolution conditions maintained during the studies in different dissolution medias are given below:

S.No.	Medium	Volume	Apparatus	RPM	Time intervals
1	Distilled water	900 ml	USP 2 Paddle	50	0, 30, 60, 90, 120, 150 and 180 Minutes
2	Acetate buffer pH 3.4	900 ml	USP 2 Paddle	50	0, 30, 60, 90, 120, 150 and 180 Minutes
3	Phosphate buffer pH 3.4	900 ml	USP 2 Paddle	50	0, 30, 60, 90, 120, 150 and 180 Minutes
4	2% Sodium Lauryl Sulphate (SLS)	900 ml	USP 2 Paddle	50	0, 5, 10, 15, 20, 25, 30 Minutes
5	0.1 N HCL	900 ml	USP 2 Paddle	50	0, 30, 60, 90, 120, 150 and 180 Minutes

From the above results Efavirenz drug release was more in 2% SLS solution as dissolution medium .But the actual intestinal or gastric environment does not resemble the 2% SLS solution. So we have decided to improve the dissolution profile of Efavirenz by employing novel drug delivery system .We have chosen solid dispersion technique as preliminary screening technique to test whether the drug is suitable for novel drug release system or not. Next we have chosen 0.1 N HCL as dissolution media for testing solid dispersion formulation since 0.1 N HCL resembles more of a gastric environment.

Composition of Solid dispersion:

Single component solid dispersions contained 2, 4, 6, 8 by weight of PEG 6000 and 1 part of Efavirenz.

Preparation of solid dispersions:

The fusion-solvent method:

Accurately weighed amounts of carrier was placed in an aluminum pan on a hot plate and melted, with constant stirring, at a temperature of about 60°C. A solution of drug in methanol was incorporated into the melted carrier with stirring to ensure homogeneity. The mixture was heated until a clear homogeneous melt was obtained. The pan was then removed from the hot plate and allowed to cool at room temperature.

Table 2: Composition of Solid dispersion.

Carrier	Drug: Carrier	Method
Drug:PEG 6000	1:2 1:4 1:6 1:8	Fusion-Solvent

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Dissolution rate determination:

An ELECTROLAB dissolution test apparatus type II (Paddle) at rotation speed of 50 rpm was used for the study. Dissolution of the drug and solid dispersion was carried out on an equivalent of 100 mg of the Efavirenz in 0.1N HCL as dissolution media. The volume and temperature of the dissolution media were 900 ml and 37 ± 0.2 0C, respectively. After fixed time intervals, 10 ml of samples were withdrawn and replace the same fresh dissolution media so as to maintain sink condition. The samples were filtered through 0.2µm filters and further diluted with methanol in 25 ml volumetric flasks and these samples were assayed UV spectroscopy at 246.5 nm. To increase the reliability of the observations, the dissolution studies were performed in triplicate.

RESULTS AND DISCUSSION

Dissolution testing of Efavirenz marketed tablets in different dissolution media:

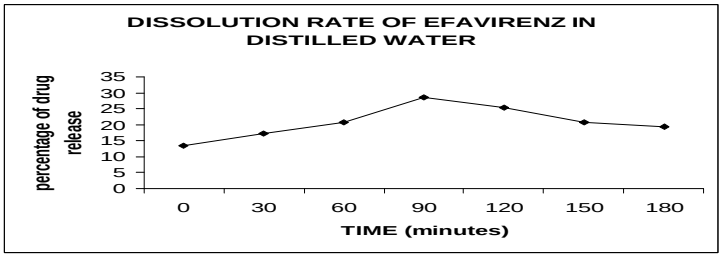

Fig.1 Dissolution of efavirenz in distilled water

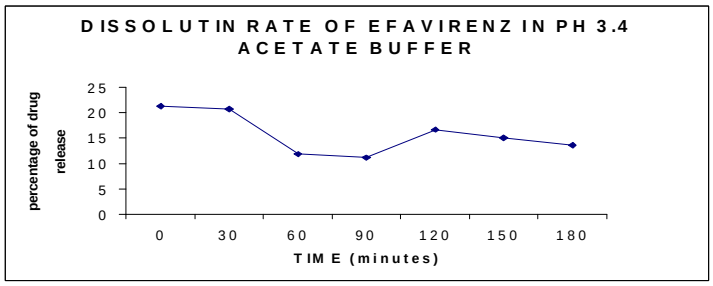

Fig.2 Dissolution of efavirenz in Acetate buffer pH 3.4

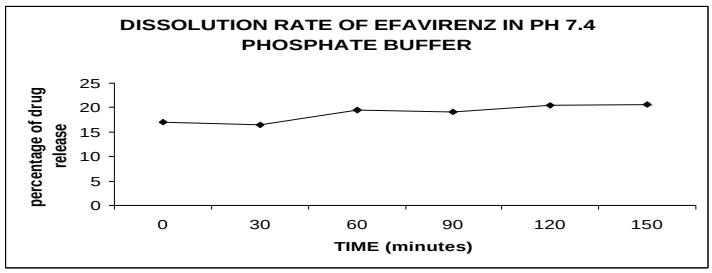

Fig.3 Dissolution of efavirenz in Phosphate buffer

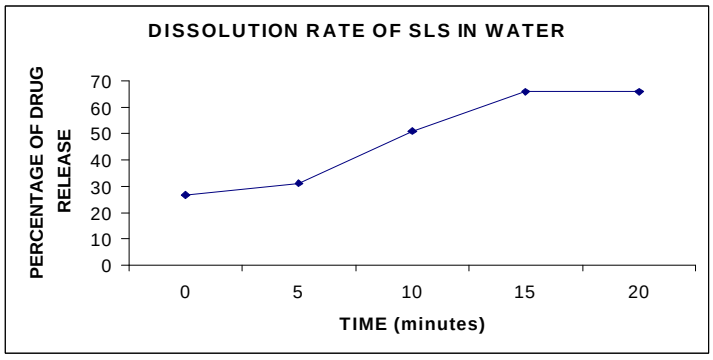

Fig.4 Dissolution of efavirenz in 2% SLS in water

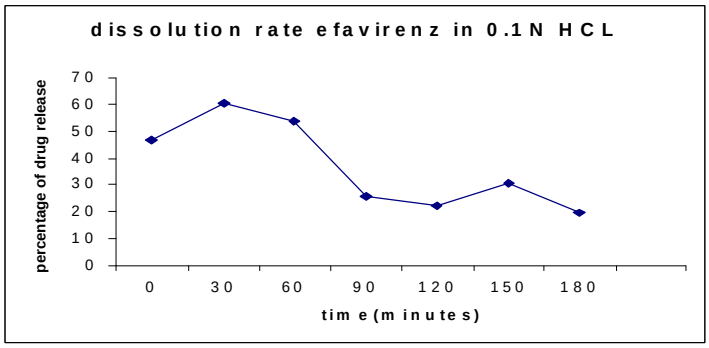

Fig.5. Dissolution of efavirenz in 0.1 N HCl

***In Vitro* Dissolution Study of Solid Dispersion:**

The dissolution of Efavirenz from different drug-polymer ratio (Efavirenz / PEG 6000) is shown in Fig.1. The dissolution rate of Efavirenz from solid dispersion method was significantly higher than Efavirenz alone. This demonstrates the solubilizing effects of the PEG 6000. The dissolution profiles of solid dispersions prepared using PEG 6000 exhibited significant increase in rate of dissolution in the 0.1 N HCl.

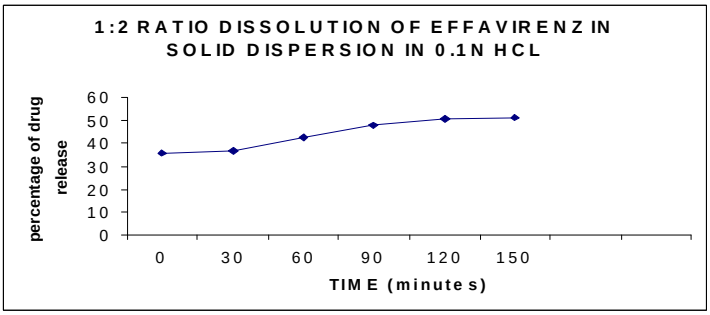

Fig.6. Dissolution of efavirenz in solid dispersion in 1:2 ratio

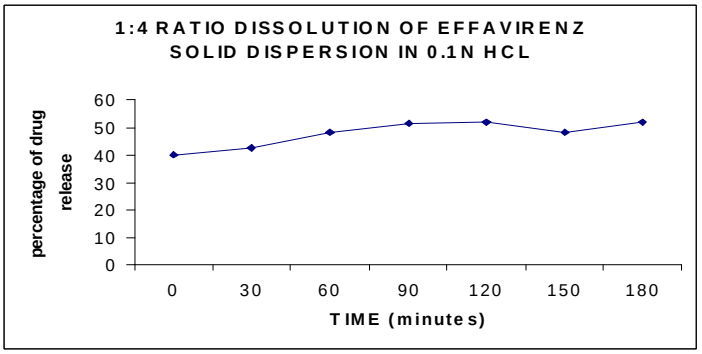

Fig.7.Dissolution of efavirenz in solid dispersion in 1:4 ratio

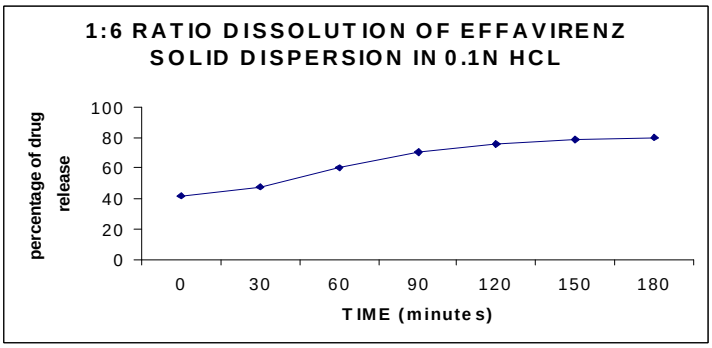

Fig.8. Dissolution of efavirenz in solid dispersion in 1:6 ratio

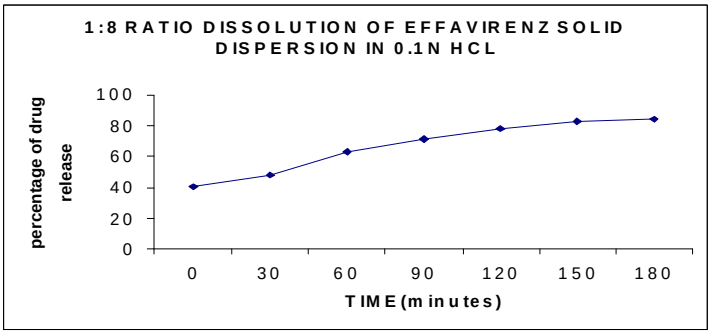

Fig.9 Dissolution of efavirenz in solid dispersion in 1:8 ratio

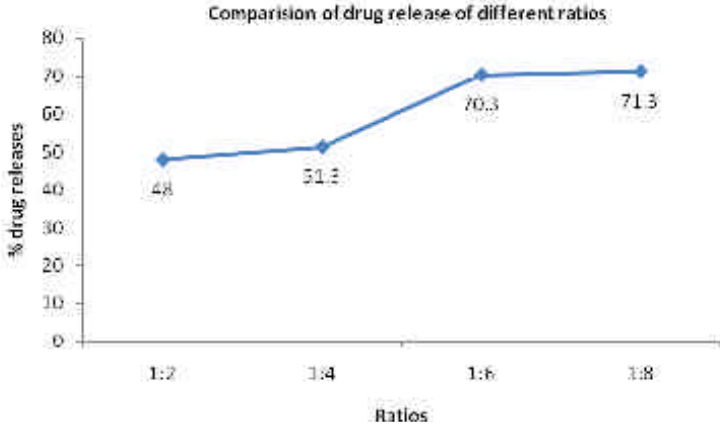

Figure 10: *In vitro* dissolution profile of Efavirenz alone and physical mixtures in the ratio of drug with PEG 6000 (1:2, 1:4, 1:6 and 1:8)

The dispersions prepared by the fusion-solvent method shows the higher dissolution rate of drug then drug alone. The dispersion prepared with 8 parts of PEG 6000 had the highest dissolution at 180 min of 95%, which is significantly greater than the drug alone. In this method, the values exhibited is direct proportionality with the amount of PEG 6000 contained in the solid dispersions.

CONCLUSION

In conclusion, solid dispersions increase dissolution rate of Efavirenz. Solid dispersions of PEG 6000 had the maximum effect on the rate and extent of dissolution of Efavirenz. The results of this study clearly suggest that fusion-solvent method of solid dispersions is ideal for poorly water soluble drugs. The adsorption of Efavirenz does not leave any residual solvent in the final formulation because of elimination of use of solvent from the preparation of solid dispersion.

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