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ENHANCEMENT OF SOLUBILITY OF EFAVIRENZ EMPLOYING β -CYCLODEXTRIN, POLOXAMER 407 AND PVP K30: PHASE SOLUBILITY AND FACTORIAL STUDIES

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ABSTRACT

The objective of the study is to evaluate the effects of β cyclodextrin (βCD), surfactant (Poloxamer 407) and PVP K30 and their concentrations on the solubility of efavirenz by phase solubility studies and to evaluate the individual main effects and combined (or interaction) effects of βCD, Poloxamer 407 and PVP K30 on the solubility of efavirenz in a 2^3 factorial experiment. The solubility of efavirenz in the selected fluids containing βCD, Poloxamer 407 and PVP K30 as per 2^3 factorial study was determined.

The aqueous solubility of efavirenz was increased linearly as a function of the concentration of βCD as well as Poloxamer 407 and PVP K30. The phase solubility diagram of efavirenz-βCD complexes can be classified as type A_L. The increase in solubility was due to the formation of a 1:1 M complex in solution with βCD. The apparent stability constant (K_c) was found to be 251.6 M^{-1} indicating that the complexes formed between efavirenz and βCD are quite stable. The individual and combined effects of βCD, Poloxamer 407 and PVP K30 in enhancing the solubility of efavirenz were highly significant ($P < 0.01$). βCD alone gave a 3.5 fold increase in the solubility of efavirenz. Combination of βCD with Poloxamer 407 and PVP K30 resulted in a much higher enhancement in the solubility of efavirenz, 14.08 fold with βCD- Poloxamer 407 and 7.16 fold with βCD- PVP K30 complexes. Poloxamer 407 and PVP K30 alone also gave a higher enhancement in the solubility of efavirenz. Hence a combination of βCD with Poloxamer 407 and / or PVP K30 or Poloxamer 407 and PVP K30 alone is recommended to enhance the solubility of efavirenz, a BCS class II drug.

Key words: Efavirenz, β Cyclodextrin, Poloxamer 407, PVP K30, Phase Solubility Studies

INTRODUCTION

Efavirenz, a widely prescribed HIV- 1 specific non – nucleoside reverse transcriptase inhibitor drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. It is practically insoluble in water and aqueous fluids. As such its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. Several techniques[1] such as micronization, cyclodextrin complexation, use of surfactants and solubilizers, solid dispersion in water soluble and dispersible carriers, use of salts, prodrugs and polymorphs which exhibit high solubility, micro emulsions and self emulsifying micro and nano disperse systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble drugs. Among the various approaches complexation with cyclodextrins has gained good acceptance in recent years in industry for enhancing the solubility and dissolution rate of poorly soluble drugs. Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and a lipophilic central cavity which can accommodate a variety of lipophilic drugs. As a consequence of inclusion process many physico-chemical properties such as solubility, dissolution rate, stability and bioavailability can be favourably affected[2,3]. Cyclodextrins have been receiving increasing application in pharmaceutical formulation in recent years due to their approval by various regulatory agencies[4,5]. Poloxamer 407 is a polyethylene oxide - polypropylene oxide - polyethylene oxide triblock co-polymer of non-ionic nature and is used as a solubilising agent[6-8]. Poly vinyl pyrrolidone (PVP K 30) is also reported[9, 10] to enhance the solubility and dissolution rate of poorly soluble drugs.

Though cyclodextrin complexation and use of surfactants and PVP for enhancing the solubility and dissolution rate of poorly soluble drugs have been investigated individually, no reports are available on their combined use in enhancing the solubility and dissolution rate. The objective of the study is to evaluate the effects of β cyclodextrin (βCD), surfactant (Poloxamer 407) and PVP K30 and their concentrations on the solubility of efavirenz by phase solubility studies and to evaluate the individual main effects and combined (or interaction) effects of βCD, Poloxamer 407 and PVP K30 on the solubility of efavirenz in a 2^3 factorial experiment.

EXPERIMENTAL

Materials

Efavirenz was a gift sample from M/s. Eisai Pharmatechnology and Manufacturing Pvt. Ltd., Visakhapatham. β Cyclodextrin was gift sample from M/s. Cerestar Inc., USA. Methanol (Qualigens), poly vinyl pyrrolidone (PVP K30) and Poloxamer 407 were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Methods

Estimation of Efavirenz

A UV Spectrophotometric method based on the measurement of absorbance at 245 nm in water containing 2 % Sodium lauryl sulphate (SLS) was used for the estimation of efavirenz. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 0-10 µg/ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.85% and 1.20 % respectively. No interference by the excipients used in the study was observed.

Phase Solubility Studies:

Solubility studies were performed according to the method reported by Higuchi and Connors[11]. Excess drug (50 mg) was added to 15 ml of each fluid taken in a 25 ml stoppered conical flask and the mixtures were shaken for 24 h at room temperature (28±1°C) on Rotary Flask Shaker. After 24 h of shaking, 2 ml aliquots were withdrawn at 2 h interval and filtered immediately using a 0.45 µ disk filter. The filtered samples were diluted suitably and assayed for efavirenz by measuring absorbance at 245 nm. Shaking was continued until two consecutive estimations are the same. The solubility experiments were replicated for four times each (n=4).

Analysis of Data

Solubility data were analyzed by Analysis of Variance (ANOVA) as per 2^3 factorial studies.

RESULTS AND DISCUSSION

Complexation with β cyclodextrin (βCD) and use of Poloxamer 407 and PVP K30 were tried to enhance the solubility of efavirenz. The effects of βCD, Poloxamer 407 and PVP K30 and their concentrations on the solubility of efavirenz were investigated by phase solubility studies in each case. The phase solubility diagrams showing the effects of βCD, Poloxamer 407 and PVP K30 and their concentrations on the solubility of efavirenz are shown in Figs. 1 – 3. The aqueous solubility of efavirenz was increased linearly as a function of the concentration of βCD as well as Poloxamer 407 and PVP K30.

The phase solubility diagram of efavirenz-βCD complexes (Fig. 1) can be classified as type A_L according to Higuchi and Connors[11]. Because the straight line had a slope <1, the increase in solubility was due to the formation of a 1:1 M complex in solution with βCD. The apparent stability constant (K_c) was calculated from the slope of the linear plot of the phase solubility diagram according to the equation, K_c = Slope/S_o (1-Slope), where S_o is the solubility of the drug in the absence of CD. The estimated K_c value was found to be 251.6 M^{-1}.The value of K_c indicated that the complexes formed between efavirenz and βCD are quite stable.

Poloxamer 407 and PVP K30 also increased the solubility of efavirenz. As the concentration of Poloxamer 407 and PVP K30 was increased the solubility of efavirenz was also increased linearly (Figs. 2-3). Poloxamer 407 gave markedly higher enhancement in the solubility of efavirenz when compared to PVP K30. Thus the phase solubility studies indicated that the solubility of the efavirenz could be increased by the use of βCD, Poloxamer 407 and PVP K30.

The individual main effects and combined (interaction) effects of βCD (Factor A), Poloxamer 407 (Factor B) and PVP K30 (Factor C) on the aqueous solubility of efavirenz were evaluated in a 2^3-factorial experiment. For this purpose, two levels of βCD (0, 5 mM), two levels of Poloxamer 407 (0, 2%) and two levels of PVP K30 (0, 2%) were selected in each case and the corresponding eight treatments involved in the 2^3-factorial study were purified water (1); water containing 5 mM βCD (a); water containing 2% Poloxamer 407 (b); water containing 5 mM βCD and 2% Poloxamer 407 (ab); water containing 2% PVP K30 (c); water containing 5 mM βCD and 2% PVP K30 (ac); water containing 2% Poloxamer 407 and 2% PVP K30 (bc) and water containing 5 mM βCD and 2% of each of Poloxamer 407 and PVP K30 (abc).

The solubility of efavirenz in the above mentioned fluids was determined (n=4) and the results are given in Table 1.

The solubility data were subjected to Analysis of variance (ANOVA) to find out the significance of main and combined effects of βCD, Poloxamer 407 and PVP K30on the solubility of efavirenz. The results of ANOVA indicated (Table 2) that the individual and combined affects of βCD, Poloxamer 407 and PVP K30 in enhancing the solubility of efavirenz were highly significant ($P < 0.01$). βCD alone gave a 3.5 fold increase in the solubility of efavirenz. Combination of βCD with Poloxamer 407 and PVP K30 resulted in a much higher enhancement in the solubility of efavirenz, 14.08 fold with βCD-Poloxamer 407 and 7.16 fold with βCD-PVP K30, than with βCD alone. Poloxamer 407 and PVP K30 alone also gave a significant enhancement, 4.42 and 9.75 fold respectively in the solubility of efavirenz.

Table 1: Solubility of Efavirenz in Various Fluids as per 2^3 - Factorial Study

Fluids (Code as per 2^3 - Factorial Experiment)	Solubility (mg/ml) (n=4) ($\bar{x}$) (cv)	Increase in Solubility (Number of Folds)
Distilled water (1)	0.12 (1.2)	-
Water containing 5 mM βCD (a)	0.42 (1.1)	3.50
Water containing 2% Poloxamer (b)	0.53 (0.9)	4.42
Water containing 5 mM βCD and 2% Poloxamer (ab)	1.69 (1.4)	14.08
Water containing 2% PVP (c)	1.17 (0.8)	9.75
Water containing 5 mM βCD and 2% PVP (ac)	0.86 (1.4)	7.16
Water containing 2% Poloxamer and 2% PVP (bc)	1.68 (1.6)	14.0
Water containing 5 mM βCD, 2% Poloxamer and 2% PVP (abc)	1.78 (1.4)	14.83

Table 2: ANOVA of Solubility Data of Efavirenz in Various Fluids as per 2^3 – Factorial Study (βCD - Poloxamer 407 – PVP K30)

Source of variation	D.F	S.S	M.S.S	F-Ratio	Significance
Total	31	11.93	0.383		
Treatments	7	11.60	1.657	120.152	P<0.01
A	1	0.81	0.81	58.48	P<0.01
b	1	4.79	4.79	347.56	P<0.01
ab	1	0.82	0.82	59.52	P<0.01
c	1	3.68	3.68	267.10	P<0.01
ac	1	1.36	1.36	98.51	P<0.01
bc	1	0.03	0.03	2.45	P>0.05
abc	1	0.10	0.10	7.44	P<0.05
Error	24	0.33	0.0055		

$F_{0.01\ (7,\ 24)} = 3.50$; $F_{0.05\ (7,\ 24)} = 2.43$; $F_{0.01\ (1,\ 24)} = 7.82$; $F_{0.05\ (1,\ 24)} = 4.26$

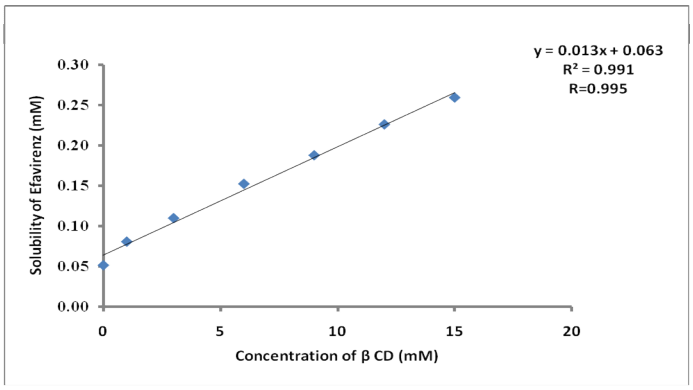

Fig. 1: Phase Solubility Studies- Effect of βCD Concentration on the Solubility of Efavirenz

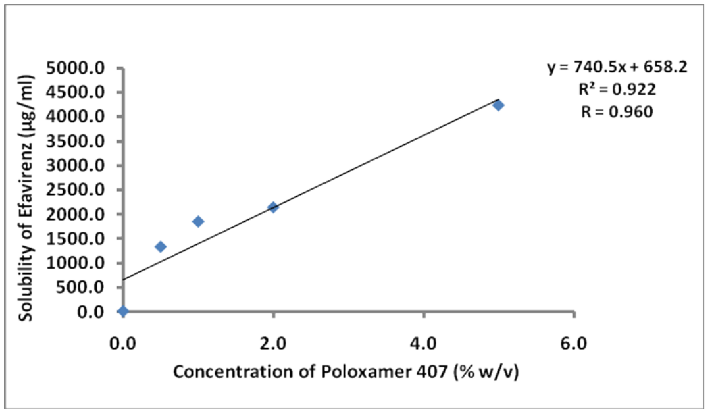

Fig. 2: Phase Solubility Studies- Effect of Poloxamer 407 Concentration on the Solubility of Efavirenz

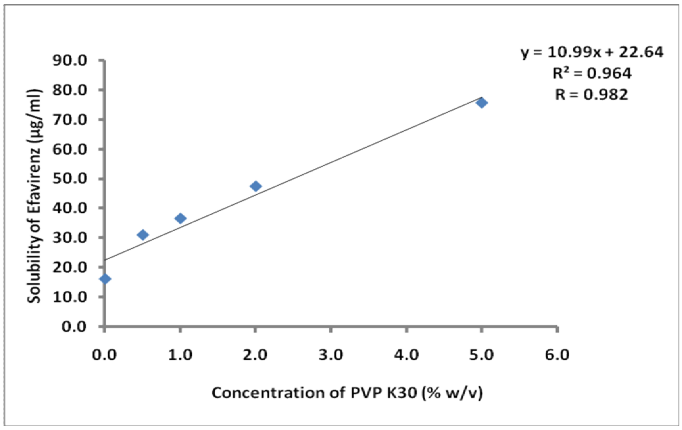

Fig. 3: Phase Solubility Studies- Effect of PVP K30 Concentration on the Solubility of Efavirenz

CONCLUSIONS

1. The aqueous solubility of efavirenz was increased linearly as a function of the concentration of βCD as well as Poloxamer 407 and PVP K30.
2. The phase solubility diagram of efavirenz-βCD complexes can be classified as type A_L. The increase in solubility was due to the formation of a 1:1 M complex in solution with βCD. The apparent stability constant (K_c) was found to be 251.6 M^{-1} indicating that the complexes formed between efavirenz and βCD are quite stable.
3. The individual and combined effects of βCD, Poloxamer 407 and PVP K30 in enhancing the solubility of efavirenz were highly significant ($P < 0.01$).
4. βCD alone gave a 3.5 fold increase in the solubility of efavirenz. Combination of βCD with Poloxamer 407 and PVP K30 resulted in a much higher enhancement in the solubility of efavirenz, 14.08 fold with βCD- Poloxamer 407 and 7.16 fold with βCD- PVP K30 complexes.
5. Poloxamer 407 and PVP K30 alone also gave a higher enhancement in the solubility of efavirenz.
6. Hence a combination of βCD with Poloxamer 407 and / or PVP K30 or Poloxamer 407 and PVP K30 alone is recommended to enhance the solubility of efavirenz, a BCS class II drug.

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