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ENHANCEMENT OF SOLUBILITY OF EFAVIRENZ EMPLOYING β CD AND SLS: OPTIMIZATION BY 2^2 FACTORIAL DESIGN

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ABSTRACT

Efavirenz, a widely prescribed HIV-1 specific, non nucleoside reverse transcriptase inhibitor (NNRTI) drug belong to Class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Its oral absorption is dissolution rate limited and it requires enhancement in solubility for increasing its oral bioavailability and therapeutic efficacy. The objective of the present study is to enhance the solubility of efavirenz by employing β-cyclodextrin (β CD) and sodium lauryl sulphate (SLS) .The individual main and combined (interaction) effects of β CD and SLS on the solubility of efavirenz were evaluated in a 2^2 factorial study. The solubility of efavirenz in the selected four fluids as per 2^2 factorial design was determined (n=3). Optimization of factors (β CD and SLS) to achieve the desired solubility of efavirenz was done by fitting a polynomial equation to the observed data. The solubility of efavirenz was markedly increased by both β CD and SLS. The main and combined effects of β CD and SLS in enhancing the solubility of efavirenz were highly significant ($P < 0.01$). SLS alone and in combination with β CD gave higher enhancement in the solubility of efavirenz. The increasing order of solubility observed with various fluids was $F_{ab} > F_b > F_1 > F_a$. The polynomial equation describing the relationship between the response ,Y and the variables, X_1 and X_2 based on the observed data was found to be $Y = 184.75+15.75 (X_1) +113.75 (X_2) + 45.75 (X_1 X_2)$. SLS ($X_2$) has greater effect in increasing the solubility of efavirenz, followed by combination of β CD and SLS ($X_1 X_2$) and β CD (X_1). Based on the above polynomial equation two optimized solutions, one with high solubility (260mg / 100ml) and the other with moderate solubility (200mg / 100ml) of efavirenz were prepared and the solubility of efavirenz in the two solutions was determined (n=3). The experimentally determined solubility values are in close agreement with the predicted or optimized solubility

values. The results indicated validity of the optimization technique employed and the polynomial equation developed could be used to develop solutions with any desired solubility specification.

KEYWORDS: Efavirenz, Solubility, β cyclodextrin, Sodium lauryl sulphate, Optimization, Factorial design.

INTRODUCTION

About 95% of all new potential therapeutic drugs (APIs) exhibit low and variable oral bioavailability due to their poor aqueous solubility at physiological pH and consequent low dissolution rate. These drugs are classified as class II drugs under BCS with low solubility and high permeability characters. These BCS class II drugs pose challenging problems in their pharmaceutical product development process. Efavirenz, a widely prescribed HIV-1 specific, non nucleoside reverse transcriptase inhibitor (NNRTI) drug belong 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. Its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability and therapeutic efficacy.

Several techniques[1] such as micronisation, cyclodextrin-complexation, use of surfactants, solubilizers and super disintegrants, solid dispersion in water soluble and water dispersible carriers, microemulsions and self emulsifying micro and nano disperse systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble BCS class II drugs. Among the various approaches cyclodextrin complexation[2,3] and use of surfactants are simple industrially useful approaches for enhancing the solubility of poorly soluble drugs in their formulation development.

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] Surfactants also increase the solubility of lipophilic water-insoluble drugs by micellar solubilization.

The objective of the present study is to enhance the solubility of efavirenz by employing β-cyclodextrin (β CD) and sodium lauryl sulphate (SLS) .The individual main and combined (interaction) effects of β CD and SLS on the solubility of efavirenz were evaluated in a 2^2 factorial study. Optimization of factors (β CD and SLS) to achieve the desired solubility of efavirenz was done by factorial design.

Optimization[6] involves choosing and combining ingredients that will result in the desired product with certain prerequisite characters. The application of optimization techniques is relatively new to the practice of pharmacy. The optimization procedure is facilitated by applying factorial designs and by the fitting of an empirical polynomial equation to the experimental results. The predicted optimal formulation has to be prepared and evaluated to confirm its quality.

EXPERIMENTAL

MATERIALS

Efavirenz was a gift sample from M/s. Eisai PharmaTechnology Ltd., Visakhapatnam. β-cyclodextrin was a gift sample from M/s. Nalco Pharma Ltd., Hyderabad. Sodium lauryl sulphate (Merck) was procured from commercial sources. All other materials used were of pharmacopoeial grade.

METHODS

Estimation of Efavirenz

An UV Spectrophotometric method based on the measurement of absorbance at 245nm in 0.1N sodium hydroxide 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 1 – 10 µg/ ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.9% and 1.25% respectively. No interference by the excipients used in the study was observed.

Determination of Solubility

Excess drug (25 mg) was added to 8 ml of each of aqueous solutions containing β CD and SLS as per 2^2 factorial design taken in a series of 15 ml stoppered test tubes and the mixtures were shaken thoroughly for 24 h at room temperature (28 ^oC). After 24 h of shaking to achieve equilibrium, the mixtures were filtered using 0.45 µ nylon disc filters. The

filtered samples were diluted with 0.1N sodium hydroxide suitably and assayed at 245 nm.The solubility experiments were replicated three times each (n=3).

RESULTS AND DISCUSSION

The objective of the present study is to enhance the solubility of efavirenz by employing β-cyclodextrin (β CD) and sodium lauryl sulphate (SLS) .The individual main effects and combined (interaction) effects of β CD (Factor A) and SLS (Factor B) on the aqueous solubility of efavirenz were evaluated in a 2^2-factorial experiment. For this purpose, two levels of β CD (1, 20 mM) and two levels of SLS (1, 5%) were selected in each case and the corresponding four treatments involved in the 2^2-factorial study were water containing 1 mM β CD and 1%SLS (1); water containing 20 mM β CD and 1%SLS (a); water containing 1 mM β CD and 5%SLS (b) and water containing 20 mM β CD and 5%SLS (ab). The solubility of efavirenz in the above mentioned four fluids was determined (n=3) and the results are given in Table1. The solubility data were subjected to Analysis of Variance (ANOVA) to find out the significance of main and combined effects of β CD and SLS on the solubility of efavirenz.

The solubility of efavirenz was markedly increased by both β CD and SLS. ANOVA of solubility data (Table 2) indicated that the main and combined effects of β CD and SLS on the solubility of efavirenz were highly significant ($P < 0.01$). SLS alone and in combination with β CD gave higher enhancement in the solubility of efavirenz. The increasing order of solubility observed with various fluids was $F_{ab} > F_b > F_1 > F_a$.

For optimization, solubility (mg/100 ml) was taken as response (Y) and level of β CD as (X_1) and level of SLS as (X_2). The polynomial equation describing the relationship between the response ,Y and the variables, X_1 and X_2 based on the observed data was found to be $\mathbf{Y = 184.75+15.75\ (X_1) +113.75\ (X_2) + 45.75\ (X_1\ X_2)}$. The coefficients in the polynomial equation indicate the effects of the factors involved, the main effects of factor A (β CD), B (SLS) and combined effect of AB (β CD - SLS). As such SLS (X_2) has greater effect in increasing the solubility of efavirenz, followed by combination of β CD and SLS (X_1 X_2) and β CD (X_1).

Based on the above polynomial equation, the following two optimized solutions, one with high solubility and the other with moderate solubility of efavirenz were worked out.

(i)Solution with a solubility of 260 mg of efavirenz per 100ml could be prepared employing β CD at 10.5mM and SLS at4.32% concentrations (solution 1) .(ii) Solution with a solubility of 200 mg of efavirenz per 100 ml could be prepared employing β CD at 19.62mM and SLS at 3.0% concentrations (solution 2) . To verify, the above two optimized solutions were prepared and the solubility of efavirenz in the two solutions was determined (n=3). The solubility of efavirenz was found to be 263mg / 100ml and 197mg / 100ml respectively in the case of solutions 1 and 2. The experimentally determined solubility values are in close agreement with the predicted or optimized solubility values. These results indicated validity of the optimization technique employed and the polynomial equation developed could be used to develop solutions with any desired solubility specification. Hence formulation of solutions with any desired solubility specification could be optimized by 2^2 factorial design.

Table1: Solubility of Efavirenz in Aqueous Fluids Containing β CD and SLS as per 2^2 Factorial Design

Trial	Solubility(mg / 100ml)			
	F_1	F_a	F_b	F_{ab}
1	102	40	236	359
2	99	41	240	363
3	104	41	234	359
$\bar{x}$	101.6	40.6	236.6	360.3
s.d.	2.05	0.47	1.79	1.88

Table 2: ANOVA of Solubility Data

Source of Variation	df	Sum of Squares (S.S)	Mean Sum of Squares (M.S.S)	F-Ratio	Significance
Total	11	183606	_____	_____	
Treatments	3	183562.9	61187.6	11357.3	P<0.01
a	1	2945.3	2945.3	546.69	P<0.01
b	1	155041.3	155041.3	28777.9	P<0.01
ab	1	25576.3	25576.3	4747.3	P<0.01
Error	8	43.1	5.3875	_____	

$F_{0.01}(3,8) = 7.59$ $F_{0.01}(1,8) = 11.3$

CONCLUSIONS

1. The solubility of efavirenz was markedly increased by both β CD and SLS.
2. The main and combined effects of β CD and SLS in enhancing the solubility of efavirenz were highly significant ($P < 0.01$).
3. SLS alone and in combination with β CD gave higher enhancement in the solubility of efavirenz. The increasing order of solubility observed with various fluids was $F_{ab} > F_b > F_1 > F_a$.
4. The polynomial equation describing the relationship between the response ,Y and the variables, X_1 and X_2 based on the observed data was found to be **$Y = 184.75+15.75 (X_1) +113.75 (X_2) + 45.75 (X_1 X_2)$**.
5. SLS (X_2) has greater effect in increasing the solubility of efavirenz, followed by combination of β CD and SLS ($X_1 X_2$) and β CD (X_1).
6. Based on the above polynomial equation two optimized solutions, one with high solubility (260mg / 100ml) and the other with moderate solubility (200mg / 100ml) of efavirenz were prepared and the solubility of efavirenz in the two solutions was determined (n=3). The experimentally determined solubility values are in close agreement with the predicted or optimized solubility values.
7. The results indicated validity of the optimization technique employed and the polynomial equation developed could be used to develop solutions with any desired solubility specification.

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