Cosolvents and Surfactants Effect on the Rate Constant (Log K) of Efavirenz in Aqueous Solution

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ABSTRACT

Efavirenz is a non-nucleoside reverse transcriptase inhibitor clinically used for the treatment of patients with human immunodeficiency virus (HIV) as it is effective in reducing viral load in HIV-positive patients. The objective of the present study was to investigate cosolvents and surfactants effect on efavirenz under basic conditions. The breakdown of efavirenz in basic aqueous solution of cosolvents and surfactants at 60°C ±0.2 was studied. The breakdown was determined by UV spectrophotometry. The drug was seen to follow the apparent first order rate kinetics and rate constant for the degradation were obtained from plot of logarithm percent drug remaining versus time. The kinetic reaction was shown to be hydroxide ion catalysed. A significant increase in the stability of efavirenz was noted with the cosolvents and surfactants investigated. The results obtained from the study suggested that cosolvents and surfactants could be used to formulate and stabilise liquid pharmaceutical dosage forms of efavirenz under basic conditions.

Key Words: *Efavirenz, Cosolvent, Surfactant, Rate constant, Degradation, Vehicles.*

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INTRODUCTION

Efavirenz is a non-nucleoside reverse transcriptase inhibitor [1, 2] clinically used for the treatment of patients with human immunodeficiency virus (HIV) [3] as it is effective in reducing viral load in HIV-positive patients [4].

Its mechanism of action involves the restriction of viral replication by binding non-competitively to the hydrophobic region of the HIV-1 reverse transcriptase through an allosteric mechanism that alters the enzyme conformation, and prevents the access to the substrates [5, 6].

Efavirenz (Figure 1), chemically is known as (S)-6-chloro-(cyclopropylethynyl)-1, 4-dihydro-4-(trifluoromethyl)-2H-3, 1-benzoxazin-2-one. Efavirenz is a crystalline powder that could be white or slightly pink.

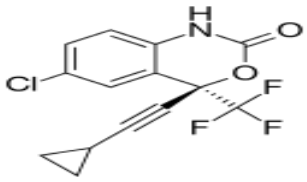

Figure 1. Chemical structure of efavirenz

Efavirenz is an antiviral drug with poor aqueous solubility and high permeability [2, 7]**,** belonging to class II of the Biopharmaceutics classification system. Its low solubility in aqueous medium limits the absorption and biodistribution of the drug from the gastrointestinal tract.

The solubility of poorly soluble drugs in water can be increased by mixing it with some water miscible solvent called cosolvent in which the drug is readily soluble [8]. Reports have indicated that cosolvents have the ability to significantly influence the rate constants of chemical compounds [9, 10]. Surfactants are composed of hydrophilic polar moiety (head) and hydrophobic non-polar moiety (tail), and are capable of forming colloidal-sized clusters in solutions, called micelles [11]. Studies [12] have shown that surfactants can significantly affect the rate constants of chemical compounds.

Previous studies [13, 14] have reported that efavirenz undergoes degradation under basic conditions. Literature review has also indicated that no study has been carried out to investigate the effect of cosolvents and surfactants on efavirenz degradation. Thus, the present study was aimed at determining the cosolvents and surfactants'

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effect on the rate constant of efavirenz in aqueous solution by investigating its degradation kinetics in a basic aqueous medium.

MATERIALS AND METHODS

Materials

Efavirenz (Strides Arcolab Limited, India), glycerol, propylene glycol, sodium lauryl sulphate and polysorbate 80 (tween 80) were all purchased from Sigma-Aldrich, USA. Methanol, hydrochloric acid and sodium hydroxide (Fisher Scientific, USA. UV/Vis Spectrophotometer (Shimadzu, Japan)

Sample preparation

A 200 µg/ml standard stock solution of efavirenz was prepared by dissolving an accurately weighed 10 mg of efavirenz in methanol in a 50ml volumetric flask, and diluting to volume with methanol. The stock solution was used to obtain the maximum absorption wavelength of the drug by scanning with a UV/V Spectrophotometer. Stock solution was diluted to obtain concentrations of 1, 2, 3, 4 and 5µg/ml; respectively. The absorbance of these concentrations was taken at the wavelength of 250 nm to obtain the calibration curve of efavirenz.

Vehicle preparation

A 0.1 M NaOH solution was prepared by diluting 4.0 g in distilled water, and diluted to 1000 ml with distilled water. Stock solution of 25% w/v of the two cosolvents employed in the study were prepared by weighing 25 g of each cosolvent into a beaker, dissolving in distilled water, and the volume was made up to 100 ml in a volumetric flask with distilled water. Dilution of the stock solution was made in 0.1 M NaOH solution to obtain the concentrations of 20% w/v, 15% w/v, 10% w/v, 5% w/v; respectively. In the same vein, a stock solution of 2.0% w/v of the two surfactants used were prepared by weighing 2 g of each surfactant into a beaker, and dissolving in distilled water, and the volume was made up to 100 ml in a volumetric flask with distilled water. Dilution of the stock solution was made in 0.1 M NaOH solution to have concentrations of 1.0% w/v, 0.5% w/v, 0.2% w/v, 0.1% w/v; respectively.

Kinetic study

The kinetic study was performed by adding 1 ml of the drug stock solution (200 µg/ml) into a 10 ml volumetric flask, diluted to volume with various percentage solutions of the cosolvent and surfactant; respectively. The solutions were transferred into vials, capped and placed into a water bath at a temperature of 60°C. At 30 min intervals, the samples were withdrawn from the water bath and analysed spectrophotometrically at a maximum wavelength of 250 nm. The rate constant was obtained by plotting log percent remaining of the drug versus time.

RESULTS

The calibration graph of efavirenz was obtained by plotting absorbance versus concentration, and it gave a linear curve. Beer's law was obeyed in the concentration range of 1-5µg/ml. The regression equation for the linear graph was A= 0.0505C + 0.002.

The results of the kinetic studies of efavirenz in cosolvent basic solutions have been presented in Figures 2-3 while that of surfactant solutions have been given in Figures 4-5. The results showed that the plot of logarithm of percent efavirenz remaining versus time gave linear curves for all the vehicles studied. The effects of the cosolvents and surfactants on the rate constant have been presented in Tables 1 and 2; respectively. The results showed that all the vehicles studied decreased the constant rate.

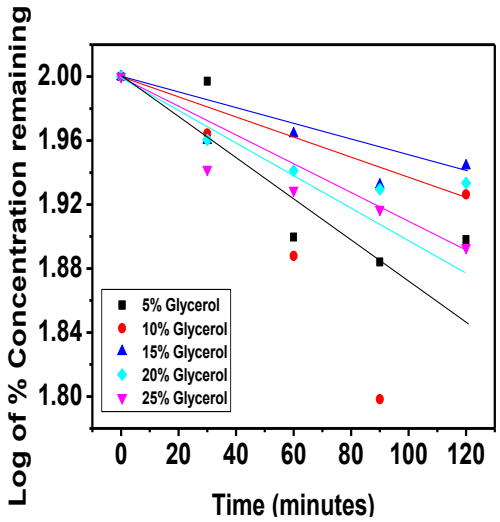

Figure 2: Effect of glycerol on the degradation kinetics of efavirenz

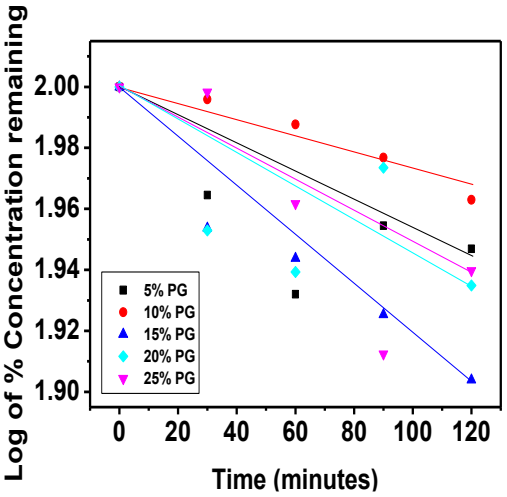

Figure 3: Effect of propylene glycol on the degradation kinetics of efavirenz

Table 1: Effect of cosolvents on the rate constant of efavirenz

% Cosolvent	Rate constant (k)	
	Glycerol	Propylene glycol
5.0	0.00244	0.00169
10.0	0.00239	0.00159
15.0	0.00183	0.00089
20.0	0.00126	0.00084
25.0	0.00107	0.00071

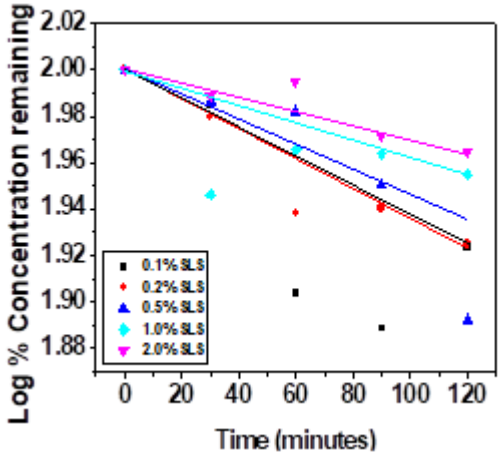

Figure 4: Effect of SLS on the degradation kinetics of efavirenz

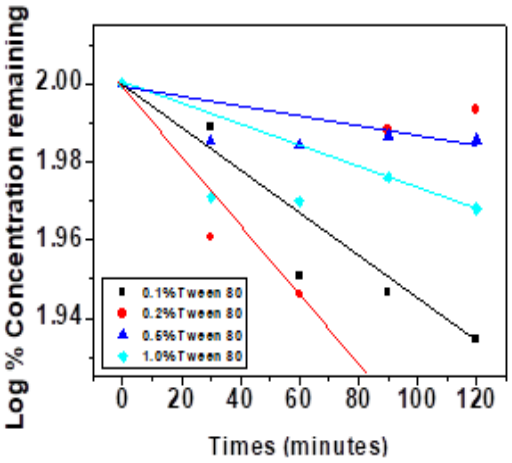

Figure 5: Effect of tween 80 on the degradation kinetics of efavirenz

Table 2: Effect of surfactant on the rate constant of efavirenz

% w/v Surfactant	Rate constant (k)	
	Polysorbate 80	Sodium lauryl sulphate
5.0	0.00133	0.00193
10.0	0.00045	0.00182
15.0	0.00021	0.00145
20.0	0.00011	0.00068
25.0	0.00008	0.00056

DISCUSSION

The chemical stability of drugs affects the efficacy and safety of the drug product. Cosolvents and surfactants are among the techniques employed to stabilize drug degradations. The regression correlation coefficient (R2) value of 0.964 suggested the linearity of the calibration curve. In the kinetic investigation, a plot of logarithm of percent drug remaining versus time gave a linear graph for each vehicle studied. The slopes of the linear curves permitted the rate constants to be calculated. The rate constant obtained in 0.1 M NaOH solution was used as a control in evaluating the effect of the studied vehicles on the rate constant of efavirenz. Plots of logarithm of percent drug remaining versus time have been used to calculate kinetic rate constants of drugs [14, 15].

A general hypothetical rate equation for efavirenz degradation as a function of 0.1 M NaOH can be written as, $k_{obs}=k_o + k[OH^-]$, where k_{obs} is the overall observed rate constant, k_o is the water catalysis rate constant, $k[OH^-]$, is the hydroxide ion catalysis rate constant. The water catalysis rate constant was an apparent first order rate constant, while the hydroxide ion catalysis rate constant was the second-order rate constant.

The degradation of efavirenz in these vehicles followed first-order rate kinetics. The rate constant was observed to decrease as the concentration of each vehicle was increasing. It was also noted that propylene glycol showed the most decreasing effect on the rate constant of efavirenz than glycerol cosolvent system at the maximum concentration (25% w/v) studied. The stabilization effect of the cosolvent on efavirenz degradation may be due to the decrease in dielectric constant and polarity as well as changes in viscosity of the solutions.

A plot of logarithm of the rate constant versus cosolvent concentration showed a linear relationship. Similarly, it was found that polysorbate 80 (tween 80) showed more decreasing effect on the rate constant of efavirenz than sodium lauryl sulphate at the maximum concentration of (2.0% w/v). A linear relationship was also observed when logarithm of the rate constant versus surfactant concentration was plotted. The surfactants' effect on the rate constants might be due to micelle formation or a combination of micelle formation and pH effects.

In the present study, no attempt was made to investigate the effects of buffers, ionic strength, pH, and the temperature on the degradation of efavirenz or characterize the degradation products since the information on them has been reported [14, 16].

The plausible mechanism of degradation of efavirenz has been the opening of the lactone/lactam ring. However, the influence of trifluoro methyl group and cyclo – propyl – ethylene group respectively on the ring suggested that it is the lactone ring that would preferentially open in the presence of hydroxide ion.

CONCLUSION

The breakdown of efavirenz was found to be first-order rate kinetics, and the hydrolytic reaction was hydroxide ion catalysed. Propylene glycol exhibited greater stabilizing effect on the constant rate of efavirenz than glycerol. Likewise, polysorbate 80 (tween 80) showed greater stabilizing effect on the rate constant of efavirenz than sodium lauryl sulphate. Finally, the study suggested that incorporating cosolvents or surfactants studied into liquid pharmaceutical dosage forms containing efavirenz would enhance the stability of the drug under basic conditions.

Conflict of Interest

Authors declared there was no conflict of interest.

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