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# Co-solubilization of Lamotrigine by Complexation and Micellization in Binary Solvent Mixtures

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ABSTRACT

The present work was carried out with the purpose of evaluating the effect of β-cyclodextrin (β-CD), sodium lauryl sulfate (SLS) and polyethylene glycol 200 (PEG 200) on the solubilization of lamotrigine by means of phase-solublility studies and solubility prediction using Jouyban-Acree model.

The experimental solubility values of various mixtures were fitted to the equation and fitting accuracy of solubility data to this model was evaluated. A quantitative relationship between the solubilizing agents was assessed and the predictive accuracy of the Jouyban-Acree model and its applicability assuring reliable prediction of the model in binary systems was studied. The significance of the simultaneous presence of SLS and β-CD on lamotrigine solubility was studied in binary solvent mixture.


## 1. Introduction

Poor aqueous solubility and dissolution rate of drug molecules remain to be one of the frequently encountered challenges in pharmaceutical development. A number of methodologies are adapted to enhance dissolution and apparent solubility of poorly soluble drugs and further to improve drug bioavailability. Many attempts have been made to overcome poor aqueous solubility of drug molecules; some of the most utilized techniques include cosolvency, complexation, micellization and pH adjustments (Bai et al., 2006; Jouyban, 2008; Li et al., 1999a).

An effective way of increasing aqueous solubility is by the cosolvency concept. Cosolvency has great application in designation of parenteral, topical and other drug delivery systems. Co-solvents are mixtures of water with one or more water miscible solvents used extensively in pharmaceutical technology. Commonly used cosolvents such as polyethylene glycol (PEG), propylene glycol and ethanol have good solubilizing capacity and low toxicity. Presence of functional groups, hydroxyl, and ether, in repeat unit can help PEG increase drug solubility and stability as well as enhance drug bioavailability (Bai et al., 2006; Jouyban et al., 2014a; Rao et al., 2006; He et al., 2003).

Cyclodextrins (CD) are cyclic oligomers of α-D-glucose in a ring formation with hydrophilic exterior and hydrophobic inner cavity that takes the shape of a truncated cone. Due to

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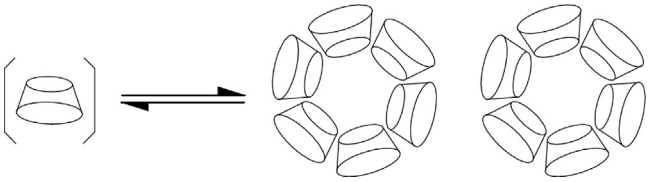

**Fig. 1 – Schematic image of CD and its aggregation.**

this special molecular structure, CDs are capable of forming inclusion complexes with many drugs and other compounds by taking up a lipophilic guest molecule (or its hydrophobic part) of the appropriate size into their cavity. CDs have long been valued in the pharmaceutical field to improve the aqueous solubility, dissolution and release rates of various drug molecules as well as act as penetration enhancer to promote drug permeation across membrane (Fig. 1). Some of the solubilizing potential of these molecules may be related to their surfactant-like properties and their ability to reduce surface tension. Among CDs, β-cyclodextrin (β-CD) is widely used because of its suitability for common pharmaceutical drugs and its cost effectiveness (Fathi Azarbayjani et al., 2010; Yang et al., 2004; Viernstein et al., 2003; Li et al., 2011).

Single approach for solubilization may not always enhance drug solubility to the desired extent. Applying certain solubilization techniques has been studied. These approaches have resulted in greater solubility enhancement. Addition of sodium luryl sulfate (SLS) to drug-polyethylene glycol dispersion has been observed to enhance drug solubility (Sjokvist et al., 1991). Addition of polyvinylpyrrolidone increased the solubilizing effect of 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) (Loftsson et al., 1994). Solubility enhancement was also achieved by PEG and temperature adjustments (Bai et al., 2006). Complexation and cosolvency may synergistically increase drug solubility (Stella et al., 1999). While other studies reported competing effect for solvent and CD cavity (Li et al., 1999b; Pitha and Hoshino, 1992).

The effect of cosolvency or pH and complexation could either decrease or enhance solubility compared with either method used alone. The synergistic and antagonistic effects of cosolvency and complexation on drug solubility have been studied using a mathematical model. Total drug solubility was calculated by employing solubility of free drug, drug–ligand binary complex, ternary complex of drug–ligand–cosolvent (assuming ratio of 1:1:1), as well as cosolvent solublizing power, apparent complexation constant, intrinsic complexation constant and destabilizing power of the cosolvent. The proposed model was validated and the shortcoming of this study was thought to be the large number of constant values and solubility data that limit its application as a prediction tool (Li et al., 1999a,b). A two-phase theoretical model has been developed to describe total solubility of poorly soluble drugs in the presence of surfactants and CDs. The proposed model takes into account all possible interactions between surfactant monomers and micellar aggregates, drug–CD complexation, inclusion complexation of micelles and their equilibrium. Universal applicability of this model is limited due to large number of constants and data points needed, as well as the effect of monomer concentration, impurities and ionic strength on solubility results (Rao et al., 2006).

Accurate measurement and interpretation of poorly soluble drugs in the presence of surfactants or complexing agents can be complicated and time-consuming. Well established experimental design and computation needs to be carried for correct interpretation of solubility behavior.

The aim of this paper is to determine the significance of the simultaneous presence of SLS and β-CD on lamotrigine solubility in the binary solvent system. The effect of solvent composition, complexing agent as well as micellization by surfactant is investigated on the solubility of lamotrigine by phase solubility method. The principal objectives of the study were therefore to develop a quantitative relationship between the solubilizing agents and to estimate the predictive accuracy of the Jouyban-Acree model and assess the applicability domain assuring the reliable prediction of the model in binary systems.

## 2. Methods and Materials

### 2.1. Materials

Lamotrigine of pharmaceutical grade was purchased from Arastoo company (Tehran, Iran) complying with United States Pharmacopeia. PEG 200 (purity of 0.99), β-CD (purity of 0.99) and SLS (purity of 0.99 m/m) were obtained from Merck (Germany). Double-distilled water was used for preparation of the solutions and ethanol (mass fraction purity of 0.935) from Jahan Alcohol Teb (Arak, Iran) was used for dilution of the saturated solutions for spectrophotometric analysis.

### 2.2. Experimental methods

The binary solvent systems of PEG 200 and water were prepared in various molar ratios. Various solubility determination procedures were reviewed in our recent work (Jouyban and Fakhree, 2012). Lamotrigine solubility was determined using saturating shake-flask method of Higuchi and Connors (Higuchi and Connors, 1965). Briefly, an excess amount of drug was added to screw capped 5 mL vials containing solvent mixtures, SLS and/or β-CD. Binary solvent mixture containing complexing agent (5,10 mM β-CD), micellizing agent (69, 138 mM SLS) or a combination of both were prepared and placed in a shaker-incubator equipped with a temperature-controlling system (298.2 ± 0.2 K). After equilibrium (>3 days), the saturated solutions were centrifuged in 10,000 rpm for 10 min (MSEMicro Center MSB010.CX2.5, Sanyo, Japan). Appropriate dilutions with ethanol in water were made to determine concentration in the filtrate samples by a UV–vis spectrophotometer (Beckman DU-650, Fullerton, California, USA) according to its calibration curve. Solubility data of lamotrigine in binary mixture of PEG 200 + water mixtures and PEG 200 + water + 10 mM β-CD were collected from our previous data (Jouyban, 2008; Jouyban et al., 2014a).

### 2.3. Computational methods

The solubility enhancement ratios (SER) were calculated according to the following equation:

$$\mathrm{SER} = \frac{\text{Solubility in particular solution}}{\text{Solubility in control}} \quad (1)$$

The solubilization power ($\omega$) of a cosolvent was calculated according to (Jouyban and Fakhree, 2007):

$$\omega = \frac{\log\left(S_{m,\max}/S_{\min,T}\right)}{m_{1,\max}} \quad (2)$$