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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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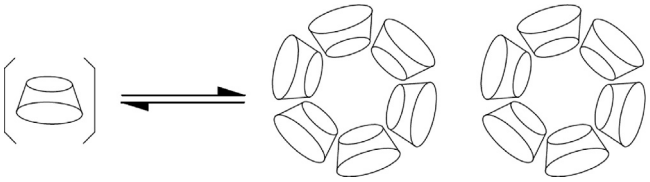

Fig. 1 – Schematic image of CD and its aggregation.

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 (ω) of a cosolvent was calculated according to (Jouyban and Fakhree, 2007):

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

in which $S_{m,max}$ is the maximum observed solubility and $m_{1,max}$ is the fraction of the cosolvent providing $S_{m,max}$. $S_{min,T}$ is the minimum solubility, i.e. aqueous solubility of drugs in the absence of β-CD in this study. The equation could be modified to apply for combined solubilizing systems such as cosolvent + β-CD, cosolvent + SLS, or cosolvent + β-CD + SLS by considering the maximum solubility in these solubilizations systems.

Solubility prediction by cosolvent systems has been the main focus of our group for many years. The Jouyban-Acree model has been employed to predict the solubility of drugs in binary solvent mixtures at various temperatures (Jouyban, 2008):

$$\log X_{m,T} = m_1 \log X_{1,T} + m_2 \log X_{2,T} + \sum_{i=0}^{2} J_i \left[\frac{m_1 m_2 (m_1 - m_2)^i}{T} \right] \quad (3)$$

where $X_{m,T}$ is the mole fraction solubility of the solute in solvent mixture, $X_{1,T}$ and $X_{2,T}$ denote the solubility in the mono-solvents at temperature T (K), m_1 and m_2 are mass fractions of solvents 1 and 2 in the absence of the solute, respectively, and J_i terms are the model constants. This model requires two solubility data in the mono-solvents and at least three data points in mixed solvents as input values. Eq. (3) is able to represent the effects of solvent composition and β-CD concentration on the solubility of a drug in mixed solvent system within an acceptable error range. The main reason for this capability is the existence of $X_{1,T}$ and $X_{2,T}$ terms in the equation. Solubilizing effect of mono-solvents 1 and 2, could be altered by β-CD addition. Solubility values in mono-solvents plus a given concentration of β-CD, $X_{1,T}$ and $X_{2,T}$, could be employed to study the enhancing/reducing effect of β-CD on the solubility of a drug in solvent mixture. The J terms of the model represent the mixing behavior of the saturated drug solutions in the mono-solvents containing β-CD (Jouyban et al., 2014b).

The experimental solubility data of drug in PEG 200 + water mixtures in the presence of β-CD and SLS were fitted to Eq. (3). The fitted data, $X_{m,exp}$, in the studied systems and the back-calculated solubilities, $X_{m,cal}$, were used to calculate the accuracy of fitness using mean relative deviation (MRD) calculated by:

$$MRD = \frac{100}{N} \sum \left| \frac{X_{m,cal} - X_{m,exp}}{X_{m,exp}} \right| \quad (4)$$

in which N is the number of data points in each set.

3. Results and Discussion

3.1. Phase solubility

3.1.1. Cosolvency and its influence on lamotrigine solubility

Phase solubility of lamotrigine in various molar ratios of PEG + water is shown in Fig. 2. Lamotrigine is a weak basic compound with an intrinsic solubility of $S_0 = 0.00073$ M and $pK_a = 5.7$ (Soltani et al., 2013). The concentration of dissolved lamotrigine increased upon the addition of co-solvent. Mole fraction solubility of lamotrigine was found to be highest in neat PEG 200 (0.034) and lowest in pure water (1.35×10^{-5}). Around 2518 fold enhancement in lamotrigine solubility was found in PEG 200 solution when compared with its aqueous solubility in pure water. Over all, mole fraction solubility of lamotrigine increased with increase in mass fraction of co-solvent. Solubilization capacity of PEG 200 shows a concentration-dependent increase in drug solubility. As the concentration of PEG 200 increases the transfer enthalpy and entropy of drug raise resulting in increased drug solubility (Bai et al., 2006). This effect is probably due to their lowest and highest polarities in water and PEG 200 solvent system, respectively (Viernstein et al., 2003). Cosolvents such as PEG 200 can reduce solvent polarity of the medium and help to increase drug solubility (He et al., 2003; Kawakami et al., 2006).

3.1.2. Effect of micellization on lamotrigine solubility

Aqueous solubility of molecules can increase via micelar solubilization of surfactants.

When surfactant concentration in aqueous medium is greater than its critical micellar concentration (CMC), micelles are formed to help solubilize poorly water soluble drugs by incorporating them into their interior cavity. CMC is an important factor in drug solubilization. It is observed that drug

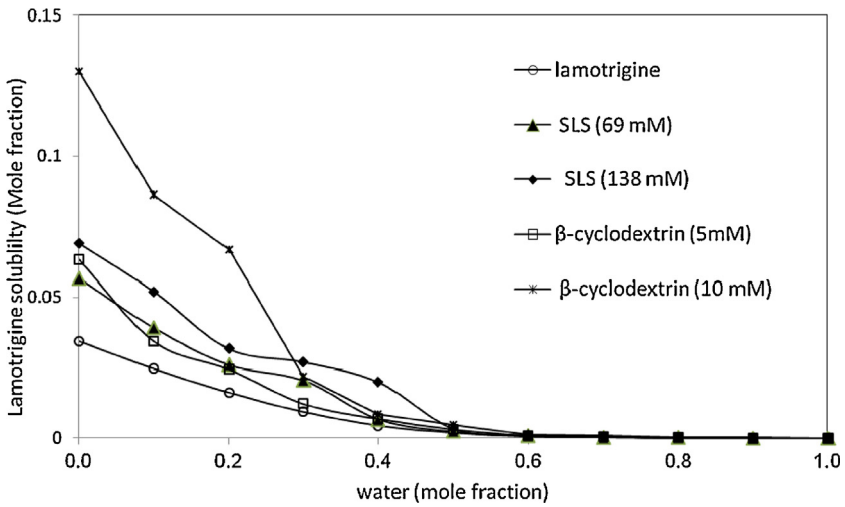

Fig. 2 – Mole fraction solubility of lamotrigine in PEG 200 + water solution containing β-CD and at 25 °C.

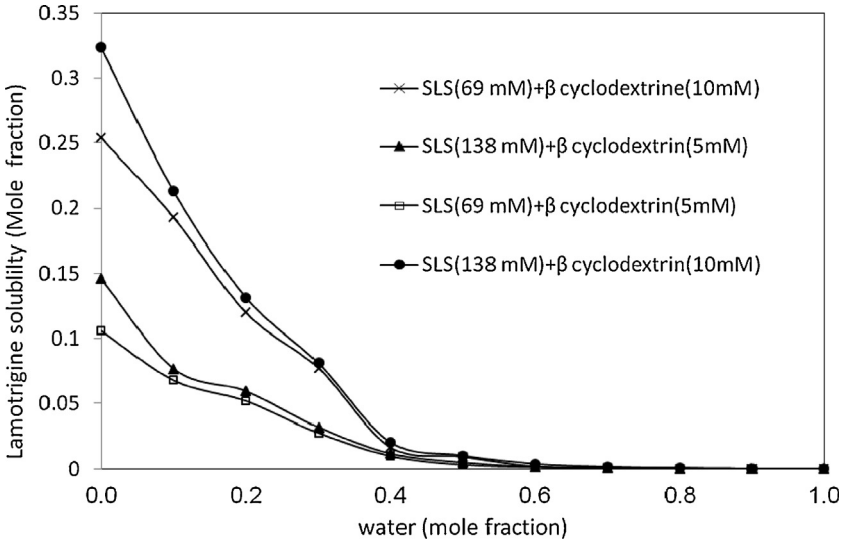

Fig. 3 – Solubilization profile of lamotrigine by combined use of β-CD and SLS at 25 °C.

solubility increases with surfactant concentration above its CMC value (He and Yalkowsky, 2006; Andreaus et al., 1997).

The CMC value of SLS in water is estimated to be anywhere between 1 and 10 mM (Rao et al., 2006). In the presence of co-solvents such as PEG 200, surface tension of the solution decreases. Therefore, the presence of ionized groups in the co-solvent system may slightly increase the CMC value of surfactant disfavoring micelle formation (Kawakami et al., 2006; Sarkar et al., 2013).

Lamotrigine phase solubility in the presence of SLS is illustrated in Fig. 2. It can be observed that SLS used at concentrations well above its CMC value, 69 and 138 mM, increased drug solubility. A linear increase in drug solubility is due to solubilization of lamotrigine in SLS micelles. SER is calculated as the maximum solubility of a particular solution over maximum solubility of the drug in control group. As seen from Figs. 2 and 3, in all solvent systems studied maximum solubility is achieved when molar fraction of PEG 200 is 1 (water = 0). Thus, SER in all systems studied is in samples where PEG 200 ratio is 1. From Table 1, SER was found to be 1.65 and 2.01 compared with binary solvent mixture of PEG and water without any surfactant. This agrees well with the behavior reported in the literature. It is found that the linear increase in drug solubility at concentrations above CMC is due to the formation of micelles (Rao et al., 2006; Yang et al., 2004; Veiga and Ahsan, 2000).

3.1.3. *Solubility enhancement by inclusion complexation with β-CD*

Solubility enhancement by inclusion complexation is shown in Fig. 2. Solubility of lamotrigine is increased by the host–guest interaction with β-CD.

Drug solubility increased linearly with a slope of 0.014, 0.031 ($r = 0.991$, 0.993) respectively for 5 and 10 mM β-CD. The slope value of phase solubility diagram shown in Table 1 is below unity, indicating complexation of first order and suggesting a 1:1 mol:mol lamotrigine-CD stoichiometry, Formation of a 1:1 inclusion complex has been reported for β-CD and lamotrigine (Seridi and Boufelfel, 2011).

In the presence of 5 and 10 mM β –CD, drug solubility appears to increase 1.84 and 3.78 folds, respectively, when compared with the drug solubility without β-CD (Table 1).

Solvent polarity is an important factor that influences its ability to increase drug solubility. Combination of co-solvency and complexation has been used to improve drug solubilization. In such systems, as the PEG concentration increases, the magnitude of lamotrigine solubility also raises. This phenomenon is due to the reduction in solvent polarity that helps to keep out non-polar molecules from the CD cavity (Li et al., 1999a; Viernstein et al., 2003; Li et al., 1999b).

The combined effect of complexant and cosolvent on drug solubility was studied. It was found that as the molecular size of the co-solvent increases and its polarity decrease, the binary drug–CD complex is reduced, which causes a decline in drug solubility (He et al., 2003).

3.1.4. *Effect of micellization and complexation on lamotrigine solubility in solvent mixture*

Fig. 3 illustrates the solubility of lamotrigine in binary solvent mixture in the presence of both β -CD and SLS. According to the phase solublilty diagram in all cases, drug solubility increased linearly as a function of PEG concentration. Co-presence of SLS (69, 138 mM) increased the solubilizing properties of β-CD as

Table 1 – Linear regression for lamotrigine solubility versus mole fraction of water/PEG 200 for Figs. 1 and 2. Slope information, solubility enhancement ratio (SER) and solubilization power of co-solvent (ω).

Solvent system	SER[a]	Slope (±S.E.)	R^2	ω^b
PEG + SLS (69 mM)	1.65	0.012 ± 0.001	0.994	3.66
PEG + SLS (138 mM)	2.01	0.012 ± 0.001	0.996	3.74
PEG + β-CD (5 mM)	1.84	0.014 ± 0.001	0.991	3.71
PEG + β-CD (10 mM)	3.78	0.031 ± 0.001	0.993	4.02
PEG + β-CD (5 mM) + SLS (69 mM)	3.09	0.023 ± 0.001	0.987	3.93
PEG + β-CD (5 mM) + SLS (138 mM)	4.24	0.031 ± 0.001	0.992	4.07
PEG + β-CD (10 mM) + SLS (69 mM)	7.39	0.059 ± 0.001	0.984	4.31
PEG + β-CD (10 mM) + SLS (138 mM)	9.40	0.074 ± 0.001	0.994	4.41

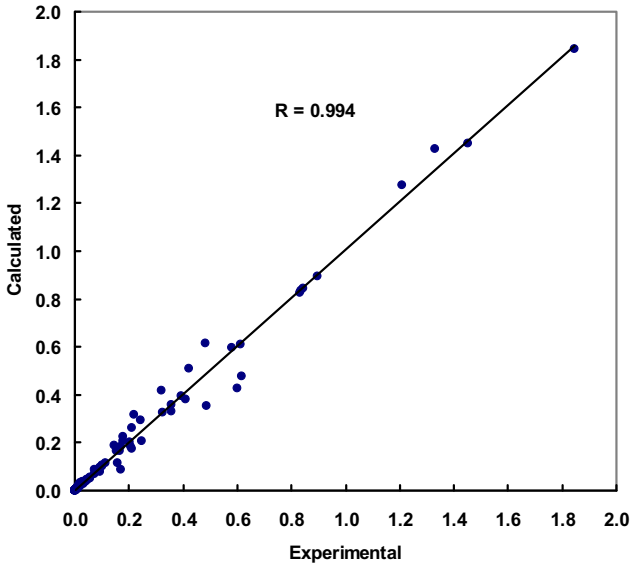

Fig. 4 – Correlation between predicted and experimental mole fraction solubility values at 25 °C.

Table 2 – Numerical values of adjusted parameters (J_0,J_1) of Jouyban-Acree model and mean relative deviation (MRD) of fitted data.

Solvent system	J_0	J_1[a]	MRD
PEG + SLS (69 mM)	135.30	668.20	9.6
PEG + SLS (139 mM)	196.99	832.86	18.8
PEG + β-CD (5 mM)	194.05	254.90	14.4
PEG + β-CD (10 mM)	-122.94	519.46	11.7
PEG + β-CD (5 mM) + SLS (69 mM)	145.17	606.29	8.3
PEG + β-CD (5 mM) + SLS (139 mM)	163.95	384.41	9.2
PEG + β-CD (10 mM) + SLS (69 mM)	-11.38	823.86	15.3
PEG + β-CD (10 mM) + SLS (139 mM)	58.48	544.26	7.2
		Overall MRD	11.3

[a] J_2 is not significant.

appears from Table 1. From the results, it is observed that a significant increase in solubility was obtained when β-CD and SLS were used simultaneously.

3.2. *Mathematical representation of experimental data*

Here, we test Jouyban-Acree model for solubility prediction of lamotrigine in binary solvent mixture in the presence of β-CD and SLS. The accuracy and predictability of the model are tested using the experimental solubility data.

The experimentally determined solubility data and data points from our previous work were used to test the model (Soltanpor and Jouyban, 2013). Model constants and fitting data are shown in Table 2. Overall, the performance of the model with the test sets is quite good demonstrating the strength of the model (11.3%). Adjustable parameters were calculated and applied to the equation and the predicted solubility data where compared with the experimental parameters and the correlatives are shown in Fig. 4 ($r = 0.994$). The model exhibited relative desired predictive performance.

Solubilities of diazepam, atenolol and lamotrigine in propylene glycol + water mixtures in the absence (Shayanfar et al., 2009) and presence (Soltani et al., 2013) of β-CD (10 mM) were reported in our earlier works. Results indicate that the addition of β-CD to binary solvent mixtures of propylene glycol/PEG 200 and water improved the solubility of poorly soluble drugs. This behavior was explained in terms of possible formation of a ternary complex (Jouyban et al., 2014a; Soltani et al., 2013).

4. Discussion

Combined use of solubilizing agent may have synergistic/antagonistic effect on drug solubility (Rao et al., 2006; Viernstein et al., 2003). The results of the solubility study allow us to conclude that the co-solubilization of lamotrigine in the presence of SLS (above its micellar concentrations) and β-CD is synergistic.

The synergistic improvement on drug solubility is clearly higher than the corresponding solubility values given by the sum of solubility of each system alone.

It is found that CD can induce SLS aggregation at concentrations lower than its CMC value in pure water causing a decrease in surfactant CMC (Zhao et al., 2015). When surfactants and β-CD are used together drug solubility decreases until micelles are formed. This initial descending portion of the curve is due to the displacement of drug molecule from CD cavity caused by surfactant monomers (shown in Fig. 5).

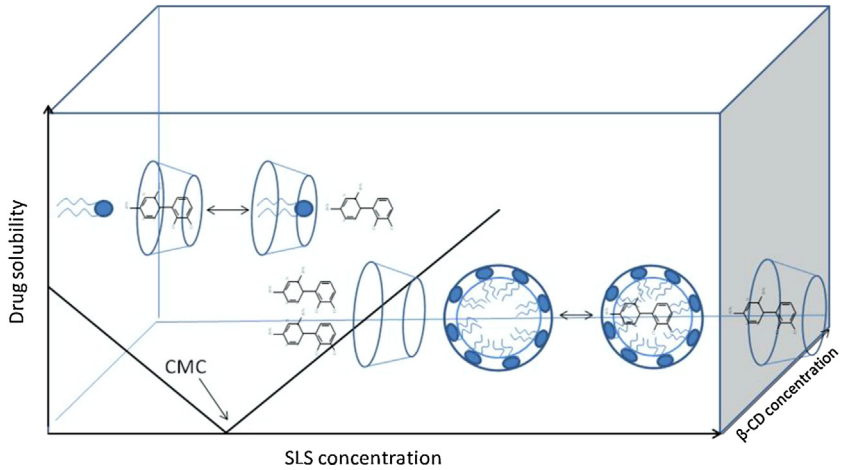

Fig. 5 – Schematic image of drug co-solubilization by SLS and β-CD.

This could be due to the formation of a 1:2 complex between CD and SLS, which may cause drug displacement from the CD cavity (He and Yalkowsky, 2006). At concentrations beyond its CMC value monomeric to micellar transition occur, which may help to synergistically increase drug solubility in a linear manner causing a V-shaped solubilization curve (Rao et al., 2006; Yang et al., 2004; Andreaus et al., 1997).

In recent years, the Jouyban-Acree is one of the commonly used mathematical models able to correlate between experimental and theoretical solubility data of various drug molecules in binary and ternary solvent systems (Jouyban, 2008; Jouyban and Fakhree, 2007, 2012; Kawakami et al., 2004).

Various prediction models have been proposed to correlate solubility enhancement of complexation and co-solvency (Li et al., 1999b), complexation and micellization (Rao et al., 2006) and micellization and co-solvency (Kawakami et al., 2006). A two-phase model was proposed for solubility prediction of drug molecule under combined use of co-solvent and surfactant. The fitting procedure was found to be poor for SLS system. Also its applicability to various co-solvents varied and it was not able to explain the solubilization behavior of ethanol and glycerol co-solvent system (Kawakami et al., 2006; Jouyban, 2006).

In this work, we offer a mathematical model to predict the interplay and to make more intelligent and less empirical process in formulation development. Due to the relatively small size of the available data, the most reliable application of this model is limited to the available data. More experimental observations will allow expanding the model to binary and ternary solvent systems containing various co-solubilizing agents. The influence of various surfactants/co-solvents on drug solubilization in CD inclusion forms and their solubilizing power remains to be elucidated and will be object of further studies.

5. Conclusion

The present work was carried out with the purpose of evaluating the effect of β-CD, SLS and PEG on the solubilization of lamotrigine by means of phase-solublility studies and solubility prediction using Jouyban-Acree model. Applications of all solubilizing agents lead to an improvement in drug solubility. The largest increase in solubility was obtained when CD and surfactant were used simultaneously.

Micellization and complexation show a synergistic effect on drug solubility improvement. The experimental solubility values of various mixtures were fitted to the equation and fitting accuracy of solubility data to this model was evaluated. Excellent agreement was obtained between experimental and calculated data.

References

Bai, T.C., Yan, G.B., Hu, J., Zhang, H.L., Huang, C.G., 2006. Solubility of silybin in aqueous poly(ethylene glycol) solution. Int. J Pharm. 308, 100–106.

Jouyban, A., 2008. Review of the cosolvency models for predicting solubility of drugs in water–cosolvent mixtures. J. Pharm. Pharm. Sci. 11, 32–58.

Li, P., Zhao, L., Yalkowsky, S.H., 1999a. Combined effect of cosolvent and cyclodextrin on solubilization of nonpolar drugs. J. Pharm. Sci. 88, 1107–1111.

Jouyban, A., Sajed-Amin, S., Panahi-Azar, V., 2014a. Solubility of atenolol, amiodarone HCl and lamotrigine in polyethylene glycol 200 + water mixtures in the presence of β-cyclodextrin. J. Drug Deliv. Sci. Technol. 24, 543–547.

Rao, V.M., Nerurkar, M., Pinnamanei, S., Rinaldi, F., Raghavan, K., 2006. Co-solubilization of poorly soluble drugs by micellization and complexation. Int. J. Pharm. 319, 98–106.

He, Y., Li, P., Yalkowsky, S.H., 2003. Solubilization of fluasterone in cosolvent/cyclodextrin combinations. Int. J. Pharm. 264, 25–34.

Fathi Azarbayjani, A., Lin, H., Yap, C.W., Chan, Y.W., Chan, S.Y., 2010. Surface tension and wettability in transdermal delivery: a study on the in-vitro permeation of haloperidol with cyclodextrin across human epidermis. J. Pharm. Pharmacol. 62, 770–778.

Yang, G., Jain, N., Yalkowsky, S.H., 2004. Combined effect of SLS and $(SBE)_{7M}$-β-CD on the solubilization of NSC-639829. Int. J. Pharm. 269, 141–148.

Viernstein, H., Weiss-Greiler, P., Wolschann, P., 2003. Solubility enhancement of low soluble biologically active compounds-temperature and cosolvent dependent inclusion complexation. Int. J. Pharm. 256, 85–94.

Li, H., Sun, J., Wang, Y., Sui, X., Sun, L., Zhang, J., He, Z., 2011. Structure-based in silico model profiles the binding constant of poorly soluble drugs with β-cyclodextrin. Eur. J. Pharm. Sci. 42, 55–64.

Sjokvist, E., Nystrom, C., Alden, M., 1991. Physicochemical aspects of drug release. The effect of sodium dodecylsulphate additions on the structure and dissolution of a drug in solid dispersions. Int. J. Pharm. 68, 53–62.

Loftsson, T., Frilfriksdottir, H., Sigurlfardottir, A.M., Ueda, H., 1994. The effect of water-soluble polymers on drug-cyclodextrin complexation. Int. J. Pharm. 110, 169–177.

Stella, V.J., Rao, V.M., Zannou, E.A., Zia, V., 1999. Mechanisms of drug release from cyclodextrin complexes. Adv. Drug Deliv. Rev. 36, 3–16.

Li, P., Tabibi, S.E., Yalkowsky, S.H., 1999b. Solubilization of flavopiridol by pH control combined with cosolvents, surfactants or complexants. J. Pharm. Sci. 88, 945–947.

Pitha, J., Hoshino, T., 1992. Effects of ethanol on formation of inclusion complexes of hydroxypropylcyclodextrins with testosterone or with methyl-orange. Int. J. Pharm. 80, 243–251.

Shayanfar, A., Acree Jr., W.E., Jouyban, A., 2009. Solubility of lamotrigine, diazepam, clonazepam, and phenobarbital in propylene glycol + water mixtures at 298.15 K. J. Chem. Eng. Data 54, 1153–1157.

Soltani, N., Shayanfar, A., Djozan, D., Jouyban, A., 2013. Solubility of three basic drugs in propylene glycol + water mixtures in the presence of β-cyclodextrin. J. Drug Deliv. Sci. Technol. 23, 187–190.

Jouyban, A., Shayanfar, A., Ghafourian, T., Acree, W.E., 2014b. Solubility prediction of pharmaceuticals in dioxane + water mixtures at various temperatures: effects of different descriptors and feature selection methods. J. Mol. Liq. 195, 125–131.

Jouyban, A., Fakhree, M.A.A., 2012. Experimental and Computational Methods Pertaining to Drug Solubility. In: Acree Jr., W.E. (Ed.), Toxicity and Drug Testing. InTech Publisher, New York.

Higuchi, T., Connors, K.A., 1965. Phase solubility techniques. Adv. Anal. Chem. Instrum. 4, 117–122.

Soltanpor, Sh., Jouyban, A., 2013. Solubility of lamotrigine in binary and ternary mixtures of N-methyl pyrrolidone and water with polyethylene glycols 200, 400, and 600 at 298.2 K. J. Mol. Liq. 180, 1–6.

Jouyban, A., Fakhree, M.A.A., 2007. A new definition of solubilization power of a cosolvent. Pharmazie 63, 317–319.

Kawakami, K., Oda, N., Miyoshi, K., Funaki, T., Ida, Y., 2006. Solubilization behavior of poorly soluble drug under combined use of surfactants and cosolvents. Eur. J. Pharm. Sci. 28, 7–14.

He, Y., Yalkowsky, S.H., 2006. Solubilization of monovalent weak electrolytes by micellization or complexation. Int. J. Pharm. 314, 15–20.

Andreaus, J., Draxler, J., Marr, R., Lohner, H., 1997. The effect of sodium dodecyl sulphate and M-α-cyclodextrin on the solubility and partitioning of Xylenes in aqueous solutions. J. Colloid Interf. Sci. 185, 306–312.

Sarkar, B., Ravi, V., Alexandridis, R., 2013. Micellization of amphiphilic block copolymers in binary and ternary solvent mixtures. J. Colloid Interf. Sci. 390, 137–146.

Veiga, M.D., Ahsan, F., 2000. Influence of surfactants (present in the dissolution media) on the release behavior of tolbutamide from its iclusion complex with β-cyclodextrin. Eur. J. Pharm. Sci. 9, 291–299.

Seridi, L., Boufelfel, A., 2011. Molecular modeling study of Lamotrigine/β-cyclodextrin inclusion complex. J. Mol. Liq. 158, 151–158.

Kawakami, K., Miyoshi, K., Ida, Y., 2004. Solubilization behavior of poorly soluble drugs with combined use of Gelucire 44/14 and cosolvent. J. Pharm. Sci. 93, 1471–1479.

Jouyban, A., 2006. Solubility prediction of drugs in water-PEG 400 mixtures. Chem. Pharm. Bull. 54, 1561–1566.

Zhao, D., Chen, Y., Liu, Y., 2015. Comparative studies on molecular induced aggregation of hepta-imidazoliumylβ-cyclodextrin towards anionic surfactants. Chinese Chem. Lett. 26, 829–833.