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Prediction of the solubility in lipidic solvent mixture: Investigation of the modeling approach and thermodynamic analysis of solubility

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ABSTRACT

Self-micro emulsifying drug delivery system (SMEDDS) is one of the methods to improve solubility and bioavailability of poorly soluble drug(s). The knowledge of the solubility of pharmaceuticals in pure lipidic solvents and solvent mixtures is crucial for designing the SMEDDS of poorly soluble drug substances. Since, experiments are very time consuming, a model, which allows for solubility predictions in solvent mixtures based on less experimental data is desirable for efficiency. Solvents employed were Labrafil® M1944CS and Labrasol® as lipidic solvents; Capryol-90®, Capryol-PGMC® and Tween®-80 as surfactants; Transcutol® and PEG-400 as co-solvents. Solubilities of both drugs were determined in single solvent systems at temperature (T) range of 283–333 K. In present study, we investigated the applicability of the thermodynamic model to understand the solubility behavior of drugs in the lipiodic solvents. By using the Van't Hoff and general solubility theory, the thermodynamic functions like Gibbs free energy, enthalpy and entropy of solution, mixing and solvation for drug in single and mixed solvents were understood. The thermodynamic parameters were understood in the framework of drug–solvent interaction based on their chemical similarity and dissimilarity. Clotrimazole and Fluconazole were used as active ingredients whose solubility was measured in single solvent as a function of temperature and the data obtained were used to derive mathematical models which can predict solubility in multi-component solvent mixtures. Model dependent parameters for each drug were calculated at each temperature. The experimental solubility data of solute in mixed solvent system were measured experimentally and further correlated with the calculates values obtained from exponent model and log-linear model of Yalkowsky. The good correlation was observed between experimental solubility and predicted solubility.

1. Introduction

Highly potent, but poorly water-soluble, drug candidates are common outcomes of contemporary drug discovery programs; *combinatorial chemistry (CC) and high-throughput screening (HTS)* (Alam et al., 2012; Lipinski, 2000; Lyckman et al., 1965; Rane and Anderson, 2008). The oral bioavailability of an active depends on several factors such as, aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, pre-systemic metabolism. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability and more 50–60% of new chemical entities (NCEs) (Constantinides, 1995; Craig et al., 1995; Gershanik and Benita, 2000; Kawabata et al., 2011) developed in pharmaceutical industry are practically insoluble in water. Hence, solubility is major factor that influences the drug efficacy, its future development and formulation efforts (Sharma et al., 2009). Solubility is the rate limiting step for the BCS class II drugs (low solubility and high permeability) so increasing the solubility in turn increases the bioavailability for BCS class II drugs (Williams et al., 2013).

There are various well known techniques are used for enhancement of solubility of poorly soluble drugs which include physical and chemical modifications of drug and other methods like Solid dispersions (Alam et al., 2012; Leuner and Dressman, 2000; Murtaza et al., 2014), co-crystallization (Kim and Park, 2004; Miroshnyk et al., 2009; Shan and Zaworotko, 2008), particle size reduction like micronization and nanosuspension (Charoen chaitrakool et al., 2000; Chen et al., 2011; Liversidge and Cundy, 1995), cryogenic techniques (Charoenchaitrakool et al., 2000), complexation (Brewster and Loftsson, 2007; Loftsson and Brewster, 1996), salt formation (Blagden et al., 2007; Serajuddin, 2007), use of adjuvants like surfactants, solubilizers, co-solvents, and novel lipidic excipients (Blagden et al., 2007; Savjani et al.,

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2012). Of all, one of the contemporary approaches is Lipid based drug delivery systems (LBDDS) like self-microemulsifying DDS (SMEDDS) which usually present the drug to the stomach in a solubilized state, unlike tablets (Constantinides, 1995; Gao and Morozowich, 2006; Kommuru et al., 2001; Pouton and Porter, 2008). They can keep drug in dissolved state until it is completely absorbed thereby overcoming barrier of GI dissolution rates. A microemulsion is a thermodynamically stable system composed of water, oil and surfactant/co-surfactant or polyglycolyzed glycerides and the drug, giving a transparent and thermodynamically stable system whose droplet size is in range of 10–140 nm (Nigade et al., 2012). The partitioning of drug to aqueous or non-aqueous is decided by its lipophilicity. The choice of SMEDDS often depends on the intrinsic drug properties, its solubility and dissolution profile during *in vitro* screening with a number of excipients (Douroumis and Fahr, 2012; Jouyban, 2010).

One of the most important criteria for the successful design of a lipidic formulation is adequate solubility of the drug in the dosage form. Solubility data of new drugs are frequently not available in the literature and at an early stage of a drug process development solubility prediction of an active substance in a single or combination of solvents is mainly an experimental approach (Rane and Anderson, 2008). However, experiments are product as well as time consuming. Apart from experimental determination, *Phase diagrams* have been empirically used to show drug solubility in pure and mixed solvent system for Lipid based formulations (Charman et al., 1992; Gershanik and Benita, 2000; Khan et al., 2012; Matsuda et al., 2010; Millard et al., 2002). Although, cosolvency models were presented from 1960 to 2007 but such models were discussed only for water-cosolvent mixtures (Jouyban, 2008). The models were, Hilderbrand solubility approach (Chen and Crafts, 2006b; Jouyban, 2008; Li et al., 2012), Log-linear model of Yalkowsky, William-Amidon model, Jouyban-Acree model and modified Wilson model with their own limitations. These theoretical models provide some evidence for better understanding of solubility behavior for drugs in mixed solvents. Nonetheless, such models have not been reported in case of Lipid based formulations so far. The ability to predict lipid solubility is an important step in being able to identify the right excipients to solubilize and formulate drugs in lipid formulations (Dahan and Hoffman, 2008; Porter and Charman, 2001). But predicting the solubility in lipidic emulsions may be quite complicated due to the interfacial nature of these systems, the distribution of the drug in the continuous/dispersed phase, sometimes preferred location at the surfactant interface and also complexity of the solvents used in the formulation (Chen and Crafts, 2006b; Constantinides, 1995). Moreover, solubility may be affected by microstructure as well as by the physicochemical properties of oil, surfactant, co-solvent and the drug. The microstructure of the lipid-based systems is depended on the type and concentration of oil, surfactant and co-surfactants, micelles, microemulsions (w/o or o/w), bicontinuous or mesomorphous phases. The surface properties of lipidic and emulsion phases are depended on the microstructure. Microstructure of lipid mixtures has a bearing on drug solubilization potential, drug release kinetics, drug permeability and bioavailability (Rane and Anderson, 2008). Structural organization of these phases in microemulsions may create additional domain which further improves the solubility. Relationships between solubility and lipid microstructure have also been reported for lutein (Amar et al., 2003), phytosterols and cholesterol (Spernath et al., 2003), and celecoxib (Garti et al., 2006). Thus, mathematical models can be helpful tool to estimate solubility in pure oils, or oil–surfac tant/co-surfactant mixtures. By measuring solubility in few representative solvents it is possible to characterize drug based on its surface interaction property and further predict solubility in any solvent or mixture of solvents which also helps to discriminate between good solvent and anti-solvent candidates and further contributes for estimation of yield and productivity (Chen and Crafts, 2006a). The factors governing lipid solubility can be better understood by conceptualizing the thermodynamic components involved in solubilization. Generally, solubility of a solute in any solvent is determined by the minimum in free energy of mixing, which should be negative in order to favor the mixed state. However, this determination requires an understanding of both molecular interactions determining free energy in both solution and pure crystalline solute (Grant and Higuchi, 1990).

The goal of this work was to investigate the predictability of proposed mathematical models for the solubility in lipidic mixtures and to understand the solubilization behavior applying thermodynamic concepts. Fluconazole and Clotrimazole were used as model poorly soluble drugs. The solubility of the solute was modeled in framework of mathematical models with co-solvent fraction and temperature as the dependent parameters. We also evaluated the effect of the cosurfactant composition on solubility and solution thermodynamics. Thermodynamic aspects of solubility were understood by the Van't Hoff model, Gibbs free energy and relative solvation at different temperatures. The applicability of the thermodynamic approach for the understanding of drug solubilization in lipidic solvents has been expanded. The exponential, Yalkowsky and activity coefficient based models were used to predict the solubility of essentially poorly soluble drugs in mixture of solvents used in SMEDDS. The linear, log linear and power mixing rules were applied to the model dependent parameters to derive predictive model. The predicted solubility values deduced from mathematical models were compared and validated with experimental results with help of statistical analysis.

2. Materials and methods

2.1. Materials

Fluconazole (FCZ) and Clotrimazole (CLZ) were kindly gifted by Endoc Life care Private Ltd. Delhi, India and their chemical structures are reported in Table 1. Oleoyl macrogol-6 glyceride (Labrafil® M1944CS, Batch # 140539), caprylocapryol macrogol-8 glyceride (Labrosol® Batch # 142605), propylene glycol monocaprylate type II (Capryol™ 90 Batch # 139506), propylene glycol monocaprylate type I (Capryol™ PGMC Batch # 131823), highly purified diethylene glycol monoethyl ether (Transcutol®HP Batch # 143339) were supplied by Gattefossé Co. (Saint-Priest, Cedex, France). Polysorbate 80 (Tween 80) was purchased from Fagron Inc. (Saint Paul, MN). Polyethylene glycol 400 was purchased from Avantor Performance Materials (Center valley, PA). Ethyl alcohol 190 proof and purified water were of HPLC grade.

2.2. Methods

2.2.1. Thermal analysis

Melting data of FCZ and CLZ were obtained by Differential scanning calorimetry (DSC Q200, TA instruments, USA). The enthalpy of fusion (ΔH_{fus}) and the melting temperature (T_m) was recorded for modeling purpose. Aluminum pans were used to hermetically seal samples (7–8 mg) of solid. Dry nitrogen gas was used as the purge gas through the DSC cell at a flow rate of 50 ml/min. The run was set at a temperature range of 293.15–453.15 K at heating rate of 5 K/min. The instrument was prior calibrated with indium according to the procedure provided by the manufacturer.