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Solubility of salbutamol and salbutamol sulphate in ethanol + water mixtures at 25 °C

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ABSTRACT

Experimental solubilities of salbutamol and salbutamol sulphate in ethanol + water mixtures at 25 °C are reported. The solubility of salbutamol was found to increase with the addition of ethanol, and reached a maximum value at an ethanol volume fraction of 0.8. The solubility of salbutamol sulphate decreased with increasing ethanol concentration, and reached a minimum value in ethanol. The Jouyban–Acree model correlated the measured salbutamol and salbutamol sulphate solubility data to within mean relative deviations (MRD) of 3.4% and 13.4%, respectively. Solubilities were predicted using previously trained models developed for crystalline non-electrolyte and electrolyte solutes. The trained models for non-electrolytes and electrolytes produced the prediction MRDs of 22.4% and 19.8%, respectively.

1. Introduction

The solubility data of drugs both in the molecular solid and salt form in ethanol + water mixtures is essential and critical in undertaking preformulation studies. Mixed solvent systems are commonly employed in many investigations to overcome problems associated with limited aqueous solubility. Ethanol is commonly added to water to improve the extraction efficiency of biologically active compounds in the pharmaceutical and/or food industries [1–3]. Ethanol is one of the most common cosolvents used in the preparation of liquid drug formulations [4]. The concentration of ethanol in pharmaceutical preparations should be kept as low as possible. The method used to optimize the composition of solvent mixtures for dissolving a desired amount of a drug in a given solution volume is usually iterative and employs a trial-and-error approach; which is time-consuming and expensive. Solubility data of pharmaceutical compounds in cosolvent and water mixtures are available as comprehensive databases [5]. In addition, the experimental solubility data, a number of mathematical models have been presented for predicting the solubility of drugs in aqueous–organic solvent mixtures. The various mathematical models and their advantages and limitations were recently reviewed [6].

Of the numerous models developed in recent years, the Jouyban–Acree model is perhaps one of the most versatile models. The model provides an accurate and realistic mathematical description for how the solute solubility varies with both temperature and solvent composition. The model is [6]:

$$\log C_{m,T}^{Sat} = \varphi_1 \log C_{1,T}^{Sat} + \varphi_2 \log C_{2,T}^{Sat} + \frac{\varphi_1\varphi_2}{T}\sum_{i=0}^{2} J_i(\varphi_1 - \varphi_2)^i \quad (1)$$

where $C_{m,T}^{Sat}$ is the solute solubility (mol L^{-1}, g/L or other units) in the binary solvent mixtures at temperature T/K, φ_1 and φ_2 are the volume fractions of solvents 1 (ethanol) and 2 (water) in the absence of the solute, $C_{1,T}^{Sat}$ and $C_{2,T}^{Sat}$ denote the mol L^{-1} solubility of the solute in neat solvents 1 and 2, respectively, and J_i are the constants of the model representing two-body and three-body interactions in the solution [7] and computed by regressing $(\log C_{m,T}^{Sat} - \varphi_1 \log C_{1,T}^{Sat} - \varphi_2 \log C_{2,T}^{Sat})$ against $\frac{\varphi_1\varphi_2}{T}$, $\frac{\varphi_1\varphi_2(\varphi_1-\varphi_2)}{T}$ and $\frac{\varphi_1\varphi_2(\varphi_1-\varphi_2)^2}{T}$ [6]. Computations of the model constants require experimental solubility data in the cosolvent + water mixtures and are derived from a training process which can limit the model's predictive application in early drug discovery studies as the required solubility data may not be readily available. This version of the model could be considered as a specific model, since it is valid only for one drug dissolved in ethanol + water mixtures. This limitation could be resolved by using a general trained version of the model specific for ethanol + water mixtures. The trained version of the Jouyban–Acree

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model for prediction of solubility of various non-electrolyte (molecular) drugs in ethanol + water mixtures at temperature (T) is Eq. (2) [8]:

$$\log C_{m,T} = \varphi_1 \log C_{1,T} + \varphi_2 \log C_{2,T} + \left(\frac{\varphi_1\varphi_2}{T}\right)\{558.45 + 358.60E + 22.01S - 352.97A + 130.48B - 297.10V\} + \left(\frac{\varphi_1\varphi_2(\varphi_1-\varphi_2)}{T}\right)\{45.67 - 165.77E - 321.55S + 479.48A - 409.51B + 827.63V\} + \left(\frac{\varphi_1\varphi_2(\varphi_1-\varphi_2)^2}{T}\right)\{-493.81 - 341.32E + 866.22S - 36.17A + 173.41B - 555.48V\} \quad (2)$$

where E is the excess molar refraction, S is dipolarity/polarizability of solute, A denotes the solute's hydrogen-bond acidity, B stands for the solute's hydrogen-bond basicity and V is the McGowan volume of the solute [8]. Eq. (2) was trained using 66 solubility data sets of non-electrolyte drugs dissolved in ethanol + water mixtures [8] and could be considered as a global model for solubility prediction of drugs in ethanol + water mixtures at various temperatures.

Eq. (2) cannot be used to predict the solubility of electrolytes in ethanol + water mixtures. In a recent study [9] we proposed a new predictive model based on the Born equation:

$$\log C_{m,T}^{Sat} = \log C_{2,T}^{Sat} + \left(\frac{A_T}{T}\right)\left(\frac{1}{\varepsilon_{2,T}} - \frac{1}{\varepsilon_{m,T}}\right) \quad (3)$$

in which A_T is a constant value computed by:

$$A_T = \log\left(\frac{C_{1,T}^{Sat}}{C_{2,T}^{Sat}}\right)\left(\frac{T}{\left(\frac{1}{\varepsilon_{2,T}} - \frac{1}{\varepsilon_{1,T}}\right)}\right) \quad (4)$$

where $\varepsilon_{1,T}$, $\varepsilon_{2,T}$ and $\varepsilon_{m,T}$ are the dielectric constants of solvent 1, solvent 2 and mixed solvent at temperature T. This predictive method employs the solubility of a drug in mono-solvents at temperature of interest (T), i.e. $C_{2,T}^{Sat}$, and the dielectric constants of the solute-free solvent mixtures as input data. Dielectric constants of ethanol + water mixtures at various temperatures (20, 40, 50, 60 and 80 °C) expressed as mass fraction compositions of the solvents were reported by Akerlof [10]. The measured dielectric constants of ethanol + water mixtures as a function of temperature and solvent composition can be accurately described by the following mathematical equation [9]:

$$\log \varepsilon_{m,T} = (2.179 - 0.000732\cdot T)\varphi_1 + (2.497 - 0.002039\cdot T)\varphi_2 + 106.8\left(\frac{\varphi_1\varphi_2}{T}\right) - 9.6\left(\frac{\varphi_1\varphi_2(\varphi_1-\varphi_2)}{T}\right) - 22.3\left(\frac{\varphi_1\varphi_2(\varphi_1-\varphi_2)^2}{T}\right) \quad (5)$$

In the present study, we have measured the experimental solubility of salbutamol (base form) and its sulphate form in binary ethanol + water mixtures at 25 °C. The measured data is used to assess the ability of the Jouyban–Acree model to mathematically represent the solubility behavior of dissolved crystalline solutes in binary aqueous–organic solvent mixtures. In addition, we have compared the measured solubility data to predictions based on previously published models developed for non-electrolyte and electrolyte solutes dissolved in ethanol + water mixtures in order to test further the applications and limitations of each model.

2. Experimental method

2.1. Materials

Salbutamol (>99% in mass fraction) and salbutamol sulphate (>99% in mass fraction) were purchased from Cipla, India. Absolute ethanol was purchased from Fisher Scientific Ltd, Loughborough, UK. Distilled water was obtained from Purelab™, ELGA, UK.

2.2. Apparatus and procedures

The binary solvent mixtures were prepared by mixing the appropriate volumes of water and ethanol with the uncertainty of 0.001 volume fraction. The solubility was determined by equilibrating excess amounts of the solids in mixed solvents at 25 °C using a shaker (Grant Instruments, Cambridge Ltd, England) placed in an incubator equipped with a temperature-controlling system maintained constant to within ±0.2 °C. After sufficient equilibration time (>24 h), the saturated solutions of the drugs were filtered using hydrophilic Durapore filters (0.45 μm, Millipore, Ireland), diluted with water, and then assayed spectrophotometrically (V-530 UV–Vis spectrophotometer, Jasco, Japan) at wavelengths (225 and 276) nm for salbutamol and salbutamol sulphate, respectively. The preliminary investigations showed that the filter did not absorb the solutes through the filtration process. Concentrations of the diluted solutions were determined from the calibration curves. Each experimental data point represents the average of at least three repetitive experiments.

2.3. Computational methods

The experimental solubility data of each drug was fitted to Eq. (1) and the back-calculated solubilities were used to calculate the accuracy of the fit. The solubilities of the drugs were predicted using Eqs. (2) and (3) employing the experimental solubilities of drugs in ethanol + water at 25 °C. The mean relative deviation (MRD) was

$$MRD = \frac{100}{N}\sum\left\{\frac{\left|\left(C_{m,T}^{Sat}\right)_{pred} - \left(C_{m,T}^{Sat}\right)\right|}{\left(C_{m,T}^{Sat}\right)}\right\} \quad (6)$$

used to assess the accuracy of the predictions, where N is the number of data points in each set.

3. Results and discussion

Table 1 lists the experimental solubilities of salbutamol and salbutamol sulphate in ethanol + water mixtures at 25 °C along with the correlated and predicted values. Visual examination of the numerical values in the first and second columns of Table 1 reveals that the solubility of salbutamol increased with increasing ethanol concentration, and reached a maximum value at $\varphi_1 = 0.800$. This solubility pattern has been observed for many pharmaceutical non-electrolytes and/or weak electrolyte drugs [11 and references herein]. The solubility of salbutamol sulphate, on the other hand, was found to decrease with increasing ethanol concentration over the entire concentration range, reaching its minimum value in neat ethanol. The pattern of decreasing solubility with ethanol concentration has been observed for the solubility of most salts and/or zwitterionic solutes in ethanol + water mixtures where ionization and solvation of the ionized forms play an important role in the solubilization process.

The measured solubilities of salbutamol and salbutamol sulphate were fitted to Eq. (1). All adjusted model constants for the investigated drugs in ethanol + water mixtures are listed in Table 2 along with the MRD values based on the back-calculated solubilities. These correlation results could be employed to evaluate the experimental solubility data for detecting possible outliers. Any data point producing very high error in the back-calculation process could be considered as an outlier. The predictive version of the Jouyban–Acree model for the solubility of drugs in ethanol + water mixtures, i.e. Eq. (2), predicted the solubility of salbutamol with reasonable MRD value (22.4%). The numerical values of the Abraham solvation parameters of salbutamol (E = 1.43,