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PLENARY LECTURES

ORAL PRESENTATIONS: ADVANCING THE CHEMICAL AND BIOLOGICAL ENGINEERING FUNDAMENTALS

Pure solvent solubility of some pharmaceutical molecules

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Introduction

During the search for novel or improved therapies, new drugs are proposed. Solubility of drug-candidates is important both for drug production and its therapeutic use. Many separation processes in the pharmaceutical industry are based on the solubilities in different solvents. Solvation plays an important role in the organism in each stage of drug transport and delivery. Properties like lipophilicity, hydrophilicity, the ability to establish hydrogen bonds and other interactions of the molecules with the surrounding media play an important role in the solvation process. Although some predictive thermodynamic tools can be used to determine drug solubility, the availability of experimental data is still fundamental for an appropriate model development and evaluation.

In this work, solubilities of some drugs, such as paracetamol, budesonide, furosemide and allopurinol, were measured in the temperature range between 25 ºC and 42 ºC, in pure solvents (water, ethanol, acetone, n-hexane, ethyl acetate and carbon tetrachloride). The Non-random Two-Liquid Segment Activity Coefficient (NRTL-SAC) equation (Chen and Song 2004), one of the most successful models for the representation of drug solubility, was used to model the data. The obtained agreement is very satisfactory (root mean square deviation of 0.051).

Experimental

All the solubility experiments were carried out using the isothermal saturation shake-flask method at five different temperatures: 25, 30, 37, 40 and 42ºC. Samples from the saturated liquid phase were removed with isothermal syringe filtration and its drug composition determined by liquid chromatography (HPLC). Melting data (melting temperature and enthalpy of fusion) of the pure drugs were also obtained by differential scanning calorimetry (DSC).

Modelling

The temperature dependence of solubility in pure solvents can be described by the following general equation, considering that the heat capacity difference between the liquid and the solid phase is negligible (Prausnitz et al. 1999):

$$\ln x_2 = -\frac{\Delta_{fus}H}{R}\left(\frac{1}{T}-\frac{1}{T_m}\right)-\ln\gamma_2$$

where x_2 is the solubility, $\Delta_{fus}H$ is the enthalpy of fusion, R the gas constant, T the absolute temperature, T_m the melting temperature and γ_2 is the activity coefficient of the solute calculated by the NRTL-SAC model.

The NRTL-SAC model is a modification of the polymer NRTL equation, where the combinatorial term is calculated from the Flory-Huggins approximation for the

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combinatorial entropy of mixing and the residual term is set equal to the sum of the local composition interaction contribution for each segment. For each solute and solvent molecule, it describes their effective surface interactions in terms of three types of conceptual segments.

Results and Discussion

Among the studied drugs, only for paracetamol there is data available in the open literature (Bustamante et al. 1998; Granberg and Rasmuson 1999; Hojjati and Rohani 2006). In general, the agreement between paracetamol data measured in this work and published in the literature is good, showing the adequacy of the method for drug solubility measurements.

Experimental and modelling results in water are presented in Figure 1 where it can be seen that NRTL-SAC is an appropriate tool for the solubility modelling of aqueous solutions of these complex molecules.

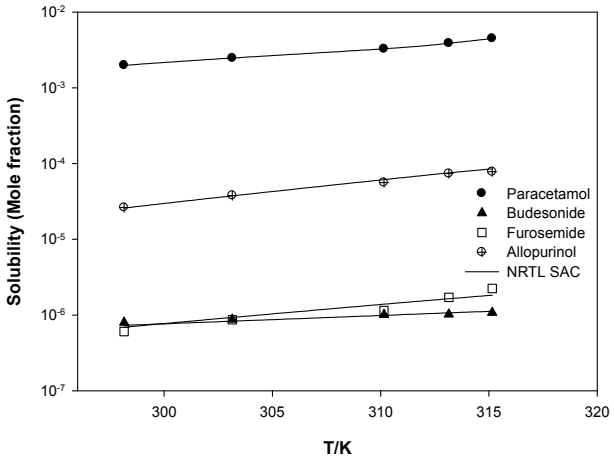

Figure 1 – Experimental aqueous solubility data of the studied compounds.

Conclusions

Solubilities of some pharmaceutical compounds in pure solvents were measured, at five temperatures, in the range 25ºC - 42ºC, using the shake-flask method. The NRTL-SAC model showed to be an appropriate tool to represent the solubility of these molecules.

Ackowledgments

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