Fluid Phase Equilibria 458 (2018) 84–101

Contents lists available at ScienceDirect

Fluid Phase Equilibria

journal homepage: www.elsevier.com/locate/fluid

Solubility of diazepam in water + *tert*-butyl alcohol solvent mixtures: Part 2. Correlation using Scatchard-Hildebrand and combined Scatchard-Hildebrand/Flory-Huggins excess Gibbs energy models

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ARTICLE INFO

Article history:
Received 31 August 2017
Received in revised form
18 October 2017
Accepted 6 November 2017
Available online 8 November 2017

Keywords:
Diazepam
tert-butyl alcohol
Solubility
Excess Gibbs energy model
Thermodynamic correlation

ABSTRACT

The aim of this work is to evaluate the performances of two excess Gibbs energy models, namely the Scatchard-Hildebrand model and the combined Scatchard-Hildebrand/Flory-Huggins model, in correlating the composition and temperature dependence of the solubility of diazepam in water + *tert*-butyl alcohol solvent mixtures. The dependence of the pure component properties required as input data to the models on temperature was considered as well as that of the adjustable binary interaction parameters. For this purpose, a set of twenty-seven model versions containing from three up to six adjustable parameters and differing from one another by the dependence of at least one binary interaction parameter on temperature was generated for the two excess Gibbs energy models investigated. To rank and weight among these different model versions, second-order Akaike's information criterion corrected for small sample size was used. The correlative performances of the most parsimonious versions of the Scatchard-Hildebrand and combined Scatchard-Hildebrand/Flory-Huggins models selected from this approach were then evaluated, compared and discussed.

1. Introduction

Solvent mixtures are of widespread use in the pharmaceutical industry as reaction, crystallization, extraction, separation or formulation media [1]. Over the past decades, water + *tert*-butyl alcohol solvent mixtures have been received an increasing interest from scientists in both academic and industrial settings as lyophilization vehicle for the preparation of freeze-dried pharmaceutical compositions [2–4]. In addition to be fully miscible with water under ambient temperature and pressure conditions, *tert*-butyl alcohol is a low toxicity [5] and environmentally friendly solvent relatively safe in use [6] which exhibits suitable physical properties with regard to the freeze-drying process including a high fusion temperature, a high solid vapor pressure and a low sublimation enthalpy [2–4]. Binary mixtures of this monohydric alcohol with water share these desirable properties as well so that, unlike other aqueous organic cosolvent systems, they can be frozen under operating conditions for conventional industrial-scale freeze-dryers [7–11] and, for identical process parameters, they sublime faster than neat water [12,13].

The first step in the manufacturing process of most lyophilized pharmaceutical compositions consisting in preparing a homogeneous solution of the ingredients to be dried, the use of water + *tert*-butyl alcohol solvent mixtures is especially valuable when considering freeze-drying of high-dosage hydrophobic drugs, for which the concentration in the solution to be lyophilized must be high enough to make the whole process economically viable for a large-scale production [2–4]. Rational design of such poorly water-soluble drug formulations intended to be freeze-dried obviously requires, among many others, knowledge of the solubility of the drug of interest in water + *tert*-butyl alcohol solvent mixtures. However, it is unlikely to be found in the literature, let alone under temperature conditions of interest, since at this time, solubility data of drugs in this cosolvent system are very scarce and often limited to a narrow solvent composition range [14–16]. Even if experimental values are always desirable,

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https://doi.org/10.1016/j.fluid.2017.11.011
0378-3812/

experimental determination of drug solubility is a time-consuming and cost-effective procedure being mostly unworkable for drug candidates in the early stages of development [17–19]. Fortunately, a countless number of mathematical expressions have been developed and expanded in the past allowing modeling solid-liquid equilibrium data. Among thermodynamic models, the Scatchard-Hildebrand equation [20,21], the Wilson equation [22], the non-random two liquids equation [23] and the universal quasi-chemical equation [24] have been widely used in their original or modified forms to describe solubility of a large variety of drugs in either pure or mixed solvents. Above and beyond their capabilities and limitations, one common feature of these excess Gibbs energy models is that they are all parameterized in terms of binary interaction parameters, characteristic of a given pair of unlike molecules. Hence, they can be employed not only to correlate the solubility of drugs in either pure or mixed solvents, but also to predict the solubility of drugs in mixed solvents from binary equilibrium data. Nevertheless, determination of the binary interaction parameters set for a given multicomponent system from global regression of multicomponent equilibrium data commonly yields a better representation of the phase equilibria under specified temperature and pressure conditions than from regression of binary equilibrium data for all possible contributing binary subsystems, as discussed elsewhere [25].

In the first part of this work [26], solubility data of the poorly water-soluble drug diazepam (7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one) in water + *tert*-butyl alcohol solvent mixtures in the temperature range from 293.15 to 313.15 K were reported. From these, the changes in thermodynamic quantities of diazepam upon fusion and mixing as well as the excess thermodynamic quantities of the drug in the different saturated solvent compositions over the temperature range investigated were determined using classical thermodynamic approaches. As a direct continuation, the aim of the present study is to evaluate the performance of the Scatchard-Hildebrand model, both corrected and uncorrected for relative difference in molar volume of individual components in the liquid phase, in correlating the dependence of the solubility of diazepam in water + *tert*-butyl alcohol solvent mixtures on solute-free binary solvent composition and system temperature. Unlike local composition theory-based excess Gibbs energy models, the Scatchard-Hildebrand equation, combined or not to the Flory-Huggins equation for the excess molar combinatorial entropy of mixing, contains only one adjustable binary interaction parameter per pair of unlike molecules but due to the assumptions underlying the model, its use in the chemical engineering literature is traditionally restricted to liquid mixtures into which the only intermolecular interactions existing are instantaneous dipole-induced dipole forces [27–32]. In the pharmaceutical literature, however, a modified form of the Scatchard-Hildebrand model introduced by Martin and coworkers [33–35] is widely used to correlate the solubility of drugs in mixed solvents, included hydrogen-bonded cosolvent systems such as that presently investigated [36,37]. In this approach, the Scatchard-Hildebrand expression for the activity coefficient of a component in a binary mixture is employed, irrespectively of the real number of components in the saturated liquid phase, and the cosolvent system is considered as a pure component so that the resulting equation does contain only one adjustable parameter, but this depends on both the qualitative and quantitative composition of the mixed solvent. In the present work, the use of this approach was avoided in order to preserve the capability of the model to predict multicomponent equilibrium data from binary equilibrium data only. Furthermore, it was considered that the capability of the excess Gibbs energy models investigated in correlating the solubility of diazepam in water + *tert*-butyl alcohol solvent mixtures over the temperature range under consideration could be enhanced by taking into account not only the temperature dependence of the pure component properties required to their use, but also that of the binary interaction parameters and for this purpose, an approach based on information-theoretic concepts was employed. The correlative performances of the most parsimonious versions of the Scatchard-Hildebrand and combined Scatchard-Hildebrand/Flory-Huggins models selected from this approach were evaluated, compared and discussed, before providing some practical recommendations for their use.

2. Theory

2.1. Solid-liquid equilibria

Provided that the solid phase is made of pure k and presents a single crystalline form, the solubility of component k in either a pure or a mixed homogeneous solvent at the system temperature and pressure is given by the following general expression [38,39]:

$$\ln x_k^{\text{sat}} = -\left\{ \frac{\Delta_{\text{fus}} H_{\text{m},k}\left(T_{\text{fus},k}\right)}{RT}\left[1-\frac{T}{T_{\text{fus},k}}\right] + \frac{1}{RT}\int_{T_{\text{fus},k}}^{T} \Delta C_{p,\text{m},k}\left(T'\right) dT' - \frac{1}{R}\int_{T_{\text{fus},k}}^{T} \Delta C_{p,\text{m},k}\left(T'\right)\frac{dT'}{T'} \right\} - \ln \gamma_k^{\text{sat}} \tag{1}$$

where $x_k^{\text{sat}} = x_k^{\text{sat}}(\text{l}, T, P, X)$ and $\gamma_k^{\text{sat}} = \gamma_k^{\text{sat}}(\text{l}, T, P, X)$ are respectively the mole fraction solubility and the symmetrical activity coefficient of component k in the saturated liquid phase of composition X at the system temperature T and pressure P, $\Delta_{\text{fus}} H_{\text{m},k}(T_{\text{fus},k}) = H^*_{\text{m},k}(\text{l}, T_{\text{fus},k}, P) - H^*_{\text{m},k}(\text{cr}, T_{\text{fus},k}, P)$ is the molar fusion enthalpy of pure component k at its fusion temperature at the system pressure $T_{\text{fus},k} = T_{\text{fus},k}(P)$, $\Delta C_{p,\text{m},k}(T') = C^*_{p,\text{m},k}(\text{l}, T') - C^*_{p,\text{m},k}(\text{cr}, T')$ is the differential molar heat capacity at constant system pressure between the hypothetical pure supercooled liquid and crystalline solid forms of component k at any temperature T' comprised in the range $[T\,;\,T_{\text{fus},k}]$, R is the molar ideal gas constant, the superscripts * and sat stand respectively for pure component and mixture saturation condition, the subscript fus refers to fusion process whereas cr and l indicate the state of aggregation of the phases as crystalline solid and liquid, respectively. Computation of the mole fraction solubility of component k in a solvent at a given system temperature and pressure from Eq. (1) hence requires, in addition to knowledge of its thermophysical properties in the pure state, a model allowing to appropriately describe the excess Gibbs energy of the mixture in order to compute its activity coefficient in the saturated liquid phase.

2.2. Excess Gibbs energy models

2.2.1. Scatchard-Hildebrand model

Derived on the basis of the works of van der Waals [40] and van Laar [41–43] by assuming, among others, ideal behavior with respect to entropy and volume changes upon mixing of pure liquid components under constant temperature and pressure conditions, the Scatchard-Hildebrand model [20,21,44,45] for the excess molar Gibbs energy $G_{\text{m}}^{\text{E}} = G_{\text{m}}^{\text{E}}(\text{l}, T, P, X)$ of a multicomponent mixture into which the only intermolecular interactions existing are instantaneous dipole-induced dipole forces is as follows: