



Excess specific volume of water + *tert*-butyl alcohol solvent mixtures: Experimental data, modeling and derived excess partial specific thermodynamic quantities



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ABSTRACT

The aim of this work is to develop a model for the dependence of the excess specific volume of the water + *tert*-butyl alcohol system on both composition and temperature under the temperature and pressure conditions relevant to the manufacturing and processing of poorly water-soluble drug formulations intended to be freeze-dried. For this purpose, experimental excess volumes of binary solvent mixtures were obtained from density measurements performed with a vibrating-tube density meter and carried out at atmospheric pressure for thirty-nine compositions covering the whole composition range and at five temperatures over the range from 293.15 to 313.15 K. For every temperature investigated, experimental excess volume data were fitted by a Redlich-Kister-based equation. By considering the temperature dependence of the regression coefficient estimates thus determined, the complete model equation was obtained and further validated by testing its correlative and predictive capabilities against data from this work and those from literature, respectively. Then, it was used to derive expressions for the excess partial thermodynamic quantities and their variations with respect to composition and temperature were discussed in terms of molecular interactions and structural arrangements in solution.

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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 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]. Since the first step in the manufacturing process of most lyophilized pharmaceutical compositions consists 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 [2–4,14]. To further increase the concentration of such drugs, the solubilization step is preferably carried out with slight heating [15,16], provided that the drug dissolution in the excipient-free and/or -containing binary solvent mixture of defined composition is an endothermic process, and that the stability of the individual solute components in the resulting solution at the selected temperature is ensured until completion of pre-lyophilization unit operations.

These multicomponent liquid mixtures, comprising at least water, *tert*-butyl alcohol and a hydrophobic drug, but more generally also including one or more hydrophilic and/or amphiphilic excipients [15–20], are expected to exhibit strong deviations from ideal mixing behavior. Indeed, in addition to the difference in size

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and shape of individual mixture components, a wide range of specific intermolecular interactions is very likely to occur in such solutions since, on the one hand, both solvent components are associated liquids, and on the other hand, most drug and excipient molecules present single or multiple hydrogen bond acceptor and/or donor functional groups in their structures. Although precise knowledge of excess thermodynamic properties of these multicomponent liquid mixtures is essential for both theoretical and practical considerations, they are unlikely to be found in the literature, let alone under temperature conditions of interest, owing to the large number of possible qualitative and quantitative mixture compositions. Experimental determination of excess thermodynamic properties of liquid mixtures becoming increasingly more difficult, time-consuming and cost-intensive with each additional component, the development of model equations enabling to reliably estimate them has always been an overarching goal of research in solution thermodynamics [21–24] and a countless number of empirical and semi-empirical expressions have been proposed and evaluated in the past with this aim [25–39]. Above and beyond their capabilities and limitations, one common feature of these mathematical models is that they are all built-up in such a way that the excess thermodynamic properties of a multicomponent liquid mixture of defined composition can be predicted only from knowledge of those of every possible contributing binary subsystem, commonly parameterized using the Redlich-Kister formalism [27]. Therefore, generating highly accurate excess thermodynamic data for the water + *tert*-butyl alcohol binary system and providing a suitable analytical representation of their dependencies on both mixture composition and temperature are essential steps toward predicting excess thermodynamic properties of drug formulations intended to be freeze-dried from this cosolvent system.

Among thermodynamic properties of liquid mixtures, volumetric and related derived quantities as well as the extent of their deviations from ideal mixing behavior are of special importance from both fundamental and applied viewpoints [40]. Indeed, knowledge of volumetric properties is not only indispensable for properly converting volume-based quantities into mass- or amount-of-substance-based quantities and performing all material balance calculations required for designing, operating, controlling and scaling-up technological processes, but also provides insights into the nature of intermolecular interactions taking place in the mixed systems. Although a great number of volumetric data at atmospheric pressure for the water + *tert*-butyl alcohol binary mixture have been reported by numerous investigators over the last sixty years [41–55], it was necessary for us to perform complementary experiments in the temperature range relevant to the industrial manufacturing of pharmaceutical composition freeze-dried from this cosolvent system, which is the field in which we are focus in this work. As a matter of fact, as pointed out by Egorov and Makarov [54], most of these experimental data were obtained either at a single temperature, or over limited composition and/or temperature ranges, or over the whole composition and/or wide temperature ranges but with large intervals, and even in some instances, they were only graphically displayed. To remedy these shortcomings, these authors carried out density measurements at atmospheric pressure on up to thirty-six water + *tert*-butyl alcohol binary mixture compositions per temperature, ranging from 274.15 to 348.15 K [54], and also performed isothermal compressibility measurements over the temperature range from 278.15 to 323.15 K and pressures up to 100 MPa [56,57]. However, despite the substantial amount of experimental data provided in these studies, those covering the whole composition range under atmospheric pressure conditions are available only for four temperatures, of which solely one is inside the range from 293.15 to 313.15 K in which we are interested in, whereas the remaining three are

substantially higher than the said upper temperature range limit. Furthermore, although from these data modeling of the isothermal dependence of the excess volume of the water + *tert*-butyl alcohol system on composition was performed, that of its dependence on both temperature and composition was not considered, so that no extrapolation beyond the temperature range covered can be made. Nevertheless, even if this were practicable, it would be unwise unless the reliability in as such extrapolated excess volume values were assessed, which in turn would require availability of sufficient experimental data covering the whole composition and relevant temperature ranges to ensure a fair evaluation.

The aim of this study is to provide a single equation allowing for the simultaneous modeling of both the composition and temperature dependence of the excess volume of the water + *tert*-butyl alcohol system under the temperature and pressure conditions relevant to the manufacturing and processing of poorly water-soluble drug formulations intended to be freeze-dried. For this purpose, experimental excess volumes of binary solvent mixtures were obtained from density measurements performed with a vibrating-tube density meter and carried out at atmospheric pressure on thirty-nine compositions covering the whole composition range and at five temperatures over the range from 293.15 to 313.15 K. The model equation was developed by considering, first, the composition dependence of excess volume of the liquid mixture on composition under isothermal conditions, and second, the temperature dependence of the model parameter estimates, and was further validated by testing its correlative and predictive capabilities against data from this work and those from literature, respectively. Finally, the changes in derived excess partial thermodynamic quantities with respect to the composition and temperature were computed and discussed in terms of molecular interactions in the light of findings from structural and dynamical studies published to date. Before proceeding further, one should specify that throughout this work, specific units were preferred over molar units to express thermodynamic quantities because, in addition to be more convenient for practical purposes in the field, they allow to detect [50,58] and model [54] more subtly extrema in the composition dependence of excess partial thermodynamic quantities. Although less conventional, this does not represent any particular issue since conversion of data provided in this work from mass units to molar ones is straightforward.

2. Material and methods

2.1. Chemicals

Ultra-pure water, otherwise known as type 1 water, ([CAS 7732-18-5], 18.2 M Ω -cm resistivity at 298.15 K, total organic carbon < 10 ppb, sodium < 1 ppb, chlorine < 1 ppb and silica < 3 ppb, W, component 1) was produced by a Synergy water purification system (Merck Millipore, Molsheim, France) whereas *tert*-butyl alcohol (2-methylpropan-2-ol, [CAS 75-65-0], purity: 0.99 in mass fraction, TBA, component 2) was purchased from Fisher Scientific (Loughborough, United Kingdom) and used as received with no further purification. Overview of chemicals used in this study is summarized in Table 1.

2.2. Solvent mixtures preparation

Since pure TBA is in the solid state at room temperature, the original container was warmed in a water bath a few degrees above its fusion temperature until the entire content was melted and was further homogenized prior to use. Samples of 100 g of W + TBA solvent mixtures were prepared by gravimetric method using a CP225D analytical balance (Sartorius, Goettingen, Germany) with

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