Fluid Phase Equilibria 374 (2014) 1–8

Contents lists available at ScienceDirect

Fluid Phase Equilibria

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

Modelling polylactide/water/dioxane systems for TIPS scaffold fabrication

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ARTICLE INFO

Article history:
Received 14 November 2013
Received in revised form 7 April 2014
Accepted 11 April 2014
Available online 21 April 2014

Keywords:
PC-SAFT
Induced association
Liquid–liquid-equilibria
Ternary systems
TIPS
Scaffolds

ABSTRACT

The representation of liquid–liquid equilibria (LLE) in ternary systems composed by water, 1,4-dioxane and different grades of poly(lactic acid) (PDLLA and PLLA), has been addressed through the PC-SAFT equation of state (EoS), in which the scheme of induced association is used to represent the interaction between solvent (dioxane) and non-solvent (water). The model parameters devoted to the description of pure component properties, as well as those pertinent to the representation of thermodynamic behaviour of solvent/non-solvent mixtures, were tuned on the basis of specific pressure–volume–temperature (PVT) data for the corresponding systems. Only the binary parameters for polymer–solvent and polymer/non-solvent pairs were adjusted to obtain a useful representation of experimental LLE data for the ternary systems. A suitable description of the thermodynamic properties of ternary mixtures was obtained using temperature-independent binary interaction parameters in the range 25–80 °C, and the consistency of the approach in the entire composition range was verified against experimental solubility data specifically measured for the polymer/non-solvent pair. The model shows good ability in the description of the thermodynamic properties of the system and it represents a reliable tool for the prediction of LLE also at conditions different from those considered for its set-up. This approach thus represents a useful designing tool for processes, such as thermally induced phase separation (TIPS), used in the preparation of microporous polymeric scaffolds.

1. Introduction

Poly(L-lactic acid) (PLLA) and poly(D,L-lactic acid) (PDLLA) are biocompatible and biodegradable polymers that can be used for the fabrication of porous scaffolds suitable for tissue engineering applications. Phase separation methods seem to be adequate for producing porous structures with pore size distribution compatible with tissue growth [1–5], and it is believed that the pore size distribution and pores topology can be tailored by adjusting the thermodynamic and kinetic parameters of the process. Thermally induced phase separation (TIPS) processing of polylactides (PLA) can be exploited by controlled cooling of solution of PLA in 1,4-dioxane, that is a good solvent of the polymer, containing a given amount of water, that acts as a non-solvent. Upon cooling, the system will demix and, together with a polymer lean solution, a polymer rich phase will appear that will ultimately result in the solid phase of interest. Although in the case of optically pure PLLA it is known that crystallization plays a major role in the formation of the solid phase, knowledge of the liquid–liquid equilibria of the ternary solution is fundamental in every modelling or optimization effort of the whole TIPS fabrication process. Liquid–liquid equilibria (LLE) of ternary systems comprising a macromolecular component is a challenging task for every thermodynamic model. Moreover, the presence of water and its peculiar role as non-solvent that promotes phase separation upon cooling, calls for the use of a model that can endow the underlying physics of hydrogen bonding.

The phase behaviour of binary mixtures formed by 1,4-dioxane and water cannot be modelled efficiently by the most commonly used activity coefficient models, as shown by Mannella et al. [6]. Moreover, it seems that even the equations of state (EoS) based on statistical mechanics theory, like the Sanchez Lacombe EoS [7], are deeply challenged by the problem of the representation of thermodynamic properties of this mixture. The perturbed chain-statistical associating fluid theory (PC-SAFT) is a model based on a well-defined picture of the intermolecular interactions that has been shown to be able to predict pure substances properties and phase equilibria of water, polar substances, macromolecular species and components of biological interest [8–14]. In the present work,

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http://dx.doi.org/10.1016/j.fluid.2014.04.007
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we discuss the representation of thermodynamic properties of ternary systems poly(lactic acid)/dioxane/water by means of PC-SAFT, using pure component and binary data to tune the model parameters.

In the next section a brief description of PC-SAFT will be given, to the aim of introducing the specific parameters entering the corresponding expression of free energy of fluid mixtures used in this work. A specific analysis of pure component volumetric data will then be performed, in order to retrieve the corresponding pure component parameters for the case of poly(L-lactic acid) (PLLA), poly(D,L-lactic acid) (PDLLA) and 1,4-dioxane. Then, binary vapour–liquid equilibrium (VLE) data for the water/1,4-dioxane mixtures will be considered to determine the corresponding binary model parameters, which account for the non-associating interactions between unlike molecules in the mixtures. The corresponding binary parameters for polymer/solvent and polymer/non-solvent pairs will then be used as adjustable parameters to describe LLE conditions in ternary systems. A comparison between model predictions and experimental binary data for water solubility in poly(lactic acid), specifically measured in this work, will finally be performed to verify the internal consistency of the model. From the comparison with several sets of experimental data available in the literature [4,15–21] it will be shown that the PC-SAFT describes very well the thermodynamic properties of this very complex system, correctly depicting the underlying physics.

2. The PC-SAFT equation of state

2.1. The molecular picture and the perturbation approach

In PC-SAFT, the reference fluid is an ensemble of molecules formed by chains of tangent hard spheres, where repulsive interactions take place between segments of different molecules. The attractive, dispersive and association interactions between the chains are expressed as perturbations from this reference fluid. Thus, the residual Helmholtz free energy of a fluid is computed by summation of the perturbation terms to the hard-spheres-chain term, as is shown in Eq. (1)

$$\tilde{A}^{\text{res}} = \tilde{A}^{\text{hc}} + \tilde{A}^{\text{disp}} + \tilde{A}^{\text{assoc}} \tag{1}$$

where superscripts hc, disp and assoc, respectively, label the “hard spheres chain”, “dispersion” and “association” contributions.

2.2. Modelling non associating systems

For the case of mixtures of non-associating components only hard spheres chain and dispersion terms contribute to the expression of residual Helmholtz free energy density. Together with molar mass M_i, the specific model parameters for single component i involved in corresponding function of temperature and species mass density are: number of segments per unit mass m_i', segment diameter σ_i and the energy parameter for segment–segment interaction ε_i.

The dispersion contribution to Helmholtz free energy for mixtures is calculated according to the so-called one fluid theory, for which the binary parameters for characteristic length and energy in interaction potential between segments of unlike species i and j are estimated from corresponding value for pertinent pure components, after a suitable set of mixing rules. In all calculations performed in this work, mixing rules depicted in Eq. (2) were used:

$$\sigma_{ij} = 0.5\left(\sigma_i + \sigma_j\right) \tag{2a}$$

$$\varepsilon_{ij} = \sqrt{\varepsilon_i \varepsilon_j}\left(1 - k_{ij}\right) \tag{2b}$$

In application of PC-SAFT model, the interaction parameter k_{ij} in Eq. (4) is, in fact, used as an adjustable binary parameter that introduces a correction to the default geometric-mean rule for the pair potential energy.

2.3. Modelling associating systems

In PC-SAFT, association phenomena are addressed assuming that molecules of an associating component i may contain one or more association sites ($A_i, B_i, \ldots$) giving rise to short-range specific attractive interactions, that can be idealized by a square-well potential acting to the off-centre association sites. It is also assumed the temporary bonding can take place only when the sites get closer than a characteristic width. In the simplest association scheme for single self-associating component systems, two different site types (A and B) are present, which can form one (AB) association pair. Correspondingly, the PC-SAFT description of the self-association requires two specific parameters, namely the depth of association square potential ε^{AB} and the association volume factor κ^{AB} pertinent to the characteristic width.

In the case of mixtures of self-associating components, cross association phenomena must also be taken into account resulting from interaction of A-type and B-type sites belonging to different species. To describe Helmholtz free energy contribution from this, a set of mixing rules is adopted for the representation of cross association energy and volume, accounting for pertinent self-association parameter. Expressions in Eq. (3), in which subscripts i and j refer to ith and jth component in the mixture, are simple examples of relations proposed to this aim [10], which involve pure species association factors, without using any correction parameters.

$$\varepsilon^{\text{A}_i\text{B}_j} = \frac{\left(\varepsilon^{\text{A}_i\text{B}_i} + \varepsilon^{\text{A}_j\text{B}_j}\right)}{2} \tag{3a}$$

$$\kappa^{\text{A}_i\text{B}_j} = \sqrt{\kappa^{\text{A}_i\text{B}_i}\kappa^{\text{A}_j\text{B}_j}} \times \left(\frac{\sqrt{\sigma_{ii}\sigma_{jj}}}{1/2\left(\sigma_{ii} + \sigma_{jj}\right)}\right)^3 \tag{3b}$$

2.4. Induced association

A specific case, in PC-SAFT, refers to the model description of those polar components that do not self-associate, but whose sites can act as proton donor or proton acceptor when mixed with associating components. The phenomenon is here referred to as “induced association”. In the simplest scheme of this kind, type A and type B sites are present in the molecule of the polar component, but their reciprocal specific interaction does not contribute significantly to energy and entropy of the system in pure component conditions. On the other hand, the same sites participate to meaningful cross association phenomena when the same component is mixed to self-associating species. For the evaluation of characteristic energy and volume factor in cross-association interaction in the latter kind of mixtures, Kleiner and Sadowski [11] proposed the following set of mixing rules:

$$\varepsilon^{\text{A}_i\text{B}_j} = \frac{\varepsilon^{\text{A}_i\text{B}_i}}{2} \tag{4a}$$

$$\varepsilon^{\text{A}_i\text{B}_j} = \varepsilon^{\text{A}_i\text{B}_i}\left(\frac{\sqrt{\sigma_{ii}\sigma_{jj}}}{1/2\left(\sigma_{ii} + \sigma_{jj}\right)}\right)^3 \tag{4b}$$

in which indexes i and j label the self-associating and the polar non-self-associating components in the mixture, respectively. The above relations correspond, in fact, to conditions represented by Eq. (3) in the case $\varepsilon^{\text{A}_j\text{B}_j}$ is set to 0 and $\kappa^{\text{A}_j\text{B}_j}$ is set equal to the corresponding value for the associating component ($\kappa^{\text{A}_j\text{B}_j} = \kappa^{\text{A}_i\text{B}_i}$). Mixing rules in Eq. (4) were used in calculations performed in this work to describe induced association phenomena and it is worthwhile to notice here that they do not include any adjustable