J. of Supercritical Fluids 109 (2016) 166–176

Contents lists available at ScienceDirect

The Journal of Supercritical Fluids

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

Solvation free energy and solubility of acetaminophen and ibuprofen in supercritical carbon dioxide: Impact of the solvent model

Javad Noroozi[a,*], Cyrus Ghotbi[a], Jaber Jahanbin Sardroodi[b], Javad Karimi-Sabet[c], Marc A. Robert[d]

[a] Department of Chemical and Petroleum Engineering, Sharif University of Technology, Tehran, Iran
[b] Molecular Simulation Lab, Azarbaijan Shahid Madani University, Tabriz, Iran
[c] Jaber Ebne Hayyan National Research Laboratory, NSTRI, Tehran, Iran
[d] Department of Chemical and Biomolecular Engineering, Rice University, United States

ARTICLE INFO

Article history:
Received 11 August 2015
Received in revised form 9 November 2015
Accepted 10 November 2015
Available online 23 November 2015

Keywords:
Supercritical carbon dioxide
Solubility
Molecular dynamics simulations
Solvation free energy
Quadrupole moment

ABSTRACT

Classical molecular dynamics simulations are used to compute the solvation free energy of two pharmaceutical solids, namely ibuprofen and acetaminophen in carbon dioxide (CO_2), over the density range of interest in supercritical processes. In order to examine the influence of the solvent model on the resulting free energies, three popular CO_2 models (Zhang, EPM2, and TraPPE) are studied. Relatively large discrepancies for the solvation free energy exist between these CO_2 models, suggesting that the former is sensitive to the different balances between dispersive and electrostatic forces used in these models. In particular, for the solvation of the highly polar (dipole moment of ~5.2 Debye) acetaminophen molecule, such discrepancies are more pronounced than for the moderately polar ibuprofen (dipole moment of ~1.6 D) molecule. Since there is an exponential relationship between the solvation free energy and solubility, the choice of the solvent model substantially affects the predicted solubility. For the solubility of the studied solutes, the value obtained using the TraPPE model is the highest, that of the EPM2 model is intermediate, and that of the Zhang model is the lowest. Generally, the simulations results show that the model with the largest quadrupole moment leads to a more negative solvation free energy and a higher solubility over the entire density range. Further, the decomposition of the solvation free energy into contributions stemming from electrostatics and dispersion interactions shows that the electrostatic interactions are important for a quantitative prediction of solid solubility, while the Lennard–Jones parameters of the solute and solvent are more important for qualitative agreement. Additionally, the infinite-dilution partial molar volume of the two solutes is estimated from the pressure derivative of the solvation free energies. With density increasing beyond the value corresponding to the zero partial molar volume of the solute (minimum solvation free energy), the repulsive part of Lennard–Jones potential wins over the attractive interactions, and the solvent strength of supercritical CO_2 decreases; however, due to the increase in the chemical potential of the pure solid (effect of the Poynting correction), the solubility further increases. Overall, these results demonstrate the importance of a proper choice of quadrupole moment of the solvent model, which is crucial for quantitative predictions of the solid solubility in supercritical CO_2.

1. Introduction

Supercritical fluids (SCFs) are an important class of solvents in many separation and purification processes, including in the pharmaceutical industries [1–4]. In this context, CO_2 is the preferred supercritical solvent because of its mild critical condition and environmental benefits. In contrast to conventional aqueous and organic solvents, the solvation power of SCFs can be easily tuned with slight change in density. Many supercritical micronization and extraction processes exploit this feature. For processing of bioactive compounds, knowledge of the phase behavior is crucial for optimizing particle diameters and morphology, and proper design and operation of these processes are often hampered by the difficulty in predicting phase equilibria [5,6].

Different approaches have been used to predict the solubility of solids in SCFs, among which are the widely used semiempirical models and conventional cubic equations of state (EoS) [7–10].

* Corresponding author.
E-mail addresses: jnoroozi@che.sharif.ir, noroozi.javad@ymail.com (J. Noroozi).

http://dx.doi.org/10.1016/j.supflu.2015.11.009
0896-8446/

These approaches require extensive experimental solubility data to determine the necessary model parameters, and the number of fitting parameters increases with addition of cosolvent or cosolute to the system. Moreover, supercritical solutions are often highly asymmetric in that there are large differences in the molecular size and interaction energy parameters of the components, which makes solubility predictions with common EoS very sensitive to the employed combining (mixing) rules [11]. The empirical models often are unable to provide a molecular-scale explanation for observed solubility trends, and the presence of empirical parameters or mixing rules limits their transferability to different conditions. Other approaches such as activity coefficient models and regular solution theory (based on the concept of solubility parameter) need to be coupled to an EoS to make high-pressure phase equilibrium predictions [12–14]. Advanced EoS based on the statistical associating fluid theory (SAFT) and nonrandom hydrogen-bonding (NRHB) theory, or on more theoretically based models such as the conductor-like screening model (COSMO), are rarely used [15–22].

Because the necessary parameters of these EoS are unavailable for many molecules of pharmaceutical interest, molecular simulations are a potential tool for predicting solid solubility solely from the knowledge of intermolecular forces. Although molecular simulations have been used extensively to investigate the phase equilibria, thermophysical, and transport properties of pure CO_2 and its mixtures, surprisingly there appears to be no study to directly simulate solid-SCFs phase equilibria [23–28].

This is mainly due to challenges associated with solid phase simulations, the unavailability of the crystalline structure of most solids and the deficiency of conventional force fields (usually parametrized to reproduce solution phase properties) to predict solid-phase properties [29–32]. As a notable exception, Albo and Müller tried to directly model the diffusion of naphthalene into supercritical CO_2 using a single-site potential model, which includes a quadrupole description [33]. The authors found that the adapted model for naphthalene was unsuccessful (despite excellent performance in the supercritical phase). This may be partly resolved with using a different force field for the solid phase than the one used for the solute in the supercritical solution.

To circumvent the challenges associated with crystal simulations, the solid fugacity $f^s(T,p)$ may be obtained from the knowledge of its pure hypothetical liquid state fugacity $f^0(T,p)$, enthalpy of fusion $\Delta H^{fus}(T_m,p)$ and melting point T_m of the solute [34]:

$$\ln\frac{f^s(T,p)}{f^0(T,p)} = \Delta H^{fus}(T_m,p)\left[\frac{1}{T_m}-\frac{1}{T}\right] \quad (1)$$

Fusion properties are easy to measure with simple differential scanning calorimetry or can be estimated from a suitable group contribution model [35]. The hypothetical liquid fugacity may be obtained from self-solvation free energy calculations in the subcooled liquid. This procedure was recently used by Ahmed and Sandler to estimate the subcooled liquid state vapor pressure of nitroaromatic energetic compounds [36,37]. However, most pharmaceuticals are solids at temperatures of interest to supercritical processes, so that simulation of their hypothetical subcooled liquid state requires special sampling strategies, and may yield erroneous results. Therefore, calculations should be performed at elevated temperatures, between the solute's normal boiling and melting points and then extrapolated to subcooled conditions [35].

Alternatively, as it is commonly done in the literature, the fugacity of the pure solid may be taken from experiment, and simulations can be performed only in the supercritical phase to predict the solution phase fugacity of the solute [33,38–51]. To avoid any errors may be introduced in this aspect of the solubility calculation, we use experimental values for the pure solute fugacity, and attempt to accurately predict the solution-phase fugacity from molecular dynamics simulations. Previous studies used simplified potential or group contribution site models [42–52], and a few attempts have been made to use more realistic force fields [38–41]. As a notable study, Su and Maroncelli used the test-particle insertion method to investigate the solvation free energy of typical solutes in CO_2 and other supercritical fluids [38]. Ignoring the pressure effects on the chemical potential of the solid (at 10 MPa, this could introduce around 0.3 kcal error in the evaluated solvation free energy of naphthalene), they found an accuracy level of 0.5 kcal/mol for all-atom potentials based on ab initio calculations and the OPLS-AA parameter set.

Anderson and Siepmann used the TraPPE force field with Monte Carlo (MC) simulations in the osmotic ensemble to investigate the solubility of hexamethylbenzene and benzoic acid in pure and modified SC-CO_2 [39]. They found that the Poynting correction is the most important factor leading to an increase in solubility at high density, where the solvation free energy is little effected by density. Their MC simulations provided a 20–40% accuracy in the prediction of solubilities in pure CO_2. More recently, Frolov and Kiselev have carried out extensive calculations of solvation free energies of monofunctional simple organic molecules in pure and cosolvent modified CO_2 to establish a relationship between solvation free energy and strength of solute–solvent interactions [40,41]. They found that the cosolvent effect, as expressed by Cosolvent Induced Solubility Enhancement (CISE), strongly depends on the number of hydrogen bonds formed between solute and solvent. In cases polar cosolvents do not form hydrogen bonds with solutes, the CISE correlates with the dipole moment of the solute. Accurate predict of solvation free energy has been a central concern in all previous simulations.

The knowledge of the equilibrium fugacity would be particularly useful for estimation of sublimation pressures of pharmaceutical compounds which require specialized techniques to be measured experimentally. Combining the solvation free energy of the solute with experimental solubility data, one may estimate the sublimation pressure of the solute [53]. Experimental solubility data of SCFs-solid have significantly increased in the last decade, and thus with the development of theoretical methods to predict the solid fugacity in the supercritical phase, one may exploit a large body of solubility data to estimate sublimation properties of solids. In this context, molecular simulation is the best-suited tool, and solvation properties of complex molecular solids can now be determined very precisely using atomistic free energy calculations in solution.

The accuracy, however, depends on a number of force field parameters and sampling strategies. The present study aims at comparing three CO_2 force fields to evaluate the sensitivity of the predictions to the adopted solvent model. Based on this study, insight is gained into how to select potential parameters to yield accurate estimate of the equilibrium fugacity of solids in supercritical CO_2.

2. Methodology

The residual chemical potential of a solute is conventionally defined as the difference between its chemical potential in the mixture and that of an ideal gas mixture at the same temperature, pressure, and composition.

For a system of N molecules composed of N_1 solvent molecules (component 1) and N_2 solute molecules (component 2), a slightly unconventional definition of the residual chemical potential of the solute μ_2^{res} is (see Ref. [38]),

$$\beta\mu_2^{res}(T,p,N_1,N_2) = \beta\mu_2(T,p,N_1,N_2) - \beta\mu_2^{ig}(T,v'(N_1,N_2-1)) \quad (2)$$