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Modeling of drug solubility in supercritical carbon dioxide using equation of state based on hole theory with molecular surface charge density

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A B S T R A C T

Equation of state based on hole theory with molecular surface charge density was developed for the modeling of drug solubility in supercritical carbon dioxide. In the hole theory, the density change of supercritical carbon dioxide can be represented by the number of holes in the system. The molecular interaction energy parameter was estimated using the interactions of segments on the molecular surface given by a quantum calculation using conductor-like screening model. The only one parameter, coordination number around a molecule was fitted to the experimental data of the drug solubility in supercritical carbon dioxide. The solubilities of the eighteen drugs in supercritical carbon dioxide were modeled by the equation of state with the molecular surface charge density. The effect of the molecular pair for the coordination number on the correlated results was investigated. It is found that the results using the fitted parameter of the solute–solute pair coordination number result in the modeling performance better than those of carbon dioxide–solute coordination number. The results of the modeling of drug solubility in supercritical carbon dioxide are compared with the experimental data. The average absolute relative deviation between the experimental and calculated results of the solubility for the drug composed of C, H and O atoms acetylsalicylic acid, benzoic acid, ferulic acid, (*S*)-naproxen, *p*-benzoquinone, propyl gallate, salicylic acid and vanillic acid is 0.38 smaller than those for compounds including N, F, I and S atoms, amical-48, benzocaine, caffeine, carbamazepine, (±)-flurbiprofen, methimazole, phenazopyridine, theobromine, theophylline and uracil, 0.59.

Keywords: Hole theory; Supercritical carbon dioxide; Drug solubility; Coordination number; Molecular surface charge; Equation of state

1. Introduction

Supercritical fluid is expected to be a useful solvent in various processes, such as separation, reaction, extraction and crystallization. Carbon dioxide has been commonly used as supercritical fluid due to the unique properties, such as the low critical temperature and pressure (T_c = 304.1 K, P_c = 7.38 MPa), nonflammable and non-toxic to human body. Many research groups have reported the material processes for the drug particle formation using supercritical carbon dioxide (Phillips and Stella, 1993; Reverchon, 1999; Charoenchaitrakool et al., 2000; Türk et al., 2002a,b; Huang et al., 2005; Chiou et al., 2007; Chow et al., 2007; Bolten and Türk, 2012; Samei et al., 2012; Hiendrawan et al., 2014; Chen et al., 2010; Ahern et al., 2013; de Matos et al., 2013). Rapid expansion of supercritical solution (RESS) method is the one of the crystallization technique for preparation of the nano-sized drug particle using supercritical fluid (Phillips and Stella, 1993; Charoenchaitrakool et al., 2000; Türk et al., 2002a,b; Huang et al., 2005; Chiou et al., 2007; Bolten and Türk, 2012; Samei et al., 2012; Hiendrawan et al., 2014; Chen et al., 2010). The micronization of carbamazepine by RESS method was investigated by Bolten and

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Türk (2012). It was reported that the particle size of carbamazepine processed in RESS was reduced up to 60 times smaller than that unprocessed. Samei et al. (2012) studied the RESS processing for the nanoparticle formation of megestrol acetate that is a poorly water-soluble steroid drug. The particle size of megestrol prepared in the RESS process was changed from 7 μm to 120 nm. Hiendrawan et al. (2014) have reported the RESS process for the micronization of fenofibrate that is used for the reduction of cholesterol levels. The supersaturation in RESS process affects largely the particle size and particle size distribution (Sanli et al., 2012). Knowledge of drug solubility in supercritical carbon dioxide can be useful and important for the nano-sized particle design and the optimization of operation condition in RESS process.

Experimental data of drug solubility in supercritical carbon dioxide are reported systematically in various temperatures and pressures as given in the literatures (Chen et al., 2010; Škerget et al., 2011; Hosseini et al., 2010; Shojaee et al., 2013; Rajaei et al., 2013). The theoretical modeling can be also a useful tool to understand the drug solubility in supercritical carbon dioxide as reported by some research groups (Hosseini et al., 2010; Shojaee et al., 2013; Rajaei et al., 2013; Tabernero et al., 2013; Tsivintzelis et al., 2009; Hezave et al., 2013). Hosseini et al. (2010) investigated the correlation of the solubility of clozapine and lamotrigine in supercritical carbon dioxide using the three types of the density-based models (Kumar, 1988; Chrastill, 1982; Bartle et al., 1991). In these correlations, the three parameters in these models were fitted to the experimental data for the solubility calculations. The solubility of piroxicam in supercritical carbon dioxide is correlated by a model in which the solubility is a function of temperature, pressure and carbon dioxide density (Shojaee et al., 2013). Tabernero et al. (2013) have investigated the correlations of the drug solubility in supercritical carbon dioxide using enhancement factor and a group contribution method. The experimental 2300 data of the drug solubility in supercritical carbon dioxide were correlated. It is reported that the deviations between experimental and correlated results are about 5% in the average absolute relative deviation. Non-random hydrogen-bonding (NRHB) theory was applied for the modeling of the phase behavior for the mixture of carbon dioxide and drug (Tsivintzelis et al., 2009). The equation of state based on NRHB theory was adopted for the solubility correlation of the drugs in supercritical carbon dioxide. The parameters of the hydrogen bonding were introduced into the equation of state. The solubility of the six drugs in supercritical carbon dioxide were correlated by this equation of state with the one temperature independent binary parameter fitted to the experimental data. The reduction of the fitting parameters in the correlation model of the solubility in supercritical carbon dioxide allow to extend the application of the model to the system that few experimental data are available. The activity coefficient models based on conductor-like screening model (COSMO) (Klamt and Schüürmann, 1993) were developed by Klamt (1995) and Lin and Sandler (2002). These activity coefficient models have the advantage that no data fitting was required for the phase equilibrium calculation. Shimoyama and Iwai (2009) have extended the COSMO-based activity coefficient model, COSMO-vac, the application to the supercritical fluid mixture by using the vacancy model in which the density change of the supercritical fluid can be represented by the number of the vacancy. The solubilities of 16 drugs in supercritical carbon dioxide were predicted by COSMO-vac method without the data fitting.

In this work, the solubility of drug in supercritical carbon dioxide were correlated by using an equation of state based on hole theory (Ishizuka et al., 1980). The molecular interaction parameter was estimated from the molecular surface charge density by COSMO calculation (Klamt and Schüürmann, 1993). The molecular surface area and volume from the COSMO calculation were also used for the estimation of the other parameters, the solid molar volume and external degree of freedom of the molecule in the equation of state. The correlation of the solubility in supercritical carbon dioxide in this work were conducted using the only one fitting parameter of the coordination number for solute–solute or carbon dioxide–solute pair. The effect of the fitted coordination number on the solubility correlation was investigated.

2. Fundamental of solubility of solid solute in supercritical carbon dioxide

Solubility of solid solute in supercritical carbon dioxide can be calculated by a relationship of solid–gas equilibria given as follows:

$$f_2^S = f_2^G \tag{1}$$

where f_2 denotes the fugacity of drug compound. The superscripts S and G are solid and gas phases, respectively. The fugacity in solid phase of drug compound including the pressure effect is obtained from the following equation (Uchida and Kmijo, 2010):

$$f_2^S = f_2^{SCL} \exp\left[\frac{\left(v_2^S - v_2^{SCL}\right)(p - p_{tp})}{RT} + \frac{\Delta h_2^{fus}}{RT_{tp}}\left(1 - \frac{T_{tp}}{T}\right)\right] \tag{2}$$

p and T are the pressure and temperature. The superscript SCL means the sub-cooled liquid phase. $\Delta h_2{}^{fus}$ is the heat of fusion of the drug compound. $v_2{}^S$ and $v_2{}^{SCL}$ are the molar volume of drug compound in solid and sub-cooled liquid phases, respectively. The subscript tp presents the triple point of the drug compound. In this work, the pressure and temperature at the triple point of the drug compound are assumed to be the atmospheric pressure and the melting temperature. The solid molar volume of the drug compound $v_2{}^S$ was the estimated from the molecular volume by COSMO calculation (Klamt and Schüürmann, 1993). The fugacity and molar volume of the drug compound $f_2{}^{SCL}$ and $v_2{}^{SCL}$ in the sub-cooled phase and the fugacity in the gas phase $f_2{}^G$ were calculated by the equation of state based on the hole theory (Ishizuka et al., 1980) described as follows. The heat of fusion $\Delta h_2{}^{fus}$ and melting temperature $T_2{}^{fus}$ of the drug compound interested in this work are cited from the literature (Su and Chen, 2007; Škerget et al., 2002). The values are listed in Table 1.

3. Modeling

3.1. Equation of state

In the hole theory (Ishizuka et al., 1980), the equation of state can be obtained by the following equation: