Thermochimica Acta 549 (2012) 95–101

Contents lists available at SciVerse ScienceDirect

Thermochimica Acta

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

Solubility of capecitabine and docetaxel in supercritical carbon dioxide: Data and the best correlation

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ARTICLE INFO

Article history:
Received 13 March 2012
Received in revised form 4 September 2012
Accepted 7 September 2012
Available online 17 September 2012

Keywords:
Supercritical carbon dioxide
Solubility
Semiempirical
Capecitabine
Docetaxel
5-Fluorouracil

ABSTRACT

The solubility values of some chemotherapeutic agents such as capecitabine (CPT), docetaxel (DTX), and 5-fluorouracil (5-FU) were evaluated in supercritical carbon dioxide ($SC-CO_2$) at pressures in the range of 15.2–35.4 MPa and temperatures ranging from 308 to 348 K, using a simple static method. The solubility values observed ranged from $y = 0.37 \times 10^{-4}$ to 7.02×10^{-4} for DTX and $y = 0.32 \times 10^{-5}$ to 15.88×10^{-5} for CPT. The mole fraction solubility of 5-FU was less than 10^{-6} and was not detectable by the proposed solubility determination method. The solubility values measured for pure drugs were correlated using semiempirical density-based models (Chrastil's, VA, Yu's, Gordillo's, Jouyban's, Bartle's, MST, KJ, and Tan's models). The results showed that these models, with an overall average absolute relative deviation (AARD%) lower than 21%, could be applied for satisfactory solubility prediction at different pressures and temperatures. Among different models, the Tan's equation is more suitable to describe the solubility of CPT and DTX in $SC-CO_2$.

1. Introduction

Capecitabine (CPT) and docetaxel (DTX) are both chemotherapeutic drugs that may be used together for extra effect. Capecitabine is a drug designed to be converted within cancer cells to an anticancer drug that has been used for some time (this drug is called 5-fluorouracil or 5-FU). It was designed to achieve the same effects as 5-FU with fewer side effects. DTX is made from an extract of the European yew tree [1].

Supercritical fluids (SCFs) possess the advantages of both the gas and the liquid, such as great solubility, favorable mass transfer capacity, and satisfactory permeability. It is known that a subtle change in temperature or pressure could cause marked variation in solubility nearby the critical point. Carbon dioxide is the most frequently used supercritical fluid.

Although applications of SCFs in pharmaceutical industries are numerous, there is a lack of sufficient data for scaling-up, especially for particle formation processes. The solubility and phase behavior are critical parameters that contribute to yield and product quality.

Solubility data in supercritical fluids are the most important information and first step for the design of pharmaceutical processes, such as particle size reduction of drugs, preparation of drug-loaded microspheres and microemulsions and development of drug delivery systems. A soluble substance in the supercritical carbon dioxide ($SC-CO_2$) can be easily processed by SCF solvent. Moreover, the drugs that are non-soluble in $SC-CO_2$ can be processed by antisolvent techniques. By definition, the mole fraction solubility of soluble compounds in $SC-CO_2$ must be above 10^{-5} and for non-soluble compounds; it is less than 10^{-5} [2]. The solubility behavior of a drug in SCF is an important key to obtain a suitable method for producing nano or microparticles of drugs in a reasonable time by consumption less supercritical fluid [3–6]. According to the solubility of the drug in SCF, the particle design techniques could be classified into two categories: rapid expansion of supercritical solution (RESS) and the supercritical antisolvent process (SAS) [3].

On the other hand, creating equilibrium SCF phase at high pressures and temperatures is very difficult and expensive. So, expansion and reform of the existing models are very useful for obtaining suitable data for solubility of different solutes in SCF under various conditions [7].

Given the importance of solubility in $SC-CO_2$, to achieve optimum operating conditions for the high cost experiments, the modeling solubility has been considered widely in the supercritical region. Semiempirical models were successfully used to correlate the experimental data [4]. In thermodynamic models, SCF is considered as a high pressure gas [8]. In the regular solution theory model, correlating the solubility value of complex

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http://dx.doi.org/10.1016/j.tca.2012.09.010

pharmaceutical compounds in SC-CO_2 was the application of solution model. In this model, the SC-CO_2 was taken as the liquid solvent, and an infinite dilution activity coefficient was employed to account for the nonideal behavior of solid–liquid equilibrium [9]. The equation of state (EOS) model requires critical parameters of the solute; thus, restricts its application. Several authors have noticed that the logarithm of solid compound solubility is approximately a linear function of the SCF density. This observation allows the prediction of the solubility values of different analytes by semiempirical models, based on density rather than pressure. These relations are very useful because the knowledge of the above-mentioned physical properties (e.g. critical temperature, critical pressure, acentric factor, and sublimation pressure) is not necessary [10–13].

In the present study, the solubilities of CPT, DTX, and 5-FU in SC-CO_2 were obtained using a very simple static method. The solubility data obtained correlated with appropriate equations. Also a comparison between the nine most used semiempirical equations was performed (Chrastil's, VA, Yu's, Gordillo's, Jouyban's, Bartle's, MST, KJ and Tan's models) and the parameters of each equation were calculated and reported.

2. Review of semiempirical models

2.1. Chrastil model

Chrastil [14] proposed an expression for dependence of the solubility on density of a pure SC-CO_2 and the absolute temperature. This model is based on the assumption that each solute molecule A is surrounded by k molecules of solvent B so as to form a complex AB_k that exists in equilibrium with the ambient medium.

According to this model (denoted as the Chrastil' model):

$$\ln\ S = k\ \ln\ \rho + \frac{\alpha}{T} + \beta \tag{1}$$

where S is the solubility (g/L); ρ is the SC-CO_2 density (g/L); k is the degree of association. The relationship between S (solubility) and y (mole fraction) are as follows [15]:

$$S = \frac{\rho M_{w\ \ \text{Solute}}}{M_{w\ \ \text{Solvent}}} \times \frac{y}{1-y} \tag{2}$$

2.2. Valle and Aguilera model

A different modification was proposed by del Valle and Aguilera [16], improving the fit obtained by Chrastil's model in prediction of the solubility of vegetable oils in SC-CO_2. They took into account the change of the enthalpy of vaporization with the temperature, considering the association number k independent of density. The del Valle and Aguilera's equation (denoted as the VA model) can be expressed as follows:

$$\ln\ S = k\ \ln\ \rho + \frac{\alpha_1}{T} + \frac{\alpha_{11}}{T^2} + \beta \tag{3}$$

The constants of linear Eqs. (1) and (3) have been obtained from experimental data.

In Chrastil's and VA models, although the SC density is a function of temperature and pressure, the pressure factor is not explicitly entered in the model. In other words, these two equations are the most suitable ones for the isobar conditions.

2.3. Yu et al. model

In this model, mole fraction can be assumed to be independent of the temperature and pressure by the following equation (denoted as the Yu's model):

$$y = C_0 + C_1P + C_2P^2 + C_3PT(1-y) + C_4T + C_5T^2 \tag{4}$$

According to Yu's model [17], the solubility shows a curvilinear behavior with pressure at a constant temperature and with temperature at a constant pressure. In addition, the solubility is affected by the interaction between pressure and temperature.

2.4. Gordillo et al. model

Gordillo et al. [18] made modification upon the previous equation to improve the fit in the solubility of Penicillin G in SC-CO_2. The following equation symbolizes the Gordillo's equation (denoted as the Gordillo' model):

$$\ln\ \ y = D_0 + D_1P + D_2P^2 + D_3PT + D_4T + D_5T^2 \tag{5}$$

Constants of the above linear equation are obtained from fitting of experimental data in it.

2.5. Jouyban et al.'s model

With reviewing the laboratory data and models presented, Jouyban et al. concluded that:

1. A linear relationship is observed between $\ln y$ and pressure in isotherm conditions.
2. There is a nonlinear relationship between the temperature and $\ln y$ in isobar conditions.
3. A linear relationship is observed between $\ln y$ and $\ln \rho$ in various temperatures and pressures.

Considering the above considerations and to achieve a high precision, the following empirical equation was presented by Jouyban et al. (denoted as the Jouyban' model):

$$\ln\ \ y = M_0 + M_1P + M_2P^2 + M_3PT + \frac{M_4T}{P} + M_5\ln\ \ \rho \tag{6}$$

In Eq. (6), M_0–M_5 are constants. Jouyban et al. [19] fitted five semiempirical equations to 106 published solubility data obtaining the minimum error with Eq. (6).

2.6. Bartle's model

Bartle et al. [20] related the enhancement factor (ratio of the actual solubility to the ideal solubility) of the solute and the density of the solvent (Eq. (7))

$$\ln\left(\frac{yP}{P_{\text{ref}}}\right) = A + C(\rho - \rho_{\text{ref}}) \tag{7}$$

$$A = a_1 + \frac{a_2}{T} \tag{8}$$

$$\ln\left(\frac{yP}{P_{\text{ref}}}\right) = a_1 + \frac{a_2}{T} + C(\rho - \rho_{\text{ref}}) \tag{9}$$

In Eq. (7) (denoted as the Bartle's model), ρ_{ref} is a reference density (a value of 700 g/L was chosen) and P_{ref} is the reference pressure, typically taken as 0.1 MPa. The values of A and C are obtained from Eq. (7) under isothermal conditions. Also, a_1 and a_2 are obtained from Eq. (8) under isobar conditions.

2.7. MST model

Mendez-Santiago et al. [21] started with Henry's constant of the dilute solution and demonstrated that the solubility plotted as $T\ln(yP)$ versus the density of the solvent would yield a single line. They later incorporated a Clausius–Clapeyron equation for the sublimation pressure and derived an empirical expression for