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Phase equilibrium and micronization for flufenamic acid with supercritical carbon dioxide

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ABSTRACT

The solubility data of flufenamic acid (FFA, a fluorinated and non-steroidal anti-inflammatory drug) in supercritical carbon dioxide were measured with a semi-flow type phase equilibrium apparatus at temperatures from 313.2 K to 333.2 K and pressures up to 21 MPa. Over the experimental conditions, the solubility values are between 0.8×10^{-6} and 2.13×10^{-4} in mole fraction. These solid–gas equilibrium data were correlated with the Chrastil model, Mendez-Santiago and Teja model, and the Peng–Robinson equation of state to average absolute relative deviations of 11.4%, 21.1%, and 7.8%, respectively. Since the solubility of FFA can be as high as 10^{-4}, rapid expansion of supercritical solution (RESS) method is favorable for preparing ultra-fine FFA particles. The experimental results of the RESS micronization show that extraction pressure, pre-expansion temperature, and dimension of capillary tube are the key factors to govern the morphology and the mean size of the resultant particles. While sticky agglomerates were obtained from lower extraction pressures with larger and/or longer capillary tube, needle-like particles were produced at higher extraction pressures with smaller and/or shorter capillary tube. Moreover, operating at lower pre-expansion temperatures and higher crystallization temperatures yielded longer and thinner needle-like crystals. Under higher extraction pressure (*e.g.*, 21 MPa), the mean size of the generated FFA particles distributed from 0.5 to 5.1 μm and from 0.1 to 1.1 μm for the lengths of major and minor axes, respectively. It is also found that the particulate FFA converts from original form I into form III after the RESS processing.

1. Introduction

Accordingly more than 40% newly developed pharmaceuticals are categorized as poorly water-soluble drugs [1]. The hydrophobic nature of these drugs has low dissolution rate and solubility in gastrointestinal fluids and may lead to limited absorption in human body and thus with low bioavailability. How to improve the dissolution rate and/or solubility of poorly water-soluble drugs is an important issue to enhance the bioavailability. Micronization is one of the feasible methods to reduce the particle size of drugs and thus increase the surface area for dissolution [2,3]. Moreover, more than 90% of pharmaceutical products, such as tablets, aerosols, capsules, suspensions, and suppositories, contain drug in particulate form. However, conventional micronization processes, such as milling, lyophilization, grinding, granulation, salting out, and spray-drying, suffer from several drawbacks including thermal and chemical degradations, large particle size, broad particle size distribution, solvent residues, etc. [4,5]. The release of heat and the presence of solvent may also induce the conversion of drug's polymorphism and thus may affect its therapeutic efficacy [6]. Therefore, it is essentially needed for the development of alternative micronization methods for producing sufficiently small and solvent-free particles with uniform size distribution and without the risk of degradation. Among several others, the rapid expansion of supercritical solution (RESS) technique is one of the novel methods to meet the requirements as mentioned above. Being capable of controlling the particle morphology and polymorphic form of drug substance by varying the RESS operating parameters are additional advantages that reported in the literatures [2,3,6].

In the RESS processes, the solid solute (*i.e.*, target material) is dissolved firstly in a supercritical fluid or supercritical fluid mixture at elevated pressures. After reducing pressure through an expansion device, ultra-fine particles may be produced from this low pressure stream due to decreasing in the solute solubility and thus inducing high supersaturation of the solute in the dense-gas medium [2-3,6,7]. The solubility data of solute compound in supercritical carbon dioxide is the most important thermophysical information for developing the RESS processing technology. High solubility of pharmaceutical compounds in supercritical fluid is required for using the RESS micronization technique to effectively

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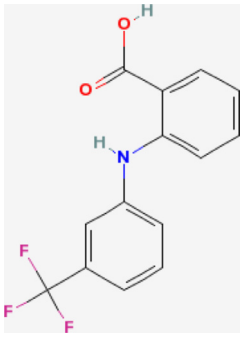
Table 1
Physical properties of FFA.

Formula	MW	T_m (K)	T_c (K)	Molecular structure	
$C_{14}H_{10}F_3NO_2$	281.23	405.15–408.15[a]	846.4[b]		
P_c (MPa)	Ω	V_2^S (cm³/mol)	P_2^S (Pa)[e]		
			$T = 313.2$ K	$T = 323.2$ K	$T = 333.2$ K
2.2[b]	0.89[c]	201.5[d]	3.16×10^{-4}	1.31×10^{-3}	4.96×10^{-3}

[a] Provided by the supplier.
[b] Estimated by the Wilson and Jasperson method [16].
[c] Estimated from the Ambrose–Walton corresponding states method [17].
[d] Taken from ChemSpider website [18].
[e] Extrapolated from the experimental saturated vapor pressures of Perlovich et al. [19].

generate sufficiently small and solvent-free particles with uniform size distribution. Moreover, the efficacy and economy of the RESS process are also dependent on the solute solubility in supercritical fluid. The drug in particulate form and with a narrow particle size distribution gains additional benefit to design drug delivery systems that are less invasive such as oral, transdermal and inhalation formulation [2,3,6]. Carbon dioxide is widely used in the supercritical micronization processes, especially for the applications in food and pharmaceutical areas, because it is non-toxic, non-flammable, plentiful, inexpensive, biocompatible, environmentally benign, and its critical temperature (T_c = 304.1 K) near ambient condition.

Flufenamic acid (FFA) is a non-steroidal anti-inflammatory drug (NSAIDs) with anti-inflammatory and analgesic-antipyretic activity. It is prescribed for the treatment of inflammatory rheumatoid arthritis (RA) and osteoarthritis (OA). However, FFA has limited solubility in water and other common organic solvents. It is known to have at least seven polymorphic forms [8,9]. Only form I (melting point T_m = 407 K) and form III (T_m = 399 K) are able to exist at room temperature and can be found from commercial products [8-12]. Thermodynamically, forms I and III are enantiotropically related, with form III being the stable form below the transition temperature of 315 K, and form I being stable above 315 K [10]. Visual observation from the appearance, form I is white powder, and form III exists as yellow powder. Infrared absorption of FFA can be used to identify the polymorphic forms I and III. The NH stretching bands of form I and form III are at 3321–3322 cm^{-1} and 3315–3316 cm^{-1}, respectively [11].

In the present study, solubility data of FFA in supercritical carbon dioxide were measured by using a semi-flow type phase equilibrium apparatus at temperatures from 313.2 K to 333.2 K and pressures up to 21 MPa. These data are still unavailable from literature. The solubility data were correlated with the Chrastil equation [13], Mendez-Santiago and Teja equation [14], and the Peng–Robinson equation of state [15]. Ultra-fine particles with narrow particle size distribution of FFA were produced by the RESS technique to enhance the bioavailability. The effects of extraction temperature and pressure, pre-expansion temperature, crystallization temperature, nozzle length and inside diameter, and spraying distance on the morphology, mean size, and particle size distribution (PSD) of the resultant particles were investigated experimentally. Furthermore, the polymorphism of the original FFA and the RESS processed samples were characterized by Fourier transform infrared spectrometer (FTIR) and differential scanning calorimeter (DSC) complementarily.

2. Materials and methods

2.1. Materials

Flufenamic acid (FFA, 97+%, CAS: [530-78-9]) was purchased from Sigma-Aldrich (USA) and its physical properties are given in Table 1 [16-19], where T_m, T_c, P_c, ω, V_2^S, P_2^S are the melting temperature, critical temperature, critical pressure, acentric factor, solid molar volume, and sublimation pressures of FFA, respectively. Carbon dioxide (99.5+%) was supplied by Liu-Hsiang Gas Co. (Taiwan). Ethanol (HPLC grade) was purchased from Fisher Scientific (UK). Potassium bromide (KBr, IR grade, 99+%) was purchased from Acros Organics (USA) for preparing FTIR samples. All the chemicals were used without further purification.

2.2. Apparatus and procedure

2.2.1. Solubility of FFA

A semi-flow type apparatus is used in the present study to extract FFA with supercritical carbon dioxide. The solid–gas equilibrium data are also measured with the same apparatus by running the extraction experiments under sufficiently long contact time. The schematic diagrams of the extraction apparatus and the experimental procedure have been given elsewhere [20]. The uncertainties of the measured variables are 0.1 mg for mass, 0.02 K for temperature, 0.1% for pressure, and 0.25% for total volume of collected carbon dioxide by wet test meter.

During the equilibrium measurements, the mass flow rate of carbon dioxide is regulated slower than 0.0014 g/s and the amount of packed FFA in the extractor is about 2 g. Under these circumstances, the flow rate was found sufficiently slow to ensure that FFA can be saturated in carbon dioxide before leaving the extractor. The attainment of equilibrium has been verified by measuring the concentrations of FFA in carbon dioxide at different lengths of contact time. At least four replicates are taken at each experimental condition. The saturated solubility is obtained by

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