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Original Research Paper

Measurement of solid solubility of warfarin in supercritical carbon dioxide and recrystallization study using supercritical antisolvent process

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ABSTRACT

The solid solubility of an anticoagulant, warfarin, in supercritical CO_2 was measured using a semiflow type apparatus at 308.2, 318.2, and 328.2 K from 10 to 18 MPa. The data were correlated using the Chrastil equation and the Méndez-Santiago and Teja equation. The average deviations for calculated and measured solubilities were approximately 10%. Warfarin was recrystallized using a supercritical crystallization process. Because of the extremely low solubility of warfarin in supercritical CO_2 (mole fraction on the order of 10^{-6}), the supercritical antisolvent (SAS) process was adopted. The effects of SAS operating parameters were compared and discussed including the operating temperature, operating pressure, solution concentration, spraying nozzle diameter, CO_2 flow rate, and solution flow rate. The experimental results proved that low operating temperatures, high solution concentrations, high CO_2 flow rates, and low solution concentrations produce small warfarin crystals, whereas the effects of operating pressure and spraying nozzle diameter are negligible. Warfarin crystals with regular habit and mean particle size of 6.6 m were successfully obtained. Further comparison on solid-state property of warfarin before and after SAS operations was investigated by PXRD, DSC, TGA and FTIR analysis.

1. Introduction

Supercritical fluid crystallization, an intensified crystallization process, has been used in pharmaceutical applications over the last few decades for manipulating the solid-state properties of active pharmaceutical ingredients (APIs) and designing novel drug delivery systems [1–3]. According to the crystallization mechanism and role played by the supercritical fluid, supercritical fluid crystallization processes can be classified as rapid expansion of supercritical solution (RESS), supercritical antisolvent (SAS), particle from gas saturated solutions (PGSS), and supercritical assisted atomization (SAA) processes [4,5]. In RESS, SAS, PGSS, and SAA processes, a supercritical fluid is used as the supercritical solvent, supercritical antisolvent, dissolved gas solute, and spraying-assisted cosolvent, respectively. Due to its advantages of low toxicity, low cost, and relatively mild supercritical conditions, carbon dioxide (CO_2) is the most commonly used fluid in supercritical fluid crystallization processes.

In the literature, the feasibility of SAS has been proved in the control and modification of the solid-state properties of APIs, such as baicalein, curcumin, etoposide, indomethacin, mangiferin, palmitoylethanolamide, quercetin, tetracycline, mefenamic acid, primidone, and sulfasalazine [6–16]. SAS methods can be compared favorably with more conventional crystallization methods; by using SAS methods, crystals with micron to submicron size, narrow size distribution, and regular crystal habit can be produced. These improved crystal properties benefit the downstream drug formulation process by enhancing the dissolution rate and favoring the powder handling procedure. In addition, SAS processes can be efficient for screening novel crystal forms and creating intellectual property during drug discovery.

For successful recrystallization of an API through a SAS process, understanding the thermodynamic properties, such as the solid solubility of the API in the supercritical fluid, is essential. For example, for proper design of the SAS operation, the target API and supercritical antisolvent must be almost insoluble to achieve satis-

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factory yield and build extremely high supersaturation. In other words, SAS processes are available and suitable for processing of APIs that demonstrate extremely low solubility (mole fraction lower than 10^{-5}) in supercritical fluids. In the literature, some solubility data of organic solids in supercritical fluids have been reviewed by Škerget et al. and Lucien and Foster [17,18]. However, according to those sources, solid solubility data for biological compounds, especially for APIs in supercritical fluids, are still scant, and more experimental measurements and thermodynamic correlations are required for data extrapolation.

In this study, warfarin was selected as a model API. Warfarin is an oral medication that is used as an anticoagulant. It treats blood clots such as deep vein thrombosis and pulmonary embolism, and to prevent stroke who have atrial fibrillation, valvular heart disease or artificial heart valves. The common side effect of warfarin is bleeding due to accidental overdose or interactions. For designing and developing oral medication with better bioavailability and lower side effect, control and modification of the solid-state property of active pharmaceutical ingredient such as crystal habit, particle size characteristics and crystal form are crucial. In this study, recrystallization of warfarin by a novel crystallization platform, supercritical crystallization technology, were investigated. In addition, the solid solubility data of warfarin in supercritical CO_2 at different temperatures and pressures using a semiflow apparatus were measured, and then correlated using semiempirical equations. According to the experimental measurements of solid solubility, a suitable supercritical recrystallization process was selected and the effects of operating parameters were investigated and compared. The solid-state properties of warfarin before and after recrystallization operations, particularly crystal habit, particle size characteristics, and crystal form, were compared and are discussed.

2. Materials and methods

2.1. Chemicals

In this study, CO_2 purchased from Cheng-Feng Gas Co. (Taiwan) with a minimum purity of 99.5% was used as the supercritical antisolvent. The model API warfarin was purchased from Sigma-Aldrich Co. with a minimum purity of 99%. In SAS operations, solvent selection is crucial. The selected solvent must be miscible with the supercritical antisolvent and must exhibit reasonable affinity. According to the high-pressure-phase behaviors of solvents and CO_2 and the solvent selection guidelines of the pharmaceutical industry (ICH Q3C guidelines), seventeen solvents, namely acetic acid, acetone, acetonitrile, anisole, dichloromethane (DCM), *N*,*N*-dimethylacetamide (DMAC), *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), ethanol, ethyl acetate, ethyl glycol, *n*-heptane, methanol, methyl ethyl ketone (MEK), *N*-methyl-2-pyrrolidinone (NMP), tetrahydrofuran (THF), and toluene, were considered for screening in this SAS study. All these organic solvents had a minimum purity of 99% and were purchased from Sigma-Aldrich, Echo Chemical, and J. T. Baker. All chemicals were used without further purification. Relevant information regarding the chemicals used in this study is summarized in Table 1.

2.2. Solid solubility measurement and data correlation

The experimental apparatus for solid solubility measurements, which contained three sections for supercritical CO_2 delivery, solute extraction, and solubility analysis, is shown in Fig. 1. CO_2 from the gas cylinder was liquefied by a cooler and then pressurized using a high-pressure pump. The system pressure was regulated to a desired value by using a back-pressure regulator. CO_2 at the desired pressure was passed through a preheating coil immersed in a thermostatic water bath to reach a supercritical state. Supercritical CO_2 from the preheating coil was charged into the pre-equilibrium and equilibrium cells, which were packed approximately 10 g of the API and with glass beads. The system temperature was controlled by a thermostatic water bath. The temperature and pressure were measured using a thermometer and a pressure transducer with resolutions of 0.1 K and 0.01 MPa, respectively. Following API extraction with supercritical CO_2, the solute-saturated supercritical solution was expanded to atmospheric pressure through a needle valve. This needle valve was wrapped with a heating tape to avoid blockage. After expansion, the total volume of CO_2 was recorded using a wet test meter, and the solid was separated from the gaseous phase and was dissolved in ethyl acetate in a flask. The API concentration in the collected solution in the flask was finally analyzed using a UV/Vis spectrometer. Prior to solubility measurement of warfarin, the feasibility and assurance of the experimental system and procedure were validated by measurement of solid solubility of salicylic acid in supercritical CO_2 at 313.2 K. The measured solubility values were consistent with literature reported data. The published solubility value at a given temperature and pressure was averaged from three independent measurements. The repeated measurements were obtained at various flow rates of effluent CO_2 between 3 and 10 L/h to ensure that data on saturated solubility were obtained.

In addition to solubility measurement, the measured solubility data were correlated using two semiempirical equations, the Chrastil equation and Méndez–Santiago and Teja (MST) equation, in their dimensionless forms [19–21]. The dimensionless Chrastil equation is expressed as:

$$\ln S_2^* = k^* \ln \rho_{r,1} + \frac{a^*}{T_r} + b^* \tag{1}$$

$$S_2^* = \frac{S_2}{\rho_{c,1}} \tag{2}$$

The dimensionless MST equation is expressed as:

$$T_r \ln y_2 P_r = c^* + d^* \rho_{r,1} + e^* T_r \tag{3}$$

where S_2 is the solute concentration (kg/m^3) of warfarin in the supercritical solution; y_2 is the solid solubility of warfarin in mole fraction; $\rho_{r,1}$ is the reduced density of pure CO_2; $\rho_{c,1}$ is the critical density of pure CO_2; T_r is the reduced temperature; P_r is the reduced pressure; and k^*, a^*, b^*, c^*, d^*, and e^* are empirically fitted model parameters.

2.3. SAS recrystallization study

Fig. 2 illustrates the SAS experimental apparatus used in this study. It included two high-pressure pumps for CO_2 and warfarin solution (or pure solvent) delivery. The CO_2 flow rate was measured using a rotameter under ambient conditions at the exit of the precipitator and was adjusted using a micrometering valve. Pressure in the precipitator was regulated using a back-pressure regulator. The temperature of precipitator was controlled by an electrical heating jacket. A stainless-steel frit with a pore size of 0.5 μm was installed at the bottom of the precipitator for collecting produced crystals.

For SAS operations, the supercritical CO_2 and pure solvent are first delivered into the precipitator until the SAS system reaches a steady state. The solution feed is then switched from pure solvent to warfarin solution. After a sufficient quantity of the warfarin solution has been injected, the solution injection procedure is stopped, and the residual solvent inside the precipitator is

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