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Parametric analysis of homogeneous and heterogeneous nucleation in subcritical CO_2-mediated antisolvent crystallization

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ABSTRACT

The present work investigates the tunability of antisolvency effect of subcritical carbon dioxide (CO_2), in a solution of cholesterol in acetone, which facilitates high and rapid supersaturation needed for producing cholesterol micro-particles. A thermodynamic analysis is proposed for selection of operating conditions that result in high solid solute supersaturation. This is further coupled to a computational analysis of homogeneous and heterogeneous nucleation, and crystal growth kinetics. A numerical strategy has been evolved and for verifying its consistency the predicted particle size has been compared with that obtained experimentally. In addition, the effects of pressure (60–70 bar), temperature (291–303 K), initial solute concentration (90–100%), specific dissolution rate of CO_2 (0.095–6.0 min^{-1}), and nuclei-substrate contact angle (30–50°) on average particle size have been ascertained. In the case of homogeneous nucleation, the particle size increases with temperature, while pressure has a negligible effect. Further, the particle size decreases when the antisolvent dissolution rate and initial solute loading in solvent are increased. For heterogeneous nucleation, an enhancement in contact angle increases the particle size. These trends are in agreement with the experimental observations reported in the literature. The computational method thus elucidates a generalized approach for engineering desired particle size in subcritical CO_2-mediated antisolvent crystallization.

1. Introduction

Production of ultra-fine particles of controlled size has been a challenge to the chemical and pharmaceutical industries for many years (Dodds et al., 2007; Elvassore et al., 2003; Jung and Perrut, 2001; Subramaniam et al., 1997; Tabernero et al., 2012). Conventional techniques employed for synthesizing ultra-fine particles include jet milling, freeze-drying, spray-drying, liquid antisolvent process and thermal cooling (Elvassore et al., 2003; Martín and Cocero, 2008; Subramaniam et al., 1997). However, one of the relatively recent techniques, with considerable potential for use in pharmaceutical industries, is crystallization employing supercritical or subcritical carbon dioxide (CO_2) as an antisolvent. CO_2 is used as an antisolvent because it is inert, safe, nonflammable, environment-friendly green gas, and highly soluble in many organic solvents (Esfandiari and Ghoreishi, 2013; Subramaniam et al., 1997; Tabernero et al., 2012). Processes that use supercritical CO_2 as an antisolvent have been explored widely (Subramaniam et al., 1997; Tabernero et al., 2012). Examples of such processes include precipitation with compressed antisolvent (PCA), supercritical antisolvent (SAS), and solution enhanced dispersion with supercritical fluids (SEDS) (Elvassore et al., 2003; Tabernero et al., 2012). Those employing subcritical CO_2 include precipitation by pressure reduction of gas expanded liquid (PPRGEL) (Dalvi and Mukhopadhyay, 2009) and gas antisolvent (GAS) process (Elvassore et al., 2003).

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Nomenclature

A_p	surface area of the particle [m^2]
C_3	instantaneous solid concentration [mol/m^3]
C_3^*	equilibrium solid concentration [mol/m^3]
D_p	diameter of the particle [m]
$\overline{D}_p$	average diameter of the particle [m]
D_{32}	diffusion coefficient of the solid solute [m^2/s]
h	width of the cap-shaped particle [m]
J	nucleation rate [$\#.m^3/s$]
k_B	Boltzman's constant [J/K]
k_g	mass transfer coefficient [m/s]
MW_3	molecular weight of solid solute [g/mol]
N_A	Avogadro's number [mol^{-1}]
n_n	number of moles of solid precipitated due to nucleation [mol]
n_g	number of moles of solid precipitated due to growth [mol]
N_p	number of nuclei formed [–]
P	pressure [bar]
R	universal gas constant [J/mol/K]
r_c	critical radius of the nuclei [m]
r_0	molecular radius of the solid solute [m]
r_p	radius of the particle [m]
S	solid solute supersaturation [–]
S_{ab}	absolute solid solute supersaturation [–]
T	temperature [K]
v_L	molar volume of the liquid [m^3/mol]
V	total volume of the vessel [m^3]
V_L	initial volume of the solvent [m^3]
$\overline{v}_2$	partial molar volume of the solvent [m^3/mol]
v_m	molar volume of GEL solution [m^3/mol]
V_c	critical volume of the nuclei [m^3]
V_t	total volume of GEL [m^3]
V_p	volume of the particle [m^3]
r_b	base radius of the cap-shaped particle [m]
$x_1{}^{max}$	maximum CO_2 mole fraction when vessel is completely filled [–]
$x_1{}^*$	equilibrium CO_2 mole fraction [–]
Y_f	pre-defined solid solute yield [%]

Greek symbols

θ	three-phase contact angle
ρ_3	solute density [kg/m^3]
η	mixture viscosity [Pa s]
σ_{cl}	solid solute-GEL interfacial tension [N/m^1]
σ_{cs}	solid solute-substrate interfacial tension [N/m^1]
σ_{sl}	substrate–GEL interfacial tension [N/m^1]

Abbreviations

GAS	gas antisolvent process
GEL	gas-expanded liquid
ISC	initial solute concentration
RESS	rapid expansion of supercritical solutions
SDR	specific dissolution rate
SC CO_2	supercritical carbon dioxide

The present paper focuses on a parametric analysis of subcritical CO_2-mediated antisolvent crystallization of cholesterol particles from acetone solution. In this process the solid solute to be precipitated is pre-dissolved in a suitable organic solvent and subcritical CO_2 is added to it. The dissolution of CO_2 progressively expands the solution forming a gas expanded liquid (GEL), which is accompanied by substantial reduction in the solvent power for the solid solute, which in turn enhances the solute supersaturation and then precipitates the solute (Bakhbakhi et al., 2005; Dodds et al., 2007; Esfandiari and Ghoreishi, 2013; Muhrer et al., 2002). Several researchers have studied the effects of operating parameters on the characteristics of the cholesterol particles precipitated using different supercritical carbon dioxide ($SCCO_2$) processes. Subra et al. (2004) investigated cholesterol particle formation using rapid expansion of supercritical solutions (RESS) and supercritical antisolvent (SAS) processes. For the RESS process the particle morphology was needle-like and the average size ranged from 1–15 μm. However, in the SAS process the particle morphology and sizes were influenced by flow rates and concentration. The morphology varied from needle-shaped particles to curved or flat elongated structures. In another work, Liu et al. (2002) produced cholesterol particles from acetone solution via the GAS process. The morphology of cholesterol particles varied depending on the CO_2 injection rate. Low injection rate produced needle-like crystals whereas rapid injection rate resulted in flattened tabular crystals. Dalvi and Mukhopadhyay (2009) studied the effects of various process parameters on the particle size and yield of cholesterol particles when precipitated from its acetone or ethanol solutions using subcritical CO_2 by the PPRGEL process. Particle size ranged from 200 nm to 7 μm, and the morphologies were near-spherical to needle-like depending on the operating conditions.

In general, formation of ultra-fine particles requires attainment of very high and rapid supersaturation of the solid solute in the solution, followed by its nucleation. Subsequent growth of the nuclei occurs due to diffusion of solute molecules from solution to the nuclei surface followed by their surface integration (Myerson, 2002). The nucleation process may be either homogeneous or heterogeneous. In the existent literature, the antisolvent crystallization has largely been addressed by considering homogeneous nucleation which may involve primary and secondary nucleation (Bakhbakhi et al., 2005; Dodds et al., 2007; Erriguible et al., 2015; Esfandiari and Ghoreishi, 2013; Muhrer et al., 2002). For example, Erriguible et al. (2015), developed a mathematical model for the estimation of nucleation and growth parameters of naproxen + nicotinamide cocrystals precipitated from acetone solution using the GAS process. This was achieved by fitting the predicted particle size distribution data to that obtained experimentally. In general, however, the nature of nucleation occurring during crystallization has not been rigorously justified in the literature. As it is well-known, the homogeneous nucleation can occur only when the solution is absolutely free of foreign particles (i.e., dust, impurities), which typically is not obtained in most practical crystallization processes (Kashchiev and van Rosmalen, 2003; Mersmann, 2001; Mullin, 2001; Nývlt, 1984). This is because impurities that may be usually present in the system can always provide sites for heterogeneous nucleation.

In their study on heterogeneous nucleation, Liu (2000) investigated the effect of foreign particles on nucleation of paracetamol from aqueous solution, both in the absence and presence of additives. It was concluded that the greater is the affinity between the foreign particle and the crystalline phase, the lower is the supersaturation required for the