MODELING OF PARTICLE FORMATION
IN SUPERCRITICAL ANTI-SOLVENT PROCESSES:
DILUTED AND CONCENTRATED REGIME

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In this work, a theoretical investigation on particle formation taking into account mass transfer and thermodynamic for ternary systems solvent-antisolvent-solute, and solute precipitation kinetic is presented for both diluted and concentrated polymeric solutions. A mathematical model of mass transfer between a droplet of polymeric organic solution and a compressed anti-solvent is solved for fully miscible conditions. The generalized Maxwell-Stefan diffusion equation is used. To fairly describe the thermodynamic of chain-like solutes, such as polymers, both the volumetric and equilibrium properties are represented by the perturbed-hard-sphere-chain-theory equation of state. For concentrated solution, where only one polymeric solid particle is generated from the initial organic-solution droplet, a simple solute precipitation kinetic gives radial profiles of solute and solvent composition, and precipitated solute as a function of time. Depending on the process variables, the solute precipitation can occur either at the initial droplet surface or internally leading either to a hollow sphere or to a compact particle, respectively.

The simulation presented in this work provides the precipitated solute distribution as a function of radial coordinate and time. Process operative variables and mass transfer pathways could strongly affect the overall final particle morphology. Results are presented for solutes with different solubility and kinetic parameters.

INTRODUCTION

Supercritical antisolvent (SAS) techniques represent an alternative route for micronizing thermo-sensitive compounds. In particular, supercritical antisolvent precipitation-recrystallization processes, where a solute precipitates from an organic solution upon contact with a supercritical antisolvent fluid, are interesting for producing micro- and nano-particulate solid materials. The rational understanding of thermodynamic and phase behavior, mass transfer [1], jet hydrodynamics and particle formation kinetics in the GAS process are of fundamental importance in controlling the morphology of the final product.

The aim of this work is to simulate the isothermal and isobaric mass transfer between a thread or a droplet of polymeric organic solution in a supercritical CO_2 environment. Following the density profile inside the droplet, in particular the onset precipitation density, that is the density at which the solute starts to precipitate, the polymer precipitation process can be predicted as a function of the process variables, such as the type of organic solvent, pressure and temperature. A fundamental analysis of this mass transfer problem can be made under some important assumptions. In this work, it was assumed that the condition at which most of the GAS experiments were performed are supercritical, so that the solvent and antisolvent are fully miscible, and a defined interface does not exist.

MODEL FORMULATION

Modeling the mass transfer in the supercritical anti-solvent process requires the time dependent conservation equations and an equation of state (EOS). The species equations in molar basis for component i are obtained from the continuity equations:

$$\frac{\partial}{\partial t}(\boldsymbol{r}_f x_i) + \nabla \cdot N_i = 0 \tag{1.}$$

with the boundary conditions:

$$\frac{\partial(\boldsymbol{r}_f x_i)}{\partial t}(r=0,t) = 0 \quad \boldsymbol{r}_f x_i(r=\infty,t) = 0 \tag{2.}$$

and the initial conditions:

$$x_i(r,0) = f(r) \tag{3.}$$

where x_i is the mole fraction of i-component in the fluid phase, $\boldsymbol{r}_f(r,t)$ the molar density of fluid phase, N_i the molar flux of i-component, $f(r)$ the initial composition profile and r the radial coordinate. In this work, subscript A refers to the antisolvent, B to the solvents and C to the solute, f to the fluid phase and s to the solid phase.

For multi-component systems, the molar flux N_i can be expressed by:

$$N_i = x_i N_f + J_i \tag{4.}$$

where N_f is the convective flux and J_i the diffusive molar flux of component i. The solution of the species equations requires the knowledge of convective flux as a function of the density variations. The overall continuity equation and the relative boundary condition are as follows:

$$\frac{\partial \boldsymbol{r}_f}{\partial t} + \nabla \cdot N_f = 0 \tag{5.}$$

$$N_f(r=0) = 0 \tag{6.}$$

The molar density profile in each phase is obtained using an equation of state with good density agreement: Carnahan-Starling EOS or other perturbation theory EOS, derived from the same reference equation, are suitable for this propose. Here the perturbed hard sphere chain (PHSC) EOS [2] is used:

$$\boldsymbol{r}_f = f_{PHSC}(\boldsymbol{r}_f, T, P, x_1, x_2, ..., x_n) \tag{7.}$$

where n is the number of system components and f_{PHSC} is a density implicit function that has to be solved for each value of the system composition.

Using the Generalized Maxwell-Stefan (GMF) diffusion equation it is possible to write the expression of (J) as follows [3]:

$$(J) = -\boldsymbol{r}_f [B]^{-1} [\Gamma](\nabla x) \tag{8.}$$

The matrix $[B]$ of dimension $(n-1, n-1)$ contains the GMF diffusion coefficients, $\hat{D}_{ij}$, and is defined as:

$$B_{ii} = \frac{x_i}{\hat{D}_{in}} + \sum_{\substack{k=1 \\ k \neq i}}^{n} \frac{x_k}{\hat{D}_{ik}}; \quad B_{ij} = -x_i \left(\frac{1}{\hat{D}_{ij}} - \frac{1}{\hat{D}_{in}} \right) \quad i \neq j = 1,2,...,n-1 \tag{9.}$$

The thermodynamic correction matrix, $[\Gamma]$, is defined as:

$$\Gamma_{ij} = \boldsymbol{d}_{ij} + x_i \frac{\partial \ln \boldsymbol{f}_i}{\partial x_i} \quad i = 1,2,\ldots,n-1 \tag{10.}$$

For ideal gas mixtures, matrix $[\Gamma]$ reduces to identity matrix. By comparison with the generalized Fick's law formulation, the matrix of practical diffusion coefficient can be expressed by $[D] = [B]^{-1}[\Gamma]$.

By substituting equation (8) in (1), a system of three partial differential-algebraic equations can be obtained.

In the case of ternary solvent-CO_2-solute system with solute precipitation, an additional overall continuity equation for the solid phase has to be written. Assuming that the precipitated pure solid phase does not follow the convective flux of the system:

$$\frac{\partial(c_s)}{\partial t} = \overline{R} \tag{11.}$$

where c_s is the concentration of solid phase for unit of system volume (mol/cm^3) and $\overline{R}$ is the solute precipitation rate.

$$\begin{cases} \overline{R} = K_p S & x_C \geq x_C^{sat} \\ \overline{R} = 0 & x_C < x_C^{sat} \end{cases} \tag{11.}$$

where K_p is a simple precipitation kinetics, x_C^{sat} the solute molar fraction at saturation condition and $S = (x_C - x_C^{sat})/x_C^{sat}$ is the supersaturation. For describing solid precipitation the contribution $\overline{R}$ have to be included in the solute continuity equation (1).

Transport properties

The diffusion coefficient dependence on compositions is estimated by the Vignes equation [4]. The infinite-dilution diffusion coefficient at infinite dilution of CO_2 in organic solvent was calculated using the Tyn-Calus method [4]. The infinite-dilution diffusion coefficient of organic solvents in CO_2 is calculated using the method of Fuller with the Takahashi correction for high pressure [4]. The diffusivity of solute is estimated from the Stokes-Einstein equation [5].

Thermodynamic properties

The perturbed-hard-sphere-chain equation of state describes a system composed by freely jointed chains of tangent sphere and gives the effect of chain length on the thermodynamic properties of both equilibrium and volumetric properties. For the volatile components, i.e. supercritical fluid and organic solvents, characteristic parameters were obtained by fitting both vapor pressure and saturated liquid densities above 1 bar (or PVT data at 1 bar when the temperature is under the normal boiling point) as reported in Table (1). The regressions were performed in the temperature range typically used in gas anti-solvent process of 300-400 K. For heavy compounds, i.e. the polymer, the characteristic parameters are obtained by a group contribution method proposed by Elvassore et al. [6], whose application requires the knowledge of molecular structure of compounds in term of their functional groups only.

One temperature-independent binary interaction parameter is used for fitting organic solvent-CO_2 vapor-liquid equilibrium data. The PHSC EOS well correlates experimental vapor-liquid data and, interestingly, it fairly predicts the experimental saturated-liquid density.

Numerical aspects

To obtain the numerical solution, the system of partial differential-algebraic equations are reduced to a system of ordinary differential-algebraic equations using the finite volume

approximations for the radial coordinate. For the numerical solution of this equation system a double-precision differential algebraic system solver (DDASSL) based on the Petzold-Gear backward differentiation formulas was used. Following the procedure reported by Werling and Debenedetti [1], in order to cluster mesh points in the region were the density changes rapidly, a constant mesh was used for the region near the droplet center (200 nodes between 0.0 and 4.0 initial droplet radius) and an exponential mesh away from the droplet center (50 nodes between 4.0 and 10.0 initial droplet radius). To improve the accuracy and the stability of the numerical solution the equations were written in dimensionless form. The simulation show that this mesh refinement leads to an efficient and accurate computing. Consistency of the overall mass balance was checked at each time integration step ensuring that the initial mass of the components was preserved. To speed up the numerical solution, the thermodynamic properties, such as density and fugacity coefficient derivatives, were interpolate using B-spline routines of IMSL Fortran 90 library; bi-dimensional grid of 40 knots were used.

RESULTS

Thermodynamic of the ternary system is of fundamental importance in governing the mass transport of GAS precipitation process. Figure 1 shows the good correlation between PHSC EOS and experimental VLE data. However, for simulating the fully miscible condition the pressure and temperature must be above the critical points and vapor-liquid coexistence surface of the ternary system. For example, the dimethylsulfoxide-CO_2-polyethyleneglycol system with maximum polymer concentration of 10 w/w % shows fully miscible condition at 150 bar at 298 K.

Figure 2 shows the effect of the polymer concentration in the droplet lifetime. Because no interface can be defined, we follow the evolution of the CO_2 molar concentration at which the polymer is likely to precipitate in the solid phase. Note that, in dilute solution, the polymer does not substantially affect the mass transfer.
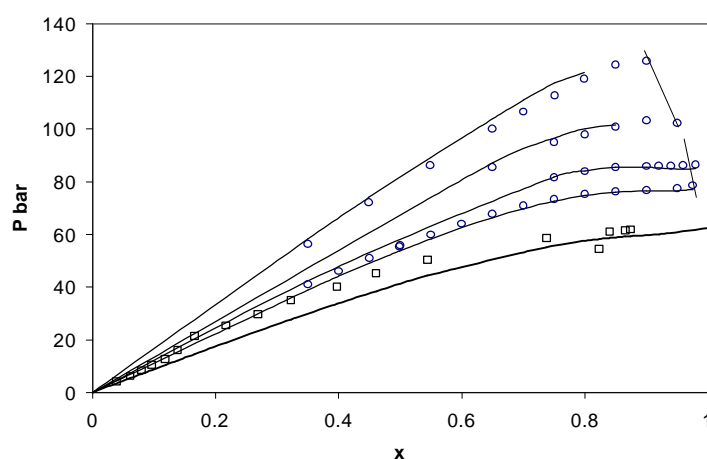

Figure 1. Vapor-liquid equilibria for the system CO_2-dimethylsulfoxide at 298-328 K. Circles are experimental data from Gonzalez et al. [7]; squares are from Kordikowski et al. [8]; lines are calculated by PHSC EOS. Segments trace the experimental mixture critical point.
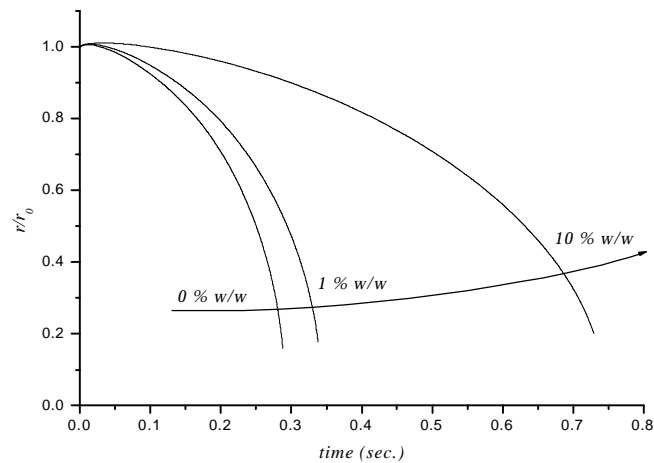
Figure 2. Evolution of CO_2 molar composition of 0.8 at 298 K, 150 bar and different polymer concentrations.
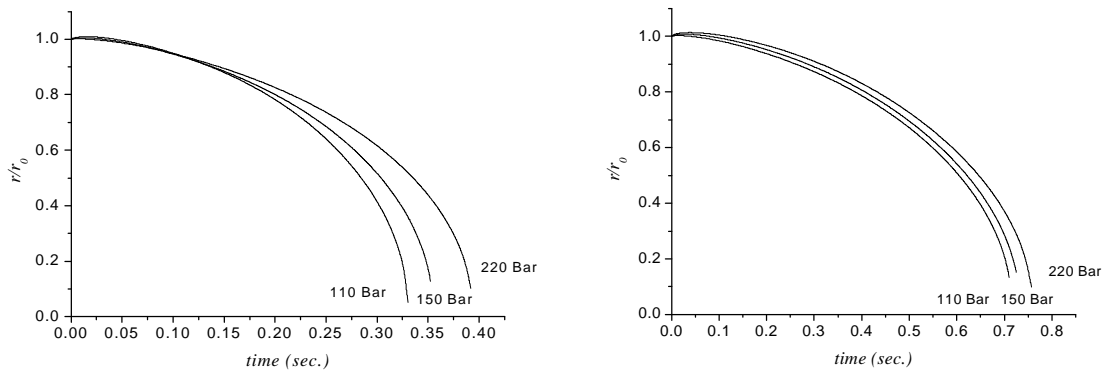

Figure 3. Evolution of CO_2 molar composition of 0.8 at 298 K, different pressure and: (a) 1 %w/w polymer concentration; (b) 10 %w/w polymer concentration.

Figure 3 shows the effect of pressure for two solutions at different polymer concentration. When operating at high polymer concentration, the droplet lifetime presents similar behavior for all pressures considered due to the vanishing of the diffusion coefficients of the ternary system approaching to the critical region.

Figure 4 gives an example of the 3-dimensional solid distribution that can be obtained performing the simulation for the system CO_2-dimethylsulfoxide-polyethyleneglycol at 298 and 150 bar. The solid is homogeneously distributed along the radial coordinate.

Figure 5 compares the solid distribution for a case of low solubility (Figure 5a) and high solubility compounds (Figure 5b). In the first case, the solid mostly precipitated on the external surface of the droplet leading to a capsule-like particles. On the other hand, fully and compact particles can be obtained when compounds with higher solubility in organic solvent-CO_2 system is treated in the GAS process, as shown in Figure 5b.

It is worthwhile to underline that other phenomena such jet hydrodynamics may also influence the final characteristics of the products. However, the simulations presented in this work are very useful to evidence the conditions at which the mass transfer could be too slow due to the polymer concentration, and to record how the precipitation kinetics and solute solubility influences the final morphology of the products.
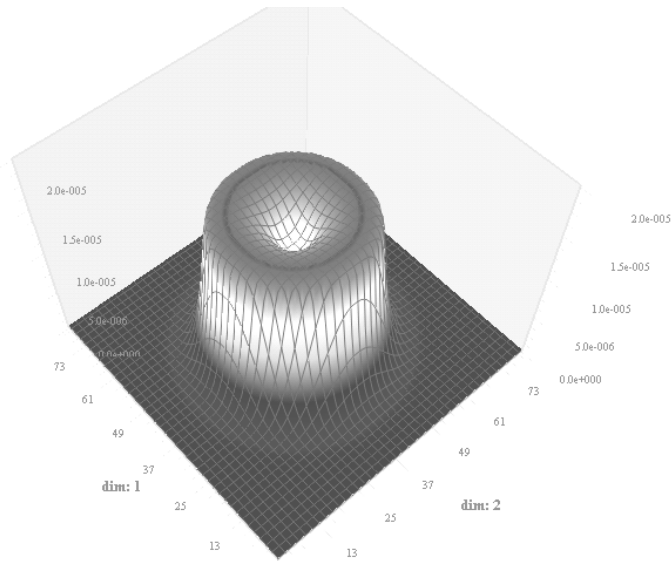
Figure 4. Example of final solid distribution produced at 298 K and 150 bar for the system DMSO-CO_2-PEG.
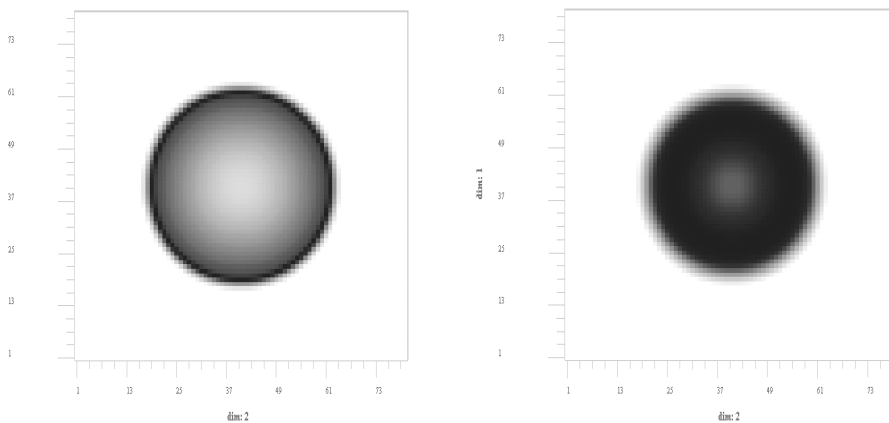

Figure 5. Example of final solid distribution produced at 298 K and 150 bar for: (a) low soluble solute x_{CO2}=0.2; (b) high soluble solute x_{CO2}=0.8. Intensity of the color are proportional to the solid concentration.

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