



Interactions of phase equilibria, jet fluid dynamics and mass transfer during supercritical antisolvent micronization

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ABSTRACT

Supercritical antisolvent (SAS) precipitation has been successfully used in the micronization of several compounds. Nevertheless, the role of high-pressure vapor–liquid equilibria, jet fluid dynamics and mass transfer in determining particle size and morphology is still debated. In this work, CO₂ has been adopted as supercritical antisolvent and elastic light has been used to acquire information on jet fluid dynamics using thin wall injectors for the investigation of the liquid solvents acetone and DMSO at operating conditions of 40 °C in the pressure range between 6 and 16 MPa. The results show that two-phase mixing after jet break-up is the phenomenon that characterizes the jet fluid dynamics at subcritical conditions. When SAS is performed at supercritical conditions a transition between multi-phase and single-phase mixing is observed by increasing the operating pressure. Single-phase mixing is due to the very fast disappearance of the interfacial tension between the liquid solvent and the fluid phase in the precipitator. The transition between these two phenomena depends on the operating pressure, but also on the viscosity and the surface tension of the solvent. Indeed, single-phase mixing has been observed for acetone very near the mixture critical point, whereas DMSO showed a progressive transition for pressures of about 12 MPa.

In the second part of the work, a solute was added to DMSO to study the morphology of the microparticles formed during SAS precipitation at the different process conditions, to find a correlation between particle morphology and the observed jet. Expanded microparticles were obtained working at subcritical conditions; whereas spherical microparticles were obtained operating at supercritical conditions up to the pressure where the transition between multi- and single-phase mixing was observed. Nanoparticles were obtained operating far above the mixture critical pressure. The observed particle morphologies have been explained considering the interplay among high-pressure phase equilibria, fluid dynamics and mass transfer during the precipitation process.

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1. Introduction

Supercritical antisolvent (SAS) micronization has been largely studied because of its wide potential of producing micrometric and nanometric particles with controlled particle size and morphology [1,2] that can be applied in several industrial fields. The process is commonly performed at temperatures ranging between 35 and 60 °C. Therefore, it is particularly useful when thermo-labile compounds have to be micronized, as in the case of pharmaceutical, cosmetic and polymeric applications. For example, reviewing SAS characteristics, Reverchon et al. demonstrated that this process is able to produce micrometric particles in the range from 1 to

20 μm for various materials [3] and to produce nanoparticles down to a mean diameter of about 50 nm [4]. The process has also been successfully scaled to pilot and semi-industrial GMP (Good Manufacturing Practice, in pharmaceuticals applications) scales [5,6]. Nevertheless, a relatively few works have been published, aimed at the understanding of the fundamental mechanisms that control the generation of the various particle morphologies during the SAS precipitation [7–11].

The SAS process is complex, since it involves the knowledge of:

1. high-pressure phase equilibria of the binary system (solvent/antisolvent) or ternary system (solvent/antisolvent/solute);
2. jet mixing, when the liquid solution is injected in the precipitator; and
3. mass transfer to and from the injected liquid phase, which causes the supersaturation and precipitation of the solute.

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1.1. High-pressure phase equilibria

The ternary system formed by solvent, solute and antisolvent should in principle be taken into account. However, SAS is based on the assumption that the solute is practically not soluble in the mixture solvent–antisolvent; if this hypothesis is verified, the presence of solute can be neglected and the fluid phase system formed in the precipitator can be treated as a binary one. Therefore, the considerations about position of the process operating point can be performed on the corresponding p – x isothermal diagram and typical SAS will be operated at pressures above the binary mixture critical point (MCP).

If the presence of solute in the fluid phase formed in the precipitator cannot be neglected (for example, if it was practically not soluble in the supercritical fluid, but it has a non-negligible solubility in the mixture antisolvent plus solvent) the phase equilibria can be largely different with respect to the corresponding binary system. For example, at the same pressure, the operating point in the ternary diagram could be located at subcritical conditions or inside a biphasic region. As a consequence, different equilibrium conditions apply and different transient interfacial tensions are obtained during the precipitation.

The influence of phase equilibria and of their possible modifications, due to the presence of solutes, on particle formation and morphologies has been reported by Reverchon et al. [3,4,12]. These authors tried to describe the different mechanisms involved in the SAS formation of nanoparticles, microparticles and expanded microparticles and to describe the switching between the various morphologies based on the literature data and on specifically performed experiments. Other authors used similar observations as a reference to obtain selected lysozyme particle morphologies [13].

1.2. Jet mixing

In the SAS related literature there is a general agreement about the flow regimes observable when a liquid is injected in a vessel, which is filled with the supercritical antisolvent. Lengsfeld et al. [11] has been the first group that investigated fluid dynamics of the SAS process. They studied the evolution and disappearance of the liquid surface tension of immiscible, poorly miscible and miscible fluids injected in supercritical (sc)-CO₂, to determine whether the liquid atomizes into droplets or evolves as a gaseous jet. They concluded that in the case of miscible fluids (i.e., at supercritical conditions), the surface tension vanishes before an appreciable jet break-up is obtained. Consequently, a gas-like jet is formed after the jet break-up.

Sarkari et al. [14], Badens et al. [7], Gokhale et al. [10] and Obrzut et al. [15] also concluded that turbulent single-phase mixing dominates at well developed supercritical conditions. However, the transition between multi-phase (formation of droplets after jet break-up) and single-phase mixing (no formation of droplets after jet break-up) could not be located at the pressure of the mixture critical point. Dukhin et al. [16] and Gokhale et al. [10] found that jet break-up into droplets still takes place at pressures slightly above the MCP. Particularly, Gokhale et al. [10] observed at these conditions the formation of small droplets that rapidly dissolve in sc-CO₂. Due to the non-equilibrium conditions during mixing, a dynamic (transient) interfacial tension exists that decreases between the inlet of the liquid and its transformation to a gas-like mixture.

Some authors attempted to connect the observed flow or mixing regimes to the morphology of the precipitated particles. Lee et al. [17] injected a solution of dichloromethane (DCM) and PLA at subcritical conditions in the dripping and in the Rayleigh disintegration regimes and observed the formation of uniform PLA microparticles. Other authors [10,15] did not find relevant differences in the various precipitates obtained, perhaps, as a result of using a poly-

mer (PLA and PVP, respectively) as the solute. As a rule, polymers show a rather limited variety of precipitate morphologies in the SAS literature. Particularly, PLA morphologies showed to be insensitive to the SAS processing conditions [18,19]. This characteristic could be assigned to the high molecular weights and to the large modifications of the solution properties induced by the presence of a polymer. Moreover, polymers tend to form aggregated particles because of the reduction of the glass transition temperature in sc-CO₂.

In all the studies commented until now, jet characteristics were studied using shadowgraphic techniques. Shadowgraphy is an optical method to obtain information on non-uniformities in transparent media, independently if they arise by temperature, density or concentration gradients. All of these inhomogeneities refract light which causes shadows.

It is important to mention that light scattering experiments give insight about jet mixing, which cannot be gained by applying techniques like shadowgraphy. Especially considering atomized sprays (very droplet laden sprays) and dense jets (gas-plumes), shadowgraphy cannot differentiate between them. This is due to the fact that both the droplet laden spray and the dense “gas-plume” result in a dark shadow. On the contrary, using a light scattering technique, it is possible to clearly differentiate between an atomized very droplet laden spray and a dense “gas-plume”.

1.3. Mass transfer

When droplets are formed, as a result of the jet break-up, mass transport of CO₂ into the droplet and solvent evaporation into the bulk sc-CO₂ are the two phenomena that characterize the SAS process. The mass transfer of sc-CO₂ inside the droplets is particularly fast, since CO₂ is highly soluble in organic solvents and shows gas-like diffusion properties that are characteristic for supercritical fluids.

The modeling works of Werling and Debenedetti [20,21] illustrated the mass transfer inside and outside a toluene spherical droplet below and above the MCP of the system toluene/CO₂. Convective mass transfer inside and outside the spherical fluid element was not considered during their investigations. Particularly, at subcritical conditions they predicted the rapid expansion of the droplet. Chavez et al. [22] also showed that the precipitation process confined in the droplet can occur according to two different mechanisms. The first is a diffusion limited regime that produces a precipitation front and the second is a nucleation-limited regime in a homogeneously mixed droplet. These mechanisms can influence the micro–nano-structure of the precipitated particles, especially considering that the nucleation process is simultaneously promoted in many parts inside the droplet [9] and can produce fine aggregates of nanoparticles.

Although the action of the single mechanisms has been elucidated, the potential superposition of the various mechanisms indicates that the overall process could be successfully described only, if the interactions among phase equilibria, fluid dynamics and mass transfer are taken into account all together. These mechanisms concur to the production of the precipitates and hence are responsible for the great variety of particle morphologies and sizes obtainable by SAS precipitation.

The role of mass transfer mechanisms seems to be relatively well demonstrated even if the limitation of non-considering convection inside and outside the droplets can be relevant. The contribution of phase equilibria and particularly of the SAS operating point (pressure, temperature and overall composition) has been stressed by some authors. What is generally missing is the connection between jet fluid dynamics, phase equilibria and mass transfer on the morphology and the dimensions of the generated particles.

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