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Thesis in Chemical Engineering

MICRONIZATION BY SUPERCRITICAL ANTISOLVENT PRECIPITATION PROCESSES

Abstract

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In the last decade, the application of microparticles, nanoparticles and composite microparticles involved several industrial fields. Conventional micronization techniques, such as jet milling, spray drying, liquid antisolvent precipitation and solvent evaporation are sometimes not suitable, since the produced particles are irregular, with broad size distribution, could be degraded due to mechanical or thermal stresses and polluted with organic solvents or other toxic substances. In this context, supercritical fluids (SCFs) based techniques have been proposed as an alternative to traditional processes thanks to the specific characteristics of SCFs, mainly solvent power and liquid-like densities with gas-like transport properties, that can be tuned varying pressure and temperature. Among supercritical assisted micronization techniques, Supercritical Antisolvent (SAS) precipitation has been successfully used to obtain microparticles and nanoparticles of several kinds of compounds, such as pharmaceuticals, coloring matters, polymers and biopolymers. In this process carbon dioxide (CO_2) is used as an antisolvent at supercritical conditions: a solution containing the product to be micronized is injected into the precipitation chamber, saturated with supercritical carbon dioxide under the chosen conditions of temperature and pressure. CO_2, in contact with the solution, forms a mixture in which the product is insoluble, causing the precipitation.

Some aspects of SAS process that are still little examined have been investigated in depth: the influence of the kind of solvent on particle morphology, the polymer/drug coprecipitation and the processing of water soluble compounds.

In order to identify the correlation between the kind of solvent and particle morphology, the jet behavior of solvent mixtures in contact with CO_2 was studied using elastic light scattering and Raman scattering techniques. It has been observed that for some solvents, like dimethylsulfoxide (DMSO), N-methyl-2-pyrrolidone (NMP) and ethanol (EtOH), the transition from the two-phase mixing (subcritical conditions) to the single-phase mixing (supercritical conditions) with the bulk CO_2 occurrs on a large pressure range; whereas, for other solvents, like acetone (AC) and chloroform (CHF), the transition occurs on a narrow pressure range. Analyzing the evolution of the interface between the injected solvent and bulk CO_2 for solvent mixtures AC/DMSO, AC/EtOH and AC/NMP, it was observed that they show intermediate behaviors between the two solvents during SAS processing. Moreover, precipitation experiments performed on two model compounds, cellulose acetate (CA) and polyvinylpirrolidone (PVP), demonstrated that it is possible to modulate the morphology of SAS precipitates using the appropriate solvent mixture. This part of the thesis was carried out on in collaboration with the Applied Raman Scattering (ARS) Laboratory of the Erlangen

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SAS coprecipitation applicability, limitations and the possible precipitation mechanisms were investigated studying the effect of all the operating parameters, to elucidate the conditions for a successful coprecipitation. Well separated microspheres for the systems PVP/folic acid, PVP/β-carotene and PVP/corticosteroids were obtained. Moreover, a coprecipitation mechanism was postulated: using PVP as carrier to retard crystal growth and working near above the mixture critical point (MCP) of the binary system solvent/antisolvent, i.e. when microparticles are produced, coprecipitation is successful because all the content of the droplet concurs the formation of the final particle. Dissolution tests confirmed the occurred coprecipitation: the produced composite microspheres showed a significant increase of the active compound dissolution rate with respect to the dissolution rate of the unprocessed compound.

In order to process water soluble compounds, a modification of SAS process, called Expanded Liquid Antisolvent precipitation (ELAS), was used because of the limited solubility of water in CO_2 at ordinary SAS operating conditions (313-333 K, 10-25 MPa). ELAS allows the processing of hydrosoluble compounds using a mixture of CO_2 and a polar organic solvent, called co-antisolvent, at expanded liquid conditions. In this work the applicability of this technique was tested on bovine serum albumin, lysozyme, sodium alginate and polyvinyl alcohol using different co-antisolvents, like ethanol, acetone and isopropanol (iPrOH). For each compound, it has been investigated the effect of all the operating parameters on morphology, mean size and particles size distribution. Nanoparticles, microparticles and expanded microparticles were successfully produced varying the kind of co-antisolvent and the process parameters. In particular, it was found that the use of EtOH/CO_2 antisolvent mixtures led to the production of micro and nanoparticles with narrow particle size distributions; the use of AC/CO_2 and iPrOH/CO_2 as antisolvent mixtures, instead, led mainly to the production of microparticles and expanded micro-particles. Moreover, it was hypothesized that the distance of the operating point with respect to the ternary high pressure vapor-liquid equilibria (VLE) can condition the morphology of the precipitates: increasing the co-antisolvent mole fraction, this distance increases, the mean size of the particles decreases and the particle size distribution become narrower. The analyses confirmed that the obtained particles are characterized by good biological activity, unaltered conformational structure and negligible solvent residue.