



Organic nanoparticles recovery in supercritical antisolvent precipitation

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ABSTRACT

One of the major problems in dry nanoparticles production and handling is their recovery. Indeed, they tend to disperse in all the precipitation chamber and, due to their dimensions, are very difficult to collect.

Supercritical antisolvent precipitation (SAS) was frequently used to produce nanoparticles at very mild conditions of pressure and temperature, but the issues of sedimentation mechanisms and nanoparticles recovery as single units, have not been evaluated yet.

In this work, SAS nanoparticles were produced for samarium acetate, rifampicin, astemizole, amoxicillin trihydrate, tetracycline hydrochloride, clemastine, cellulose acetate and disperse red 60; the powders were collected as aggregates, due to the specific sedimentation mechanism that characterizes the process. SAS produced nanoparticles of the previously listed materials were precipitated from different organic solvents. Then, they were post-processed by ultrafiltration, ultracentrifugation and ultrasound based techniques, demonstrating that they can be easily separated in single nano-units. Nanoparticles showed mean diameters in the range 50–150 nm.

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1. Introduction

Nanomaterials are engineered materials with at least one dimension measuring 100 nm or less though less restrictive definitions are frequently adopted, depending on the specific field of interest. They include nanoparticles, nanofibers and nanotubes, composite and nano-structured materials [1].

In this work, the term nanoparticle (np) refers to a homogeneous primary particle of a compound soluble in an organic solvent. These nanosized materials can be of wide importance in several industrial fields; it will be possible to produce explosives with a potential closer to the ideal one, colouring matters with brighter colours, toners with a higher resolution, polymers and biopolymers with improved functional and structural properties, drugs with enhanced pharmaceutical activity or for different delivery routes [2].

Nanoparticles can be obtained from a great variety of processes; the commonly used methods are: physical and chemical vapor deposition, colloidal chemistry approach, mechanical alloying techniques, mechanical milling, microemulsions based techniques and sol–gel techniques [3–5]. However, these methods, with the exclusion of microemulsions, cannot be applied to the production of

organic np_s because of the (extremely) high temperatures required for processing. In the case of microemulsions, the major drawback is the aging time of several hours required for the complete processing of particles, that can induce particle coalescence and growth [6]. Frequent problems in traditional techniques are:

- nanoparticles agglomeration, that can be reversible or irreversible, depending on the technique adopted and on the material treated [7,8];
- the large kinetic energy possessed by np_s when they are produced, that induces problems in their collection [9].

Furthermore, dry np_s recovery and handling are also very difficult. Most np_s production processes create dispersions of np_s in aqueous or organic mediums, and, in some cases, the content in np_s of the suspension obtained is quite low. Therefore, these suspensions are further processed to concentrate the product or to produce dry powders [9].

The use of supercritical fluid (SCF) assisted techniques has also been proposed to produce np_s, trying to take advantage of some specific properties of these fluids, mainly the very fast (gas-like) mass transfer. The most widely used supercritical fluid is carbon dioxide (CO₂), that is cheap, not polluting and whose critical temperature and pressure parameters are simple to be obtained in an industrial apparatus; the mild process temperature conditions are compatible with the thermal stability of many organic thermolabile compounds to be used in food, pharmaceutical and cosmetic industries [2]. However, ammonia, alcohols, light hydrocarbons and

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water have also been proposed for nanomaterials production at supercritical conditions [10,11]. For example, supercritical water (SCW) provides an excellent reaction medium for hydrothermal synthesis, producing very small nanometric particles; however, this process requires challenging operative conditions, since supercritical point for water is located at 373.94 °C and 220.59 bar. It means that this process is applicable only to compounds that are stable at high temperatures. To operate in SCW, stainless steel with special characteristics is required, due to the simultaneous application of high pressures and temperatures. Moreover, SCW is a strong oxidizing agent, not only for processed materials, but also for the elements of the plant that are in contact with it [2].

Nanoparticles have been obtained using the Rapid Expansion of Supercritical Solutions (RESS) [5,12]; it consists of the saturation of the supercritical fluid with a solid substrate; then, the depressurization of the solution through a heated nozzle into a low pressure chamber produces a rapid nucleation of the substrate in form of very small particles that are collected from the gaseous stream [13]. This process is particularly attractive due to the absence of organic solvents. Unfortunately, many solid compounds with high molecular weight and polar bonds, that could be candidate to organic nanoparticles generation, show a very low or negligible solubility in SC-CO₂, and show a reduced solubility in many other compounds that could be good candidates to act as SCF. Np_s recovery can be cumbersome owing to the electrostatic forces, that bind the particles to the walls of the precipitator [14]. Problems of particles coalescence and growth also limit the minimum dimensions of the particles produced by this technique.

A variation of the RESS process is the Rapid Expansion of a supercritical solution into a liquid SOLVENT (RESOLV), that consists of spraying the supercritical solution into a liquid [15] to block the particles growth in the precipitator, improving the RESS performance [16]. Another variation of the RESS process is the Rapid Expansion from Supercritical to Aqueous Solutions (RESAS). The supercritical solution is expanded through an orifice directly into an aqueous solution containing a stabilizer (a surfactant) to minimize the particle aggregation during the free jet expansion [17].

A completely different SCF based technique, that has largely demonstrated the possibility of producing nps, is the supercritical antisolvent precipitation (SAS). In this process, supercritical carbon dioxide is used as an antisolvent and two requisites have to be respected: the solute has to be soluble in the solvent and not soluble in the solution formed by SC-CO₂ and the organic solvent; SC-CO₂ and the liquid solvent have to be completely miscible at the process operating conditions. SAS process can produce nps of several materials, like pharmaceuticals, colouring matters, polymers, etc., with mean diameters ranging between 45 and 150 nm [18]. Nevertheless, SAS as process itself has been poorly-considered until now for nps production, and the sedimentation mechanisms involved in the nanoparticles production by SAS have been completely ignored.

A common lack of knowledge in this field is that, while several papers in the literature discuss of the potential of the supercritical antisolvent based techniques in producing nps [19–23], the issue of their coalescence and efficiency of recovery (collection) have been usually underestimated. In some cases, the authors only looked at the nanometric units forming large micrometric aggregates; but, the possibility of their de-agglomeration has not been considered. A certainly relevant problem is that nps generated in some processes have a large kinetic energy, and, therefore, they give difficulties in sedimentation and tend to disperse along the walls of the precipitation vessel [8,24].

Therefore, the scope of this work is to demonstrate that, not only SAS can generate reproducible nps, but, through the analysis of nps sedimentation mechanism, that the produced nps can be easily collected from a macroscopic point of view and that form disconnectable microscopic aggregates. This special characteristic

could be very useful to perform an easy and quantitative collection of the nps that will recover their single particle identity only when required, during the industrial application.

2. Experimental

2.1. Materials

Samarium acetate (purity 99.9%), rifampicin (purity 97%), astemizole (purity 98%), amoxicillin trihydrate (purity 97%), tetracycline hydrochloride (purity 96%) and clemastine (purity 96%) were supplied by Sigma–Aldrich (Italy). Cellulose acetate was kindly provided by British & American Tobacco (England). Disperse Red 60 (purity 99.9%) was supplied by Sun Chemicals (USA).

Dimethyl sulfoxide (DMSO, purity 99.5%), acetone (AC, purity 99.8%), methanol (ME, purity 99.5%), dichloromethane (DCM, purity 99.5%), chloroform (CLF), ethyl acetate (EtAc, purity 99.5%) and N-methyl 2-pyrrolidone (NMP, purity 99.5%) were supplied by Sigma–Aldrich (Italy). CO₂ (purity 99%) was purchased from SON (Italy).

2.2. SAS apparatuses and techniques

The SAS laboratory apparatus consists of an HPLC pump (Gilson, mod. 805), equipped with a pulse dampener, used to deliver the liquid solution, and a diaphragm high-pressure pump (Milton Roy, mod. Milroyal B) used to deliver carbon dioxide. A cylindrical vessel with an internal volume of 500 cm³ is used as the precipitation chamber. The liquid mixture is delivered to the precipitator through a thin wall 200 μm diameter stainless steel nozzle. A second collection chamber located downstream the precipitator at a lower pressure (20 bar) is used to recover the liquid solvent. Typical liquid solution flow rates ranged between 0.5 and 2.0 mL/min, and SC-CO₂ flow rates were correspondingly adapted to produce a X_{CO₂} ≈ 0.97. Further information on this apparatus have been given elsewhere [25].

A windowed precipitator has also been used to investigate the evolution of the SAS process. In this case, the precipitator has an internal volume of 375 mL and is equipped with quartz windows that allow the visual observation of the jet break-up and of the precipitation phenomena.

A SAS experiment begins by delivering supercritical CO₂ to the precipitation chamber until the desired pressure is reached. Antisolvent steady flow is established; then, pure solvent is sent through the nozzle to the pressurized chamber with the aim of obtaining steady state composition conditions during the precipitation process. At this point, the flow of the organic solvent is stopped and the liquid solution is delivered through the nozzle. The experiment ends when the delivery of the liquid solution to the chamber is interrupted. However, supercritical CO₂ continues to flow for 90 min to wash the chamber from the liquid solubilized in the supercritical antisolvent. If the final purge with pure CO₂ is not performed, the liquid solvent condenses in the precipitator during the depressurization and can modify the morphology of the powder. More details on these procedures have been given elsewhere [25].

2.3. Analytical methods

Samples of the precipitated material were observed by a field emission scanning electron microscope (FESEM, mod. LEO 1525, Carl Zeiss SMT AG, Oberkochen, Germany). Powders were dispersed on a carbon tab previously stuck to an aluminum stub (Agar Scientific, United Kingdom); then, were coated with gold-palladium (layer thickness 250 Å) using a sputter coater (mod. 108 A, Agar Scientific, Stansted, United Kingdom).

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