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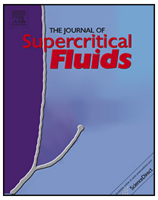

Supercritical fluids based techniques to process pharmaceutical products difficult to micronize: Palmitoylethanolamide

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ABSTRACT

Palmitoylethanolamide (PEA) is a relevant anti-inflammatory and neuroprotective drug whose poor solubility is currently addressed by micronization with traditional fluid technology. In this work, three different supercritical carbon dioxide based techniques were used to improve PEA particle size reduction down to 1–5 μm range; we used supercritical antisolvent (SAS), supercritical assisted atomization (SAA) and supercritical emulsion extraction (SEE) processes and various organic solvents. SAS was substantially unsuccessful since PEA was in some cases extracted and in some other precipitated in form of very long needle-like crystals. SAA and SEE were successful in the micronization of PEA in some cases: the problem to overcome was the very fast crystallization rate of this compound that tends to form flat crystals, more than amorphous microparticles. However, the selection of the proper solvents and operative conditions strongly reduced this inconvenience, since it was possible to limit the evolution of the liquid droplets, that operating as confined reactors, restrained the solidification/crystallization of PEA within the limits of the droplets boundaries. Quasi-spherical PEA microparticles with a mean diameter of 1.48 μm were produced at the most successful micronization conditions.

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1. Introduction

Palmitoylethanolamide (PEA) is an endogenous fatty acid amide, belonging to the class of nuclear factor agonists. It has been studied extensively for its anti-inflammatory and neuroprotective actions [1]. As an endogenous compound, PEA has no adverse effects at pharmacological doses, while possessing a therapeutic effect. It has recently been demonstrated that PEA exerts neuroprotection in central nervous system (CNS) pathologies and that treatment with PEA significantly reduces inflammatory secondary events associated with spinal cord injury (SCI) [2]. Some scientific work has been done to try to describe the physiologic properties of this endogenous modulator and its pharmacologic and therapeutic profile [3]. Given to their lipidic nature and large particle size in the native state, molecules such as PEA have limitations in terms of water solubility and bioavailability.

Micronization techniques are frequently used in the pharmaceutical field for dissolution enhancement of poorly water-soluble drugs, since the dissolution rate of a drug is proportional to its surface area, major benefits of microparticles formulations are enhanced rate of dissolution and reduced variability of drug absorption when orally administered [4]. A recent research paper showed superior anti-inflammatory action exerted by, orally administered, micronized PEA and ultramicronized PEA obtained by air jet-milling, in the rat paw carrageenan model of inflammatory pain [5]. Therefore, it could be very interesting to find a technique that allows the production of PEA micro and nanoparticles to test the possible enhancement of its therapeutic activity.

A possible approach for the preparation of micron-sized drugs is the mechanical comminution (crushing, grinding and milling) of previously formed larger particles. PEA is currently processed on the industrial scale by traditional air-jet milling and reaches interesting particle size distribution: 0.5–10 μm, despite fat and plastic texture of its native crystals. Alternative approaches to microparticles production are based on the precipitation of the solute from a solution in an organic solvent, by nanoprecipitation, solvent evaporation of emulsions and spray drying. These techniques show some drawbacks, such as the difficulty in the removal of toxic solvents, batch layout and difficulties in controlling particles size distributions [6].

Summarizing, lipidic compounds are very difficult to micronize: since they tend to plasticize during comminution processes. Furthermore, they are frequently characterized by a very fast crystallization rate that obstacles liquid based and encapsulation processes.

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The application of supercritical fluids (SCFs) to the precipitation of pharmaceuticals and natural substances has attracted great attention due to the peculiar properties of these fluids [7]. SCFs show liquid-like densities with gas-like transport properties and solvent power that can be continuously adjusted by changes in pressure and temperature. Several precipitation methods have been proposed that can take advantage of the possibility of tuning the properties of SCFs to produce fine powders with a narrow particle size distribution. In some SCF processes used, which can be completely removed from the product due to the high solubility of these solvents in SCF. The contamination of the product is, therefore, avoided. When supercritical carbon dioxide (SC-CO_2) is used, the process can be carried out at near-ambient temperatures, thus avoiding thermal degradation of the substance. For these reasons, SCF processes have been extensively studied during the last years, for applications that include pharmaceuticals, enzymes, natural substances, pigments, superconductor precursors and explosives [8,9]. SCF most frequently used precipitation processes are [10]: the rapid expansion of supercritical solutions (RESS) process [11]; the supercritical anti solvent process (SAS) [12–14] the supercritical emulsion extraction (SEE) [15,16]; the supercritical assisted atomization (SAA) [17]. These processes have been applied successfully to the micronization of pharmaceutical compounds, obtaining micro and nanoparticles with narrow particles size distributions.

In the SAS process, micronization is obtained using CO_2 as the antisolvent to extract the solvent from a solution in which the solute is solubilized. The general rule is that the solvent has to be completely miscible with the anti-solvent; whereas, the solute has to be not soluble in it. This process has been applied to many molecules [18–21]. Modulating the operating conditions (pressure, temperature, concentration of the liquid solution, the ratio between the CO_2 and liquid solution flow rates), different morphologies: nanoparticles (30–200 nm), microparticles (0.5–5 μm), and balloons (5–50 μm) have been obtained.

In the SAA process, the SC-CO_2 is used to improve the atomization of a solution, containing the solute to be micronized. Improved microparticles formation and control of particles size distribution is obtained due to the expanded liquid formed before atomization, that is characterized by reduced surface tension and viscosity. These are two cohesive forces in the jet break-up mechanism and, in the classical atomization, do not allow the production of smaller droplets. Microparticles ranging between 0.2 and 5 μm have been consistently produced [22,23].

During the SEE process, particles are formed as a consequence of the extraction of the organic solvent of an oil in water (o/w) emulsion. The solute is dissolved in the oil phase where also a polymer can be dissolved, in the case of coprecipitate particles production. Extracting the solvent of the oil phase of the emulsion a particles suspension is obtained. Thanks to the enhanced mass transfer of SC-CO_2, the extraction process is completed in a few minutes resulting in homogeneous particles size distribution, avoiding aggregation phenomena. Higher entrapment efficiency is obtained with respect to conventional processes. Furthermore, the extraction can be performed at lower temperatures preserving thermolable compounds from thermal degradation. Another advantage of this process is the possibility to work in continuous with the counter-current extraction tower, that allows a robust and reproducible processing [24–26].

Due to the specific characteristics of SCF-based processes, they could be able to overcome the limitations in PEA micronization. At present PEA has been never tested by SCF-based techniques; therefore, the objective of this work is to test different supercritical fluids based processes for the micronization of PEA, to obtain a micronized product with controlled particles size distribution, that can largely improve its bioavailability. For this reason, we will process PEA using the SAS, SEE and SAA process. It is the first time that different supercritical assisted based processes are tested on the same compound, to select the most efficient technique. Considerations about their efficiency and possible application to different compound families will be also proposed.

2. Apparatus, materials and methods

2.1. Apparatus

2.1.1. Supercritical antisolvent processes (SAS)

SAS apparatus consists of an HPLC pump (Gilson, model 305) used to deliver the liquid solution to the precipitation vessel. A cylindrical vessel of 500 cm^3 internal volume is used as precipitation chamber. The liquid mixture is delivered to the precipitator through a 100 μm internal diameter stainless steel nozzle. Supercritical CO_2 is delivered, using a high pressure pump (Milton Roy, mod. Milroyal B), through another inlet port located on the top of the chamber. Before entering the precipitator, CO_2 is heated at the process temperature. The precipitator is electrically heated using thin band heaters. The pressure in the chamber is measured using a test gauge manometer and regulated by a micrometering valve located at the exit (bottom) of the chamber. This valve is heated by a cable heater connected to a controller. A stainless steel filter (pore diameter of 0.1 μm) located at the bottom of the chamber is used to collect the produced powder. A second vessel located downstream the micrometering valve is used to recover the liquid solvent. A backpressure valve regulates the pressure in this vessel. At the exit of the second vessel a rotameter and a dry test meter are used to measure the CO_2 flow rate and the total quantity of antisolvent delivered, respectively. A schematic representation of the plant and a detailed description are reported elsewhere [27].

2.1.2. Supercritical assisted atomization (SAA)

SAA process is based on the solubilization of controlled quantities of SC-CO_2 in liquid solutions in which the solute to be micronized has been previously dissolved. The solution is atomized through a nozzle. Microparticles are obtained by droplets evaporation using warm Nitrogen. SAA laboratory apparatus, used in this work, consists of two high-pressure pumps (model 305, Gilson) delivering the liquid solution and liquid CO_2 to a heated bath and, then, to the saturator. The saturator is a high pressure vessel (internal volume: 25 cm^3) loaded with stainless steel perforated saddles which assure a large contact surface between liquid solution and CO_2, thus enhancing the dissolution of the gaseous stream into the liquid solution. Typically, volumetric flow rates of the liquid solution of about 4–5 mL/min are used, that produce long residence times (from 4 to 5 min) in the saturator, leading to near-equilibrium conditions. The solution produced in the saturator is sprayed through a thin wall 80 μm diameter injection nozzle into the precipitator. A controlled flow of N_2 is taken from a cylinder, heated in an electric heat exchanger and sent to the precipitator to facilitate liquid droplets evaporation. The precipitator is a stainless steel vessel (internal volume: 3 dm^3) operating at atmospheric pressure. The saturator and the precipitator are electrically heated using thin-band heaters. A stainless steel filter located at the bottom of the precipitator allows the powder collection and the gaseous stream flow out. SAA apparatus layout, a schematic representation of the postulated SAA process mechanism and further details on the experimental procedures were published elsewhere [22,28].

2.1.3. Supercritical emulsion extraction (SEE)

In the SEE process, micro and nanoparticles are obtained starting from emulsions [29,30], via solvent extraction of the oily solvent using supercritical CO_2, producing an aqueous suspension of particles. The apparatus used for the extraction is a 1.2 m tall packed

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