J. of Supercritical Fluids 105 (2015) 92–98

Contents lists available at ScienceDirect

The Journal of Supercritical Fluids

journal homepage: www.elsevier.com/locate/supflu

Supercritical anti-solvent precipitation of ethyl cellulose

R. Djerafi [a], Y. Masmoudi [a], C. Crampon [a], A. Meniai [b], E. Badens [a,*]

[a] Aix Marseille Université, CNRS, Centrale Marseille, M2P2 UMR 7340, 13451, Marseille, France
[b] Laboratoire de l'Ingénierie des Procédés de l'Environnement, Université Constantine 3, Algeria

ARTICLE INFO

Article history:
Available online 6 March 2015

Keywords:
Ethyl cellulose
Supercritical anti-solvent
Micronization
Ethyl acetate

ABSTRACT

Supercritical anti-solvent (SAS) process is considered to be a clean technology suitable for particle design. It is generally used in order to micronize compounds of interest under mild operating conditions of temperature and with very low residual solvent traces in the end-product. By varying the process parameters, the properties of the produced powders can be adjusted with defined size (generally micron or nanometer sized particles), morphology and a narrow particle size distribution. There is currently a growing interest for the elaboration of controlled delivery systems. For this purpose, the SAS process can also be applied in order to co-precipitate molecules of interest with biocompatible and/or biodegradable polymers.

An experimental study dealing with supercritical anti-solvent (SAS) precipitation has been carried out in order to micronize a biocompatible polymer, ethyl cellulose, widely used as a drug carrier in controlled delivery systems for oral administration. Supercritical carbon dioxide was used as anti-solvent for the polymer and ethyl acetate (EtAc), generally recognized as safe (GRAS) by the FDA (Food and Drug Administration) as solvent. The influence of the variation of the main operating parameters upon the characteristics of the micronized polymer was evaluated. In particular, the temperature (308, 318 and 333 K), the polymer concentration (1, 3 and 4 wt%), the EtAc/CO_2 molar ratio (5 and 8 mol%) and the capillary tube diameter (127 and 254 μm) while pressure was kept constant and equal to 10 MPa. Using a low organic solution concentration of 1 wt% and at a temperature of 308 K, ethyl cellulose was successfully micronized in submicron particles with a mean size of 300 nm. However, increasing the temperature or the polymer concentration in the organic solution favored the particle coalescence and even led to fiber formation.

© 2015 Elsevier B.V. All rights reserved.

1. Introduction

The design of fine particles with controlled morphology and particle size distribution is required in the pharmaceutical industry. The conventional techniques such as milling, spray-drying and solvent evaporation are not always suitable for producing fine and pure particles. There are practical problems associated with many of the aforementioned processes: spray-drying can thermally denature compounds, milling produces broad size distribution and solvent/emulsion evaporation techniques often leave residual solvents that are difficult to remove [1,2].

Supercritical fluid (SCF) processes represent alternative techniques to conventional routes of particle generation (micronization and coprecipitation/coating). Indeed, these processes allow the formation of smaller particles with a narrower particle size distribution as well as an accurate control over polymorphic purity and particle morphology [3]. Furthermore, the reduction in the quantity of the required organic solvent or even its elimination leads to a cleaner and a more compact process. Thanks to the mild temperature conditions that could be applied especially when CO_2 is the SCF (T_c = 304.21 K), thermosensitive drug molecules can be manipulated without degrading their properties. These methods use SCFs, generally $scCO_2$, either as a solvent in rapid expansion from supercritical solution processes (RESS), as an anti-solvent in supercritical anti-solvent (SAS) processes or as a solute in particles from gas-saturated solution processes (PGSS). The most studied SCF micronization technique is the SAS process. This technique is used to precipitate solutes (generally polar compounds) with low solubility in supercritical fluid by taking advantage of the miscibility of $scCO_2$ with several organic solvents. Moreover SAS process using $scCO_2$ allows us to obtain controlled particle size and distribution that are not achievable by conventional methods.

Several kinds of compounds have been processed using the supercritical anti-solvent (SAS) precipitation including polymers, bio-polymers, pharmaceutical molecules, organic and inorganic materials (coloring matters, catalysts, precursors of

* Corresponding author. Tel.: +33 685543017.
E-mail address: elisabeth.badens@univ-amu.fr (E. Badens).

http://dx.doi.org/10.1016/j.supflu.2015.02.033
0896-8446/© 2015 Elsevier B.V. All rights reserved.

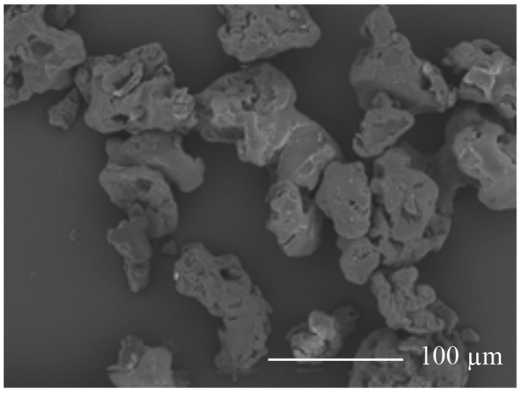

Fig. 1. SEM image of unprocessed ethyl cellulose.

superconductors, etc.) and others either for particle micronization [4], or micro or nano-composites formation [5,6]. For all these applications, it is important to mention that the operating parameters (i.e. pressure, temperature, solvent/carbon dioxide molar ratio, organic solution concentration, hydrodynamic conditions and jet characteristics, etc.) play a key role on the precipitate formation and its physical characteristics (i.e. particle size, morphology, crystal polymorphism, etc.).

For drug delivery systems, the properties of the excipient, often a biocompatible and/or biodegradable polymer matrix, play an extremely important role in the drug release pharmacokinetics [7]. Cellulose derivatives are among the most commonly used for better drug delivery efficiency, reduced toxicity and improvement in patient compliance [8,9]. Ethyl cellulose (EC) is a biocompatible polymer used for the coating of solid dosage forms [10]. This polymer has garnered considerable attention since it is non-toxic, stable and hydrophobic. It can be used as a binder, a dispersing agent, a stabilizer, a water conserving agent, as well as for sustained release products, including film coated tablets, microspheres, microcapsules and matrix tablets for both soluble and poorly soluble drugs [11]. It has been reported that EC has been successfully used in the microencapsulation of different drugs with conventional methods: acetylsalicylic acid [12], propranolol hydrochloride [13], and theophylline [14].

Few authors have attempted the micronization of ethyl cellulose (micro or nanoparticles) using supercritical fluid methodologies. Li et al. [15] have precipitated micrometric particles with sizes comprised between 1.07 and 9.87 μm with a $scCO_2$ spray-drying process using acetone as the organic solvent and $scCO_2$ as the dry medium. The results indicated that the average particle size increased with increasing the gas to liquid ratio, the temperature or the solution concentration, while it decreased with increasing the pressure. Montes et al. [16] reported the same trend using methylene chloride as the organic solvent. Indeed, agglomerated micrometric particles were obtained in supercritical conditions (8 MPa and 308 K). The concentration of the polymer in the organic solution was the only factor that was varied. An increase in the initial concentration of the polymer solution from 10 mg/mL to 40 mg/mL led to an increase in particle size from 3.8 to 5 μm.

The aim of this work was to study the influence of the variation of different operating conditions of the SAS process on the properties of micronized ethyl cellulose (EC). More particularly, the studied parameters were the temperature, the polymer concentration in the organic solution, the solvent/CO_2 molar ratio and the capillary diameter while the pressure was kept constant and equal to 10 MPa. The interest of this work is the use of GRAS ethyl acetate (EtAc) as a solvent and $scCO_2$ as an anti-solvent. This research is a part of a study on the coprecipitation of pharmaceutical active ingredients with ethyl cellulose, in order to obtain stable formulations suitable for sustained drug delivery.

2. Materials and methods

2.1. Materials

Ethyl cellulose (CAS 9007-57-3) was purchased from Sigma–Aldrich (France) and ethyl acetate (purity 99%) from CARLO ERBA Reagents (Italy). Carbon dioxide (purity 99.7%) was supplied by Air Liquide (France).

SEM observation of the raw ethyl cellulose was performed as a comparison for the SAS precipitation results. The morphology of unprocessed ethyl cellulose particles is shown in Fig. 1. Raw particles consist of irregular shaped particles with a rather broad distribution and a large dimension higher than 50 μm.

2.2. Experimental methods

The experimental set-up used for the SAS process is illustrated in Fig. 2. This versatile equipment was built in the laboratory and is mainly composed of a 1 L high pressure precipitation vessel (Top Industrie S.A., France) equipped with a double jacket connected to

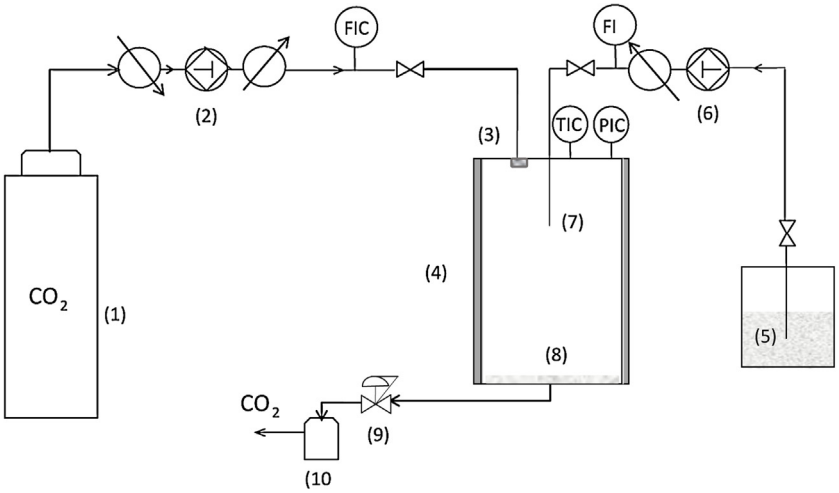

Fig. 2. Schematic diagram of the SAS experimental set-up: (1) CO_2 cylinder, (2) HPLC pump, (3) CO_2 frit filter, (4) high pressure precipitator, (5) organic solution, (6) liquid pump, (7) capillary, (8) metal frit filter, (9) back pressure regulator (BPR), (10) solvent trap.

Download English Version:

https://daneshyari.com/en/article/230179

Download Persian Version:

https://daneshyari.com/article/230179

Daneshyari.com