MICRONISATION OF ETHYL CELLULOSE BY SUPERCRITICAL ANTI-SOLVENT PROCESS

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ABSTRACT

Supercritical Anti-Solvent (SAS) process is considered as a clean technology suitable for particle design, micron or nanometer sized. It is generally used to micronize compounds of interest in mild operating conditions of temperature and nearly without any residual solvent traces in the end-product. By varying the process parameters, the properties of the produced powders can be adjusted with a defined size, morphology and a narrow size distribution. There is currently a growing interest for the elaboration of controlled delivery systems. For this purpose, SAS process can be also applied to co-precipitate molecules of interest with biocompatible and/or biodegradable polymers.

In this study, SAS process was applied to micronize a biocompatible polymer, Ethyl Cellulose, widely used as a drug carrier in controlled delivery systems for oral administration. Carbon dioxide was used as an anti-solvent while Ethyl acetate, low in toxicity, was used as a solvent under 10 MPa and at 308 K. The influence of the process parameters upon the characteristics of the micronized polymer was evaluated by varying several parameters: the polymer concentration in the organic solution (from 1 up to 4 wt.%), the solvent/CO_2 molar ratio (from 5 to 8 mol%) and the capillary tube diameter (127 and 254 µm). Ethyl cellulose particles were produced with a narrow mean distribution, in a range comprised between 0.2 and 2.2 µm.

Keywords: Supercritical Antisolvent, Micronisation, Ethyl cellulose.

INTRODUCTION

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 size distribution. Furthermore, an accurate control over polymorphic purity and particle morphology could be achieved [1]. In addition to the reduction or even the elimination of residual solvent content which leads to a cleaner and more compact process, thanks to the mild temperature conditions that could be used, thermosensitive drug molecules can be manipulated without degrading their properties. These methods use SCFs, generally SC-CO_2 either as a solvent: Rapid Expansion from Supercritical Solution (RESS), as an anti-solvent: Supercritical Anti-Solvent (SAS) or as a solute: Particles From Gas-Saturated Solution (PGSS). The most studied SCF micronization technique is the SAS process. This technique is used to precipitate solutes by using two convenient properties of SCFs; the solvent power of SC-CO_2 to dissolve the non-polar organic solvents as well as the

low solubility of the compounds of interest (which are polar) in SC-CO_2, resulting in the precipitation with controlled particle size and distribution that are not achievable by conventional methods.

Ethyl cellulose (EC) is a biocompatible polymer used for the coating of solid dosage forms [2]. This polymer has garnered considerable attention since it is a non-toxic, stable, and hydrophobic polymer, that can be used as a binder, dispersing agent, stabilizer, water conserving agent, and for sustained release products, including film coated tablets, microsphere, microcapsules and matrix tablets for both soluble and poorly soluble drugs [3]. It has been reported that EC has been successfully used in microencapsulation of different drugs with conventional methods: aspirin [4], propranolol hydrochloride [5], and theophylline [6].

The aim of this work is to study the influence of different operating conditions on the precipitation of ethyl cellulose through SAS process using ethyl acetate (EtAc) as a solvent and CO_2 as an antisolvent. This work is the first step in the study of the co-precipitation and encapsulation of drugs with this bio-polymer, in order to obtain stable formulations suitable for pharmaceutical applications.

MATERIALS AND METHODS

1- Materials

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

2- Experimental methods

The experimental set-up used for the SAS process is illustrated in figure 1. It is mainly composed of a 1 liter high pressure precipitation vessel (Top Industrie S. A., France) equipped with a double jacket connected to a thermostated bath. This autoclave is fed with CO_2 through a regulated high pressure piston pump (LGP50, Separex, France) and with the organic solution through a HPLC pump (Gilson 307, France). The outlet of the autoclave is equipped with a back pressure regulator (Tescom, Germany) to control the pressure during the experiments.
In a typical SAS experiment, the autoclave is first set to the desired temperature and then fed with preheated CO_2 with a regulated mass flow rate. The pressure inside the autoclave is controlled by adjusting the aperture of the back pressure regulator. When the operating parameters, i.e. pressure, temperature and CO_2 flow rate are reached, the organic solvent was dispersed through a capillary nozzle (inner diameter of 254 μm) in a co-current SC CO_2 stream to reach the desired solvent/CO_2 molar ratio in the vessel. The organic solvent is then replaced with the organic solution. Precipitation process is then carried out for a fixed time defined by the final quantity of product to collect. Finally, a washing step was realized by flowing pure CO_2 in the autoclave in order to renew its content, removing the remaining solvent. Once the washing completed, the autoclave is slowly depressurized, and micronized particles are

recovered. The morphology and particle size of micronized ethyl cellulose particles were characterized using a Scanning Electron Microscope (Hitachi TM3000).

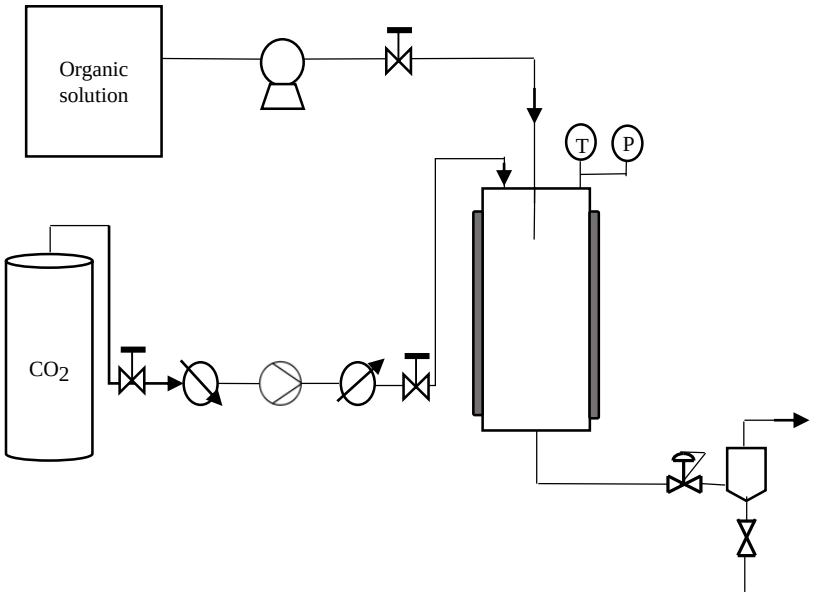

Fig. 1. Schematic diagram of the SAS experimental set-up.

EXPERIMENTAL RESULTS

Raw ethyl cellulose presents irregular shape particles with size ranging between 50 to 100 µm and a rather broad distribution of widths as illustrated in Figure 2.

The influence of several parameters on the supercritical micronization of ethyl cellulose were studied by varying the solvent/CO_2 molar ratio, the capillary diameter as well as the concentration of EC in the organic solution, The tested experimental conditions are summed up in Table 1. For all the experiments, the pressure and the temperature were kept constant at 10 MPa and 308 K respectively. In these conditions, ethyl acetate and CO_2 are completely miscible [7].

Table. 1
Summary of the experimental conditions tested

Experiment	P (MPa)	T (K)	$C_{polymer}$ (wt%)	Ratio EtAc/CO_2 (mol%)	Injection velocity ($m.s^{-1}$)	Capillary diameter (µm)
1	10	308	1	8	1	254
2	10	308	1	5	1	254
3	10	308	1	8	1	127
4	10	308	3	8	1	254
5	10	308	4	8	1	254

The so micronized particles were characterized through SEM observations. Comparing to unprocessed polymer, two distinct features can be revealed. First, the mean size of the EC particles is significantly reduced from 50-100 µm to submicrometric range of 0.2 to 2.2 µm. Secondly, the morphology of the micronized particles has changed from irregular shape to well-defined spheres. These changes are shown in figure 2 where the morphology of unprocessed and SAS-processed ethyl cellulose particles are presented.

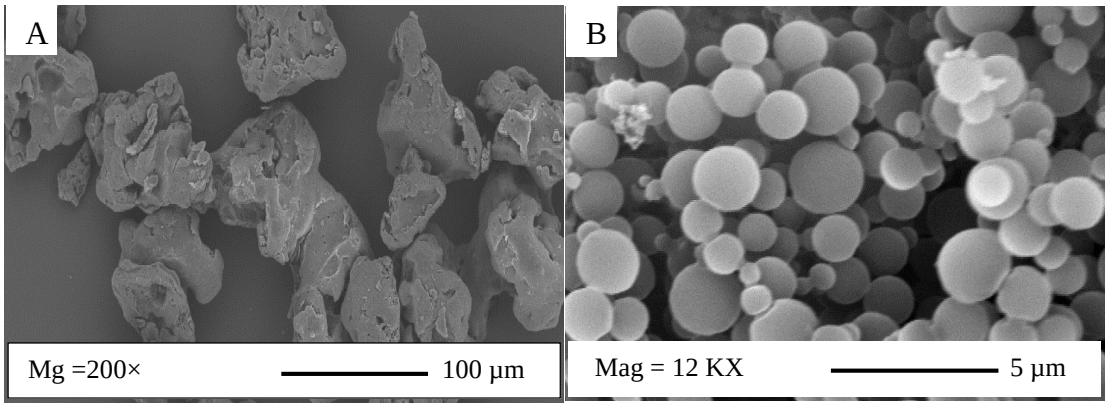

Fig. 2. SEM images of Ethyl cellulose particles before (A) and after (B) SAS process.

1. **Influence of the molar ratio solvent/CO_2**

Experiments with different EtAc/CO_2 molar ratios (5 and 8%) were carried out with a capillary diameter of 254 µm and an organic solution concentration of 1wt% (experiments 1 and 2 in table 1). In our experimental conditions, varying the solvent/CO_2 molar ratio in the explored range does not influence the morphology, the size (approximatly 0.2 to 0.4 µm) or the coalescence of the resulting particles (figure 3)

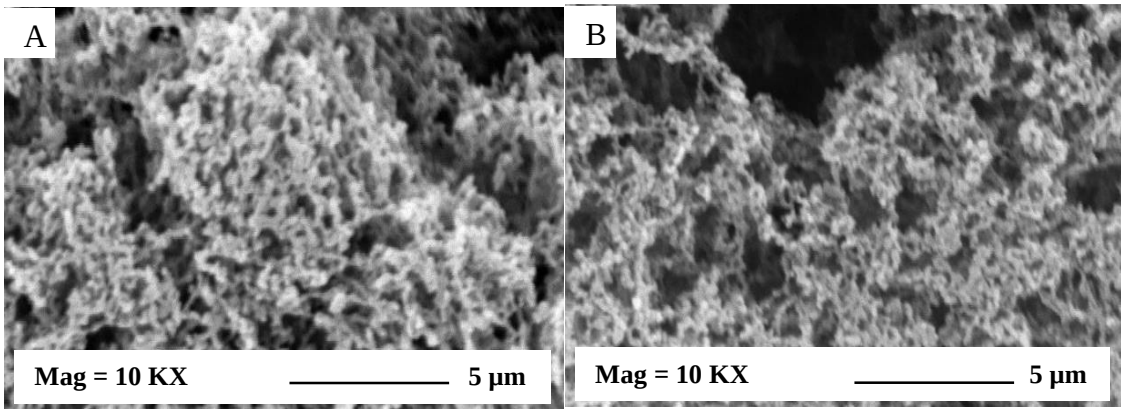

Fig. 3. SEM images of micronized EC with different molar ratios 5% (A) and 8% (B), from solution concentration (EC in EtAc) of 1 wt% and injection velocity of 1m.s^{-1}.

2. Influence of the capillary diameter

Two different capillary diameters, 127 and 254 µm, were also used keeping the processing conditions constant at a pressure of 10 MPa and a temperature of 308 K with 1wt% initial ethyl cellulose solution concentration and a velocity of 1 $m.s^{-1}$ (experiments 1 and 3 in Table 1). The morphology of so micronized EC particles are shown in figure 4 where SEM images obtained at the same magnification are presented. These images show that sub-micrometric particles are produced both with the small and the largest capillary injector and there is no significant variation in the morphology and the size diameter of the resulting particles. On the basis of SEM images the mean particles size were measured and are ranging from 0.2 to 0.4 µm.

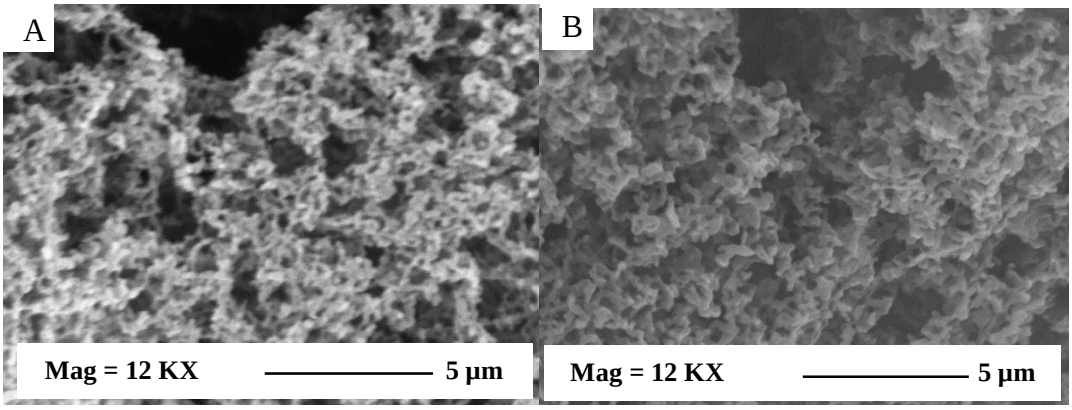

Fig. 4. SEM images of micronize EC with different capillary diameters 127µm (A) and 254 µm (B), from solution concentration (EC in EtAc) of 1 wt% and injection velocity of 1$m.s^{-1}$.

3. Influence of the organic solution concentration

The influence of the initial concentration of the polymer in the injected solution on micronized EC particles was studied by carrying out a series of experiments with different concentrations: 1wt%, 3wt% and 4wt% (experiments 1, 4 and 5 in Table 1). The Solvent/CO_2 molar ratio was kept constant and the velocity of the injected solution through a capillary of 254 µm was of 1 $m.s^{-1}$.

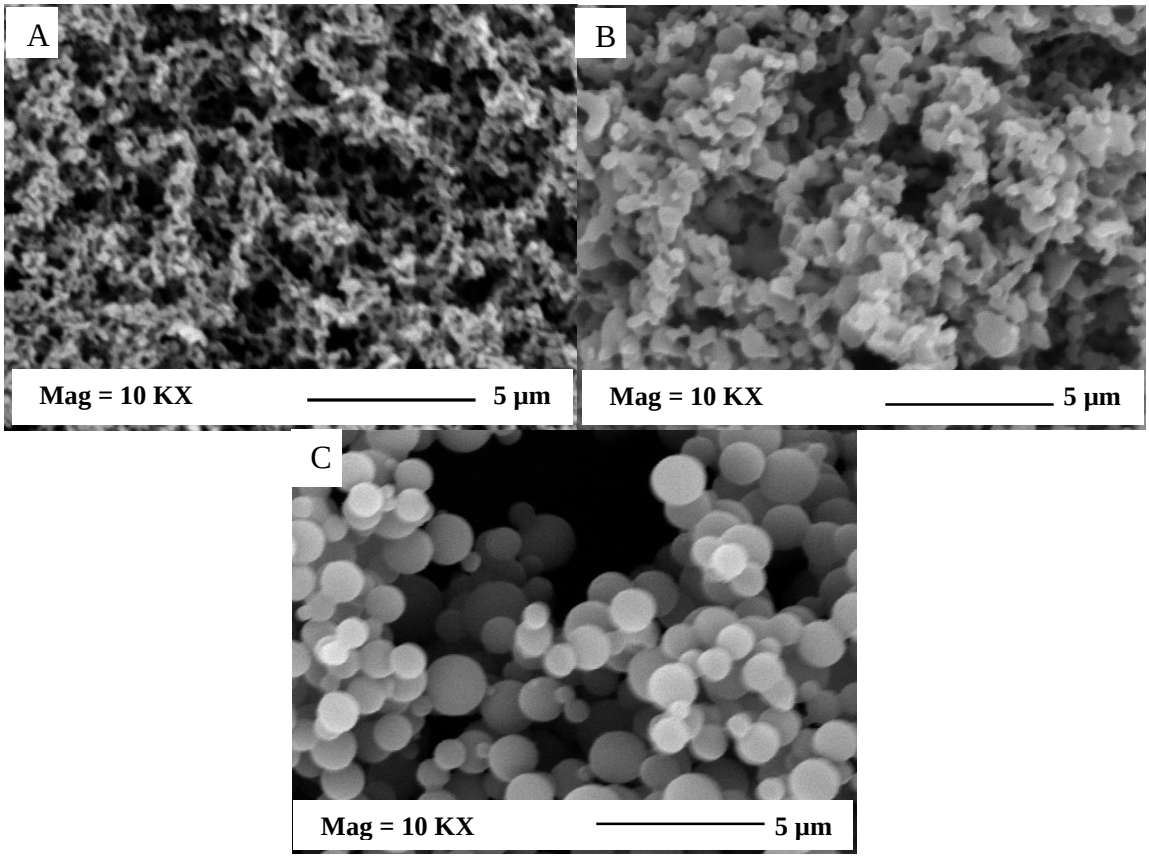

Fig. 5. SEM images of micronized EC with different initial organic solution concentrations (EC in EtAc), 1 wt% (A), 3 wt% (B) and 4 wt% (C), with a capillary diameter of 254 µm and a solution velocity of 1m.s^{-1}.

An increase in the initial concentration of the injection solution has two opposing effects : on the one hand, higher supersaturations from higher concentration tend to decrease the particle size due to high nucleation frequency; and on the other hand, higher growth rate from higher concentration tend to increase the particle size. In our case, increasing the polymer concentration in the organic solution results in an increase in particle sizes. Indeed, at lower concentrations, supersaturation of the polymer is reached more slowly and, therefore, the precipitation delays and nucleation dominate growth, producing smaller particles. By increasing the concentration, supersaturation occurs earlier, with growth dominating over the nucleation process, thus producing larger particles. This result is consistent with those obtained by Reverchon *et al.* [8] and Montes *et al.* [9].

CONCLUSION

The micronization of ethyl cellulose from ethyl acetate solutions with a supercritical anti-solvent process was successfully performed. Spherical microparticles with diameters ranging from 0.2 to 2.2 µm were obtained. The effect of different operating conditions on the particles size was studied. Particles size increased by increasing the polymer concentration in the organic solution. However, neither the molar ratio solvent/CO_2 in the studied range nor the capillary

diameter of the injection solution, influence the obtained particle morphology. These first results will be used in order to study the co-precipitation and the encapsulation of pharmaceutical compounds.

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