

EFFECTS OF TEMPERATURE ON THE CO- PRECIPITATION OF AMOXICILLIN AND ETHYLCELLULOSE BY SAS PROCESS AND DRUG DELIVERY IN SIMULATED FLUIDS

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INTRODUCTION

The coating of microparticles finds wide applications in various important industries [1–3] as pharmaceutical, food, fertilizer, cosmetics, electronic, and biomedical. Among other it has been found to be of particular interest for the controlled release of drugs, genes and other bioactive agents. Some of the key issues that drug delivery studies try to address include increasing bioavailability of drugs, reducing side effects, controlling kinetic release profiles, increasing clinical ease of use and reducing pain from administration [4]. The necessity to deliver drugs for the efficacious treatment of diseases has resulted in significant advances in the development of drug delivery vehicles [5, 6].

Conventional techniques for the encapsulation of fine particles, such as emulsion evaporation, phase separation, spray-drying, freeze-drying and so forth, require large amounts of organic solvents, surfactants and other additives, a situation that leads to volatile organic compound emissions and other waste streams.

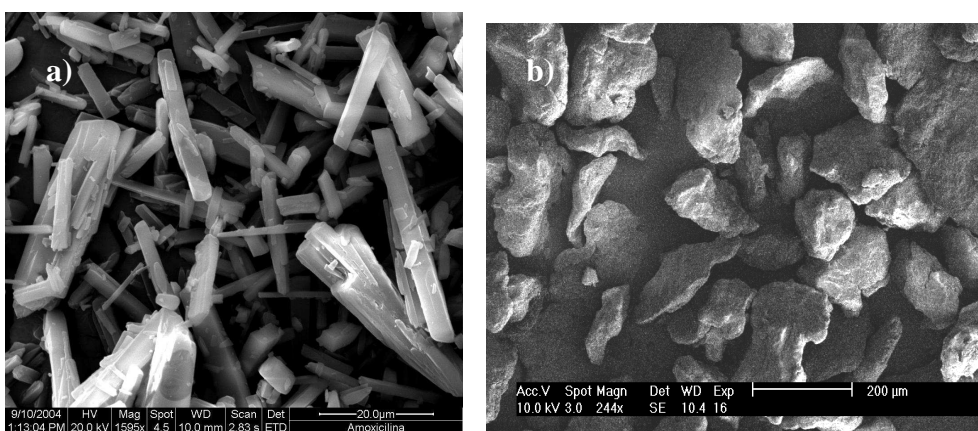
The application of supercritical fluids (SCF) as an alternative to the conventional precipitation processes has been an active field of research and innovation during the past two decades [7–9]. In particular, in the supercritical antisolvent process (SAS) the supercritical fluid, normally CO₂ should be completely miscible with the liquid solvent, at the process conditions, whereas the solute should be insoluble in the SCF. Therefore, contacting the liquid solution with the SCF induces the formation of a solution and produces supersaturation and precipitation of the solute. The formation of the liquid mixture is very fast due to the enhanced mass transfer rates that characterize the supercritical fluids and, as a result, micro- and nanoparticles could be produced.

In this work, commercial amoxicillin (AMC) and ethyl cellulose (EC) have been dissolved in organic solvent mixture, dichloromethane (DCM) and dimethyl sulfoxide (DMSO), and have been sprayed into the vessel mixing with supercritical CO₂. The drug and polymer have been co-precipitated due to a higher supersaturation produced by diffusion of the organic solvent into the supercritical CO₂.

MATERIALS AND METHODS

Dichloromethane (purity 99.5%) and dimethyl sulfoxide (purity 99.9%) were purchased from Sigma-Aldrich (Spain). CO₂ with a minimum purity of 99.8% was supplied by Linde (Spain). Amoxicillin (purity ≥ 97%) and ethyl cellulose (48.0-49.5% (w/w) ethoxyl basis) were purchased from Sigma-Aldrich (Spain). SEM images of the amoxicillin and ethyl cellulose composite powders precipitated on the vessel wall were obtained using a JEOL scanning electron microscope. Prior to analysis the samples were placed on carbon tape and then covered with a coating of gold using a sputter coater. SEM images of commercial amoxicillin and ethyl cellulose are shown in Figure 1.

Figure 1. SEM image of a) unprocessed amoxicillin, and b) ethyl cellulose

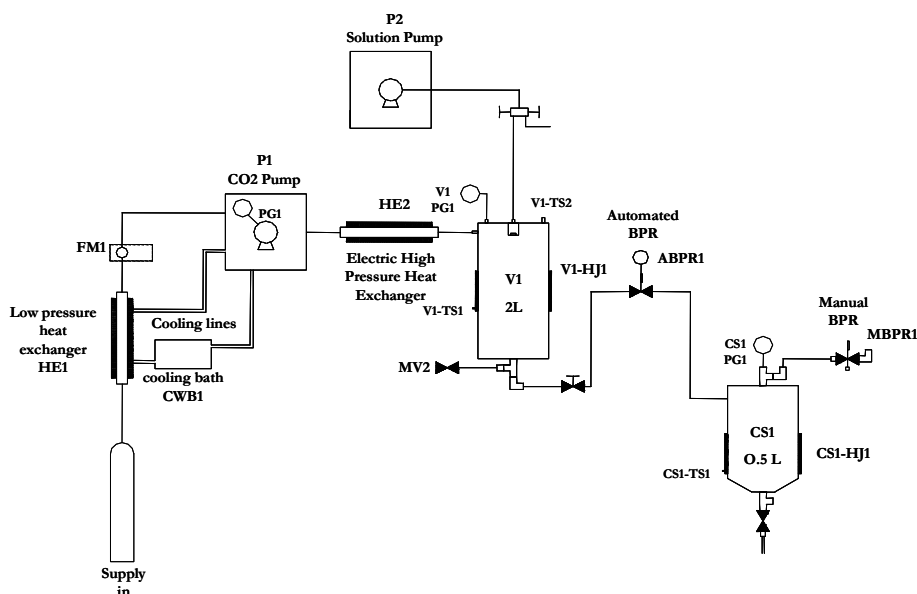


X-ray photoelectron spectroscopy (XPS) (Kratos Axis Ultra DLD) was used for the chemical analysis of the surface of the microspheres. The powder samples were mounted on double sided adhesive conducting polymer tape and analysed without any further treatment. Elemental analysis (EA) (CHNS-932 LECO) was used to confirm the presence of amoxicillin in the precipitates obtained.

The experiments were carried out in a pilot plant developed by Thar Technologies® (model SAS 200). A schematic diagram of this equipment is shown in Figure 2. This plant was described in detail in a previous publication [10].

Amoxicillin and ethyl cellulose commercials in a solution of DCM/DMSO (85/15) have been used to precipitate ethyl cellulose (EC) and amoxicillin (AMC) composites by SAS process using CO₂ as antisolvent, at the amoxicillin: ethyl cellulose ratio 1:7.5 w/w. The temperature effect has been evaluated and in this way experiments with temperatures from 308 to 333 K into the vessel have been carried out (Figure 3). Pressure of 200 bar, CO₂ flow rate of 11g/min, sample flow rate of 2 ml/min, washing time of 120 minutes and a nozzle of 100 μm of diameter to spray the solution into the vessel have been held in all the experiments.

Figure 2. Pilot plant schematic diagram

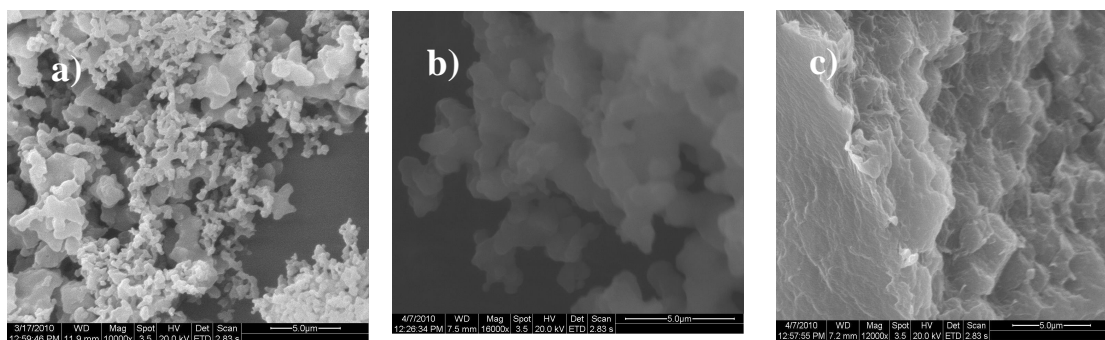


The drug release profile into simulated gastric fluids (SGF) and simulated intestinal fluids (SIF) have been carried out adding 40 mg of amoxicillin into 20 ml of fluid. The samples have been recovered periodically and measured by UV Shimadzu 1240 spectrophotometer at 288 nm. The release medium (3.0 ml) was removed for analysis at given time intervals using a syringe, and replaced with the same volume of fresh preheated SGF and SIF respectively. Corrected concentration of released amoxicillin have been calculated according to Zhu et al [11].

RESULTS

All experiments led to a successful precipitation of amoxicillin and ethyl cellulose. SEM images of these co-precipitation experiments are shown in Figure 3. The morphology of the particles changed from rectangular or irregular blocks (raw material) to spherical microparticles in the experiments a) and b). The shape of the particles is different in the runs at higher temperature. So, when temperature is increased from 308 to 328 K, the particle size of the composites is increased as it is shown in Figure 3, but an agglomerated of particles formed by irregular block is observed when the temperature experiment is 338 K.

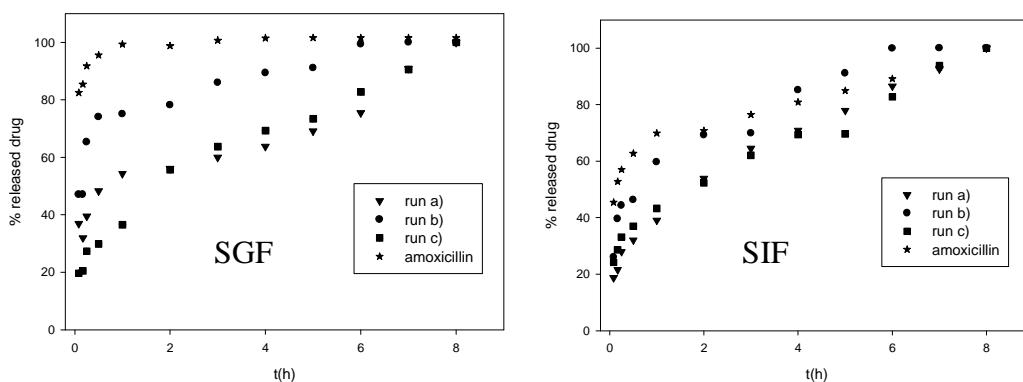
Figure 3. SEM images of the amoxicillin and ethyl cellulose co-precipitated powder at a) 308K, b) 323K and c) 338K



XPS has been used to determine the location of the drug by the chemical analysis of the particles in the polymer surface. The elements that differentiate amoxicillin from ethyl cellulose are sulphur and nitrogen. Therefore, these elements can indicate the location of the drug in the precipitated powders. Run a) and b) presented nitrogen on surface but run c) did not, so in this case the polymer surrounded amoxicillin particles. The presence of amoxicillin in the precipitates obtained has been confirmed by elemental analysis.

On the other hand, the drug delivery profile into simulated gastric fluid (SGF) and simulated intestinal fluid (SIF), for these composites have been obtained and can be observed in Figure 4. The obtained precipitated at 323 K have the highest slopes so the faster release, in both fluids. Then, a relationship between the presence of nitrogen on the precipitated surface and its release profile was established. The release of amoxicillin from runs a) and b) in which nitrogen was present on the surface is faster than run c) where nitrogen was not present. This fact is evident in Figure 4. Anyway the co-precipitated released allowing a slower drug release than pure drug.

Figure 4. Release profile of the amoxicillin and ethyl cellulose co-precipitated in SGF and SIF



CONCLUSION

All experiments led to a successful precipitation of amoxicillin and ethyl cellulose. The shape and size of the particles are influenced by temperature, so when temperature is increased from 308 to 328 K, the particle size of the composites is increased and agglomerated particles are obtained at 338 K. The release of amoxicillin from runs where nitrogen was present on the surface is faster than run where was not present. Co-precipitated systems released allowing a slower drug release than pure drug.

Acknowledgment

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