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Supercritical fluid assisted production of HPMC composite microparticles

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ABSTRACT

Supercritical fluid technology has recently been proposed in literature to obtain drug controlled release systems as alternative to conventional techniques. In this work, the Supercritical Assisted Atomization (SAA) is proposed to produce hydroxypropyl methylcellulose (HPMC) based composite microparticles using ampicillin trihydrate as model drug.

Successful micronization of HPMC alone and, then, coprecipitation of HPMC and ampicillin were obtained using a buffer solution as solvent. Well-defined micrometric particles with spherical or "doughnut-like" morphology were produced in both cases, with a sharp particle size distribution: diameters ranged between about 0.05 and 5.20 μm. SAA composite microparticles were characterized by differential scanning calorimetry (DSC), Scanning electronic microscopy-energy dispersive X-ray spectroscopy (SEM-EDX) and UV–vis analysis. A solid solution of HPMC and ampicillin was produced; a stabilizing effect of the polymer on the drug was observed, resulting in the protection of ampicillin from thermal degradation. Coprecipitates were produced at different drug/polymer ratios and two kinds of formulations for oral drug delivery were explored to verify ampicillin controlled release from HPMC: tablets and gelatine capsules of coprecipitated microparticles. Tablets released 97% of AMP in more than 72 h, allowing a slower drug release than capsules, that released 100% of AMP in 8 h. Drug release mechanisms characteristic of swelling-controlled systems were observed, with ampicillin release rate dominated by the erosion of HPMC matrix.

1. Introduction

Hydrophilic based microparticle systems are one of the most novel and advanced release devices currently developed and are an extremely important type of dosage form for oral drug delivery. In general, microparticulate drug delivery offers high efficacy and flexibility of administration. According to the pharmaceutical target, microparticles can be used as oral delivery systems if encapsulated into gelatine capsules or compressed into tablets; as subcutaneously injected, inhalatory, parental or transdermal delivery systems if used as free powder. Particularly, the oral route of drug delivery is typically considered the preferred and most patient-convenient mean of drug administration.

Hydroxypropyl methylcellulose (HPMC) is a semi-synthetic ether derivative of cellulose that is widely used in many fields. In particular, it is frequently used in the formulation of controlled release devices because of its non-toxic nature and easy to manufacture [1,2]. HPMC belongs to the swellable hydrophilic matrix systems, which form a gel layer when exposed to aqueous media. It has been reported that drug release from HPMC matrices is affected: (i) by the physical character of the polymer, such as polymer viscosity, particle size, and drug/polymer ratio; (ii) by the physicochemical properties of the drugs, such as solubility, particle size, and drug loading; (iii) by manufacturing factors, such as compression force, tablet shape, hardness, formulation excipients, coatings, and processing techniques, as well as by the testing medium [3–9]. For example, Heng et al. [10] observed that particle size of HPMC plays an important role in determining the release behavior of aspirin from tablets made of HPMC and aspirin: the polymer particle size affects drug release mechanism. The tablets showed three different release characteristics as particle size decreased: disintegration at large particle size level, diffusion at medium size level and a combination of both erosion and diffusion at fine size level.

Several processes are currently studied to design composite particles, such as solvent evaporation, coprecipitation

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emulsification–evaporation, emulsification–diffusion and salting-out method [11–13]. However, conventional processes have some drawbacks, such as the high temperatures required and the limited size control during spray drying, or manufacturing complexity of current emulsion techniques. Moreover, the organic solvents used to dissolve polymers are difficult to be removed and, therefore, several further operations are necessary to reduce the solvent residues below the regulatory limits.

Supercritical fluid (SCF) based processes are promising technologies able to overcome many drawbacks presented by conventional methods [14–16]. At present, very few works on HPMC microparticles production using SCF based processes are reported in literature. In particular, Moneghini et al. [17] produced HPMC-theophylline coprecipitates using Supercritical Antisolvent Precipitation to obtain sustained release of the drug. However, no morphological analysis neither particle size distribution on precipitates is reported in their work; moreover, they used a dichloromethane/ethanol mixture as solvent, but no solvent residue analysis was performed on coprecipitates.

One of the favourable HPMC characteristics is that it is water-soluble; thus, if water or aqueous solution are used instead of organic solvents, problems of solvent residues in the micronized powders can be avoided, with the consequent safe pharmaceutical and biomedical application of coprecipitates. But, supercritical fluid based processes taking advantage of the antisolvent effect of CO_2 cannot efficiently employ water as solvent, since supercritical CO_2 is not an effective solvent for aqueous solutions. On the other hand, processes based on the solvent effect of CO_2 (such as RESS-based processes) cannot be successfully applied to HPMC because of the very limited solubility of this polymer in SC-CO_2 [18].

Among SCF techniques, Supercritical Assisted Atomization (SAA) is an efficient process based on the solubilization of controlled quantities of SC-CO_2 in liquid solutions [19–21]. One of SAA advantages is the possibility to use either organic solvents either water or aqueous solutions as the process solvent. Moreover, it is possible to avoid chemical and thermal degradation; it provides a good particle size and particle size distribution control with the production of microparticles with mean diameters strictly ranging between 0.05 and 5 μm. These characteristics, joined to the quality of a green and not aggressive process with respect to the substances treated, allowed the SAA technique able to successfully micronize several compounds until now: pharmaceuticals, catalyst and superconductor precursors, cyclodextrins and polymers [19–26].

In a recent paper, SAA has also been proposed for the production of composite materials, such as microspheres. Coprecipitation of chitosan/ampicillin trihydrate has been obtained and composite microspheres with the amorphous drug homogeneously dispersed into the polymer matrix have been produced [27].

In this work, the possibility of extending SAA field of applications to obtain coprecipitates for drug controlled release has been further investigated. In particular, the SAA production of HPMC and HPMC-based composite microparticles is proposed. Ampicillin trihydrate (AMP) has been selected as model drug for the coprecipitation of HPMC/AMP microspheres. Water has been used to solubilize both HPMC and AMP. Morphological, granulometric, solid state and drug release analyses have been performed on microparticles to investigate the processability of this multi-component system and the distribution of the drug inside the particles. The effect of the polymer/drug ratio on drug release rate has been evaluated as well. Drug release studies have been performed on two possible formulations for oral delivery of the drug: tablets prepared by direct compression of coprecipitates and gelatine capsules containing the coprecipitated powder.

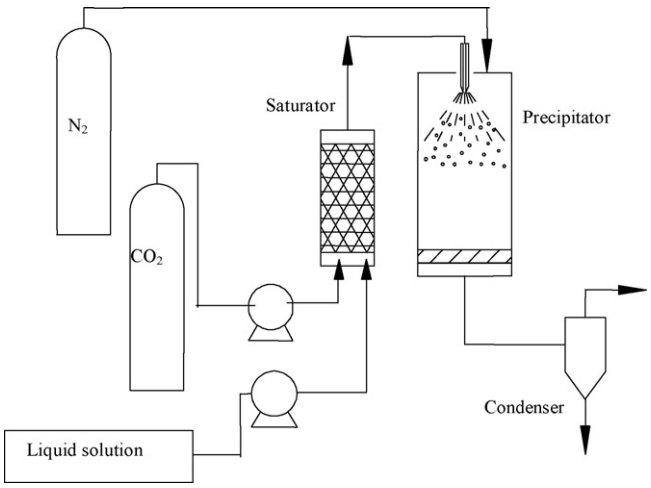

Fig. 1. Schematic representation of the SAA apparatus.

2. Experimental apparatus, materials, methods

2.1. SAA process and apparatus

In SAA process, SC-CO_2 acts both as co-solute being miscible with the solution to be treated, as well as pneumatic agent to atomize the solution in fine droplets. This process is based on the use of a packed saturator that contains high surface packings and ensures long residence times; thus, a near-equilibrium solution is formed between the liquid solution (solute + solvent) and SC-CO_2; then, it is atomized through thin wall injector and sprayed into the precipitator. A two-step atomization is obtained: primary droplets produced at the outlet of the injector (*pneumatic atomization*) are further divided in secondary droplets by CO_2 expansion from the internal of the primary ones (*decompressive atomization*). The subsequent evaporation of the solvent from the droplets produces the microparticles precipitation.

SAA laboratory apparatus consists of two high-pressure pumps (mod. 305, Gilson, Middleton, USA) delivering the liquid solution and liquid CO_2 to a heated bath (Forlab mod. TR12, Carlo Erba, Milan, Italy) and, then, to the saturator. The saturator is a high pressure vessel (internal volume: 25 cm^3) loaded with stainless steel perforated saddles. 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. The solution obtained 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 (mod. CBEN 24G6, Watlow, St. Louis, USA) 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. A schematic representation of the SAA apparatus is reported in Fig. 1. Further details on the experimental procedures were published elsewhere [19–23].

About 500 mg of powder was produced in each experiment with a yield of about 95% (calculated as the ratio between the powder collected and the solutes fed to the apparatus). The remaining part of the injected material was lost on the walls of the precipitator.