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Ibuprofen–polymer precipitation using supercritical CO_2 at low temperature

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ABSTRACT

A process for the SAS coprecipitation of ibuprofen with the polymers poly(L-lactic acid) and Eudragit L100 was successfully carried out. The particle size was reduced to micrometer and near nanometer ranges. The morphology of the raw material changed to spherical upon processing for both poly(L-lactic acid)/ibuprofen particles and eudragit/ibuprofen particles. The eudragit-based particles were significantly smaller than those obtained with poly(L-lactic acid). Ibuprofen release profiles were determined for simulated gastric and intestinal fluids in order to study the effect of the polymer and to identify the appropriate systems for different administration routes. The in vitro release profiles for both polymer/drug systems showed a slower and more controlled release in comparison to the unprocessed ibuprofen. Moreover, the effects of pressure, temperature, initial concentration of the solution and drug-to-polymer ratio on the particle size and morphology of these drug/polymer systems have been evaluated. According to the XRD, DSC and FTIR data, physicochemical interactions do not occur between ibuprofen and the polymers and a proportion of the ibuprofen molecules probably remained on the microparticle surface.

1. Introduction

Supercritical fluid techniques have been widely used to produce a variety of pharmaceutical compounds and the processing of numerous kinds of micro- and nanoparticles is currently carried out [1–8]. This approach is particularly important for drugs with poor water solubility, such as ibuprofen (IBU) – one of the most commonly used nonsteroidal anti-inflammatory drugs for the treatment of inflammatory processes. The use of microparticles of any active substance with a controlled size makes it possible to increase the bioavailability and decrease the therapeutic dosage of the drug, thus improving its efficiency. For this reason, in a previous study [9] the particle size reduction of IBU obtained on using supercritical CO_2 was investigated. The influence that the experimental conditions had on morphology, particle size (PS) and particle side distribution (PSD) was also investigated in the Rapid Expansion of Supercritical Solutions (RESS) process. The direct administration of IBU can lead to irritation of the digestive tract and could cause or aggravate pre-existing ulcers. In order to avoid these harmful side effects, biocompatible polymers have been successfully used to obtain carrier/IBU systems [10–17]. However, the processes used to obtain these systems often suffer from drawbacks such as high residual solvent concentrations, high levels of waste streams, the need for post-processing steps for purification and moderate temperatures. The use of supercritical fluid technology overcomes these drawbacks and prevents possible thermal and chemical solute degradation while providing a high quality product with control of the PS and PSD. Numerous authors have carried out successful encapsulation experiments using supercritical fluids in the pharmaceutical field [18–20]. In particular, IBU has been encapsulated by exploiting the fact that polymers can be plasticized by supercritical CO_2, a process that results in the complete molecular dispersion of IBU molecules. In this way, spherical particles of IBU and poloxamers, gelucire and glyceryl monostearate with sizes in the range 50–200 μm were produced by the Particles from Gas Saturated Solutions (PGSS) approach [21]. On the other hand, Hussain and Grant [22] carried out the impregnation of IBU into submicron films (25–250 nm) of poly(methyl methacrylate) (PMMA) and poly(vinyl pyrrolidone) (PVP) by solubilizing the drug with supercritical CO_2. PMMA–PLA [23] and PEG–PVP blends [24] and cyclodextrin [25,26] were also loaded with IBU by Supercritical CO_2-assisted impregnation. Hermsdorf et al. [27]

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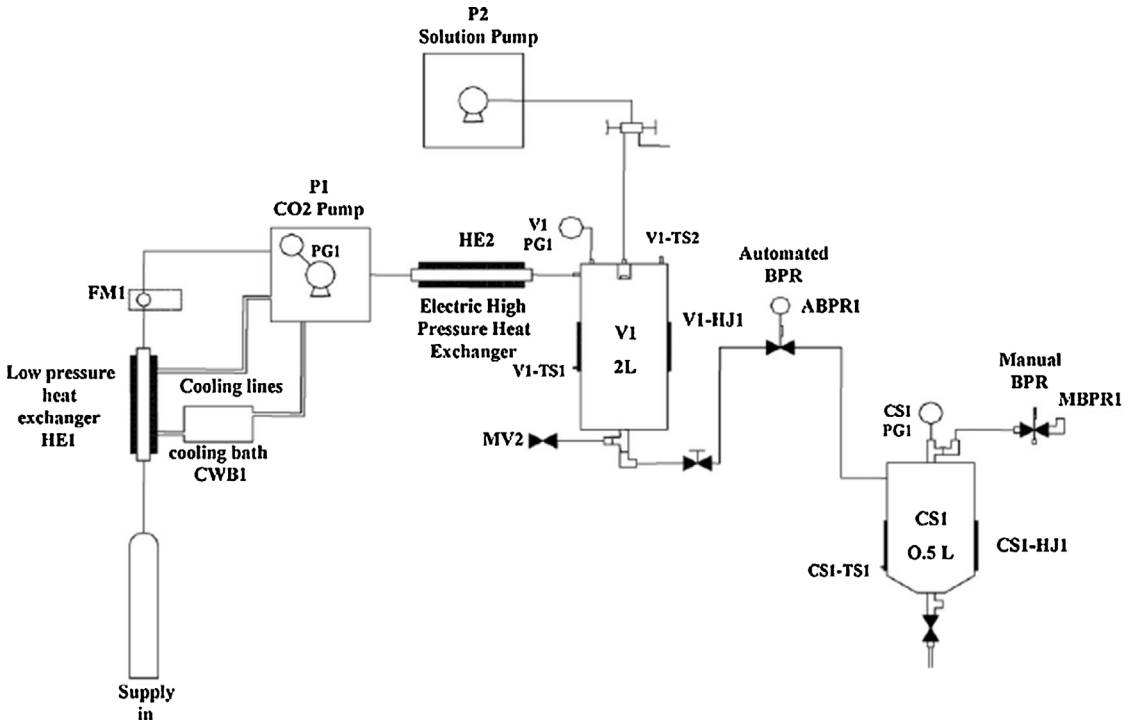

Fig. 1. Schematic diagram of SAS 200 pilot plant.

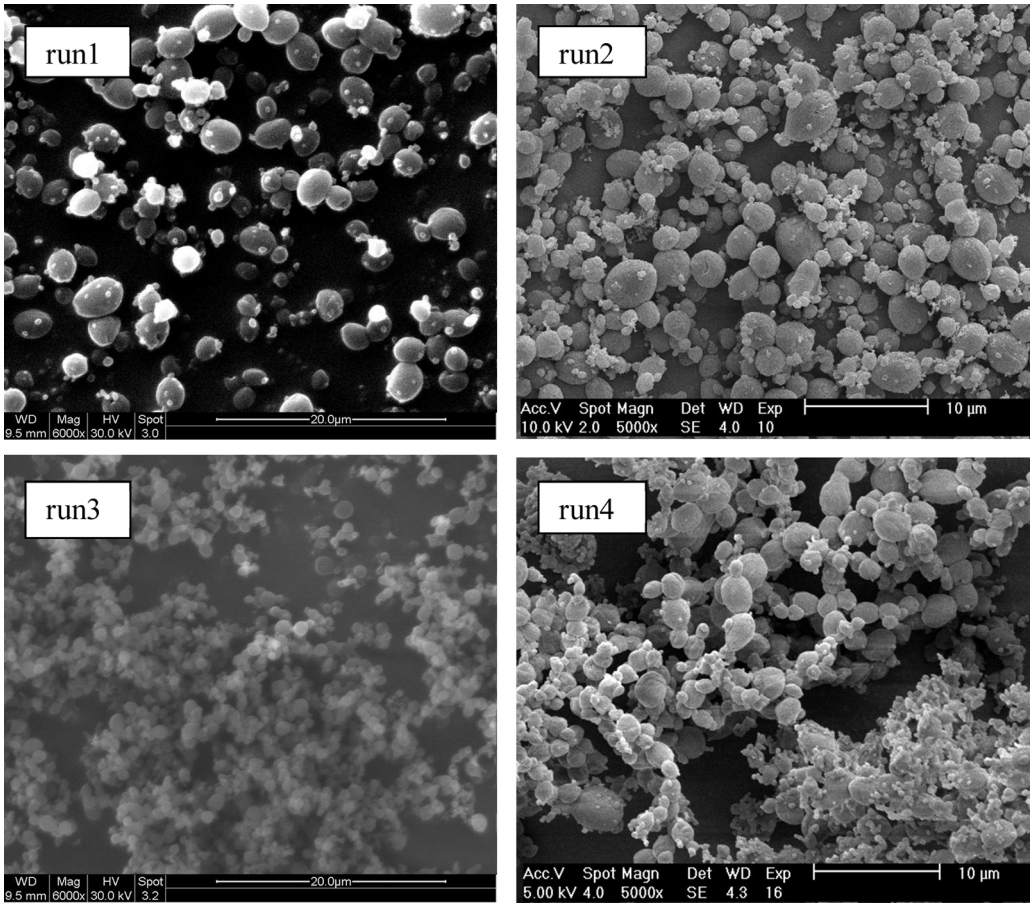

Fig. 2. SEM images of IBU–PLA particles at 120 bar and 40 °C – drug:polymer ratio effect.