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Formation of PVP/nimesulide microspheres by supercritical antisolvent coprecipitation

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ABSTRACT

In order to improve the bioavailability of poorly water soluble drugs, an effective technique is the coprecipitation of the drug with a hydrophilic polymer. In this work, the coprecipitation of polyvinylpyrrolidone/nimesulide (PVP/NIM) nanostructured microparticles using Supercritical Antisolvent (SAS) was proposed. The effects of the main process parameters, such as polymer/drug ratio, overall concentration, operating pressure and temperature were investigated to identify successful operating conditions for SAS coprecipitation. Microparticles with a mean diameter ranging between 1.7 and 4 μm (calculated in number of particles) were successfully produced; they were characterized using different analytical techniques, to demonstrate the occurred coprecipitation. Precipitation yield was found to be about 100% with respect to the amount of solute dissolved in the starting solution. Drug release analyses revealed that Nimesulide dissolution rate from PVP/NIM microparticles in a phosphate buffered saline solution (PBS) was 2.5 times faster with respect to unprocessed drug. The possible precipitation mechanisms involved in the process were discussed.

1. Introduction

Poorly water-soluble drugs are characterized by low bioavailability, which implies the use of high dosages to reach a therapeutic concentration, with consequent adverse effects on patient's health [1,2].

Nimesulide (4-nitro-2-phenoxymethanesulfonamide) (NIM) is a non-steroidal anti-inflammatory drug (NSAID), widely used in the treatment of acute pain associated with different diseases, such as back pain, toothache, postoperative pain and inflammation, headache and migraine [3]. It shows a reduced solubility in water (<0.01 mg/mL); therefore, to maintain its plasma concentration at the therapeutic level, the administration of high drug doses is needed with consequent undesired effects, like heartburn, nausea, diarrhea, vomiting, peptic ulcer and hepatic damages [4]. Considering that, for poorly soluble orally administered drugs, the rate of absorption is often controlled by the rate of dissolution [5], the attainment of a faster solubilization for those drugs indicated for various pains is required [6].

Different techniques have been proposed, such as micronization, solid dispersion and inclusion complexation to improve dissolution rate of drugs [7,8]. Among them, micronization is the most used, since the reduction of particle size leads to an increase of the surface area to volume ratio and, therefore, an increase of the drug dissolution rate is expected because of the larger surface area in contact with the solvent [7]. Several conventional micronization processes can be used: spray-drying [9], emulsification/solvent evaporation [10], liquid antisolvent precipitation [11], centrifugal extrusion [12], freeze drying [13], jet-milling [14] and coacervation [15]. These processes are characterized by several limitations: the production of coarse particles with broad particle size distribution (PDS), possible degradation of the product due to mechanical or thermal stresses and contamination of particles with organic solvents or other toxic substances [16]. Di Martino et al. [17] processed NIM using liquid antisolvent precipitation from different solvents; they obtained crystals with different habits in the range 100–200 μm and dissolution tests were not performed. Khan et al. [18] employed coacervation for the coprecipitation of NIM and Hydroxypropyl Methylcellulose; they obtained large particles in the range 117–133 μm with a wide PSD and did not report the comparison of the drug dissolution profiles between unprocessed NIM and processed powder.

The limitations of traditional techniques can be overcome by supercritical fluids (SCFs) based processes, that have been effectively proposed in micronization [19–25], extraction [26], impregnation [27,28], membranes and scaffolds production

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[29–31]. In the micronization field, nanoparticles, microparticles and expanded microparticles of different kind of materials with a good control over particles size and particle size distribution were successfully obtained by Supercritical Antisolvent (SAS) precipitation [32–37]. However, Moneghini et al. [38] observed that processing NIM by SAS using acetone, chloroform and dichloromethane as solvents, it precipitated in form of large crystals irrespective of the operating conditions.

Coprecipitation with a hydrophilic polymeric carrier could be an alternative to direct micronization. Nevertheless, coprecipitation using SAS is difficult to obtain, since generally the drug and the polymer tend to precipitate separately. Indeed, some authors attempted coprecipitation of active principles by SAS; but, they obtained irregular and coalescing particles [39], with broad particle size distributions [40,41], low drug entrapment efficiency [16,42] and, in some cases, the occurrence of coprecipitation was questionable [43–46]. Some successful examples of SAS coprecipitation were also published [47–49] in the production of composite microparticles of folic acid, β-carotene and some corticosteroids with improved dissolution rate of the active compound.

Considered the difficulties in micronizing NIM using traditional and supercritical techniques, in this work, SAS coprecipitation of NIM is proposed, trying to take advantage of PVP ability to retard crystal growth [50–52], with the aim of producing effective coprecipitated microparticles that could improve NIM dissolution rate and bioavailability. The effect of polymer/drug ratio, operating pressure, temperature and overall solute concentration will be investigated. The processed powder will be characterized to verify the success of coprecipitation and the improvement of the drug dissolution rate. An explanation of the involved precipitation mechanisms will be attempted.

2. Materials, methods and procedures

2.1. Materials

Polyvinylpyrrolidone (PVP, average molecular weight 10 kg/mol), Nimesulide (NIM, purity ≥ 98%) and Dimethylsulfoxide (DMSO, purity 99.5%) were supplied by Sigma–Aldrich (Italy). CO_2 (purity 99%) was purchased from Morlando Group s.r.l. (Italy). All materials were used as received. Solubility tests performed at 30 °C showed that: the solubility of the materials in DMSO are about 250 mg/mL in the case of PVP and 200 mg/mL in the case of NIM.

2.2. SAS apparatus

The homemade SAS laboratory plant used for the experiments performed in this work consists of two high pressure pumps used to deliver the supercritical CO_2 and the liquid solution, respectively. The precipitator is a cylindrical vessel of 500 cm^3 internal volume (I.V.) (i.d. = 5 cm). The temperature control is assured by a PID controller connected with electrically thin bands and the pressure in the vessel is measured using a test gauge manometer and regulated by a micrometering valve. Carbon dioxide, after a preheating, is cocurrently delivered through another port to the chamber. The liquid mixture is delivered to the precipitator through a thin wall 100 μm internal diameter stainless steel nozzle. A stainless steel filter with a pore diameter of 0.1 μm, located at the bottom of the precipitator, is used to collect the produced powder, allowing the CO_2-solvent-solution to pass through. The liquid solvent is then recovered in a second collection vessel located downstream the micrometering valve, whose pressure is regulated by a backpressure valve. At the exit of the second vessel, CO_2 flow rate and the total quantity of antisolvent delivered, are measured by a rotameter and a dry test meter, respectively.

2.3. SAS procedure

At the beginning of the SAS experiment, CO_2 is delivered to the precipitation vessel to reach the desired pressure; then, pure solvent is sent through the nozzle to obtain steady state composition conditions during the solute precipitation. At this point, the solvent flow is stopped and the liquid solution is delivered through the nozzle, producing the precipitation of the solute. At the end of the injection step, supercritical CO_2 continues to flow, to eliminate residual content of liquid solubilized in the supercritical antisolvent. If the final purge with pure CO_2 is not performed, the organic solvent contained in the fluid phase condenses during the depressurization step and can solubilize or modify the precipitates. At the end of the washing step, CO_2 flow is stopped, the precipitator is depressurized down to atmospheric pressure and the precipitated powder is collected for analysis.

2.4. Analytical methods

Samples of the precipitated material were observed by a Field Emission Scanning Electron Microscope (FE-SEM, mod. LEO 1525, Carl Zeiss SMT AG, Oberkochen, Germany). Powder was dispersed on a Carbon tab previously stuck to an Aluminum stub (Agar Scientific, United Kingdom); then, was coated with Gold (layer thickness 250 Å) using a sputter coater (mod. 108A, Agar Scientific, Stansted, United Kingdom).

Particle size distribution (PSD) of the powders was measured from FE-SEM photomicrographs using the Sigma Scan Pro image analysis software (release 5.0, Aspire Software International Ashburn, VA). Approximately 1000 particles, taken at high enlargements and in various locations inside the precipitator, were analyzed in the elaboration of each particle size distribution. Histograms representing the particle size distributions were fitted using Microcal Origin Software (release 8.0, Microcal Software, Inc., Northampton, MA).

X-ray diffractograms were recorded using an X-ray powder diffractometer (model D8 Discover; Bruker, USA) with a Cu sealed tube source. Samples were finely milled in a mortar, placed in the holder and flattened with a glass slide to ensure a good surface texture The measuring conditions were: Ni-filtered CuKα radiation, λ= 1.54 Å, 2θ angle ranging from 5° to 30° with a scan rate of 3 s/step and a step size of 0.2°.

Drug dissolution studies were performed using an UV/vis spectrophotometer (model Cary 50, Varian, Palo Alto, CA) at a wavelength of 396 nm. Accurately weighted samples containing an equivalent amount of NIM (1.5 mg) were suspended in 2 mL of phosphate buffered saline solution (PBS) and placed into a dialysis sack; they were then incubated in 300 mL of PBS at pH 7.4, continuously stirred at 200 rpm and 37 °C. Each analysis was carried out in triplicate and the proposed curves are the mean profiles.

Precipitation yield (PY%) of each sample was measured by UV–vis analysis, measuring the absorbance obtained in the release medium at the end of the drug release; i.e., when all NIM was released from the microspheres to the outer water phase. The absorbance was, then, converted into NIM concentration, using a calibration curve. Therefore, PY% was calculated comparing the amount of NIM in the initial solution and the amount of NIM in the SAS processed powder, as shown below:

$$PY\% = \frac{mg\ NIM\ processed\ \ sample}{mg\ NIM\ \ initial\ solution} \cdot 100$$

DMSO residues were measured using a headspace sampler (model 7694E, Hewlett Packard, USA) coupled to a gas chromato-