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Microparticles formation of anti-inflammatory drug with bio-degradable polymer

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1. Summary

In the present study, preliminary experiments on the formation of micro particles for pharmaceutical purposes have been carried out by employing the GAS technique. The drug of an interest was diclofenac sodium, a non-steroidal active substance that acts anti-inflammatory, with prolonged release, used in the treatment of rheumatic disorders. The substance, 2- [(2,6-Dichlorophenyl) amino]benzeneacetic acid sodium salt is a salt of a weak acid with a pKa of 4 and a partition coefficient (n-octanol/aqueous buffer, pH 7.4) of 13.4. Different copolymers can be used as the drug carrier to reach the right physical and chemical properties and adjust polymer degradation and erosion. As a first step, a linear biodegradable polyester poly (lactide), biochemical inert, nontoxic with FDA approval and not too expensive was used. The experiments were performed by using dimethyl sulfoxide (DMSO) and a mixture of DMSO, dichloromethane (DCM) as solvent and supercritical carbon dioxide as anti-solvent. The work was focused on the exploration of favorable operating conditions to yield the appropriate micro-particles.

Keywords: supercritical antisolvent precipitation, poly(lactide), dimethylsulfoxide, diclofenac sodium

2. Introduction

Supercritical antisolvent precipitation, a semicontinuous precipitation technique, is widely used to produce micrometric and sub-micrometric particles of pharmaceutical and related compounds like hydrophobic enzymes, anti-inflammatory drugs, antibiotics, biopolymers. Employing SCF-GAS technique, where the application of an antisolvent decreases the solubility of a material dissolved in the solution, micro-particles can be formed, where the drug is embedded into a degradable polymer matrix. This technique is applicable to the material, if the compound is insoluble (or slightly soluble) in the gas and the gas is (very) soluble in the liquid. For a successful

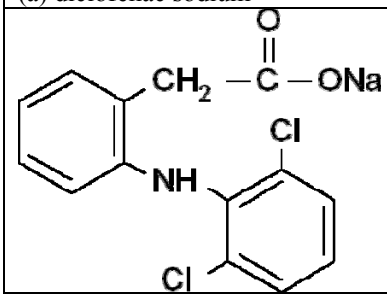
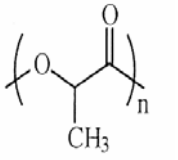
operation, a good solvent-antisolvent combination has to be chosen. The solubility of solid substances in the chosen solvents is essential for evaluating the feasibility of a process and for establishing optimum process conditions.

3. Experimental

3.1. Materials

Diclofenac sodium was kindly supplied by Krka, d.d., Novo mesto (Pharmaceutical Company, Novo mesto, Slovenia) and used as received. The water content of the original powder of the drug was determined in triplicate using the Karl Fischer titration method. The water content was 0,487%. The solvents dimethyl sulfoxide and dichloromethane were analytical or chromatographic grade, supplied by Merck.
Poly(lactid acid) (PLA) produced at NIC, Department for Polymer Chemistry and Technology was used with the following physical properties: M_w= 80 000 – 100 000 g/mol, T_g= 55°C, T_m= 145°C, polydispersity P=1.7 (without cleaning) and P= 1.3 (with cleaning). In addition, some experiments with Poly (L-lactide) (L-PLA) from Aldrich were performed, in which polymer was found to be more crystalline and less soluble.

Figure 1. Molecular structure of substances

(a) diclofenac sodium	(b) PLA
	

3.2. Apparatus

Experiments were performed in a batch operation mode, in the autoclave with internal volume of 2 L, equipped with the sapphire windows that can be applied up to 150 bars. The autoclave was filled with SC CO_2 at desired temperature T and to desired pressure P, followed by the discontinuous injection of the liquid solution. Because of the very fast diffusion of SC CO_2 into the solvent, and the organic solvent counter diffusion in the gas phase, the liquid density of the drop was lowered until the critical value was reached, what caused the solute precipitation. The precipitation in a supercritical fluid rich phase occurred. The solution was removed by venting through the frit and fresh CO_2 was continuously added to keep the pressure constant in the autoclave and to remove the rest of the solvent from the particles (washing step). The solid particles were captured by the filter unit at the bottom of the autoclave. The particles were collected from the filter and dried in the vacuum oven at room temperature.

Series of GAS experiments with PLA solution without a drug was carried out in order to optimize the operating conditions. Experiments were performed also with the drug alone and the drug and PLA together in the entering solution.
The morphology of the polymer precipitates was examined by scanning electron microscopy (SEM).
Particle size distribution of powders from ethanol was also determined.

3.3. The solubility of solids in fluids

For the evaluation and design of different crystallization processes solubility data is required of solids in solvent or mixtures of a solvent and SCF CO_2. In the literature the solubility data of PLA in SC-CO_2 at different conditions [1, 2] were found as well as solubility data of diclofenac sodium in SC- CO_2 [3]. The solubility of diclofenac sodium in DMSO at different temperatures was measured by Fele et al. [4, 5].
The phase behavior of the binary system DMSO/CO_2 was presented by Kordikowski et al. [6], Reverchon et al. [7, 8], and it is of Type I. The phase diagram may be used for the explanation of the precipitation process, under assumption that PLA or PLA and the drug, present in small concentration, will not affect the phase behavior of the DMSO/CO_2 system.

3.4. Microparticles morphologies

Figure 2. Scanning electron micrograph of PLA (NIC) particles produced

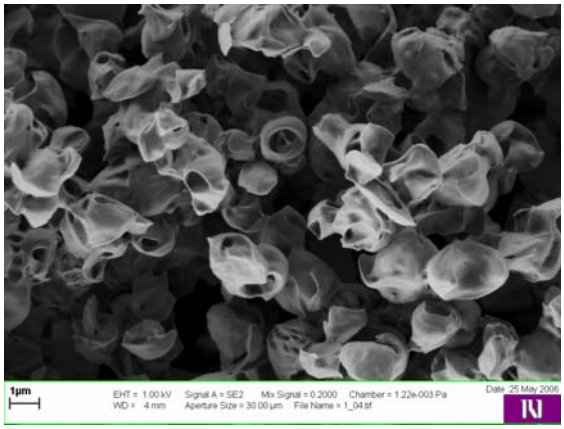
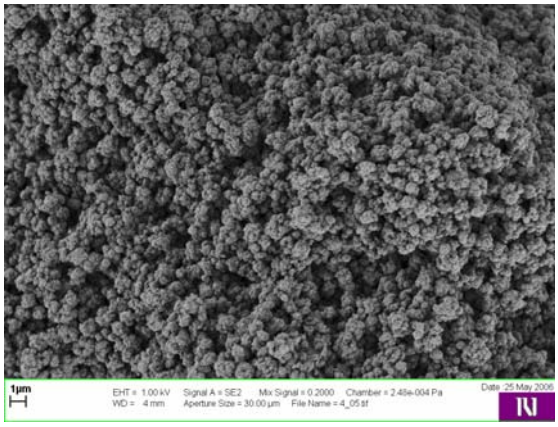


Figure 3. Scanning electron micrograph of drug particles



Using the GAS method, irregularly formed particles of PLA were obtained. The feed solution with approx. 1 wt% and 0.4 wt% of polymer, produced at NIC and Aldrich, respectively, in solvent was used.
Because of the temperature and pressure influence on the phase behavior and on the mean particle size, experiments were performed by changing slightly the operating conditions.
In Figure 2 and Figure 3 scanning electron micrographs are shown for the microparticles produced according to GAS procedure.
Very fine particles were obtained by supercritical processing of diclofenac sodium from dimethyl sulfoxide at temperature of 48°C and pressure of 150 bar by using a

proper rinsing procedure at the end of the process. In spite of extensive rinsing, some agglomeration of the particles was observed.
Leaf-form particles were generated from L-PLA dissolved in mixed solvent DMSO/DCM from a supercritical mixture.
Experiments were conducted also from solution (DMSO/DCM) containing L-PLA and the drug. The drug has precipitated randomly on the surface of the polymer particles from a supercritical mixture. The operating conditions were not optimized so far, since further studies like biological activity of the drug has to be determined.

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