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Investigation of the rapid expansion of supercritical solution parameters effects on size and morphology of cephalexin particles

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ABSTRACT

The particle size of organic and inorganic materials is vital parameter to determine its final use. Most of the newly developed pharmaceutical materials are poorly soluble or insoluble in the aqueous media such as biological fluids. Particle size reduction of such pharmaceuticals is one of the clues to improve the dissolution rate, adsorption and bioavailability. In this study, the effect of extraction and expansion parameters of the RESS process such as extraction temperature (313–333 K), extraction pressure (140–230 bar), effective nozzle diameter (450–1700 μm), nozzle length (2–15 mm) and spraying distance (1–7 cm) on the size and morphology of the precipitated particles of cephalexin were investigated. The morphology and particle size of the unprocessed and processed (precipitated) particles were examined by the SEM images. The mean particle size of the precipitated particles was between 0.86 and 7.22 μm depending upon the different experimental conditions used. The precipitated cephalexin particles were close to spherical form while the unprocessed particles were irregular or needle in shape.

1. Introduction

Supercritical fluid technology has been widely used for various applications such as extraction, reaction, chromatography and material processing. Several authors have reviewed the applications of supercritical fluid on the preparation of nano-materials (Reverchon & Adami, 2006), green chemical synthesis (Beckman, 2004) and processing of semiconductors (King & Williams, 2003). Classification and selection of supercritical particle formation processes have been reviewed by several authors (Bahrami & Ranjbarian, 2007; Jung & Perrut, 2001; Perrut & Clavier, 2003). These technologies were found attractive for the production of sub-micron and nano-particles in pharmaceutical application. The application of supercritical fluid process for particle formation may reduce the use of organic solvent or avoid the heat effect in traditional mechanical treatment (Su, Tang, & Chen 2009) Production of nano-particles or micro-particles with narrow PSD, however, requires creation of a very rapid, uniform and extremely high super-saturation in the solution. This has been made possible in recent years by using carbon dioxide (CO_2) as a supercritical fluid due to its excellent thermodynamic and transport properties. Supercritical carbon dioxide (SC-CO_2) acts as a solvent for rapid expansion of the supercritical solution (RESS) or for precipitation from a gas-saturated solution (PGSS) and as an anti-solvent in crystallization processes such as GAS, SAS, PCA, SEDS and ASES (Azevedo, Jun, & Veciana 2003; Kappler, Leiner, Petermann, & Weidner 2003; Knez, 2003; Pathak, Meziani, Desai, & Sun 2005; Rodrigues et al., 2004; Subra, Berroy, Sauriana, & Domingo 2004; Thakur & Gupta, 2006a).

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The RESS process consists of extraction and precipitation unit. A substance is solubilised in a supercritical fluid (SCF) at the extraction unit, than the supercritical solution is suddenly depressurized in a nozzle causing fast nucleation and fine particle formation. Due to the rapid expansion of supercritical solution through a nozzle, the large decrease in density, and hence decreasing the SCF solvating power. The solute becomes supersaturated and then precipitated. The driving force of the nucleation process is super-saturation. Higher super-saturation leads to increase the nucleation rate (J, particles/cm^3 s) and tends to decrease the particle size (Hirunsit, Huang, Srinophakun, Charoenchaitrakool, & Kawi, 2005; Türk, 2000).

Advantages of RESS process are that nano or microparticles are produced, providing a solvent-free product and controllable particle size. The morphology and size distribution of the precipitated material is related to pre-expansion and expansion conditions, extraction parameters, spray distance and nozzle design (Knez & Weidner, 2003; Sihvonen, Jarvenpa, Hietaniemis, & Huopalahti, 1999).

In the pharmaceutical industry many drugs exhibit poor solubility in biological media. Solubility of drugs affects on the rate of dissolution and their absorptions in the gastrointestinal tract are limited by their dissolution rates. Poorly soluble compounds causes risk of precipitation at the injection point and slow dissolution in serum also. Therefore the bioavailability of poorly soluble compounds is also limited by solubility. The meaning of bioavailability is the ratio of drug absorbed in target area by body to initial dosage. The drug must first be dissolved in order to be absorbed. Based on the Noyes–Whitney equation, the dissolution rate of compounds is a function of the surface area of the particles. And, the surface area can be determined through the control of the particle size (Kayrak, Akman, & Hortacu, 2003; Perrut, Jung, & Lebpeuf, 2005; Vasukumar & Bansal, 2003).

Also, it has been shown that dissolution rate, absorption rate, content uniformity, color, taste, texture and stability depend to a varying degree on particle size and particle size distribution (Ravin & Radebaugh, 1990). For poorly soluble drugs (The BCS group, poorly soluble compounds as class II (compounds is featured poorly solubility and high permeability) and class IV drugs (poor solubility and poor permeability)), bulk active pharmaceutical ingredient (API) having small particles size should be used to enhance in situ dissolution. In general, the particle size of API is recommended to reduce to 50% less than 10 μm and 90% less than 30 μm.

Generally, micronization of pharmaceutical compounds is one of the most important processes in pharmaceutical industry for improving the dissolution rate of the active pharmaceutical ingredient (API). Pharmaceutical solids with high dissolution rate provide the advantages of high efficiency, low dosage requirement and avoiding possible side effects. In this study, the feasibility of the RESS processes for the micronization of cephalexin was assessed. The RESS experiments involved the investigation of the effects of extraction temperature and pressure, nozzle geometry and spraying distance on the particle size and morphology.

Cephalexin (API drug) has the molecular formula $C_{16}H_{17}N_3O_4S \cdot H_2O$ and the molecular weight is 365.41 g/gmole. Cephalexin is a semisynthetic cephalosporin antibiotic intended for oral administration.

The crystalline form of cephalexin that is available is a monohydrate. It is a white crystalline solid having a bitter taste. Solubility in water is low at room temperature; 1 or 2 mg/mL may be dissolved readily, but higher concentrations are obtained with great difficulty. Cephalexin is used to treat urinary tract infections, respiratory tract infections, and skin and soft tissue infections. It is also sometimes used to treat acne.

In addition, cephalexin (also called Cefalexin) is a first generation cephalosporin antibiotic. It is one of the most widely prescribed antibiotics, often used for the treatment of superficial infections that result as complications of minor wounds or lacerations. It is effective against most gram-positive bacteria.

2. Experimental

2.1. RESS setup

The setup used in this study mainly consists of an extraction unit, and a precipitation unit in which the precipitated particles are collected. The reliability of the used apparatus was checked before however some modifications are introduced to the apparatus (Esmaeilzadeh & Goodarznia, 2005). The description of the used apparatus is as follows:

Carbon dioxide was supplied from a gas cylinder and passed through a 0.5 μm in-line filter to remove any particles that might be present in the gas tank. Then the gas was liquefied through a cooler and pressurized to the desired pressure by means of a reciprocating oil-free water-free high pressure manual pump. The flow prior to entering the extraction vessel enters to a surge tank which dampened the pressure fluctuations produced by operation of the pump. Both the surge tank and extraction vessel are wrapped by a circulating water jacket and heated to the desired temperature. The pressure in the stainless steel homemade extraction vessel was monitored by a pressure gauge ranged up to 400 bar with the division of 1 bar. In addition, the extraction column is suitable for use up to 400 bar. It has an internal volume of 180 cm^3. The temperature of the both extraction vessel and surge tank was controlled by the PT-100 controller with precise of $\mp 1\,^{\circ}C$. Inside the equilibrium cell, there is a cylindrical wire netting, which was packed with alternate layers of glass wool, glass beads and the 15 g of cephalexin to keep the solute in place. Glass wool was used on both the ends of the equilibrium cell to avoid any undissolved material to carry over with the CO_2 flow. After obtaining the desired temperatures throughout the system, CO_2 was allowed to fill the extraction unit. After the desired pressure and temperature were achieved in the extraction unit, the supercritical solution was left in the extraction unit for 2 h to attain equilibrium. The equilibrated