초임계 유체를 이용한 이트라코나졸 미세입자의 재결정

유진희, 류 정, 이용철*
성균관대학교 화학공학과
(yclee@yurim.skku.ac.kr*)

Recrystallization of itraconazole micro- and nano-particles by supercritical antisolvent precipitation

Jin Hee Yoo, Jung Ryu, Yong Chul Lee*
SungKyunKwan University Chemical engineering
(yclee@yurim.skku.ac.kr*)

Introduction

The technology progress in many industrial fields is intimately dependent on the ability of conceiving materials with unusual combinations of properties. The successful development frequently depends on new processing media and schemes. Supercritical fluids have been extensively used for the past two decades in attempts to gain accurate and detailed knowledge of fundamental properties[1].

Such knowledge is essential to the utilization and optimization of supercritical fluid technology in materials preparation and processing. Among the most important properties of a supercritical fluid are the low and tunable densities that can be varied between those of and a normal liquid and the local density effects observed in supercritical fluid solutions(most strongly associated with near-critical conditions)[1].

Carbon dioxide is commonly used because the critical points are quite close to air temperature, nontoxic, nonflammable and cheap though.

Supercritical fluids applications developed to produce micro and nano-particles start from these considerations. Indeed, very large supersaturation ratios, very fast precipitation, solventless products are some of the potential properties of supercritical fluid based processes. Very small particles down to nanoscale and a good control of particle size distribution are also promised[2].

The most promising supercritical fluids based process cloud be the supercritical antisolvent (SAS) precipitation that has been successfully tested for several kinds of compounds. Micronized powders of some pharmaceuticals, polymers and biopolymers, superconductors and catalyst precursors, colouring matters and explosives have been produced by supercritical antisolvent (SAS). The results obtained by the different authors frequently do not converge in the indication of the influence of the various process parameters on the powder morphology, particle size (PS) and particle size distribution (PSD). The role of the different process arrangements is also obscure and sometimes strongly dependent on the nature of the compounds and of the mixtures involved in the process[3].

The supercritical antisolvent (SAS) process has been frequently applied to pharmaceutical compounds, since it is easy to separate and to recover the solvent and antisolvent, and the consequent high purity of the product are favourable for this kind of process. Moreover,

controlled particle sizes and particle size distributions are expected to be obtainable using this process. However, until now supercritical antisolvent (SAS) precipitation has been performed only is laboratory apparatus with very small production rate[3].

The choice of a satisfactory scale-up procedure requires a in deep understanding of the controlling steps of the process. Werling and Debenedetti noted that it is difficult to isolate the effect of thermodynamics, mass transfer, jet hydrodynamics and nucleation kinetics, as being responsible for a given trend in particle properties. Until now only a very limited number of papers have been published on pilot scale supercritical antisolvent (SAS). Since the realization of large scale production of micro- and nano-particles for commercially viable fine chemicals is of increasing interest, the study of the supercritical antisolvent (SAS) precipitation process on a pilot scale plant has been considered[3].

In that Work temperature, pressure, flow rate conditions and kinds of solvent were selected in order to obtain particles of controlled particle size (PS) and particle size distribution (PSD). The effect of the injection device and of the jet hydrodynamics on the particle size (PS) and morphology has been considered in this study.

Theory

1.Analysis of supercritical fluid based technique(Semi-continuous operation)

The liquid solution and the supercritical anti-solvent are continuously delivered to the precipitation vessel in co-current or counter-current mode. In this operation mode, flow rates and their ratio can be important for the evolution of the precipitation process[2].

A key role in the semi-continuous operation is played by the liquid solution injection device. The injector is designed to produce liquid jet break-up and the formation if small micronic droplets that expand in the precipitator. The solid solute is released when its local concentration exceeds the saturation limit. So various injection devices are proposed by lots of authors. Some authors proposed the adoption of a nozzle. Other authors used small internal diameter capillaries or vibrating orifices. Coaxial devices have been also proposed in which two capillary tubes continuously deliver the liquid solution and the supercritical anti solvent. The formation of small droplets in this case depends on the turbulent mixing of the two flows. Complex geometries formed by more than two capillaries and different disposition of the liquid and supercritical fluid (inside-outside) have also been tested[2].

The washing step with pure supercritical anti solvent at the end of the precipitation process is fundamental also for continuous operation to avoid the condensation of the liquid phase that otherwise step rains on the precipitated powder modifying its characteristics. A method to calculate the length of washing is to consider the precipitation as a continuous stirred tank reactor (CSTR).

2. Pharmaceutical principles

Pharmaceutical principles are a field in which small particles with controlled particle size and particle size distribution are required to improve/modify the therapeutic action of several drugs. Using controlled size microparticles it is possible it increase the bioavailability of active principle or decrease the therapeutic dosage or change the drug delivery system. Among the others, transdermal, tracheobronchial and pulmonary delivery systems can be used that can improve efficiency of the drug and eliminate undesired secondary effect resulting from oral assumption of pharmaceutical compounds.

Experimental

The apparatus used is a continuous co-current precipitation in which the supercritical antisolvent and the liquid solution are separately fed the top of the chamber and continuously discharged from the bottom.

A schematic representation of the SAS apparatus is shown in Fig, 5. It consists of two high pressure pumps (Ilshin Autoclave co,.) respectively used to deliver the liquid solution and the liquid carbon dioxide. The pump used for supercritical fluid was modified to avoid cavitation from compressible-fluid pumping by adding a cooling head. The precipitation chamber is a cylinder vessel which has about 300ml, internal volume and the inside of the chamber can be seen through the sight glass which is placed on the chamber body. The liquid solution was delivered into the precipitation chamber through a 100㎛ diameter, stainless steel nozzle. Supercritical carbon dioxide was delivered by another inlet point located on the top of the chamber. CO_2, Before entering the precipitation chamber, was heated in the coiled pipe in the dry oven. The precipitation chamber was also heated in the dry oven. The pressure in the chamber was measured by the pressure regulator which is placed over the dry oven. and it was regulated by a back pressure regulator located at the exit of the chamber. This valve was heated in the water bath to avoid being stuck by chilling. A filter can was used to collect the precipitated particles in the precipitation chamber. A second collection chamber located at downstream of the back pressure regulator was to recover the liquid solvent and CO_2. and it was operated under low pressure condition.

A typical SAS experiment was started by delivering supercritical CO_2 to the precipitation chamber until the desired pressure was reached. Before this, the chamber and pipe lines heated to desired experimental temperature.

Then, pure liquid solvent was sent through the nozzle to the chamber at a flow rate of around 1㎖/min and supercritical CO_2 flow was regulated at 20 ml/min. This procedure was aimed at obtaining steady state operating condition during solute precipitation. Pure solvent was fed to chamber for 10 min. First objective is to give an about 90% approach to the steady state concentration of liquid solvent in the supercritical CO_2 contained in the precipitation chamber, supposing the contents of this to be perfectly mixed and second objective is to avoid the closure of the nozzle due to the precipitation of solute inside it during the start up procedures. As soon as the flow of the pure liquid solvent was stopped, the liquid solution was delivered through the nozzle at the same rate, 1㎖/min. Supercritical CO_2 flowed , being maintained at 20 ml/min. During this period, particles were precipitated in the filter can.

This stage took 10 min or more to allow the collection of solid in a quantity sufficient to perform the analysis of precipitate. This experiment finished when the desired solution was ended. However, supercritical CO_2 was continuously delivered for 90 min more to wash the residual content of liquid solvent in the precipitation chamber and particles solubilized into the supercritical antisolvent.

The washing time of 90min was calculated as that required to remove 98% of the liquid solvent from the chamber, assuming the contents of this to be perfectly mixed. If the final delivery of pure supercritical CO_2 is not operated, the liquid solvent condenses in particles during the chamber depressurization and partly solubilizes the particle in the filter can,

modifying its morphology.

When the washing process was completed, the CO_2 flow was stopped and the chamber was depressurized down to atmospheric pressure.

Result and discussion

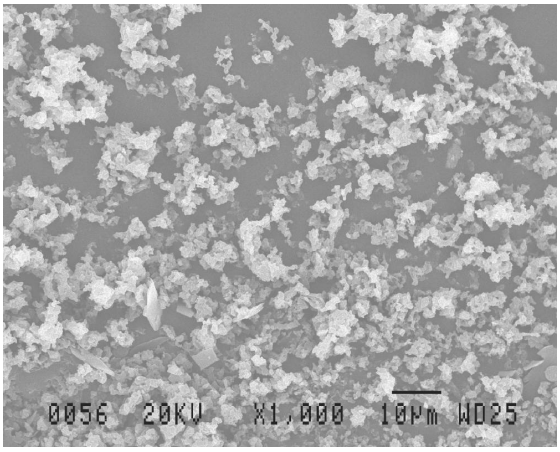

Fig. 1. SEM image at 150bar, 45℃, 0.5㎖/min

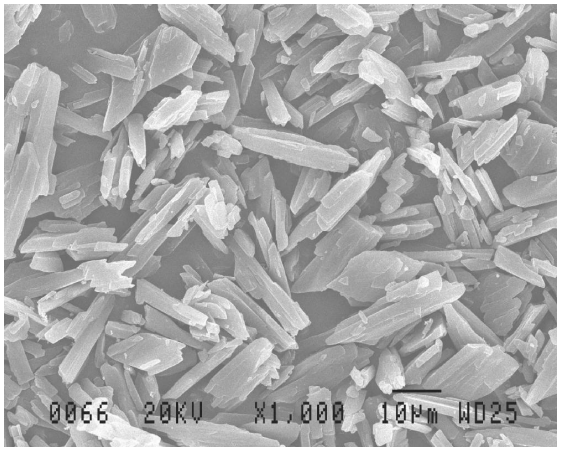

Fig. 2. SEM image of untreated itraconazole

Use of the influence of feed rate of CO_2 condition was optimized by previous experiment but in this work we tried to find out the influence of feed rate of solution, pressure and temperature on particle distribution and shape.

The experiment was performed under variable feed rate condition of solution such as 0.2, 0.5, 1, 5㎖/min at the condition of 35~55℃ and 100~150bar.

After the process, all the particles were smaller than initial itraconazole and we could see that the particles were depended on feed rate on solution. If the feed rate of solution was slower, the particle size was smaller.

But in the case of feeding solution at 0.2㎖/min, the particle was conglomerated. So we could assume that there was the second growth of particles. According to this work, the optimum feed rate of solution was 0.5㎖/min.

Reference

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