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Rapid Communication

Controlled Expansion of Supercritical Solution: A Robust Method to Produce Pure Drug Nanoparticles With Narrow Size-Distribution

Jenni Pessi [1,2,*], Ilkka Lassila [2], Antti Meriläinen [2], Heikki Räikkönen [1], Edward Hæggström [2], Jouko Yliruusi [1]

[1] Division of Pharmaceutical Chemistry and Technology, Faculty of Pharmacy, University of Helsinki, Viikinkaari 5e, 00790 Helsinki, Finland
[2] Division of Material Physics, Department of Physics, University of Helsinki, Gustaf Hällströmin katu 2a, 00560 Helsinki, Finland

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We introduce a robust, stable, and reproducible method to produce nanoparticles based on expansion of supercritical solutions using carbon dioxide as a solvent. The method, controlled expansion of supercritical solution (CESS), uses controlled mass transfer, flow, pressure reduction, and particle collection in dry ice. CESS offers control over the crystallization process as the pressure in the system is reduced according to a specific profile. Particle formation takes place before the exit nozzle, and condensation is the main mechanism for postnucleation particle growth. A 2-step gradient pressure reduction is used to prevent Mach disk formation and particle growth by coagulation. Controlled particle growth keeps the production process stable. With CESS, we produced piroxicam nanoparticles, 60 mg/h, featuring narrow size distribution (176 ± 53 nm).

Introduction

Particle production based on supercritical carbon dioxide ($scCO_2$) is efficient, inexpensive, and ecological.[1] These kinds of bottom-up technologies form particles by recrystallization.[2] CO_2 is the most common solvent in supercritical processes because its critical temperature and pressure are relatively low, 31°C and 74 bar.[3] Furthermore, CO_2 is “Generally Recognized As Safe” by the Food and Drug Administration; it is neither flammable nor toxic. The prepared particles are pure, and the obtained polymorph can be controlled.[4-6] Supercritical particle production allows using a 1-step preparation process.[2] This simplifies the particle production, which, for example, in common industrial ball milling techniques requires many steps and excipients. Moreover, current nanoparticle technologies feature limited batch size and often require organic solvents.[7]

Particle production techniques using $scCO_2$ use $scCO_2$ as solvent, as solute, or as antisolvent.[5,8] Rapid expansion of supercritical solutions (RESS) is a solvent- and excipient-free production method.[9] It has been used to micronize pharmaceutics[1,4,10] and to produce nanomicron- and submicron-size drug particles.[11-21] For example, piroxicam, the model compound in our research, has been micronized with RESS resulting in particles with Ø = 1.52-8.78 μm.[22]

The processes using $scCO_2$ as a solvent have been modified by changing process parameters (e.g., ultrahigh pressure,[23] nozzle construction,[24] or by expanding the $scCO_2$ in a liquid environment[25]). However, since invented, particle production using $scCO_2$ as solvent is based on rapidly decreasing the pressure.[26] Although promising also for nanoparticle production, the results have not always been satisfactory regarding particle size and product uniformity.[27]

In RESS, the supercritical solution is expanded through a nozzle,[28,29] and the subsequent rapid decrease in solvent density reduces the solvent power.[30] Particles are generated as solute precipitates, and the particle formation, the creation of a single spherical particle of radius *r*, can be understood using the reduced Gibbs energy in a closed system (Eq. 1).[31]

* *Correspondence to:* Jenni Pessi (Telephone: +358503810225).
E-mail address: jenni.pessi@helsinki.fi (J. Pessi).

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$$\frac{\Delta G}{k \cdot T} = \frac{4 \cdot \pi \cdot \sigma \cdot r^2}{k \cdot T} - \frac{4 \cdot \pi \cdot r^3}{3 \cdot v_{2,S}} \left(\ln S - v_{2,S} \left(p - p_{2,sub} \right) \Big/ (k \cdot T) \right) \quad (1)$$

where $\Delta G(kT)^{-1}$ is the reduced Gibbs energy, k Bolzmann constant, T temperature, σ the interfacial tension of the solute, $v_{2,s}$ the molecular volume of the solid phase, p_2 the partial pressure of the solute, and S the supersaturation. The parameter to alter in the expansion of a supercritical process is the supersaturation (Eq. 2).[32]

$$S = \frac{y_{2,E}(T_E,\ p_E) \cdot \Phi_2 \left(y_{2,E}\ (T_E, p_E) \right)}{y^*{}_2(T, p) \cdot \Phi_2 (y_2^*(T,\ p))} \quad (2)$$

where $y_{2,E}\,(T_E,p_E)$ is the mole fraction of the solute at postexpansion temperature and pressure, $y^*_2\,(T,p)$ the equilibrium mole fraction of the solute at the extraction temperature and pressure, and Φ_2 the solute fugacity coefficient relating the ideal gas pressure and the effective pressure of a real gas. The molar ratios determining the degree of supersaturation directly depend on the preexpansion and postexpansion pressure and temperature. A steep drop in pressure and temperature decreases the density and solvent power of CO_2 significantly, resulting in a high degree of supersaturation. The higher the degree of supersaturation, the more numerous and smaller the formed nuclei.[33]

After nuclei formation, particles grow by 2 mechanisms: condensation where free molecules are deposited onto the nuclei surface and coagulation where particles grow by colliding.[34,35] In RESS, the time available for particle growth by condensation is limited to microseconds.[36]

The key RESS parameters that affect the end product are nozzle geometry, preexpansion temperature and pressure, and the postexpansion pressure and temperature.[30,34] In RESS, the ratio of preexpansion to postexpansion pressures exceeds 10, the ejection velocity is sonic at the nozzle, and later supersonic.[37] The supersonic free jet ends with a Mach disk beyond which the velocities again are subsonic.[35,37]

Particle precipitation in the RESS process mainly takes place after the nozzle exit and in the shear layer of the jet.[38] The inlet pressure determines the exact location at which the particle formation begins.[39] The particle concentration is highest at the Mach disk, and the main mechanism for particle growth is coagulation in the subsonic free jet.[18] The flow in the collection chamber of a RESS system is often complicated because of time varying thermal and hydrodynamic conditions and changing density, temperature, pressure, and flow velocity. This velocity can reach 700 m/s before the Mach disk.[38] Particle growth is accelerated beyond the shock in the expansion jet, and thus, theoretical predictions of particle size often deviate from the size of the actual particles.[39]

Our experiments indicate that nanoscale particles can also be produced in opposite conditions: *slow depressurization and with low degree of supersaturation*, using a method developed in this research, CESS. CESS essentially differs from RESS and uses controlled mass transfer, controlled flow, controlled pressure reduction, and finally particle collection in dry ice (Table 1). The core of the technology is to allow larger initial nuclei size and particle growth by condensation. This avoids the variation in temperature, pressure, and density, as well as the particle growth by coagulation.

Materials and Methods

Piroxicam, a nonsteroidal anti-inflammatory drug, (Hawkings Inc.) and CO_2 ($\geq$99.8% AGA, Helsinki, Finland) were of analytical grade and used as received.

Table 1
Essential Differences Between RESS and CESS Techniques

Feature	RESS	CESS
Pressure drop	Rapid	Controlled
Ratio of pressure drop	>10	<10
Flow velocities	Supersonic	Subsonic
Degree of supersaturation	High	Low
Formation of Mach disk	Yes	No
Particle formation	Mainly beyond exit nozzle	Mainly before exit nozzle
Main mechanism for particle growth	Coagulation	Condensation

A specific pressure and temperature profile is created with a system consisting of a high-pressure pump (SFT-10; Supercritical Fluid Technologies Inc.), a 100-mL custom-made high-pressure chamber, a heater/mixer (MR 2002, Heidolph, Germany), needle valve (Swagelok), 40-cm outlet tube (Sandvik, Sweden), a main nozzle and 2 additional nozzles (Mist&More Inc.), and a collection chamber (Fig. 1). The pressure chamber was loaded in room temperature with a surplus of piroxicam (300 mg) and filled with liquid CO_2. Saturated solution of piroxicam was made as the pressure was increased to 200-350 bar and the temperature to 60°C-70°C. A magnetic mixer (1500 rpm) ensured proper mixing. The valve temperature was kept at 40°C with proportional-integral-derivative—controlled (16S, Meyer) resistors.

The pressure reduction in the system occurs in 2 steps. The first step takes place along the outlet tube connecting the pressure chamber to the collection chamber. The flow is controlled by a needle valve. At the valve, the pressure decreases from 230-250 bar to 30-45 bar, whereas the temperature is kept constant. The particles are formed as the pressure decreases. The flow rate inside the outlet tube is kept at 24 mL/min. The second pressure reduction step occurs at the exit nozzle as the formed particles are transferred from the outlet tube into the collection chamber. As the volume increases, the pressure drops from 30-45 bar to 4 bar, the counter pressure in the collection chamber (Fig. 2). The nozzle at the end of the outlet tube maintains the pressure in the outlet tube and controls the flow. The particles are collected in dry ice formed by the Joule—Thomson effect and enhanced with 2 additional CO_2 sprays (15° angle relative to the main nozzle). Solid dispersion consisting of nanoparticles and dry ice is formed. This further prevents particle growth by coagulation and inhibits aggregation.

The nanoparticles can be stored within the dry ice to increase stability. Alternatively, the dry ice can be sublimated in nitrogen atmosphere, and the particles collected as dry nanoparticle powder. The production rate of the nanoparticles with our small laboratory-scale device is 60 mg/h.

Particle size and morphology of 3 nanoparticle batches and bulk piroxicam were examined by scanning electron microscopy (Quanta 250 FEG, FEI Inc.). Samples were collected on a generic stainless steel metal net and sputter coated with a 5-nm-thick platinum layer (Q150T Quomm, Beijing, China). The particle size was determined by diameter measurements and analysis with the ImageJ freeware (National Institutes of Health).

Results and Discussion

The pressure, flow, and the rate of solid dispersion formation within the collection chamber are constant. Therefore, the collection and particle production processes are stable. The robustness, stability, and reproducibility of the process were proven by preparing 3 batches of similar product. The