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Micronization and characterization of drug substances by RESS with supercritical CO_2

Jung-Teag Kim, Hong-Lyong Kim, and Chang-Sik Ju†

Department of Chemical Engineering, Pukyong National University, Busan 608-739, Korea
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Abstract−A RESS (rapid expansion of supercritical solution) process for the preparation of ultra-fine drug particles with no organic solvent has been developed with supercritical CO_2. Three drug substances with different solubility in supercritical CO_2 were used, and orifice disks and capillary tubes were adapted as an expansion device. The solubilities of drug substances in supercritical CO_2 and the effects of various operating parameters on the characteristics of the particles prepared by RESS process were experimentally investigated. The solubility of the drug substance in supercritical CO_2 had a major effect on the average diameter of the particle prepared by RESS process, and the particle diameter decreased with the solubility for all the drugs and operating conditions. The particle diameter also decreased with pre-expansion temperature and increased with the hole diameter of the orifice nozzle and aspect ratio (L/D) of the capillary tube.

Key words: RESS, Drug Substances, Micronization, Solubility, Supercritical

INTRODUCTION

A fluid becomes supercritical when it is compressed and heated to conditions above its critical point, where it exhibits densities close to those of liquids and viscosities close to those of vapors. The resultant supercritical fluid (SCF) has a much increased solvent capacity for many nonvolatile and thermally labile compounds. And SCFs are unique and useful as extracting agents because their solvent power can be manipulated over a wide range by adjusting temperature and pressure [1,2].

Among the numerous applications of SCFs, crystallization might be potentially promising. The advantages of crystallization at supercritical conditions over conventional crystallization are very clear, when nonvolatile, thermally labile substances are to be crystallized [3].

CO_2 is the most widely used SCF because it has a relatively low critical temperature and a moderate critical pressure. In addition, it is inexpensive, leaves no toxic residue, and is not flammable. Since the critical temperature of CO_2 is near ambient, supercritical CO_2 as a non-contaminating solvent might be attractive alternative to conventional organic solvent for processing heat-sensitive flavors, pharmaceuticals, labile lipids, and reactive monomers [4].

Rapid expansion of a supercritical solution (RESS) is a promising process for the production of small, uniform and solvent-free powders of solutes with high solubility in SCFs [5-7]. The RESS process is advantageous because it can produce fine particles of a wide range of inorganic, organic and polymeric materials and has a low operation temperature and single step processing. Furthermore, RESS with supercritical CO_2 is especially attractive for drug substances because it can produce fine particles without any solvent residues.

†To whom correspondence should be addressed.
E-mail: csju@pknu.ac.kr

In the RESS process, ultra fine particles with narrow particle size distribution (PDS) can be produced because crystallization of the dissolved material results from a fast decompression and instantaneous very high degree of supersaturation by the expansion of the supercritical solution through a well-defined expansion device.

Many research groups have studied the RESS process to produce various kinds of fine particles with uniform particle size distributions.

Thakur et al. [5] and Helfgen et al. [8] reported micronization of pharmaceutical substances by the RESS process and a model focused on the flow through the nozzle, the supersonic free-jet, the Mach shock and particle growth in the expansion unit.

Preparation of nanoscale semiconductors [9] and microencapsulation of protein [10,11] and metal fine powders [12] are interesting and promising applications of the RESS process.

The objective of this study is to develop techniques controlling the morphology and size of the drug particles by the RESS process with supercritical CO_2. Some experimental researches [5,6,13] were preformed on the RESS process with supercritical CO_2 preparing fine particles of some drug substances with different solubility. Besides extraction temperature and pressure comprising the major operating parameters of the RESS process, we examined the effect of solutes and some operation parameters including expansion devices on the morphology and size of the fine particles.

EXPERIMENTAL

1. RESS Apparatus

A schematic of the experimental apparatus for the RESS process with supercritical CO_2 is shown in Fig. 1. The apparatus consists of an extraction unit and a precipitation unit including high-pressure pump (Milton Roy) and auxiliary facilities.

Liquid CO_2 is cooled in low temperature water bath and compressed to the desired pressure by high-pressure pump. Before it

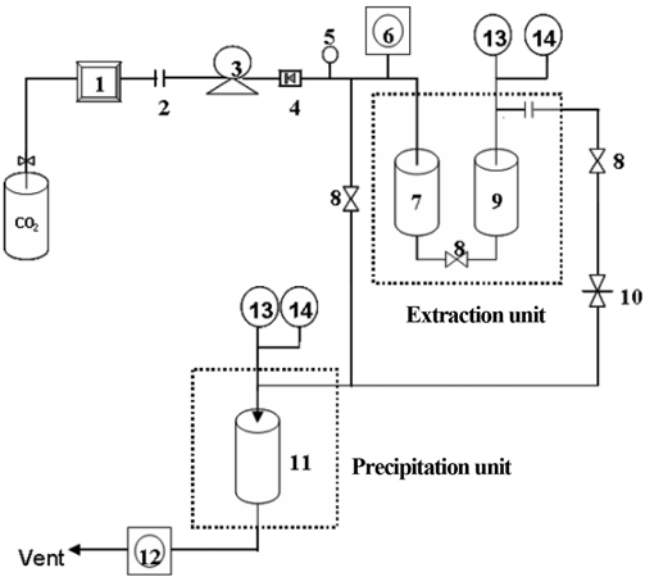


Fig. 1. Schematic experimental apparatus for the RESS process with supercritical CO_2.

1. Low temp. water bath
2. Filter
3. High pressure pump
4. Check valve
5. Safety fin
6. Flow meter
7. Storage tank
8. Valve
9. Extraction tank
10. Quick connector
11. Crystallization tank
12. Gas meter
13. Pressure gauge
14. Temperature gauge

enters the stainless steel extraction tank, pressure fluctuation is eliminated in the storage tank. The extraction temperature and pressure are maintained at the desired value by PID temperature controller and back-pressure regulator, respectively. The liquid CO_2 enters the extraction tank packed with the drug substance and becomes supercritical, where it provides efficient mixing and prevents entrainment of solid solute. Supercritical CO_2 is saturated with drug substance in the extraction tank, and the saturated solution flows to the precipitation unit wrapped with double-insulated heating tape. The purpose of expansion unit is to heat the solution to prevent phase changes upon expansion and choking problems in the expansion device caused by premature precipitation of solute or solid CO_2.

Following the heating at the expansion unit, the supercritical solution is allowed to expand into atmosphere through the expansion device. Orifice disks with different hole diameter and capillary nozzles with different L/D ratio are adapted as expansion devices. The solution is rapidly depressurized by expansion, resulting in a dramatic decrease in the saturation concentration of the drug substance. And the resultant high supersaturation produces fine drug particles instantaneously.

Prior to each run, CO_2 is purged through the bypass section of the extraction unit and continues to flow through the precipitation unit to remove solute residue.

2. Solubility Measurement and Analysis

Three drug substances with different solubility in supercritical CO_2, such as lidocaine, benzoic acid and griseofulvin, are adapted as drug substances. Solubilities of the drug substances used in this research were also measured by the apparatus shown in Fig. 2.

Liquid CO_2 was cooled in the low temperature water bath and

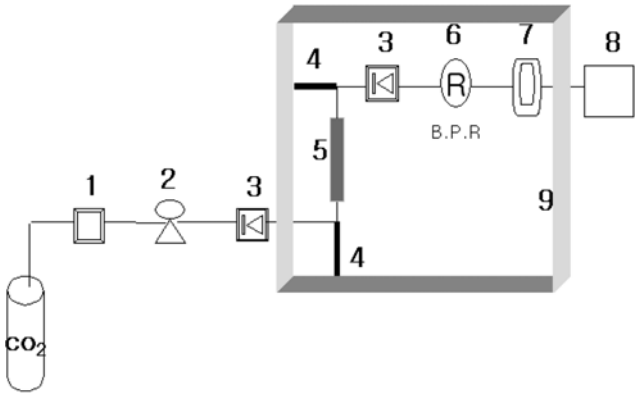


Fig. 2. Schematic experimental apparatus for measuring solubilities of drug substances in supercritical CO_2.

1. Low temperature water bath
2. High pressure pump
3. Check valve
4. Thermometer
5. Extraction tube
6. Back pressure regulator
7. Collector
8. Gas meter
9. Thermostated chamber

compressed by high pressure metering pump (Thar Design). The extraction tube, back pressure regulator and collector were placed in the thermostated chamber to keep constant temperature. The extraction tube containing 5.0 g of drug substance was equilibrated with supercritical CO_2, where the pressure was maintained constant by a back pressure regulator. The cumulative weight of the drug substances deposited in collector was precisely measured with time and the flow rates of vent gas were also measured by gas meter. The extraction tube was precisely weighted after each run to be sure that some drug remained undissolved.

Precipitated fine drug particles are collected in expansion unit, and the morphology, size and particle size distribution are measured by scanning electron microscope (SEM, Hitachi S-2400), particle size analyzer and Zeta Potential Analyzer (Brookhaven, ZetaPlus).

For the particle size analysis with Zeta Potential Analyzer, 0.1% v/v aqueous dilute suspension of the particles was prepared and placed in an acrylic square cell. Just a few minutes are required for the sam-

Table 1. The comparative solubilities of drug substances in supercritical CO_2

Material	Temp. (°C)	Press. (bar)	Solubility (mole fraction)
Benzoic acid	45	200	3.18×10^{-3}
	45	350	4.87×10^{-3}
	55	200	3.83×10^{-3}
	55	350	7.17×10^{-3}
Griseofulvin	45	200	1.3×10^{-5}
	45	300	4.3×10^{-5}
	55	200	2.4×10^{-5}
	55	300	5.3×10^{-5}
Lidocaine	45	240	6.7×10^{-2}
	45	360	6.4×10^{-2}
	55	240	7.0×10^{-2}
	55	360	6.6×10^{-2}

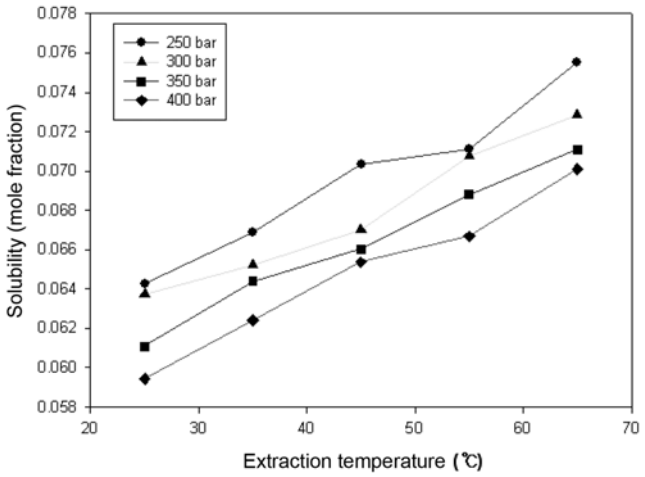


Fig. 3. The effect of extraction temperature on the solubility of lidocaine in supercritical CO_2 at different pressures.

ple and cell to equilibrate with the environment inside the analyzer.

RESULTS AND DISCUSSION

1. Solubilities of Drug Substances

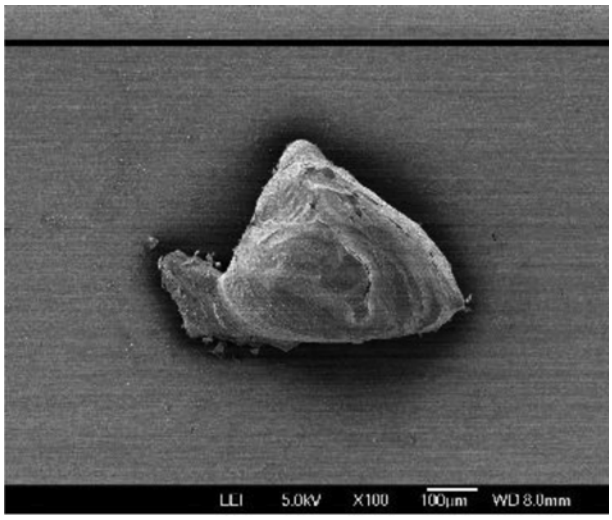
The solubilities of drug substances in supercritical CO_2 used in this research are compared in Table 1. Table 1 shows lidocaine has a far higher solubility in supercritical CO_2 than any other drug substances. And the solubility (mole fraction) of griseofulvin in supercritical CO_2 is very small, ranging from 1.3×10^{-5} to 5.3×10^{-5}, whereas that of benzoic acid is in the medium range of 3.18×10^{-3} to 7.17×10^{-3}. We adapted these three drug substances as target materials because of the big differences in solubility in supercritical CO_2.

Fig. 3 shows the effect of extraction temperature and pressure on the solubility of lidocaine in supercritical CO_2. As shown in Fig. 3, the solubility of lidocaine increases with extraction temperature and decreases with extraction pressure. However, it's well known that the solubility of solutes in supercritical fluids normally increases with extraction pressure and temperature even though retrograde (crossover pressure effect) behavior exist.

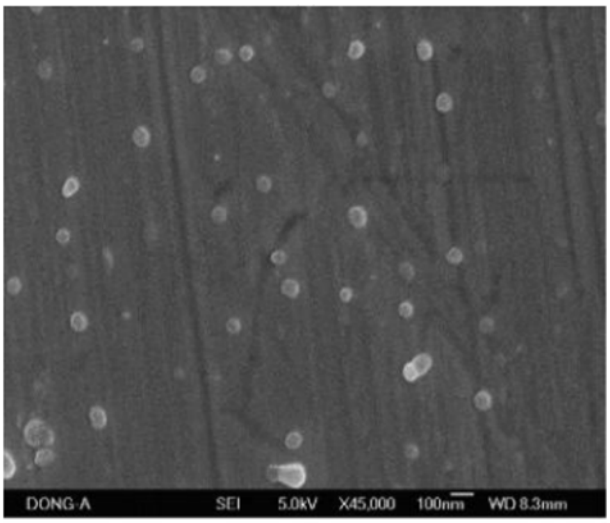
Morante et al. [14] reported the solubility of imipramine HCl in supercritical CO_2 decreases with pressure beyond a given pressure and explained this decreasing solubility with pressure might be attributed to a limitation of the technique at high pressure. However, similar decreasing solubilities of drug substances in supercritical CO_2 were reported by several researchers. Vandana and Taja [15] observed the decreasing solubility of paclitaxel in supercritical CO_2 and N_2O and Frank and Ye [13] also reported decreasing solubility of the insoluble drugs with pressure. Therefore, we believe this interesting decreasing solubility with pressure shown in Fig. 3 is not attributed to a limitation of the technique at high pressure but the correct result.

2. Effect of Process Parameters on Particle Properties

The RESS process with supercritical CO_2 prepared fine drug substances in a wide range of experimental conditions. Especially in the case of lidocaine, nano-sized spherical particles were prepared from lidocaine raw material with particle diameter of 350-550 μm. Representative SEM photos of raw and processed lidocaine particles are shown in Fig. 4, and photos of griseofulvin [16] and benzoic acid [17] particles are shown in our previous papers.



(a)



(b)

Fig. 4. Representative SEM photos of lidocaine particles. (a) Raw particle. (b) After RESS process at 50 ºC 250 bar.

Lidocaine has a far higher solubility of 6.4×10^{-2}-7.0×10^{-2} in supercritical CO_2 than other drugs examined and produced finer nano-sized spherical particles with relatively narrow PSD whose average particle diameter is 100-300 nm. On the other hand, griseofulvin [16] produced relatively big particles with wide PSD whose average particle diameter is 1,800-3,300 nm because of its low solubility.

The PSD and average particle diameter of lidocaine prepared by RESS process were measured by zeta potential analyzer and the representative overlaid PSD curves are shown in Fig. 5 and 6. As shown, the peaks of the PSD curve move steadily downward (to smaller diameter) with extraction temperature and upward with extraction pressure. The PSD curves, as a whole, become narrow with extraction temperature and broaden with extraction pressure. These effects of extraction temperature and pressure on the particle diameter are explained below.

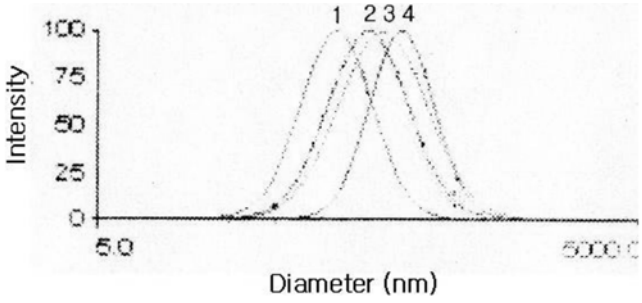


Fig. 5. The effect of extraction temperature on the PSD curve of lidocaine particles by Zeta Potential Analyzer at 250 bar.
1. 70; 2. 60; 3. 50; 4. 40

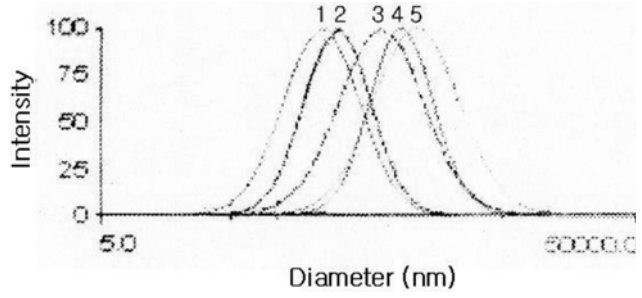


Fig. 6. The effect of extraction pressure on the PSD curve of lidocaine particles by Zeta Potential Analyzer at 50 °C.
1. 150 bar; 2. 200 bar; 3. 250 bar; 4. 300 bar; 5. 350 bar

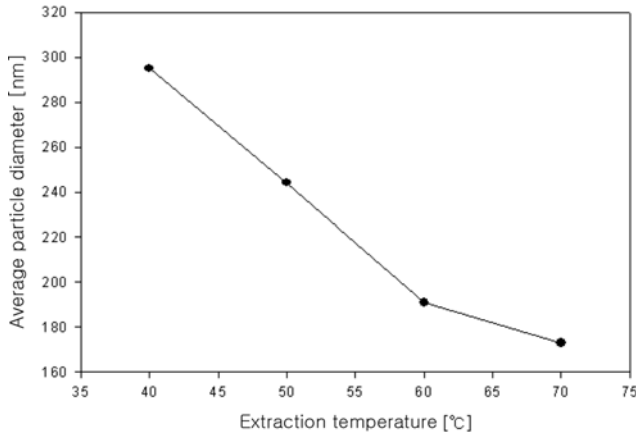


Fig. 7. The effect of extraction temperature on the average particle diameter of lidocaine prepared by RESS process at 250 bar.

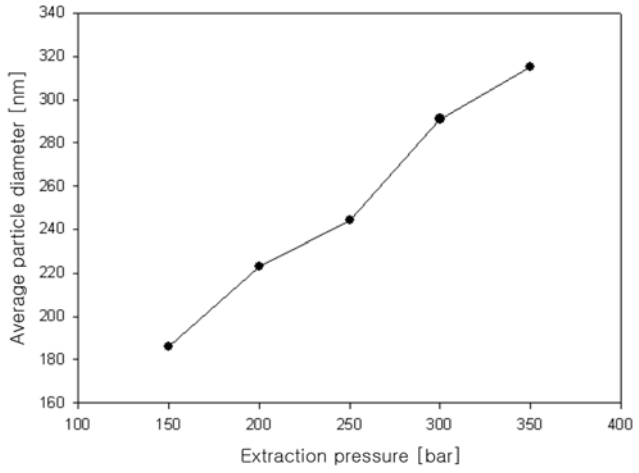


Fig. 8. The effect of extraction pressure on the average particle diameter of lidocaine prepared by RESS process at 50 °C.

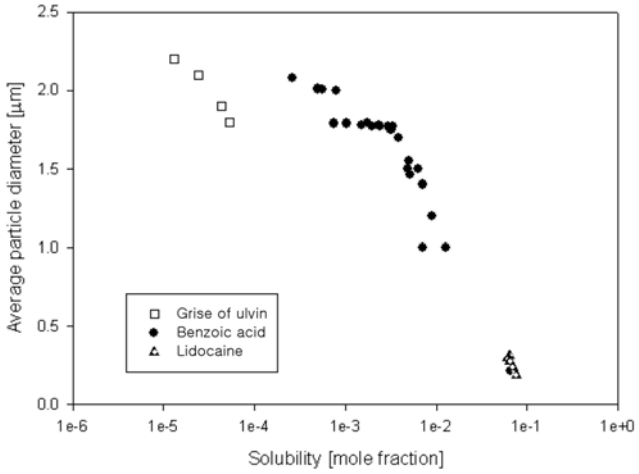


Fig. 9. The effect of solubility on the average particle diameter of drug substances prepared by RESS process.

Figs. 7 and 8 represent the effects of extraction temperature and pressure on the average particle diameter of lidocaine prepared. As shown, the average particle diameter decreases with extraction temperature and increases with extraction pressure. These results may be explained by the solubility effect on the particle formation. The solubility of lidocaine in the supercritical CO_2 increases with the extraction temperature and decreases with extraction pressure, as shown in Fig. 3. The high solubility produced at high temperature and low pressure causes a high lidocaine concentration in supercritical solution, and the high lidocaine concentration makes instantaneously high super-saturation during the rapid expansion through the expansion device. Resultant high super-saturation induces high nucleation potential and produces more nuclei and small particles with narrow PSD.

For the purpose of investigation on the general relationship between drug solubility in supercritical CO_2 and average diameter of particles produced by RESS process, the average particle diameters of three drug substances used in this research are plotted against their solubilities in Fig. 9. Fig. 9 clearly shows the general tendency that average particle diameter decreases with solubility of the solutes, even though data for benzoic acid are more or less scattered. Considering the fact that the extraction temperature and pressure determine the solubility of the solute, this result shows the solubility is major factor controlling the average particle diameters, regardless of used solute.

For the purpose of preventing phase changes and choking problems in the expansion device caused by premature precipitation of solute or solid CO_2, pre-expansion temperature was controlled by heating tape and PID controller. The pre-expansion temperature also

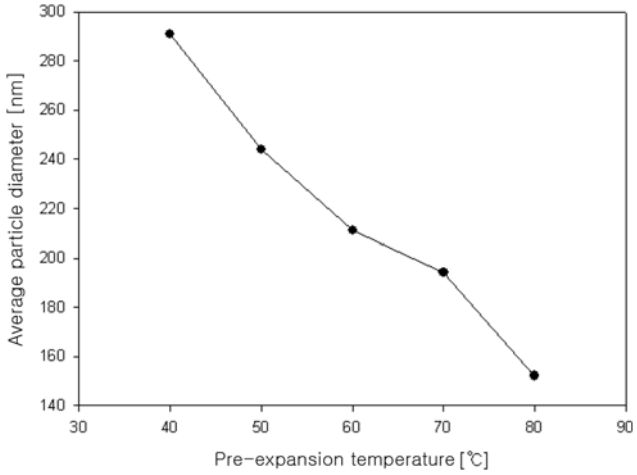


Fig. 10. The effect of pre-expansion temperature on the average particle diameter of lidocaine prepared by RESS process at 50 ℃ and 250 bar.

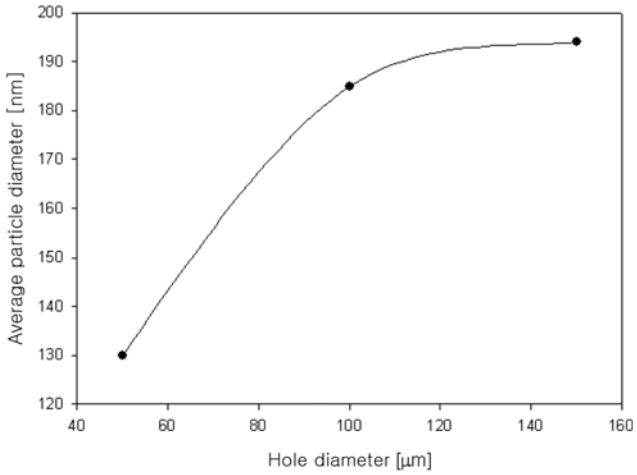


Fig. 11. The effect of hole diameter on the average particle diameter of lidocaine prepared by RESS process at 50 ℃, 250 bar.

has a significant effect on the average particle diameter of produced lidocaine. As shown in Fig. 10, the average particle diameter significantly decreases with pre-expansion temperature. This result might be attributed to the reduced supersaturation and prolonged precipitation period by premature precipitation caused by low solubility at low pre-expansion temperature.

The average particle size of prepared lidocaine is also affected by the configuration of expansion devices, such as hole diameter of a orifice disk and length to diameter ratio (L/D) of capillary tube.

Fig. 11 shows the effect of hole diameter of a orifice disk on the average particle diameter. As shown, the average diameter increases with the hole diameter. This result might be attributed to moderate concentration gradient of lidocaine around expansion device. The increase in hole diameter causes a moderate concentration gradient of lidocaine around the expansion device, and the concentration gradient causes premature precipitation and low supersaturation producing large particles due to the prolonged precipitation period.

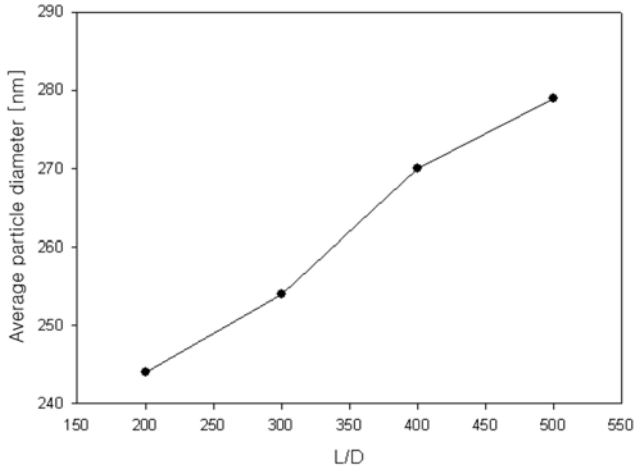


Fig. 12. The effect of aspect ratio (L/D) on the average particle diameter of lidocaine prepared by RESS process at 50 ℃, 250 bar.

The effect of L/D ratio on the average diameter of prepared lidocaine particles is shown in Fig. 12. The average particle diameter also increases with L/D ratio. This result is coincident with those of Ju et al. [16] and Kim et al. [17] for griseofulvin and naproxen, respectively. They have reported the average particle diameter increases with L/D ratio for L/D >200, and it is not easy to make an expansion device whose L/D ratio is less than 200 because of the very short capillary length.

This result might be explained by the concentration gradient of a solute in a capillary tube. The increase in L/D ratio causes a moderate concentration gradient and premature precipitation in the capillary tube and produces large particles due to the prolonged precipitation period.

CONCLUSIONS

A RESS process for the preparation of ultra-fine lidocaine particles with no organic solvent has been developed with supercritical CO_2. Lidocaine has a far higher solubility in supercritical CO_2 and the solubility increases with extraction temperature and decreases with extraction pressure.

The RESS process produces lidocaine fine particles with average particle diameter of 100-300 nm in these experimental conditions. The average particle diameter of lidocaine produced by the RESS process decreases with extraction temperature and increases with extraction pressure. The particle diameter also decreases with pre-expansion temperature, and increases with hole diameter of orifice nozzle and aspect ratio (L/D) of capillary tube.

Regardless of drug substances, the average particle diameter decreases with solubility of drug in supercritical CO_2.

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