ABSTRACT

ULTRA-FINE PARTICLE FORMATION USING PRINCIPLE OF RAPID EXPANSION OF SUPERCRITICAL SOLUTIONS

by
Miraj Minesh Sheth

There are indications in the chemical and pharmaceutical industries that the reduction in size of a crystalline particle can lead to better performance of the drug compound, particularly for water insoluble drugs, in the final dosage form. Many particle formation techniques have been investigated in recent years by researchers to obtain desired particulate sizes and size distributions. Supercritical fluid technologies have been successfully investigated for particle formation due to its unique gas/liquid properties in the supercritical state. In this report, results of particle formation using the principles of Rapid Expansion of Supercritical Solutions (RESS) have been documented.

In the RESS process, the solution is rapidly expanded through a well-defined nozzle which leads to formation of ultra-fine particles. An extensive parametric study was conducted in order to obtain an optimized set of experimental parameters to formulate ultra-fine particles with narrow particle size distribution. Particles in the nano / sub-micron range were obtained. Modifications of the RESS process were also explored. Particles obtained from the RESS process were characterized using tools such as scanning electron microscopy, light scattering, and, Raman Spectroscopy. This work illustrates that the RESS processes can be successfully used to produce ultra-fine particles.

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by
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CHAPTER 1

INTRODUCTION

In 1999, Dr Richard Smalley, Nobel laureate in chemistry, mentioned in US Congress Testimony [that],

> "The impact of nanotechnology on health, wealth, and the standard of living for people will be at least the equivalent of the combined influences of microelectronics, medical imaging, computer-aided engineering, and man-made polymers in this century".[1]

The field of nanotechnology is growing at a fast rate with a focus on the creation of functional materials, devices, and systems through the control of matter at the nanometer scale, and the exploitation of novel phenomena and properties at that length scale. The rapid development of nanotechnology is equally supported by major scientific and technological advances in microscopy, material science, molecular-level manipulation, and scientific understanding at the borderline between classical and quantum physics.[2]

Over the past decade, spending on nanotechnology R&D has increased almost exponentially both in the public and private sector of the industries. In the 2001 fiscal year, a national nanotechnology initiative was introduced in the United States of America, making it a top science and technology priority. A 21st century National Nanotechnology Research and Development Act was signed into law by President George W. Bush in December 2003 which authorized $3.7 billion to be spent in the 4-year period beginning October 2005 on nanotechnology initiatives with an aim to establish interdisciplinary research centers and accelerate technology transfer into the private sector. The five participating federal agencies included National Science

Foundation (NSF), Department of Energy (DOE), NASA, National Institute of Standards and Technology (NIST), and Environmental Protection Agency (EPA).[3]

1.1 Definition of a Nanoparticle

Nanotechnology is the science of creation and utilization of functional materials, devices, and systems through the control of matter on a nanometer-length scale. A nanometer (nm) is one billionth (10^{-9}) of a meter. By definition, any particle with a size smaller than one micrometer can be referred to as a nanoparticle. However, several national initiatives are encouraging the development of particles less than 100 nanometers to be referred to as nanoparticles as they tend to demonstrate some unique physical properties at the threshold where quantum physics takes over. From a pure physics point of view, when one dimension of the structure is on the nanometer scale, the structure is referred to as a quantum well. Moreover, if two sides are of nanometer length, the structure is referred to as quantum wire, and a quantum dot is used for a structure with all three sides in the nanometer range. The change in properties arises due to the quantum-mechanical nature of physics in this small (nano) field.[3] In this report, particles within the size range of 1nm to 1000nm will be considered as nanoparticles since the question of the precise size range is still a debate.

1.2 Nanotechnology and Pharmaceuticals

The unique properties of nanoparticles have led to new applications and developments within the pharmaceutical and medical field. The dosing and efficacy of drug compounds have improved due to the emergence of nanotechnology. Since the absorption profiles

increases, smaller quantities of the drug need to be administered. This in turn reduces the chances of side effects in the patients. Drug delivery through oral, injective, inhalers, respirators and, solutions mode have now been made possible at the nanoscale level. Novel technologies are being developed for targeted drug delivery.

In the pharmaceutical industry, the actives (active pharmaceutical ingredients) in approximately eighty percent of all medicines are administered in the solid state. In addition to that, about forty percent of the active pharmaceutical ingredient (API) currently in the industry pipelines exhibit poor solubility and bioavailability. The majority of these drug substance falls under biopharmaceutical specification class II (BSC II) classification. Drugs of class II exhibit high permeability but the rate limiting step is a function of low solubility, which can be correlated with the dissolution velocity. Therefore, there is a critical need in the industry to develop formulations with increased dissolution rates, which can thereby enhance absorption and bioavailability. One of the ways to achieve this is by reducing the particle size to the nano or sub-micron range. According to the Noyes-Whitney equation, the poor solubility can be correlated with the low dissolution velocity.

$$\frac{dW}{dt} = \frac{DA(C_s - C)}{L}$$

where, dW/dt is the rate of dissolution, A is the surface area of the solid, C is the concentration of the solid in the bulk dissolution medium, C_s is the concentration of the solid in the diffusion layer surrounding the solid (saturation solubility), D is the diffusion coefficient, and L is the diffusion layer thickness. This equation shows that the increase dissolution velocity is directly proportional to the increase in surface area of the particle.

This increase in surface area, and thus increase in dissolution velocity can be achieved by decreasing the particle size of the substance. For instance, the surface area of the particle would increase by a factor of 10, by micronizing a 50μm particle to 5μm. There is an additional increase by a factor of 100 if the same particle is micronized to 500nm. Furthermore, when the size is below 1 μm, there is additional increase in saturation solubility (C_s) by a factor of about 2 to 4-6. It is also worth noting that many drug substances can currently be formulated at a nano-scale level.[4, 5, 6, 7]

1.3 Techniques for Particle Formation

Conventional techniques for particle formation, particle size reduction and material processing used currently in the industries include milling, high pressure homogenization, spray-drying, freeze-drying and crystallization.

1.3.1 Milling

There are several milling techniques used in the industry. Two of the most common techniques used in the pharmaceutical industry are discussed below.

1.3.1.1 Ball / Pearl Milling. A ball / pearl mill is one of the oldest means of grinding materials. The milling is primarily affected by the mill's rotational speed, length of milling time, quantity of milling medium as well as quantity of the powder. In a ball / pearl mill, the milling medium (i.e., balls) along with the powder (e.g., drug powder) is placed in the cylinder and is rotated on a set of rotating wheels. The degree of comminution, or size reduction, can be increased by increasing the milling time, rotating the mill at a faster speed, and/or by using a larger ratio of ball weight to powder weight.

While there are advantages to using these techniques, there are also disadvantages which can be critical in pharmaceutical industry. Ball / pearl milling can change the morphology of a solid; a crystalline solid can become amorphous. Moreover, strong grinding can increase the solid's surface energy and can distort the crystal lattice. Another critical issue with ball / pearl milling is the erosion from the milling medium during the milling process. There are also issues of high thermal energy resulting from the particle-particle and particle-milling medium collisions inside the chamber which can be critical for thermolabile (heat-sensitive) drug substances.[8]

1.3.1.2 Jet Milling. During jet milling, the process material is driven at near sonic velocity around the perimeter of a chamber by multiple jets of air or steam. High-velocity collisions particles comprising the powder cause the reduction in size. The chamber is constructed such that it allows the recirculation of the larger particles which in turn enhances the effect of this collisions.[9] This type of technique is of limited use to the production of nano powders. For typical jet milling processes, the final size distributions are usually within the size range of about 0.1 to 20 μm, and thus contains a very small fraction (about 10%) in the nanometer range.[4, 6]

1.3.2 High Pressure Homogenization

Homogenization is a mechanical process that uses high pressure to break down particles in the suspension. The suspension is usually passed through a specially designed tiny homogenizing gap which results in high shear, compression, acceleration, pressure drop and collision forces acting in this highly turbulent fluid in the gap possessing a high kinetic energy and eventually causing the breakup of particles and dispersion. The

pressure required for homogenizing process ranges from 100 to 1500 bar, which can be a critical issue for temperature and pressure sensitive drug substances. One advantage of high pressure homogenization over ball / pearl milling is absence of the milling medium. This technology requires the drug powder to be in the micronized state as well as in liquid suspension. Researchers have also looked at a combination technique where the resulting suspension from a precipitation technique is subsequently homogenized in order to minimize the disadvantages of the crystal growth and stability issues due to precipitation. [4, 10]

1.3.3 Spray Drying

Spray drying is a subsequent technique to a process like homogenization wherein once the powder is micronized, the water needs to be removed from the suspension to obtain a stable dry powder. In the spray drying technique, the solution is placed with contact of hot air in a drying chamber during which the sprays are produced by either rotary or nozzle atomizers. Dry particles produced due to the evaporation of moisture from the droplets are then collected in a collection chamber. A schematic example of the combination technique of homogenization followed by spray drying is shown in Figure 1.1.

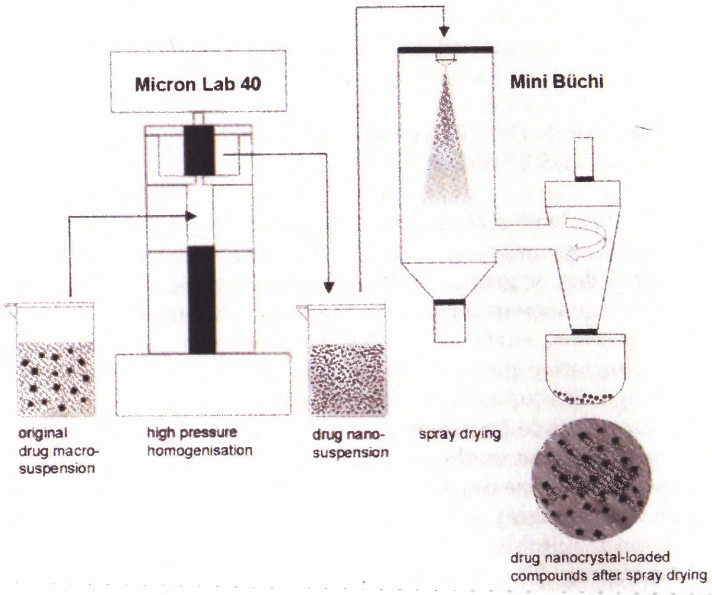


Figure 1.1 Two-step process of production of drug nano-particles[4].

1.3.4 Freeze Drying

Freeze drying is also a subsequent step to a process like homogenization. In freeze drying, the material is allowed to freeze at first and then the material is dried using two-step drying process. In the first drying step (primary drying), the pressure is lowered and enough heat is supplied to the material so that the water sublimates from solid (ice) to gaseous phase. The second drying step (secondary drying) is performed to sublimate the water molecules that are adsorbed during the freezing process. In this step the temperature is raised even higher and the pressure is often dropped lower (than primary drying) to break any physico-chemical interactions between the frozen material and water molecules. This technique is both complex and expensive.[11]

1.3.5 Liquid Antisolvent (LAS)

The use of liquid antisolvent techniques to crystallize solid compounds has been prevalent in many industries. This technique has become one of the most promising particle production techniques in the pharmaceutical industry beecause this technique eliminates the use of thermal energy which can lead to the degradation of biological activity of drug particles. In the most common procedures, a poor solvent of a particular solute is added to the solution in order to precipitate the solute. Water is most commonly used as an antisolvent for hydrophobic drug compounds, whereas organic solvents are used for hydrophilic compounds. Precipitation of the solute takes place when the antisolvent is gradually mixed with solution. The working principle behind this technique is that during mixing, there is an increase in the molar volume of the solution that results in decrease in solubility power of the solute and hence the precipitation. Even though it has been widely used in industry, there is minimal control over the crystal morphology and size distribution, as well as the presence of residual solvent which is undesirable.[12]

1.4 Motivation

There is a growing interest in pharmaceutical industry to develop efficient drug delivery system for controlled / sustained release using ultra-fine drug particles. Fine and ultra-fine particles possess unique properties that improve dosing (reduced drug dosage), efficacy of drugs (high therapeutic effect) and bioavailability of the drug. There are many particle formation processes available in the literature. Although few of these processes have been used successfully in the pharmaceutical industry for several years,

they all hold various drawbacks due to either the application of heat, development of electrostatic charges and/or residual organic solvents. Also, the processes suffer from poor control of particle size as well as PSD. In order to overcome this researchers have started focusing on unconventional techniques to reduce the particle size of the drugs. Supercritical fluid technologies have shown promising results in order to produce fine particles with controlled size distribution and morphology.

1.5 Problem Definition

Among the supercritical processes such as Rapid Expansion of Supercritical Solutions, (RESS), Gas Anti-Solvent (GAS), Supercritical Anti-Solvent (SAS), and Solution-enhanced Dispersion by Supercritical Fluids (SEDS), RESS process have shown promising results for producing fine particles with narrow size distributions without the use of any organic solvents. Therefore, RESS process was used in this study as a means to produce nano / sub-micron particles. Effect of various parameters on precipitation of drug substance was examined in this study in order to optimize the parameters to obtain ultra-fine particles.

1.6 Thesis Structure

The first chapter gave a brief introduction on nanotechnology in pharmaceutical industry. Chapter 2 is a review on particle engineering using supercritical fluid technologies. A concise background on RESS technique is given in chapter 3. Chapter 4 explains the experimental setup, nozzle geometries and characterization techniques used during the study. Discussion of the experimental results is in chapter 5. The scale-up related issues are discussed in chapter 6 followed by the concluding remarks in chapter 7.

CHAPTER 2

PARTICLE ENGINEERING USING SUPERCRITICAL FLUIDS TECHNOLOGY – A REVIEW

The thrust to gain an accurate and detailed understanding of supercritical fluids have been ever increasing since the past two decades. Initial interest in supercritical fluid technologies was aroused due to the environmental benefits because of the replacement of organic solvents as well as their unique liquid-like and gas-like properties. Recently, due to advancement of research it was found that supercritical fluids possess many unique properties that can improve many chemical processes.

2.1 Definition of Supercritical Fluid

A substance is considered as a supercritical fluid when its thermodynamic state is above its critical pressure and temperature. At a reduced pressure (P/P_c) ranging from 1.01 to 1.05 and a reduced temperature (T/T_c) from 1.01 to 1.11, a substance is considered a supercritical fluid. The pressure-temperature phase diagram in Figure 2.1 illustrates the supercritical region.[14]

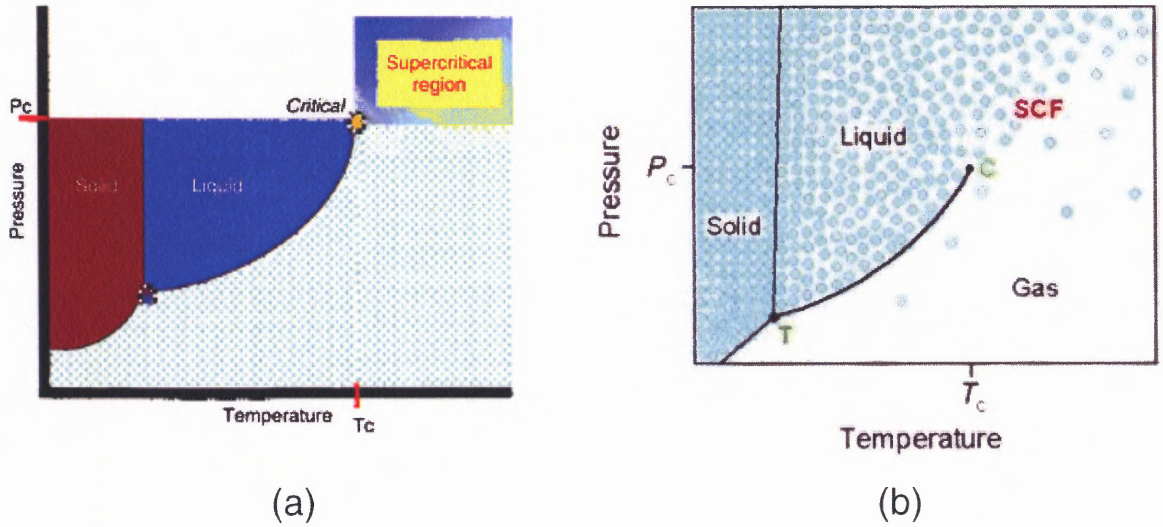


Figure 2.1 (a) Pressure-Temperature phase diagram[14] (b) Phase diagram at molecular level[15].

Within the supercritical region, a substance's liquid and vapor phases are indistinguishable starting at their respective critical temperatures (T_c) and pressures (P_c). In this stage, the supercritical fluid exhibits properties corresponding to both the liquid and gaseous state, with liquid-like densities, and gas-like flow properties. The density of supercritical fluids, which is greater than those of gases, allows for more considerable solvation power. The diffusivity of solutes in supercritical fluids (of the order of 10^{-3} cm^2/sec) is higher than those in liquids (10^{-5} cm^2/sec) due to its lower viscosity (of the order of 10^{-4} g/cm/sec and approximately 100-fold lower than that of liquids) which results in enhanced mass transfer rates comparable to conventional solvents. An important property for particle formation is that the supercritical fluids possess gas-like compressibility properties particularly near the critical point. This results in a very sensitive solubilizing power; small changes in temperature and/or pressure can tailor its solvent capacity suited for a particular application.[13, 16]

2.2 Supercritical Carbon Dioxide

All gases can reach a supercritical state if they are thermodynamically above the specified critical temperature and pressure. However, some gases gain supercritical state at extremely high temperature and pressures which can be significantly high for thermolabile (heat-sensitive) solids. Several gases in the supercritical state have been used for particle formation in industries. Table 2.1 lists several supercritical fluids studied for research in academia and industry.

Table 2.1 – Critical Constants and Safety Data for Several Supercritical Solvents[4]

Supercritical Fluid	Tc (°C)	Pc (bar)	Safety hazard
Ethylene	9.3	50.3	Flammable gas
Trifluoromethane (fluoroform)	25.9	47.5	
Chlorotrifluoromethane	28.9	39.2	
Ethane	32.3	48.8	Flammable gas
Carbon dioxide	31.1	73.7	GRAS
Dinitrogen monoxide (laughing gas)	36.5	72.6	Not combustible but enhances combustion of other substances
Sulfur hexafluoride	45.5	37.6	
Chlorodifluoromethane (HCFC 22; R22)	96.4	49.1	Combustible under specific conditions
Propane	96.8	43.0	Extremely flammable
Ammonia	132.4	112.7	Flammable and toxic
Dimethyl ether (wood ether)	126.8	52.4	Extremely flammable
Trichlorofluoromethane (CFC 11; R 11)	198.0	44.1	
Isopropanol	235.2	47.6	Highly flammable
Cyclohexane	280.3	40.7	Highly flammable
Toluene	318.6	41.1	Highly flammable
Water	374.0	220.5	

The selection of the supercritical fluid is largely based on the physico-chemical properties of the compound of interest and also the chemical process. For pharmaceutical applications, the most commonly used supercritical fluid is carbon dioxide because of its

low critical temperature (T_c = 31.1 °C) and reasonable critical pressure (P_c = 73.7 bar). Supercritical carbon dioxide is nontoxic, nonflammable, has GRAS ('generally recognized as safe') status, and is relatively inexpensive. It also doesn't react strongly with many organic solvents and can be recycled at the end of a process.

2.3 Supercritical Fluid Techniques for Particle Formation

The need for unconventional particle formation techniques has been given a great deal of attention in the chemical and pharmaceutical industries due to ever growing interest in nanotechnology as well as the search for more environmentally friendly technologies. The increase in interest for small particles with a narrow particle size distribution can be explained due to a need for most sophisticated drug delivery systems and the effect of particle size on the solubility, dissolution rate, targetability, and bioavailability of drug compounds. Furthermore, the appropriate aerodynamic size, shape, and apparent density are prime requirements to ensure the best drug delivery to the lung. The use of supercritical fluids for particle formation applications has gained a lot of momentum in past decade. Figure 2.2 summarizes several supercritical fluid technologies researched till date for particle formation.

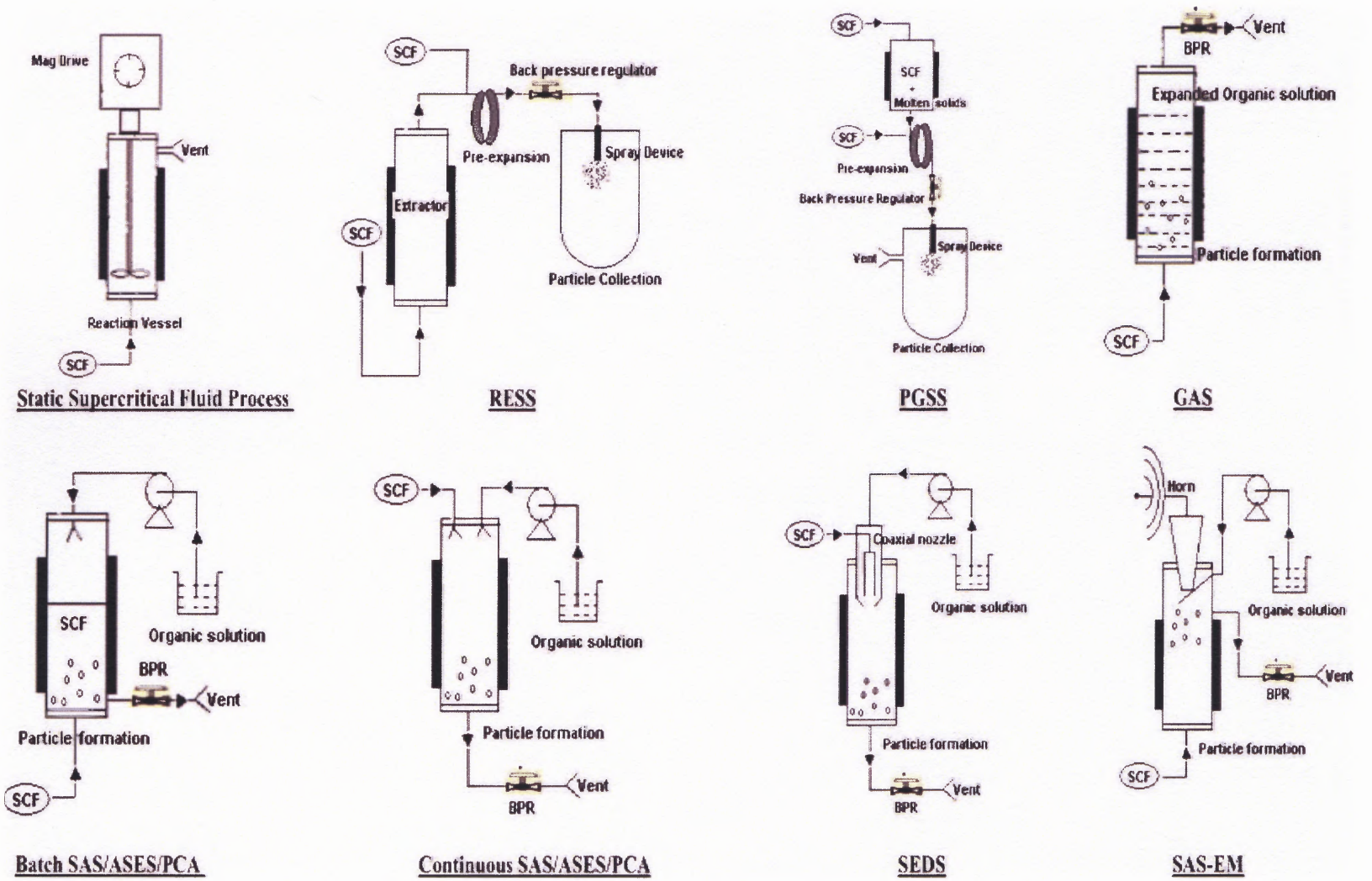


Figure 2.2 Schematic of supercritical fluid technology processes for particle formation.[28]

2.3.1 Gas Anti-Solvent (GAS) Process

In this batch precipitation process, a compound with low solubility is dissolved in an organic solvent before a miscible gas is added as an anti-solvent. This process requires steady addition of a supercritical fluid into a liquid organic solution containing the particular solute (drug) and is dependent on the ability of the liquids to solubilize a large amount of gases. As the supercritical fluid significantly expands, the volume of the organic solvent reduces its density and the dissolved drug precipitates. The precipitation is caused by the volumetric expansion of the organic solution which is accompanied by a sudden drop of liquid solvent strength. The GAS process possesses several advantages over other conventional and unconventional particle formation techniques, but also includes some drawbacks. There are chances of residual traces of organic solvent in the final product which can lead to a serious limitation in pharmaceutical industry. A broader particle size distribution can result due to variable supersaturation ratios caused by the gradual increase of supercritical fluid volume. An additional drying phase is required after GAS process since the particles are mainly produced in the liquid phase. The process scale-up can be a challenge since the conditions of the pressure are transient.[16]

2.3.2 Supercritical Anti-Solvent (SAS) Process

In this process, the supercritical fluid is substituted as the liquid anti-solvent which causes the precipitation of the solute dissolved in the primary solvent. The process is carried out at the specific temperature and pressure conditions at which the primary liquid solvent and supercritical anti-solvent are completely miscible. A rapid supersaturation of solute

dissolved in the liquid results due to the diffusion of supercritical fluid into the liquid solvent. This, in turn, results in the precipitation of micronized particles. This process differs from the GAS process in that the precipitation during the SAS process occurs in a supercritical fluid-rich phase. However, like the GAS process, it is difficult to obtain particles with a narrow particle size distribution. The complexity arises due the formation of droplets as well as mass transfer into and out of the droplets. In order to produce smaller particles, the mixing or mass transfer of the solvent and anti-solvent (supercritical fluid) needs to be faster than the SAS process.[4, 17]

2.3.3 Solution-enhanced Dispersion by Supercritical Fluids (SEDS)

The SEDS process works on a similar principle as that of SAS, in which the supercritical fluid and the organic solution are introduced concurrently in the reactor, and the added anti-solvent leads to the precipitation of the solid. However, in the SEDS process, a coaxial nozzle is used in which the liquid solution is introduced in the inner channel while the supercritical fluid flows in the outer tube. The premixing of the two channels before the injection point allows the dispersion of the organic solution and supercritical fluid and allows for better mass transfer. This process has been successful to produce fine particles. However, one of the drawbacks of this process is the difficulty to produce particles without any trace of solvent.[17]

2.3.4 Rapid Expansion of Supercritical Solution (RESS)

The RESS process is one of the very few supercritical technologies which do not involve the use of an organic solvent. This process relies on the solvent properties of the

supercritical fluid. This process has been successfully used to produce fine particles with a narrow particle size distribution. When the supercritical solution is rapidly expanded through the nozzle, the pressure and temperature drops suddenly based on Joule-Thompson expansion phenomenon. This leads to high supersaturation, and nucleation and growth of the ultra fine particles with narrow size distribution.

2.4 Remarks

The RESS process for particle engineering has been explored in this study for the following reasons. First and foremost, the RESS process does not involve the use of any organic solvent. This provides an utmost advantage in pharmaceutical industry where any trace of organic solvent in the drug compound is undesirable. Another significant advantage is that RESS process has a capability to precipitate ultra fine particles (nano / sub-micron range) with narrow size distribution. Additional advantages of RESS process are discussed in the subsequent chapters.

CHAPTER 3

RAPID EXPANSION OF SUPERCRITICAL SOLUTIONS – A REVIEW

3.1 History

Rapid Expansion of Supercritical Solutions technology has been investigated by researchers for about a century. In 1879, Hannay and Hogarth first described the process using a basic concept of RESS as,

> "When the solid is precipitated by suddenly reducing pressure, it is crystalline, and maybe brought down as a 'snow' in the gas, or on the glass as a frost,..."[17, 18]

However, this technology has not been really focused on as a phenomenon to produce particles with desired size and size distribution until about the early 1980s. In 1983, the first of the many patents related to RESS process was approved which demonstrated processes and apparatus for formulating fine powders of solid materials. Results were found using polymers and silica systems.[18] Since then, the rapid expansion of supercritical solutions technology has been investigated by many researchers around the world as a means to formulate particles with desired particle size and narrow particle size distribution. Lately, many more researchers have been exploring this process to produce fine particles for pharmaceutical drug substances. The utmost benefit of RESS process is that it is free of any organic solvent and hence, the solvent wastes can be greatly reduced. This process has been successfully used to fabricate particles in nano / sub-micron particle size range with controlled size distribution. Also, the operating conditions, particularly the temperature, are reasonably mild. Thus, this process is very

attractive to the pharmaceutical industry, since there is minimal thermal degradation of the thermolabile drug (API) substances.[17, 18]

3.2 Definition of RESS

When a supercritical solution, comprised of a solute (usually drug or polymer) is dissolved in supercritical solvent, is expanded through a specially designed nozzle, the characteristic speed of the expansion in the nozzle is approximately on the same order of magnitude as the speed of sound. Due to the rapid nature of this process, it is referred to as Rapid Expansion of Supercritical Solution. The process follows the principle of Joule-Thomson expansion (isenthalpic expansion) wherein the sudden pressure drop at constant enthalpy, leads to a drop in temperature resulting in very high supersaturation. The high supersaturation of solute causes high nucleation rates and hence reduces the growth of fine particles as shown in Figure 3.1.

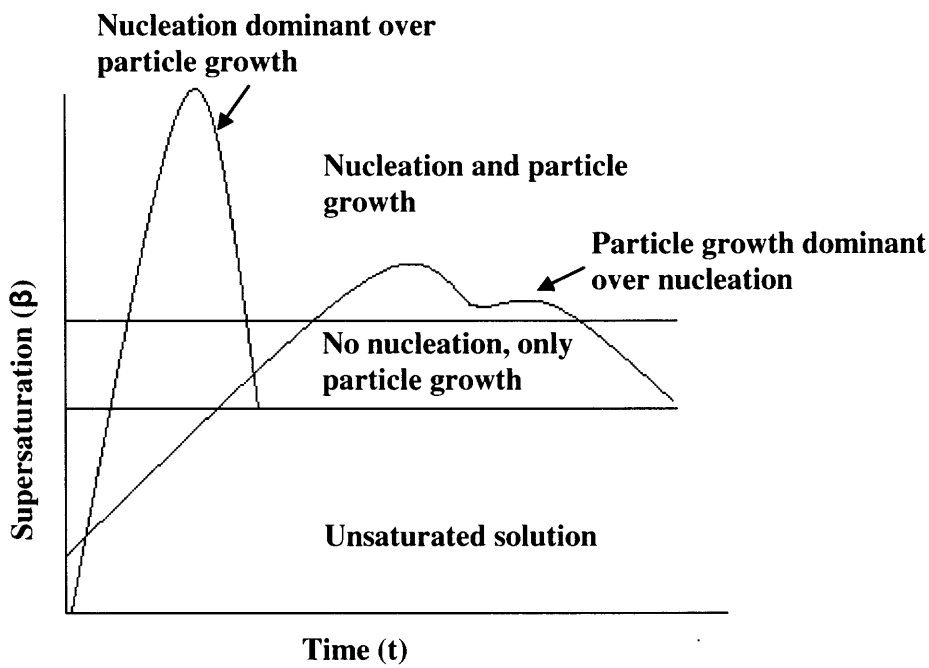


Figure 3.1 Qualitative supersaturation profiles corresponding to a precipitation process[19]

A graphic representation of expansion phenomenon (Figure 3.2) has been well demonstrated in the papers of Dr. Ram Gupta and his group at Auburn University.[20] The next section (Section 3.3) describes the process in greater detail.

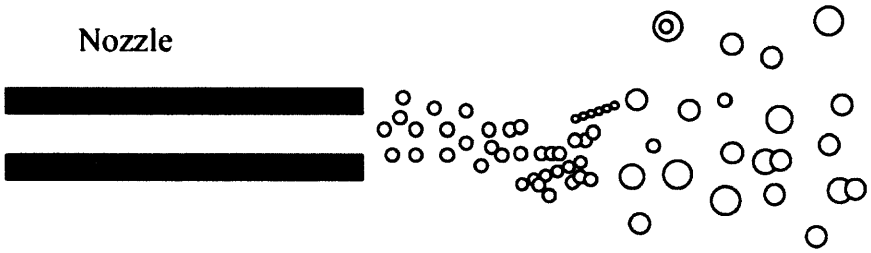


Figure 3.2 Schematic of RESS process[20].

3.3 Process Description

Figure 3.3 schematically presents four steps involved in the RESS process.

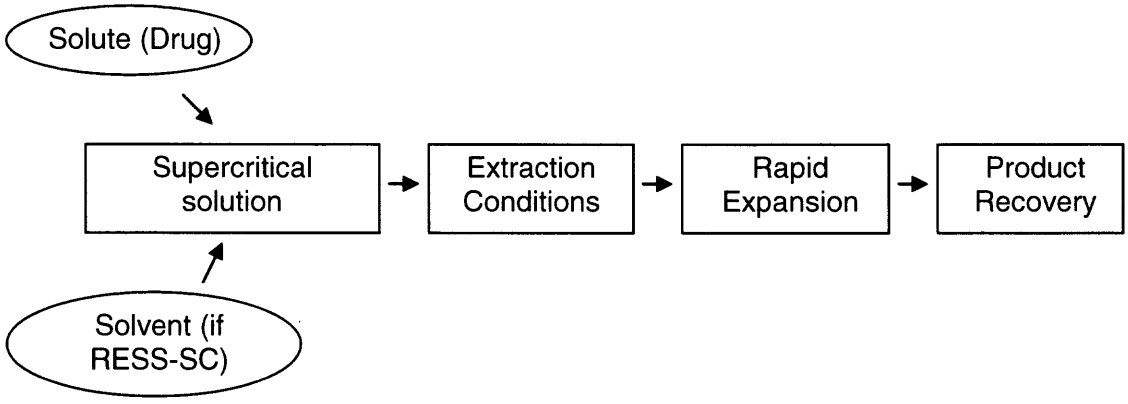


Figure 3.3 Schematic Flow diagram of RESS process[21].

3.3.1 Rapid Expansion of Supercritical Solution (RESS)

The first step in the RESS process is the dissolution of a solute (drug/API) in supercritical fluid (SCF). A solvent, at conditions higher than T_c and P_c, is pumped from the cylinder to an extraction chamber. The dissolution properties of the solute depend on the

extraction conditions (temperature and pressure) as well as the chemical characteristics which includes polarity of the solute. Therefore, it is essential to estimate the solute solubility in the supercritical solution. The challenge arises especially for pharmaceutical compounds due to the lack of availability of the data for the specific drug compounds in the literature. The solubility of the solute in supercritical solution can be determined experimentally or calculated by modeling solid-fluid equilibria using the equation of state (EOS) approach. The extraction conditions are determined based on the solubility results. The goal is to attain equilibrium concentration of solute in SCF at a given pressure and temperature (usually referred to as P_{ext} and T_{ext}) and mean residence time. This can be achieved easily by small changes in pressure and/or temperature. It is also essential to ensure the equilibrium conditions in order to obtain a high yield of the particles.[21-23, 30]

3.3.2 Rapid Expansion of a Supercritical Solution into a Liquid Solvent (RESOLV)

The RESOLV process is a slight modification of the conventional RESS process in that the supercritical solution is expanded into the liquid solvent instead of ambient air. The rationale behind this modification is to inhibit the particle growth in the expansion jet that is found in RESS process. The liquid solvent used as an expansion medium is usually de-ionized water; however, other liquids in which the solute is insoluble can also be explored. There is a potential challenge particle agglomeration in the suspension may arise which can be prevented by addition of a stabilizing agent.[21, 22]

3.3.3 Rapid Expansion of Supercritical Solutions with Solid Cosolvent (RESS-SC)

Generally, high molecular weight solids have low solubility in supercritical carbon dioxide (SC-CO_2) as CO_2 is non-polar. The introduction of a solid cosolvent into a RESS process can enhance the solute (drug) solubility to some extent as well as prevent the growth by reducing the intra-particle interactions. The cosolvent in this case is solid at nozzle exit conditions. The growth by coagulation is inhibited due to the presence of excess solid co-solvent in the expansion chamber. Figure 3.4 schematically represents this phenomenon. The choice of solid cosolvent depends on its solubility in supercritical fluid, its vapor pressure (which should be high), non-reactivity with drug or supercritical fluid, and the cost. The solid cosolvent can be removed later by using techniques such as freeze-drying or sublimation. Menthol is one of the solid compounds that satisfies the above requirements and also is an acceptable additive in food and pharmaceutical industry.[4, 20]

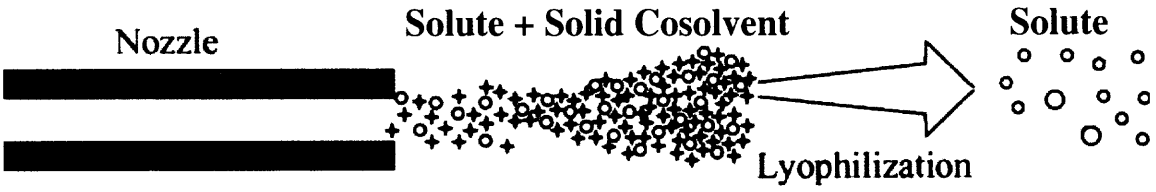


Figure 3.4 – Schematic of RESS-SC process[4, 19]

CHAPTER 4

EXPERIMENTAL SECTION

4.1 Materials

Fenofibrate ($C_{20}H_{21}ClO_4$, ≥99%, pure), and Ibuprofen ($C_{13}H_{18}O_2$, ≥98%, pure), were purchased from Sigma Aldrich. Tween 80 (from non-animal source) was purchased from Sigma Aldrich. All these chemicals were used without any further purification. Carbon dioxide (high purity SCF grade) was purchased from Welco Gas Products. Water was deionized and purified using Milli-Q® Ultrapure Water Purification Systems.

4.2 RESS Apparatus

The RESS experimental setup at can be seen in Figure 4.1. The setup allows it to be used for the modifications of RESS processes (i.e., RESOLV and RESS-SC).

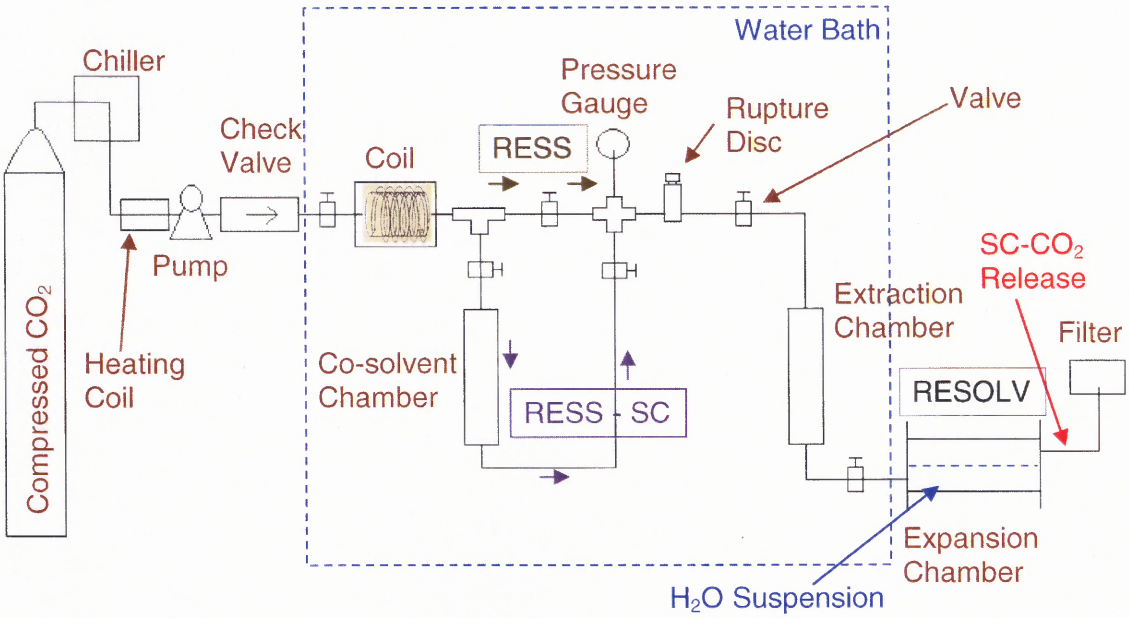


Figure 4.1 Schematic of RESS apparatus at New Jersey Institute of Technology.

The setup consists of a high pressure pump for pressure generation and pressure maintenance during the rapid expansion process. The check valve is followed by a heating coil. The T-junction allows the supercritical fluid to travel to a cosolvent chamber if RESS-SC process is performed which is controlled by the valves. The pressure gauge monitors the operating pressure maintained in the setup. The rupture disc rated at 7000psi is installed in the supercritical fluid pump and right before the extraction chamber as a safety precaution. The dissolution of the solute (drug/API) in SC-CO_2 takes place in the extraction chamber. The chamber is followed by a valve attached to the nozzle for depressurization. The nozzle can be attached to the expansion chamber containing aqueous liquid (deionized water) in order to run experiments for RESOLV process.

4.3 Nozzle Geometry

The two distinct nozzle geometries (Nozzle 1 and Nozzle 2) used to examine their effect on the particulate size, particle size distribution (PSD) and morphology are shown in the Figure 4.2.

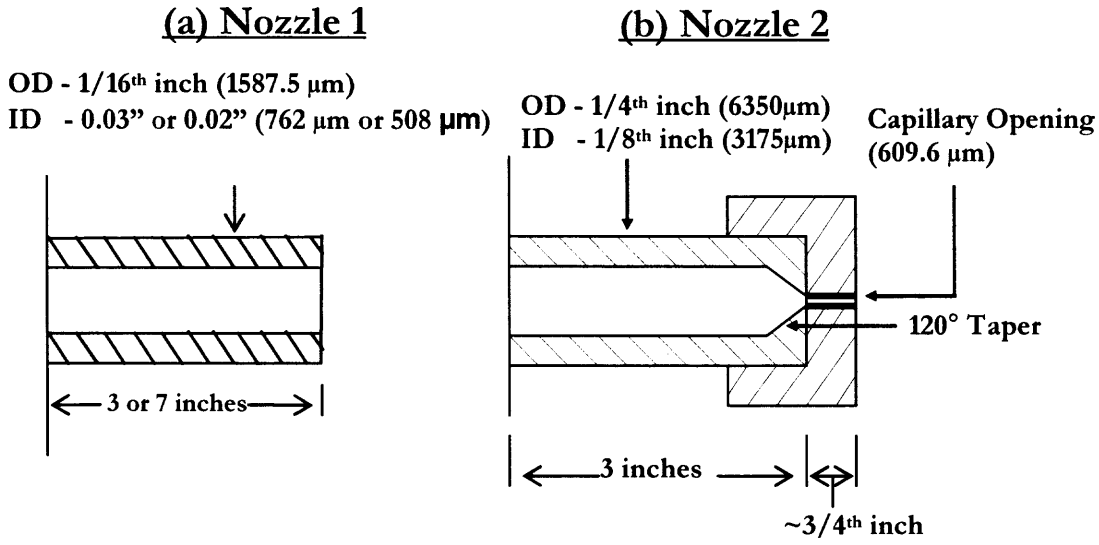


Figure 4.2 Schematic of nozzle geometries.

4.4 Characterization

Characterization of the particles produced using the RESS processes was performed using scanning electron microscopy (SEM), light scattering (LS) and raman spectroscopy.

4.4.1 Scanning Electron Microscopy (SEM)

SEM (LEO 1520 VP FESEM) was used to perform a qualitative analysis of the particles obtained from the RESS processes. The particle size and morphology were analyzed. For the analysis, the particles were collected on the carbon tape located on the top of aluminum stubs. For the analysis of the sample from aqueous liquid suspension (0.1% v/v tween 80 / DI-water), the solution was first sonicated for approximated 20 minutes and few droplets were added on the SEM stub. The stub was then placed under vacuum in dessicator to ensure the sample was dry before analysis. SEM micrographs from

different regions of the stubs were captured. Image processing and analysis software (ImageJ by NIH) was used to perform particle size analysis. This was done in order to obtain a particle size distribution for the particles directly collected on the SEM stub. Multiple images for each experiment were processed in order to get a statistically valid representation of the particles. Image analysis results were compared with light scattering (where available) results and were found to be significantly similar.

4.4.2 Light Scattering

Light scattering (Beckman Coulter LS 230) was used to measure the hydrodynamic diameter of aqueous solution of drug and deionized water. Polarization Intensity Differential Scattering (PIDS) was also performed using the Fraunhofer diffraction model. For the RESS process, after the collection of particles, deionized water was added along with approximately 0.1% of Tween 80 and sonicated for twenty minutes before performing the analysis. One of the challenges faced for light scattering was that the solution was very dilute for some experiments. Image processing was performed for these experiments.

4.4.3 Raman Spectroscopy

Raman spectroscopy (Mesophotonics SE1000) was used to compare the physical characteristics of drug substances before and after processing. The instrument is equipped with 785nm (N-IR) laser beam. The laser power is ~300mW. Raman gives the fingerprint of the molecule and the peaks represent the bonding interactions of the molecules.

CHAPTER 5

RESULTS AND DISCUSSION

An extensive parametric study has been conducted to explore the effect of parameters on size, PSD, and morphology of the particles precipitated by Rapid Expansion of Supercritical Solutions and its modifications. The effect of nozzle geometry (nozzle 1 and nozzle 2), extraction pressure (100 – 200bar), initial solute amount (100 – 300mg), and heated nozzle temperature (20 – 60°C), for RESS process has been studied. Light scattering and scanning electron microscopy were used to characterize the crystals. Table 5.1 presents the details of the experiments, process conditions, and particle size and morphology of precipitated powders.

The RESOLV process has also been examined in this study. The effect of extraction pressure (100 – 250bar) on particle size, size distribution and morphology has been investigated while maintaining all other parameters constant. The results obtained from the study are discussed in this chapter.

Table 5.1 – Tabulated Experimental Results

	Extraction Conditions			Expansion Conditions							Results		
Exp.	**Pressure (bar)**	**T (°C)**	**Drug Amount (mg)**	**Pressure (bar)**	**Nozzle T (°C)**	**Nozzle Type**	**Nozzle Length (inches)**	**Nozzle Diameter (μm)**	**Process**	**LS**	**Average Particle Size (μm)**	**Range (μm)**	**Morphology**
1	100	60	100	ambient	ambient	1	7	762.0	RESS	N/A	2.385	0.50 - 11.35	quasi-cubicle
2	100	60	100	ambient	ambient	1	3	762.0	RESS	N/A	0.766	0.24 - 5.39	quasi-cubicle
3	100	60	100	ambient	ambient	1	3	508.0	RESS	N/A	4.112	1.66 - 13.78	rod-like
4	100	60	100	ambient	60	1	3	762.0	RESS	Yes	1.232	0.415 - 7.85	quasi-cubicle
5	100	60	100	ambient	60	2	3/4	609.6	RESS	Yes	0.289	0.06 - 3.57	quasi-cubicle
6	150	60	100	ambient	60	2	3/4	609.6	RESS	Yes	5.521	1.25 - 23.99	quasi-cubicle
7	200	60	100	ambient	60	2	3/4	609.6	RESS	Yes	4.977	3.13 - 25.52	quasi-cubicle
8	100	60	200	ambient	60	2	3/4	609.6	RESS	Yes	2.169	0.25 - 10.89	quasi-cubicle
9	100	60	300	ambient	60	2	3/4	609.6	RESS	Yes	5.302	0.86 - 24.15	quasi-cubicle
10	100	60	100	ambient	40	2	3/4	609.6	RESS	Yes	1.826	0.69 - 14.18	quasi-cubicle
11	100	60	100	ambient	ambient	2	3/4	609.6	RESS	Yes	8.466	1.68 -32.11	quasi-cubicle, rod-like, needle-shaped
12	100	60	100	ambient	ambient	1	7	762.0	RESOLV	Yes	3.451	1.12 - 8.09	quasi-cubicle
13	150	60	100	ambient	ambient	1	7	762.0	RESOLV	Yes	13.749	0.71 - 56.54	quasi-cubicle
14	200	60	100	ambient	ambient	1	7	762.0	RESOLV	Yes	7.923	0.61 - 23.35	quasi-cubicle
15	250	60	100	ambient	ambient	1	7	762.0	RESOLV	Yes	14.676	2.66 - 124.5	quasi-cubicle

5.1 Effect of Nozzle Geometry

The effect of nozzle geometry has been examined using Fenofibrate as a solute for the RESS process. The effect of nozzle length (L = 7 inches and L = 3 inches) has been studied.

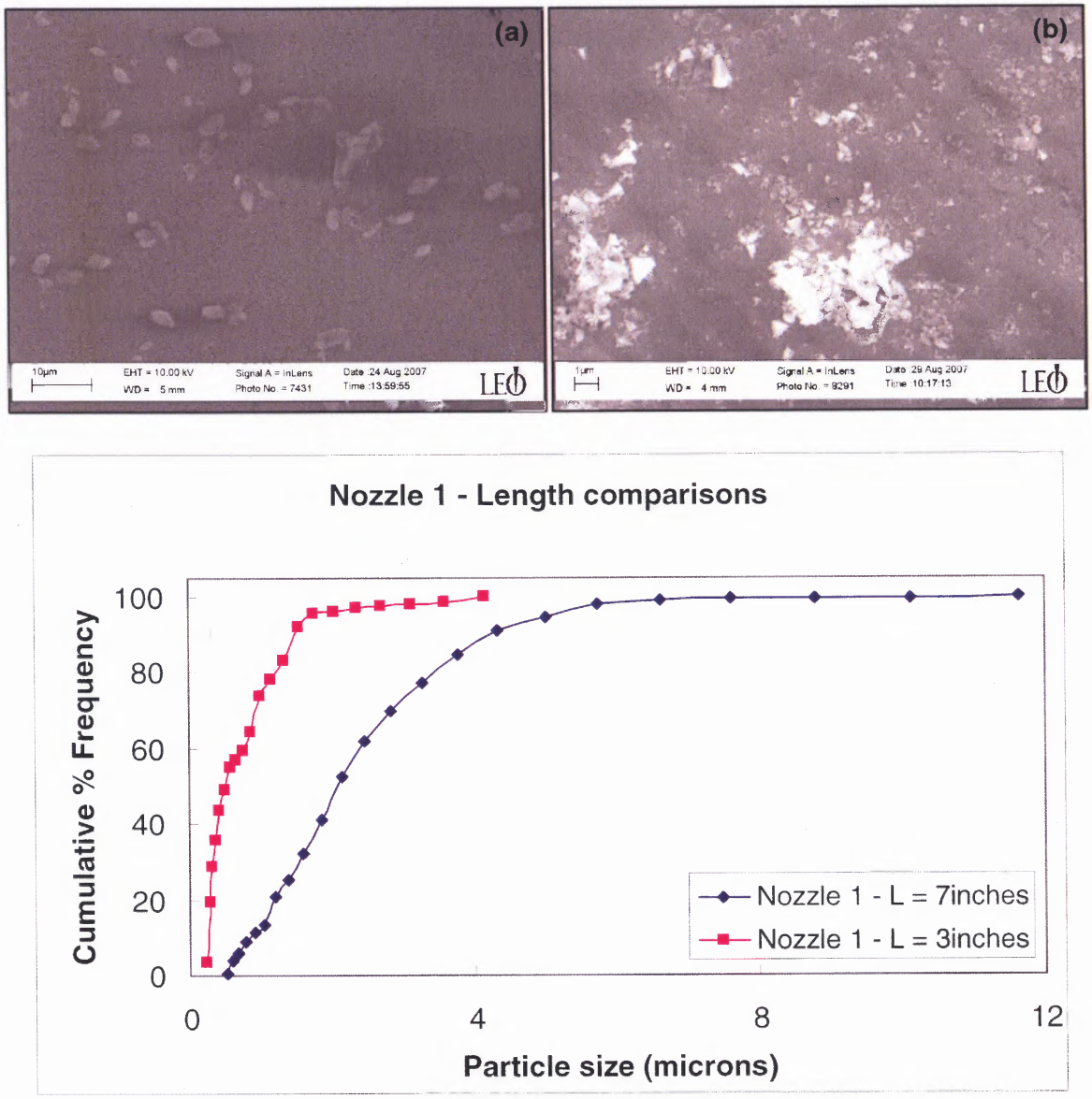
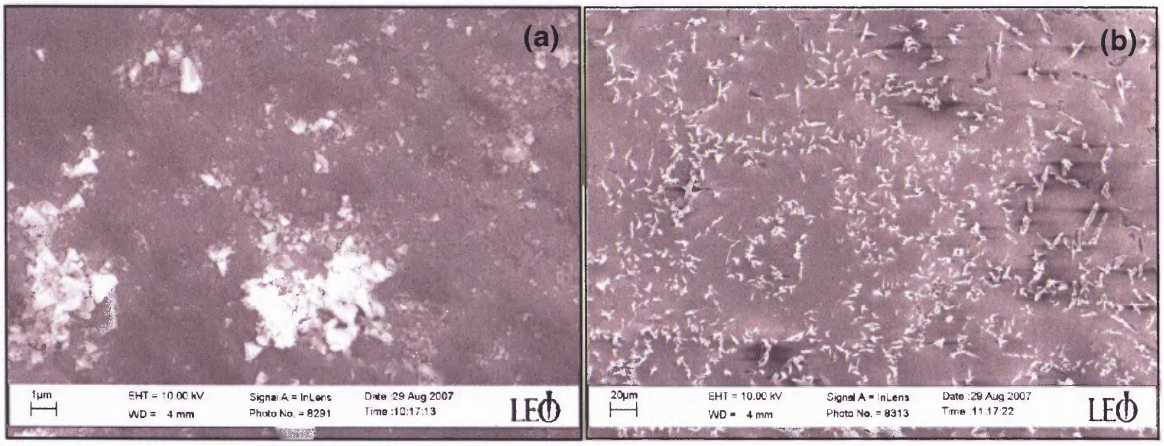


Figure 5.1 SEM micrographs and cumulative PSD for particles precipitated by RESS (a) exp 1 (b) exp 2.

The particles in these set of experiments (exp. 1 & 2) have been directly collected on the SEM stub with carbon tape attached to it. The inner diameter (ID) of the nozzle was constant for both the lengths at 762μm. As seen in Figure 5.1, approximately 50% of the particles collected using a nozzle with length, L = 3 inches were below 0.550 μm, whereas for the nozzle with length, L = 7 inches about 50% were below 2.5 μm. Also, the mean size of particles decreases from 2.385 μm to 0.766 μm with a decrease in nozzle length from 7 inches to 3 inches as shown in Figure 5.1. The increase in particle size and PSD can be attributed to the extra particle growth due to the increase in their residence time in the longer nozzle.

The next set of experiments (exp. 2 and 3) has been conducted in order to examine the effect of nozzle diameter. For these experiments, the nozzle length was constant at 3 inches while two nozzle diameters D = 508 μm and D = 762 μm have been used. Fenofibrate is used as a solute and all other parameters are kept constant. Figure 5.2 shows the results obtained from the experiment. It can be seen that with the increase in nozzle diameter from 508 μm to 762 μm for nozzle 1 the particle size decreases from 4.112 μm to 0.766 μm. It is observed that for nozzle with diameter D = 508 μm, the morphology of precipitated particles is rod-like shape while for D = 762 μm , it is quasi-cubicle. At this point, there is no reasonable explanation for the change in morphology. The experiment for nozzle diameter D = 508 μm has been repeated to eliminate a possibility for error; however, similar morphology was obtained. The results contradict the findings of Huang et al who reports that a change in nozzle diameter had no significant change in the morphology or size of precipitated aspirin.[24] It was also shown in the literature that there was no significant effect of nozzle diameter on morphology or

morphology or particle size of naphthalene when precipitated using RESS.[27] Domingo et al performed RESS process on several organic compounds in which they reported needle-like morphology for benzoic acid crystals, salicylic acid crystals and aspirin crystals using a capillary and a frit nozzle.[26]



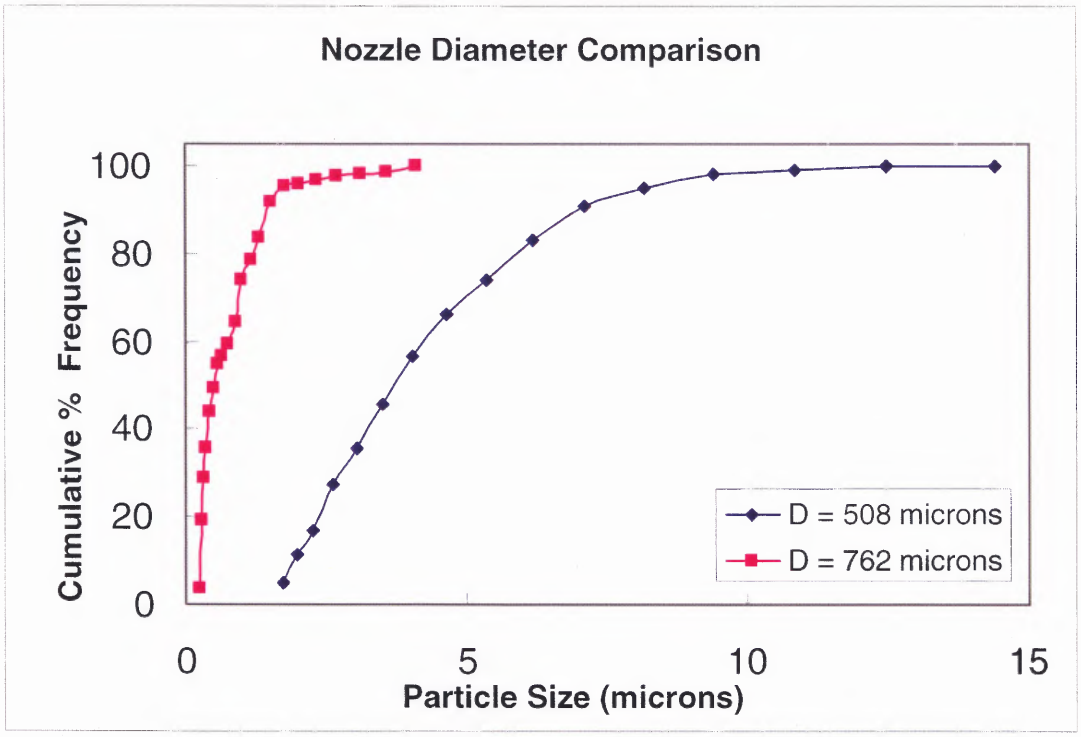


Figure 5.2 SEM micrographs and cumulative PSD for particles precipitated by RESS (a) exp 2 (b) exp 3.

The effect of two distinct nozzle geometries (as shown in Figure 4.2) on particle size, PSD and morphology has also been explored (exp. 4 & 5). The rationale behind designing a new nozzle (Nozzle 2) was that the sudden decrease in the capillary diameter results in very high velocity. This leads to almost zero difference in the residence time for the particle growth to occur in the nozzle. This would minimize the time for the particle growth in the capillary which may lead to small particle size with narrow distribution.

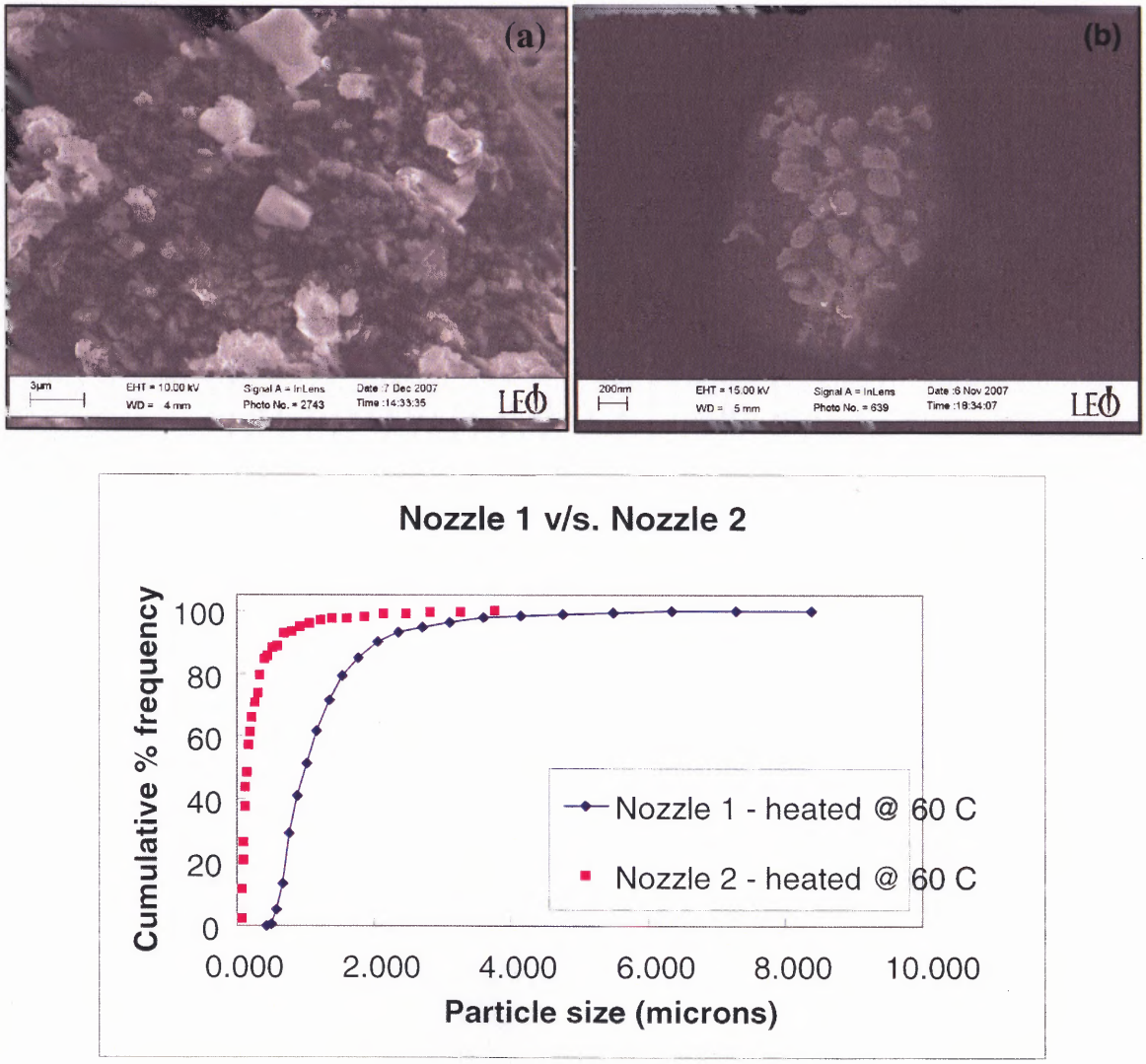


Figure 5.3 SEM micrographs and cumulative PSD for particles precipitated by RESS (a) exp 4 (b) exp 5.

For these experiments the particles (Fenofibrate) were collected in an empty flask. The nozzle was heated at 60 °C during expansion. After the expansion, 0.1% aqueous solution of Tween 80 in deionized water was added and was sonicated for 20 minutes. The particles deposited on the sides of the flask were scrapped off using a spatula. It is evident from the SEM micrographs that some particles were agglomerated after the addition of deionized water due to the hydrophobic nature of the solid. This resulted in a slightly broader particle size distribution. The results of image processing were comparable to that of light scattering. From the cumulative plot in Figure 5.3, it can be seen that ~50% of crystal precipitated from nozzle 2 are below 0.170 μm; while for nozzle 1, 50% of the crystals are below 1 μm. The average size of the particles precipitated from nozzle 1 is 1.232 μm while that from nozzle 2 is 0.289 μm. Moreover, the size distribution of crystals obtained using nozzle 2 was much narrower than those precipitated from nozzle 1. For these reason, nozzle 2 was used for all the remaining parametric study in this report.

5.2 Effect of Extraction Pressure

The effect of extraction pressure (exp. 5, 6 & 7) has been explored for the RESS process while keeping all the remaining parameters constant. The pressures examined were 100, 150 and 200 bars for Fenofibrate as a solute.

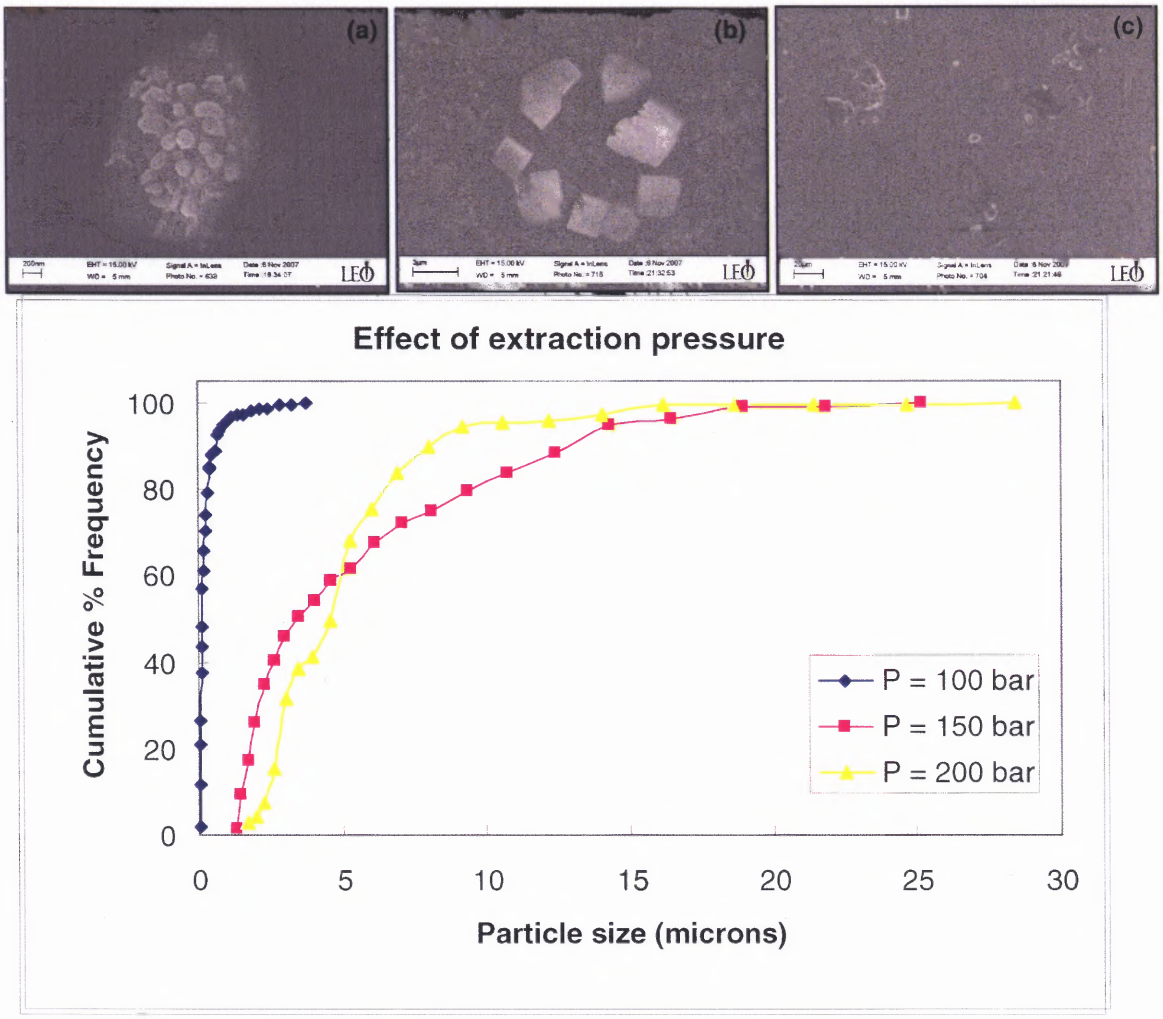


Figure 5.4 Effect of extraction pressure on fenofibrate precipitation. SEM micrographs of fenofibrate particles precipitated (a) exp 5 (b) exp 6 (c) exp 7.

An increase in extraction pressure resulted in the increase in the particle size of fenofibrate drug substance. The particle size distribution was also found to be widened with an increase in pressure. Figure 5.4 shows the SEM micrographs and the cumulative distribution at 100bar, 150bar, and 200bar. The average particle size at 100bar was found to be 0.289 μm, which increases to 5.521 μm at 150bar and 4.977 μm at 200bar. Similar trend was also obtained using ibuprofen as the drug solute. The results obtained from these experiments were in the similar lines of the previous literatures. Huang et al.[24] and, Hirunsit et al.[25] have shown in their respective research that as the extraction

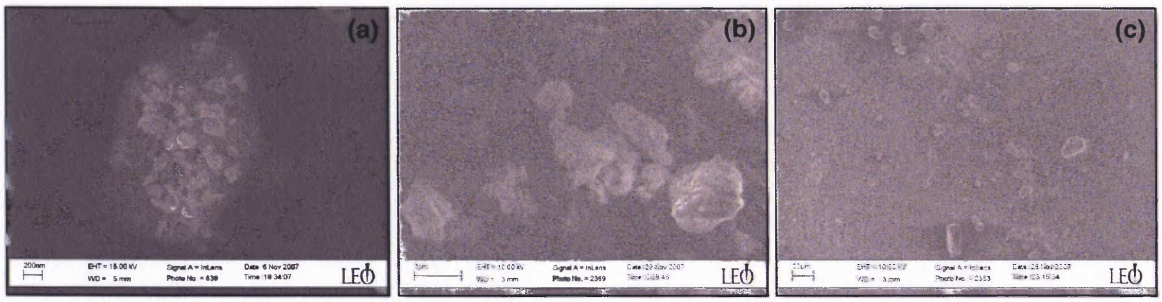
research that as the extraction pressure (P_{ext}) increases at constant temperature (T_{ext}), the solubility of the drug substance also increases, i.e. the initial solute concentration increases. The higher initial solute concentration results in higher supersaturations upon expansion which leads to higher nucleation. The nucleation rate is inversely proportional to the particle volume. Finer particles are obtained as P_{ext} increases due to higher supersaturation and subsequent higher nucleation rates. Nucleation is followed by growth process which in turn leads to wider particle size distribution.

5.3 Effect of Extraction Temperature

It is been reported that lower extraction temperature results in early nucleation along the nozzle leading to larger particle size. Domingo et al.[26] have reported similar results for aspirin, benzoic acid, and phenanthrene. However, contrasting results have been reported by Mohamed et al.[27] saying there is no effect on particle size with variations in extraction temperature when the solute concentration is kept high. Hirunsit et al.[25] also reports that for Ibuprofen at different extraction temperature, very high velocity and very close initial nucleation leads to almost zero difference in the residence time for the particle growth to occur in the nozzle. Therefore, there is minimal effect on the particle size of Ibuprofen. In this study the extraction temperature was kept constant for all the experiments.

5.4 Effect of Initial Solute Concentration in SCF

The effect of initial solute concentration has also been examined in this study. The initial amount of drug placed in the extractor has been varied as 100mg, 200mg and 300mg.



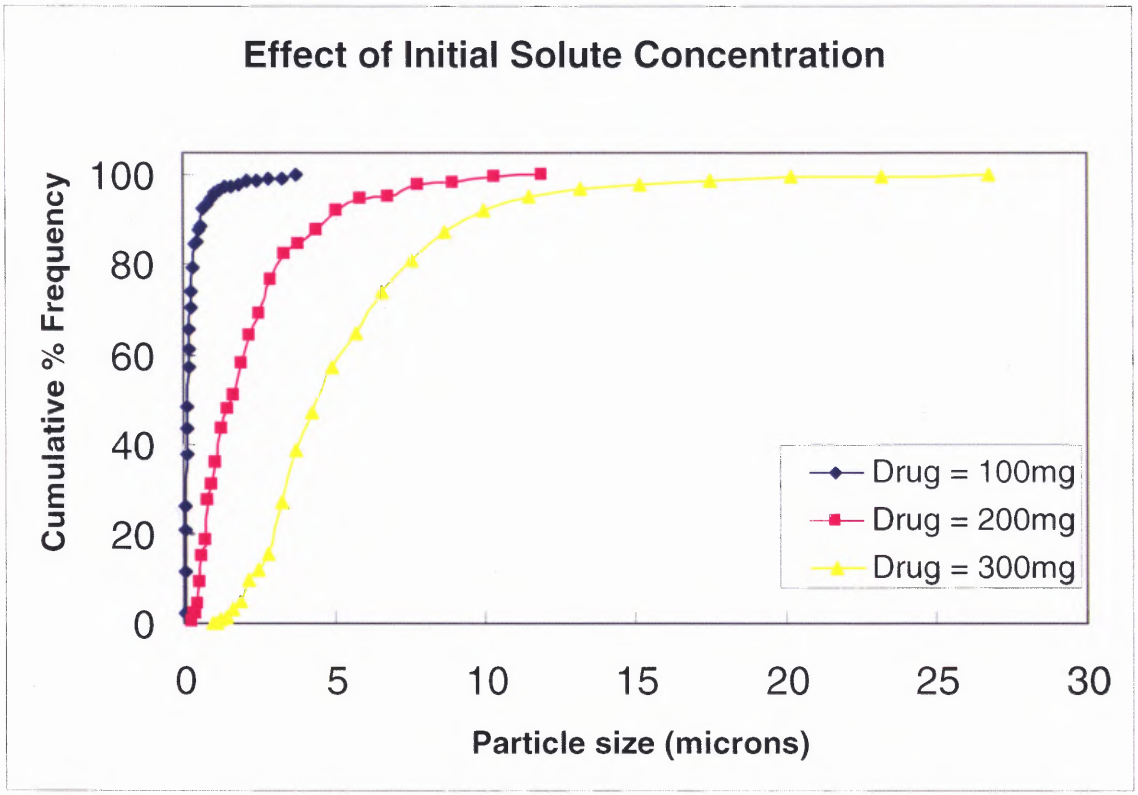


Figure 5.5 Effect of initial solute concentration in SCF on Fenofibrate precipitation. SEM micrographs of fenofibrate particles precipitated (a) exp 5 (b) exp 8 (c) exp 9.

It is reported that initial solute amount in the extractor plays a part in particle formation process using RESS.[27] It was found that increase in initial fenofibrate concentration results in increase in particle size as well as the size distribution (exp. 5, 8 & 9). Figure 5.5 shows the results at 100mg, 200mg and 300mg solid concentration. The

average particle size for 100mg drug amount was found to be 0.289 μm, which increases to 2.169 μm for 200mg and 5.302 μm for 300mg. Decrease in the initial amount of solid placed in the extractor decrease in the amount of the fenofibrate dissolved in SC-CO_2. This reduces supersaturation, lowers nucleation rates and makes less fenofibrate available for growth and lower particle size is obtained. However, it is dependent on other extraction conditions. Similar observations were reported by Ginosar et al. where they observed smaller particles are produced at lower solute concentration. They found that at higher solute concentration of phenanthrene in RESS resulted in bimodal distribution of primary nanoparticles and larger micron-sized aggregates.[27] At lower final solute concentration, the supersaturation and nucleation rate are lower which may prevent the growth of the particles resulting in smaller particles.

5.5 Effect of Heated Nozzle Temperature

Effect of heated nozzle temperature on the particle size, size distribution and morphology has been examined(exp. 5, 10. & 11). Nozzle was heated using the heating tape controlled by the Dimerstat. The thermocouple was attached to the nozzle to monitor the temperature of the nozzle.

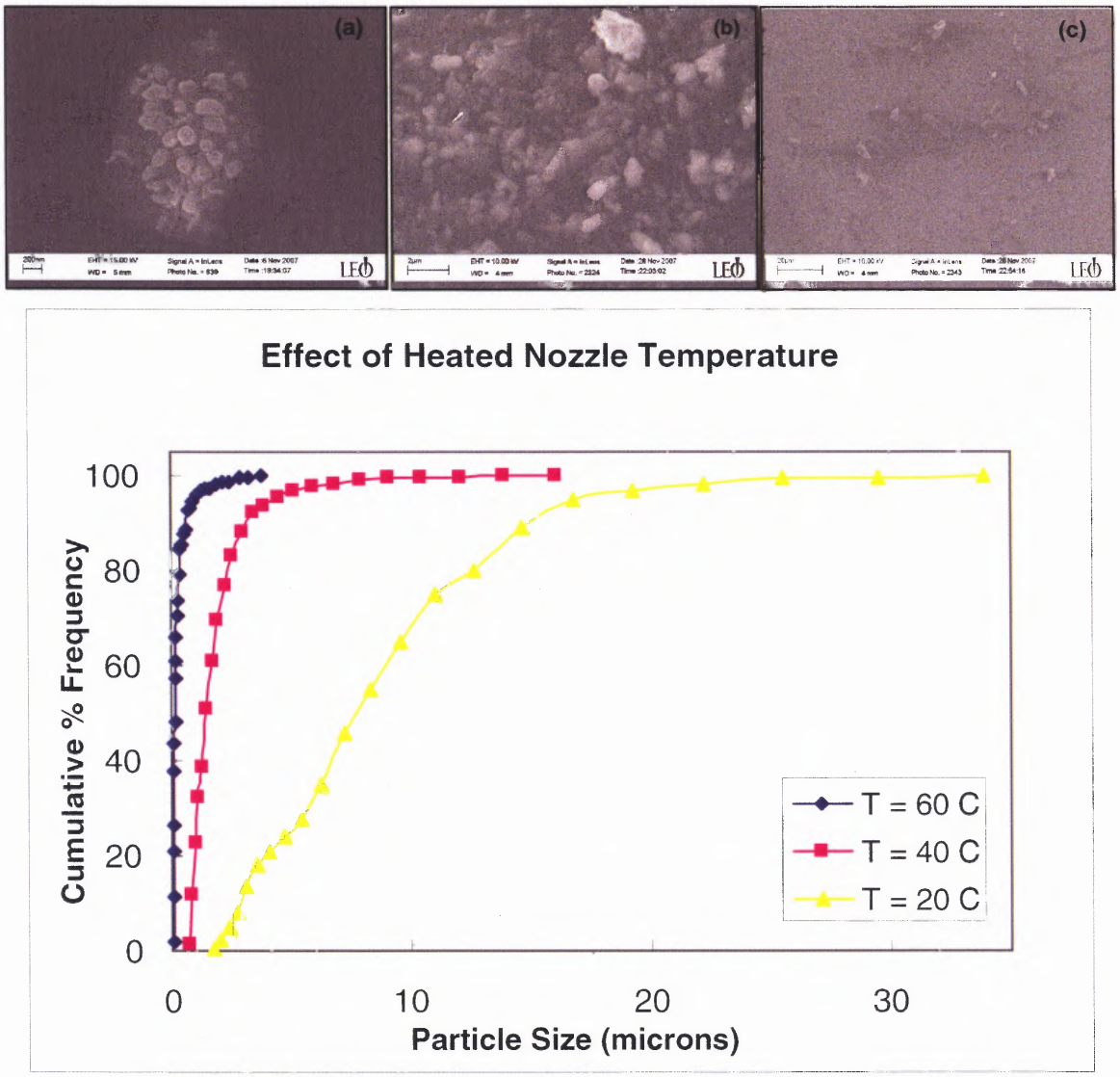


Figure 5.6 Effect of heated nozzle temperature on Fenofibrate precipitation. SEM micrographs of fenofibrate particles precipitated (a) exp 5 (b) exp 10 (c) exp 11.

Heating of nozzle during expansion resulted in significant change in particle size, distribution and the morphology of the precipitated particles of fenofibrate. When the nozzle was kept at the ambient temperature (~20 °C), mixed morphology of the crystals was observed. SEM micrograph in Figure 5.6(c) shows the existence of combination of needle-shape, rod-like and cubical crystals. The crystal size of the particles and the size distribution was also significantly larger as compared with the crystals precipitated when

the nozzle temperature was maintained at 40 °C as well as 60 °C. Approximately 50% of crystals were smaller than 0.170 μm and 1.40 μm for 60 °C and 40 °C respectively, whereas for ambient temperature 50% particles were smaller than 8.5 μm. The average particle size was found to be 0.289 μm at 60 °C nozzle temperature, which increases to 1.826 μm at 40 °C and 8.466 μm at ambient conditions. An increase in nozzle temperature increases the solid solubility in SC-CO_2 which increases the supersaturation and at the same time growth is also restricted. This reduces the particle size by inhibiting the particle growth as less solute is available for particle growth.

5.6 RESOLV

Experiments were conducted on RESOLV process (exp. 12-15) in order to compare its results with conventional RESS process. It is reported by Y. P. Sun's group that expansion of the supercritical solution in aqueous solution inhibits the growth of particles after nucleation. This result in formation of crystals in nano and/or sub-micron range suspended in aqueous solution.[21, 22] In this study, the effect of extraction pressure on the particle size, size distribution and morphology of the particles were examined at 100, 150, 200 and 250 bars. Figure 5.8, 5.9, 5.10, and 5.11 corresponds to the SEM micrographs of experiments at the respective extraction pressures. The micrographs show that the particles tend to agglomerate in the RESOLV process. This is due to hydrophobic nature of the solute, fenofibrate. Because of the hydrophobic nature, these particles tend to form agglomeration in order to reduce the interactions with water molecules. There was a distinct trend seen from the image analysis and light scattering results. As the extraction pressure increased the agglomerate size and the size

results. As the extraction pressure increased the agglomerate size and the size distribution increased. Figure 5.7 confirms that as the extraction pressure increased from 100bar to 150bar, the agglomeration increased and so did the agglomerate size distribution. There was no distinct change as pressure was increased from 150bar to 200bar, however, at 250bar; there was again an increase in agglomeration size and size distribution. The pattern is confirmed by the SEM micrographs. The micrographs show that the individual particle size is in nano / sub-micron range for extraction pressure of 100bar and increases is the extraction pressure increases. It is evident from the Figure 5.11(b) that at extraction pressure of 250bar, there were particles below 2μm size, however; it is impossible to obtain a representative individual particle size as they are agglomerated. Y.P. Sun and group have reported that the introduction of stabilizers such as surfactants, or polymers has shown to reduce the amount of agglomeration and obtain particles in nano / sub-micron range.[22] Future work is planned to investigate addition of stabilizers in the aqueous liquid to avoid agglomeration.

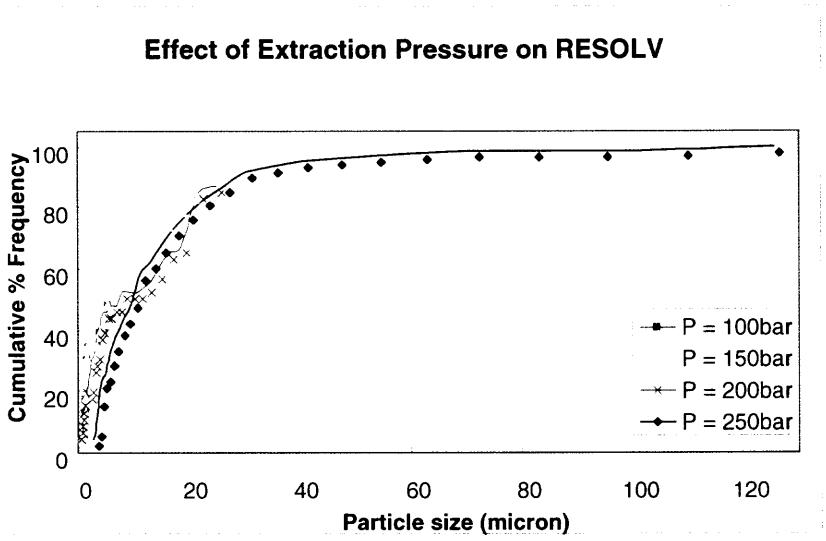


Figure 5.7 Cumulative frequency of the agglomerate size distribution at respective extraction pressures.

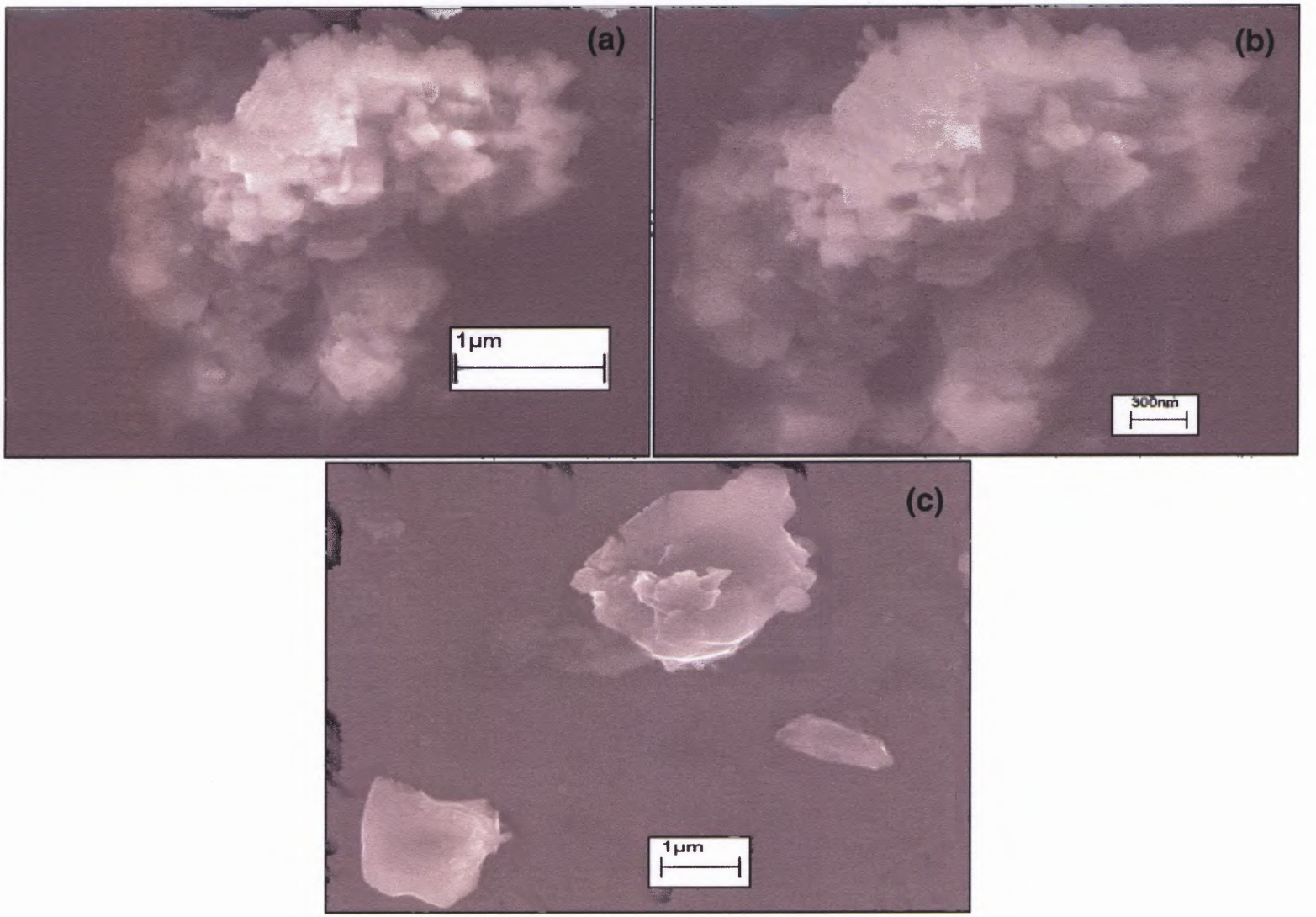


Figure 5.8 SEM micrographs for precipitated fenofibrate particles using RESOLV process at P_{ext} = 100bar.

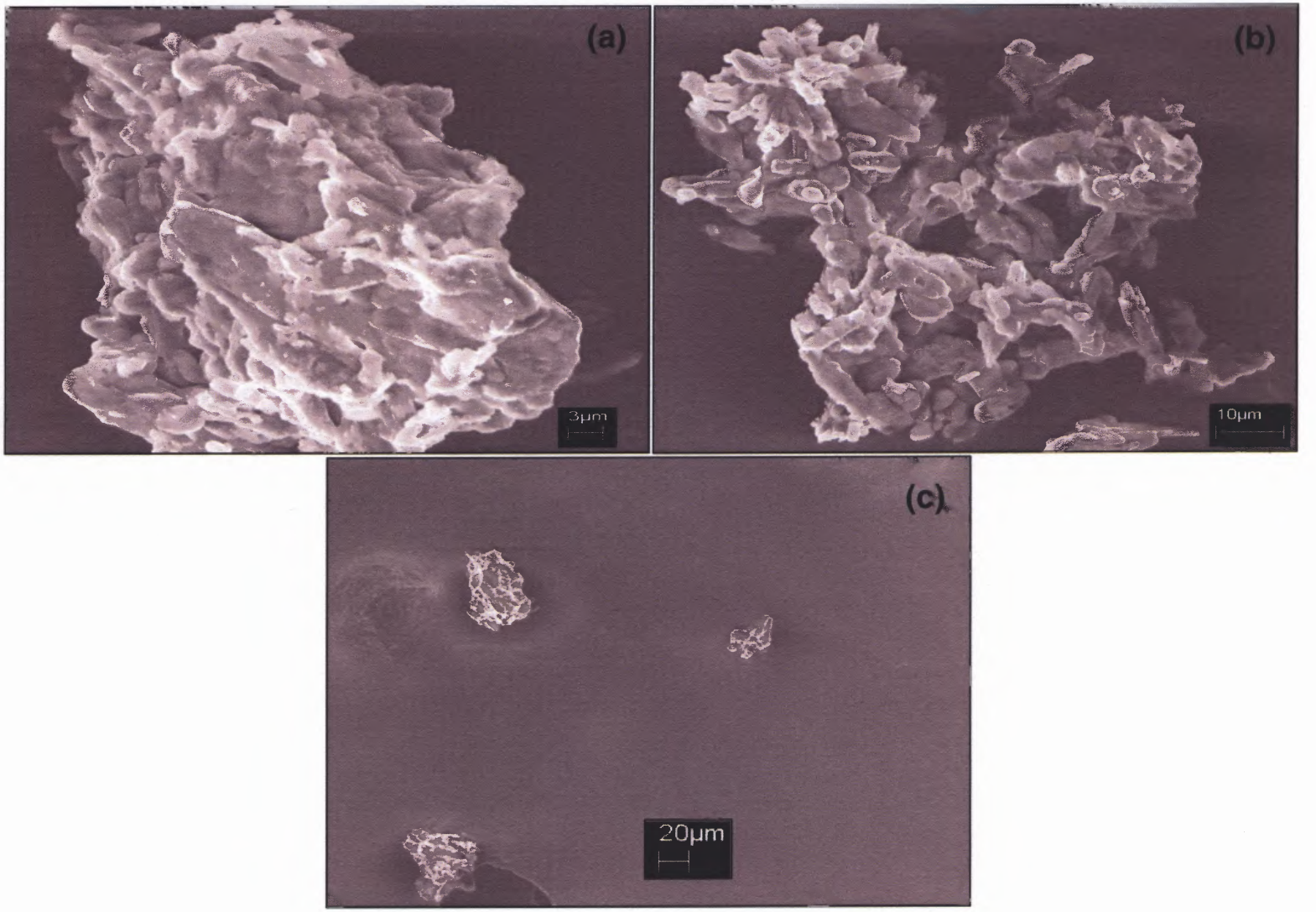


Figure 5.9 SEM micrographs for precipitated fenofibrate particles using RESOLV process at P_{ext} = 150bar.

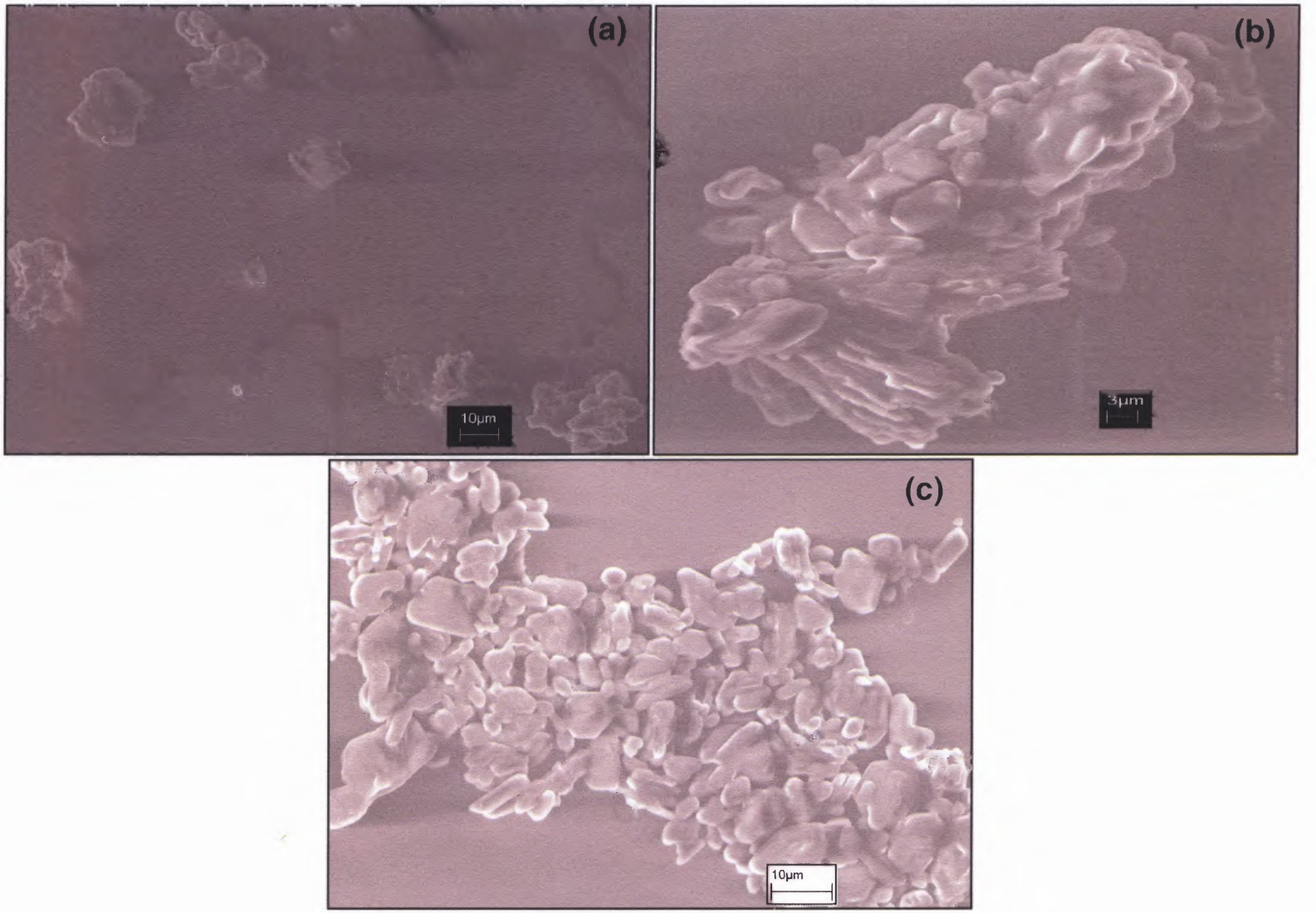


Figure 5.10 SEM micrographs for precipitated fenofibrate particles using RESOLV process at P_{ext} = 200bar.

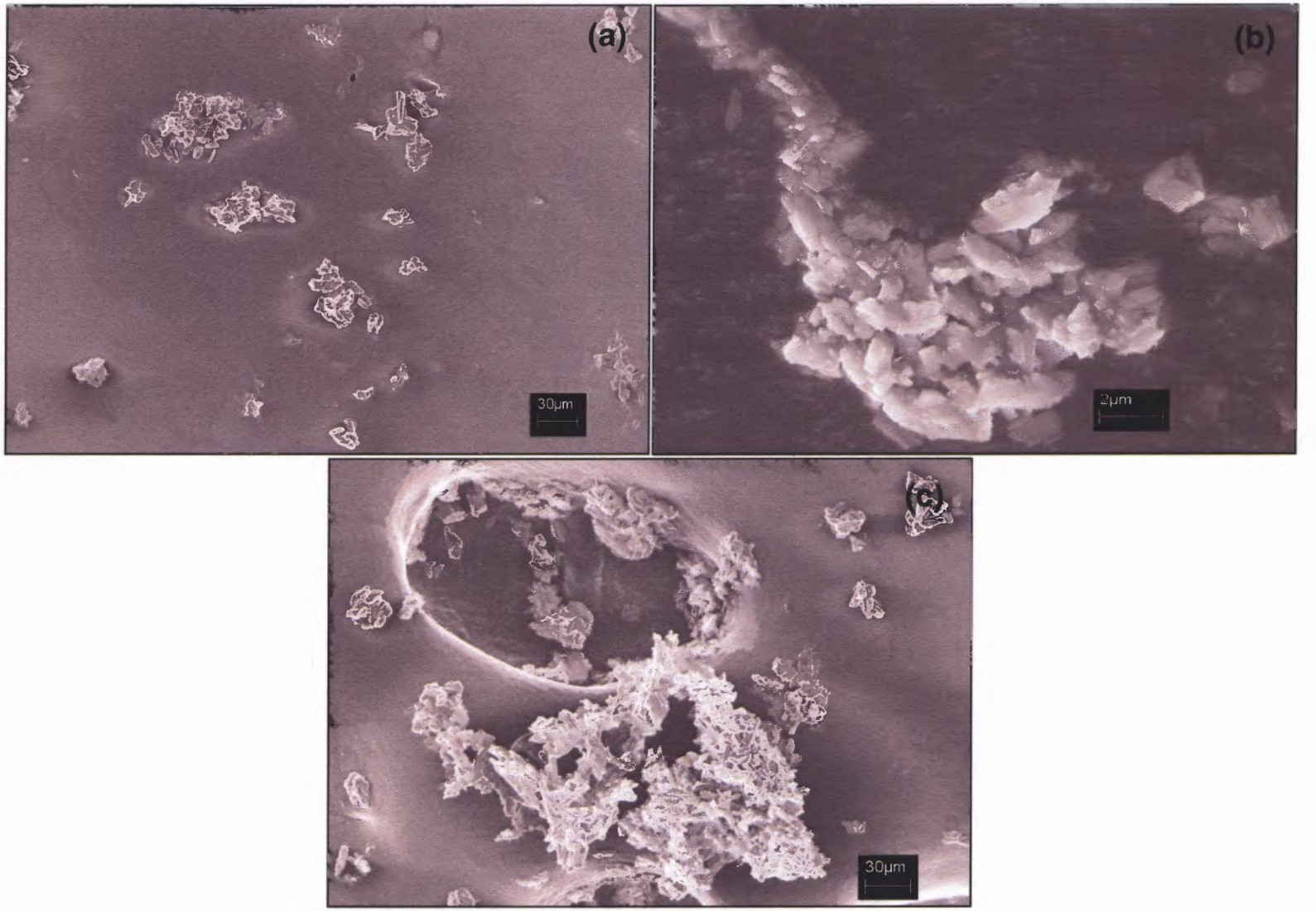


Figure 5.11 SEM micrographs for precipitated fenofibrate particles using RESOLV process at P_{ext} = 250bar.

5.7 Raman Analysis

The crystallinity of the drug substance affects its bioavailability, physical and chemical stability. The chances of the crystalline nature of the drug to be affected using the RESS process are reasonable due to the influence of high pressure and temperature. In this study, Raman spectroscopy was performed on unprocessed and processed drug substance.

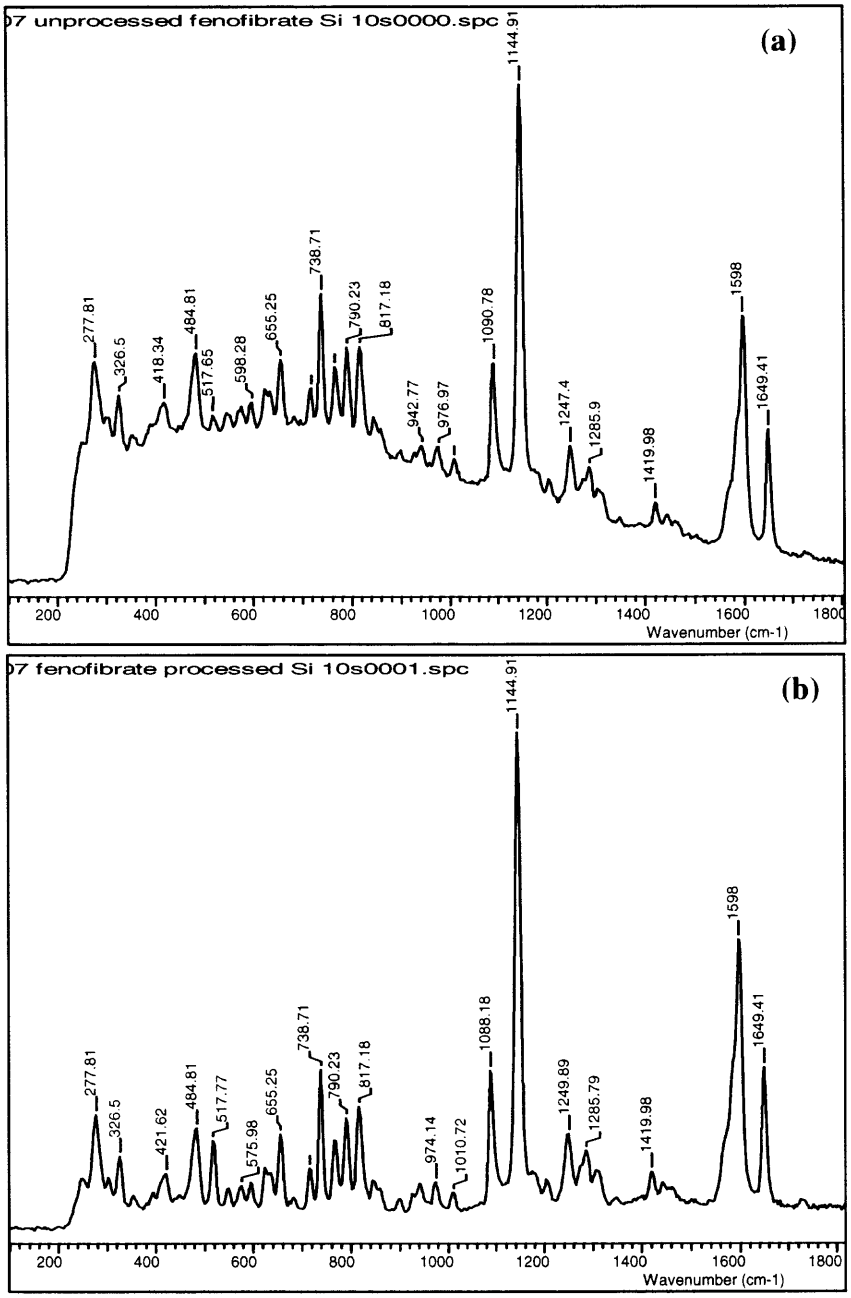


Figure 5.12 Raman spectra plots for fenofibrate (a) unprocessed (b) processed.

Figure 5.12 shows the comparisons of Raman spectra for the (a) unprocessed and (b) processed fenofibrate. From the spectra it can be seen that there is a slight chance that the starting material may be in amorphous phase, which disappeared after processing for Fenofibrate. The level of crystallinity of the processed drug would be important factor to be analyzed. It is previously reported that the precipitated drug substance retains its crystalline structure after RESS processing.[20] Further work is planned to perform the analysis at New Jersey Institute of Technology.

CHAPTER 6

SCALE-UP OF RESS PROCESS

Scale-up of supercritical fluid technologies is a challenging issue in the industry. However, large commercial high-pressure extraction plants are already employed in the food industry for decaffeination of coffee beans that are compliant with the current good manufacturing practice (cGMP) standards administered by food and drug administration (FDA). Therefore, scaling up the supercritical technology for pharmaceutical industry would not require anything novel.[20]

Even though promising results are being obtained on the laboratory scale, commercial implementation of these processes is a rarity at this stage. Two of the most important factors influencing the scale-up implementation of these processes are safety and economical issues. The high pressure equipments of supercritical processes cost much higher than those for the conventional processes. In the pharmaceutical industry, the formulation of fine particles does not require scale-up on a very large scale. For example, Palakodaty et al. in their chapter, *"Pharmaceutical and Biological Materials Processing with Supercritical Fluids"*, reports that annual requirements for salbutamol sulfate, an antiasthmatic drug, in United States is in the region of 500-1000 kg. This substantially reduces the capital costs associated with high pressure equipments.[20, 28]

The experiments in this study were conducted at the laboratory scale. 0.10g drug substance gave the best results with corresponding process parameters. For processing 0.10g of drug (fenofibrate) in one batch at P_{ext} = 100bar and T_{ext} = 60 °C, approximately 7.2g of SC-CO_2 was consumed for extraction. Rough calculation for straight scale-up of

RESS to process 500g of drug (fenofibrate) in one batch at the above conditions shows that the extraction chamber will have to be of 60L capacity which will consume approximately ~36kg (60L) of SC-CO_2. There is also a possibility to perform RESS as a semi-continuous or continuous process. Multiple extraction vessels can be arranged in a sequence for a semi-continuous process. This allows other vessels to run in an uninterrupted extraction while one vessel is loading or unloading. The examples of designs for a commercial extraction process used in soil industry were shown in Alonso E., et al[31]. The extractor volume for these designs ranged from 90L, 163L, and 244L with carbon dioxide flow rates of 452, 538 and, 1138 kg/h^{-1} respectively. Up to four extraction chambers were used simultaneously in order to run the process in semi-continuous fashion. Therefore, by using a 90L vessel for RESS process, up to 750g of drug can be processed using one batch process (i.e., ~195 kg/year). The total processing can increase for semi-continuous batch process where more than one batch can be processed per day.

The operating temperatures for RESS process are generally lower as compared to several other conventional pharmaceutical operations. This eliminates the possibility of burn-related risks associated with the processes. The inclusion of pressure-relief mechanisms, pressure rupture discs on supercritical fluid pump, and high pressure vessels provides protection against over pressurizing the mechanical components of the system. In RESS process like any other supercritical technologies, the process takes place in the closed system. Therefore, the entire process equipment does not need to be in a controlled environment. The equipment including the high pressure pump and carbon dioxide recycling system can be outside the clean room in the explosion proof room.

Only the particle collection equipment (expansion chamber) is required to be in the controlled environment to prevent contamination of the drug substance. RESS process does not utilize any other solvent apart from carbon dioxide, which is GRAS acclaimed. This prevents the exposure risk of the personnel working on the process. Moreover, absence of any other solvent allows the fluid (usually carbon dioxide) to be recycled and a cost-effective measure. Most high pressure equipments are manufactured using 316L stainless steel, which are least durable for long-term due to its corrosion proof nature and can be cleaned easily using organic solvents.[20, 28, 29]

Thus, the RESS process can be scaled-up and adapted to the cGMP compliance in a straightforward manner with major difficulty for the low-volume pharmaceutical fine particle formation. A successful scale-up of RESS will depend on the proper understanding of the thermodynamics of nucleation and coagulation process as well as the relationship between the process parameters and the physical and chemical characteristics of resulting particles.

CHAPTER 7

CONCLUSIONS

This study has engaged the use of rapid expansion of supercritical solutions (RESS) process for formation of fine particles. The effect of nozzle length, diameter and geometry, extraction pressure, initial solute concentration, and heated nozzle temperature were studied for RESS process. The effect of extraction pressure was explored for RESOLV process. It was found that all of the above factors had an effect on particle size and size distribution. It was also found that the lower nozzle diameter (D = 508 μm), length (L= 3inches), and ambient nozzle temperature resulted in the rod-like morphology different from the other nozzle geometries. The extraction pressure (P_{ext} = 100bar), extraction temperature (T_{ext} = 60 °C), initial solute concentration (100mg), and nozzle temperature (T_N = 60 °C) using nozzle 2, gave nano / sub-micron particles and a narrow size distribution. The average particle size was found to be 0.289 μm. Particle size and the size distribution increases with an increase in extraction pressure, initial solute concentration, nozzle length, as well as decrease in nozzle temperature. The study confirms that claims that RESS process can be used to formulate very fine particles, with a controlled size distribution, and most importantly for pharmaceutical industry, it is a solvent free technique.

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