CHAPTER II

LITERATURE REVIEWS

Particle Formation Using Supercritical Fluid Technology

Introduction

Small-particle engineering enables an active pharmaceutical ingredient to be incorporated into formulation for targeted drug delivery. Powder micronization can also be used to increase the dissolution rates of poorly water soluble drugs. Micronization procedures can modify particle size, porosity, and density, and the active ingredient may be mixed with pharmaceutical excipients using small-particle technologies to maximize delivery to the desired target for drug administration. Particle formation technologies may be classified as either mechanical micronization processes or solution-based phase separation processes. The most common mechanical micronization methods include ball and jet milling. However, friction generated during these milling processes may lead to either thermal or mechanical degradation of the active ingredient. Spray-drying is another common method used to micronize drug substances alone or with pharmaceutical excipients. This method requires extremely high temperatures, on the order of 150 ^{o}C, to remove the solvent from the drug following atomization. The elevated temperatures may accelerate degradation of the active ingredient.

Relatively new solution-based particle formation techniques involve the use of conventional liquids, compressed gases, near-critical liquids, or supercritical fluids functioning as solvents, antisolvent. These techniques involve phase separation of solvent and active ingredient by evaporation, rapid expansion and change in solvent composition. The spray configuration in many of these processes produces atomized droplets with high surface areas. Thus, phase separation and rapid nucleation result in small primary particles or highly porous microparticles (Roger et al. 2001).

Principle

The use of supercritical fluids as media for the formation of microparticles for therapeutic application is a very recent development. Interest in this new field is driven by the important advantages that supercritical fluids offer over conventional microparticulate formation route: mainly, the mildness of the operating temperatures, the purity of the products, and the avoidance of organic solvents. Conventional techniques for particle size reduction include mechanical comminution (crushing, grinding, and milling), recrystallization of the solute particles from solution using liquid antisolvent, freeze-drying, and spray-drying. Among the limitations associated with these processes are excessive solvent use and disposal, thermal and chemical degradation of products, trace residues and interbatch particle size variability. Therefore, the production of contaminant-free microparticles with controlled particle size and desired product qualities in an environmentally responsible manner continues to be a major challenge (Subramaniam et al. 1997).

The selective solvating power of supercritical fluids makes it possible to separate a particular component from a multicomponent mixture. Small changes in pressure or temperature near the critical point strongly affect the density and, hence, the solubilising power of the supercritical fluid. This behaviour of supercritical fluids has been used for purification and separation purposes in the food processing and distillation industries for many years. It has also been used for applications in analytical chemistry.

Supercritical fluids (SF) are those gases and liquids at temperatures and pressures above their critical points (T_c – critical temperature; P_c –critical pressure). In Figure 2-1 the critical point is located at the upper end of the liquid: gas-vapour pressure curve and the phase area in excess of this point is the SF region. Of particular interest for SF application are the ranges $1 < T/T_c < 1.1$ and $1 < P/P_c < 2$. In this region, the SF exists as a single phase with several advantageous properties of both liquids and gases (Table 2-1). SF have density values that enable appreciable solvation power, whilst the viscosity of solutes in SF is lower than in liquids and the diffusivity of solutes is higher, which facilitates mass transfer. Also, and importantly for particle formation, SF are highly compressible, particularly near the critical point,

and their density and thus the solvation power can be carefully controlled by small changes in temperature and/or pressure (York 1999).

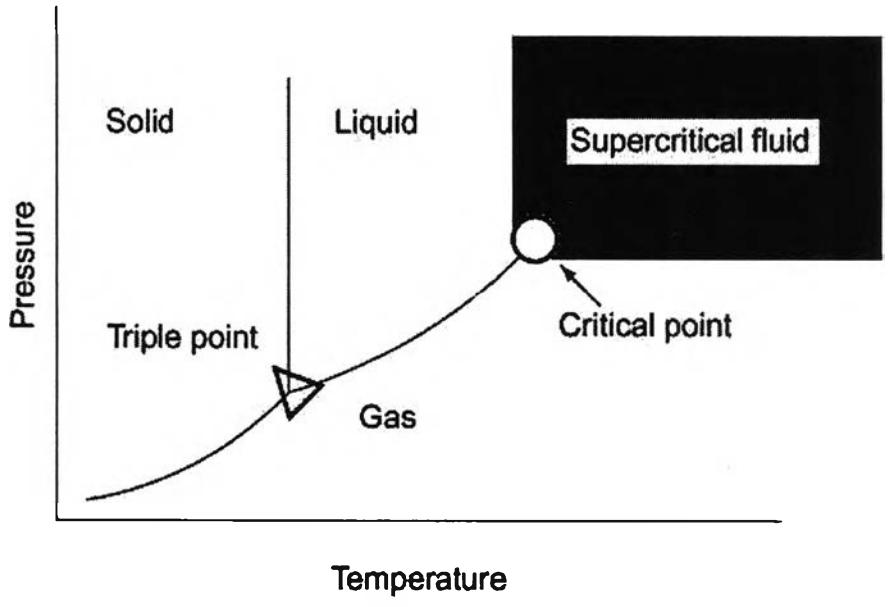

Figure 2-1 The phase diagram of a pure substance.

Table 2-1 Physical properties of gas, liquids and supercritical fluids.

	Density (kg/m^3)	**Viscosity ($N\text{-}s/m^2$)**	**Diffusivity (cm^2/s)**
Gases	1	10^{-5}	10^{-1}
Liquids	10^{3}	10^{-3}	10^{-5}
Supercritical fluids	700	10^{-4}	10^{-4}

(Knutson et al. 1996)

For pharmaceutical applications, carbon dioxide is an ideal processing medium. Because of its relatively mild critical temperature (31.1 °C), it is possible to exploit the advantages of near-critical operation at temperatures lower than 35 °C. Furthermore, carbon dioxide is nontoxic, nonflammable, relatively inexpensive, recyclable, and "generally regarded as safe". Even though the critical pressure (73.8 bar or 1070 psi) of carbon dioxide is relatively high, such operating pressures and operating equipment thereof are fairly routine in large-scale separation processes

involving supercritical carbon dioxide such as the decaffeination of coffee beans and the extraction of hops. Carbon dioxide is a nonpolar solvent. A common rule of thumb is that if a compound dissolves in hexane, then that compound should also dissolve in supercritical carbon dioxide. While this rule is valid for many low molar mass compounds that have appreciable vapor pressures, it fails in the case of polymers which have negligible vapor pressures. As such, carbon dioxide is essentially a nonsolvent for many lipophilic and hydrophilic compounds (which covers most pharmaceutical compounds). Supercritical carbon dioxide has been exploited both as a solvent and as a nonsolvent or antisolvent in pharmaceutical applications. The ability to rapidly vary the solvent strength, and thereby the rate of supersaturation and nucleation of dissolved compounds, is a unique aspect of supercritical technology for particle formation. Table 2-2 shows critical temperature and critical pressure of other solvent.

Table 2-2 Critical conditions for some solvent.

Solvents	Critical temperature °C	Critical pressure psi	(MPa)
Ammonia	132.5	1636	(11.28)
Benzene	289	709	(4.88)
Carbon dioxide	31.1	1070	(7.37)
Trichloromonofluoromethane	198.1	640	(4.41)
Dichlorotetrafluoromethane	146.1	522	(3.60)
Dichlorodifluoromethane	111.7	579	(4.00)
Chlorodifluoromethane	96	725	(5.00)
Chlorotrifluoromethane	28.9	569	(3.92)
Cyclohexane	280.3	590	(4.07)
Ethane	32.2	708	(4.88)
Ethylene	9.3	731	(5.04)
Isopropanol	235.2	690	(4.75)
Nitrous oxide	36.5	1050	(7.24)
P-Xylene	343.1	511	(3.52)
Propane	96.7	616	(4.25)
Propylene	91.9	670	(4.62)
Toluene	318.6	596	(4.11)
Trichlorofluoromethane	198	640	(4.41)
Water	373	3200	(22.06)

(Knutson et al. 1996)

Classifications of Techniques Used in Pharmaceutical Processing

The advantage of using supercritical fluids for the precipitation of pharmaceuticals is that dry particles with low solvent residues can be obtained in one processing step. Further, the use of CO_2 as an antisolvent, which has a relatively low critical temperature, allows processing to be conducted at moderate to low temperatures. Carbon dioxide is also nontoxic, readily available and inexpensive. In addition, the solvent and antisolvent can be recovered and recycled. The techniques using supercritical fluids can be categorized into four groups:

1. Rapid Expansion of Supercritical Solutions Process (RESS)
2. Gas Anti-solvent Recrystallization (GAS).
3. Precipitation with a Compressed Antisolvent (PCA) / Aerosol Solvent Extraction System (ASES) / Supercritical Antisolvent process (SAS) / Solution-enhanced Dispersion by Supercritical Fluids (SEDS).
4. Particles from Gas-Saturated Solutions (PGSS).

1. Rapid Expansion of Supercritical Solutions Process (RESS).

The RESS process is a method of recrystallization, particle size reduction, and component mixing. A schematic diagram of a typical apparatus used for the RESS process is shown in Figure 2-3. In this process, the solute is first dissolved in a supercritical fluid (SCF), which is then subjected to rapid depressurization by being passed through a nozzle. During expansion, the density and solvation power of the dense gas decrease dramatically, resulting in a high degree of solute supersaturation and subsequent precipitation of solute particles free of residual solvent. The combination of high supersaturation ratios and a rapidly propagating mechanical perturbation is a distinguishing characteristic of the RESS process.

The major limitation of using RESS in pharmaceutical applications is that most pharmaceutical materials are polar or high-molecular-weight substances, such as proteins and polymers, and are relatively insoluble in dense CO_2 at moderate conditions (<60 °C and 300 bar). The low solubility necessitates either using large quantities of the dense gas or using polar cosolvents, which can complicate the phase

behavior of the system and result in residual solvent in the final product (Jung and Perrut, 2001).

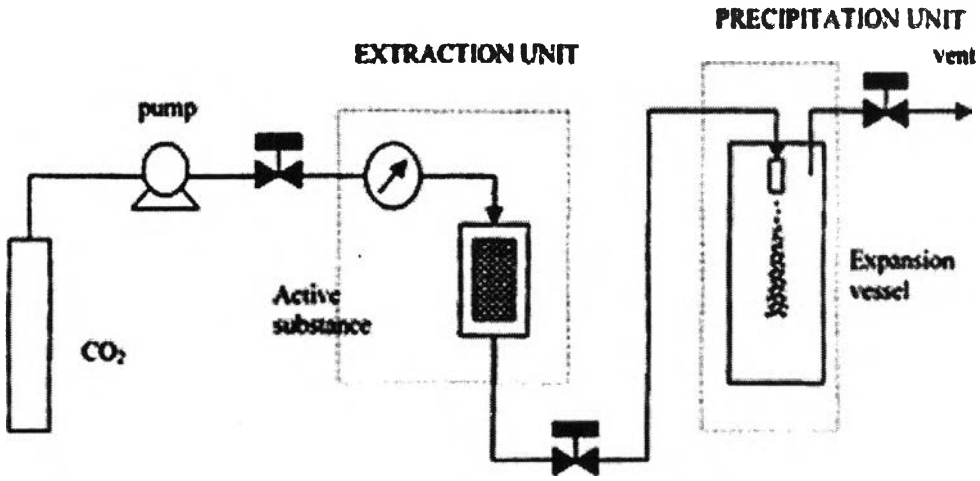

Figure 2-2 Schematic diagram of the RESS process. (Knutson et al. 1996)

Parameters that can be modified to affect the resulting micronized powder particle size and morphology include pre- and postexpansion temperature and pressure, nozzle geometry, and solution concentration (Subramaniam et al. 1997; Tom and Debendetti 1991; Philips and Stella 1993). Preexpansion temperature can be increased for high pressures to enable a higher drug loading concentration in the supercritical solution prior to atomization. At a given temperature, the pressure of the supercritical CO_2 can be increased to raise the solvent density and active ingredient solubility. Postexpansion temperature can be increased to accelerate the evaporation rate of the supercritical CO_2 following atomization. The postexpansion pressure is typically at atmospheric conditions. Nozzle geometry can also be modified to achieve intense atomization. At a small nozzle length-to-diameter ratio, the pressure drop occurs closest to the free jet, resulting in micronized active ingredient particles.

2. Gas Anti-solvent Recrystallization (GAS).

Gas antisolvent (GAS) precipitation is a batch process that has been used to process explosives, low molecular weight organic compounds, proteins, and polymers (Reverchon 1999). A diagrammatic representation of a GAS apparatus is shown in Figure 2-3. The precipitator is partially filled with the solution of active substance. CO_2 is then pumped up to desired pressure and introduced in the vessel, preferably from the bottom to achieve a better mixing of the solvent and anti-solvent. After a holding time, the expanded solution is drained under isobaric conditions to wash and clean the precipitated particles.

The GAS precipitation process involves the addition of CO_2 as an antisolvent to an organic solution containing an active ingredient and, if necessary, additional pharmaceutical excipients (Subramaniam et al. 1997; Benedetti et al. 1997). CO_2, in the gaseous, liquid, or supercritical fluid states, must be significantly soluble in the solvent and the active ingredient and excipients must not be soluble in the excess CO_2 phase above the solvent-rich phase. The CO_2 mole fraction in the solution can reach 50% or more. When the gaseous antisolvent is dissolved into the organic solution, the solvent strength decreases significantly, precipitating the drug. If additional pharmaceutical excipients are present in the solution, the active ingredient will precipitate inside a matrix of the excipients. The precipitate is then flushed with fresh CO_2 to eliminate trace organic solvent.

A major challenge of the GAS precipitation process is the need to filter the precipitate from the organic solvent solution without particle growth and agglomeration. The rate of addition of the CO_2 to the organic solution influences the particle size. Both bimodal and unimodal particle size distributions have been formed in the same GAS-processed batch. If elevated temperatures are required to expand the organic solvent phase sufficiently, thermal degradation of the active ingredient can occur (Roger et al. 2001).

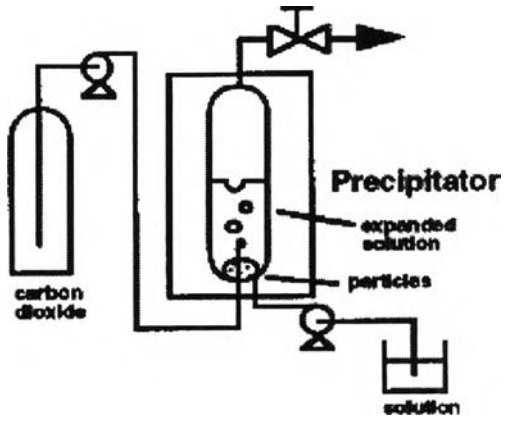

Figure 2-3 Schematic diagram of the GAS process. (Subramaniam et al. 1997)

3. Precipitation with a Compressed Antisolvent (PCA) / Aerosol Solvent Extraction System (ASES) / Supercritical Antisolvent process (SAS) / Solution-enhanced Dispersion by Supercritical Fluids (SEDS).

In contrast to the GAS batch process, PCA is a semicontinuous technique. The two processes differ in terms of mass transfer pathways and atomization. The PCA process is shown schematically in Figure 2-4. The organic feed solution containing the active ingredient is atomized into an excess flowing continuum of supercritical or liquid CO_2. The high surface area atomized droplets allow intimate contact with the excess antisolvent. In contrast to the unidirectional mass transfer of the CO_2 diffusion into the organic phase in the GAS process, active ingredient phase separation in PCA occurs by two-way mass transfer. The organic solvent diffuses into the CO_2 phase, and the CO_2 diffuses into the organic dispersed domains. Both rates are much faster than conventional organic liquid antisolvent. The faster mass transfer rates result in more rapid nucleation of the active ingredient and smaller final particle sizes. The dry, micronized powder is available for collection following depressurization of the CO_2 (Dixon et al. 1993, Subramaniam et al. 1997, Bodmeier et al. 1995).

Precipitation utilizing the PCA technique depends heavily on the efficiency of atomization of the organic solution into the supercritical antisolvent,

with more intense atomization resulting in a higher surface area and more rapid two-directional mass transfer (Dixon et al. 1993)

The Weber number N_{We} describes the degree of atomization of the feed stock solution into the supercritical antisolvent. The N_{We} is a dimensionless ratio of inertial forces to surface tension forces, given by

$$N_{We} = (\rho_A v^2 D)/\sigma$$

where ρ_A is the antisolvent density, v is the relative velocity, D is the droplet diameter, and σ is the interfacial tension. The greater the value of the N_{We} for a given Reynolds number ($\rho\ vD/\mu$) the more intense the degree of atomization into smaller droplets (Dixon et al. 1993, Palakodaty and York 1999). A detailed theoretical model of the spray process that describes mixing and precipitation has appeared recently.

Other antisolvent processes that have also been investigated have been referred to as aerosol solvent extraction system (ASES) (Engwich et al 1999; Bleich etal. 1993), solution-enhanced dispersion by supercritical fluids (SEDS), and the supercritical antisolvent process (SAS) (Tom et al. 1993). The diffusion coefficient of a particular organic solvent into compressed liquid or supercritical CO_2 is a function of temperature and density of the compressed antisolvent. It has also been found that under certain conditions, other effects such as mass transfer can dominate the precipitation process. An example of this behaviour was reported by Randolph et al. (1993). The production of larger polymer particles (from 0.61 to 1.4 μm) as the density of CO_2 was increased from 0.65 to 0.76 g/ml suggests that the reduced diffusivity of the antisolvent was a more dominant factor influencing particle size.

Thies and Muller (1998) found that the size of L-PLA particles precipitated from a 3% w/v methylene chloride solution decreased dramatically from 50 to 6 μm when the antisolvent density was increased from 0.25 to 0.69 g/ml, which was consistent with hydrodynamic theory. At higher carbon dioxide density (higher pressure), the increase in deforming pressure forces necessary to break up the liquid droplet into smaller droplets would be expected to result in the precipitation of smaller particles.

The system commonly operates at conditions under which the solvent and antisolvent are miscible and thus form a homogeneous phase. Upon extraction of the solvent from the solution, supersaturation in the system occurs, and the solute

precipitates. After the solute has precipitated, it is washed with the dense gas antisolvent to remove solvent residue before the system is finally depressurized and the product is collected. The optimization of the operating parameters makes these processes more flexible than other precipitation techniques. A high supersaturation in the solutions can be generated rapidly, leading to the formation of small and uniform particles.

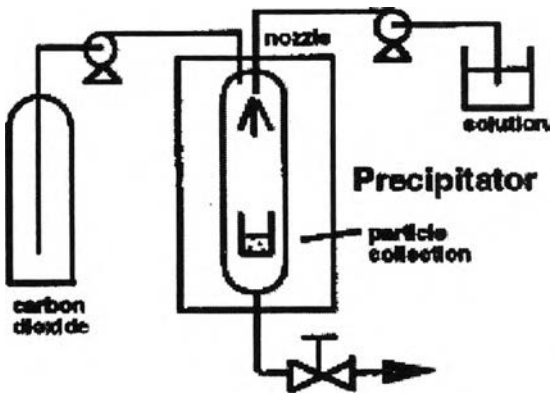

Figure 2-4 Schematic diagram of the PCA/SAS/ASES process. (Subramaniam et al. 1997)

The method, known as solution enhanced dispersion by supercritical fluids (SEDS) was developed in order to achieve smaller droplet size and intense mixing of supercritical fluid and solution for increased transfer rates. Indeed the supercritical fluid is used both for its chemical properties and as 'spray enhancer' by mechanical effect: a nozzle with two coaxial passages allows to introduce the supercritical fluid and a solution of active substance(s) into the particle formation vessel where pressure and temperature are controlled (Figure 2-5). The high velocity of the supercritical fluid allows to break up the solution into very small droplets. Moreover, the conditions are set up so that the supercritical fluid can extract the solvent from the solution at the solution at the same time as it meets and disperses the solution.

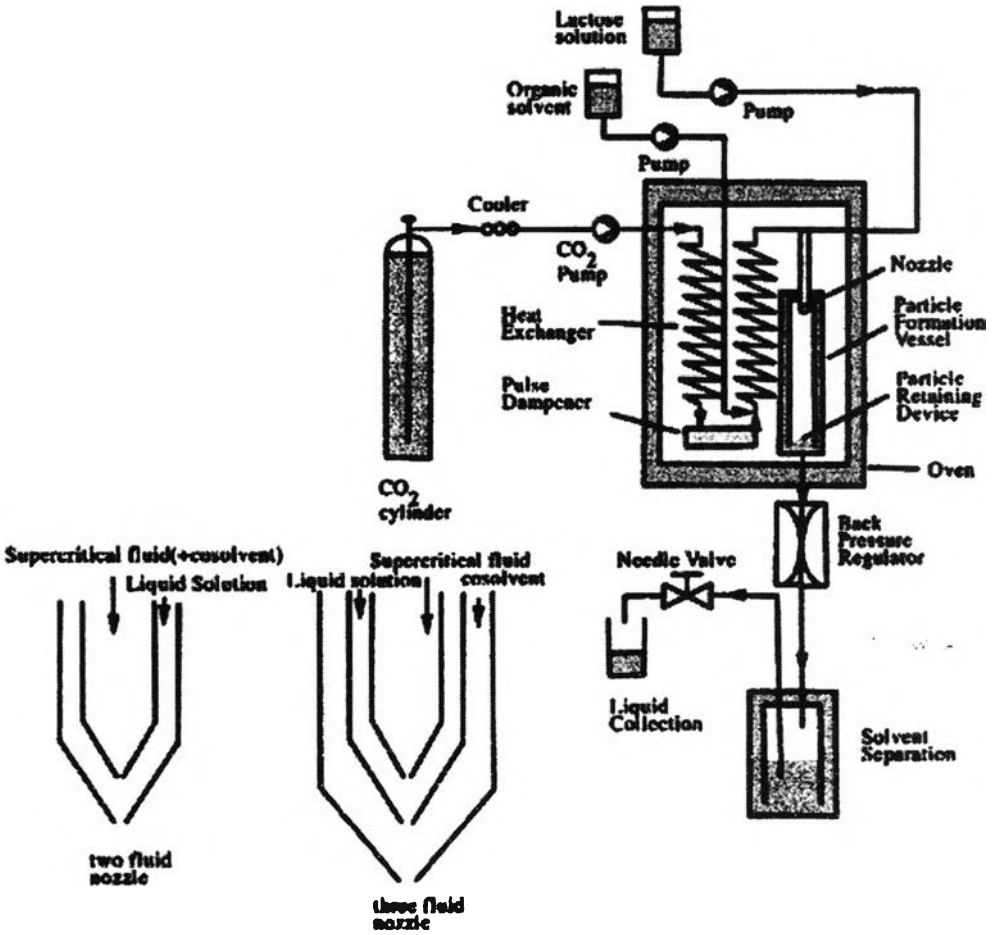

Figure 2-5 Schematic flow diagram of the SEDS process along with the cross section of the co- and triaxial fluid nozzles. (Palakodaty and York 1999)

Figure 2-5 contains a drawing of a coaxial nozzle that is used in the SEDS precipitation technique. The organic solution is fed through one axis, and the prepressurized liquid or supercritical CO_2 is fed through the second axis. The two feed liquids meet in the mixing chamber prior to exiting the nozzle. The turbulence created in the mixing chamber by the collision of the high-speed CO_2 with the feedstock solution stream causes an intense atomization into primary feedstock microdroplets, followed by homogenization of the feedstock droplets and antisolvent. As a result, there is a highly efficient two-way mass transfer that results in rapid precipitation. The primary particle size of the powder can be manipulated by adjusting the relative velocity between the two streams.

Although pharmaceutical protein and peptide powders have been precipitated using the GAS and PCA/SEDS/ASES/SAS processes (Winters 1996), many organic solvents used to dissolve the active ingredient also denature proteins and peptides. Therefore, most of the PCA techniques may not lead to biologically active micronized protein powders. The PCA technique has been modified by Hanna and York to allow the dissolution of the pharmaceutical protein in an aqueous medium prior to spraying into CO_2. Previous supercritical precipitation processes utilized only organic solvents due to the poor solubility of water in CO_2. In the SEDS process, a triaxial nozzle is used to introduce separately the aqueous solution containing the protein, the compressed CO_2, and an organic solvent, thus minimizing contact time between the protein and solvent. A schematic drawing of the triaxial nozzle is shown in Figure 2-5. The organic solvent dissolves the water from the aqueous protein solution. The water/organic solvent mixture then become miscible with the compressed antisolvent. Following depressurization of the system, the CO_2/organic solvent/water mixture evaporates, leaving the dry, micronized protein powder. This triaxial nozzle enables proteins to be micronized using a compressed antisolvent precipitation process while minimizing the extent of denaturation.

4. Particles from Gas-Saturated Solutions (PGSS).

The PGSS process is based on the ability of dense gas to diffuse into an organic compound, thereby lowering the melting point and decreasing the viscosity of the compound as the concentration of the dense gas in the melt increases. The concentration of a gas in a molten solute increases with increasing pressure, and a gas-saturated solution can be formed. If such a solution is depressurized, for example through a nozzle, particles can be formed as the gas is released from the condensed phase. A schematic diagram of the typical PGSS process is shown in Figure 2-6. The system includes a high-pressure vessel for the pressurization and melting of the solute and an expansion chamber with a nozzle assembly for particle formation. In the PGSS process, fine particles can be formed through the atomization and temperature reduction experienced by the gas-saturated solution during the expansion, which rapidly generates a high degree of supersaturation. The particle

size distribution and crystallinity can be controlled by the process parameters such as nozzle diameter, temperature, and pressure (Foster 2003).

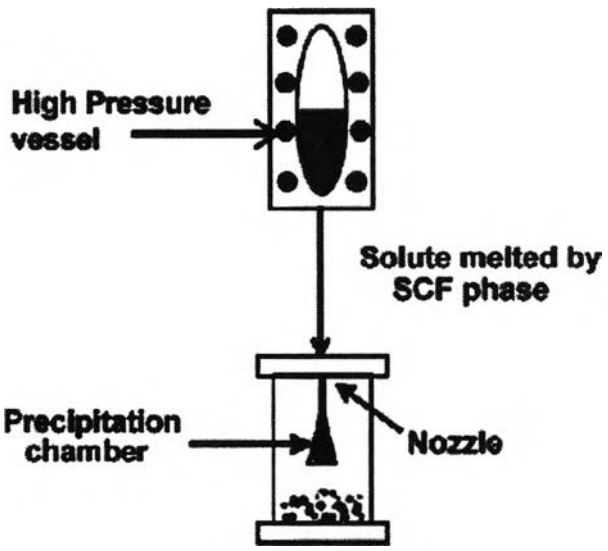

Figure 2-6 Schematic diagram of the PGSS process. (Foster 2003)

Applications in Pharmaceutical Technology

Supercritical carbon dioxide offers several attractive technologies for pharmaceutical processing that could result in significantly reduced usage of conventional liquid solvents and the production of relatively contaminant-free products. The research using supercritical fluids techniques in the experiments are classified by its pharmaceutical applications follow as:

1. Micronization
2. Protein and Peptide Microparticles
3. Polymer-Microparticles, Polymer-Drug Microparticles and Microencapsulation

1. Micronization

The particle micronization with supercritical carbon dioxide offers a unique technology for producing micron and submicron particles with controlled particle size and purity. The antiinflammatory drug ibuprofen was successfully micronized by the RESS technique using supercritical CO_2. The particle size reduction of the processed powder led to a remarkable increase in the rate of drug dissolution. The particle size of the original ibuprofen was as high as 250 μm. The size of ibuprofen particles precipitated by the RESS process was reduced to 3 μm. The dissolution rate of processed ibuprofen was also found to be 4 times higher than the unprocessed material, as shown in Figure 2-7. X-ray diffraction (XRD), differential scanning calorimetry (DSC), and intrinsic dissolution studies confirmed that the original polymorphic form of the ibuprofen and the degree of crystallinity were retained after processing by the RESS technique. Therefore, the improved dissolution property was related solely to the particle size reduction (Charoenchaitrakool et al. 2000).

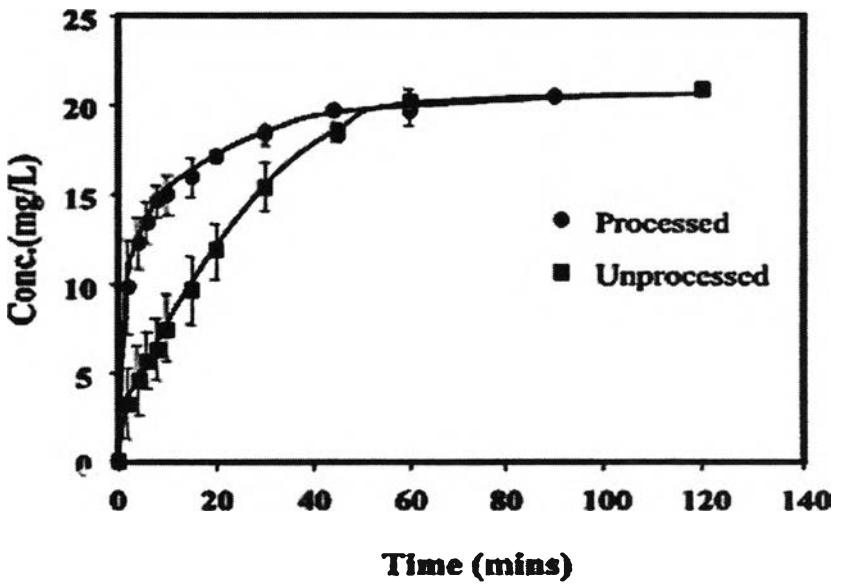

Figure 2-7 Dissolution profile of ibuprofen before and after processing by the RESS technique. (Charoenchaitrakool et al. 2000)

Moneghini et al. (2001) showed the effect of the GAS- micronization of carbamazepine (CBZ), an anti-convulsant drug, on its bioavailability by measuring the rates of dissolution in water of treated and untreated CBZ. Also, they showed that the coprecipitation of CBZ with polyethylene glycol (PEG), a hydrophilic polymer, as fine particles using the GAS process could significantly increase the rate of dissolution of the drug. They used acetone as the solvent and CO_2 as the anti-solvent. sing the GAS process, the particle size of the pure drug was reduced from 284 to 31 μm.

Corrigan and Crean (2002) applied the GAS process for producing hydrocortisone-polyvinylpyrrolidone (PVP) particles. They compared the particles produced using the GAS process with the particles produced by coprecipitation and spray drying. Their study showed that the particles produced by the GAS process had a dissolution rate lower than those prepared by the spray drying, but equivalent dissolution with those prepared by coprecipitation. The pure hydrocortisone particles produced from the GAS process and the coprecipitation had the same crystallinity of the original materials, while the particles produced using spray drying were amorphous.

Reverchon and coworkers applied the SAS process for micronizing some drugs namely, salbutamol (Reverchon et al. 2001), rifampicin (Reverchon et al. 2002) and amoxicillin (Reverchon et al. 2003). They investigated the influences of the SAS operating parameters on morphology, particle size and particle size distribution.

The antihypertensive drug nifedipine is an example of a pharmaceutical processed through PGSS using dense CO_2. The particle size was between 15 and 30 μm, and the dissolution rate of the micronized nifedipine was more rapid than that of the untreated material. The amount of PGSS-precipitated drug that dissolved in 30 min was 5 times higher than the amount dissolved for the untreated nifedipine. (Sencar-Bozic et al.1997).

Drug particles with a narrow particle size distribution,and a typical mass median aerodynamic diameter (MMAD) less than 5 μm are required for the application in inhalation therapy with a dry powder inhaler (DPI), a metered dose inhaler (MDI) or a nebuliser for an effective drug delivery to the lungs (Hinds, 1982). The micronization of drugs could be obtained by controlled crystallization out

of organic solvents leading to solvent incorporation into the drug crystals. Jet milling of drugs is inappropriate or ineffective for unstable or wax-like substances particularly if they are unstable at higher temperature. Glucocorticoids for inhalation therapy of lung diseases are often very hydrophobic and have an insufficient wettability in water. Steckel et al. (1997) using the aerosol solvent extraction system (ASES) produced the steroids, beclomethasone-17,21-dipropionate, betamethasone-17-valerate, budesonide, dexamethasone-21-acetate, flunisolide, fluticasone-17-propionate, prednisolone and triamcinolone acetonide, for inhalation. They used spraying solution contained 1% (w/w) of drug; the solvents were dichloromethane, methanol or a mixture of both. The median particle size of the steroid particles was in most cases lower than 5 μm and consequently within the respirable range. HPLC-analysis showed no chemical decomposition of the drug during the process but the crystal properties of certain investigated drugs changed. Most of the steroids used could be micronized by means of the ASES-process with residual dichloromethane content lower than 350 ppm in all cases.

2. Protein and Peptide Microparticles

The low critical temperature of CO_2, which is commonly employed as the antisolvent for the ASES process, enables thermally labile compounds to be processed at very moderate temperatures without degradation. The interest in this process has involved the processing of a range of proteins including insulin and lysozyme (Yeo et al. 1993 and Winters et al. 1996) for which an important factor is that both the structural integrity and biological activity are unaffected. Yeo et al. (1993) dissolved insulin in dimethylsufloxide (DMSO) or *N*,*N*-dimethylformamide (DMF) and these solutions were sprayed into a crystallizer with a continuous feed of supercritical carbon dioxide. Particle formation from 5- and 15 mg/ml-insulin-DMSO solutions and 5-mg/ml-insulin-DMF solutions was investigated. In preparing insulin-DMF solutions, solubilization of the protein was achieved by adjusting the pH to 7.3 with 1N HCl. The CO_2 antisolvent and protein solutions were contracted at 86.2 bar and 25 °C or 35 °C by the cocurrent technique. Over this range of experimental conditions and solvent systems, spherical and spheroidal insulin particles were produced. The morphology of the SAS-produced powders differs

significantly from the polyhedral aspect of the crystalline commercial insulin. Antisolvent expansion of the solvent droplets caused the formation of insulin particles, of which 90% were less than 4 μm and 10% less than 1 μm. It was more significant that the insulin in these powders maintained its bioactivity.

Microencapsulation experiments were then performed on a model protein, lysozyme, from dimethylsulfoxide (DMSO) solutions. Young et al. (1999) used ASES process to encapsulate the protein lysozyme, which was suspended in an organic solution containing poly (DL-lactide-co-glycolide) (PLGA) dissolved within dichloromethane. Following atomization of the suspension into excess CO_2, the PLGA precipitated onto the surface of the suspended lysozyme as the CO_2 expanded the dichloromethane. Because the protein was suspended and not dissolved in the organic solvent, denaturation may be expected to be much less severe. The actual drug loadings of the particles were not reported.

Elvassore et al. (2001a, 2001b) produced insulin-loaded biodegradable polymer-based nanoparticles using the SAS process (they called this the semi-continuous GAS process). Since the poly(lactide) (PLA) used in their research had low biodegradability and high hydrophobicity, Elvassore et al. (2001a) showed that by adding PEG to the drug/PLA mixture, the bioavailability and biodegradability of the nanoparticles are improved. The resulting nanoparticles had an average range of 400–600 nm in size distribution. In order to achieve particulate products with narrow size distribution and homogeneous drug dispersion into the polymeric carrier and to avoid the jet break-up during liquid injection into the precipitation chamber, the insulin/PEG/PLA mixture was dissolved in a 50:50 dichloromethane (DCM)/dimethylsulfoxide (DMSO) mixture.

3. Polymer-Microparticles, Polymer-Drug Microparticles and Microencapsulation.

Supercritical fluids are promising extraction media for the formation of microparticles of drugs and pharmaceutical excipients (Subramaniam et al. 1997). There are several reports of the production of microparticles of biodegradable polymers using different supercritical fluid extraction methods (Bleich et al. 1993; Tom et al. 1993; Bodmeier et al. 1995; Ghaderi et al. 1998). The production of pharmaceuticals, such as the precipitation of bioerodible polymers (Randolph et al. 1993 and Bodmeier et al. 1995) are primary interest.

Bleich et al. (1993) treated several biodegradable polymers: Poly(L-lactide) (L-PLA), Poly(β- hydroxybutyric acid) (PHB), Poly(DL-lactide) (DL-PLA) and Poly(DL-lactide)-*co*-glycolyde (PLGA) by precipitation from methylene chloride, operating in continuous mode. Spherical particles were obtained for L-PLA with $X_{50\%}$ particles ranging between 1 and 10 μm. Using DL-PLA and PLGA no particle formation was obtained since the polymer was extracted during the process and precipitated in the liquid collection vessel. Poly(L-lactide) has also been show to consistently precipitate from the ASES process as discrete microspheres, which are desirable for pharmaceutical applications.

Dixon et al. (1994) used a precipitation vessel that was only partly charged with liquid CO_2; the remaining part contained gaseous CO_2 in equilibrium with the liquid phase. Discontinuous injection of the liquid solution was performed. Bodmeier et al. (1995) used the same arrangement to test various pharmaceutically acceptable polymers: ethyl cellulose, poly-methylmethacrylate (PMMA), poly-caprolactone (PCL), DL-PLA and L-PLA. Ethyl cellulose and L-PLA do not swell in carbon dioxide, and, therefore, are suitable candidates for micronization. L-PLA microspheres were obtained in methylene chloride; they were smaller than 5 μm with a narrow particle size distribution. However, high polymer concentration produced fibers. Chlorpheniramine maleate and indomethacin in methylene chloride were dissolved in the polymer solution before the spraying process. The drug loading of the resulting microspheres was low. Probably the solubility of drugs in CO_2 increased owing to the presence of methylene chloride producing the drug extraction from the microspheres during the drying step.

The RESS micronization technique can be used to precipitate active ingredient alone, or it can be used to form a coprecipitate formulation of the drug embedded in a polymeric matrix. Tom et al. (1993) found that an unacceptable coprecipitate was formed when using the RESS process to micronize lovastatin and DL-PLA (DL-poly-lactide) due to the formation of needlelike crystals of drug protruding from the polymeric matrix instead of a molecularly homogeneous continuum. In another study, Kim et al. (1996) discovered that higher preexpansion temperatures and pressures (>114°C and >190 bar, respectively) produced homogeneous naproxen/L-PLA microspheres following RESS processing, while lower system temperatures and preexpansion pressures allowed phase separation prior to precipitation. The requirement of elevated temperatures to produce homogeneous precipitates may enhance degradation of thermally labile drugs processed using the RESS technique. Another major disadvantage of the RESS process is the low solubility of most organic solids in supercritical CO_2. Low drug loading into the supercritical CO_2 results in low production rates of powders.

The potential of the ASES process for microencapsulation was first realised by Bleich et al. (1994). Their work involved the microencapsulation of a model drug, hyoscine butylbromide, with poly(L-lactide) by precipitation from a solution of methanol and methylene chloride. The drug loading determined from unwashed samples was 14.7– 15.3 %. The low critical temperature of CO_2, which is commonly employed as the antisolvent for the ASES process, enables thermally labile compounds to be processed at very moderate temperatures without degradation. A study of the microencapsulation of ionic compounds gentamycin, naloxone and naltrexone with poly(L-lactide) from methylene chloride was published by Falk and Randolph (1998).

Tu et al. (2002) used the ASES process to micronize and microencapsulate parahydroxy benzoic acid (p-HBA) and lysozyme with L-PLA from various organic solutions. The effect of various parameters, such as pressure, temperature solution concentration and spraying velocity on the nature of the particles were determined. They used a multiple nozzle for encapsulating the model drugs by the biodegradable polymer, L-PLA. They suggested that for reaching higher encapsulation efficiency, the contact between the drug and polymer phases should be maximized during the rapid precipitation process by changing the nozzle geometry.

It was found that the high-molecular-weight compounds, L-PLA and lysozyme, precipitated as microspheres and nanospheres, whereas the lighter-weight compound, parahydroxybenzoicn acid (p-HBA), precipitated as crystalline particles resembling platelets averaging 3 μm in length. The encapsulation efficiencies for lysozyme and p-HBA/L-PLA particles obtained were 15.6% and 9.2% respectively. Other authors reported higher drug loading values, for example 50–60%, and efficiencies of 22%, but with the copolymer poly(D,Llactide-co-glycolide) (PLGA) (Engwicht et al. 1999; Ghaderi et al. 2000). Higher encapsulation efficiency was perhaps due to the fact that PLGA is a more amorphous polymer compared to L-PLA, and was, therefore, able to encapsulate core material during plasticisation by CO_2.

The biodegradable polymers, poly(D,L-lactide-co-glycolide): copolymer composition 50:50 (DL-PLGA), poly(L-lactide) (L-PLA), poly(D,L-lactide) (DL–PLA) and polycaprolactone, were used for preparation of microparticles by a modified SEDS process (Ghaderi et al 1999).The combination of supercritical N_2 and CO_2 led to a more efficient dispersion of the polymer solutions than CO_2 alone (Ghaderi et al. 2000). Discrete spherical microparticles with a mean volumetric diameter of less than 10 μm were produced from DL-PLGA, DL–PLA and L–PLA. Hydrocortisone was successfully entrapped within the DL-PLG microparticles.