3

Supercritical Fluid Technology for Particle Engineering

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INTRODUCTION

Design and fabrication of pharmaceutical particulate systems is still largely an art as opposed to a fundamental science. However, a more systematic design and manufacture of particulate systems including nanoparticles is being enabled by the application of novel technologies, such as supercritical fluid (SCF) technology, which is the focus of this chapter (1). A fluid is supercritical when it is compressed beyond its critical pressure (P_c) and heated beyond its critical temperature (T_c). SCF technology has emerged as an important technique for particle manufacturing. In many industrial applications, it is poised to replace the conventional recrystallization and

Table 1 Critical Constants and Safety Data for Various Supercritical Solvents

SCF	T_c (°C)	P_c (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	
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; R 22)	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	

Abbreviation: SCF, supercritical fluid.

milling processes, mainly because of the quality and the purity of the final particles and environmental benefits. There are a variety of SCFs available as listed in Table 1. T1

SUPERCRITICAL CO_2

Out of the fluids listed in Table 1, carbon dioxide is the SCF of choice because it is nonflammable, nontoxic, inexpensive, and has mild critical temperature. Hence, much of the attention has been given to supercritical carbon dioxide for pharmaceutical particle formation.

No amount of compression can liquefy the SCF. In fact, pressure can be used to continuously change the density from

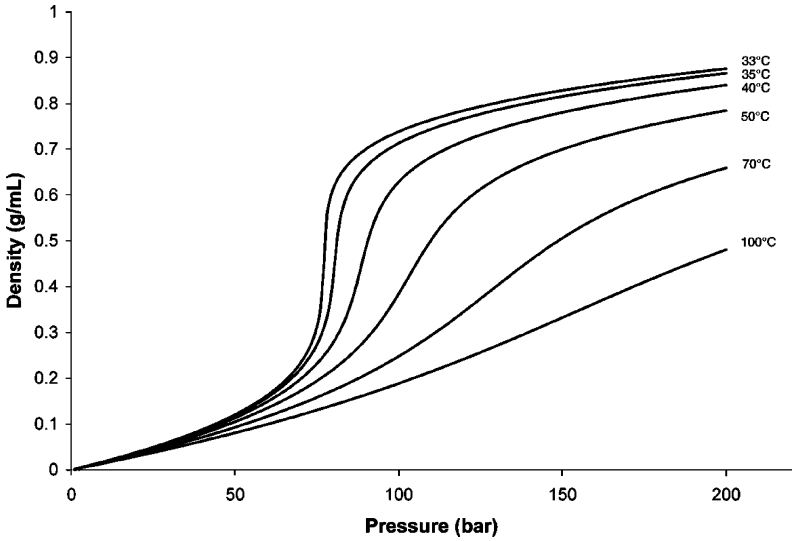

Figure 1 Density dependence of carbon dioxide at various temperatures.

gas-like conditions to liquid-like conditions. Near the critical region, small changes in the pressure can give rise to large changes in the density. Figure 1 shows how density of carbon dioxide is varied by pressure at different temperatures. F1

In addition to density, diffusivity of the SCFs is higher than that of liquid solvents, and can be easily varied. For typical conditions, diffusivity in SCFs is of the order of 10^{-3} cm^2/sec as compared to 10^{-1} for gases and 10^{-5} for liquids. Typical viscosity of SCFs is of the order of 10^{-4} g/cm/sec, similar to that of gases, and about 100-fold lower than that of liquids. High diffusivity and low viscosity provide rapid equilibration of the fluid.

SOLUBILITY IN SUPERCRITICAL CO_2

Carbon dioxide (O=C=O) is a nonpolar molecule with a small polarity due to the quadrupole moment. Hence, nonpolar or light molecules (e.g., menthol, methanol, acetone, toluene, and hexanes) easily dissolve in CO_2, whereas the polar or

heavy molecules (e.g., griseofulvin, paclitaxel, tetracycline, and dexamethasone phosphate) have a very poor solubility. For example, solubility of menthol in CO_2 is as high as 5 mol% (Fig. 2), whereas the solubility of griseofulvin in CO_2 is only about 18 ppm (Fig. 3). Solubilities of other pharmaceutical compounds are shown in Figures 4–6. A comprehensive compilation of solubility data in supercritical CO_2 is given in a recent book by Gupta and Shim (6).

Three important factors that govern drug solubility in supercritical CO_2 are the vapor pressure of drug, drug–CO_2 interaction, and density of CO_2. Drug vapor pressure is a function of temperature (T), and CO_2 density is a function of pressure (P) and T. (Fig. 7). Mendez–Santiago and Teja (8) observed that the solubility (y_2 μmol/mol) can be correlated using the following equation:

$$y_2 = \frac{10^6}{P}\exp\left(\frac{A}{T} + \frac{B\rho_1}{T} + C\right) \quad (1)$$

where P is in bars, T is in Kelvin, ρ_1 is CO_2 density in moles per milliliter. Constants A, B, and C are listed in Table 2

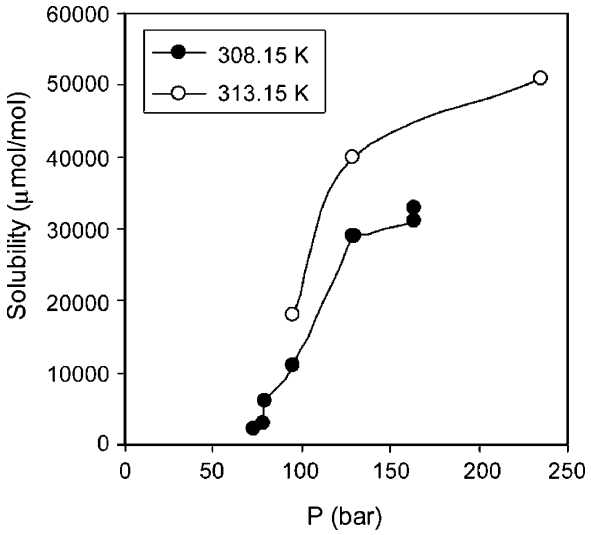

Figure 2 Solubility of menthol in CO_2. *Abbreviation*: CO_2, carbondioxide. *Source*: Ref. 2.

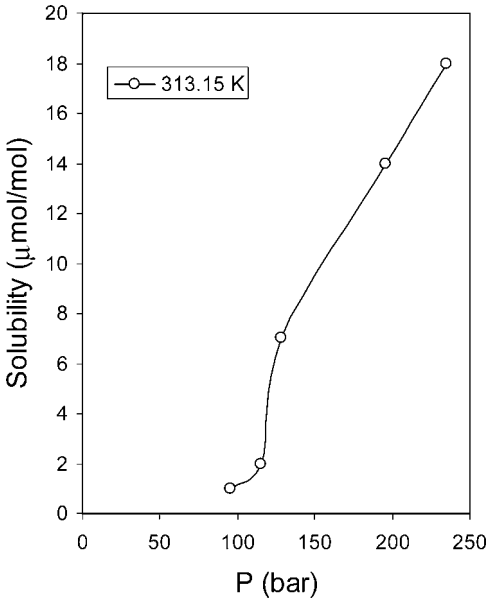

Figure 3 Solubility of griseofulvin in CO_2. *Source*: From Ref. 2.

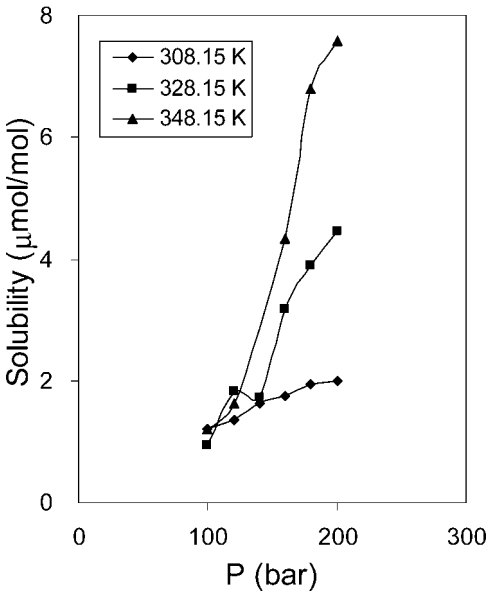

Figure 4 Solubility of nicotinic acid in CO_2. *Source*: From Ref. 4.

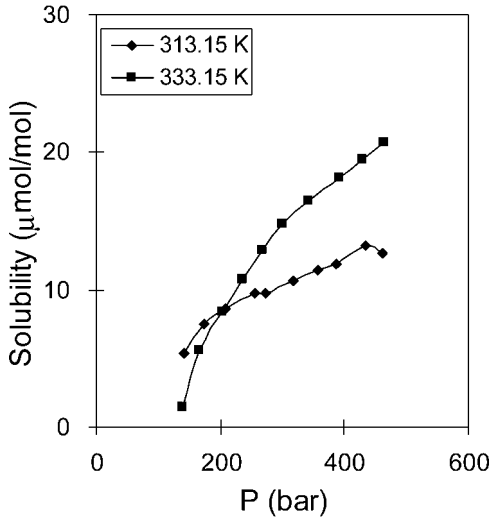

Figure 5 Solubility of chloramphenicol in CO_2. *Source*: From Ref. 5.

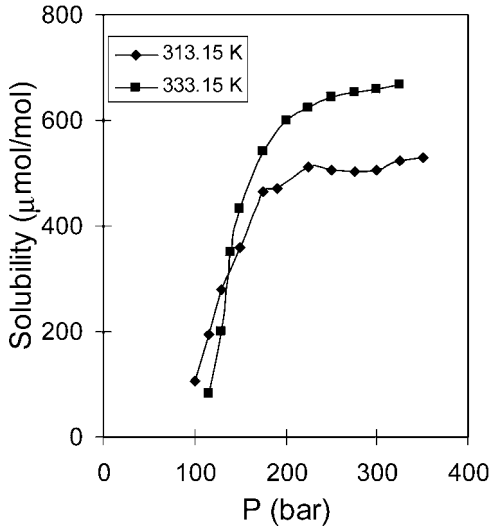

Figure 6 Solubility of salicylic acid in CO2. *Source*: From Ref. 3.

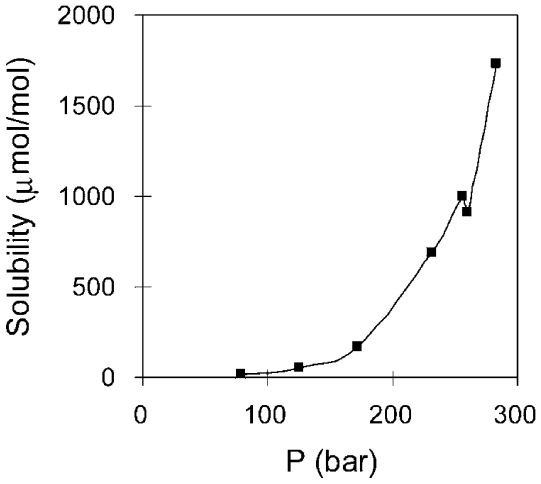

Figure 7 Solubility of α-tocopherol in CO_2 at 333 K. *Source*: From Ref. 7.

for selected drugs. Density of pure CO_2 can be obtained from NIST Standard Reference Database (http://webbook.nist.gov/chemistry/) at the desired T and P. Alternatively, the following empirical expression can be used (9):

$$\rho_1 = \frac{1}{44}\exp\left(-27.091 + 0.609\sqrt{T} + \frac{3966.170}{T} - \frac{3.445P}{T} + 0.401\sqrt{P}\right) \quad (2)$$

RAPID EXPANSION OF SUPERCRITICAL SOLUTION FOR PARTICLE FORMATION

From the previous section it is evident that the solubility of pharmaceutical compounds is highly dependent on CO_2 pressure. As the pressure is reduced, solubility decreases because of a reduction in the CO_2 density, which is closely related to its solubility power (8–11). At a high pressure, the drug can be dissolved in CO_2 and if the pressure is reduced to ambient, the drug precipitates out as fine particles. The depressurization

Table 2 Values of the Constants for Equation (1)

Drug	*A*	*B*	*C*
7-Azaindole	−8,412	87,110	20.66
Behenic acid	−4,473	61,240	6.80
Biphenyl	−10,200	132,800	25.75
Brassylic acid	−10,860	146,100	21.01
Capsaisin	−7,172	70,830	19.54
Cholecalciferol	−9,784	172,500	18.42
Diphenylamine	−18,720	397,100	33.40
Eicosanoic acid	−15,990	161,600	36.97
1-Eicosanol	−14,530	122,500	36.15
Endrin	−9,912	167,800	20.29
Ergocalciferol	−1,092	173,500	21.51
Flavone	−11,430	110,100	27.38
D(−)-Fructose	−871.2	10,740	−4.29
D(+)-Glucose	847.1	2,471	−9.12
3-Hydroxyflavone	−9,746	81,530	21.31
Ketoprofen	−12,090	157,500	24.72
Medroxyprogesterone acetate	−10,270	186,100	17.77
Methoxychlor	−12,670	184,100	27.38
Monocrotaline	−10,440	8,057	20.28
Mystiric acid	−17,250	173,100	44.84
Naproxen	−9,723	122,900	18.11
Narasin	−8,529	124,900	13.86
Nifedipine	−10,020	168,500	15.92
Nimesulide	−13,820	186,900	28.14
Nitrendipine	−9,546	151,400	15.91
Octacosane	−19,860	123,000	52.555
1-Octadecanol	−17,290	141,000	45.32
Palmityl behenate	−8,378	59,180	18.44
Penicillin V	−6,459	73,730	13.29
Phenylacetic acid	−13,730	14,450	35.78
Piroxicam	−10,560	18,130	17.57
Progesterone	−12,090	21,040	23.43
t-Retinol	−8,717	168,900	16.60
Salinomycin	−18,990	185,500	42.05
Stigmasterol	−13,010	169,000	25.23
Testosterone	−14,330	238,300	26.42
Theobromine	−7,443	114,000	8.31
Theophyline	−6,957	94	760
Triacontane	−22,965	199,800	57.22
Trioctylphosphine oxide	−9,378	211,900	17.65
Vanillin	−7,334	136,500	14.53

Source: From Ref. 8.

can be done very fast; so fast that CO_2 comes out of the nozzle at the speed of sound. The fast depressurization results in a very fast rate of precipitation providing small drug particles. This process is termed as rapid expansion of supercritical solution (RESS) and has been tested for a wide variety of drugs. A schematic of the RESS process is shown in Figure 8. F8

The bulk drug is solubilized in CO_2 in a high-pressure chamber. The solution is then passed through a nozzle to rapidly reduce the pressure. In some applications, the nozzle is also heated to avoid clogging due to freezing of CO_2 by sudden expansion. The precipitated drug particles are collected in an ambient pressure bag filter. The morphology of the resulting particles (crystalline or amorphous) depends on the molecular structure of the drug and RESS process conditions (solubilization temperature, expansion temperature, pressure drop across nozzle, nozzle geometry, impact distance of the jet against collection surface, etc.).

Most of the drug particles produced by RESS, have been in the 1–5 μm-size range. The rapid expansion of supercritical CO_2 does produce nuclei 5–10 nm in diameter, but these nuclei grow because of coagulation and condensation to produce the final micrometer-size particle. The micronized drugs include 2–5 μm aspirin, 3–5 μm caffeine, 2–3 μm cholesterol, 2 μm ibuprofen, 1–3 μm nifedipine, 2–5 μm progesterone, 1–5 μm salicylic acid, 2–5 μm testosterone, 4–12 μm theophyline, and 1–2 μm α-tocopherol (3,12–19).

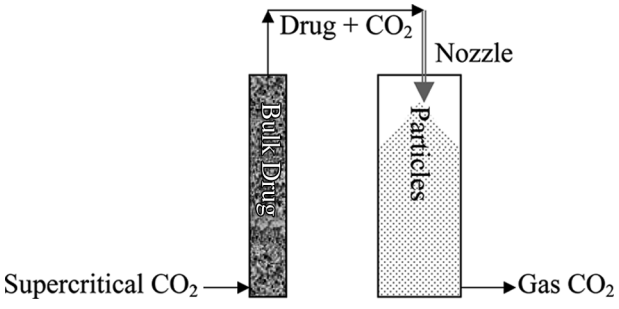

Figure 8 Schematic of RESS process. *Abbreviation*: RESS, rapid expansion of supercritical solution.

For a few drugs, nanoparticles have also been obtained using RESS. These nanonized drugs include 100 nm lidocaine, 200 nm griseofulvin, 200 nm β-sitosterol (20,21). Recently, by expanding the drug CO_2 mixture in a liquid medium containing stabilizers, Pathak et al. (22) have obtained small nanoparticles of ibuprofen and naproxen.

As the obtained particles are free of organic solvents and the high-pressure part of the equipment is not too expensive, theoretically RESS process is very useful. Unfortunately, for most drugs, nanoparticles are not obtained. Instead, oriented-fused particles are obtained (Fig. 9). F9

Another major drawback of the RESS process is the low solubility of most drugs in supercritical carbon dioxide. For example, solubility of griseofulin is only 18 ppm. Hence, to obtain 18 mol of griseofulvin, one needs to use one million mol of CO_2 (i.e., 1 g griseofulvin particles from about 7 kg CO_2). The worst part is the collection problem. For the earlier example, 1 g of powder would be dispersed in 3573 L of gaseous CO_2 requiring efficient filtration.

Addition of cosolvents, such as methanol, acetone, or ethanol, can enhance the drug solubility to some extent.

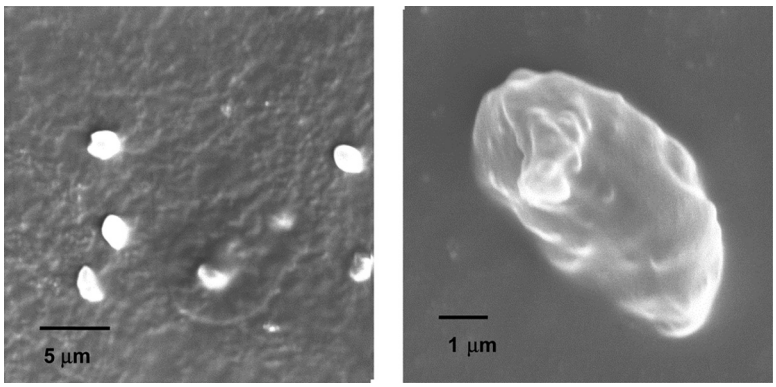

Figure 9 Scanning electron micrograph of griseofulvin particles obtained from RESS process (solubilization in CO_2 was done at 196 bar, 40°C). *Abbreviation*: RESS, rapid expansion of supercritical solution.

But, the presence of such a cosolvent in the expansion chamber is not desired, as it will lead to solubilization of the particles in the cosolvent.

RESS WITH SOLID COSOLVENT FOR NANOPARTICLE FORMATION

Recently, Thakur and Gupta (2,23) have addressed both the challenges of RESS (low solubility and growth by coagulation) by utilizing a cosolvent that is solid at the nozzle exit conditions. The solid cosolvent (SC) enhances the solubility in supercritical carbon dioxide and provides a barrier for coagulation in the expansion chamber. The SC is later removed from the solute particles by lyophilization (sublimation). The new process is termed as RESS–SC.

In RESS, all the nuclei or small particles of solute are surrounded by the same kind of particles as in Figure 10(A). F10
But in the RESS–SC process, nuclei or small particles of the solute are surrounded by excess SC particles. This reduces the probability of solute particle growth by coagulation. The

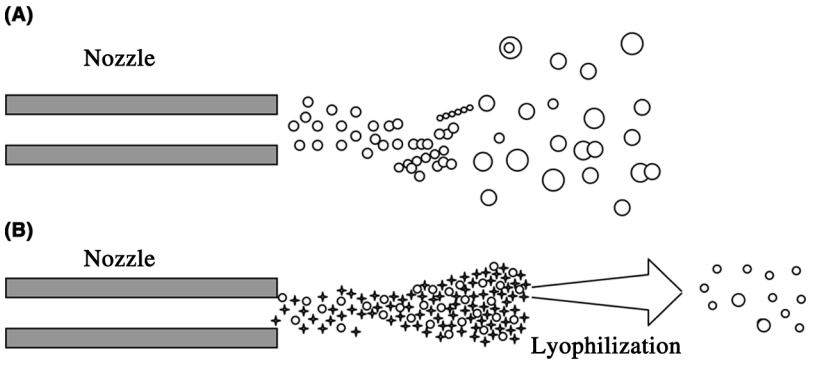

Figure 10 (**A**) Magnified view of the RESS nozzle. (**B**) Schematic of RESS–SC process. Circles represent drug particles, whereas stars represent solid–cosolvent particles. *Abbreviations*: RESS, rapid expansion of supercritical solution; RESS–SC, rapid expansion of supercritical solution solid cosolvent.

RESS–SC concept is depicted in Figure 10(B). The lyophilization step shown in the figure is carried out separately after the expansion.

The choice of a proper SC is the key for successful RESS-SC. Various requirements for the selection of the SC are

- good solubility in supercritical CO_2,
- solid at nozzle exit condition (5–30 °C),
- good vapor pressure for easy removal by sublimation,
- should be nonreactive with drugs or CO_2, and
- inexpensive.

Menthol is a solid compound (melting point, 42°C) that satisfies the requirements mentioned earlier. It has appreciable solubility in CO_2 (Fig. 2) and can easily sublime under vacuum. Menthol naturally occurs in mint-flavored plants, and is widely used in antipruritic agents, mouthwashes, nasal sprays, food, etc. Because of its wide use in food and pharmaceutics, menthol does not seem to possess harmful effects and its use as a cosolvent with supercritical carbon dioxide still carries the benign benefit of the technology. The following are two examples of the RESS-SC process using menthol solid cosolvent.

Griseofulvin Nanoparticles

Using menthol cosolvent, griseofulvin solubility can be enhanced by up to 28-fold, as shown in Table 3. T3

The nanoparticles obtained from the RESS–SC process are in the size range of 50–250 nm (Fig. 11), which is about 10-fold smaller than in RESS. In addition, due to the solubility enhancement, the CO_2 requirement is about 28-fold lower. F11

Aminobenzoic Acid Nanoparticles

By using menthol cosolvent, the solubility of 2-aminobenzoic acid can be enhanced by up to 100-fold as shown in Figure 12 (23). F12

The RESS–SC process produced ~80 nm size nanoparticles, which is significantly smaller than the ~610 nm size nanoparticles obtained from the RESS process. Menthol is

Table 3 Solubility of Griseofulvin in Supercritical CO_2 with Menthol Cosolvent

P (bar)	T (°C)	Menthol amount (μmol/mol)	Griseofulvin solubility (μmol/mol)	Enhancement factor[a]
96	40	21,000	27	28
117	40	25,000	71	–
130	40	37,000	133	20
198	40	42,000	217	15
239	40	60,000	266	15
96	50	5,000	2	15
130	50	24,000	43	12
164	50	34,000	110	15

[a]Ratio of griseofulvin solubility in menthol/CO_2 to that in pure CO_2.
Abbreviation: CO_2, carbondioxide.

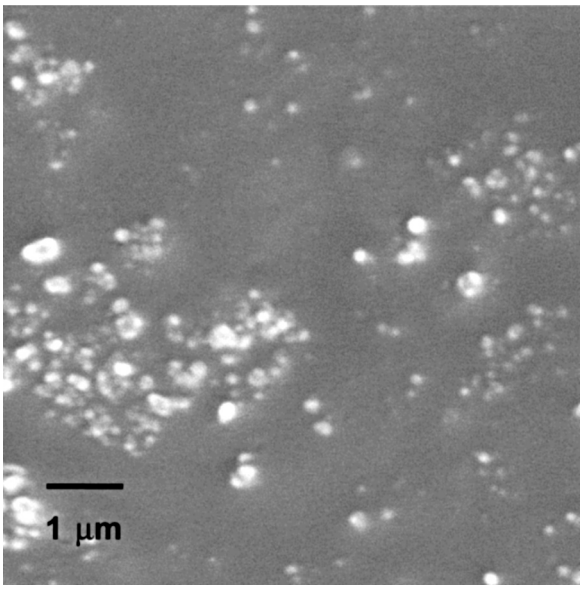

Figure 11 Griseofulvin nanoparticles from RESS–SC process. *Abbreviation*: RESS–SC, rapid expansion of solid supercritical solution solid cosolvent.

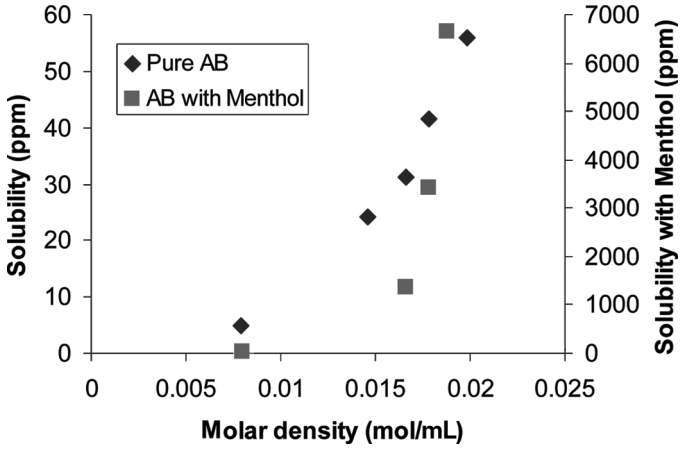

Figure 12 Solubility of 2-aminobenzoic acid in pure CO_2 and with menthol cosolvent versus fluid density. *Abbreviation*: CO_2, carbon-dioxide.

easily removed from 2-aminobenzoic acid nanoparticles by sublimation (lyophilization) (Fig. 13). F13 AQ2

SUPERCRITICAL ANTISOLVENT PROCESS FOR PARTICLE FORMATION

Before the invention of the RESS–SC process, the low-solubility aspect of supercritical CO_2 was utilized to produce particles by its antisolvent action. The drug is dissolved in an organic solvent, and then the solution is injected into supercritical carbon dioxide. The SCF, due to its high diffusivity, rapidly extracts the solvent precipitating the drug particles. A schematic of the supercritical antisolvent (SAS) concept is shown in Figure 14. F14

The SAS process has been proposed with numerous acronyms (SAA, SEDS, GAS, ASES, etc.,) in the literature, but the basic concepts remain the same. Typically, 50–200 μm nozzles have been utilized in SAS. When the injection of the drug solution is complete, a washing step is carried out to remove the organic solvent so as to prevent it from condensing during

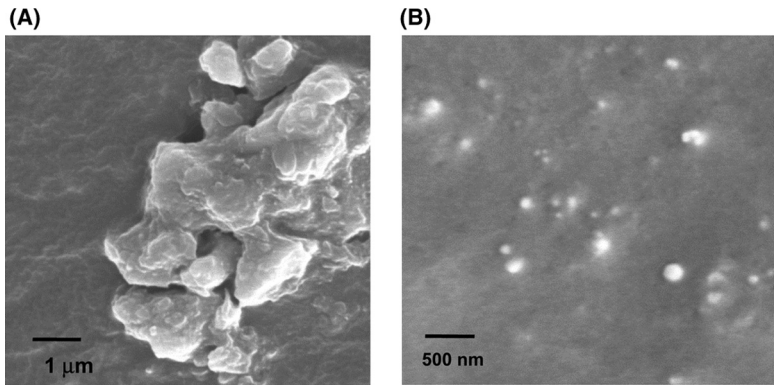

Figure 13 2-Aminobenzoic acid particles from (**A**) RESS and (**B**) RESS–SC processes. *Abbreviations*: RESS, rapid expansion of supercritical solution; RESS–SC, rapid expansion of supercritical solution solid cosolvent.

the depressurizing step. For this purpose, the feed of supercritical CO_2 is maintained to carry out the residual solvent. Once all the residual solvent is removed, the vessel pressure is reduced to atmospheric pressure, and the solid particles are collected on a filter at the bottom of the vessel. A review of SAS-based processes is provided by Jung and Perrut and by Charbit et al. (24,25). A polymer can be coprecipitated along with the drug to obtain controlled release formulation (26,27).

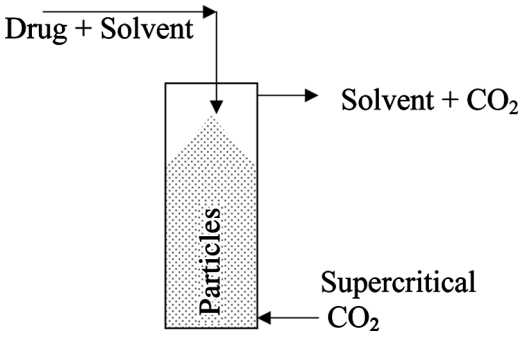

Figure 14 Schematic of SAS process. *Abbreviation*: SAS, supercritical antisolvent.

The particle size and morphology depends on the nozzle geometry, solution velocity, CO_2 pressure, and the type of organic solvent used. The SAS process provides mostly 15 μm drug particles. Examples include 10–40 μm acetaminophen from ethanol, 1–10 μm ascorbic acid and aspirin from ethanol, 1.2–2 μm budesonide from methylene chloride, 0.5–20 μm camptothecin from dimthyl sulfoxide, 1–5 μm chlorpeniramine maleate from methylene chloride, 1.7 μm fluticasone-17-propionate from methylene chloride, 14 μm ibuprofen from methanol, 1–5 μm indomethacine from methylene chloride, 1–10 μm insulin from hexafluoro isopropanol, 1–5 μm insulin from dimethyl sulfoxide, 0.5–5 μm insulin from ethanol, 1–5 μm lysozyme from dimethyl sulfoxide (Winters #115), 1–10 μm paracetamol and saccharose from ethanol, 2–20 μm sulfathiazole from acetone and methanol, and 1.5 μm trypsin from ethanol (27–38).

A few SAS studies have produced nanoparticles. These are listed in Table 4, along with the process conditions used. T4

In SAS, the inability to form small nanoparticles and to have a narrow size distribution can be attributed to particle growth after nuclei formation. The main phenomenon in

Table 4 Drug Nanoparticles from SAS-Based Precipitation Processes

Drug	Solvent	*P* (bar)	*T* (K)	Particle size (nm)	References
Albumin	Water/ethanol			50–500	39
Amoxicillin	*N*-Methylpyrrolidone	150	313	300–1200	40
Gentamicin/PLA	Methylene chloride	85	308	200–1000	41
Hydrocortisone	Dimethyl sulfoxide	100	308	600	29
Ibuprofen	Dimethyl sulfoxide	100	308	500–1000	29
Naloxone/l-PLA	Methylene chloride	85	308	200–1000	41
Insulin	Water/ethanol			50–500	39
Naltrexen/l-PLA	Methylene chloride	85	308	200–1000	41
Nicotinic acid	Ethanol			400–750	42
RhDNase	Ethanol			50–500	39
Salbutamol	Methanol/acetone	100	333	500	42

Abbreviation: SAS, supercritical antisolvent.

RESS is the high rate of pressure reduction, where in SAS, it is the high diffusivity of supercritical CO_2. The antisolvent action (mixing or mass transfer of solvent and antisolvent) needs to be even faster than SAS, in order to produce smaller particles of < 300 nm in size.

SA WITH ENHANCED MASS (EM) TRANSFER (SAS-EM) PROCESS FOR NANOPARTICLE FORMATION

A significant improvement in the SAS process is introduced by Gupta and Chattopadhyay leading to nanoparticles of controllable size that are up to an order of magnitude smaller than those resulting from the conventional SAS process, and have a narrower size distribution (43). Like the SAS, this process, SAS–EM, utilizes supercritical carbon dioxide as the antisolvent, but in this case the solution jet is deflected by a surface vibrating at an ultrasonic frequency that atomizes the jet into much smaller droplets. Furthermore, the ultrasound field generated by the vibrating surface enhances mass transfer and prevents agglomeration through increased mixing. The particle size is controlled by varying the vibration intensity of the deflecting surface, which in turn is easily adjusted by changing the power supplied to the attached ultrasound transducer. The SAS–EM process is shown in Figure 15. F15

The SAS–EM process has been demonstrated by the formation of tetracycline, griseofulvin, lysozyme, and dexamethasone phosphate nanoparticles (44–46). The size is easily varied from 100 to 1000 nm by the power supply knob on the ultrasonic processor. These results are summarized in Table 5. T5

SAS–EM has been scaled up by Thar Technologies (www.thartech.com) for production at pilot scale (Fig. 16). F16 This unit can produce up to 1 kg nanoparticle/day. It has one precipitation vessel and two separate collection vessels. One collection vessel can be used to collect the nanoparticles, while the other can be used to remove the nanoparticles for final use. The system is fully automated and can provide nanoparticles

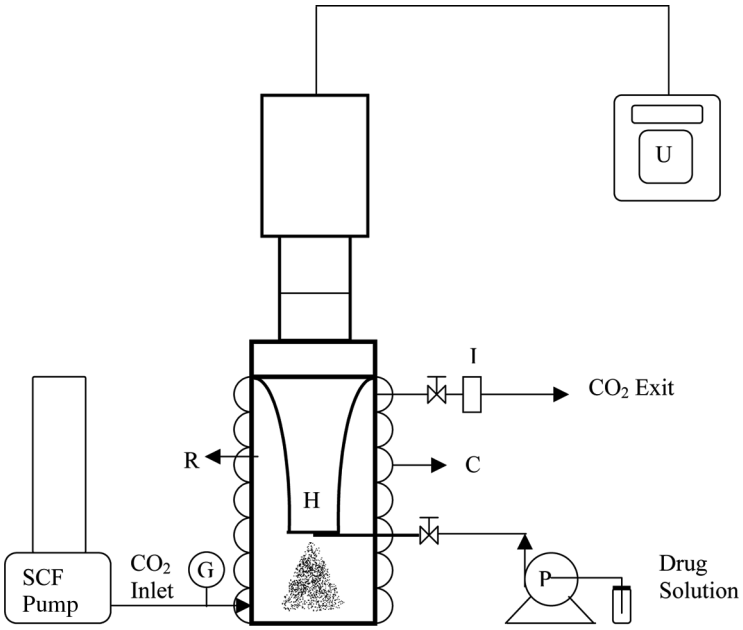

Figure 15 SAS-EM process. R, precipitation chamber; SCF pump, supply of supercritical CO_2; I, inline filter; U, ultrasonic processor; P, pump for drug solution; G, pressure gauge; C, heating coil with temperature controller. *Abbreviations*: SAS–EM, supercritical antisolvent with enhanced mass transfer; SCF, supercritical fluid. AQ3

continuously. The ultrasound power supply is controlled by a computer, which in turn controls the nanoparticle size.

FUNDAMENTALS GOVERNING PARTICLE FORMATION WITH RESS AND SAS

Both SAS and RESS are complex processes involving the interaction of jet hydrodynamics, phase equilibrium, nucleation and growth (48,49). In SAS, additional complexity arises because of droplet formation, and mass transfer into and out of the droplets. In both cases, a high supersaturation is achieved, which results in rapid precipitation of the dissolved drug. In RESS, a sudden change in the fluid pressure causes

Table 5 Drug Nanoparticles from SAS–EM Process

Drug	Solvent	P (bar)	T (°C)	Ultrasound power (W)	Particle size (nm)	References
Dexamethasone phosphate	Methanol	102	40	90	175	46
Griseofulvin	Dichloromethane	96.5	35	90	510	47
Griseofulvin	Dichloromethane	96.5	35	150	520	47
Griseofulvin	Dichloromethane	96.5	35	180	310	47
Griseofulvin	Tetrahydrofuran	96.5	35	120	200	47
Griseofulvin	Tetrahydrofuran	96.5	35	150	280	47
Griseofulvin	Tetrahydrofuran	96.5	35	180	210	47
Lysozyme	Dimethylsulfoxide	96.5	37	12	730	45
Lysozyme	Dimethylsulfoxide	96.5	37	30	650	45
Lysozyme	Dimethylsulfoxide	96.5	37	60	240	45
Lysozyme	Dimethylsulfoxide	96.5	37	90	190	45
Tetracycline	Tetrahydrofuran	96.5	37	30	270	44
Tetracycline	Tetrahydrofuran	96.5	37	60	200	44
Tetracycline	Tetrahydrofuran	96.5	37	90	184	44
Tetracycline	Tetrahydrofuran	96.5	37	120	110	44

rapid precipitation, whereas in SAS the sudden diffusion of CO_2 into a drug solution causes drug precipitation. For RESS, the nanoparticle population balance equation accounting for particle nucleation and growth dynamics is as follows (50).

$$\frac{\partial n}{\partial t} = J(\nu^*)\delta(\nu - \nu^*) - \frac{\partial(G_g n)}{\delta\nu} + \frac{1}{2}\int_0^{\nu} \beta(\nu - \bar{\nu}, \bar{\nu}) n(\nu - \bar{\nu}, t) n(\bar{\nu}, t) d\bar{\nu} - n(\nu, t) \times \int_0^{\infty} \beta(\nu, \bar{\nu}) n(\bar{\nu}, t) d\bar{\nu} \quad (3)$$

to obtain the number concentration of the particles from nucleation, condensation, coagulation, and decoagulation. Where n is the number concentration, t is the time, J is the nucleation

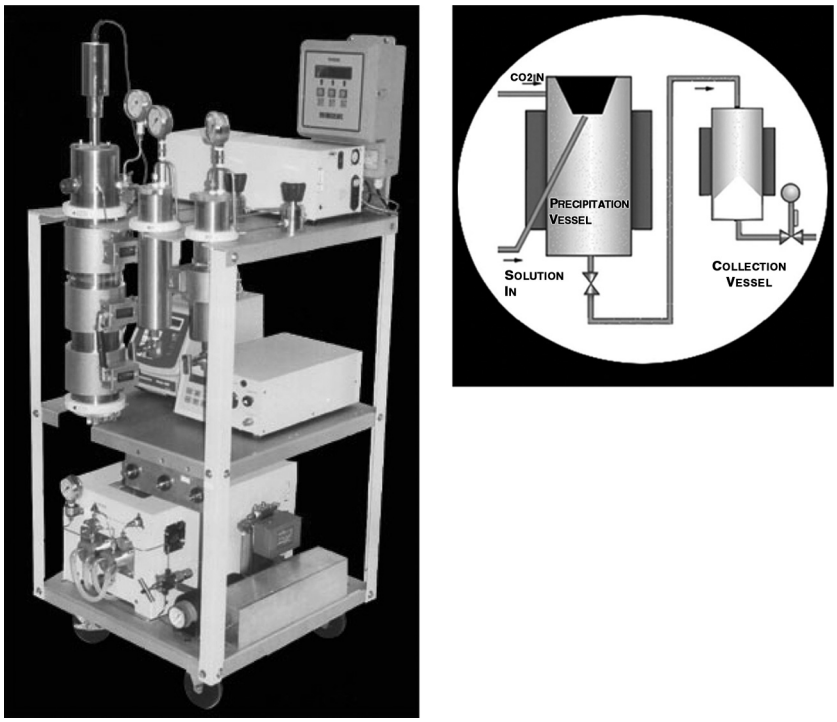

Figure 16 SAS–EM commercial unit by Thar Technologies, Inc. *Abbreviation*: SAS–EM, supercritical antisolvent with enhanced mass transfer.

rate, δ is the delta function, v is the nanoparticle volume, G_g is the condensation rate, and β is the coagulation function.

Nucleation rate, J, is obtained from supersaturation (51)

$$J = 2N_2 \frac{Py_2}{\sqrt{2\pi m_2 kTL^{-1}}} \sqrt{\frac{\sigma\left(v_2^s\right)^2}{kT}} \exp\left\{ -\frac{16\pi}{3} \left(\frac{\sigma\left(v_2^s\right)^{2/3}}{kT} \right)^3 \times \left[\frac{1}{\ln S - Ky_2^{eq}(S-1)} \right]^2 \right\} \tag{4}$$

where y_2 is the actual drug mole fraction in CO_2 phase; y_2^{eq} is the equilibrium drug mole fraction over a flat surface (i.e., solubility); S is the supersaturation ratio, y_2/y_2^{eq}; k is the

Boltzmann constant; N_2 is the number concentration of the solute in the fluid phase; and P is the pressure. The equilibrium solubility can be obtained from Equation (1) as discussed earlier. It will be a function of pressure, temperature, and cosolvent if present.

Particles grow by the condensation of solute from the fluid phase onto the particle surface. The net rate of a single molecule condensation onto a spherical particle is given by (52),

$$G_g = G_g = 2\pi d_p D\left[N_2 - N_2^{eq}(g)\right] \tag{5}$$

where d_p is the diameter of spherical particles containing g molecules and D is the diffusion coefficient for the solute molecule in the fluid phase.

The particle size and concentration can also change by coagulation and decoagulation. For coagulation of two particles (1 and 2), rate of coagulation (J') can be expressed as (53)

$$J' = K_{12}N_1N_2 \tag{6}$$

where N_1 and N_2 are the number concentrations of the coagulating particles and K_{12} is the effective coagulation coefficient given as

$$K_{12} = \left[\frac{2kT}{3\mu}\frac{\left(D_{p1}+D_{p2}\right)^2}{D_{p1}D_{p2}}\right] + \left[\frac{du}{dy}\frac{\left(D_{p1}+D_{p2}\right)^3}{6}\right] + \left[\left(\frac{\pi\varepsilon_k}{120v}\right)^{1/2}\left(D_{p1}+D_{p2}\right)^3\right] \tag{7}$$

which is the sum of Brownian, laminar shear, and turbulent coefficients. And

$$N_i(r,t) = N_i(0)\left[1 - \frac{D_{p1}+D_{p2}}{2r}erfc\left(\frac{2r-\left(D_{p1}+D_{p2}\right)}{4\sqrt{D_{12}t}}\right)\right] \tag{8}$$

where du/dy is the velocity gradient in the case of laminar flow; ε_k is the rate of dissipation of kinetic energy per unit mass; ν is the kinematic viscosity of the fluid; r is the distance of the particle from the center of the fixed particle; and D_{12} is the effective diffusion coefficient.

OTHER APPLICATIONS OF SCFs FOR PARTICLE ENGINEERING

SCFs can be applied to a variety of other applications where nano- and microdimensions of the drug material in excipient are important for drug release (54). These include the following.

Porous Particles and Polymer Foams

Since a fast removal of dissolved CO_2 can be achieved by rapid depressurization, this behavior can be used to create foams, especially that of poly(lactide–*co*–glycolide) (PLGA) polymer, because CO_2 has a good solubility in this approved polymer. Hile et al. (55) prepared PLGA foam capable of sustained release of basic fibroblast growth factor for tissue engineering applications. To prepare the foam, a water-in-oil microemulsion consisting of an aqueous protein phase (typical reverse micelle domain size of 5–10 nm) and an organic polymer solution was prepared. The microemulsion was filled in molds and then placed in a pressure vessel. Now, the pressure vessel was pressurized with supercritical CO_2, to extract the organic phase, causing the polymer to precipitate onto the protein droplets. Now the vessel is purged with more CO_2 to remove the solvent from the system. Finally, the vessel is depressurized in 10–12 sec causing rapid removal of the CO_2 that was dissolved in the polymer, making a porous foamy structure.

Koushik and Kompella (56) employed an SCF pressure-quench technique to create porous peptide (deslorelin) encapsulating PLGA particles (Fig. 17). On SC CO_2 treatment (1200 psi, 33°C for 30 min) of deslorelin, PLGA particles prepared using emulsion–solvent evaporation, the mean particle size of the deslorelin PLGA microparticles increased from 2.2 to 13.8 μm, the mean porosity increased from 39% to 92.38%, the mean bulk density reduced from 0.7 to 0.082 g/cm^3, mass spectrometry indicated structural integrity of released deslorelin, the circular dichroism spectrum indicated stabilization of β-turn conformation of the peptide, and the scanning elec- F17 AQ4

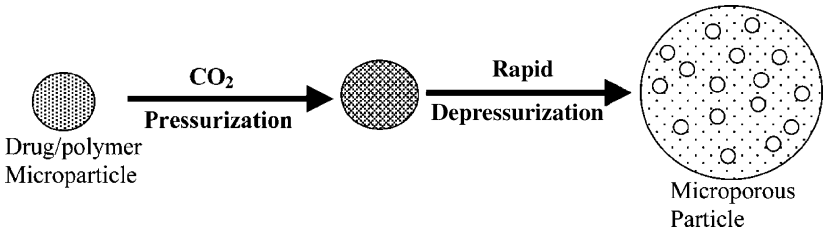

Figure 17 Supercritical-fluid pressure-quench technique to create porous microparticles. *Abbreviation*: CO_2, carbon dioxide. *Source*: From Ref. 56.

tron microscopy confirmed increased particle size and pore formation. Further, the deslorelin release was sustained during the seven-day study period and the residual solvent content was reduced from 4500 ppm to below the detection limit (< 25 ppm).

Liposomes

Liposomes, in which nanodomains of drug are stabilized using lipids, are useful drug carriers for both small and macromolecular drugs. Unfortunately, the conventional methods of making liposomes require large amounts of organic solvents and have difficulty with scale-up for hydrophilic drugs. Lipids actually have some solubility in supercritical CO_2, and this behavior has been used to form liposomes without using organic solvents. For example, Frederekseen et al. (52) dissolved a phospholipid (1-palmitoyl-2-oleoylphosphatidylcholine) and cholesterol in supercritical CO_2 using 7% ethanol cosolvent. The mixture is expanded into an aqueous state containing fluorescein isothiocyanate (FITC)–dextran at low pressure. Because of the sudden reduction in the solubility of the phospholipid and the cholesterol at the nozzle tip, liposome-encapsulating FITC–dextran was formed. The process yielded 200-nm-size liposomes (termed as critical fluid liposomes) with 20% encapsulation efficiency. The main benefit of this process is the significantly reduced use of organic solvent. Later, Castor and Chu (57) prepared liposomes

containing hydrophobic drugs, such as paclitaxel, camptothecins, doxorubicin, vincristine, and cisplatin. These formulations including 150–250-nm paclitaxel liposomes are claimed to be more effective against tumors in animals compared to commercial formulations.

Inclusion Complexes

Inclusion compounds, such as inclusion of poorly water-soluble drugs in cyclodexin, are useful in enhancing bioavailability. Basically, the lipophilic drug is included in the lipophilic interior of the cyclodextrin molecule. The exterior of the cyclodextrin molecule is hydrophilic, and hence the whole complex can be dissolved in water. Inclusion can be achieved when both the drug and the cyclodextrin molecules are in a dissolved state, i.e., have a higher molecular mobility as compared to the solid forms. In conventional technique, both are dissolved in an organic solvent and then the solvent is removed. Unfortunately, the concentration of the residual solvent is high in the final product (58).

Supercritical CO_2 processes allow preparation of drug–cyclodextrin inclusion complexes without the use of organic solvents. This is because the interaction of supercritical CO_2 with solid cyclodextrin makes the cyclodextrin molecules more fluid. This interesting plasticizing effect of supercritical CO_2 has been well known for organic polymers, for which the glass transition or melting can be achieved at a lower temperature with SC CO_2. To make inclusion compounds, the physical solid mixture of the drug and cyclodextrin is exposed to supercritical CO_2, and then rapidly CO_2 is removed by depressurization.

Bandi et al. (59) prepared budesonide and indomethacin hydroxypropyl–cyclodextrin (HPBCD) complexes using an organic solvent-free SCF process (59,60). The process involved the exposure of drug–HPBCD mixtures to supercritical carbon dioxide. The ability of the SCF process to form complexes was assessed by determining drug dissolution using a high-performance liquid chromatography assay, crystallinity using powder x-ray diffraction (PXRD) and differential scanning

calorimetry, and drug–excipient interactions using Fourier transform infrared spectroscopy (FTIR). The SC CO_2 process did not alter the dissolution rate of pure drugs but resulted in two- and threefold higher dissolution rates for budesonide and indomethacin–HPBCD mixtures, respectively. SCF-processed mixtures exhibited a disappearance of the crystalline peaks of the drugs (PXRD), a partial or a complete absence of the melting endotherm of the drugs (DSC), and a shift in the C=O stretching of the carboxyl groups of the drugs (FTIR), consistent with the loss of drug crystallinity and the formation of intermolecular bonds with HPBCD. Thus, budesonide and indomethacin–HPBCD complexes with an enhanced dissolution rate can be formed using a single-step, organic solvent-free SC CO_2 process. Similar inclusion complexes were also reported for piroxicam using a supercritical CO_2 process (61).

Solid Dispersions

In many delivery applications, molecularly intimate mixtures (i.e., solid dispersion) of drug with excipients, such polymers are needed. An organic solvent, which can dissolve both, does bring the two in intimate contact while in solution. Unfortunately, when the solvent is removed by evaporation or by addition of a liquid antisolvent, the drug and the polymer phases precipitate out or separate. Hence, the dispersion of the two is poor in the solid state. Supercritical CO_2 antisolvent induces the precipitation about 100-fold faster than the liquid antisolvent, not allowing enough time for the drug and the polymer domains to separate out. Thus, supercritical CO_2 precipitation can provide a more dispersed solid mixture. Supercritical CO_2-based precipitation is superior to the liquid-based precipitation or the milling process. For example, a solid dispersion of carbamazepine in polyethyleneglycol (PEG)-4000, produced by CO_2 method, increased the rate and the extent of dissolution of carbamazepine (62). In this method, a solution of carbamazepine and PEG4000 in acetone was loaded in a pressure vessel, in which supercritical CO_2 was added from the bottom to obtain solvent-free particles.

SAFETY AND HEALTH ISSUES

When dealing with supercritical carbon dioxide, there are two safety and health issues that are to be kept in mind when designing and operating the extractor: (i) the high pressure involved requires that personnel is protected from the plant by proper isolating walls and (ii) if carbon dioxide is released in the closed atmosphere it can lead to asphyxiation, as it can replace the oxygen in the surroundings.

CONCLUSIONS

For particle formation, SCF technology offers two processes: (i) RESS for drugs that are soluble in supercritical CO_2 and (ii) SAS for drugs that are poorly soluble in supercritical CO_2. In RESS, a sudden change in the fluid pressure causes rapid precipitation, whereas in SAS the sudden diffusion of CO_2 into a drug solution causes drug precipitation. Conventionally, both the technologies have produced microparticles in the 1–5-μm-size range. With enhancement in mixing, SAS-EM process produces nanoparticles of controllable size. With the reduction in particle coagulation, the RESS–SC process produces nanoparticles with a high yield. The RESS–SC equipment is expected to be cheaper than SAS–EM, because the residence time of the drug in the high-pressure chamber is lower in the former. The particle formation techniques can also be employed for the preparation of liposomes and solid dispersions of drugs and solubility enhancing carriers. In addition, SCF exposure or pressure-quench techniques can be employed to form porous structures or inclusion complexes and to remove residual solvents in pharmaceutical particulate systems.

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