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Review Article

Rapid expansion from supercritical solutions: application to pharmaceutical processes

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Introduction

Although supercritical fluid (SCF) technology has been successfully applied on a large scale in the food and petroleum industries (ie. the decaffeination of coffee beans, the polymerization of polyethylenes and the fractionation of petroleum products), its potential in the pharmaceutical industry has yet to be realized (Larson and King, 1986). This paper describes the precipitation of material using supercritical fluid technology and relates this technique to filling a specific pharmaceutical processing need. Rapid expansion from supercritical solutions (RESS) will be reviewed as a possible technique for producing very small and monodisperse crystalline drug for incorporation into pulmonary delivery devices. The nonideality of the current milling techniques and the potential advantages and shortcomings of RESS is discussed.

Drug is delivered to the pulmonary region either in solid or solution form. The solid is delivered either from a suspension type metered dose inhaler (MDI), or as a powder from a dry powder inhaler. In both cases, the very small particle size of the solid material is critical to ensure delivery of a sufficient amount of material to the lung (respirable dose). Jet milling (micronizing) is used to produce particles with sizes targeted to 2–3 μm with the majority of drug less than 10 μm. However, this process tends to produce very high internal temperatures that may adversely affect the polymorphic form of a crystalline material, change its percent crystallinity and produces particles that are log-normally distributed.

A log-normal particle size distribution is often characterized by a median diameter and geometric standard deviation, σ_g, which is a measure of the degree of dispersity of the material. The range of particle sizes in a distribution increases with σ_g. In practice, it is difficult to reproduce the size and size distribution of micronized material and the collection efficiency of this process is poor. In respiratory drug delivery, changes in the median size or degree or dispersity of the micronized material may result in unacceptable variations of the respirable dose and, in some cases, may even predispose the suspension formulation to physical instability, rendering the formulation therapeutically ineffective. Ideally, the pulmonary delivery scientist would like a technique that efficiently and reproducibly generates small

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particles with a very narrow degree of dispersity, $\sigma_g < 2$. Rapid expansion from supercritical solutions may fulfil this need.

What are Supercritical Fluids?

For every solvent there exists a temperature, its critical temperature (T_c), above which no applied pressure can force the solvent into its liquid phase. Above its T_c and corresponding critical pressure, P_c, the solvent is in its supercritical state and is described as a supercritical fluid (SCF). SCFs are highly compressible in the range of 1.0–1.2 T_c, have densities that are liquid-like and transport properties that are gas-like. Small changes in the temperature or pressure near the critical point results in large changes in the fluid's density and, hence, its solubilizing power. Table 1 lists some common SCFs and their corresponding critical temperatures. Carbon dioxide (CO_2) is by far the most common SCF because it is nontoxic, nonflammable, inexpensive, 'generally recognized as safe' and has a fairly low critical temperature making it attractive for use with heat labile solutes. For an excellent introduction to the properties of supercritical fluids the reader is encouraged to consult the book by McHugh and Krukonis (1986).

TABLE 1

Critical conditions for some supercritical solvents

Solvent	Critical temperature T_c (°C)	Critical pressure P_c (psi)
Ethylene	9.3	730
Carbon dioxide	31.1	1070
Ethane	32.3	709
Nitrous oxide	36.5	1050
Propyelene	91.9	670
CFC-22 [a]	96.0	725
CFC-11 [b]	198.1	640
CFC-12 [c]	111.7	579
CFC-114 [d]	146.1	522
Ammonia	132.3	1636
Water	374.2	3200

[a] CFC-22, chloro-difluoromethane.
[b] CFC-11, trichloro-monofluoromethane.
[c] CFC-12, dichloro-difluoromethane.
[d] CFC-114, dichloro-tetrafluoromethane.

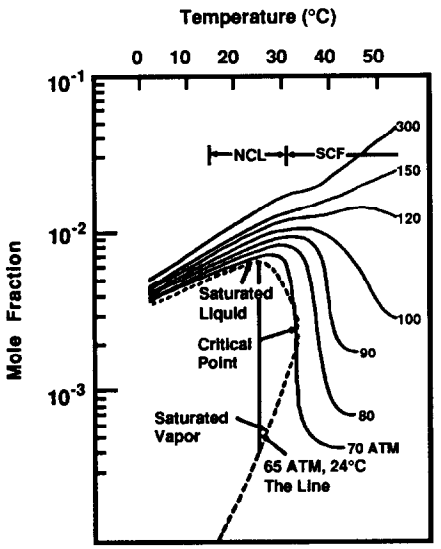

Fig. 1. Solubility of naphthalene in supercritical carbon dioxide. Adapted from McHugh and Krukonis (1986).

The most attractive features of SCFs are enhanced solubilizing powers compared to regular gases, sensitivity to small changes in either temperature or pressures and fairly mild operating conditions. The solubility of naphthalene in supercritical (SC) CO_2 (Fig. 1) demonstrates these features quite nicely. Near the critical point (T_c 31°C, P_c 70 atm), the solubility of naphthalene is 0.0027 mole fraction. When the pressure is increased to 80 atm, at constant temperature, the solubility is increased to 0.008, reflecting the increased density of the SCF. However, a temperature increase from 31 to 35°C, at a constant pressure of 70 atm, results in a naphthalene solubility decrease from 0.0027 to 0.0006. As the temperature is increased at constant pressure, the frequency of collisions of the CO_2 molecules is increased and the density of the fluid is decreased. This phenomenon, decreased solubility with increasing temperature, is known as retrograde solubility (Tom and Debenedetti, 1991a). A mechanistic interpretation of this phenomenon is discussed by Debenedetti and Kumar (1988). However, at pressures greater than 120 atm, the solubility of naphthalene does increase with tem-

perature. While a decrease in the SCF density still occurs, this is offset by the contribution of the solute's own sublimation pressure. Although each compound has its own unique solubility-temperature profile, the same general trend is observed for crystalline solids as seen with naphthalene. Naphthalene solubility in SC ethylene was estimated to be 16 000 times greater than its calculated solubility in ethylene acting as an ideal gas (McHugh and Krukonis, 1986). The enhanced solubility of materials in SCFs is attributed to the highly compressible, nonideal behavior of the fluid.

The nonreactive nature of CO_2 has resulted in few reports of chemical interaction between SC CO_2 and the extracted material. A notable exception is the reaction between SC CO_2 and β-carotene (Chang and Randolph, 1989). Some proteins and peptides were denatured in humid SC CO_2 but water and heat were the responsible agents (Weder, 1984). Indeed, many researchers are experimenting with SC CO_2 as a medium for biochemical reactions (Chi et al., 1988; Erickson et al., 1990; Nakamura, 1990; Steytler et al., 1991).

Rapid Expansion from Supercritical Solutions (RESS)

The potential to precipitate materials from SCFs was recognized as early as 1879 by Hannay and Hogarth; however, until recently the use of SCFs has focused largely on extraction. The precipitation of materials from SCFs was reported in the 1980's by Krukonis who termed the process 'supercritical fluid nucleation'. The U.S. patent for RESS was awarded in 1986 (Smith, 1986). Scientists at Batelle Research Labs have extensively studied RESS for the preparation of inorganic films and microfine ceramic powders (Petersen et al., 1986; Matson et al., 1989, 1987). Research has extended to include the preparation of polymeric films (Krukonis, 1985), fibers (Petersen et al., 1987; Lele and Shine, 1992), microspheres (Tom and Debenedett, 1991a,b) and the recrystallization of many organic materials (Loth and Hemgesberg, 1986; Mohamed et al., 1989a,b; Tavana and Randolph, 1989; Ohgaki et al., 1990).

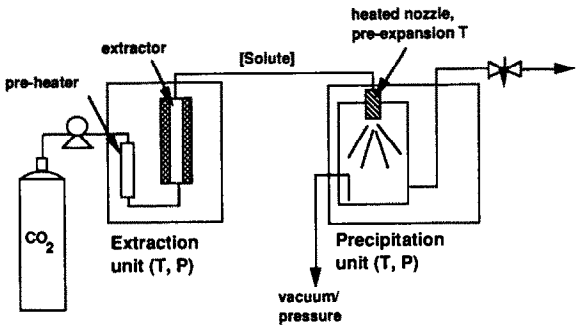

Fig. 2. Generic schematic of RESS system. The concentration of solute entering the precipitation unit is a function of extraction unit temperature and pressure.

Fig. 2 depicts a simplified, generic RESS system. The solid material to be reprecipitated is incorporated into an extraction vessel and the supercritical solvent is charged into the vessel at a particular temperature and pressure via a preheater. The resultant supercritical solution is introduced into the precipitation unit by expansion through a capillary or laser drilled nozzle. This unit is maintained at conditions where the solute has a much lower solubility in the SCF, typically the temperature is the same as that in the extractor but the pressure is reduced. During expansion, (decompression) the density and solubilizing power of the SCF decreases dramatically. This leads to high degrees of solute supersaturation and subsequent precipitation. Referring again to Fig. 1, if naphthalene were extracted at 150 atm and 35°C and expanded into a chamber maintained at the same temperature but 70 atm then its solubility in SC CO_2 would decrease from 0.012 to 0.0006 mole fraction, and the supersaturation ratio (S^{150}/S^{70}) would approach 20. Because decompression can occur at the speed of sound, the solution becomes almost instantaneously, homogeneously supersaturated and the degree of supersaturation is often much greater than that achieved by thermal perturbations. The combination of large, rapid and uniform supersaturation is the major advantage of RESS and has the potential to produce very uniform particle sizes if traditional nucleation and growth theory is followed. Another attractive feature of RESS is

the potential to recompress and reuse the SC fluid in a continuous process. The morphology and size distribution of the precipitated material is a function of its pre-expansion concentration and expansion conditions, as discussed in more detail below.

Pre-expansion concentration

Appreciable solubility of the material in the SCF is the major criteria for the use of RESS. The amount of material extracted into the SCF will depend on: the density and structure of the SCF; the solute chemical structure and, in some cases, the SCF-solute contact time in the extraction unit. Many studies have been conducted to determine and predict (Stahl and Willing, 1980; Kurnik et al., 1981; Kwiatkowski et al., 1984; Schmitt and Reid, 1986a; Smith et al., 1987) the solubility of materials in SCFs. Investigators have correlated solubilities with SC densities (Chrastil, 1982; Kumar and Johnston, 1988; Lemert and Johnston, 1990), thermodynamic relationships (Kurnik et al., 1981; Kurnik and Reid, 1982; Dobbs et al., 1986; Schmitt and Reid 1986a; Neau et al., 1990) and modified solubility parameters (Czubryt, 1970; Allada, 1984; King and Friedrich, 1990).

Table 2 lists the solubility of naphthalene and some relevant compounds in SCFs. As a general rule, low molecular weight hydrocarbons and

TABLE 2

Solubilities of some pharmaceutically relevant compounds in SCFs

Solute	SC solvent	Solubility (% w/w)	Extraction conditions (°C, psi) [b]	Cosolvent	Reference [a]
Naphthalene	CO_2	7.4	45, 3200	–	Mohamed, 1989a
		16.3	55, 5200	–	Mohamed, 1989a
Mevinolin	CO_2	0.04	40, 5500	–	Mohamed, 1989b
		0.45	40, 5500	5% MeOH [c]	Larson, 1986
Imipenem	CO_2	0	40, 5000	H_2O, MeOH	Larson, 1986
Efrotomycin	CO_2	0.03	40, 5000	–	Larson, 1986
Steroid [d]	CO_2	5.9	not specified	3% MeOH	Larson, 1986
Griseofulvin	CO_2	0.012	50, 3500	–	Sugiyama, 1985
Digoxin	CO_2	0.003	50, 3500	–	Sugiyama, 1985
β-Carotene	ethylene	0.17	50, 5500	–	Chang, 1989
		0.23	70, 5500	–	Chang, 1989
Testosterone	CO_2	0.09	45, 5150	–	Coffey, 1988
		0.11	95, 5150	–	Coffey, 1988
Progesterone	CO_2	0.50	45, 4400	–	Coffey, 1988
		1.10	95, 4400	–	Coffey, 1988
L-PLA [e]	CO_2	0.0427	45, 4350	–	Tom, 1991b
		0.0738	65, 4350	–	Tom, 1991b
		0.157	45, 4350	1% acetone	Tom, 1991b
		0.368	65, 4350	1% acetone	Tom, 1991b
Sitosterol	CO_2	0.65 [f]	60, 12300	–	Stahl, 1980
Codeine	CO_2	0.09 [f]	40, 1160	–	Stahl, 1980
Coumarin	CO_2	0.74 [f]	40, 1470	–	King, 1990
Salicylic acid	CO_2	0.045 [f]	40, 1470	–	King, 1990
Cholesterol	CO_2	0.334	60, 3970	–	Wong, 1986
		0.376	60, 3970	MeOH	Wong, 1986

[a] First author of reference cited.

[b] Pressure values were converted from various units and rounded off to the nearest 10 psi (14.7 psi = 1 atm).

[c] MeOH, methanol.

[d] Merck compound L-636-028 (Larson and King, 1986).

[e] Poly(L-lactic acid) M_W = 5500 (Tom and Debenedetti, 1991b).

[f] Values were estimated from graphs.

lipophilic organics, such as esters, ethers, lactones are easily extracted up to 4500 lb/inch^2 (psi; 1 atm = 14.7 psi). However, the presence of polar groups, such as hydroxyl or carboxyl functionalities on the molecule, reduces their solubility. In a preliminary investigation into the use of RESS for the production of small particle sizes, Coffey and Krukonis (1988) examined the solubility of testosterone and progesterone in SC CO_2 and chlorodifluoromethane (CFC-22). Progesterone was approx. 5 times more soluble in SC CO_2 than testosterone (Table 2). The hydroxyl group in the 17 position of the testosterone molecule facilitates intermolecular hydrogen bonding and therefore decreases the solubilizing power of CO_2. Progesterone is without the hydroxy group and thus has a much higher solubility in CO_2, 0.5% w/w at 45°C at 4400 psi. With a slightly more polar SC solvent, CFC-22, testosterone solubility approached 16% w/w at 45°C and 4400 psi.

Researchers have met with limited success in extracting sugars, amino acids (imipenem, Table 2) and glycosides using pure SCFs. The use of cosolvents to enhance the solubility of materials in SCFs (Dobbs et al., 1986, 1987a,b; Schmitt and Reid, 1986b; Tavana et al., 1989; Lemert and Johnston 1991) has been investigated. For comparison, the solubility of some materials in the presence of cosolvents is included in Table 2. While solubility enhancement with cosolvents may make a process feasible (Cygnarowicz and Seider, 1990), the presence of a cosolvent complicates the phase behavior of the system and makes predictions of solubility much more complex. The cosolvent may also react or complex with the extracted solute. Tavanna et al. (1989a) proposed a screening method to determine the best cosolvent for solubility enhancement; however, the choice of cosolvent for pharmaceutical compounds is severely limited when its regulatory acceptability is considered. Furthermore, the presence of nonvolatile cosolvents will effect the expansion behavior of the SC solution and subsequent precipitation of the solute. For example, the concentration of mevinolin in SC CO_2 was increased by an order of magnitude with the addition of 5% methanol as a cosolvent and the resultant precipitated material had particle sizes ranging from 10 to 50 μm (Larson and King, 1986). However, further research (Mohamed et al., 1989a) indicated that the precipitated mevinolin dissolved and recrystallized in the methanol, which had condensed upon expansion. The absence of cosolvent decreased the solution concentration, but precipitated particle sizes were much smaller, of the order 0.1–1 μm. Thus, while cosolvents may enhance the RESS process by increasing solution concentrations, they can also adversely effect morphology and crystal size.

The effect of pre-expansion concentration on final crystal size distribution is demonstrated in the precipitation of naphthalene from SC CO_2. Naphthalene is the compound of choice for the study of RESS because a wealth of empirical data exists on its solubility in various SC solvents and it has appreciable solubility in SC CO_2. When extraction conditions were adjusted to increase the concentration of naphthalene (from 7.4 to 16.3% w/w), holding all other operating variables constant, the crystal size decreased from 30–135 to 4–38 μm. These results were in good agreement with classic nucleation and crystal growth theory. Both nucleation and growth are thought to be dependent upon the degree of supersaturation, increase supersaturation and increase the rate of nucleation. When many nuclei are formed there is less material remaining in solution to precipitate on the existing nuclei and although the number of crystals is many, their size is small.

Expansion conditions

While the formation of monodisperse aerosols by vapor condensation in nozzles is well understood (Pratsinis, 1988; Turner et al., 1988), the expansion behavior of SCFs has, as yet, only been described in a qualitative fashion. In RESS, nucleation and crystal growth take place in a highly compressible medium which has physical properties (density and viscosity) intermediate between liquids and gases.

Supercritical solutions expand in the precipitation unit via capillary nozzles or laser drilled orifices. Orifice diameters range from 25 to 150 μm and the length of the nozzle is as short as possible to prevent pressure drops. The nozzle is maintained at a pre-expansion temperature to

prevent condensation to the liquid phase and/or premature precipitation of the solute. As the SC solution exits the nozzle, the jet temperature drops as the fluid expands. Expansion occurs on a time scale of 10^{-8}–10^{-5} s, facilitating very rapid and homogeneous nucleation. The molecules at the leading edge of the expanding fluid collide with background gases causing the formation of a shock front known as thc Mach disk. Within this region, molecular collisions heat and break up any small solvent clusters that may have formed.

The pre-expansion temperature and pressure, the precipitation pressure and the orifice dimensions influence the expansion characteristics, which in turn, define the nucleation mechanism. If solvent droplet formation is avoided, solute nucleation may be homogeneous and will result in formation of fine powders. Observation of pure SCFs escaping from capillary nozzles indicated (Petersen et al., 1987) the formation of a single gaseous phase when the temperature of the nozzle was maintained at a reduced temperature of approx. 1.3 (a reduced value equals the ratio of experimental value to critical value, i.e., $T_r = T/T_c$). However, a SC CO_2 solution containing 5% methanol as a cosolvent was observed to produce liquid solvent droplets at pre-expansion temperatures as high as 70°C ($T_r = 70/31 = 2.3$). Mohamed and colleagues (1989a,b) studied the effect of expansion conditions on the resultant crystal size of naphthalene and mevinolin. At moderate naphthalene solution concentrations (7.4%), a decrease in the pre-expansion temperature from 170 to 110°C reduced particle size; however, this effect was not observed at higher (16.4%) naphthalene solution concentrations. A decrease in the post expansion temperature (the temperature in the precipitation unit) was accompanied by a reduction in particle size, again probably because of greater supersaturation ratios.

The effect of changing the post-expansion pressure (the pressure in the recrystallizer) on crystal size is less conclusive. An increase in the post expansion pressure resulted in a decrease of naphthalene crystal size. The authors suggested that the decrease in supersaturation ratio (due to the smaller pressure differential) was offset by the increase in nucleation rate due to the increase in the solute's partial pressure. Similar results were observed (Tavana and Randolph, 1989b) in the batch recrystallization of benzoic acid precipitated from SC CO_2. The surface areas of particles expanded to ambient and sub-critical pressures were compared. Because they were equivalent, suggesting similar particle sizes, it was concluded that expansion below the critical pressure was not necessary for the production of small particles. However, it remains to be seen if these findings are also true for compounds with lower sublimation pressures than naphthalene and benzoic acid. The potential benefit of expanding solutions into higher pressure environments is a decrease in recompression costs for the reusable SC solvent. With this in mind, Debenedetti (1990) predicted the nucleation profiles, based on classic nucleation and growth theory, for various expansion pathways. He concluded that nucleation profiles would be shallow because of the competing effects between large supersaturation ratios and decreased solute concentration and fluid temperature due to expansion. However, he indicated that a significant portion of the maximum nucleation rate could be achieved by expanding into an above-ambient pressure environment.

Expansion conditions effect crystal size as well as morphology and crystal habit. Ohgaki et al. (1990) precipitated fine, amorphous stigmasterol particles under low pre-expansion pressures, but whisker-like crystals were obtained under high pre-expansion pressures. Petersen et al. (1987) precipitated polystyrene, cellulose acetate and polypropylene from SC pentane solutions. Fibers were formed when the pre-expansion temperature was near the melting point of the polymers (T_m) while particles were formed at temperatures above and below the polymer melting points. When the expansion temperature was below T_m, particle formation followed traditional nucleation and growth theory, while at $T > T_m$ liquid polymer droplets formed which quickly solidified within the recrystallization unit. Lele and Shine (1992) also observed the transition from powder to fiber formation with a decrease in pre-expansion temperature for polymethyl methacrylate (PMMA), polycaprolactone, and a styrene/methyl methacrylate block copolymer. However, they dis-

agreed with the proposed correlation of polymer melting point and fiber formation because PMMA fibers were formed from 110°C pre-expansion temperatures eventhough amorphous PMMA has no melting point. Alterations in pre-expansion pressure, solute concentration and orifice diameter also affected polymer morphology for all three of these polymers. Poly(L-lactic acid) (L-PLA) precipitated from SC CO_2 (Tom and Debenedetti, 1991b) displayed various morphologies as a function of processing time, presence of cosolvent, pre-expansion temperature and crystallizer temperature.

RESS of pharmaceuticals and polymers

Pharmaceutical compounds that appear particularly well suited for RESS are the steroids. Steroids are frequently used as first line therapy for asthma, but their polymorphic form and degree of crystallinity may be altered during the milling process (Tuladhar, 1983; Otsuka, 1986). RESS may overcome this problem and the fairly simple structure of many steroid compounds indicates they can be solubilized to an appreciable degree in CO_2. Progesterone and testosterone crystals precipitated from SC CO_2 to ambient conditions had 2–5 μm particle sizes with an apparently narrow size range, as determined by optical microscopy (Coffey and Krukonis, 1988). A cursory examination of the effect of post-expansion pressure on the resultant crystal size was performed but because of the preliminary nature of the work, no strong conclusions were drawn except to recognize that operating conditions did effect final crystal size. Steroid crystals having an upper size of 5 μm would be acceptable for inclusion in a pulmonary delivery device, however a thorough particle size analysis of material produce by RESS has yet to be performed. Larson and King (1986) precipitated a steroidal compound (Merck identifier, L-636–028) with approximately the same size distribution as material obtained by conventional milling. X-ray diffraction patterns before and after RESS indicated retention of crystalline structure; however, variations in the intensity of the patterns suggested some amorphous content.

Other pharmaceutical compounds precipitated by RESS include phenacetin, β-estradiol, mevinolin and β-carotene. Loth and Hemgesberg compared the physical properties and aqueous dissolution properties of phenacetin micronized by jet milling and RESS techniques. Similar melting points, thermograms and dissolution kinetics were observed between the two lots of material, despite obvious differences in the physical appearance and specific surface area between the jet milled and RESS precipitated material. Coffey and Krukonis (1991) reported the production of submicron to micron size β-estradiol particles by expanding the SC CO_2 solution from 50°C and 5000 psi to ambient conditions. The size of the bulk material was up to 100 μm acicular crystals. RESS precipitated mevinolin and β-carotene particles were highly aggregated. Mevinolin crystal size was less sensitive to changes in operating conditions than naphthalene (Mohamed et al., 1989b) but the precipitated drug formed aggregates with elementary units of 0.1–1 μm. The aggregated powder was sonicated in heptane to reveal particle sizes of approx. 0.1–0.3 μm. Similarly, β-carotene precipitated from SC ethylene at atmospheric conditions produced aggregated particles whose mean size was determined to be 1.0 μm after sonication in a nonsolvent (Chang and Randolph, 1989). When the β-carotene/SC ethylene solution was expanded into a 10% aqueous/gelatin solution the resultant mean size was 0.3 μm. However, the use of a dispersing medium and/or a deaggregating step would negate the attractiveness of the RESS process. Further work should focus on why some crystalline compounds precipitate as strongly aggregated material and why the resultant particle size of other crystalline material is less sensitive to changes in operating conditions.

The RESS of polymers may be of particular interest to pharmaceutical scientists since polymers are used in tablet coating, capsule formation, as emulsifying agents and as matrices in controlled delivery devices. Polymers have very large molecular weights compared to simple organic molecules and many have molecular weight distributions. These large molecular weight molecules have virtually no vapor pressure and

do not readily dissolve in SC CO_2. Poly(methylmethacrylate), polycaprolactones and cellulose acetate were not soluble in SC CO_2 but did dissolve in CFC-22 (Lele and Shine, 1992). However, the phasing out of chlorofluorocarbons by 1996 eliminates their viability as SC solvents. Although many other processes involving extraction and fractionation of polymers use SC ethylene, or SC propylene, these are not acceptable for pharmaceutical polymers because of residual solvent impurity and toxicity concerns.

There are, however, a few reports of RESS success with pharmaceutical polymers. Mueller and Fischer (1989) patented a process that precipitated drug containing microspheres of poly-(DL-lactic acid) (DL-PLA) from an organic solvent using countercurrent flow of SC CO_2. Tom and Debenedetti (1991b) took this process one step further by eliminating the organic solvent and precipitating L-PLA, DL-PLA and poly(glycolic acid) (PGA) from supercritical CO_2 solutions. They performed solubility experiments as a function of CO_2 addition and found that the lower molecular weight portions of all three polymers preferentially dissolved. Subsequently, the molecular weight of the precipitated product was less than the commercial material. Precipitated L-PLA polymer had a higher glass transition temperature and lower melting point than the starting material. While the results were reproducible, the complexity of RESS of polymers is demonstrated by the fact that three very different precipitates were produced from L-PLA alone. At present, researchers cannot easily predict what polymer morphology will be produced for a given set of extraction and expansion conditions.

A complementary technique to RESS may prove more feasible for the precipitation of polymers. Gas-anti solvent recrystallization is discussed in a subsequent paper for the production of polymeric microspheres for controlled drug delivery. Briefly, polymer is precipitated from an organic solution that is expanded using carbon dioxide as an anti-solvent. The expanded solvent has a decreased solubilizing capacity forcing the precipitation of the dissolved solute. The insoluble nature of polymers ensures that preferential dissolution in the gas phase will not occur. This technique is potentially advantageous over current microsphere preparation techniques because it uses fewer organic solvents, has the potential to recycle many components and is, therefore, more environmentally acceptable.

Conclusions

While the concept of RESS is fairly straightforward, application to commercial processes requires a thorough understanding of the nonideal behavior of the expanding SCF, and the operating variables that affect the rates of nucleation and crystal growth as well as the physical form of the material. The criteria of appreciable solubility in SC CO_2 will eliminate several pharmaceutical compounds from RESS consideration. For those materials with sufficient solubility in SC CO_2 (i.e., steroids and other low molecular weight hydrophobic compounds), the effect of operating conditions on resultant size, morphology and crystal habit must be thoroughly investigated. The small size, narrow degree of dispersity and apparent retention of crystalline structure for two model steroids supports the further investigation of RESS as a replacement technique for jet milling. Only very low molecular weight, simple polymers will sufficiently dissolve in SC CO_2. The resultant size and morphology of RESS precipitated polymers is less predictable.

Acknowledgements

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