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Review

Design and process aspects of laboratory scale SCF particle formation systems

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Abstract

Consistent production of solid drug materials of desired particle and crystallographic morphologies under cGMP conditions is a frequent challenge to pharmaceutical researchers. Supercritical fluid (SCF) technology gained significant attention in pharmaceutical research by not only showing a promise in this regard but also accommodating the principles of green chemistry. Given that this technology attained commercialization in coffee decaffeination and in the extraction of hops and other essential oils, a majority of the off-the-shelf SCF instrumentation is designed for extraction purposes. Only a selective few vendors appear to be in the early stages of manufacturing equipment designed for particle formation. The scarcity of information on the design and process engineering of laboratory scale equipment is recognized as a significant shortcoming to the technological progress. The purpose of this article is therefore to provide the information and resources necessary for startup research involving particle formation using supercritical fluids. The various stages of particle formation by supercritical fluid processing can be broadly classified into delivery, reaction, pre-expansion, expansion and collection. The importance of each of these processes in tailoring the particle morphology is discussed in this article along with presenting various alternatives to perform these operations.

Keywords: Supercritical fluid equipment; SCF; Particle formation; Design; Vendors

Contents

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1. Introduction

The central role of solvents in the processing of pharmaceutical materials is widely accepted since the origin of modern pharmaceutical processing. It is only in the recent past that the adverse effects of the residual solvents from both processing and environmental standpoints have been recognized. Strict regulations on the use of organic solvents and their residual level in the end products form a major limitation to the traditional processing techniques. In an effort to reduce the use of volatile organics, search for alternative techniques of material processing developed as a new facet to pharmaceutical research. Supercritical fluid (SCF) technology is an outcome of such research with particular emphasis in the green synthesis and particle formation. Particle formation using supercritical fluids involves minimal or no use of organic solvents, while the processing conditions are relatively mild. In contrast to the conventional particle formation methods, where a larger particle is originally formed and then comminuted to the desired size, SCF technology involves growing the particles in a controlled fashion to attain the desired morphology. The adverse effects originating from the energy imparted to the system to bring about size reduction can thus be circumvented. Typical among the adverse events are the formation of non-crystalline domains, phase changes in the physical form, high surface energy and static charge and occasional chemical degradation. Growing particles from a solution in a controlled fashion, on the other hand, means that the rigid solid particle, once formed, does not have to undergo the thermal and mechanical stresses. This feature makes supercritical fluid technology amenable to produce biomolecules and other sensitive compounds in their native pure state.

Growing demands on the particle and crystalline morphologies of pharmaceutical actives and excipients, coupled with the limitations of current methods, brought wide attention to SCF technology (York, 1999). The technology is rapidly evolving, as reflected by the number of modified processes reported since its inception. These include static supercritical fluid process (SSF) (Lindsay and Omilinsky, 1992), rapid expansion of supercritical solutions (RESS) (Matson et al., 1987), particles from gas-saturated solutions (PGSS) (Weidner et al., 1995), gas antisolvent process (GAS) (Gallagher et al., 1989), precipitation from compressed antisolvent (PCA) (Bodmeier et al., 1995), aerosol solvent extraction system (ASES) (Bleich et al., 1993), supercritical antisolvent process (SAS) (Bertucco et al., 1996), solution enhanced dispersion by supercritical fluids (SEDS) (York and Hanna, 1995) and supercritical antisolvent process with enhanced mass transfer (SAS-EM) (Gupta and Chattopadhyay, 2001). Refer Table 1 and Fig. 1 to distinguish various processes and to identify the critical attributes controlling the particle morphology. Adaptations to the above generic processes also exist, among which the notable ones are ferro micron mix (Mandel, 2002), carbon dioxide-assisted aerosolization (Sellers et al., 2001, polymer liquefaction using supercritical solvation

Table 1
Distinguishing various supercritical fluid processes

Process	Acronym	Solute (x1)	Solvent (x2)	Antisolvent (AS)
Rapid expansion of supercritical solutions	RESS	Drug or drug mixture	Pure or modified SCF	Absent
Particles from gas-saturated solutions	PGSS	Compressed gas/SCF	Melt of drug/drug mix	Absent
Gas antisolvent system	GAS	Drug or drug mixture	Liquid organic solvent	SCF/compressed gas
Precipitation using compressed antisolvent	PCA	Drug or drug mixture	Liquid organic solvent	SCF/compressed gas
Aerosol solvent extraction system	ASES	Drug or drug mixture	Liquid organic solvent	SCF/compressed gas
Supercritical antisolvent system	SAS	Drug or drug mixture	Liquid organic solvent	SCF
Solution enhanced dispersion by supercritical fluids	SEDS	Drug or drug mixture	Organic solvent with/without water	SCF
Supercritical antisolvent system with enhanced mass transfer	SAS-EM	Drug or drug mixture	Liquid organic solvent	SCF

Method		Mechanism of particle precipitation	Factors affecting particle morphology
RESS	Solution of x1 + x2 rapidly expanded	Loss of SCF solvent power after rapid evaporation	T, P of extraction, pre-expansion, collection; geometry of spray device and collection vessel
PGSS	Solution/dipserion of x1 + x2 rapidly expanded	Phase change in x1 + Joule–Thompson cooling	T, P of Rxn, pre-expansion, collection; geometry of spray device and collection vessel
GAS	AS bubbled through solution of x1 + x2	Volumetric expansion of solvent by gas	Choice of x2; rate and extent of as addition; T, P, geometry of Rxn vessel
PCA	x1 + x2 sprayed into AS (batch) or x1 + x2 and AS sprayed in co/counter-current modes into Rxn vessel (continuous)	Extraction of x2 by AS + x2 evaporation into AS	Choice of x2; relative rates of addition of x1 + x2 and AS; T, P, geometry of Rxn vessel
SEDS	x1 + x2 and AS flowed through coaxial nozzle	Dispersion of x1 + x2 by AS + extraction of x2 by AS + x2 evaporation into AS	Choice of x2; relative flow rates of x1 + x2 and AS; geometry of co-axial nozzle; T, P of Rxn Vessel
SAS-EM	x1 + x2 atomized into AS using a vibrating surface	Atomization of x1 + x2 by vibrating surface + extraction of x2 by AS + x2 evaporation into AS	Choice of x2; Amplitude of vibrating surface; T, P of Rxn vessel

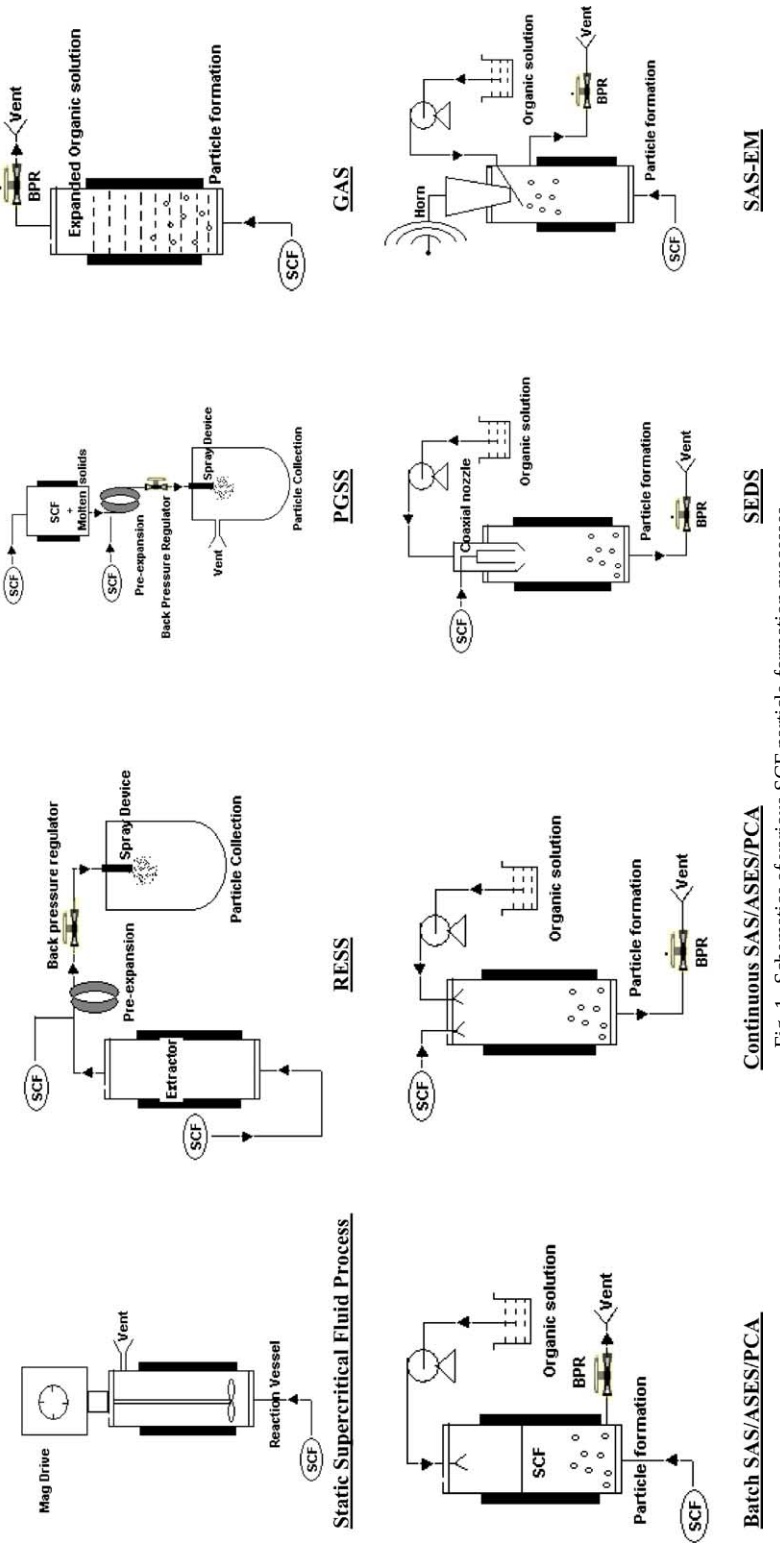
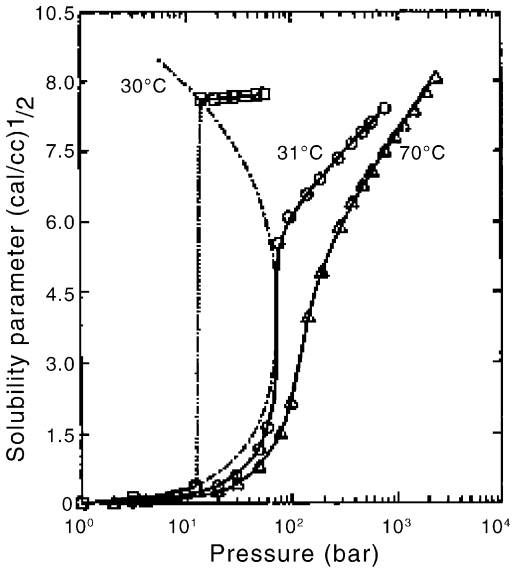


Fig. 1. Schematics of various SCF particle-formation processes.

(Shine and Gelb, 1998) and biorise (Carli et al., 1999) technologies. While it is not the intent of this article to dwell on the subtle differences in the above techniques, it serves as an efficient means of following the chronological developments of the technology as new understanding emerged. Further, the existence of so many closely related patents serves as a testimonial to the current interest in SCF particle formation and the restrictions on the freedom to operate.

A common feature in all the above particle formation techniques is the function of SCF as a reprecipitation aid. The basic advantages like rapid and uniform nucleation of solute(s) remain the same in all the processes, although the mode and mechanism of particle precipitation varies depending on the manner in which the SCF is used to precipitate particles. Essentially, all the abovementioned techniques can be classified depending on whether the SCF is used as (i) a solvent, e.g. RESS (ii) a solute, e.g. PGSS and (iii) an antisolvent, e.g. SAS. Refer to Table 1 and Fig. 1 for further details of this classification. Solubilization, plasticization and diffusion properties of supercritical fluids are utilized in static supercritical fluid process, RESS and PGSS processes. On the other hand, rapid mass transport between SCF and the continuous phase carrying the material to be processed is of interest while dealing with the antisolvent precipitation processes.

Carbon dioxide is regarded as a favorable processing medium and is the commonly used SCF for pharmaceutical applications. It is generally regarded as safe (GRAS), chemically inert, non-flammable, inexpensive, has a low critical temperature and pressure and exhibits solubilization and plasticization effects that can be varied continuously by moderate changes in pressure and temperature. The solvent properties of supercritical carbon dioxide are reported to resemble those of hexane, toluene, isopentane and methylene chloride depending on the pressure and temperature conditions of the fluid (see Fig. 2) (Hyatt, 1984; Dandge et al., 1985; Dobbs et al., 1987; Ting et al., 1993). From a feasibility standpoint, compounds exhibiting significant solubility behavior in the SCF of interest are most suitable for RESS process (for example, lipophilic compounds with low molecular weight and high vapor pressure for SC CO_2). PGSS is ideal for processing low melting compounds that exhibit negligible interaction with the SCF and more importantly, significant thermal stability. Antisolvent processes, on the other hand provide



Solubility parameters of common organic solvents in (cal/cc)^1/2: Hexane-7.24; Toluene-8.91; Isopentane-6.80; Ethyl Acetate-9.10; $MeCl_2$-9.93; MeOH-14.28; EtOH-12.92

Fig. 2. Solvent properties of supercritical carbon dioxide (from Perry's Chemical Engineers' Handbook, Mc Graw-Hill, New York, 7th ed., 1997).

more flexibility in choosing the precipitation conditions through the use of solvents and solvent mixtures and by manipulating the solvent extraction conditions of SCF. Excepting ferro micron mix (Mandel, 2002), PGSS (Mura and Pozzoli, 1995) and SEDS (Bonner, 2000) processes, which have been scaled up to the tune of producing 1 t particulate solids per year, the progress with other techniques is by far only limited to the research laboratories. For the purposes of clarity in this manuscript, lab-scale and pilot-scale particle formation systems are distinguished on the basis of their product throughputs. Lab-scale systems typically produce few grams of particulate solids per hour while the throughput of pilot scale systems are of the order of few kilograms per hour.

Scale-up of RESS process is limited by the poor solubilities of many pharmaceutical actives and excipients in commonly used supercritical fluids. While a semi-pilot scale particle production of saquinavir was demonstrated in a Roche patent (Bausch and Hidber, 2001), the solute throughputs are still prohibitively low to earn commercial value for RESS scale-up. Antisol-

Table 2
Potential applications of SCF processes in solid drug processing

Application	References
Micronization	Donsi and Reverchon, 1991, Kerc et al., 1999, Snavely et al., 2002
Nanoparticles	Mohamed et al., 1989a, Gupta and Chattopadhyay, 2002, Elvassore, 2001
Microencapsulation	Kim, 1996, Bleich and Muller, 1996, Young et al., 1999, Tu et al., 2002
Particle coating	York, 1995, Subramaniam et al., 1998, Wang et al., 2001
Crystal modification	Robertson et al., 1996, Weber et al., 1997, Vemavarapu et al., 2002
Solid dispersions	Mura, 1995, Kerc, 1999, York et al., 2001, Sethia and Squillante, 2002, Juppo et al., 2003
Dissolution enhancement	Loth and Hemgesberg, 1986, Van Hees et al., 1999, Moneghini et al., 2001, Charoenchaitrakool et al., 2002, Turk, 2002
Amorphous conversion	Ohgaki et al., 1990, Jaarmo et al., 1997, Reverchon and Della Porta, 1999, Reverchon et al., 2002
Infusion/impregnation	Berens et al., 1989, Carli, 1999, Shine, 1998, Zia et al., 1997
Liposomes	Frederiksen et al., 1997, Castor and Chu, 1998, Imura et al., 2003
Granulation	Lindsay, 1992, Mandel, 1999
Polymorph separation	Edwards et al., 2001, Kordikowski et al., 2001, Velaga et al., 2002, Beach, 1999
Extrusion	Lee et al., 1998, Daly et al., 2001, Breitenbach and Baumgartl, 2000
Polymerization	Rajagopalan and McCarthy, 1998, Muth, 2000

vent processes, on one hand provide more flexibility in the variety of compounds that can be processed. The downside however stems from the agglomeration of the particles containing un-extracted residual solvents. Means of containing the agglomeration to retain the original particle characteristics have been the subject of interest in several closely related patents (Sievers and Karst, 1997; Kulshreshtha et al., 1998; Schmitt, 1998; Hanna and York, 2001; Pace et al., 2001; Merrified and Valder, 2000; Gupta and Chattopadhyay, 2002) and form the scope of GAS, PCA, ASES, SAS, SEDS and SAS-EM processes. Associated scale-up issues with the various antisolvent processes have been extensively covered in a recent publication by Thiering (Thiering et al., 2001). While large inroads remain to be made, the potential for SCF technology appears

Table 3
SCF particle formation in pharmaceutical industry

Pharma/drug delivery company (1)	SCF research group	Representative patent
Skye Pharma (formerly RTP Pharma)	Phasex Corporation[a]	US6177103, 2001
Skye Pharma (formerly RTP Pharma)	University of Texas	WO 97/14407, 1997
Nektar (Formerly Inhale)	Bradford Particle Design[a]	US6440337, 2002
Bristol Myer Squibb	Bradford Particle Design	WO 01/15664, 2001
Glaxo Smithkline (formerly Glaxo)	Bradford Particle Design	WO 95/01324, 1995
Astra	Bradford Particle Design	WO 98/52544, 1998
Lavipharm	Separex[a]	EP1244514, 2002
Ethypharm	University of Angers/Mainelab	US6183783, 2001
Eurand	Vector Pharma	WO 99/25322, 1999
Crititech	University of Kansas	US5833891, 1998
Alcon	Phasex Corporation	US5803966, 1998
Thar	Auburn University	US0000681, 2002
Glaxo Smithkline (formerly Smithkline Beecham)	–	WO 00/37169, 2000
Hoffman-La Roche	–	US6299906, 2001
Pharmacia and Upjohn	–	US5707634, 1998
Schwarz Pharma	–	US5043280, 1991
Rohm andHass	–	US6228897, 2001
Aphios	–	US5776486, 1998
BASF	–	US0000036, 2001

[a] Acquired by (1).

Table 4
Vendor information of supercritical fluid equipment and accessories

Item	Representative vendors
Gas suppliers	Air Products, PA; BOC Gases, NJ; Matheson, PA
Gas pumps	Haskel, CA; Isco, NE; Jasco, MD
Liquid metering pumps	Eldex, CA; Ivek, CA
Heat exchanger/chiller	Lytron, MA; Polyscience, IL
Tubing/fittings	Vici Valco, TX; High Pressure Equipment Company, PA
Reaction vessels	Thar, PA; Pressure Products Industries, PA; Autoclave Engineers, PA
View-thru vessels	Clark-Reliance Corp.OH; Chandler Eng. Company LLC, OK
Valves	High Pressure Equipment Company, PA; Vici Valco, TX
Back pressure regulators	Tescom, MN; Thar Designs, PA; Jasco, MD
Mixing loops	Thar Designs, PA; Autoclave Engineers, PA
Whole units	Supercritical Fluid Technologies, DE; Thar Designs, PA
Phase monitors	Supercritical Fluid Technologies, DE; Thar Designs, PA
Pressure transducers	Texas Instruments, TX; Omega, CT
RTD/theromcouples	Omega Engineering, CT
Flow meters	Dwyer, IN; Porter Instruments, CA; Coriolis Liquid Controls, IL
Nozzles	Thar Designs, PA; Applied Surface Technologies, NJ; BPD, UK
Sapphire windows	Thermo Oriel, CT; Mindrum Precision, CA; Insaco, PA
Toll processing	Thar Designs, PA; Lavipharm, NJ; Bradford Particle Design, UK
Technical consultants	Phasex, MA; Supercritical fluid technology Consultants, PA

immense as reflected by the wide gamut of pharmaceutical applications reported to date. Further, the appearance of a number of reviews on this subject in the recent pharmaceutical literature is a testimony to its potential. (Subramaniam et al., 1997; York, 1999; Kompella and Koushik, 2001; Jung and Perrut, 2001; Tan and Borsadia, 2001). Table 2 summarizes the various applications of supercritical fluid technologies in pharmaceutical material processing. The initiatives of major pharmaceutical industries in tapping this potential through acquisitions or co-developmental work with diverse supercritical research groups are illustrated in Table 3.

Given the commercialization of SCF technology in the extraction of coffee, hops, flavors etc. and in analytical chromatography, the majority of the currently available off-the-shelf SCF instrumentation is designed for extraction purposes. Only a few selective vendors appear to be in the early stages of manufacturing equipment specific to particle formation (Table 4). A general practice however, as reflected from the reported publications and patents, is to reconfigure a commercially available system specific to the end use. It is the purpose of this article to provide such information and resources necessary for startup research involving particle formation using supercritical fluids. The various stages of supercritical particle formation can be broadly classified into delivery, reaction, pre-expansion, expansion and collection and SCF recycling. The importance of each of these processes from the standpoint of tailoring the particle morphology is discussed in the following sections while also providing various alternatives to perform these operations. Issues on the safety are an integral part of any high-pressure operation and are addressed in the final section of this manuscript.

2. Supercritical fluid delivery

The critical point for any pure substance is defined by the temperature and pressure coordinates, above which no physical distinction exists between the liquid and gaseous states. Substances above the critical point are referred to as ‘supercritical fluids’. In contrast to the other transitions of state, the phase change from the liquid or gaseous state to the supercritical fluid state is not a first-order phenomenon, although most physical and transport properties change abruptly around the fluid’s critical point. Accurate determination of the solvent critical point is therefore not a straightforward task and often relies on a number of complimentary techniques involving the study of critical opalescence, mixture phase behavior, acoustic measurements and theoretical equations of state (McHugh and Krukonis,

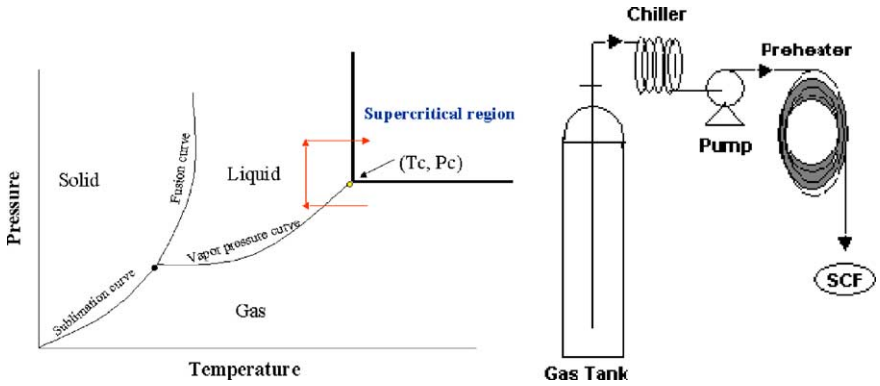


Fig. 3. Supercritical fluid delivery.

1994). The critical phase behavior, however for a number of frequently used supercritical fluids and fluid mixtures can be readily obtained from scientific literature (Walas, 1985; Ziegler et al., 1995; Chester and Haynes, 1997).

For typical pharmaceutical applications involving the use of SC CO_2, the most common and economic route of reaching the supercritical region is from a gas through the liquid state into the SCF phase (Fig. 3). Compressed CO_2 is readily available in large quantities with a high level of purity and is reasonably priced. This is liquefied by passing through cooling lines prior to charging the pump (Fig. 3). Delivering the fluid to the pump in a liquid state ensures effective pressurization without any cavitation problems. Frictional forces from the pump and the heat of compression can raise the temperature of the fluid, thereby inducing phase change and needs to be compensated using a heat exchanger. While circulating a coolant in an external chill-can surrounding the pump head can be an option, more sophisticated pumps rely on improving efficiency by internal coolant circulation or through the use of low thermal conductivity ceramic/polymer pistons and other pump accessories (Koebler and Williams, 1993). Refer to Table 4 for details of major gas suppliers and pump vendors. This table only provides a representative set of vendors of various SCF-related equipment and services. Refer to trade magazines such as Pharmaceutical Processing, Pharmaceutical Technology, AAPS Buyers Guide etc. for more detailed listings of vendors. Given that CO_2 is the SCF of choice in a number of reported pharmaceutical applications, pumps that efficiently perform up to 690 bar are most commonly used. For applications that do not require high pressures or instances where the difference between the properties of fluids at sub and supercritical states is not distinctive, liquid tanks with a dip tube can be readily obtained from a number of suppliers that can be directly connected to a preheater.

Pressurized liquid from the pump is then brought to the supercritical state by passing through a heat exchanger (preheater). Owing to the high thermal conductivities of these fluids (Perry, 1997), supercritical temperatures are easily reached although the residence time of fluids in the preheater is not long. A lengthy piece of coiled tubing up to 5 m in length is typically used as a heat exchanger to raise the temperature of compressed CO_2 (1–5 °C) to supercritical state (>31 °C). The temperature of the coil is controlled using either a temperature bath/oven or a heating tape and is chosen such that equilibrium supercritical temperatures are attained by the time the fluids exit the coil. The flow of the SCF at this point is pulsed depending on the efficiency of the pump, further being exacerbated by the high kinetic energies of the fluids. Steady flow rates of SCFs assist in creating uniform conditions for nucleation and are therefore of interest in the context of particle formation. Wherever uniformity in flow rates is considered important, pulse dampeners or snubbers can be used to buffer these pulsations. Alternatively, an additional vessel can be placed upstream of the reaction vessel that dampens the pulsation and thereby stabilizes the flow rates. Flow measurement of the fluid in supercritical state is relatively difficult considering the high pressures that the flow meters need to handle. Gas

flow meters are typically used to monitor the supercritical fluid flow rates and are placed downstream of the particle collection vessel where the fluid is in gaseous state. Allowing the gas to flow through a lengthy tubing would not only assist in dropping any residual solutes or solvents well before the gas enters the flow meter but also helps in the equilibration of temperature. In instances that require measurement of mass flow rates in supercritical state, a rather expensive Coriolis flow meter can be used. The vibrating tube of this meter can also serve in measuring the density of the supercritical fluid in-line. Various flow meters are currently available, and the choice of the meter should take into account such factors as the operating range, sensitivity, type of fluid, moisture levels of the gas, inlet temperature and pressure, costs etc. While applications requiring accurate measurement such as the measurement of solute solubility in supercritical fluids require sensitive meters (e.g. Thermo mass flow meter, Coriolis) with the totalizing function, other applications can function as well with inexpensive rotameters.

In operations involving the use of co-solvents, the phase behavior of the resulting supercritical mixture needs to be developed. A liquid metering pump is additionally required to deliver the co-solvent and can be purchased off-the-shelf from vendors dealing with the liquid chromatographic systems. It is noteworthy that such a metering pump should be capable of pumping the co-solvent against the head pressure of the compressed fluid. Check valves are placed in the paths of SCF and co-solvent streams just before the point where the fluids meet. Mixing of the fluids can then be affected at the junction where they meet in T-configuration or more effectively, through the use of a sampling loop. The fluid mixture can then be delivered to the preheater that raises the temperature of the resulting mixture to the supercritical state.

3. Processing

The processing vessel (also called as pressure vessel or a reaction vessel) is where the supercritical fluid is brought in contact with the material(s) to be processed. Essential requirements for a processing vessel are chemical inertness, ability to withstand the operating temperature and pressure conditions and ASME-specified design. Several designs of the pressure vessels are currently available and in general are distinguished by the type of closures. Different closures vary in the nature and site of formation of the seal to contain the supercritical pressures. Finger tight closures with a ‘c’ cup seal formed of a graphite reinforced Teflon ring containing an energized spring (Kumar, 1998) can withstand pressures up to 690 bar and are frequently used in pharmaceutical applications. Refer to Table 4 for particulars of some of the vendors of pressure vessels and reactors.

Pressure vessels made for pharmaceutical applications are typically made of stainless steel (316 SS) due to the sturdiness and chemical inertness of the material. Among various components, the processing vessel is typically the largest reservoir of pressurized SCF at any one time. Good safety procedures should therefore include (i) shielding the vessel from the operator and (ii) providing a pressure-relief mechanism by placing a rupture disc on the vessel. Controlled conditions of temperature and pressure in the processing vessel are important to attain reproducible results and can be achieved through the use of a backpressure regulator, sensitive pressure transducers and temperature-measuring devices. The temperature of the vessel can be regulated either by using a heating mantle or a temperature-controlled bath/oven. The temperature of the contents in the vessel can be accurately controlled through a proper choice of the heaters and temperature controller and by an appropriate placement of the thermocouple(s). On the other hand, the required pressure in the processing vessel is attained using the supercritical pump. Loss of pressure upstream of the point where the supercritical fluids are depressurized is compensated by using a backpressure regulator (BPR). While simple designs use restrictors or micrometering valves as BPRs, more sophisticated designs rely on a mechanical or electronic feed back to the pump (Chordia, 1997). Independent control of supercritical fluid flow rates and pressures is made possible through the latter designs. A common problem seen with the use of backpressure regulators in SCF particle formation processes is the precipitation of solutes and/or dry ice (in SC CO_2 applications) in the BPR. Joule–Thompson cooling as a result of the large volumetric expansion across the BPR leads to drop in temperature of the supercritical solutions and is the cause for such precipitations. This leads to inconsistent flow rates on one end and plugging of the lines in severe conditions. Independent

temperature control of the BPR is therefore essential to prevent such problems. For lab-scale processing involving CO_2 (with gas flow rates through the system in the range 2–20 SLPM and a pressure drop between 73.8–689 bar), the BPR is usually maintained at approximately 50 °C higher than the temperature of the processing vessel.

Intimate mixing of the supercritical fluid with the material to be processed is critical in SCF material processing (Shekunov et al., 2001; Kim et al., 2000). The effects are particularly pronounced in rapid expansion of supercritical solution (RESS) and particles from gas-saturated solutions (PGSS) processes. Channeling of the supercritical fluid in continuous operations of RESS and PGSS processes limits the contact of the fluid with the material(s) of interest. Packing of solute(s) in the processing vessel is therefore critical in these processes and should maximize the interaction while limiting the entrainment of solute. Mixing the material with glass beads (e.g. 10/90% by weight of material/glass beads), viton seals and glass wool prior to loading it to the processing vessel is used to improve the degree of interaction. The glass beads not only help in improving the contact of materials with SCFs, but also assist in dampening the flow pulsations by reducing the free volume in the reaction vessel. Alternatively, stirring or agitation in the processing vessel can be provided using an impeller. Extrusion of the commonly used seals (typically made of Buna N, Teflon, Kalrez™, Aflas™ and other composite materials) due to the sorption of gases into the polymers at relatively high temperatures forms a major limitation to using ordinary devices. Moreover, the wear and tear of the moving parts of the mixing device is exacerbated by the high pressures of the SCF process. To overcome these limitations, magnetic mixing devices have been designed that effectively provide a leak-proof agitation in a pressure vessel without the use of polymeric seals and other moving parts. Patented devices for mixing in pressure vessels such as PPI dyna magnetic mixers and ferro micron mixers are available as off-the-shelf items (Table 4).

For investigative studies requiring the physical observation of events taking place in the processing vessel, view cells can be fitted in the vessel caps. Commonly used view cells are made of such materials as quartz, sapphire, lexan® etc. The compatibility of the cells and the seals with supercritical fluids needs to be verified prior to their use. Sorption of SCFs into the o-rings combined with the leaching capability of the fluids is a frequent cause of leakages inherent in supercritical systems. Preventive maintenance of the system should therefore include replacing the seals at frequent intervals of time. For studies involving milder operating conditions, a Jerguson gauge (Clark-Reliance Corporation, OH) can be used as a processing vessel and also to qualitatively view the events of the reaction. Solubility and phase behavioral events of the pharmaceutical materials in supercritical fluids can be developed using the above-mentioned designs, although special devices (phase monitor/phase equilibrium analyzer) are designed and frequently used for such studies.

4. Pre-expansion

The composition and phase of the supercritical solution from which particles precipitate is found to have a major effect on the particle morphology in RESS and PGSS processes and is controlled during the pre-expansion stage (Weidner et al., 1996; Helfgen et al., 2000). Independent control of the temperature and pressure during the pre-expansion stage is therefore critical in these processes. Additionally, the phase changes in the supercritical solutions, which often lead to plugging of the lines, can be eliminated through the use of a controlled pre-expansion line. While one end of the pre-expansion line is connected to the reaction vessel, the other end feeds the supercritical solution through a backpressure regulator to the expansion device (Fig. 1). The composition of the solution in this line may not only be controlled by changes in temperature, but also by adding fresh SCF solvent to the line. Typically, the pre-expansion device is a lengthy coiled tubing having the same dimensions as the other lines with a port for the addition of fresh solvent. It is usually maintained at approximately 50 °C higher than the temperature of the reaction vessel using a heating tape or a temperature bath/oven. Pre-mature precipitation of solutes in the lines can thus be avoided excepting situations where the solute exhibits retrograde behavior in this temperature range. In such instances, plugging can be prevented by the addition of fresh supercritical solvent to dilute the supersaturated solution. The fluids can be effectively mixed through the use of mixing loops that are most commonly used in pre-column reactions of HPLC analysis.

5. Spray configurations

In supercritical fluid particle formation, the fluids are expanded through a restriction device in a controlled fashion. Two critical aspects of rapid expansion that are of interest in the context of controlling particle morphologies are: (i) the supersaturation profile of solutes as temperature, pressure, phase and composition changes during the expansion (thermodynamics) and (ii) mechanical shear that a particle undergoes in the subsonic and supersonic regions of the expanding supercritical fluids (aerodynamics). A restriction device is designed to support the large pressure drop that occurs across it, while maintaining suitable conditions for precipitation. The geometry of the restriction device has been shown to influence the morphology of the particles to varying degrees and by different mechanisms (Matson et al., 1987; Debenedetti et al., 1993; Subramaniam et al., 1998; Weber et al., 2002). In RESS and PGSS processes, the device controls the growth of particle after the nucleation process by affecting the dynamics of jet expansion. Joule–Thompson cooling, resulting from the large volumetric expansion across the restriction device causes a drop in temperature, thereby affecting a phase change and subsequently leads to plugging of the device. The restriction devices are therefore heated to compensate for such effects. While stainless steel nozzles are most frequently used owing to their strength to withstand the large pressure differential, they are limited by their poor thermal conductivities. Wherever necessary, they can be replaced with sapphire nozzles that provide better heat transfer to the fluid while also maintaining the material strength. The devices, for the most part are custom designed according to the specific needs of the researcher. Off-the-shelf devices with standard configurations can also be obtained from selective supercritical fluid vendors (Table 4). Using computational fluid and aerosol dynamics, several authors have attempted to model the supersaturation and growth of particles during the rapid expansion (Turk, 1999, Helfgen et al., 2000; Weber et al., 2002). While an absolute theoretical model still remains as a distant goal, the current level of understanding qualitatively delineates the critical parameters that affect the particle size.

On the other hand, the restriction device in antisolvent processes affects particle morphology by controlling the initial droplet size and also the rate of solvent extraction by the SCF (Subramaniam et al., 1998; Werling and Debenedetti, 1999). Various configurations have been used to date, namely capillaries, nozzles, laser-drilled discs and valves. For investigative purposes, capillaries are preferred to other specialized designs due to their easy availability, cost and the flexibility of changing the geometry of the device in house (Kim et al., 1996). Typical aspect ratios (length/diameter) of the restriction devices evaluated to date are in the range 6–20, with orifices from 20 to 1600 μm in diameter. Other coaxial nozzles that are specific to the SEDS process are patent-protected and can be purchased for purposes notwithstanding the claims of the patent (Hanna and York, 1999).

6. Particle collection

Retaining the original characteristics of the particles produced by supercritical fluid process is as critical as forming the particles and constitutes the particle collection step. This step is critical in that the distinct characteristics of the particles can be completely lost owing to a poor collection technique (Turk, 1999). Although it is recognized that the issues of particle collection will become more apparent during the process scale-up, very little research has been directed toward this problem to date. Laboratory-scale particle-formation systems mostly utilize filters and baskets to collect the particles. Due caution should therefore be exercised while translating the results obtained by in situ measurements to the actual characteristics of the product produced on a pilot scale.

In rapid expansion of supercritical solution and particles from gas-saturated solution processes, the rapidly expanding supercritical fluids impart high kinetic energies to the particles produced. Insufficient path for expansion can therefore result in the agglomeration of particles. The agglomeration is even worse in the presence of residual amounts of co-solvent in RESS process or uncongealed portions in PGSS process. Design of particle collection vessel in these processes should be such that agglomeration is kept to a minimum by providing a sufficient path for expansion of the supercritical fluids. While a logical solution is to make the collection vessel very large, the collection

of small amounts of material from a relatively larger vessel can be difficult, resulting in low yields. This problem can be circumvented in part by inserting detachable baskets inside the vessel. The baskets can be taken apart at the end of the process to collect the particles. Other potential designs of particle collection involve the use of high-efficiency filters, cyclone separators and electrostatic precipitators (Thiering et al., 2001). The utility of these devices, however, needs to be examined in greater detail in SCF particle formation. While precipitating the solutes into a non-solvent containing a surfactant is another solution to agglomeration (Bausch and Hidber, 2001), it adds one more step to an otherwise continuous unit operation. An optimum balance between the ease of collection and the expansion path of the SCFs should be reached in designing the particle collection vessel. Other design factors that merit consideration include: surface finish of the inside of the baskets/vessel, shape of the vessel, alignment etc. (Matson et al., 1987; Turk, 1999). In principle, the post-expansion conditions in RESS and PGSS processes control particle growth by affecting the dynamics of jet expansion. Although true, experimental results reported to date mostly have found such effects to be inconclusive or relatively insignificant, perhaps obscured by the inaccuracies arising from particle agglomeration. Excepting situations where post-expansion conditions are significant (Mohamed et al., 1989b), or where fluid recompression costs are a factor, the collection vessels in RESS and PGSS processes are therefore maintained at atmospheric conditions.

The collection of particles in the antisolvent processes occurs in the same vessel where solvent extraction takes place. The particles are retained at the bottom of the vessel by placing filters while the solvents are removed with the flowing supercritical fluid. Additionally, a drying cycle is performed at the end of particle precipitation. As part of this cycle, generous amount of SCF is passed through the powder to remove any un-extracted solvent. Particle agglomeration and solvent removal from the vessel in these processes are relatively less dependent on the design of the vessel and are outweighed by other spray/thermodynamic effects. The design of collection vessels used for antisolvent applications should, however, take into account the interaction between the materials and the supercritical fluids without plugging the lines (Hanna and York, 1999).

7. Recycling

The commercial viability of a technology depends not only on its scientific virtues but also on the cost of instrumentation and operation. High-pressure operations with such sensitivity as supercritical fluids require sophisticated control systems for precision and safety. Apparently, the associated costs of building such instrumentation are high. The capital costs for building a developmental non-cGMP supercritical fluid plant capable of processing 20 kg/day are estimated to be 2 million dollars (Personal Communication). On the other hand, the operating costs of SCF processing (taking into account the cost of SCF plus other utility costs) are projected to reach $10–20/kg product. One means of compensating for such high operating costs that was taken advantage of, in the SCF extraction industry, is solvent recycling. The rapid change in the solvent strength of SCFs with moderate adjustments in pressure and temperature, in theory, can be utilized to recover the supercritical fluid. Although economical, complete removal of solutes from SCF cannot be affected by adjusting the temperature alone. While fluid recompression costs are substantial, pressure reduction is more efficient in recovering pure supercritical fluids devoid of solutes.

While alternative ways to recover and purify SCFs using other solvent systems may be possible in extraction (for example, by passing SC CO_2 laden caffeine through water in SCF decaffeination), particle formation relies on the rapid expansion of SCFs as a result of depressurization. Recompression therefore significantly contributes to the overall cost of SCF-based particle formation. The processing virtues of this technology should therefore be balanced against the rather high costs of implementing this technology in evaluating its commercial viability. Majority of the lab-scale systems, however, are designed to vent out the used supercritical fluids in addressing greater technological challenges at hand.

8. Safety

In a recent publication (Lucas et al., 2003), Lucas et al. have presented an excellent treatise on the safety aspects of supercritical processing in general and extraction in specific. The authors have not only laid out

the potential areas of hazard while dealing with SCF equipment, but also performed a model-based safety analysis. While the above work should be treated as a primary reference in developing the safety guidelines, the present discussion attempts to specifically cover aspects related to particle formation at a laboratory scale.

Particle formation experiments involving pharmaceuticals typically use CO_2 as the supercritical fluid and are conducted in the temperature and pressure regimes of 31–100 °C and 73.8–690 bar, respectively. The discussion on the safety of SCF particle formation equipment will therefore be reserved to the above operating conditions. Carbon dioxide is considered a GRAS solvent with a TLV-TWA value of 5000 ppm. (TLV-TWA is the threshold limit value time weighted average concentration for a normal 8 h workday or 40 h workweek, to which all healthy workers may be repeatedly exposed, day after day, without adverse effect). While this is otherwise not an issue, combinations of CO_2 along with other solvents may pose a risk and can be addressed through the use of proper hardware combined with adequate shielding. SCF-produced particles are typically of the respirable size range and appropriate powder handling procedures need to be employed. These include the use of personal protective equipment such as a respirator, gloves, lab coat, safety glasses etc. Additionally, performing the particle collection and other solvent operations in a laminar flow hood or a vented enclosure under negative pressure is a good practice to contain any inadvertent leaks.

The operational temperatures in SCF particle formation are lower compared to several other pharmaceutical operations. Burn-related hazards are therefore infrequent while dealing with SCF particle formation. On the other hand, generating and containing pressures up to 690 bar from gases at room temperature are not routine to pharmaceutical labs and requires special training. Refer to the National Safety Council's data sheet titled "Pressure vessels and pressure systems in the research and development lab" for details on the design and operation of high-pressure systems (NSC Data Sheet I-678-Rev-85). SCF particle-formation operations not only require the use of hardware rated for high pressures, but also the employment of multiple pressure-relief mechanisms and safety practices. Pressure-rated rupture-disc assemblies are typically placed on the SCF pump, pressure vessels and at additional positions containing high pressure. These provide protection against over pressurizing the mechanical components of the system. In addition to the abovementioned, procedures should be laid in place for accommodating process uncertainties and preventing hazards. These include adequate level of shielding of high-volume components, training personnel on operation and preventive maintenance and more importantly, working within the rated pressures. Given that the volumes of pressurized fluids are of the order of few hundred milliliters when dealing with lab-scale particle-formation systems, the hazards of over pressurization are relatively insignificant compared to a pilot-scale system. The downside, however, stems from the fact that smaller components and seals that are rated for the same higher pressures are relatively expensive and require frequent replacement. In summary, safety is an important factor while dealing with the supercritical particle formation systems, and the design of such equipment should take all the abovementioned factors into account.

9. Summary

Current advances in pharmaceutical research have not only contributed to the discovery of various new technologies but also identified the potential limitations of the conventional techniques of material processing. Among the different nascent technologies currently under investigation, supercritical fluid-aided particle formation is reported to operate under relatively mild conditions making the process amenable to sensitive molecules, enzymes, proteins and other macromolecules (Yeo et al., 1993; Moshashaee et al., 2000; Elvassore et al., 2001). Different SCF processes have been demonstrated to produce particles with residual solvent content below the FDA-permitted levels (Steckel et al., 1997). Further, control over the morphology and crystallographic purity of the particles is shown to be better than several other conventionally used processes (Beach et al., 1999). Particle formation using SCFs as a continuous unit operation is conducted in an enclosed system under positive pressure, which inherently lends itself to cGMP conditions. Further, the modularity of particle-formation systems made up of components that have been time tested for cGMP applications is a testimony to this fact. The potential for SCF technology in the pharmaceutical realm manifests from

all the abovementioned features combined with the feasibility of producing particles under cGMP conditions. Deriving all these virtues from a nascent technology also means that a greater number of challenges need to be addressed in the development stage. Noteworthy among these are predictive models of general applicability, material throughputs, nozzle designs, particle collection systems and continuous processing. The information provided in this article is intended to assist investigative researchers in addressing such challenges either through setting up a particle-formation system in house or by contracting the work to established supercritical fluid consultants.

References

Bausch, A., Hidber, P., 2001. Process of making sub-micron particles. US Patent 6299906.

Beach, S., Latham, D., Sidgwick, C., Hanna, M., York, P., 1999. Control of the physical form of salmeterol xinafoate. Org. Process Res. Dev. 3, 370–376.

Berens, A.R., Huvard, G.S., Korsmeyer, R.W., 1989. Process for incorporating an additive into a polymer and product produced thereby. United States Patent 4820752.

Bertucco, A., Pallado, P., Benedetti, L., 1996. Formation of biocompatible polymer microspheres for controlled drug delivery by a supercritical antisolvent technique. Process Technol. Proc. High Press. Chem. Eng. 12, 217–222.

Bleich, J., Muller, B.W., Wabmus, W., 1993. Aerosol solvent-extraction system: a new microparticle production technique. Int. J. Pharm. 97, 111–117.

Bleich, J., Muller, B.W., 1996. Production of drug loaded microspheres by the use of supercritical gases with the aerosol solvent extraction system (ASES) process. J. Microencapsul. 13, 131–139.

Bodmeier, R., Wang, H., Dixon, D.J., Mawson, S., Johnston, K.P., 1995. Polymeric microspheres prepared by spraying into compressed carbon dioxide. Pharm. Res. 12, 1211–1217.

Bonner, J., June 2000. A particularly fine way of making drugs. Chem. Ind., 391.

Breitenbach, J., Baumgartl, H., 2000. Solid foamed active substance preparations. United States Patent 6150424.

Carli, F., Colombo, I., Alessi, P., Kikic, I., Cortesi, A., 1999. Pharmaceutical compositions having the shape of powders of crosslinked polymers loaded with drugs and related preparation process by supercritical fluids. International Patent Publication WO 99/25322.

Castor, T.P., Chu, L., 1998. Methods and apparatus for making liposomes containing hydrophobic drugs. United States Patent 5776486.

Charoenchaitrakool, M., Dehghani, F., Foster, N.R., 2002. Utilization of supercritical carbon dioxide for complex formation of ibuprofen and methyl-b-cyclodextrin. Int. J. Pharm. 239, 103–112.

Chester, T.L., Haynes, B.S., 1997. Estimation of pressure– temperature critical loci of CO2 binary mixtures with methyl-*tert*-butyl ether, ethyl acetate, methyl-ethyl ketone, dioxane and decane. J. Supercrit. Fluids 11, 15–20.

Chordia, L.M., 1997. Variable restrictor and method. United States Patent 5694973.

Daly, A.T., Decker, O.H., Wursthorn KR, Houda, F.R., Grundowski, L.T., Ernst. C.W., 2001. Continuous processing of powder-coating compositions. United States Patent 6228897.

Dandge, D.K., Heller, J.P., Wilson, K.V., 1985. Structure solubility correlations: organic compounds and dense carbon dioxide binary systems. Ind. Eng. Chem. Prod. Res. Dev. 24, 162–166.

Debenedetti, P.G., Tom, J.W., Kwauk, X., Yeo, S.D., 1993. Rapid expansion of supercritical solutions (RESS): fundamentals and applications. Fluid Phase Equilib. 82, 311–321.

Dobbs, J.M., Wong, J.M., Johnston, K.P., 1987. Modification of supercritical fluid phase behavior using polar cosolvents. Ind. Eng. Chem. Res. 26, 56–65.

Donsi, G., Reverchon, E., 1991. Micronization by means of supercritical fluids: possibility of application to pharmaceutical field. Pharmaceutica Acta Helvetica 66, 170–173.

Edwards, A.D., Shekunov, B.Y., Kordikowski, A., Forbes, R.T., York, P., 2001. Crystallization of pure anhydrous polymorphs of carbamazepine by SEDS. J. Pharm. Sci. 90, 1115–1124.

Elvassore, N., Bertucco, A., Caliceti, P., 2001. Production of insulin-loaded PEG/PLA nanoparticles by gas-antisolvent techniques. J. Pharm. Sci. 90, 1628–1636.

Frederiksen, L., Anton, K., Hoogevest, P.V., Keller, H.R., Leuenberger, H., 1997. Preparation of liposomes encapsulating water-soluble compounds using supercritical carbon dioxide. J. Pharm. Sci. 86, 921–928.

Gallagher, P.M., Coffey, M.P., Krukonis, V.J., Klasutis, N., 1989. Gas antisolvent recrystallization: new process to recrystallize compounds insoluble in supercritical fluids. In: Johnston, K.P., Penninger, JML. (Eds.), Supercritical Fluid Science and Technology, ACS Symposium Series 406. American Chemical Society, Washington DC, pp. 334–354, Chapter 22.

Gupta, R.B., Chattopadhyay, P., 2002. Method of forming nanoparticles and microparticles of controllable size using supercritical fluids and ultrasound. United States Patent Application US20020000681 A1.

Hanna, M., York, P., 2001. Method of particle formation. International Patent Publication WO 01/03821 A1.

Helfgen, B., Turk, M., Schaber, K., 2000. Theoretical and experimental investigations of the micronization of organic solids by rapid expansion of supercritical solutions. Powder Technol. 110, 22–28.

Hyatt, J.A., 1984. Liquid and supercritical carbon dioxide as organic solvents. J. Org. Chem. 49, 5097–5101.

Imura, T., Otake, K., Hashimoto, S., Gotoh, T., Yuasa, M., Yokoyama, S., Sakai, H., Rathman, J.F., Abe, M., 2003. Preparation and physicochemical properties of various soybean lecithin liposomes using supercritical reverse phase evaporation method. Colloids Surf. B: Biointerfaces 27, 133–140.

Jaarmo, S., Rantakyla, M., Aaltonen, O., 1997. Particle Tailoring with Supercritical Fluids: Production of Amorphous Pharmaceutical

Particles. In: Proceedings of the 4th International Symposium on Supercritical Fluids, May 11–14, pp. 263–266.
Jung, J., Perrut, M., 2001. Particle design using supercritical fluids: Literature and patent survey. J. Supercrit. Fluids 20, 179–219.
Juppo, A.M., Boissier, C., Khoo, C., 2003. Evaluation of solid dispersion particles prepared with SEDS. Int. J. Pharm. 250, 385–401.
Kerc, J., Srcic, S., Knez, Z., Sencar-Bozic, P., 1999. Micronization of drugs using supercritical carbon dioxide. Int. J. Pharm. 182, 33–39.
Kim, J.H., Paxton, T.E., Tomasko, D.L., 1996. Microencapsulation of naproxen using rapid expansion of supercritical solutions. Biotechnol. Prog. 12, 650–661.
Kim, T.H., Lim, D.Y., Yu, B.S., Lee, J.H., Goto, M., 2000. Effect of stirring and heating rate on the formation of TiO_2 powders using supercritical fluid. Ind. Chem. Eng. Res. 39, 4702–4706.
Koebler, D., Williams, G., 1993. Liquefied carbon dioxide pump. United States Patent 5193991.
Kompella, U.B., Koushik, K., 2001. Preparation of drug delivery systems using supercritical fluid technology. Crit. Rev. Ther. Drug Carrier Syst. 18, 173–199.
Kordikowski, A., Shekunov, T., York, P., 2001. Polymorph control of sulfathiazole in supercritical CO_2. Pharm. Res. 18, 682–688.
Kulshreshtha, A.K., Smith, G.G., Anderson, S.D., Krukonis, J., 1998. Process for sizing prednisolone acetate using a supercritical fluid anti-solvent. United States Patent 5803966.
Kumar, L.M., 1998. Pressure vessel seal with self-energizing seal. United States Patent 5850934.
Lee, M., Tzoganakis, C., Park, C.B., 1998. Extrusion of PE/PS blends with supercritical carbon dioxide. Polym. Eng. Sci. 38, 1112–1120.
Lindsay, A.D., Omilinsky, B.A., 1992. Method of preparing mixtures of active ingredients and excipients using liquid carbon dioxide. United States Patent 5169433.
Loth, H., Hemgesberg, 1986. Properties and dissolution of drugs micronized by crystallization from supercritical gases. Int. J. Pharm. 32, 265–267.
Lucas, S., Alonso, E., Sanz, J.A., Cocero, M.J., 2003. Safety study in a supercritical exraction plant. Chem. Eng. Technol. 26, 449–461.
Mandel, F.S., 1999. Mixing system for processes using supercritical fluids. United States Patent 5993747.
Mandel, F.S., 2002. Controlled release pharmaceuticals prepared by supercritical fluid processing techniques. International Patent Publication WO 02/20624 A1.
Matson, D.W., Fulton, J.L., Petersen, R.C., Smith, R.D., 1987. Rapid expansion of supercritical fluid solutions: Solute formation of powders, thin films and fibres. Ind. Eng. Chem. Res. 26, 2298–2306.
McHugh, M.A., Krukonis, V.J., 1994. Supercritical Fluid Extraction, 2nd ed. Butterworth-Heinemann, Newton, MA.
Merrified, D.R., Valder, C.E., 2000. Process and apparatus for producing particles using a supercritical fluid. International Patent Publication WO 00/37169.
Mohamed, R.S., Halverson, D.S., Debenedetti, P.G., Prud'homme, R.K., 1989a. Solids formation after the expansion of supercritical mixtures. Supercritical fluid science and technology. In: Johnston, K.P., Penninger, JML. (Eds.), ACS Symposium Series-406. American Chemical Society, Washington DC, pp. 355–378.
Mohamed, R.S., Debenedetti, P.G., Prud'homme, R.K., 1989b. Effects of process conditions on crystals obtained from supercritcal mixtures. AIChE J. 35, 325–328.
Moneghini, M., Kikic, I., Voinovich, D., Perissutti, B., Filipovi-Grcic, J., 2001. Processing of carbamazepine-PEG 400 solid dispersions with supercritical carbon dioxide: preparation, characterization and in vitro dissolution. Int. J. Pharm. 222, 129–138.
Moshashaee, S., Bisrat, M., Forbes, R.T., Nyqvist, H., York, P., 2000. Supercritical fluid processing of proteins. I: lysozyme precipitation from organic solution. Eur. J. Pharm. Sci. 11, 239–245.
Mura, G., Pozzoli, S., 1995. Process for the production of powders with controlled particle sizes and powdery product so obtained. European Patent Application 0661091A1.
Ohgaki, K., Kobayashi, H., Katayama, T., 1990. Whisker formation from jet of supercritical fluid solution. J. Supercrit. Fluids 3, 103–107.
Pace, G., Vachon, M.G., Mishra, A.K., Henrikson, I.B., Krukonis, V., 2001. Process to generate submicron particles of water-insoluble compounds. United States Patent 6177103.
Perry, 1997. Perry's Chemical Engineers' Handbook, 7th ed. Mc Graw-Hill, New York.
Rajagopalan, P., McCarthy, T.J., 1998. Two-step surface modification of chemically resistant polymers: blend formation and subsequent chemistry. Macromolecules 31, 4791.
Reverchon, E., De Marco, I., Della Porta, G., 2002. Rifampicin microparticles production by supercritical antisolvent precipitation. Int. J. Pharm. 243, 83–91.
Reverchon, E., Della Porta, G., 1999. Production of antibiotic micro- and nano-particles by supercritical antisolvent precipitation. Powder Technol. 106, 23–29.
Robertson, J., King, M.B., Seville, J.P.K., 1996. Novel techniques for particle production from supercritical solutions. In: IChemE Research Event Conference of Young Research Che. Eng., vol. 2, Institute of Chemical Engineers, Rugby, UK, pp. 988–990.
Schmitt, W.J., 1998. Finely divided solid crystalline powders via precipitation into an anti-solvent. United States Patent 5707634.
Sellers, S.P., Clark, G.S., Sievers, R.E., Carpenter, J.F., 2001. Dry powders of stable protein formulations from aqueous solutions prepared using supercritical CO_2-assisted aerosolization. J. Pharm. Sci. 90, 785–797.
Sethia, S., Squillante, 2002. Physicochemical characterization of solid dispersions of carbamazepine formulated by supercritical carbon dioxide and conventional evaporation method. J. Pharm. Sci. 91, 1948–1957.
Shekunov, B.Y., Baldyga, J., York, P., 2001. Particle formation by mixing with supercritical antisolvent at high Reynolds numbers. Chem. Eng. Sci. 56, 2421–2433.
Shine, A.D., Gelb, J., 1998. Microencapsulation process using supercritical fluids. United States Patent 5766637.
Sievers, R.E., Karst, U., 1997. Methods for fine particle production. United States Patent 5639441.
Snavely, W.K., Subramaniam, B., Rajewski, R.A., Defelippis, M.R., 2002. Micronization of insulin from halogenated alcohol solution using supercritical carbon dioxide as an antisolvent. J. Pharm. Sci. 91, 2026–2039.

Steckel, H., Thies, J., Müller, B.W., 1997. Micronizing of steroids for pulmonary delivery by supercritical carbon dioxide. Int. J. Pharm. 152, 99–110.

Subramaniam, B., Rajewski, R.A., Snavely, K., 1997. Pharmaceutical processing with supercritical carbon dioxide. J. Pharm. Sci. 86, 885–890.

Subramaniam, B., Saim, S., Rajewski, R.A., Stella, V., 1998. Methods for a particle precipitation and coating using near-critical and supercritical antisolvents. United States Patent 5833891.

Tan, H.S., Borsadia, S., 2001. Particle formation using supercritical fluids: pharmaceutical applications. Expert Opin. Ther. Patents 11, 861–872.

Thiering, R., Dehghani, F., Foster, N.R., 2001. Current issues relating to anti-solvent micronization techniques and their extension to industrial scales. J. Supercrit. Fluids 21, 159–177.

Ting, S.S.T., Macnaughton, S.J., Tomasko, D.L., Foster, N.R., 1993. Solubility of naproxen in supercritical carbon dioxide with and without cosolvents. Ind. Eng. Chem. Res. 32, 1471–1481.

Tu, L.S., Dehghani, F.L., Foster, N.R., 2002. Micronization and microencapsulation of pharmaceuticals using a carbon dioxide antisolvent. Powder Technol. 126, 134–149.

Turk, M., 1999. Formation of small organic particles by RESS: experimental and theoretical investigations. J. Supercrit. Fluids 15, 79–89.

Turk, M., 2002. Micronization of pharmaceutical substances by RESS: a promising method to improve boavailability of poorly soluble pharmaceutical agents. J. Supercrit. Fluids 22, 75–84.

Van Hees, T., Piel, G., Evrard, B., Otte, X., Thunus, L., Delattre, L., 1999. Application of supercritical carbon dioxide for the preparation of a piroxicam-β-cyclodextrin inclusion compound. Pharm. Res. 16, 1864–1870.

Velaga, S.P., Berger, R., Carlfors, J., 2002. Supercritical fluids crystallization of budesonide and flunisolide. Pharm. Res. 19, 1564–1571.

Vemavarapu, C., Mollan, M.J., Needham, T.E., 2002. Crystal doping aided by rapid expansion of supercritical solutions. AAPS PharmSciTech 3, article 29.

Walas, S.M., 1985. Phase Equilibria in Chemical Engineering. Butterworth Publishers, Stoneham, MA.

Wang, T.J., Tsutsumi, A., Hasegawa, H., Mineo, T., 2001. Mechanism of particle coating granulation with RESS process in a fluidized bed. Powder Technol. 118, 229–235.

Weber, A., Beutin, M., Tschernjaew, J., Kummel, R., 1997. Compressed fluid antisolvent crystallization for controlled particle design. Cryst. Growth Org. Matter 4, International Workshop, 214–221.

Weber, M., Russell, L.M., Debenedetti, P.G., 2002. Mathematical modeling of nucleation and growth of particles formed by the rapid expansion of a supercritical solution under subsonic conditions. J. Supercrit. Fluids 23, 65–80.

Weidner, E., Knez, Z., Novak, Z., 1995. Process for preparing particles or powders. International Patent Publication WO 95/21688.

Weidner, E., Steiner, R., Knez, Z., 1996. Powder generation from polyethyleneglycols with compressible fluids. In: Rudolf von Rohr, P., Trepp, C. (Eds.), Process Technology Proceedings 12. High-Pressure Chemical Engineering. Elsevier Science B.V., pp. 223–228.

Werling, J.O., Debenedetti, P.G., 1999. Numerical modeling of mass transfer in the supercritical antisolvent process. J. Supercrit. Fluids 16, 167–181.

Yeo, S.D., Lim, G.B., Debenedetti, P.G., Bernstein, H., 1993. Formation of microparticulate protein powders using a supercritical fluid antisolvent. Biotechnol. Bioeng. 41, 341–346.

York, P., Hanna, M., 1995. Salmeterol Xinafoate with controlled particle size. International Patent Publication WO 95/01324.

York, P., 1999. Strategies for particle design using supercritical fluid technologies. Pharm. Sci. Technol. Today 2, 430–440.

York, P., Wilkins, S.A., Storey, R.A., Walker, S.E., Harland, R.S., 2001. Coformulation methods and their products. International Patent Publication WO 01/15664.

Young, T.J., Johnston, K.P., Mishima, K., Tanaka, H., 1999. Encapsulation of lysozyme in a biodegradable polymer by precipitation with a vapor-over-liquid antisolvent. J. Pharm. Sci. 88, 640–650.

Zia, H., Dondeti, P., Needham, T.E., 1997. Comparison of nasal insulin powders prepared by supercritical fluid and freeze-drying techniques. Part. Sci. Technol. 15, 273–301.

Ziegler, J.W., Dorsey, J.G., Chester, T.L., Innis, D.P., 1995. Estimation of liquid–vapor critical loci for CO_2–solvent mixtures using a peak-shape method. Anal. Chem. 67, 456–461.