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Formation of polymer particles with supercritical fluids: A review

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Abstract

Recent developments on particle formation from polymers using supercritical fluids have been reviewed with an emphasis on articles published during 2000–2003. First, a brief description of the basic operating principles of the various particle formation processes is presented. These include the rapid expansion of supercritical solutions (RESS), the gas antisolvent process (GAS), supercritical antisolvent process (SAS) and its various modifications, and the particles from gas-saturated solution (PGSS) processes. An account of the general review articles that have been published in previous years is then provided. The publications that have appeared over the past 4 years have been reviewed under two groupings, one involving the production of particles from pure polymers, and the other involving the production of polymer particles that contain active ingredients, especially those that pertain to pharmaceuticals. The majority of the efforts in the current supercritical particle formation technology is indeed on the production of polymer particles that are of pharmaceutical significance. In each grouping, the publications were further categorized according to the primary role played by the supercritical fluid in the process, namely whether it was used as a solvent, or as an antisolvent, or as a solute. This review is the first comprehensive review specifically focused on the formation of particles from polymers.

Keywords: Polymers; Particle formation; Supercritical fluids; Pharmaceuticals; Review

1. Introduction

Interest in supercritical fluids and their potential use for process improvements has significantly increased in the past decade. These fluids, the properties of which can be tuned by changing the fluid density between those of liquid and gases, have been adopted or are being explored as: (a) alternative solvents for classical separation processes such as extraction, fractionation, adsorption, chromatography, and crystallization, (b) as reaction media as in polymerization or depolymerization, or (c) simply as reprocessing fluid as in production of particles, fibers, or foams. Some of the extraction processes such as decaffeination, and some polymerization and foaming processes have become commercial. Particle formation will most likely be the next major commercial application area that uses supercritical fluids.

The particle formation technology that uses supercritical fluids has evolved in many different forms during the last 20 years. Several review articles have already appeared in the literature [1–12]. A wide variety of organic and inorganic materials have been processed in the form of particles, fibers, films, and foams, employing the supercritical fluids as solvents or as antisolvents. Supercritical fluids were used as solvents, for example, to crystallize a supercritical fluid-soluble compound [13–35], or as non-solvents to precipitate supercritical fluid-insoluble materials [36–54]. In some cases, these fluids were employed as cosolvents or coantisolvents along with an organic liquid solvent to produce particles with a targeted morphology [31]. The versatile operating conditions that are possible with supercritical fluids and their mixtures, provide the flexibilities in controlling the size of the particles that span from microns to nanometers. Indeed, the recent advances in these techniques are opening new horizons for the supercritical fluid technology in the area of particle design by extending the utilization domain to nanotechnology-based applications.

Among the various organic and inorganic compounds that have been processed with supercritical fluids, polymers have been of special interest and significance. A variety of polymers including polyolefins [14], fluoropolymers [25],

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polyamides [37], and biopolymers [45] have been explored. A range of protocols and flow arrangements and their influence on the particle size and shapes have been reported. General observations from these studies have been that the external shape of the resulting particles is relatively insensitive to process variables, and that the particle morphology depends more strongly on the properties of the polymer itself. For example, if the polymer is semicrystalline such as polyesters, particles are found to be spherical [46], and if molecules have stiff chains such as polyamides, fibrous forms are likely to be formed [37]. It remains a challenge to design for a specific particle shape and size in "any" targeted range for "every" type of polymer. Even though many forms of particles may be generated, finding their niche use areas presents another challenge. Therefore, the knowledge that is being generated is shifting more towards those applications where polymer particles that are produced have more clearly identifiable use areas, such as the case with pharmaceutical applications. In this respect, the more attractive polymers are the biopolymers. Particles of various biodegradable polymers have been produced for applications of drug delivery, or for use in agricultural and biological applications [8]. An important objective of the particle formation with biopolymers is to encapsulate a biologically active ingredient in the polymer matrix to be used for a controlled release of the compound to a targeted location. Two approaches are common, one is the formation of pure biopolymer particle which is then impregnated with the active ingredients, and the other is the coproduction of the polymer and other active ingredients. Many technical methods were developed to control the concentration of the active compounds inside the polymer particles. The variation of experimental conditions and contacting mechanism between supercritical fluids and liquid solutions that contain polymers and biologically active compounds result in different loading efficiencies in the polymer particles. The key challenge in these techniques is to successfully impregnate the active ingredient into polymeric matrix at a target concentration, or when coproduced, to overcome the segregated particle formation of the two components upon their coprecipitation.

The objective of the present review is to provide a critical account of the current state of formation of particles from polymers with a special focus on pharmaceutical applications. This is the first comprehensive review that is specifically devoted to particle formation from polymers. We first briefly describe the various supercritical particle formation technologies that have been developed, and then survey the previously published review articles on the supercritical particle formation processes that cover processing of not only polymers but also other organic and inorganic materials. Next, we present a review of the recent technical papers on polymer particle production with an emphasis on developments in the last 4 years. The review is presented in subsections according to the type of polymer particles generated, and the role of supercritical fluids in the experimental technology used. The review describes the recent advances made in the formation of particles from pure polymers, followed by coprocessing of polymers with non-polymeric materials. The focus is more on the practical applications, especially the pharmaceutical applications of this technology. Articles on chemical reaction-based particle formation such as particle formation in polymerization under supercritical conditions were excluded from the review. Even though the focus is on pharmaceutical applications of polymer particles, we hope that this review demonstrates the significant strides that are being made in the supercritical fluid-based particle formation technology for the downstream processing of polymer products in general.

2. Summary of supercritical particle formation methodologies

Twenty years of usage of supercritical fluids in the particle formation technology has given birth to a number of modified processes that use different nucleation and growth mechanisms of precipitating particles. These are summarized in Table 1 and are briefly described in the following sections.

2.1. Rapid expansion of supercritical solutions (RESS)

This process is used when the polymer has some degree of solubility in supercritical fluids. The polymer is dissolved in a supercritical fluid and this high-pressure solution is rapidly depressurized through an orifice to lead to polymer precipitation at a low pressure. The process is based on the solubility difference of the polymer in supercritical fluids at high and low pressures, respectively. The governing principle is pressure-induced phase separation as illustrated in Fig. 1. Along with the pressure quench, the solution experiences a temperature quench as well. Depending upon the process temperature, and the glass and/or the melting transition temperature of the polymer and the degree to which these transitions may have been lowered, and the path followed from the homogeneous one-phase region, the particle formation may come about from crossing the fluid–solid boundary (F–S), or the system may first undergo a liquid–liquid (L–L) phase separation followed by solidification.

2.2. Gas antisolvent process (GAS)

This process is devised to recrystallize solid compounds that are not soluble in supercritical fluids. The technique is especially suitable for polymers because majority of polymers are not soluble in supercritical fluids or gases. The polymer is first dissolved in a liquid organic solvent and a gas is employed as an antisolvent for the polymer. The gas is injected into the solution in a closed chamber and the particle precipitation occurs as the gas concentration in solution increases with pressure. In this process, the antisolvent gas does not have to be at supercritical condition. The governing principle

Table 1
Summary of the particle formation technologies using supercritical fluids

Process	Role of supercritical fluid	Role of organic solvent	Mode of phase separation
RESS	Solvent	Cosolvent	Pressure/temperature-induced
GAS	Antisolvent	Solvent	Solvent-induced
SAS	Antisolvent	Solvent	Solvent-induced
SEDS	Antisolvent/dispersing agent	Solvent/non-solvent	Solvent-induced
PGSS	Solute		Pressure/temperature/solvent-induced

is solvent-induced phase separation as illustrated in Fig. 2. Upon introduction of the antisolvent, the fluid–solid and the liquid–liquid phase boundaries are shifted to higher temperature or higher pressures, respectively. As a result, the system which was initially in the one-phase homogeneous region finds itself in the two-phase region upon which undergoes phase separation leading to particle formation. A significant difference between the GAS and the RESS processes is that in the RESS process one is dealing with a binary system of polymer + supercritical fluid, whereas in the GAS process, the system becomes a ternary system of polymer + organic solvent + antisolvent gas.

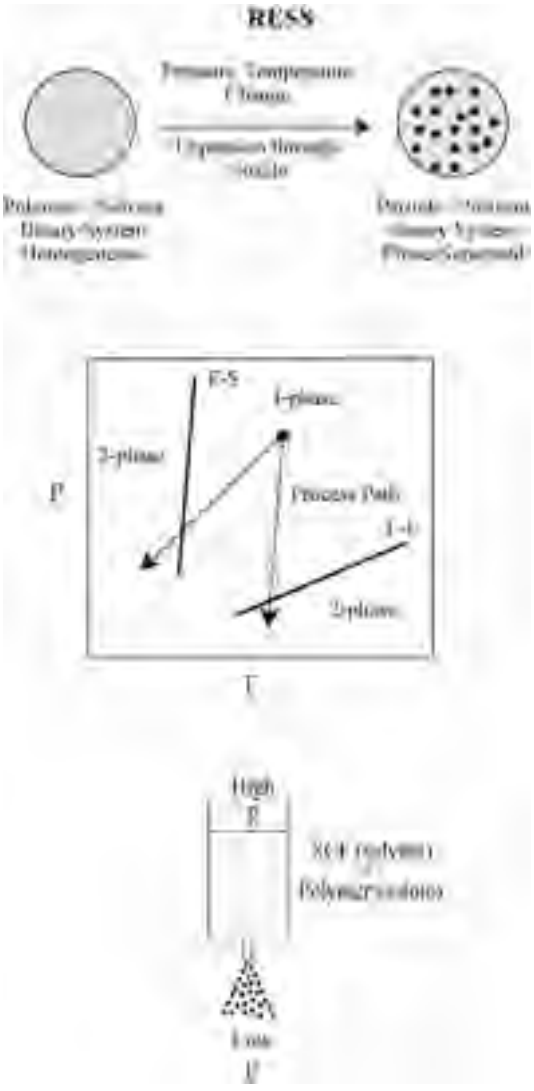

Fig. 1. Schematic representations of the RESS process and its operational principles. The process involves rapid expansion from supercritical solutions which is accompanied with a pressure and a temperature drop. This is demonstrated by the dotted lines representing the process pathways in the *P–T* projection. The process takes the system from a homogeneous solution into a phase-separated state, typically as a result of crossing the fluid–solid phase boundary (F–S). The possibility of crossing the liquid–liquid phase boundary (L–L) is also illustrated. The expansion is carried out through a nozzle. The nozzle diameter and length are among the factors that influence the particle size generated.

2.3. Supercritical antisolvent process (SAS)

This technique is also known as the aerosol solvent extraction system (ASES) or precipitation with a compressed antisolvent (PCA) process. In these techniques, a supercritical fluid acts as an antisolvent for polymer solutions as in the GAS process, but the contacting mechanism is different than that employed in the GAS process. Polymer is dissolved in a liquid solvent and the solution is sprayed into a chamber where a supercritical fluid (antisolvent) already exists, causing rapid contact between the two media. This generates higher supersaturation ratio of the solution, resulting in fast nucleation and growth, and consequently creates smaller particles. A special advantage of this technique is its adaptability for continuous operations, which is important for large-scale mass production of particles. The governing principle for this system is still the solvent-induced phase separation, or compositional quench as described in Fig. 2.

2.4. Solution enhanced dispersion by supercritical fluids (SEDS)

This process is a modified version of the SAS process in which the liquid solution and supercritical fluid are sprayed together using a specially designed coaxial nozzle. Two-channel and three-channel nozzles are used for the precipitation of single and binary compounds, respectively. Here, the supercritical fluid serves a multiple purpose in that it is used both as an antisolvent and as a dispersion medium. The spontaneous contact of high-speed streams of a liquid solution and a supercritical fluid generates the finely dispersed mixture and a prompt particle precipitation. Adoption of three processing media such as two different supercritical fluids and one organic solvent can create more versatile operating variables. Aqueous solutions can also be processed in this technique for forming particles from water-soluble compounds such as proteins and sugars. As in the GAS and SAS processes the

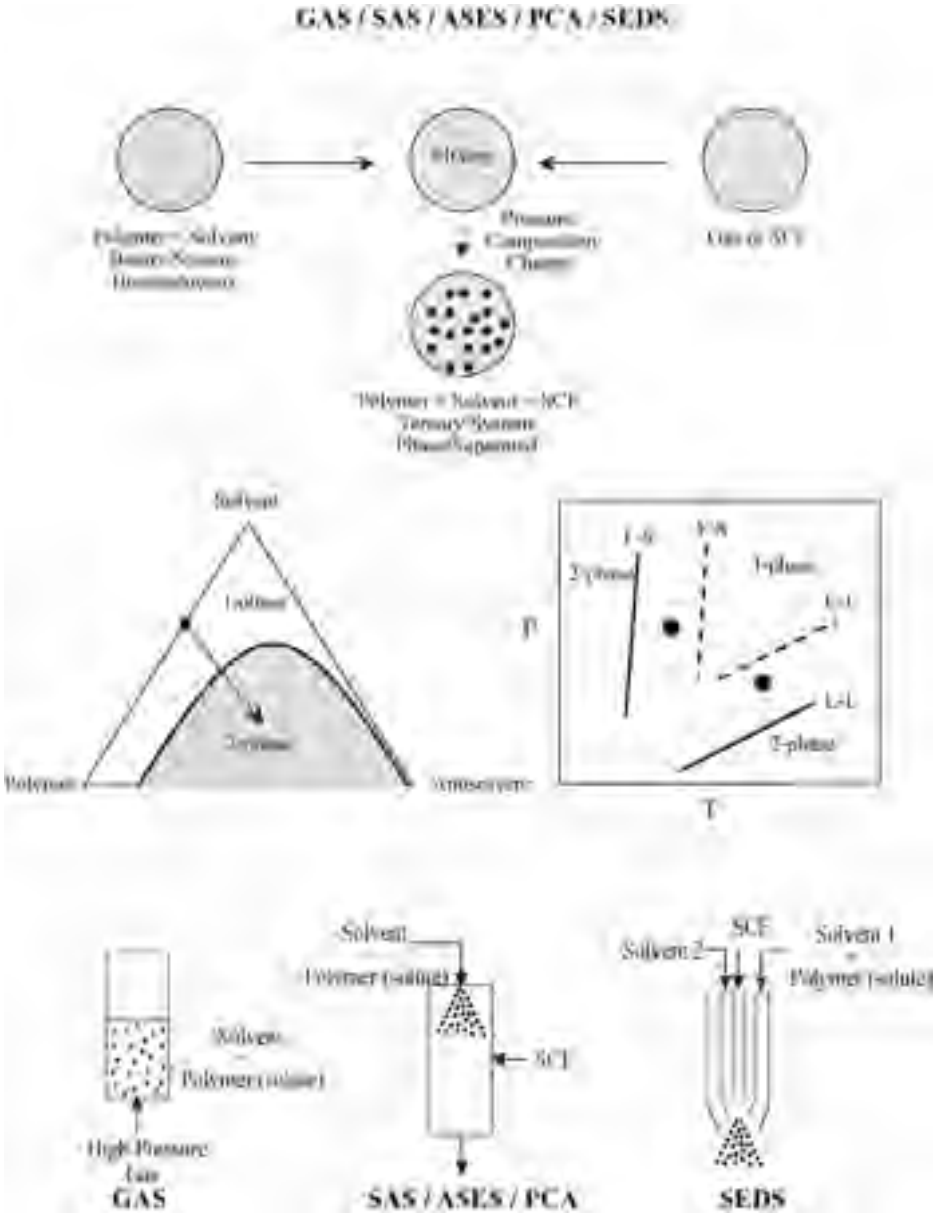

Fig. 2. Schematic representation of the GAS, SAS, ASES, PCA, and SEDS processes and their basic operational principles. These processes involve mixing a polymer solution with a gas or supercritical fluid that functions as an antisolvent. What is different in these processes with different acronyms is the mode of contacting the solution with the antisolvent which are illustrated in the lower part of the figure. From a thermodynamics standpoint, any one of these processes takes a homogeneous polymer solution into a phase-separated state along a process path like the dotted arrow shown in the ternary phase diagram. In a *P–T* projection the consequence of adding the antisolvent to the system is equivalent to moving the L–L boundary to higher pressures (solid line vs. dotted line), or the F–S boundary to higher temperatures, as a result of which a system which was initially in the homogeneous region (as illustrated with the filled circles) will find itself in a phase-separated, heterogeneous domain.

basic principle here is also solvent-induced phase separation. Particles are formed due to a compositional quench (Fig. 2).

2.5. Particles from gas-saturated solutions (PGSS)

This process is designed for making particles of materials that absorb supercritical fluids at high concentrations. Even though the running industrial applications may currently be mostly on non-polymeric materials, the technique has great promise and is highly suitable for polymer powder production, particularly for powder coating applications. A supercritical fluid is dissolved in the molten polymer or in liquid-suspended solutions, and the high-pressure mixture is rapidly depressurized through a nozzle leading to particle formation by precipitation. This process is found especially useful for the impregnation of active ingredients in polymer matrices. The governing principles involve both the pressure and temperature- and solvent-induced phase separation (Fig. 3).

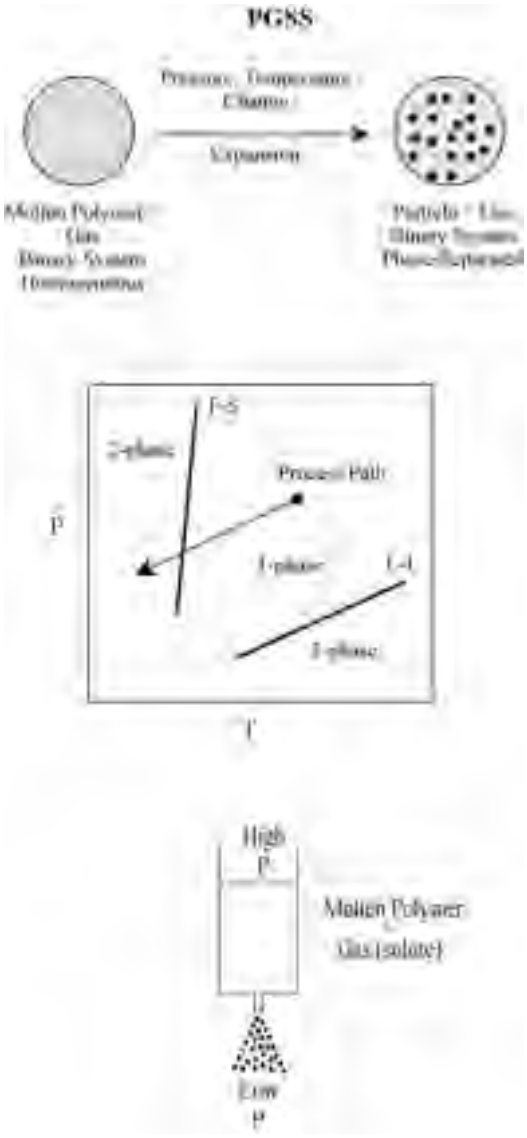

Fig. 3. Schematic representation of PGSS process and its basic operational principles. The process path involves a pressure and a temperature drop.

2.6. Particle formation via polymerization-induced phase separation (PIPS)

These processes lead to production of particles through synthesis in a supercritical fluid medium, such as polymerization (Fig. 4). The common methodologies are the precipitation, dispersion, or the emulsion polymerizations. In precipitation polymerization, the chains grow, and with sufficient increase in degree of polymerization, the miscibility conditions are altered upon which the system enters the two-phase regions that lead to particle formation. In dispersion polymerization, the system is heterogeneous and remains heterogeneous, while the stability is sustained by using specially designed surfactants. Emulsion polymerizations are also heterogeneous. In these polymerizations, the initiator, however, is preferentially dissolved in the continuous phase and not the monomer phase, and the monomer does not have high solubility in the continuous phase. Polymerization is a rapidly expanding field of application for supercritical fluids, however, as already indicated, polymerisation-induced particle formation has been excluded from the present review.

3. Previous review articles

Several review articles on supercritical fluid-based particle formation technology have been published during the past decade. These are listed in Table 2. These reviews have concentrated either on a particular experimental technique or on a specific type of material being processed. A survey of these earlier review articles is of value since their appearance, in some measure, correlates with the expansion of interest in the relevant technology within academic institutions and industry. They identify the trends, and also highlight the need for future research for solving the current problems. In this section, we provide an account of the key review papers on the supercritical particle formation technology that have been previously published.

The supercritical particle formation phenomenon has been known for a long time, but the first process that visibly introduced the term “supercritical” in its name is the RESS process that was developed in mid 1980s [13–16]. In 1991, Tom and Debenedetti [1] published the first review article on the RESS process. This article reviewed the fundamentals, experimental methods, and applications of the process and summarized the available results of the related studies conducted from 1984 to 1990. In this early period, materials that were processed by RESS included ceramics, organics, pharmaceuticals, and polymers. The supercritical fluids that were used to dissolve these materials included water, ethylene, ethanol, pentane, propane, ethylene, and carbon dioxide. Among these applications, the production of polymer particle was identified as an area where RESS offers a real promise for bringing about improvements over existing approaches. Investigations ranged from hydrocarbon-derived polymers (polypropylene, polystyrene, polyphenyl sulfone, and poly(methyl methacrylate) (PMMA)) to biodegradable polymers (poly(L-lactic acid) (L-PLA) and polycaprolactone (PCL)). From a fundamental perspective, in their review the authors also examined the theoretical developments to understand the underlying physical phenomena so that the process conditions can be effectively related to the end-product characteristics, and thus can be used for improvements for practical implementations. Two important points were addressed in this article; first, the authors noted that the RESS technique had considerable potential to combine particle size reduction and material blending in one processing step for production of loaded biopolymer microspheres. This realization has lead to the many developments in RESS and other supercritical particle formation technologies in the controlled release drug delivery applications in which composite materials of polymer and biolog-

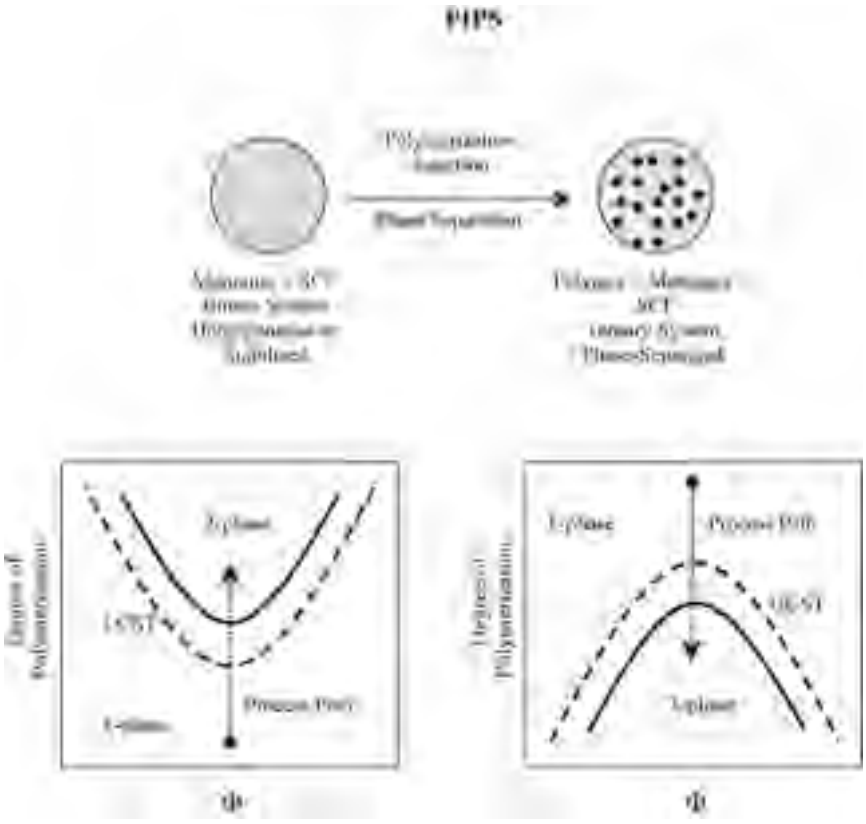

Fig. 4. Schematic representation of polymerization-induced phase separation and the related phase diagrams. This is a process in which, as a result of polymerization and chain growth, the system enters the two-phase region. An alternative way to look at the process is to link the phase separation process with lowering of the lower critical solution temperature (LCST) or increasing the upper critical solution temperature (UCST) with an increase in the degree of polymerization which takes the system into the phase-separated state with reaction time.

ically active compounds are involved. Second observation was the limited productivity with the RESS process, which is linked to the low solubility of materials in supercritical fluids, which led to the development of other methods that enable the mass production of particles. As a result, the research focus began to shift to processes such as GAS and SAS in which the supercritical fluids were used as antisolvents that are more suitable for mass production of particles.

In 1997, Subramaniam et al. [2] reviewed the particle formation technologies for pharmaceutical compounds that employ supercritical carbon dioxide. This review paper emphasized the use of environmentally benign media that can eliminate the concerns over trace residues of toxic organic solvents in pharmaceutical end-products. In addition, the disadvantages involved in conventional particle size reduction methods for drug compounds, such as excessive solvent use and problems with disposal, thermal and chemical degrada-

Table 2
Review articles on the supercritical particle formation processes

Review subject	Year	Corresponding author	Journal
RESS (general review)	1991	Debenedetti [1]	Journal of Aerosol Science
RESS, GAS, SAS (pharmaceutical processing)	1997	Subramaniam [2]	Journal of Pharmaceutical Science
GAS, SAS (general review)	1999	Reverchon [3]	Journal of Supercritical Fluids
RESS, SAS, SEDS, PGSS (phase behavior)	1999	York [4]	Pharmaceutical Research
RESS, GAS, PGSS (general review)	2000	Marr [5]	Chemical Engineering and Processing
RESS, SAS, SEDS (polymer processing)	2000	Cooper [6]	Journal of Materials Chemistry
RESS, SAS, SEDS, PGSS (general review)	2001	Perrut [7]	Journal of Supercritical Fluids
RESS, GAS, SAS (drug delivery system)	2001	Kompella [8]	Critical Review in Therapeutic Drug Carrier Systems
RESS, GAS, SAS, SEDS (pharmaceutical powders)	2001	Williams III [9]	Drug Development and Industrial Pharmacy
RESS, SAS, SEDS, PGSS (pharmaceutical application)	2001	Tan [10]	Expert Opinion on Therapeutic Patents
RESS, GAS, SAS, PGSS (drug delivery, polymer)	2002	Foster [11]	Australian Journal of Chemistry
RESS, SAS (nanomaterials)	2003	Wai [12]	Journal of Chemical Education

tion of products, and inter batch particle size variability were addressed. The particle formation technologies were classified as a process using carbon dioxide either as a solvent (RESS) or as an antisolvent (GAS/SAS). The basic principles and the major limitations associated with each process were described. The list of pharmaceutical compounds that have been processed by these techniques up to date were presented along with experimental conditions and the resulting particle size information, which included lovastatin, efrotomycin, imipenem, stigmasterol, and theophylline (drug compounds) and L-PLA, poly(glycolic acid), and poly(D,L-lactic acid) (polymers) by RESS process, and insulin, chlorpheniramine maleate, indomethacin, hycosine butylbromide, piroxicam, thymopentine, hydrocortisone, methylprednisolone acetate, salmeterol xinafoate, lysozyme, and trypsin (drug compounds) and L-poly(lactic acid), poly(glycolic acid), D,L-poly(lactic acid), and hyaluronic acid benzylic ester (polymers) by antisolvent processes.

In 1999, Reverchon [3] published a review article that focused on the particle precipitation processes in which the supercritical fluids were used as antisolvents. As already indicated, among the six supercritical processes mentioned, three processes (GAS, SAS, and SEDS) and some of the polymerisation-induced particle formation processes are based on the antisolvent properties of the fluid. In some ways, this implies that supercritical fluids are more applicable for the particle formation technology when they are employed as antisolvents rather than solvents. This review article covered the experimental techniques, the process mechanisms and the potential applications of the GAS and SAS processes. The effect of experimental variables such as the volume expansion rate, the injection mode of the antisolvent, the pressure and temperature conditions, and the chemical compositions of solvent and solute were fully discussed. The review includes particles from materials in quite different categories, such as explosives, high propellants, polymers, pharmaceuticals, pigments, catalysts, superconductors, and inorganic compounds. The processing ability of such a variety of solid compounds shows the high applicability of the antisolvent processes. The experimental conditions that might affect the morphology and size distribution of the particles were discussed. This review highlights the need for fundamental data on phase behavior and mass transfer as well as theoretical models that can be validated with reliable sets of experimental data for scale-up. Such fundamental information and modeling capability will take these processes to their next level, that is, commercialization.

Recognizing the importance of phase behavior, a review on the fluid phase behavior and its influences on the various supercritical particle formation processes was published by Palakodaty and York [4] in the same year. In this article, the basic principles of RESS, GAS, SAS, SEDS, and PGSS processes and the phase behavior of different systems encountered in particle formation processes pertaining to pharmaceutical applications have been reviewed. These systems may consist of mixtures of solutes, organic solvents and supercritical fluids, and their phase behavior is governed by the number of components in the system and their concentrations, and by the operational variables such as temperature and pressure. The paper highlights the importance of understanding the correct phase separation (precipitation) path leading to particle formation. A specific point is the consequence of the phase separation path on the porosity of the particles that are formed. Porosity is emphasized to be particularly important in impregnating a drug substance into the polymer matrix for controlled release applications. This review raises the awareness of the need for improved understanding of thermodynamics and fluid phase equilibria pertaining to these multicomponent systems that are encountered in particle formation for pharmaceutical applications.

The brief review by Marr and Gamse [5] published in 2000 focuses on the particle formation processes for the pharmaceuticals industry as well. One aspect that is brought to greater attention in this review is the need for producing particles with a narrow size distribution that is especially important for inhalation sprays.

Another review which appeared in 2000 by Cooper [6] is an extensive review on polymer synthesis and processing using supercritical carbon dioxide. The article covers all areas of polymerization and polymer processing that employs not only chemical but also physical phenomena in which supercritical fluids play an important role. Even though the polymer synthesis has been excluded from our current review, it is important to emphasize that as long as polymer compounds are concerned, polymerizations such as precipitation and dispersion polymerizations under supercritical conditions are important techniques to produce polymer particles. In this review, the author summarizes the existing technologies (RESS, SAS, and SEDS) and presents the types of polymers processed by supercritical carbon dioxide. Majority of works were focused on the particle formation of biodegradable polymers such as L-PLA, D,L-PLA, poly(glycolic acid) (PGA), D,L-poly(lactic acid-co-glycolic acid) (D,L-PLGA), and polysaccharides. In addition to the biopolymers, particles or fibers of other polymers such as polystyrene, aromatic polyamides, and PMMA were included. Various efforts that are being made to encapsulate various pharmaceutically active compounds inside biopolymer particles were reviewed. This review puts a special emphasis to impregnation of drugs and pigments in polymer particles, which is highlighted as the most promising application area of supercritical particle formation technology.

In 2001, Jung and Perrut [7] published an integrated review paper on the particle design using supercritical fluids. They thoroughly surveyed the related literature including the patent activity, and illustrated the existing particle formation processes suggesting a strategy on how to choose a proper process leading to the desired particles. The review provides extensive compilations of materials that have been processed, along with the techniques that were employed. The number of compound that appear in these lists include 11 polymers, 24 inorganic and organic materials, and 25 pharmaceutical

compounds where supercritical fluids were used as solvents. For the case where supercritical fluids were used as antisolvents, the authors have listed processing of 4 explosives, 14 polymers, 15 inorganic and organics, 39 pharmaceuticals, and 17 composite materials. In addition, this review includes examples where chemical reactions in supercritical media lead to particle formations such as the thermal decomposition of inorganic precursors. This review also points to the rapid developments in controlled delivery systems that resulted in intensified application of the particle formation technology in manufacturing of composite microspheres and microcapsules. The materials that have been embedded in microspheres include adhesives, agrochemicals, live cells, enzymes, flavors, fragrances, and pharmaceuticals. The review discusses particle coating technologies using supercritical fluids for these applications. Productions of the composite microspheres by the existing processes were reviewed, and formations of microcapsules using particle coating techniques were illustrated. A special value of this particular review article is that the authors point out the advantages and potential drawbacks of each technique that may be of value in selecting a process that may optimize the product quality.

The review papers mentioned earlier clearly identified that the particle formation from biopolymers, drugs, and their composites is the most significant and active application area of supercritical particle formation technology. Therefore, it should be no surprise that a number of investigators whose primary research is in pharmaceuticals have become engaged in supercritical fluid methodologies in recent years, and have published review articles in pharmaceutical journals. In 2001, Kompella and Koushik [8] reviewed the preparation of drug delivery systems using supercritical fluid technology. This review article focuses on the formulation of pure polymer particles, drug-containing polymer particles and plain drug particles. First they describe the conventional techniques for preparing drug and polymer composites and point out the associated disadvantages such as the wide size distribution of particles, and the use of large amounts of organic solvent and surfactants that is not conveniently removed. Drawbacks of the traditional size reduction techniques such as jet milling are also mentioned which include high internal temperature rise that can affect the stability, polymorphism, and degree of crystallinity of drug particles. The review provides tabulated lists of the type of polymers and drugs processed along with the description of experimental conditions and morphology of the resulting particles. The listed polymers included L-poly(lactic acid), poly(glycolic acid), D,L-poly(lactic acid), D,L-poly(lactic acid-co-glycolic acid), poly(methyl methacrylate), polycaprolactone, poly(β-hydroxybutyric acid) (PHB), polyacrylonitrile (PAN), polystyrene, and hyaluronic acid benzylic ester (HYAFF-11). The authors also reviewed the preparation of protein powders, solute-containing liposomes (spherical lipid-based vesicles consisted of layers enclosing an aqueous volume) and inclusion complexes of drug and carriers. The factors that influence the particle properties such as physical property of drugs, nucleation and growth rate, and characteristics of polymers, were analyzed. The operational parameters for RESS and antisolvent processes such as the pre-expansion temperature and pressure, nozzle geometry, density of antisolvent, and the flow rates of solute and antisolvent streams were also described. This review provides a critical assessment of issues that are yet to be fully investigated and notes that: (a) although supercritical technology appears to offer the advantages for particle engineering, it is unlikely to be an option for processing all pharmaceutical compounds, (b) supercritical technology is unlikely to fully replace conventional methods because it has not completely eliminated the use of organic solvents, and (c) to be commercially viable, particles should be produced in a large scale with desired product characteristics and consistency.

Rogers et al. [9] published a review article in 2001 on solution-based particle formation of pharmaceutical powders by supercritical carbon dioxide and cryogenic spray-freezing technologies which appeared in a pharmaceutical journal. This paper emphasized the supercritical technology as a new micronization method that can overcome the disadvantages associated with high temperature spray-drying and milling which cannot be used to process thermolabile or physically unstable drug substances. They however indicate that the low product yields is a major drawback of supercritical particle formation technology, suggesting the cryogenic micronization process as an alternative. Tan and Borsadia [10] reviewed the processes for particle formation using supercritical fluids with respect to pharmaceutical applications. The supercritical fluid-based particle formation technology is presented as an alternative to possibly overcome the common limitation of conventional particle formation methods with respect to particle size and morphology control, polymorphic purity, batch consistency, and regulatory compliance. Potential applications areas that were suggested include size reduction of drug particles, encapsulation of proteins, peptides and vaccines, targeted delivery of biologicals, and metered dose and dry powder inhaler applications. From the pharmaceutical point of view, the emerging supercritical processes were classified according to the characteristics of the active substances and excipients as: (a) carbon dioxide soluble, (b) organic solvent soluble, (c) water soluble, and (d) carbon dioxide dispersible. Illustrative descriptions of each process were provided, and related patents were also reviewed.

Stanton et al. [11] reviewed how to improve the drug delivery using polymers and supercritical fluid technology. They focused on the application for polymers in pharmaceutical industry and illustrated the so-called dense gas techniques for micronization, coprecipitation, impregnation, and encapsulation, in order to overcome the problems encountered with conventional processing methods. The article shows the experimental concepts of each process and briefly reviews papers on particle formation from polymers along with polymer/drug composites. Recently, Ye and Wai [12] published an article on making nanomaterials in supercritical fluids. They summarized physical as well as chemical processes for

preparing nanoparticles, nanowires, and thin solid films using supercritical fluids. RESS and SAS processes were illustrated as the key physical technologies for these applications, and the other modified processes such as chemical RESS method (RESS combined with chemical reaction), microemulsion reaction, and physical and chemical deposition processes were described.

In summary, the particle formation processes have evolved in the sequence from RESS, to GAS, SAS, SEDS, and PGSS, and many incorporated modifications to these basic processes such as chemical reactions. For particle production, supercritical fluids have been used as solvents (RESS), as antisolvents (GAS, SAS, and SEDS), and as solutes (PGSS). In the earlier years, the processed materials covered a wide variety of inorganic and organic compounds, but in later years the focus has gradually moved to pharmaceutically important polymers and drug compounds. The frequent appearance of the recent review papers in the pharmaceutical journals reflects these trends. The supercritical fluid-based processes are being filtered through the criticism of pharmaceutical scientists, who are evaluating the possibilities for replacing the conventional particle formation methods in pharmaceutical area. Even though the supercritical fluid technology may not be an answer for processing of all drug compounds, it provides new opportunities. The increasing interest in using supercritical fluid technology in producing nanosize materials is also paving the road for supercritical nanotechnology.

4. Formation of particles from pure polymers

The small size particles of a pure polymer find use in chromatographic applications, as solid adsorbents, as standards for particle sizers and counters, as catalytic support materials, and in other applications where uniformly distributed polymer microparticles are needed. Production of micro- or nanoparticles of polymers using supercritical technology is especially attractive for providing alternative solutions to various problems encountered in traditional techniques. For example, the inherent plasticity of polymers often prohibits producing particles with a uniform size distribution by mechanical size reduction methods such as milling. The polymer's high affinity to organic solvents and difficulty of complete removal of residual solvents from the end-product is a concern with particle formation processes that are based on solvent evaporation. In pharmaceutical applications, there are stringent requirements as to the type of solvents that can be used and the allowable level of residual solvent. The low solubility of polymers in supercritical fluids provides suitable conditions to employ these fluids as an antisolvent. Even in the case where polymer has some degree of solubility in the fluid, the limited mutual solubility between polymers and supercritical fluids accelerates the complete separation of supercritical solvents and polymers upon pressure reduction.

As already noted, there is an increasing demand for biopolymer particles in drug delivery application and the feasibility for producing drug-loaded polymer particles. For these applications, particle formation from pure polymers is a crucial step and forms a base for further preparation of the drug-loaded polymer composite particles. In the following sections we present a review of the recent literature on particle formation from pure polymers where supercritical fluids are used as solvents and as antisolvents.

4.1. Polymer particle formation using supercritical fluids used as solvents

The RESS process was the first supercritical process to produce polymer particles in which the supercritical fluid was employed as a solvent. The early studies reported on formation of particles from hydrocarbon-based polymers such as polypropylene [13,14], polystyrene [15], polyphenyl sulfone [16], and PMMA [14] using propylene, pentane, and propane as supercritical fluids which have high solvating power for these polymers. A concern with these early studies has been the use of the flammable solvents, and therefore the focus has continually moved to the processing of polymers that dissolve in non-flammable supercritical fluids such as carbon dioxide. In 1990s, biopolymers such as lactic acid-based polymers (L-PLA, D,L-PLA) [17,18], polysaccharide (HYAFF-11) [19], and PGA [20] were processed using carbon dioxide, and PCL [21] was processed using chlorodifluoromethane as a solvent. The solubilities of these compounds in carbon dioxide were often enhanced by adopting cosolvents such as acetone and ethanol.

In 2000s, the interest in application of RESS process for polymers shifted to coatings. Coating is a form of particle formation in which the particles precipitates onto a solid surface and then adhere as a thin deposition. Coating is an area where low productivity with the RESS process for producing particles for mass production arising from the low solubility of polymers in supercritical fluids is not such a drawback. Indeed, the formation of thin layers of polymer coating does not require large quantities of particles. For coating applications, the traditional volatile organic solvents are not completely replaced, but their amounts are reduced with carbon dioxide, thereby reducing the negative impact on the environment [23].

Carbon dioxide-soluble polymers such as siloxanes and fluoropolymers have received special attention for exploration of coating applications through the RESS process, some of which aimed at novel applications. For example, Tepper and Levit [24a] have reported on depositing poly(dimethylsiloxane) films onto a sensing surface of a microfabricated transducer using supercritical carbon dioxide as the solvent. These transducers are aimed at developing chemical sensors such as surface acoustic wave (SAW) devices, for which uniform thin deposition of the polymer layer is critical. Fulton et al. have reported on coating of complex geometries such as cardiovascular stents with fluoroacrylate polymers that are soluble in carbon dioxide using an electrostatic RESS technique [24b]. Chernyak et al. [25] reported

on the production of droplets of perfluoropolyether diamide from carbon dioxide solutions for coating of porous materials encountered in monumental and civil infrastructures. The effects of polymer concentration, pre-expansion temperature and pressure, and the nozzle geometry (length and diameter of capillary) on the spray characteristics and droplet size distributions were examined. Glebov et al. [26] investigated the coating of fused silica substrates and aluminum and magnesium powders by poly(vinylidene fluoride) and poly(4-vinylbiphenyl) using carbon dioxide. The polymers were initially dissolved in carbon dioxide at high temperature and precipitated onto metal particles upon cooling and subsequent depressurization. The thickness of polymer films was evaluated using UV absorption spectroscopy revealing an average thickness in the range 1–30 nm. Henon et al. [27] coated surfaces of porous marble, sandstone, and limestone samples with perfluorinated polyethers. The diffusivity of water vapor through coated stones was measured, and the penetration depths of the polymers and the percentages of blockage of the pores were estimated.

Low-molecular-weight polymers such as paraffin wax materials which have reasonably high solubility in supercritical carbon dioxide have also been popular for explorations with coating experiments using RESS. The homogeneous solutions of paraffins in carbon dioxide were sprayed into a fluidized bed, previously loaded with silica particles and glass beads, in order to achieve an even distribution of the coating material onto the solid particles. Depending on the experimental conditions, the coating layer thickness in the range 40–4000 nm have been reported [28,29].

In addition to the coating applications, particles and fibers of a fluoropolymer (poly(heptadecafluorodecyl acrylate) were produced by the RESS process using pure carbon dioxide as a solvent to investigate the effect of the polymer concentration and the degree of saturation on particle size and morphology [30].

The RESS processing of carbon dioxide-insoluble polymers was made possible by adopting three different modifications, i.e. the use of organic cosolvents to increase solubility, the formation of polymer dispersion in carbon dioxide using a stabilizer, and the use of organic solvents as supercritical fluids. Matsuyama et al. [31] used ethanol as a cosolvent (up to 30% ethanol in carbon dioxide by weight) to dissolve polystyrene-b-(poly(methyl methacrylate)-co-poly(glycidyl methacrylate)), polyethylene glycol, bisphenol epoxy resin, PMMA, and poly(oxyalkylene) alkylphenyl ether in carbon dioxide, and the mixtures were rapidly expanded to form microspheres. The cosolvency effect was utilized, that is the solubility of polymer is extremely low in either carbon dioxide or ethanol but becomes higher in a mixture of the two. Because ethanol is non-solvent for the polymers, dry powders of polymer could be obtained upon precipitation from the supercritical mixtures. Wang et al. [32] used a modified RESS process for coating of glass beads with poly(vinyl chloride-co-vinyl acetate) and hydroxypropyl cellulose using carbon dioxide with acetone as a cosolvent. In this study, the pressure and temperature of post-expansion stream (instead of pre-expansion stream) were regulated to control the resulting morphology. Shim and Johnston [33] synthesized poly(2-ethylhexyl acrylate) suspension in carbon dioxide using a siloxane-based surfactant as a stabilizer. The high-pressure mixture was rapidly expanded into water containing a hydrophilic surfactant to form stable aqueous latexes, which can be used for coatings and adhesives. Han et al. [34] used propane as a supercritical fluid to dissolve both isotactic polypropylene and ethylene–butene copolymers. The RESS process of the binary mixtures produced the blend of the two polymers with the resulting morphology of microfibers and a trace of microparticles. It was revealed that the phase domain size of ethylene–butene copolymer in the blends decreased as the content of ethyl branches in the copolymer increased. Blasig and Thies [35a] produced particles and fibers of cellulose triacetate, a semicrystalline polymer, using ethyl acetate as a supercritical solvent. The effects of polymer concentration and degree of saturation on particle size and morphology were examined. There is the possibility to replace the harmful solvents such as methylene chloride used in the traditional spinning process.

These studies are summarized in Table 3. The interest in the RESS process using supercritical fluids as solvents for the polymers will clearly continue with pharmaceutical applications with a desire to produce well defined microspheres of biopolymers, and with a desire to make polymer processing operations for particle formation, coating and spinning more environmentally friendly by reducing or replacing the use of harmful traditional solvents with environmentally benign fluids such as carbon dioxide.

4.2. Polymer particle formation using supercritical fluids as antisolvents

As long as carbon dioxide is the fluid of choice, more polymers can be processed by using carbon dioxide as an antisolvent rather than using it as a solvent, because most of the polymers have very limited or nearly zero solubility in carbon dioxide. Moreover, the relatively high solubility of polymers in ordinary liquid organic solvents may provide ideal conditions to employ both the organic solvents and supercritical fluids as solvents and as antisolvents, respectively. The key factor for the supercritical antisolvent process is the selection of a proper combination of an organic solvent and supercritical fluid for a particular polymer component. A large number of fluid mixtures have been investigated with respect to their volume expansion characteristics in relation to the gas antisolvent processes [35b]. The organic solvent should have a reasonable solubility towards the polymer and also have to show high mutual solubility with supercritical fluid under moderate operating pressure and temperature. In fact, most of the organic solvents used to dissolve a particular polymer show high mutual solubility or complete miscibility with carbon dioxide in the near- and supercritical region. This is the primary reason why the variety of antisolvent processes has

Table 3
Particle formation from pure polymers using supercritical fluids as solvents (RESS) during 2000–2003

Polymer	Solvent/cosolvent	Year	Reference
Poly(dimethylsiloxane)	CO_2	2000	[24]
Perfluoropolyether diamide	CO_2	2001	[25]
Poly(vinylidene fluoride), poly(4-vinylbiphenyl)	CO_2	2001	[26]
Perfluorinated polyether	CO_2	2002	[27]
Poly(heptadecafluorodecyl acrylate)	CO_2	2002	[30]
Polystyrene-b-PMMA-co-poly(glycidyl methacrylate), polyethylene glycol, bisphenol epoxy resin, PMMA	CO_2/ethanol	2001	[31]
Poly(oxyalkylene)-alkylphenyl ether			
Poly(vinyl chloride-co-vinyl acetate), hydroxypropyl cellulose	CO_2/acetone	2002	[32]
Poly(2-ethylhexyl acrylate)	CO_2	2002	[33]
Polypropylene, ethylene–butene copolymers	Propane	2000	[34]
Cellulose triacetate	Ethyl acetate	2003	[35a]

been developed in polymer processing area. Regardless of the type of antisolvent process, it is essential to understand the phase behavior of the ternary mixtures that contain polymer, solvent, and antisolvent, to locate the phase separation boundary and hence to determine the correct operating conditions for the polymer precipitation. Upon understanding these fundamentals, the antisolvent process could be conducted by contacting the polymer solution and antisolvent in order to achieve the particle formation.

Investigations conducted in the initial stage of early- to mid-1990s explored the possibility of particle formation of polymers in different categories such as amorphous polymer (polystyrene [36]), rigid-chain crystalline polymer (aromatic polyamide [37]), semicrystalline polymer (polyacrylonitrile [38]), and biopolymers (L-PLA, D,L-PLA, PLGA [39,40]). Organic solvents used for these polymers include toluene, dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), and methylene chloride. Carbon dioxide was employed as an antisolvent in all of these experiments. The earlier studies did not aim to manufacture polymer particles or fibers in any desired size and morphology. The researchers rather focused on the phenomenological observations pertaining to these novel processes. Different mixing methods for the polymer solution and antisolvent were explored, and the effects of adjustable experimental variables were investigated. It was found that the morphology and dimension of the produced polymer particles were controllable by changing the flow configurations and process variables such as temperature, pressure, flow rates, and polymer concentration. A commonly observed problem was the particle agglomeration which might be caused by the decreased glass transition temperature of polymer due to the addition of carbon dioxide. Overall observation of these studies revealed that particle morphology strongly depends on the inherent characteristics of polymer molecules. For example, the semicrystalline polymers tend to form spherical shape while highly crystalline polymers likely produce fibrous or spherulitic morphologies [37]. Moreover, molecular weight of the polymers, which governs the chain dimension of the molecules, also affect the resulting morphology. The valuable outcome of these studies have been that many of the investigated biodegradable polymers could be produced in spherically shaped particles with a reasonable size and size distributions, which could ultimately be used as carriers of other biologically or chemically active ingredients. These results motivated the research on antisolvent processes conducted from the late 1990s to be concentrated on particle formation of industrially significant biopolymers [41]. Furthermore, it has been recognized that even if both the RESS and antisolvent processes could be used to produce particles of the same type of biopolymers such as lactic acid-based polymers [17,39], the antisolvent processes may be more promising in terms of high product yield and diversity of process variables.

In 2000s, the major effort in the supercritical antisolvent processes has been in producing biodegradable polymer particles. Reverchon et al. [42] used the SAS process to produce particles of natural biopolymers such as dextran and inulin together with poly(hydroxypropylmethacrylamide) (HPMA) and the other polymers such as L-PLA [43] of biological significance. DMSO and methylene chloride were used as organic solvents for these polymers. Overall, spherical microparticles of the biopolymers were consistently obtained. The study emphasized that even though there is an effect of the experimental variables such as concentration, pressure, and temperature on particle size and morphology, the primary factors influencing the outcome are the properties of the specific polymers being processed. Sarkari et al. [44] generated L-PLA particles using not only carbon dioxide but also carbon dioxide-philic fluorinated liquids (HFE-7100 (3M specialty fluid)), vertrel (decafluoropentane), and traditional organic liquids (ethanol and hexane) as antisolvents in SAS process. The liquid antisolvents were selected by considering the solvent polarity. The solutions of L-PLA in methylene chloride were sprayed through a nozzle into carbon dioxide at high pressure as well as into the liquid antisolvents at atmospheric pressure. The kinetic studies on the spray processes in the various types of antisolvents revealed that the turbulent mixing caused by the spraying, not solution atomization caused by nozzle, dominated the particle formation mechanism. This result reflects the relative insensitivity of particle size to the spraying conditions. In addition, the use of carbon dioxide-philic liquid antisolvents offers an alternative to supercritical

fluids that may be developed as a non-pressurized particle formation process. Elvassore et al. [45] used GAS and SAS processes to obtain various morphologies of several types of hyaluronic acid ester biopolymers (HYAFF-11, HYAFF-7, and HYAFF-302) employing DMSO as a solvent. Threads and fibrous morphologies were obtained by injecting polymer solutions into the continuous carbon dioxide phase (SAS), and the sponges and particles were produced by introducing carbon dioxide into bulk polymer solutions (GAS). This study highlights the important effect of contacting mechanism between polymer solution and antisolvent on the resulting polymer morphology. In GAS process, where the carbon dioxide is injected into the bulk of polymer solution, systems with the polymer concentrations higher than the chain overlap threshold value result in sponges, while systems with low polymer concentrations lead to microparticles. In SAS process, the continuously injected polymer solution forms a laminar jet inside the carbon dioxide phase inducing the shear force between the stream of polymer solution and the stationary carbon dioxide phase. The prompt polymer precipitated under the influence of the shear force tended to form fibers or threads.

Breitenbach et al. [46] reported on the relationship between the morphology of SAS processed biopolymers and their physical properties. This is an important study in that unlike the earlier studies that have focused on either modifying the flowing modes of the polymer solution and the antisolvent, or on changing the experimental conditions in order to achieve a target morphology (mostly microspheres) of existing biopolymers, this study concentrated on modifying the chemical and physical properties of biopolymers in order to obtain the spherically shaped microparticles precipitated in a given antisolvent process. The linear polyesters (L-PLA and D,L-PLA) and branched polyesters prepared with a poly(vinyl alcohol) (PVA) such as PVA–D,L-PLA, PVA–D,L-PLGA, PVA–L-PLA, and PVA–D,L-PLGA were synthesized and subjected to the SAS process. It was found that the high degree of polymer crystallinity was the key factor for successful microsphere formation. In relation to this work, Shekunov et al. [47] investigated the structural change and plasticization effect of L-PLA particles produced by carbon dioxide in SEDS process, with the aim of understanding the mechanism of precipitation and particle agglomeration. The tendency of the biopolymer particles to form agglomerates was explained by a combination of a kinetic mechanism during nucleation and a slower process of structural changes occurred after the nucleation. In order to avoid the agglomeration, it was suggested to optimize the process conditions such as nucleation rate, solution viscosity and quality of the solvent for polymer. Pérez et al. [48] also attempted to solve the agglomeration problem occurred in conventional SAS process by using a T-mixer type spraying device. Dextran was precipitated from DMSO solutions and the particle size was manipulated from several nanometers to tenths of microns. The mixing device was based on the finding that the formation of droplets in SAS operation is not due to the atomization of DMSO solution but rather to the formation of a new polymer-rich liquid phase when the solution and carbon dioxide get in contact. The spherical morphology of particles was explained by the formation of droplets of polymer solutions in the continuous antisolvent phase.

Efforts have been extended to understand the hydrodynamics and kinetics and their influence on the particle formation of biopolymers. Carretier et al. [49] investigated the mixing behavior of sprayed L-PLA solutions in methylene chloride and carbon dioxide in SAS process. The precipitation vessel was considered as a well-mixed reactor auto-agitated by the sprayed liquid phase, and the residence time distribution of the polymer solution in the vessel was experimentally measured. It was found that the particle morphology changed from fibrous to spherical as the liquid flow rate increased. The direct visualization of the spraying process, correlated with the particle morphology, allowed for an estimation of the L-PLA precipitation time, which turned out to be in the order of few milliseconds. Elvassore et al. [50] investigated the particle formation kinetics by measuring UV absorbance of precipitating L-PLA particles in GAS process. The technique monitors the attenuation of light due to the scattering of the suspended particles at different carbon dioxide injection rates. The precipitation kinetics was rationalized by developing a population balance model considering particle nucleation, growth, aggregation, and settling, and the kinetic parameters were estimated based on the spectroscopic data. The model was used to predict the particle size distribution which was strongly affected by the aggregation mechanism. Owens et al. [51] studied the particle formation mechanism of diacrylated polyethylene glycol in a process that combines the principles of SAS and photopolymerization processes. A solution containing the solvent, a monomer, and a photo-initiator was sprayed into carbon dioxide while simultaneously illuminating the precipitation chamber with UV light. The particle formation occurred under the action of both antisolvent precipitation and polymerization. The analysis on the particle size distribution and the calculation of nucleation and growth rate revealed that the particle formation mechanism was dominated by the phase behavior of the solvent, antisolvent and monomer ternary system.

In addition to biopolymers, some difficult-to-process polymers were also investigated to explore the possible use of the supercritical antisolvent processes as an alternative to conventional methods. Li et al. [52] explored the particle formation from poly(ethylene terephthalate) (PET) using phenol as a solvent in a GAS process. Different size particles were obtained by changing experimental conditions, and the morphological variations were attributed to the phase behavior of carbon dioxide–phenol–PET ternary systems. Park et al. [53] generated the particles of Nylon 66 using formic acid as a solvent in a SAS process. Spherical particles were consistently obtained without any significant effects of the operating conditions. Hsu et al. [54] used SAS process to produce particles of cycloolefin copolymers employing toluene and HFC-134a as a solvent and as an antisolvent, respectively. Microspheres

Table 4
Particle formation from pure polymers using supercritical fluids as antisolvents (GAS/SAS/SEDS) during 2000–2003

Polymer	Process	Solvent/antisolvent	Year	Reference
L-PLA	SAS	Methylene chloride/CO_2	2002	[43]
L-PLA	SAS	Methylene chloride, chloroform/CO_2	2000	[44]
HYAFF	GAS, SAS	DMSO/CO_2	2001	[45]
D,L-PLA, PVA	SAS	Methylene chloride/CO_2	2000	[46]
L-PLA	SEDS	Methylene chloride/CO_2	2003	[47]
Dextran, inulin, HPMA	SAS	DMSO, methylene chloride/CO_2	2003	[48]
L-PLA	SAS	Methylene chloride/CO_2, ethanol	2003	[49]
L-PLA	GAS	Methylene chloride/CO_2	2003	[50]
Diacrylated polyethylene glycol	SAS	Methylene chloride/CO_2	2003	[51]
Poly(ethylene terephthalate)	GAS	Phenol/CO_2	2000	[52]
Nylon 66	SAS	Formic acid/CO_2	2002	[53]
Cycloolefin copolymers	SAS	Toluene/HFC-134a	2002	[54]

and fibers were generated depending on the polymer concentrations, and the morphology variation was explained by the different precipitation mechanisms. The microspheres were obtained in the low polymer concentration range where the nucleation and growth mechanisms occurred, while the fibers were produced at high polymer concentrations which induced the spinodal decomposition.

These recent studies are summarized in Table 4. They demonstrate that with appropriate modifications, the antisolvent processes can be effectively utilized in formation of particles from a range of polymers. Majority of the effort appears to be once again on biopolymers for pharmaceutical applications. There is an acceleration of investigations for deeper understanding of the particle formation mechanism, and the influence of factors such as the hydrodynamics of mixing, particle precipitation kinetics, phase separation path, and clearly the influence of polymer properties on the end-morphology. Some advances have been made to address the chronic problems such as particle agglomeration. There is a need for improved understanding of the fundamentals related to mixing (contact between polymer solution and antisolvent) and demixing (precipitation of solid phase from fluid mixtures) processes. There is a greater awareness of the importance of understanding the thermodynamics and kinetics of these mixing and demixing phenomena before making an attempt to modify the operational variables such as flow configurations and to design the contacting device for the polymer solutions and supercritical antisolvents.

5. Formation of polymer particles containing active ingredients

The successful production of microspheres of pure biopolymers has fueled the interest in generation of polymer particles containing active ingredients that can be used for controlled release applications. Additives such as pharmaceuticals, cosmetics, and agricultural chemicals can be incorporated into the biopolymer particles in order to achieve the delivery of these active ingredients to a targeted location in a controlled manner either by a diffusional process or by degradation of the host biopolymers. The supercritical fluid-based particle formation techniques used for the production of composite polymer microspheres employ either coprecipitation, or particle coating as the basic methodology. In the coprecipitation process, both the polymer and other ingredients are precipitated together from their solutions. These are complex systems that may display multiple phases upon phase separation. For example, if a biopolymer and a drug compound are precipitated together from a homogeneous solution, depending upon the conditions that are employed, one may encounter the following possibilities: (a) a pure polymer and a pure drug phase can separately form, and (b) a drug-containing polymer (polymer-rich) and a polymer-containing drug (polymer-lean) phase can form. If there is absolutely no affinity between the polymer and the active chemical compound (i.e. drug molecule), it is likely that they will undergo independent precipitation. If the nucleation and growth of the polymer particles take place first followed by that of the drug compound, there is very little chance to form drug-containing polymer particles. The preferred goal is to produce the drug-containing polymer phase. In the particle coating process, on the other hand, polymer microcapsules instead of composite particles are generated. Pure polymer is precipitated from the solution onto the pre-existing non-polymeric particle surface to form a thin coating film. Depending on the solubility of the coating agent (polymer) in supercritical fluids, the RESS process or one of the antisolvent processes is implemented.

5.1. Formation of polymer particles containing active ingredients using supercritical fluids as solvents

The typical coprecipitation of polymer and active ingredient can be achieved in RESS process when both components are soluble in a supercritical fluid. RESS process might be the most recommendable process that brings about a simultaneous size reduction and impregnation without the worry over residual organic solvent. However, the application is limited because it is not easy to achieve reasonable solubilities for both compounds in a single supercritical fluid at a given experimental condition. Therefore, the RESS process is often carried out in a modified way in which a polymer solution

in supercritical fluid that contains a suspension of the active ingredient microparticles is rapidly expanded. In coprecipitation by RESS, it is very difficult, if not impossible, to control over the degree of incorporation, i.e. concentration of the active ingredient in polymer phase. In this extremely rapid particle forming process, a very rigorous manipulation of experimental conditions such as sequence of supersaturation of the two compounds becomes essential to minimize the formation of unwanted solid phases (pure solids and polymer-lean phases).

The pharmaceutical compounds have been the most widely studied active ingredients in RESS coprecipitation experiments. The earliest studies in 1990s explored the coprecipitation of biopolymer/drug pairs such as D,L-PLA/lovastatin [18] and L-PLA/naproxen [55]. In these studies, the polymer and drug binaries were dissolved in carbon dioxide together and expanded to atmospheric pressure. Analysis of the produced particles showed that depending upon the experimental conditions spherical polymer particles with embedded drug ingredients were generated along with some pure polymer or drug particles. As already noted, due to difficulties with traditional RESS approach in producing uniformly coprecipitated particles, the particle coating approach has been the more active area of research. This technique is especially useful when the active ingredients (typically proteins) are absolutely insoluble in carbon dioxide. In this respect, Mishima et al. [56] conducted RESS experiments to produce biopolymer microparticles containing proteins by using particle coating method. A suspension of proteins (lysozyme and lipase) in carbon dioxide that contains a cosolvent (alcohols) and a dissolved polymer (polyethylene glycols, PMMA, L-PLA, and D,L-PLGA) was sprayed to atmospheric pressure, resulting in polymer coated protein microcapsules. The study takes advantage of the solubility difference of protein (insoluble) and polymer (soluble) in carbon dioxide and cosolvent mixtures. The polymer coating thickness was controlled by changing the feed compositions. This technique was also used to encapsulate medical compounds (*p*-actamidophenol, acetylsalicylic acid, 1,3-dimethylxanthine, flavone, and 3-hydroxyflavone) in biopolymers [57a]. In a recent study, Türk et al. describe simultaneous coprecipitation of β-sitosterol/Eudragit (an ethyl acrylate–methyl methacrylate copolymer) by RESS process which lead to finely divided particles with less than 500 nm in diameter [57b].

Other than polymers, coating materials that have high solubility in carbon dioxide, such as lipids, were effectively processed by using supercritical solvents. Dos Santos et al. [58] produced protein (bovine serum albumin) microparticles coated with commercially available lipids (trimyristin and a mixture of glycerides and fatty acid esters). The lipids were dissolved in carbon dioxide in the presence of suspended protein particles using a closed vessel equipped with an impeller. Upon reduction of pressure and temperature, the lipid precipitated from the supercritical solution and formed coating films on the surface of protein particles. The coated protein particles were characterized with respect to their morphology, protein content and in vitro release profile. It was shown that the protein did not undergo any degradation after the carbon dioxide treatment under supercritical conditions.

The major limitation to coprecipitation method (low solubilities of multiple components in carbon dioxide) could be overcome by employing organic supercritical solvents. Pestov et al. [59] conducted RESS coprecipitation experiments using chlorodifluoromethane as a supercritical fluid. A fluorescent sensor material (2,5-distyrylpyrazine (DSP)) was dissolved with either diethyl *p*-phenylenediacrylate (EPA) or fluorinated polyacrylate (FAA), and sprayed to atmospheric pressure to induce the coprecipitation of the binary materials. Nanospheres of DSP–FAA or DSP–EPA composites were generated.

Besides the coprecipitation and particle coating methods, drug-loaded polymer particles could also be generated by impregnating drug materials into polymer matrix. Cristini et al. [60] produced microcomposites of ibuprofen in the particles of α-lactose and β-cyclodextrin by using RESS impregnation technique. The carbon dioxide solution containing dissolved ibuprofen was sprayed into a stirred vessel, at atmospheric pressure, where a known amount of the biopolymer particles was previously introduced. The precipitation of ibuprofen in the presence of polymer particles with the vigorous agitation allowed the impregnation of drug into the polymer. The dissolution rate of impregnated ibuprofen in the composite particles was found to be enhanced compared to plain drug particles. This improvement was attributed to a reduction of surface tension of drug resulting from impregnation.

In summary, coprecipitation, particle coating, and impregnation methods, employing supercritical fluids as solvents, have been used to produce polymer particles loaded with active ingredients. These recent studies discussed earlier are summarized in Table 5. The supercritical carbon dioxide-based solutions with extremely low concentrations of polymers or drug compounds may find special applications in generating thin polymer films loaded with active ingredients and this aspect of RESS will likely be investigated further in the coming years.

5.2. Formation of polymer particles containing active ingredients using supercritical fluids as antisolvents

The polymer particles loaded with active ingredients can be produced by three different methods employing supercritical fluids as antisolvents: (1) A polymer and an active ingredient can be dissolved in an organic solvent, and the solution of binary compounds is contacted with supercritical antisolvent. This method is feasible when the both compounds are soluble in a single organic solvent. The formation of composite particle is governed by the coprecipitation mechanism. (2) A polymer solution containing suspended active substance is contacted with supercritical antisolvent. This method can be used when the polymer is soluble and active compound is insoluble in a particular organic solvent.

Table 5
Formation of polymer particles that incorporate active ingredients using supercritical fluids as solvents (RESS) during 2000–2003

Polymer/active compound	Solvent/cosolvent	Year	Reference
PGA, PMMA, L-PLA/lysozyme, lipase	CO_2/ethanol	2000	[56]
L-PLA, PEG, PMMA, ethyl cellulose/*p*-actamidophenol, acetylsalicylic acid, flavone, 1,3-diemthylxanthine, 3-hydroxyflavone	CO_2/ethanol	2003	[57a]
Lipids/albumin	CO_2	2003	[58]
Fluorinated polyacrylate/2,5-distyrylpyrazine	Chlorodifluoromethane	2003	[59]
Lactose, cyclodextrin/ibuprofen	CO_2	2003	[60]

Upon contact of the solution and antisolvent, the polymer precipitates in the presence of solid particles that brings about the encapsulation of active compound with polymer. This can be considered as solvent-induced particle coating process. This process is useful in an application such as encapsulation of proteins with biodegradable polymers, because proteins are practically insoluble in most of organic solvents while the organic solvents may dissolve polymers. (3) A polymer and an active ingredient are separately dissolved in two different solvents and both solutions simultaneously contacted with supercritical antisolvent. Organic liquid solvent, water, and another supercritical fluid can be used as solvents for each of the compound. Mixing of the three solutions causes the co-precipitation of the polymer and the active compound while their solvents are depleted from the precipitated composites under the action of supercritical antisolvent. Employing an additional solvent, this method extends the applicability of supercritical antisolvent processes to handle more diverse materials, particularly enables to produce polymer composite particles loaded with water-soluble compounds such as proteins. Among these antisolvent techniques, the first two operations can be performed in typical GAS and SAS processes and the third method can be realized in SEDS process.

The pharmaceutical compounds are once again the major active substances that have been loaded in polymer particles by using supercritical antisolvent techniques. The earlier studies in 1990s employed GAS- or SAS-type processes to prepare drug-loaded polymer particles by coprecipitating various lactic acid-based biopolymers along with a number of drug compounds such as chlorpheniramine maleate, indomethacin [61], naproxen [62], gentamycin, naloxone, naltrexone [63], albumin, and estriol [64]. In these investigations, the biopolymer and the drug compound were dissolved in an organic solvent and the solution was brought in contact with supercritical carbon dioxide either by spraying the solutions into carbon dioxide phase or by injecting carbon dioxide into the solution phase. The polymers and drugs were coprecipitated from the solutions and the drug compounds were expected to be entrapped in polymer particles upon precipitation. Quality of the composite particles was determined by measuring the efficiency of drug loading on polymer matrix. General observations indicated that the drug loading efficiency was highly dependent on the nature of drug compounds such that lipophilic or carbon dioxide-soluble compounds were difficult to be incorporated. Therefore, in order to overcome the difficulties arising from the nature of the drug and to enhance the loading efficiency, additional ingredient such as anionic detergents were sometimes added to the system to induce the ion paring of drugs [63]. In these studies, the performance of the final products was tested by measuring the drug release behavior into host solutions for practical application of the polymer composite particles.

In 2000s, improved antisolvent techniques led to significant progress on drug incorporation into polymer particles. Ghaderi et al. [65] used SEDS process to entrap hydrocortisone in D,L-PLGA microparticles. Here, two supercritical fluids, carbon dioxide and nitrogen were co-introduced into a three-channel nozzle together with a polymer solution which also contained a dissolved drug compound. The use of nitrogen improved the dispersion effect of the polymer solution, resulting in the successful entrapment and further reduction of particle size. Upon coprecipitation, hydrocortisone was loaded in the polymer particles at around 20% of entrapment efficiency, which is defined as the ratio of entrapped amount to initially added. The results were claimed to be quite promising compared to the previous studies [61,64] with respect to optimizing the drug loading efficiency. Taki et al. [66] used the SAS process to load a herbicide (diuron) in L-PLA particles. The diuron and polymer were dissolved in methylene chloride at different concentrations and the solution was sprayed into carbon dioxide to induce coprecipitation. It was found that the initial concentration of diuron and polymer in methylene chloride is the critical parameter that controls the degree of loading. Spherical particles of diuron-loaded L-PLA were successfully generated at concentrations of L-PLA and diuron in the feed solution lower than 3.0 and 0.1%, respectively. When the diuron concentration was higher than this, diuron precipitated earlier and resulted in the separated formation of acicular (needle-like) diuron particles followed by spherical L-PLA particles.

Elvassore et al. [67] encapsulated insulin in L-PLA particles using the SAS process. A mixture of DMSO and methylene chloride with 50% ratio was used as a solvent giving the homogeneous solutions of the two compounds. The composition of the initial solution was 1% of polymer in solution and 5% of insulin with respect to polymer. The solution was sprayed into carbon dioxide resulting in the coprecipitation of the protein and polymer. In all experimental conditions investigated, a very high protein incorporation yield was found. The result suggested that more than 80% of ini-

tially fed insulin was loaded and it was finely dispersed into the polymeric matrix. In addition, insulin extracted from the composite particle was found to fully maintain the activity after injection to diabetic mice. Sze Tu et al. [68] encapsulated *p*-hydroxybenzoic acid (*p*-HBA) and lysozyme in L-PLA particles employing the SAS apparatus equipped with the three-channel nozzle. Here, two types of experiment were conducted. First, a mixed solution of methanol and methylene chloride containing both *p*-HBA and polymer were sprayed with carbon dioxide using only two channels in the nozzle. Second, the *p*-HBA and polymer were dissolved in methanol and methylene chloride, respectively, and these two separated solutions were sprayed with carbon dioxide using the three channels. In case of lysozyme, DMSO was used as a solvent. In both experiments, the encapsulation efficiencies were relatively low and the results were practically unaffected with the use of multiple nozzle. Observations indicated that the encapsulant, L-PLA was precipitating earlier than the core material, *p*-HBA, thus making encapsulation of the drug difficult. Moreover, the precipitated *p*-HBA particles were too large for entrapment by the much smaller L-PLA microspheres. The higher loading efficiency was achieved in lysozyme entrapments, which was most likely due to the formation of smaller particles of lysozyme that could be encapsulated compared to *p*-HBA. Authors concluded that the encapsulation might slightly improve when the process parameters were varied, however, the drug loading may depend more on the type of system, such as the crystallization/precipitation behavior of both the drug and polymer. Chattopadhyay and Gupta [69a] produced magnetite-encapsulated D,L-PLGA, PMMA, and Eudragit RS microparticles using SAS process. The magnetite-encapsulated particles can be used for site-specific delivery of drugs using external magnetic fields. The polymers were dissolved in methylene chloride in the presence of suspended magnetite particles and fatty acid surfactant, and brought in contact with carbon dioxide. The experiment was also conducted to precipitate indomethacin-loaded magnetically responsive polymer particles. The methylene chloride solutions containing polymer, indomethacin and suspended magnetite was injected into carbon dioxide resulting in composite particles of the three compounds. For higher mass transfer, the solution sometimes was sprayed onto a vibrating surface to enhance the atomization of solution. It was found that there was no morphological and size difference between indomethacin-loaded polymer/magnetite composite particles and unloaded polymer particles. Release studies of the drug-loaded polymer particles showed sustained release and 30% of drug was released over a period of 9 h. A recent article describes a model study using silica nanoparticles as host particles and Eudragit RL polymer as the coating material [69b].

Pellikaan et al. [70] performed SAS experiments to produce chitosan (*N*-trimethyl chitosan chloride (TMC)) particles loaded with a peptide drug (buserelin acetate), which are suitable for pulmonary administration. Chitosan is a polysaccharide that enhances the absorption of peptide and protein drugs through skin in the acidic environments. Two compounds were coprecipitated from DMSO solutions upon injection into carbon dioxide. Spherical TMC particles loaded with peptide drug were produced in the size range of 0.2–5 μm, with the loading efficiency of nearly 100%. Drug degradation and residual DMSO in the final product were not detected. The study showed that the experimental conditions of SAS process were mild enough to keep the conformation of the peptide unaffected. Vega-González and Subra [71] encapsulated a steroid (cholesterol) in particles of PMMA/PCL blend using SAS process. Both the drug and polymer were dissolved in methylene chloride and sprayed into carbon dioxide. The polymer blend was chosen as a carrier of drug because the polymer composites usually show improved characteristics compared to their separate components. Morphology of loaded polymer particles was affected by operating pressure. As pressure decreased, the morphology changed from flocculated microspherical to acicular structure. Authors confirmed the presence of polymer blend and cholesterol in the precipitants regardless of the morphological modifications. Grassi et al. [72] studied release kinetics from tablets made up from a compressed drug-loaded polymer powders obtained by SAS coprecipitation. Poly(hydroxypropyl methylcellulose) (HPMC) was loaded with a model drug (theophylline) using a mixed solution (50/50 mixture of methylene chloride/ethanol) as a solvent and carbon dioxide as an antisolvent. HPMC is a hydrophilic polymer that frequently used in formulation of controlled release devices for the application in aqueous media. Drug release profiles obtained from SAS processed materials were compared with those from untreated ones. The significantly slower drug release rate was found in SAS processed materials, due to the broader contact of the drug with carriers and the subsequent change in the internal morphology of drug exist in the composite.

These studies, summarized in Table 6 have shown that depending upon the system (type of drug and polymer) studied, the loading efficiency of drug on polymer matrix vary in a wide range while the process parameter such as temperature, pressure, and concentration have only minor effect on the loading capacity. The drug incorporation processes are based on the principle of coprecipitation of the binary compounds from their solutions under the action of supercritical antisolvents. These processes are therefore basically solvent-induced physical blending processes. Indeed, the degree of blending or mixing of two different materials strongly depends on the similarity of the compounds. Polymer/drug pairs are often chemically dissimilar systems, and supercritical antisolvent technology may not be applicable to every pair of drug/polymer composites to achieve a desired level of drug loading in polymer. Therefore, current focus of the antisolvent-based research is aimed at either identifying those drug/polymer systems that have high mutual miscibility, or developing new experimental methodologies to overcome the inherent chemical incompatibility of a given system.

Table 6
Formation of polymer particles that incorporate active ingredients using supercritical fluids as antisolvents (GAS/SAS/SEDS) during 2000–2003

Polymer/active compound	Process	Solvent/antisolvent	Year	Reference
D,L-PLGA/hydrocortisone	SEDS	Methylene chloride, acetone, ethyl acetate, hexane, isopropanol/CO_2, nitrogen	2000	[65]
L-PLA/diuron	SAS	Methylene chloride/CO_2	2001	[66]
L-PLA/insulin	SAS	DMSO, methylene chloride/CO_2	2001	[67]
L-PLA/*p*-HBA, lysozyme	SAS	Methanol, methylene chloride/CO_2	2002	[68]
D,L-PLGA, PMMA/magnetites	SAS	Methylene chloride/CO_2	2002	[69a]
Chitosan/buserelin acetate	SAS	DMSO/CO_2	2003	[70]
PMMA–PCL blend/cholesterol	SAS	Methylene chloride/CO_2	2003	[71]
HPMC/theophylline	SAS	Methylene chloride, ethanol/CO_2	2003	[72]

5.3. Formation of polymer particles containing active ingredients using supercritical fluids as solutes

The limitations encountered in particle formation and drug encapsulation techniques include the low productivity of the RESS process and the concern over organic solvent residues in the end-product due to the unavoidable use of organic solvents in antisolvent processes. These two problems are eliminated in PGSS process in which the supercritical fluid is used as a solute. In PGSS process, supercritical fluid is solubilized in a molten substance, and the mixture is sprayed through a nozzle. As a result of the large cooling effects that accompany expansion along with pressure reduction, the substance is solidified, resulting in particle formation [73a,b,c,d]. Aqueous solutions also can be processed by PGSS in which the solute-containing solution is saturated with supercritical fluid and expanded through a capillary to form micron size aerosols, and the subsequent evaporation of water and precipitation of the dissolved solutes. Microparticles of water-soluble pharmaceuticals and inorganic materials can be generated in this way [74]. PGSS is especially useful for particle formation from polymers because the solubility of supercritical fluids in polymers is a strong function of pressure so that the particle formation, i.e. the phase separation can easily be achieved by pressure manipulation. This technique has been used to produce pure polymer particles such as polyethylene glycol [75a,b], polyethylene [76], and polyester [77]. The special feature of this process is that in addition to being useful in production of pure polymer particles, it is particularly suitable for producing polymer composite particles embedded with guest materials. The basic principle of PGSS process, i.e. the mixing of supercritical fluid and polymer under high pressure followed by the separation of two materials upon rapid depressurization, can be successfully applied to incorporate active ingredients in polymer particles. In this case, supercritical fluid is dissolved in the polymer in the presence of insoluble guest particles (active ingredients). The dissolution of supercritical fluid in the polymer induces the depression of its glass transition temperature (polymer is plasticized), and a substantial reduction in the viscosity of the polymer, allowing efficient incorporation of guest substances with a homogeneous distribution throughout the polymer matrix [78a]. The technique has indeed been used for the encapsulation and inclusion of active substances in various polymer matrices. A recent article provides modeling of the PGSS process and droplet formation by considering the hydrodynamic equations of two phases. The model simulates the profiles for pressure, density, temperature and velocity along the nozzle [78b].

Kerc et al. [79] used PGSS process to micronize water insoluble drugs (nifedipine and felodipine) and to incorporate the drug particles in hydrophilic polymer (polyethylene glycol) with the aim to increase dissolution rate of the drugs. Carbon dioxide was dissolved in a mixture of molten drug and polymer and expanded through a nozzle. Coprecipitation of the two compounds resulted in drug/polymer composite particles. The effect of process parameters on particle size was examined, and it was found that with increasing pre-expansion pressure the mean particle size was decreased. The dissolution rate of drugs from the composite particle was much higher than from the unprocessed ones. The enhanced dissolution rate was explained by the combined factors including particle size reduction, interaction between the drug and polymer, and the solubilization effect of the hydrophilic polymer carrier.

Watson et al. [80] incorporated proteins (avidin-rhodamine and ribonuclease A) into polymer scaffolds (used in tissue engineering) which was made of D,L-PLA powders. This study focused on loading of drug ingredients in polymer matrix in the very low biological concentrations down to the order of parts per billion. First, the proteins were dissolved in water at very low concentrations. The aqueous solution was then dropped onto the surface of polymer scaffolds and the samples were freeze-dried, which results in dried protein particles adsorbed on the surface of the polymer matrix. This polymer sample was placed in a heated autoclave in which supercritical carbon dioxide was introduced, and the mixture was maintained to equilibrate for around half an hour before slowly venting to atmospheric pressure. In this process, the dissolution of carbon dioxide in polymer induces the swelling of the polymer and plasticizes the sample allowing the penetration of proteins from surface to the bulk of the polymer. The protein is incorporated with a uniform distribution throughout the polymer particles. The release behavior of protein showed that the protein from the freeze-dried scaffolds released very quickly with nothing remaining after 2 days, while the pro-

tein from the carbon dioxide processed sample exhibited stabilized release behavior for about 3 weeks.

Recently, a number of studies have been reported on the preparation of the composites by impregnation, which is referred to as inclusion complex of a drug in polymer matrix, for the purpose of improving the dissolution rate of poorly water-soluble drugs in the actual biological environment. The β-cyclodextrins (cyclic oligosaccharide) are commonly used as hydrophilic polymers that enhance the solubility of impregnated active compounds. In these studies, carbon dioxide was used as a solvent for drug compounds and as a solute with respect to polymers. The role of carbon dioxide is to penetrate into bulk polymer and provide a suitable environment for the active compounds to form an inclusion. Earlier, Van Hees et al. [81] explored the inclusion of an anti-inflammatory drug (piroxicam) into β-cyclodextrin particles. Carbon dioxide was charged to a high-pressure cell that was previously loaded with a physical mixture of the drug and the polymer. After the carbon dioxide charging was completed, the cell was left for few hours at elevated temperatures (>150 °C) and pressures (>450 bar) allowing the inclusion of drug take place. The experiment was finished by rapidly venting the carbon dioxide to atmospheric pressure. In this process, the drug is first dissolved in carbon dioxide and then is transferred into polymer matrix to form an inclusion. Quantitative assay of UV spectroscopy revealed that the inclusion yield reached up to 99% indicating the most of drug initially loaded in the cell was included in the polymer particles. Authors suggested that the mechanism of drug inclusion in polymer is a substitution mechanism of the pre-existing water molecules in the cavity of polymer by the less polar guest compound (drug) in the presence of carbon dioxide.

Charoenchaitrakool et al. [82] prepared the inclusion complex of ibuprofen in β-cyclodextrin particles. In this study, carbon dioxide was first passed through a bed of ibuprofen, producing drug-laden carbon dioxide, and then the stream was brought into contact with β-cyclodextrin in a second cell. The cell was isolated and left in a static mode up to 24 h at 35 °C for the inclusion occurred. Authors observed that during the inclusion, the polymer inside the cell is in the melt state due to the melting point depression in the presence of carbon dioxide. Upon depressurization of the system, particles of ibuprofen-included polymer were generated. Characterization of the product revealed that the drug that gets incorporated in the polymer complex exists in an amorphous form while the unprocessed ibuprofen is in the crystalline state. The comparison of dissolution rate into aqueous media showed that the dissolution rate of ibuprofen from the inclusion complex was much higher than from the physical mixture of drug and polymer. The enhancement in dissolution could be attributed to the amorphous character of the complex and the improved wettability.

Marongiu et al. [83] included imazalil into β-cyclodextrin in order to increase the solubility of the fungicide in water for the agricultural application. The inclusion experiments were performed in a batch autoclave by loading the fungicide, polymer and carbon dioxide together into the chamber, and leaving the system in a static mode up to 6 h. After the inclusion was completed, the carbon dioxide was rapidly vented. The results showed that the inclusion efficiency increased with contact time and operating pressure, which may be due to the increased solubility of imazalil in carbon dioxide. Regarding the temperature effect, an optimum temperature for the highest inclusion was observed. At this temperature, the solubility of fungicide in carbon dioxide was maximized under the combined effect of carbon dioxide density and vapor pressure of imazalil. These results suggested that the solubility of guest compound in carbon dioxide was a critical factor for the successful inclusion. The formation of inclusion complex of imazalil in β-cyclodextrin was confirmed by the NMR spectroscopy analysis.

Table 7
Formation of pure polymer particles and polymer particles that incorporate active ingredients using supercritical fluids as solutes (PGSS) during 2000–2003

Polymer/active compound	Solute	Year	Reference
Polyethylene glycol	CO_2	2003	[75a]
Polyethylene	CO_2	2003	[76]
Polyester	CO_2	2003	[77]
D,L-PLA, PLGA, PCL/ribonuclease A, catalase, β-D-galactosidase	CO_2	2001	[78a]
β-Cyclodextrin/piroxicam	CO_2	2002	[80]
β-Cyclodextrin/ibuprofen	CO_2	2002	[82]
β-Cyclodextrin/imazalil	CO_2	2003	[83]

These reports, summarized in Table 7, demonstrate that carbon dioxide can be used as a transferring medium to bring a solute such as a drug compound from fluid phase into the polymer internal structure. The role of carbon dioxide is to change the physical state of polymer so that polymer becomes more flexible and receptive to guest molecules under moderate pressures and temperatures. Recent studies demonstrate that the encapsulation in polymer is possible for carbon dioxide-soluble [81–83] as well as carbon dioxide-insoluble [80] drug compounds. In case of carbon dioxide-soluble compounds, the inclusion efficiency depends on the solubility of drug in carbon dioxide, which can be controlled by pressure. Therefore, this technology can fully utilize the special feature of supercritical fluids such as their pressure-tunable solvent power in order to control the degree of encapsulation. The advantages of this technology over the conventional methods include not only the simplicity of process that needs only one-step operation but also the capability of complete removal of the processing medium from end-product, which is useful for the organic solvent-sensitive applications.

6. Concluding observations and future trends

This review which covered the recent articles published during 2000–2003 clearly is not and was not meant to be exhaustive. Since the initial submission of this manuscript several new reviews on the broader aspects of particle for-

mation has appeared in the literature [84–86]. The studies included in the present and in these other reviews have addressed a variety of issues such as particle size reduction, narrowing the particle size distribution, creation of homogeneous particle morphology (especially the spherical form), prevention of particle agglomeration, and control over the loading of active ingredients in desired concentrations. The major use area for polymer particles produced by supercritical fluid technology currently resides in the pharmaceutical area. There is no doubt that this will continue to be the case in the near future.

Numerous polymer particles have been generated by utilizing the various features of supercritical fluids: (1) Their tunable solvent power towards selected polymers which enables them to be used as adjustable solvents. The ability to control the solubility of polymers from nearly zero to a reasonable level by adjusting the operational variables such as the temperature and pressure and the amount of cosolvents, make supercritical fluids as a versatile process media to dissolve and to precipitate the polymer particles. (2) Their high miscibility with many ordinary organic solvents makes supercritical fluids effective antisolvents towards polymers dissolved in the organic solvents that lead to phase separation. The high affinity of supercritical fluids with organic solvents accelerates the removal of solvents from the precipitated polymers resulting in solvent-free dry powders. (3) Lowering of the viscosity of polymer solutions and melts facilitates their processing with supercritical fluids through transport channels and nozzles used in many particle formation systems. (4) High diffusivity along with the moderate solubility in polymer combined with plasticization of the polymer provides the proper environment for guest materials to migrate into the polymer matrix to generate the active ingredient-loaded particles with reasonable loadings. (5) Low toxicity and environmental acceptability are features that keep the interest in applying the technology to pharmaceutical products.

Clearly a wide range of polymers can be processed whether or not they are soluble or insoluble in supercritical fluids by modifying the operational methods and employing additional physical and chemical factors. The methods must take into consideration the physicochemical characteristics of the polymer and the morphological features that are aimed for the final product. Thermal transitions play a significant role. The consequences of various quench processes on the final product morphology and the relationship with the kinetics of the phase separation processes are yet not fully documented. In view of the fact that during solidification or crystallization, transient structures are locked in, the connection between the process conditions and the kinetics of the underlying transformations must be better described. Process dynamics must be considered along with polymer chain dynamics and the transitional phenomena in polymers.

As demonstrated in this review, some of the recent developments such as inclusion studies, or the PGSS process depend greatly on our ability to know (or assess) the amount of carbon dioxide (or the supercritical fluid of choice) that dissolves in the polymer, and the extent to which the glass transition and/or the melting transitions and the viscosities are lowered, and the extent to which other transport properties such as the mass and heat transfer characteristics are altered. We anticipate many studies addressing these issues will appear in the coming years.

Even though not discussed in detail, crystallization of polymers from supercritical fluids at high pressure often leads not only to different solid–fluid boundary conditions [87], but also to different crystalline morphologies with multiplicity of melting transitions that is only recently receiving attention [88]. We anticipate that new explorations in the future will not be just on the particle size and shape and their broad appearance under SEM, but will include more information on the additional details of the crystalline morphology. These studies will deal with both the crystalline morphology of the polymer as well as the additives that may be incorporated. As already noted, in some studies, ibuprofen that is impregnated into polymer matrices have been demonstrated to be amorphous and easier to be released than if they were simple mixtures where they exist in their crystalline forms [82].

Even though we have not included polymerization-induced particle formation in this review, powder coatings constitute an important area of growth. Processes that combine polymerization and particle formation based on PGSS methodology to produce powders of reactive compounds have been described in the literature [73c,d,75b]. In these processes, the binders for powder coatings are prepared by polymerization in supercritical fluids. A specific example is formation of the copolymer hydroxypropyl methacrylate–methyl methacrylate–styrene in supercritical carbon dioxide. The polymer-rich phase is then processed to recover the polymer as powder.

Another important aspect of polymerization-induced particle formations is the opportunity to design systems in which the polymer physicochemical properties can be modified for suitability for particle formation. In a recent study conducted in our laboratory [89], we designed special copolymers with different comonomers to alter the properties from a crystalline homopolymer to a set of glassy copolymers of different compositions (and thus different glass transition temperatures), and demonstrated how a given set of conditions fail to lead to free-flowing particles with greater degree of insertion of the comonomer with lower glass transition temperature into the backbone chain.

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