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Supercritical Fluid Technology: An Emphasis on Drug Delivery and Related Biomedical Applications

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Abstract

During the past few decades, supercritical fluid (SCF) has emerged as an effective alternative for many traditional pharmaceutical manufacturing processes. Operating active pharmaceutical ingredients (APIs) alone or in combination with various biodegradable polymeric carriers in high-pressure conditions provides enhanced features with respect to their physical properties such as bioavailability enhancement, is of relevance to the application of SCF in the pharmaceutical industry. Herein, recent advances in drug delivery systems manufactured using the SCF technology are reviewed. We provide a brief description of the history, principle, and various preparation methods involved in the SCF technology. Next, we aim to give a brief overview, which

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provides an emphasis and discussion of recent reports using supercritical carbon dioxide (SC-CO_2) for fabrication of polymeric carriers, for applications in areas related to drug delivery, tissue engineering, bio-imaging, and other biomedical applications. We finally summarize with perspectives.

Keywords

bioavailability enhancement; biomedical applications; drug delivery; polymeric carriers; supercritical fluids; tissue engineering

1. Introduction

The supercritical fluid (SCF) technology is perhaps one of the most renowned high-pressure techniques so far to obtain products with better performances. This technology has been commercially used for many years in the pharmaceutical, textile, and food industries.[1] The reasons behind the wide adoption of this technology are not only due to its environmentally benign nature in various processes but also because of its economically promising character.[2] While many conventional pharmaceutical products rely on the use of organic solvents,[3] the SCF technology, by contrast, takes advantage of benign solvents such as CO_2 and water to replace the organic solvents, therefore serving as an alternative in synthesizing delivery systems.

Drug delivery relies on various formulations and strategies for transporting pharmaceutically active compounds to achieve desired therapeutic effects.[4] However, it has been associated with challenges related to solubility and diffusion.[5] Regarding this, the biopharmaceutical classification system (BCS) has clearly categorized all drugs, and specific formulations based on their physical and chemical properties as well as their pharmacokinetics and pharmacodynamics.[5a,6] New chemical entities also suffer from poor solubility and stability and require frequent administration.[7] To overcome these issues, excipients such as biodegradable polymers are utilized in many pharmaceutical formulations to encapsulate the core materials such as active pharmaceutical ingredients (APIs) or drugs, which coalesce to form matrices/frameworks.[7b,8] Particles synthesized via micronization can be administered through various routes such as intravenous, intramuscular, pulmonary, and others, in addition to oral delivery.[8a] Furthermore, the use of particles helps to protect the sensitive agents from the harsh environments in the body.[7b,9]

According to a formulator anticipation, the ideal drug delivery system should carry a high payload to the desired site and release in a controlled manner, which reduce the frequency of dosage.[6,9c] In few instances, chemical modification of drug or attachment to macromolecules such as polymers or polysaccharides to increase the drug encapsulation efficiency may be chosen to accomplish the design.[4a,7b,10] More often, sustained delivery of drugs from encapsulating polymeric particles such as those micro- or nanoscale in size also improves the efficacy and reduces the undesired side effects.[11] These advancements have integrated materials science with drug delivery to deal with controlling parameters (such as morphology) and manufacturing process of particle formation.[5b] However, conventional particle fabrication technologies have a few limitations, such as thermal and

chemical degradation of drugs, the use of large amounts of organic solvents, broad particle size distribution, and solvent residues in the end products.[8b,12] To overcome these limitations, an efficient production platform applying particle engineering at industrial scale is necessary.[7b,13] To this end, the compressed/pressurized fluid bottom-up technique utilizing supercritical solvents has largely addressed the challenges. This technology precipitates micro-[14] as well as nano-sized particles[15] with large surface areas, controlled uniform particle sizes, and smooth surfaces,[5b,14,16] which eventually augment drug bioavailability.

Recently, the application of the SCF technology has attracted interest of many researchers as it is non-toxic, non-flammable, non-reactive, economical, and non-polluting.[17] This green technology has a potentially high impact in the pharmaceutical field to overcome the curbs of various conventional methods such as spray-drying and others.[12,18] Indeed, SCF exists as a single phase beyond critical conditions (i.e., temperature and pressure). Furthermore, the physical properties (density, diffusivity, and viscosity) of the SCF are intermediate between liquid and gas and can be easily manipulated by adjusting the temperature and pressure during operations.[3,6,16c,17] In general, CO_2 is the most used supercritical solvent and is recognized as safe by the United States Food and Drug Administration (US-FDA) in the pharmaceutical processing,[19] i.e., drug delivery applications, because of its low toxicity, low cohesive energy, as well as low density. Supercritical CO_2 (SC-CO_2) is a cost-effective solvent operated at mild conditions (critical temperature (T_c = 31.1 °C) and low critical pressure (P_c = 7.38 MPa)) at gaseous standard state under ambient circumstances (Figure 1). It has been extensively used as a solvent, anti-solvent, and plasticizer for synthesis, modification, and purification of both natural and synthetic polymers.[17] Moreover, other SCFs include water[20] and solvents such as acetone, CO_2/ethanol (EtOH) mixture, chlorodifluoromethane, diethyl ether, nitrous oxide, propane, and trifluoromethane operated at their respective supercritical conditions.[20e,21] Recent literature have already reported the properties including solubility and critical parameters of several commonly used supercritical solvents.[22]

SCF is dense, but can be highly compressible, where the solvation power and pressure changes merely result in density alteration at the critical point.[3] The high diffusivity of SCF results in the ease of penetration of CO_2 into the polymers, and the fluctuation in diffusivity determines the supercritical status of the fluid with the non-homogenous distribution of molecules in the space.[13b,17] In the SCF-assisted process, the mechanism lying behind the particle formation or crystallization is the attainment of a high degree of supersaturation state of the material in non-equilibrium conditions of temperature and pressure, which leads to nucleation, crystal growth, and eventually agglomeration.[13b] The control over the critical conditions during operation is highly advantageous over conventional process. Since it is operated at extreme conditions using pressurized gasses and solvents, this process usually requires safety rules and stringent regulations such as Current-Good Manufacturing Practices (cGMP) to control the mechanical and chemical hazards.[3]

Despite many reviews[1,2,3,5b,8b,9a,12,13,17,18b,20d,e,23] published on the potential of the SCF technology, very few focused on the use of it for fabrication of particulate delivery systems.[1,3,5b,23b,e] Few reports focused only on carriers intended for one of the drug delivery routes

or the SCF process of particle formation, and critical analysis on a theoretical basis.[23d,h,p] Herewith, we present a perspective on an extensive survey of the past two decades on the use of the SCF technology in drug delivery and related biomedical applications.

2. Supercritical Processes for Particle Formation

Conventional methods (i.e., mechanical or chemical) for synthesizing polymeric particles have several limitations, such as heterogeneous particle size distribution, particle damage by shear forces, and others.[24] Indeed, utilizing the SCF technology in pharmaceutical manufacturing and processing, the internal obstacles caused by conventional approaches can be minimized. Further, this technology has probably become the most sustainable process for addressing environmental concerns.[21a,23c,d] The first report of the SCF technology was from Hannay et al. in 1879,[25] following which variants in the technology have been developed to fabricate drug delivery vehicles. Different processes (Figure 2) of particle formation are categorized based on the behavior of SCF as *solute* (particle formation from gas-saturated solutions (PGSS)); *solvent* (rapid expansion of supercritical solutions (RESS));[26] *anti-solvent* (supercritical anti-solvent (SAS),[27] gaseous anti-solvent (GAS),[28] aerosol solvent extraction system (ASES),[21a] precipitation with compressed anti-solvent (PCA),[29] supercritical anti-solvent with enhanced mass transfer (SAS-EM),[30] solution enhanced dispersion by supercritical fluids (SEDS),[31] suspension-enhanced dispersion by supercritical fluids (SpEDS)[32]); and *others* such as depressurization of an expanded liquid organic solution (DELOS)[1a,33] and the supercritical-assisted atomization (SAA) process, etc.[34] SCF acts as a re-precipitation aid for rapid and uniform nucleation of solute in all the above-mentioned methods of fine particle formation. The performance efficiency of this technology is based on proper solvent selection and by adjusting critical parameters (temperature and pressure) during operations.[12] Herewith, we discuss these various supercritical processes involving particle formation in brief.

2.1. PGSS Process

SCF acts as a solute in the PGSS method (Figure 2a).[35] The SC-CO_2 is compressed and dissolved in a molten polymer after autoclave treatment, where the solution expands and becomes cooled by the Joule-Thomson effect.[21a] Microparticles are formed when operated at a relatively low pressure.[21a] This approach is advantageous over other SCF techniques since it uses low volumes of SCF.[21a,35] However, the application of this process is limited due to particle agglomeration and nozzle blockage.[23f]

2.2. RESS Process

In a RESS process, SCF acts as a solute carrier, and this solution is expanded adiabatically leading to a rapid drop in temperature and pressure and further generation of small-sized particles after spraying through a nozzle (Figure 2b).[21a,26,36] In designing this process, the solubility of the material plays a crucial role in particle formation and processing since most of the pharmaceutical substances such as polymers, drugs, and high-molecular weight proteins are polar in nature. In few instances, small amounts of organic solvents are added to improve the affinity of polar drug molecules.[23b] RESS is the simplest and an efficient method in the SCF technology, but it is limited in its application because of its relatively

high cost and poor solubility of polymers in non-polar SC-CO_2. High amounts of SC-CO_2 are preferred at industrial scale to address this issue.[24] Further, the advancements in the RESS process have been made to overcome certain limitations. One of them is the RESS process in an aqueous solution containing a surfactant or other reducing agents known as the rapid expansion of a supercritical solution into a liquid solvent (RESOLV) process (Figure 2c),[21b] where the SCF is expanded into a liquid medium. This modified process inhibits the particle agglomeration in the expansion jet.[37] The other modified process is the rapid expansion of a supercritical solution with solid co-solvent (RESS-SC), which results in smaller-sized particles. During synthesis, the added co-solvent improves the solubility of the APIs to a greater extent by avoiding superficial contact between particles, which increases the surface area of exposure to SCF and eventually, lyophilization can remove the co-solvent.[38] Despite its advancements, RESS still has certain limitations that are surpassed by the altered SCF behavior as anti-solvent in the reaction vessel.

2.3. SAS Process

The SAS process is proposed to process the molecules with poor solubility in SCF. This process predominantly utilizes an organic solvent such as acetone, dichloromethane (DCM), and dimethyl sulfoxide (DMSO), to dissolve the materials, where SCF behaves as a non-solvent to solute/API.[6] During the process, the mixture expands to supersaturation and results in fast nucleation, demonstrating the high mass transfer ratio due to the low viscosity and high diffusivity of SCF.[6] The outcome of this process utterly depends on the order of addition of solvent, SCF, and other substrates. Additionally, factors such as temperature, pressure, chemical composition of solute (drug, polymer), as well as organic solvent are required to be optimized. SAS has gained better drug loading than the RESS process, enabling the formation of fine particles.[23b] Other SAS processes comprise of GAS, which is based on the recrystallization of SCF insoluble solute and has a flexibility of choosing organic solvent to improve the solubility. This process has less operational problems compared to the conventional SAS method and is easy to scale-up in the manufacturing.[28] Recent advancements in SAS micronization techniques include, i.e., expanded liquid anti-solvent (ELS)[39] and the supercritical-assisted injection in a liquid anti-solvent (SAILA) methods;[40] however, deep analyses on these processes yet remain to be reported. ELS is operated using SCF and an organic solvent at expanding liquidity conditions.[39] The other modified SAS techniques include ASES,[21a] SCF-assisted extraction of emulsions (SFEE),[41] SAS-EM,[30] SEDS,[14,42] and SpEDS.[32]

2.4. ASES Process

Particle generation in ASES happens to be favorable at high anti-solvent-to-solvent ratio after spraying the drug/polymer solution into SCF via an atomization device. Further, the mass transfer of SCF depends on atomization efficiency, while solvent mass transfer relies on dispersing and mixing of SCF and organic solvent. This process is not suitable to load high amounts of drugs due to their usually high affinity towards organic solvent, which eventually reduces the loading amount in polymer after organic solvent extraction.[23b] Furthermore, a slight modification of ASES, known as the PCA manufacturing process (Figure 2d) effectively produces particles with a narrow size distribution.[23p] This process has been reported as a single-step technique operated to precipitate proteins.[23p]

2.5. SFEE Process

SFEE has emerged as a modified SAS process to encapsulate poorly water-soluble drugs. SCF interacts with the emulsion droplets and extracts the organic solvents/oily phase and leads to rapid precipitation of microparticles.[43] The advancement is to minimize the separation of the solid phase and agglomeration of particles during the SAS process.

2.6. SAS-EM Process

SAS-EM is an advanced SAS process to overcome the existing limitations of the SAS process.[30] The modification of the technique is that it utilizes a vibrating ultrasonic processor to atomize the solution jet into micro-droplets (Figure 2e). This processing method yields high turbulence, which enhances the mixing operation and subsequently the mass transfer and generates smaller-sized particles.[44]

2.7. SEDS Process

SEDS is another important process of SAS technique operated at a lesser drying time and increased mass transfer rates, which minimize the ASES process limitations. In a typical SEDS process (Figure 2f), the dispersed components are sprayed through a specially designed co-axial nozzle to control the particle morphology.[23b] Mass transfer of SCF into the sprayed droplet determines the particle formation by the rate of solvent transfer into SCF phase. A high mass transfer allows a faster nucleation and results in smaller particle sizes with less agglomeration.[23p] In fact, the polymer processing using organic solvents is highly accessible with this process because of solubility problems. Moreover, the continuous SEDS operation has extended the shelf life of polymeric materials. Water-soluble compounds can also be dealt with by introducing organic solvent through a co-axial three-compartment nozzle.[45]

2.8. SpEDS Process

SpEDS is an advancement of the SEDS process to overcome its processing damage issues.[32a] The apparatus and operation of both processes are almost similar, but SpEDS has an auxiliary injector setup to effectively pump the loaded suspension (Figure 2g).[32a] This process is designed to obtain core-shell structured microparticles with higher drug encapsulation efficiency and longer sustained drug release property compared to other SCF-assisted co-precipitation processes.[46]

2.9. Others

DELOS is another process of operation utilizing traces of organic solvent for the precipitation of particles.[23h] In this process, SCF acts as a co-solvent and is suitable for thermo-sensitive substances over various SAS methods. Other advantages of this process include minimum CO_2 consumption and easier scalability of micronization of drugs.[33b]

Other important processes include the SAA process[34] and the CO_2-assisted nebulization with a bubble dryer (CAN-BD) process[47] for aerosolization of particles, where SCF assists the nebulization for processing. Despite the similarity, CAN-BD requires no sophisticated setup for processing and is more suitable for thermolabile substances. An SAA approach

resembles the DELOS process except that SAA uses water during operation. Moreover, by introducing a hydrodynamic cavitation mixer, the hybridized supercritical-assisted atomization-hydrodynamic cavitation mixer (SAA-HCM) was developed to improve the mixing operation during synthesis.[48] Several other methods such as microemulsion method, drying medium in the sol-gel process, and metal particles in SCF as the reaction medium, among others, are under practice as well.[49]

Drugs are also successfully encapsulated using the supercritical solvent impregnation (SSI) process involving a series of steps.[50] Initially, the drug is dissolved/saturated in SCF and then mixed with the polymer, and further optimization of operation parameters at the time of impregnation results in higher drug loading efficiency. Co-solvency is also used to support better drug impregnation; however, a better understanding is necessary.[9a]

SCF-assisted spray-drying (SASD) process is another method developed as a valid alternative technique to the conventional spray-drying (SD) process and SAS process for the preparation of nanoparticles. Herewith, SCF plays multiple roles such as co-solvent and partially miscible solvent, and and in addition, as a pneumatic agent to generate fine particles through atomization.[51] In another case, the SCF process is hybridized with a conventional method of particle formation results in SCF processing (SCP), which acts as an alternative to solvent evaporation method for manufacturing very tiny particles.[52] SCF-expansion depressurization (SFED) process is another innovative technique, which has shown great potential in micronization of water-soluble drugs, where SCF acts neither as solvent nor anti-solvent; however, when SCF is in contact with ternary phase mixture, it starts dissolving in the solution.[53]

The supercritical hydrothermal process is another process of the SCF technology, which is treated as an extension of the conventional hydrothermal technology operating just near or above the supercritical temperature of water.[20e,54] One of the advantages of this process during particle formation is the higher reaction rates, which lead to fast nucleation and result in small-sized particles.[54] Adschiri et al. pioneered this technique for the preparation of metal oxide nanomaterials for bio-imaging applications.[20e]

All these methods and their properties have been utilized for the production of the pure drug and composite (polymer-drug) particles for different deliveries, with the added advantages of impurity separation, selective precipitation, and control of crystalline forms. Basic safety hazards and precautionary measures should be strictly followed while operating SCF equipment.

3. Drug Delivery

Solid dosage forms are of primary choice for drug formulations and are mostly administered through the oral route.[3,7b] However, they face manufacturing hurdles such as physical instability during particle formation.[4a] Moreover, traditional methods undergo a multi-step process to manufacture dosage forms. Increased demand of pharmaceutical industries in developing new approaches for drug delivery, has evidenced the SCF technology as an alternative[55] for the syntheses of micro-[35,56] as well as nano-size particles[20d,e,57] with

homogenous size distribution and high-performance.[21a] Indeed, this technology has been used to manufacture various formulations of different drug categories such as those treating anesthesia,[58] antibiotics,[53,59] asthma,[60] cancer,[61] central nervous system,[62] cardiovascular system,[31a] diabetes,[28] diuretics,[63] inflammation (steroidal[64] and non-steroidal anti-inflammatory agents[65]), lipid-lowering,[66] among others, administered through oral,[67] intravenous,[41] ophthalmic,[68] pulmonary,[47] transdermal,[61c] and polymeric implants for sustained delivery.[69] Revercheon et al. have highlighted the production of various nanoconstructs such as nanoparticles,[70] nanofibers,[71] nanowires,[72] nanotubes,[73] and other nanostructured materials using supercritical-based techniques.[20d] In addition, Adschiri et al. explored the adaptive properties of SCF for the synthesis of advanced nanomaterials include carbon nanotubes (CNTs), fullerenes, magnetic particles, quantum dots, phosphors, nanocomposites (e.g., peptide/hydroxyapatite (HAp)), and gold nanoshells for drug delivery and other biomedical applications such as imaging, sensing, and cancer theranostics.[20e]

The SCF processing of drugs improves bioavailability with also a significant increase in the surface area of the particles after micronization. However, the solubility of the drug in SCF and size of the particles depend on the density of the fluid and the pre-expansion concentration of the solute, respectively.[71] Eventually, to improve the drug dissolution characteristics, the amorphous form of poorly water-soluble drugs and their uniformly sized particles are feasible, because of their higher surface area exposure to solvent. The high surface area increases dissolution rate and subsequently, results in higher efficacy and lower dosage requirement for administration.[74]

3.1. Polymeric Carriers for Controlled Drug Release

To improve the fate and performance of a drug,[75] a protein,[76] or a vaccine,[77] a suitable carrier is required to change its delivery pattern.[72,78] Recently, controlled delivery using various polymers has garnered increasing interest, which prolongs the drug effect by maintaining the levels in the therapeutic window. In addition, targeted delivery such as magnetically directed[30,79] or using targeting ligands[61b,80] is anticipated to make APIs available at the desired sites with minimum adverse effects.[7b,61b,c] Several efforts are being made to address various challenging issues in preparing delivery systems by tailoring the morphology of polymeric carriers. Impurities-free biodegradable polymers are the best choice due to their versatility for encapsulation and efficiency in delivering various pharmaceutical agents in the body to a specific site in a controlled fashion. Spray-drying, emulsions, ionic gelation, phase separation, polyelectrolyte complexation, and SCF-assisted precipitation are the most preferred processes for polymeric micro-/nano-encapsulation.[23l] The adaptive properties of SCF are quite promising, and this green technology has emerged for particle design with low residual solvent in the product. Polymer selection is crucial based on its solubility in SCF and other solvents to overcome its separation during the manufacturing process. Further, the physical properties of polymer and operation conditions should be optimized to generate particles with different desired morphologies.[1]

As depicted in Table 1, many APIs have been encapsulated in biodegradable polymers to synthesize different sizes of particles for controlled delivery.[26,65a,b,81] Generally, the drug

encapsulation in the polymeric shell involves sequential steps as follows. In the case of non-polar or low-molecular weight drugs, the API is initially soluble in SCF. Subsequently, the polymer is added for impregnation. Eventually, the SCF is separated to remove the free drug, followed by the extraction of organic solvent, if used. In few cases, multiple drugs were also impregnated through this technology.[62b] In fact, large molecules such as proteins are difficult to be absorbed when administered through non-invasive routes and are usually compromised by using absorption enhancers. The SCF technology has created a new path in fabricating sustain delivery carriers for the transport of large molecules with structural stability.[18a,24,82] Eventually, this strategy has surpassed the drawbacks of conventional processes such as solubility and recrystallization issues.

In general, drugs with poor oral bioavailability, i.e., either with low solubility or low intestinal permeability, are opted to improve by optimizing the conditions of the manufacturing process.[4a,5b] Numerous studies with respective to delivery systems using the SCF technology are compiled and tabulated focusing on the relevant parameters related to the purpose of delivery and method of preparation (Table 1). Few of the studies have reported the micronization of APIs alone[81d,83] and few were impregnated in various water-soluble polymeric matrices such as polyvinylpyrrolidone (PVP), starch derivatives, modified cellulose, and some other synthetic polymers.[1,3,5b,23b,e,61b,84]

Polymers are highly advantageous as carriers because of easy drug impregnation, ability to carry a high payload of drugs, biocompatibility, biodegradability, and sustainability of drug release from the matrix.[7b,85] Polymers are chosen based on polarity and thermosensitivity. The key feature is the polymer solubility in SCF, which favors the reduction of polymer melting temperature and subsequently decreased viscosity[86] guided by the molecular structure, i.e., functional group, and its morphology. Polymers usually have low solubility in SCF. However, the increase in pressure or temperature results in enhancement of their solubility.[23b] Notably, few polymers are soluble only in the organic solvents, whose industrial applicability is limited.[87] To this end, phase mixing in a combination of solvents can be pursued to overcome this issue.[88]

During the supercritical process, polymeric particle formation undergoes sequential steps: initially, nucleation phase, which results in the formation of the polymeric nucleus and then followed by growth phase yielding desired particles.[13b] In fact, altered operating conditions (i.e., temperature, pressure, and solution flow rate) result in different shapes of polymeric composites such as microspheres and microfibers. The various shapes with altered critical conditions result in changes in the polymeric physical properties such as reduction in melting point and solubility improvement in relatively high-pressure systems.[89]

Most of the microencapsulated systems are prepared using biodegradable polylactic acid (PLA),[84b,90] since it is suitable for controlling delivery of short half-life drugs or highly potent drugs due to its long in vivo degradation time. For example, paclitaxel (PTX) was loaded in a synthetic biodegradable diblock copolymer poly(ethylene glycol)-PLA (PEG-PLA), and subsequently conjugated with folic acid (FA) in the PEG terminal ends to form FA-PEG-PLA complex (Figure 3). The hydrophobic drug-loaded microparticles for use as the tumor-targeted delivery system (PTX-FA-PEG-PLA) were produced via the SEDS

process, which resulted in a spherical shape and presented significantly higher cellular uptake than FA-free carriers (PTX-PEG-PLA) in the tumor tissue. This study and others demonstrate that the semi-crystalline and amorphous forms of PLA, and amorphous poly(lactide-*co*-glycolide) (PLGA) are all suitable in the SCF technology for particle formation.[61b,84a]

Among all the SCF methods for particle formation, the SAS process is one of the most efficient to produce microparticles with desired morphologies, where SCF acts as the anti-solvent, and the alternative organic solvent is used to dissolve the polymer. Further, the SCF miscibility with organic solvent leads to its expansion and subsequent reduction in density and the solvation capacity. These consequences enable supersaturation, solute nucleation, and particle formation.[8b] Different linear polyesters of lactic acid (e.g., PLA) and their co-polymers with polyvinyl alcohol (PVA) such as PVA-PLA and PVA-PLGA are processed through the SAS method.[8b,91] Solvent selection plays a crucial role in polymer dissolution and mutual miscibility with SCF.

In addition to micro-size particles, SCF can generate nanometric domains with improved therapeutic efficacy. In a case, Zare et al. prepared nanometric domains of celecoxib by SC-CO_2 extraction from a volatile oil-in-water microemulsion (Figure 4a). Celecoxib and PLGA (lactide:glycolide = 75:25) were dissolved in the dispersed phase (*n*-butyl acetate); concomitant extraction yielded solid powder composed of spherical nanoparticles with an average size of 110 nm (Figure 4b and c). In addition, these polymeric nanocarriers were dispersed in an injectable crosslinked hydrogel (Figure 4d) composed of biocompatible and biodegradable polymers, PVA (Mw = 89–98 KDa, 10 wt.%) and PVP (Mw ≈ 40 KDa, 3 wt. %). Celecoxib was capable of inducing angiogenesis in normally perfused and ischemic organs, and the intravenously administered nanoparticle formulation profoundly worked for improving therapeutic angiogenesis.[31a]

The SCF technology is rather the alternative to treat/encapsulate large molecules such as proteins due to its promising operating conditions. Polymeric carriers such as biodegradable PLGA microspheres are usually chosen to encapsulate and deliver because of their sensitivity and relatively fast degradation behavior.[17,23b,31a] This impregnation of proteins surpasses limitations such as agglomeration and limited solubility of proteins in organic solvents.[92] Most of the proteins processed as inhalation powders for therapeutic delivery are prepared using SAS[93] and its associated processes.[94]

In addition, polymeric particle formation in PGSS is easier after solubilizing SCF in polymers (i.e., PEG and polyethylene (PE)) through rapid depressurization and their phase-separation by pressure alteration. Polymer plasticization upon SCF treatment results in substantial reduction in its viscosity and results in smaller particles and allows effective immobilization of drugs.[8b] This reduction in particle size demonstrates the effective dissolution of particles and exhibits controlled release of drugs from the hydrophilic polymer matrix. Out of all processing techniques operated to synthesize drug delivery vehicles using the SCF technology, PGSS holds several advantages over others, such as no organic solvent requirement for solubilizing polymers, and eventually no extraction process for solvent removal.[17]

In general, the SCF technology is operated using any one of the supercritical solvents available. Few instances, combination of SCFs are preferred to minimize severe flocculation of polymeric microparticles due to plasticizing effect of residual SCF and this approach also results in fine-sized particles.[95] Eventually, these green solvents are also utilized to extract the residual organic solvent at <100-psi pressures from the conventional preparations, which enables increasing the particle porosity.[96]

During particle fabrication, the SCF technology offers many advantages over other processes such as colloid chemistry, microfluidics, spray-drying, and electrospray. Unlike these conventional processes, the SCF technology does not rely on the use of organic solvents. This green technology precipitates micro- and nano-sized particles with narrow size distribution by altering critical conditions (i.e., temperature and pressure) and flow rate of SCF and others.[5b,20d,21a,23r] The SCF possesses unique properties such as its solvating power, anti-solvent effect, and large compressibility.[3] The SCF technology provides many ways of particle fabrication (See Section 2) such as rapidly exceeding the saturation point of a substrate and rapid depressurization, among others.[1,21a,23e] These SCF processes yield smaller-sized particles usually faster than other techniques such as those based on microfluidics. The polymeric particles fabricated by the SCF processes can be completely dispersed in most cases, unlike various colloidal particles that rely on certain interaction forces such as electrostatic, steric, and van der Waals forces to disperse.[97] Another advantage of the SCF technology is that it allows single-step fabrication of particles that are difficult to obtain by traditional techniques.

Despite the efficiency of SCF in producing particulate delivery systems, poor solubility of polar substrates (i.e., drugs and polymers) in SCF has remained as a challenge.[98] Several alternatives can overcome this issue, such as pre-mixing of substrates and usage of organic solvent. Pre-mixing involves the mixing of all the substrates, i.e., drug and polymer, as well as other excipients, before the SCF treatment.[98] In addition, the drug is dissolved in an organic solvent before pressurizing CO_2. Further, the resultant solution is supplied to a polymer, which facilitates the impregnation of drug in the swollen polymer.[99] Eventually, the organic solvent traces can be removed post-fabrication, which results in unaltered surface properties of the particles.[17]

In addition to carrier design, the SCF technology is also used to synthesize certain biodegradable polymers by rapid depressurization at the end of polymerization.[100] Indeed, the SAS process is preferred to co-precipitate desired molecules of interest and is beneficial over other conventional methods. The plasticization phenomena of polymers in compressed SCF has a great impact on their physical and mechanical properties, which alters glass transition temperature of the polymer and allows to design advanced materials.[23g] Molecular imprinting (MIP) is one such method to synthesize polymers using various polymerization mechanisms. It has enormous applicability in different fields, which has also inspired the pharmaceutical field to design controlled release systems with high encapsulation efficiency.[101] This technique is very precise and easy to tailor the polymer because monomer is chosen based on the requirement to obtain the desired polymer.[68] Copolymer MIP process is also applied in the manufacturing process to attain control over the therapeutic release and the nature of interaction confinement during self-assembly to

direct the drug release, which depends on molecular recognition of functional monomers.[102]

In addition to polymers, cyclodextrins (CD) are the most used pharmaceutical delivery vehicles to produce solid-state inclusion complexes.[3,103] Inclusion approach alters the physicochemical properties such as solubility and dissolution rate to enhance the bioavailability of poorly soluble drugs.[103f] The specific interactions present between the host and guest molecules direct the release rate of the drug.[104] Several conventional methods in the past were used to prepare the CD complexes, which were time-consuming multi-stage processes and resulted in traces of organic solvents after preparation.[103f] The SCF technology is probably the most suitable method for the preparation of inclusion complexes using various CDs (Table 2). Following the solubilization of the drug in SCF, inclusion of the drug is possible by partitioning the dissolved drug with the SCF phase and hydrophobic CD cavity and establishes the molecular interactions such as hydrogen bonding.[103e] The SCF technology has remained as the most advantageous method of preparation over traditional methods to load large molecules in CD complexes.[103g,h]

Liposomes are the versatile delivery systems formed by the colloidal association of amphiphilic lipid substances,[23i,106] which are suitable for delivering both hydrophilic and hydrophobic drugs[107] as well as proteins.[108] Most of the genes are delivered using adenoviral or liposomal vectors, in addition to non-viral vectors known as polymers.[109] SCF has received considerable attention as a green alternative in liposome scale-up because conventional processes require large amounts of organic solvents.[3,105,106b,110] The SCF-treated liposomes resulted in higher encapsulation efficiency[3,106b,108] than the conventional liposome preparation methods.[111] Two ways have been used to prepare liposomes, one of them is performed by mixing all components, i.e., phospholipids, SCF, and organic solvent together followed by decompression, and the other is by mixing phospholipids, SCF, and organic solvent and pumping the mixture into an aqueous phase.[23]

Zhao et al. prepared liposomes utilizing modified supercritical process involving the equilibration of phospholipid suspension in water with the high-pressure CO_2 and the CO_2-expanded liquid phase at a constant depressurization rate. The mechanism behind the liposome yield is simultaneous pressurization and depressurization phenomena, which leads to a dispersing effect of CO_2 in phospholipids and released upon depressurization.[105] Eventually, due to hydrophobic interactions, phospholipids aggregate to yield spherical bilayers (Figure 5). This is similar to conventional homogenization process; however, the heat is removed from the phospholipid suspension, resulting in a temperature drop and cooling effect in the liposome suspension.[105] These lead to nano-sized particles at elevated pressure while higher depressurization rates contribute to enhanced uniformity.

Lipid delivery vehicles manufactured through the SCF technology (Table 3) possess different physicochemical properties with high stability and narrow particle size distribution.[106b] The single-step continuous mode is under operation to improve the process,[112] which has no interference in encapsulation efficiency and no loss of entrapped drug. High drug entrapment efficiency in liposomes is yielded when they are prepared from unsaturated phospholipids.[113] This approach was later utilized to develop various drug formulations

using SCF after optimization of formulation variables.[114] Although much research has been done in preparing liposomes through the SCF technology, the scalability and industrial implementation of these processes are expensive.[105,106b]

3.2. Mechanisms of Drug Release

Drug delivery systems generally consist of a drug encapsulated within a biocompatible polymeric matrix, which is intended to release the drug through various mechanisms in the body. The release mechanism depends on a few factors such as the type of polymer used and the method of preparation of any formulation.[4a,6] These factors influence successful encapsulation of drug in the polymeric matrix or a micro-reservoir either in a laboratory or during scale-up, while other factors such as pH of the target environment also play a crucial role in its release.[4a] The incorporated drug can be released through two major ways of diffusion and burst-out phenomena.[6] In a diffusion process, the high affinity or specific interactions between the encapsulated drug and the polymeric matrix are weakened and the polymeric matrix becomes porous and subsequently releases the drug in a controlled fashion. The other way is the burst release, where the drug in the polymeric matrix is weakly bound and after exchange of the surrounding fluid it results in burst-out release of almost the entire drug cargo. The burst-out phenomena can be achieved through pH-/temperature-sensitive polymers used for encapsulation.[76] In addition, surface-adsorbed drug molecules during co-precipitation process may result in their immediate release. Currently, drug delivery vehicles have been designed to contain different payload of single/multiple drugs in a formulation possessing various release characteristics such as initial burst release from the outer layer and sustained release pattern from the inner layer within the same vehicle.[23c] Others include micro-reservoir-like vehicles, where the mode of release is modulated through a microchannel array.[115]

3.3. Pulmonary Delivery

Pulmonary delivery of drugs has become an attractive target in healthcare as the lung is suitable for absorption of many drugs due to its high surface area,[116] receipt of the entire cardiac output, low enzyme activity,[23a] and lack of the first-pass metabolism.[117] This non-invasive route is now used for the administration of various drugs and proteins for systemic as well as localized therapy through pressurized metered-dose inhalers (MDIs), nebulizers, and dry powder inhalers (DPIs) containing very tiny particles (<7 μm) for efficient deposition in lungs.[51,118] These formulations should provide excellent aerodynamic performance with suitable electrostatic charge and morphology, as well as long shelf-life stability and high deposition rate.[23j] In addition to aerodynamic performance, inter-particulate interactions are also considered, which significantly depends on the particle dispersibility to define the overall particle size distribution and deposition after inhalation.[23j] These aerosol formulations are produced widely by traditional ways, such as milling or spray drying;[51] however, the end product of these methods has few limitations such as remnants of solvents and sensitive molecules (proteins, and genes) encapsulated are susceptible to degradation.[51] In addition, selection of suitable excipients also remains a challenge for formulating sustained-release pulmonary delivery systems.[119]

Researchers have applied the SCF technology using CO_2 and other solvents to synthesize fine particles of drugs,[51,59a,60,64,83,103c,120] proteins,[28,93b,c,121] and genes[122] for inhalation delivery (Table 4). Many inhalation formulations are produced at a high yield using a single-step SCF process, which can fine-tune the particle morphology, size, and charge after optimizing of all parameters.[23a] The ease of modulations has resulted in product with excellent aerodynamic performance as well as pulmonary deposition after nebulization.[23f] Particle size plays a crucial role in sustained pulmonary delivery, where larger-sized particles face difficulty in attaining bronchial penetration,[123] and small-sized particles are prone to alveolar macrophages uptake.[124] The SAS-EM technique is optimum to improve the particle size distribution in sub-micron range using the ultrasonic frequency vibrations.[93a]

DPIs are one of the most used inhalation formulations, and their clinical performance completely depends on the inspiratory flow of a patient.[17,23a,f,p] DPIs prepared using SCF are less susceptible to flow patterns than others. Further, the formulation is tolerant to physical stress, but the particles can break down upon inhalation.[125] During the processing of proteins for inhalation formulation, conditions should be optimized in the SCF technology to yield the end product with no significant change in protein conformation.[23a,126] In addition, poorly soluble proteins are also facilitated to increase their solubility in the supercritical atmosphere, suggesting the new path for bioavailability improvement in formulating protein powders. Most of the protein inhalation formulations are prepared by the SAS process, where SCF acts as an anti-solvent and an organic solvent is chosen for protein precipitation.[28,93b,c,121a] DMSO is one the most commonly used organic solvents to disperse proteins, because of its ability of expansion with pressure.[93b,127] DMSO usually disrupts the protein conformation; however, proteins such as lysosome and trypsin refold on rehydration of inhaled powders.[23a] The resultant protein product is very fine, uniform, and discrete particles (<4 μm in size) with relatively insensitive morphology and no loss of bioactivity at the varied conditions of temperature and pressure. Similar to SAS, the SFEE process also results in the formation of uniform crystalline drug particles for inhalation formulation and helpful in coating of microparticles to prevent agglomeration, which is a serious consequence in conventional coating techniques.[128]

In a comparative study involving powder formulation of salmon calcitonin (sCT) from both the conventional SD and the innovative SASD methods to investigate the role of CO_2 in the particle formation process,[51] Various formulations were designed with both the methods utilizing stabilizer (inulin, trehalose) and absorption enhancers (chitosan, sodium taurocholate, β-CD) (Figure 6). Particle size distribution of the SASD process was in a nanometric range, whereas SD resulted in >2 μm in size on average in all the formulations, and failed to detect the size of pure sCT particles accurately by zetasizer due to its poor dispersibility. The particle formation in SASD involves the origination of secondary droplets from the first droplets, which are generated by atomization through a nozzle. These secondary particles are the resultant droplets due to the rapid expansion of CO_2 within the primary droplets (decompressive atomization). In vivo absorption capacity of SASD-processed sCT in rats showed much higher nasal absorption than unprocessed and SD-processed sCT, demonstrating that the preparation of fine nasal powder with a proper absorption enhancer using the SCF process could be a promising approach.[51]

Optimization of the physical parameters for better performance of inhalation powders is still under development.[129] Few alternatives were discussed to improve the performance, for example, different constituents (polymer and drug) in a formulation have different solubility rate, which can be addressed by optimizing the amounts and solvent admixture preparation.[130] Furthermore, the addition of lower-molecular weight PEG can enhance the drug release because of its dissolution and concomitant pore formation.[131] Moreover, albumin addition can affect the particle morphology, which results in aerosolization improvement and consistency in lung deposition.[129]

Genes have also been formulated using the SCF technology (Table 4) for better stability during preparation, storage, and delivery[109,122,132] via the pulmonary route to avoid degradation in blood, and reduce the dosage.[23a,109] Eventually, the SCF technology is anticipated to be successful in fabricating various drug, protein, and gene formulations for pulmonary delivery.

3.4. Transdermal Delivery

The transdermal delivery has been a major route of drug administration in pharmaceutics, due to advantages such as pain-free self-administration, minimal frequency of dosing, and avoidance of hepatic first-pass metabolism by escaping from various metabolic enzymes.[3,133] Nevertheless, it is yet to be an alternative to oral or parenteral delivery since it is limited to delivery of drugs with narrow therapeutic ranges.[133] Many synthetic polymers such as PE, PLA, PLGA, poly(urethanes) (PU), polycaprolactone (PCL), poly(acrylonitrile) (PAN), silicone rubbers, and natural polymers (such as cellulose, chitosan, alginate, collagen, and gelatin) are utilized to prepare these topical delivery systems.[133,134] Although polymeric carriers have shown potential in delivering drugs, the penetrating ability of the therapeutic molecules is still limited. Further, this delivery system has progressed with very few active strategies to deliver therapeutic moieties and cosmetic application[135] for enhanced percutaneous permeation studies including electroporation,[136] iontophoresis,[137] microneedle,[138] and ultrasound pretreatment[139] and others.[133] However, these methods have their own limitations such as inflammation in the microneedles technique and skin rupture due to electric field associated devices such as electroporation.[61c]

Bioactive molecule impregnation using SCF holds several advantages over conventional processing systems such as high drug diffusivity into a matrix, high solubility and plasticizing effect, reduction of residual solvent, and uniform particle size distribution.[140] Chen et al. proposed a synergistic approach through the combination of methotrexate-loaded silk fibroin (SF) magnetic nanoparticles using the SpEDS process with stationary/alternating magnetic fields to achieve transdermal drug delivery.[61c] Upon supersaturation, the SF polymer precipitated on methotrexate-deposited Fe_3O_4 nanoparticles, and eventually, the permeation flux of drug was significantly enhanced under the influence of an applied magnetic field (Figure 7). This altered stationary and alternating magnetic field acted as the massage-like effect on the skin, which would significantly broaden the application of transdermal drug-delivery systems. Further advances in its manufacturing process are under progress.[61c]

3.5. Polymeric Implants

Despite its efficacy, the systemic administration is not the first choice of treatment for all types of ailments, since few of them depend on the intensity or type of the treatment, physical properties, pharmacokinetics, as well as toxicity profile of the drug and patient compliance.[69] Drug administration using medical implants with improved results has partially overcome the limitations associated with systemic routes of drug administration.[69] Implants are the medical devices pre-loaded with APIs and surgically mounted in the body for long-term therapy to avoid post-operative complications.[23c] Several traditional manufacturing processes have been developed to produce drug-eluting implants such as hot-melt extrusion and solvent casting.[23c] However, these suffer from few limitations such as high processing temperature and large amounts of organic solvent utilization. To minimize these drawbacks, the SC-CO_2-assisted impregnation process has garnered strong attention in manufacturing the drug-eluting implants.[141] The SC-CO_2-assisted impregnation process takes the advantages such as good solvating power and high diffusivity properties of SCF.[17] In this process, SC-CO_2 is first injected into a reactor to solubilize the drug and then CO_2 plus drug are allowed to contact polymer for impregnation of drug (Figure 8). Various factors such as solubility of the drug in CO_2, absorption of SCF into the polymer, and affinity between drug and polymer influence the drug loading process may affect the properties of the final products.[23c] Numerous APIs (drugs, genes, or proteins) have been packed into various biocompatible polymeric reservoirs (PLA, PLGA, PCL, poly(methyl methacrylate) (PMMA), and others), chitosan derivatives, and silicone-based copolymers (Table 5).[68,142] These implants have considerable mechanical strengths and have been envisioned for various biomedical applications such as ophthalmic and other implantable reservoirs to increase the bioavailability of the drugs.[68,69,141–143]

The SC-CO_2-assisted impregnation process has been used to prepare drug-eluting implants by impregnating drugs into polymeric matrices.[23c] Among the studies that investigated the SCF-assisted impregnation process, few of them were highlighted specific to their applications. The SC-CO_2-assisted impregnation process has been applied widely in preparing ocular devices such as lenses (intraocular lenses (IOL) and soft contact lenses (SCL)) as well as conjunctival implants to create implantable drug reservoirs (Figure 8).[68,142a,b,143] These reservoirs are applied to extend the residence time of the drugs in the aqueous humor, which enhance the bioavailability of the drugs.[23c] In addition, the drug loading efficiency through the SCF impregnation process is higher than the conventional aqueous soaking process due to the higher solubility of drugs in SCF compared to water.[143c] Recently, polymeric blends for implantable drug delivery were designed to create degradable subconjunctival implants, at which in vitro release experiments have shown both initial burst release for first 8 hours and progressive controlled release for a month.[141]

In addition to drug-eluting implants, few patents have been reported based on the SC-CO_2-assisted impregnation process in preparation of catheters and stents with antibacterial and anti-fungal drugs.[23c] Another promising application of this SCF process can be expected in the development of polymeric endoprostheses such as hip and knee prosthesis.[23c]

4. Tissue Engineering

Tissue engineering has attracted significant attention since the conception of the field due to the increase in the demand for organ replacement therapies and a shortage of donor organs.[144] This field integrates various disciplines, including but are not limited to chemistry, material science, engineering, and biology for the generation of functional tissue substitutes.[145] In addition, the tremendous progress in the past few decades has evidenced the advancements of various methods in generating three-dimensional (3D) porous scaffolds.[144] The use of these scaffolds oftentimes constitutes an important pre-requisite of tissue engineering, which are essential to repair/improve the control over the microenvironment for cell and tissue growth.[44,144,146]

Various techniques such as solvent casting–particle leaching, freeze-drying–particle leaching, thermally induced phase separation, foaming, self-assembly, compression molding, extrusion, electrospinning, sacrificial templating, and injection molding are also available to produce 3D porous scaffolds.[17,23t,144,147] However, the applications associated with some of these approaches have been limited due to the need for large amounts of organic solvents utilized during the preparation of scaffolds in many cases.[23n,147] These organic solvents may damage bioactive molecules such as growth factors during the fabrication procedure, while the residues may also subsequently affect the cells and the surrounding tissues.[33a] In addition, the solvent residues might result in the inflammatory responses after implantation.[148] Some other techniques such as self-assembly are not able to control of internal scaffold structure and achieving the microarchitecture is challenging.[147] The bioactive molecules such as proteins incorporated by an adsorption-associated freeze-drying process are remained on the surface of the scaffolds, and their release is rapid upon delivery.[8b,149] To this end, the SCF technology has attracted the attention in designing porous polymeric scaffolds, overcoming the above-mentioned disadvantages of the conventional scaffold fabrication methods. The SCF processes involve the interaction of highly dense gas with polymers, which enables precise control over the porous morphology by tuning the operation conditions and produces scaffolds upon depressurization.[33a,150] Moreover, SCF-assisted preparations lead to generation of stable scaffolds such that the structure remains unchanged during drying and the incorporated bioactive molecules such as proteins are distributed homogenous throughout the scaffold.[8b,149,151] The only minor disadvantage is that the end-products may possess denser surfaces with less interconnected porosity than the internal space, which usually has a high porosity with interconnected and open pores. However, the surface can be subsequently removed to expose the interior before application.[152]

Out of all SCFs operated, SC-CO_2 is the most suitable solvent to generate porous polymeric scaffolds, since it holds strong interactions with the carbonyl groups of polymers such as PLA and PLGA.[153] Gas-foaming, and phase-inversion are the mostly used SCF techniques to prepare tissue-engineered scaffolds. In the gas-foaming method, SCF plasticizes the glassy biomaterials after saturation and results in foaming of the polymers for the formation of the porous scaffolds and sponges[154] with normal porosity. Polymers from natural (alginate,[155] chitosan[154b,156]) and synthetic (poly(methyl vinyl ether-*co*-maleic anhydride) (PVM-MA),[85a,154a] PLA,[152] PLGA[157]) origin and bioceramics such as

HAp[158] act as a template to promote tissue growth.[23t,33a,159] This foaming of biodegradable polymers has numerous advantageous[160] and applicable in various fields of tissue engineering such as periodontal regeneration, bone formation, cartilage development, repair of nasal and auricular malformations, as artificial corneas, in ligament replacement, in tumors, and in tendon repair.[17,33a,140,161] In addition, natural deep eutectic solvents also used as enhancers in producing polymeric foams in the SCF technology.[162] In the SCF-assisted phase-inversion process, SCF acts as a non-solvent, which after in contact with polymer solution results in polymeric scaffolds through phase separation.[163] In this case, altered critical operating conditions can tailor the properties of SCF, which result in subsequent changes in the morphology and size of the porous scaffolds.[33a] After phase separation, the organic solvent is removed by flushing SCF.

Another SCF process for tissue engineering applications is the emulsion-templating method, which is effective in preparing hydrophilic porous polymeric scaffolds.[164] The pores are generated after removal of the internal phase from the oil-in-water emulsion. This platform is highly advantageous in processing heat-sensitive biomolecules over conventional approaches due to the ability to use low amounts of solvents if necessary and operation at low temperature. Herewith, SC-CO_2 acts as the internal phase, which can generate well-organized interconnected pores in surfactant-polymer complex, further increase in the internal phase and surfactant concentration leads to increase in porosity and open, interconnected pores, respectively.[164] In another way, proteins are incorporated by dispersing in water and polymer in the oil phase followed by their saturation with SC-CO_2, and subsequent depressurization results in porous scaffolds for controlled release of protein.[165] The double-emulsion method is preferred for creating homogenous matrix to encapsulate multiple proteins in polymeric scaffolds.[166]

Polymeric foams generated at both supercritical as well as subcritical temperatures are chosen to sinter biological moieties such as cells based on the crystalline behavior of the polymer.[33a,167] Initially, the selected polymer is subjected to compressed CO_2 treatment at a constant temperature and pressure until it attains a stable swollen state. Subsequently, the pressure and/or temperature are altered, leading to phase separation and eventually pore generation. In general, different porosity range in the polymeric scaffolds is utilized for different biomedical applications.[168] For generation of pores and better interconnectivity, elutable porogens such as sodium chloride, sucrose, or other porogens with low decomposition temperature such as ammonium carbonate are added during the preparation of porous scaffold.[151] Few studies have also reported significant pore interconnectivity without using any porogen. For example, the cartilage repair was performed using poly(ethyl methacrylate)/tetrahydrofurfuryl methacrylate (PEMA/THFMA) polymeric scaffold, which possessed a significant pore interconnectivity to culture chondrocytes and to form a 3D environment for tissue generation without any porogen.[169] In addition, post-processing of solvent-free ultrasound technique also improved the interconnectivity of pores generated from gas-foamed scaffolds with increase in pore size.[170] Further, mechanical properties of the scaffolds were altered by changing the SCF processing conditions and utilized for various tissue engineering applications.[171]

More often, polymer content variation results in the change in morphology of pores yielding heterogeneous pores.[134b] In addition, various drugs have also been impregnated into polymers using SCF for the self-healing process in tissue engineering and regeneration.[134a] Interestingly, Cardea et al. demonstrated the SCF-assisted phase-inversion process for the preparation of ibuprofen-loaded cellulose acetate (CA) structures at a short processing time (Figure 9).[134b] In this study, CA-loaded structures were different with increasing polymer concentration in the starting solution. At the lower concentration, it yielded microparticles (Figure 9a,b) to a bicontinuous one with macrovoids at moderate concentration (Figure 9c,d), and to a cellular one at an extreme higher concentration (Figure 9e). Nevertheless, the ibuprofen presence had no effect on the void formation.[134b] In addition, from the drug release point of view, the pore size of the CA structures was indirectly proportional to the pressure applied, where the high pressure resulted in small pore size and eventually controlled the drug release and vice versa.

A work from Duarte et al. addressed the preparation of bio-compatible polymeric scaffolds made of blends of natural and synthetic polymer using the SCF technology, which mimic the functions of extracellular matrix (ECM).[172] These biocompatible scaffolds are available in the form of the 3D porous matrix, non-fibrous matrix, polymeric hydrogel, or porous micro-sphere, which enables cell attachment throughout the space in the matrix and promotes its integration with the host tissue with a potential of rapid angiogenesis facilitated by cell migration and nutrient transfer.[153a] These scaffolds prepared by the SCF-based technology tend to show biological acceptance and function as a temporary support for the tissue regeneration by preserving the ability of cells to proliferate, as well as controlling cell function, growth, reorganization, and possibly neovas cularization.[33a,158,173] Apart from cell attachment, these porous scaffolds prepared by SCF processes are also utilized to release precise amounts of guest species[23t] i.e., essential growth factors such as vascular endothelial growth factor (VEGF),[174] transforming growth factor-beta 3 (TGF-β3),[175] basic fibroblast growth factor (bFGF),[176] and others.[177] All these preparations by homogeneously incorporating various signaling moieties promote cell infiltration, adhesion, migration, expansion, and differentiation.[33a,178]

5. Bio-Imaging

Bio-imaging allows visualization of biological structures as well as functional analysis often taking advantage of contrast agents.[20e] Since tracing of a targeted system is a prolonged course, inorganic constructs are most preferred to organic molecules because of their long biological half-lives. For example, phosphor-containing nanoparticles such as those made of rare earth phosphates and semiconductor nanoparticles such as quantum dots have attracted attention, since their optical emission wavelengths can be conveniently controlled by compositions and particle sizes.[20e,179] Inorganic metal oxides have also garnered potential interest for use as contrast agents and others, whose application potential is dictated by their surface, particle size, and shape.[20e] The supercritical hydrothermal process has been used for the generation of metal oxide nanoparticles such as those of zinc oxide (ZnO), iron oxide (Fe_3O_4), titanium oxide (TiO_2), gadolinium vanadate ($GdVO_4$), and others, for bio-imaging purposes. Surface modification is preferred either by immobilizing various organic or heat-labile carriers for better performance.[20e,180]

Out of various metal oxides obtained by the SCF technology, magnetic (iron oxide) nanocarriers have profoundly attracted the attention in numerous biomedical applications such as magnetic resonance imaging (MRI) contrast agents[20e] and targeted drug delivery purposes.[30,61c,79] Although in its infancy, SCF-assisted nanoparticle preparation is anticipated to possess widespread biomedical applications.

6. Miscellaneous Applications

Apart from the generation of drug delivery carriers and 3D porous scaffolds for various biomedical applications, the SCF technology can also be utilized in other applications during pharmaceutical processing such as coating of delivery systems, sterilization of products, and extraction of solvents and active gradients. In this section, we present a brief overview on these aspects.

The process of coating of any drug delivery system is to mask its unpleasant taste or odor, to control the delivery site, and to protect the formulation both physically and chemically.[181] In a conventional process, the coating material is dissolved in either water or an organic solvent and is eventually sprayed over the particles. This procedure has its own disadvantages such as long drying time, chances of agglomeration, limited solubility of coating substance, toxicity and inflammability of the residual organic solvents.[182] The organic solvent-free SCF technology thus has the capability to coat various APIs to improve the hydrophobicity of certain moisture-sensitive biodegradable materials.[181] A fluidized bed coating process has been applied based on a multi-step RESS process through optimization of various parameters such as temperature, pressure, and solidification of coating material on the surface, which play key roles in an effective coating strategy.[181] This process is highly advantageous to coat sensitive materials such as proteins.[183]

Another application of SCF is sterilization, which is already in practice in the food, pharmaceutical, and biotechnological industries where contamination is a major concern.[184] Since sterilization is a preliminary concern of these fields, it is mandated to ensure that every component such as glassware, raw materials, and final products is free from contamination. In addition to traditional methods of sterilization, SCF has been utilized to inactivate a wide variety of microbes and their spores providing suitable conditions (14–21 MPa, 30–45 °C for 0.6–4 h). The inactivation of microbes involves a series of mechanisms in disrupting the integrity of the cells. Unique mass transfer property of SCF creates an ability to enter the cells by extracting cell wall lipids, further damaging cell membrane and inducing cytoplasmic pH change and metabolic enzyme inactivation intracellularly.[184]

SCF leads to the efficient green synthesis of biodegradable polymers, ideal for pharmaceutical applications. In few instances, high productivity of polymers has been evidenced by using various metal catalysts and organic solvents.[100b] Extraction of these co-solvents, however, is critical during the processing of the porous scaffolds for subsequent applications in drug delivery or tissue engineering due to that the trace amounts can significantly affect the tissue response and mechanical properties of the scaffolds. SCF is advantageous in removing the traces relatively quicker than the traditional vacuum drying approach with no significant alteration in the scaffold architectures.

In addition, pre-cleaning of scaffolds using SCF may also minimize the adverse responses as well as to improve the bio-compatibility. This pre-treatment does not alter any biochemical or biomechanical properties of the scaffolds, and would thus improve their integration with the surrounding tissues post-implantation through relieved immunological responses.[33a] Recently, single-step supercritical defatting and sterilization of human bone allograft powder has also been proposed.[185]

The SCF technology is also used to extract bioactive ingredients such as polyphenols, terpenoids from the natural products and is potentially more advantageous over conventional methods, which usually involve the usage of organic solvents.[186] The advancement of the SCF-assisted extraction processes and examples discussing the pharmacological benefits of the active moieties were compiled by da Silva et al.[187] These mild operating conditions provided by SCF are more appropriate to recover various sensitive ingredients.[188] Further, the hybridization of impregnation to the supercritical extraction process resulted in the high encapsulation efficiency of extracted active moieties.[188] So far, SCF extraction of solvent is under practice in various fields such as food processing, agriculture, and others.[189]

7. Conclusions and Remarks

In summary, this critical review has highlighted and discussed various SCF processes in producing controlled drug release carriers such as micro- as well as nano-sized polymeric particles, liposomes and CDs for the application focusing oral, and pulmonary and transdermal routes of administration. These polymeric carriers produced by the eco-friendly SCF technology are advantageous over those fabricated by conventional methods of preparation with high efficiency. In addition, we also gave an overview of SCF-assisted preparation of products intended for related biomedical applications such as tissue engineering and bio-imaging, among others.

Despite its success at laboratory scale, the applications of the SCF technology at industrial scale is still in infancy due to the lack of fundamental studies accurately describing the phase behavior of the multi-component mixtures including biodegradable complex compounds. Recently, steps have been taken for commercialization of these processes for pharmaceutical application. Pierre Fabre CDMO Supercritical Fluids, a France-based SC-CO_2 GMP unit for pharmaceutical applications, has been performing pre-formulation studies of various APIs through patented processes such as Formulcoat, Fomulplex, and Formuldisp. However, no established marketed product manufactured by the SCF technology is yet available to date.

We anticipate that integrating SCF with a conventional process such as spray drying or others may result in the advancement of the carriers. It may open a new paradigm in the field of pharmaceutical science to reduce the complexity of manufacturing process and a better understanding of the product behavioral characteristics and performance. It is anticipated that with further optimization, the SCF technology can create novel opportunities not only in laboratory research but also for the industrial processing of delivery systems in the future.

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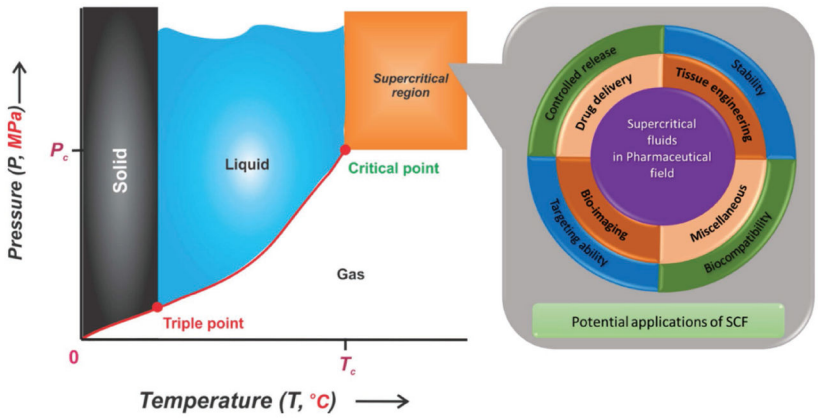

Figure 1.

Schematic representation of CO_2 phase diagram elucidating CO_2 existence as various phases along with the supercritical phase beyond the critical point (T_c = 31.1 °C, P_c = 7.38 MPa) (**Left**). Graphic illustration elucidating the potential applications of SCF (**Right**).

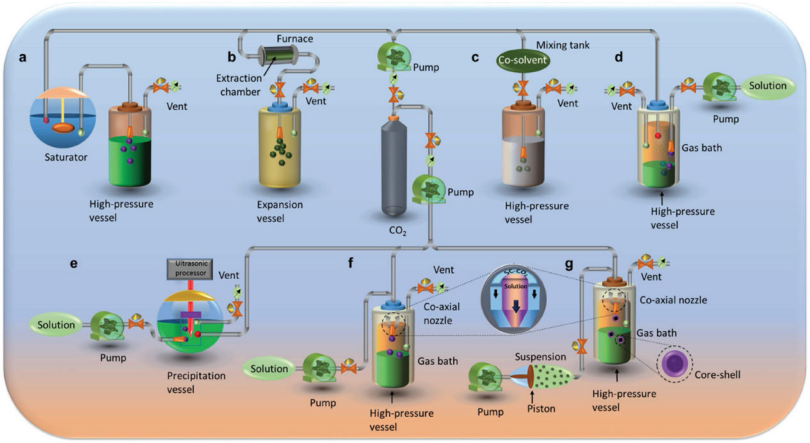

Figure 2.

Conceptual representation of various processes of particle formation using SC-CO_2. a) Particle formation from gas saturated solutions (PGSS). b) Rapid expansion of supercritical solutions (RESS). c) Rapid expansion of a supercritical solution into a liquid solvent (RESOLV). d) Precipitation with compressed anti-solvent (PCA)/Aerosol solvent extraction system (ASES). e) Supercritical antisolvent with enhanced mass transfer (SAS-EM). f) Solution enhanced dispersion by supercritical fluids (SEDS). g) Suspension enhanced dispersion by supercritical fluids (SpEDS).

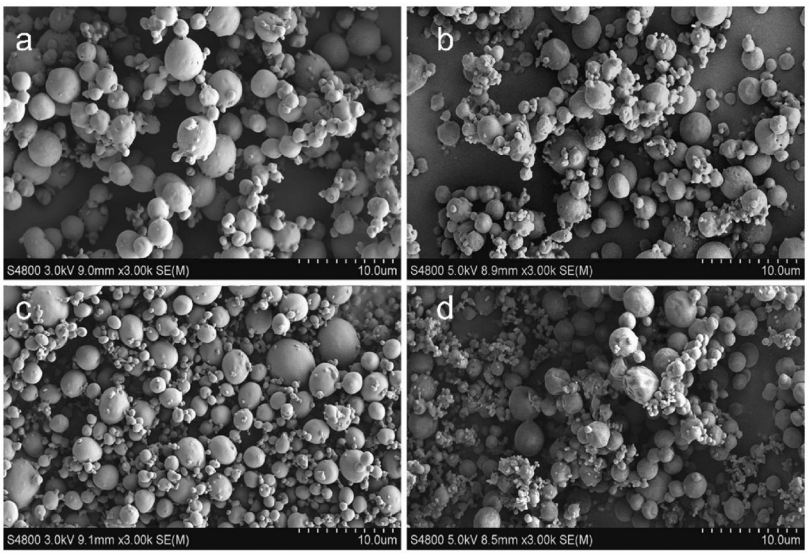

Figure 3.

SEM images showing microparticles prepared by the SEDS process. a) FA-PEG-PLA, b) PTX-loaded FA-PEG-PLA, c) PEG-PLA, and d) PTX-loaded PEG-PLA particles. Reproduced with permission.[61b] Copyright 2015, Springer.

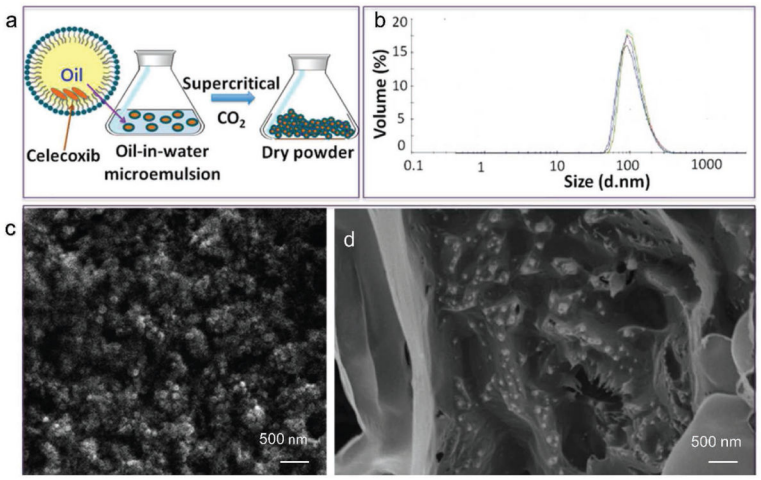

Figure 4.

Celecoxib nanoparticles formation and characterization. a) Schematic representation of nanoparticle formation process. b) Particle size measurements in water by dynamic light scattering (DLS). c) SEM image of nanoparticles in powder. d) SEM image of nanoparticles embedded in hydrogel (dried). Reproduced with permission.[31a] Copyright 2015, American Chemical Society.

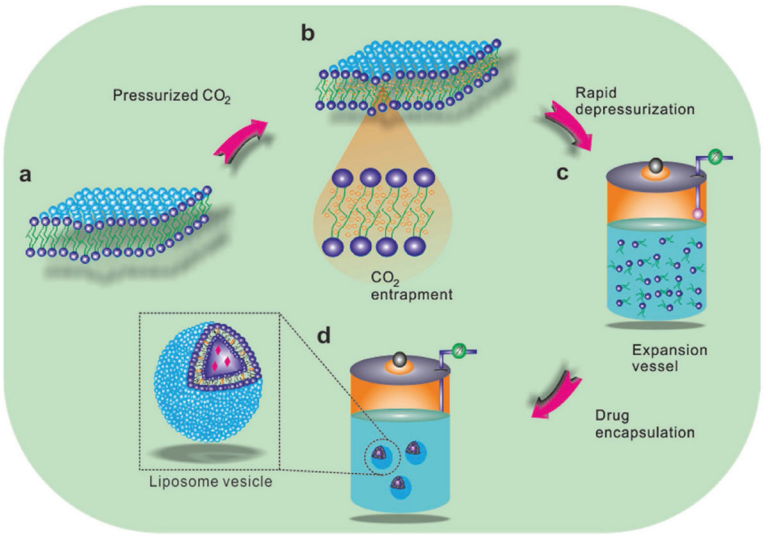

Figure 5.

Schematic mechanism of liposome formation by the modified supercritical method. a) Phospholipid curvatures present at ambient condition, b) formation of expanded phospholipid bilayers after pressurization and equilibration with CO_2, c) formation of an instantaneous dispersion of discrete phospholipid molecules during depressurization and release of CO_2, and d) formation of liposome vesicle due to hydrophobic interactions after depressurization. Reproduced with permission.[105] Copyright 2015, Elsevier.

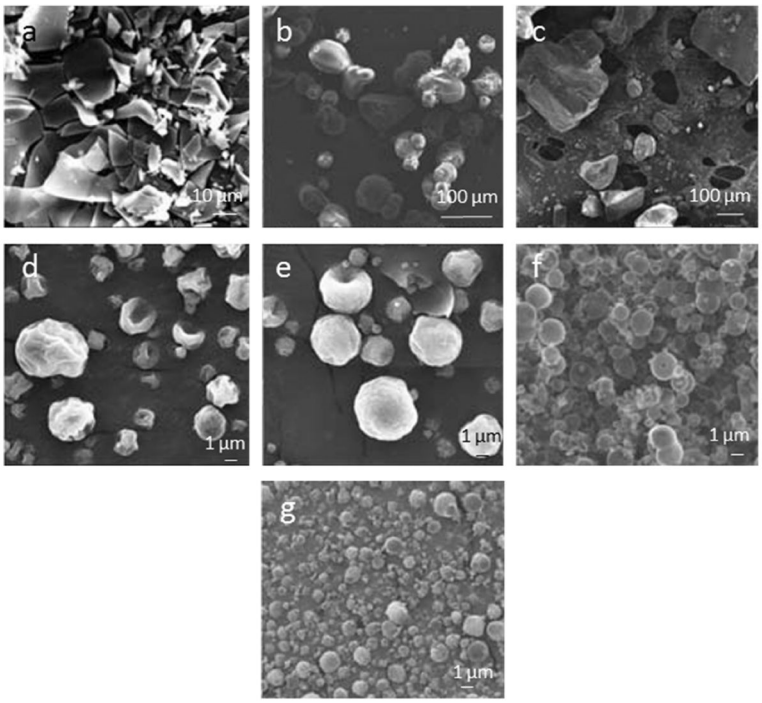

Figure 6.

SEM images of (a) raw salmon calcitonin, (b) raw inulin, (c) raw trehalose, formulations prepared by (d,e) SD method, and (f, g) SASD method. Reproduced with permission.[51] Copyright 2015, Elsevier.

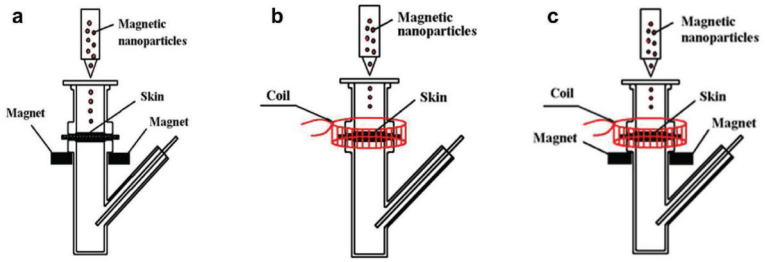

Figure 7.

The experimental setup of permeation studies. a) Diffusion cell with the stationary magnetic field. b) Diffusion cell with the alternating magnetic field. c) Diffusion cell with stationary/alternating magnetic fields. Reproduced with permission.[61c] Copyright 2015, Dove Press.

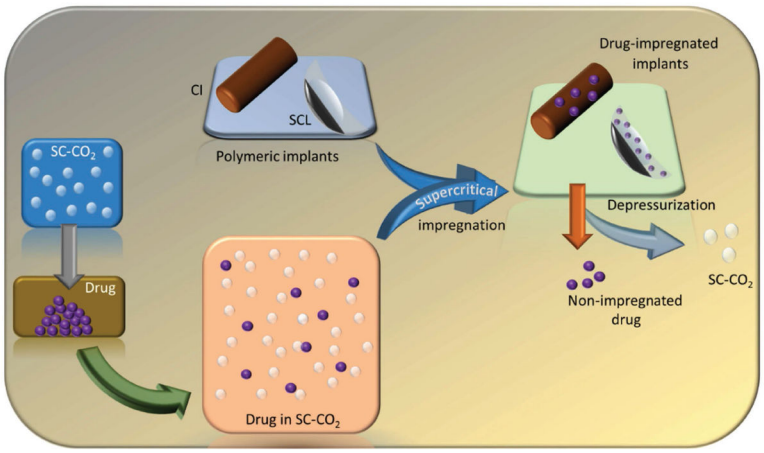

Figure 8.

Graphical illustration of drug impregnation into polymeric implants (SCL-Soft contact lens, CI- Conjunctival implants) by using SCF technology.

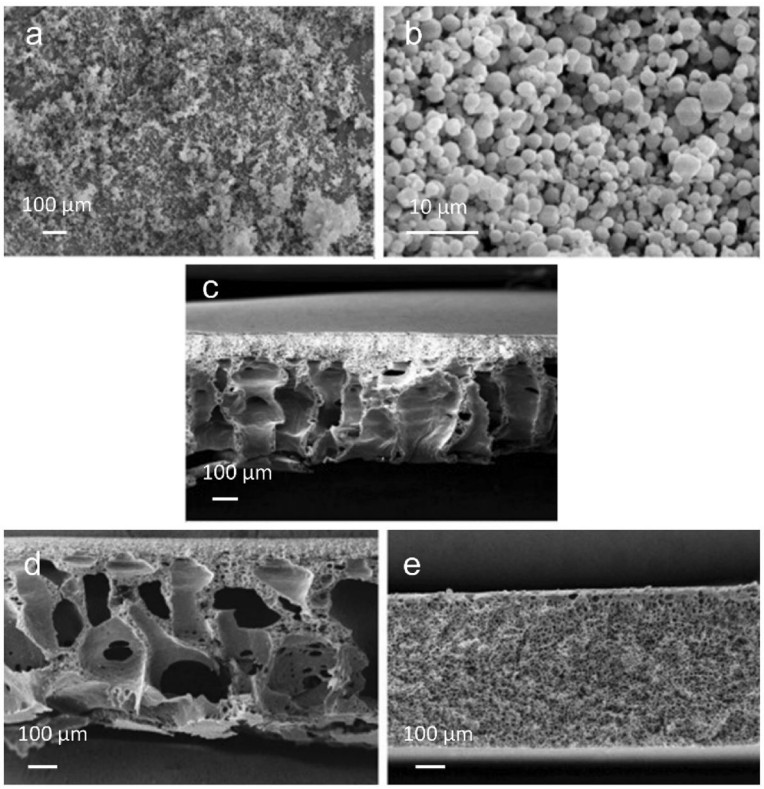

Figure 9.

CA structures loaded with ibuprofen at 10% w/w, obtained at 250 bars and 35 °C, starting from different polymer concentrations. a–b) 5% w/w, c) 10% w/w, d) 15% w/w, and e) 20% w/w. Reproduced with permission.[134b] Copyright 2016, Elsevier.

Table 1

Polymeric drug delivery systems synthesized using various methods of preparation with the SCF technology.

Pharmaceutical compound	SCF Process	Polymer	Solvent	Purpose	Reference
2,6-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-3-hydroxymethylimidazo-[1,2-a] pyridine mesylate	SEDS	Eudragit® E100, Mannitol	Acetone, DMSO, MeOH	Bioavailability enhancement	[42a]
5-Aminosalicylic Acid	SEDS	Eudragit® S100	Acetone, DMSO	Bioavailability enhancement	[190]
5-Fluorouracil	SEDS	PLA	DCM	Controlled release	[61a]
		PLA, Silica	DCM		[191]
		PEG, PLA–PEG	Acetone, DCM, Water		[192]
	SAS + SSI	PLA	EtOH		[18a]
	SCP	PLGA	-		[85b]
		PLA	EtOH		[193]
17α-Methyltestosterone	SAS	PCL, PLA	DCM	Controlled release	[27]
α-Tocopheryl acetate	SSI	MCM-41-type silica	EtOH, Toluene	Controlled release	[194]
β-Carotene	SFEE	PCL	DCM	Controlled release	[195]
	SEDS	PHBV	-		[196]
β-Estradiol	SCP	PLGA	-	Controlled release	[85b]
		PVP	EtOH		[197]
β-Sitosterol	RESS	-	Trifluoromethane	Bioavailability enhancement	[81d]
Acetaminophen	RESS-N	EC, PEG, PEG-PPG-PEG, PLA, PMMA	EtOH	Controlled release	[81b]
	SAS	Eudragit® RL100	Acetone		[75]
Adefovir dipivoxil	RESS	-	-	Bioavailability enhancement	[13c]
Ampicillin	SAA	-	Acetone, MeOH	Bioavailability enhancement	[34a]
	SAS	-	DMSO, EtOH, NMP		[198]
	SAS	EC	DCM, DMSO	Controlled release	[199]
	SAA	HPMC	Phosphate buffers		[200]
Amoxicillin	SAS	-	NMP	Injectable	[83a]
		-	DMSO, EtOH		[201]
	SCF-PI	PMMA	Acetone, DMSO	Controlled release	[202]
		PVDF–HFP	Acetone		[203]
	SEDS	Chitosan	-	Bioavailability enhancement	[204]
Arbutine	SAS	-	EtOH	Topical administration	[205]

Pharmaceutical compound	SCF Process	Polymer	Solvent	Purpose	Reference
Artemisinin	RESS	PVP-K25	DCM	Oral delivery	[81a]
		-	-	Bioavailability enhancement	[206]
	SCP	Silica, Sodium alginate, and Starch aerogels	EtOH, Isopropanol		[207]
Aspirin	RESS-N	PEG	EtOH	Controlled release	[81b]
	SCF-MIP	P(DEGDMA)			[101]
Avidin	SCP	PLA	–	Controlled release	[149]
Azacytidine	SAS	PLA	DCM, DMSO	Controlled release	[208]
Baicalein	SEDS	–	Acetone, DMSO, EtOH	Bioavailability enhancement	[209]
Bevacizumab	SCF-PQT	PLA, PLGA	DCM	Controlled release	[50]
BSA	SEE-C	PCL, PLA, PVA	Acetone, Glycerol, Water	Controlled size	[210]
	SSI	Chitosan, PNIPAAm	Acetic acid	Stimuli-responsive release	[76]
	PGSS	Chitosan, PEG, PLGA	–	Controlled release gastroretentive system	[67]
	SAA	PLA	Chloroform	Stability improvement	[211]
Bupivacaine HCl	SAS	PLA, PLGA	DCM, EtOH	Controlled release	[91]
Calcitonin (Salmon)	SASD	Chitosan glutamate	EtOH, Water	Bioavailability enhancement	[51]
Camptothecin	SAS	Dextran	DMSO	Targeted delivery	[80]
Carbamazepine	SSI	PVP	–	Controlled release	[98a]
	GAS	PEG	Acetone	Bioavailability enhancement	[212]
	SCP	Gelucire, PVP-K30, TPGS	MeOH		[52]
Celicoxib	SEDS	PLGA	*n*-Butyl acetate	Injectable	[31a]
Cefuroxime axetil	SEDS	HPMC, PVP-K30	DCM, EtOH	Bioavailability enhancement	[213]
Chelerythrine	SEDS-PA	–	MeOH	Bioavailability enhancement	[214]
Chlorohexidine diacetate	SSI	PEMA, THFMA	–	Polymeric foam	[215]
Cilostazol	SAS	–	DCM	Bioavailability enhancement	[216]
Cholesterol	SSI	PCL, PMMA	–	Controlled release	[217]
Cu_2(indomethacin)$_4$DMF$_2$	ASES, GAS	–	DMF	Bioavailability enhancement	[21c]
Curcumin	SEDS	–	Acetone	Bioavailability enhancement	[218]
		SF	HFIP		[219]
Dexamethasone	SAA	–	Acetone, MeOH	Bioavailability enhancement	[34a]
Diclofenac sodium	SFEE	PLGA, PVA	EA, Water	Injectable	[41]
Dihydroquercetin	SCP	Starch aerogels	EtOH	Oral delivery	[207]

Pharmaceutical compound	SCF Process	Polymer	Solvent	Purpose	Reference
Dithranol	SCP	Silica aerogels	ACN, MeOH	Oral delivery	[220]
Docetaxol	SCP	PVP-K17	Myristyl alcohol	Bioavailability enhancement	[221]
Erlotinib HCl	SAS	–	MeOH	Bioavailability enhancement	[74]
		HPMC-phthalate	DMSO		[222]
Felodipine	PGSS	PEG-4000	–	Bioavailability enhancement	[35]
	SAS	HPMC	DCM, EtOH		[223]
Fenofibrate	PGSS	PEG-4000	–	Bioavailability enhancement	[35]
	RESOLV	Alginate, HPMC, PLGA	–		[37]
	SCP	Silica matrix	–		[224]
		Fumed silica	–		[225]
		Silica SBA-15	–		[226]
Fenprofen	RESS	–	–	Bioavailability enhancement	[227]
Fluconazole	SAS	–	Acetone, DCM, EtOH	Bioavailability enhancement	[228]
Flufenamic acid	SCF-MIP	Methacrylic acid, NIPAAm cross-linked EGDMA	–	Controlled release	[102]
Fulvestrant	SAS	–	EA	Bioavailability enhancement	[74]
Furosemide	SAS	PVP	Acetone, EtOH, MeOH	Bioavailability enhancement	[63]
Gentamycin	PCA	PLA	DCM	Controlled release	[29]
		PVM-MA	Acetone		[85a]
		PLGA	Acetone	Intracellular targeting	[229]
Griseofulvin	RESS	–	Trifluoromethane	Bioavailability enhancement	[81d]
	RESS-SC	–	DCM, Menthol		[38]
	SFEE	PVA, PVP	DCM, EA		[230]
	SCP	Silica aerogels	ACN, MeOH	Oral delivery	[220]
Human growth hormone	SEDS	–	Isopropanol	Bioavailability enhancement	[231]
Hydrocortisone	SEDS	PCL, PLA, PLGA	Acetone, DCM, EA, Hexane, Isopropanol	Controlled release	[95]
	SFEE	PLGA	DMSO, EA, EtOH		[232]
Ibuprofen	SSI	PVP	EtOH	Controlled release	[65a]
		PMMA, PVP	EtOH, Toluene		[233]
		Chitosan, PNIPAAm	Acetic acid	Stimuli-responsive release	[76]
		Gelatin, Silica	Acetone	Controlled release	[234]
	SCFS	PCL, Starch	Menthol		[235]

Pharmaceutical compound	SCF Process	Polymer	Solvent	Purpose	Reference
	RESOLV	PEG, PVA, PVP	–		[70a]
	SCP	PLA	Chloroform		[145a]
	PGSS	Gelucire, Glyceryl Monostearate, Pluronic F127	Water		[236]
	SCF-PI	CA	Acetone		[134b]
	SCP	PCL	–		[237]
		PEG, PVP	EtOH		[98b]
		MCM-41-type silica	–		[238]
		Silica, Sodium alginate, and Starch aerogels	EtOH	Oral delivery	[207]
Immunoglobulin G (IgG)	SAS	–	EtOH	Biopharmaceutical powders	[239]
Indinavir	SAS	–	Acetone	Bioavailability enhancement	[240]
Indomethacin	SAS, SAS-EM	Eudragit® RS 100, Magnetite, PLGA, PMMA	DCM	Magnetically responsive drug release	[30]
	SFEE	Eudragit RS®, PLGA	EA	Controlled release	[96b]
	SEDS	PLA, PLGA	DCM		[14]
		Iron oxide, PLA	DCM	Magnetically responsive drug release	[241]
	SSI	Chitosan	–	Controlled release	[81c]
		HPMC	–		[242]
		PLA, PLA-PEG, PLGA	Acetone, Water		[243]
Insulin	SAS	PLA	DCM, DMSO	Subcutaneous delivery	[130]
	GAS	PEG, PLA	DMSO	Controlled release	[131]
		PEG, PLA	DCM, DMSO		[244]
	SFEE	PLGA	–		[245]
	SCP	Chitosan, PAA, PEO	–	Bioavailability enhancement	[246]
Itraconazole	SCP	HPMC, PVP	Cetyl alcohol	Bioavailability enhancement	[247]
Ketoprofen	SSI	PVP-K10	–	Bioavailability enhancement	[248]
		Gelatin, Silica	Acetone	Controlled release	[234]
	PGSS	Gelucire, PEG	–		[65c]
	SCF-IP, SSI	PVP	–	Oral delivery	[115a]
	SFEE	PLGA	EA	Bioavailability enhancement	[249]
		Eudragit RS®, PLGA		Controlled release	[96b]
	SCFD	Alginate	EtOH	Oral delivery	[250]
	SCP	PLGA	–	Controlled release	[251]

Pharmaceutical compound	SCF Process	Polymer	Solvent	Purpose	Reference
		Silica aerogels	ACN, MeOH	Oral delivery	[220]
Levothyroxine sodium	GAS, ARISE	–	EtOH	Bioavailability enhancement	[252]
Lipase	RESS-N	PEG, PEG-PPG-PEG, PLA, PLGA, PMMA	Acetone, EtOH, MeOH, Propanol, Toluene	Bioavailability enhancement	[87]
Loratidine	SCP	Silica, and Starch aerogels	EtOH, Isopropanol	Oral delivery	[207]
Lovastatin	RESS	PLA	-	Bioavailability enhancement	[55]
Lutein	SEDS	Zein	Acetone, DMSO	Controlled release	[253]
Lysozyme	SFEE	PLGA	DMSO, EA	Bioavailability enhancement	[254]
	RESS-N	PEG, PEG-PPG-PEG, PLA, PLGA, PMMA	EtOH, Toluene		[87]
	ASES	PLA	DMSO		[255]
	PCA	PLA, PLGA	DCM		[92]
	SEDS	PEG, PLA	DMSO		[256]
Mangiferin	SAS	–	Acetone, DMSO, EtOH, NMP	Bioavailability enhancement	[257]
Megestrol acetate	SAS	HPMC, PVP, PEG	DCM, EtOH	Bioavailability enhancement	[258]
Methotrexate	SpEDS	Iron oxide, SF	DCM, HFIP	Transdermal delivery	[61c]
		PEG, PLA	Acetone, DMSO	Controlled release	[32a]
		Iron oxide, PEG, PLA	DCM	Targeted Controlled release	[46]
	SEDS	–	DMSO	Bioavailability enhancement	[259]
Miconazole	SCP	Silica aerogels	ACN, MeOH	Bioavailability enhancement	[220]
Minocycline	SAS	–	EtOH	Bioavailability enhancement	[260]
Morphine	SEDS	PLA-PEG-PLA	DCM, MeOH	Controlled release	[261]
		PLA	DCM, EtOH, Water		[262]
Naloxone	PCA	PLA	DCM	Controlled release	[29]
Naphthalene	SSI	PMMA	–	Controlled release	[263]
Naproxen	SAS	EC, Methyl cellulose	DCM, DMSO	Oral delivery	[264]
	RESS	PLA	–	Bioavailability enhancement	[65b]
	SCP	Ethylene-vinyl-acetate, Eudragit® E100	DCM	Transdermal controlled delivery	[99]
Naltrexone	PCA	PLA	DCM	Controlled release	[29]
Niclosamid	SCP	Silica aerogels	ACN, MeOH	Oral delivery	[220]
Nifedipine	PGSS	PEG-4000	–	Bioavailability enhancement	[35]
Nilotinib	SAS	HPMC-phthalate,	Acetone, Chloroform, DMSO	Bioavailability enhancement	[222]
Nimesulide	SAS	–	Acetone, Chloroform, DCM	Bioavailability enhancement	[265]

Pharmaceutical compound	SCF Process	Polymer	Solvent	Purpose	Reference
	SSI	PDMS	–	Controlled release	[266]
Olanzapine	RESS, RESSAS	HPMC, PEG	–	Oral delivery	[267]
Oxaliplatin	SCP	–	Myristyl alcohol	Oral delivery	[268]
Oxeglitazar	SAS	PEG, Poloxamer 188 and 407, PVP-K17	Chloroform, DCM, DMSO, EtOH, NMP, THF	Oral delivery	[25]
pDNA	SCF foaming	Chitosan, PLGA	–	Controlled release	[156]
Paclitaxel	SSI	PLA	EtOH	Controlled release	[269]
	SEDS	PEG-PLA	DCM	Targeted delivery	[61b]
		PLA, PLGA	DCM	Controlled release	[270]
	GAS, SCF-PI	Basil seeds mucilage	DMSO, EtOH	Bioavailability enhancement	[271]
	RESOLV	PVP	–		[272]
Phenytoin	RESS-SC	–	Menthol	Bioavailability enhancement	[62a]
Piroxicam	SAILA	PLA, PLGA	–	Controlled release	[40b]
	SSI	PDMS	–		[266]
	SFEE	PLGA, PVA	EA, Water	Injectable	[41]
	PCA	PVP	–	Bioavailability enhancement	[273]
Progesterone	SCP	PEG, Gelucire 44/14 TPGS	–	Transdermal delivery	[274]
	PGSS		–	Bioavailability enhancement	[275]
Puerarin	SEDS	PLA	DCM	Bioavailability enhancement	[15,276]
Quercetin	SFEE	Pluronic L64, Soybean lecithin	EA	Bioavailability enhancement	[43]
Retinyl acetate	SFEE	PLGA	Acetone	Sustained release	[277]
Retinyl palmitate	RESOLV	PLA	–	Bioavailability enhancement	[278]
Rhodamine	SFEE	PLA	EA	Controlled release	[279]
Rifabutin	SCP	Silica, Sodium alginate, and Starch aerogels	EtOH, Isopropanol	Oral delivery	[207]
RNA	SEDS	PEG, PLA	DCM	Transdermal controlled delivery	[280]
Salbutamol	SCFD	Chitosan	EtOH	Controlled release	[281]
Salicylic acid	SCF-MIP	P(DEGDMA)	EtOH	Controlled release	[101]
	SSI	Alumina, Amberlite, Silica gel	-		[62b]
Silymarin	SEDS	Phospholipids	DCM, EtOH	Bioavailability enhancement	[282]
Simvastatin	RESS	-	Trifluoromethane	Bioavailability enhancement	[66]
Sulfamethizole	SAS	-	Acetone, DMF	Ultrasound application	[283]
Sulfathiazole	SAS	-	Acetone, MeOH	Bioavailability enhancement	[284]

Pharmaceutical compound	SCF Process	Polymer	Solvent	Purpose	Reference
Terfenadine	SCP	Silica aerogels	ACN, MeOH	Oral delivery	[220]
Tetanus toxoid	SCP	PLA	-	Sustained release	[77]
Theophylline	SAS	HPMC	-	Controlled release	[285]
	RESS-N	EC, PEG	EtOH		[81b]
Timolol maleate	SSI	Chitosan derivatives	EtOH	Ophthalmic delivery	[142c]
		PCL, PCL/POE, PCL/PEVA	THF	Controlled release	[141]
Tolfenamic acid	SAS	-	Acetone, EA	Bioavailability enhancement	[286]
Triclabenzadol	SAA	-	Acetone, MeOH	Bioavailability enhancement	[34a]
Triflusal	SCP	PMMA	Acetone	Controlled release	[287]
		PMMA, Silica	-	Bioavailability enhancement	[70b]
	SSI	Gelatin, Silica	Acetone	Controlled release	[234]
Trypsin	SAA-HCM	Chitosan	Water	Controlled release	[82]
Vitamins (2-methyl-1, 4-naphthquinone (vitamin K3) cholecalciferol (vitamin D3))	SSI	Sodium alginate aerogels	EtOH	Controlled release	[288]
Zidovudine	SAS	PLA	DCM, EtOH	Bioavailability enhancement	[289]

Abbreviations: 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), Acetonitrile (ACN), Aerosol solvent extraction system (ASES), Atomized rapid injection solvent extraction process (ARISE), Bovine serum albumin (BSA), Cellulose acetate (CA), Continuous-Supercritical emulsions extraction (SEE-C), D-alpha tocopheryl polyethylene glycol-1000 succinate (TPGS), Dichloromethane (DCM), Dimethylformamide (DMF), Dimethylsulfoxide (DMSO), Ethanol (EtOH), Ethyl acetate (EA), Ethyl cellulose (EC), Ethylene glycol dimethacrylate (EGDMA), Gas anti-solvent (GAS), Hydroxypropyl methylcellulose (HPMC), Methanol (MeOH), Mobil composition of matter (MCM), N-methylpyrrolidone (NMP), Particle formation from gas saturated solutions (PGSS), Poly(3-hydroxybutyrate-*co*-3-hydroxy valerate) (PHBV), Polycaprolactone (PCL), Polydimethylsiloxanes (PDMS), Poly(lactide-*co*-glycolide) (PLGA), Polyethylene glycol (PEG), Poly(ethyl methacrylate)/tetrahydrofurfuryl methacrylate (PEMA/THFMA), Poly(ethylene-vinyl acetate) (PEVA), Polyethylene oxide (PEO), Polylactic acid (PLA), Poly(methyl methacrylate) (PMMA), Poly(diethylene glycol dimethacrylate) P(DEGDMA), Poly(methyl vinyl ether-*co*-maleic anhydride) (PVM-MA), Poly(N-isopropylacrylamide) (PNIPAAm) Poly(oxyethylene) (POE), Polypropylene glycol (PPG), Poly-vinyl alcohol (PVA), Poly(vinylidene fluoride-*co*-hexafluoropropylene) (PVDF–HFP), Polyvinylpyrrolidone (PVP), Precipitation with Compressed anti-solvent (PCA), Rapid expansion of a supercritical solution into a liquid solvent (RESOLV), Rapid expansion of supercritical solutions (RESS), Rapid expansion of supercritical solutions into aqueous solution (RESSAS), Rapid expansion from supercritical solution with a non-solvent (RESS-N), Rapid expansion of supercritical solution with solid co-solvent (RESS-SC), Santa Barbara Amorphous (SBA), Silk fibroin (SF), Solution-enhanced dispersion by supercritical fluids (SEDS), Solution-enhanced dispersion by supercritical fluids-prefilming atomization (SEDS-PA), Supercritical-assisted injection in a liquid anti-solvent (SAILA), Supercritical anti-solvent (SAS), Supercritical anti-solvent with enhanced mass transfer (SAS-EM), Supercritical-assisted atomization (SAA), Supercritical-assisted atomization-hydrodynamic cavitation mixer (SAA-HCM), SCF-assisted molecular imprinting (SCF-MIP), SCF-assisted spray drying (SASD), SCF-drying (SCFD), SCF-assisted extraction of emulsions (SFEE), SCF-inkjet printing (SCF-IP), SCF-phase inversion process (SCF-PI), SCF-pressure-quench technology (SCF-PQT), SCF-assisted processing (SCP), SCF-assisted sintering (SCFS), Supercritical solvent impregnation (SSI), Suspension-enhanced dispersion by supercritical fluids (SpEDS), Tetrahydrofuran (THF).

Table 2

Inclusion complexes of various cyclodextrins synthesized using various methods of preparation with the SCF technology.

Pharmaceutical compound	SCF Process	CD	Solvent	Purpose	Reference
Benzocaine	SCI	β-CD	EtOH	Bioavailability enhancement	[58]
Budesonide	SEDS	γ-CD	EtOH	Bioavailability enhancement	[103g,h]
	SCI	HP-β-CD	-		[103e]
Bupivacaine HCl	SCP	β-CD	EtOH	Bioavailability enhancement	[58]
Curcumin	ARISE	HP-β-CD	Acetone, EtOH	Inhalation powders	[290]
Econazole	SCI	β-CD	-	Bioavailability enhancement	[291]
Eflucimibe	SAS	γ-CD	DMSO	Bioavailability enhancement	[292]
Fluconazole	SCI	β-CD	-	Bioavailability enhancement	[291]
Flurbiprofen	SCP	Trimethyl-β-CD	EtOH	Bioavailability enhancement	[293]
Ibuprofen	SCI	Methyl-β-CD	-	Bioavailability enhancement	[103d]
		β-CD	-		[103f,294]
Imazalil	SCI	β-CD	-	Bioavailability enhancement	[295]
Indomethacin	SCI	HP-β-CD	-	Bioavailability enhancement	[103e]
		Methyl-β-CD	-		[296]
Itraconazole	ASES	HP-β-CD	DCM, EtOH	Bioavailability enhancement	[297]
	SCI	β-CD	-		[291,298]
Ketoprofen	SCI	Methyl-β-CD	-	Bioavailability enhancement	[103b]
Mepivacaine	SCI	β-CD	EtOH	Bioavailability enhancement	[58]
Miconazole	SCI	β-CD	-	Bioavailability enhancement	[299]
		HP-γ-CD	-		[300]
Naproxen	ASES	HP-β-CD, Methyl-β-CD	Acetone, DMSO, EtOH	Pulmonary delivery	[103c]
	SCP	Trimethyl-β-CD	EtOH	Bioavailability enhancement	[293]
	SCI	β-CD	-		[301]
Olanzapine	SCI	Methyl-β-CD	-	Bioavailability enhancement	[104]
Piroxicam	SCI	β-CD	-	Bioavailability enhancement	[299,302]
			Acetone, EtOH		[303]
Quercetin	PGSS	HP-β-CD	-	Bioavailability enhancement	[304]
Simvastatin	SAS	HP-β-CD	DCM, EtOH	Bioavailability enhancement	[305]

Pharmaceutical compound	SCF Process	CD	Solvent	Purpose	Reference
Tocopherol	PGSS	HP-β-CD	-	Bioavailability enhancement	[304]

Abbreviations: Aerosol solvent extraction system (ASES), Atomized rapid injection solvent extraction process (ARISE), Cyclodextrin (CD), Dichloromethane (DCM), Dimethylsulfoxide (DMSO), Ethanol (EtOH), Hydroxypropyl-β-cyclodextrin (HP-β-CD), Particle formation from gas saturated solutions (PGSS), Polyvinylpyrrolidone (PVP), Solution-enhanced dispersion by supercritical fluids (SEDS), Anti-solvent (SAS), SCF-assisted processing (SCP), Supercritical inclusion (SCI) method.

Table 3

Liposomes as drug delivery carriers synthesized using various methods of preparation with the SCF technology.

Pharmaceutical compound	SCF Process	Lipid	Solvent	Purpose	Reference
BSA	SuperLip	Phospholipids	EtOH	Controlled size	[108,306]
	DELOS	PEG, Phospholipids	-	Targeted delivery	[33b]
Cyclosporin A	SAS	Cholesterol, Phospholipids	EtOH	Stability improvement	[111]
	SCP	Phospholipids	-	Ocular delivery	[307]
Docetaxol	SAS	Cholesterol, PEG, Phospholipids	Chloroform, MeOH	Controlled release	[114]
Human growth hormone	SAA	PEG, Phospholipids, Tristearin	DMSO	Oral delivery	[308]
Insulin	SAA	PEG, Phospholipids	DMSO	Oral delivery	[308,309]
Ketoprofen	PGSS	Glycerolipids	-	Controlled release	[310]
Miconazole	ASES	Phospholipids	DCM, MeOH	Pulmonary delivery	[311]
Ribonuclease A	PGSS	PEG, Phospholipids	DCM, DMSO	Controlled release	[312]
Silymarin	SEDS	Phospholipids	DCM, EtOH	Bioavailability enhancement	[282]
Theophylline	PGSS	Hydrogenated palm oil	-	Controlled release	[313]

Abbreviations: Aerosol solvent extraction system (ASES), Bovine serum albumin (BSA), Depressurization of an expanded liquid organic solution (DELOS), Dichloromethane (DCM), Dimethylsulfoxide (DMSO), Ethanol (EtOH), Methanol (MeOH), Particle formation from gas saturated solutions (PGSS), Polyethylene glycol (PEG), Solution-enhanced dispersion by supercritical fluids (SEDS), Supercritical anti-solvent (SAS), Supercritical-assisted atomization (SAA), Supercritical-assisted liposome formation (SuperLip), SCF-assisted processing (SCP).

Table 4

Drug delivery systems intended for pulmonary route of administration synthesized using various methods of preparation with the SCF technology.

Pharmaceutical compound	SCF Process	Polymer	Solvent	Purpose	Reference
5-Fluorouracil	SAS	α-Lactose monohydrate	Acetone, DCM, EtOH, MeOH	Inhalation powders	[314]
Amphotericin B	CAN-BD	–	EtOH	Pulmonary delivery	[47]
Albuterol sulfate	SEDS	α-Lactose monohydrate	DCM, MeOH	Inhalation powders	[315]
Amoxicillin	SAS	–	NMP	Inhalation powders	[83a]
		–	DMSO, EtOH		[201]
		–	DMSO, NMP	Pulmonary delivery	[120a]
Beclomethasone-17, 21-dipropionate	GAS	–	Acetone, EtOH, MeOH	Pulmonary delivery	[316]
	ASES	–	DCM, MeOH	Pulmonary delivery	[64]
Betamethasone-17-valerate	ASES	–	DCM, MeOH	Pulmonary delivery	[64]
BSA	ASES	PLA-PLGA	DCM, MeOH, TFE	Pulmonary delivery	[317]
	SAA-HCM	–	Water		[48]
Budesonide	ASES	–	DCM	Inhalation powders	[83b]
		–	DCM, MeOH	Pulmonary delivery	[64]
	SEDS	–	Acetone, MeOH	Inhalation powders	[318]
		α-Lactose monohydrate	Acetone		[315]
Calcitonin (Salmon)	SASD	Chitosan glutamate	EtOH, Water	Nasal powders	[51]
Celicoxib	SCF-PQT	PLGA	–	Sustained release	[124]
Cyclosporin A	RESS, PGSS	–	–	Inhalation powders	[319]
Curcumin	ARISE	HP-β-CD, PVP	Acetone, EtOH	Inhalation powders	[290]
Dexamethasone	ASES	–	DCM, MeOH	Pulmonary delivery	[64]
Flunisolide	ASES	–	DCM, MeOH	Pulmonary delivery	[64]
	SEDS	–	Acetone, MeOH	Inhalation powders	[318b]
Fluticasone-17-propionate	ASES	Heptafluoropropane-227	DCM	MDI	[120c]
		–	DCM, MeOH	Pulmonary delivery	[64]
Hydrocortisone	SEDS	–	Acetone, MeOH	Inhalation powders	[320]
Insulin	SAS	Mannitol	DMSO	Pulmonary delivery	[93b]
	SCFD	Trimethyl chitosan, Dextran			[321]
	SAS	–	HFIP	Inhalation powders	[121a]

Pharmaceutical compound	SCF Process	Polymer	Solvent	Purpose	Reference
	GAS	–	DMF, DMSO		[28]
Ipratropium bromide	ASES	–	DMF, EtOH	Pulmonary delivery	[129,322]
Ketoprofen	SFEE	Starch	EtOH	Aerogels	[128]
Levofloxacin hydrochloride	SAA-HCM	–	MeOH	Pulmonary delivery	[323]
Lysozyme	SAS	–	DMSO	Aerosol delivery	[93c]
	PCA	PLA	DCM	Pulmonary delivery	[324]
	SEDS	–	DMSO		[94]
	SAA-HCM	–	EtOH, Water		[325]
	SAS-EM	–	DMSO	Controlled release	[93a]
Miconazole	ASES	Cholesterol, Phospolipids, Poloxamer 407	DCM, MeOH	Pulmonary delivery	[311]
Nalmefene	SAS	–	EtOH	Pulmonary delivery	[21a,326]
Naproxen	ASES	HP-β-CD, Methyl-β-CD	Acetone, DMSO, EtOH	Pulmonary delivery	[103c]
	CAN-BD	–	EtOH		[47]
Nicotinic acid	SEDS	–	MeOH	Pulmonary delivery	[327]
pDNA	SEDS	Mannitol	Isopropanol, Water	Inhalation powders	[122]
	SCP	Chitosan, Mannitol	EtOH, Water		[109,132]
	SFEE	PLGA	EA, Water	Pulmonary delivery	[328]
Prednisolone	ASES	–	DCM, MeOH	Pulmonary delivery	[64]
Rifampicin	SAS	PLA	DCM	Inhalation powders	[59a]
		–	DMSO		[120g]
	SAA	–	MeOH		[329]
RNA	SCP	Chitosan, Mannitol	EtOH	Inhalation powders	[119]
Salbutamol	SAS	–	DMSO, MeOH, EtOH	Pulmonary delivery	[60]
	SCP	–	Menthol	Inhalation powders	[125,330]
Salmeterol xinafoate	SEDS	–	Acetone, MeOH, THF	Inhalation powders	[331]
Terbutaline	SAA	–	Water	Aerosol delivery	[120d]
	ASES	–	DMF, EtOH	Pulmonary delivery	[129]
	SEDS	α-Lactose monohydrate	EtOH, MeOH, Water	Inhalation powders	[120e]
Tetracycline	SAS	–	NMP	Pulmonary delivery	[120f]
	SFED	–	EtOH, Water	Inhalation powders	[53]
	SAA	–	Water		[329]

Pharmaceutical compound	SCF Process	Polymer	Solvent	Purpose	Reference
Triamcinolone acetonide	ASES	–	DCM, MeOH	Inhalation powders	[64]

Abbreviations: 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), 2,2,2-Trifluoroethanol (TFE), Aerosol solvent extraction system (ASES), Atomized rapid injection solvent extraction process (ARISE), Bovine serum albumin (BSA), Carbon dioxide-assisted nebulization with a bubble dryer (CAN-BD), Cyclodextrin (CD), Dichloromethane (DCM), Dimeth-ylformamide (DMF), Dimethylsulfoxide (DMSO), Ethanol (EtOH), Ethyl acetate (EA), Gas anti-solvent crystallization technique (GAS), Hydroxypropyl-β-cyclodextrin (HP-β-CD), Metered dose inhaler (MDI), Methanol (MeOH), N-methylpyrrolidone (NMP), Particle formation from gas saturated solutions (PGSS), Poly(lactide-*co*-glycolide) (PLGA), Polylactic acid (PLA), Polyvinylpyrrolidone (PVP), Precipitation with Compressed anti-solvent (PCA), Rapid expansion of supercritical solutions (RESS), Solution-enhanced dispersion by supercritical fluids (SEDS), Supercritical anti-solvent (SAS), Supercritical anti-solvent with enhanced mass transfer (SAS-EM), Supercritical-assisted atomization (SAA), Supercritical-assisted atomization-hydrodynamic cavitation mixer (SAA-HCM), SCF-assisted spray drying (SASD), SCF-assisted drying (SCFD), SCF-expansion depressurization (SFED), SCF-assisted extraction of emulsions (SFEE), SCF-pressure-quench technology (SCF-PQT), SCF-assisted processing (SCP), Tetrahydrofuran (THF).

Table 5

Implantable drug delivery systems synthesized using various methods of preparation with the SCF technology.

Pharmaceutical compound	SCF Process	Polymer	Solvent	Purpose	Reference
Acetazolamide	SSI	Silicone-based hydrogels	EtOH, Water	Ophthalmic delivery	[143a]
Cefuroxime sodium	SSI	PMMA	EtOH	Ophthalmic delivery	[142a]
Ciprofloxacin	SSI	P-HEMA	EtOH	Extended ocular delivery	[143b]
Dexamethasone	SSI, SFE	SCL	EtOH	Extended ocular delivery	[68]
	SSI	P-HEMA	-	Ophthalmic delivery	[143b]
Flurbiprofen	SSI	SCL	EtOH	Ophthalmic delivery	[143c]
	SSI, SFE	SCL	-	Extended ocular delivery	[68]
	SSI	Chitosan derivatives	-	Ophthalmic delivery	[142c]
	SCP	P(MMA-EHA-EGDMA)	-		[143d]
Ibuprofen	SSI, SFE	SCL	EtOH	Extended ocular delivery	[68]
Ketoprofen	SCP	Alginate, Gelatin	EtOH	Ureteral stents	[155]
Norfloxacin	SSI	HEMA, BEM	-	Ophthalmic delivery	[142b]
Paclitaxel	SCF foaming	PLGA	DCM	Post-surgical implants	[332]
Roxithromycin	SSI	PLA	DCM	Polymeric implants	[69]
Timolol maleate	SSI	SCL	EtOH	Ophthalmic delivery	[143c]
		Chitosan derivatives	-		[142c]
		Silicone-based hydrogels	-		[143a]
		PCL, PCL/POE, PCL/PEVA	THF	Conjunctival implants	[141]

Abbreviations: 2-butoxyethyl methacrylate (BEM), 2-hydroxyethyl methacrylate (HEMA), Dichloromethane (DCM), Dimethylsulfoxide (DMSO), Ethanol (EtOH), Poly(2-hydroxyethyl methacrylate) (P-HEMA), Polycaprolactone (PCL), Poly(lactide-*co*-glycolide) (PLGA), Poly(ethylene-vinyl acetate) (PEVA), Polylactic acid (PLA), Poly(co-ethyl hexyl acrylate-methylmethacrylate-*co*-ethylene glycol-dimethacrylate) (P(MMA-EHC-EGDMA)), Poly(methyl methacrylate) (PMMA), Poly(oxyethylene) (POE), Soft contact lenses (SCL), SCF-assisted processing (SCP), Supercritical freeze extraction (SFE), Supercritical solvent impregnation (SSI), Tetrahydrofuran (THF).