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Review

Supercritical Fluid Technology: Concepts and Pharmaceutical Applications

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ABSTRACT: In light of environmental apprehension, supercritical fluid technology (SFT) exhibits excellent opportunities to accomplish key objectives in the drug delivery sector. Supercritical fluid extraction using carbon dioxide (CO_2) has been recognized as a green technology. It is a clean and versatile solvent with gas-like diffusivity and liquid-like density in the supercritical phase, which has provided an excellent alternative to the use of chemical solvents. The present commentary provides an overview of different techniques using supercritical fluids and their future opportunity for the drug delivery industry. Some of the emerging applications of SFT in pharmaceuticals, such as particle design, drug solubilization, inclusion complex, polymer impregnation, polymorphism, drug extraction process, and analysis, are also covered in this review. The data collection methods are based on the recent literature related to drug delivery systems using SFT platforms. SFT has become a much more versatile and environmentally attractive technology that can handle a variety of complicated problems in pharmaceuticals. This cutting-edge technology is growing predominantly to surrogate conventional unit operations in relevance to the pharmaceutical production process.

KEYWORDS: Drug delivery, Nanoparticle, Carbon dioxide, Antisolvent, Particle size, Supercritical

LAY ABSTRACT: Supercritical fluid technology has recently drawn attention in the field of pharmaceuticals. It is a distinct conception that utilizes the solvent properties of supercritical fluids above their critical temperature and pressure, where they exhibit both liquid-like and gas-like properties, which can enable many pharmaceutical applications. For example, the liquid-like properties provide benefits in extraction processes of organic solvents or impurities, drug solubilization, and polymer plasticization, and the gas-like features facilitate mass transfer processes. It has become a much more versatile and environmentally attractive technology that can handle a variety of complicated problems in pharmaceuticals. This review is focused on different techniques that use supercritical fluids and their opportunities for the pharmaceutical sector.

1. Introduction

The pharmaceutical industry has advanced as one of the largest and most exciting sectors by keeping pace with the rapid growth of research, technology, and the global economy. The success of drug products mainly bank on the development and implementation of robust, scaleable, and economical production processes. Many of the conventional unit operations in pharmaceutical manufacturing rely highly upon processing at high temperatures and/or the reckless use of organic solvents, which is an impediment to the final safety and proper activity of the drug products. The sector is looking for rapid methods of drug development and purification and a predictable scale-up that influence the success of the product by both financially and strategically improving quality and safety and reducing environmental hazards. With this, a significant

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industrial development is forecasted for the near future. Research data reveals that the exponential trend in the number of scientific publications pertaining to the use of supercritical fluids (SCFs) in the pharmaceutical field in last two decades is almost reaching maturity (1).

Supercritical fluid technology (SFT) is a distinct concept that utilizes solvent properties of the SCFs above their critical temperature and pressure conditions. A SCF is a phenomenon whose temperature and pressure values eventuate above its critical point synchronously. Alongside the supercritical region, SCFs exhibit dense as well as highly compressible properties. Critical temperature (T_C) is the highest temperature at which a gas can be converted into a liquid by an increase in pressure. Critical pressure (P_C) is the highest pressure at which a liquid can be converted into a traditional gas by an increase in the liquid temperature. Very unique characteristics can be observed at the state wherein both critical pressure and temperature conditions have either been reached or exceeded. In other words, a SCF can behave as either a liquid or a gas, but is actually neither. The supercritical status corresponds to a region where the physicochemical properties such as density, viscosity, diffusion coefficient, and heat conductivity values of the substance are intermediate between those of the liquid and the gas. In the critical region the liquid and gaseous phases are identical and homogeneous, as the substance exhibits a liquid-like density and gas-like viscosity and diffusivity, allowing for good mixing and mass transfer. Above such critical points SCFs exhibit both liquid-like and gas-like properties, which can enable many pharmaceutical applications. For example, the liquid-like properties provide benefits in extraction processes of organic solvents or impurities, drug solubilization, and polymer plasticization, and the gas-like features facilitate mass transfer processes and reaction selectivity (2–6).

Several organic solvents show desirable features such as low viscosity and high solvent power under the influence of SCF conditions. Almost all gases can be transformed into SCFs above their specific critical pressure and temperature values. In some cases extremely high temperatures and pressures are required to attain the SCF state. The critical pressure and temperature values increase with the molecular weight, intermolecular hydrogen bonding, or polarity. Indeed, carbon dioxide (CO_2) is the most accepted SCF in pharmaceutical applications. Almost 98% of applications have been developed using CO_2 as the SCF because of its low critical temperature (31.2 °C) and pressure (7.4 MPa), which is beneficial in relatively simple processing and manufacturing for pharmaceutical products. Due to increasingly stringent environmental regulations, supercritical CO_2 (SC-CO_2) has gained wide acceptance in recent years as an alternative to toxic solvents, as it is non-toxic, non-combustible, recyclable, abundantly available, eco-friendly, and cost-efficient in usage (7–10). While there are other SCFs such as xenon (Xe) and sulfur hexafluoride (SF_6) that have low critical temperature and pressure values, they are restricted for commercial applications because of their high cost of production. Safety concerns confine the usage of gases such as nitrous oxide (N_2O) or ethane even if they possess low critical values (3). Overall, to qualify as a SCF for pharmaceutical processing, safety and commercial viability need to be considered. Critical temperature and pressure values of certain SCFs are presented in Table I (6, 11).

2. Supercritical Fluid Technology (SFT) Techniques

SFT is primarily classified into two broad categories based on the expansion of a supercritical solution containing a solute: (1) The SCF is used as a good solvent, and (2) the precipitation of a solute dissolved in an organic solvent by means of SCF used, that is, the SCF is used as an antisolvent.

2.1. Supercritical Solution as a Solvent

2.1.1. Rapid Expansion of Supercritical Solution (RESS): The rapid expansion of supercritical solution (RESS) represents one of the simple and earlier methods in SFT to produce drug-encapsulated particles (10). This method consists of a saturation of the SCF with a solid substrate followed by the rapid depressurization and then expansion of a supercritical solution through a heated capillary or laser-drilled nozzle into a low-pressure chamber. In the process, when passing substrate-loaded SCFs from supercritical to ambient conditions, pressure drops rapidly and uniformly, diminishing the solvent power. This results in a decompression of the solution, which leads to supersaturation, super-fluid nucleation, and hence uniform particle generation. The most commonly used solvent in the RESS method is SC-CO_2. Other solvents used are propane, chlorodifluoromethane, pentane,

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TABLE I
Critical Temperature and Pressure Values of Supercritical Fluids

Supercritical Fluid	Chemical Formula	Critical Temperature (T_C) °C	Critical Pressure (P_C) MP_a
Water	H_2O	374	22
Xenon	Xe	16.6	5.9
Sulpha hexafluoride	SF_6	45.5	3.8
Nitrous oxide	N_2O	36.5	4.1
Ethylene	C_2H_4	9.1	5.1
Trifluormethane	CHF_3	25.9	4.7
Carbon dioxide	CO_2	31.2	7.4
Propene	CH2=CHCH3	36.5	4.6
Methane	CH_4	19.0	4.6

ethanol, acetone, diethyl ether, and nitrous oxide. The controlling parameters in this process are solute solubility in SC-CO_2, temperature, pressure, capillary design angle, and impact of the capillary jet against the surface. The attained particles are completely dry, solvent free, and do not need further processing. The method is already used in pharmaceutical applications such as preparation of microparticles and films. The merits of the RESS method are that it is a relatively simple process by virtue of its control parameters in the absence of a solvent system and it is easy to implement as a lab scale component. The most important limitations associated with RESS are low solubility of many pharmaceutical compounds in SCF, poor prediction control of particle size and morphology, tendency toward particle agglomeration, and difficulty in exploration at production scale (4, 10, 12, 13).

2.1.2. Rapid Expansion of a Supercritical Solution into a Liquid Solvent (RESOLV): Rapid expansion of a supercritical solution into a liquid solvent (RESOLV) is a modified method of conventional RESS that aims to minimize the aggregation formed during particle production. This method involves depressurizing or expanding SCFs containing solid substrate through a laser-drilled orifice into a collection chamber containing an aqueous solution at room temperature. Additionally, various water-soluble polymers or surfactants are added to the aqueous medium as a stabilizer (4, 14, 15).

2.2. Supercritical Solution as an Antisolvent

Antisolvent-based techniques were generally employed to process poorly soluble compounds in SCFs. Here the pressurized CO_2 acts as an antisolvent for precipitating a solute from an organic solvent. This process makes it feasible to keep a check on the particle agglomeration in the precipitator, thus improving RESS process performance. The supercritical antisolvent techniques offer greater flexibility and therefore have been studied more thoroughly for preparation of drug delivery systems (16).

2.2.1. Gas Antisolvent Recrystallization (GAS): The gas antisolvent recrystallization (GAS) method was developed in order to accomplish a reduction in particle size of the hydrophobic materials that are unsuitable for processing using the RESS technique due to their poor solubility in SCF. The GAS technique utilizes a SCF as an antisolvent. It involves the precipitation of solute present in an organic solvent by introducing an antisolvent SCF. In this technique, the CO_2 diffuses into the organic solvent leading to its evaporation into the gaseous phase, an expansion in volume, and a reduction in solvent density. This lowers the solvent power of the organic solvent, which will no longer be a good solvent for the solute. The overall process favors the onset of nucleation, bringing on precipitation of the solute. The ideal situation for the GAS technique is when the SCF is completely miscible with the solvent, and the solute is insoluble in the SCF (4, 15, 17–19).

2.2.2. Supercritical Antisolvent Recrystallization (SAS) and Precipitation with Compressed Antisolvent (PCA): The classical antisolvent nature of SCFs can be applied by spraying an organic solution containing drug and polymer through an orifice into a compressed gas or SCF. In both methods, CO_2 is

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pumped into the high-pressure vessel until the system reaches the desired pressure and temperature conditions. The organic solution loaded with an appropriate drug and polymer concentration is sprayed through a nozzle into the vessel containing the SCF. By controlling critical parameters such as pressure and temperature, the formation of particles takes place, which are collected on a filter attached at the bottom of a precipitation vessel. The precipitation with compressed antisolvent (PCA) utilizes either a liquid or supercritical antisolvent, whereas the supercritical antisolvent recrystallization (SAS) makes use of SCFs as an antisolvent. High-pressure vapor-liquid equilibrium and mass transfer between the liquid and SCF also play a relevant role in SAS (3, 6).

2.2.3. Aerosolized Solvent Extraction System (ASES): The aerosolized solvent extraction system (ASES) is very closely associated with SAS. ASES uses SCFs as an antisolvent and can be processed by the spraying of the solution and the antisolvent. The passage of the SCF into the liquid droplets is accompanied by a large volume expansion and simultaneous reduction in the liquid solvent power, causing a sharp rise in the supersaturation within the liquid mixture and the consequent formation of small and uniform particles. A high-pressure pump is employed to spray the SCF into the high-pressure vessel. Once the system attains a steady state, the compound in solution is introduced into this vessel through an orifice of definite size. It is imperative that the solution be pumped at a higher pressure than the vessel operating pressure to obtain small liquid droplets. The particles are collected at the filter surface fitted onto the bottom of the vessel (6, 15).

2.2.4. Solution-Enhanced Dispersion by Supercritical Fluids (SEDS): The basic principle of solution-enhanced dispersion by supercritical fluids (SEDS) involves dispersion of the polar organic solvent. The SCF and the aqueous solution are introduced as a separate stream inside the particle formation vessel containing a three-channeled coaxial nozzle. The design of the nozzle allows the process to work at high Reynold's numbers (good mixing) and low Weber numbers (small droplet size) by increasing the velocity of the fluid. In this process, the use of a mixing chamber provides a higher mixing surface area, which results in an increase in the mass transfer rates. The high mass transfer rates favor fast nucleation rates and yield smaller particles with less aggregation. Here, the solvent plays a dual role as a precipitating agent and a modifier, facilitating the non-polar CO_2 to remove the water. The SEDS process is best used to overcome problems associated with poorly soluble compounds in SCFs. Various types of compounds, organics, biopolymers, etc., have been used with SEDS technology for the production of micron to nanosize stuffs. It is a highly controlled and reproducible technique compared to other antisolvent-based SCF processes. The SEDS technique has proved to be uniquely suitable for its scaling-up potential and manufacturing according to good manufacturing practices (GMP) conditions (3, 9, 15, 17, 20).

A schematic representation of various SCF techniques is depicted in Figure 1.

3. Pharmaceutical Applications of SCF Technology

3.1. Particle Design in Drug Delivery Applications

The majority of existing pharmaceutical processes in the area of particle generation and pretreatment operations are still fairly primitive, inefficient, and seriously limited. The traditional particle-size reduction method by high-energy milling is inept and is vulnerable to morphological and crystallographic modifications. Such changes can alter the physicochemical stability of the downsized material. The alternative strategy of using SFT for crystal and particle engineering of pharmaceutical materials and drug delivery systems shows great promise in this area. The limitations of traditional processes can be overcome by efficient utilization of the supercritical technologies to produce micron- and submicron-sized particles. In the recent years, the SAS process has shown great potential to produce micron-sized particles for a series of compounds, such as insulin, lysozyme, trypsin, methylprednisolone, and hydrocortisone (21). In one such application, budesonide and polylactic acid (PLA) microparticles were prepared by incremental change in temperature and pressure utilizing the precipitation with a compressed antisolvent (PCA) technique. The drug solution and antisolvent were introduced through a capillary tube, and the mean diameters obtained by budesonide-PLA microparticles were in the range of 1–2 μm (22). A modified SAS process was successfully employed to fabricate controlled-release matrices for paclitaxel. The results suggest that the process allows fabrication of sub-micron particles without the requirement of specialized nozzles or high temperatures. It was shown that the application of ultrasonication to the SAS process greatly enhances the mixing

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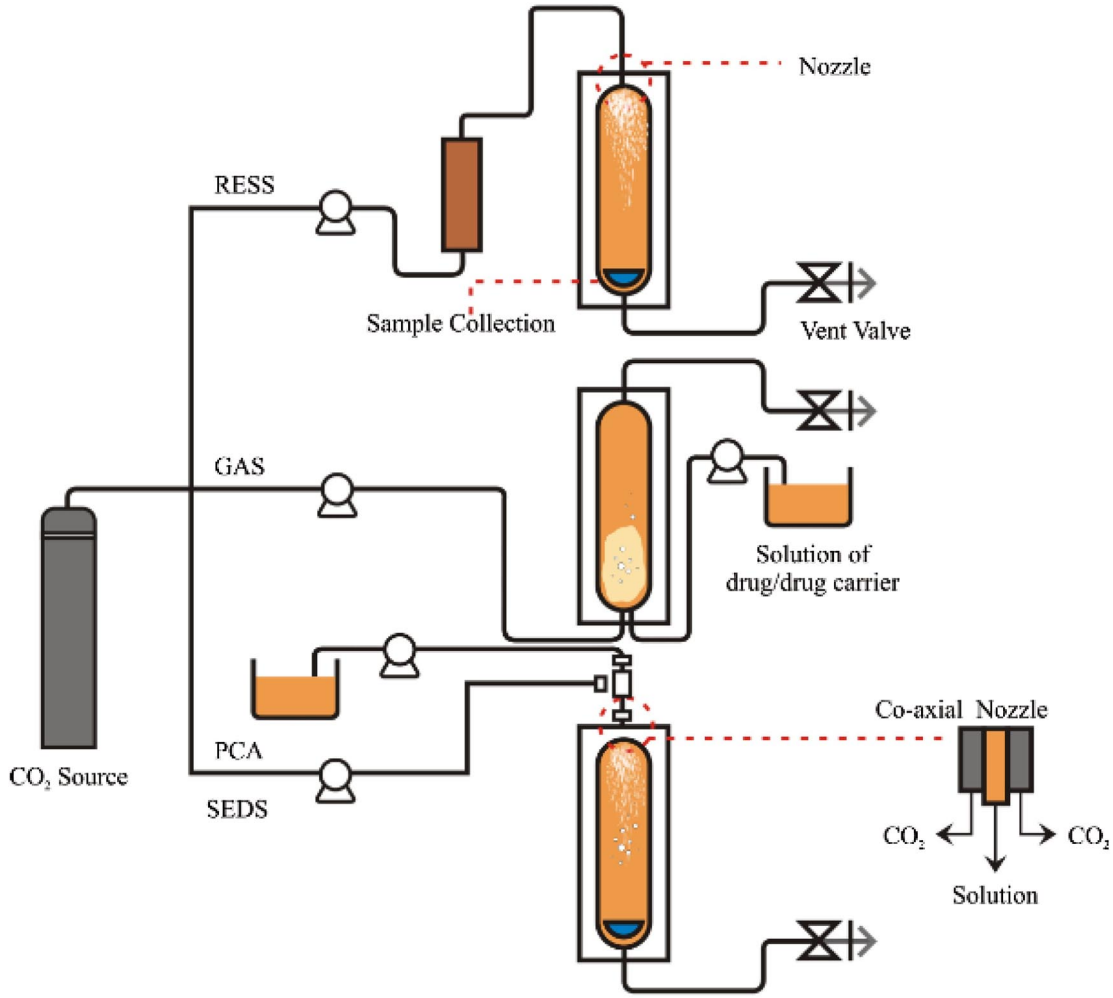

Figure 1

Schematic representation of various supercritical fluid techniques. Reprinted from Kompella, U. B.; Sunkara, G. Drug delivery applications of supercritical fluid technology. *Drug Dev. Deliv.* 2002, *2* (1), 33–34. Reprinted with permission.

of the organic solvent with CO_2 phases, leading to significantly smaller particles (2). For micronization of the hydrophilic compounds, the supercritical-assisted atomization (SAA) process has shown to be promising. Cefadroxil microparticles were prepared successfully from a combination of water and ethanol solvent by SAA (23). Particles of lysozyme in the range of 0.1–5 μm were generated by high-pressure CO_2 or nitrogen (N_2) from aqueous ethanol solutions using an atomization process similar to the SAA technology (24). Padrela *et al.* demonstrated the potential of SFT as a screening method for cocrystals with possibilities for particle engineering. Particulate indomethacin-saccharin cocrystals with different morphologies with micron to nano sizes were produced using SFT (25). Poorly water-soluble drug, nifedipine, was micronized down to the size range of 15–30 μm utilizing the gas-saturated solution technique (2, 26). Using the SAA technique, griseofulvin particles were micronized, and the mean diameters of spherical particles were obtained in the range of 0.5–3 μm (27). Preparation of naproxen-loaded microspheres for controlled-release applications using SFT has demonstrated significant advantages compared to the routine techniques. In particular, the SAS technique has shown greater benefits compared to the conventional ones. The obtained naproxen-loaded microparticles have a smaller as well as a uniform particle size distribution (28). In a work presented by Reverchon *et al.,* the SAA technique is used to produce

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hydroxypropyl methylcellulose (HPMC)–based microparticles using ampicillin trihydrate as a model drug. Using a buffer solution as a solvent micronization of HPMC alone, co-precipitation of HPMC with ampicillin was achieved. Uniform particle size distribution with a diameter range between 0.05–5.20 μm was generated. The particles obtained were of spherical or doughnut-like morphology (29). In another approach, Pathak *et al.* utilized RESOLV-based techniques for the nanosizing of ibuprofen molecules. Here, initially formed nanoparticles were allowed to expand in the aqueous medium containing various hydrophilic polymers. The effect of different stabilizing agents on the properties of nanoparticles was also studied using the RESOLV technique (30). Kim *et al.* successfully prepared amorphous atorvastatin calcium nanoparticles using the SAS process. By optimization of various process parameters such as drug solution concentration, feeding rate of CO_2 and drug solution, and the pressure and temperature conditions of the precipitation vessel, mean particle sizes ranging between 152–863 nm were obtained. The particles showed uniform distribution with spherical morphology. Compared to the crystalline nature of the unprocessed drug, the obtained amorphous atorvastatin calcium nanoparticles showed enhancement of solubility and thereby intrinsic dissolution rates. These results were attributed to the reduction of particle size and hence increased specific surface area (31). Falk *et al.* adopted a PCA-based technique for preparation of controlled-release products. The process utilized PLA as a polymer to produce gentamicin, naltrexone, and rifampicin nanoparticles. These obtained nanoparticles were spherical in shape with a particle size range of 200–1000 nm (32).

3.2. Preparation of Pharmaceutical Powders

The inherent properties of SC-CO_2 in SFT can be used for processing of macromolecules such as proteins, peptides, and nucleic acids. The method has advantages over the conventional lyophilization methods. Advantages include incorporation of delicate biologicals without loss of biological activity and control over the morphology of the powder particles. Several studies have shown that diverse types of particles can be obtained when processing aqueous protein solutions into powders by using SCFs. Tservistas *et al.* formulated the plasmid DNA-loaded pharmaceutical powders using SEDS technology (33). Debenedetti *et al.* used an antisolvent method to prepare microparticles of insulin and catalase; the SCF expanded and nucleated with the liquid solvent, thereby facilitating the formation of submicron protein particles (34).

3.3. SCF in Drug Solubilization Applications

Solubility of drugs is one of the governing parameters of drug delivery design. A multitude of pharmaceutical substances are often insoluble in aqueous media, and the applications of these drugs are often limited by their low bioavailability. A promising method to improve the solubility and thereby bioavailability of pharmaceutical agents can be achieved by SFT. A number of authors explored the application of SFT in the enhancement of solubility. Turk *et al.* showed that the RESS processing of griseofulvin leads to a significantly improved dissolution rate of the drug, resulting in improved bioavailability (35). Sanganwar *et al.* increased the dissolution rate of a poorly water-soluble fenofibrate by adsorbing it onto silica. The adsorption is accomplished by first dissolving the fenofibrate in SC-CO_2 and then depressurizing the solution onto silica. The obtained product was assessed by in vitro dissolution studies. The results revealed a significant increase in the dissolution rates of silica-adsorbed drug product compared to micronized fenofibrate. This can be attributed to an increase in the surface area and decrease in the crystallinity of drug after adsorption onto silica. From the stability point of view the obtained crystalline fenofibrate is also proved to be more stable than the amorphous form of the compound. In this process, solvents are not used in the drug-loading process, hence the final product obtained was free from any residual solvents (36). In work carried out by Badens *et al.,* oxeglitazar, a poorly water-soluble compound, was formulated using excipients such as poloxamer, polyethylene glycol, and polyvinylpyrrolidone (PVP) and processed using the SAS technique. The drug-and-polymer-blended feed solutions were passed through a capillary nozzle in SC-CO_2. Formulations were superior in terms of particle morphology, particle size, crystallinity, polymorphic purity, precipitation yield, and specific surface area. The authors of the study accomplished with an improved dissolution kinetics of the study compound oxeglitazar (37). In addition to these studies, several experimental results confirm that SFT is promising for the formation of submicron particles and that the improved dissolution performance is influenced by particle size, surface area, and wettability of the processed powders.

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3.4. SCF in Inclusion Complexes

Another approach to improve dissolution properties of drugs by SFT is to load or complex the poorly aqueous soluble drugs into a solid carrier, thereby improving the water solubility of the drug (38). For example, piroxicam/β-cyclodextrin complexes were prepared at a solid state by means of SC-CO_2. The influence of several operating variables was analysed. The best results were achieved by keeping physical mixtures of piroxicam/β-cyclodextrin/l-lysine in the molar ratio of 1:2:1.5 for 2 h in contact with CO_2 at 150 °C and 15 Mpa (39). Solid dispersions of carbamazepine in PVP K30 were prepared by either a conventional solvent evaporation or a SCF process and characterized by intrinsic dissolution rate. The best intrinsic dissolution rate was obtained for supercritically processed carbamazepine/PVP K30, which was 4-fold higher than pure carbamazepine. The supercritical-based process produced solid dispersions with intrinsic dissolution rates better than conventional solid dispersions (40). Bounaceura *et al.* carried out the complexation between ketoprofen (KP) and a β-cyclodextrin (CD) using SC-CO_2. They also extensively discussed the process controls involved in SFT. The results suggest explanations for the phenomena involved in inclusion formation. An increase in the process-related parameters such as pressure, temperature, maturation period, agitation, and density of SC-CO_2 resulted in an increase in the association rate of KP with CD in all cases. The mass ratio of the SC-CO_2 mixture played an important role in the formation of the complex. It was observed that the use of higher volumes of CO_2 resulted into dilution of KP and was deleterious to the complexation rate. By appropriate control of the operating conditions of SC-CO_2 (pressure, temperature, maturation period, agitation, and density), the process resulted in a higher percentage of complexation without the use of organic solvents (41). Another hydrophobic drug, simvastatin (SV), was also studied by inclusion complex with hydroxypropyl β-cyclodextrin (HP-β-CD) using the SAS process. The results affirmed the enhancement of aqueous solubility, dissolution rates, and bioavailabilty of SV. The authors confirmed the usefulness of the SAS process for the preparation of the inclusion complexes (42). Thus, from all the above findings by several research groups, it can be confirmed that the SCF process appears to be efficient and is a suitable choice for the preparation of inclusion complexes for poorly water-soluble pharmaceutical active compounds.

3.5. Polymer Impregnation

Polymer impregnation comprises placing a polymeric substrate into a pressure vessel at atmospheric pressure while simultaneously mixing the polymeric substrate with a mixture of a carrier liquid and an impregnation additive, wherein the impregnation additive is substantially insoluble in a SCF. Simultaneously, all these components (polymeric substrate, mixture of the carrier liquid, and impregnation additive) were exposed to a SCF in the closed pressure vessel for a sufficient time and allowed to swell the polymeric substrate. After closed pressure vessel exposure, the pressure in the vessel is released so that the carrier liquid diffuses out of the swollen polymeric substrate, wherein an amount of the impregnation additive is entrapped within the polymeric substrate (43). A variety of polymeric substrates can be used, including lactic acid, glycolic acid, polyolefin, polyamide, polyurethane, silicone, and protein derivatives. In some of the processes a suitable combination of polymeric substrates in an appropriate ratio can also be used. This also applies to carrier liquids, in that it can be selected from the group alone or in combination with water, methanol, ethanol, isopropanol, or hexane. Dye, protein, polypeptide, nucleotide, drug, or monomer can be used as impregnation additives (44). Many research papers have addressed the utilization of polymer impregnation in drug delivery applications. Uzer *et al.* presented a polymer impregnation technique using SC-CO_2 for formulation of controlled-release delivery systems. In the process of impregnation, polymeric component, polymethylmethacrylate (PMMA), and compound naphthalene were used. Impregnation and swelling steps were achieved at temperature conditions of 35–45 °C and pressure values of 80–150 bar. At these conditions, impregnated samples swelled 2- to 4-fold, and impregnation loads were found between 103.7 and 289 mg naphthalene/g of PMMA (44). A desired amorphous form of piroxicam was obtained by the impregnation method in a work carried out by Banchero *et al.,* in which PVP K-15 and piroxicam samples were impregnated at a pressure of 300 bar and a temperature of 100 °C. The amorphous nature of the piroxicam exhibited a significant increase in the dissolution rates in comparison to the simple physical mixtures (45). In another application, a hydrogel-type ophthalmic drug delivery was developed using a supercritical solvent impregnation (SSI) technique. Different chitosan derivatives [*N*-carboxymethyl chitosan (CMC), *N*-carboxybutyl chitosan (CBC) and *N*-succinyl chitosan (SCC)] were impreg-

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nated with the anti-inflammatory drug flurbiprofen and the anti-glaucoma drug timolol maleate. Impregnation experiments were carried out from 9.0 to 14.0 MPa and at 303.0, 313.0, and 323.0 K. The results revealed that the drug delivery systems for the ocular therapy can be successfully prepared by the impregnation process (46). In the recent work carried out by Dias *et al.,* polymeric biomaterials like *N*-carboxybutylchitosan (CBC) and agarose (AGA) were loaded with two different natural-origin bioactive compounds, quercetin (anti-inflammatory) and thymol (anaesthetic properties), using a SSI method. Impregnation experiments were carried out using SC-CO_2 at 10 and 20 MPa, and at 303 and 323 K. Release kinetics results showed that higher amounts of quercetin and/or thymol were loaded when higher pressures and temperatures were employed. The authors also concluded that the SSI process additionally promoted the size reduction of the loaded quercetin particles, which helps significantly in the improvement of solubility parameters (47). Consequently, the application of impregnation methodology in the formation of polymer-drug composites using SC-CO_2-assisted infusion for a range of drugs can work toward improving the solubility of the drugs and drug dissolution kinetics.

3.6. SCF in Liposomal Formulations

The requirement of large amounts of organic solvents in liposomal production and the low encapsulation efficiency are among the major limitations of liposomal manufacturing. These problems can be overcome by exploiting SC-CO_2 as a co-solvent for liposomal preparations (6). One of the efficient supercritical techniques was developed by Otake *et al.* The reverse-phase evaporation method using SC-CO_2 employed by the research group was free of any organic solvents for the preparation of liposomes. The group prepared aqueous dispersions of liposomes through emulsification by introduction of a fixed amount of water into a homogeneous mixture of SC-CO_2/l-α-dipalmitoylphosphatidylcholine/ethanol with sufficient stirring and subsequent pressure reduction. The study concluded that the supercritical reverse-phase evaporation method is the technique of choice, one which permits one-step preparation of large unilamellar liposomes with high entrapment efficiency (48). Amphotericin B–intercalated liposomes were prepared by a process where amphotericin B and purified phosphatidyl choline were solubilized in a suitable solvent and precipitated in SC-CO_2 by the anti-solvent technique to obtain microsized particles. The particle size distribution was studied using the laser technique and showed nanosize particles with a narrow range of size distribution and a higher intercalation efficiency of prepared liposomes (49). The ASES process can also be used to prepare liposomes in a dry and reconstitutable form. Dry liposomes containing miconazole as a model drug were prepared by an optimized ASES process with various compositions of spraying solution containing phosphatidylcholine, cholesterol, and poloxamer 407. The process yielded partially crystalline, spherical, and nonporous microparticles varying from a few to 40 μm. The microparticles also fall into a desired limit of residual solvents (50). Several methods using SCFs can be successfully adapted to produce liposomal preparations to overcome drawbacks associated with the routine production methods.

3.7. Purification and Polymorphism

The synthesis of the active pharmaceutical ingredients (APIs) minus the impurities is extremely important. The presence of even traces of impurities can result in an alteration of chemical properties aside from the physical instabilities of compounds. Recently, SFT came out as an excellent tool to assist in the isolation of certain process impurities in APIs. Furthermore, SFT is also key in the API industry for its application in polymorph isolation and chiral control. Several reports are available in the literature regarding the usage of the gas anti-solvent recrystallization (GAS) process for separation and purification purposes. These include the purification of β-carotene, cholesterol, anthracene, bilirubin, citric acid, and proteins and for fractional crystallization of mixtures of anthracene and anthraquinone and lecithin from egg yolk, phenanthrene and naphthalene, natural products, hydroxybenzoic acid isomers, and racemic mixtures. Furthermore, SC-CO_2 crystallization has been used to investigate fractionalization of polystyrene by chain length and for separating semi-crystalline and amorphous poly (l-lactic acid) (51).

In solid state pharmaceuticals, polymorphic forms of a crystalline material can have distinctly different physical and chemical properties such as melting point, solubility, and even bioavailability. Different research groups reported control of the polymorphic form by processing in SC-CO_2, including the separation of polymorphs of paracetamol, carbamazepine, terbutalin sulphate, deoxychloric acid, sulfathiazole, and salmeterol xinafoate. Critical operations such as granula-

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tion, drying, spray drying, homogenization, lyophilization, and compression are inevitable during pharmaceutical production. The impact of these processes on solid states is highly prone to the undesirable conversion of polymorphs, desolvation of solvates, solvates formation, etc., which can be avoided by the use of SFT tools (51).

3.8. Drug Extraction Process and Analysis

The extensive development of the field of SFT has attracted significant attention for drug extraction processes and analysis. Extraction and fractionation of natural compounds using supercriticals has already gained popularity. Over the last decade, studies on the extraction of classical compounds such as essential and seed oils from various sources—seeds, fruits, leaves, flowers, rhizomes, etc.—with or without the addition of a co-solvent have been published (52).

Supercritical fluid extraction (SFE) was employed to analyze drugs in plasma by Klime *et al.* Evaluation of anti-inflammatory drugs such as ibuprofen, indomethacin, and flufenamic acid was performed using the high-performance liquid chromatography (HPLC) method in combination with SFE. The process was carried out with the magnitude of the CO_2 pressure suitable for drug extraction. The results of this study determined the optimal procedure for the SFE of ibuprofen, indomethacin, and flufenamic acid from plasma (53). Apart from this, several benzodiazepines were separated from the matrices of their standard dosage forms using SFE (54). Several chromatographic techniques in combination with SFE are used for the separation and/or estimation of pharmaceutical compounds. The SFE liquid chromatography techniques aim to separate analytes of high polarity and molecular weight that cannot be addressed by either method alone. A preferred combination method widely used is SFE gas chromatography because of the high sensitivity, flexibility, and compatibility of the detectors (6).

4. Scale-up and GMP Processing

From a GMP perspective, several attractive features of SFT are apparent, especially in providing a totally enclosed, single-step process for controlled particle formation. A mechanistic understanding of SCF particle formation processes and rigorous descriptions of mass transfer and nucleation processes will form the basis for the efficient scale-up of laboratory processes. Several pharmaceutical products, including polymeric microparticles and nanoparticles, drug powders, drug polymorphs, and liposomes, can be developed using SFT. For significant commercial feasibility, a demonstration of the processes that can be scaled to produce sufficient quantities of practical yield in production batches is required. For the antisolvent-based systems, the best processing equipment for the single stage provides a totally enclosed process that is free of moving parts and is constructed from high-grade stainless steel with clean-in-place facilities available for larger-scale equipment (6, 21). The unique properties of SC-CO_2 technology make it an outstanding choice in relation to the conventional technologies such as spray-drying and freeze-drying. Therefore, GMP compliance is not a true obstacle to SCF processing in commercialization. In fact many pharmaceutical companies have already developed particle-design plants at both the pilot and industrial scale under stringent quality assurance and according to GMP-compliant principles. In this regard, an interdisciplinary approach must be sought by merging engineering, physicochemical, pharmaceutical technology, and biopharmaceutical expertise.

5. Concluding Remarks

SFT is no longer in its infancy, it is growing at a fast pace, but the major challenges now are to ensure that real commercial opportunities are developed in the pharmaceutical industry. Taking advantage of the specific properties of SFT, such as more simplified and flexible processes and a reduced environmental impact, makes it ideally suited for developing processes for extracting, purifying, and recrystallizing fine chemicals and pharmaceuticals and seeing better performances in particle-size engineering for drug delivery. SFT can also be used for the modification of the dissolution-rate enhancement of drugs, especially poorly soluble active substances, and for many other applications such as the formation of microparticles and nanoparticles, polymer impregnation, drug extraction, co-crystallization, and complexes with host molecules. Importantly, a number of academic research papers have reported successful applications of SFT but surprisingly also note a lack or very low commercial output to date. Further research and development of SCF processing for pharmaceuticals is required to strengthen the current understanding of SFT and ultimately to use it competently in industrial applications.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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