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Review Article

An Overview of supercritical carbon dioxide processing of pharmaceutical drugs and polymers

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Abstract

Supercritical carbon dioxide (SC-CO_2) has emerged as a green, versatile and sustainable processing medium for the pharmaceutical industry, offering a promising alternative to conventional organic solvent-based methods that are often toxic, expensive and environmentally hazardous. Carbon dioxide reaches its supercritical state at a relatively mild critical temperature of 31.1 °C and critical pressure of 73.8 bar, where it exhibits unique hybrid properties intermediate between a liquid and a gas, including liquid-like density and solvating power, gas-like diffusivity and viscosity, near-zero surface tension and tunable solubility by simple variation of pressure and temperature. These properties, combined with its non-toxicity, non-flammability, chemical inertness, low cost, abundance and easy removal by simple depressurization, leaving no solvent residue, make SC-CO_2 particularly attractive for processing thermolabile pharmaceutical drugs and biodegradable polymers. This review provides an overview of SC-CO_2 processing of pharmaceutical drugs and drug-polymer particles, focusing on the fundamental principles and processing techniques. The solubility of a drug in SC-CO_2 depends on its molecular weight, polarity, vapour pressure and the density of CO_2. The review then systematically categorized the major SC-CO_2 particle formation techniques into three groups: processes using SC-CO_2 as a solvent, notably Rapid Expansion of Supercritical Solutions (RESS) and its modifications such as RESS with solid co-solvent, RESS with non-solvent and Supercritical Assisted Atomization; processes using SC-CO_2 as an anti-solvent, including Supercritical Anti-Solvent (SAS), Gas Anti-Solvent (GAS), Solution Enhanced Dispersion by Supercritical Fluids (SEDS) and Aerosol Solvent Extraction System (ASES). Despite remaining challenges in solubility, scale-up and cost, continued advances in process understanding, modelling, in-line characterization and equipment design are expected to accelerate its industrial adoption for next-generation drug delivery systems.

Keywords: *Biomedicine, Nanoparticles, Pharmaceuticals, Polymers, Supercritical carbon dioxide*

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INTRODUCTION

Green chemistry is important due to the fact that supercritical CO_2 (SC-CO_2) is an environmentally friendly, acceptable replacement for petroleum-based solvents [1]. There are many adverse effects associated with residual solvents, especially in processing and environmental

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industries. This has limited the application of these traditional techniques in the pharmaceutical industry. Organic solvents have been replaced with supercritical fluids, especially in the area of nanoparticle fabrication, extraction and processing of polymers [2].

Conventional particle formation methods such as freeze-drying involve the formation of a large particle which is subsequently reduced to the desired shape, whereas the supercritical fluid (SCF) technology requires the attainment of the desired morphology via controlled growth of the particles [3]. One of the reasons why SCF technology is preferred is that no further processing is required on the formed particles; thus, it is suitable for biomolecular production. Although many scientists are eager to know the greenhouse effect of CO_2, it is still the preferred alternative to available organic solvents because CO_2 is recyclable and there is no tangible change in the net load on the atmosphere [4].

There are different techniques deployed in the development of these nanoparticles. They consist of the following: solvent evaporation, jet-milling, freeze-drying, spray-drying and coacervation [5]. The traditional processes make use of toxic organic solvents, elevated temperatures and long post-process treatments. Challenges associated with high process temperatures include degradation of the active compound and incomplete removal of the solvent from the final product. Many studies have documented the possibility of using supercritical CO_2 in overcoming these challenges [6-10]. The supercritical fluid state of a pure substance is defined as the state where the temperature and pressure are above their critical values, as illustrated in Figure 1 [11].

Nanoparticle production techniques via the application of SC-CO_2 as a solvent

There are different techniques that have been used over the years in the production of nanoparticles. They include:

a. Rapid expansion of supercritical solution (RESS)
b. Rapid expansion of supercritical solutions with solid co-solvent (RESS-SC)
c. Rapid expansion of a supercritical solution into a liquid solvent (RESOLV)

The RESS was the first technique that deployed the use of SC-CO_2 as a solvent. This technique involves the dissolution of a certain amount of solute with the help of the supercritical fluid. The solute is dissolved by feeding the SC-CO_2 into the vessel. The dissolution of the solute involves a specific temperature and pressure. The supercritical solution is delivered into a pre-expansion zone, which occurs at a higher temperature than that reached in the extractor. After the solute has been solubilized in $SCCO_2$, a fast expansion of the mixture occurs via a nozzle in the collection chamber as illustrated in Figure 2.

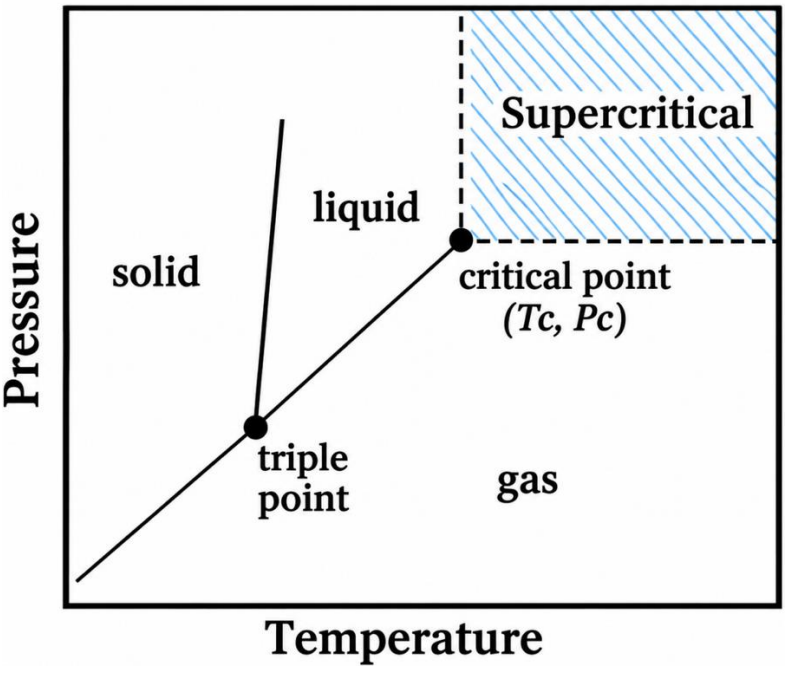

Figure 1: Graphical illustration of a simplified phase diagram. Adapted with permission from Franco and De Marco [11]

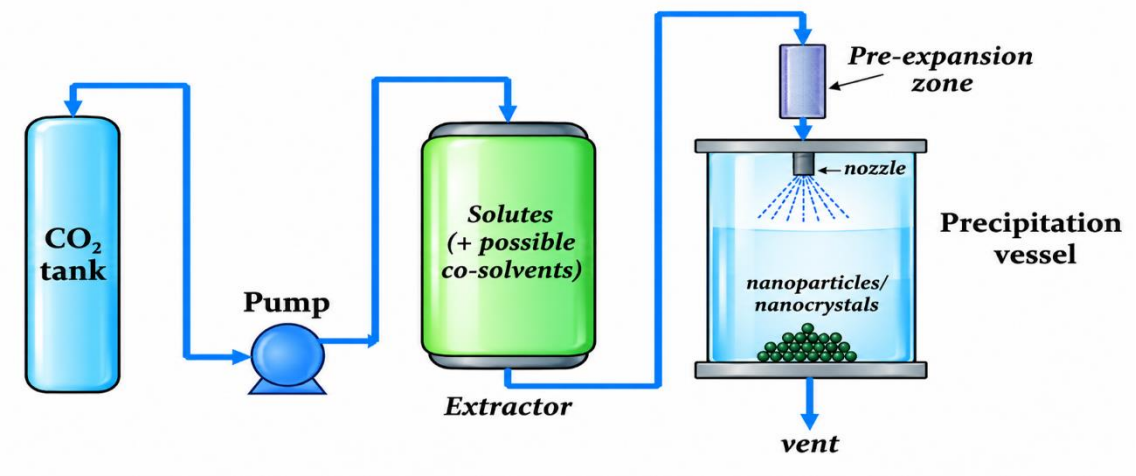

Figure 2: A sketch of the rapid expansion of supercritical solution (RESS) process, adapted with permission from Franco and De Marco [11]

According to Kim *et al,* they produced naproxen nanocrystals by using polylactic acid (PLA) [12]. Also, Sharma *et al* produced ibuprofen nanoparticles using different surfactants [13]. The results indicated that sub-microparticles were obtained by using polyethyleneimine (PEI) with a molecular weight of 1300 Da and Tween 40®. Some of the major challenges associated with the RESS process are due to the low solubility of polar drugs in $SCCO_2$ and the possible agglomeration of particles in the expansion zone [14]. This challenge was overcome by modification of the RESS technique using solid co-solvents such as menthol [15, 18]. The solid co-solvent should possess certain characteristics such as high vapor pressure, inertness, nonflammability, non-toxicity, and economic feasibility. According to Uchida *et al*, they produced theophylline nanocrystals using vanillin as a solid co-solvent [16].

In the RESOLV process, the expansion of the supercritical mixture, which contains the solutes to be nanosized, takes place in a liquid solvent [17, 19, 20]. One of the challenges associated with the RESOLV process is the issue of aggregation of the nanoparticles [21, 22]. This has been resolved by coupling ultrasonication with RESOLV in order to improve drug nanonization [23]. According to Sodeifian and Sajadian, they employed two main polymers, namely polyvinyl pyrrolidone (PVP) and hydroxypropyl methyl cellulose (HPMC), in order to stabilize drug particles [21]. The use of supercritical CO_2 in the production of pharmaceutical nanoparticles has been documented. Its applications range from oral and topical to intravenous injections and infusions [24-27]. Table 1 depicts an overview of the production of nanoparticles using CO_2 as a solvent, while Table 2 depicts an overview of the production of nanoparticles using CO_2 as an antisolvent.

Table 1: An overview of nanoparticles produced using CO_2 as a solvent

Types	Main compound	Co-solvent	Conditions of operation	Sizes	Ref
RESS	Cholesterol, caffeine	Alcohol	35- 45 °C P_{EXT} 14-20 MPa	81-169 nm	[26]
RESS	Deferasirox	Alcohol	T_{EXT} 35-45 °C 14-20 MPa	50 nm	[27]
RESS	Digitoxin	Ethanol	T_{PREEX} 90-110 °C P_{EXT} 10 Mpa	91-255 nm	[29]
RESS	Naproxen	methanol	T_{PREEX} 60-100 °C T_{PREEX} 45-100 °C P_{PREEX} 15-30 MPa	60-220 nm	[30]
RESS-SC	Aspirin	Menthol	T_{EXT} 35 °C P_{EXT} 7.3 -8.5 MPa T_{PREEX} 30-70 °C.	Nanocrystal, nanoparticle	[28]

Rapid expansion of supercritical solution (RESS), Rapid expansion of supercritical solutions with solid co-solvent (RESS-SC), Rapid expansion of a supercritical solution into a liquid solvent (RESOLV), T_{PREEX}: Pre-expansion temperature, T_{EXT}: Expansion temperature, P_{PREEX}: pre-expansion pressure, P_{EXT}: extraction pressure

Nanoparticle production techniques via the application of SC-CO_2 as an antisolvent

Different techniques used in the production of pharmaceutical nanoparticles using SC - CO_2 as an antisolvent include: Aerosol solvent extraction system (ASES), Supercritical gas antisolvent (GAS), Precipitation with compressed fluid antisolvent (PCA), and Supercritical antisolvent precipitation (SAS). The supercritical antisolvent precipitation (SAS) method uses SC-CO_2 as an antisolvent. It involves the use of some liquid solvents that are miscible with SC-CO_2, which include methanol, acetone and dimethyl sulfoxide (DMSO). Figure 3 is an illustration of the supercritical antisolvent precipitation process that is commonly deployed in the industrial sector.

The production of nanoparticles in the SAS process involves low temperature (35-50 °C) and pressure ≥ 9 MPa. One major advantage associated with the SAS technique over the conventional processes is that it is more suitable for obtaining smaller particles [2,3]. A study conducted by Park *et al*, after formulation, showed that the particle size of cefdinir nanoparticles was smaller than that of cefdinir microparticles (2.32 ± 1.76 µm) which were produced by spray-drying [10]. Some modifications of the SAS process occur in the form of ASES, GAS and solution-enhanced dispersion by supercritical fluids (SEDS) techniques [31-34].

The GAS process involves the introduction of the SC-CO_2 into the precipitation vessel, which contains the liquid solution [35-37], while the SEDS process involves the injection of both the SC-CO_2 and the liquid solution via a coaxial nozzle. This ensures that better mixing occurs between the solution and the antisolvent in order to produce finer powders when compared to those produced by the conventional SAS process. The supercritical fluid extraction of emulsions (SFEE) technique involves the use of SC-CO_2, which acts as an antisolvent suitable for oil-in-water (o/w) or water-in-oil (w/o) emulsions [37,38]. The use of o/w emulsions involves the dissolution of the hydrophobic active compounds in the oily phase, as shown in Figure 4.

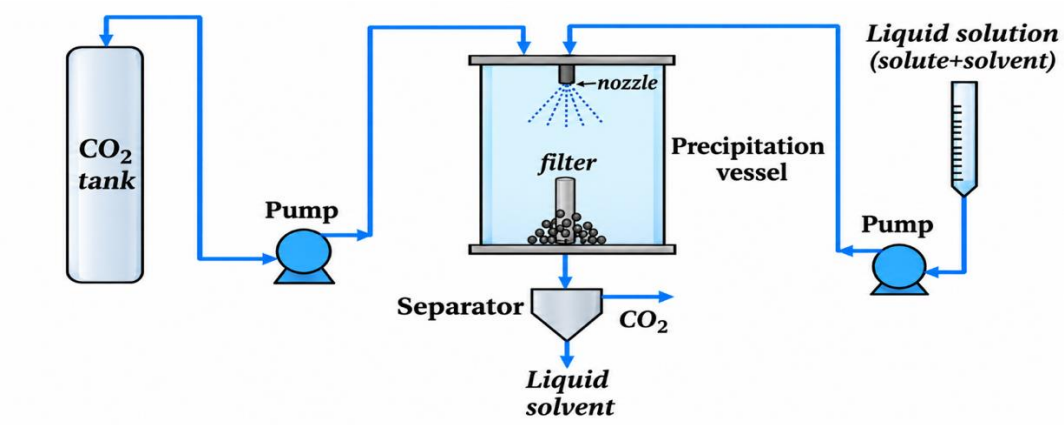

Figure 3: Supercritical antisolvent precipitation process. Adapted with permission from Franco and De Marco [11]

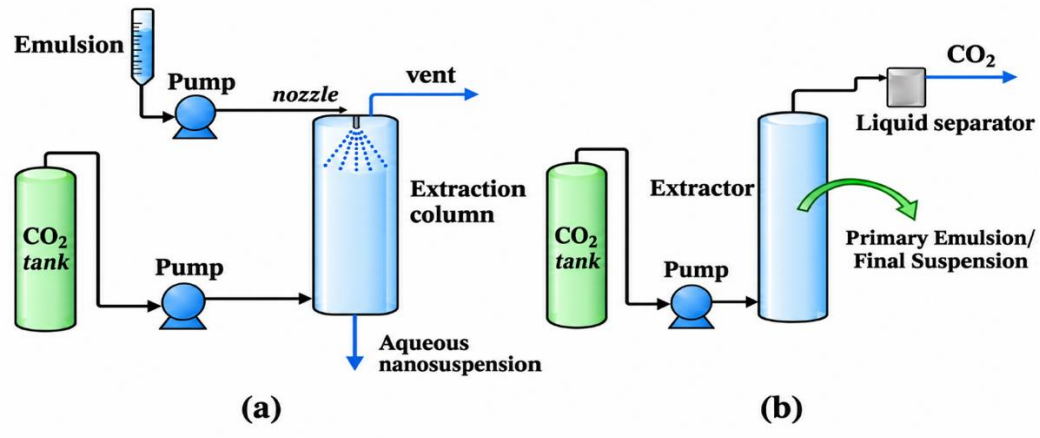

Figure 4: A sketch of the supercritical fluid extraction of emulsions: (a) continuous and (b) batch SFEE. Adapted with permission from Franco and De Marco [11]

Table 2: An overview of nanoparticles produced by using CO_2 as an antisolvent

Types	Main compound	Polymer	Solvent	Conditions of operation	Size	Reference
ASES	Itraconazole	HPMC	Ethanol	12-15 MPa 45-60 °C	Nanoparticle (220-430 nm)	[34]
GAS	Ampicillin	HPMC	DMSO	9-15 MPa 34-46 °C	Nanoparticle (180-300 nm)	[39]
GAS	Lysozyme	HPMC	DMSO	19-35 °C.	Nanoparticle (300 nm)	[35]
PCA	Gentamicin	PVM/MA	AC	10 MPa 25 °C.	Nanoparticle (200 nm)	[40]
SAS	Diclofenac sodium	Zein	DMSO	9 MPa	140 nm	[41,42]

HPMC: Hydroxypropyl methyl cellulose, AC: acetone, DMSO: dimethyl sulfoxide, ASES: Aerosol solvent extraction system, GAS: supercritical gas antisolvent, PCA: Precipitation with compressed fluid antisolvent, SAS: Supercritical antisolvent precipitation. PVM/MA: Poly(methyl vinyl ether-co-maleic anhydride), PVP: Polyvinyl pyrrolidone

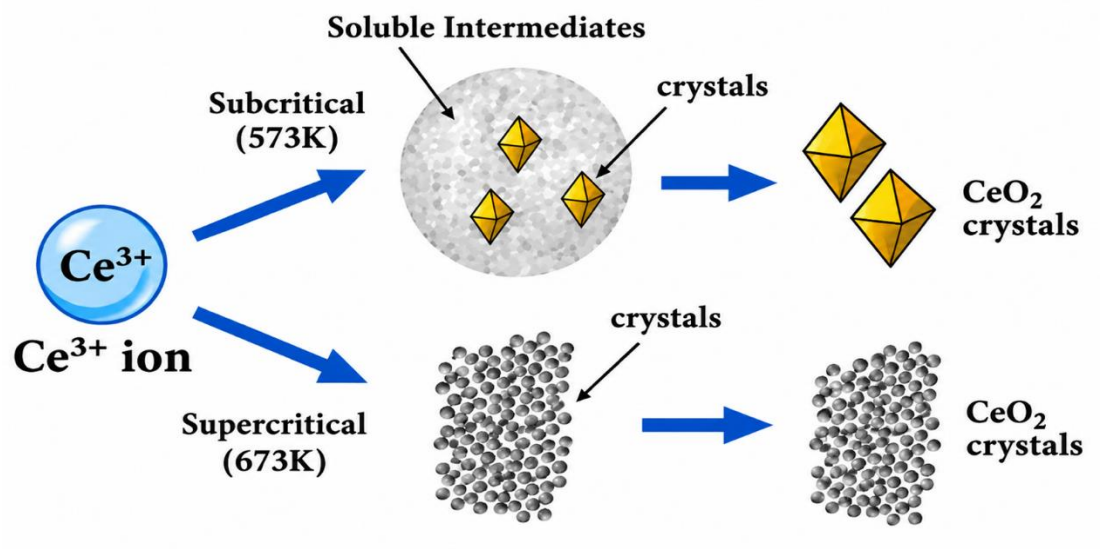

Figure 5: Mechanisms of CeO_2 nanoparticle formation under supercritical conditions. Adapted with permission from Byrappa *et al* [48]

Nanoparticle production techniques via the application of SC-CO_2 as a co-solute

Different techniques used in the production of pharmaceutical nanoparticles using SC-CO_2 as a co-solute include Particles from gas-saturated solutions (PGSS), Supercritical-assisted atomization (SAA), and supercritical-assisted injection in a liquid antisolvent (SAILA).

The PGSS method consists of mixing scCO_2 and molten substances (e.g., drug and polymer), usually in a static mixer. It involves the mixing of SC-CO_2 and molten substances together in a precipitation chamber [43,44]. One major advantage associated with the PGSS is that organic solvents are not needed in the processing of active compounds. The SAA process is suitable for controlling particle morphology and particle size distribution, with limited use of liquid solvents [45,46]. One of its limitations is the high temperature, which is not suitable for thermolabile materials.

In the SAILA process, the SC-CO_2 and an organic solvent help in the formation of an expanded liquid solution. This leads to the depressurization of the ternary solution. The aqueous phase is pumped into the vessel, which causes recovery of the nanoparticle suspension. There are two principles governing the SAILA process. They include the solubility of the solute in the organic solvent and the miscibility of water and the organic solvent. The CO_2 becomes the co-solute, while the water becomes the antisolvent [47,48].

Synthesis of metal oxide nanoparticles

Three properties influence the application potential of metal oxide nanoparticles. They include shape, particle size and nature of the

surface. Figure 5 depicts the mechanisms of CeO_2 nanoparticle formation under supercritical conditions

Although highly crystalline nanoparticles can be obtained with SCF technology, the challenge usually stems from large size and coagulation. Some organic ligands such as surfactants and capping agents can be suitable for controlling the nanoparticle size and morphology [48].

CONCLUSION

The use of SC-CO_2 for synthesizing metal nanoparticles and metal oxides offers a promising, environmentally friendly and versatile approach with tunable properties. By optimizing process parameters and precursor chemistry, SC-CO_2 can be used to produce nanoparticles with controlled size, shape and distribution.

DECLARATIONS

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Ethical approval

Not applicable.

Use of Artificial intelligence/Large language models

We also declare that we did not use Generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Conflict of interest

No conflict of interest is associated with this work.

Contributions of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. CFC: conceived the study, drafted the manuscript; CAE: Supervised the review; ECO: drafted the manuscript; OEO: drafted the manuscript; Joel OO: Drafted the manuscript; EOO: Conceived the study, drafted the manuscript. All authors read and approved the final manuscript for publication.

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