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An overview on the application of supercritical carbon dioxide for the processing of pharmaceuticals

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Abstract

Supercritical carbon dioxide ($scCO_2$) application in the pharmaceutical industry is still undeveloped regardless of significant research interests in this processing medium shown in the last decades. $ScCO_2$ technologies can improve drug solubility, bioavailability, and therapeutic effect. These technologies can lead to the development of new formulations that will contribute to a decrease in drug dose, medication frequency, and increase patients' well-being. Considering the significant decrease in the price of high-pressure equipment and society's growing need for cleaner production and safer products, it is expected that symbiosis between supercritical fluid and pharmaceutical technologies will happen soon. Therefore, this review was focused on the latest contributions of $scCO_2$ technologies to the pharmaceutical field. The main aim was to bring these technologies closer to pharmaceutical specialists. For this purpose, the most commonly used technologies were explained and discussed: the preparation of solid dispersions, polymer impregnation with drugs, and drug micro/nanoparticle production using $scCO_2$.

Key words: supercritical CO_2, solid dispersion, supercritical impregnation, particle generation

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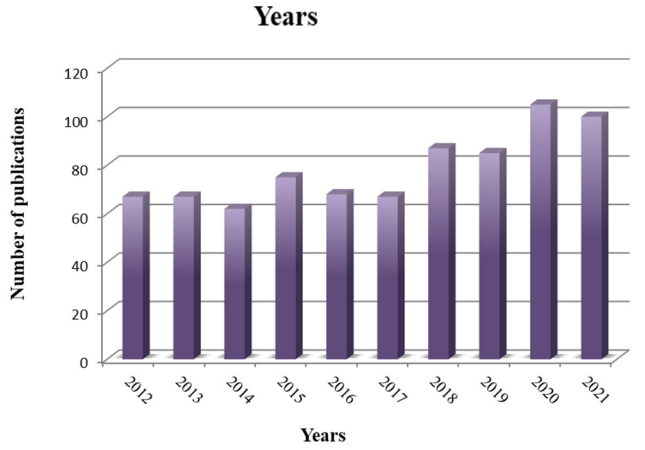
Introduction

Supercritical carbon dioxide ($scCO_2$) found its application in the food/beverage industry, mostly for the extraction from several types of plant materials, and in the textile industry for fabric dyeing. However, its application in the pharmaceutical industry is still undeveloped, although it has been a subject of debate in the last decades. The reason for this could be high investment costs, as well as the lack of sufficient interdisciplinary collaboration between scientists from different fields, which resulted in fragmented knowledge, severely jeopardizing the development of next-generation drug formulations. Considering the significant decrease in the price of high-pressure equipment and society's growing need for cleaner production and safer products, it is expected that symbiosis between supercritical CO_2 technologies and pharmaceutical technology will happen soon. Until then, the research interests and efforts shown for these technologies are expected to grow, as previous years have shown (Figure 1). According to a scientific literature survey, based on the Web of Science database (WOS), 783 research and review articles on the processing of drugs using $scCO_2$ were published from 2012–2021, with an increase in the number of paper in the last four years. Based on the WOS categories, 38.7% of the published papers are in the domain of chemical engineering, followed by 25.5% in physical chemistry, and 18.9% in pharmacy. The increased interest in $scCO_2$-assisted processes is mostly due to well-known technical features that have numerous advantages. In addition, sustainable, “green”, safe, and “environmentally friendly” properties of $scCO_2$ are increasingly important subjects for the pharmaceutical industry (1). Contrary to the number of published articles, the number of registered patents decreased starting from the 2018 year (Figure 1c).



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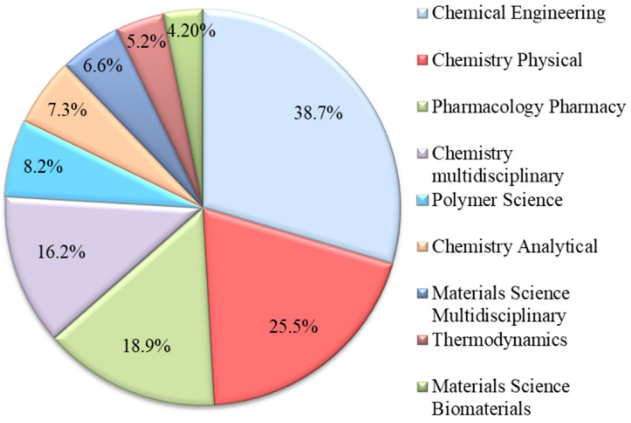

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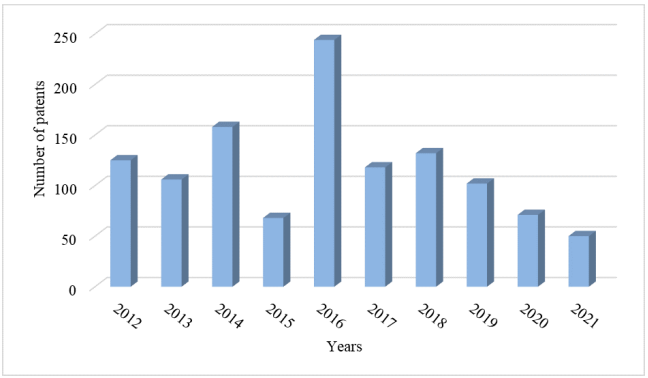

(c)

Figure 1. **(a) Survey on research reports number, (b) research areas, and (c) survey on patents numbers for $scCO_2$ application in drug processing for the 2012–2021 period based on the Web of Science database (keywords used: supercritical CO_2 AND drug) on 25th August 2022**

Slika 1. **(a) Pregled broja istraživačkih radova, (b) istraživačkih oblasti i (c) pregled broja patenata na temu primene $nkCO_2$ za procesiranje lekova koji su objavljeni u periodu 2012–2021 na osnovu baze podataka "Web of Science" (upotrebljene ključne reči: "supercritical CO_2" i "drug") 25. avgusta 2022.**

Supercritical carbon dioxide

Properties of supercritical carbon dioxide

Fluid is in a supercritical state when pressure and temperature conditions are above the fluids' critical point. Above the critical point, distinct liquid and gas phases do not exist (1, 2). Phase change with pressure and temperature conditions can be seen in the CO_2 phase diagram in Figure 2. At the supercritical state, above the critical temperature (*T*c) and pressure (*P*c), a fluid is homogeneous with unique physicochemical properties. Diffusivity, viscosity, density, heat conductivity, and dielectric constant values of a supercritical fluid are between those of a gas and a liquid (Table I) (2, 3). As the temperature of the liquid rises, it becomes less dense, and as the pressure of the gas rises it becomes denser, and it becomes equal at the critical point. The liquid-like nature enables supercritical fluids to act as solvents, while their gas-like properties allow quick and easy diffusion through the material.

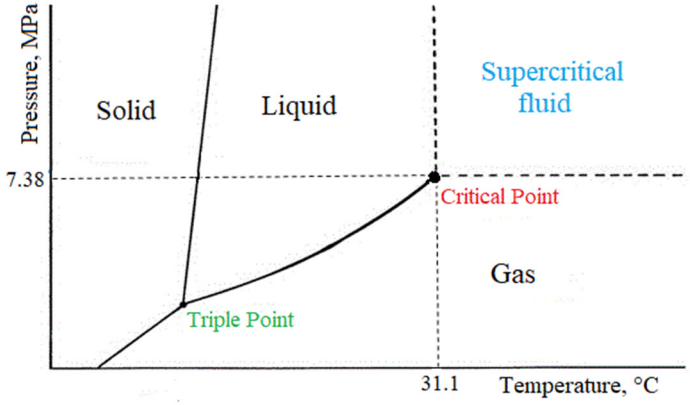

Figure 2. Phase diagram of carbon dioxide
Slika 2. Fazni dijagram ugljenik(IV)-oksida

Table I Characteristic values of some physical parameters of fluids in different phases
Tabela I Karakteristične vrednosti pojedinih fizičkih parametara fluida u različitim fazama

	Density (kg/m^3)	**Diffusivity (cm^2/s) ·10^6**	**Viscosity (g/cm s) ·10^5**
Gas			
P= 101.3 KPa *T*= 15−30 ºC	0.6−2.0	100000−400000	10−30
Supercritical fluid			
P= *P*c, *T*= *T*c	200−500	700	10−30
P= 4*P*c, *T*= *T*c	400−900	200	30−90
Liquid			
P= 101.3 KPa *T*= 15−30 ºC	600−1600	2−20	200−3000

Processes that employ $scCO_2$ as a solvent have generally attracted attention primarily due to green, environmentally friendly, sustainable, and safe features (1). The main reasons for the wide use of $scCO_2$ are its unique and easily tunable physicochemical properties, availability, and low cost (1, 4). $ScCO_2$ is considered an ideal medium for pharmaceuticals processing because it has relatively mild critical parameters (7.38 MPa, 31.1 °C), it is an environmentally benign solvent, non-toxic, non-flammable, chemically inert, fully recyclable, can be easily removed from the product just by pressure reduction, leaving no residues, and is "generally regarded as safe" (2).

When CO_2 is in the region above the critical point, its density is close to the liquid. The value of $scCO_2$ density can be easily changed and adjusted by a small variation in operational pressure and/or temperature, thus allowing adjustment of its solvation powers towards different compounds (1, 5). Contrary to values of density, values of diffusivity and viscosity are close to the one of the gas (5) enabling good transport properties. In addition, low values of $scCO_2$ surface tension and dielectric constants, combined with excellent heat transfer properties, high compressibility, and recyclability make it an ideal processing medium that does not contribute to a greenhouse effect (1). Relatively low operating temperatures needed for $scCO_2$ processes not only allow a lower energy demand, but also help avoid the degradation of heat-sensitive compounds. The unique properties of $scCO_2$ and its tunable solvent power make it superior to conventional solvents and an excellent medium for the processing of different compounds/matrices. Since the final material does not contain potentially toxic solvent residues and there is no generation of solvent waste, $scCO_2$-assisted processes are considered green techniques.

The versatility of supercritical carbon dioxide

The unique properties of $scCO_2$ and the environmental benefits of $scCO_2$-assisted processes have led to a variety of its applications. $ScCO_2$ processes on a laboratory scale are mostly used for (a) separation of bioactive extracts from plant material (4, 6) to avoid the use of organic solvents and/or high temperatures (7), (b) supercritical drying to remove liquids from gels without a change in the wet gel matrix (8, 9), (c) polymer impregnation with bioactive components (10, 11), (d) both natural and synthetic textile dyeing (7), (e) modification/functionalization of inert inorganic solids (12), and (f) distribution of drugs into solid polymer matrices (13–15). In the field of polymeric processing, $scCO_2$ can act as a plasticizer of semicrystalline and amorphous polymers and induce polymer foaming (16). $ScCO_2$ technologies on a lab-scale in the pharmaceutical field are usually used for the processing of poorly water-soluble drugs to improve their properties (14, 17) or for masking the unpleasant taste of drugs (18).

Several $scCO_2$-assisted processes were developed on an industrial scale for food and cosmetic applications. These $scCO_2$ processes include the separation of hop extracts for the beer industry and the separation of caffeine from tea or coffee for the beverage industry. Caffeine obtained in the decaffeination process is further used by the cosmetic industry (it is a common ingredient in cellulite creams) (7). However, there is still a lack of application of sc-CO_2 technologies in the pharmaceutical industry.

Methods for drug processing using supercritical carbon dioxide

$ScCO_2$ technologies most often reported for processing of pharmaceutical drugs are: preparation of solid dispersion with various polymeric carriers, polymer impregnation, preparation of particles from gas saturated solutions (PGSS), rapid expansion of supercritical solutions (RESS), and supercritical anti-solvent (SAS) process.

Preparation of solid dispersions

Production of solid dispersion (SD) implies the dispersion of an active ingredient in an inert and solid carrier matrix for the improvement of drug dissolution (19). SDs increase the dissolution of poorly water-soluble drugs by a reduction in the size of drug particles, change of the drug state from crystalline to amorphous, production of particles with higher porosity, or improving particle wettability (14, 19, 20). Conventional methods for SD preparation are solvent evaporation and melting or their combination (14, 21). This includes freeze drying, spray drying, hot-melt extrusion, and electrospinning (19, 22 ,23). Although melting methods are relatively easily adapted for the application in the pharmaceutical industry, their major drawback is the need for thermostable drugs and polymers. Moreover, these drugs and polymers need to be compatible and miscible at the high process temperature (14, 24). It was reported that SDs prepared by the melting methods can go through phase separation during the cooling phase, could have poor flowability, and poor compressibility (14). Although some of these issues may be resolved by using solvent evaporation methods, these methods usually require the use of organic solvents (14, 24). The main disadvantage of these methods is the lack of complete solvent evaporation, which might lead to instability of the SD upon storage or toxicity issues for consumers (14, 21, 23). These shortcomings can be overcome by utilization of the $scCO_2$ technology, which allows the drug formulation preparation in the absence of oxygen, reducing the possibility of oxidative degradation, and results in a product with no residual organic solvent (14, 22). Moreover, $scCO_2$ technology solved drying issues and issues related to heat liability (24, 25).

SDs can be prepared in a single-step process by exposure of drug-polymer physical mixtures to $scCO_2$ at desired pressure and temperature conditions during a certain period (13–15). In this process performed in a static regime, $scCO_2$ promotes the mixing of a drug and polymer by acting as a molecular lubricant and, at the same time, potentially acting as a temporary plasticizer (14). During decompression (outgassing), $scCO_2$ is fully leaving the system and the obtained SDs are solvent-free. Numerous drugs have been processed using $scCO_2$ for SD preparation such as eflucimibe (26), carbamazepine (20), tacrolimus (24), nimodipine (27), etc. Several drugs, polymeric carriers, and conditions for SDs preparation using $scCO_2$ that were reported in the last 5 years are listed in Table II.

Table II Examples of drug solid dispersions prepared via the $scCO_2$ technique in the last 5 years

Tabela II Primeri čvrstih disperzija lekova pripremljenih upotrebom $nkCO_2$ tehnike u poslednjih 5 godina

Drug	Carrier	Conditions	Results	Ref
Carvedilol	PVP, HPMC, Soluplus®, Eudragit®	100 °C 30 MPa 2 h static	Drug amorphization and increase of release rate to more than 80% in 0.1 N HCl after 10 min.	(14,15)
Valsartan	Soluplus®, Eudragit®, HPMCAS	100 °C 30 MPa 2 h static	Drug formulations retained buoyancy up 24 h in 0.1 M HCl solution.	(13)
Atorvastatin	PVP, PEG, Soluplus®, Chotosan	40–80 °C 10–15 MPa 1 h static	Increased drug solubility up to 20-fold and zero-order release of up to 95%.	(25,86)
Cefixime trihydrate	PEG 4000, PEG 6000	40 °C 9–11 MPa 2 h static	Drug solubility in 0.05 M potassium phosphate buffer increased up to 20%	(19)
Bicalutamide	PEG 6000, Poloxamer® 407	50,60 °C 15,16 MPa mixing	Drug crystallinity was decreased. Dissolution rate increased up to 70%.	(21)
Simvastatin	Soluplus®	40,50 °C 10–30 MPa 1,2 h static	Drug dissolution rate increased up to 100% in PBS within 45 min.	(23)
Ibuprofen	Kollidon®	40 °C 25 MPa 18 h static	Dissolution performance significantly improved. Remarkably high drug concentrations in blood.	(87)

PVP– polyvinylpyrrolidone; HPMC– hydroxypropyl methylcellulose; Soluplus®– polyvinyl acetate and polyvinyl caprolactam copolymer; Eudragit®– poly-(*N*-dimethylaminoethyl methacrylate-*co*-methyl methacrylate-*co*-butyl methacrylate; HPMCAS– hydroxypropyl methylcellulose acetate succinate; PEG– polyethyleneglycol

Alternatively, methanol or ethanol can be added to the polymer-drug mixture before exposure to $scCO_2$ (19, 20, 25). Alsmadi et al. (25) reported that this enabled the formation of a hydrogen bond between the carbonyl group of Soluplus® and the hydroxyl group of atorvastatin, which led to a loss of atorvastatin crystalline form during exposure to $scCO_2$. As a result, the dissolution of atorvastatin increased by more than 20-fold (from 61.6 to 1305.0 μg/mL) when tested in vitro. Moreover, the developed SD enabled higher and more consistent exposure to atorvastatin after oral administration (even in pathophysiological changes induced by inflammatory bowel disease and irritable bowel syndrome).

Impregnation of drugs into polymers

Supercritical solvent impregnation (SSI) implies the introduction of $scCO_2$ at desired pressure and temperature into the system with a drug and polymer that are physically separated, dissolution of a drug in $scCO_2$, and diffusion of the obtained solution into the polymer matrix. System depressurization enables the complete separation of $scCO_2$ from a drug and polymer, while a drug remains in/on the polymer matrix due to precipitation, hydrogen bonding, or chemical interaction. The SSI process takes advantage of both the solvent power and diffusivity properties of $scCO_2$ previously mentioned.

The SSI process that employs $scCO_2$ has attracted significant interest in a variety of research fields due to the compliance with the Green Chemistry rules, lack of organic solvent use, lower energy demands, and zero waste generation (17). Besides, when $scCO_2$ acts as a polymer plasticizer, it facilitates impregnation. Additionally, an amount and distribution of a drug into a polymer matrix can be easily controlled by variations in process parameters such as pressure, temperature, contact time, and decompression rate (28–30).

Numerous drugs have been impregnated into polymer carriers using $scCO_2$, and several of them reported in the last 5 years are listed in Table III. Usually, the drug aimed for oral delivery is molecularly dispersed into/onto the polymer matrix and its bioavailability and dissolution rate are enhanced after the $scCO_2$ impregnation process. Beside oral drugs intended to be dissolved and absorbed in the upper or lower gastrointestinal tract, pulmonary drugs can be also impregnated into nanoporous carriers using $scCO_2$. Alsmadi et al. (31) impregnated cisplatin for lung cancer treatment into chitosan-alginate nanoporous carriers and obtained a formulation that reduced cisplatin lung toxicity. This enabled a significant reduction in the mortality rate. It also prevented weight loss in rats when compared to free cisplatin after intratracheal administration. Impregnation of ophthalmic drugs into commercial contact lenses using $scCO_2$ was reported for the preparation of innovative ophthalmic drug delivery systems. These ophthalmic devices maintained adequate therapeutic levels for a longer period and overcame the limitations that were associated with conventional ocular drug formulations (32–34). In addition, the $scCO_2$-assisted impregnation process has been used to prepare drug-containing biomedical implants, such as sutures (5, 35), scaffolds for tissue engineering (36, 37), stents, and endoprosthesis to decrease the infection risks and increase tissue regeneration (5).

Table III An overview of the $scCO_2$ impregnation technique used for drug processing in the last 5 years

Tabela III Pregled $nkCO_2$ tehnike impregnacije upotrebljene za procesiranje lekova u poslednjih 5 godina

Drug	Carrier	Conditions	Results	Ref
Ibuprofen	MCC	40–60 °C 10–25 MPa 2–24 h	The highest drug loading was achieved at 25 MPa and 40 °C after 24 h (9.43%).	(17)
	mcl-PHA	40 °C 15,20 MPa 0.5–3 h	The highest drug content was obtained at 20 MPa after 1 h (90.8 mg/g carrier).	(88)
Cisplatin	CHT-ALG	40 °C 9.9 MPa 2–4 h	60% of drug was released within 2 h following sustained first-order release over 6 h.	(31)
Ketoprofen	PLLA	80, 90 °C 30, 35 MPa 3 h	Process conditions controlled drug loading and the release profile (from 3 days up to 3 months).	(35)
	PLA	35–75 °C 10–30 MPa 6–72 h	Drug release profiles were dependent on the specific pressure and temperature conditions	(42)
Aspirin	PLLA LLDPE	8 °C 30 MPa 3 h	Loading up to 3.4% for PLLA and up to 0.6% for LLDPE with drug release up to 74 days.	(89)
Methotrexate	Acrylic intraocular lenses	35 °C 8–25 MPa 0.5–4 h	Drug release lasted more than 80 days when tested in human donor capsular bags.	(32)
Gemcitabine	PLGA	25, 40 °C 12, 20 MPa 0.5–4h	Release process was controlled by external diffusion, internal mass transfer, and polymer degradation.	(37)
Lansoprazole	HPMC PVP	35–55 °C 15–25 MPa 1–3 h	The best results were obtained after 3 h at 25 MPa and 55 °C with loadings up 1.3%.	(90)
Ketoconazole	PVP	35–55 °C 15–25 MPa 1–3 h	The dissolution rate of poorly water-soluble drug was remarkably enhanced.	(91)
Fenofibrate	Aerosil® 200	45 °C 15 MPa 0.5 h	SSI provided the highest dissolution rate and amorphous drug with 151 nm size.	(92)

MCC– microcrystalline cellulose; mcl-PHA–medium-chain-length Polyhydroxyalkanoates; CHT– chitosan; ALG– alginate; PLLA– poly(L-lactic acid); LLDPE– linear low-density polyethylene; PLGA– poly(lactic-co-glycolic) acid; HPMC– hydroxypropyl methylcellulose ; PVP– polyvinylpyrrolidone.

A variety of polymers, such as polyesters, polysaccharides, cellulose, silicon-based copolymers, polyurethane, etc., have been used as drug carriers. Polysaccharide (starch, alginate, chitosan) aerogels have been regarded as perspective biocompatible and biodegradable carriers for different drugs. Their tailor-made properties enable improved drug pharmacokinetics (38–41). In addition, aerogels are outstanding lightweight materials with high open porosity and surface area, suitable as carriers of high drug amounts that improve drug stability, enhance drug bioavailability, and control drug amorphous form (38). Among biodegradable polymers, poly-l-lactide (PLLA) and poly-d,l-lactide (PDLLA) are the most studied for the development of implants that release drugs in a controlled manner during a prolonged period (42, 43). Drug loading, as well as its release rate from an impregnated polymer, can be easily tuned by adjusting the high-pressure process operating conditions (28–30). Indeed, Champeau et al. (35) confirmed this statement and also showed that drug release could be tuned in the same manner (the release of ketoprofen from sutures varied from 3 days to 3 months due to variations in impregnation conditions).

Methods for micro and nano-particles production

RESS, PGSS, and SAS are the main $scCO_2$-assisted processes for the production of fine powders (22). Conventional processes for powder production, like crushing/milling, crystallization/precipitation, and high-pressure homogenization are still in use (1, 22, 44–47). Typical issues associated with conventional methods for drug particle production are unwanted particle morphologies, undesired amorphous or crystalline forms, long operating time (due to a significant number of grinding, homogenization, and sieving cycles), difficulties associated with nano-sized particles production, adhesion of drug particles to mills/balls/beads, particle agglomeration issues, use of organic solvents, residual solvents and surfactants/stabilizers, energy-consuming drying steps (for wet milling and homogenization methods), thermal and chemical degradation of labile drugs, high or ultra-high pressures requires for homogenization methods (up to 150 or 400 MPa, respectively), etc. (1, 44, 46–48). Supercritical fluid technology for particle formation avoids most of these drawbacks. $ScCO_2$-assisted processes can produce micro/nanoparticles with a narrow size distribution, high purity, controlled morphology, and crystal polymorphism control. Moreover, these techniques can be used for processing thermolabile molecules, can be performed in a single step, and can have an easy downstream operation (18, 22, 49).

Numerous $scCO_2$ techniques have been developed for the production of drug particles as variations of RESS, SAS, and PGSS processes. Some of the variations on the RESS process are the rapid expansion of supercritical solutions into a liquid solvent (RESOLV), into an aqueous solution (RESSAS), with a non-solvent (RESS-N), or with a solid co-solvent (RESS-SC). Other techniques include continuous powder coating and spraying process (CPCSP), gas-assisted melting atomization (GAMA), precipitation by pressure reduction of gas-expanded liquids (PPRGEL), CO_2-assisted nebulization with a bubble dryer (CAN-BD), supercritical-assisted injection in a liquid antisolvent (SAILA), supercritical-assisted atomization (SAA), supercritical-assisted spray-drying (SASD), supercritical-assisted atomization using hydrodynamic cavitation mixer (SAA-HCM),

supercritical-enhanced atomization (SEA), depressurization of an expanded-liquid organic solution (DELOS), and particle formation from gas-saturated solutions with drying (CSS) or concentrated powder form (CPF). The mentioned techniques are described elsewhere (1, 50, 51).

Rapid expansion of supercritical solutions (RESS)

The RESS technique has been developed for the processing of solid solutes that are thermo-labile and require a controlled particle size or particle size distribution (52). The process is performed by introducing $scCO_2$ in a vessel that contains a drug, at pressure and temperature conditions that allow drug dissolution in the supercritical phase. The next step is a fast depressurization or expansion of the obtained solution through a specially constructed nozzle into a vessel that maintains lower pressure (usually atmospheric). This leads to a decreased solubility of the drug, supersaturation, and its precipitation (1, 46, 47, 53). Uniform conditions for particle formation can be reached in the nucleating solution since the pressure reduction during depressurization is a mechanical perturbation traveling at the speed of sound (52). The combination of supersaturation and mechanical perturbation leads to the formation of small drug particles that have a narrow size distribution (46, 47, 52). Several variables can influence the RESS: pressure and temperature in the pre-expansion and post-expansion chamber, residence time, the nozzle geometry, selection of drug, drug concentration, and drug-$scCO_2$ interaction (52, 54). The RESS technique is strongly influenced by the phase behavior of drug-$scCO_2$ and its physicochemical properties (such as interfacial tension), as well as by the specific mechanisms of drug particle nucleation and growth (1). The advantages of RESS technology are the production of high purity particles, semi-continuous processing, easy scalability, low/mild processing temperatures, possibility of nanoparticles formation, controlled recrystallization that can tailor particle morphology, absence of additional washing and drying steps, etc. (1, 46, 54).

Some drugs have low solubility in $scCO_2$, restricting their processing by the RESS technique. However, solubility can be improved by adding solid co-solvents, stabilizers, or surfactants to a drug before the introduction of $scCO_2$ into the system. In addition, the dissolution of a drug in $scCO_2$ could be augmented by the addition of glass/steel beads (to improve fluid flow and buffer turbulent flow) or by using ultrasounds (1, 46). Numerous drugs have been processed using the RESS process. Most articles report the production of single-compound drug particles such as caffeine (55), risocaine (56), mefenamic acid (54), nabumetone (54), paracetamol (54), tolbutamide (54), olanzapine (57), etc. Several drugs and conditions for nanoparticle generation using the RESS technology that have been tested in the last 5 years are listed in Table IV.

Table IV An overview of the RESS technique used for drug processing in the last 5 years

Tabela IV Pregled RESS tehnike upotrebljene za procesiranje lekova u poslednjih 5 godina

Drug	Co-solvent / Carrier	Conditions	Results	Ref
Fenofibrate	Aerosil® 200	45 °C 15 MPa	Improved dissolution rate, amorphous form, 194 nm size drug with 107 m^2/g surface area.	(92)
SRT	/	35–65 °C 20–29 MPa 2.4 L/h	Particle size of 185–842 nm enabled dissolution rates 18 times greater compared to original SRT.	(93)
Aprepitant	Menthol	35–65 °C 15–33 MPa 2.4 L/h	Particle size of 23 nm enabled enhanced dissolution rate by 8.2 folds.	(47)
Letrozole	Menthol	45–75 °C 12–36 MPa 2.4 L/h	Drug solubility was increased 7.1 times. The smallest average particle size was 19 nm.	(94)
Theophylline	/	40–60 °C 14–22 MPa 2.4 L/h	The mean particle sizes were in the range of 200–300 nm.	(95)
Lonidamine	DCM	35–55 °C 10–30 MPa 1 mL/min	Processed drug was amorphous, solubility was improved and in vitro antiproliferative effects enhanced.	(96)
Molsidomine	PAc-β-CD	45–60 °C 34.5 MPa	Increase in temperature and decrease of nozzle diameter increase the average particle size.	(97)

SRT– Sertraline hydrochloride; DCM– Dichloromethane;

PAc-β-CD– peracetyl-β-cyclodextrin

Supercritical antisolvent (SAS)

The SAS technique is the most popular antisolvent method that employs $scCO_2$ as a processing medium for the production of drug nanoparticles (1). It implies the dissolution of a drug in a solvent and contact of the resulting solution with $scCO_2$. The supercritical fluid acts as an anti-solvent for a drug and removes a drug solvent (58). The concentration of a drug in the remaining solvent rises, reaches saturation, and then supersaturation, which leads to drug nucleation and the formation of micro/nanoparticles (53). The SAS technique is more complicated compared with the RESS process due to the involvement of at least three components (drug, organic solvent, and $scCO_2$) in three aggregation states (solid, liquid, gas), which makes the assessment of thermodynamic boundary conditions time consuming and expensive (53).

The choice of the organic solvent for the SAS process is crucial. It has to have good miscibility with the $scCO_2$ at the selected process conditions. Moreover, the drug has to be soluble in the selected solvent, but insoluble in the solution formed by the solvent and

$scCO_2$ (48). One of the most important considerations for the selection of the solvent is human safety. It usually belongs to class 3 (nontoxic) solvent of the pharmaceutical guidelines (22). One of the disadvantages of the SAS process that may arise with the non-adequate selection of solvent is the addition of a residual solvent removal step with the fresh anti-solvent flow. This additional step can be complicated by the drug-solvent affinity leading to drug extraction in some cases (22).

The versatility of SAS ensures the future development of very different types of materials (22). The advantages of this technique include the production of high-purity particles with narrow size distributions, low or mild processing temperatures, and the possibility of nanoparticle formation (<100 nm). Besides, solvent and $scCO_2$ can be recovered and re-used, the process can be easily adapted for continuous operations, and drug recrystallization and particle morphology can be controlled by process variables. SAS process reduces the use of organic solvents compared with traditional solution-based processes, has straightforward production conditions, and enables cost/energy efficiency (1).

Numerous drugs, such as tadalafil (59), ibuprofen (58), azithromycin (60), sirolimus (61), itraconazole (62), etc., have been processed using the SAS technology. It was shown that the particle morphology could be easily tailored by controlling the process pressure, temperature, selection of organic solvent, drug solution concentration, and nozzle geometry (58, 59, 63). Park et al. (59) reported that the mean particle size of tadalafil particles decreased from 900 to 200 nm with a decrease in temperature (from 50 to 40 °C) and drug solution concentration (from 15 to 5 mg/mL). Particle size also decreased with an increase in pressure (from 9 to 15 MPa). Several drugs, carriers, and conditions for particle preparation using SAS that were reported in the last 5 years are listed in Table V.

Table V An overview of the SAS technique used for drug processing in the last 5 years

Tabela V Pregled SAS tehnike upotrebljene za procesiranje lekova u poslednjih 5 godina

Drug	Drug solvent	Carrier	Conditions	Results	Ref
Nimesulide	DCM Methanol	HPMC PVP	40 °C 8 MPa 100 mL/min	Obtained powders were spherical microparticles. Drug completely transformed into amorphous state. Drug yield was 94%. Solubility in PBS increased more than 5-folds.	(63)
GnIH	Ethanol	Pluronic F-127	40 °C 10–18 MPa 30 g/min	Obtained GnIH particles had a generally spherical form. The smallest particle size was 0.2 μm. The highest amount of drug was obtained at pressure of 10 MPa.	(98)
SRT	DMSO	/	40,50 °C 10–20 MPa 3 g/min	Particle size from 115–500 nm. Dissolution rates 50 times higher compared with the original SRT. Chemical structure of drug remained unchanged.	(93)
Prednisolone	Ethanol	PVP	40 °C 9 MPa 440 kg/h	Particles diameters 1–10 μm. Life cycle analysis gave guidelines how to reduce impact by 85.8%.	(85)

Drug	Drug solvent	Carrier	Conditions	Results	Ref
Imiquimod	Acetic acid	/	40–60 °C 12–15 MPa 10–20 mg/mL	An increase concentration and pressure lead to an increase in particle size and a reduction in drug yield. Particles diameters was in the range 6–925 μm. No improvement in drug dissolution rate.	(99)
Glimepiride	DCM	L-arginine	60 °C 120 MPa 30 mL/min	Particles diameters 5–79 μm. Drug solubility increased from 0.6 to 84.2 μm/mL. Glimepiride and L-arginine showed intermolecular interactions.	(100)
Nimesulide Ketoprofen	DMSO	β-CD	40 °C 9–15 MPa 30 g/min	Particle size from 0.3–4.8 μm were obtained. Inclusion complexes with β-CD produced enhanced drug dissolution rate up to 21 times.	(48)
5-fluorouracil	Methanol	urea thiourea	40 °C 7–15 MPa 2.5,5 mg/mL	Drug co-crystals with urea and thiourea were produced. Particles showed the stoichiometric amount of the co-crystal components.	(101)
	DMSO DCM	PLLA	35,50 °C 12–25 MPa 15,20 g/min	Mean particle size of drug was in the range from 220 to 670 nm. Drug loading ranged from 18 to 42% w. Release rate was substantially reduced when compared with the pure drug.	(102)
Tosufloxacin	DCM	HP-β-CD	35–55 °C 8–16 MPa	The optimum conditions for obtaining inclusion complex were pressure 12 MPa, temperature 45 °C, molar ratio 1:1, and mixed solvent 20% DCM resulting in the efficiency of 15%.	(103)
Ivermectin	Acetone	PMMA	40,50,60 °C 9,10,11 MPa 20 mg/mL	The encapsulation efficiency was 73%.The in vitro release kinetics showed controlled release of approximately 100 h. Mean particle size ranged from 60.6 to 167.2 nm.	(104)
Fisetin	Ethanol DCM	PVP	45 °C 10 MPa 35 g/min	Drug release as well as in vitro cytotoxicity evaluations indicated augmented performance efficiency compared to the free drug. Mean particle size ranged from 71.7 to 357.4 nm.	(105)
Cetirizine Ketotifen	DMSO	Zein	40,45,50 °C 9 MPa 50 mg/mL	Drug release was significantly prolonged. Mean particle size was in the range from 0.7 to 8.8 μm.	(106)
Diclofenac	DMSO	Zein	35–60 °C 8.5–15 MPa 5–50 mg/mL	Particles having mean diameter from 0.1– 3.0 μm were obtained. At zein/diclofenac sodium 30/1 ratio, a successful co-precipitation that results in a prolonged drug release can be achieved.	(107)

DCM– Dichloromethane; HPMC– hydroxypropyl methylcellulose; PVP– polyvinylpyrrolidone; GnIH– gonadotrophin inhibitory hormone; SRT– Sertraline hydrochloride; DMSO– dimethylsulfoxide; CD– cyclodextrin; PLLA– poly(Llactide); HP-β-CD– hydroxypropyl-β-cyclodextrin; PMMA– poly(methyl methacrylate).

Particles from gas-saturated solutions (PGSS)

The PGSS process implies the formation of particles from a melt or a solution using $scCO_2$. Firstly, substances intended for pulverizing are melted or dissolved (in an extruder or a vessel) and transferred using a dosing system to a static mixer. Secondly, compressed CO_2 is pumped into the same static mixer where both flows are homogenized. Finally, a

gas-saturated solution is depressurized through a nozzle into a spray tower (22, 64, 65). Usually, pressures in front of the nozzle are in the range of 10 to 35 MPa, while the pressure in the spray tower is ambient. The nozzle construction enables the formation of fine droplets, which are solidified due to the cooling effect of the expanding gas. In the end, the obtained fine powder is separated from the gas CO_2 (64). High concentrations of $scCO_2$ in the liquefied drug/polymer phase lead to a significant reduction of melt/solution viscosity and interfacial tension. This helps with the spraying of substances that are hardly or even not sprayable under conventional conditions (53). The advantages of the PGSS technology compared with conventional ones for particle formation include the production of amorphous particles with high purity and high encapsulation/co-precipitation efficiencies that are solvent-free. Particles can be produced at moderate pressures and low/mild processing temperatures, solvents (when used) can be recovered and re-used, and $scCO_2$ can be rapidly removed without lengthy drying steps. In addition, lower amounts of $scCO_2$ are usually required, smaller volume vessels are needed, and scale-up of the process is relatively easy (1, 66).

Although research interest in the last years has shifted towards the development of particles from waxes, plant extracts, extract components, and supplements using the PGSS technology (67–79), there are reports in the available literature on the development of drug particles that are listed in Table VI. Usually, produced drug particles consist of two (44, 45, 80, 81) or several compounds (82, 83). The size of the particles and controlled release of a drug can be tailored by variations in pressure, temperature, and nozzle diameter. For example, particles containing drugs with a diameter from 20 nm (44) to 1423 μm (80) can be obtained by the PGSS technique.

Table VI An overview of the PGSS technique used for drug processing

Tabela VI Pregled PGSS tehnike upotrebljene za procesiranje lekova

Drug	Carrier	Conditions	Results	Ref
Nimodipine Fenofibrate	Brij S100 PEG 4000	60 °C 10–25 MPa 1 h	Mean particle size 45.5–70.6 μm. The loading efficiency up to 99%.	(49)
Lidocaine	GMS 40-55 type II	67 °C 17 MPa 1 h	Particle diameter was 20–120 μm. Encapsulation efficiency (70–79%). Drug content (0.7–7.5 wt.%).	(108)
Ibuprofen	PEG 6000	50–80 °C 10–25 MPa	Spherical drug nanoparticles with diameter of 20–500 nm. Faster dissolution of the ibuprofen nanoparticles compared with the raw material	(44)
Caffeine	Lumulse GMS K	62 °C 13 MPa	Mean particle size 5.5 μm. Particles were loaded with 140 mg of caffeine/g of particle.	(45)
Fenofibrate	Gelucire® 50/13	50 °C 8 MPa 15 min	Mean particle size 1.4–1423.3 μm. Drug content 90.0–100%. Bulk density 0.12–0.30 g/cm^3.	(80)

Drug	Carrier	Conditions	Results	Ref
Nifedipine	PEG 4000	50–185 °C 12–19 MPa	Mean particle size 15–30 μm. Enhanced dissolution rate with no degradation products.	(81)
Caffeine Ketoprofen	Lumulse® GMS-K, WTG Cutina® HR, s-TiO_2	72 °C 13 MPa 1 h	Encapsulation efficiency of caffeine was small. Ketoprofen had sustained release. Particles were loaded with s-TiO_2 and caffeine, glutathione or ketoprofen in percentages of 4.2, 5.6 and 16.1 wt% for the respective drugs.	(82)
Ibuprofen	Pluronic® F127, L64, Gelucire® 43-01, Lumulse® GMS-K	40–62 °C 10–20 MPa 30 min	Mean particle size 40–220 μm. Drug encapsulation efficiencies up to 90%. Poloxamer carrier provided an increased solubility of ibuprofen, while Gelucire® and GMS provided a slower, controlled release of the drug.	(83)

Brij S100– Polyoxyethylene (100) stearyl ether; PEG–Polyethylene glycol; GMS– glyceryl monostearate; WTG– waxy triglyceride; sTiO_2– silanized TiO_2.

Future perspectives

The application of $scCO_2$ for drug processing has been under investigation since the 1990s (1, 84). After decades of active research and process development, $scCO_2$ technologies are reaching maturity. It is expected that very soon drug formulations processed by $scCO_2$ or produced by mentioned $scCO_2$ processes are likely to appear on the market. Although $scCO_2$ technologies still undergo fundamental and applied advanced research, several controversial issues remain, such as high-pressure process thermodynamics and mass transfer in supercritical systems (53). This includes the influence of operating parameters on the properties of the processed drug (size, morphology, polymorphism, dissolution, and release), nucleation phenomenon, crystal growth, particle agglomeration, as well as comprehension of the process dynamics, the process scaling up, etc. Described $scCO_2$ technologies for drug processing can be relatively easily transferred from a lab-scale up to an industrial scale (especially PGSS) (53) because operating conditions and parameters can be easily optimized to facilitate the process scaling up (84). Besides, advances in scaling-up and high-pressure plant design for continuous operation, coupled with modeling/prediction of thermo-physical properties, strengthen comprehensive approaches to industrial production of drug formulation using $scCO_2$ (1). Furthermore, capital costs for the high-pressure equipment and $scCO_2$ processes compliance with GMP guidelines are not real obstacles for the pharmaceutical industry that is used to dealing with them. Large-scale units that employ $scCO_2$ have been successfully working for decades in the food and textile industry. Therefore, it is only a matter of time when the pharmaceutical industry will use the capabilities and advantages offered by these $scCO_2$ technologies. This transfer of technology could be accelerated by establishing more specific and technology-oriented collaborations between the pharmaceutical industry and academia (specifically with researchers working on a lab-scale with these technologies and drugs). One of the

approaches that could ease the scale-up is the evaluation of the quantitative impacts of processes and products through the life cycle assessment (LCA) (85). LCA analysis of $scCO_2$ processes could evaluate all phases of the production process that have a significant impact on the environment. It can be used to optimize the production parameters to improve environmental sustainability, as well as the economics of the process. In addition, the emergence of several companies as service providers that offer scale-up studies, the production of drug clinical batches that are required for clinical studies, and even the production of commercial batches, significantly contribute to the transition of $scCO_2$ technologies from a laboratory to an industry (84). The existence of these companies allows the development of a new drug formulation without requiring high-pressure unit investment costs.

Conclusion

Supercritical CO_2 ($scCO_2$) technologies have made significant progress in recent years regarding the development of lower-cost industrial units, as well as new scientific reports on drug-$scCO_2$-polymer interactions. Combining this with the concepts of "green chemistry" and "sustainable technology" contributes greatly to making the potential pharmaceutical industrial applications of $scCO_2$ technologies closer than ever. The most commonly used $scCO_2$ technologies for the processing of drugs on a laboratory scale are the production of solid dispersion, polymer impregnation with drugs, and drug micro/nanoparticle production. It has been proven numerous times that these processes are more efficient and have a large number of advantages when compared with conventional methods for the preparation of drug formulations. Therefore, it can be concluded that $scCO_2$ technologies have a promising future and can be easily foreseen for a number of industrial pharmaceutical applications. The most important application of $scCO_2$ technologies is the development of new formulations that enhance the bioavailability of a drug, ease its delivery, and enable its controlled release.

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Pregled mogućnosti primene natkritičnog ugljenik(IV)-oksida u proizvodnji lekova

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Kratak sadržaj

Primena natkritičnog ugljenik(IV)-oksida ($nkCO_2$) u farmaceutskoj industriji je još uvek nerazvijena, bez obzira na značajan istraživački interes za ovaj procesni medijum pokazan u poslednjim decenijama. $NkCO_2$ tehnologije mogu poboljšati rastvorljivost lekovite supstance, njenu bioraspoloživost i terapijski učinak. Ove tehnologije mogu dovesti do razvoja novih formulacija koje će doprineti smanjenju doze leka, učestalosti uzimanja leka i poboljšati dobrobit pacijenata. S obzirom na značajno smanjenje cene opreme za rad pod visokim pritiscima i sve veću potrebu društva za čistijom proizvodnjom i sigurnijim proizvodima, očekuje se da će uskoro doći do simbioze između natkritičnih i farmaceutskih tehnologija. Stoga je ovaj pregledni rad bio fokusiran na najnovije doprinose $nkCO_2$ tehnologija farmaceutskoj oblasti. Glavni cilj bio je približiti ove tehnologije farmaceutskim stručnjacima. U tu svrhu objašnjene su i diskutovane najčešće korišćene tehnologije: priprema čvrstih disperzija, impregnacija polimera lekovitim supstancama i proizvodnja mikro/nanočestica lekovitih supstanci upotrebom $nkCO_2$.

Ključne reči: natkritični CO_2, čvrsta disperzija, natkritična impregnacija, generisanje čestica