WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 2, 1922-1931. **Review Article** ISSN 2277– 7105

SUPERCRITICAL FLUID TECHNOLOGY: A REVIEW

***Anuru Sen and Dr. Dhrubo Jyoti Sen**

Department of Pharmaceutical Chemistry, School of Pharmacy, Techno India University,
Salt-Lake City, Sector-V, EM-4, Kolkata-700091, West Bengal, India.

Article Received on
21 Dec. 2021,
Revised on 11 January 2022,
Accepted on 01 Feb. 2022
DOI: 10.20959/wjpr20222-23185

***Corresponding Author**
Anuru Sen
Department of
Pharmaceutical Chemistry,
School of Pharmacy,
Techno India University,
Salt-Lake City, Sector-V,
EM-4, Kolkata-700091,
West Bengal, India.

ABSTRACT

Supercritical fluid technology. Supercritical fluid technology is commonly utilized to prepared nanoparticles from drug solutions. The various methods including the supercritical solution process (RESS), the supercritical antisolvent process and precipitation with compressed antisolvent process (PCA) can be utilized. Unlabelled: 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. 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.

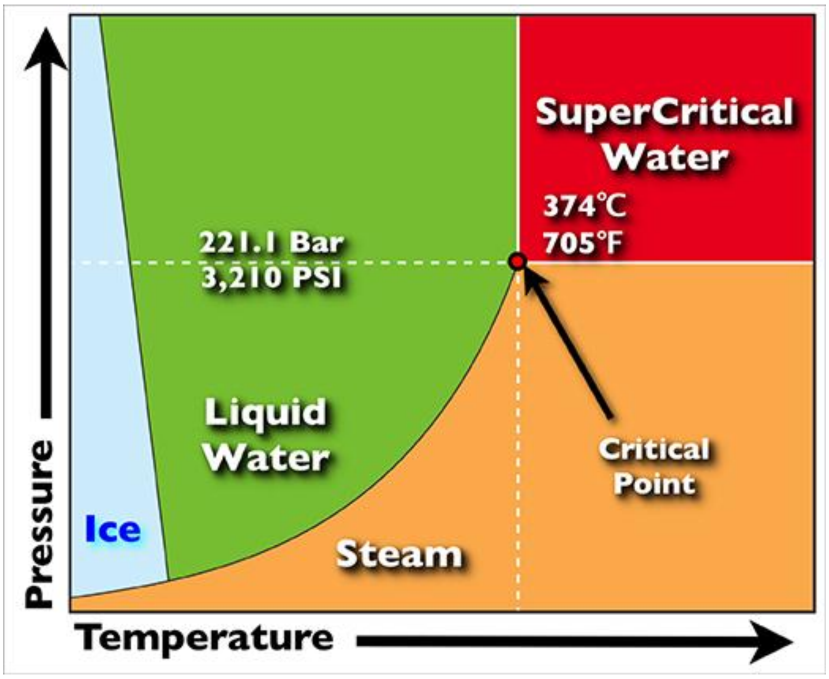
KEYWORD: Supercritical fluid, nanoparticles, drug delivery, carbon dioxide, Antisolvent, particle size.

INTRODUCTION

Supercritical fluid technology is **commonly utilized to prepared nanoparticles from drug solutions**. The various methods including the supercritical solution process (RESS), the supercritical antisolvent process and precipitation with compressed antisolvent process (PCA) can be utilized.

A **supercritical fluid** (**SCF**) is any substance at a temperature and pressure above its critical point, where distinct liquid and gas phases do not exist, but below the pressure required to compress it into a solid. It can effuse through porous solids like a gas, overcoming the mass transfer limitations that slow liquid transport through such materials. SCF are much superior to gases in their ability to dissolve materials like liquids or solids. In addition, close to the critical point, small changes in pressure or temperature result in large changes in density, allowing many properties of a supercritical fluid to be "fine-tuned".

Supercritical fluids occur in the atmospheres of the gas giants Jupiter and Saturn, the terrestrial planet Venus, and probably in those of the ice giants Uranus and Neptune. Supercritical water is found on Earth, such as the water issuing from black smokers, a type of underwater hydrothermal vent. They are used as a substitute for organic solvents in a range of industrial and laboratory processes. Carbon dioxide and water are the most commonly used supercritical fluids; they are often used for decaffeination and power generation, respectively.



Examples of supercritical fliud are- Many pressurized gases are actually supercritical fluids. For example, **nitrogen** has a critical point of 126.2 K (−147 °C) and 3.4 MPa (34 bar). Therefore, nitrogen (or compressed air) in a gas cylinder above this pressure is actually a supercritical fluid. These are more often known as permanent gases.

PROPERTIES OF SUPERCRITICAL FLUID

A supercritical fluid is a substance with **both gas-and liquid-like properties**. It is gas-like in that it is a compressible fluid that fills its container, and is liquid-like in that it has comparable densities (0.1–1 g ml^{-1}) and solvating power.

The properties between those of a liquid and gas and do not have surface tension

Supercritical fluids are useful in the precipitation of micro- to nanorange of particles in pure and encapsulated forms. Carbon dioxide is most widely utilized supercritical fluid. There is no surface tension in a supercritical fluid, as there is no liquid/gas phase boundary. By changing the pressure and temperature of the fluid, the properties can be "tuned" to be more liquid-like or more gas-like. One of the most important properties is the solubility of material in the fluid. Solubility in a supercritical fluid tends to increase with density of the fluid (at constant temperature). Since density increases with pressure, solubility tends to increase with pressure. The relationship with temperature is a little more complicated. At constant density, solubility will increase with temperature. However, close to the critical point, the density can drop sharply with a slight increase in temperature. Therefore, close to the critical temperature, solubility often drops with increasing temperature, then rises again.

Table 1: Critical properties of various solvents.

Solvent	Molecular mass	Critical temperature	Critical pressure	Critical density
	g/mol	K	MPa (atm)	g/cm^3
Carbon dioxide (CO_2)	44.01	304.1	7.38 (72.8)	0.469
Water (H_2O)†	18.015	647.096	22.064 (217.755)	0.322
Methane (CH_4)	16.04	190.4	4.60 (45.4)	0.162
Ethane (C_2H_6)	30.07	305.3	4.87 (48.1)	0.203
Propane (C_3H_8)	44.09	369.8	4.25 (41.9)	0.217
Ethylene (C_2H_4)	28.05	282.4	5.04 (49.7)	0.215
Propylene (C_3H_6)	42.08	364.9	4.60 (45.4)	0.232
Methanol (CH_3OH)	32.04	512.6	8.09 (79.8)	0.272
Ethanol (C_2H_5OH)	46.07	513.9	6.14 (60.6)	0.276
Acetone (C_3H_6O)	58.08	508.1	4.70 (46.4)	0.278
Nitrous oxide (N_2O)	44.013	306.57	7.35 57	0.425

MIXTURE

supercritical fluids are completely miscible with each other, so that a binary mixture forms a single gaseous phase if the critical point of the mixture is exceeded. However, exceptions are known in systems where one component is much more volatile than the other, which in some cases form two immiscible gas phases at high pressure and temperatures above the component critical points. This behavior has been found for example in the systems N_2-NH_3, NH_3-CH_4, SO_2-N_2 and n-butane-H_2O.[7]

The critical point of a binary mixture can be estimated as the arithmetic mean of the critical temperatures and pressures of the two components,

$$T_{c(mix)} = \chi_A \times T_{c(A)} + \chi_B \times T_{c(B)}$$

where χ_i denotes the mole fraction of component i.

For greater accuracy, the critical point can be calculated using equations of state, such as the Peng-Robinson, or group-contribution methods. Other properties, such as density, can also be calculated using equations of state.

SUPERCRITICAL CO2

Carbon dioxide (CO_2) is the most widely used supercritical fluid. This is because CO_2 is cheap, chemically inert, non-toxic, non-flammable and readily available at high purities and at low costs. Besides, the critical point of CO_2 is easily accessible (critical temperature 31°C and critical pressure 74 bar) allowing the fluid to be used at mild conditions of temperatures (40-60°C) without leaving harmful organic residues. Due to its interesting properties Supercritical CO_2 can be described as a "green" solvent.

PHASE DIAGRAM OF SUPERCRITICAL FLUID

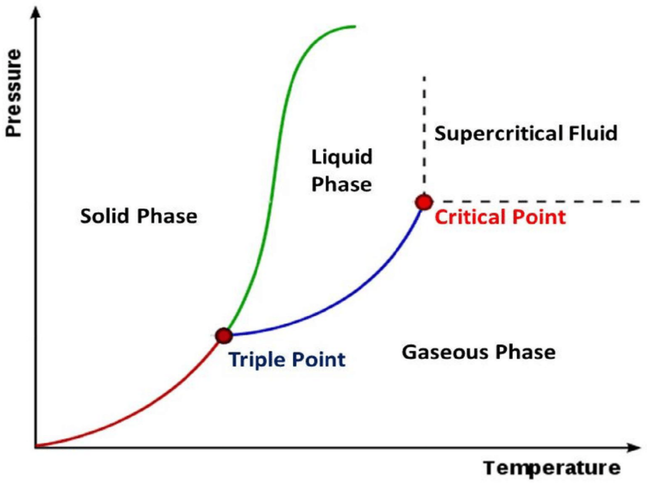
The two-dimensional projections of a phase diagram. In the pressure-temperature phase diagram. the boiling curve separates the gas and liquid region and ends in the critical point, where the liquid and gas phases disappear to become a single supercritical phase. The appearance of a single phase can also be observed in the density-pressure phase diagram for carbon dioxide. At well below the critical temperature, e.g., 280 K, as the pressure increases, the gas compresses and eventually (at just over 40 bar) condenses into a much denser liquid, resulting in the discontinuity in the line (vertical dotted line). The system consists of 2 phases in equilibrium, a dense liquid and a low density gas. As the critical temperature is approached (300 K), the density of the gas at equilibrium becomes higher, and that of the liquid lower. At the critical point, (304.1 K and 7.38 MPa (73.8 bar)), there is no difference in density, and the 2 phases become one fluid phase. Thus, above the critical temperature a gas cannot be liquefied by pressure. At slightly above the critical temperature (310 K), in the vicinity of the critical pressure, the line is almost vertical. A small increase in pressure causes a large increase in the density of the supercritical phase. Many other physical properties also show large gradients with pressure near the critical point, e.g. viscosity, the relative permittivity and the solvent strength, which are all closely related to the density. At higher temperatures, the fluid starts to behave more like an ideal gas, with a more linear density/pressure relationship. For carbon dioxide at 400 K, the density increases almost linearly with pressure.

Many pressurized gases are actually supercritical fluids. For example, nitrogen has a critical point of 126.2 K (−147 °C) and 3.4 MPa (34 bar). Therefore, nitrogen (or compressed air) in a gas cylinder above this pressure is actually a supercritical fluid. These are more often known as permanent gases. At room temperature, they are well above their critical temperature, and therefore behave as a nearly ideal gas, similar to CO_2 at 400 K above.

However, they cannot be liquified by mechanical pressure unless cooled below their critical temperature, requiring gravitational pressure such as within gas giants to produce a liquid or solid at high temperatures. Above the critical temperature, elevated pressures can increase the density enough that the SCF exhibits liquid-like density and behaviour. At very high pressures, an SCF can be compressed into a solid because the melting curve extends to the right of the critical point in the P/T phase diagram. While the pressure required to compress supercritical CO_2 into a solid can be, depending on the temperature, as low as 570 MPa, that required to solidify supercritical water is 14,000 MPa.

The Fisher-Widom line, the Widom line, or the Frenkel line are thermodynamic concepts that allow to distinguish liquid-like and gas-like states within the supercritical fluid.

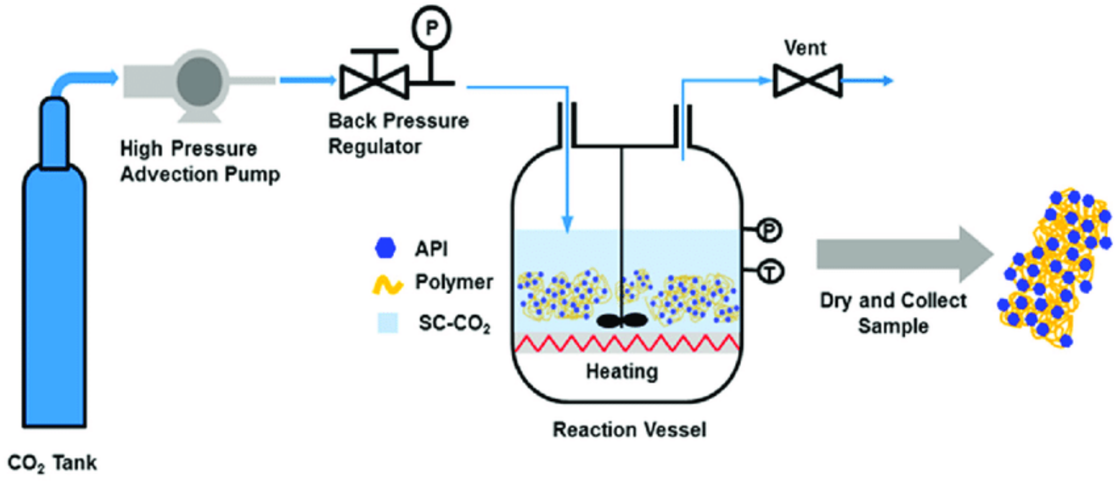
In recent years, a significant effort has been devoted to investigation of various properties of supercritical fluids. This has been an exciting field with a long history since 1822 when Baron Charles Cagniard de la Tour discovered supercritical fluids while conducting experiments involving the discontinuities of the sound in a sealed gun barrel filled with various fluids at high temperature. More recently, supercritical fluids have found application in a variety of fields, ranging from the extraction of floral fragrance from flowers to applications in food science such as creating decaffeinated coffee, functional food ingredients, pharmaceuticals, cosmetics, polymers, powders, bio- and functional materials, nano-systems, natural products, biotechnology, fossil and bio-fuels, microelectronics, energy and environment. Much of the excitement and interest of the past decade is due to the enormous progress made in increasing the power of relevant experimental tools. The development of new experimental methods and improvement of existing ones continues to play an important role in this field, with recent research focusing on dynamic properties of fluids.



APPLICATION FOR SUPERCRITICAL FLUID

Supercritical fluids have been applied to **mass-transfer processes, phase-transition processes, reactive systems, materials-related processes, and nanostructured materials**. Some applications are already at industrial capacity, whereas others remain under development.

Extraction of bioactive species from various plant matrices by means of supercritical fluids has been widely investigated during the last few decades. In this chapter, recent advances of mass transfer models for representing kinetics of supercritical fluid extraction processes have been summarized. The mass transfer models reviewed here include the most successful broken and intact cell model, the shrinking core model, the microstructured mathematical model, the heat analogue diffusion model and other relatively simple models. Supercritical fluid extraction of botanical matters may be influenced by the solute solubility limitation, solute–solid interactions, solid phase mass transfer coefficient and fluid phase mass transfer coefficient, along with axial dispersion coefficient. Due to the limitations arising from complicated microstructures of plant matrices, sample pretreatments and optimization methods, further attempts are still requiring for developing theoretical mass transfer models for scaling-up and commercialization design of kinetic supercritical fluid extraction processes. **phase-transition processes-**During the supercritical process, heat and pressure are applied to carbon dioxide gas. When the supercritical point is reached, **carbon dioxide gas changes from a liquid** to a supercritical phase. The substance proposed to convert in nanoparticle is dissolved in the supercritical carbon dioxide.



CONCLUSION

Supercritical fluid reaction has been shown to have several advantages compared to conventional catalytic reaction in biodiesel production. The **absence** of catalysts in supercritical-based reaction simplifies the reaction route and downstream processes significantly.

REFFERNCES

1. Marre S, Roig Y, Aymonier C. (2011) Supercritical microfluidics: Opportunities in flow-through chemistry and materials science. , *J. Supercrit. Fluids, Inpress.*
2. I M Al-fagih, F K Alanazi, G A Hutcheon, I Y Saleem. (2011) Recent Advances Using Supercritical Fluid Techniques for Pulmonary Administration of Macromolecules via Dry
3. J F Brennecke, C A Eckert. (1989) Phase Equilibria for Supercritical Fluid Process Design, & quot;., *Am. Inst. Chem. Eng. J.*, 35: 1409-1427.
4. Yasuji T, Takeuchi H, Kawashima Y. (2008) Particle design of poorly water-soluble drug substances using supercritical fluid technologies. Adv. Drug Deliv. Rev., 60: 388-398.
5. P J Sinko.Martin’s physical pharmacy and pharmaceutical sciences; physical chemical and biopharmaceutical principles. *in the pharmaceutical sciences, 5th ed.; Lippincott Williams and Wilkins: 351 West Camden, street Baltimore, MD.*
6. Vasukumar K, K A Bansal. (2003) Supercritical fluid technology in pharmaceutical research., *Curr. Res. Infor. Pharm. Sci.*, 4: 8-12.
7. W J Schmitt, Reid R C. (1986) The use of entrainers in modifying the solubility of phenanthrene and benzoic acid in supercritical carbon dioxide and ethane. Fluid Phase Equilibria, 32: 77-99.
8. Brunner E J Chem Thermochim, 1985; 17: 672-679.

9. Pasquali I, Bettini R, Giordano F. (2008) Supercritical fluid technologies: An innovative approach for manipulating the solid-state of pharmaceuticals. , *Adv. Drug Deliv. Rev.*, 60: 399-410.
10. Reverchon E, Adami R. (2006) Nanomaterials and supercritical fluids. , *J. Supercrit. Fluids,* 37: 1-22.
11. E M Phillips, V J Stella. (1993) Rapid expansion from supercritical solutions: application to pharmaceutical processes. , *Int. J. Pharm,* 94: 1-10.
12. Kayrak D, Akman U, Hortacsu O. (2003)., *Micronisation of ibuprofen by RESS.J. Supercrit. Fluids,* 26: 17-31.
13. Jung J, Perrut M. (2001) Particle design using supercritical fluids: literature and patent survey. , *J. Supercrit. Fluids,* 20: 179-219.
14. Date A A, Patravale V B. (2004) Current strategies for engineering drug nanoparticles., *Curr. Opin. Colloid Interface Sci.,* 9: 222-235.
15. Reverchon E, Pallado P. (1996) Hydrodynamic modeling of the RESS process., *J. Supercrit. Fluids,* 9: 216-221.
16. York P. (1999) Strategies for particle design using supercritical fluid technologies. *Pharm. Sci. Technolo. Today,* 2: 430-440.
17. Thakur R, R B Gupta. (2006) Formation of phenytoin nanoparticles using rapid expansion of supercritical solution with solid cosolvent (RESS-SC) process., *Int. J. Pharm, 308: 190-199.*
18. Domingo C, F E Wubbolts, Rodríguez-Clemente R, Rosmalen G M V. (1999) Solid crystallization by rapid expansion of supercritical ternary mixtures. , *J. Cryst. Growth, 198:* 760-766.
19. Chen A-Z, Zhao Z, Wanga S-B, Li Y, Zhao C et al. (2011) A continuous RESS process to prepare PLA–PEG–PLA microparticles., *J. Supercrit. Fluids,* 59: 92-97.
20. A H-J Chiou, Yeh M-K, Chen C-Y, Wang D-P. (2007) Micronization of meloxicam using a supercritical fluids process., *J. Supercrit. Fluids,* 42: 120-128.
21. Weidner E, Petermann M, Knez Z. (2003) Multifunctional composites by high-pressure spray processes., *Curr. Opin. Solid State Mater. Sci.,* 7: 385-390.
22. Almeida A J, Souto E. (2007) Solid lipid nanoparticles as a drug delivery system for peptides and proteins. Adv. Drug Deliv. Rev., 59: 478-490.
23. M J, Pathak P, Beacham F, L F Allard, Sun Y-P. (2005) Nanoparticle formation in rapid expansion of water-in-supercritical carbon dioxide microemulsion into liquid solution., *J. Supercrit. Fluids,* 34: 91-97.

24. Reverchon E, Adami R. (2006) Nanomaterials and supercritical fluids., *J. Supercrit. Fluids*, 37: 1-22.