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Supercritical Fluid Technology: Green Chemistry for the 21st Century

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ABSTRACT

A supercritical fluid has both the gaseous property of being able to penetrate anything, and the liquid property of being able to dissolve materials into their components. In addition, it offers the advantage of being able to change density to a great extent in a continuous manner. On this account, use of carbon dioxide or water in the form of a supercritical fluid offers a substitute for an organic solvent. Supercritical fluids provide exciting opportunities to the scientists, as they cater to various processing needs. They can be applied in a number of fields such as drug delivery, chromatography, synthesis, purification, extraction, etc.

Key words: *Supercritical fluids, chromatography, synthesis, purification, extraction.*

INTRODUCTION

The Green Chemistry program of the Environmental Protection Agency (EPA) was recently created to support benign by design principles in the design, manufacture, and use of chemicals and chemical processes [1].This Design for the Environment (DfE) program features R & D efforts related to innovative technologies, in order to assist industries with the development of environmentally benign products and processes. Such an initiative harmonizes with the Pollution Prevention Act of 1990 that was created to focus on source reduction of pollutants; a concept that is often overlooked due to the industrial focus on waste management and pollution control. In 1992, the EPA's Office of Pollution Prevention and Toxics (OPPT) teamed up with the National Science Foundation (NSF) to jointly fund worldwide green chemistry research. Since its inception in 1977, the OPPT has been responsible for assuring that chemicals for use or sale do not pose any adverse effects to human health or the environment. To date, the OPPT-NSF partnership has awarded tens of millions of dollars in the form of grants for fundamental research in green chemistry to groups throughout the world [2].Much of the recent funding has been directed to research that exploits the unique properties of supercritical fluids (SCFs), as a alternative to traditional solvents.

Under the Federal Resource Conservation and Recovery Act (RCRA), industries that use organic solvents must comply with strict regulations concerning on-site storage, recycling/disposal, and off-site waste transport.3 Together with the Federal Clean Air Act (CAA), these regulations are intended to suppress pollution that would occur through excessive solvent evaporation, or improper disposal to contaminate soil and/or water resources. It would be an extremely attractive proposition to have media that would serve as a versatile solvent, without carcinogenic properties or the potential for environmental degradation. Indeed, this goal has been brought to fruition with the advent of supercritical fluid technology [3].

Supercritical fluids possess properties that are intermediate between liquids and gases. This unique phase is obtained through the exertion of pressures and temperatures greater than the critical point (**Fig. 1**). Near the critical point of fluid, minute changes in pressure or temperature significantly alters the physico-chemical properties of the SCF (e.g., density, diffusivity, or solubility characteristics). This is especially important for synthetic applications, where reaction conditions (e.g., selectivities, rates, pathways) may be sensitively manipulated. Such reaction control is impossible using traditional organic-based solvents. Further, due to the deleterious effects that many organic solvents have on the environment and/or one's health, media such as halogenated hydrocarbons (e.g., chloroform, dichloromethane) are being phased out of use, and benign replacements are being developed. Supercritical carbon dioxide (sc-CO2) is an attractive alternative, since it is extremely inexpensive and poses no threat to the environment or human health. However, depending on the application, a variety of other SCFs may be more attractive; **Table 1** lists common fluids that have been utilized for applications as diverse as extraction/chromatography, inorganic/organic synthesis, catalysis, materials processing, and even dry-cleaning [4].

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Supercritical Fluids:

A supercritical fluid has both the gaseous property of being able to penetrate anything, and the liquid property of being able to dissolve materials into their components. In addition, it offers the advantage of being able to change density to a great extent in a continuous manner. On this account, use of carbon dioxide or water in the form of a supercritical fluid offers a substitute for an organic solvent [5]. Supercritical fluids provide exciting opportunities to the scientists, as they cater to various processing needs. They can be applied in a number of fields such as drug delivery, chromatography, synthesis, purification, extraction, etc.

The critical properties of various solvents are shown in **Table 1**. **Fig. 1** shows the region for supercritical fluids.

Table No. 1: Critical properties of various solvents

Fluid	Critical Temperature (K)	Critical Pressure (bar)
Carbon dioxide	304.1	73.8
Ethane	305.4	48.8
Ethylene	282.4	50.4
Propane	369.8	42.5
Propylene	364.9	46.0
Trifluoromethane (Fluoroform)	299.3	48.6
Chlorotrifluoromethane	302.0	38.7
Trichlorofluoromethane	471.2	44.1
Ammonia	405.5	113.5
Water	647.3	221.2
Cyclohexane	553.5	40.7
n-Pentane	469.7	33.7
Toluene	591.8	41.0

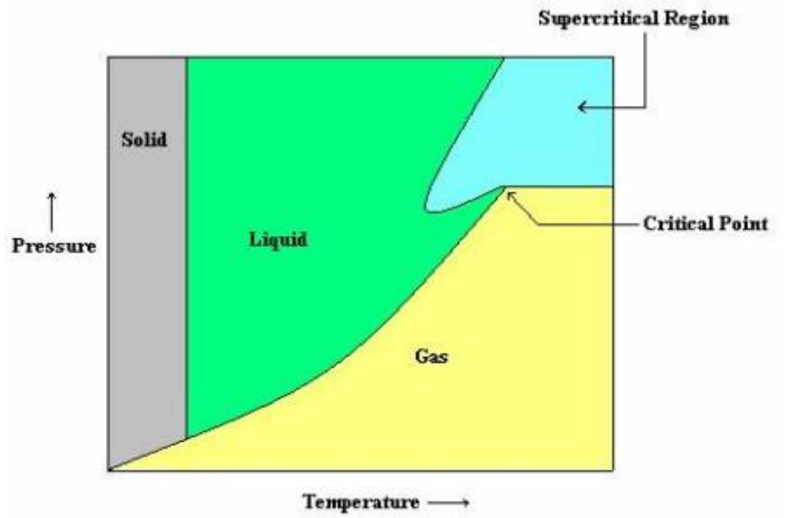

Fig. 1: Phase Diagram showing Supercritical Region

Applications of Supercritical Fluid Technology:

1. ***Drug Delivery:***

- **Particle Size Reduction of Drugs:**

Supercritical fluid technology provides a better control over the particle size distribution and morphology, which makes this technology advantageous compared with conventional techniques [6, 7]. A comparison of supercritical fluid particle designs technology with conventional technology is shown in **Table 2**.

Table No. 2: Comparison of Supercritical Fluid Particle Designs Technology with Conventional Techniques

Methods	Nanoparticles	Crystallanity	Size Distribution	Residual Solvent	Encapsulation
Spray Drying	Irregular	Amorphous	Broad	Yes	May be
Milling	Yes	Irregular	Broad	Yes	No
Coacervation	No	Depends	Broad	Yes	Yes
Solvent Evaporation	Yes	Depends	Broad	Yes	May be
Lyophilization	No	Depends	Broad	Yes	No
RESS (Rapid expansion of supercritical solutions)	Yes	Depends	Narrow	No	Yes
SAS/PCA (Supercritical Anti-solvent/ Precipitation using Compressed Antisolvent)	Difficult	Crystalline (tunable)	Narrow	No	Yes
SAS-EM TM(Supercritical Anti-solvent with Enhanced Mass Transfer)	Yes	Crystalline (tunable)	Narrowest	No	Yes

i. Particulate Dosage Forms:

At certain pressures some gases cause swelling of polymers like polypropylene, polyethylene, or drug carriers, and allow migration of active material in polymer matrix to give diffusion-controlled drug delivery systems. This type of behavior can be exploited for various purposes replacing the spray drying, solvent evaporation and freeze-drying. This solvent-free approach can be utilized to develop novel drug delivery systems and deposit thermolabile materials such as peptide drugs into the polymers [8].

ii. Particle Coating:

The supercritical fluid technology is also applied for particulate coating to replace traditional methods. Solubilization of coating component is done beforehand in the supercritical fluid, and contact with the powder is done in a chamber similar to fluid bed dryer.

iii. Micelle and Microemulsions:

Microemulsions formed in liquid and supercritical CO_2 have emerged as a new type of solvent for industrial-scale processes. Such w/o microemulsions have potential applications in reaction or separation processes where the high diffusivities and strongly pressure-dependent phase behavior of the fluid combined with the capability to solubilize highly polar or ionic solutes may be used to significant advantage [9].

iv. Amorphous Drug Preparation:

Supercritical fluids technology to improve the solubility of a poorly soluble drug and handling of highly brittle crystalline excipients is to convert them to amorphous or non-crystalline forms.

v. Materials Processing:

Use of a supercritical fluid will make it possible to manufacture specially structured products and high-functional, high-quality materials, which are difficult to produce with conventional manufacturing methods. Examples are fine-graining, thin-filming, fiber refining using the RESS method, as in the manufacture of whisker-shaped fine particles.

2. Supercritical Fluid Chromatography:

One of the most successful application areas of supercritical fluids and a commonly used analytical technique for the separation and analysis of drug molecules is supercritical Fluid Chromatography (SFC). For drug analysis, SFC is useful when the solute can be dissolved in a supercritical fluid and has a high diffusion coefficient. Multiple gradients can be used in contrast to gas chromatography (GC) and high-performance liquid chromatography (HPLC) methods. Various factors to be considered for SFC and so, proper selection of pressure, temperature, pressure reduction ratio, density or co-solvent and solvent gradients is important for optimized separation and analysis [10].

3. Supercritical Fluid Extraction:

Principle of Supercritical Fluid Extraction (SFE) is that when the feed material is contacted with a supercritical fluid than the volatile substances will partition into the supercritical phase. After the dissolution of soluble material in supercritical fluid, the dissolved substance is removed from the feed material. Then the extracted component is completely separated from the supercritical fluid by means of a temperature and/or pressure change. The supercritical fluid is then may be recompressed to the extraction conditions and recycled. CO_2 is the most widely used fluid in SFE. Beside CO_2, water is the other applied solvent. Various applications of supercritical fluid extraction are shown in **Table 3**.

Table No. 3: Applications of Supercritical Fluid Extraction

Fields	Applications
Pharmaceuticals	Particle formation Extraction of biologically active ingredients Fermentation broth extraction Protein purification
Neutraceuticals	Vitamin extraction Anti-oxidant extraction Concentration of active ingredients
Chemistry	Precision machined components Silicon wafers Medical implants Electronic components
Polymers	Flavor extraction and concentration Extraction of fragrance Processing essential oils Flavor and fragrance infusion
Polymers Chemistry	Renewal of monomers and oligomers Infusion of component Removal of binder from powered metals
Reaction Chemistry	Reactions and organic product synthesis Hydrogenation reactions Polymerization reactions and synthesis
Food and flavoring	Decaffeinication of tea and coffee Extraction of essential oils and aroma materials from spices
Petrol chemistry	Handling of the distillation residue of the crude oil In regeneration procedures of used oils and lubricants
Environmental protection	Elimination of residual solvents from wastes. Purification of contaminated soil.
Plant extractions	Production of denicotined tobacco.
Nanotechnology	Post fermentation biomass or in situ extraction of inhibitory fermentation products Extraction of biological compounds In the bioprocessing industries
Remediation Technology	Remediation of soils contaminated with petroleum or polyaromatic hydrocarbons, heavy metals, organic and inorganic compounds
Milk	Determination of total fat in milk and soy-based infant formula powder

4. Supercritical Fluid Oxidation:

Supercritical water is now recognized for its capacity to destroy toxic or hazardous materials. Supercritical water is also an important medium for chemical synthesis. In the supercritical oxidation process a solution containing the toxic or hazardous component is heated to near-critical or supercritical conditions in the presence of appropriate oxidizers. Since the critical point of water is relatively high (374°C) waste components can be burned to simple byproducts. Under hydrothermal processing conditions the main components of the waste are converted to three harmless byproducts; carbon dioxide, nitrogen and water. By varying the temperature or pressure of the supercritical or near-critical solution significant control over the reaction can be obtained [11].

5. Supercritical Friedel Crafts Alkylations:

It is possible to overcome many of problems associated with conventional Friedel-Crafts reactions, both from an environmental and a practical standpoint by using supercritical fluid, a heterogeneous catalyst and a continuous flow reactor. Advantages of supercritical Friedel Crafts alkylations are: high product selectivity, easy product separation, clean technology, and longer catalyst lifetime [12].

6. Forensic Science:

Supercritical fluid extraction and chromatography is also applied in forensic science. The forensic use of supercritical fluid technology is in the sample preparation and separation of drugs of abuses particularly cannabinoids, opiates, cocaine, and sedatives. Supercritical fluid technology can be used for both time-of-death-related drug analysis and for obtaining information relating to long-term drug abuse. The uses of supercritical fluids in two other major forensic areas are fingerprinting, and the extraction and separation of explosives from both bombing events and gunshot residues [13].

7. Terminal Sterilization:

Use of Supercritical fluid technologies has been explored in the inactivation of medical contaminants. In particular, ScCO$_2$ is appealing for sterilization due to the ease at which the supercritical state is attained, the non-reactive nature, and the ability to readily penetrate substrates. The development of a ScCO$_2$ based sterilization process capable of achieving rapid inactivation of bacterial endospores while in terminal packaging is reported. Moreover, this process is gentle; as the morphology, ultra structure, and protein profiles of inactivated microbes are not altered [14].

a. Drying of Biological Specimens:

Traditional freeze-drying or spray-drying processes are often harmful to labile proteins and could be replaced by supercritical fluid drying to produce particles with defined physicochemical characteristics. By this way stabilization of proteins in dry powder formulations are possible.

b. Polymer Synthesis:

It is difficult to produce polymers with narrow molecular weight distributions by traditional methods. And they require a post-polymerization fractionation technique to obtain the desired narrow molecular weight distributions. Supercritical fluid technology is more properly applied to overcome the conventional methods, as the solubility parameter of supercritical fluid can be tailored, and selective extraction and fractionation are possible from multi-component mixtures. Recently, there has been intense interest in developing ScCO$_2$ as a solvent for dispersion polymerization. ScCO$_2$ shows great promise as a versatile, environmentally acceptable replacement for conventional solvents, and a viable route to extremely low residue polymers. The key to making high quality polymers is to ensure precise control of molecular weight and polydispersity at high yield, whilst keeping residual contaminants below acceptable tolerance levels [14].

C.Parts and Garment Cleaning:

The combination of the liquid carbon dioxide and the surfactants emerges a new cleaning system. Soap-like properties are created when these polymers form micelles that trap dirt particles and carry it away (similar to the way conventional soap works in water). At the end of the cleaning process, the carbon dioxide is returned to a gas, the dirty residues contained, and the surfactant collected. Both the CO2 and the surfactants are recycled for continued cleaning operations.

i. Textile Processing:

Both liquid and supercritical carbon dioxide can be used as a replacement solvent for water and exploit its property of existing as a gas at room temperature. The development of a nonaqueous-based textile processing represents a redesign of the current process. The advantage of the process from the beginning is that a true zero discharge manufacturing operation can be achieved through the use of a supercritical fluid.

ii. Green" Alternative to Soxhlet for Fat Determination in Food:

Supercritical fluid extraction (SFE) was used to determine total fat and fat-soluble vitamins in Parmigiano cheese and salami. The results were compared with results obtained by traditional methods (Soxhlet). The quantity collected by SFE was statistically equivalent to the Soxhlet extraction.

iii. Medical Implant Cleaning Using Supercritical Fluids:

Today's modern medicine allows many of us to have longer, healthier and more productive lives than our ancestors ever could have dreamed. One key part of this advancement is the use of medical implants that are made to replace and act as a missing biological structure within the body.

D. Non-Toxic Enzymatic Esterification:

Esters of fatty acids and alcohols are used in the food, beverage, cosmetic and pharmaceutical industries as flavor and fragrance compounds. Applied Separations has recently synthesized fatty acid esters using an immobilized lipase in a carbon dioxide medium without the use of toxic organic solvents. Various esters have been synthesized using the "green" supercritical process including citronellol laurate, isoamyl acetate, and octyl oleate.

i. Solvent-Free Essential Oils:

RosehipOil:

Rosehip oil is a valuable natural product for the cosmetic industry, yet conventional methods of extraction are often time consuming and rely heavily on the use of chemical solvents. Traditionally, the determination of oil in rosehip seeds is accomplished by soxhlet extraction. Since rosehip seeds contain a relatively low percentage of oil compared to other seeds this extraction method is labor intensive and requires a significant quantity of organic solvent, such ashexane.

SCF is an alternative technique using supercritical carbon dioxide to extract rosehip seed oil quickly and naturally in the laboratory. It eliminates the use, exposure to, and disposal of hazardous solvents, while providing comparable extraction results in less time [13, 14].

ii. Clean Extraction of Essential Oils – Flavors and Fragrances:

The use of essential oils has become "essential" for modern living. Essential oils can be primary ingredients in perfumes for cosmetics or soaps and detergents. They form the basis of the spices in our foods. Using supercritical fluids to extract the essential oils is more efficient and leaves no solvent residue [15].

iii. Environmentally Friendly Textile Dyeing:

The conventional dyeing of textiles requires that an excess of dye is dissolved or in some way "taken-up" in an aqueous or solvent solution. The dye mix is then pumped into a vat containing holding the textile. Typically there is agitation or the dye is recirculated several times through the cloth. At the end of the cycle, the dye mix is pumped to the waste treatment facility. Dyes are notoriously difficult to treat. The process is decidedly unfriendly to the environment.

Fig. 2: The use of supercritical CO_2 in textile dyeing is an environmentally friendly alternative

iv. "Green" Process for the Extraction of Natural Products:

The term natural products has become the "catch-all" for any compound that has been produced by a living being, e.g. plant, animal, algae. The extracted compounds are used in, or are themselves, foods, medicinals, pigments, fragrances. The process for many years was to extract from the matrix material by solvents: aqueous and petroleum based. The first large scale use of supercritical fluids in extracting natural products was the decaffeination of coffee in 1979 and since then thousands of compounds have been extracted commercially [15].

v. Environmentally Friendly Debinding in Metal Injection Molding:

Metal injection molding, or MIM, is a manufacturing process which combines the versatility of plastic injection molding with the strength and integrity of machined, pressed or otherwise manufactured small, complex, metal parts. The process involves combining fine metal powders with binders which allow the metal to be injected into a mold using standard plastic injection molding machines. The binders must be removed before the part can be used.

Applications in Materials Synthesis:

Nanometer metal powders are expected to have applications as burn rate modifiers in propellants, as well as components in fuel air explosives, energetic structural materials, and high-density explosives. Powders of some transition metals and their alloys are used in thick-film technology for the production of conductive pastes for hybrid integrated circuitry and for the metallization of multilayer ceramic (MLC) capacitors. Metal powders are prepared by a variety of methods such as powder mixing/calcination, metal-organic decomposition from nonaqueous solutions, and precipitation from aqueous solutions of metal salts. However, these methods generally give a nonuniform size distribution that requires milling of the agglomerated powders. Spray pyrolysis has also been utilized to generate metal alloy particles possessing diameters in the range 100-1000 nm. However, only in the last two years have researchers begun to utilize SCFs as a medium for nanoparticle growth.

Once a component is dissolved in a supercritical fluid, the particles may easily be isolated from the fluid by decreasing the system pressure. If the medium is sc-CO_2, gaseous CO_2 is released from the system (often being recycled), and the dissolved components are deposited as extremely fine particles, due to the rapid expansion of the supercritical solution (RESS). Another method for nanoparticle formation uses microemulsions, whereby an aqueous metal salt solution, reducing agent, and surfactants are added to the SCF. The resultant metal nanoparticles are deposited by RESS after the SCF is vented from the system. Particles formed through this simple procedure are shown to be free of atomic incorporation and are extremely homogeneous in size.

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