IJPSR (2012), Vol. 3, Issue 07 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 17 February, 2012; received in revised form 27 April, 2012; accepted 13 June, 2012

SUPERCRITICAL FLUID TECHNOLOGY: NASCENT CONTRIVANCE FOR PHARMACEUTICAL PRODUCT DEVELOPMENT

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Keywords:
Supercritical fluid (SCFs),
RESS,
SSI,
RESOLV,
GAS,
PCA,
SAS,
SEDS,
PGSS

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ABSTRACT

A supercritical fluid (SF) can be defined as a dense non condensable fluid. A fluid reaches the supercritical status when its temperature and pressure exceed the relevant critical temperature and pressure. At the critical point only a single phase exists which has some properties typical of liquids (density) and some of gases (viscosity, compressibility, and mass diffusion coefficient). For pharmaceutical applications, the most widely used SF is carbon dioxide (more than 98% of the applications have been developed using this fluid) because of its low and easily accessible critical temperature (31.2°C) and pressure (7.4MPa), non-flammability, non-toxicity and inexpensiveness. The physical and thermal properties of SCFs fall between those of the pure liquid and gas. SCFs offer liquid-like densities, gas-like viscosities, gas-like compressibility properties and higher diffusivities than liquids. The properties of SCFs, such as polarity, viscosity, and diffusivity, can be altered several-fold by varying the operating temperature and/or pressure during the process. This flexibility is enabling the use of SCFs for various applications in the food and pharmaceutical industries, with the drug delivery system design being a more recent addition.

INTRODUCTION: The past 20 years have indeed been a remarkable journey for supercritical fluids research, which has been beyond anyone's initial imaginations. During this time, the application areas continually expanded and experienced an explosive growth. The applications that were initially focused on extraction of natural materials, expanded in a very dramatic way into inorganic materials, polymers, emulsions, biomedical applications, hydrothermal processes, reactions, catalysis, environmental remediation, alternative energy, nanotechnology and hybrid materials.

Many of researchers provide different perspectives on particle formation, and co-precipitation processes and their applications in food, pharmaceuticals, cosmetics and drug formulations. Bioavailability of drugs can be enhanced by producing submicron particles via RESS (rapid expansion of supercritical solutions).

Co-precipitation techniques allow encapsulation of proteins in biodegradable polymers. PGSS process (particles from gas-saturated solutions) is now a commercial process employed to form powdered lecithin.

Apart from the key of using supercritical fluid as an efficient solvent at its critical point has been shown its applicability in various types processing such solvent for some specialized chemical reaction. SCF technology is making in-roads in several pharmaceutical industrial operations including crystallization, medium for particle design and engineering, particle size reduction, preparation of drug delivery systems, coating, and product sterilization.

It has also been shown to be a viable option in the formulation of particulate drug delivery systems, such as micro particles and nanoparticles, liposomes, and inclusion complexes, which control drug delivery and/or enhance the drug stability.

Fundamentals:

Supercritical Fluids: A supercritical fluid (SF) can be defined as a dense non condensable fluid. A fluid reaches the supercritical status when its temperature and pressure exceed the relevant critical temperature and pressure. At the critical point only a single phase exist which has some properties typical of liquids (density) and some of gases (viscosity, compressibility, and mass diffusion coefficient) and well explained by **figure 1**.

Therefore, a SF can behave as a solvent, since the solvent power is proportional to density. A SF is dense but compressible and any change of pressure alters its density and consequently the solvent power. Moreover, the high mass diffusion coefficient and low viscosity imply that SCFs can have good transport properties [1].

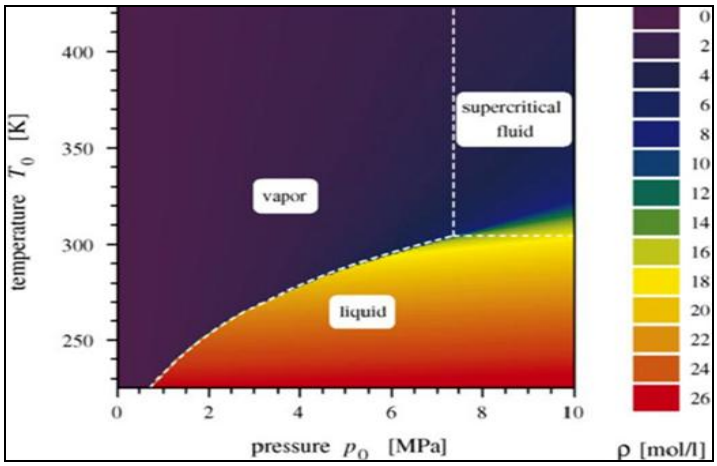

FIG. 1: PHASE DIAGRAM OF CARBON DIOXIDE DEPICTING THE PHASE BOUNDARIES BETWEEN THE GASEOUS, LIQUID, AND SUPERCRITICAL PHASE

For pharmaceutical applications, the most widely used SF is carbon dioxide (more than 98% of the applications have been developed using this fluid) because of its low and easily accessible critical temperature (31.2°C) and pressure (7.4MPa), non-flammability, non-toxicity and inexpensiveness. The physical and thermal properties of SCFs fall between those of the pure liquid and gas. SCFs offer liquid-like densities, gas-like viscosities, gas-like compressibility properties and higher diffusivities than liquids.

The properties of SCFs, such as polarity, viscosity, and diffusivity, can be altered several-fold by varying the operating temperature and/or pressure during the process. This flexibility is enabling the use of SCFs for various applications in the food and pharmaceutical industries, with the drug delivery system design being a more recent addition. Commonly used supercritical solvents include carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water (**Table 1**). Of these, CO_2 is a widely used SCF in the pharmaceutical processing due to its unique properties [2].

TABLE 1: CRITICAL CONDITIONS FOR SOME SOLVENT

Substance	Pc,K	Pc,atm	Density (g/ml)
Ammonia	405.6	112.5	0.24
Benzene	562.1	48.3	0.30
Carbon dioxide	304.2	72.9	0.47
Ethane	305.5	48.2	0.20
Ethanol	516.6	53.0	0.28
Methane	190.6	45.8	0.26
Propane	370.3	41.9	0.22
Chloroform	299.3	47.9	0.62
Water	647.3	213.3	0.32

Supercritical Fluids Properties: A pure component enters the supercritical status when both temperature and pressure are above its critical P and T values. In this region, the SCF exists in an intermediate phase between liquid and gas phases. The macroscopic appearance of the SCF is a homogeneous and opalescent system without phase separation (single phase) since, at this point, the density of the gas and liquid is the same. Nevertheless, a SCF does not show a specific aggregation state. In fact, its physicochemical properties are intermediate between liquid and gas. Like a liquid, the SCF shows a density value appreciable for the solvation power, while the viscosity and diffusivity similar to a gas facilitate the mass transfer [3].

The SCF is dense but highly compressible, particularly near the supercritical region. Thus, any change of pressure alters its density and consequently the solvent power. While the solvent-like properties are beneficial to drug solubilization, polymer plasticization, and extraction of organic solvents or impurities, the gas like properties significantly enhance the diffusion related phenomena. Although these unique and complementary physical characteristics allow the development of efficient and versatile processes, it should be underscored that the SCF cannot be considered as the universal "super-solvent" [3].

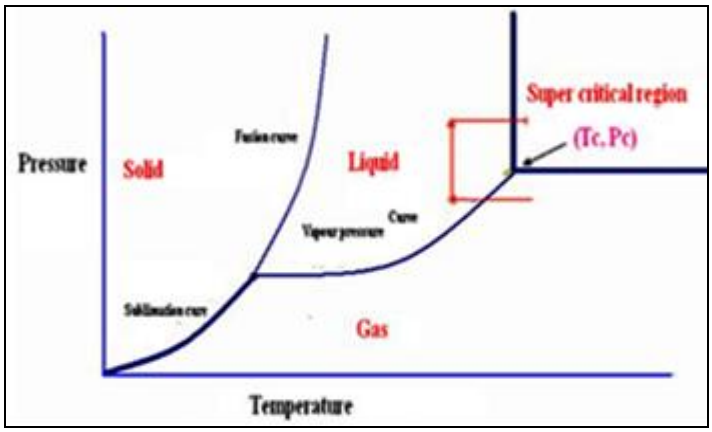

FIG. 2: PHASE DIAGRAM OF PURE SUBSTANCE

Fig. 2 shows a schematic projection of the phase diagram of a pure substance on the pressure-temperature plane. The three lines divide the diagram into three regions: solid, liquid and gas. Along the lines, two phases are in equilibrium and the three states of aggregation coexist at the triple point.

The discontinuous transition from liquid to gas ends at the critical point (T, P,). Beyond this point, a low density gas can be compressed into a dense fluid continuously. Strictly speaking, a fluid whose temperature and pressure are simultaneously higher than at the critical point is supercritical. In practice, the term is reserved for the description of fluids in the relative vicinity of the critical point.

In this region, the thermo physical properties exhibit very high rates of change with respect to temperature and pressure. At the critical temperature (Tc) and pressure (Pc), a substance's liquid and vapor phases are indistinguishable. A substance whose temperature and pressure are simultaneously higher than at the critical point is referred to as a supercritical fluid (Fig. 2).

As a consequence, the entire supercritical region is characterized by very large compressibility's. At the same time, fluid densities can be very close to liquid-like. The distinguishing feature of supercritical fluid is the fact that, though almost liquid-like in density, it possesses a very high compressibility.

This allows the use of pressure as a very sensitive means of manipulating and controlling the solvent's characteristics (in particular, its solvent power), spanning the continuum range from gas like to liquid.

Advantages of CO_2 as a Solvent for Pharmaceuticals: Carbon dioxide as a solvent has many advantages. Probably the most important advantage is that it is a GRAS solvent that leaves no traces in the product. After extraction, the carbon dioxide is recycled and any trace carbon dioxide in the product dissipates to the atmosphere within a few hours. Also, unlike solvent extraction, the carbon dioxide is readily recycled by pressure and temperature adjustment, which is very mild and does not harm the product [4].

Another advantage of supercritical fluid extraction is the capability of fractionating products to create co-products. Solvent extraction requires a distillation step, (in which top notes are lost and distillation notes are created), that many times alters the taste, aroma and chemical composition of the product. Also, trace quantities of residual organic solvent are usually present in the product.

Supercritical carbon dioxide is finding broad acceptance in the food, flavor, fragrance, pharmaceutical and nutraceutical industries because it does not harm products and produces higher concentration (quality) extracts [4].

Solubility of materials in Super Critical CO_2: Since particle design using $SCCO_2$ technology employs rapid changes in solubility as the chief means of substance manipulation, solubility in $SCCO_2$ is very important for the success of processes, such as rapid expansion of supercritical fluid (RESS), gas anti-solvent (GAS), supercritical anti-solvent (SAS), and particle from a gas-saturated solution (PGSS) [5].

When $SCCO_2$ is used as a *solvent* for materials (e.g. RESS), checking the solubility of the materials under various conditions (pressure and temperature) is

absolutely necessary for particle production, as $SCCO_2$ should dissolve the materials to be micronized. The mixture of materials with $SCCO_2$ is usually expanded in a reactor and precipitated as a solid formulation [6].

When $SCCO_2$ is used as an *anti-solvent*, the key to producing the particles is generally considered to be the super saturation of the solution of materials via the counter-diffusion of SC-CO_2 and the solvent. The solubility of the materials in $SCCO_2$ influences the degree of this super saturation.

In the case of PGSS, $SCCO_2$ should be soluble in melted material, but this material is not required to be soluble in $SCCO_2$. As stated above, the degree of solubility is critical for controlling the properties during $SCCO_2$ processing both with and without the solvent. The solubility of materials in pure CO_2 or CO_2 with solvent is the most important factor to consider when choosing the appropriate process to enhance the drug solubilization during SC-CO_2 processing [7].

Basic Techniques in SCF Technology: In conventional precipitation methods (such as solvent anti- solvent and solvent evaporation), organic solvents, surfactants, and suspending agents are required, and must be removed from the formulation before their use in vivo. Alternative techniques, such as spray drying and melt-pressing followed by grinding, involve heat, which may affect the drug's stability, and multiple processing steps.

RESS is an attractive alternative to conventional methods for the production of drug-loaded polymeric microspheres since it requires no surfactants, yields a solvent-free product (the solvent is a dilute gas after expansion), and allows processing at moderate temperatures.

In contrast, the co precipitation of bioerodible polymers and drugs by RESS can, in principle, produce drug-loaded microspheres in a single processing step, avoiding the use of liquid organic solvents, surfactants, and heat (if low-critical-temperature solvents are used). The application of the GAS process to the formation of microparticulate protein powders is a very recent development. Controlled release systems for peptides and proteins offer several advantages over conventional solution formulations.

Conventional techniques such as spray drying, milling, grinding, lyophilization, and controlled precipitation, can in principle, be used to produce small protein particles. Problems associated with these techniques can include shear or temperature-induced protein inactivation and low yield (spray drying); large (l0-50 pm) particles, broad size distributions, and denaturation (milling); electrostatically charged powders and low efficiency towards soft powders (fluid energy grinding); broad distributions (lyophilization); denaturation by organic solvents and the need for a secondary drying step (controlled precipitation with organic solvents).

The use of supercritical fluids in biomedical applications is a new, virtually unexplored field. In this review, a possible general classification of SCF based techniques can be proposed according to the role played by the SCF in the process.

Indeed, SCF have been proposed as solvents, solutes, anti-solvents and reaction media.

SC-CO_2 as Solvent:

Rapid Expansion of Supercritical Solutions (RESS): A supercritical solvent saturated with a solute of interest is allowed to expand at a very rapid rate, causing the precipitation of the solute. The rapid expansion/ decompression is achieved by allowing into pass through a nozzle at supersonic speeds. This rapid expansion of supercritical solutions leads to super saturation of the solute in it and subsequent precipitation of solute particles with narrow particle size distributions. This process is also known as supercritical fluid nucleation (SFN).

Fig. 3 provides schematic view of the rapid expansion of supercritical solutions (RESS) process. The SCF is pumped through a pre-heater into the vessel containing the solid solute at a particular temperature and pressure. The SCF dissolves and gets saturated with the solute, and the resultant solution is introduced into a precipitation chamber by expansion through capillary or laser-drilled nozzle [8].

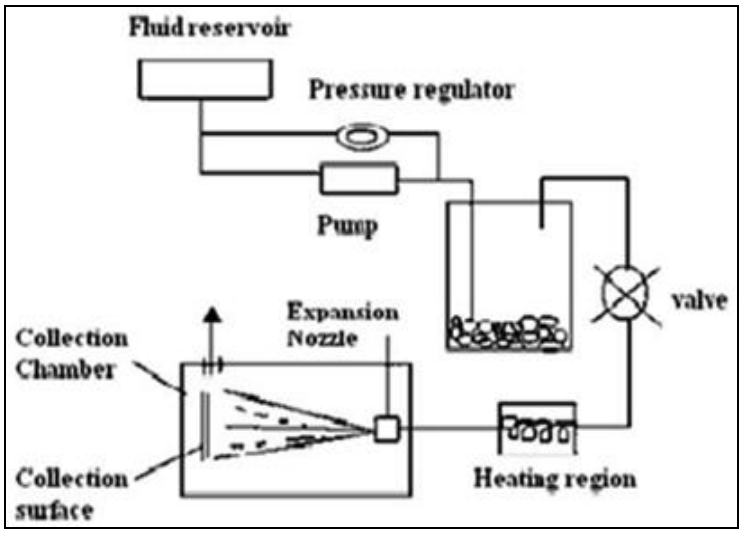

FIG. 3: PRESS APPARATUS

Typically, by altering the pressure, the precipitation unit is maintained at conditions where the solute has much lower solubility in the SF. During expansion or decompression phase, the density and solubilising power of the SF decreases dramatically, resulting in a high degree of solute super saturation and subsequent precipitation. The morphology and size distribution of the precipitated material is a function of its pre-expansion concentration and expansion conditions. The pre-expansion concentration is dependent on the choice of SF, nature of solute, addition of cosolvents and operating pressure and temperature. The higher the pre-expansion concentration, the smaller the particles and narrower will be the particle size range [9].

RESS process is used in two modes, batch and semi continuous.

In semi-continuous mode, the coating (and active) material(s) dissolve in SCF at high pressure in the extraction section and then the suspension (or solution) is rapidly decompressed (≤10−5 s) via a nozzle or an orifice.

In batch mode, the depressurization is within the vessel and it is slower than semi-continuous mode. High pressure and temperature are usually required in the extraction stage.

Many interested polymers have a dissolution limit in SCO_2, so sometimes co-solvents are used to increase the dissolution power of $SCCO_2$. The mass transfer in RESS process is severe and so high super saturation is produced. High super saturation causes fast nucleation and makes RESS process difficult to control and results in fine and porous composite particles [10].

Supercritical Solvent Impregnation (SSI) or Infusion of Polymers with Bioactive Materials: Some gases cause swelling of polymers or drug carriers at high pressures. This swelling behavior can be exploited for various applications, such as control delivery of drugs. Polymers can be impregnated with drugs by dissolving the drug in a supercritical fluid and then contacting the resulting fluid mixture with the polymer particles to be impregnated [11].

A schematic diagram of this process, called Supercritical Solvent Impregnation (SSI) is presented in **Fig. 4**.

The two main items of the setup are the drug column, in which SC-CO_2 is saturated with the drug, and the carrier column, in which this solution is brought into contact with the polymer. It is also possible to dissolve another substance in the CO_2 to enhance the solubility of the drug (co-solvent) or to improve the dispersion of the drug in the polymer (surfactant).

The impregnation of the drug by this mechanism is aided by the plasticization and swelling effect caused by the dissolution of CO_2 into the polymer [11].

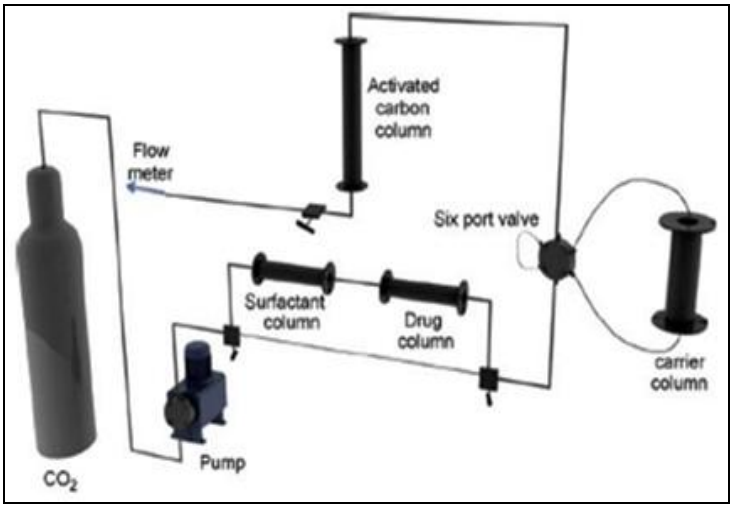

FIG. 4: SCHEMATIC OF THE SUPERCRITICAL SOLVENT IMPREGNATION (SSI) PROCESS

The polymers evaluated by this process are polypropylene, polyethylene, ethylene-vinyl acetate copolymer, ethylene-ethyl acrylate copolymer and causes the migration of active material in to the polymer [11].

Rapid Expansion of a Supercritical Solution into a Liquid Solvent (RESOLV): An interesting variation of the RESS process is the rapid expansion of a supercritical solution into a liquid solvent (RESOLV) that consists of spraying the supercritical solution into a liquid. Operating in this manner, it should be possible to quench particles growth in the precipitator, thus improving the RESS process performance [12].

The solution of the drug in liquid CO_2 is prepared inside a high-pressure syringe pump. The solution is pumped into a heating unit to attain the desired temperature before expansion through a laser-drilled orifice.

The rapid expansion of the solution occurs into an aqueous medium at ambient pressure. Various water-soluble polymers may be added to the aqueous medium for stabilizing the nanoparticle suspension. The RESOLV process, for the production of nanoparticles has also been proposed for the production of polymeric nano-fibers of poly (heptadecafluorodecylacrylate) (PHDFDA), PMMA and PLA [12].

SC-CO_2 as Anti-Solvent: In supercritical anti-solvent methods, quick mass transfer between supercritical fluids and solution of coating (and core) material(s) results in the expansion of solution. The expansion reduces the solvation power and causes a supersaturated solution from which the precipitation (co-precipitation) of coating (and core) material(s) occurs. The quick mass transfer is mainly due to high diffusion of supercritical fluid into the solution.

In supercritical anti-solvent methods, post-processing treatments are no required to remove the anti-solvent fluid in contrast to conventional liquid anti-solvent methods. In addition, the control of particle size distribution is possible and there is no need to post-process size reduction processes like milling. The main anti-solvent methods are GAS, PCA, SAS and SEDS are explained in subsequent sections [13].

Gas Antisolvent Recrystallisation (GAS): In GAS method, the SCO_2 (or compressed gas) is introduced into an organic solution, previously loaded in precipitation vessel, resulting in microspheres or microencapsules. GAS technique is a batch process and its simple set up is shown in **Fig. 5**.

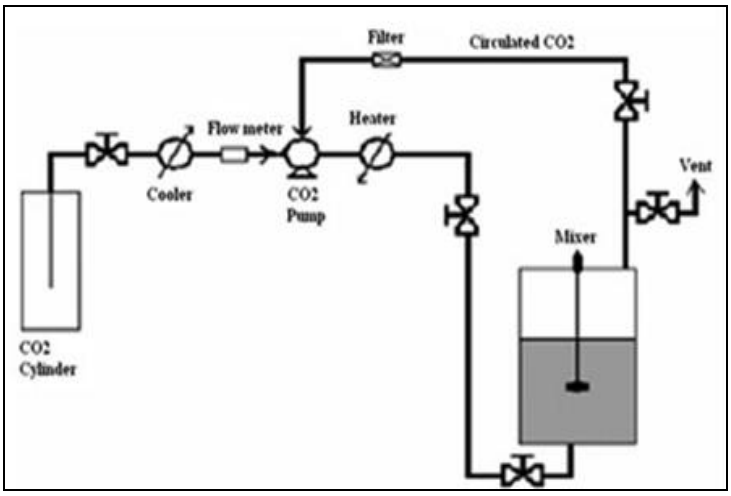

FIG. 5: SCHEMATIC OF GAS METHOD

It is a well-known phenomenon that a poor solvent of a particular solute can be added to the solution to precipitate the solute. This is called salting out and is widely used for crystallization purposes [13].

Precipitation with Compressed Fluid Antisolvent (PCA): In PCA method, mixing of organic solution and supercritical fluid (or compressed gas) is completely in contrast to GAS method. In this process, the organic solution is dispersed in a continuum of supercritical fluid or compressed gas (Fig.6). Some authors have called this method as aerosol solvent extraction system (ASES).

Unlike GAS method, PCA does not need drying step. Supercritical fluid (or compressed gas) phase can be used in both modes of operations, i.e. static and continuous. Although in most of the works, a static phase was used for supercritical fluid (or compressed gas); some researchers applied a continuous phase and called the technique as PCA (or ASES) [14].

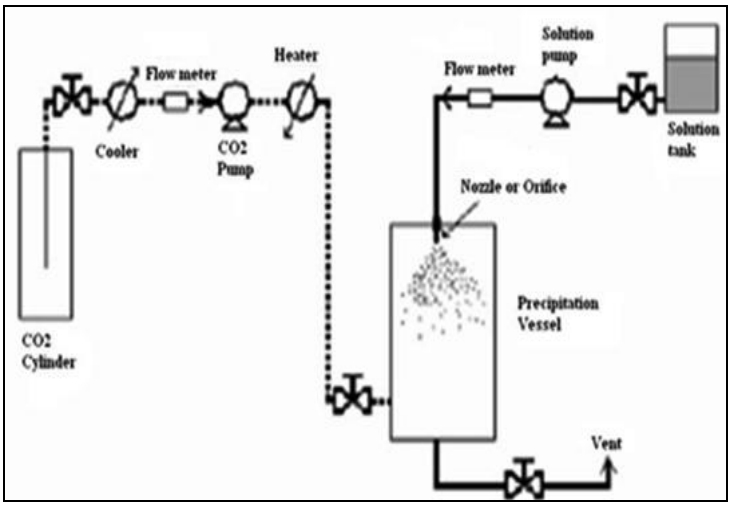

FIG. 6: SCHEMATIC OF PCA METHOD

Supercritical Anti-Solvent Method (SAS): In SAS method, the $SCCO_2$ and the organic solution are separately and continuously fed inside the precipitation chamber through the nozzles (**Fig. 7**).

In normal operation of SAS method, the SCO_2 and solution streams are co-current. In modified SASEM method the streams are brought into contact by a cross pattern. SAS is a semi-continuous process in which carbon dioxide and organic solution are continuously vented from chamber. In the SAS process, the precipitated solids accumulate inside the vessel and are collected at the end of the operation.

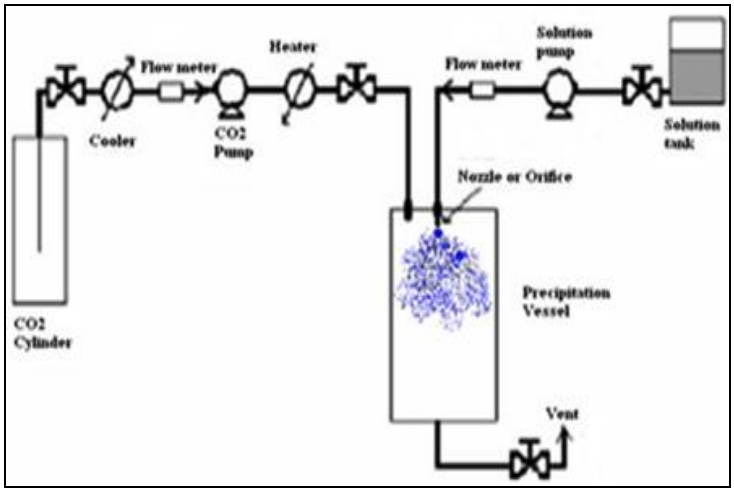

FIG. 7: SCHEMATIC OF SAS METHOD

Solution Enhanced Dispersion by Supercritical Fluid (SEDS): This technique was developed at the University of Bradford to overcome some of the limitations of the RESS and GAS methods. The drug solution and the SCF are introduced simultaneously into the arrangement causing rapid dispersion, mixing and extraction of the drug solution solvent by SCF leading to very high super saturation ratios [14].

The temperature and pressure together with accurate metering of flow rates of drug solution and SF through a nozzle provide uniform condition for particle formation. This helps to control the particle size of the product and, by choosing an appropriate liquid solvent; it is possible to manipulate the particle morphology. In SEDS method, the SCO2 and solution are co-introduced into a precipitation vessel through a coaxial nozzle (**Fig. 8**). In SEDS method, SCO_2 is the dispersing agent in addition to be an anti-solvent. In this method, more dispersion and vigorous mixing cause smaller particles than those made in SAS method.

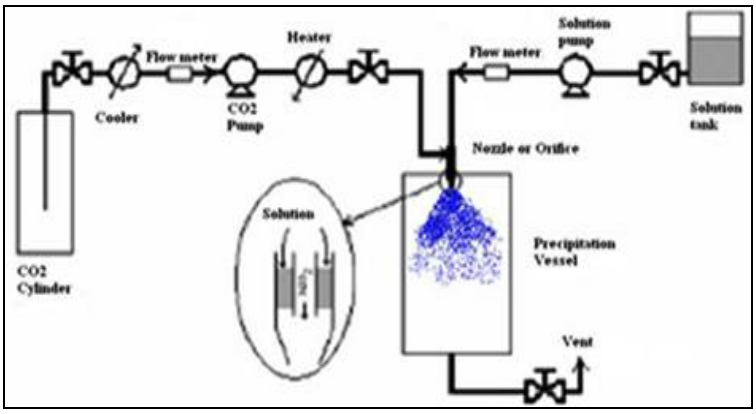

FIG. 8: SCHEMATIC OF SEDS METHOD

Supercritical Fluid Extraction Emulsions (SFEE): This is an advanced version of the micro encapsulation techniques utilizing SCF in order to overcome some of the disadvantages in these conventional ones. The unique feature of this method is that it combines the flexibility of particle engineering using different emulsion systems with the efficiency of large scale, continuous extraction ability, provided by SCF. This can produce efficiently drug-loaded polymer spheres in a well-controlled manner [14]. Using this technique production of composite (e.g., polymer-drug) micro- and nanoparticles, intended for application in sustained-release drug delivery formulations has been carried out in both the batch and continuous reactors by SCCO2 extraction of oil-in-water (o/w) emulsions [14].

SC-CO_2 as Solute:

Particle from Gas Saturated Solution/Suspension Method (PGSS): The PGSS method requires neither drug particles nor polymer to dissolve in $SCCO_2$. In PGSS technique, $SCCO_2$ dissolves in a molten or plasticized substance at high pressure, leading to a gas saturated solution. The rapid expansion of solution through a nozzle results in particles (**Fig. 9**).

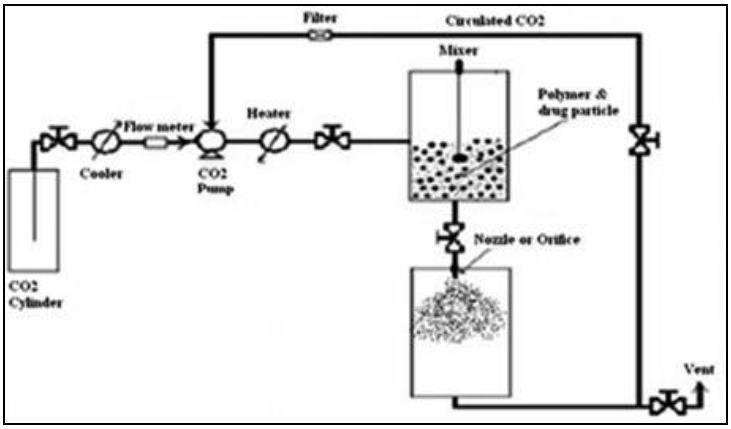

FIG. 9: SCHEMATIC OF PGSS METHOD

The consumption of CO_2 in PGSS method is lower than RESS method by an order of magnitude of 103. In addition, the requisite of RESS technique, which is the dissolution of substance in SCO_2, is eliminated in PGSS method. No organic solvent is used in PGSS method in contrast to anti-solvent techniques [14]. The PGSS method can be applied for a mixture of active ingredient(s) and polymer to produce composite particles. The absorbed $SCCO_2$ in the polymer matrices reduces the melting/glass transition temperature of polymer, so PGSS method is useful for polymers that absorb $SCCO_2$ considerably. Subsequent massive expansion of dissolved CO_2 ruptures the droplets into aerosols. Evaporation of water from aerosols follows by the precipitation of solute(s) and results in extremely fine particles. Reverchon and Spada called this method supercritical assisted atomization method (SAA).

SC-CO_2 as Reaction Medium: Sometimes $SCCO_2$ is used as a reaction medium, in which the coating material synthesizes by a chemical reaction and coats the surface of particles. Silanization is a process to coat the surface of hydrophilic particles and improve their chemical and physical properties [14]. For example, it improves the dispersion of nanoparticles within organic liquid, so reduces the aggregation of them.

Drug Delivery Applications of SCFT:

Micro Particles and Nanoparticles: Drug and polymeric micro particles have been prepared using SCFs as solvents and antisolvents. Krukonis first used RESS to prepare 5 to 100 µm particles of an array of solutes including lovastatin, poly-hydroxy-acids, and mevinolin [13, 14]. RESS process employing CO_2 was used to produce poly (lactic acid) (PLA) particles of lovastatin and naproxen. A GAS process was used to produce clonidine-PLA micro particles.

Micro Porous Foam: Using SCF technique, Hile et al prepared porous PLGA foams capable of releasing an angiogenic agent, basic fibroblast growth factor (bFGF), for tissue engineering applications. These foams sustained the release of the growth factor [13, 14].

Liposome: Liposomes are useful drug carriers in delivering conventional as well as macromolecular therapeutic agents. Frederekseen *et al*., developed a laboratory scale method for preparation of small liposome's encapsulating a solution of FITC-dextran, a water-soluble compound using supercritical carbon dioxide as a solvent for lipids. Using the SCFT process, liposomes, designated as critical fluid liposomes (CFL), encapsulating hydrophobic drugs, such as taxoids, camptothecins, doxorubicin, vincristine, and cisplatin, were prepared.

Inclusion Complexes (Inclusion complexes with Cyclodextrins): For many nonpolar drugs, previously established inclusion complex preparation methods involved the use of organic solvents that were associated with high residual solvent concentration in the inclusion complexes. Earlier, cyclodextrins were used for the entrapment of volatile aromatic compounds after supercritical extraction. Based on this principle, Van Hees *et al*., employed supercritical fluids for producing piroxicam and ß-cyclodextrin inclusion complexes. Greater than 98.5% of inclusion was achieved after 6 hours of contact with supercritical CO_2 at 15 MPa and 150°C [13, 14].

Solid Dispersions: SCF techniques can be applied to the preparation of solvent-free solid dispersion dosage forms to enhance the solubility of poorly soluble compounds. Traditional methods suffer from the use of mechanical forces and excess organic solvents. A solid dispersion of carbamazepine in polyethylene glycol 4000 (PEG4000) increased the rate and extent of dissolution of carbamazepine [13, 14].

Powders of Macromolecules: Processing conditions with supercritical CO_2 are benign for processing macromolecules, such as peptides, proteins, and nucleic acids. Debenedetti et al used an antisolvent method to form micro particles of insulin and catalase. Protein solutions in hydroethanolic mixture (20:80) were allowed to enter a chamber concurrently with supercritical CO_2. The SCF expanded and entrained the liquid solvent, precipitating sub micron protein particles [13, 14].

Coating: SCFs can be used to coat the drug particles with a single or multiple layers of polymers or lipids. A novel SCF coating process that does not use organic solvents has been developed to coat solid particles (from 20nm to 100µm) with coating materials, such as lipids, biodegradable polyester, or polyanhydride polymers [13,14].

An active substance in the form of a solid particle or an inert porous solid particle containing active substance can be coated using this approach. The coating is performed using a solution of a coating material in SCF, which is used at temperature and pressure conditions that do not solubilize the particles being coated.

Product Sterilization: In addition to drug delivery system preparation, SCF technology can also be used for other purposes, such as product sterilization. It has been suggested that high-pressure CO_2 exhibits microbicidal activity by penetrating into the microbes, thereby lowering their internal pH to a lethal level. The use of supercritical CO_2 for sterilizing PLGA microspheres (1, 7, and 20 μm) is described in US Patent No. 6,149,864.

Particulate Dosage Forms: Some gases at certain pressures cause swelling of polymers like polypropylene, polyethylene, and ethylene-vinyl acetate co-polymer and ethylene ethyl acrylate copolymer or drug carriers, and allow migration of active material in polymer matrix to give diffusion-controlled drug delivery systems [13, 14].

This approach can be utilized as a solvent-free approach to develop novel, controlled-release dosage forms and deposit thermo labile materials such as peptide drugs into the polymers.

Microspheres and Microcapsules of Proteins: Microspheres and microcapsules of proteins and genes with biodegradable polymers are promising formulations for optimizing inhalation therapy. These micro particles may provide new functions such as the sustained release of proteins, protection of proteins against enzymatic degradation, increased retention due to bioadhesive properties, and so on.

The application of supercritical SCO_2 to micro encapsulation of proteins is a promising way to prepare microspheres with low residual solvent and strong protein activity [13, 14].

Bioimaging Applications: Bioimaging using phosphor attracts keen interest among researchers. To recognize how a drug delivers inside body is essential to design a drug delivery system (DDS). Since the organic probes used in bioimaging cannot survive too long in the body, the replacement was found in some semiconductor materials showing strong photoluminescence behavior, whose wave length could be controlled with its particles size ("Quantum Size Effect"). With a same wavelength of excitation, wide range of colors can be obtained by changing the particle size of the nanoparticles of CdSe, CdTe, CdS, etc., the so called quantum dots (QD). The non-toxic metal oxide nanoparticles with photo-luminescence property are prepared using SCF technology.[15]

Application in Pharmaceutical Industries:

Medium for Crystallization: To generate high purity polymorphs, even with some morphological viz. high degree of enantiomeric enrichment. SCF technology appears to be a potential modality. Moreover, size and shape of the polymorph can be manipulated by controlling temperature and/or pressure during processing while degree of crystallization can be improved by manipulating the rate of crystallization & high degree of crystallinity.

Solubilization of Pharmaceuticals: RESS technology has been used for solubilization of pharmaceuticals. Most of pharmaceutical compounds below 60^0c and 300 bars showed a considerable higher solubility. In many a process of solubilization of polar or non-volatile compounds a limited solubility in $SCCO_2$ is fails to form a homogenous solution under practical conditions. To aid the solubilization in such cases the CO_2-philic solubilizers are being developed which rather the $SCCO_2$ insoluble substances and make them solubilize in $SCCO_2$.

Extraction and Purification: Supercritical fluid extraction technique could be utilized to separate impurities mainly organic complexes from the pharmaceuticals. Methods developed by Zoel are now widely used in industry as in caffeine production & isolation of Taxol from the bark of the Taxus brevifolia in which $SCCO_2$ is used. Purification via SCF technology gives a better alternative to all conventional purification methods as it is almost automated, quick, high yielding,

Medium for Polymerization and Polymer Processing: Supercritical fluids mainly $SCCO_2$ is rapidly becoming an alternative solvent for polymerization. Solubility plays a very important role in the synthesis of polymers. Mainly two processes are used-

- **Step growth:** $SCCO_2$ has been reported very yielding in the production of polycarbonates, polyamides, polyesters, polypyrrols, poly-phenoxides and silica gels.

- **Chain growth:** free radical polymerization of styrenics, armlets and methacrylates, cationic polymerization of isobutylene.

Supercritical CO_2 in polymerization is increased plasticization because of CO_2. The highly plasticized state of polymers is also results in increased polymerization rates by the enhanced diffusion of monomer into the polymer [16].

As a Supercritical Bio-Catalyst: Randolph et al primarily found the enzyme alkaline phosphates active in a batch reaction system that employed $SCCO_2$ as solvent. In the comparison $SCCO_2$ as the adverse effect of pressure was less profound in case of compressed propane and ethane.

Micronization of Pharmaceuticals: The RESS process has been shown to be capable of forming micron-sized particles. Krukonics, first extensively studied RESS in micronization of a wide variety of materials, including pharmaceuticals, biologicals, and polymers. He produced uniform submicron powder of estradiol.

SAS process has been successfully used to produce micron sized particles like insulin, bovine liver catalase, lysozyme, trypsin, and methylprednisolone and hydrocortisone acetate. ASES process has been studied for the preparation of a range of steroids for pulmonary delivery.

Extraction of Fermentation Broths: Supercritical carbon dioxide countercurrent column extraction is currently being investigated as a new process for the extraction of pharmaceutically active compounds from fermentation broths.This process offers an inexpensive method to extract and simultaneously fractionate compounds of interest without leaving organic solvent residues in the product.

CONCLUSION: The special properties of SCFs bring certain advantages to chemical separation technique. Several applications have been fully developed and commercialized which include food and flavoring, pharmaceutical industry, environmental protection for volatile and lipid soluble compounds, extraction of high value oils, extraction of natural aromas, recovery of aromas form fruits, meat and fish, isolations of lipid soluble compounds.

Supercritical fluid or dense gas technology can afford environmentally benign and novel processing a wide range of pharmaceutical products. The physical and chemical properties of CO_2, in particular, make it a suitable organic solvent alternative in pharmaceutical processing where biodegradable compounds are used frequently.

We expect that the transfer of supercritical fluid technology of material processing from laboratory to industry will be achieved in a near future in combining economical efficiency and sustainable development in pharmaceutical research.

REFERENCES:

1. Kiran E, Brunner G,Smith RL Jr: The 20*th* Anniversary of the Journal of Supercritical Fluids-A Special Issue on Future Directions in Supercritical Fluid Science and Technology. J Supercrit Fluids 2008; doi:10.1016/j.supflu.2008.12.001.
2. Ferdinando Giordano et.al: Solid-state chemistry and particle engineering with supercritical fluids in pharmaceutics. Eur J Pharm Sci 2006; 27:299-310.
3. Raeissi S, Diaz S, Espinosa S et.al: Ethane as an alternative solvent for supercritical extraction of orange peel oils. J Supercrit Fluids 2008; 45:306-13.
4. Vemavarapu C, Mollan MJ, Mayur L, and Thomas EN: Design and process aspects of laboratory scale SCF particle formation systems. Int J Pharm 2005; 292:1-16.
5. Yasuji T, Takeuchi H, Kawashima Y: Particle design of poorly water-soluble drug substances using supercritical fluid technologies. Adv Drug Del Rev 2008; 60:388-98.
6. Yeo SD, Kiran E: Formation of polymer particles with supercritical fluids: A review. J Supercrit Fluids 2005; 34:287-308.
7. Peter York: Strategies for particle design using supercritical fluid technologies. Research focus, PSTT 1999; 2:430.
8. Wolfgang Christen, Tim Krause, and Klaus Rademann: Transferring pharmaceuticals into the gas phase. International J Mass Spectrometry 2008; 277: 305-8.
9. Diaz MS, Brignole EA: Modeling and optimization of supercritical fluid processes. J. Supercrit Fluids 2008; doi:10.1016/j.supflu.2008.09.006.
10. Byrappa K, Ohara S, Adschiri T: Nanoparticles synthesis using supercritical fluid technology-towards biomedical applications. Adv Drug Del Rev 2008; 60:299-327.
11. Ana RC, Duarte *et al*: Supercritical fluid impregnation of a biocompatible polymer for ophthalmic drug delivery. J Supercrit Fluids 2007; 42: 373-77.
12. Reverchon E, Antonacci A: Polymer micro particles production by supercritical assisted atomization. J Supercrit Fluids 2007; 39:444-52.

13. Ferdinando Giordano et.al: Supercritical fluid technologies: An innovative approach for manipulating the solid-state of pharmaceutical. Adv Drug Del Rev 2008; 60:399-410.
14. Cocero MJ et al: Encapsulation and co-precipitation processes with supercritical fluids: Fundamentals and applications. J.Supercrit Fluids 2008; doi:10.1016/j.supflu.2008.08.015.
15. Irene Pasquali, Ruggero Bettini, Ferdinando Giordano: Supercritical fluid technologies: An innovative approach for manipulating the solid-state of pharmaceuticals. Adv Drug Del Rev 2008; 60:399-410.
16. Moneghini M, Kikic I, Voinovich D, Perissutti B, Filipovic-GJ: Processing of carbamazepine-PEG 4000 solid dispersions with supercritical carbon dioxide: preparation, characterization, and in vitro dissolution. Int. J Pharm 2001; 222(1): 129-38.
17. Pablo GD, Jean WT, Sang-DY, Gio-BL: Application of supercritical fluids for the production of sustained delivery devices. J Control Rel 1993; 24: 21-44.
18. Ana RC, Duarte et.al: Preparation of controlled release microspheres using supercritical fluid technology for delivery of anti-inflammatory drugs. Int J Pharmaceutics 2006; 308: 168–174.
19. Jacques Fages et.al: Particle generation for pharmaceutical applications using supercritical fluid technology. Powder Technology 2004; 141: 219-26.
20. Ronald TK and Robert CR: Solubility of solid mixtures in Supercritical fluids. Fluid phase equilibria 1982; 8: 93-105.
21. Kenji Mishima: Biodegradable particle formation for drug and gene delivery using supercritical fluid and dense gas. Adv Drug Del Rev 2008; 60: 411-32.
22. Jennifer Jung, Michel Perrut: Particle design using supercritical fluids- Literature and patent survey. J Supercrit Fluids 2001; 20:179-219.
23. Elaine MP Valentino JS: Rapid expansion from supercritical solutions- application to pharmaceutical processes. Int J Pharmaceutics 1993; 94: l-10.
24. Masoud B,Ranjbarian S: Production of micro and nanocomposite particles by supercritical carbon dioxide. J Supercrit Fluids 2007; 40:263-283.
25. Keenan G, Ihtesham UR, Jawwad AD: Characterization and drug release investigation of amorphous drug-hydroxypropyl methylcellulose composites made via supercritical carbon dioxide assisted impregnation. J Pharm Biomed Anal 2008; doi:10.1016/j.jpba.2008.08.031.
26. Johannes Kluge et al: Rational design of drug-polymer co-formulations by CO_2 anti-solvent precipitation. J. Supercrit.Fluids 2008; doi:10.1016/j.supflu.2008.10.005.
27. Soyoung KA, Kyoungwon L et al: Synthesis of a biocompatible polymer using siloxane-based surfactants in supercritical carbon dioxide. J Supercrit Fluids 2008; 45: 391-99.
28. A. Lopez-Periago et al: Impregnation of a biocompatible polymer aided by supercritical CO2: Evaluation of drug stability and drug-matrix interactions. J Supercrit Fluids 2008, doi:10.1016/j.supflu.2008.09.015.
29. Luigi Manna, Mauro Banchero et al: Impregnation of PVP micro particles with ketoprofen in the presence of supercritical CO2. J Supercrit Fluids 2007; 42:378-84.
30. Cocero MJ et.al: Co-precipitation of carotenoids and bio-polymers with the supercritical anti-solvent process. J Supercrit Fluids 2007; 41:138-47.
31. Martín A, Cocero MJ: Micronization processes with supercritical fluids-Fundamentals and mechanisms. Adv Drug Del Rev 2008; 60: 339-50.
32. Sun YP, Meziani MJ et.al: Nanoparticle formation in rapid expansion of water-in-supercritical carbon dioxide micro emulsion into liquid solution. J Supercrit Fluids 2005; 34: 91–97.
33. Mishima K: Biodegradable particle formation for drug and gene delivery using supercritical fluid and dense gas. Adv Drug Del Rev 2008; 60:411-32.
34. Okamoto H, Danjo K: Application of supercritical fluid to preparation of powders of high-molecular weight drugs for inhalation. Adv Drug Del Rev 2008; 60:433-46.

How to cite this article:

Wakure B.S., Yadav A.V., Bhatia N.M., and Salunke M.A.: Supercritical Fluid Technology: Nascent Contrivance for Pharmaceutical Product Development. *Int J Pharm Sci Res*, 2012; Vol. 3(7): 1872-1882

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