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Review article

A REVIEW ON SUPERCRITICAL FLUID TECHNOLOGY AND ITS APPLICATIONS IN PHARMACEUTICAL INDUSTRY

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ABSTRACT

A supercritical fluid is any substance at a temperature and pressure above its critical point, where distinct liquid and gas phases do not exist. It can effuse through solids like a gas, and dissolve materials like a liquid. In addition, close to the critical point, small changes in pressure or temperature result in large changes in density. Carbon dioxide and water are the most commonly used supercritical fluids, being used for decaffeination and power generation, respectively. Surface tension in a supercritical fluid, as there is no liquid/gas phase boundary. 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. Supercritical fluid technology (SCFT) can be classified into three broad categories depending on the way Super Critical Fluid-CO_2 is being used. Although supercritical Fluid technology is not yet widespread in the pharmaceutical industry, except for extraction of active compounds from vegetal sources (phytopharma-/nutra-ceuticals), many promising applications are now under development, especially for new drug formulations through innovative particle design.

Key Words:-Anti-solvent, Bio-catalyst, Decaffeination, Supercritical fluids.

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INTRODUCTION

As far as supercritical fluid technology (SCFT) is in use from late 19th century as a tool to understand the natural mineralization, the commercial exploitation of SCF technology has began in the 1970s. This was particularly motivated by environmental concern, capability of some SCFs for replacing toxic industrial solvent and finally, the SCF processes might be economical to liquid extraction and distillation methods.

A fluid is said to be supercritical, when its pressure and temperature exceed their respective critical value (T_c- critical temperature and P_c - critical pressure). In the phase diagram Fig. **1**, the critical point located at the right upper end and the phase area beyond of this point is the supercritical fluid (SCF) region. Above the T_c, it is not possible to liquefy a gas by increasing the pressure. In other words, a SCF can behave as either a liquid or a gas, but is actually neither. Under these conditions, the densities of the liquid and vapor are identical, and for this reason the meniscus, on the interface between the two phases, disappears.

However, the SCF has a unique thermo-physical property. As the pressure is raised, the density of the gas

increases without significant increase in viscosity while the ability of the fluid to dissolve compounds also increases. A gas may have little to no ability to dissolve a compound under ambient condition can completely dissolve the compound in supercritical range. Therefore, SCF provide a greater avenue as its solvation power is altered by careful control of changes in temperature and/or pressure (Parhi R and Padilama S, 2009; Valquíria MHY and Victor MCFB, 2016).

All gases can form SCF above specific sets of Pc and Tc values, but in most of the cases, the transition to the supercritical state occurs at high temperatures not compatible with pharmaceutical compounds (e.g. SC water). In addition, the Pc, Tc values increase with the molecular weight or intermolecular hydrogen bonding or polarity (Vasukumar K and Bansal KA, 2003). Among the number of gases tried as SCF, CO_2 is considered as the best option for SCF technique because of its low critical point (31.3 ºC, 7.4 MPa), attractiveness for heat sensitive materials, it is inert, leaves no traces behind after the process, as well as being inexpensive, non-inflammable, having GRAS (generally regarded as safe) status and being easy to recycle or to dispose off. By incorporating a small amount of volatile cosolvent, often a polar or proteic compound such as acetone or ethanol, the solvation power of a particular SCF in less soluble solvent like water can be improved (Schmitt WJ and Reid RC, 1986).

Supercritical fluid technology is a new method to produce fine drug particles and is valuable for product quality, batch consistency and the reduction of manufacturing barrier in many areas of pharmaceutical applications. The progress in SCFT is based on multidisciplinary approach and a considerable progress has been made over the last decade in the application of supercritical fluids (SCFs) to the processing of pharmaceuticals and to the preparation of drug delivery systems. SCFs have been proposed as solvents, solutes, anti-solvents and reaction media and SCFT is very attractive for manufacturing innovative therapeutic particles, either of pure active compounds or mixtures of excipient and active compounds. Certainly, pharmaceutical companies can develop pharmaceutical products of much higher yields greater purity, and quality than possible by conventional chemical engineering unit operations using SCFTs. The most commonly used SCFs for a variety of applications include supercritical fluid carbon dioxide (SC-CO_2), nitrous oxide, water, methanol, ethanol, ethane, propane, n-hexane and ammonia.

SC-CO_2 is an attractive solvent or anti-solvent as it is safe, inexpensive, readily available, and an ideal substitute for many hazardous and toxic solvents. SC-CO_2 exists when both the temperature and pressure equal or exceed the critical point of 31°C and 73 atm. and has both gas-like and liquid-like qualities, and it is this dual characteristic of SCFs that provides the ideal conditions for extracting compounds with a high degree of recovery in a short period of time. By controlling the level of pressure/temperature/modifier, SC-CO_2 can dissolve a broad range of compounds, both polar and non-polar. At present, carbon dioxide technology is one of the fastest growing new process technologies being adopted by the pharmaceutical industry. Supercritical water is a unique medium for safe destruction of dangerous waste by total oxidation due to its special physicochemical properties (Bhupinder SS, 2010).

Advantages

Selectivity

The properties of a supercritical fluid can be altered by varying the pressure and temperature, allowing selective extraction. For example, volatile oils can be extracted from a plant with low pressures (100 bar), whereas liquid extraction would also remove lipids. Lipids can be removed using pure CO_2 at higher pressures, and then phospholipids can be removed by adding ethanol to the solvent.

Speed

Extraction is a diffusion-based process, with the solvent required to diffuse into the matrix, and the extracted material to diffuse out of the matrix into the solvent. Diffusivities are much faster in supercritical fluids than in liquids, and therefore extractioncan occur faster. Also, there is no surface tension and viscosities are much lower than in liquids, so the solvent can penetrate into small pores within the matrix inaccessible to liquids. Both the higher diffusivity and lower viscosity significantly increase the speed of the extraction: An extraction using an organic liquid may take several hours, whereas supercritical fluid extraction can be completed in 10 to 60 minute (Skoog DA and Crouch FJ, 2014).

Physical properties of Supercritical Fluids

The physical properties of supercritical fluids are in-between those of a gaseous and liquid states. Typical values of different physical properties for each fluid state are listed in table1.

Kinematic viscosity defined as $\eta = \mu / \rho$

- Thermal conductivity presents maximum values in the near-critical region, highly dependent with temperature

Density and viscosity of supercritical fluids are lower than those of liquids; however diffusivities are higher. Thermal conductivities are relatively high in the supercritical state and have very large values near the critical point, because, in principle, the heat capacity of a fluid tends to infinity at the critical point. Interfacial tension is close to zero in the critical region. In general, the physical properties in the critical region enhance mass and heat transfer processes (Kurnik RT and Reid RC, 1981).

Processes using Supercritical Fluids (SCF)

SCF technology can be classified in to three broad categories depending on the way SCF-CO_2 is being used.

- SCF-CO_2 used as solvent for active substances and its excipients (RESOLV RESS, PGSS,, RESAS, DELOS)
- SCF-CO_2 used as anti-solvent for the precipitation of active substances and their excipients in organic solvent (GAS, ASES, PCA, SAS, ASAIS, SEDS)
- SCF-CO_2 assisted spray drying or aerosolization based methods (CAN-BD, SAA).

SCF as a solvent

Rapid expansion of supercritical solutions (RESS)

Rapid expansion of supercritical solutions (RESS) process is consisting of two steps; (a) dissolving the solid substance in a SCF and (b) formation of particles due to supersaturation. In the RESS process, at first SCF-CO_2 is pumped at desired pressure and temperature to extraction chamber containing solid substance(s) through heat exchanger as seen in the fig. (2). The SCF percolates and dissolves the solid substance(s) in the extractor and then the resulted solution is depressurized through a heated nozzle or capillary at supersonic speed into a low pressure chamber. The supercritical solution is expanded adiabatically in the chamber, which leads to a rapid drop in temperature and pressure and spontaneous formation of droplets/particles. During the rapid expansion of the supercritical solution, the density and solvent power decrease significantly, resulting in super saturation of the solution and consequently precipitation of desire particles free of a residual solvent. This process is also called supercritical fluid nucleation (SFN).

The parameters influencing RESS process are classified into pre-expansion and post-expansion condition. Pre-expansion condition includes equipment related parameters (temperature and pressure) and raw material related parameters like SCF, structure of solute (crystalline or amorphous, composite or pure) and cosolvent. The post-expansion condition depends on nozzle temperature, geometry, size, distance and angle of impact against the surface of the jet stream.

The advantages of RESS process are that it is simple, effective when single nozzle is used and it minimizes the use of organic solvent and reuses the SCF in continuous process. The main drawback is represented by poor solubility of most of the pharmaceutical material (e.g. polymer) in SCF-CO_2, which, in turn require large amount of fluid, and therefore, RESS increases the cost of production. Difficulty of scaling up the process because of particle aggregation and nozzle blockage caused by cooling due to the rapid expansion of the supercritical solution and also poor control over particle size distribution (Parhi R and Padilama S, 2009).

Below is presented the example of RESS micronization of lovastatin, an anti-cholesterol drug that is slightly soluble in CO_2; the nozzle geometry orients the particle size morphology from long rods generated by a capillary nozzle to spherical particles generated by a very short laser-drilled orifice (Michel P, 2002; Jung J and Perrut M, 2001).

Particle formation from gas saturated solutions (PGSS)

Many pharmaceutical materials are polar or high molecular weight substance, such as protein and peptide and due to which it is difficult to dissolve them in CO_2, which has no polarity even in supercritical state. High amount of CO_2 is needed to compromise this low solubility, which in turn increases operational cost. In PGSS process, the polymer(s) are first melted or suspended in solvent at a given temperature in an autoclave and then solubilizing SCF-CO_2 in above melted or liquid suspended substance(s), leading to a so called gas saturated solution or suspension that is further depressurized through a nozzle with the formation of droplets or solid particles Fig.(4). Unlike to RESS technique, the principle governing PGSS process involves both the pressure and temperature- and solvent-induced phase separation.

Advantages of PGSS process are

(i) Substance need not be soluble in SCF-CO_2,
(ii) Simplicity of this process, leading to low processing cost and wide range of application,
(iii) Can be used with suspensions of active ingredient(s) in polymer(s) or other carrier substance leading to composite particles,
(iv) Can be applied to process inorganic powders to pharmaceutical compounds, and
(v) low solvent gas usage and pressure than RESS process as operational condition (Weidner E *et al*., 2003)

Care must be taken for thermolabile solute and moreover this technique compromises with microparticles. Insulin SLNs of size less than 500 nm were prepared by using DMSO as solvent and the lipid mixture of tristearin, phosphatidylcholine and dioctylsulfosuccinate (Almeida AJ and Souto E, 2007).

Rapid Expansion of a Supercritical Solution into a Liquid Solvent (RESOLV)

RESOLV method consists of spraying of solution (drug in SCF-CO_2) into an aqueous medium from vessel maintain at given temperature and pressure. The rapid expansion of solution and followed by quenching leads to particle formation. Number of water soluble polymer (e.g. PVP) may be added to the aqueous medium to stabilize the particulate suspension. Finally, particles recovered from the suspension. The advantage of this method is that the possibility of stopping the particle growth in the precipitator. RESOLV method is having the same

limitation as RESS. The other problem is the recovery of particle from the aqueous solvent (Parhi R and Padilama S, 2009).

Rapid Expansion from Supercritical to Aqueous Solutions (RESAS)

This is a modification of RESS technique and is developed so that the stabilization of submicron particle in the aqueous phase became feasible. In this process, the supercritical solution (SCF with polymer and drug) is expanded through a nozzle in to an aqueous solution containing stabilizers. Usually, non-ionic surfactants such as lecithin, polysorbates and poloxamer are the choice for the stabilization because of their low toxicity. Parameters that are influencing the resultant particle size are stabilizer type, concentration of stabilizer in aqueous phase, solid to surfactant ratio and finally the temperature of the stabilizer solution. Nanosizing of particles, high drug payload and long term stability are making this technique attractive than RESOLV method. But there are some demerits like it is not a suitable method for the drug which are unstable in aqueous solution and broad particle size distribution (Huang J andMoriyoshi T, 2008; Turk M and Lietzow R, 2004).

Depressurization of an expanded liquid organic solution (DELOS)

In DELOS process, the substances are first dissolved in suitable organic solvent and then it is mixed with SCF-CO_2 in a vessel of particular temperature and pressure. This mixture is depressurized through a nozzle into a vessel to form fine particle. Here, the SCF-CO_2 is used as co-solvent to the organic solvent. The main advantage of this technique in comparison to PGSS is that the thermo-sensitive material can be handled to prepare fine particle without melting it.

SCF as an antisolvent

The low solubility of pharmaceuticals in SCFs limited the large scale production of micro/nano sized particles by PGSS and RESS method. Using SCFs as antisolvent was thought off by many researchers to solve the above problem. Here, the solute is insoluble in an antisolvent, whereas the antisolvent should be completely miscible with liquid solvent. This is based on the principle that when a solution sufficiently expanded by a gas, the liquid phase is no longer a good solvent for the solute and particle formation by precipitation occurs. The SCFs as antisolvent includes GAS, SAS, ASES, PCA and SEDS processes.

Gaseous Anti Solvent (GAS)

GAS is a batch process where the precipitator is partially filled with the solution of solute of interest and then the supercritical antisolvent is pumped into the vessel, preferably from the bottom until the fixed pressure is reached as shown on fig. (5). the particles precipitate as the gas concentration in the solution increases with pressure. After a holding time, the expanded solution is made to pass through a valve present above the precipitator to wash and clean the precipitated particles. A clear disadvantage of this technique is the lack of control on the particle formation, which prevent the formation of mono dispersed particles.

Aerosol Solvent Extraction System (ASES), Particles by Compressed Anti-solvent (PCA), Supercritical Antisolvent (SAS)

The SCF is first pumped to the top of the high pressure vessel until the system reaches a constant temperature and pressure Fig. (6)**.**Subsequently, active substance solution is sprayed as fine droplets into above SCF bulk phase through an atomization nozzle. The large volume expansion of drug solution in vessel, resulting dissolution of SCF into liquid droplets and, subsequently, in super saturation due to reduction in solvent power leading to nucleation and formation of small and mono disperse particles. Particles are collected on a filter at the bottom of the vessel. The SCF and organic solvent mixture flow down to a depressurized tank where suitable temperature and pressure condition allow gas-liquid separation. After the collection of sufficient quantity of particles, the spraying of liquid solution has to be stopped. Furthermore, to remove residual solvent, pure SCF continues to flow through the vessel. The ASES can be modified with the addition of precipitation of compressed anti solvent (PCA) which was proved to be more efficient in the production of a great variety of organic and biopolymer based particles.

Main advantage of this technique over GAS is its suitability for continuous operation, which prerequisite for large scale mass production of particles. Complex mass transfer process is one of the major limitations in SAS scale up. Complex mass transfer process is originated due to two issues. First one is the result of variety of jet dispersion patterns in the supercritical spray leading to formation of droplets of non uniform sizes. It is obvious that mass transfer within the droplets of smaller size is considerable faster than that of larger droplets owing to higher surface area of the former. Furthermore, there is more time for crystal growth in larger particles. Another problem related to mass transfer in SAS is due to residence time of particles under supercritical condition until the cycle ends. Particle may still grow, when present on the filter for separation, under above condition. To solve above problems in SAS, concentric tube anti-solvent reactor (CTAR) technique was developed. In this process, particles are formed inside a small concentric tube instead of usual spraying of drug solution into SCF. Filter is used for the harvesting of particles, which is again more problematic

owing to small concentric tube in CTAR (Parhi R and Padilama S, 2009).

Atomization of supercritical anti-solvent induced suspension (ASAIS)

This is another modification to SAS technique. In ASAIS process, anti-solvent induced precipitation occurs in a small tube, where anti-solvent mixed with the solution to generate a suspension. This suspension of particles is then sprayed into a precipitator at atmospheric condition for solvent separation, which eliminates the high volume and high pressure precipitator. In addition, very small to moderate anti-solvent concentration is required. Contrary to both SAS and CTAR process, the particles recovery is performed by cyclone separator rather than using filter. Here, the first step (suspension formation) occurs in the small tube and next step in the precipitator and finally particle recovery in cyclone separator (Rodrigues MA *et al.*, 2013).

Solution Enhanced Dispersion by Supercritical Fluids (SEDS)

This is a modification of SAS process in which the SCF and drug solution are introduced simultaneously in to the precipitation vessel at particular temperature and pressure through the coaxial nozzle. The design of co-axial nozzle is such that to facilitate the dispersion of drug solution by SCF, thereby enhancing mass transfer and formation of fine particles Fig. (8). In addition, the high velocity of SCF allows intense mixing with drug solution. Here, the SCF serves both as an anti-solvent and as a dispersion medium.

The particle formation/size by SEDS depends on the mass transfer of SCF into sprayed droplets and by the rate of solvent transfer into the SCF phase. In general, high mass transfer causes faster supersaturation and smaller particle size with less agglomeration. Most often two way coaxial nozzle is used where both drug solution and SCF are introduced into precipitation chamber as separate stream. Basic operational principle of GAS/SAS/ASES/PCA/SEDS is described as follows. A ternary system is produced by the introduction of SCF in to chamber containing polymer and solvent homogenous binary system. Upon change in pressure, compositional quenching takes place leading phase separation and particle formation.

To overcome the limitation of water solubility in SCF, SEDS has been further modified to in order to process water soluble compounds (e.g. protein and peptides). The above modification includes the use of three way coaxial nozzle to introduce aqueous drug solution, SCF and organic solvent (polar) in to particle formation chamber as separate stream. The organic solvent acts both as precipitating agent and a modifier, enabling the non-polar SCF to remove water. The use of ultrasonic nozzle is a further modification of SEDS. The formation of fine droplets is based on the induction of ultrasonic waves of frequency between 10-100 kHz, caused by the vibration of ultrasonic coaxial nozzle.

SCF-CO2 assisted spray drying (Aerosolization-based) methods

These techniques used SF to assist or enhance the nebulization or aerosolization of the solution of the substance to be processed, which is then rapidly dried in a drying atmosphere to form fine particles. There are two methods based on this principle.

Carbon dioxide Assisted Nebulization with Bubble Dryer (CAN-BD)

This process focused on the nebulization of the liquid solution rather than using dense gas (SCF) to achieve precipitation by solubility reduction for the solute to be micro- or nano-sized. At first, the solute(s), preferably in between 1% to 10%, is dissolved or suspended in aqueous or organic solvent or their mixture and then mixed intimately with near critical or SC by pumping both fluid through a near zero volume tee as shown in Fig. (9), to generate emulsion. The resultant emulsion is rapidly expanded through a flow restrictor to near atmospheric pressure to form aerosol consisting of micro droplets and micro bubbles. The aerosol is formed due to sudden dispersion of the liquid solution caused by rapid expansion of compressed gas. The drying chamber is filled with heated air or nitrogen gas to maintain the desired temperature for rapid drying of aerosol droplets or micro bubbles. Dry particles are collected on a filter placed at the outlet of the drying chamber.

Parameters influencing the particle formation are flow rate of solution (for lab scale 0.3-0.6 ml/min is sufficient), percentage of dissolved or suspended substance, inner diameter flow restrictor (50-175 μm and length ∽ 10 cm), temperature of the drying chamber, residence time of droplets or micro bubbles (as micro bubbles are dried faster than droplets).

Advantages of CAN-BD process are; (i) minimum decomposition of thermolabile drugs, (ii) preferred method for water soluble drug, (iii) organic solvent compatible with SCF can be substituted in part or totally for water, and (iv) very fine size of the produced particle (<3 μm diameter). There is need to heat tee and restrictor to a temperature in the range 50 to 100 ºC in order to avoid restrictor obstruction during expansion.

Supercritical Fluid-Assisted Atomization (SAA)

SAA process is based on the solubilization of SCF in aqueous solution to be dried and subsequently atomization through a thin wall nozzle at atmospheric pressure. The difference between SAA and CAN-BD is the

region where the mixing is achieved (Parhi R and Padilama S, 2009).

PHARMA APPLLICATIONS OF SCF-

Industrial applications of Supercritical Fluids have been mostly developed for natural products extraction/fractionation, both for food and pharmaceutical products. At present time, these applications are still continuing to spread worldwide as requirements for high quality products and concerns on environment/health are growing.

Extraction

SFE from solid materials is the most developed application, mainly for food products (coffee, tea), food ingredients (hops and aromas, colorants, vitamin-rich extracts, specific lipids) and nutra-/phytopharma-ceuticals. Residual organic solvent or other impurities, like pesticides, are also removed from final active compounds (like ginseng) at large scale or residual solvents from synthetic drugs. I estimate the number of industrial-scale SFE units now under operation about 100 with a growth of about 10% per year. Some niches applications concern high-added value products, like bone delipidation for allografts, or specialty polymer stripping for medical applications.

Fractionation

SFF of liquid mixtures is designed to take profit of the very high selectivity of supercritical fluids with attractive costs related to continuous operation ; nevertheless, few industrial units are now used for aromas production from fermented and distilled beverages, fractionation of polyunsaturated fatty acids (EPA, DHA), polar lipids (ceramides, sphingolipids, glyco-lipids), specialty lipids (phytosterols) and vitamins (tocopherols), specialty polymers (hard-disk lubricants) ; the recovery of active compounds from fermentation broths may also appear as a fruitful application in the near future.

Preparative Scale Supercritical Fluid Chromatography

PSFC is operated for ultimate fractionation of very similar compounds, especially for lipids like polyunsaturated fatty acids in a few large-scale units; moreover, enantiomers resolution is paid great interest, at lab-scale until now prior to further development.

Reactions

SFR are operated in Supercritical media and very promising processes are being developed for fine highly selective synthesis, especially hydrogenation. As reaction rate and selectivity are drastically improved, a very high throughput can be obtained from rather small units, with the example of a recent start-up of a plant dedicated to hydrogenation of specialty chemicals in the UK.

Particle design and drug formulation

Particle formation processes using supercritical fluids are now subjected toincreasing interest, especially in the pharmaceutical industry with three aims : Increasing bio-availability of poorly-soluble molecules, designing formulations for sustained-release and for less invasive than parenteral drug delivery (oral, pulmonary, transdermal). The most complex challenge is related to therapeutic proteins as it is extremely difficult to deliver bio-molecules due to instability and very short half-life *in vivo*. The various stages of particle formation bysupercritical fluid processing can be broadly classified into delivery, reaction, pre-expansion, expansion and collection. The importance of each of these processes in tailoring the particle morphology has been reported along with presenting various alternatives to perform these operations. In pharmaceutical industry, fine particles (μm or nm) with uniform narrow size range are of particular interest. Various SCF processes for particle formation include RESS, SAS, PGSS, SAS, PCA, ASES and SEDS.

Co-formulation

Co-formulation of drug and excipient is one of the emerging concept in Pharma industry. SCF based PCA process provided good approach for co-formulation and quality of co-formulation product. Coformulation particles of the non-steroidal anti-inflammatory drug ketoprofen and the amorphous biodegradable polymer poly-lactic-co-glycolic acid ranging between 100 and 200 nm in size were reported by SC-CO_2 extraction of emulsions. SCFT provided co-formulated samples with a rapid and enhanced dissolution profile for poorly water-soluble drugs. The PCA process was used to maximize the drug loading in stable and fully amorphous solid dispersions of phenytoin in PVP (Schmitt WJ and Reid RC, 1986).

Drying of proteins and peptides

The number of protein such as cyclosporine, insulin, protein hydrolysate are introduced to the market, which is the result of genetic engineering (Jain GK and Jain NK, 2001). The important aspect about protein and peptide is the stabilization as they are unstable in liquid formulation because of chemical and physical degradation reaction, which necessitates to store in dry form (Manning MC *et al.*, 1989). Many traditional drying techniques, such as freeze drying, spray drying, vacuum drying and spray freezing drying, have been used for a long time to stabilize above compounds. But all the above techniques are having drawbacks. For instance, freeze drying is an expensive process due to high energy and time consumption and not providing complete recovery of the intact protein due to process induced degradation (during freezing and drying phase). SCF process is an alternative method to above due to its mild process conditions, cost effectiveness and possible sterilizing properties (Dillow AK *et al*., 1999).

Coating

An improved process for coating medical devices, particularly surgical devices such as stents with polymer or polymer and a pharmaceutical/therapeutic agent or drug using SC-CO_2 has been reported. Scientists have reported a method for forming a continuous film on a substrate surface that involved depositing particles (mean particle size of less than 1 micron) onto a substrate surface and contacting the particle-deposited substrate surface with a supercritical fluid under conditions sufficient for forming a continuous film from the deposited particles. The method may be performed in a pressure vessel containing a compressible fluid. A particle-deposited substrate was provided in the pressure vessel and the compressible fluid was maintained at a supercritical or sub-critical state sufficient for forming a film from thedeposited particles. Pierre Fabre Medicament - active ingredient division - has recently enlarged its Drug Delivery Technology portfolio based on its knowledge in supercritical fluids. Cyclodextrin complexation in SC- CO_2 is a Pierre Fabre patented technology mainly used in the bioavailability enhancement of poorly soluble APIs 58. Polymer fibers with a diameter of several ten to hundred nanometers have a very large surface area to volume ratio. Hollow fibers by electrospinning in supercritical CO_2 are likely to provide a big potential in a wide range of applications.

Solid Dispersions

Composite particle generation by SCF processes looks as a very promising solution to enhance the dissolution of poorly-soluble compounds and the most studies were conducted with hydrophilic polymers and cyclodextrins leading to size-controlled particles that rapidly release the active compound in the aqueous media. A number of drying methods such as evaporation as a baseline, freeze drying, SCF, and a novel CO_2 sublimation are available. Based on drying time and production yields for all powders tested, SCF processing and CO_2 sublimation produce, by far, the most dispersible powder. ASES process proved as a promising technique to reduce particle size and/or prepare amorphous solid dispersion of drugs in order to improve the solubility and bioavailability of poorly water-soluble drugs such as itraconazole 138. Paclitaxel solid dispersion prepared by using the SCF process showed an improved solubility, thereby, being effectively used for the preparation of paclitaxel injection and oral preparation having a high bioavailability. Dissolution studies of cefuroxime axetil solid dispersions with HPMC 2910/PVP K-30 prepared using (SEDS indicated that the dissolution rates were remarkably increased in solid dispersions compared with those in the physical mixture and drug alone. Thus, an amorphous or non-crystalline CA solid dispersion prepared using SEDS could be very useful for the formulation of solid dosage forms 140 Micronized solid dispersions containing hydrophilic carriers and a new chemical entity, YNS3107 prepared by PGSS process enhanced the rate of dissolution of YNS3107 in the solid dispersion microparticles. Precipitation with compressed antisolvent (PCA) provided an effective pharmaceutical formulation technology to improve the bioavailability of poorly water-soluble drug.

Preparation of liposome

Liposomes are non-toxic (mostly) and effective in encapsulation ofmaterials from the environment. Several studies have indeed shown that liposomes form a basis forcontrolled release food processes such as for the release of enzyme involved in cheese ripening. Liposomes can be prepared in a 50-mL autoclave equipped with a variable speed agitation device. Thegeneral protocol started with the injection of predefined quantities of the solute and phospholipids to the reactor. After heating to a specified temperature, solution was pressurized to 30.0 MPa under gentle agitation. After agitation at 100 rpm for 5 minutes, the vessel was depressurized over a period of about 45 minutes. The liposomes were finally isolated and stored at 4°C under nitrogen Encapsulation efficiency was independent of solute concentration between 10 and 50 mg/mL and of pressure above the critical pressure. However, significant effects were observed with respect to lipid concentration, temperature and initial volume of aqueous phase. Manufacturing of liposome by SCF covers three separate methods including: (i) phospholipids solvation in a near critical fluid, mixture with a protein containing buffered solution (ii) decompression of solvated phospholipids prior to injection to solution, (iii) the critical fluid decompression technique in which phospholipids are first hydrated in an aqueous buffer, mixed with SCF, with the mixture being then submitted to decompression. Several parameters can improve the characteristics of the liposomes prepared with SCF ethane. Optimization studies would be necessary to examine whether liposomes of higher quality can be made using SCF technology. Also, other SCF should be tested (Darani KK and Mozafari MR, 2009).

Impregnation

Impregnationof active compounds into excipients is easily obtained using SCF as vectors, due to their high diffusivity and tunable solvent power, either through porous matrix or inside non-porous polymeric matrixes swollen by the fluid, like pharmaceutical patches, sponges, and catheters. We recently disclosed a new process for on-line impregnation after extraction, especially for natural products impregnation into a porous excipient, leading to a free-flowing powder (Majewski W and Perrut M, 2000).

Supercritical Fluid Chromatography and its application

Supercritical fluid chromatography (SFC) uses CO_2 as mobile phase to dissolve compounds.

Unfortunately, CO_2 is not a good solvent for polar compounds. But, this problem can be corrected by adding moderate amount of organic solvent, called as modifier. The popularity of SFC lies on its advantage over HPLC such as (a) faster and more efficient separation of compounds due to lower viscosity and higher diffusivity of CO_2, (b) most of the pharmaceutical ingredients used for the synthesis purpose are as soluble or more soluble in mixture of CO2 and organic modifier, (c) recovery of purified compounds from the collected fractions is easier and economical as solubility in CO_2 decreases rapidly with decrease in pressure, (d) moreover, mobile phase, CO2, is cheaper, greener and safer as compared to organic solvent. There are, generally, two types of SFC, namely packed column and preparative scale.

The application of SFC includes: (a) chiral (enantiomer) separation e.g., separation of chiral sulfoxide belonging to thefamily of substituted benzimidazoles by using Chiralpak AD and methanol as stationary phase and modifier, respectively.Separation of 44 paires of enantiomers (β-blockers, β-agonist, benzdiazepines, non-steroidal anti-inflammatory drugs,barbiturates, free and derivatized amino acids) were carried out by using common stationary phase (Chiralcel OD and AD,ChirobiotcVandT),CO_2odified with 5-30 % of methano l. Liu et al. performed the enantiomeric separation of macr ocyclic glycopeptide (teicoplanin) and some of its common derivatives, (b) Separation of achiral compounds such as t he separation of mixture of estrogen metabolite and separat ion of phosphatidylcholine, phosphatidylethanolamine, ph osphatidylinositol and phosphatidylserine by SFC coupled with light scattering and mass spectrometric detection, (c) analysis of peptides- among the peptides separated and analyzed by SFC are cyclosporin, actinomycin D and vancomycin, gramycidin A, B, and C, (d) Coupling of SFC with mass spectroscopy, which helps to obtained good peak shape and signal in chromatogram.

Supercritical Fluid Extraction (SFE)

Supercritical Fluid Extraction near the critical point of the (SFE) is based on the fact that, solvent, its properties change rapidly with only slight variations of pressure. Supercritical fluids can be used to extract analytes from samples. The main advantages of using supercritical fluids for extractions is that they are inexpensive, extract the analytes faster and more environmentally friendly than organic solvents. For these reasons supercritical fluid CO_2 is the reagent widely used as the supercritical solvent.

Polymer processing

Specific interactions between supercritical fluids and polymers lead to many attractivedevelopment. Most polymers are swollen by SCF that act as plasticizers, decreasing sharply the glass transition temperature, what permits easy penetration of solutes impregnation) or extraction of residues (stripping), morphology modifications (foams, particles, fibers), blending alloys, grafting reactions or spinning fibers.

Ceramics and carbons manufacture

For long, ceramic binder extraction has been widely described, permitting to manufacture ceramic pieces of very good dimension stability and reproducibility with a much shorter cycle than classical binder cracking by heating. According to our knowledge, this process is getting increasing acceptance for high-duty ceramic parts.On the other hand, ceramic precursors can be prepared using SCF, either throughelaboration of the oxides powder by hydrothermal synthesis in supercritical water or SCF CO_2 fractionation of narrow cuts of polymeric precursors of C-C alloys likepolycarbosilanes or mesophase from petroleum pitch.[19] Moreover, impregnation ofthree dimension mats of carbon fibers by polycarbosilane is claimed to lead to a drastic improved C-C alloy properties (fatigue and oxidation under high stress) (Michel P, 2002).

Generation of the pharmaceutical co-crystals

For the production of the novel crystalline forms of the active pharmaceutical ingredients (also called Pharmaceutical co-crystals), Supercritical fluids technology provide the advantage of the single step production of the particles that are difficult to obtain by the traditional techniques. Solvent power, antisolvent effect and atomization improvement are few of the properties of the Supercritical fluids that signify their capability of producing the pure and dry crystals of pharmaceutical ingredients. Examples of the crystals formed utilizing the technique is formation of the Indomethacin Saccharin cocrystals (Bhardwaj L and Sharma P, 2010).

Foams and aerogels

For long, all polymeric foams were blown with CFC (R12, then R22) that are now banned and most manufacturers are now turning to light hydrocarbons or, preferably, to carbon dioxide, leading to drastic cost reduction. Injection of CO_2 in thermoplastic extruders is now common practice, especially for polystyrene foam. On the other hand, more sophisticated polymeric foam elaboration using SCF was patented: preparation of microcellular foams (2-25 mm) from most thermoplastics was claimed as soon as 1984 and, more recently, preparation of extremely small cells (< 2 mm) and extreme high cell density. Moreover, it is possible to impregnate the foam with solutes during the foaming process if the solutes are soluble in liquid or supercritical CO_2, as proposed for food Products (Dixon DJ and Johnston KP, 1997).

Other Applications

Regarding sterilization, it is known for long that CO_2 has a biocide effect on most bacteria and fungi. A recent article reviews the literature and reports attractive results showing that bacteria can be easily inactivated by exposition during a few minutes to carbon dioxide at relatively low pressure (74 bar) at 38°C; moreover, spores can be inactivated only when using high temperatures (75°C) or through a more interesting process operating at low temperature (38°C) and rapidly cycling the pressure (50 - 150 bar) during one hour (30 cycles). The authors consider that this inactivation is related to dissolution of CO_2 in the cell causing a rapid decrease of the intracellular pH and a deep modification of the membrane permeability due to the interaction with the membrane lipids.

As a Supercritical Bio-catalyst

Hydrophobic Ion Pairing was used to solubilise biomolecules in supercritical CO_2 and fluorous solvents, by pairing cationic sites on the surface of the biomolecule with fluorinated cationic surfactant forming a soluble neutral complex (Michel P, 2002).

Destruction of Industrial wastes

Several SCFs have been tested successfully on waste materials on industrial nature. For example SC-water is very reactive, corrosive, and miscible with air and oxygen. An industrial process was describes the use of SC water to treat aqueous solutions containing organic compounds (Haas GJ *et al.*, 1989). A major pharmaceutical company has described the operation of a process based on this technology to treat waste generated from recombinant fermentation (Krishna G *et al.*, 1986).

Table 1. Comparison of the physical properties of gas, liquid and supercritical fluids

Physical Property	Gas (T at ambient)	SCF (Tc, Pc)	Liquid (T at ambient)
Density ρ (kg m-3)	0.6 – 2	200 - 500	600 – 1600
Dynamic viscosity μ (mPa.s)	0.01 - 0.3	0.01 - 0.03	0.2 – 3
Kinematic viscosity ηa (106 m2s-1)	5 – 500	0.2 - 0.1	0.1 – 5
Thermal conductivity **λ** (W/mK)	0.01 - 0.025	Maximum	0.1-0.2
Diffusion coefficient ***D*** (106 m2s-1)	10 – 40	0.07	0.0002 - 0.002
Surface tension ***σ*** (dyn/cm2)	-	-	20-40

Fig 1. Typical diagram of supercritical region

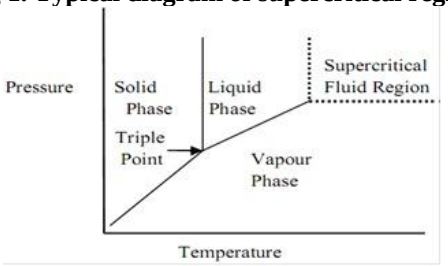


Fig 2. RESS equipment concept

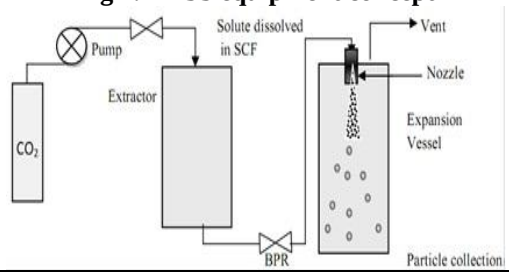
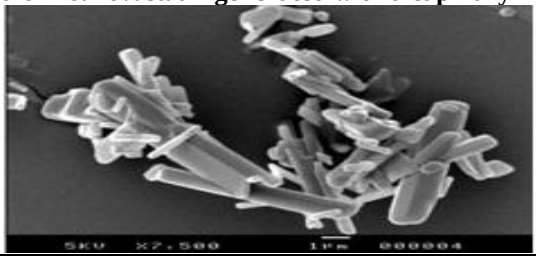


Fig 3. Lovastatin atomization by RESS

***a)Micronized lovastatin* generated with a capillary nozzle**



b) with a laser-drilled short orifice.

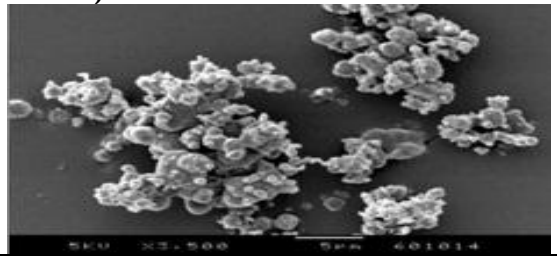


Fig 4. PGSS Equipment concept

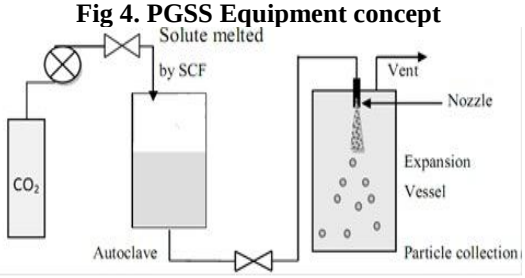


Fig 5. GAS equipment concept

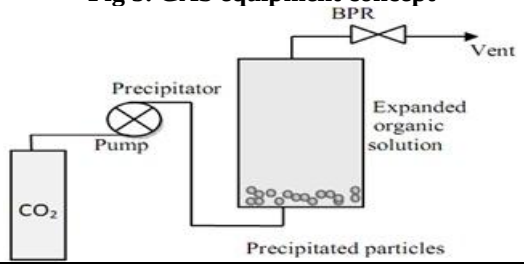


Fig 6. ASES/SAS/PCA equipment concept

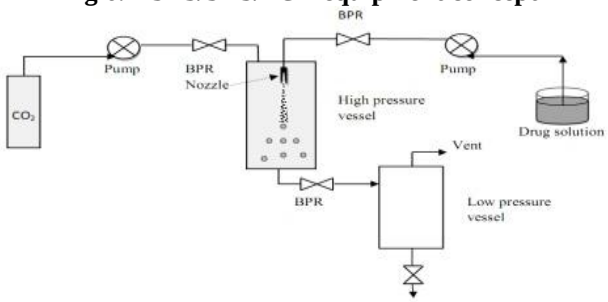


Fig 7. SEDS equipment concept

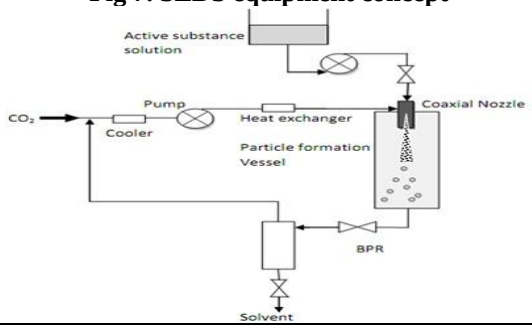
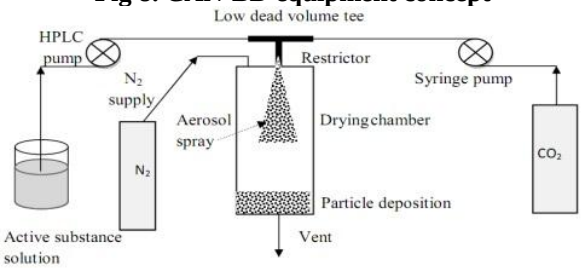


Fig 8. CAN-BD equipment concept



CONCLUSION

Supercritical fluids have unique properties, including high diffusivity, low surface tension, low dielectric constant, and continuously variable density. Also they are non-flammable, non-toxic, inexpensive and do not require special disposal. SCF provides alternatives for solvents in cleaning, extraction, and synthesis applications and provides new capability for extraction, chromatography, and toxic waste elimination, manufacturing specially structured materials, which cannot be produced conventionally. Many promising applications are now under development using SCF, especially for new drug formulations through innovative particle design. Several applications have been fully developed and commercialized which include food and flavouring, 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, isolation of lipid soluble compounds.

ACKNOWLEDGEMENT

Nil

CONFLICT OF INTEREST

No interest

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