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A review on methodology and application of supercritical fluid technology in pharmaceutical industry

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ABSTRACT

When the critical temperature and pressure of a fluid is crossed it exhibits mixed properties of gases and liquid, and at this state is called Supercritical fluid, while technique utilizing these fluids, is called Supercritical fluid technology. Supercritical fluids have good solvent power and transport capability due to their low viscosity and high diffusivity, which can be manipulated with slight variation in the temperature and pressure. Such properties of the supercritical fluid are utilized in extraction of the drugs, in analytical techniques, in chemical reactions to enhance selectivity, morphology of the particles and also in the development of the drug delivery systems. In this article, we have discussed about the properties of the supercritical fluids along with different variants of the technique and the applications in the pharmaceutical industry.

Keywords: Supercritical fluid technology, solubility, extraction, chromatography, nanoparticles.

INTRODUCTION

In present scenario of the pharmaceutical industry, advancement of various different approaches like high throughput screening, combinatorial chemistry and many others, are leading to the discovery of the new chemical entities, having good pharmacotherapeutic properties. In order to get these potent chemical entities administrable for human consumption, these are supposed to get incorporated in suitable and efficient drug delivery systems, which need the control over various physicochemical properties of particles along with their size, shape, crystalline structure and purity. These properties are key factors in order to manage technological and biopharmaceutical properties of drug products, specially, for the drug product meant to be inhaled or injected intravenously [1].

When the temperature and pressure of a fluid is above its critical point, the fluid is called to be in a supercritical region and at that stage, called Supercritical fluid. Critical temperature of a fluid may be defined as, the highest temperature at which a gas got liquefied by raising the pressure of the system, while the Critical pressure, similarly, may defined as the, highest pressure at which a liquid get converted to the gas by raising the temperature of the system. Supercritical fluids, generally, come into the existence at a reduced temperature (temperature/critical temperature) around 1.01 to 1.11 and at a reduced pressure (pressure/ critical pressure) around 1.01 to 1.5. Supercritical fluids, in critical region, where the gaseous and liquid phases are not distinguishable, shows density like liquids; viscosity & diffusivity like gases, which impart the good mixing and mass transfer properties and shows variations in the solubility of the solutes on slight changes of temperature and/or pressure. This variation of solubility at different temperature gives us the freedom for the selection of the suitable supercritical fluid as a solvent for specific application. When, such fluids at their critical temperature and pressure, are utilized for various purpose, as an integral part of the technique, it is called Supercritical fluid technology.

During earlier years of 1980s, Supercritical fluid technology was applied in the pharmaceutical industry and crystallization and precipitation techniques using Supercritical fluid was developed. Being harmless, environment friendly, cost-effective technique and processing under working conditions of low pressure and temperature make the technique attractive for pharmaceutical research.

Current applications of the supercritical fluids include extraction of drugs, qualitative or quantitative analysis, drug particle formation, micronization, production of the nanoparticle and microspheres etc.

Advantages of the supercritical fluid technology over other techniques are:
1. Enhancement of the selectivity and yield of the technique by adjusting the solvent strength.
2. High diffusion coefficient and low viscosity.
3. Faster and complete solvent recovery without any residue left.
4. Good environment compatibility and non toxicity of the solvents.
5. Retention of the actual structure and morphology of the powdered particles dried.

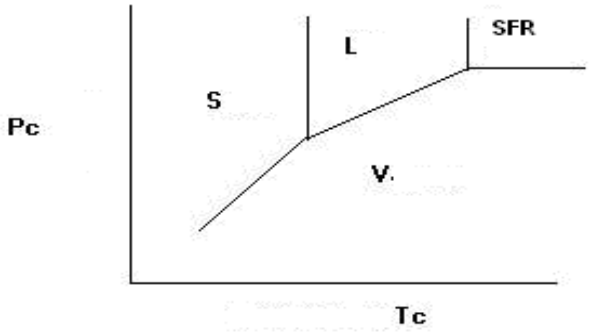
Historical Aspects [2]

Existence of a fluid in supercritical phase was first cited by Cagniard de la Tour in 1822, during visual inspection of a sealed glass container at elevated temperature, where the disappearance of the liquid- gas interphase was observed. It was followed by, in 1879, by Hannay and Hogarth, where they reported the enhanced solubility of (metal chlorides in) a supercritical fluid (Supercritical Ethanol) at low pressure. It was during early and mid 20th century, where the technology got a little attention. In 1936, Wilson et al, work on a propane based deasphalting process in which they use the increased solubility of propane at critical temperature and pressure and had provided a great boon for the selective separation of paraffin wax, asphalt, purified light oil etc. from the lube oil feed stock. The process has also lead in the development of the “Solexol process”, for purification and extraction of Vitamin A from fish oil and polyunsaturated triglycerides from vegetables, utilizing supercritical Propane. Later on, in 1971, the process was

also utilized in the decaffeination of the Coffee beans, which became the major commercialized use of the Supercritical fluid technology, during that period. In pharmaceutical industry, the use of the Supercritical fluid technology was first cited in the processing of the active pharmaceutical ingredients, where these were processed to reduce and impart homogeneity in the particle size, and hence to enhance the bioavailability. But, the major utilization of it, in pharmaceutical industry, was started during 1980-90s.

Supercritical fluids properties

Any fluid is said to be entered in a supercritical phase, when the pressure & temperature both crosses its critical pressure & temperature values. During these conditions, the Supercritical fluid depicts its existence in an intermediate phase **(fig. 1)** between gaseous and liquid phases respectively, with opalescent and homogenous consistency [3].



where , Pc: Pressure; Tc: Temperature; S: Solid phase; L: Liquid phase; V: Vapour phase; SFR: Supercritical Fluid region.

Diagram showing Supercritial Fluid region

Fig. 1: Phase diagram showing Supercritical Fluid region

Supercritical fluids have moderate to high density, but also show high compressibility, around the supercritical region. This shows, that even slight variation in applied pressure causes alteration in its density and hence in its solvency [4]. Further, the solvency power of the supercritical fluids can be compared with gases and liquids on the basis of their density and viscosity (Table 1).

Table 1: comparison of properties of Supercritical Fluid with Gas & water

Phase of the solvent	Viscosity ($gm.cm^{-1}$ sec^{-1})	Density (gm/ml)	Coefficient of diffusion	Remarks
Super critical Fluid	0.0001 to 0.001	0.1 to 1.0	0.001to 0.0001	Viscosity is similar to gas.
Gaseous	0.0001	0.001	0.1	Viscosity is similar to supercritical fluid
Liquid	0.01	1.0	Less than 0.00001	Viscosity is greater than Gas and supercritical fluid

For Supercritical fluids, solvent like properties shows its importance in drug solubilization, polymer plasticization and extraction of organic solvents or impurities while its gaseous

properties leads to enhancement of the phenomenon of diffusion. Even after having such versatile characteristics supercritical fluids cannot be declared Super solvent [5].

While, selecting the supercritical fluid for the thermolabile products like proteins and peptides, it is very important to consider its critical temperature. Carbon dioxide is the most commonly used supercritical fluids due to its low critical pressure (73.8 bar) and low critical temperature (87.98 ^{o}F), making it a very useful solvent for the heat sensitive (thermolabile) drugs and chemicals. It is also approved by the USFDA for pharmaceutical & food industry and is economical. Other supercritical solvents used in the industry are discussed in Table 2.

Table 2: Properties of common Supercritical solvents used in the industry

Solvent	Critical temperature (K)	Critical Pressure (Atm)	Density (mg/ml)
H_2O	647	218	320
CO_2	304	73	470
C_2H_5OH	517	63	280
C_6H_6	562	48	300
NH_3	406	113	240
C_2H_6	306	48	200
$CHCl_3$	299	28	620

Supercritical Carbon dioxide and supercritical water are seemed to be more environment friendly and considered as a perfect substitute for the solvents of petroleum category, which are used in the chemical and other industries on a greater extent [6]. These solvents, if present in residual amounts also pose the problem of producing adverse effects, from processing and environmental point of view.

During the last ten years, applicability of supercritical fluid technology has shown a steep growth due to its capability of being compatible with various chemical materials and has replaced organic solvents in various chemical processes not only in the pharmaceutical industry but also in the other chemical industries. Super critical fluid technology, these days is being used in the processing of food, chemical synthesis, extraction of the phyto-constituents (on large scale) from the crude drugs, manufacturing of the nanoparticles, particle coating etc [7]. In reference to traditional methods, used for the particle generation like spray drying technique, precipitation technique and freeze drying technique which produce the larger size particle followed by communition for desired particle size, Supercritical fluid technology assure the generation of the particles in more controlled manner with desired morphology. The particle so produced using supercritical fluid technology need not to be further processed, which makes this technology more useful in the production of biomolecules and other sensitive molecules. The advancement in the Supercritical fluid technology has provide a great support in the in the development of the new pharmaceutical products from small molecular size drugs to macromolecules of biological origin like peptides, proteins and nucleic acid [8].

Methods used in the Supercritical Fluid technology

Through Super critical fluid technology, it is possible to reduce the size of the particle and the content of the residue of the solvent in single step and control the various parameters related to the particle characteristics like particle size distribution, polymorphism, crystal lattice and morphology.

Depending on the use of the supercritical fluid in the system we can classify the processes in two groups as:

A.) Solvent

B.) Antisolvent.

Process in which Supercritical fluids are used as solvent

1. **Rapid expansion of supercritical solution:** It was, during the late 1970s, when first time fine particles were produced having narrow particle size distribution using the Supercritical fluid technology [9]. This technique was called rapid expansion of the supercritical fluid, which was based on the phenomenon, in which solid is first dissolved in gas and then allowed to precipitate under reduced pressure (First recorded by the Hogarth and Hannay) [10].

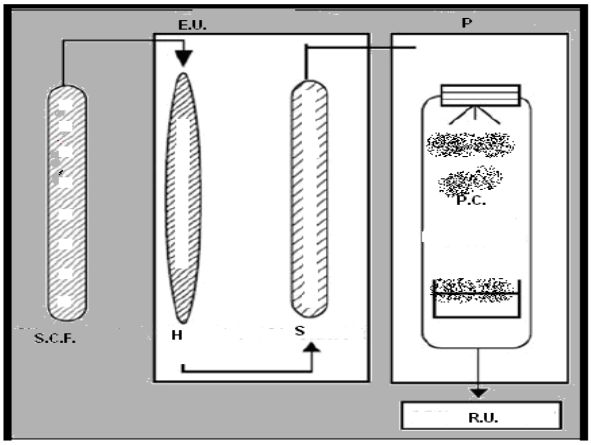


Fig. 2: Rapid expansion Supercritical solution Apparatus

The apparatus (fig. 2) used in the process typically consists of a vessel for solubilization, a precipitator and heater. In the process, first, the solute is allowed to dissolve in the supercritical fluid under pressurized condition in solubilization vessel until it gets saturated. After that, the saturated supercritical fluid is allowed to expand at a rapid rate, which leads to precipitation of the solute. The super saturation that is achieved by the supercritical fluid is the major advantage of the Rapid expansion supercritical solution technique, which occurs at rapid rate maintaining the uniformity and leads to small uniform size particle production [11].

Various parameters that affect the efficiency of the process can be divided on the basis of their time of influence in the whole process. The pre expansion conditions (before the expansion of the supercritical fluid) include the pressure and the temperature of the solubilization vessel, which affect the density of the and hence the concentration in the pre-expansion phase. Concentration, during this phase is also depends on the nature of the supercritical fluid and solute geometry (crystalline or amorphous). The post expansion conditions include the temperature of

the nozzle, size and angle of impact against the jet stream, which if not maintained accordingly, may lead to early and undesirable precipitation of the solute [12]. Advantages of the Rapid expansion supercritical solution techniques include its simplicity and easy implementation on the small scale along with environmental compatibility. While the major limitation of the technique, is inability to process insoluble or less soluble materials in the supercritical fluid used.

2. **Rapid expansion of supercritical solution in a liquid solvent:** This technique is basically employed with the liquid Carbon dioxide as supercritical fluid. In the process, inside a high pressure pump, a solution of the drug or the solute in liquid carbon dioxide is prepared. Then, in order to attain the desired temperature before expansion, the solution is pumped into a heating assembly, through an orifice and allowed to expand rapidly in an water based medium under ambient pressure condition. This technique is widely used in the production of the stabilized suspension of the nanoparticle [13].

Process in which the Supercritical fluids are used as an anti solvent

The use of supercritical fluid as antisolvent was proposed as an alternative to the rapid expansion supercritical solution technique to overcome the drawback of lack of solubility of the many organic compounds in the supercritical Carbon dioxide [14] and is based on the capability of the liquid to solubilize the higher quantity carbon dioxide gas. Low affinity of the antisolvent used to the solute while the fractional miscibility with organic part, is also an important parameter in the process. Diffusion of the antisolvent in organic solvent phase and the organic solvent evaporation in the antisolvent phase of the system direct the starting of the nucleation in the system and hence the crystal growth from the triple phase system created by the solute, organic solvent and antisolvent. Expansion of the antisolvent leads to volume expansion; hence reduce the solute solubility, while the evaporation of the organic solvent in the gaseous phase leads to higher concentration of solute within. This complete process is responsible for the occurrence of the supersaturation and formation of the particle [15].

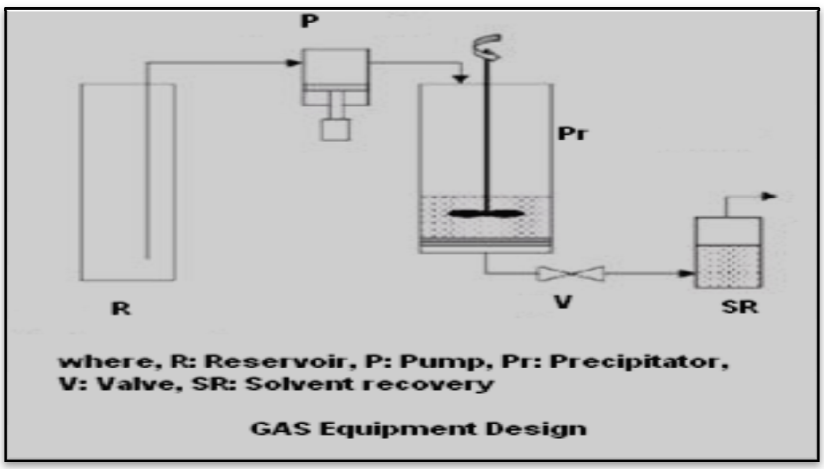


Fig. 3: Gaseous antisolvent crystallization equipment design

1. **Gaseous antisolvent crystallization:** In Gaseous antsolvent crystallization (fig. 3) technique, supercritical fluid (Carbon dioxide) is introduced steadily in a solute solution containing vessel till the desired pressure is attained. This is followed the precipitation of the

solute and is generally called Salting out. Major benefit of the process over others is that a uniform mixing of the whole system filled in the vessel is obtained when the supercritical fluid is injected from the bottom side while the poor control over the resultant particles morphology and presence of the of solvent residue limits the utilization.

2. **Precipitation using compressed fluid as antisolvent:** In this techniques, there are three variants have been developed and being used effectively which are: Particles by compressed antisolvent, Aerosol based solvent extraction system and Supercritical anti solvent system. In these techniques (fig. 4), in a high pressurized vessel system carbon dioxide gas is introduced using a pump until predefined conditions of temperature and pressure are achieved. Then, in the bulk of the supercritical fluid the organic solvent based solution is sprayed and particles so generated can be obtained from the filter at the bottom side of the vessel.

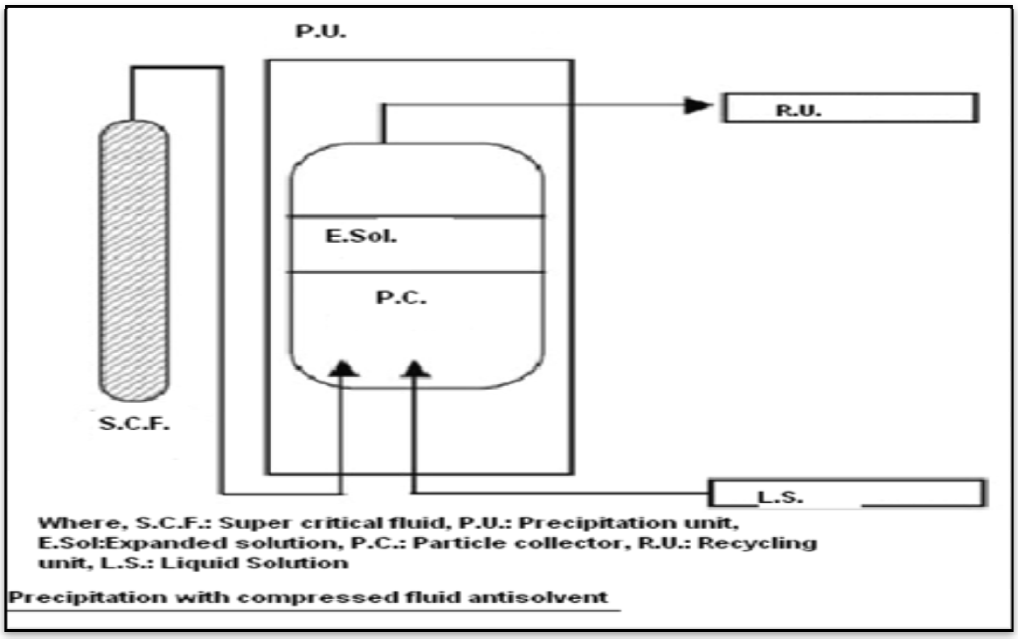


Fig. 4: Equipment design for Precipitation with compressed fluid antisolvent

3. **Solution enhanced Dispersion using supercritical fluid:** The technique (fig. 5) was developed to surmount the limitation of the Rapid expansion of the supercritical solution technique and Gaseous antisolvent precipitation technique. In the process both the solution of the solute and the supercritical fluid are introduced concurrently in the vessel meant for the precipitation of the solute particles, under the desired condition of the temperature and pressure, which leads to rapid dispersion of the solute solution , uniform mixing and extraction of the solute from the solvent solution. To obtain the particles of the uniform size distribution it is essential to maintain the rate of flow of the solute solution and supercritical fluid. Mixing of the system during the process ensure the raise in the mass transfer which in turn leads to faster nucleation and small, uniform size particle development without any aggregate mass formation [16].

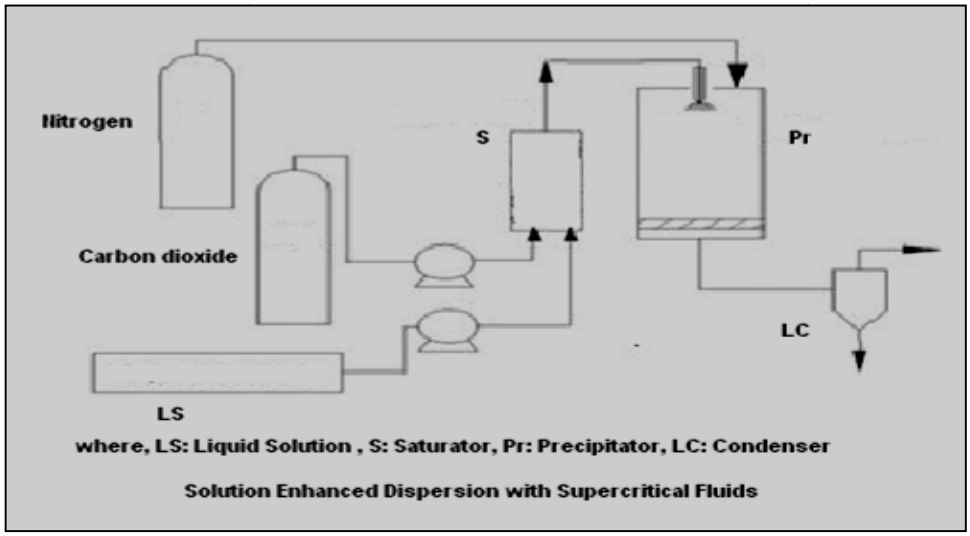


Fig. 5: Solution enhanced Dispersion using supercritical fluid

This technique is also being utilized in the processing hydrophilic solutes or drugs (eg. Proteins), where the solute solution in water or aqueous based solvent , supercritical fluid and organic solvent which is supposed to constitute for formation of the triple phase system is sprayed as individual stream in the mixing vessel.

These properties of the, Solution enhanced dispersion by supercritical fluid technique , makes it a very reproducible technique over other supercritical fluid techniques based on antisolvent system and is also considered suitable for use in the manufacturing according to the guidelines of the Good Manufacturing Properties (GMP) [17].

Applications of the Supercritical fluids technology in the pharmaceutical industry

1.) **Micronization of the drugs used:** Supercritical fluid technology is widely being used for the production of the micron size particles incuding the pharmaceuticals, biological and polymeric compounds. Rapid expansion supercritical solution techniques has been used succesively to produce the micron size particles of the phenacetin, estradiol etc., while the Supercritical antisolvent technique has been successfully used for the particle size reduction of the drugs having low solubility in the supercritical fluid, like trypsin, catalase, methylprednisolone, insulin etc. Examples of the drugs micronized using different techniques are grouped in the table follows:

Table 3: Drugs which have been micronized using Supercritical fluid techniques

Drug	Technique
5- fluorouracil	Solution enhanced Dispersion using supercritical fluid [18]
Lysozyme	Gaseous antisolvent crystallization. [19]
Atorvastatin Calcium	Supercritical anti solvent system [20]
Cyclosporine A	Precipitation using compressed fluid as antisolvent [21]

2.) **Enhancement of solubility of the drugs:** Supercritical fluid technology, specially Rapid expansion supercritical solution technique has been used for the improvement of the solubility of

the pharmaceutical drugs at temperature below 60 ºC and pressure about 300 bars [22]. Examples of the other drugs processed for enhancement of solubility are grouped in the table:
Table 4: Drugs processed for enhancement of solubility

Drug	Technique
Atenolol	Aerosol based solvent extraction system [23]
Phenytoin	Gaseous antisolvent crystallization [24]
Felodipine	Supercritical anti solvent system [25]
Naproxen	Rapid expansion Supercritical solution [26]

3.) **Development of Solid dispersion**: The traditional methods used in the production of the solid dispersion of uses the excessive shear forces and the solvent of organic origin. Supercritical fluid provides the advantage of the preparation of the solid dispersion dosage form free of the organic solvent in order to enhance the solubility of the drugs having poor solubility. Moneghini et al, (2001) developed a PEG 4000 based solid dispersion of carbamazepine in order to enhance the dissolution rate and extent [27].

4.) **Production of the Microparticles and Nanoparticles:** Supercritical fluid technology has shown good application in the production of the micron size particle of the drug utilizing supercritical fluids as solvents and antisolvents. Microparticle of size 5 to a150 micron size has been prepared for the drugs like Lovastatin, Naproxen, Mevinolin etc. Using this technology particle of range 5×10^{-9} m to 2×10^{-6} has been produced. Rapid expansion of supercritical fluid technique was used to prepare the microparticles of Naproxen with L-poly (lactic acid) using supercritical Carbon dioxide [26]. Mueller and Fisher had used the Antisolvent Supercritical fluid technique for producing microparticles of Clonidine hydrochloride encapsulated by L-poly(lactic acid) [28]. The technology has also been utilized for producing the nano size particles of the drugs. Nanoparticles of Gentamicin, Naltrexon and Rifampicin have been prepared using the Supercritical fluid technique [29].

5.) **Supercritical Fluid Extraction:** In comparison to conventional Liquid extraction technique, supercritical fluid extraction is much rapid, due to the low viscosity and high diffusivity of the supercritical fluid. Extraction procedure can be made more selective by controlling the density of the medium. Releasing of the pressure, leads to the change of the phase, that is supercritical fluid returns to the gaseous phase and evaporate, leaving behind the extracted material or constituent. Carbon dioxide is the most widely used supercritical solvent for the extraction procedure. The technique is being used for decaffeination of the coffee beans and extraction of the Hops (*Humulus lupulus*) for beer production. In pharmaceutical industry the technique is being use for the extraction of the essential oil and other pharmaceutical products from plants.

6.) **Supercritical Fluid chromatography:** Supercritical fluid chromatography provides the combined advantages of high performance liquid chromatography and gas chromatography and utilized for the non-volatile thermolabile analytes effectively. Though the advantages offered are not sufficient to replace the application of HPLC and GC, it provides good applicability in analysis of the high molecular weight hydrocarbons and in the separation of chiral molecules [30].

7.) **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 [31]. Examples of the crystals formed utilizing the technique is formation of the Indomethacin-Saccharin cocrystals [32].

8.) **Drying at various stages in the Pharmaceutical operations:** Drying is the process of the removal of solvent from the bulk mass, which has to be achieved at different phases in the development and production of a pharmaceutical product. Supercritical drying provides the benefits of removal of the solvent without appearance of the distortion and shrinkage in the solid particle that arise due to the effects of surface tension. Technique is being used in the production of the "Aerogel" (material having lowest bulk density of porous solid) and drying of the delicate materials as biological samples for electron microscopy.

Future prospects
Several pharmaceutical products can be produced using the supercritical fluid technology like drug powders, drug polymorphs, microparticles, nanoparticles etc. The techniques an also be utilized in the other processes like drying, preparation of inclusion complexes, to enhance the selectivity of the reactions specially in the production of the chiral compounds. But, the major disadvantage of the technology is its high cost of the setup and processing along with the limited availability of the solvents. So, the focus should be drawn on exploring the new application of the supercritical fluid technology and to find the other potential candidates that can act as a supercritical fluid in the defined critical temperature and pressure conditions, while the reduction in the expenditure of the scale up should also be considered, in order to improve the acceptability of the technique in the small as well as large industry set up.

CONCLUSION

Supercritical fluid technology is most pioneering and capable technique used in order to design the systems of drug delivery and also to improve the various vital characteristics of the many potential drug candidate like solubility, uniformity in particle size etc. It is clear that by appropriate regulation of the working conditions specific crystal form a material can be produced, so investigation of the effects of these factors that affects the various characteristics of the particle still deserves a respectful approach, which should be focused on the particle kinetics and thermodynamics leading the occurrence of the precipitation from the supercritical fluid. The vast prospective of future application of the Supercritical fluid technology in the improvement of the new drug development by appropriate particle designing and engineering is quite visible. Supercritical fluid technology also provides the huge advantage over conventional methods of extraction, drug particle formation and in the designing of drug delivery systems. Huge number of the developments using Supercritical fluid technology and patents applied in the pharmaceutical field utilizing it as an inherent part last few decades is showing a great prospective for the technology in the near future.

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