

A Short Preliminary Study on Pharmaceutical Particle Manufacturing using Supercritical Fluid Technology

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Abstract: *The bioavailability of solid drugs and the efficacy of their delivery systems are generally constrained by size, morphology and size distribution. As such these factors controls the solubility of the drugs in the body fluids. The micronization and microencapsulation of drugs with uniform size and uniform morphology are the two methods which requires an efficient novel technologies for producing a system which yields a controlled release of the drugs with enhanced bioavailabilty within the therapeutic range. Supercritical fluid has great potential for utilizing it as the solvent or antisolvent in these processes. The fluid is supercritical when it is compressed beyond its critical pressure (Pc) and heated beyond its critical temperature (Tc). The technology has emerged as an important technique for particle manufacturing and has replaced the conventional recrystallization and milling processes mainly because of the quality and purity of the final particles. The remarkable properties of supercritical fluids are considered as continuously adjustable by changing the pressure and temperature to achieve solvating properties with gas and liquid characteristics without actually changing the chemical structure of the compound, that is the physicochemical properties of these fluids are in the intermediate state between gas and liquid, which impart high diffusivity comparable with gas and high solubility as a liquid. Supercritical carbon dioxide as noninflammable, nontoxic, in expensive and due to its mild critical temperature and critical pressure, it is rapidly using fluid for pharmaceutical particle formation, it reveals high solubility for non polar organic compounds but there is a limitation for dissolving polar, ionic or polymeric compounds for which supercritical fluids other than carbondioxide can be used. This review focusses on the characteristics of supercritical fluids, various techniques of paharmaceutical particle manufacturing using supercritical fluids and applications of Supercritical fluid for particle manufacturing.*

Keywords: Supercritical fluid, Micronization, Rapid expansion of supercritical solution (RESS), Supercritical antisolvent process for particle formation (SAS).

1. Introduction

A critical point is called as a critical state at which phase boundary ceases to exist, there are multiple types of critical points such as vapour-liquid critical points and liquid-liquid critical points. As the critical point is approaches, the properties of the gas and liquid phases approaches one another to form one single homogeneous phase called Supercritical fluid. The most important point here is that above a critical temperature a liquid cannot be formed by an increase in pressure but with enough pressure a solid may forms thus homogeneous phase of supercritical fluid attains only if compound, mixture or element is treated above its critical temperature and critical pressure but below the pressure required to condense it into a soild¹. Extracts of aromatic herbs, spices and medicinal plants are generally used in food and pharmaceutical processing to impart flavor and other medicinal properties respectively. Traditionally, volatile essential oils from plant materials are obtained by hydrodistillation but the process is suffered by issues like hydrolytical reactions, chemical alterations and thermal degradation of products. The extracts obtained by organic solvents are generally called as oleoresin as contains all ingredients soluble in organic solvent, including volatile oils and the resins. Unfortunately, separation of plant materials from organic solvents may lead to oxidation of aroma and coloring compounds, especially in the presence of air. The supercritical fluid extraction acts as an alternative procedure to conventional extraction and steam distillation method with overcoming the drawbacks associated with such processes². Supercritical state is obtained when a fluid is

treated beyond its critical temperature and critical pressure, a critical point is called as a critical state at which phase boundary ceases to exist and as the critical point is approaches, the properties of the gas and liquid phases approaches one another to form one single homogeneous phase which is called as Supercritical fluid³. In the supercritical region, a state of liquid like density can be transforms into one of vapour like density by tuning the pressure and temperature without the appearance of an interface thus by proper control of pressure and temperature the accessibility to significant range of physicochemical properties (density, diffusivity, dielectric constant) can be attained without ever passing through a phase boundary and such intermediate ranges are not at all available at subcritical temperature and pressure. Carbon dioxide is the most commonly used supercritical fluid owing to its nontoxic, noninflammable and environmental friendly properties and mild supercritical conditions of 31.3⁰c as critical temperature and 7.4mpa as critical pressure⁴. Carbondioxide and the extract are easily separated by the pressure reduction or expansion mechanism and the extract obtained is free of any undesirable solvent. Although CO₂ is nonpolar with a dipole moment of zero, when used in SFEE its polarity can be manipulated by adding small amounts of an entraining solvent, such as methanol. The low viscosity and high diffusivity of the supercritical fluid enhances the penetrating power based on its high mass transfer rate of the solute into the fluid, allowing efficient extraction of the compounds from the raw material.

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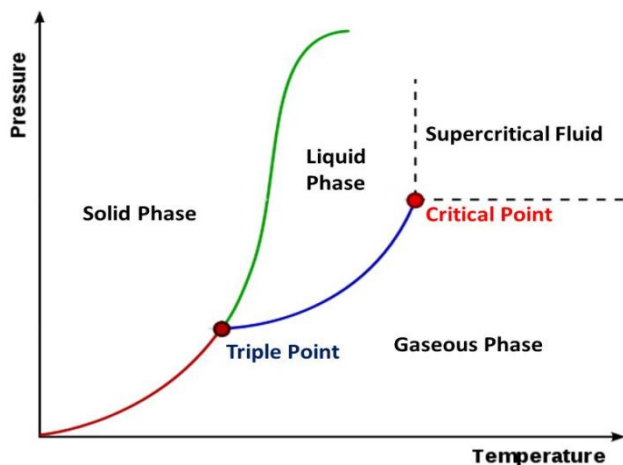


Figure 1: Phase diagram of Supercritical fluid region⁵

Characteristics of Supercritical fluids²:

- The supercritical fluid shows both of properties of liquid as well as gas but here fluid cannot be termed as vapour as vapour is defined as a gas whose temperature is below the critical temperature.
- In the supercritical region, a state of liquid like density can be transforms into one of vapour like density by tuning the pressure and temperature without the appearance of an interface thus by proper control of pressure and temperature the accessibility to significant range of physicochemical properties (density, diffusivity, dielectric constant) can be attained without ever passing through a phase boundary and such intermediate ranges are not at all available at subcritical temperature and pressure.
- The continuously adjustable solvent properties of water in supercritical region can be depicted as

Table 1: Range of properties of supercritical fluid on comparing gas and liquid³

Properties	Gas	Supercritical Fluid	Liquid
Density (g/cm ³)	10 ⁻³	0.1-1	1
Diffusion coefficient (cm ² /s)	10 ⁻¹	10 ⁻³ -10 ⁻⁴	<10 ⁻⁵
Viscosity (g/cm-s)	10 ⁻⁴	10 ⁻³ -10 ⁻⁴	10 ⁻²

From the above demonstration it can be depicted as that supercritical fluids exists in the intermediate state between gas and liquid i.e having high diffusivity comparable with a gas and high solubility as a liquid.

- Above the critical pressure (Pc) the increase in density comparable to water shows greater solubilization power.
- The increase in diffusivity comparable to gas allows for the rapid extraction of constituents.
- The decrease in viscosity comparable to gas shows the formation of molecular dispersion.
- Generate no liquid phase under any pressure change.
- Critical temperature and critical pressure of some of compounds as shown in table: 2 and according to this table Supercritical carbon dioxide is the rapidly using fluid for pharmaceutical particle formation due to its mild Tc °c and Pc.

Table 2: Critical temperature and critical Pressure of some of the compounds²

COMPOUNDS	Tc °c	Pc (MPa)
Water	374	22
Nitrogen	-147	3.39
Carbondioxide	31.3	7.4

2. Methods of Particle Production⁶

The number of novel and promising processes have been devised for the production of nanosized pharmaceutical particles as follows:

1. Rapid Expansion of Supercritical Solutions (RESS):

The RESS process is a precipitation technique of particle formation which relies on the solvent properties of carbon dioxide. The active substance to be micronized is partly solubilized in a continuous stream of pure supercritical carbon dioxide and in some cases cosolvent may be added at a high pressure, the mixture so formed is then expanded to reduce the pressure at an ambient range. This decrease in pressure leads to the evaporation of carbon dioxide and finally supersaturation and precipitation of the solid, the precipitated particles are then collected in a bag filter. The size of particles obtained may be in the range of 5-10 nanometer.

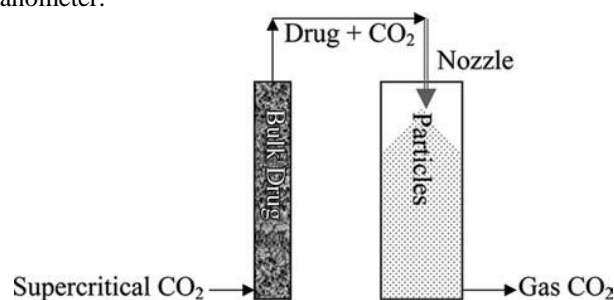


Figure 2: Schematic process of Rapid Expansion of Supercritical Solutions

2. Supercritical Antisolvent Process for Particle Formation:

This process of nanoparticle formation allows the utilization of the antisolvent nature of carbon dioxide. In this process drug is first dissolved in an organic solvent and then solution is injected into the supercritical carbon dioxide. The supercritical fluid due to its high diffusivity, rapidly extracts the solvent precipitating the drug particles to form particles of 50-100nanometer range.

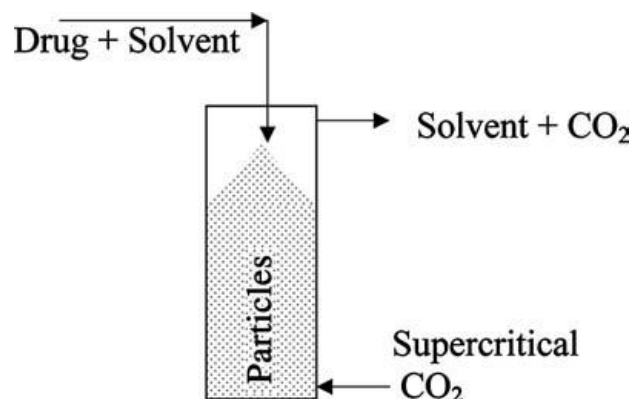


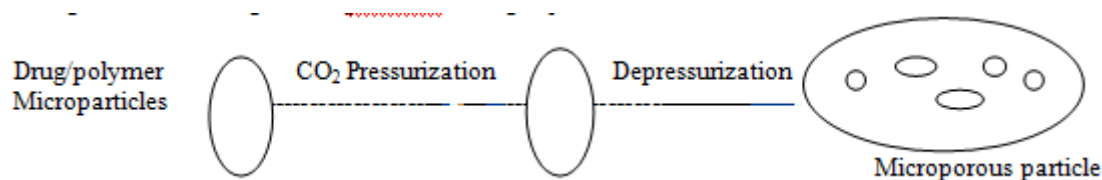
Figure 3: Schematic process of Supercritical Antisolvent Process for Particle Formation

Applications of Supercritical Fluids for Pharmaceutical Particle Manufacturing

- 1) The supercritical fluids due to their nature of intermediate range between gas and liquid allows for the efficient extraction and separation thus facilitating a potentially clean and recyclable process.
- 2) The production of pharmaceutical particles of nanometer range leads to an increase in the rate of dissolution of

drugs which are generally practically insoluble, from the dosage form in the biological fluids, which in turn allows the rapid absorption of drug from the site of absorption (increase in bioavailability).

- 3) The production of porous particles and polymer foams



- 4) Liposomes production, the conventional process involves the use of large amounts of organic solvents and have difficulty with scale-up for hydrophilic drugs. Lipids actually have some solubility in supercritical carbon dioxide and this behavior can be

3. Conclusion

For particle formation, supercritical fluid technology offers two general processes: Rapid Expansion of Supercritical Solutions for drugs that are soluble in supercritical carbon dioxide and Supercritical Antisolvent Process for drugs that are poorly soluble in supercritical carbon dioxide. Conventionally both the techniques have produced particles in microrange but with enhancement in these two techniques the particles in nanorange can be produced with much improved stability which can avoid particle agglomeration and coagulation.

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