PRODUCTION OF SUSTAINED RELEASE MICROPARTICLES BY SUPERCRITICAL FLUID TECHNOLOGY

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ABSTRACT

Microencapsulation is a widely used technique in which a thin layer of a coating agent is deposited onto a solid/liquid/gas core. Currently, the technique faces two challenges: being solvent-free and being applicable for coating particles smaller than 80 microns. An improved process for the production of polymeric microparticles using various supercritical fluids (SCFs), especially supercritical Carbon Dioxide is rapidly emerging as a solution to these problems. Role of SCF Technology in the production of Sustained Release (SR) microparticles has been reviewed here.

KEY WORDS: Microencapsulation, Microparticles, Supercritical Fluids, Sustained Release.

1.INTRODUCTION

Supercritical fluid technology encompasses a very broad field, which includes various reaction, separation and material formation processes that utilize a fluid at a temperature greater than its critical temperature and a pressure greater than its critical pressure. Supercritical fluids generally are compressed gases, which combine properties of gases and liquids in a chemically interesting manner. Supercritical fluids have physicochemical properties in between a liquid and a gas. They can have a liquid-like density and no surface tension while interacting with solid surfaces. They can have gas-like low viscosity and high diffusivity and, like a liquid, can easily dissolve many chemicals and polymers. Critical temperature (T_c) is the highest temperature at which a gas can be converted to a liquid by an increase in pressure. Critical pressure (P_c) is the highest pressure at which a liquid can be converted to a traditional gas by an increase in the liquid temperature(Martin,2006). The phase diagram of a pure substance illustrating the supercritical region is depicted in Fig. 1.

History of SCF Technology:

The observation of the supercritical phase was first cited in 1822 by Cagniard de la Tour. In 1869, Thomas Andrews(Randolph,1985) first recognized the presence of the critical point, which gave birth to a new world of critical phenomena and supercritical fluid science. Later in 1879, Hannay and Hogarth (Hammond,1985; Nakamura,1985) measured the solubility of solid in supercritical fluid. In 1895, Villard(Kamat,1995; Chulalaksananukul,1993) attempted to observe the changes in the color of I_2 dissolved in CO_2 when CO_2 passed through the critical point. In 1937, Michels (Erickson,1990) made precise measurements of the state of CO_2 near the critical point.

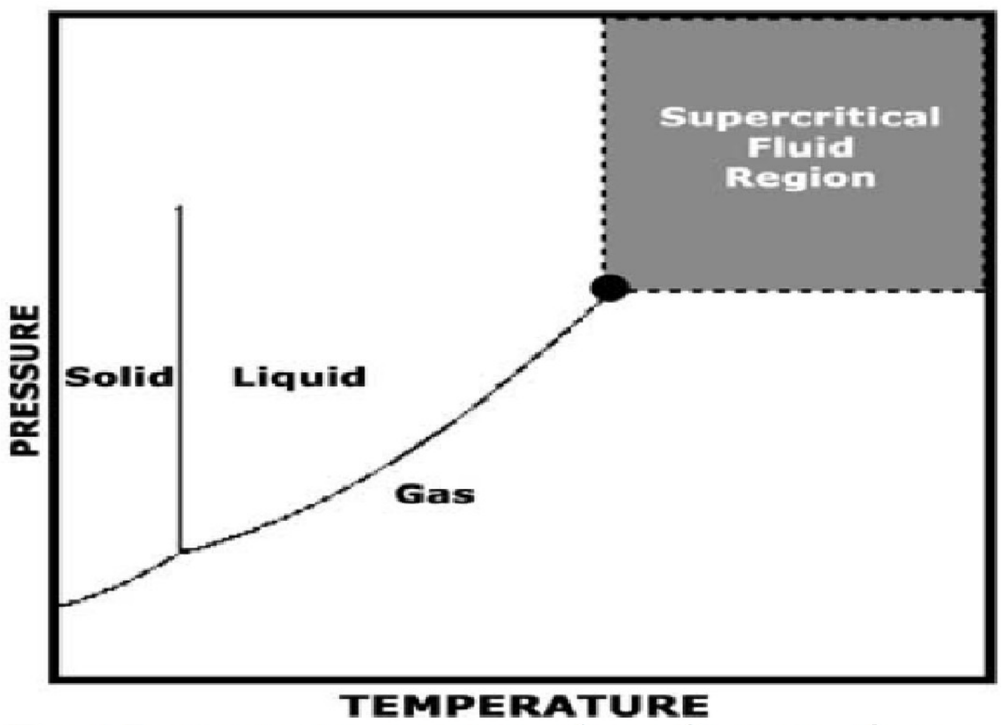

Fig. 1 Pressure–temperature phase diagram of a pure component indicating the supercritical region.

In 1950s, the solubility of dense gases was a lively topic both from the scientific and technological points of view. Since then, detailed data on solubility and thermodynamic quantities of high density gases including supercritical water have been accumulated mainly from the practical interests of chemical engineering.

In 1971, Zosel discovered that caffeine could be removed from green coffee beans in a reasonable time at moderate temperatures using CO_2 as a

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supercritical solvent for extraction. Since 1980s reviews (Randolph,1988;Nakamura,1990) on the spectroscopy and reactions in supercritical fluids have been published both from the scientific and engineering viewpoints. Researchers in the field of chemical engineering made an appreciable contribution to develop the physical chemistry of supercritical fluid.

Pharmaceutical applications of SCF processing came to fruition during the 1990s. The initial goals were to reduce drug particle size and to enhance a drug's dissolution rate and/or bioavailability. Subsequent reports addressed the coprecipitation of a drug and a biocompatible polymer. Currently, use of SCFs such as CO_2 is proving to be environmentally benign and economical, with the added advantage of reduced residual solvents in both food and pharmaceutical products(Aaron).

Microencapsulation Technology:

Microencapsulation is described as a process of enclosing micron-sized particles of solids or droplets of liquids or gasses in an inert shell, which in turn isolates and protects them from the external environment. This technology is mainly used for the purpose of protection, controlled release and compatibility of the core materials.

***Microparticles* have a variety of structures (Fig.2):**

- Particles with irregular geometry composed of an active substance in form of aggregates or molecularly dispersed solid embedded into a matrix. They are called '*microspheres*';
- Particles with spherical geometry composed of a *core* of active substance surrounded by a solid polymeric or proteic *shell*. They are called '*microcapsules*'.

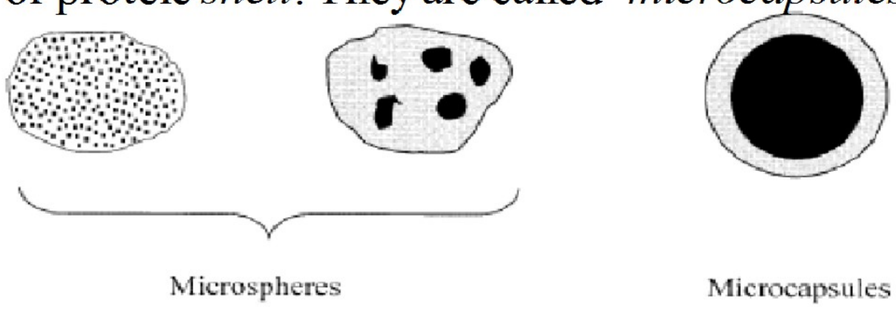

Fig. 2. Structure of the different microparticles.

Numerous preparation technologies available for the encapsulation of core material have been reported(Benita,1996;Arshady,1999;Ranney,1969). In general, microencapsulation techniques are divided into two basic groups, namely chemical and physical, with the latter being further subdivided into physico-chemical and physico-mechanical techniques. Some of the important processes used for microencapsulation are summarized in Table 1.

Table 1. Different techniques used for microencapsulation

Chemical processes	Physical processes Physico-chemical	Physico-mechanical
• Suspension, dispersion and emulsion polymerization • Polycondensation	• Coacervation • Layer-by-layer (L-B-L) assembly • Sol-gel encapsulation • Supercritical CO_2-assisted microencapsulation	• Spray-drying • Multiple nozzle spraying • Fluid-bed coating • Centrifugal techniques • Vacuum encapsulation • Electrostatic encapsulation

The present article deals with applications of SCF technology in Microencapsulation.

Fundamentals of SCF Technology:

SCF Selection

Supercritical fluids are highly compressed gasses that possess several advantageous properties of both liquids and gases. These fluids have attracted much attention in recent years, the most widely used being supercritical CO_2, alkanes (C_2 to C_4) and nitrous oxide (N_2O). They have low hydrocarbon-like solubility for most solutes and are miscible with common gases such as hydrogen (H_2) and nitrogen (N_2). A small change in temperature or pressure causes a large change in the density of supercritical fluids near the critical point – a property which enhances their use in several industrial applications. Supercritical CO_2 is widely used for its low critical temperature value, in addition to its nontoxic, nonflammable properties; it is also readily available, highly pure and cost-effective. It has found applications in encapsulating active ingredients by polymers. Different core materials such as pesticides, pigments, pharmaceutical ingredients, vitamins, flavors and dyes are encapsulated using this method(Ghaderi, 2000; Liu,2002;Chambon,2004).

Careful SCF selection is important to reduce processing time and to improve efficiency. However, the choice is usually restricted by the desire of reasonable critical parameter values and costs, chemical inertness, low toxicity and little environmental impact.

SCF Processes

The general methods of particle production by SCF technology fall in to 2 groups(Weber,2002;Jung,2001):

1. Expansion of a supercritical solution containing a solute
2. Precipitation of solute dissolved in an organic solvent utilizing SCFs as antisolvents

The most common expansion methods are:

i. Rapid Expansion of Supercritical Solutions (RESS)
ii. Supercritical Fluid Nucleation (SFN)

iii. Particles from Gas-Saturated Solutions (or Suspensions) (PGSS)

Precipitation Methods include:

i. Gas Antisolvent Recrystallization (GAS)
ii. Supercritical Antisolvent Recrystallization (SAS)
iii. Supercritical Antisolvent with Enhanced Mass Transfer (SAS-EM)
iv. Solution-Enhanced Dispersion by Supercritical Fluids (SEDS)
v. Precipitation with Compressed Antisolvents (PCA)
vi. Aerosolized Solvent Extraction System (ASES)

Detailed discussion of these can be found in the earlier review(Jung,2001).

Apart from these there is so called "Supercritical-Assisted Atomization" (SAA) (Reverchon,2002) to produce Micro- and/or Nanoparticles of Controlled Size and Distribution. It is based on the solubilization of controlled quantities of supercritical CO_2 in liquid solutions containing a solid solute and on the subsequent atomization of the ternary solution through a nozzle.

Applications in Pharmaceutical Research:

Potential applications of SCF technology in Pharmaceutical Research are discussed elsewhere (Aaron). They include:

- Drug Extraction and Analysis
- Chromatography
- Drug Analysis in Human/ Animal Tissues and Fluids
- Drug Analysis in Pharmaceutical Preparations
- Preparation of Drug Powders and Polymorphs
- Drug and Delivery System Design to produce : Microparticles (RESS), Microparticles (antisolvent processes), Porous microparticles, Microporous foams, Nanoparticles, Macromolecule powders, Inclusion complexes, Polymer impregnation, Liposomes, Polymer fractionation.

The present article deals only with the review of production of drug microparticles by SCF technology for Sustained Release (SR).

Design of SR Microparticles by SCF Technology:

SCFs are very promising for microencapsulation. Encapsulation of pharmaceutical actives in polymers allows for improvement of shelf-life and stability and achieving Sustained Release. However, the encapsulation process usually includes the use of a solvent, which could damage the active agent. Supercritical fluids are attractive alternative solvents.

2.CONCLUSION

During the last few years, application of SCFs has attracted attention of scientific community to develop new technologies like SR Drug Delivery Systems in order to substitute the traditional ones. Among all the possible SCFs, carbon dioxide is the most widely used, due to its favorable critical parameters, cost and lack of toxicity.

Table-2 summarizes the research reports on the application of SCF technology for the production of SR drug microparticles.

Drug/API	Process	Comment/Result	Reference
Naproxen	SAS	Ethylcellulose/ Methylcellulose blends were produced and impregnated with naproxen. Miscrospheres prepared have a higher loading capacity and present a slower release profile. Drug diffusion followed Fick's law of diffusion.	Ana Rita, 2006
Bovine Serum Albumin (BSA)	SAS	Poly(l-lactic acid)microparticles loaded with a model protein (bovine serum albumin) prepared. Sustained-release solvent-free microparticles were obtained.	The Preparation of BSA-PLLA,2009
Puerarin Nanoparticles	SEDS	Puerarin nanoparticles were microen-capsulated by PLLA in a modified SEDS. After a burst release at the first stage, the drug was released in a sustained process from microcapsules.	Ai- Zheng Chen, 2009
Polyactin A	GAS	Solvent-free microparticles, loaded with a polymannopeptide (polyactin A) produced prolonged release over a 24 h period from microparticles.	Preparation and anti-tumor evaluation of Polyactin, 2008
Ampicillin trihydrate	SAA	HPMC based composite microparticles using Ampicillin trihydrate were prepared; Tablets of these co-precipitates gave SR upto more than 72 hrs, whilst Gelatin capsules gave release upto 8 hrs.	Reverchon, 2008
β-estradiol	GAS	β-estradiol in $scCO_2$ was impregnated into the glassy polymer polyvinylpyrrolidone (PVPP) to get Controlled Release.	Joshua R.Bush, 2007
Theophylline	PGSS	Drug release from Microcomposites of theophylline/hydrogenated palm oil followed Higuchi's model for simple diffusional processes.	Rodrigues, 2004
Indomethacin	PGSS	Drug impregnation with poly (vinyl pyrrolidone) (PVP) and poly(vinyl acetate-co-crotonic acid)	Moolmana-2006

API- Active Pharmaceutical Ingredient
HPMC- Hydroxy Propyl Methyl Cellulose
sc Co_2 – Supercritical Carbon Dioxide
rhGH- Recombinant human growth hormone

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