

Fabrication of controlled release devices using supercritical antisolvent method

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Abstract Supercritical antisolvent with enhanced mass transfer (SASEM) method is used to process biodegradable and biocompatible polymer PLGA (poly DL lactic co glycolic acid) in an attempt to fabricate micro or nano sized particles for encapsulation of drugs for purposes of controlled release. In this process, an ultrasonic vibrating surface provides the liquid atomization in the supercritical fluid medium. The ultrasonic vibration also creates turbulence in the supercritical phase and enhances the mixing and mass transfer between the organic solvent and supercritical antisolvent. The setup has been designed for visualization of the liquid atomization and antisolvent process in the high pressure vessel. PLGA particles obtained from this process are further analyzed using SEM (Scanning Electron Microscopy). Experiments were also carried out to study the droplet size distribution from ultrasonic liquid atomization using a Phase Doppler Particle Analyzer (PDPA).

Index Terms Supercritical antisolvent, Ultrasonic liquid atomization, controlled release, PLGA (poly DL lactic co glycolic acid)

I. INTRODUCTION

IN the past few decades, much attention has been devoted to the development of micro-/nanoparticles of biodegradable polymers as drug delivery systems for chemotherapy of targeted cells [1]. The conventional methods used in fabrication of these polymeric systems include single emulsion (for hydrophobic drugs), double emulsion (for hydrophilic drugs and proteins) and spray drying. These methods usually involve the use of substantial amounts of organic solvents and provide little control of product size. A method of processing the controlled delivery devices that is versatile, provides a high yield of product, and allows control of the product size and morphology is desired. In this research, we are interested in exploring the use of supercritical fluid techniques in the

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processing and fabrication of drugs and pharmaceutical products.

Several routes exist for the production of micro/ nano sized particles using supercritical fluid techniques. The common ones are the rapid expansion of supercritical solutions (RESS) [2] and the supercritical antisolvent (SAS) [3] methods. Supercritical fluid processes provide an alternative method for the production of particles for therapeutic purposes. Supercritical fluid extraction and supercritical antisolvent processes normally takes place in the range $1.01 < T/T_c < 1.1$ and $1.01 < P/P_c < 1.5$. Supercritical fluids have the advantage of having both desirable properties of liquids and gas such as liquid-like density and gas-like viscosity and high diffusivity as illustrated in Table 1 [4]. Because the physical properties of supercritical fluids are highly dependent on pressure and temperature, it is possible to fine-tune the reaction environment. Table 2 summarizes the critical pressures and temperatures of common supercritical fluids used in extraction and particle formation processes [5]. In particular, CO₂ is the most commonly used supercritical fluid for drug delivery device development as it has many known advantages such as

TABLE 1
Comparison of the physical properties of gases, liquids and supercritical fluids [ref 4]

Property	Gas	SCF	Liquid
Density (g/ml)	10^{-3}	0.3	1
Viscosity (Pa.s)	10^{-5}	10^{-4}	10^{-3}
Diffusivity (cm ² /s)	0.1	10^{-3}	5×10^{-6}

TABLE 2
Critical conditions of commonly used supercritical solvents [ref 5]

Fluid	T _c (°C)	P _c (bar)
Ethylene	9.3	50.4
Carbon dioxide	31.1	73.8
Nitrous oxide	31.3	73.8
Ethane	32.3	48.8
Chlorodifluoromethane	96.0	51.9
Propylene	91.8	46.2
Propane	96.7	42.5
Ethanol	240.8	61.4
Water	374.1	217.7

being inexpensive and readily available, environmentally benign in nature, non-toxic, non-flammable, and the critical temperature and pressure of 31.1 deg C and 73.8 bars, respectively, are modest.

Debenedetti et al. [2] have conducted several studies on the particle formation using the RESS method and have carried out experiments for encapsulation of lovastatin in PLA polymers. The RESS method is advantageous due to its low processing temperatures and the absence of an organic solvent. However, the main obstacle to using this method is in the low solubility of most pharmaceutical compounds in scCO₂. This greatly reduces the yield and poses a big difficulty for large-scale production of the pharmaceutical product using such a method.

In recent studies, more attention has been given to the supercritical antisolvent (SAS) method. There are many variations in this method for particle formation. The main principle of the method is to dissolve the pharmaceutical in a suitable solvent which is also soluble in supercritical CO₂. The solution is then introduced into the supercritical CO₂ where the supercritical CO₂ acts as an antisolvent and rapid mass transfer takes place between the solvent and the supercritical CO₂. As a result, the solution becomes more and more saturated with the pharmaceutical and precipitation takes place. This method is commonly known as the supercritical antisolvent (SAS) method.

Different ways of contacting the solution with the supercritical fluid have been explored by various research groups using SAS. The most commonly used one is to use a specialized nozzle (small orifice) to spray the solution

into the supercritical fluid. Modifications to this process includes work done by Randolph et al. [6] and Subramaniam et al. [7], who explored the use of ultrasonic nozzles to create mono-disperse solution droplets in supercritical CO₂. Chattopadhyay and Gupta [8-11] used an ultrasonic vibrating surface to breakup the solution jet into smaller droplets and also increase the mass transfer rate between supercritical CO₂ and the solvent.

In this study, the effects of using different organic solvents in the SASEM process is investigated. The precipitation unit is specially designed to hold CO₂ at high pressures and a specialized fitting is also designed to incorporate an ultrasonic horn into the vessel. A study of the behavior of the liquid spray generated from an ultrasonic vibrating surface is also carried out.

II. EXPERIMENTAL

A. Materials

PLGA (Poly DL Lactic co glycolic acid) 50:50 (MW = 5,000 – 15,000Da) and PLGA (Poly DL Lactic co glycolic acid) 75:25 (MW = 90,000 – 126,000Da) were purchased from Sigma Aldrich. Organic solvents acetone and dichloromethane (DCM) of HPLC grade were also purchased from Sigma-Aldrich.

B. SASEM setup

The SASEM setup may be divided into 3 main units: the supercritical CO₂ feed unit, the solution feed unit, and the

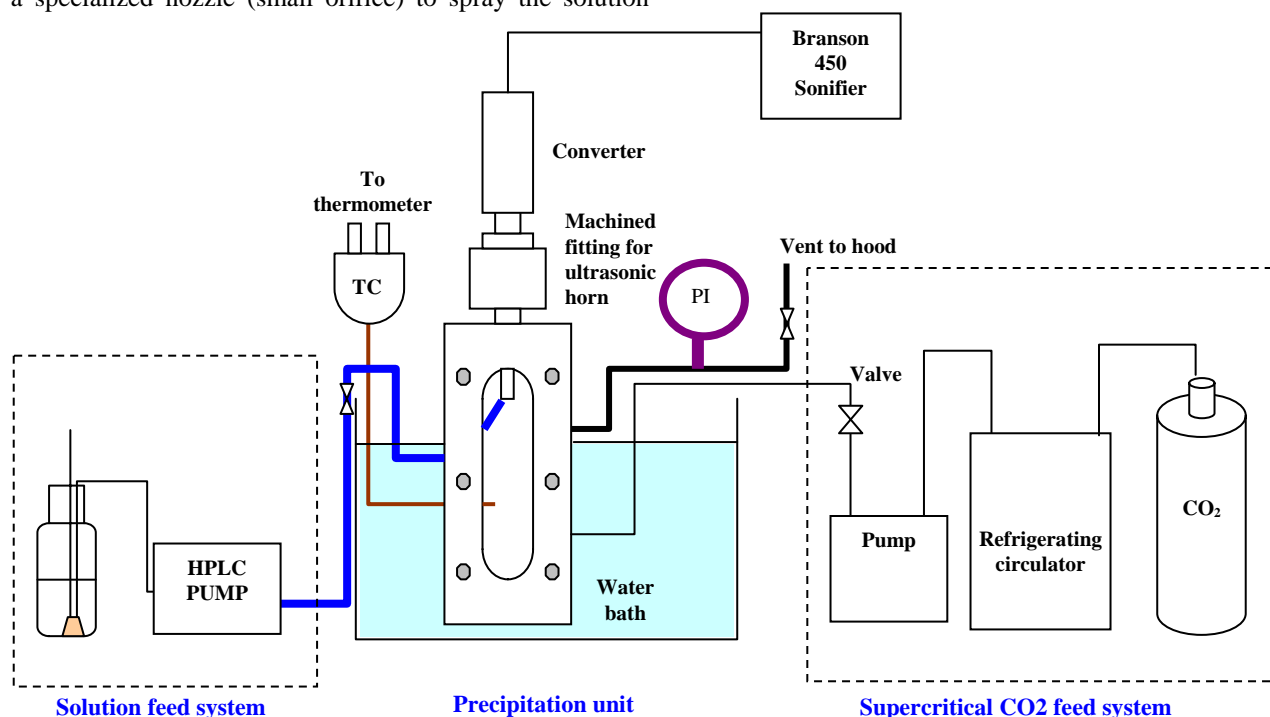


FIGURE 1. Schematic of the SASEM setup

precipitation unit, as illustrated in Figure 1. In the supercritical CO₂ feed unit, a refrigerating circulator (Cole-Parmer Model EW-12108-00, capacity = 6L) is used to liquefy the CO₂ entering the high pressure liquid pump (Eldex BBB-4, allowable pressure = 5000psi) which is used to feed high pressure CO₂ into the precipitation unit.

The solution feed system includes a feed bottle, a HPLC pump (Eldex B-100-S, allowable pressure = 5000 psi), a filter, and an inlet sparger. The solution (organic solvent + dissolved polymer) is then delivered into the vessel via a 1/16" OD stainless steel line.

The precipitation unit is a Jerguson high pressure gage (T-20-11; allowable pressure = 200 psi) heated to the required temperature by a water bath. 4 NPT ports were drilled into the sides of the vessel for (i) CO₂ feed, (ii) Solution feed, (iii) a thermocouple and (iv) a pressure gauge and valve for venting to the hood. An ultrasonic horn was connected to a sonifier (Branson 450 sonifier) attached to the top of the precipitation unit.

C. Ultrasonic atomization attachment

Two important considerations influence the design of the attachment for the ultrasonic probe (titanium probe, tip diameter = 3/8 in, Sonics and Materials). Firstly, to avoid interference with the vibration of the probe, there should be no contact of the probe with any solid surface from flange to the probe tip. Secondly, the process is to be carried out in high pressure CO₂, the fitting should allow for pressure tight sealing and be able to withstand the mechanical stresses during operation. Figure 2 is the schematic of the design of the fitting for connecting the ultrasonic probe to the vessel.

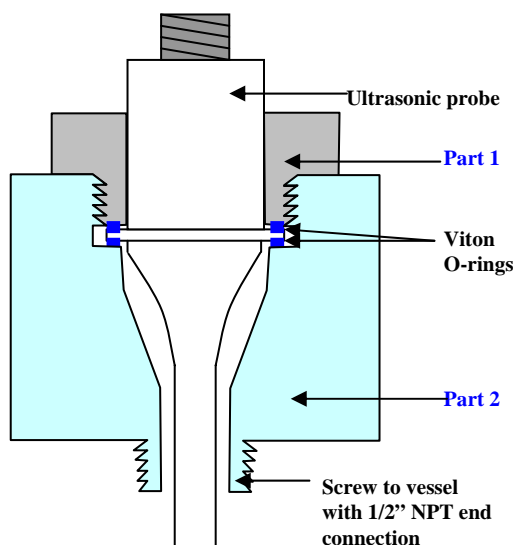


FIGURE 2.
Schematic of stainless steel fitting for ultrasonic probe
(Not drawn to scale)

D. Experimental

The SASEM process consists of 3 main stages: setup, precipitation and cleaning. The vessel is prepared for high setup pressure by setting all the bolts encasing the reactor to a torque of 32 lbft. The connections to the sides of the vessel and the ultrasonic probe have to be fitted tightly to the vessel and checked for leaks. The water bath is set to the operating temperature and the vessel is allowed to reach the operating temperature after pressurizing with CO₂.

After setting up the vessel, the sonifier is switched on to the desired power and the solution (organic solvent + polymer) is pumped into the vessel through a 1/16" stainless steel capillary tubing (ID = 0.03") onto the vibrating probe surface at an angle of approximately 45 deg. The entire process of liquid atomization and mixing of the droplets in the supercritical CO₂ can be observed through the borosilicate glass windows on the vessel.

After the precipitation process, the high pressure vessel is purged of CO₂ and flushed with fresh CO₂ for 4-5 times, after which, the vessel is opened and particles are collected from the side walls and bottom of the vessel.

E. Characterization

Particles collected from the precipitation unit were analysed using scanning electron microscopy (SEM). The JEI/Philips XL30 FEG Environmental Scanning Electron Microscope (ESEM) was used to study the surface morphology of the samples. No coating was required and images were captured in the Low Vacuum mode.

III. RESULTS AND DISCUSSION

A. Particle formation

The effects of different solvents on the properties of the particles obtained was studied. 2 common solvents used for PLGA are acetone and DCM. The SASEM method was used to process PLGA 50:50 dissolved in acetone and DCM respectively. Only 4-5 ml of organic solvent was used for each run and a polymer loading of 7.5-10% (wt/vol %) was used for the studies conducted.

When acetone was used as the organic solvent, the particles obtained at the end of the experiment were sticky and agglomerated. Most of the particles were found on the side walls of the vessel. Figure 3a shows the surface morphology of the particles obtained from side walls of the vessel. Particles obtained directly from the bottom of the vessel (on an SEM tape placed at the bottom of the vessel during the SASEM process) also showed rough surface morphology but smaller particles are obtained as shown in figure 3b. Some particles in the range of approximately 10

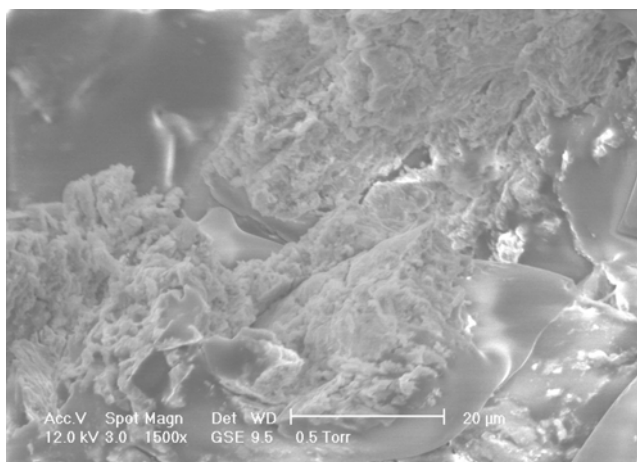


FIGURE 3A.
SEM picture of the surface morphology of PLGA 50:50 particles obtained from the side walls of the vessel

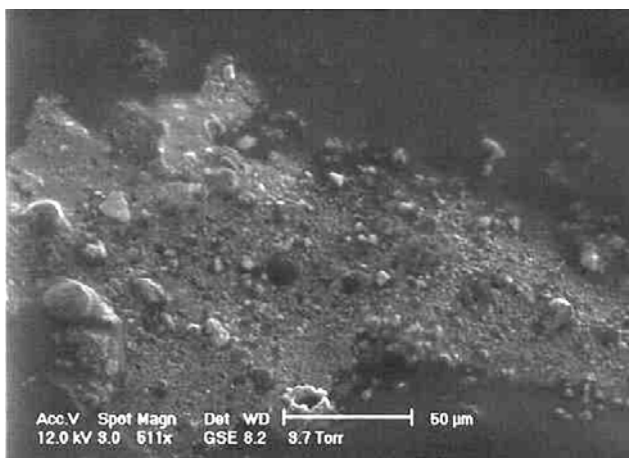


FIGURE 3B.
SEM picture of the surface morphology of PLGA 50:50 particles obtained from carbon tape placed on the bottom of the vessel

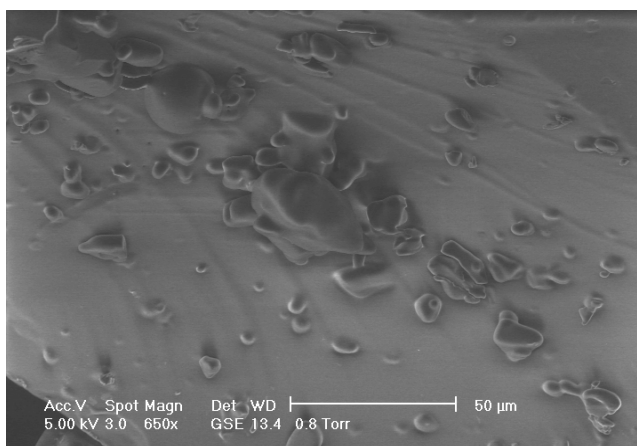


FIGURE 4A.
SEM picture of the surface morphology of PLGA 50:50 particles obtained from the side walls of the vessel

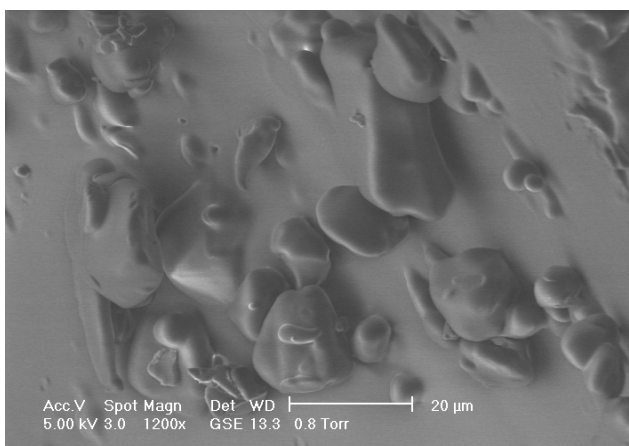


FIGURE 4B.
SEM picture of the surface morphology of PLGA 50:50 particles obtained from the side walls of the vessel (larger magnification)

μm were obtained. This is not found for the particles collected from the side walls of the vessel. This may be because droplets reaching the bottom of the vessel have the longest time in the supercritical fluid medium and therefore, the organic solvent managed to be removed before touching the surface of the vessel. Particles collected on the side walls are agglomerated mainly due to incomplete removal of organic solvent before reaching the vessel surface.

When DCM was used as the solvent, dryer particles were obtained. Particles were found mostly on the side walls of the vessel. A yield of approximately 18% was obtained. The SEM pictures of the particles are shown in figure 4a and 4b. The picture shows the particles are large agglomerates with small particles on the surface of the large particle. The particles appear to have a smooth surface morphology and the smaller particles on the

surface of the agglomerate are approximately 5-20 μm in size.

More experiments have to be carried out in order to understand the effects of using different solvents and the volume of solvent used in the SASEM process. Many factors in the SASEM process may affect the particle properties obtained. These include the atomization spray mechanism, the mass transfer between the solvent and antisolvent, and the nucleation of the polymers from the supersaturated solution to crystallize into microspheres. Werling and Debenedetti [12, 13] have constructed a numerical model of the 2-way mass transfer between a droplet (50μm) of organic solvent and supercritical antisolvent. Reverchon et al. [14] also studied the role of phase behavior and atomization in the SAS process.

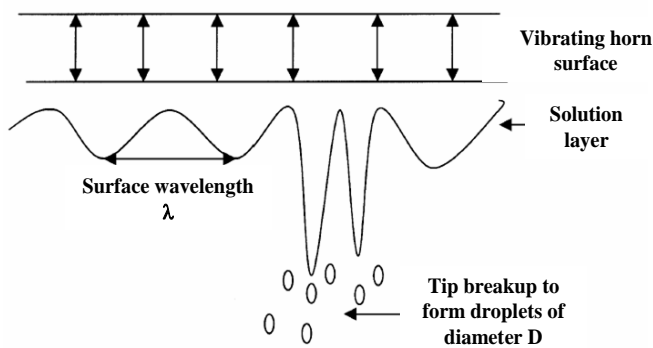


FIGURE 5.
Mechanism of the ultrasonic liquid atomization process

B. Ultrasonic atomization

Ultrasonic liquid atomization makes use of the breakup of the liquid at the tip of surface waves at the vibrating surface to produce a uniform spray. Figure 5 illustrates the droplet formation mechanism in this study. Sindayieburu and Bolle [15] carried out a stability analysis of the viscous liquid film free surface in the ultrasonic liquid atomization process.

An empirical correlation due to Lang[16] for droplet size is:

$$D = 0.34\lambda \quad \text{----- (1)}$$

where λ is a function of liquid density ρ , surface tension σ , and vibration frequency F as in equation (2):

$$\lambda^3 = 8\pi \frac{\sigma}{\rho F^2} \quad \text{----- (2)}$$

A Phase Doppler Particle Analyzer (PDPA) has been used to study the size and size distribution of the droplets created from the ultrasonic probe used in the SASSEM process. The Phase Doppler Method is based upon the principles of light scattering interferometry. The PDPA is able to measure the local velocity of each particle and the particle size distributions accurately. The signal analyzer and post-processing software (Aerometrics Real-Time Signal Analyzer, Data VIEW) can also record the number density of the measurement volume online.

A vibration frequency of 20 kHz was used for all the experiments. According to Equation (1), atomization of water at a vibration frequency of 20 kHz yields droplets of approximately 56.4 μm in diameter. For experiments using PDPA with water, the droplet size distribution is shown in figure 6. The droplet size distributions of water droplets

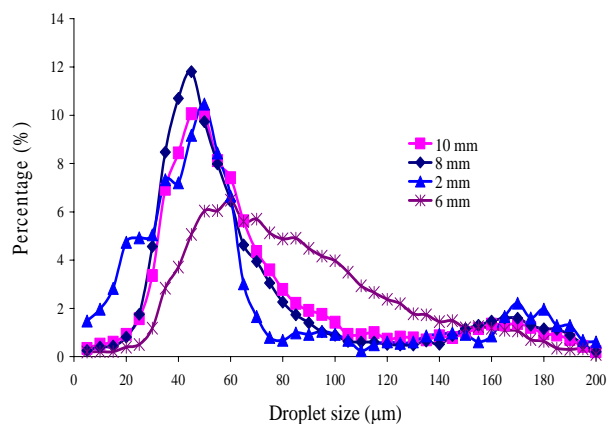


FIGURE 6.
Size distribution of droplets created by ultrasonic vibration
(Determined experimentally using PDPA)

were obtained at various positions from the surface of the vibrating surface. The droplet size distribution shows good agreement with the empirical correlation, with a high percentage of droplets between 40 – 55 μm in size.

IV. FUTURE WORK

More experimental studies will be carried out to optimize the SASSEM process to obtain smaller and more spherical polymeric particles. This includes studies to understand the ultrasonic atomization process, the phase behavior of polymer and organic solvent in supercritical CO_2 , mass transfer parameters of organic solvent in supercritical CO_2 and the nucleation process of the polymer.

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