

# Nanopowder Production

## A Comparison of Several Methods

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## **Abstract**

Several methods are available for the production of nano-powder production. The objective of this paper is to give an introduction to the basics of nanotechnology and nano-powder production using supercritical fluids (SCF) as well as a comparison of these techniques. The processes that will be compared are the Rapid expansion of Supercritical Solutions (RESS), the Supercritical Anti-Solvent (SAS), and the Particles from Gas Saturated Solutions (PGSS), and the Depressurization of Expanded Liquid Organic Solution (DELLOS). In order to achieve the aforementioned goals, literature research has been the starting point. Later this search was expanded to include the different methods of nanopowder production and a comparison of these methods.

## **Introduction**

Nanotechnology...

## **Nanotechnology**

Nanotechnology may be defined as the ability to work at the molecular level, atom by atom, to create large structure with fundamentally new molecular organization. Since this technology is developed from the scale range of  $10^{-9}$  m or 10 Å, its interaction by intermolecular and inter-atomic forces will lead to the next industrial revolution. Thus, providing the ability to control and manipulate the physical, biological, and chemical properties of a system. In other words, materials will be constructed from the bottom-up instead of conventional methods, top-down methods [1]. The ability to largely influence the properties and structure of materials has made nanotechnology a quickly developing field that has been gaining interests among the public due in part to the possibilities that this technology provides.

Many scientists suggest that nanotechnology will fuel enormous growth within the areas of Biotechnology and Bio-medical Chemistry, and Atomic Positioning [2]. Here the possibilities are endless. Using nanotechnology will play a major role in the field of Bio-medical Chemistry.

Many pharmaceutical companies are performing research to decline the particle size. If drugs were able to have smaller particle size they would be better absorbed by digestive tract lining therefore the amount necessary would be reduced making medicines more affordable. The ability to deliver antibiotics in aerosol form to the lungs would mean easier ways of treating infections like tuberculosis [3]. By decreasing particle size, the bioavailability many increase. This would lead to faster-reacting drugs and many other applications in the health industry [4].

“Nanorobots,” are imagined molecules that could be made to seek out certain cells and perform a task in that particular area of the body, for example, the seeking out of liver cells and facilitating the production of a certain proteins. By developing man-made nano-robots, it would be possible to manipulate and self-assemble cells that cause diseases and cancers and eliminate current health problems. The potential of nano-robots in the field of Biotechnology reaches beyond healing living cells. Nanotechnology experts contend that human life can be extended by nanorobots’ ability to self-copy and keep human cell replicating in normal ways, which reduce aging [2].

The ability to build materials from the smallest particles means that atomic properties can be adapted for certain purposes for example; the electronics field. The ability to manipulate properties means that these materials can be made to be better conductors leading to circuits that are smaller and faster. The circuits will in turn be able to achieve more complicated functions.

The potential for this technology is endless. For example, the National Nanotechnology Initiative have set these challenges for research scientists to accomplish: reducing entire content of the library of Congress to a sugar cube, constructing new plastics and other polymers with the strength of steel, improving computers speed by a factor of millions, and etc [2].

Improving the performance of a catalyst is very important for economical and social aspects of society. In an article discussing the economic contributions of catalysis noted that “one-third of material gross national product in the U.S. involves a catalytic process somewhere in the production chain” [5]. An example is the petroleum industry. Many of their processes heavenly depend on catalysts to produce oil, gasoline, and other

petroleum products. If a catalyst's efficiency improves by 3 %, this may lead to an increase of millions, possible billions of dollars for the petroleum industry. The social impact would be the price reduction of different petroleum products for the consumer. The environment also benefits since harmful bi-products will subside as a result of increasing the yield of a process. In order to improve catalyst, scientists are investigating the nanocatalyst as an avenue.

The advantages of using a nanocatalyst are profound. By nanocatalyst being very small in size, the particle size creates a very high surface to volume ratio [1]. This increase the performance of the catalyst since there is more surface to react with the reactants. Another advantage is that nanocatalysts are able to place where traditional catalysts will not fit.

## **Nanopowders**

The basis of nanotechnology is the ability to form nano-sized particles, for example nanopowders, which are solid particles that measure on the nanoscale, usually comprised of three to five molecules together. Nanopowders can be used in most of the aforementioned applications; therefore, they have been a field of great interest.

Nanopowders have been of extreme interest in the pharmaceutical field. Drug delivery has been impacted in several ways due to the advances in nanopowder technology. Smaller particles are able to be delivered in new ways to patients, through solutions, oral or injected, and aerosol, inhaler or respirator. New production processes allow for encapsulation of pharmaceuticals which allow for drug delivery where needed within the body. Dosing of pharmaceuticals had also improved. Smaller particles mean better absorption by the body therefore less drug is needed. Because of a combination of these, side effects are lessened due to better use of pharmaceuticals.

### **Production of Nanopowders**

Although there are many uses for nanopowders within the pharmaceutical field, the production of these powders has been of great interests. For this reason, at this point in time the research around nanopowders has been focused mostly on methods of production.

#### **Conventional Methods**

Conventional methods of particle size reduction include milling, grinding, jet milling, crushing, and air micronization. There are several drawbacks to these methods. First, they might not accomplish the desired amount of particle size reduction. The second drawback is associated with the physical and chemical properties of the materials undergoing size reduction. Certain compounds are chemically sensitive or thermo-labile, such as explosives, chemical intermediates, or pharmaceuticals which can not be processed using conventional methods due to the physical effects of these methods. Other compounds such as , polymers, pigments or dyes, etc. maybe difficult to process by conventional methods due to physical properties such as physical degradation under high pressures or temperatures, "softness", or waxy texture.

### Supercritical Fluid Nanopowder Production

The most common methods of nanopowder production involve the rapid depressurization of saturated solutions. This causes the solute to precipitate out of the solution in the form of nanopowder.

There are several methods from production of nanopowders. One of them is through a chemical route. Using the point of zero charge concept, single molecules or small packets of molecules may be synthesized, usually on a support.

\*\*homogeneous nucleation occurs at fast saturation and temperature drops  
(Encyclopedia Britannica Online: nucleation)

\*\*certain dyes, chemical intermediates, pharmaceutical and biological compounds, polymers and explosives, which are chemically sensitive, thermo-labile, waxy or soft, are difficult to powderize by conventional techniques.

\*\*Most new techniques for nanopowder production use CO<sub>2</sub> non-toxic, non-flammable, cheap and easy recyclable.

\*\* $\beta = (\text{actual concentration} / \text{saturation concentration})$

\*\*Size, size distribution, morphology, polymorphic nature all depend on evolution of  $\beta$

\*\*Where large levels of supersaturation are quickly attained small particle size distribution occurs and smaller crystals are formed due to nucleation phenomena being enhanced over crystal growth, meaning smaller particles.

\*\*The efficiency of a crystallization process is highly related to the compound solubility and solute concentration evolution, which determines the supersaturation during the crystallization process.

### **Rapid Expansion of Supercritical Fluids**

**Rapid Expansion of Supercritical Solutions (RESS) is a crystallization technique that uses the properties of a supercritical fluid, typically CO<sub>2</sub>, as a solvent to facilitate nanopowder production. The RESS process is described in two steps: solubilization and particle formation. The driving force for this process is caused by the rapid depressurization of the supercritical fluid dissolved with the solute of interest through a nozzle to cause fast nucleation and fine particle generation [ 6]**

[7].

#### RESS process operation

As showing in Figure 1, the RESS process begins by subjecting liquid CO<sub>2</sub> to high pressure and temperature in order to reach the supercritical region of the fluid. The supercritical fluid is then mixed in the extraction autoclave with the solute. At the extraction step, the flow rate plays a role since the thermodynamic equilibrium may not have been obtained [ 6]

[7]. This may affect the solvating power of the solvent since temperature fluctuations occur outside the region of thermodynamic equilibrium.

The next step involves the depressurization of the mixture from high pressure to atmospheric pressure by a nozzle. This rapid decrease in pressure causes nucleation by lowering the solvating power of solvent. Since  $\text{CO}_2$  is in the gaseous state at ambient conditions, the solute precipitates and is gathered in the collecting device. The  $\text{CO}_2$  is then purges out of the container through a valve.

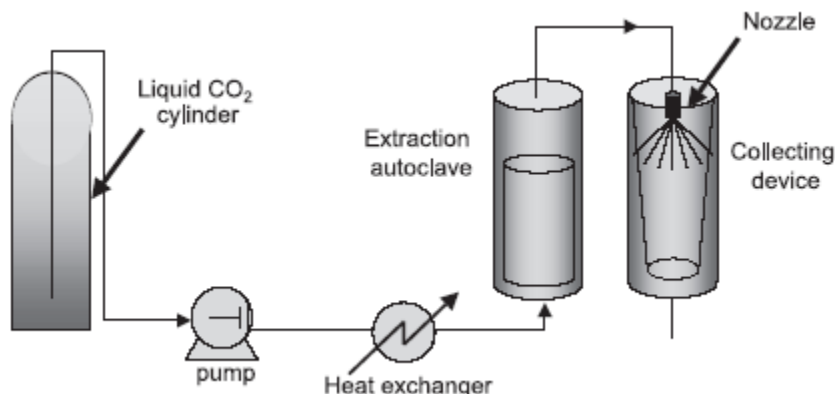


Figure 1. Schematic of the RESS process.

### Advantages and Disadvantages

There are many advantages to the RESS process. Although the process takes place at high pressures, the temperatures required are fairly low. This lowers energy costs. Another advantage is the lack of significant environmental hazards. Since  $\text{CO}_2$  is not a hazardous material when released in the quantities used in this process and it is almost pure  $\text{CO}_2$ , meaning that there is little of the solute left after the process is completed, there are almost no environmental considerations that have to be taken into account for this process. The greatest advantage of all is the ability to make extremely small particles in the micro or nano scale.

For all the advantages though there are some disadvantages to this process. The major disadvantage is the cost of operating at the high pressures required for the process. High pressures are costly due to pumping expenses as well as the equipment costs. Besides the high costs of being a high pressure process, the other major disadvantage is that the RESS process only works for solutes that are soluble in  $\text{CO}_2$ . If the solute is not soluble in  $\text{CO}_2$  then another process must be considered.

### Supercritical Anti-Solvent

The Supercritical Anti-Solvent process (SAS) uses solvent/anti-solvent binary systems to induce the formation of nano and micro-size particles. The supercritical fluid (i.e.  $\text{CO}_2$ ) acts as an anti-solvent that causes the crystallization of the solute [ 6]

[7]. The main driving force for this process is the droplet formation, which is caused by the solvent/anti-solvent interaction. Since many results are influenced by the process arrangement, an investigation of the different SAS-related processes will be discussed.

### **Batch operation**

The precipitation vessel or precipitator is loaded with a specific quantity of liquid solution, as shown in Figure 2. The supercritical fluid CO<sub>2</sub> is injected into the vessel, typically from the bottom to achieve a better solvent and anti-solvent mixture [ 6] [7]. Once injected and due to the dissolution of the compressed gas, the expanded solvent has a lower solvating power than the pure solvent. This mixture becomes supersaturated and solute precipitates to form micro-size particles. After a holding time, the expanded solution is drained under isobaric conditions to wash and clean the precipitated particles [ 6]

[7].

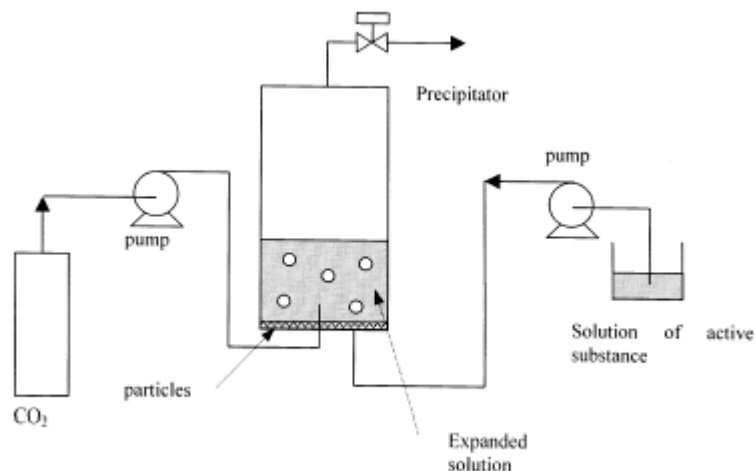


Figure 2. Schematic of Batch Operation SAS/GAS process [ 6]

[7].

### **Semicontinuous operation**

There are two different methods in which particles may be produced by semicontinuous operation. The first type is sometimes referred to as Aerosol Solvent Extraction System (ASES) and the second type is known as Solution Enhanced Dispersion by Supercritical fluids (SEDS). The difference between these types is due to the way the supercritical fluid and solution interacts within the injection device. We shall first discuss the ASES process, followed by the SEDS process.

ASES method involves spraying the solution as fine droplets into the supercritical fluid. The dissolution of the supercritical fluid is followed by a large volume expansion, which is called the anti-solvent effect. This cause a reduction in the liquid solvating

power and a sharp increase in the supersaturated within the liquid mixture, which leads to small and uniform particles [ 6] [7].

Figure 3 is a simple schematic of the ASES process. As shown in Figure 3, liquid  $\text{CO}_2$  is elevated to the supercritical region through pumps and heat exchangers. The  $\text{CO}_2$  is allowed to enter the mixing device at a constant flow until desired pressure is established. Next, pure organic solvent transverse through the mixing device with the aim of obtaining steady composition conditions during the solute precipitation. After steady composition conditions are acquired, the flow of the pure solvent is stopped and the liquid solution from the solution vessel is delivered to the mixing device. The experiment seize when the flow of liquid solution stops and the  $\text{CO}_2$  is purge. Typically, the  $\text{CO}_2$  continues to flow after the flow of liquid solution has stop in order to remove the residue on the precipitate [3].

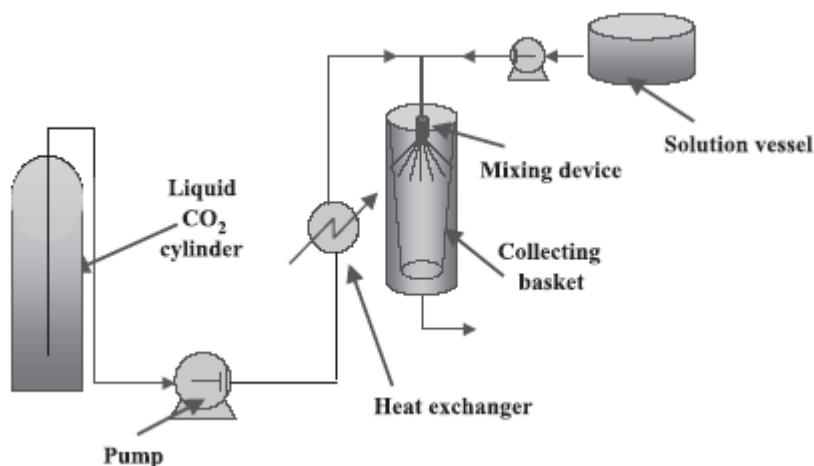
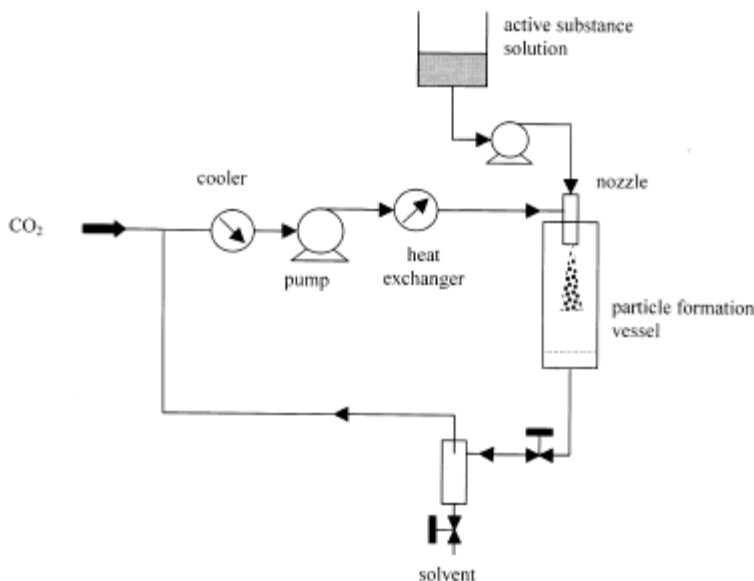


Figure 3. Schematic of ASES Process.

SEDS method was developed to achieve smaller droplet size and intense mixing of supercritical fluid and solution for increased mass transfer rates. The supercritical fluid is used for its chemical properties and as a 'spray enhancer' by mechanical effects. As shown in Figure 4, the nozzle plays an important role in particle formation. Having two coaxial passages allows the supercritical fluid and the solution to mix inside the nozzle. This means that the high velocity of the supercritical fluid assist in the break up of the solution into very small droplets. Designed conditions permit the evaporation of the solvent from the solution into the supercritical fluid [ 6] [7]. As an effect, the droplet size reduces which leads to the formation of micro and nano-size particles [ 6]



[7].

Figure 4. Schematic of SEDS process [ 6]

[7]

### Advantages and Disadvantages

**There are many advantages using the SAS process over traditional liquid antisolvent processes. The first advantage is based on the ability to completely remove the supercritical antisolvent by pressure reduction. Traditional liquid antisolvent requires complex post-processing treatments for the complete elimination of liquid residues [5]** A. T. Bell. "The Impact of Nanoscience on Heterogeneous Catalysis." Science 299 (2003): 1688-1690

[ 6]

[7] J. Jennifer, M. Perrut. "Particle design using supercritical fluids: Literature and patent survey." The Journal of Supercritical Fluids 20 (2001): 179-219

[8] E. Reverchon, G. D. Porta, "Supercritical fluids-assisted micronization techniques. Low-impact routes for particle production." Pure Appl. Chem. 73 (2001): 1293-1297

**[9], which translates into additional cost. The second advantage is due to the fact that the magnitude of the diffusivities for supercritical antisolvents may be two orders higher than liquid antisolvents. Hence, the rate of diffusion into the liquid solvent produces the supersaturation of the solute and its precipitation in the range of micronized particles to the particle diameters, which is not possible by traditional liquid antisolvent or other methods [5]** A. T. Bell. "The Impact of Nanoscience on Heterogeneous Catalysis." Science 299 (2003): 1688-1690

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[7] J. Jennifer, M. Perrut. "Particle design using supercritical fluids: Literature and patent survey." The Journal of Supercritical Fluids 20 (2001): 179-219

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[9].

One disadvantage is finding a solvent that is completely miscible with the supercritical fluid. Also, the crystallization tends to be heterogeneous, which depends on

the efficiency of the mixing with in the nozzle. A third disadvantage is that the solute after crystallization must be rinsed to remove residue on the particles.

### Applications

The SAS technique has been applied to explosives, catalysts, superconductor precursors, polymers and biopolymers, and some pharmaceutical compounds. In 1988, Schmitt produced triamcinolone particles of diameter 5-10  $\mu\text{m}$  from THF. In 1992, Krukonis et al. were able to use the SAS process for crystallization and the separation of two explosives; RDX and HMX. Debenedetti et al. were able to create catalase and insulin particles with 1-5  $\mu\text{m}$  size [10]. Reverchon et al. produced micronic and nano-meter particles of Rifampicin by varying the pressure of the process. Those were only a few examples of the applications of the SAS process

Another application of this process is the ability to allow co-precipitation of two different compounds. The advantages acquired from co-precipitation falls into terms of formulation, dissolution rate of drug releases systems [10]. Since SAS process is rapidly changing, new applications are discovered daily and the science of nano-powder is being revolutionized.

### Particle From Gas Saturated Solution

The Particle from Gas Saturated Solution (PGSS) process uses a SCF, usually  $\text{CO}_2$ , as a solute to crystallize a solution. The PGSS process can be used to create micro-sized particles with the ability to control particle size distribution. PGSS also allows for the production of particles that are solvent-free using a method that is sensitive to the chemical and physical properties of the materials. The most common use of PGSS is for the micronization or encapsulation of pharmaceuticals [1]

**G. A. Mansoori.**  
**“Advances in Atomic & Molecular  
Nanotechnology.” Tech Monitor (2002): 53-59**

[2] R. Dunkley. “Nanotechnology: social consequences and future implications.” *Futures* (2004)

[3] E. Reverchon, I. De Marco, G. D. Porta. “Rifampicin microparticles production by supercritical antisolvent precipitation.” *International Journal of Pharmaceutics* 243 (2002): 83-91

[4] P. Q. Fisher. *Mathematical Modeling of the RESS Process for Pharmaceuticals with Various EOS and Modified van der Waals Mixing Rules*. University of Illinois at Chicago

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- [10] J. Fages, H. Lochard, J. Letourneau, M. Sauceau, E. Rodier. "Particle generation for pharmaceutical applications using supercritical fluid technology." *Powder Technology* 141 (2004): 219-226

[11].

The driving force of the PGSS is a sudden temperature drop of the solution below the melting point of the solvent. This occurs as the solution is expanded from a working pressure to atmospheric conditions due to the Joule-Thompson effect. The rapid cooling of solution causes the crystallization of the solvent. The cooling is sudden and homogeneous throughout the solution; therefore, homogenous nucleation is the method of particle formation.

### Process Operation

The PGSS process is a two-step process shown in Figure 5. A solvent is created by melting the desired product under a blanket of SCF. These conditions are favorable to high solubility of the SCF into the liquid product, giving rise to a gas saturated solution. The solution is allowed to reach equilibrium and homogenize. After the solution has equilibrated, it is expanded to atmospheric conditions. A filter in the expansion chamber collects the powder produced. The product does not need to be cleansed due to its solvent-free production. The SCF may be recycled if necessary [12].

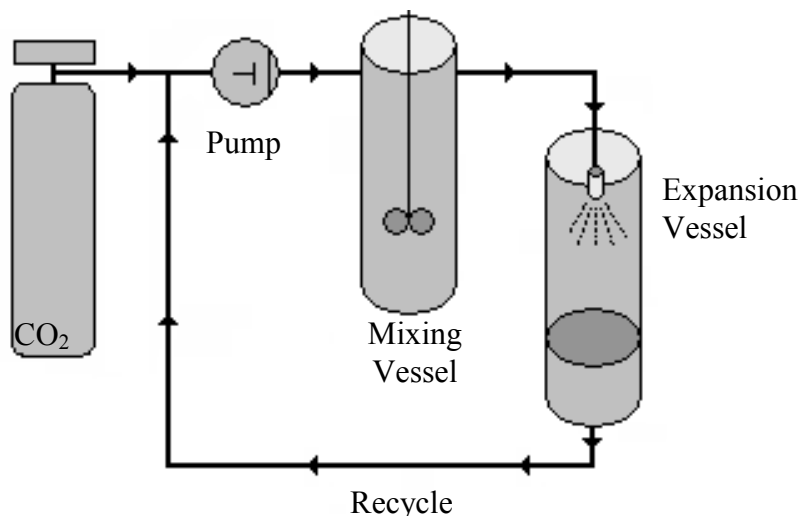
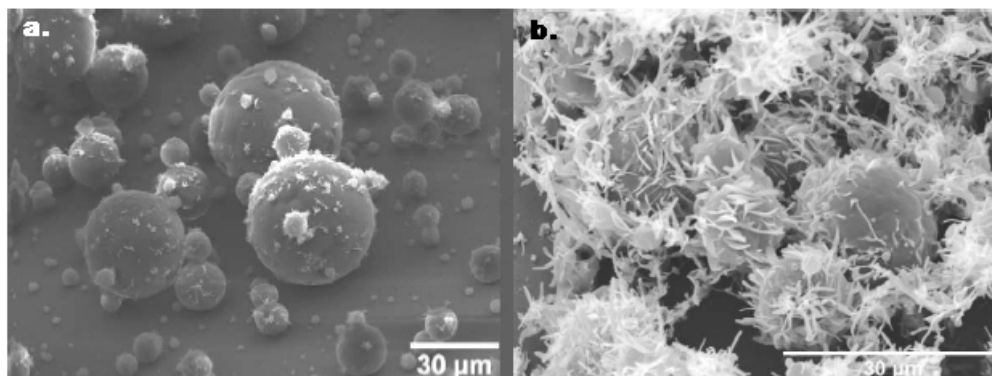


Figure 5. Schematic of PGSS Process.

Rodrigues, M. et al. have shown the most dramatic effects of working pressure changes, is a change in the morphology of the particles. At higher pressures, 16 MPa to 18 MPa, the morphology of particles seemed to mostly spherical with some aggregation. As the working pressure was lowered to 14 MPa to 12 MPa the morphology dramatically changed. Particles became flatter and developed protrusions from the surface. These protrusions are "spike" shaped and tend to become larger as pressure drops. This becomes evident in Figure 6 is a SEM image of this phenomenon. Figure 6 also make

apparent that as pressure decreases the amount of aggregation between particles also increases. These differences can be attributed to the difference of in which period nucleation begins. At lower pressures, nucleation begins earlier in the expansion process, where is large amounts of acceleration, giving rise to long thread-like structures because. Spherical particles are evidence of higher pressures, therefore, nucleation that begins at a later, less accelerated stage, of the expansion process. Although pressure has a noticeable change in particle morphology, there is no apparent effect upon the size or size distribution of particles.



**Figure 6. SEM images of theophylline/HPO composite particles formed by the PGSS process from 359 K and a. 18 MPa, b. 14 MPa to atmospheric conditions [1] G. A. Mansoori. "Advances in Atomic & Molecular Nanotechnology." Tech Monitor (2002): 53-59**

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[11].

The most evident advantage to the PGSS process is the ability to form nanopowder without the need for solvents for the products. This reduces operating costs

in two ways. First, the need for expensive chemical solvents is reduced therefore, operating costs are lowered. Second, the lack of solvents means that the product is high in purity and removal of residue or rinsing is not required.

Another advantage of the PGSS process is the ability to form micro composites or encapsulated particles. This can be achieved by the dissolution of a SCF into a mixture of two solvents, both of which will be present in the product. The process can then be run at conditions that optimal for encapsulation or for formation of micro composite particles.

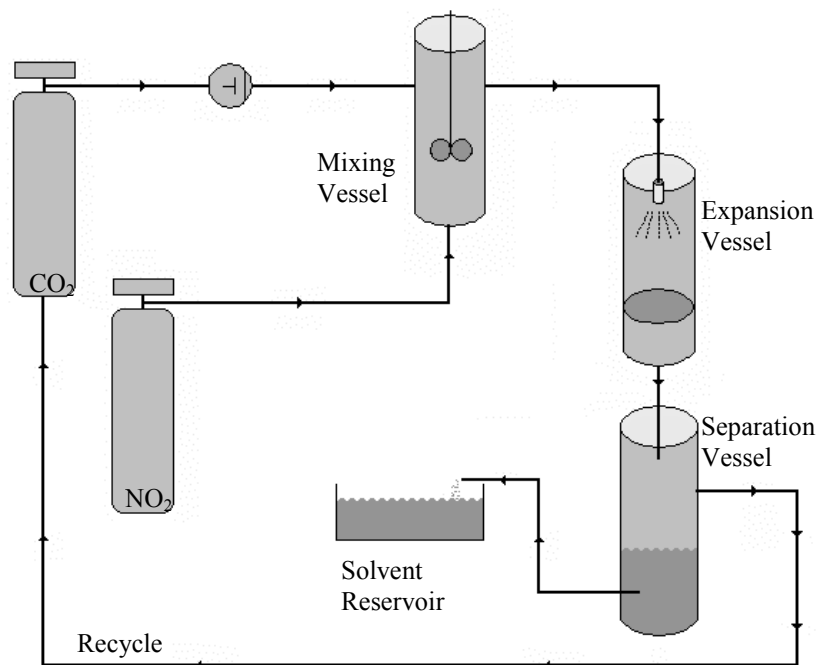
The disadvantages of the PGSS process are due to the need for a SCF to dissolve into a solvent. Although at higher working pressures dissolution becomes more effective, there are compounds for which a SCF can have low solubility. In these cases a different SCF might be an option. Another related disadvantage is the difficulty in the dissolution of a SCF into several solvents with different SCF solubilities. This becomes most important when encapsulation or micro composite particles are the desired product.

### **Depressurization of an Expanded Liquid Organic Solution**

Unlike any other method Depressurization of an expanded liquid organic solution (DELOS) is a process that uses a supercritical fluid, as a co-solvent for the formation of micro- sized particles. The DELOS process is best for organic solutes in organic solvents and it is particularly useful for pharmaceuticals, dyes, and polymers, where conventional methods of particle size reduction tend to be ineffective due to physical and chemical limitations [12].

The driving force for the DELOS process is a fast and large temperature drop. This occurs when the pressurized solution is expanded from a working pressure to atmospheric pressure. The drop in pressure and temperature is homogeneous throughout the solution due to the fact that the system is allowed to reach equilibrium before being expanded. This fast drop in temperature causes the saturation limit to drop equally as fast causing the crystallization of particles from the solution. This process therefore favors nucleation.

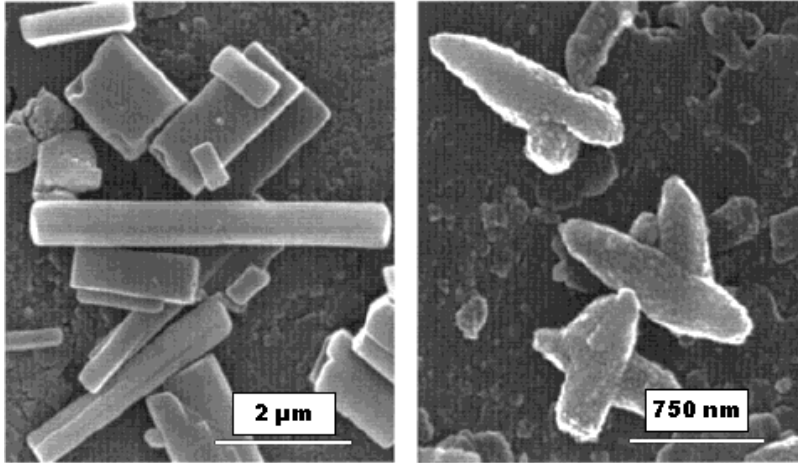
The DELOS process is a simple three-step process, shown in Figure 7. The first step is the dissolution of a solute into an organic solvent in a pressure resistant chamber that is heated to a desired working temperature. Once this is complete, a pre-heated CF is dissolved into the solution and used to achieve the desired working pressure. Sufficient time is provided for the ternary solution to reach equilibrium and the working temperature. Once equilibrium is achieved, the solution is expanded through a one-way valve into a chamber at atmospheric pressure. Pure nitrogen is pumped into the solution chamber to maintain the working pressure during expansion. A filter at the bottom of the expansion chamber collects the solute powder. The formed powder can be cleansed using the pure CF. The solvents from this process can easily be separated and recycled if deemed necessary [12].



**Figure 7. Schematic of DELOS Process.**

Since crystallization through the DELOS process is dependent on a large temperature drop, the yield can be maximized by maximizing the amount of CF used. However, there is a disadvantage; there is a limit to the amount of CF which can be used. If this limit is surpassed, the DELOS process will not be possible and instead crystallization will occur through the SAS process. The limiting amount of CF can be obtained by finding the intersection of the experimental solubility curve for the system and the working line which depicts the evolution of the solvent concentration as CF is added to the system [13].

As the working concentration of CF reaches the limit concentration, the size of particles and the size distribution are minimized. Therefore it is possible to control the particle size characteristics by controlling the working concentration of CF. This allows for the possibility of both micro- and macro- sized particles. Nano-sized particles are attainable through this procedure [13]. Figure 8



**Figure 8. SEM images of particles produced by DELOS process [13].**

It has been shown that the DELOS process is not dependent on the pressure change from the working pressure to atmospheric pressure. Ventosa, N. et al. have shown that for a given system yield, particle size, and particle size distribution are dependent on the temperature drop for the working temperature to the final depressurization temperature, therefore the main factors that control yield are the working concentration of CF and the initial solubility ratio [12]. This allows for the process to be carried out at lower temperatures without any effects. This can lead to cost reduction of running the process.

Particle characteristics or yield of the products of the DELOS process are not dependent on the flow rate of solution through the one-way expansion valve. Particle characteristics are only dependent upon the progression of the supersaturation ratio through the process [12].

Product yield for the DELOS process is directly proportional to the initial supersaturation ratio of the equilibrated solution. Since the solution is allowed to equilibrate, the saturation profile of the process is homogeneous and therefore, does not depend on the efficiency of mixing [13].

## **Conclusions**

## **Acknowledgements**

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