SCALE-UP CONSIDERATIONS IN SUPERCRITICAL ANTI-SOLVENT PROCESSES: ATOMIZATION AND MIXING

Poongunran Muthukumaran*, Lalit Chordia
Thar Technologies, Inc.
730 William Pitt way, Pittsburgh, PA 15238. USA
poongs@thartech.com Fax: 1.412.826.3215

Supercritical antisolvent recrystallization processes have been demonstrated to be advantageous over other methods for pharmaceutical powder processing. They being inherently constructive, increasingly replace traditional destructive size reduction processes. SAS-EM™ is a new antisolvent based process that produces micro and nanoparticles with better control over particle size and size distribution. This paper describes scaleup considerations involved in SAS processes in general and SAS-EM™ process in particular. Control of solution atomization and enhanced mass transfer are two main features that enable nanoparticle production in SAS-EM™ process. In the current processes, all variables including flow rate, pressure and temperature are used for size optimization. In SAS-EM™ process, particle size control is accomplished by external vibration control and crystal structure control by varying the thermodynamics of the system. Effect of atomization and mixing during scale-up of the processes is also discussed. Scanning electron microscope, X- ray diffraction results from Laboratory and Pilot scale unit are also presented.

INTRODUCTION

The formation of fine particles of desired substances in the micro- to nanometer range is an intense area of research. The processes and methods can be extended to a wide variety of materials, including catalysts, chemicals, coatings, explosives, pesticides, polymers and pharmaceuticals. Many supercritical fluid processes have been used to produce fine particles. Rapid Expansion of Supercritical Solutions (RESS) has been successful however this technique does have certain disadvantages, such as solubility issues and substantial pressure drops, which can be quite costly. Supercritical antisolvent process (SAS) is an alternative method in which fine particles can be formed. The solute is dissolved in a solvent and sprayed into another solvent in which the solute is insoluble. The result is the precipitation of particles. Building on this concept, SAS-EM™ can add energy to the SAS process to enhance atomization of the dispersion, mass transfer rate of the antisolvent into the droplet and the solvent out of the droplet through the use of a vibrating surface to atomize the solution jet. SAS-EM™ has an external variable to control the atomization. A change in the amplitude of vibrations changes the atomization without affecting system composition. This gives complete flexibility to manipulate the composition of the system for optimization and still obtain enhanced atomization.

There has been much work performed in the field of supercritical fluid particle technology starting with Krukonis et al. in 1984. Most of the research has focused on using either RESS or SAS. Some examples of the particles formed using these techniques include steroids [2], polystyrene [1], trypsin [4] and insulin [4,5] Other work has focused on the formation of fine polymeric particles that contain various

drugs for the purpose of controlled drug release. Hanna and York [8] also disclosed a method and apparatus for the formation of particles of given substances using supercritical fluids.

While much research has been performed, SAS can still only be used to produce particles in the 1-10 μm range, which is not applicable for pharmaceuticals. Therefore, attempts at modifying the SAS process have been made in order to address this issue. For example, the use of a coaxial nozzle [8] was employed to co-introduce the supercritical fluid and solution, allowing for better dispersion of the solution jet. Randolph et al. [3] used an ultrasonic nozzle in the SAS process, and this concept was disclosed in US5,833,891 and US5,874,029 [6]. Gupta et al.[7] employed a vibrating surface in order to atomize the jet into microdroplets and provide a narrow size distribution. This technique removes the nozzle dimension dependence on atomization altogether.

It is clear from these examples that while methods exist for particle formation using supercritical fluids, there is still a vast research area yet to be explored for improving upon current techniques and paving the way for a successful product manufactured through one of the antisolvent techniques.

Antisolvent processes

In supercritical antisolvent processes, an organic solvent based solution is expanded by the antisolvent, typically supercritical carbon dioxide. Carbon dioxide dissolves considerably in the solution and reduces the solvent power. This results in supersaturation and subsequent nucleation and particle precipitation. This complete process takes place in such a short time that the supersaturation is instantaneous. Such processes are referred in the literature as Gas antisolvent (GAS) or Supercritical Antisolvent(SAS). In another variation, solution is sprayed into supercritical fluid environment where the precipitation of solute occurs. Such a spray system is referred in literature with names like Precipitation in compressed antisolvents (PCA), Supercritical Antisolvent (SAS), and solvent extraction systems (ASES). For the purpose of this paper, expansion of solution using SCF is referred as GAS and spray processes are referred as SAS processes.

GAS process is strictly a batch process. The following process variables are of interest to the process development:

1. Solution concentration
2. Rate of addition of supercritical antisolvent: This is quantified by the rate of increase in pressure
3. Pressure
4. Temperature

In addition, thermodynamic information like phase behaviour of the following systems are necessary for both designing and controlling the process.

1. Antisolvent-Solvent
2. Antisolvent -Solute
3. Antisolvent -Solvent-Solute

Another data of interest is the pressure at which the antisolvent starts precipitating the solute from the solution. It is commonly referred to in the supercritical fluid literature as the cloud point.

The following variables will be important in SAS spray processes.

1. Solution concentration
2. Pressure
3. Temperature

4. Solution flow rate
5. Nozzle design/dimension
6. CO_2 flow rate

Other thermodynamic information will also be needed for SAS processes.

Scale-up requirements in Pharmaceutical Industry

Considering the high potential of antisolvent processes in pharma industry, this paper uses the requirements in pharmaceutical industry. It is reasonable to assume the following requirement for different drug administration routes.

Pulmonary Delivery: Dosages are in microgram quantities and the batch size requirement will be in the order of 10 kg. ***Injection Delivery***: (Intravenous, Intraperitonial, subcutaneous etc.) Dosages are in 1-20 mg and the batch size needed will be in the range of 10-100 kg. ***Oral Delivery:***Higher dosages are required for oral delivery. More than 20 mg will be needed in each dosage. Batch size requirement will be more than 100 kg.Above numbers are generalized for delivery routes and depending on the potency of the drug and the treatment methodology, dosages vary and accordingly batch sizes also vary.

Scale-up considerations in GAS

Scale up of GAS process is similar to a mixing operation at high pressures. Rate of addition of antisolvent need to be maintained and continuous mixing should be provided for effective precipitation and solvent removal. Removal of solvent containing antisolvent from the high pressure vessel can be accomplished by continuously purging the vessel with antisolvent at elevated pressures or other means for separating different phases. Temperature need to be carefully controlled. Most of the solutes are poor thermal conductors and as a result maintaining the temperature constant throughout the process scale vessel is an issue that needs careful consideration. If the heat input is primarily maintained by controlling the antisolvent inlet temperature, heat can disperse uniformly with well dispersed antisolvent resulting in better temperature control.

Scaleup Considerations in SAS

In the SAS spray processes, spraying step provides a control mechanism in addition to the variables available in GAS process. Several variations in spraying the solution/suspension have been investigated. Some of these variations have been patented and pave the way to commercial success of the technology. There are some issues that are common for the scale-up of all variations of spraying. Most important of them is the nozzle dependent spraying or solution jet breakup. Nozzle design and dimension plays a major role in the solution jet break up and the resultant particle size. For example, a popular antisolvent variation SEDS uses CO_2 as a dispersant in addition to being an antisolvent. Literature shows that the average particle size obtained from such SEDS process is usually more than a micron and in most cases above 2-3 microns. Grothe et al. [9] recently modified the SEDS process to incorporate a tortuous swirling path for the solution thereby increasing the turbulence in the resultant solution jet. They were also able to quantify the energy associated with such increased turbulence. Such a modification provides increased mixing of the solution jet with antisolvent and leads to submicron particles. Similarly, it is well known that changing the nozzle size changes the solution jet-breakup resulting in different particle sizes. It is necessary to increase the flow rate of the solution during the scale-up to increase the throughput. This involves increasing the nozzle size. Theoretically, classical dimensionless scale-up considerations can be used to increase the nozzle size. This includes adjusting the flow rate and other variables to maintain Reynolds, Weber and other relevant dimensionless numbers constant. In practical cases, it is difficult to

maintain the same solution jet breakup during scale-up which results in different particle sizes than what is anticipated during the laboratory development. This invariably leads to implementing multiple nozzles of smaller dimension to increase the throughput[10]. When many nozzles are used, it is difficult to control the solution jet breakup and as a result different size particles will be produced from different nozzles. This leads to a wide particle size distribution nullifying one of the main advantages of using supercritical antisolvent processes. Clogging or partial clogging of one or more nozzles also result in such problems. In pharmaceutical applications this poses various regulatory uncertainties leading to prolonged development cycles.

Mixing in the particle formation vessel provides a way to make the precipitation process uniform and to certain extend control the kinetics of recrystallization. Mixing can be achieved traditionally by employing an impeller capable of operating at high operating pressures. Impellers provide a good macromixing. Micromixing at molecular or even crystal levels is not achievable using traditional impellers.

Antisolvent flow schemes and flow patterns inside the particle formation vessel play a role in uniform temperature control throughout the collected powder and residual solvent level control. Antisolvent can be flown counter-current, cross-current and cocurrent to the flow of solution. Depending on the flow configuration, location of the exit ports and the vessel geometry, flow pattern will vary. Advanced Computational fluid dynamic tools prove to be helpful in modeling flow patterns and temperature control during the scale-up studies.

Collection of produced micro and nanoparticles is an important issue. Solid state characteristics of the powder need to be maintained while collecting in large batches. Design of collection bags and appropriate systems for sterile handling of powder after the vessel is opened are important for pharmaceutical applications.

Considering the issues in scale-up of antisolvent recrystallization processes, the following paragraphs present a new or modified antisolvent process termed as Supercritical antisolvent process with enhanced mass transfer (SAS-EM^{TM}) and describe how the new process addresses the issues of scale-up issues. This new process was invented by Gupta and Chattopadhyay[7]

SAS-EM^{TM} Process

SAS-EM^{TM} is an antisolvent process where the solute is dissolved in a solvent and applied on to a vibrating surface. This application is accomplished by directing a solution jet through a capillary tube on to a vibrating surface. Solution jet instantaneously forms a film on the vibrating surface which upon vibration breaks down as fine droplets. Film breakage is so intense that the atomization is very effective leading to small droplets and in most cases in submicron sizes. These droplets undergo antisolvent effect where supercritical carbon dioxide diffuses into the droplet, expands it, reduces the dissolving power of the solvent and precipitates the solute as nanoparticles.

Vibration in the particle formation vessel create a vibration field that makes the immediate vicinity of the vibrating surface well mixed. This thorough mixing enhances the mass transfer. This enhanced mass transfer makes the antisolvent effect to take place faster and makes sure the droplets become particles before two or more droplets coalesce together to form bigger droplets. This ensures formation of nanoparticles of the solute in the precipitates powder.

Atomization in SAS-EM^{TM}

Atomization in SAS-EM^{TM} is controlled externally by the piezoelectric or magneto restrictive method. Degree of atomization can be controlled by the amplitude of vibration of the vibrating surface. Examples have shown that by increasing the

amplitude of vibration, particle size can be decreased. This has been shown to be the case for a variety of compounds. Removing the nozzle dimension dependence on atomization is a radical change from other nozzle size dependent atomization schemes in antisolvent processes. Increasing the amplitude of vibration while simultaneously increasing the solution flow rate yields the same particle size. However, increased solution flow rates yield higher throughputs. This scale-up philosophy addresses the drawbacks in the traditional atomization scale-up involved in SAS processes.

Mixing in SAS-EM^{TM}

Vibrational field created by the vibration inside the particle formation vessel makes a well mixed zone in the vicinity of the atomization zone. Thorough mixing provides enhanced mass transfer and it is very critical especially at the immediate vicinity of the atomization zone. Even if the atomized droplets are very small, if they are left as droplets for long, they may coalesce to become bigger droplets. When the mass transfer is enhanced around the atomization zone, droplets undergo rapid antisolvent effect and precipitate as fine particles before they get a chance to coalesce. The time lines discussed here are only relative and the overall timeline is in seconds or milliseconds depending on the process conditions. Vibrational enhancement to mass transfer also makes sure that most of the residual solvent is removed from the particles by the antisolvent effectively. Residual levels are well below the ICH guidelines.

The following examples illustrate the pilot scale experimental results using SAS-EM^{TM} process. Tetracycline base is a model poorly water soluble drug. Nanoparticles of tetracycline will enhance the water solubility and hence increase the bioavailability of the drug. This reduces dosage level required for treatment. In cytotoxic compounds, this leads to less side effects and better life style for the patients.

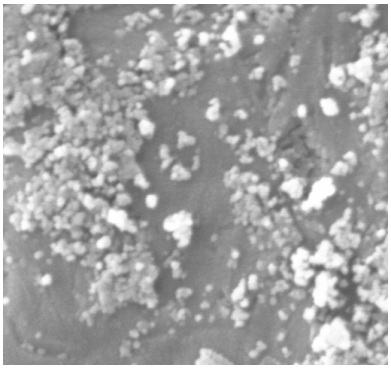


Fig. 1.Tetracyline nanoparticles from laboratory scale Size bar is 250nm.

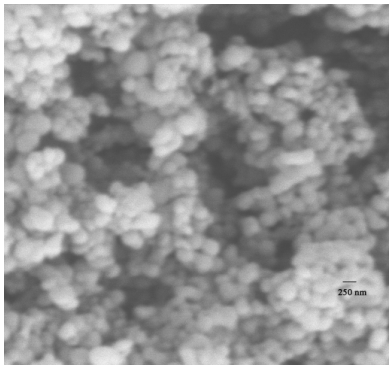
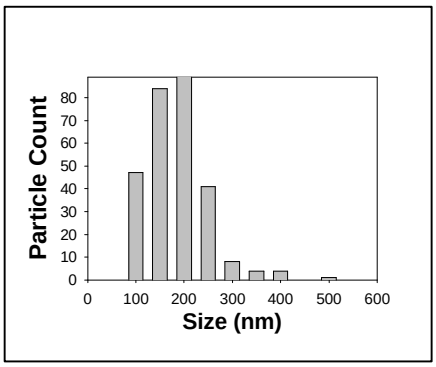


Fig 2.Tetracycline nanoparticles from pilot scale

Figure 1. and 2 show the SAS-EM^{TM} processes tetracycline nanoparticles. Figure 1 is a result from lab scale apparatus and Figure 2 is a result from a pilot scale apparatus.



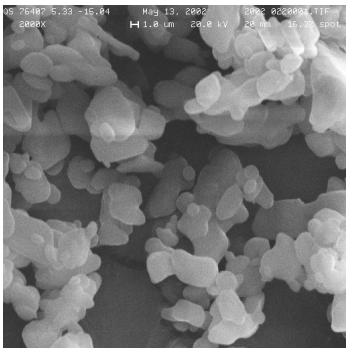


Figure 3. Particle size distribution

Figure 4. Pilot scale acetaminophen particles

Figure 3 shows the particle size distribution of tetracycline processed with SAS-EM™. Figure 4 is the SEM micrograph of acetaminophen processed in SAS-EM™ pilot scale apparatus. Nanoparticles were obtained for the same drugs using different solvents like ethanol, methanol, tetrahydrofuran, methylene chloride and more. Figure 5 shows Xray diffraction pattern of one of the SAS-EM™ processed acetaminophen samples. It compares well with the unprocessed crystalline material indicating SAS-EM™ processing is able to retain the crystalline structure during the recrystallization process.

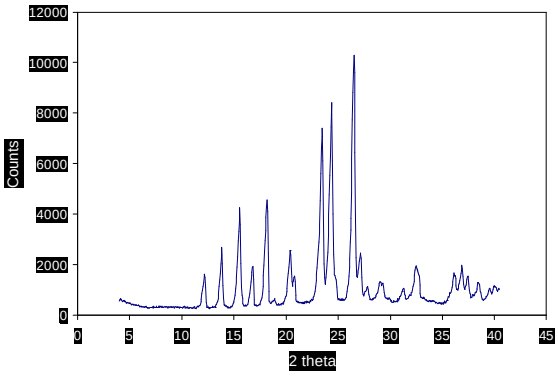


Figure 5. XRD pattern of acetaminophen

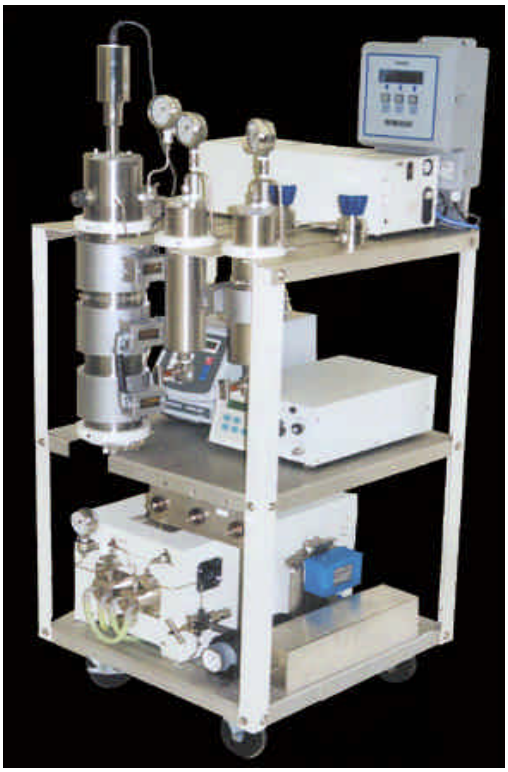


Figure 7. Pilot scale SAS-EM™ equipment

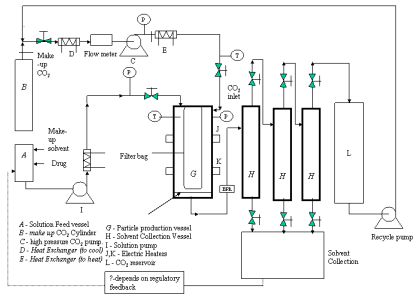


Figure 6. SAS plant setup

Figure 6 illustrates the components of an antisolvent precipitation plant for industrial scale production.

CONCLUSION

Issues involved in scale-up of antisolvent based processes are to be given consideration in early stages of process development as many are inherently process related. With appropriate considerations and employing SASEM, it is possible to commercialize this technology and provide new ways of addressing new challenges in drug delivery in of 21st century.

REFERENCES :

[1] Dixon, David J.; Johnston, Keith P. AIChE Journal (1991), 37(10), 1441-9.

[2] Larson,F.A and M.L.King, Biotechnol. Prog, 2, 1985, p73

[3] Randolph, T. W.; Randolph, A. D.; Mebes, M.; Yeung, S.. *Biotechnol. Prog.* 9, **1993**,p 429

[4] Winters, M. A.; Knutson, B. L.; Debenedetti, P. G.; Sparks, H. G.; Przybcien, T. M.; Stevenson, C. L.; Prestrelski, J. S. *J. Pharm. Sci.* **1996**, *85*, 586.

[5] Yeo, S.-F.; Lim, G.-B.; Debenedetti, P. G.; Bernstein, H.. *Biotechnol. Bioeng.* **1993**, *41*, 341

[6] Subramaniam, B.; Saim, S.; Rajewski, R. A.; Stella, V.. U.S. Patent 5,833,891, 5,874,0291997

[7] Gupta, R. B.; Chattopadhyay, P. U.S. 2002/0000681 A1

[8] York, Peter; Hanna, Mazen, WO 95/01221

[9] Grothe, Willy., Jarmer, Daniel., Lengsfeld, Corinne., Randolph, Theodore., WO03006223
[10] Sun, Chuanjing., Sun, Yunpeng., CN1314146