Particle Formation Using Supercritical Carbon Dioxide

Rodger Marentis
Supercritical Technology Consultants
PO Box 3350, Allentown, PA 18106
Tel. 610-967-2997, Fax 610-966-3877, email: rmarentis@aol

Particle formation by methods utilizing supercritical or sometimes-subcritical carbon dioxide is a subject of great interest in the pharmaceutical and fine chemical industries. Several techniques are available to form particles utilizing supercritical carbon dioxide:

Rapid Expansion from a Supercritical Solution (RESS)

If a material is highly soluble in liquid or supercritical carbon dioxide, then the process known as Rapid Expansion from a Supercritical Solution (RESS) should be considered. This is a process in which a supercritical fluid mixture is expanded into an expansion vessel through a specially designed orifice to achieve the desired mean particle size and particle size distribution. This process however is very limited in its application because very few compounds are highly soluble in supercritical carbon dioxide.

RESS can be used to precipitate mainly organic, but some inorganic, solutes upon expansion of a dilute solution from a supercritical or near critical solvent. The expansion step in RESS occurs through a throttling device such as an orifice, capillary tube or needle valve, which can support a large pressure drop without freezing. For commercial scale applications, heat should be applied to the throttling device to reduce the Joule-Thompson freezing effect that can lead to clogging of the throttling device. The RESS process can produce a variety of precipitate morphologies, including thin films, fine diameter fibers and narrow size distribution particles. Changes in pressure, throttling device dimensions, concentrations of solute in the supercritical fluid, and temperature cause wide variations in precipitate morphology, (e.g. fibers to spheres).

An increase in pre-expansion temperature under certain experimental conditions, can lead to a transition of powder to fibrous morphology. Similarly a decrease in pressure can also result in a powder to fiber morphology transition. This suggests that solutions with lower density are

more likely to produce particles of a fibrous morphology in the RESS process. In addition to the thermal dynamic variables of pressure, temperature and concentration, a fluid dynamic process variable – the diameter of the throttling device, has also been found to influence the morphology of the precipitate.

Gas Anti-Solvent (GAS)

Gas Anti-Solvent (GAS) is a far more universal process because the compounds of interest do not have to be soluble in carbon dioxide for the process to work. The GAS process can be utilized for the separation of mixtures into individual, nearly pure component fractions. The degree of separation possible is a function of the volume expansion of the liquid solvent phase. The GAS process is based on the ability of a supercritical gas to dissolve in and expand an organic solvent at moderate pressures and temperatures. Due to the dissolution of the compressed gas in the liquid solvent, the expanded solvent has a lower solvating capacity for the solute. When a solution (liquid solvent and solute) is expanded sufficiently by the supercritical solvent, the liquid solvent can no longer keep the solute in solution, and nucleation will occur. The nuclei will grow as the supercritical anti-solvent is dissolved into the solution, until the solute is essentially depleted from the solution. The complete miscibility of the organic solvent with the compressed gas is the basic requirement for applying this anti-solvent technique. Examples of applications for the GAS process are 1) the purification and comminution of energetic materials (RDX and NQ), 2) the recrystalization and purification of ß-carotene, and 3) the comminution of proteins.

Supercritical Anti-Solvent (SAS) Fractionation

Supercritical anti-solvent fractionation is an extractive process for separating polydisperse mixtures of macro molecules (e.g. polyethylene) having uniform chemical micro structure into fractions of varying average molecular weight. SAS can be a batch or continuous process performed in single-stage extraction vessel or a continuos multi-stage high-pressure column. Typically, the solvent rich extract contains a low molecular weight fraction and the polymer rich raffinate contains a high molecular weight fraction. Solvent selectivity is controlled by temperature, pressure, and solvent composition (by adjusting the anti-solvent concentration). The solvent capacity is defined as the polymer solubility in weight %, while the

solvent selectivity is defined as the ratio or partition co-efficient for the separated components (during a state of phase equilibrium).

Distinguishing SAS from GAS, in SAS the compressed gas is added to a polymer solution to induce the creation of a solvent rich liquid phase and a polymer rich liquid phase as opposed to, in GAS where the compressed gas is added to a solution to cause volumetric expansion and associated reduction in solvent power. In SAS processes, the upper critical solution temperature (UCST) and the lower critical solution temperature (LCST) are shifted to higher and lower temperatures respectively until they represent one large region of immiscibility over the whole temperature range.

In a commercial SAS fractionation process, the liquid solvent and the polymer are fed counter-currently to a multi-stage column. The polymer feed is introduced at the top stage of the column and the liquid solvent with supercritical anti-solvent is introduced at the bottom stage of the column. The mixture is allowed to separate into polymer-rich and solvent-rich phases that reach the state of phase equilibrium at each stage. The extract stream (the solvent rich phase) is obtained at the top stage and the raffinate stream (the polymer-rich stage) is obtained at the bottom stage. The SAS process would be most useful for solvent recovery in solution polymerization processes as well as for molecular weight fractionation of polymers.

Precipitation with a Compressed fluid Antisolvent (PCA) or Spray GAS

PCA (sometimes called spray GAS) is a process similar to GAS which allows the production micron-size particles. Both GAS and PCA rely on the same mechanism of the insolubility of the supercritical fluid in an auxiliary organic solvent. In both processes a solution formed from a liquid solvent and solid solute is contacted with the supercritical fluid, which acts as an anti-solvent and precipitates the solute into fine solid particles of nearly uniform particle size distribution. The difference being in how this contact between antisolvent and solution is achieved. In the GAS process the supercritical carbon dioxide antisolvent is sprayed into the liquid solution, while in PCA or spray GAS the liquid solution is sprayed into the supercritical carbon dioxide. Thus, PCA involves a second step of washing the particles by the CO_2 for the removal of the solvent and recovery of dry particles.

Solution Enhanced Dispersion of Solids (SEDS)

The SEDS or Solution Enhanced Dispersion by Supercritical fluid process incorporates the use of supercritical fluids for particle formation, as well as provide directed and reproducible control over particle characteristics. The process involves introducing a solution of a solid solute (e.g. a drug) in an organic solvent and a supercritical carbon dioxide into the particle formation vessel via a specially designed coaxial nozzle. The liquid jet of drug solution is broken by a high velocity jet of supercritical carbon dioxide, and the extraction of the organic solvent into the supercritical carbon dioxide. This leads to very high super saturated conditions and the rapid formation of particles which are retained in the particle formation vessel. The pressure and temperature of the particle formation vessel, along with the precise metering of the flow rates of the drug solution and supercritical carbon dioxide into the nozzle, provide for uniform conditions that can be used to control nucleation and particle generation. The products are micro fine particles with uniform morphology and narrow size distributions that are batch consistent, easy flowing, readily dispersible and solvent free. SEDS is primarily a particle design technology for pharmaceuticals.

Concentrated Powder Formation (CPF)

This high pressure spray process is unique because the particle size increase may also be achieved. This process comprises the following steps:

1. Dissolution of a pressurized gas into the liquid solvent, thus lowering the viscosity and surface tension of the solvent.

2. Release of the pressurized gas and liquid solvent by expansion through a nozzle that forms small droplets of the liquid solvent.

3. Simultaneous ad mixing of a solid, powderous carrier, which is intensely mixed with the droplets of the expanding gas.

4. Infiltration of the droplets into porous carriers and/or agglomeration of non-porous carrier materials by the liquid.

5. Separation of the formed particles by sedimentation, centrifugal forces, or filters.

The CPF process can be applied to low and high viscous liquids. Solid carriers with a broad range of particle sizes and bulk densities (50-850 kilograms/m^3) can be used. The pressure range is 70-200 bar. The gas consumption is 0.5-2 kg of gas/kg of powder. The CPF technology results in powderous agglomerates with an unusual high liquid content. Almost any liquid might be applied to solid carrier materials.

Particles from Gas Saturated Solutions (PGSS)

In the PGSS process, the substance to be powdered is melted in an autoclave. Next, supercritical carbon dioxide is dissolved in the melt and forms a solution. At moderate pressures (typically between 70-200 bar), gas concentrations of 5-50 wt/% in the melt solution are obtained. This gas saturated solution is expanded in a nozzle. The combination of cooling and volume increase of the released gas causes the substance to precipitate in a fine dispersed form. The powder is separated from the gas by sedimentation in a spray tower or centrifugal forces in a cyclone separator. Electrical forces or fine filters might also be used to collect small particles. PGSS offers a major advantage if large-scale production of particles is being considered: the amount of gas required is extremely low (<0.1 kg gas/1.0 kg powder) compared to RESS, GAS, PCA, and SEDS. PGSS can also use standard separator designs and can be operated as a fully continuous process.

Ferro SF MiconMix™ PGSS Process

The MicronMix™ process combines the chemical engineering unit operations of mixing and PGSS micronization in a single processing step. MicronMix™ is especially advantageous when processing viscous liquids, solid particles that become viscous liquids, or monomers that become viscous upon polymerization. The process can produce powders of tight (plus or minus 0.5 micron) and tunable mean particle size distribution that can be selected between 5 and 80 μm, (which is achieved without the need for particle size classification). Additionally, the particles can be tuned to a desirable level of porosity and surface area, in addition to being tuned for mean particle size distribution. Another important feature for manufacturing drug delivery and orthopedic matrices is that the porosity (interconnectivity of the pores) in the particles can also be controlled.

The Ferro SFMicronMix™ process is a batch process that consists of four distinct steps:

1. Materials are loaded at specified quantities into the portable-charging hopper.

2. The unmixed materials are charged from the portable-charging hopper into the supercritical fluid process vessel, and carbon dioxide is introduced into the vessel. Heat is introduced into the vessel by the wall wiping pumping mixer, so that the carbon dioxide is brought to supercritical fluid operating conditions. The viscosity of the materials is greatly reduced by a plasticization effect, which allows for the impeller to quickly and homogeneously disperse the ingredients

3. After 30-60 minutes of agitation, the wall wiping pumping mixer directs completely mixed material to a computer controlled orifice. The mean particle size distribution is controlled by a combination of the selection of appropriate orifice dimensions and selection of the pressure differential between the mixing and collection vessels.

4. The cyclone collection vessel allows the particles to separate from the carbon dioxide via tangential flow patterns that create a cyclone within the collection vessel. The particles are directed downward towards a low pressure reciprocating valve where they are periodically ejected from the collection vessel. The carbon dioxide exits from the top of the cyclone collection vessel, and is recycled.

Conclusions

Several supercritical fluid particle formation processes with different distinctive competencies are currently available for commercial exploitation to produce pharmaceuticals and fine chemicals.

References

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