

**PARTICLE FORMATION USING  
SUPERCRITICAL FLUIDS – A SHORT REVIEW\***

*Particle formation and the design of solid particles and powdery composites with unique properties is at the moment one of major the developments of supercritical fluid (synonyms: dense gases, dense fluids, high pressure) applications. Conventional well-known processes for the particle-size redistribution of solid materials are crushing and grinding (which for some compounds are carried out at cryogenic temperatures), air micronization, sublimation, and recrystallization from solution. There are several problems associated with the above-mentioned processes. Some substances are unstable under conventional milling conditions, in recrystallization processes the product is contaminated with solvent, and waste solvent streams are produced. The application of supercritical fluids may overcome the drawbacks of conventional processes, and powders and composites with special characteristics can be produced. Several processes for the formation and design of solid particles using dense gases have been studied intensively. The unique thermodynamic and fluid-dynamic properties of supercritical fluids can also be used for the impregnation of solid particles, for the formation of solid powderous emulsions, particle coatings, e.g. for the formation of solids with unique properties for use in different applications. This review will focus on the fundamentals and on recent advances of particle formation and design processes using supercritical fluids, on their applications and the technological advantages and disadvantages of various processes.*

*Key words: Micronisation, Supercritical fluids, Dense gases, Particle formation, PGSS<sup>TM</sup>.*

Conventional well-known processes for the particle-size redistribution of solid materials in the pharmaceutical industry are crushing and grinding, air micronization, sublimation, and recrystallization from solution. There are several problems associated with the above-mentioned processes. Some substances are unstable under conventional milling conditions, in recrystallization processes the product is contaminated with solvent, and waste solvent streams are produced.

The application of supercritical fluids may overcome the drawbacks of conventional processes, and powders and composites with special characteristics can be produced. Several processes for the formation and design of solid particles using dense gases have been studied intensively [1–3].

**Rapid expansion of supercritical solutions (RESS)**

Crystallization from supercritical solutions (CSS) is a special process where fine particles are formed from substances which are soluble in supercritical solvents.

When the solute-laden solution is a supercritical fluid, supersaturation may be induced not only by varying the temperature, but also by pressure variation. Thus pressure and pressure-gradients would be

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additional means for the generation of particles with the desired size, form and morphology [4,5].

The rapid expansion of supercritical solutions is another way of performing the crystallization from SCF, where small-size particles can be produced. In this process, a solid is dissolved in a pressurized supercritical fluid and the solution is rapidly expanded to some lower pressure level, which causes the solid to precipitate. This concept has been demonstrated for a wide variety of materials including polymers, dyes, pharmaceuticals and inorganic substances [6,7].

**Gas anti-solvent processes (GASR, GASP, SAS, PCA, SEDS)**

The application of supercritical fluids as anti-solvents is an alternative recrystallization technique for processing solids that are insoluble in SCF. This method exploits the ability of gases to dissolve in organic liquids and to lower the "solvent power" of the liquid for the compounds in solution, thus causing the solids to precipitate.

Gas anti-solvent processes (GASR, gas anti-solvent recrystallization; GASP, gas anti-solvent precipitation; SAS, supercritical anti-solvent fractionation; PCA, precipitation with a compressed fluid anti-solvent; SEDS, solution-enhanced dispersion by supercritical fluids) differ in the way that contact is achieved between the solution and anti-solvent [1–3].

**Particles from gas-saturated solutions (PGSS<sup>TM</sup>)**

This process allows the formation of particles from substances that are insoluble in a supercritical fluid, but absorb a large amount of gas that either swells the

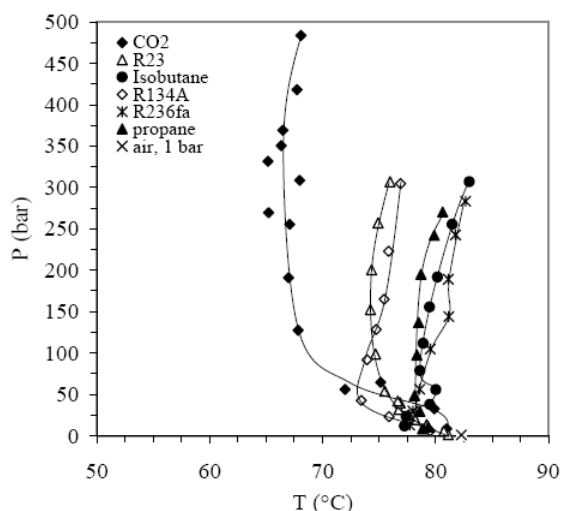


Figure 1. S-L-G behaviour of ethyl-vanillin in various gases

substance or decreases the melting (for polymers the glass transition temperature). This process can also be used for the micronization of liquids, suspensions and emulsions.

In the PGSS™ process the substance or the mixture of substances to be powdered must be converted into a sprayable form by liquefaction/dissolution. This can be achieved by melting or/and dissolving the substance or mixture of substances in a liquid solvent, or by dispersing solids or liquids in a melt or solution, and saturation of the melt/solution/dispersion with the gas [8]. Then the gas-containing solution is rapidly expanded in an expansion unit and the gas is evaporated. Due to the Joule-Thomson effect and/or the evaporation and the volume-expansion of the gas, the solution cools down below the solidification temperature of the solute and fine particles are formed. The solute is separated and fractionated from the gas stream by a cyclone and electro-filter.

When liquefaction is achieved by melting, knowledge of the P-T trace of the S-L-V equilibrium gives information on the pressure needed to melt the substance to be micronized and form a liquid phase at a given temperature, and to calculate its composition [9-11].

When the supercritical fluid has a relatively high solubility in the molten heavy component, the S-L-V curve can have a negative dP/dT slope [12]. The second type of three-phase S-L-V curve shows a temperature minimum [13]. In the third type, where the S-L-V curve has a positive dP/dT slope, the supercritical fluid is only slightly soluble in the molten heavy component and, therefore, an increase of the hydrostatic pressure will increase the melting temperature and a new type of three-phase curve with a temperature minimum and maximum may occur [14].

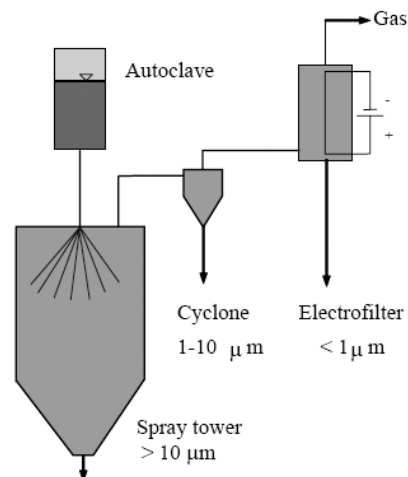


Figure 2. Basic scheme of the apparatus for PGSS™ micronisation

In general, for substances for which liquefaction is achieved by melting, a system with a negative dP/dT slope and/or with a temperature-minimum in the S-L-V curve could be processed by PGSS™ [1,2,8]. For other systems, for example the PGSS™ drying of solutions or suspensions, the mass of gas necessary for solvent evaporation is very important.

The basic scheme of the PGSS™ apparatus is presented in Figure 2. A detailed description of the apparatus and experimental procedures is presented in [1,2,8].

The PGSS™ process was tested on a pilot- and technical scale on various classes of substances. Up to the present time the application of the PGSS™ process has been investigated for polymers, waxes and resins, natural products, fats and fat derivatives, pharmaceuticals, synthetic and natural antioxidants, surface-active compounds, UV-stabilizers, composites of the mentioned substances, etc. [1,2,8].

The highly compressible fluids that have been used are carbon dioxide, propane, butane, dimethyl ether, freons, nitrogen, alcohols, esters, ethers, ketones and mixtures of the above-mentioned gases and solvents.

The powders produced show narrow particle-size distributions and have improved properties compared to conventional produced powders.

The material structure of the substance to be micronised (crystalline-amorphous, pure or composite),

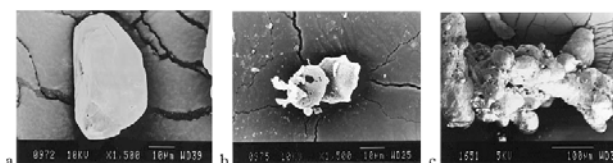


Figure 3. Nifedipine: a) original, b) PGSS processed, c) co-precipitate with PEG [15,16]

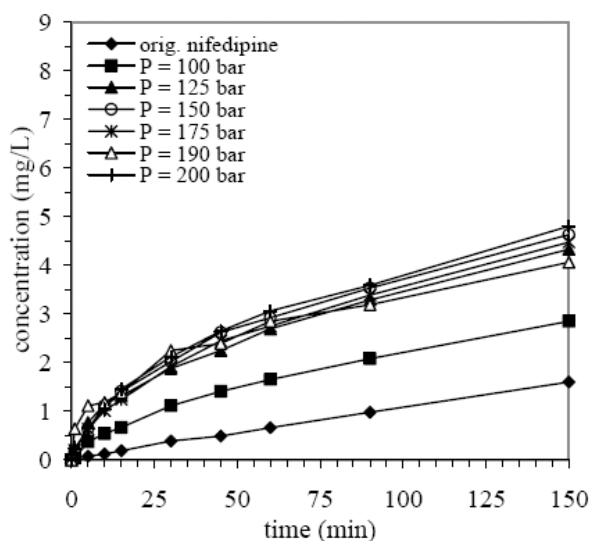


Figure 4. Dissolution profiles of nifedipine, micronized at 175°C and various pressures compared with original nifedipine [15,16] concentration (mg/L)

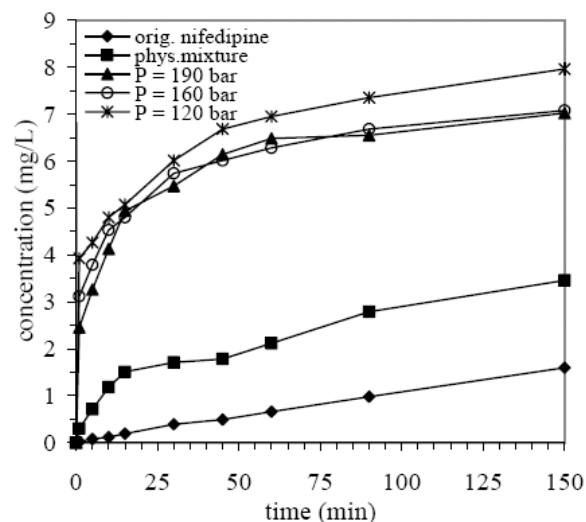


Figure 5. Dissolution profiles of coprecipitates prepared at 50°C and different pre-expansion pressures compared with original nifedipine and a physical mixture of the same composition (1:4) [15,16]

the process parameters (pre-expansion pressure, temperature, gas to substance ratio (GSR), viscosity of the melt/solution/dispersion) of the PGSS™ process and geometry of the process equipment influences the particle size, particle size distribution, bulk density, the morphology (particle shape) (Figures 4, 5) and crystalline/amorphous ratios of the processed substances.

### PGSS™ micronisation of pharmaceuticals

#### Nifedipine

The practically water-insoluble compounds nifedipine and felodipine, which are dihydropyridine

calcium-channel-blockers, were processed by the PGSS process with the aim of increasing their dissolution rate and hence bioavailability [15,16].

Using the PGSS process, nifedipine was micronized at various pressures in the range from 100 to 200 bar and at 165, 175 and 185 °C [16]. The mean particle-size of the starting nifedipine was 50 µm, and it was decreased to 15–30 µm, depending on the experimental conditions. The resulting particle size was a function of the process conditions. With increasing pre-expansion pressure, the mean particle-size was reduced and, as a result, the dissolution rate was found to be higher for samples prepared at higher pre-expansion pressures (Figure 4).

The shape of the micronized particles was irregular and, according to SEM pictures, it was assumed that the particles were porous. With particle-size reduction and, therefore, increased specific surface area (external and internal), the dissolution rate increased to some extent, but the anticipated effective surface area was probably reduced by the drug's hydrophobicity and the agglomeration of particles during and after micronization. The shape of the particles is presented in Figure 3.

In order to avoid the agglomeration of micronized particles and the thermal degradation of nifedipine at high temperatures (175 and 185 °C), the hydrophilic polymer PEG 4000 was added to nifedipine to reduce its melting point. It was found that a eutectic mixture for the system PEG 4000/nifedipine is a 80:20 mass ratio at 58 °C [15,16]. Micronization at pre-expansion temperatures between 50 and 70 °C was possible and fine powdered co-precipitates of nifedipine/PEG 4000 were obtained.

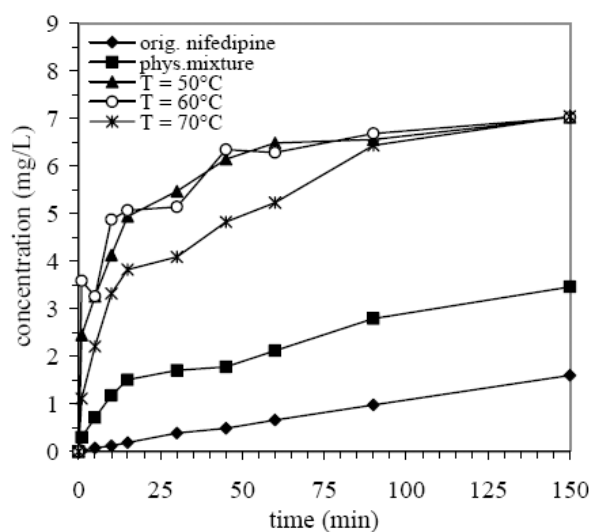


Figure 6. Dissolution profiles of coprecipitates prepared at 190 bar and different pre-expansion temperatures compared with original nifedipine and a physical mixture of the same composition (1:4) [15,16]

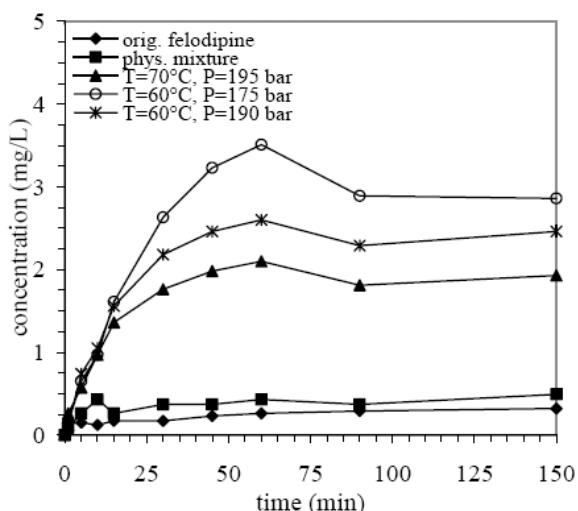


Figure 7. Dissolution of micronized felodipine PEG 4000 samples prepared at different pre-expansion pressures, compared with original felodipine and a physical mixture of the same composition (1:4) [15,16] concentration (mg/L)

Their dissolution rate was much higher compared to that for pure micronized nifedipine (Figures 5 and 6).

**Felodipine**

The mean particle size of the starting felodipine was 60 μm, and was reduced after micronization with the PGSS process to 42 μm. The specific surface areas measured using the BET method increased from 0.33 m<sup>2</sup>/g for the starting felodipine to 1.33 m<sup>2</sup>/g for the micronized felodipine. The starting felodipine, as well as the micronized felodipine, practically do not dissolve in water, due to the poor wettability of the felodipine particles. The amount of dissolved felodipine after 1 h was only 0.26 mg and 0.29 mg, for the starting felodipine and the micronized sample, respectively.

The dissolution profiles of PGSS-felodipine/PEG 4000 co-precipitates, along with the starting felodipine and its physical mixture with PEG 4000 (1:4), are presented in Figure 5. The amount of felodipine dissolved in 1 h from felodipine/PEG 4000 co-precipitates micronized at pre-expansion pressures of 175, 190 and 195 bar was 13.5-, 10-, and 8-times higher than that of the original felodipine, respectively.

The impact of the pre-expansion pressure on the dissolution behaviour of felodipine from micronized felodipine/PEG 4000 co-precipitates can be seen in Figure 7. Similar observations were noted above for nifedipine/PEG 4000 samples [15,16].

Even at a pre-expansion pressure of 175 bar, enough CO<sub>2</sub> was dissolved in the melt to cause rapid precipitation of the components. The lower dissolution rate of the sample micronized at 195 bar and 70°C could be explained by the decreased solubility of CO<sub>2</sub> in the melt at a higher temperature.

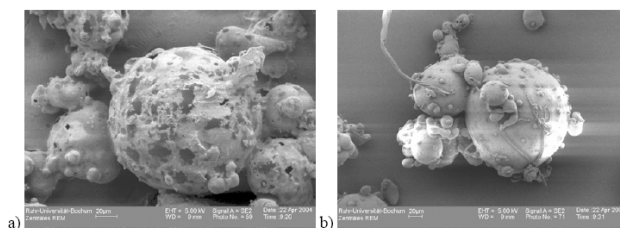


Figure 8. Solid composite particles with 50% by weight of liquid a) open structure, b) closed structure [18]

**Solids with solid composites of system solid/liquid**

The PGSS<sup>TM</sup> process enables the production of solid composite particles with up to 50% by weight of liquids. Based on the process parameters, the solids can have an open (Figure 8a) or closed structure (Figure 8b).

**Conclusion**

The removal of solvent is a problem of conventional co-precipitation or co-evaporation techniques where large amounts of organic solvents are needed and in which complete removal is often a long and difficult process. With the PGSS process, micronized drug or micronized drug/carrier can be obtained in one step without organic solvent.

Through the choice of an appropriate combination of solvent and operating conditions for a particular compound, PGSS<sup>TM</sup> can eliminate some of the disadvantages of traditional methods of particle-size redistribution in material processing. Solids formation by PGSS<sup>TM</sup>, therefore, shows potential for the production of crystalline and amorphous powders with a narrow and controllable size-distribution, thin films, and mixtures of amorphous materials. Due to the low processing costs, PGSS<sup>TM</sup> can be used not only for highly valuable, but also for commodity products.

One goal of RESS/CSS, anti-solvent processes such GAS, and the PGSS<sup>TM</sup> process, is to obtain submicron- or micron-sized particles. Although several features concerning RESS and GAS-processes scale-up are not yet very well known, it is probable that these processes are, or may be, used for producing relatively small amounts of high-value-added substances.

Restrictions arising from the difficult product- and gas-recovery in the RESS and GASR, GASP, SAS/PCA/SEDS processes are avoided by the PGSS<sup>TM</sup> process.

The PGSS<sup>TM</sup> process has several advantages, which favour its use for large-scale applications. This process has promise for the processing of low melting, highly viscous, waxy and sticky compounds, even if the obtained particles are not of sub-micron size. The process already runs in plants with a capacity of some hundred kilograms per hour. New possibilities for the generation of particles and composites based on PGSS<sup>TM</sup> and CPF<sup>TM</sup> processes are [17]:

Table 1. Experimental conditions for the micronization of nifedipine using the PGSS process

|                                |                              |
|--------------------------------|------------------------------|
| Melting point of the drug (°C) | 175–176                      |
| Pre-expansion pressure (bar)   | 100, 125, 150, 175, 190, 200 |
| Pre-expansion temperature (°C) | 165, 175, 185                |
| Nozzle diameter (mm)           | 0.4, 0.25                    |

Table 2. Experimental conditions for the micronization of felodipine using the PGSS process

|                                |         |
|--------------------------------|---------|
| Melting point of the drug (°C) | 141–145 |
| Pre-expansion pressure (bar)   | 200     |
| Pre-expansion temperature (°C) | 150     |
| Nozzle diameter (mm)           | 0.4     |

- microfoam particles via the continuously operated PGSS<sup>TM</sup> process,
- powderization of reactive compounds and immiscible substances,
  - powderous liquids via the CPF<sup>TM</sup> process,
  - powderous emulsions via jet dispersion and the CPF<sup>TM</sup> process.

Numerous other processes for particle formation and the design of composites and particle coating using supercritical fluids have been developed (UNICARB<sup>TM</sup>, VAMP<sup>TM</sup>, SAA, reactions in supercritical media leading to particle formation) have been additionally described in the literature [1,2,17,18]. The specific properties of dense gasses allow the obtaining of fine dispersed solids, especially of substances with low melting point temperatures, high viscosities and very waxy or sticky properties. Economic evaluation of the process shows that these compounds cannot be efficiently and economically processed by conventional mechanical processes and that there is a big advantage of using supercritical fluids.

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## IZVOD

### KRAĆI PREGLED PRIMENE NATKRITIČNIH FLUIDA KOD DOBIJANJA FINIH ČESTICA

(Pregledni rad)

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Danas se smatra da je primena natkritičnih fluida najznačajnija u procesima dobijanja čvrstih čestica fine strukture ili kompozitnih prahova sa tačno definisanim i projektovanim karakteristikama. Klasične metode dobijanja malih čestica ili prahova nekog materijala, koje se zasnivaju na mehaničkim procesima (mlevenje, sitnjenje i prosejavanje, mikronizacija, sublimacija, rekristalizacija iz rastvora) često se realizuju na veoma niskim temperaturama ali su pri tome uglavnom praćene različitim neželjenim efektima. Oni se odnose, pre svega, na osobinu termijske nestabilnosti materijala koji se sitni ili na primer u slučaju primene procesa rekristalizacije na pojavu neželjenog zaostalog rastvarača, često samo u tragovima, u finalnom proizvodu koji je praćen i sa sve češćim strogim propisima za uklanjanje i/ili regeneraciju korišćenog rastvarača. Primenom natkritičnih fluida moguće je eliminisati ove i druge nedostatke klasičnih procesa dobijanja finih čestica i kompozitnih prahova različitih materijala. Neki primenjeni procesi su detaljno proučavani i o njima postoji dosta podataka u literaturi.

Povoljne karakteristike natkritičnih fluida mogu se iskoristiti, između ostalog, za razvoj njihove primene u procesima impregnacije čvrstih čestica mikronske veličine ili kod prebođenja emulzije u sprašeni oblik sa jedinstvenim karakteristikama i mogućnostima različitih primena.

Ovaj pregledni rad se fokusira na analizu fundamentalnih teorijskih osnova primene natkritičnih fluida i na novija saznanja i rešenja primenjena u procesima dobijanja finih čestica različitih materijala. Takođe se analiziraju prednosti i nedostaci različitih, do danas razvijenih i u svetu, primenjenih tehnoloških rešenja dobijanja čestica i prahova mikronskih veličina zasnovanih na primeni natkritičnih fluida.

Ključne reči: Mikronizacija, Natkritični fluidi, Ugušćen gas, Stvaranje čestica, PGSSTM.