# Production of micro-particles with sc-$CO_2$: Comparison of PCA and GAS precipitation techniques for different pharmaceutical compounds

Francesco Fusaro, Markus Hänchen, and Marco Mazzotti*

Institute of Process Engineering, ETH, Swiss Federal Institute of Technology, Sonneggstrasse 3, CH-8092 Zurich, Switzerland, phone: +41/1/632 24 56, fax: +41/1/632 11 41, email: mazzotti@ipe.mavt.ethz.ch

Gerhard Muhrer

Novartis Pharma AG, Chemical & Analytical Development, CH-4002 Basel, Switzerland

Bala Subramaniam

Department of Chemical and Petroleum Engineering, University of Kansas, Lawrence, Kansas

Different pharmaceutical compounds have been processed by using the gas antisolvent recrystallization (GAS) and the precipitation with compressed antisolvent (PCA) techniques. By variation of the operating conditions, it was possible to tune the final product particle size distribution (PSD), which represents a key property of pharmaceutical products.
When paracetamol was precipitated using GAS, the average particle size decreased from 250 to 50 μm with increasing $CO_2$ addition rate. Significantly smaller particles were obtained upon PCA processing of the same compound, i.e. 3 - 8 μm depending on the experimental conditions.
The different patterns of behavior observed experimentally for the GAS process, could be reproduced using a detailed mathematical model of the process. Moreover, by incorporating PCA-typical $CO_2$ mass transfer time scales to the GAS model, it was possible to match the experimental behavior observed for paracetamol in PCA.
This analysis has led to a better fundamental understanding of the differences and similarities between GAS and PCA techniques that should help in identifying optimal operating conditions to achieve the desired product size range.

## INTRODUCTION

Dense gas anti-solvent precipitation techniques possess the significant advantage of obtaining in one process step a relatively solvent-free product at mild operating conditions and by moderate use of organic solvents with no need for further washing or drying. This work addresses the analysis of the GAS and PCA techniques, two of several high pressure gas assisted processes that have been proposed for pharmaceutical processing [1-3]. For this analysis, the anti-inflammatory drug paracetamol has been precipitated using both GAS and PCA techniques.
In the GAS (Gas Anti-Solvent recrystallization) technique, the solute is first dissolved in an organic compound and the solution loaded into the precipitator, and then the addition of $CO_2$ at constant flow rate is initiated. As pressure in the reactor increases, the solution undergoes volumetric expansion due do the dissolution of the anti-solvent into the solution, thus leading

to a decrease of its solvent power and eventually triggering precipitation of the solute. In the PCA (Precipitation with compressed Anti-solvent) technique, the solution is directly sprayed into the compressed carbon dioxide. Mass transfer between the solvent and anti-solvent leads to supersaturation of the organic solution, thus triggering precipitation of the solute. Several different injection devices such as ultrasonic dispersion devices, co-axial nozzles or two-substance nozzles have been employed to improve mass transfer between solvent and anti-solvent.

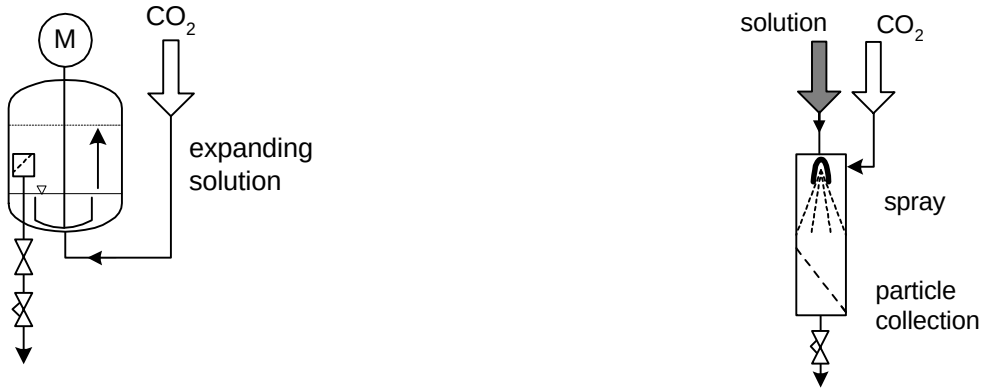


**Figure 1 : The GAS (Gas Anti-Solvent) and PCA (Precipitation with Compressed Anti-solvent) processes**

Despite the similarities between the GAS and the PCA technique, only a few reported studies comparing the particle formation mechanism in the two processes exist. In a recent work for example, Warwick et al. have experimentally investigated the precipitation of copper indomethacin using GAS and PCA, presenting a qualitative comparison [4].

The precipitation of different pharmaceutical compounds using the GAS process has recently been reported leading to three types of dependence on the $CO_2$ addition rate [5-8]. In the case of paracetamol, variation of the $CO_2$ addition rate (defined as the ratio between $CO_2$ addition rate and initial amount of solution loaded into the precipitator) over two orders of magnitude, yielded average particle sizes between 50 and 250 μm. For a proprietary pharmaceutical intermediate, it was possible to tune the average particle size between 200 nm and 10 μm, whereas nearly no effect was observed for the precipitation of lysozyme from DMSO, for which the average particle size was always around 300 nm.

In an attempt to understand better understand these differences, in this work, we compare experimental results obtained for the precipitation of paracetamol from acetone solution in both GAS and PCA using $CO_2$ as the antisovent.

## I – EXPERIMENTAL SET-UP

The experimental arrangement used to carry out the GAS paracetamol experiments is equipped with a 400 mL jacketed temperature controlled precipitator that allows for observation of the experiment through a Pyrex window ($H \approx 120$ mm). Feeding of $CO_2$ was accomplished through the impeller shaft – a mode of operation which has been shown to enhance vapour-liquid mass transfer between solvent and anti-solvent [9]. A sintered metal filter placed at the bottom of the reactor was used to collect the paracetamol crystals. A detailed description the GAS unit can be found elsewhere [7].

The PCA unit used during our experiments at University of Kansas can be seen in Figure 2. Carbon dioxide, flowing in parallel from three dip-tube cylinders, is dried in a silica gel column and compressed to the operating pressure by a pneumatically operated gas booster. After passing a surge tank immersed in a temperature-controlled water bath, where pressure fluctuations are dampened, it enters the precipitation chamber through a co-axial nozzle located inside the narrow 2-L-reactor. The solvent (acetone), containing dissolved paracetamol, is supplied at a constant flow rate by a syringe pump (Isco 314), heated up by passing through a coil immersed in the water bath, and fed through the inner capillary of the nozzle (0.19 mm) into the thermostated reactor. The co-axial $CO_2$-stream in the converging-diverging nozzle rapidly disperses the liquid jet and precipitation takes places at the exit of the nozzle. A cylindrical glass inlet tapering off into a funnel at the bottom is directing the flow towards the outlet. The particles are collected outside of the reactor on a filter unit, kept at constant temperature by being immersed in the water bath. The $CO_2$-solvent mixture is depressurised over a heated back-pressure regulator and the solvent recovered in a cyclone.

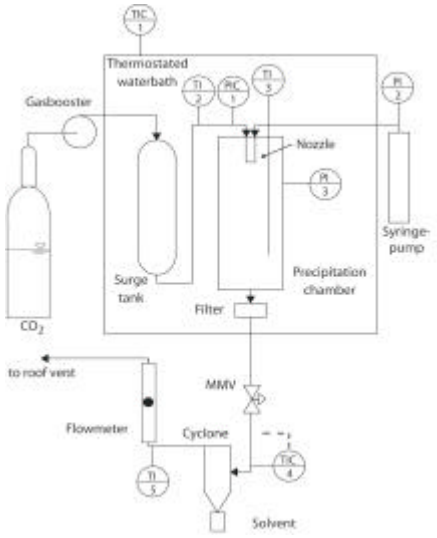


**Figure 2 : PCA experimental set-up**

## II – MATERIALS AND METHODS

For the GAS experiments, technical grade carbon dioxide (99.9% purity) and analytical grade acetone (99.7%) were purchased by PanGas (Schlieren, Switzerland) and Fluka (Buchs SG, Switzerland) respectively. Pharmaceutical grade paracetamol (= 99%) was obtained from Merck (Merck-Schuchardt, Hohenbrunn, Germany). SEM analysis was used for the determination of the characteristics of the paracetamol particle populations. Agglomeration and breakage were estimated qualitatively by observation, whereas the particle size distributions where obtained quantitatively by manual identification of the primary particles and calculation of the relevant statistics. X-ray powder diffraction measurements where carried out in order to compare the structure of GAS precipitate to the starting material. Finally the residual solvent content in the particles was measured on Waters (Milford, MA) HPLC.

For the PCA experiments, industrial grade carbon dioxide was supplied by Airgas Ltd. and paracetamol (99.3 %) was obtained by Mallincrodt U.S.P, whereas acetone (certified A.C.S.) was obtained from Fisher Scientific. The particle size distributions were measured through Aerosizer measurements (API, Amherst, USA), while the particle morphology and structural information were obtained by observations of the SEM photomicrographs.

## III – RESULTS

In the GAS precipitation technique, the specific $CO_2$ addition rate was identified as a key parameter for tuning the average particle size of the precipitate, as shown in Figure 3 and discussed in detail in ref. [5].

The specific $CO_2$ addition rate allows for the comparison of experiments carried out in vessels of different volume.

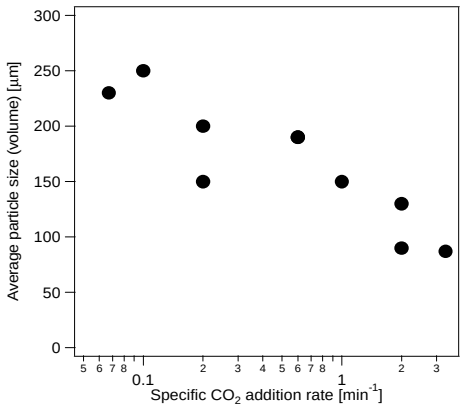


**Figure 2 : Effect of specific $CO_2$ addition rate on the paracetamol particles precipitated in GAS [5].**

As a general trend, increasing the specific $CO_2$ addition rate leads to a decrease of the average particle size. An analysis using a detailed mathematical model of the GAS process accounting for primary homogeneous nucleation and secondary nucleation has shown that this type of behaviour can be attributed to the predominance of the former [10].

As shown in Figure 3, PCA experiments were conducted in different regions of the $CO_2$ – acetone phase diagram. In agreement with referenced literature results, the particles obtained when operating above the critical locus line were prismatic and elongated in shape (designated as shape a in Figure 3); for the two runs carried out at 33 °C, 83 bar, volume weighted average particle size was 3.5 µm in both cases. In contrast, the run at the higher temperature and pressure (38 °C and 95 bar), an increase to 7.5 µm was observed with a columnar, more elongated shape of the crystals as in the corresponding SEM microphotograph shown in Figure 4 [11]. In contrast, for the runs closer to critical locus, the crystals were spherical in shape and slightly smaller (designated as shape b in Figure 3). Three runs were carried out at 38 °C, 83 bar, and average particle sizes were between 2.5 µm and 4.5 µm. Increasing the temperature to 47 °C but maintaining pressure constant in yielded an average particle size around 7 µm. As pointed out by other authors [12-14], due to the vanishing interfacial tension between the solvent and anti-solvent phases, the mixing mechanism in the region of full miscibility differs considerably from the one in the two phase regions, where solvent droplets and anti-solvent bulk phase coexist for a finite time period. These differences may explain the changes in the observed particle morphology and in average particle size in the two regions. These results indicate that the average size of the paracetamol particles obtained via the two processes, GAS and PCA, differs by one to two orders of magnitude. This aspect is further discussed in the following section.

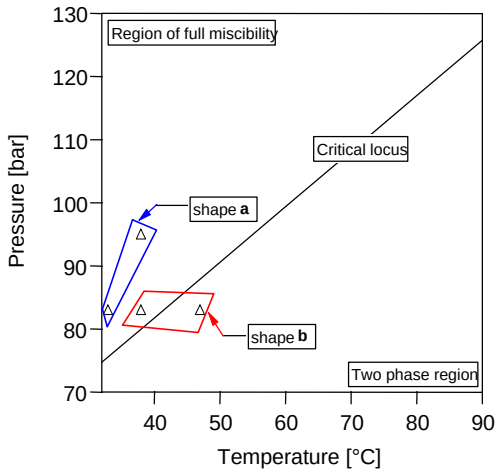


**Figure 3 : Location of the PCA experimental points in the phase diagram $CO_2$ – acetone.**

## III – DISCUSSION AND CONCLUSION

The common feature of the two processes is that supersaturation is created by mass transfer between the anti-solvent and the solution containing the solute to be precipitated. The analysis using the mathematical model of the GAS process has shown that increasing the $CO_2$ addition rate leads to higher supersaturation levels at which nucleation occurs [10]. In order to quantify the differences in the mass transfer rates between the two processes, we define a

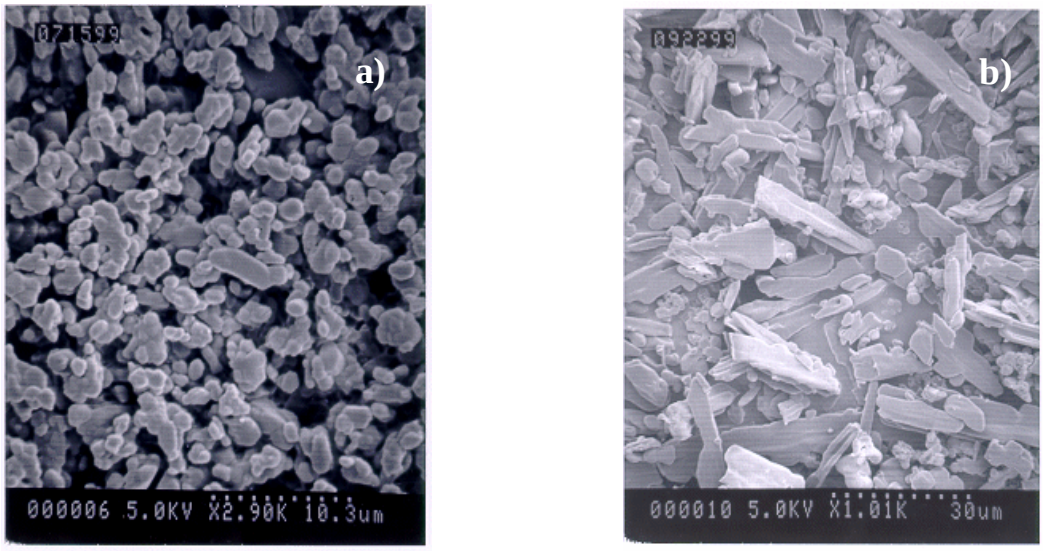


**Figure 3 : SEM photomicrograph of paracetamol samples precipitated with PCA : a) particles obtained at 38 °C, 83 bar ; b) particles obtained at 38 °C, 95 bar.**

characteristic mass transfer time for the GAS process as the ratio of the initial solution volume $V_0$ and the average mass transfer flux during the process. In a recent work, we have shown theoretically and experimentally that the average mass transfer rate during GAS expansion is equal to the $CO_2$ addition rate, $Q_A$, thus leading to the following expression of the characteristic mass transfer time for GAS:

$$t_{mt}^{GAS} = \frac{V_0}{Q_A} \qquad \textbf{(1)}$$

Since the initial volume of solution as well as the $CO_2$ addition rate can be varied in a GAS process, typical characteristic times for our GAS experiments fall between 10 and 600 s. This broad range of characteristic mass transfer times corresponds to the broad range of particle sizes that has been observed in paracetamol precipitation!

In the case of the PCA process, let us consider the contact region between the solution and the anti-solvent. In the sub-critical case, this region will consist of droplets of the solution in the antisolvent phase, while in the supercritical range this region may be envisioned to have defined areas with high solvent concentration embedded in the bulk anti-solvent. Both cases were considered by Werling and Debenedetti who calculated the time evolution of a droplet in the subcritical phase or of the high concentration zone for the toluene – $CO_2$ system [13, 14]. For this discussion, only the sub-critical case is considered. Initially, $CO_2$ penetrates into the droplet swelling it to a maximum value. The maximum swelling volume $?V$ can be related to the corresponding swelling time $?t$, thus defining an average $CO_2$ mass transfer flux into the droplet. We base the average mass transfer flux on the initial droplet volume $V_0$ thus defining a characteristic mass transfer time for PCA as follows:

$$t_{mt}^{PCA} = \frac{?t \cdot V_0}{?V} \qquad \textbf{(2)}$$

For 50 μm droplets and pressures between 75 and 87 bar at 318 K, one can calculate, following the approach suggested by Werling and Debenedetti, characteristic mass transfer times around 0.02 s. Clearly, the swelling volume as well as the swelling time depends on the pressure and temperature of the system. Moreover, writing the equations in dimensionless form shows that the characteristic mass transfer time increases with the square of the initial radius of the droplet divided by the diffusivity. Therefore the typical range of characteristic

mass transfer time for PCA lies between 0.02 and 0.2. This range is several orders of magnitude smaller than the corresponding mass transfer times obtained for GAS. We therefore argue that this disparity in time scales leads to the observed difference in the particle sizes in the GAS and PCA processes.

These results suggest that the PCA and GAS processes allow access to widely different mass transfer time regimes, and hence different supersaturation levels. To prove this, we use the mathematical model of the GAS process for the phenanthrene – toluene – $CO_2$ model system to simulate the PCA process [10]. We select a high value of the $CO_2$ addition rate so that the characteristic mass transfer time is comparable to that obtained in the PCA process. The results obtained for such a series of simulations are shown in Figure 5, where the average particle size is plotted versus the corresponding characteristic mass transfer time. It is readily observed that in the range of mass transfer time values characteristic of the GAS process the same behaviour observed experimentally for paracetamol is obtained, i.e. particle size increases with increasing mass transfer time.

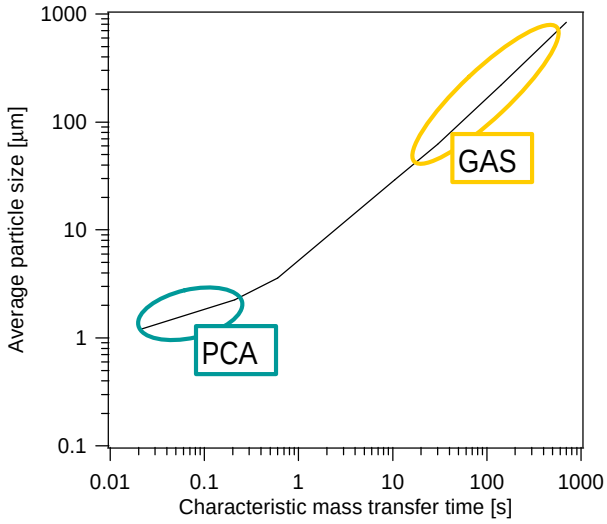


**Figure 4 : Effect of characterisitc mass transfer time on the average particle obtained in the GAS model simulations**

At PCA conditions, the mass transfer time is much smaller, and accordingly the final average particle size is smaller than in the GAS process. Remarkably, this size range brackets the range observed experimentally for paracetamol. We believe that understanding and recognizing the significant differences and similarities between the GAS and PCA processes presented here will help in rationally tuning the properties of nano- and micro-particles for biopharmaceutical applications.

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