

Communication presented at the 4th International Symposium
on High Pressure Technology and Chemical Engineering, VENICE (Italy), Sept. 2003

SOLID STATE MORPHOLOGY OF PARTICLES PREPARED BY A SUPERCRITICAL FLUID PROCESS

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The solid state morphology of many compounds is a key-parameter for their further utilization when several forms can co-exist either as crystalline and amorphous, and/or as different polymorphs (allotropes) ; this is particularly important for pharmaceutical drugs as their morphology can have a significant impact on their bio-availability and stability. Supercritical Fluid (SCF) technology is now considered to be an innovative and promising way to design particles, as reviewed by Kompella and Koushik (2001) and Jung and Perrut (2001). We present a review of the results already published in literature and our own results on morphology changes and stability of particles generated by SCF processes, focusing on neat particles and not on composite ones.

INTRODUCTION :

Generally, a dramatic change of the solid morphology is observed after processing by SCF : Average particle size and size distribution, particle shape and porosity, and consequently, specific area and dissolution rate, are often completely different from those of the starting material. However, it seems that, in most cases, the crystal pattern is not modified, although relatively few results, attested by XRD and DSC measurements, have yet been published.

1. SCF CONTACT :

Surprisingly, contacting a solid with a SCF induces a re-crystallization with crystalline morphology modification in certain cases, as shown in several documents. In a patent granted to Graser and Wickenhaeuser (1984), a process for re-crystallization of finely divided crude organic pigments in C3-C5 alkanes or alkenes, or C1-C3 chloro-alkanes, is claimed to lead to pigments with deeper and more brilliant colorations than the starting material. Recently, the conversion of *carbamazepine* (an anticonvulsant drug) by contacting the solid with SCF carbon dioxide was reported by Bettini et al. (2001). This drug presents four polymorphs and a dihydrate forms ; Form I (m.p. 190°C) and form III (m.p. 177°C) – the commercial product - form an enantiotropic pair : Form III is stable at ambient temperature whereas form I is stable at higher temperature (>70°C). Different mixtures of Form I : Form III were contacted with supercritical carbon dioxide in static conditions, that causes a rapid conversion of Form I into Form III although not complete. The authors suspect that this transformation results from the fact that these two forms have different solubilities in SCF carbon dioxide. It is to be noted that Kikic

et al. (2000) reported a significant increase in dissolution rate in water after anti-solvent re-crystallization of *carbamazepine* from acetone solution either in crystalline form (the polymorph was not identified), or in composite micro-spheres of PEG 4000.

We can propose the following “qualitative” interpretation : When a solvent is contacted with a solid, it gets saturated into this compound ; but this saturation is not “static” : In permanence, molecules are exchanged between the solid and the fluid phases, especially in SCF solvents where mass transfer is fast, causing a “re-crystallization” of the solid into the more stable polymorph at the operating temperature, the transformation being limited by the kinetic of dissolution/re-crystallization.

2. SCF Atomization :

The three main processes using SCF for atomizing pure compounds in order to reduce the particle size, lead to solid morphology changes or not, depending on the compound, and the process operating conditions.

2.1 RESS :

Few publications deal with scientific evaluation of the microscopic solid morphology :

- The first evaluation of the solid formed by RESS was published by Larson and King (1986) : The XRD patterns of the starting material and the RESS-atomized particles of *naphthalene*, *Mevinolin* (anti-cholesterol drug) and an undisclosed *steroid* show “that crystalline materials retain their crystallinity after precipitation from supercritical fluids” ; however, the diffraction patterns vary somewhat, possibly due to the presence of amorphous material.
- DSC characterization of *Griseofulvin* particles shows that particles obtained by RESS (using CHF₃) exhibit the same melting temperature and the same melting enthalpy as the micronized crystalline material (Martin et al., 2000).
- *Anthracene* and *Phenanthrene* were either precipitated or co-precipitated by RESS from a SCF CO₂ solution by Nagahama and Liu (1997), forming dendritic particles of anthracene while the starting material was in form of hexagonal crystals and phenanthrene needles. But coprecipitation of a mixture leads to a *solid solution* different from a simple eutectic as attested by XRD.
- *Ibuprofen* (a chiral non-steroidal anti-inflammatory drug) was micronized from SCF CO₂, leading to micro-particles exhibiting the same XRD pattern as the starting material, although the peak intensities seemed lower, which shows “the decrease in the degree of crystallinity” according to Kyrak et al. (2001).
- *Para-Hydroxybenzoic acid* was micronized from solutions in SCF CO₂ or SCF CO₂ added with methanol (3.5 wt%) by Jaarno et al (1997), leading to crystalline nano-particles and a few large irregular non-crystalline particles.

We just obtained very attractive results according to a process described in a recent patent (Perrut et al., 2002). *Celecoxib* (a COX-2 inhibitor registered for arthritis cure) was dissolved in SCF CO₂ (50°C, 29 MPa) and the solution rapidly depressurized to atmospheric pressure ; we operated either according the classical way where the atomization vessel is maintained at around 20°C (sample a), or by injecting an additional stream of liquid CO₂ in order to generate carbonic snow that trapped the particles (sample b) at very low temperature immediately after their

nucleation, as described in an earlier patent (Perrut, 1999). On figure 1, is presented a SEM picture after dry ice evaporation, showing fluffy agglomerates of elementary nano-particles.

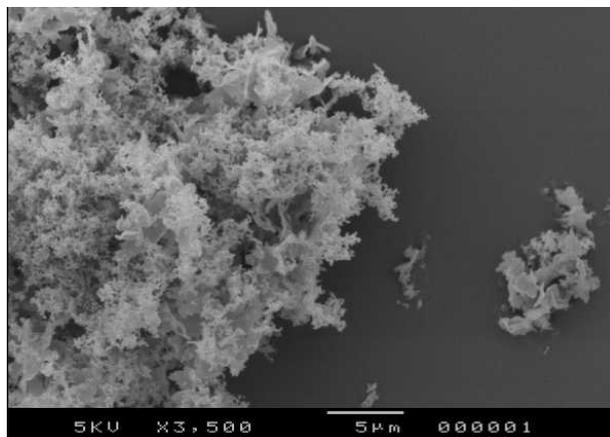


Figure 1 : SEM picture of Celecoxib particles (sample b).

The XRD patterns of these particles after storage at low temperature during one day (sample b : lower curve and sample a : intermediate curve) are compared on figure 2 with the starting material one (upper curve), the two latter curves being presented with an offset of 2,000 and 3,000 counts per second respectively for ease of interpretation. It clearly appears that the starting material is highly crystalline and the generated particles are completely amorphous when the temperature in the atomization vessel is kept low, and mostly amorphous – but not free of crystals - when this temperature is near ambient. We consider that the very short RESS nucleation leads to amorphous material that immediately tends to re-crystallize during the particle residence time in the atomization vessel and on the collection filter, if the temperature is not kept lower than a “re-crystallization temperature” that is much below (at least 30°C according to some estimations) the solid glass transition temperature. So, the amorphous morphology must be “frozen” just after particle generation in order to prevent any re-crystallization.

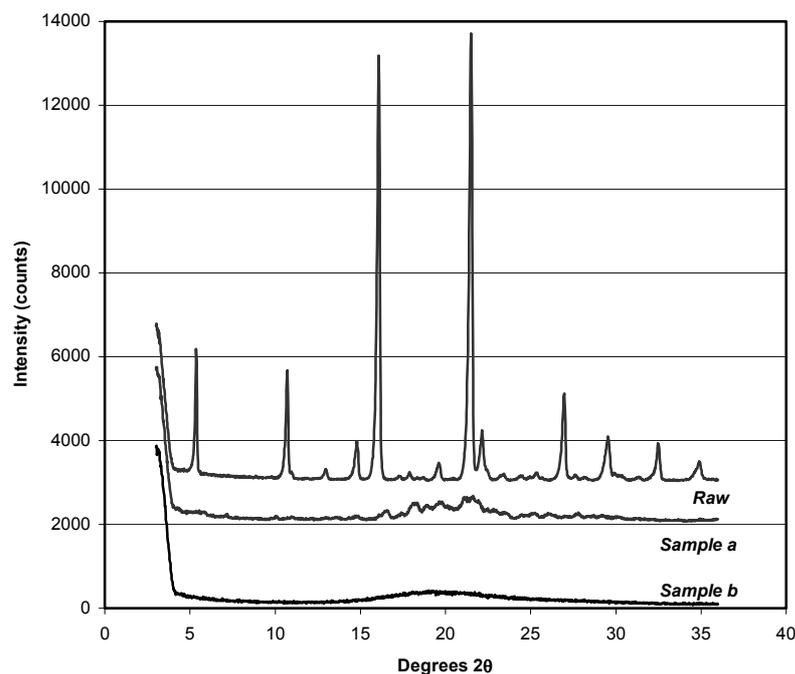


Figure 2 : XRD profiles for Celecoxib raw material and RESS-CO₂ samples.

2.2 Anti-Solvent :

- **Salmeterol xinafoate** polymorphic forms can be controlled by varying the anti-solvent crystallization parameters, according to Hanna and York (1995) and Hanna et al. (1998) ; using the SEDS technology, this compound was re-crystallized from acetone or methanol solutions using SCF CO₂ at various temperatures and pressures : At temperatures below 60°C, only the pure Form I was obtained meanwhile polymorphic transformation to Form II was observed since 60°C and is complete at 90°C. It is to be noted that this anti-solvent process permits to reach this Form II at a much lower temperature than by heating Form I alone (the transformation happens near to the melting temperature of Form I which is 124°C). Moreover, the authors claim that the pure Form II obtained by SEDS is extremely stable when stored free from light during 5 years. This demonstrate that anti-solvent re-crystallization can be used to obtain very pure polymorphs that are the more stable because no other polymorph “impurity” may induce transformation to the other form(s).
- **Sugars** can be re-crystallized from aqueous solutions using SEDS as reported by Hanna and York (1996), Hanna et al. (1998) and Palakodati et al. (1998) : **Lactose** was obtained in crystalline form with different particle shapes, **maltose** and **trehalose** in form of spongy spheres of amorphous nature as shown by XRD, and **sucrose** as a free-flowing crystalline powder.
- **Sulfathiazole** was subjected to the most detailed study on polymorphism control by Kordikowski et al. (2000), by SEDS of a methanol solution in SCF CO₂. SEM, XRD and DSC showed temperature is the key-parameter : Three pure polymorphs (Form I over 80°C, Form III around 40°C, Form IV below 0°C) and mixtures of polymorphs at intermediate temperatures were obtained.

- *Ibuprofen*, *ketoprofen*, *salicylic acid* and *nicotinic acid* were recrystallized in the same morphology by a SCF process where the compound is primarily dissolved or suspended into a first SCF, and this solution/suspension is contacted with a second fluid (nitrogen) which causes precipitation of the compound into fine particles, as disclosed by Hanna et al. (1999).
- *Acetomiphen* and *P-Acetoxyacetanilide* were co-crystallized by SEDS from an ethanol solution of both compounds by Shekunov (2000) in form of a solid solution with incorporation of PAA in the crystals of A (XRD and DSC).
- Subramaniam et al. (1997) reported GAS recrystallization in the same morphology (by DSC) of *phenytoin* by bubbling CO₂ into an acetone solution.
- Similarly, Lee et al (2000) observed by XRD that crystal morphology is always identical to the starting material one when re-crystallizing *NTO* (Nitrotrazolone) from a DMF solution in CO₂ under various conditions.
- On the contrary, Jaarno et al (1997) prepared either crystalline or amorphous particles of *Sodium Cromoglycate* starting a methanol solution : The crystalline particles are very similar to the commercial product (same polymorph according XRD) ; completely amorphous spherical micro-particles were also obtained and did not show any crystallinity after 5-month storage. The authors stated that the most important parameter affecting crystallinity and stability was the residual concentration of methanol that can be drastically reduced by adding a small amount of water to the organic solution.
- Thiering et al. (1998) reported comparative results on re-crystallization of *Para-Hydroxybenzoic acid* using GAS and ASES (and RESS : see before) ; the particle shape, size and crystallinity strongly depend on the temperature, the organic solvent, and the rate of addition of the anti-solvent in the batch GAS process (crystalline particles at low addition rate and amorphous ones at high addition rates), as a result of different nuclei formation kinetics.
- Murher et al. (2001) recently presented results obtained by GAS on an undisclosed pharmaceutical showing that either amorphous (with Ethanol) or crystalline forms (with Acetone or Acetonitrile) can be reached.

2.3 DELOS :

The DELOS (Depressurization of an Expanded Liquid Organic Solution) process, very recently disclosed by Sala et al. (2001) and Ventosa et al. (2001a, 2001b), consists in precipitating a solute dissolved in an organic solvent by the fast and homogeneous temperature decrease caused by depressurizing the organic solution previously expanded by a compressed gas. This can be considered as an original variant of RESS as the expanded liquid phase is homogeneous. Provided that a “solute/organic solvent/SCF” system existing as a homogeneous liquid solution can be found, this process leads to nano-/micro-particles. For several compounds, the particles showed a high degree of crystallinity, with XRD patterns similar to those of the starting material:

- *Aspirin* and *Colorant Solvent Blue 35* from Acetone/CO₂ solutions ;
- *Acetomiphen* from Ethanol/ CO₂ solutions.

2.4 PGSS :

Few results have been published on morphology of particles generated from Gas-Saturated Solutions. Weidner et al. (1994) and Knez (2000) obtained particles of *nifedipine* (a calcium antagonist) that are significantly different from the starting material in size, shape and dissolution

rate ; the authors suspected that the processed particles “have a more amorphous character compared with the product obtained by conventional process”. However, no structure measurement supported this assessment.

References

- Bettini R., I. Casini, D. Zhou, A. Rossi, A. Gazzaniga, D. Grant, F. Giordano, 2001, Proceed. of the Sixth Conf. On Supercritical Fluids, Maiori (It), 401.
- Graser F., G. Wickenhaeuser, 1984, US patent 4,451,654.
- Hanna M., P. York, 1995, World patent WO 95/01221
- Hanna M., P. York, T. Shekunov, 1998, Proceed. of the 5th Meet. on Supercritical Fluids, Nice (France), 325.
- Hanna M., P. York, 1996, World patent WO 96/00610.
- Hanna M., P. York, Hanna M.H., 1999, World patent WO 99/59710.
- Jaarno S., M. Rantakyla, O. Aaltonen, 1997, Proceed. of the 4th Int. Symp. on Supercritical fluids, Sendai (Japan), 263.
- Jung J., M. Perrut, 2001, The Journal of Supercritical Fluids, 20, 179.
- Kayrak D., U. Akman, O. Hotacsu, 2001, Proceed. of the Sixth Conf. On Supercritical Fluids, Maiori (It), 337.
- Kikic I., M. Moneghini, B. Perissutti, D. Voinovich, 2000, Proceed. of the 7th Meet. on Supercritical Fluids, Antibes (France), 95.
- Knez Z., 2000, Proceed. of the 7th Meet. on Supercritical Fluids, Antibes (France), 21.
- Kompella U.D., K. Koushik, 2001, Crit. Rev. Therapeutic Carrier Systems, 18(2), 173.
- Kordikowski A., T. Shekunov, P. York, 2000, Proceed. of the 7th Meet. on Supercritical Fluids, Antibes (France), 117.
- Larson K.A., M.L. King, 1986, Biotechnology Progress, 2(2), 73.
- Lee S.-Y., G.-B Lim, K.-K Koo, B.-S. Park, H.-S. Kim, 2000, Proceed. of the 7th Meet. on Supercritical Fluids, Antibes (France), 123.
- Martin H.-J., P.C. Schmidt, M.A. Wahl, 2000, Proceed. of the 7th Meet. on Supercritical Fluids, Antibes (France), 53.
- Muhrer G., C. Lin, M. Mazzotti, 2001, Proceed. of BIWIC 2001 Workshop, 106.
- Nagahama K., G.-T. Liu, 1997, Proceed. of the 4th Int. Symp. on Supercritical fluids, Sendai (Japan), 43.
- Palakodaty S., P. York, M. Hanna, J. Pritchard, 1998, Proceed. of the 5th Meet. on Supercritical Fluids, Nice (France), 275.
- Perrut M., 1999, French patent FR 2 802 445.
- Perrut M., J. Jung, F. Leboeuf, 2002, French patent application FR-02 05046.
- Sala S., N. Ventosa, J. Veciana, 2001, Proceed. of the Sixth Conf. On Supercritical J., Fluids, Maiori (It), 325.
- Shekunov B.Y., Bristow, P. York, A.H.L. Chow, 2000, Proceed. of the 7th Meet. on Supercritical Fluids, Antibes (France), 111.
- Subramaniam B., R. Rajewski, V. Stella, 1997, World patent WO 97/31691.
- Thiering R., M. Charoenchaitrakool, L. Sze Tsu, F. Deghani, A.K. Dillow, N.R. Foster, 1998, Proceed. of the 5th Meet. on Supercritical Fluids, Nice (France), 291.
- Ventosa N., S.Sala, J. Veciana, J. Libre, J. Torres, 2001a, Proceed. of the Sixth Conf. on Supercritical Fluids, Maiori (It), 343.
- Ventosa N., S.Sala, J. Veciana, J. Libre, J. Torres, 2001b, Proceed. of the Sixth Conf. on Supercritical Fluids, Maiori (It), 349.
- Weidner E., Z. Knez, Z. Novak, 1994, Proceed. of the 3rd Int. Symp. on Supercritical Fluids, Nice (France), Tome 3, 229.