The different pathways of crystallization in Supercritical Anti-Solvent (SAS) process

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Supercritical carbon dioxide has been used as an anti-solvent of drug recrystallization for more than thirty years. For a given studied compound, particles with a wide range of characteristics can be obtained depending on thermodynamics and hydrodynamics' conditions [1]. When a crystalline form of a pure drug compound is obtained, the resulting powder can be formed either of individual single crystals resulting from a classical pathway of nucleation and growth, or of aggregates of small crystals, resulting from an orientated or a non-orientated aggregation of crystals. It is worth noting that such different pathways have been described for conventional crystallization for which it has been reported that individual crystals are obtained by Monomer-by-Monomer Addition (MMA) occurring during nucleation and growth of the crystal while aggregates of crystals are formed following a Crystallization by Particle Attachment (CPA) [2]. A specificity of SAS crystallization is that spherical aggregates of small crystals can also be obtained, this morphology resulting from a CPA followed by a droplet drying mechanism, already described for the SAS process [3].

The study presented here comprises two parts:

(1) An experimental work dedicated to the recrystallization of a drug (sulfathiazole) using SAS process at 10 MPa and 313 K. The flow rates of the fluid phases and the drug concentration have been varied, as well the nature of the organic solvent. Four solvents have been used: acetonitrile, acetone, tetrahydrofuran and acetic acid. Powders exhibiting a pure polymorphic form (either the most stable form or the less stable one) have been obtained. For the most stable polymorphic form of sulfathiazole, powders exhibiting the different morphologies described above have been obtained, the morphology being dependent on the solvent nature.

(2) A modeling study focused on crystal habit prediction depending on the growth environment. The modeling investigates the adsorption of the solvents on the different drug crystal faces. Three different solvent adsorption behaviors have been highlighted with modeling, namely (i) CO_2 and acetonitrile do not adsorb onto any of the crystal faces (ii) Acetone and tetrahydrofuran adsorb on a given set of crystal faces which may hinder their growth and (iii) Acetic acid exhibits a strong affinity with all the crystal faces.

The comparison of the experimental results with the modeling highlights that when the solvent does not adsorb onto any of the crystal faces, the drug powder formed is composed of individual single crystals while when there is adsorption of the solvent on some crystal faces, aggregates of crystals are obtained. The individual single crystals result from a Monomer-by-Monomer Addition (MMA) like classical nucleation and growth mechanism while the aggregates may result from a Crystallization by Particle Attachment (CPA) mechanism (see Figure 1). The main conclusion is that, for the studied system, the adsorption of the solvent may induce the CPA pathway. Since it is possible to predict the adsorption behavior by modeling, it is thus feasible to induce a specific crystallization path so as to obtain a targeted powder morphology.

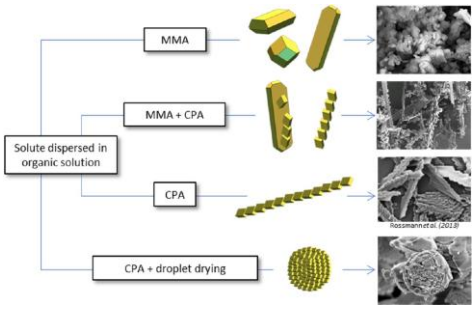

Figure 1. Crystallization pathways (MMA: Monomer-by-Monomer Addition; CPA: Crystallization by Particle Attachment) [4].

[1] E. Badens *et al.,* Current situation and perspectives in drug formulation by using supercritical fluid technology, J. Supercrit. Fluid, vol. 134, 2018.
[2] J.J. De Yoreo *et al.*, Crystallization by particle attachment in synthetic, biogenic, and geologic environments, Science, vol. 349, 2015.
[3] E. Reverchon *et al.*, Mechanisms controlling supercritical antisolvent precipitate morphology, Chem. Eng. J., vol. 169, 2011.
[4] S. Clercq *et al.*, Prediction of crystal-solvent interactions in a supercritical medium: A possible way to control crystal habit at high supersaturations with molecular modeling, Cryst. Growth Des., 20,10, 6863-6876, **2020**.