NUMERICAL SIMULATION OF A SUPERCRITICAL CO-CRYSTALLIZATION PROCESS

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ABSTRACT

In this work, we propose a simulation of a co-crystallization process with supercritical antisolvent. Simulations are performed in 3D configuration for the system naproxen/ nicotinamide/acetone in supercritical CO2 with the home-made Computational Fluid Dynamic code “Thetis”. By implementing further the equilibrium data for the solute to recrystallize and a population model, the spatial and time-dependent supersaturation field and the particle size distribution were issued as well.

INTRODUCTION

In the pharmaceutical sector, a new strategy at nanoscale for modulating the physical and chemical properties of drugs at macroscale is the formation of cocrystals, i.e. multicomponent assemblies of drug (API) and coformer held together by noncovalent interactions. Meanwhile, the need for improved manufacturing technologies is getting more and more crucial, notably because of the emergence of the generics that are less expensive than the original drugs and of the growing social concerns for environment protection and global change that motivate the emergence of alternative products and manufacturing routes. Crystallization assisted by CO2, and especially the so-called SAS (Supercritical Antisolvent) process has emerged years ago as a promising alternative route for a better control of the particle size. Experimentally, the task is fastidious, and consequently promotes the development of simulation to better identify important parameters and to go off the case-by-case approach. In a previous work, the Gaseous Anti-Solvent (GAS) technique was used to produce cocrystals of naproxen (NPX) and nicotinamide (NCTA) in acetone using CO2 as an anti-solvent [1]. Powder characterization evidenced the same stoichiometry (NPX2:NCTA1) and hydrogen-bond network than cocrystals synthetized by cooling or grinding techniques.
A complete description of the Supercritical Antisolvent Process requires the modeling of several complex physical phenomena such as heat and mass transfer, hydrodynamic, phase equilibria of ternary or quaternary, and nucleation /growth of the species to be precipitated. Simulations are performed in 3D configuration for the system naproxen/ nicotinamide/acetone in supercritical CO2 with the home-made Computational Fluid Dynamic code “Thetis”. The classical Navier-Stokes model is coupled with the Fick’s law to take into account the diffusion of the species. As a first assumption, we are going to consider that a complex 2:1 of naproxen and nicotinamide is formed in the liquid phase so the co-crystal is going to be considered in the simulation as a single “pseudo-species” with the properties of the two components according to the stoichiometry 2:1. Let us mention that due to the importance of the micromixing, turbulence was considered using a Large Eddy simulation model. By implementing further the equilibrium data for the solute to recrystallize and a population

model, the spatial and time-dependent supersaturation field and the particle size distribution were issued as well.

MODELLING AND NUMERICAL METHODS

1. Hydrodynamic and mass transfer

In the conditions investigated in this work, the pressure is above the critical pressure of the CO2-acetone mixture so the two fluids are fully miscible and merge as a monophasic flow. The flow is considered as incompressible since the variation of density is only due to the variation of the mixture composition. The equation of continuity and conservation of momentum for turbulent flow are described in a previous article [2]. The effect of pressure and composition on the fluid density is described through the Peng Robinson equation of state with classical quadratic mixing rules. The species continuity equations are expressed by taking into account the diffusion of species according to the Fick's law for the solvent and for the pseudo-species “co-crystal”.

$$\rho\frac{\partial x_s}{\partial t}+\nabla\cdot\left(\rho x_s\bar{\mathbf{u}}-\rho\left(D_s+D_t\right)\nabla x_s\right)=0 \qquad (1)$$

$$\rho\frac{\partial x_{cc}}{\partial t}+\nabla\cdot\left(\rho x_{cc}\bar{\mathbf{u}}-\rho\left(D_{cc}+D_t\right)\nabla x_c\right)=S_{cc} \qquad (2)$$

With x_s and x_{cc} the mole fractions of solvent and co-crystal, respectively, D_s and D_{cc} the diffusion coefficients of solvent and co-crystal in solvent/CO2, respectively estimated by Hayduck-Minhas and Wilke and Chang equations [3], and S_{cc} a source term that represents the quantity of solute produced by nucleation and growth, determined by the resolution of the population balance equation determined hereafter.

2. Nucleation and growth

The general dynamic equation for nucleation and condensation is solved with the standard method of moments assuming that the particle size distribution follows a log-normal distribution. Assuming that the velocity particles is equal to the fluid velocity, the population balance equation remains to solve the fourth first moments of the distribution, it leads to:

$$\rho\frac{\partial m_j}{\partial t}+\nabla\cdot\left(\rho m_j\bar{\mathbf{u}}\right)=\rho\left(0^j B_{hom}+jGm_{j-1}\right)\qquad \text{for } j=0,1,2,3 \qquad (3)$$

where m_j is the j^{th} moment of the distribution. B_{hom} and G represent the nucleation and the growth rates, respectively defined by:

$$B_{hom}=1.5D_b\left(C_{sat}SN_a\right)^{7/3}\sqrt{\frac{\sigma}{k_bT}}V_m\exp\left(-\frac{16\pi}{3}\left[\frac{\sigma}{k_bT}\right]^3\frac{V_m^2}{\ln^2(S)}\right) \qquad (4)$$

$$G=k_gC_{sat}\left(S-1\right) \qquad (5)$$

where S represents the supersaturation, the driving force of the precipitation process estimated by the following relation:

$$S=\frac{2x_{cc}}{x_{sat}^{NPX}} \qquad (6)$$

The solubility of the naproxen x_{sat}^{NPX} in presence of nicotinamide was determined experimentally by Revelli et al. [4] for the operating conditions of our study.
The mean particle size d_{32} are calculated by the following relationship:

$$d_{32} = \frac{m_3}{m_2} \qquad (7)$$

3. Numerical methods

The numerical tool is the home-made CFD code "Thétis" developed at the I2M/TREFLE Department. The approximation of the model described in the previous section is realized by the finite volumes method on a fixed staggered grid. More details about numerical schemes can be found in [2].

RESULTS

The experimental conditions were of 308 K for temperature, 10 MPa for pressure, 8.37 $mg.ml^{-1}$ for nicotinamide concentration, 31.47 $mg.ml^{-1}$ for naproxen concentration in the initial solution and 6 $ml.min^{-1}$ for the solution flow rate. As a first results and in these conditions, particles of about 200 µm as mean size are calculated. In the figure 1, the instantaneous supersaturation profile in the meridian plane of the domain is shown. As expected and yet observed in classical SAS conditions, the high levels of supersaturation are localized at periphery of the jet where the solvent content is lower. In a next step, we are going to fit nucleation and growth parameters with experimental results and validate the simulation of the co-crystallization process.

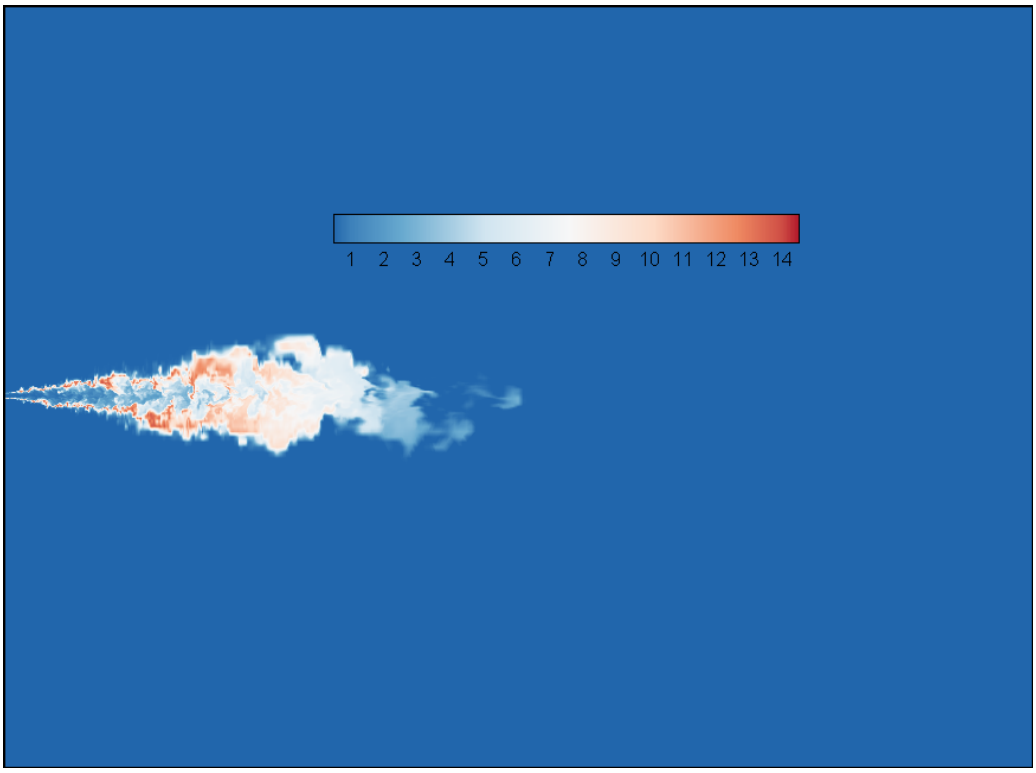

Figure 1: Instantaneous supersaturation profile in the meridian plane of the domain

CONCLUSION

We have proposed here a 3D simulation of a co-crystallization process for a better understanding of all the phenomena which occur in the process. The turbulence was considered using a Large Eddy simulation model in order to take into account with precision the micromixing between the injected solution and the supercritical antisolvent. Population balance equation was implemented to obtain finally the particle size distribution. The next step will consist in the validation of the computational code with experimental results.

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