SELECTIVE MANIPULATION OF CRYSTAL SHAPE BY COMBINED CRYSTALLIZATION, MILLING, AND DISSOLUTION STAGES – AN APPROACH FOR ROBUST PROCESS DESIGN

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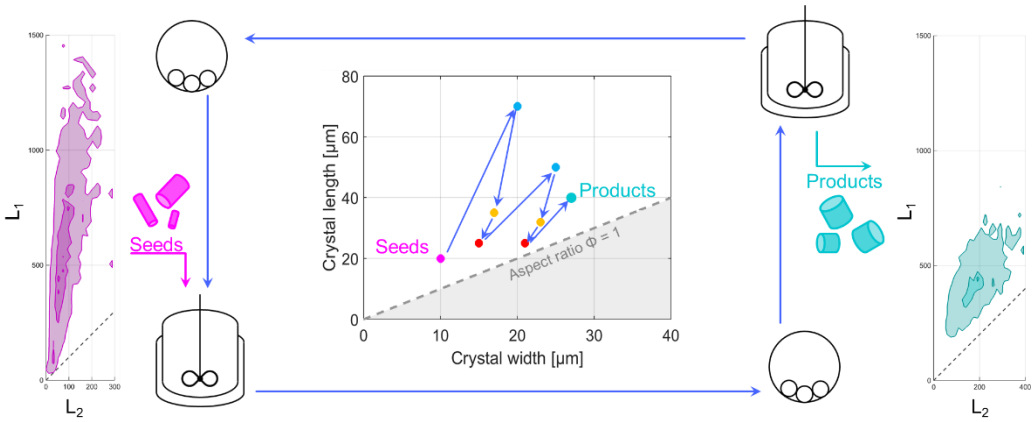

Figure 1 - Conceptual design of the 3-stage process

Key Words: Particle morphology, Process monitoring, Process modelling, Crystallization, Milling.

Solid formulations are nowadays extremely important in everyday life, especially concerning food and pharmaceutical products. Particularly in the latter case, the size and shape of the active pharmaceutical ingredients play a major role in determining their properties, both in terms of processability and bioavailability. For this reason, the interest in the crystallization community is driven nowadays more and more towards the identification of solutions to control the morphology of the particles during crystallization processes. Currently, the use of additives and antisolvents, as well as milling the particles after crystallization, are techniques commonly applied in industry. In order to avoid chemical impurities and fines in the final products, processes involving temperature cycles, eventually combined with a feedback controller, have also proved to be an interesting alternative. In this work, a new technique based on the combination of crystallization, milling and dissolution is proposed to control the shape of crystals. The crystallization stage is used to recover the solute from solution, while milling is used to break particles lengthwise, therefore reducing their length and leading to more equant shaped crystals. The fines formed during rupture are subsequently removed by dissolving them and the three stages are repeated for the desired number of cycles.

The approach used for a successful process design is thoroughly explained. First of all, it is necessary to develop devices to reliably and accurately measure multidimensional particle size and shape distributions. This is fundamental for a precise characterization of the basic phenomena occurring during the different stages. To this aim, the flow-through cell, an in-house built device, is used to monitor and measure populations of crystals and characterize them in terms of length and width; on top of that, a hot-stage microscope is used to investigate phenomena at the single particle scale. The experimental observation is used to develop a mathematical model, based on population balance equations. This model allows to describe phenomena typically occurring during crystallization processes, such as breakage and nucleation, hence allowing for an accurate prediction of experimental outcomes.
The mathematical model developed proves to be a reliable tool for the investigation of the feasibility of the proposed process. After the identification of process variables, particular focus is placed on the effect of the amount of mass dissolved, the milling intensity and the number of cycles performed, by considering and comparing both average properties and the whole particle size and shape distributions. A parametric analysis is used to identify general process trends and possible tradeoffs, as well as close-to-optimality conditions. To conclude, a comparison with a single crystallization stage and cooling crystallization followed by milling is carried out, highlighting benefits and limitations of the new process on the alternatives proposed.