Process Development for Size and Shape Manipulation of Elongated Crystals

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Crystallization

Crystallization is a separation and purification technique that is widely employed in pharmaceutical, agrochemical, and fine chemical industries. *Active Pharmaceutical Ingredients* (APIs), that are solid at ambient temperature and pressure, undergo at least one or more crystallization steps in their production chain. Therefore, the design of a process that includes the crystallization step, is critical to enable the availability of any given drug in the market at scale.

The crystallization step leads to particulate matter (or powders) that is composed of an ensemble of crystals exhibiting a plethora of sizes and shapes, described by the so called *Particle Size and Shape Distribution* (PSSD). Additionally, these crystals can also exhibit different internal crystal structures (polymorphism). The focus of the proposed project is on the former, i.e. the PSSDs. It is well known that the PSSD is a major factor in dictating the downstream processability (e.g. filterability, flowability, tabletability) of a powder.[1] In reality this translates to a scenario, where equant (e.g. spherical or cubes) shaped particles are always preferred over nonequant particles (e.g. elongated or plate-like particles). Alas, in practice not all APIs that are crystallized exhibits an equant shape. Therefore, there is a need to develop strategies to manipulate the size and shape of ensembles of nonequant particles.

Particle Size and Shape Manipulation

In literature one can find a variety of size and shape manipulation approaches. The simplest approach employs strategies to manipulate the supersaturation (the driving force for the crystallization step).[2–4] Another alternative is to employ a process cyclic that involves either temperature cycling (cycles of heating and cooling), mechanical action (milling), or a combination of these.[5–8] The choice of the process and therefore its performance depends heavily on the compound being used. In the absence of a pronounced size and shape change by employing the aforementioned approaches, antisolvents or additives can be employed to vary the supersaturation and/or to influence the growth rates of the facets of the compound.[9–11]

Multistage Process for Particle Size and Shape Manipulation

The proposed project aims to explore the role of antisolvents/additivies to effectively manipulate the size and shape of a population of elongated crystals and eventually design a batch/semi-batch process incorporating them. The PhD student will work on the:

1. Development of a multidimensional mathematical model to describe the process (*Year 1*)
2. Estimation of the multidimensional growth/dissolution kinetics of a model compound in the presence of antisolvents/additives (*Year 1-2*)
3. Fine-tuning the process using the estimated kinetics, optimizing the process in a modeling framework, and testing the performance in an experimental setting (*Year 2-3*)

To achieve the goals of the project, the PhD candidate will be exposed to state-of-the-art experimental (microscopic and multiprojection imaging devices)[12,13] and computational tools (population balance equation solvers, parameter estimation tools).[14,15] Additionally, the potential to employ machine learning/hybrid modeling techniques for the mathematical modeling part of the project will be considered. The student will also have the opportunity to work in a tight collaboration with the group of Dr. Aurora Cruz-Cabeza.

Additional Notes

Applicants for this project will be placed in the group of Dr. Ashwin Kumar Rajagopalan in the Department of Chemical Engineering and Analytical Science. The applicants should have or expect to achieve at least a 2.1 honors degree or equivalent in chemistry, physics, chemical engineering, or related subject. Prior relevant experience in imaging, mathematical modeling, and/or crystallization processes will be desirable.

For further information about the project or any informal enquiries, please contact Dr. Ashwin Kumar Rajagopalan at ash23win@gmail.com and/or visit ash23win.github.io. Please contact the admissions team at pgr-ceas@manchester.ac.uk for any queries regarding the application process.

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