# Engineering Downstream Processes to Enhance Processability of Crystallized Products

## Rationale of the Project

In the production chain of active pharmaceutical ingredients (API), a crystallization step is an integral part for separation and purification purposes. A typical solution crystallization step is followed by the so-called downstream processing steps. These correspond to a solid-liquid separation step, i.e. filtration, a washing step to remove the mother liquor from the filter cake, and finally a drying step to evaporate the wash solvent. The dried powder is eventually blended with excipients and in some cases formulated as tablets or granules to obtain the final solid product.[1] The performance of these steps is often dictated by the crystallization step, namely through the particle size and shape distribution (PSSD), the moisture content, the surface properties (e.g. cohesive/adhesive interactions), to name a few, of the crystallized product.

The aforementioned downstream steps have been studied both experimentally and computationally in detail for many different applications, e.g. pharmaceuticals, agrochemicals, paper and pulp, etc. Experimental and modeling studies that aim to provide a empirical relationship between the PS(S)D (mostly on size and rarely on shape) and the final filter cake porosity have been reported.[2,3] Despite its significance, washing has been scarcely explored over the years, with the focus being on developing rules of thumb and empirical models that work under a narrow range of operating conditions for specific compounds.[4–6] When it comes to drying, many of the reported works have looked into understanding the impact of the solvent/wash solvent content, agitation of filter cakes, size of particles, to name a few, on the effectiveness of the drying process in terms of time and the extent of breakage or agglomeration.[7–9] Even though these downstream steps have been studied for a long time, they have not been done in an integrated framework with the upstream crystallization step. Much less studied is the impact of the PSSD of the crystallized product on the downstream processability of the product.[10,11] This can be mainly attributed to the unavailability of reliable and accurate size and shape characterization tools.[12,13] Most importantly, even if this link is established there are only a handful of processes reported in the literature that have the ability to tune the size and shape of the crystals to enhance its downstream processability.[14,15]

## Engineering Downstream Processing Steps for APIs

This project is aimed at bridging the gap between the upstream crystallization step and the downstream steps by using a multiscale approach. We will develop predictive microscopic and macroscopic models backed by experimental data for all the three aforementioned downstream steps to improve our understanding and in turn develop efficient processes. These models will pave way to integrate the entire process chain, where given a PSSD one could quantitatively gauge the processability of the crystallized product in terms of both processing time and energy consumption.

To this aim, the PhD student will work on the:

1. Characterization of filter cakes and refining the scope of existing models (developed in house) to describe filtration processes (*Year 1*)
2. Development of microscopic and macroscopic models to describe washing and drying of the filter cake (*Year 2-4*)
3. Validation of the developed washing and drying models using a thorough experimental campaign (*Year 2-4*)

To achieve the goals of the project, the PhD candidate will be exposed to state-of-the-art experimental (microscopic and multiprojection imaging devices, agitated filter-dryer, tomographic devices)[16–18] and computational tools (population balance equation solvers, parameter estimators, molecular modeling, packed bed models).[18–21] The student will will be jointly supervised by Dr. Ashwin Kumar Rajagopalan and Dr. Carlos Avendaño. The project

is an industrial CASE studentship, hence will benefit from working closely with our industrial partner, AstraZeneca with the potential of placement for a few months at the company site.

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