POPULAR SCIENTIFIC ABSTRACT

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Crystallization of active pharmaceutical ingredients: novel process analytical technology (PAT) enabled strategies for process optimization and scale-up

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The pharmaceutical industry has in recent years been faced with the challenge of rethinking their business and Research and Development (R&D) models due to expiring patents competition from generic products, tighter regulations and a decrease in profits from their own products. The resulting decline in profitability has led to reduced reinvestment in R&D. One way of rethinking the R&D model is to speed up the pharmaceutical development process to reduce energy costs, operating costs and waste. In this PhD thesis, the focus is on the crystallization process.

Crystallization is a significant separation and purification technique widely used in the chemical, agrochemical, cosmetic and pharmaceutical industries, where more than 90% of active pharmaceutical ingredients (APIs) are produced by this process step. Crystallization serves as the link between synthesis and downstream processes such as filtration and tableting, where performance and processability depend on properties of the crystal product such as size and shape.

The current project presents a comprehensive study combining the application of process analytical technology (PAT) tools and multivariate analysis leading to PAT-enables strategies and systematic approaches. In the first part of the project, five different crystallization strategies were applied for crystallization of a biopharmaceutical and the thermodynamic relative stability between the anhydrate and hydrate of this compound was established. In the second part of the project, three proof-of-concept articles are presented for the first time showing the implementation of the principles of Quality-by-Design and direct design approach to facilitate scale-up. It was successfully shown that the properties of the crystal product could be maintained across scales using this new strategy and by the application of supersaturation control and direct design. Finally, in the last part of the project, the shift from batch crystallization to continuous crystallization was investigated and a risk assessment conducted for antisolvent crystallization. Two novel level control approaches were implemented: one by ultrasound and one by image analysis. The implementation of level control showed to increase the robustness of the process.