VYSOKÁ ŠKOLA
CHEMICKO-TECHNOLOGICKÁ
V PRAZE

Fakulta chemicko-inženýrská

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Návrh a řízení farmaceutických krystalizačních procesů

DISERTAČNÍ PRÁCE - ABSTRAKT ANGLICKY

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STUDIJNÍ OBOR	**Léčiva a biomateriály**
ROK	**2015**

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Title: Design and Control of Pharmaceutical Crystallisation Processes
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Study programme: Drug Synthesis and Production
Subprogramme: Drugs and Biomaterials

SUMMARY

It is estimated that more than 80% of pharmaceutical products involve at least one crystallization step in their manufacturing process. Thus, the development of better methods for the design and operation of crystallization processes is essential for technological advancement of the pharmaceutical industry in both the "originators" and the "generics" sectors. The most important parameters of the active pharmaceutical ingredient (API), in terms of material quality, are particle size distribution, crystal shape, purity and yield of the crystallization process.

The primary motivation of the present work was to investigate the crystallization of APIs in situations where the solid state has an "unusual" form, such as co-crystals of metastable polymorphs, and to improve the quality of the crystallizing material with regard to subsequent treatment through the design of an inherently robust crystallization process, in line with the Quality by Design (QbD) concept.

The experimental results are divided into three parts, all of which are essential in the development of the required solid form with the desired physical and chemical properties.

The first part demonstrates the combination of solvent selection and co-crystal ternary phase diagram prediction on the basis of solubility measurements into a single methodology that can be integrated into the pharmaceutical process development workflow. A suitable solvent for the co-crystallization process of agomelatine and citric acid has been chosen on the basis of co-crystal solubility, which is connected to the yield of the crystallization process. Furthermore, the quality of final crystals from the crystallization experiments was evaluated.

The second part deals with the kinetics of the crystallization process, i.e. with the interplay between the rates of nucleation and growth with regard to particle size distribution and the crystal morphology. The solubility curves and the meta-stable zone width were determined and the effect of cooling rate and seeding policy on the crystallization process was then systematically investigated. A mathematical model of the crystallization process, consisting of the population and mass balance, was formulated and the similarities and differences between classical single-component crystallization and co-crystallization were discussed.

In the third part, the crystallization of agomelatine metastable form X as an alternative to the agomelatine co-crystal has been developed using a novel crystallization process that combines the principles of both antisolvent and cooling crystallization. The influence of process conditions on the polymorphic antisolvent crystallization and transformations during cooling crystallization of agomelatine metastable form X from water/methanol solution has been investigated with a view of designing a robust process that includes not only crystallization but also filtration, filter cake washing and drying.