Crystallization of Active Pharmaceutical Ingredients

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Introduction

The pharmaceutical industry is large and has for years had very good profits from their drugs on the market but are now facing challenges. These challenges include patents expiring, generic competition, harsher price controls and tighter regulation [1],[2] and the pharmaceutical industry therefore has to rethink their business model. One strategy could be to decrease the time of process development and optimization. An area which could have great potential of being optimized is the crystallization process step, which is used in more than 90% of processes concerning small molecular active pharmaceutical ingredients (APIs). The Food and Drug Administration (FDA) initiated in 2004 the use and implementation of process analytical technology (PAT) in the processing of APIs. By implementing PAT into the crystallization process it makes it possible to analyze, control and design the process during the actual processing [3]. This project is part of the ProPharm project which is a collaboration between SDU, DTU, LeoPharma and Lundbeck. The aim of this project is to develop a PAT platform based on a multi-sensor system and a use chemometrics to gain insight into the mechanisms involved in the crystallization of the model API.

Critical property attributes of a crystalline API

- Purity
- Polymorphic form
- Crystal shape
- Crystal size distribution (CSD) [4]

PAT tools for crystallization processes

- Attenuated total reflection-fourier transform infrared spectroscopy (ATR-FTIR)
- Focused beam reflectance measurement (FBRM)
- Raman spectroscopy
- In-line and off-line imaging of particle shape and size
- Chemometrics used to interpret data

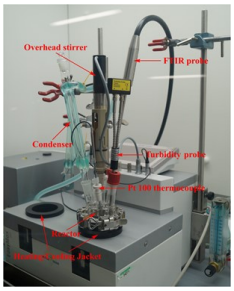

Figure 1: Experimenal set-up for crystalization in lab-scale [5].

Benefits of applying PAT

- Analyze the process to gain a more in depth understanding of the crystallization process
- Identify root causes of product/process deviations and control the crystallization process so unwanted processes are eliminated [6]
- Quality by design (QbD) so the desired quality of the product is obtained by designing the crystalization process in the most appropriate way [7]

Materials and Methods

- Solubility and polymorphism in the first stage of the research will be conducted in lab scale by using solvents such as methanol, propanol, acetone, water and ethanol at isothermal conditions
- The temperature dependency of solubility will be investigated for given solvents
- Concentration of dissolved compound will be investigated by HPLC and the remaining crystalline compound will be investigated by Raman spectroscopy and XRPD. Different PAT tools will be used in stage 2

Project outline

- Solubility investigation
- Applying different PAT tools
- Multi-sensor system
- Gain insight into the effects of the key operation parameters
- Predictive models will be developed and verified based on the in-line and off-line collected information of the process

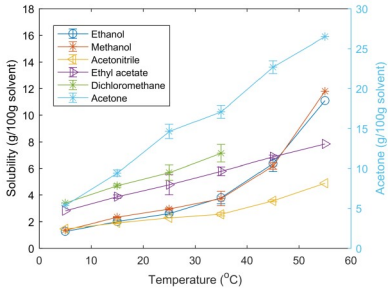

Figure 2: Solubility of IMC (γ form) in different solvents [5].

Project stages

1. Solubility and polymorphism investigation of the chosen API
2. Investigation of the crystalization of the chosen API by implementing PAT tools and the use of chemometrics for characterization of the key properties of the crystalline API
3. Outcome of stage 2 may lead to possible development of new crystallization strategies

References

[1] PwC, "From Vision to Decision - Pharma 2020," 2012.
[2] Deloitte, "2017 Global life sciences outlook : Thriving in today's uncertain market," 2017.
[3] M. Birch, S. J. Fussell, P. D. Higginson, N. McDowall, and I. Marziano, "Towards a PAT-based strategy for crystallization development," *Org. Process Res. Dev.*, vol. 9, no. 3, pp. 360–364, 2005.
[4] C. Lindenberg, M. Krättli, J. Cornel, M. Mazzotti, and J. Brozio, "Design and Optimization of a Combined Cooling/Antisolvent Crystallization Process," *Cryst. Growth Des.*, vol. 9, no. 2, pp. 1124–1136, 2009.
[5] C. R. Malwade and H. Qu, "Cooling crystalization of Indomethacin fromn different organic solvents," *BIWIC 24th Int. Work. Ind. Cryst.*, no. 24, pp. 40–45, 2017
[6] L. X. Yu, R. A. Lionberger, A. S. Raw, R. D'Costa, H. Wu, and A. S. Hussain, "Applications of process analytical technology to crystallization processes," *Adv. Drug Deliv. Rev.*, vol. 56, no. 3, pp. 349–369, 2004.
[7] E. Simone, W. Zhang, and Z. K. Nagy, "Application of Process Analytical Technology-Based Feedback Control Strategies To Improve Purity and Size Distribution in Biopharmaceutical Crystallization," *Cryst. Growth Des.*, vol. 15, no. 6, pp. 2908–2919, 2015.