Pharmaceutical Process Engineering

Pharmaceutical Process Engineering at the Institute for Pharmaceutical Technology is performed as an engineering science that converts drug substances, excipients and/or their formulations. Projects focus mainly on particulate systems or solid drug forms; hence, physical processes are in the foreground. Main objectives are reaching pre-determined product properties in the first place - or optimization of products and processes - by targeted and systematic variation of process and geometrical parameters. Scale of machines and apparatus used in the Pharmaceutical Process Engineering cover the range from lab- to lower kilo-range.

Furthermore, scale-up procedures are developed, production processes are evaluated or optimized. Efficiency, reproducibility and robustness of either single process steps or process chains are the major concern.

Projects of the Pharmaceutical Process Engineering can be allocated to the following fields:

- Nanomilling - wet milling in the sub-micron range with stirred bead mills
    - *Size Reduction of Liposomes with a novel Type of Stirred Bead Mill*
    - *Optimization of product properties by targeted nano-milling*

- Co-processing - e.g. dry milling and crystal modification at the same time
    - *Investigation of a jet mill for milling and mechanical activation of APIs*

- Extrusion - hot melt extrusion of granulation
    - *Online Measurement of Drug Substance Crystallinity during Hot Melt Extrusion*
    - *Cooling of Pharmaceutical Hot Melts with a Rotary Drum Cooler*

- Spray drying - of solutions or suspensions
    - *Spray drying of poorly water soluble plant extract from organic solution*
    - *Production of microparticles containing nano-sized drug substance for pulmonary application*

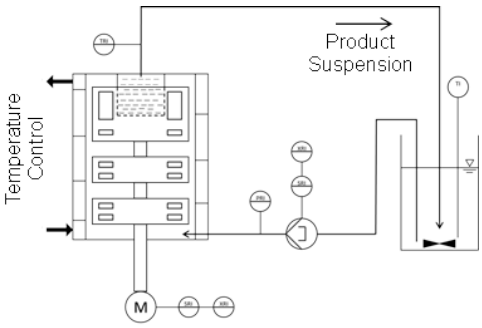
- Isolators - Optimization of operation robustness in pharmaceutical production plants
    - *Quantification of isolator decontamination efficiency*

- Production logistics - lean management
    - *Operational excellence and lean principals – applications and workshops*

Size Reduction of Liposomes with a novel Type of Stirred Bead Mill (Nanomill)

The potential of liposomes as carriers for drug delivery and drug targeting has frequently been reported but the production of liposomal formulations on an industrial scale remains a challenge. Consequently a novel nano-milling unit has been developed and investigated. The new nanomill fulfils the GMP standards of the pharmaceutical industry and is ready for SIP/CIP as this unit remains closed for filling, bead and product emptying, or cleaning. This new milling unit allows fast batch changes and short cycle times so that production can be more efficient and cost-effective. The machine was designed and constructed by the industrial partner Willy A. Bachofen AG Maschinenfabrik, Muttenz CH.

Novel type of stirred bead mill (Nanomill)



Experimental set-up

Milling unit

The influence of the main operating parameters necessary for the size reduction of liposomes with nanomills was determined. It has been revealed that the result of size reduction with this type of mill can be described by the concept of the stress number which, consequently, can be used to control the size reduction of soft organic particles. Furthermore this mill has been developed not only to meet the requirements of liposome production but also the requirements of the pharmaceutical industry with regard to the nano-milling of poorly water soluble drug substances.

Project Team: *Martin Studer, Berndt Joost*

Partner: *Willy A. Bachofen AG Maschinenfabrik, Muttenz CH*

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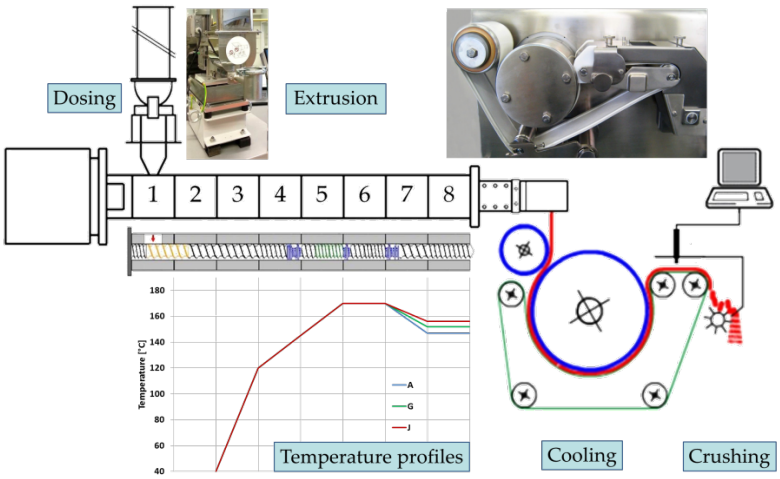
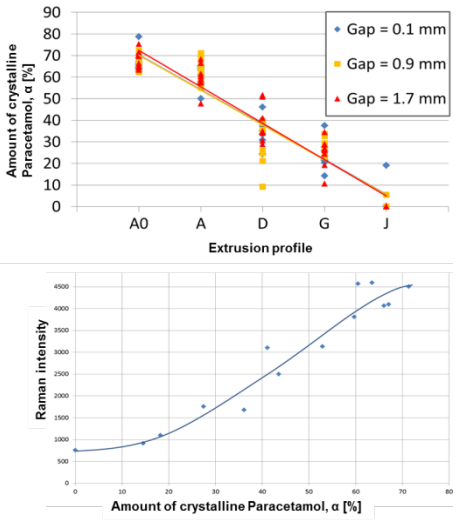
Cooling of pharmaceutical hot melts with a rotary drum cooler

Extrusion is a recognized manufacturing process for solid dispersions and other innovative dosage forms. Especially for poorly water-soluble drug substances in solid excipients, hot melt extrusion has become a commonly used processing method. Nevertheless, the necessary cooling of the extruded melt remains a challenge, since the cooling rate of the melt has an impact on the final product quality and therefore on its shelf-life. From the variety of possible cooling systems - air, inert gases, liquids or conveyor belt systems - a chill roll cooler was chosen and the operating parameters of the cooler were varied systematically. Furthermore, online information about the quantity of crystallized product present in the cooled melt is of major importance for quality recording or quality control during production.



Experimental set-up



Crystallinity vs Extrusion profile
Crystallinity vs online Raman intensity

With the experimental set-up it was possible to measure the amount of crystalline drug substance in the final extrudate online during production. A Raman online method was used to investigate the impact of different operating parameters of a rotary drum cooler on the crystallinity of Paracetamol in a final extrudate. The results indicate that an operating space between a lower and an upper discharge temperature threshold exists, in which the share of crystalline drug substance in the extrudate can be influenced just by varying the operating parameters of the rotary drum cooler.

Improved process understanding and deepened knowledge about operating parameters' interaction with final drug product quality allow shorter development cycles and thus more efficiency and cost-effectiveness.

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