Research Center Pharmaceutical Engineering (RCPE) – Overview

I2APM Emerging Pharmaceutical Manufacturing Summit
Malta 2017
RCPE – Key Facts

- **Research Center Pharmaceutical Engineering GmbH**
  - Independent research center for pharmaceutical process and product development
  - A nationally-supported, public-owned Institute configures and operates as a private organisation
  - Located in Graz, Austria

- **Our objectives:**
  - Develop innovative science-driven platform knowledge for process and product design & development
  - Reducing costs and time in pharmaceutical development
  - Create business advantages for our partners
Our Definition of Advanced Pharmaceutical Manufacturing

- **Controlled**: Quality is ensured by real-time monitoring of CQAs and “state of control” is maintained by advanced process control methods
- **Understood**: Mechanistic understanding of process and associated process models exist
- **Robust**: CQAs can be achieved for a broad range of materials, scales and operating conditions. Not overly sensitive to changes in materials attributes
- **Intensified**: Multiple physical and chemical transformations are carried out simultaneously (e.g., co-processing, melting and mixing)
- **Scalable**: Process is flexible with respect to the amount of product made and process can be scaled easily (e.g., time-scaling of continuous processes)
- **Economic**: Complex products and materials can be made using the processes in an economic way
Systems View of Pharmaceutical Product Development

Materials
- PSD, shape, BET, porosity, \( \rho \)
- Morphology
- Solid state, \( T_g, T_m \)
- Chemical stability
- Mechanical props.
- Flowability (ffc, etc.)
- Solubility, pKa, etc.
- Hydro/lipophilicity

Product
- Structuring
  - Molecularly mixed
  - Dispersed
  - Layered
  - Particle mix
- Mechanical interaction (friction, adhesion, etc.)
- Chemical interaction
- Thermodynamics

Processing
- Mechanical effects
  - Compaction, hardness, porosity
  - Change of morphology
- Particle/pellet synthesis (granulation, mechanofusion)
- Melting/solidification
- Redistribution

Biopharmacy
- Bioavailability
  - Liberation
  - Absorption
  - Metabolism
  - Distribution
  - Elimination
- Nano-particle uptake
- Distribution and clearance

Experimental
- Pore sizer
- X-ray
- Texture analyzer, etc.
- TEM
- DSC
- Powder rheology, etc.
- Compaction simulator
- Small-scale equipment
- Pilot lab
- In-vitro model (human cells)
- Ex-vivo model (tissue)
- In-vivo model (animal/human)

Simulation
- MD, DFT, MC
- Group-contribution models
- MD, DFT, MC
- Group contribution methods
- CFD, DEM, CFD-DEM
- FEM, SPH
- IVIVC
- GastroPlus
- PBPK models
RCPE Organization

**Executive Board of Directors**
- Business Development
- Licensing in/out
- Strategic Leadership
- Scientific targets
- Finance
- HR
- Internal and External Consulting
- IPRs

**Key facts**
- 140 Researchers,
- Legal entity is GmbH
- Clear IPR strategy
- 11 MIO per year turnover
- 30 peer-reviewed publications per year

**Laboratories and Pilot Plant**
- OEB 3-4 and controlled substances
- Material Science
- Analytical Science
- Stability
- Pre-clinical and clinical manufacturing in collaboration with AMS

**Program Committee**
- Program Commission

**Supervisory / Strategy Board**

**Scientific Advisory Board**

---

**Area I: Modeling and Prediction**
- Advanced Modeling & Simulation
- Scale up
- *In silico* prediction

**Area II: Advanced Products and Delivery**
- Material Science
- Biopharmaceutics
- Dosage Form Design & Development

**Area III: Process Engineering**
- Continuous Manufacturing
- Processing engineering Development & Scale Up
- QbD/PAT

---

**ITT1: New Platform Technologies**

**ITT2: Drug Quality and Safety Technologies**

**ITT3: Personalized Medicine e.g. Geriatrics**

---

**OEB 3-4**

---

**08.05.2017**

---

**I2APM Emerging Pharmaceutical Manufacturing Summit, Malta 2017**
RCPE Scientific “Space”

Products
- Oral dosage forms
- Inhaled dosage forms
- Advanced forms
- Biopharmaceuticals

RCPE

Process Science
- Particle engineering
- Particle processing
- Process modeling & simulation
- PAT & process control
- Primary manufacturing

Methods
- Material science
- Biopharmaceutics
- In silico methods
- Regulatory strategy
The Centre of Excellence for Pharmaceutical Formulation & Manufacture provides a “one-stop shop” that combines model-based analytical technology and experimental services.

This helps accelerate the development of drugs and design of their manufacturing processes.
Process Analytical Technology (PAT)

Optical Coherence Tomography

NIR Imaging

Figure: tablets in manufacturing stream

OCT Pharma 1D probe in hygienic design

In-line evaluation software
Continuous Manufacturing at RCPE

- **European Consortium on Continuous Pharmaceutical Manufacturing (ECCPM):** RCPE leads consortium with AZ, UCB, Bayer, GEA, Siemens, Automatik, EVK, University of Gent, U. of Eastern Finland, U. of Duesseldorf, TU Graz

- **International Institute for Advanced Pharmaceutical Manufacturing:** RCPE (A), CMAC (UK), C-SOPS (USA)

- **Continuous Hot-melt Extrusion and Pelletization:** Bayer (D)

- **Continuous filtration, cake washing & particle drying:** Novartis (CH)

- **Continuous drying of crystallization slurries:** Novartis (CH)

- **Fully continuous plant for dry, wet and melt granulation:** LLB Bohle Germany (D)

- **Integrated upstream-downstream continuous process**

- **Continuous capsule filling system**

- **Printing of Drugs**
ECCPM - Structure

ECCPM

RCPE Scientific and Communication Lead: Wen-Kai Hsiao

Pre-Competitive: Work Shop Series

Use-case I
Hot Melt Extrusion
Bayer
Maag Automatik
Siemens
EVK
IPPT
RCPE
KR: Johannes Khinast
RCPE: Jakob Rehrl
Isabella Aigner

Use-case II
Wet Granulation
UCB
GEA
Ghent University
RCPE
KR: Thomas de Beer
RCPE: Dave Doughty
Wen-Kai Hsiao

Use-case III
Direct Compaction
Astra Zeneca
University of Eastern Finland
RCPE
KR: Jarkko Ketolainen
Ossi Korhonen
RCPE: Wen-Kai Hsiao

Company Specific

Pre-Competitive: Work Shop Series

Company Specific

Company Specific

Prof Johannes Khinast
Scientific Director

Massimo Bresciani
Director BD/Sci Op

Company Specific

Company Specific
ECCPM – Workshop Series

- Successful workshop September 2015 on PAT & RTR
- Successful workshop July 2016 on process control and control strategy
- More than 45 participants at each workshop
- High level speakers
  - Steve Hammond, Pfizer Inc. (USA)
  - Sonja Sekulic, Pfizer Inc. (USA)
  - Martin Warman, Vertex Pharmaceuticals Inc. (USA)
  - Mauricio Furtan, Janssen (USA)
  - Jochen Thies, Glatt (CH)
ECCPM - Industrial Use Cases

Use Case 1: Hot-melt Extrusion

- Hot-melt extrusion/pelletizing is inherently continuous
- Solubility enhancement for poorly water soluble compounds with IR tablet as targeted product

Challenges:
- Formulation and process development for successful pelletizing
- Formulation for fast dissolution (pellet)
- Formulation and process development for successful tableting (elastic pellet)
- Develop PAT solution and control strategy

Use Case 2: Wet granulation

- CM equipment available based on wet extrusion granulation (GEA ConsiGma)
- Support migration from batch to continuous processing
- QbD approach to process development

Challenges:
- Formulation and process development to mitigate variability in API batches
- Individual unit operation trial and optimization
- Technology/process transfer
- Full line operation support

Use Case 3: Direct compaction

- Simplest process path to CM
- Minimal back-mixing and buffer to damp out disturbance
- Highly dependent on material processability

Challenges:
- Interfaces (residues and dead zone)
- Long run process robustness/effects
- In-line PAT method development
Evolving Challenges for CM

Upstream or Primary Processes
- Unit Op.
- Unit Op.
- Unit Op.
- Unit Op.

Downstream or Secondary Processes
- Unit Op.
- Unit Op.
- Unit Op.
- Unit Op.

Costs
Supply chain
Material science

Interfaces
Control & PAT
Regulatory

Supply chain
Costs
Data standard
Regulatory

Costs
Simulation
Control & PAT
Regulatory

Costs
Supply chain
Patient-centricity
Continuous Manufacturing – What’s Next?

- Integrating CM early on in pharmaceutical development, i.e., “What formulation strategies enable CM?” or “How can CM simplify formulations?”
- Standardization of selected materials for CM (e.g., MCCs, MgSt, etc.) with USP
- Integrating continuous API synthesis and secondary manufacturing (e.g., spray drying and filling into capsules or NANEX)
- Co-processing and multi-functional materials
- Individual manufacturing for patients based of personal needs, i.e., “fresh medicines”
- Adaptive formulations based on excipient variability
- Open innovation
- ECCPM 2.0
ECCPM 2.0

- Consolidation of lesson learnt
- Develop platform knowledge, i.e. tool kits to facilitate CM implementation (e.g. material science knowledge base, long-term PAT dynamics, etc.)
RCPE – Expanding Collaboration

Industrial partners

Scientific partners

Support partners
Contacts

Prof. Dr. Johannes G. Khinast
Director – Science
e-mail: khinast@tugraz.at
phone: +43/316/873/30400

Dr. Thomas K. Klein
Director – Legal and Finance
e-mail: thomas.klein@rcpe.at
phone: +43/316/873/30900

Massimo Bresciani
Director BD and Sci Ops
e-mail: massimo.bresciani@rcpe.at
phone: +43/316/873/30915