Mechanistic Model-based Digital Design framework for individual and integrated manufacturing steps

David Slade (Process Systems Enterprise)
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ADDoPT scope – a reminder

**Improve / optimise for impact**

- Product and Process Design
- Upstream
  - Materials properties
  - Manufacturing classification
  - Processing rules
- Primary Manufacturing - Secondary Manufacturing
  - Active Ingredient (API)
  - Crystallisation Filtration Washing Drying
  - Milling Blending Compaction Coating
- Downstream
  - Product Performance
  - Quality systems
  - Release profiles
  - Particle attributes
  - Formulation

**Processes**
- Design and control of optimised development & manufacturing processes through data analysis and first principle models

**Products**

**Patients**

- A systems-based approach to pharmaceutics
- **Horizontal integration:** Manufacture → Product Performance (breaking down silos)
- **Vertical integration:** Length Scales & Design → Operation
gPROMS Formulated Products – a new PSE product enabled by ADDoPT
Enabling platform - gPROMS

Platform functionality

Process modelling
- Equation-oriented solution power
- Custom model construction
- Steady-state and dynamic simulation
- Powerful optimisation, including mixed-integer
- Advanced parameter estimation
- Global system analysis
- High-performance computing

Materials modelling
- Molecular & ionic species
- Complex species & mixtures
- Gas, liquid, solid phases
- Phase & reaction equilibrium

A single powerful software platform
- R&D → engineering design → operations
- Formulation → manufacture → product performance
Enabling platform - gPROMS

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Model libraries in gPROMS FormulatedProducts

### Active Ingredient Manufacture
- Membrane separation
- Heat treatment
- Evaporation
- Solar pond operations
- Well-mixed crystallizer
- CSTR
- AFD
- PFR
- VL & VLL Flash
- Plug flow crystallizer
- Wet mill
- Distillation
- Extraction
- Pressure filter
- Centr. filter
- nD pop balance crystallization framework

### Formulation Manufacture
- Feeder
- Dry mill
- Fluid-bed drying
- Roller compactor
- Jet mill
- Spray drying
- Agglomerator
- Twin screw granulator
- High shear wet granulator
- Fluid-bed granulation
- Hot melt extruder
- 2D pop balance granulation framework
- Lyophilization

### Product Performance
- In-vitro dissolution and precipitation
- Oral absorption in GI tract
- Pharmacokinetics
- Solid form stability
- Parenteral stability

### Properties DB
- Multizonal (gFP:CFD)
- Multizonal (gFP:DEM)

### Data import and processing
- External model validation
- Parallelisation of GSA and PE

### Global Sensitivity Analysis
- Introduced with gPROMS FormulatedProducts 1.3

### Parallelisation of GSA and PE
- Introduced with gPROMS FormulatedProducts 1.3

### Available in gPROMS FormulatedProducts 1.2
- On roadmap

28th March 2019
ADDOPT DIGITAL DESIGN SHOWCASE, LONDON
Tracking material structure evolution across the system

- Unit operations effect transformations of complex materials
- Material description reflects earlier processing

- Reaction
- Crystallization
- Blending
- Dry Granulation
- Tabletting
- Oral Absorption

Primary particles, e.g.
- Impurities
- Shape

Granule structure, e.g.
- PSD of primary particles (API & excipient)
- Porosity or liquid content

Tablet structure, e.g.
- Granule PSD
- Extra granular excipient
- Ungranulated API / excipient
Properties and equipment databases

- Flexible database structure compatible with
  - PSE provided databases
Example of models developed in ADDoPT using the latest science & workflows

Ability to model the particle size and shape evolution during crystallization processes supported by new Morphological Crystallizer and Morphological PSD sensor models

Twin screw granulation - case study with AZ establishes model validation workflows and requirements, value proposition
- Perform fewer, more targeted experiments.
- Determine optimal screw configuration for desired granule PSD.

Models from academia and industry implemented and applied using new framework, establishing workflows complimentary to existing or challenging current practice
Hybrid modelling

- Combining mechanistic and data driven models
- Rationale for this approach outlined earlier today

Development of digital design and digital operation tools using mechanistic understanding, big data and hybrid approaches

- Data is typically not ubiquitous nor cheap to generate at the R&D and Engineering stages
- Use targeted data driven approaches to fill gaps in mechanistic understanding:
  - E.g. flowability, compressibility, bulk density
- Hybrid models
An interface for hybrid data-driven & mechanistic models
Integration of gPROMS Formulated Products and PharmaMV

Will be presented in more detail later today at 3.25pm by
• Andy Mitchell (Perceptive) & Niall Mitchell (PSE)
Applying the gPROMS FormulatedProducts systems framework
CMAC Digital Design example

A Design Tool for End-to-End Process

Multi unit operation and objective design space
• Using validated model to explore design space
• Linking operations to see the impact between processes
• Limit operating space by considering quality (content uniformity), manufacturing (filtration time) and economic (yield)

11.6 days (only experiment run time), 250 kg experimental vs 4 hr simulations

Applied also to
• RTD across multiple unit ops &
• Effect of Disturbances
Applying the gPROMS FormulatedProducts systems framework
CMAC Digital Design and Digital Operation example

A Continuous Microfactory Module – 5 stage MSMPR development

Aim: design & build flexible, modular processing module
- Output includes:
  - **Physical**: PAT – data – automation - control
  - **Digital**: equipment & process models
- Make as ease as possible to deploy on new processes

- Siemens- PCS7-SiPAT + Perceptive MPC control framework
- Expand to incorporate full process stream
- 3DP used for rapid prototyping
- VR/AR being developed
Further case studies

Talks today from

- Next: Marta Moreno-Benito, Pfizer, *Solid Drug Product and Process Design using Multi-Scale Interconnected Flowsheet Modelling and Global System Analysis*

- 4.05pm: Gavin Reynolds, AZ, *Application of hybrid models for Advanced Process Control of a Twin Screw Wet Granulation Process*

Demo booths in lobby:

- Morphological crystallizer, jet mill, integrated system

Anyone from PSE...
A mechanistic model-based digital design framework, gPROMS FormulatedProducts, has been created for

- Horizontal integration: Manufacture $\rightarrow$ Product Performance (breaking down silos)
- Vertical integration: Length Scales & Design $\rightarrow$ Operation

Enabling the creation of a Digital Twin of both complex formulated products and their manufacturing processes

These Digital Twins can be used for virtual DoEs (design space exploration), tech transfer and as a basis for Digital Operation
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