Continuous Pharmaceutical Manufacturing: from powder to tablet

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BACKGROUND

Health sector is facing major challenges in Europe: Population ageing creates need for

- new type of medicines
- more medication per capita
- more personalized and targeted medicinal products
CHALLENGES

- increasing financial pressure to keep up the standards of the European public health system

- competition from generic pharmaceutical companies (public health care system will benefit from efficient and low-cost medication)

- Increasing interest to outsource activities into low-cost countries + more and more R&D activities to Asian countries
CHALLENGES

- number of new molecules reaching the market ↓
- not enough new blockbuster molecules in pipelines of European pharma
  
  optimize the few new molecules + maximize value of already existing ones + streamline related dosage form design and manufacturing
- new molecules are larger and more challenging from processing point of view

European pharmaceutical sector with long and successful history is close to a most severe crisis during its existence

Europe must focus on building up the future technologies
“The pharmaceutical industry has a little secret: Even as it invents futuristic new drugs, its manufacturing techniques lag far behind those of potato-chip and laundry-soap makers.”

Wall Street Journal (Sep 3, 2003)

- still partly applicable today

- manufacturing of pharmaceuticals is conservative and old-fashioned field of engineering

- heavy documentation based regulatory structure ensuring the quality of the final product
INNOVATION IN PHARMACEUTICAL MANUFACTURING

CURRENT WAY OF MANUFACTURING

**BATCH PROCESSING**
- specific quantity of materials processed
- if quality is not met ➔ batch rejection

**off-line quality control in QC lab**
- sampling during each unit operation
- limited number of samples
- no real-time information
- no process understanding
- no real-time release

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**CONTINUOUS PROCESSING**
*a radically different system*

- SYNTHESIS
- CRYSTALLIZATION
- BLEND-ING
- GRANULATION
- DRYING
- TABLET-ING
- COATING

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**Input Variable**
- Fixed

**Process**
- Black - Box

**Output**
- [Waveform]
CONTINUOUS PROCESSING

A radically different system

- ‘one in, one out’- principle
- less scale-up issues
- lower cycle time
- faster release of manufactured goods

Process Analytical Technology (PAT)

- in-line / real-time quality control
- risk-based manufacturing
- improved process understanding
- increase of process efficiency
- real-time release possible
Continuous processing has major impact on:

- **workspace**
  - smaller systems
- less QC areas
- smaller warehouses (up to 65% reduction)
- **waste**: less batches rejected (up to 85% reduction)
- **manpower**: less personnel required in operations, maintenance, QA, logistics (up to 60% reduction)
- **operational costs** (up to 50% reduction)
A. API manufacturing

API manufacturing

several chemical reactions (e.g.; introduction of functional groups)

intermediates

downstream processing (filtration, distillation, ...)

final reaction mixture

downstream processing (multiple steps)

final API

unit operations:
- filtration
- distillation
- precipitation
- crystallisation
- drying
- milling

continuous:
- milling
- filtration
- distillation
B. Drug Product Manufacturing

Historically: conventional manufacturing = several unit operations

Each unit operation modulating certain material properties

BUT: some unit operations are continuous by design
Fully continuous: Collette Consigma system
granulation liquid

A: transport zones
B: kneading zones
Consigma: how does it work?
CONTINUOUS PRODUCTION PROJECT – Laboratory of Pharmaceutical Process Analytical Technology

1. PhD student Margot Fonteyne

- real-time monitoring of critical process and product parameters
  - interfacing of suitable sensors
- increasing the understanding of material behaviour in the process environment
derived from the data supplied by the process sensors

- in this presentation:
  - in-line monitoring of drying unit
  - prediction of critical quality attributes after drying

end product
1. In-line monitoring of drying unit

**Formulation**

- Anhydrous theophylline 30%
- Lactose 60.7%
- Polyvinylpyrrolidone 2.5%

Granulation liquid:
- Aqueous solution of SodiumLaurylSulfate 0.5% (w/v)

IN LINE MONITORING –

FEED-BACK & FEED-FORWARD CONTROL

TO THE MARKET
Raman spectroscopy
solid state changes of theophylline
NIR Spectroscopy
in-line moisture content
First experiment

15 different drying runs with varied
- drying time
- drying air temperature
- drying air flow

different moisture contents at the end of the run

after each run:

20 NIR-spectra

Karl-Fisher Moisture Determination

PLS-model
* 6 drying experiments
* 30° - 40° - 50° - 60° - 70° - 80° C
* in-line monitored NIR-spectra
* NIR-Spectra → PLS-model → moisture content prediction

![Graph showing moisture content over drying time with Karl Fisher result after drying at 12.5 min.]
1. In-line monitoring of drying unit

12.5 min
2. prediction of granule properties after drying based on in-line measurements

**Methods**

- Continuous twin-screw wet granulation and continuous drying

**Formulation**

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- Lactose 60.7%
- Polyvinylpyrrolidone 2.5%

Granulation liquid:

- Aqueous solution of SodiumLaurylSulfate 0.5% (w/v)

**Experimental design**

- Two-level full factorial design

<table>
<thead>
<tr>
<th>Run order</th>
<th>Barrel temperature (°C)</th>
<th>Powder feed rate (kg/h)</th>
<th>Drying temperature (°C)</th>
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<td>25</td>
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<tr>
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</table>

Factors/Process parameters:

- Barrel temperature
- Powder feed rate
- Drying temperature

Granules in-line measured using:
- Flashsizer (size and shape)
- Raman
- NIR
### Methods

#### In-line measurements
- **FlashSizer3D**
  - Roughness (shape)
  - $d_{10}$
  - $d_{50}$
  - $d_{90}$
- **NIR**
  - 4500 – 10000 cm$^{-1}$
  - Mean-centering and SNV pre-processing
  - PCA
- **Raman**
  - 100 – 1800 cm$^{-1}$
  - Mean-centering and SNV pre-processing
  - PCA

#### Off-line measurements
1. **Moisture content**
   - Karl Fischer titration
2. **Bulk and tapped density**
   - PhEur
   - To calculate Compressibility index (CI) and Hausner ratio (HR)
3. **Flowability**
   - PhEur
4. **Angle of repose**
   - PhEur

---

**Flowability**
- 11 granulation runs
- Flowability
- Bulk and tapped density
- Karl Fischer titration
- PhEur
- Compressibility index (CI) and Hausner ratio (HR)
- Angle of repose
- PhEur
REAL-TIME DATA PROCESSING

- Temp
- Pressure
- Speed
- RM Attribute 1
- RM Attribute 2
- NIR
- Raman
- WTC

Quantitative result

Qualitative result

SIEMENS

SIEMENS
## RESULTS AND DISCUSSION

### X-variables

<table>
<thead>
<tr>
<th>NIR</th>
<th>Raman</th>
<th>FlashSizer3D</th>
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</thead>
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<tr>
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- **NIR**
  - PC1 74.70%
  - PC2 16.09%
  - PC3 5.07%

- **Raman**
  - PC1 39.81%
  - PC2 25.06%
  - PC3 18.47%

- **FlashSizer3D**

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<tr>
<td>Responses</td>
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RESULTS AND DISCUSSION

MC = moisture content
CI = compressability index
HR = Hausner ratio
Flow = flowability
AR = angle of repose

summary of predictive abilities of the PLS model (2 PLS components)
Imaging (Flashsizer): size and shape information

samples are imaged through a glass window

2 light sources, placed 180° from each other in horizontal plane

FlashSizer 3D

current process imaging system facts:
  • pixel resolution 10 um
  • image area 1.2x1.6 cm
  • optimal size range 50-2000um
  • 5-20 images/sec
  • calculations ~50ms
**Combination of 2 images for 3D visualization and PS data extraction:**
RESULTS AND DISCUSSION

SAMPLING ISSUES: FLASHSIZER3D

Examples

Run 9 t1
Run 9 t2
Run 11 t1
Run 11 t2

Same sample / different time of measurement or different sample points

Difficult sampling

- Finer granules are retained in the first layer
- Larger granules are hidden
2. PhD student Séverine Mortier

- development and validation of mechanistic models based on physical and chemical patterns increase the fundamental process knowledge
- better understanding of process and product parameters upon process progress and product quality
- process control
- process simulations

- *in this presentation*: drying behaviour of continuously produced wet granules
Drying of pharmaceutical granules

1. Fast drying period

\[ \dot{m}_v = h_D (\rho_{v,s} - \rho_{v,\infty}) A_d \]  

\( h_D \) = mass transfer coefficient, \( \rho_{v,s} \) = partial vapour density over the droplet surface, \( \rho_{v,\infty} \) = partial vapour density in the ambient, \( A_d \) = surface area of droplet

2. Slow drying period

\[ \dot{m}_v = -\frac{8\pi \varepsilon \beta D_{v,cr} M_w p_g}{\Re (T_{cr,s} + T_{wc,s})} \ln \left[ \frac{p_g - p_{v,i}}{p_g - \left( \frac{\Re}{4\pi M_w h_D R_p^2} \dot{m}_v + \frac{p_{v,\infty}}{T_g} \right) T_{p,s}} \right] \]  

\( \varepsilon \) = crust porosity, \( \beta \) = power coefficient, \( D_{v,cr} \) = vapour diffusion coefficient (crust pores), \( M_w \) = molecular weight of the liquid, \( p_g \) = pressure of drying agent, \( T_{cr,s} \) and \( T_{wc,s} \) = temperature of crust outer surface and of the crust-wet core interface, \( p_{v,i} \) and \( p_{v,\infty} \) = partial vapour pressure at the crust-wet core interface and in the ambient, \( h_D \) = mass transfer coefficient, \( R_p \) = particle radius

First drying period: weakly bound water
Second drying period: strongly bound water
Validation

3 independent drying experiments at 3 different drying temperatures

45° C

55° C

65° C

- Modelprediction: Linear
- Modelprediction: Quadratic
- Modelprediction: Exponential
- Experimental data: first drying period
- Experimental data: second drying period
3. CONCLUSIONS AND FUTURE PERSPECTIVES

- manufacturing of dosage forms will radically change in the upcoming years

- there is an urgent need to improve efficiency and productivity within the drug manufacturing area

- there is an urgent need to employ innovation and cutting edge formulation, engineering and scientific know-how to respond to those manufacturing challenges

- continuous pharmaceutical manufacturing may offer pharma industry a chance to remain productive, profitable and able to meet global competitive challenges

- if we want to keep pharma manufacturing industry in Europe alive, it is urgent that industrial partners and academics join efforts in order to meet the challenges of the future
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