The potential of Continuous Processing in secondary manufacturing

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Today’s Pharmaceutical World…

- low efficiency
  - example: secondary manufacturing
    - large batch equipment, inefficiently used
    - low equipment utilisation (30% - 40% avg)
    - low product yields
    - long production lead time (intermediate QCs)
    - individually controlled equipment
    - high inventory volumes & cost
    - space consumption & add-on utilities
    - scrap & rework
    - labour intensive
    - improvement perceived limited by regulatory
Oral Solid Dosage manufacturing today

High inventory including “work in progress”, long changeovers, disconnected processes, high process losses, off line analysis, low asset utilization, …
PAT: Key Enabler for Continuous Manufacturing and Real Time Product Release

Right First Time
Real time release

- Blender
- Granulator
- Dryer
- Tablet press
- Coating
- In/At line check
- Quality check
- SIPAT
- Raw Material
PAT Basics – Holistic Approach

Advanced Control → Quality built in by design → Right First Time

Closed loop control → Temp., Speed, Liquid addition, Compression Force, ...

Classic control

monitoring product quality

mathematical translation

monitoring process data

Real-Time Release

Lab

LIMS

Hold / release

Sample

Process output

Process Analyzer

PAT

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ConsiGma™ Continuous Tabletting Line example
ConsiGma™ Continuous Tabletting Line example

Materials Handling

Feeding

Blending

Granulating

Drying

Milling

Extra Granular additions

Coating

Compression

Lubrication

Extra Granular additions
PAT/QBD in solid dosage

- Drying control
- Process parameters

- Blending / Lubrication control
- Process parameters

- Compression control
- Process parameters

- Coating control
- Process parameters

- Dispense & Blend control
- Process parameters

- Wet Granulation control
- Process parameters

- Loss On Drying

- Particle size

- Content Uniformity

- Bulk Physical Defects

- Sampling & Off-line analysis

- Test against specifications

- Bulk Physical Defects

- Content Uniformity

- Packaging control
- Process parameters

- Coating solution

- Particle size
SIPAT Data Flow principle
focus on-line data acquisition and processing

- Data alignment
- Contextualization
- Rules separating non-representative data
- Statistical RT Models
  - e.g. PLS, PCA
  - Chemometrics (Umetrics, Matlab,...) engine embedded in SIPAT
- Aggregation of CQA over process context
  - Average
  - Standard deviation
- On line Monitoring
- Out of control detection
- Deviation tracking
High Level System Architecture

- **Supervisory & Control**
  - Alarm handling
  - Line Recipe handling
  - Trending **Univariate** Data
  - Deviation Tracking Critical Process Parameters

- **Control Analyzers**
- **Multivariate** Data handling
- On-line monitoring of the Critical to Quality Attributes (CQA)
- Deviation Tracking CQA
- Out of Control Detection & input to APC

- **Real Time Release reporting**

- **Process**

- **Line**

- **SITE**

- **MES**

- **LIMS**

- **SCADA**

- **SIPAT**

- **PLC / Motion Control**

- **ANALYZERS**

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Data Driven Manufacturing

• SIPAT allows to measure inline the CQA’s, real time

• Increased number of measurements

  Test case of 50hrs run @25kg/hr=1250kg material

  - Moisture measured 960 times
  
  - Particles size distribution measurements: 960 times
  
  - Content uniformity: 100 times
  
  - Tablet weight: each tablet (1,8 Mio)
  
  - Enhanced product security
  
  - Data correlation across units
Material Residence Time distribution
Product Plug tracking

Ingredients
- API
- Excipient 1
- Excipient 2

Granulation

Drying

Milling/Blending

Compression

Coating

Output

Time

Drum 1

Drum 2

Drum 3
Material Residence Time distribution
Real Time Release floating window

Ingredients
- API
- Excipient 1
- Excipient 2

Granulation

Drying

Milling/Blending

Compression

Coating

Output

Drum 1
Drum 2
Drum 3

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Page 14  Oct 6st, 2010  Ivo Backx  Industry Sector
Granulation/Drying/Milling Equipment Comparison

Batch Process room requirements
- 70 m²
- 490 m³

Continuous Process room requirements
- 6.25 m²
- 22.5 m³

Legend:
1. = granulator
2. = dryer
Cleaning philosophy

Granulation unit: Wash in place - Wash off line
Drying unit: Wash in place - Wash off line
Granule conditioning unit: Cleaning in place
Investment & Running Cost: Case Study

Commercial manufacture of compound X in plant Y, using base case 1.5 bn tablets/yr

- Conventional Batch Approach (all inclusive) 42 mio euro
- Continuous (all inclusive) 17 mio euro

A continuous line requires **30% of manufacturing space** (70 m² vs. 18,75m²)

- Cost of direct labour for conventional plant 3,471,000 euro
- Cost of indirect labour for conventional plant 1,066,000 euro

**40% saving on labour costs expected**

- Material saved via raised yield @ ½ % of 450 ton/yr = 2,250 kg material
  
  2,250 kg @ 900 euro/kg = 2,025,000 euro/yr

- Reduced space requirement reduces HVAC costs, smaller surface area contact parts reduces cleaning utility requirements, this is estimated to be worth 115,000 euro/yr
Why Continuous Manufacturing?

Why move towards CM operation?

Many advantages perceived in CM

- Smaller equipment
- Smaller facility
- Easier scale-up
- Better control
- Improved yield
- Reduced waste
- Improved Safety
- Flexible Manufacturing
  - For personalized medicine/Targeted therapies
- Reduced cost
- Improved quality
Faster to Market

Benefits to late stage process development

- Equipment scale development=manufacturing
- Faster process understanding and optimization through Automation and integrated data management
- PAT/ Controls developed simultaneously
- Faster to market
Good Collaboration makes this happen

End-User
- **Product Know-How**
  - Specify required machinery to fulfill a specific production operation
  - Equipment must comply with the own specific norms and standards
  - Focus on the optimized functioning of the complete production line
  - Easy integration of the control level into Plant-IT

Siemens
- **Industry know How**
  - Standard platform
  - Scalable solutions
  - Easy integration
  - GMP supporting functions
  - Cost effective solutions
  - Long term Support (investment protection)
  - Worldwide Product Support

OEM
- **Process Know-How**
  - Supply specific equipment + instrumentation to handle a specific production operation
  - Focus on equipment specific optimization
  - Equipment automation specification (PLC, HMI, drive, instrumentation, ...)
  - Equipment validation
  - Equipment specific 21 CFR Part 11 functionality
  - Worldwide Packaged Unit Support
Thank you for your attention!

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