Fluid Bed Best Practices For Multiparticulate (MP) Formulations

The Importance of Computational Design and Process Analytical Technology

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Intended Outcomes and Importance to Quality

• Accelerate formulation development by reducing traditional iterative trial and testing practices in development

• Support robust formulation development using computational design tools and PAT technology

• Reduce formulation and process risk throughout product lifecycles
Multiparticulate (MP) Dosage Forms Offer Formulation and Process Opportunities

- **Taste Mask Coatings**
  - pH-Independent Coating
  - pH-Dependent Coating

- **Controlled Release Coating**
  - Diffusion Controlled

- **pH-Trigger Release Coatings**
  - Enteric / pH-Dependent Coating

- **Fixed Dose Combination Products**
  - IR Formulation / MR Formulation

**Note:** Image Adapted from "An Introduction to Multiparticulates," M. Shaffer, July 2018.
Best Practices for Multiparticulate Success

Substrate (Core)
- Particle Morphology
- Size
- Friability
- Sphericity
- SA/FT Ratio (MDD)
- Drug Layering
- API Morphology
- Binder Selection

Equipment
- Maintenance / Parts
- Static / Grounding
- Process Air Conditioning
- Filter Selection (Exhaust)
- Bottom Plate and Retention Screen Selection
- Spray Nozzle Set-up

Coating
- SA/FT Ratio
- Fluidization (Product Flow)
- Temperature (Tg)
- Agglomeration
- Droplet Size (air volume)
- Spray Nozzle Performance
- Optimization (DoE / Risk Analysis)

Process
- Static
- Fluidization (Product Flow)
- Agglomeration
- Process Tracking
- Scale-up
- Δ P
- Partition Height (Product Flow)
An ‘Inside Out’ Approach to Consistency Starts with the Core

- Robust formulations start at the core
- Consistency of coating layers depends on the consistency of the starting core
- Uniform size and shape of the stating core allows a more uniform application of coating layers
What are the Critical Quality Attributes

- Particle Size Distribution
- Sphericity
- Friability
Drug Release Primarily by Diffusion Through the Semipermeable Membrane

- Rate of drug release is modified by:
  - Increasing or decreasing the amount of polymer applied (film thickness)
  - Altering the permeability of the polymer barrier membrane coating

Fick’s 1st law of diffusion:

$$J = \frac{dM}{dt} = \frac{DSK(C_d - C_r)}{h}$$

- \(S\) = surface area (cm\(^2\))
- \(C\) = concentration
- \(D\) = diffusion coefficient
- \(K\) = partition coefficient
- \(h\) = thickness of barrier
- \(J\) = Flux

![Graph of SA/FT versus Time 50% Release](image)
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Design and Process Tools for MPs

- **My Dosage Design™ Tool (Colorcon)**
  - Calculator for the development of MP Dosage Forms
  - Estimates important product characteristics
  - Compare multiple formulation scenarios
  - Incorporate known information where possible

- **Dynamic Image Analysis**
  - Lab based instrument for offline measurement
  - Inline fluid bed measurements

Images courtesy of Horiba and Innopharma Technology.
Computational Design Using My Dosage Design™
Observed Consistent Process Control and Film Thickness Growth Throughout Coating

- Film thickness (um) as a factor of predicted weight gain percentage
- Observable, consistent growth between sample points
- Steady process trend and no process interruptions.
Innopharma Technology & the Eyecon\textsubscript{2} Particle Analyser

Chris O’Callaghan
Innopharma Technology & the Eyecon\textsubscript{2} Particle Analyser

- Chris O’Callaghan
- Head of Engineering, Innopharma Technology Ltd.

- Section Overview
- About Innopharma & our products
- The importance of PAT
- The Eyecon\textsubscript{2}
  - Applications
  - Tech Specs
  - Direct Imaging – Method of Operation
Innopharma Technology Company Background

• Founded in 2009
• Three divisions:
  • Education & Upskilling
  • Technology to Enable Advanced Manufacturing / Process Analytical Technology
  • Technical Services
• Currently ~75 employees experienced in STEM, Pharma development and manufacturing operations, IT & Software Development
Innopharma Technology - Our Products

**Direct Imaging Particle Analyser**
- Particle analyser for powders and bulk solids
- Detect Fluid bed Pellet (Wurster) Coating Thickness.
- Determine why a process is failing or reducing yield in-line
- Capture manufacturing consistency automatically
- Particle size and shape analysis software EyePASS™ included

**Multi-point NIR Spectrometer**
- Near infrared spectrophotometer for measuring changes in process in real-time, in-line
- Highly effective in monitoring moisture content from 0 to 27 ± 0.8%.
- Analyse component concentrations and material density
- User Friendly chemometrics package included – Quanta Model Developer™

**Vertically integrated platform for Smart Process development and Manufacture**
- Functional insight and control
- Integration and storage of all process
- Analytical data in a single, easy access view
- Pre-configuration of experimental and DoE
- Higher resolution of in-process data
- Understanding of design space
- Scale up control to commercial manufacturing

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## Journey of PAT, Sensors & Advanced Manufacturing Platforms

### PAT, Sensors and Platforms for Advanced Manufacturing

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<td>multieye₂</td>
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### Advanced Manufacturing - Pharma 4.0

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<td>SmartX for fluid bed granulation / coating</td>
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<td>SmartX for crystallisation</td>
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<tr>
<td>SmartX for twin screw granulation</td>
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The Importance of PAT

- Improving productivity and product quality is one of the biggest challenges Pharmaceutical companies are facing.
- PAT tools are used to enable better understanding of the processes by providing valuable data from the process in real-time.
- Better process understanding leads to more robust reliable processes with optimal control which is key to assuring final product quality and maximum yield for pharmaceutical products.
- Optimizing the processes by reducing the cycle/process time and increasing the yield can have bigger impact on the final price of the product and it’s accessibility to the patients.
Particle Size Analyser: Eyecon$_2$

- Real-time particle size distribution and shape
- Use in:
  - Research & development (QbD/DoE/CPP/CQA)
  - Scale up
  - Tech transfer
  - Manufacturing
    - Batch
    - Continuous
- Use in:
  - Fluidised bed coating, granulation, drying
  - Twin screw granulation
  - Roller compaction / milling
  - Extrusion - spheronisation
EyePASS – Particle Analysis Software

Material: Gran_171001_R2
Sublot: 1
Starting operator: admin
Elapsed time: 06:01:22.06

Batch Number: attempt2
Configuration: Config_170022_Gran
Time started: 2017-10-24 14:35:13
Integration Period: 120s

Size Distribution

Volumetric:
- Dv10: 597.10
- Dv50: 1016.25
- Dv90: 1534.09

Eccentricity:
- AVG: 0.4607
- RSD: 0.4529

% of Total

100.0% 95.0% 80.0% 60.0% 40.0% 20.0% 0.0%

Particle size

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**Eyecon\textsubscript{2} Technical Specifications**

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<th>Specification</th>
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<tr>
<td>Size Range</td>
<td>50 to 5500 µm</td>
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<tr>
<td>Casing materials</td>
<td>304 Stainless Steel, Glass, Silicon (gaskets)</td>
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<td>Imaging Area</td>
<td>11.25 x 11.25 mm</td>
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<td>Output</td>
<td>PDF session report. CSV, full PSD from D5-D95, JPEG (images)</td>
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<td>Instrument Ratings</td>
<td>GMP Compliant Design</td>
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<td>EyePASS is both 21 CFR part 11 &amp; GAMP5 Compliant</td>
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<td>Ethernet and USB</td>
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Method of Operation: Image Capture

- A flash-imaging technique is used with an extremely short light-pulse to illuminate moving particles for image capture.

- Red, Green and Blue LEDs illuminating the sample from different angles for accurate detection of particle boundaries.
Method of Operation: Image Analysis

- Each particle initially identified
- Best-fit ellipse calculated
- Major & minor diameters computed
- PSD/D-values determined
Particle Size

- The D-values are computed from the group of ellipses estimated from the particles.

- D50 value, also known as mass-median-diameter (MMD) is the diameter which divides the particles into two groups with equivalent weight / mass.

- Similarly, the mass of particles with diameters smaller than D10, D50, D90 equals to 10%, 50%, 90% of the total mass.
Case Study: Particle Size Growth Measurement MP Coating
Use of Dynamic Image Analysis Tools
**Formulation / Equipment / Process**

- BCS Class I Freely Soluble API (133 mg g\(^{-1}\))
- Suglets\(^\circledR\) (Sugar Sphere, NF) 850-1000 µm
- Glatt GPCG2 (7” Wurster)

<table>
<thead>
<tr>
<th>Batch Size (kg)</th>
<th>Inlet Air Temp (°C)</th>
<th>Product Temp (°C)</th>
<th>Spray Rate (g min(^{-1}))</th>
<th>Air Volume (m(^3) hr(^{-1}))</th>
<th>Atm Air (bar)</th>
<th>Orifice Plate</th>
<th>Partition Ht. (mm)</th>
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<tr>
<td>2</td>
<td>70-75</td>
<td>44-46</td>
<td>15-20</td>
<td>100 – 110</td>
<td>1.6</td>
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GPCG 2, Image courtesy of Glatt Air Techniques.
Overview of Study Response Variables

- In-process particle size analysis
  - Eyecon\textsubscript{2} (in-line)
  - Camsizer (at-line)
- Particle morphology
- Film thickness
- Assay
- Dissolution testing
- Relationship between dissolution & PSD

Image courtesy of Colorcon and Innopharma Technology.
Particle Size Distribution and Substrate Flow in a Wurster Column

- Bias toward coating larger particles
  - cross-sectional area
  - particle mass
  - fluidization pattern
- Larger particles gain more coating
- Impact of agglomerates
- Starting substrate of narrow particle size distribution (Suglets®) minimizes effect
Consistent Film Thickness Growth Observed Throughout Coating

- Film thickness (um) as a factor of predicted weight gain percentage
- Observable, consistent growth between sample points
- Steady process trend and no process deviations.
Dissolution Results

- Dissolution curves at 5%, 10%, 15%, and 20% weight gain or 5 – 35 micron film thickness.
- Two additional curves illustrate impact of a post-coating thermal treatment or curing step.
- Slight decrease in release was observed for the cured samples
- Dissolution results in agreement with the observed particle size growth between sample points and steady process trend during coating.
Relationship Between Dissolution & Film Thickness

Film Thickness versus Dissolution

\[ y = -0.0235x^2 - 0.2502x + 101.83 \]
\[ R^2 = 0.9987 \]

- Film Thickness vs Dissolution @120 minutes
- Poly. (Film Thickness vs Dissolution @120 minutes)
Relationship Between Dissolution & Film Thickness

Film Thickness vs. Dissolution

- Film Thickness vs Dissolution @15 minutes
- Film Thickness vs Dissolution @60 minutes
- Film Thickness vs Dissolution @240 minutes
- Film Thickness vs Dissolution @600 minutes
- Poly. (Film Thickness vs Dissolution @15 minutes)

- Film Thickness vs Dissolution @30 minutes
- Film Thickness vs Dissolution @120 minutes
- Film Thickness vs Dissolution @480 minutes
- Film Thickness vs Dissolution @720 minutes
- Poly. (Film Thickness vs Dissolution @30 minutes)

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Dissolution: Predicted versus Actual

Predicted Dissolution with Analytical Results Overlaid
Best Practices

- MP Dosage forms offer formulation flexibility and patient friendly features.
- Robust formulations start with the core.
- Computational design and PAT (Eyecon2) offer enhanced formulation and process insight.
- Opportunities to improve outcomes, speed development, and helps ensure product robustness.
Designing your multiparticulate product and manufacturing process with a set of Best Practices in mind, will expedite the development process and help ensure a trouble-free lifecycle.

Jason Hansell
Senior Area Technical Manager, Colorcon
Industry Collaboration to Meet Formulators Needs

- Piyush Patel, Formulation Technology at Colorcon
- Ed Godek, Process Technology at Glatt Air Techniques
- Chris O’Callaghan, Head Of Engineering at Innopharma Technology
- Jeff Bodycomb, Product Manager at Horiba Scientific

A Best Practice Approach Offers Opportunities to Improve Development Outcomes.

Fluid Bed Best Practices for Multiparticulate Formulations