Fluid Bed Best Practices For Multiparticulate (MP) Formulations

The Importance of Computational Design and Process Analytical Technology

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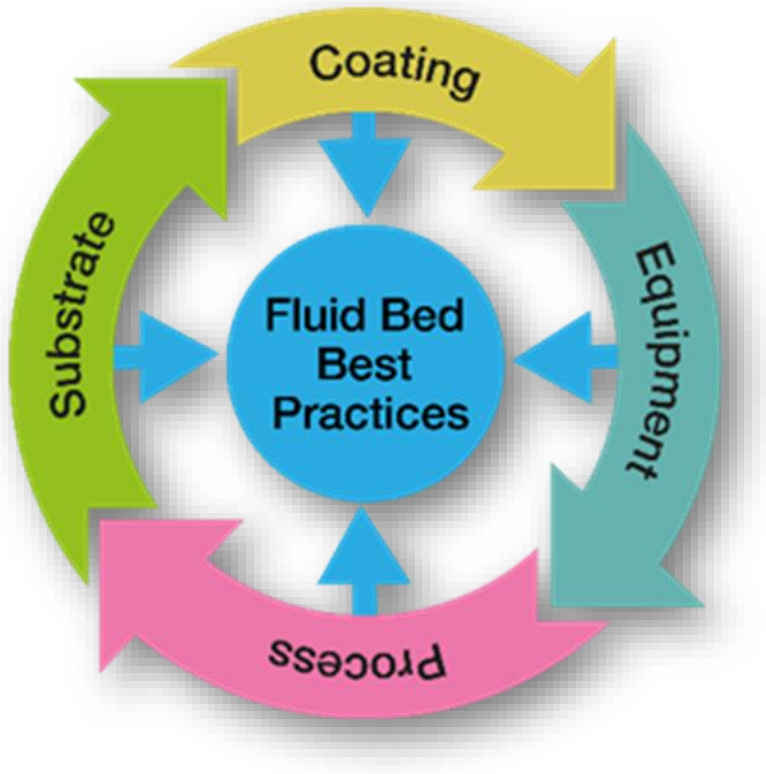
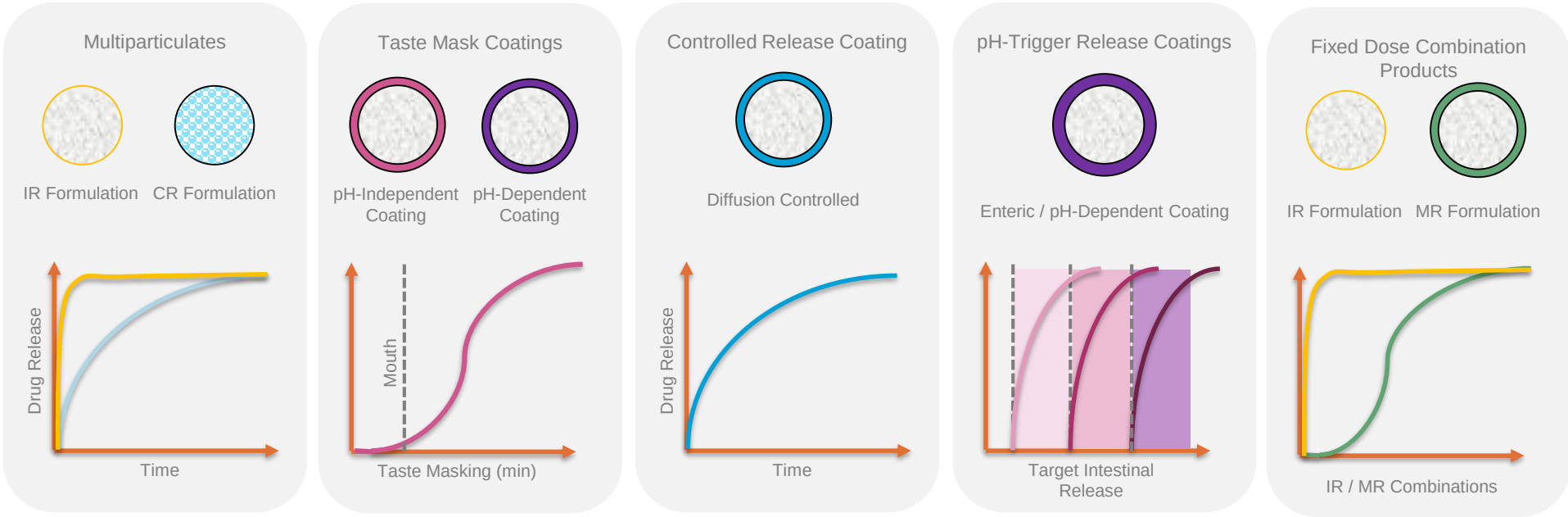
Intended Outcomes and Importance to Quality

- 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



Note: Image Adapted from *An Introduction to Multiparticulates*, M. Shaffer, July 2018.

Best Practices for Multiparticulate Success

Substrate (Core)

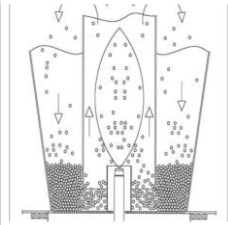
- Particle Morphology
  - Size
  - Friability
  - Sphericity
- SA/FT Ratio (MDD)
- Drug Layering
- API Morphology
- Binder Selection

Equipment

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

Coating

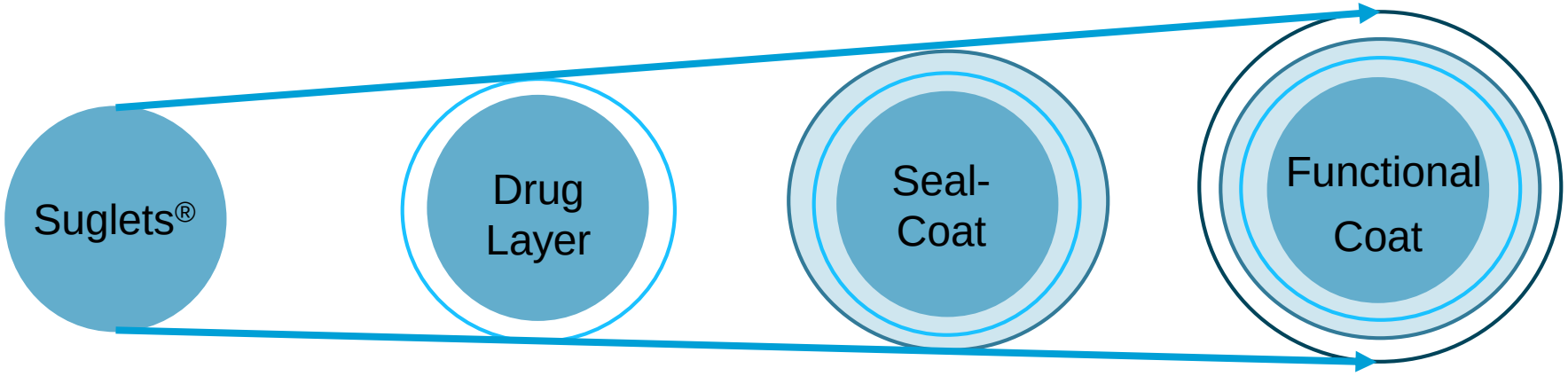
- SA/FT Ratio
- Fluidization (Product Flow)
- Temperature (Tg)
- Agglomeration
- Droplet Size (air volume)
- Spray Nozzle Performance
- Optimization (DoE / Risk Analysis)



Process

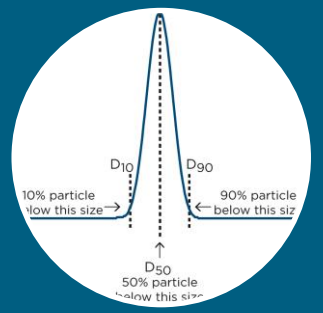
- Static
- Fluidization (Product Flow)
- Agglomeration
- Process Tracking
- Scale-up
- Δ P
- Partition Height (Product Flow)

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

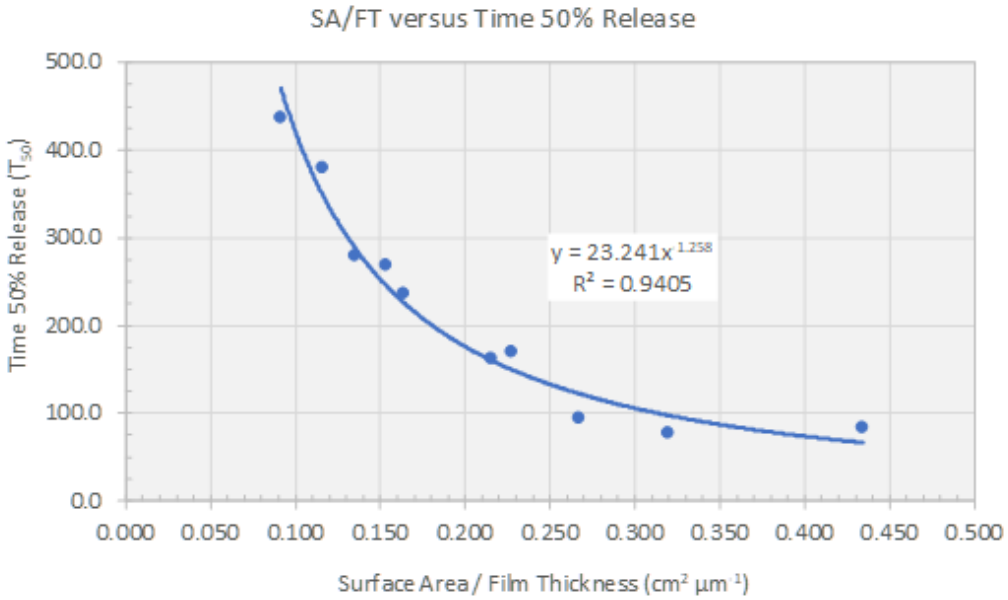
Drug Release Primarily by Diffusion Through the Semipermeable Membrane

- 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)
D = diffusion coefficient
h = thickness of barrier
C = concentration
K = partition coefficient
J = Flux



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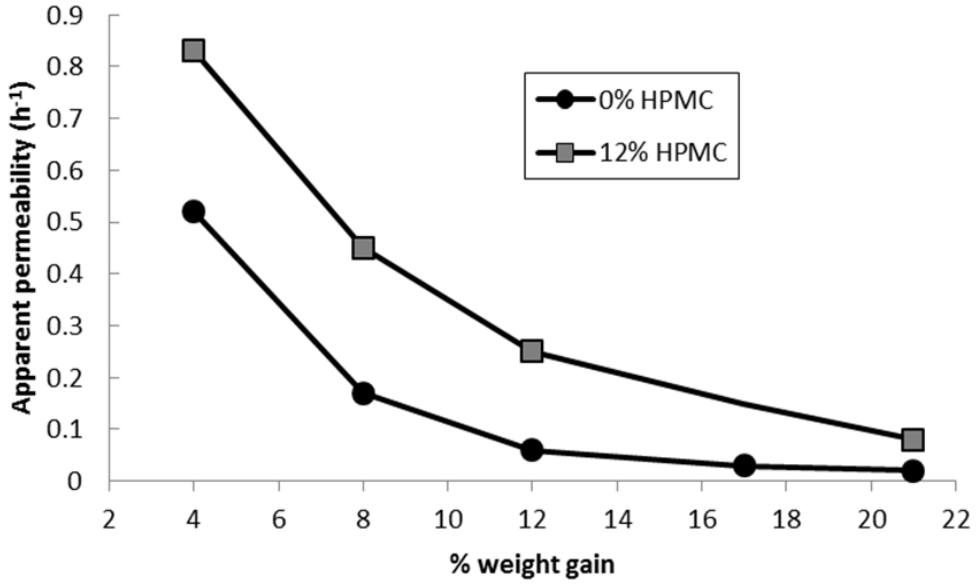
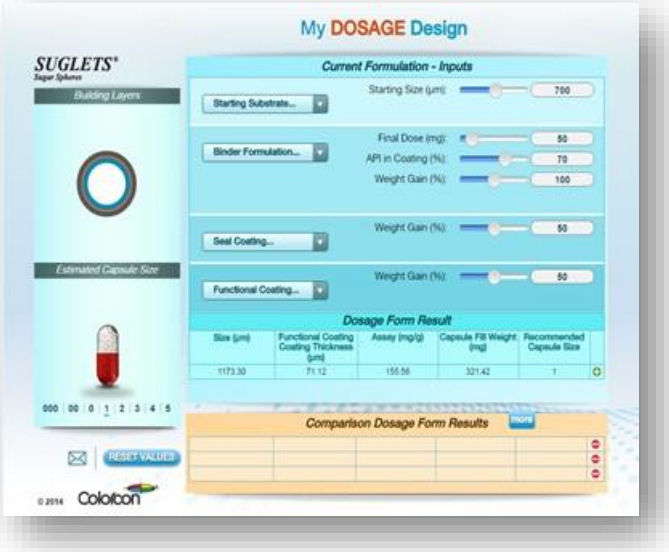


Reference: Lijuan Tang, Joseph B. Schwartz, Stuart C. Porter, Roger L. Schnaare & Rodney J. Wigent (2000) Drug Release from Film-Coated Chlorpheniramine Maleate Nonpareil Beads: Effect of Water-Soluble Polymer, Coating Level, and Soluble Core Material, ***Pharmaceutical Development and Technology***, 5:3, 383-390, DOI: 10.1081/PDT-100100554

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™

My DOSAGE Design

SUGLETS®
Sugar Spheres

Building Layers

Estimated Capsule Size

3

000 | 00 | 0 | 1 | 2 | 3 | 4 | 5

RESET VALUES

Current Formulation - Inputs

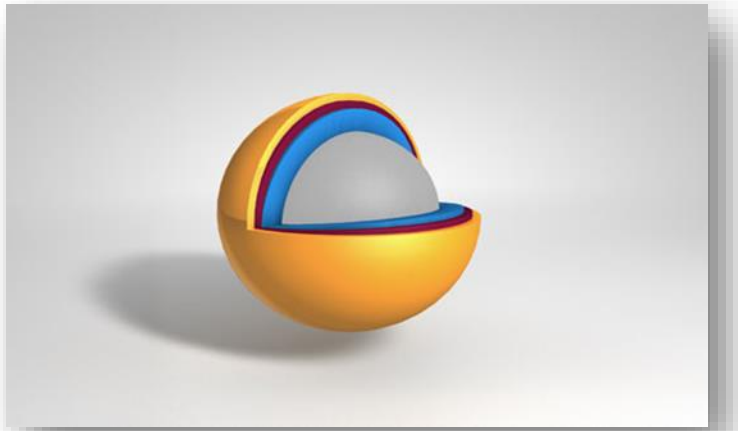
Suglets® 25/30	Starting Size (µm):	674
Opadry® 03A	Final Dose (mg):	12
	API in Coating (%):	53
	Weight Gain %:	17
Opadry® 03A	Weight Gain %:	5
Surelease®	Weight Gain (%):	12

Dosage Form Result

SIZE	FUNCTIONAL COATING THICKNESS (MM)	ASSAY (%)	CAPSULE FILL WEIGHT (MG)	RECOMMENDED CAPSULE SIZE
784.63	20.03	69.85	171.80	3

Comparison Dosage Form Results more

771.73	13.59	69.85	171.80	3
778.23	16.84	69.85	171.80	3
784.63	20.03	69.85	171.80	3



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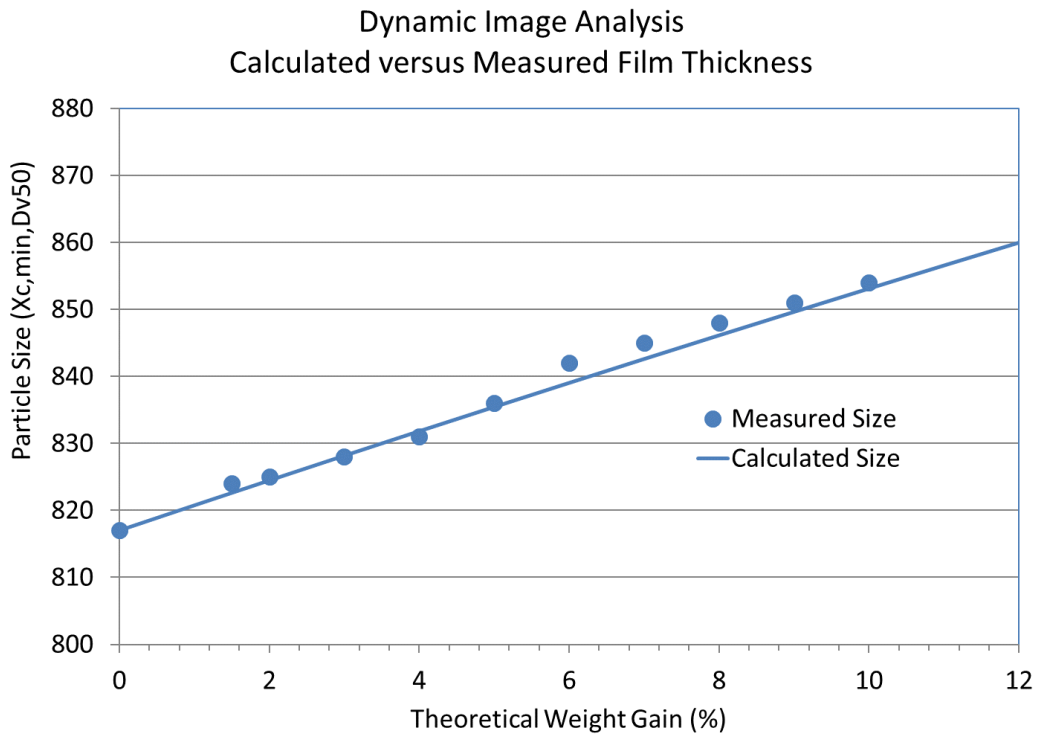
Observed Consistent Process Control and Film Thickness Growth Throughout Coating



- 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$_2$ Particle Analyser

Chris O'Callaghan

Innopharma Technology & the Eyecon$_2$ Particle Analyser

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

- Section Overview
- About Innopharma & our products
- The importance of PAT
- The Eyecon$_2$
  - 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

eyecon₂

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

multieye₂

Multi-point NIR Spectrometer

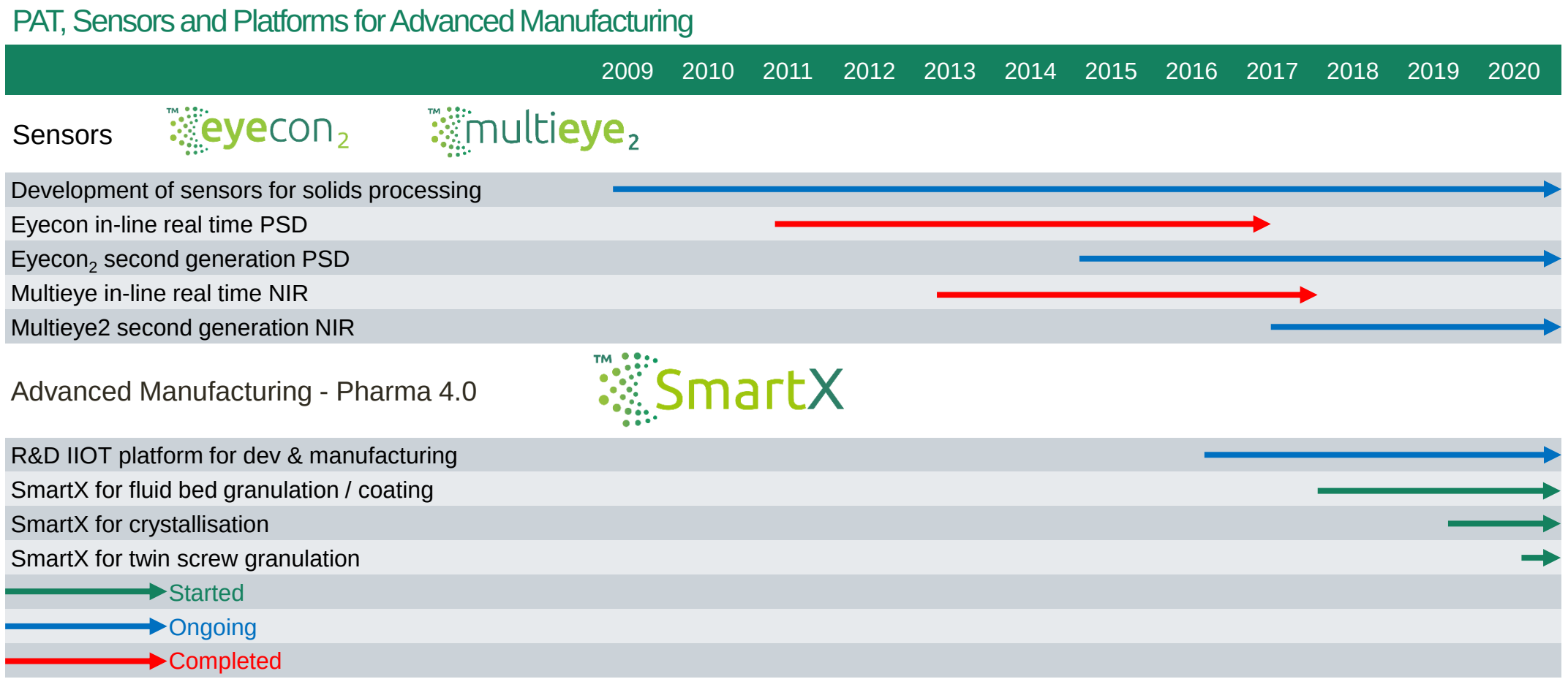
- Near infrared spectrophotometer for measuring changes in process in real-time, in-line
- Highly effective in monitoring moisture content from 0 to 27 ± 0.8%.
- Analyse component concentrations and material density
- User Friendly chemometrics package included – Quanta Model Developer™

SmartX

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

Journey of PAT, Sensors & Advanced Manufacturing Platforms

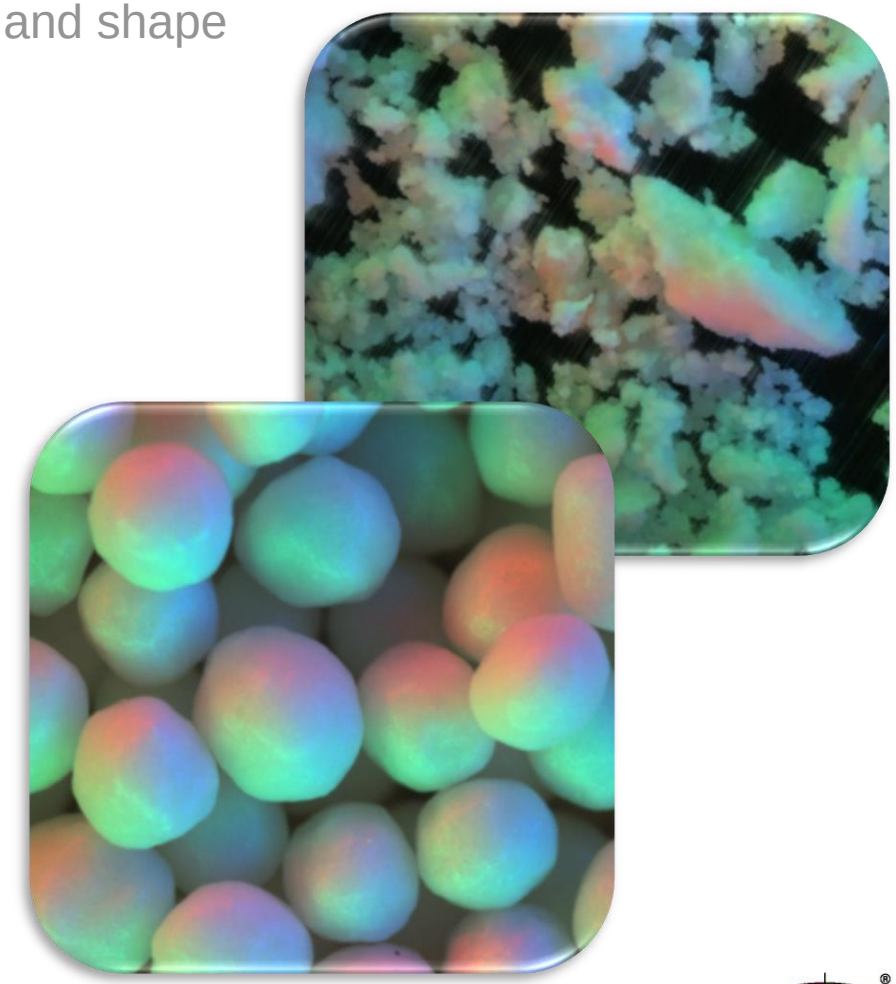


The Importance of PAT

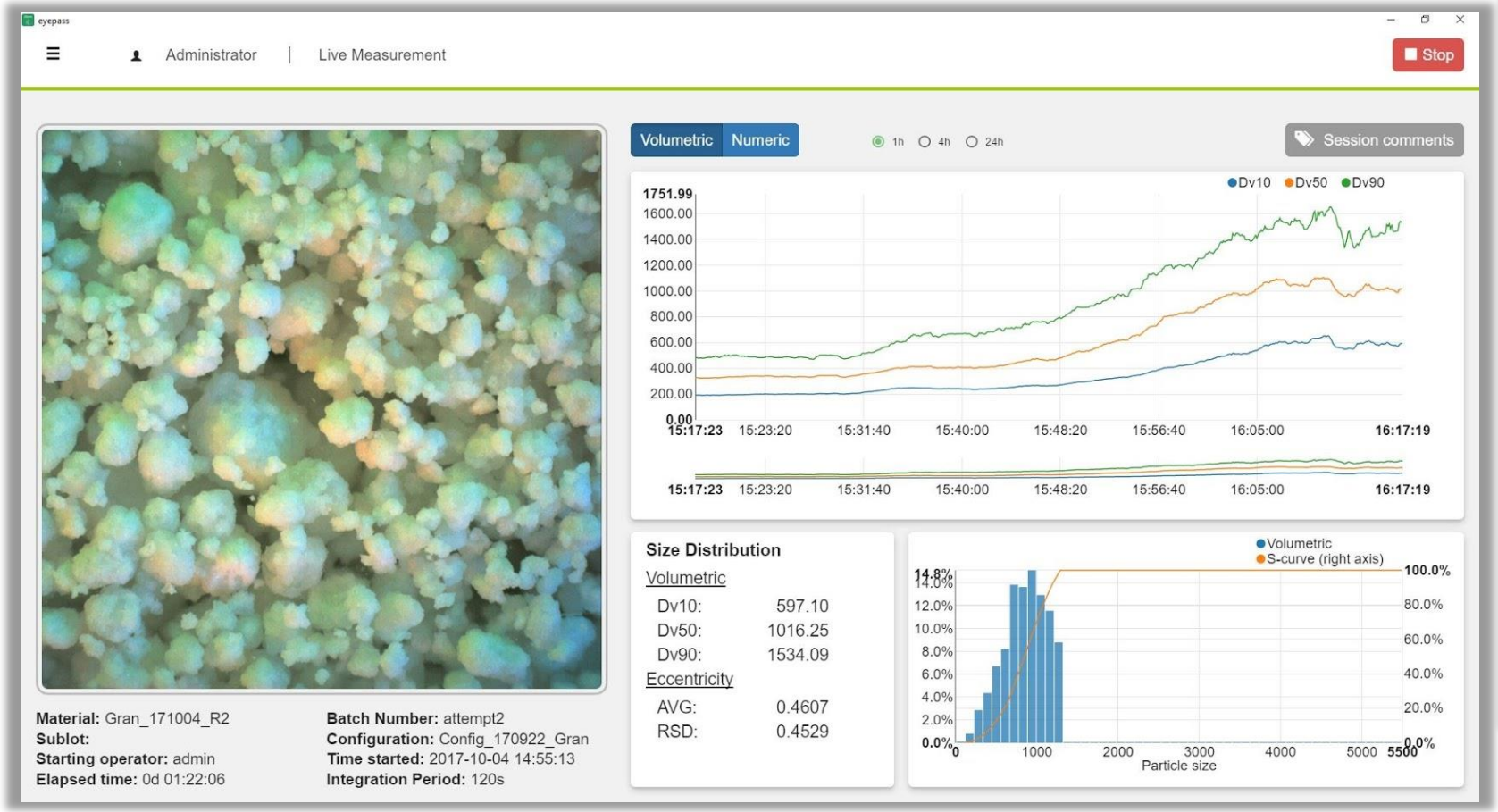
- Improving productivity and product quality is one of the biggest challenges Pharmaceutical companies are facing
- PAT tools are used to enable better understanding of the processes by providing valuable data from the process in real-time
- Better process understanding leads to more robust reliable 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

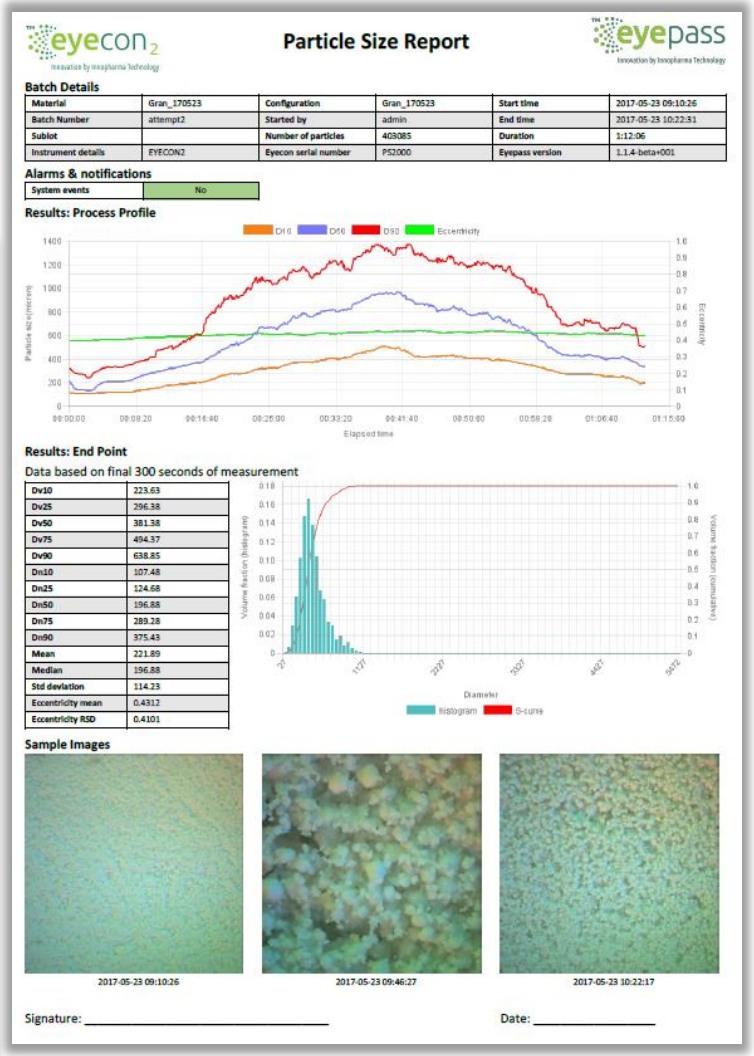
Particle Size Analyser: Eyecon$_2$

- 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



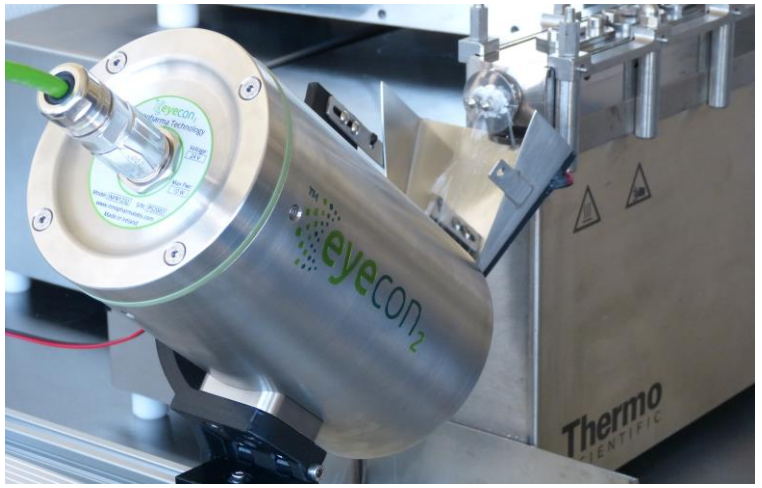
EyePASS – Particle Analysis Software



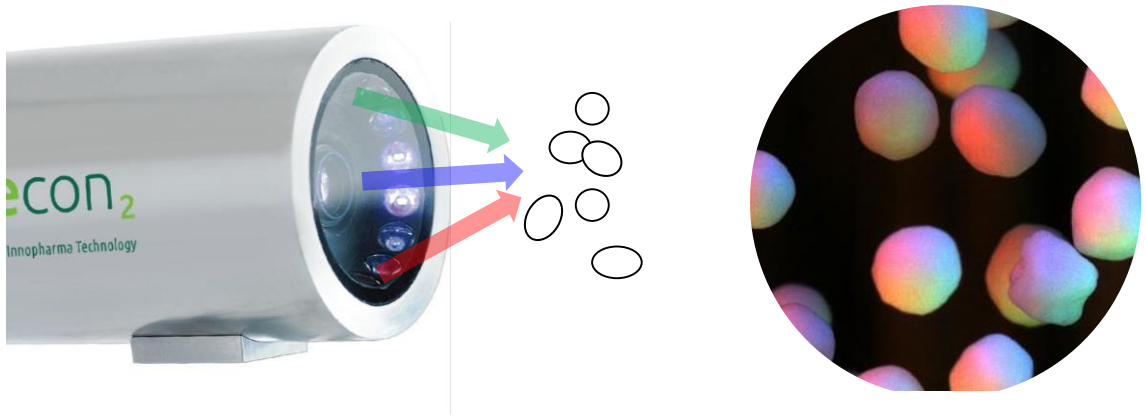


Eyecon$_2$ Technical Specifications

Size Range	50 to 5500 µm
Casing materials	304 Stainless Steel, Glass, Silicon (gaskets)
Imaging Area	11.25 x 11.25 mm
Output	PDF session report. CSV, full PSD from D5-D95, JPEG (images)
Instrument Ratings	GMP Compliant Design EyePASS is both 21 CFR part 11 & GAMP5 Compliant CE Marking ATEX zones 2/22, IP65.
Configurations	In-line and at/off-line
Communication	Ethernet and USB OPC UA, OPC DA 3.0



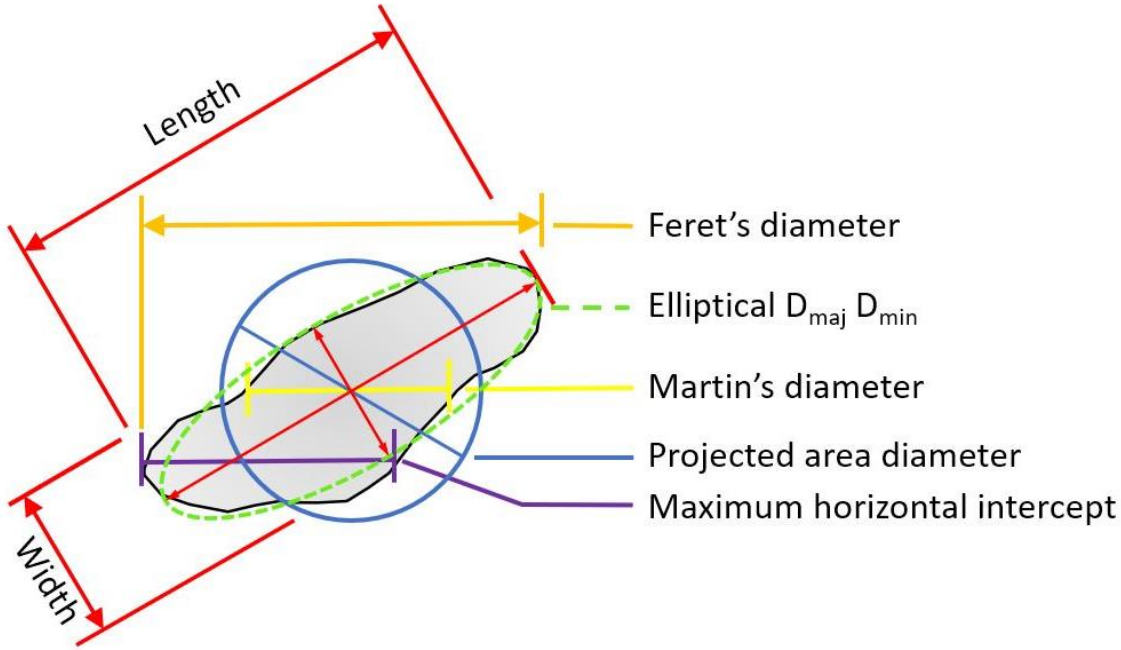
Method of Operation: Image Capture

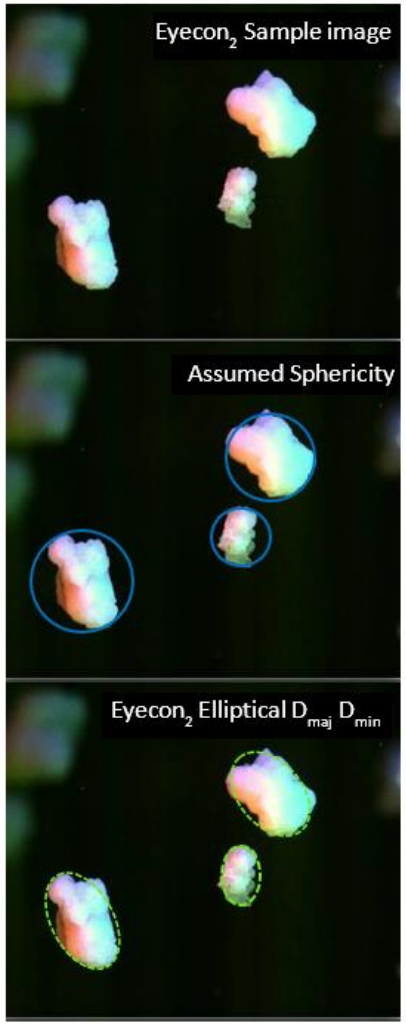


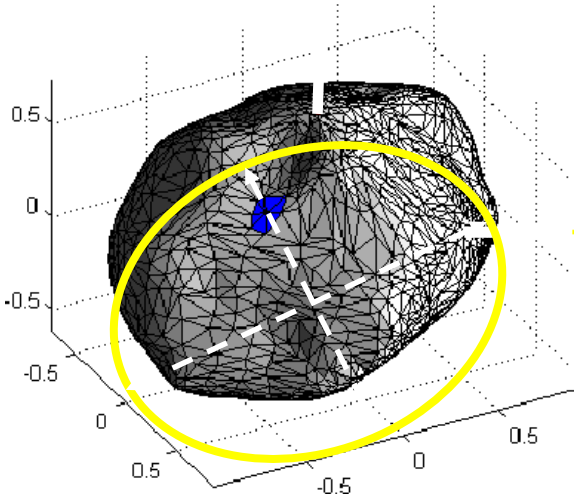
- A flash-imaging technique is used with an extremely short light-pulse to illuminate moving particles for image capture

- Red, Green and Blue LEDs illuminating the sample from different angles for accurate detection of particle boundaries

Method of Operation: Image Analysis



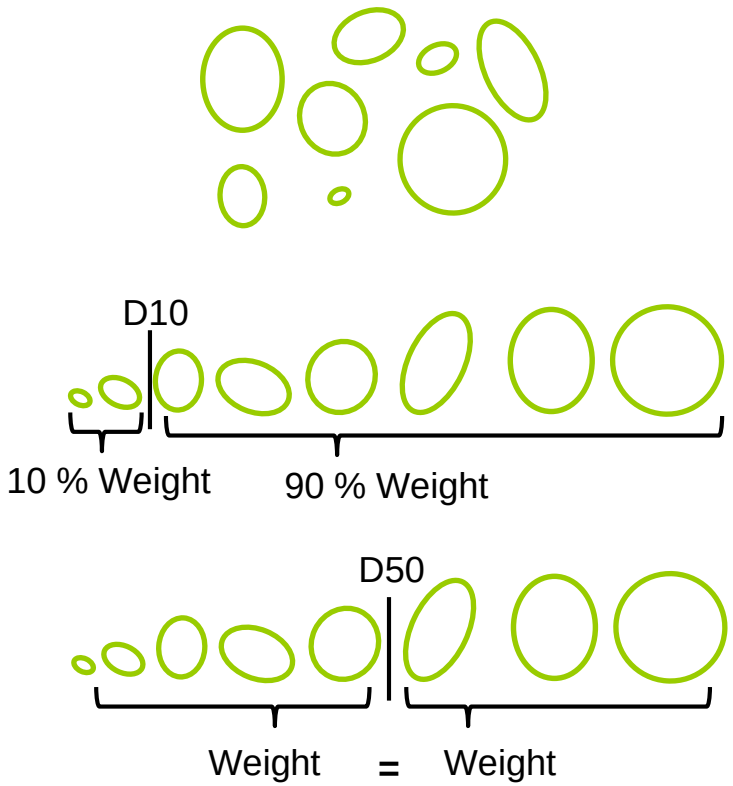




- Each particle initially identified
- Best-fit ellipse calculated
- Major & minor diameters computed
- PSD/D-values determined

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® (Sugar Sphere, NF) 850-1000 µm
Glatt GPCG2 (7'' Wurster)

GPCG 2, Image courtesy of Glatt Air Techniques.

SURELEASE®
ETHYLCELLULOSE DISPERSION TYPE B NF

OPADRY® EC
Ethylcellulose Organic Coating System

Batch Size (kg)	Inlet Air Temp (°C)	Product Temp (°C)	Spray Rate (g min^{-1})	Air Volume (m^3 hr^{-1})	Atm Air (bar)	Orifice Plate	Partition Ht. (mm)
2	70-75	44-46	15-20	100 – 110	1.6	B	30

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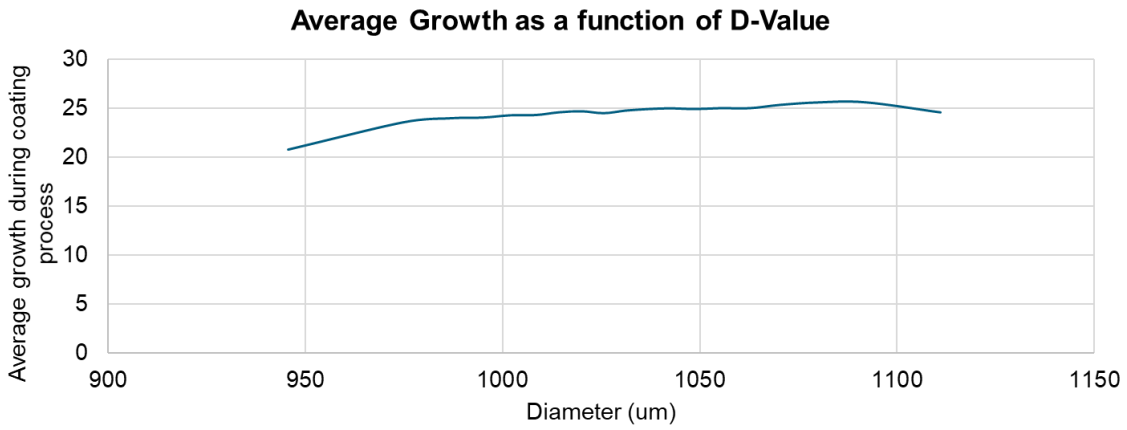
Overview of Study Response Variables

Image courtesy of Colorcon and Innopharma Technology.

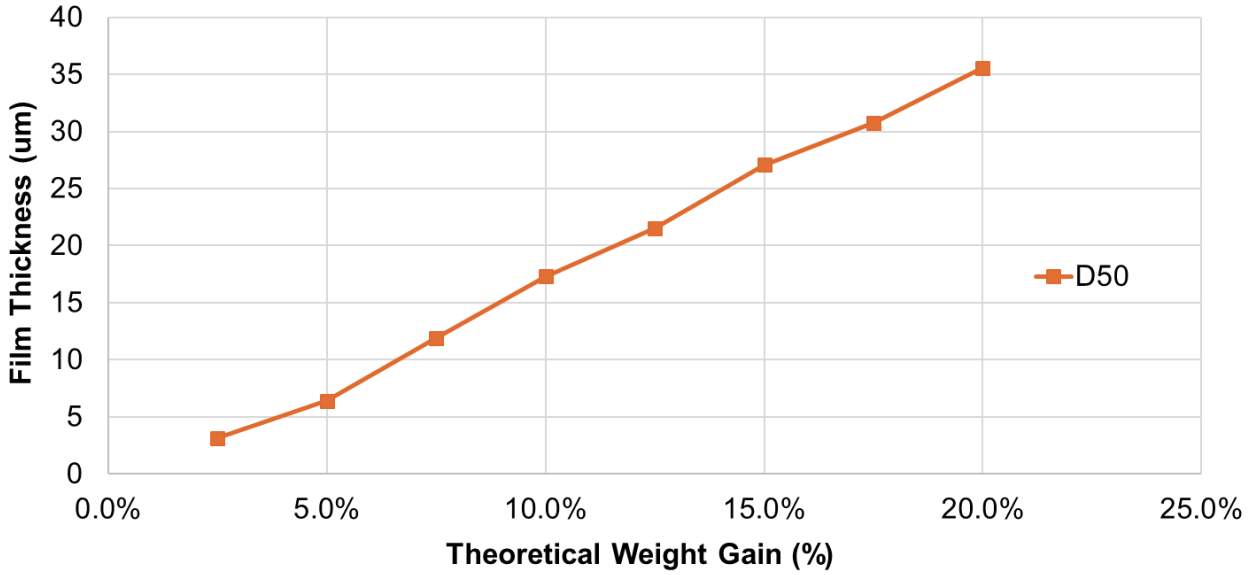
- In-process particle size analysis
  - Eyecon$_2$ (in-line)
  - Camsizer (at-line)
- Particle morphology
- Film thickness
- Assay
- Dissolution testing
- Relationship between dissolution & PSD

Particle Size Distribution and Substrate Flow in a Wurster Column



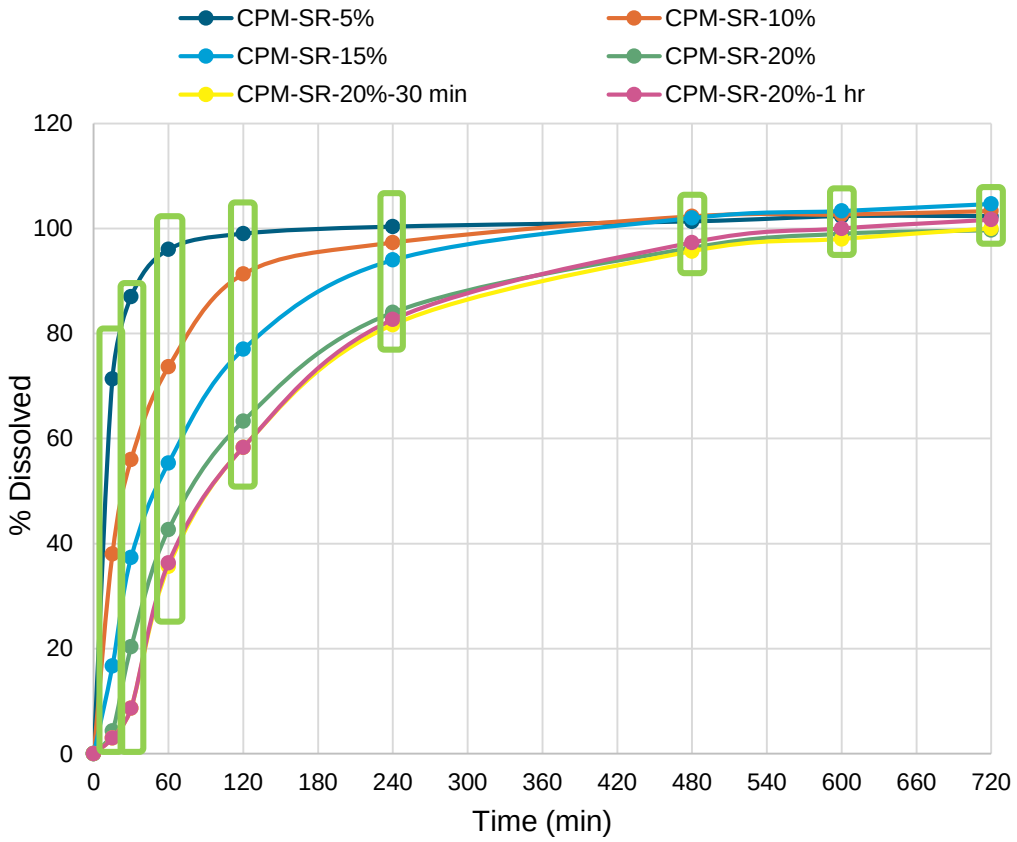
- Bias toward coating larger particles
  - cross-sectional area
  - particle mass
  - fluidization pattern
- Larger particles gain more coating
- Impact of agglomerates
- Starting substrate of narrow particle size distribution (Suglets®) minimizes effect

Consistent Film Thickness Growth Observed Throughout Coating



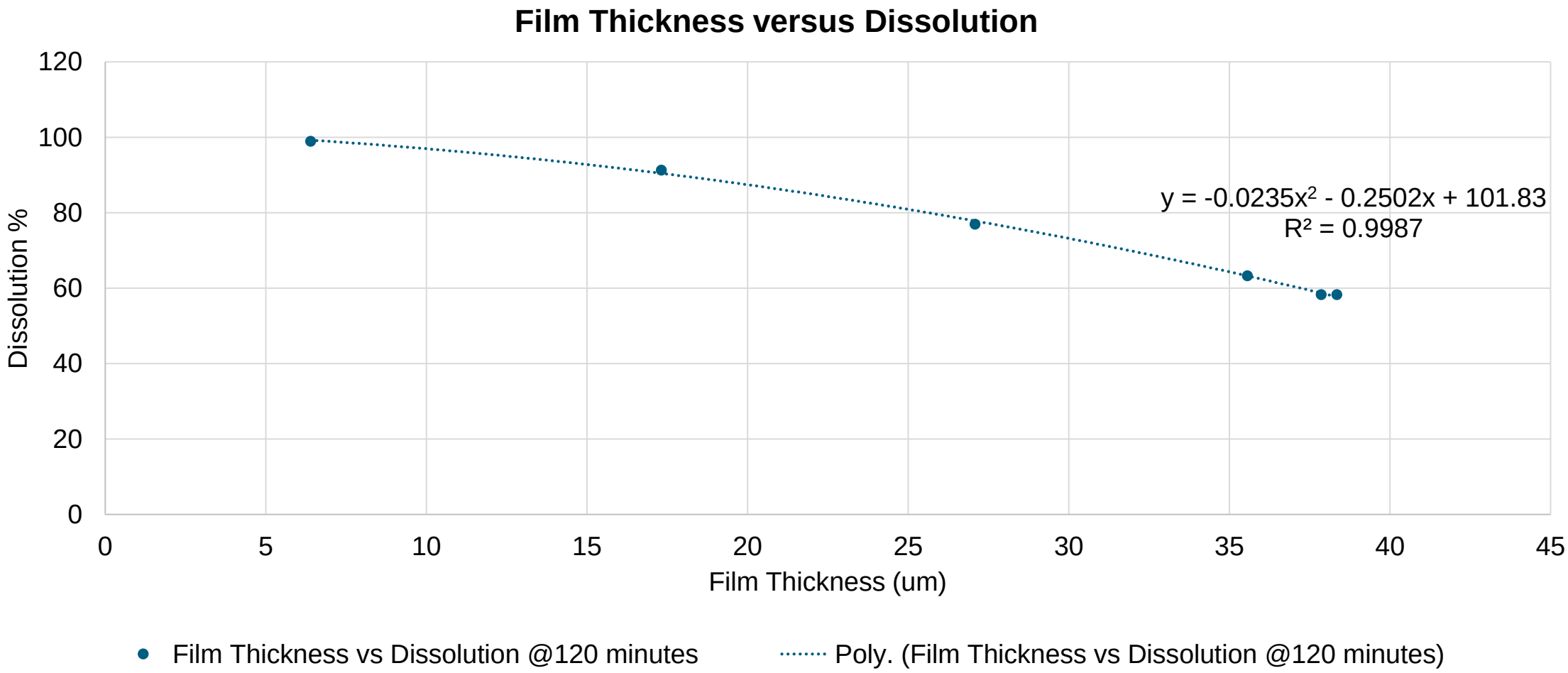
- Film thickness (um) as a factor of predicted weight gain percentage
- Observable, consistent growth between sample points
- Steady process trend and no process deviations.

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



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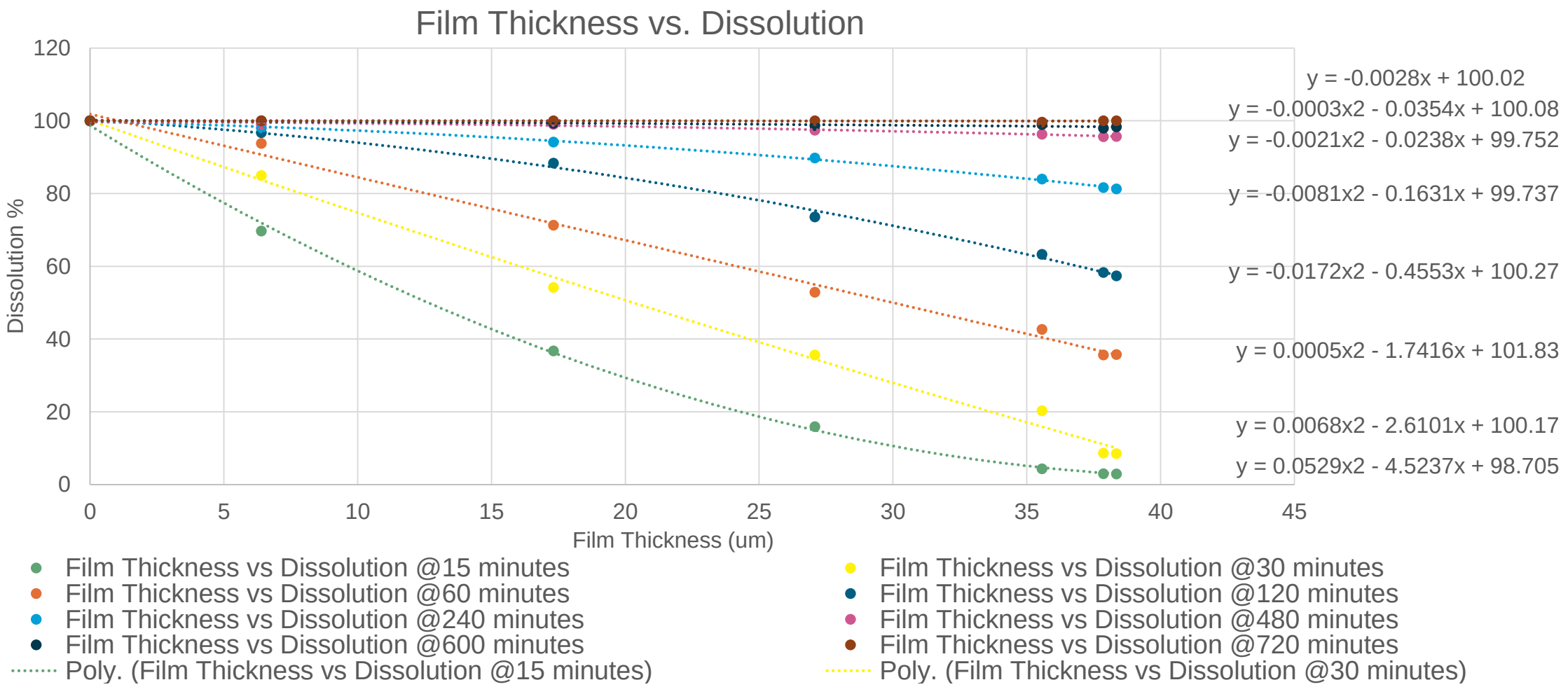
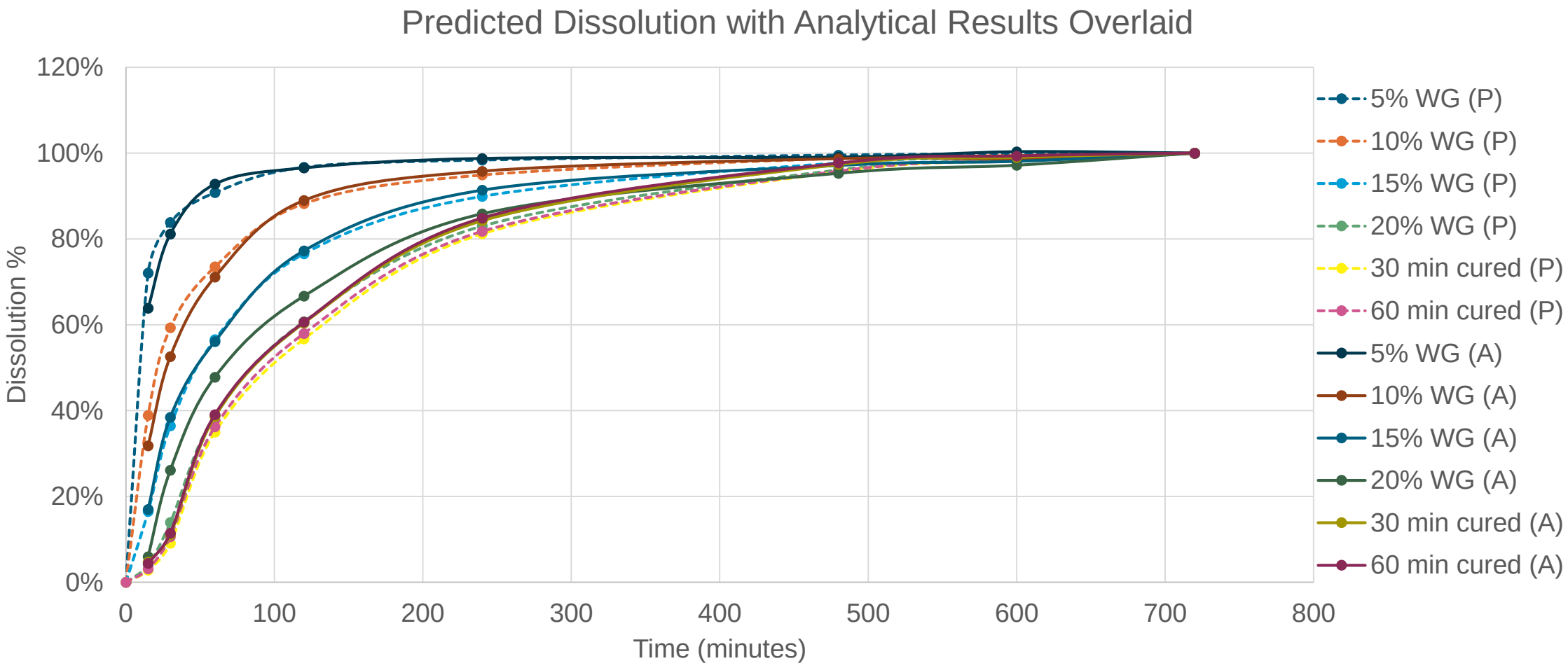
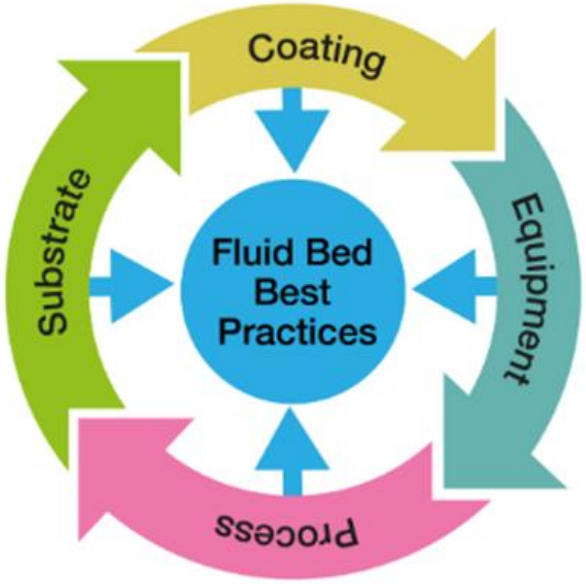


Dissolution: Predicted versus Actual



Best Practices

- ✓ MP Dosage forms offer formulation flexibility and patient friendly features.
- ✓ Robust formulations start with the core.
- ✓ Computational design and PAT (Eyecon$_2$) 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

My Dosage Design Tool Predicts, Process Analytical Technology Confirms Film Thickness of Fully Formulated Aqueous and Organic Ethylcellulose Coating
(reference: Colorcon AAPS Poster, 2017)

Colorcon

A Best Practice Approach Offers Opportunities to Improve Development Outcomes.

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