The Value of Real-time Imaging: Integrating Particle Size Analysis onto Fluid Beds, Twin Screw Granulators and Roller Compactors

Darren McHugh & Chris O’Callaghan – Innopharma Technology
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Overview

- **Innopharma Introduction**
  - **Eyecon$_2$** – Direct Imaging System for In-line Particle Size Measurement
- **Practical Considerations for Implementation**
  - or Interface with Process Equipment
- **Application**
  - TSG, Milling, FBG
  - Deep Dive – Wuster Coating the Real-Time Prediction of Polymer-Coated Multiparticulate Dissolution.
  - **Review**
  - **Q&A**

Innopharma Company Background

- Founded in 2009
- Three divisions:
  - Education & Upskilling
  - Technology to Enable Advanced Manufacturing/Process Analytical Technology
  - Technical Services
- Currently ~60 employees experienced in STEM, Pharma development and manufacturing operations, IT & Software Development

Innopharma Technology - Our Products

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™ 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

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PAT, Sensors and Platforms for Advanced Manufacturing

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020

Sensors — eyecon₂ multieye₂

- Development of sensors for solids processing
- Eyecon in-line real time PSD
- Eyecon$_2$ second generation PSD
- Multieye in-line real time NIR
- Multieye2 second generation NIR

Advanced Manufacturing - Pharma 4.0 — SmartX

- R&D IIOT platform for dev & manufacturing
- SmartX for fluid bed granulation / coating
- SmartX for crystallisation
- SmartX for twin screw granulation

Started

Ongoing

Completed

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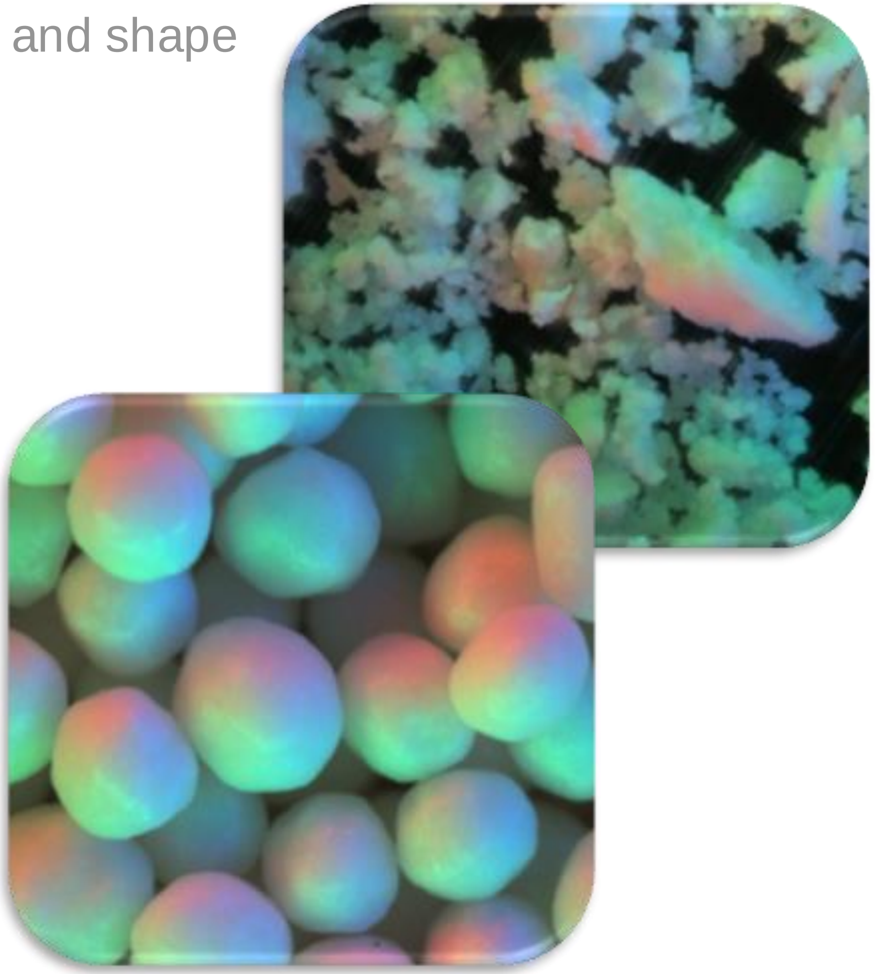
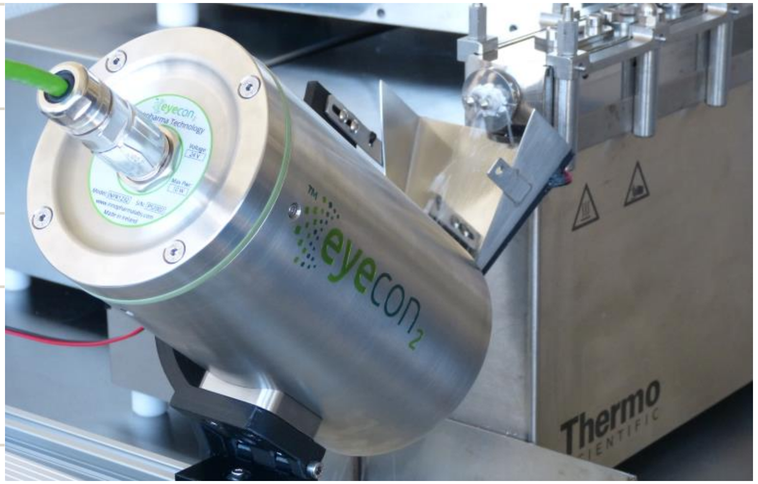
Particle Size Analyser: Eyecon$_2$

- Real-Time particle Size Distribution and shape
- Use in:
  - Research & development (QbD/DoE/CPP/CQA)
  - Scale up
  - Tech transfer
  - Manufacturing
    - Batch
    - Continuous
- Use on:
  - Fluidised Bed Coating, Granulation, Drying
  - Twin Screw Granulation
  - Roller Compaction/Milling
  - Extrusion, Spheronisation



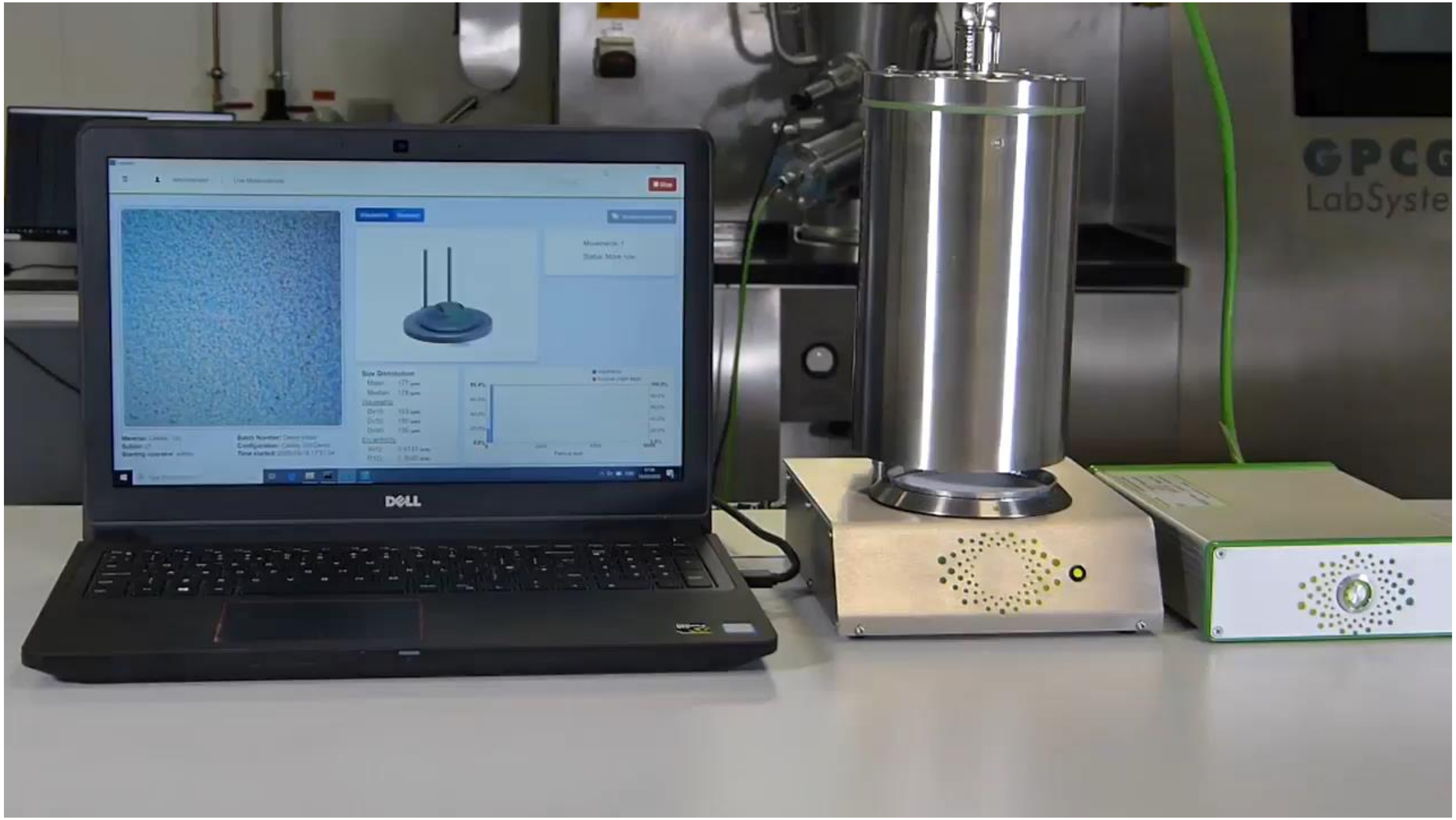
Eyecon$_2$ Technical Specifications

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/offline
Communication	Ethernet and USB OPC UA, OPC DA 3.0



Device Overview Video

Benchtop



Inline

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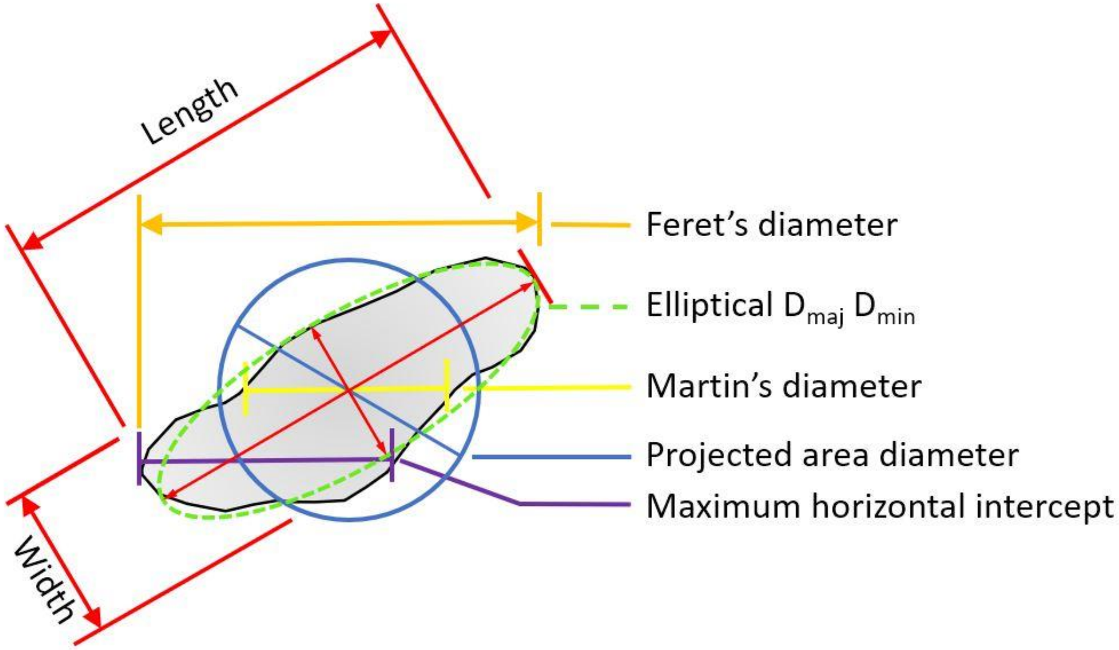
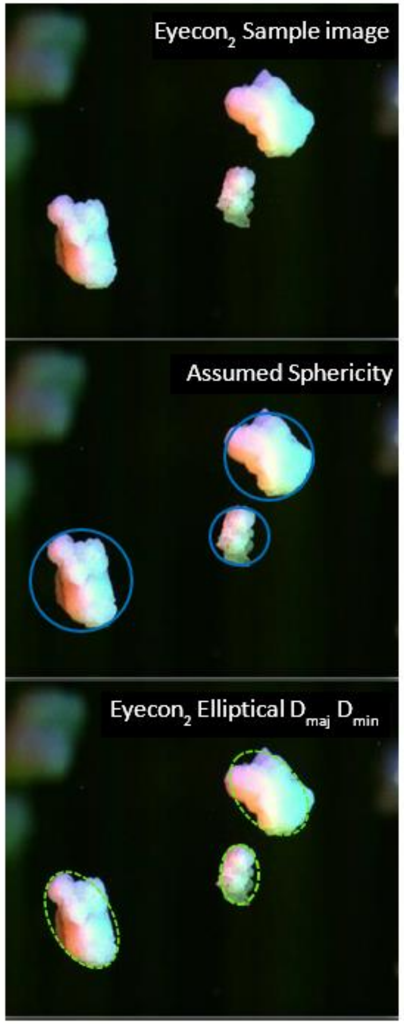
Method of Operation: Image Capture

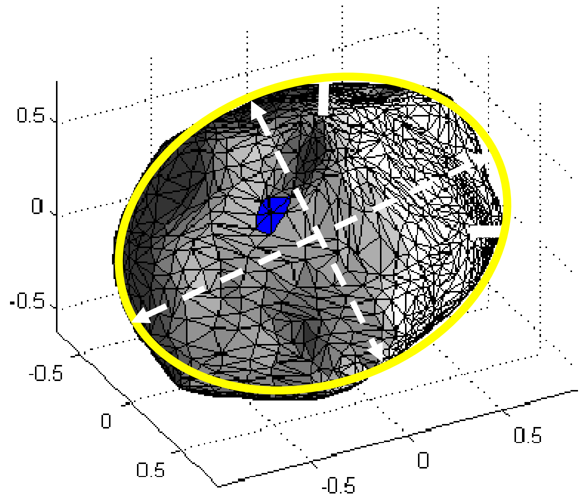
- A flash-imaging technique is used with an extremely short light-pulse to illuminate moving particles for image capture

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

Method of Operation: Image Analysis



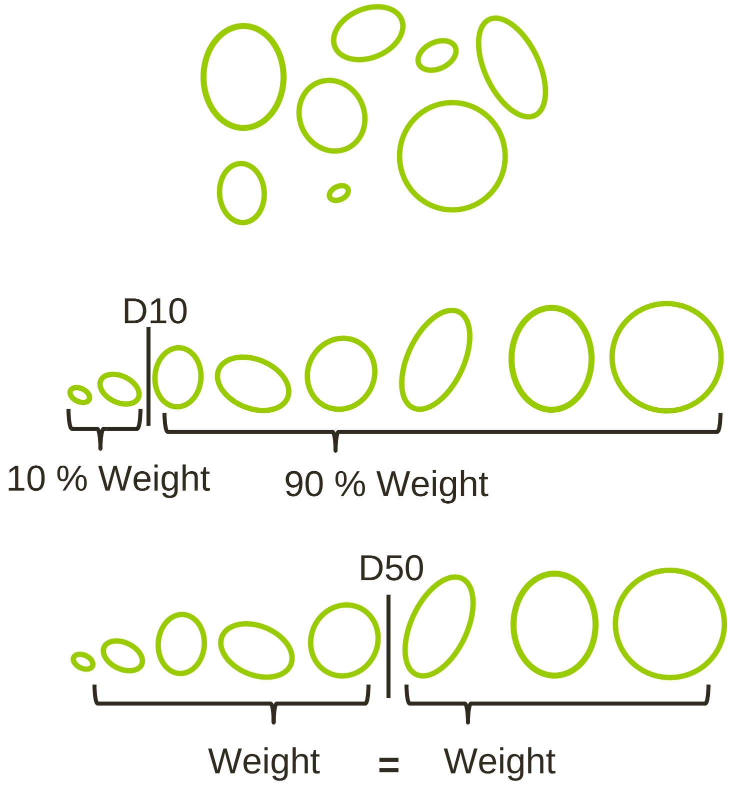




- Each particle initially identified
- Best-fit ellipse calculated
- Major & minor diameters computed
- PSD/D-values determined

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



Eyecon$_2$ Data Output

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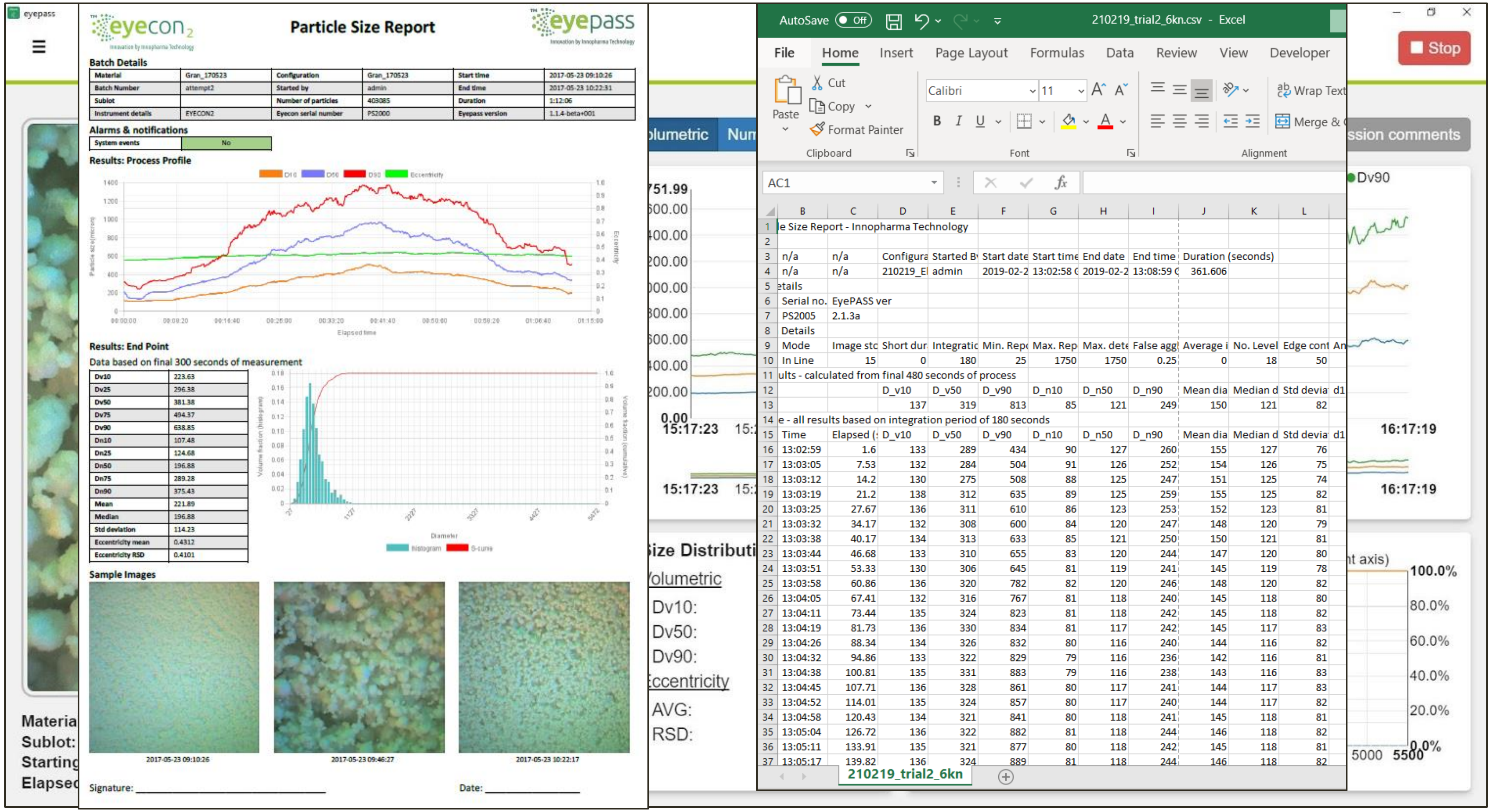
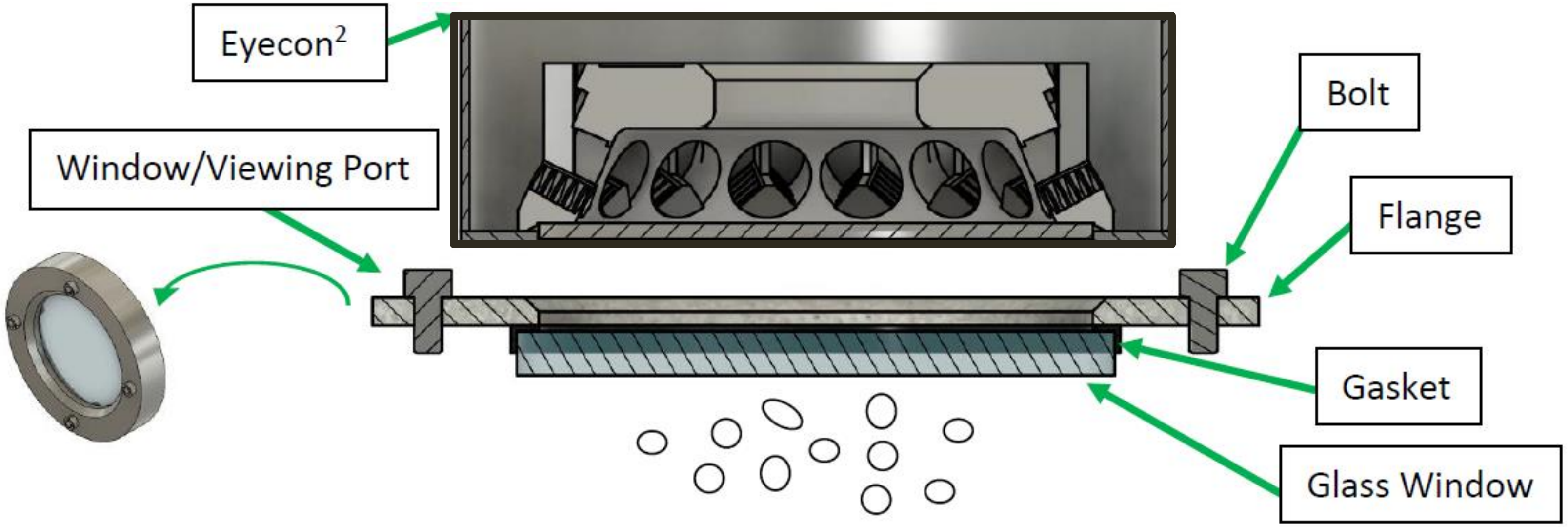


Geometry of Illumination



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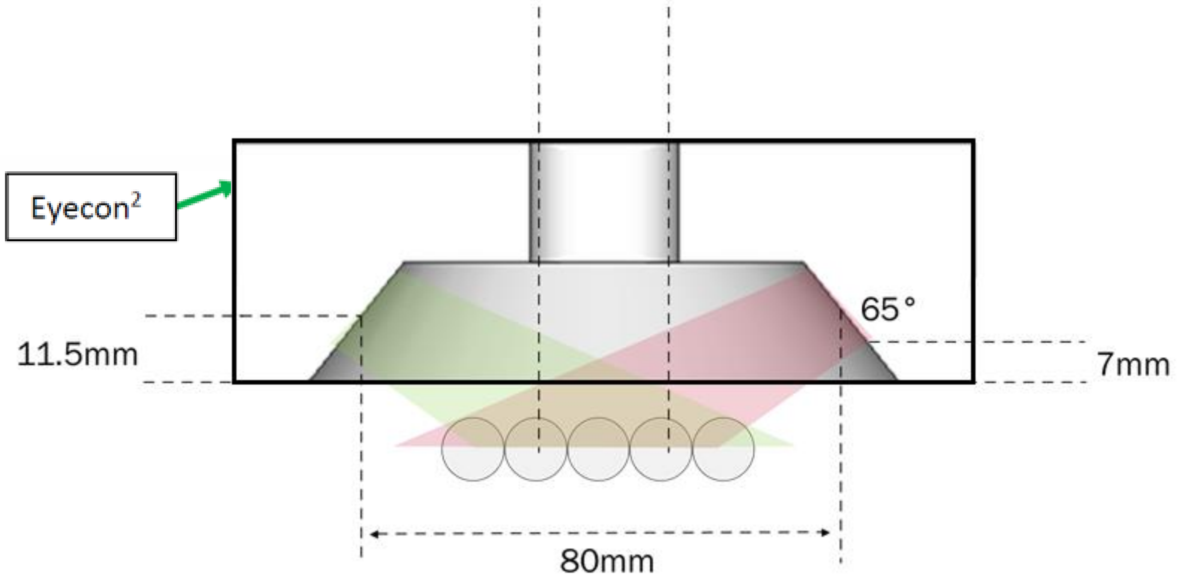
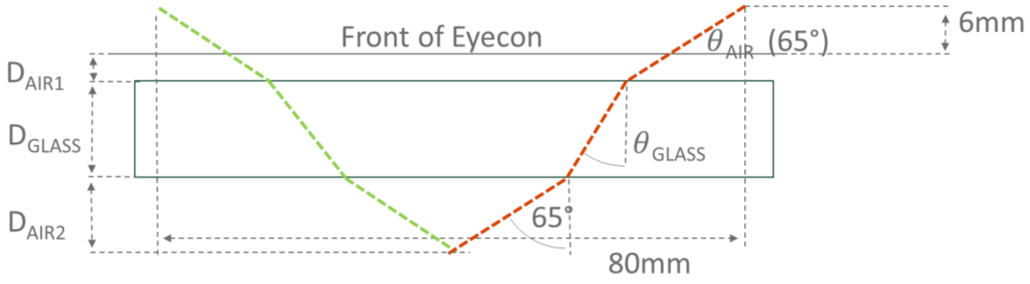


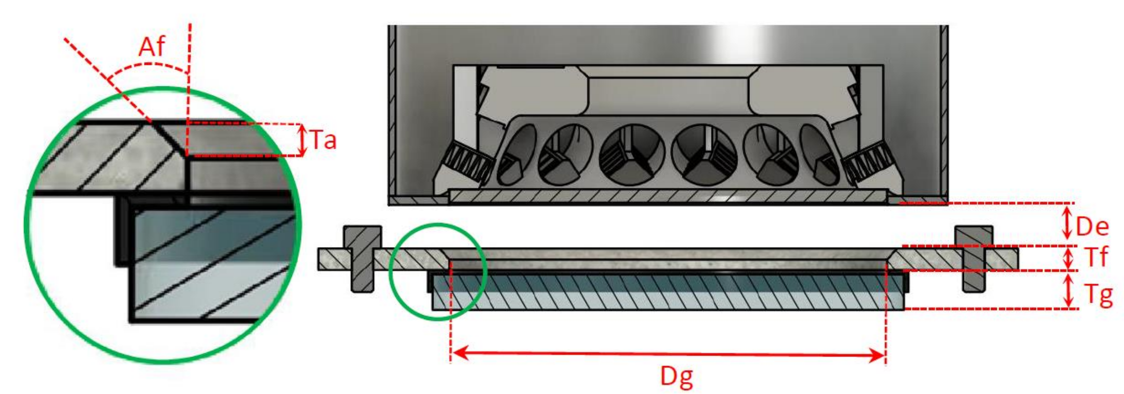


Snell's Law: $\frac{n_{air}}{n_{glass}} = \frac{\sin \theta_{glass}}{\sin \theta_{air}}$

$$\theta_{glass} = \sin^{-1}\left(\frac{n_{air}.\sin \theta_{air}}{n_{glass}}\right) \approx 38°$$

Typical values: $n_{air} = 1$ $n_{glass} = 1.47$

Illumination Calculator



Viewing Port Parameters (altering these values to achieve measurement requires equipment modification)

Tg	12	glass thickness
Dg	52	glass aperture diameter (minimum diameter if non-circular)
Tf	4	overall flange thickness (0 if no protruding flange)
Af	0	flange angle (0 if no chamfer)
Ta	0	thickness of flange chamfer (0 if no chamfer)
Glass type, n_r	Boriscillicate, 1.47	type of glass used in viewing port

Eyecon Position

De	1	Eyecon distance: illumination ring to flange

Intermediate Calculations

Measurement dist in air (trigonometric)	9.048668
Measurement dist in air (experimental)	12
Measurement dist in air (max experimental)	18
Outside aperture	52
Light angle in glass	38.06361
Air dist to glass	5
Equivalent air dist in glass	8.814249
Protrusion / shortfall (trigonometric)	-4.76558
Protrusion / shortfall (experimental)	-1.81425
Protrusion / shortfall (max experimental)	4.185751

Results

Incident light angle (must be >25°) — 25.62 degrees

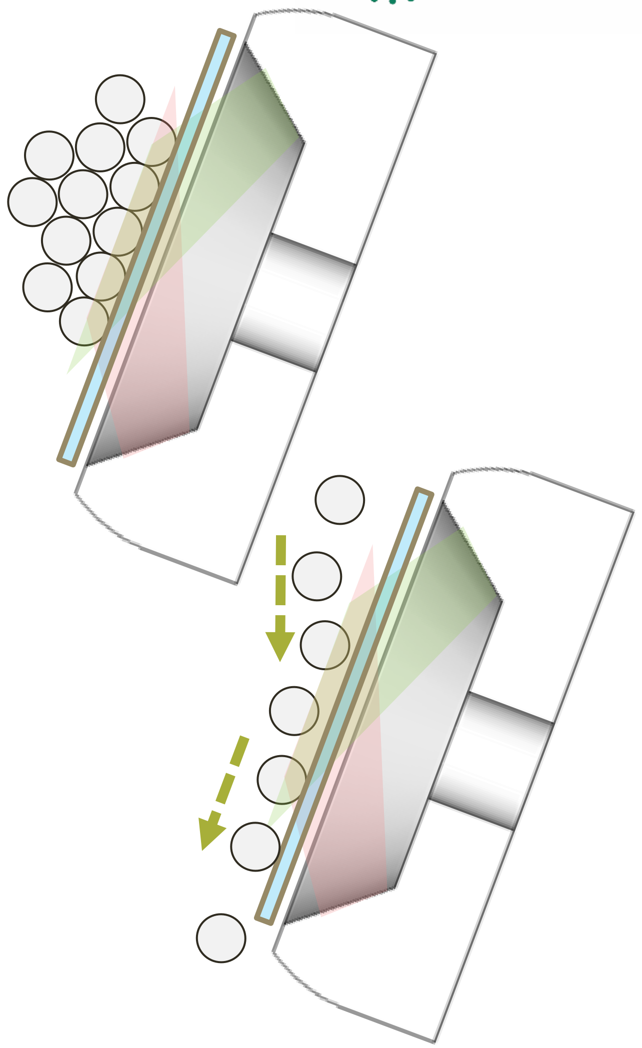
To increase this try the following:
Increase De (Eyecon distance to flange)
Add a chamfer to the flange of depth Ta...
and angle of up to 65 degrees (Af)

Protrusion beyond glass (must be ±2mm) — -1.81 mm

To increase this try the following:
Decrease De (within above constraint)
Increase Dg (aperture diameter) if possible
Use thinner flange (Tf)
Use denser glass in window (n Glass)
Use thinner window (Tg)

Presenting Particles for Imaging: 1

- Particles imaged directly behind surface of window
- Applicable with quasi-static bodies of material e.g. fluid bed, and with flowing materials
- Window helps to ensure particles are optimally presented within the depth of field



Challenges

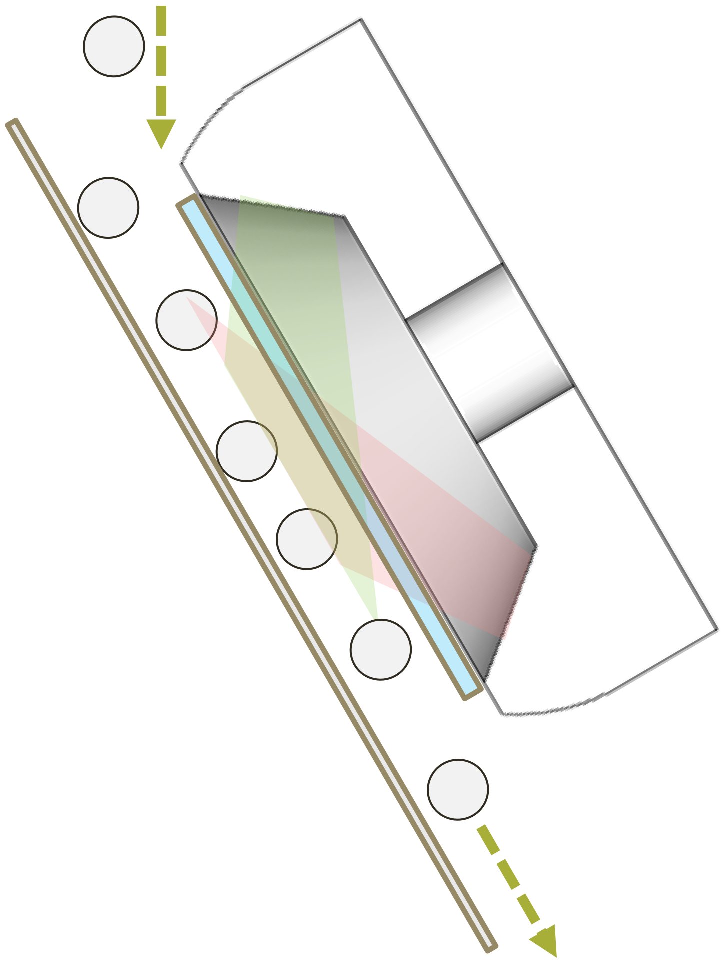
- Wide PSD – smaller particles obscure larger
- Differential particle speeds & bouncing – angle
- Fouling of window
- Agglomeration – sticking or static

Presenting Particles for Imaging: 2

- Particles imaged flowing between window & chute (typically stainless steel)
- Applicable only to flowing material
- Useful with wetter / stickier materials as backing surface can have greater resistance to fouling than window

Challenges

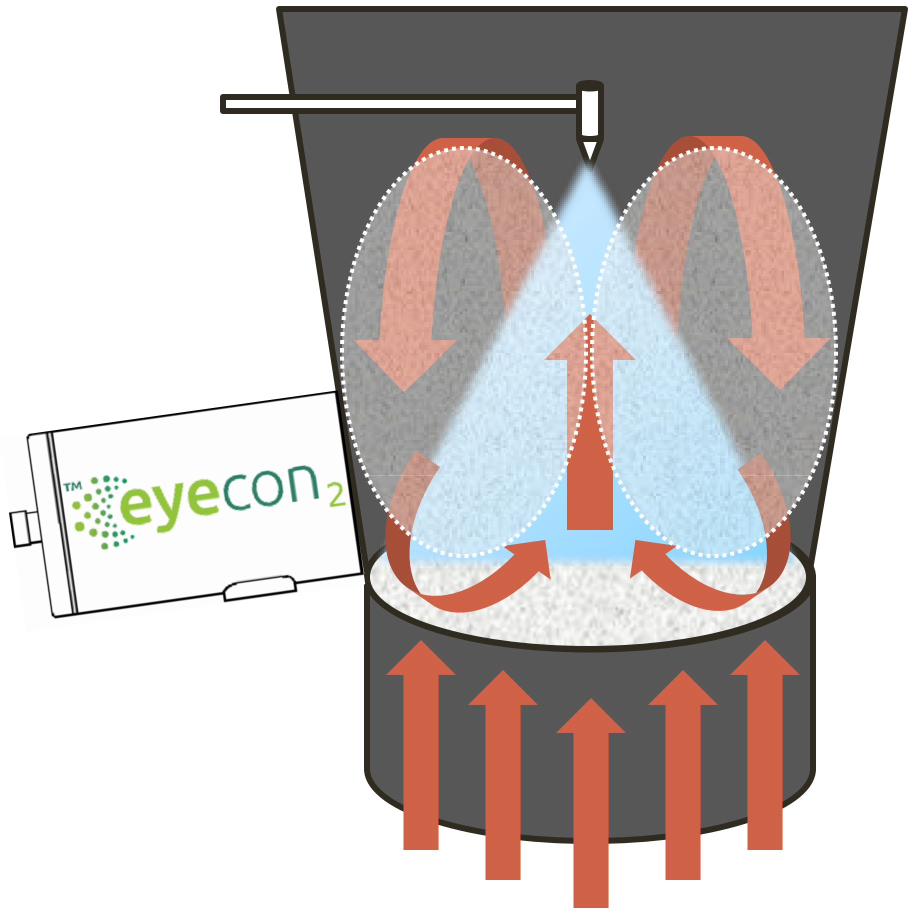
- Constraining flow within degrees of freedom while minimising risk of blocking
- Differential particle speeds & bouncing – angle
- Fouling of window & backing surface – accessibility for clearing fouling & blockages



Equipment Integration Solutions

- What to consider
  - Presentation
  - Representation

  - Maintain consistent presentation of material
    - For FB position below material bed level
    - For TSG image onto backing surface
  - Maximise number of particles captured per image
  - Optimise positioning in focal plane
  - Minimise fouling



Fluid Bed Interfaces

Lab → Pilot → Manufacturing

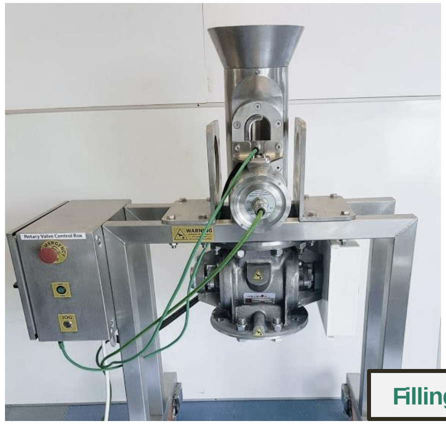
Interface Examples

Develop → Scale Up → Manufacturing

Dev. Scale Conti. Line

Twin-Screw Granulation

Drier Outlet



Filling

Milling

Roller Compaction

Fouling

- Fouling Control
  - Prevent the ingress of the fouling material
  - Low-fouling surfaces (for example, very smooth, implanted with ions, or of low surface energy like Teflon) are an option for some applications.
  - Anti-static
  - Sapphire (Low coefficient of friction)
  - Purge valves
  - The conditioning of the glass and its orientation

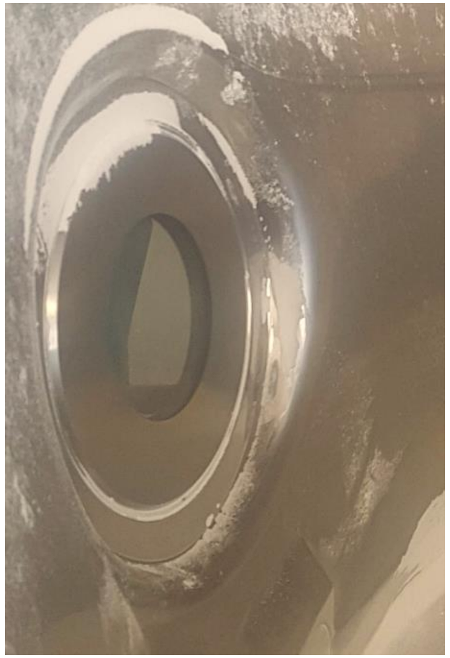
Fouling Control

Issue

Solution

Issue

Solution



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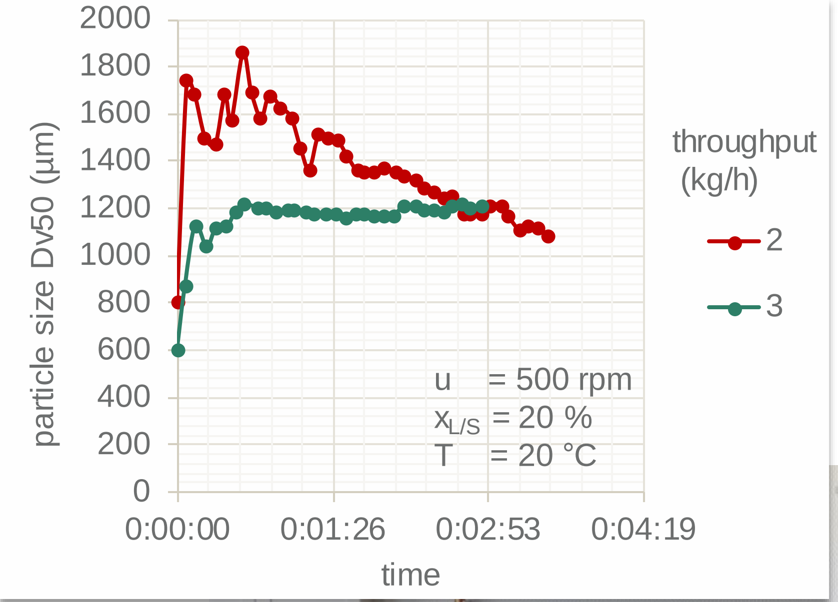
Eyecon$_2$ In-Line Application Examples

Chris O’Callaghan, Head of Engineering
ocallaghanc@innopharmalabs.com

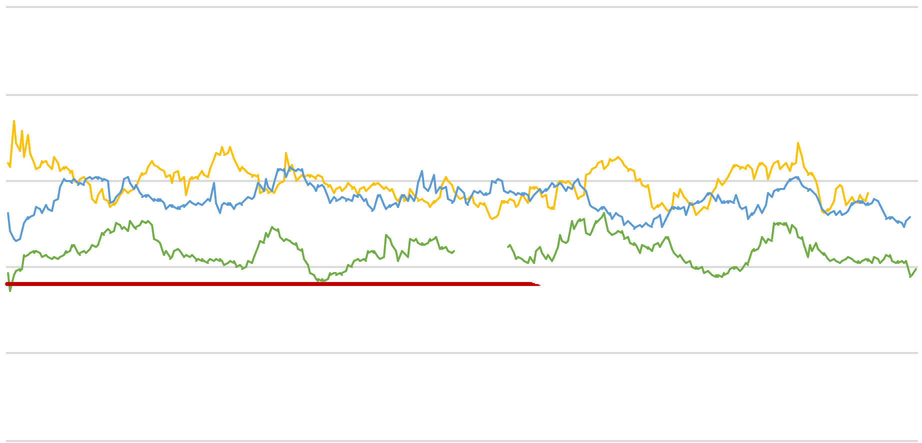
Twin-Screw Wet Granulation

- Continuous granulation – measurement of wet particles directly at outlet
- Polished, heated chute to reduce sticking
- Quick DoEs: 5~7 minutes per experiment
    - No stops between experiments
    - No time required for sampling, drying, offline analysis
- Start-up dynamics and atypical runs rapidly & clearly identifiable



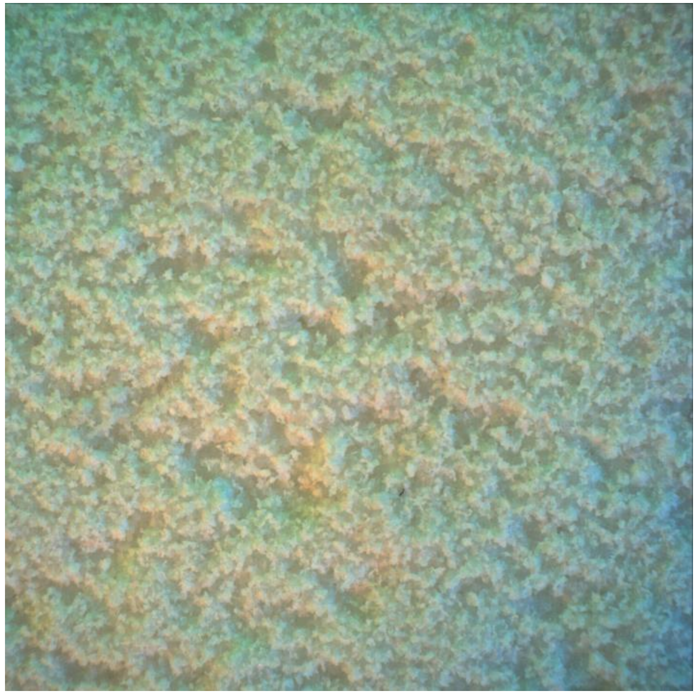
Milling

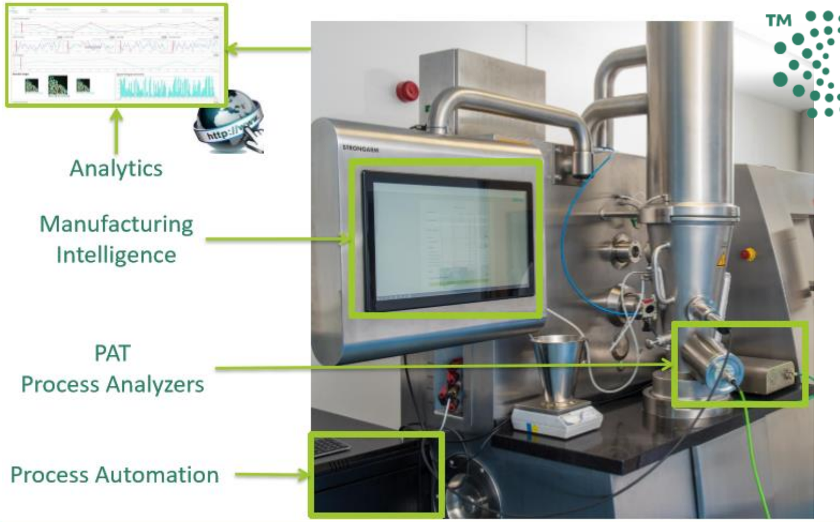
- HME, pelletisation and milling DoE (Hosokawa Alpine 100)
  - Varied mesh size and RPM
  - Aim to determine optimum parameter setpoints to minimise risk of O.O.S. material
- Eyecon integrated directly after Mill outlet
- Measured impact of parameter changes and process fluctuations in real time



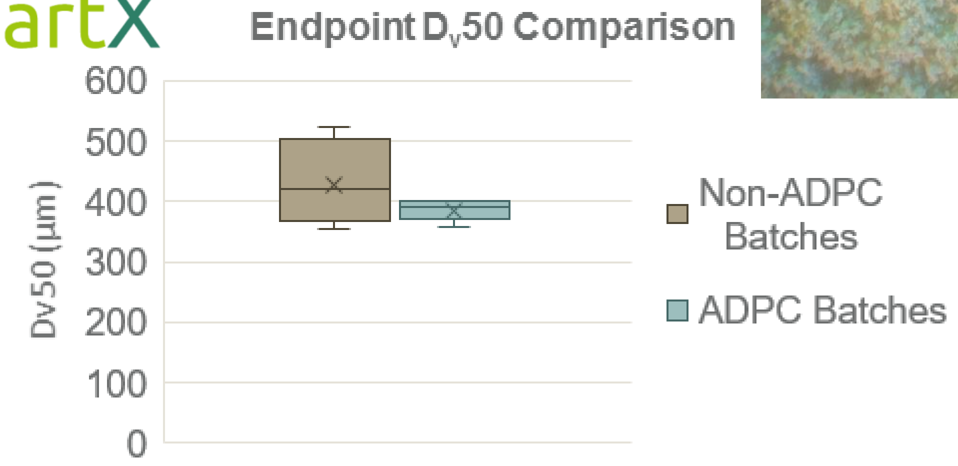
Fluid Bed Granulation

- Automation of a fluid bed wet granulation process using Innopharma's SmartX advanced control platform
- Eyecon$_2$ provided real-time particle measurement used for phase end-point determination – greater control of end-product quality
- Subsequent study in progress on linking inlet velocity to real-time particle size to optimise between fluidising & transport velocities





SmartX



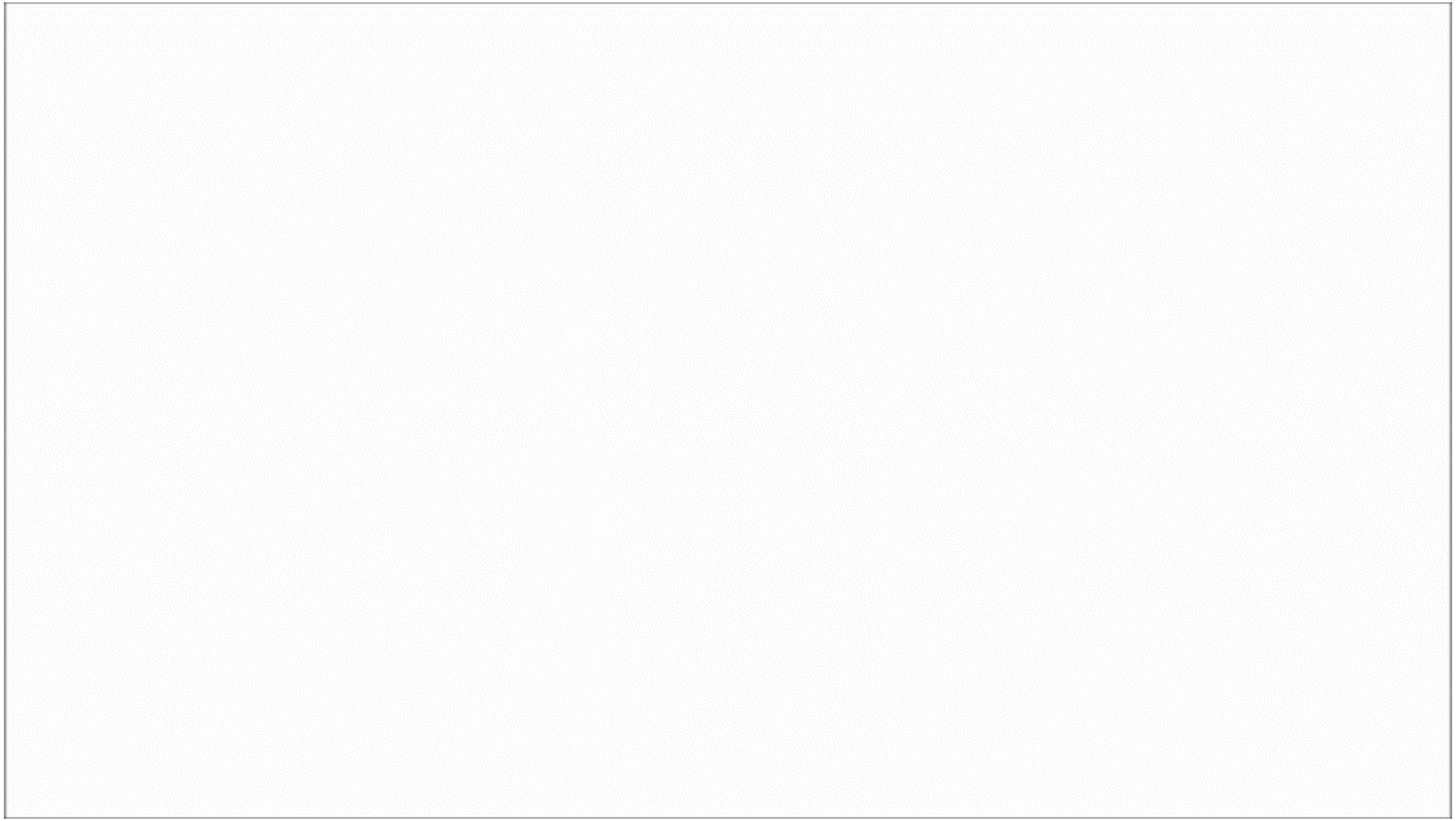
Application Deep Dive: Wurster Coating

- Dissolution Prediction Example published in Pharmaceutical Technology April 2017 issue, Pharma Focus Asia Issue 33, presented at IFPAC 2017

Modified Release Products

- Formulations where the in-vitro release time or location of the drug are engineered to meet therapeutic objectives
  - Release location
  - Patient convenience
- Controlled release / sustained release / delayed release…
- In oral solid dosage forms typically accomplished with functional coating on tablet / minitablets / pellets

The Wurster Coating Process



Control of Coating Processes

- Current methods use little to no inline CQA monitoring
- Typically controlled by spraying a fixed quantity of coating factor

- Coating is an additive process - as coating is applied a particle size increase is expected
- Directly related to weight gain
- Size increase -> film thickness -> predictor of dissolution performance

Presenting Particles for Imaging: 1

- Particles imaged directly behind surface of window
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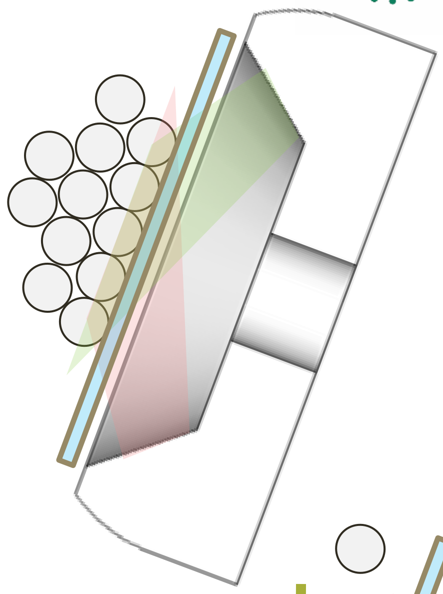
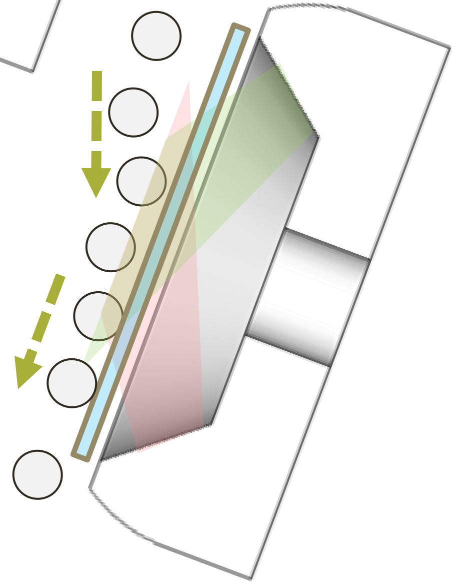
- Window helps to ensure particles are optimally presented within the depth of field

- Challenges
  - Wide PSD – smaller particles obscure larger
  - Differential particle speeds & bouncing – angle
  - Fouling of window
  - Agglomeration – sticking or static





Dissolution Prediction Study: Equipment & Formulation

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- Glatt GPCG2 with 7” expansion chamber extension
- 6” PAT-compatible Wurster product container Fitted with $Eyecon_2$

Material	Amount/batch
CPM layered Sugar Spheres (12 mg) - 18/20 mesh	2000 g
Surelease – aqueous ethylcellulose dispersion	1408 g
Opadry Clear	88 g
DI Water	1437 g

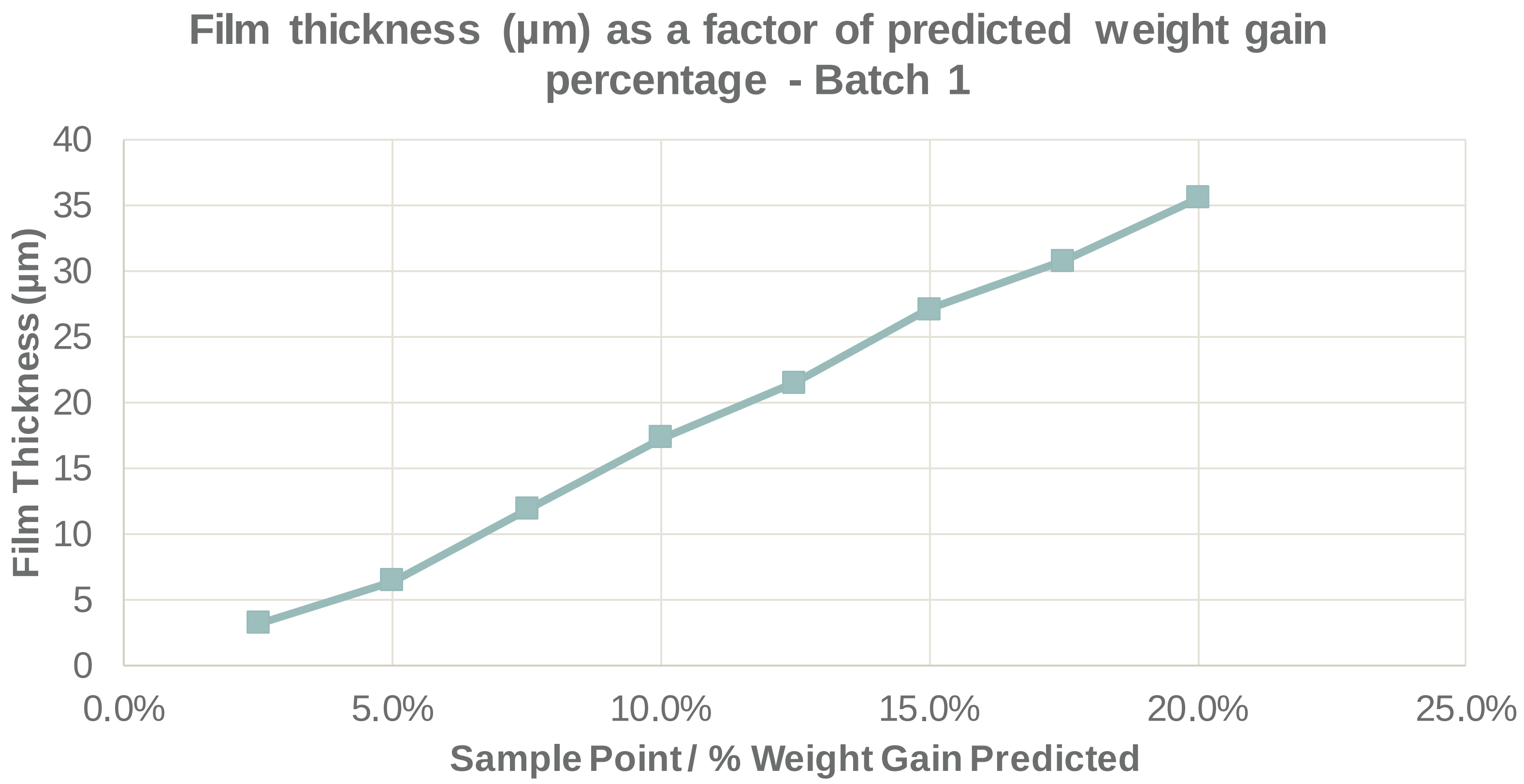
Batch Size (kg)	Inlet Air Temp (°C)	Product Temp (°C)	Spray Rate (g/min)	Air Volume (CMH)	Atm Air (bar)	Orifice Plate	Partition Ht. (mm)
2	70-75	44-46	15-20	100 – 110	1.6	B	30

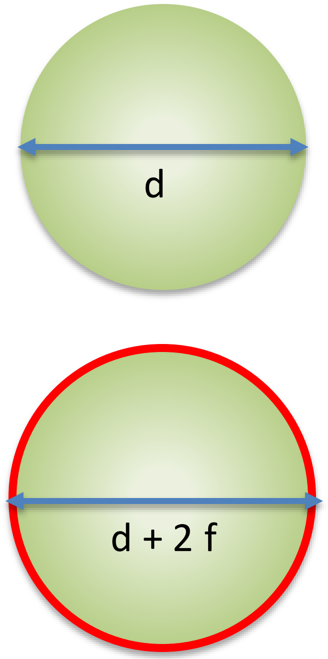
DOE & Sampling Strategy

- Duplicate experiments conducted
  - CPM-SR-1 – develop basic model
  - CPM-SR-2 – validate basic model & improve
- Coated to 20% weight gain
- Samples taken at 2.5% w.g. intervals
- Additional samples after 30 & 60 minutes curing time
- Offline analysis
  - Camsizer
  - Dissolution testing

In-Line PSD during Wurster Coating: Film Thickness

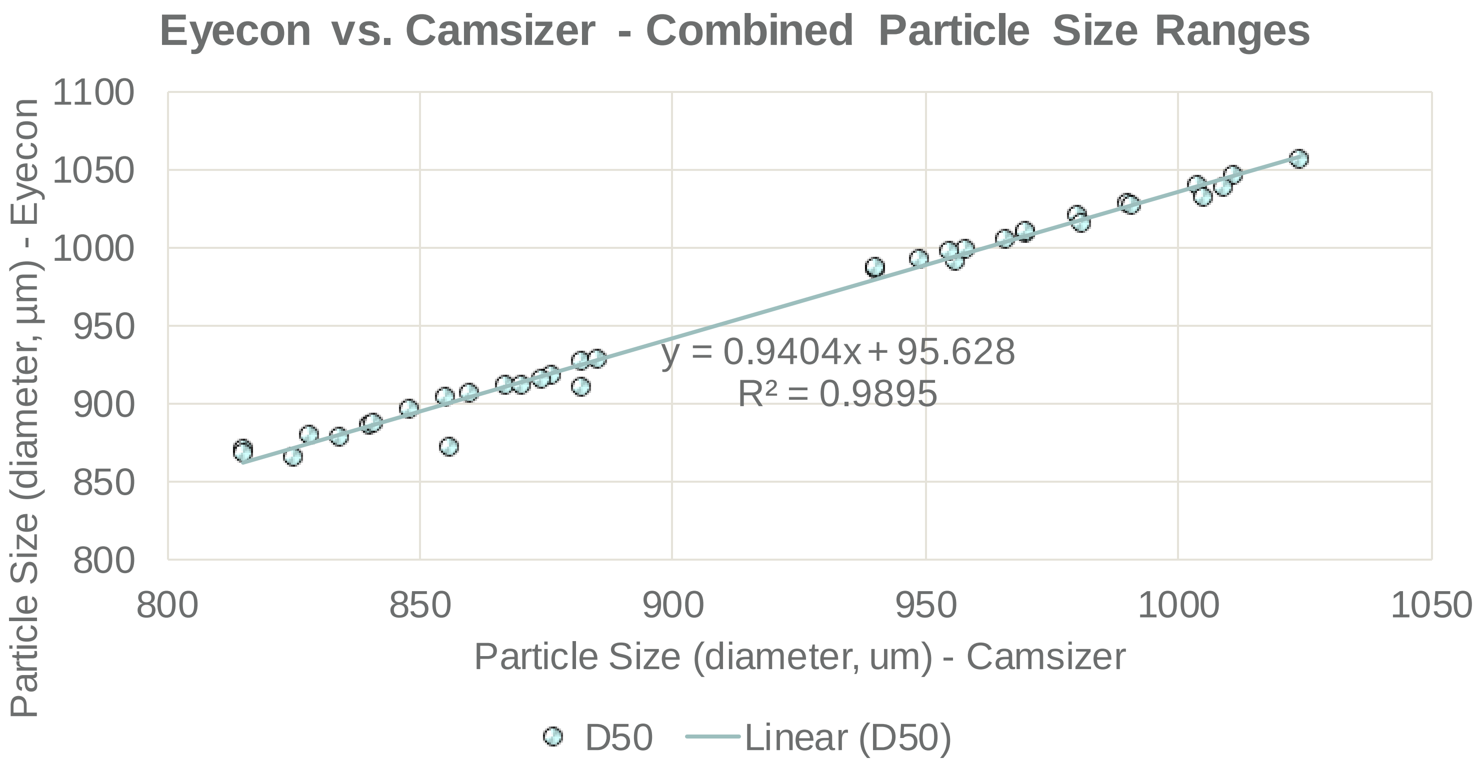
- Observable, consistent growth between sample points



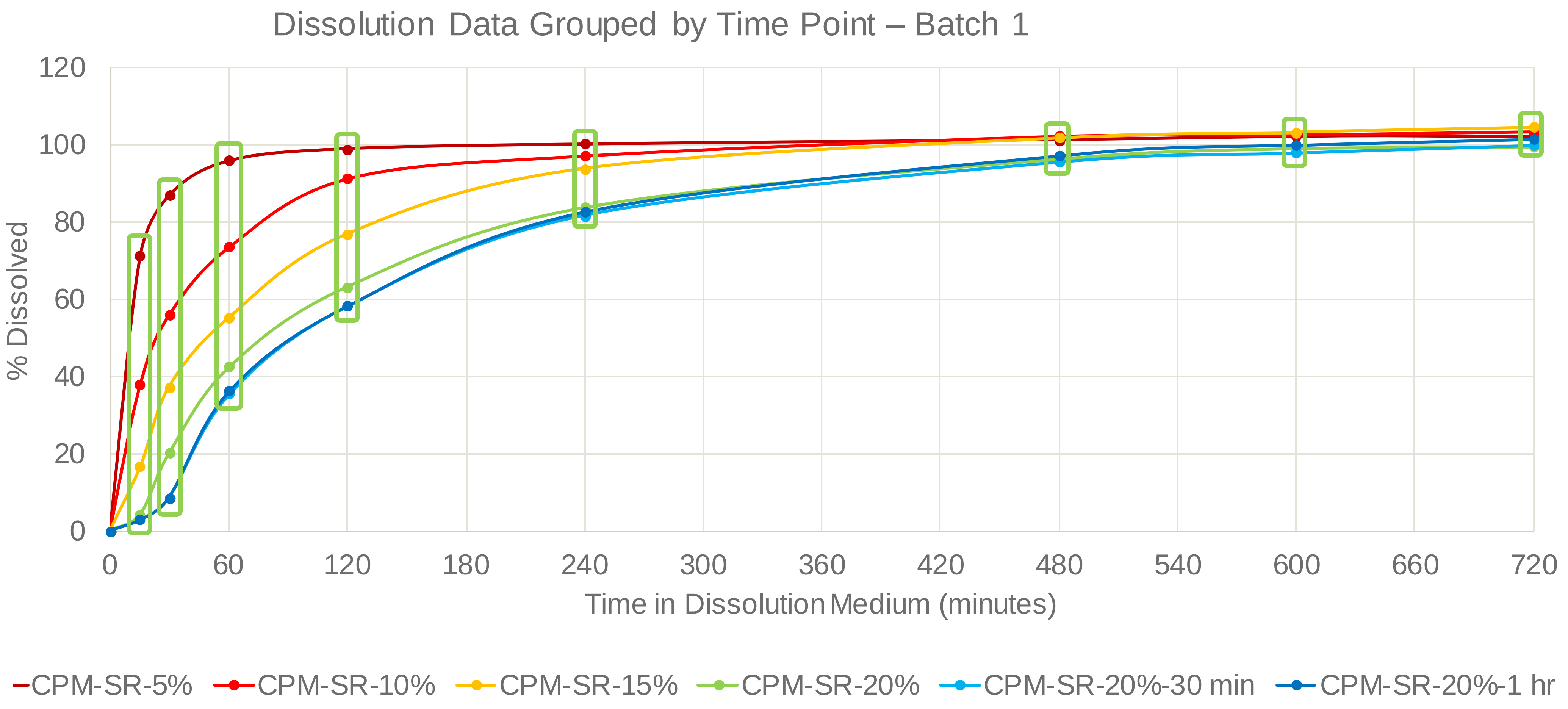


At-Line – In-Line PSD Validation

- $R2 = 0.9895$
- Strong correlation between Eyecon & Camsizer

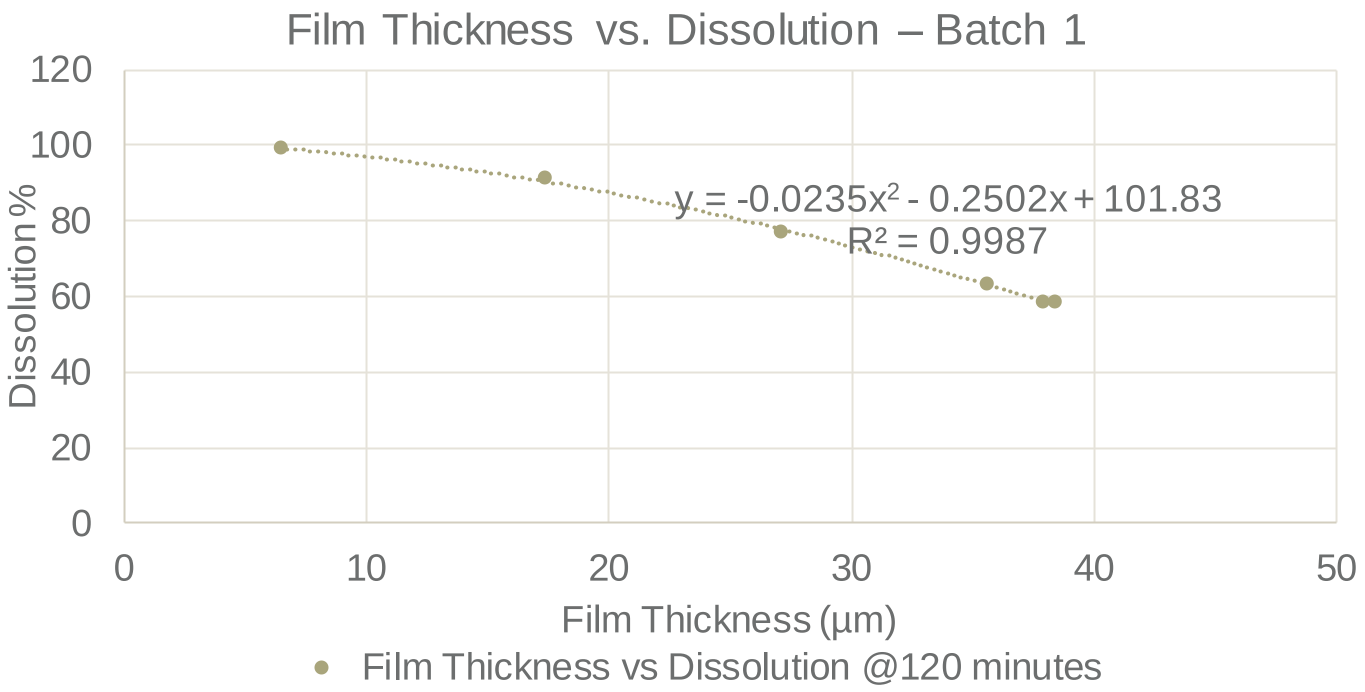


In-Line PSD during Wurster Coating: Dissolution Data

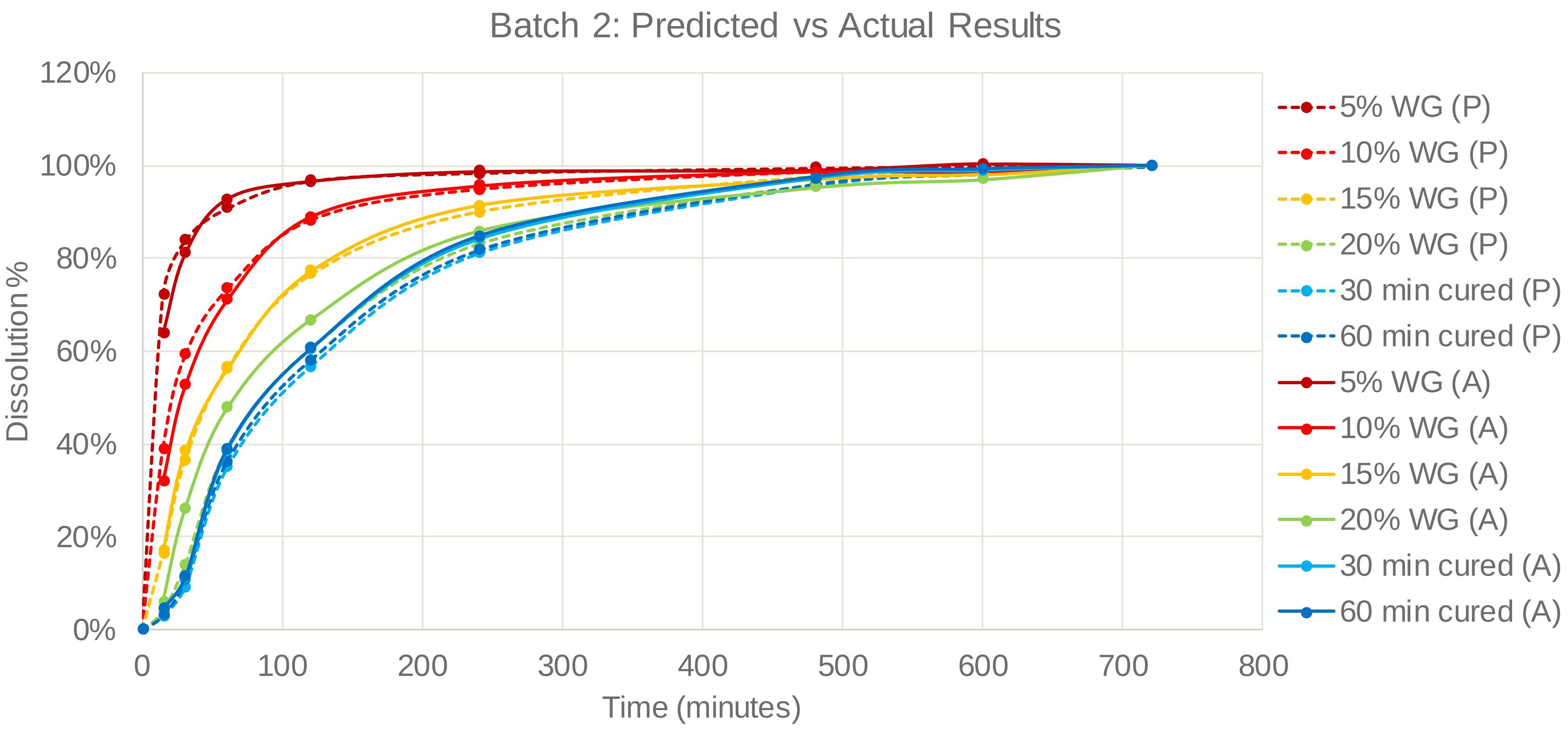


In-Line PSD during Wurster Coating: Relationship Between Dissolution & Film Thickness

- Polynomial fit between PSD & dissolution for varying film thickness
- Shows possibility of model-based real-time measurement / prediction of dissolution!



In-Line PSD during Wurster Coating: Predicted Dissolution vs Actual



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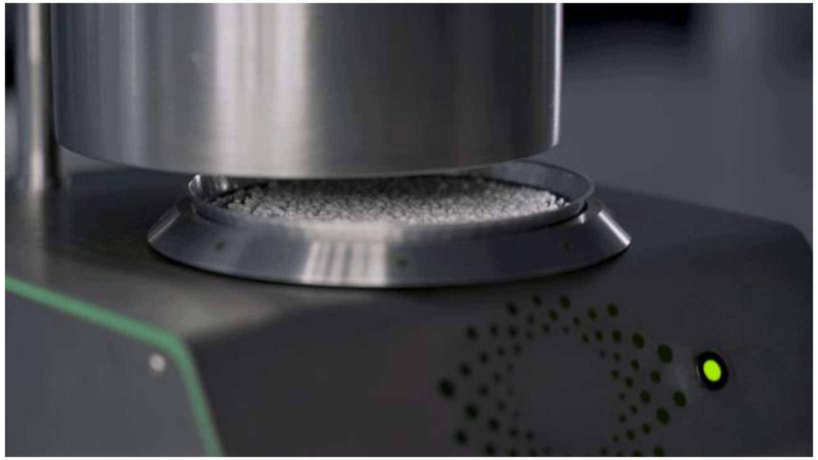
HORIBA Instruments announces exclusive distribution in the Americas

Thank you!

Thank you for listening!

Questions?



Darren McHugh
Product Manager
Innopharma Technology Ltd
mchughd@innopharmalabs.com

Chris O'Callaghan
Head of Engineering
Innopharma Technology Ltd
ocallaghanc@innopharmalabs.com