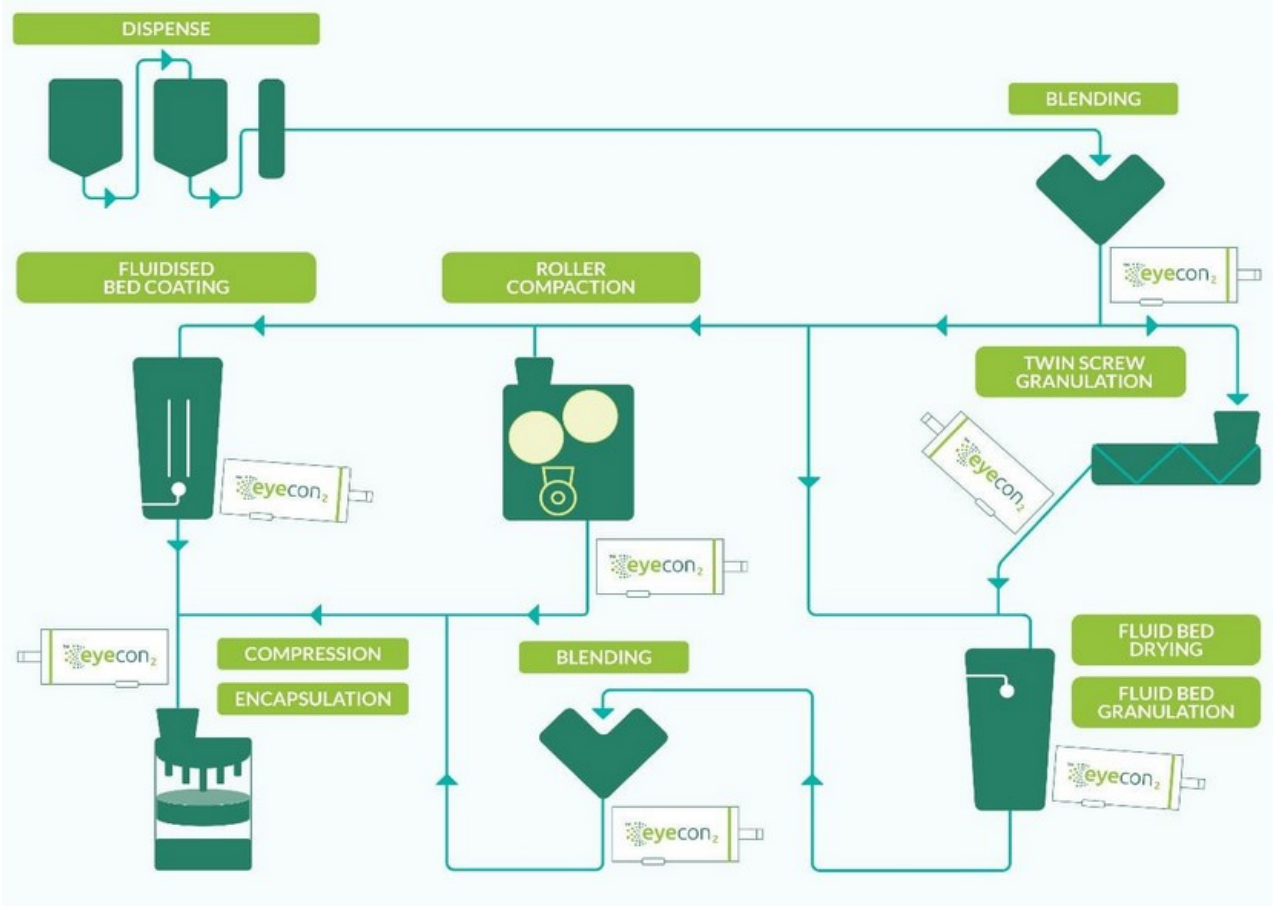
Particle Size Analysis

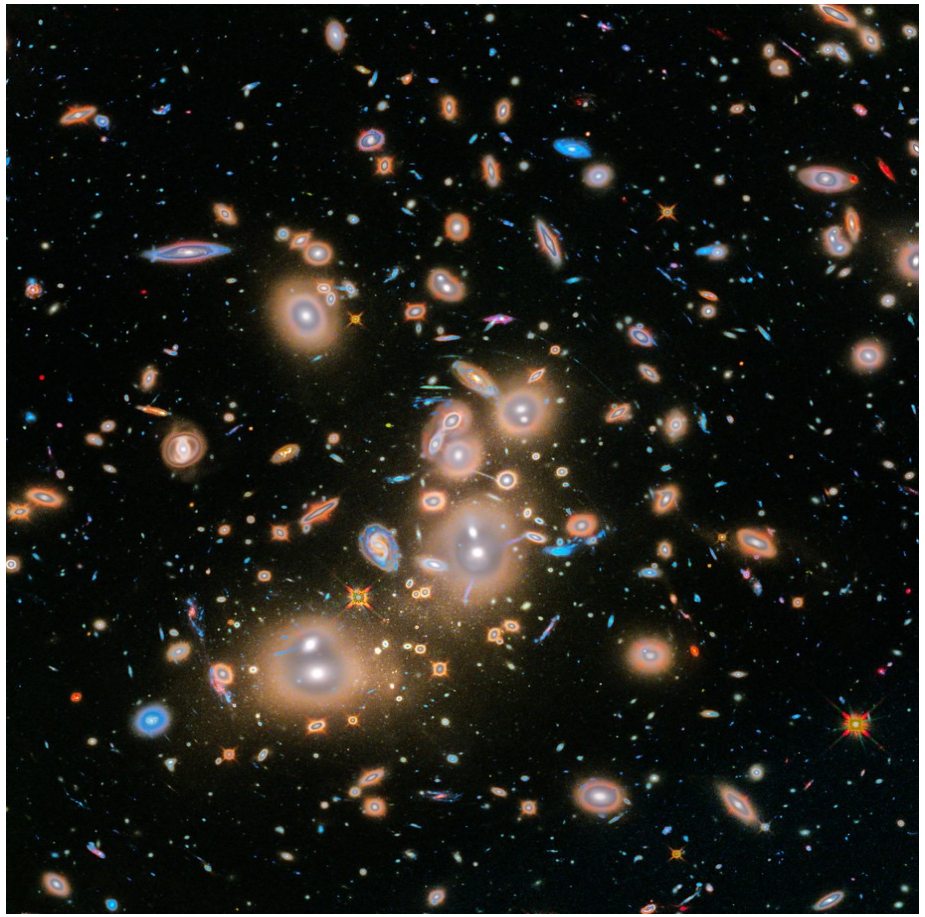
Interpretation of results and correlation with orthogonal methods

Particle size analysis webinar goals

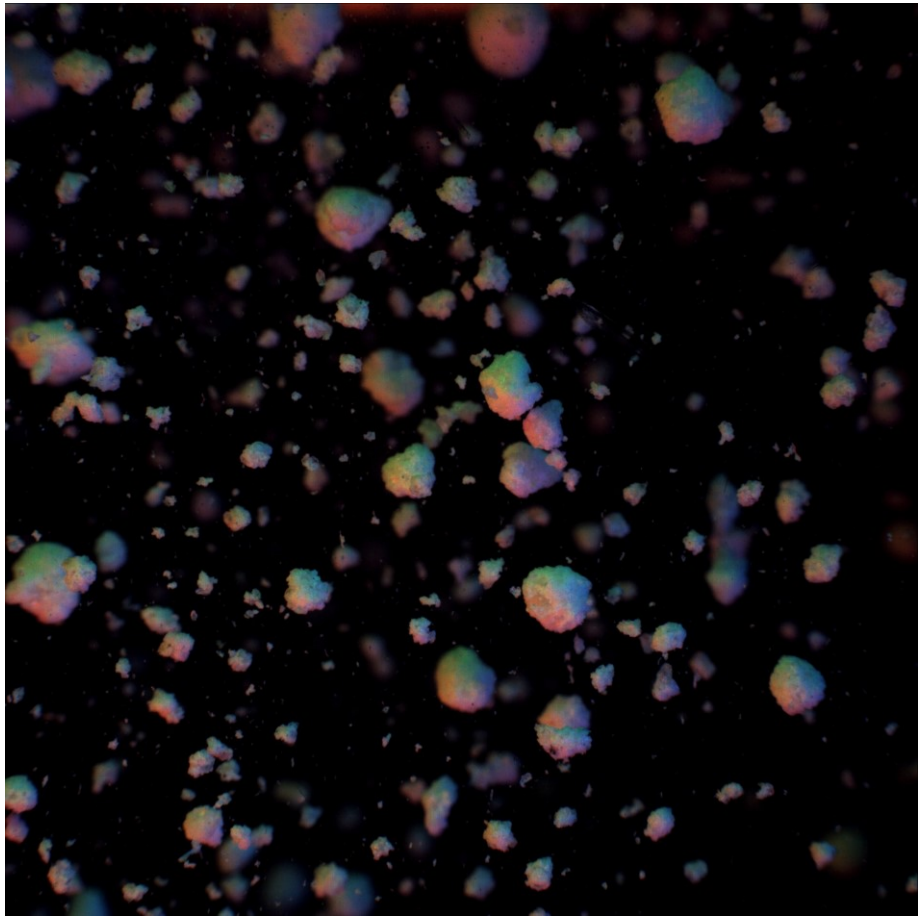
- The importance of Particle size
- Live from the Lab
  - Real time Image analysis – Eyecon2 PSD
  - Sieve
- All particle size results are not created equally so correlate.
- Correlation with orthogonal methods
  - Death by Excel
- Interpretation of results
- FDA Guidance - Alternative analytical procedures



The small matter of particle size



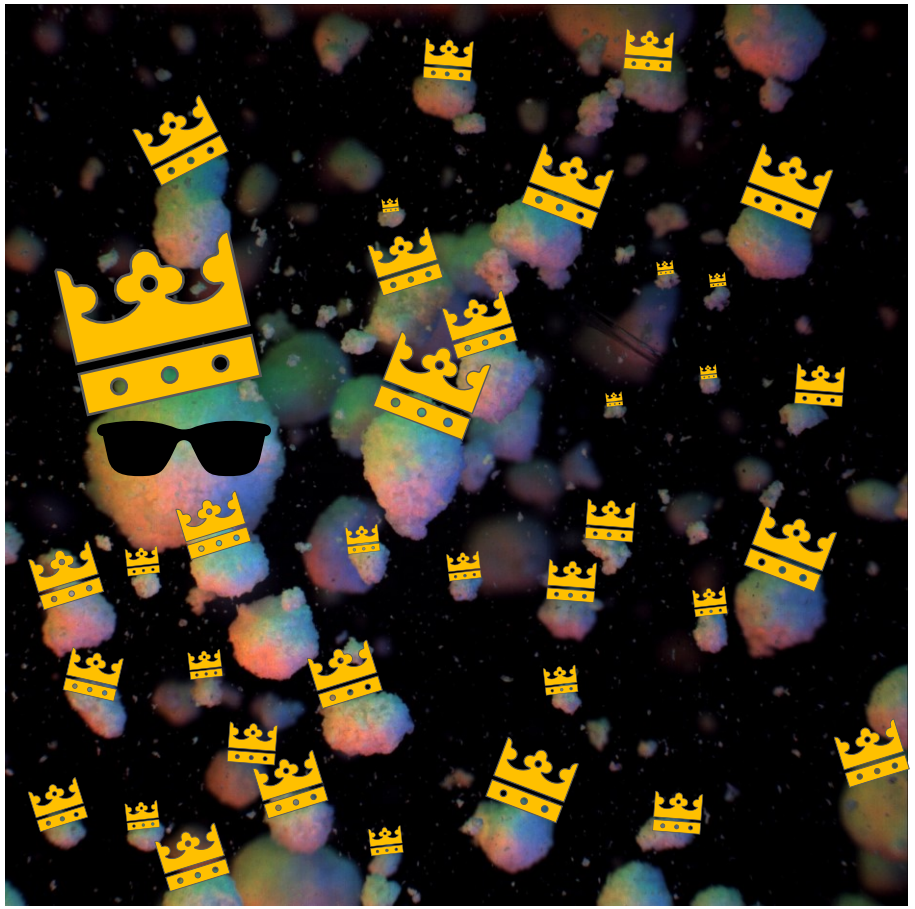
Hubble Space Telescope image of the galaxy cluster Abell 2744.



Eyecon2 particle sizer, micron image of fluidised granulate

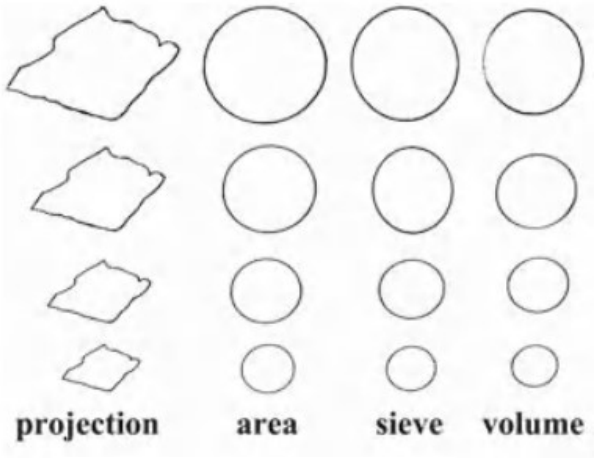
Particle size, the importance in powder and bulk solid manufacturing.

Particles the VIP



Particle size methods

Particle size methods are not created equally, they all have their advantages and disadvantages

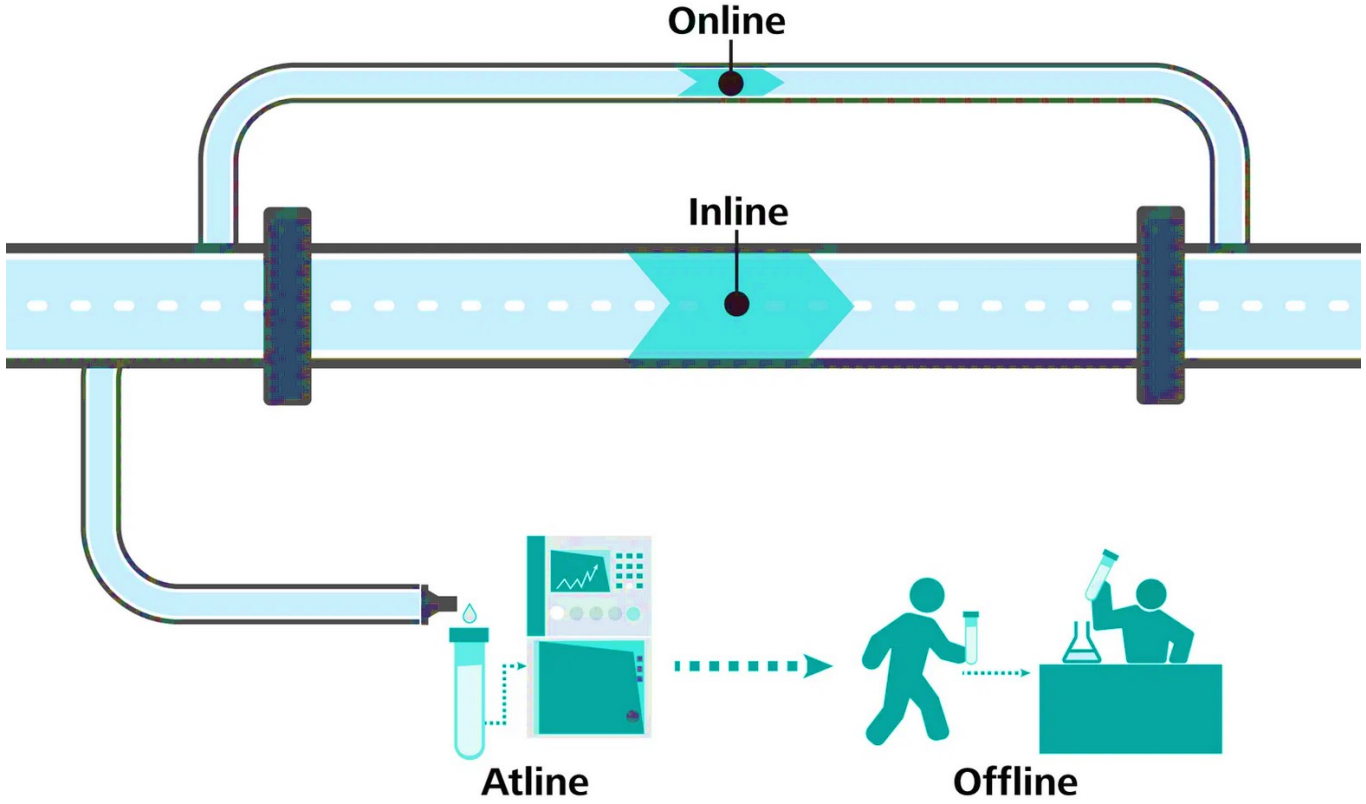


2.1 Particle Size

Fig. 2.2 Equivalent sphere concept for arbitrary particles

From: Particle Size Measurements, Fundamentals, Practice, Quality,Henk G. Merkus

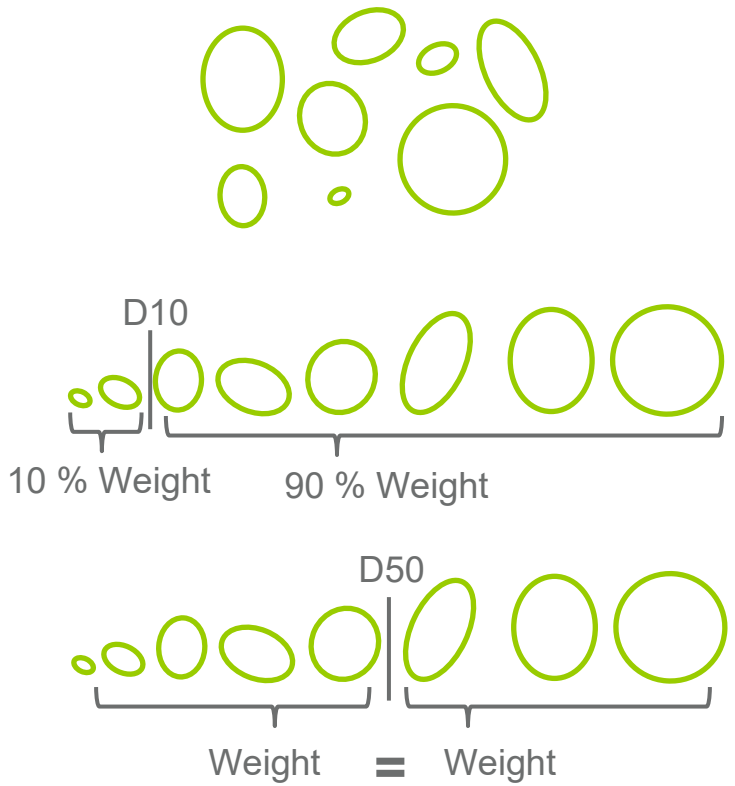
Configurations:



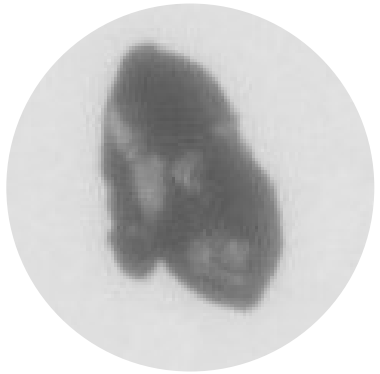
by Alyson Lanciki | Jan 30, 2020

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

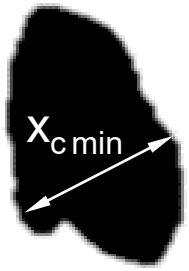


Particle Size



$x_{c\,min}$

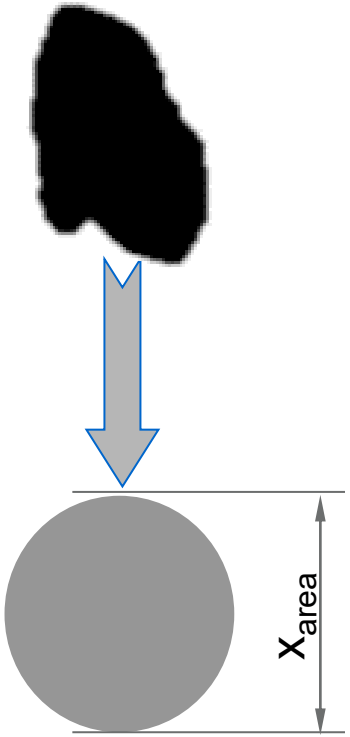
"width"



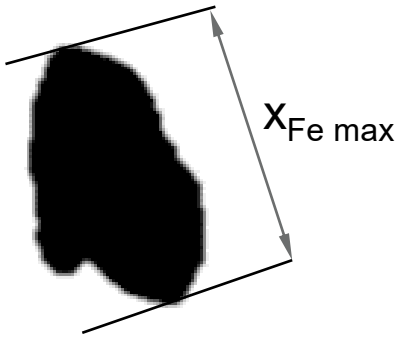
Xcmin is comparison with sieves

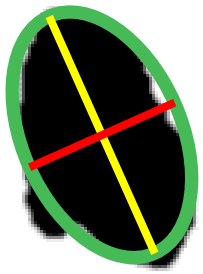
x_{area}

"diameter over projection surface"



"length"



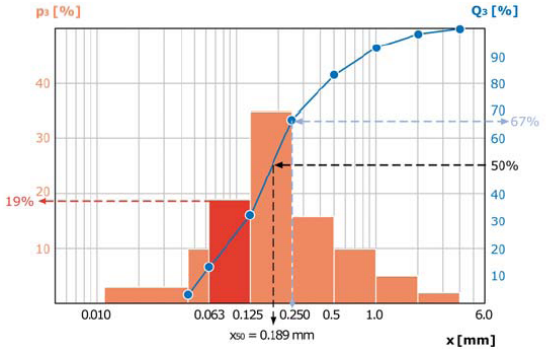


Major, minor diameters

Shape parameters can be calculated!

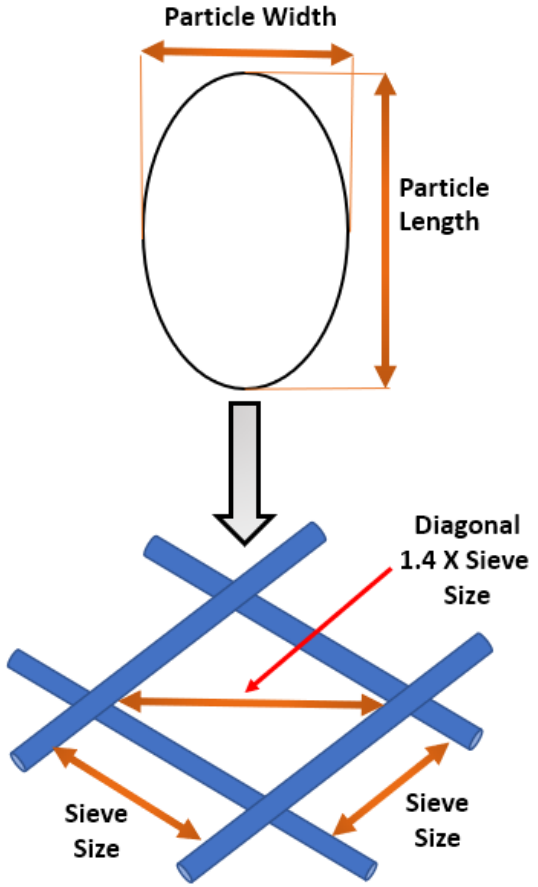
Sieve Analysis

- Each sieve is weighed, and the volume of each fraction is calculated in percent by weight, providing a mass-related distribution.
- The resolution of sieve analysis is restricted by the number of obtainable size fractions.
- A standard sieve stack accommodates a maximum of eight sieves which means that the particle size distribution is based on just eight data points



Size class [mm]	p_3 [%]	Q_3 [%]
< 0.045	3.0	3.0
0.045 - 0.063	10.0	13.0
0.063 - 0.125	**19.0**	**32.0**
0.125 - 0.250	35.0	67.0
0.250 - 0.500	16.0	83.0
0.500 - 1.000	10.0	93.0
1.000 - 2.000	5.0	98.0
2.000 - 4.000	2.0	100.0
> 4.000	0.0	100.0

x_{50} = 0.189 mm



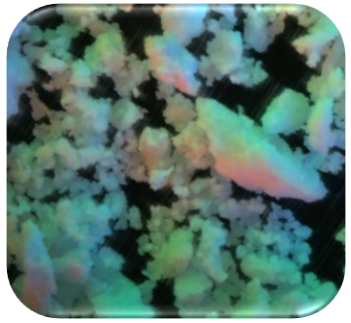
Elongated particles pass through the sieve screen end-on

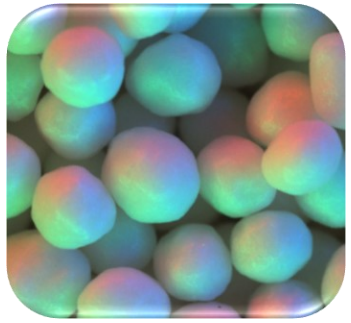
Eyecon$_2$ - Real-Time particle size and shape

- Research & development (QbD/DoE/CPP/CQA)
- Scale up
- Tech transfer
- Batch
- Continuous

Processes:

- Fluidised Bed Coating, Granulation, Drying
- Twin Screw Granulation
- Roller Compaction/Milling
- Extrusion, Spheronisation





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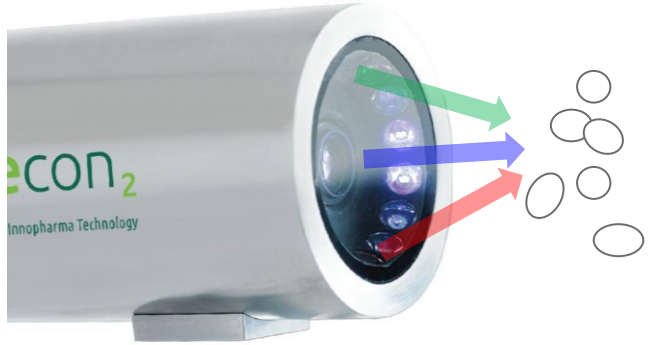
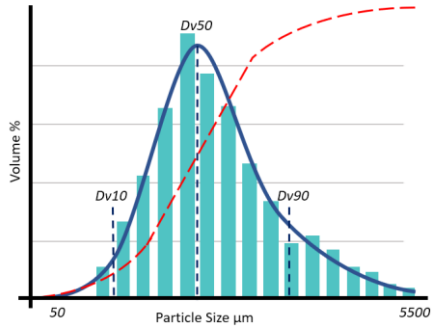
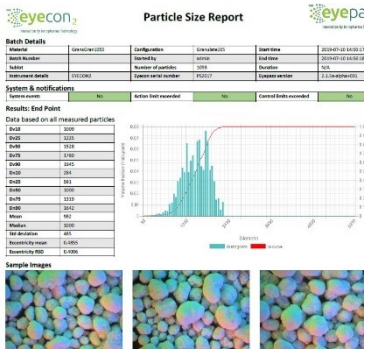
Size Range	50 to 5500 µm
Imaging Area	11.25 mm^2
Pixel Size	5.5 µm
Output	PDF. CSV, Jpeg PSD D5-D95
Instrument Ratings	GMP 21 CFR part 11 GAMP5 CE Marking ATEX 2/22 IP65.
Configurations	In-line, at-line
Casing materials	304 Stainless Steel, Glass, Silicon (gaskets)
Communication	Ethernet, USB OPC UA, DA 3.0

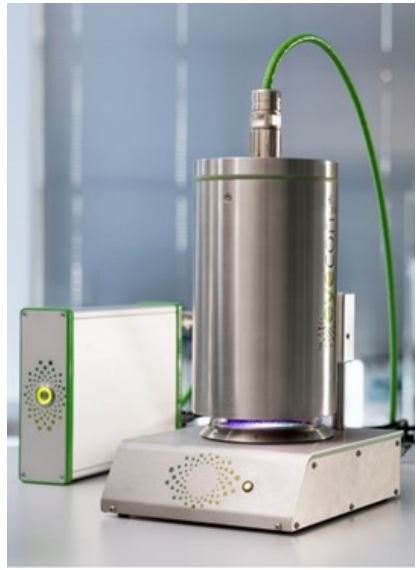
Eyecon$_2$ Real-Time particle size and shape Analysis

- At-Line and In-line
- Dynamic, Non-Product Contact, Real time, digital, no drift, no model building
- Removing/reduce the need for sampling
- Insight what CPP changes the CQA
- Pharma 4.0 ready

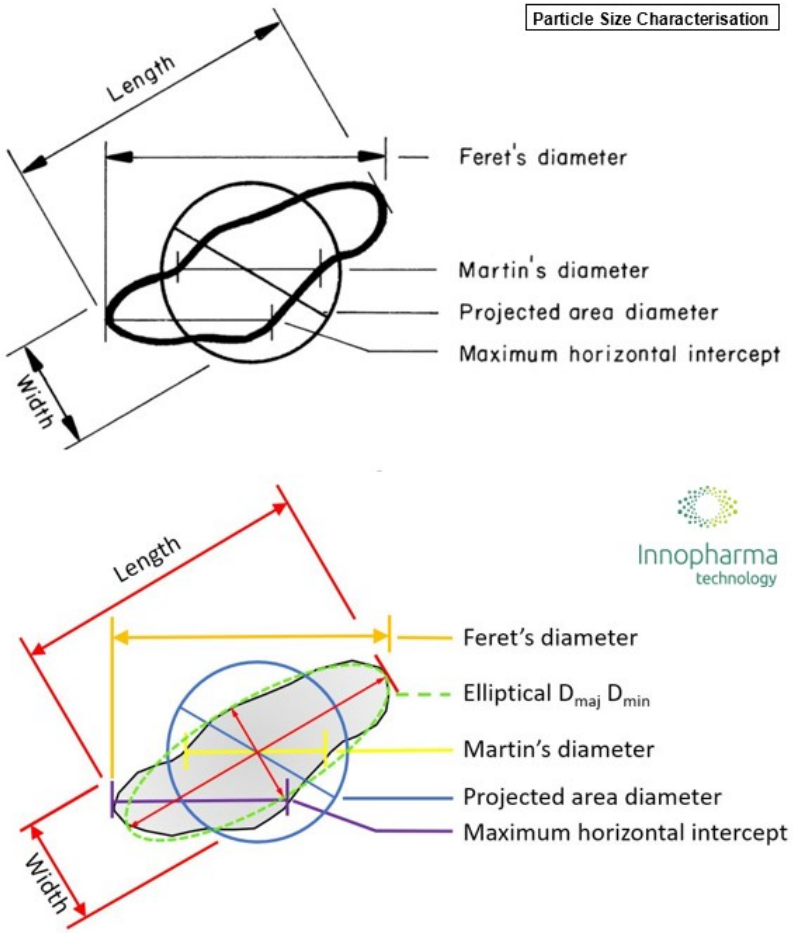


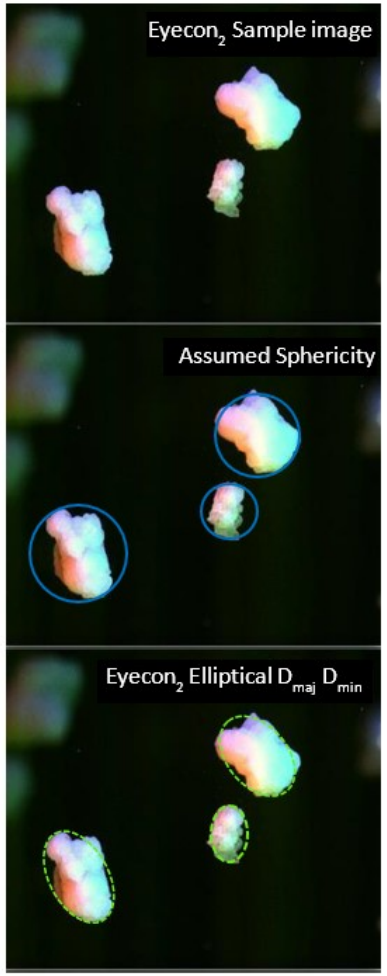


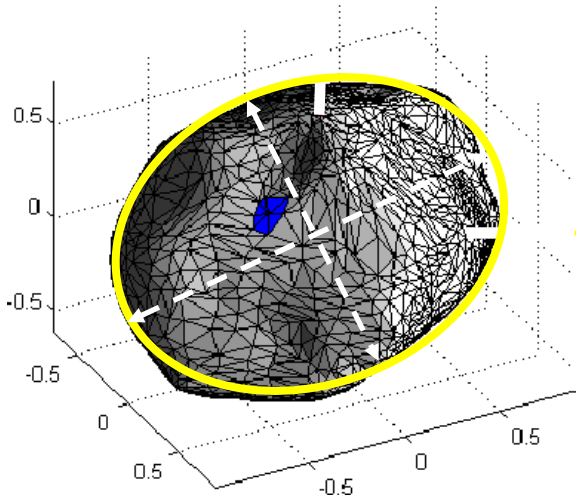




Method of Operation: Image Capture



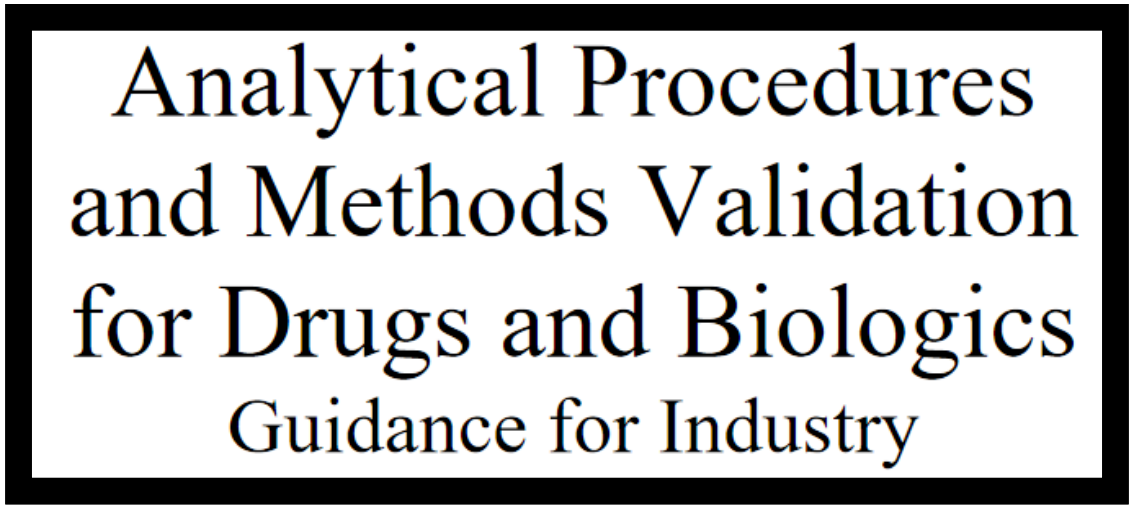




- Each particle initially identified
- Best-fit ellipse calculated
- Major & minor diameters computed
- PSD/D-values determined

Analysis & the FDA

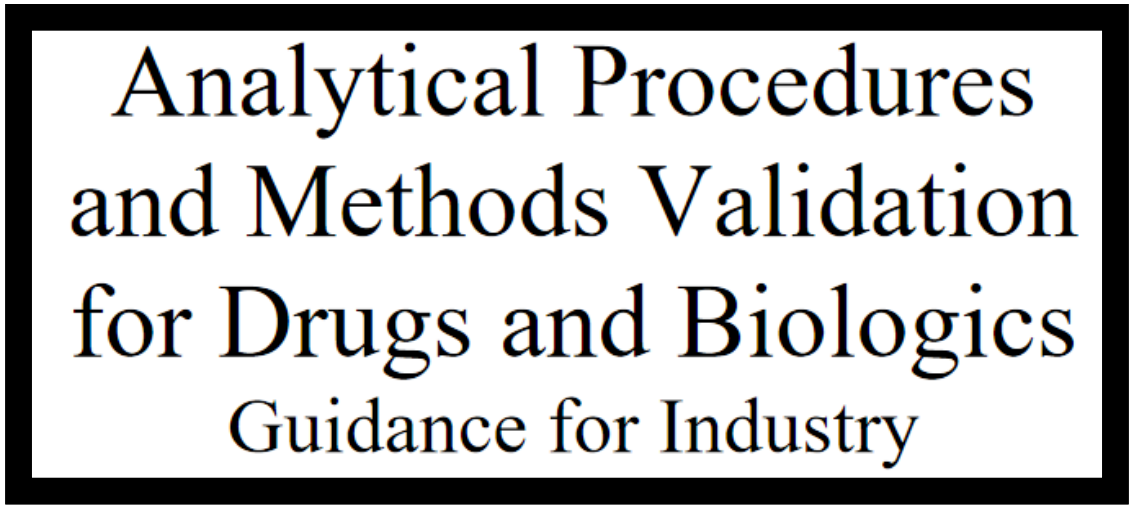
"This guidance…provides recommendations on how you, the applicant, can submit analytical procedures and methods validation data to support the documentation of the identity, strength, quality, purity, and potency of drug substances and drug products."



https://www.fda.gov/regulatory-information/search-fda-guidance-documents/analytical-procedures-and-methods-validation-drugs-and-biologics

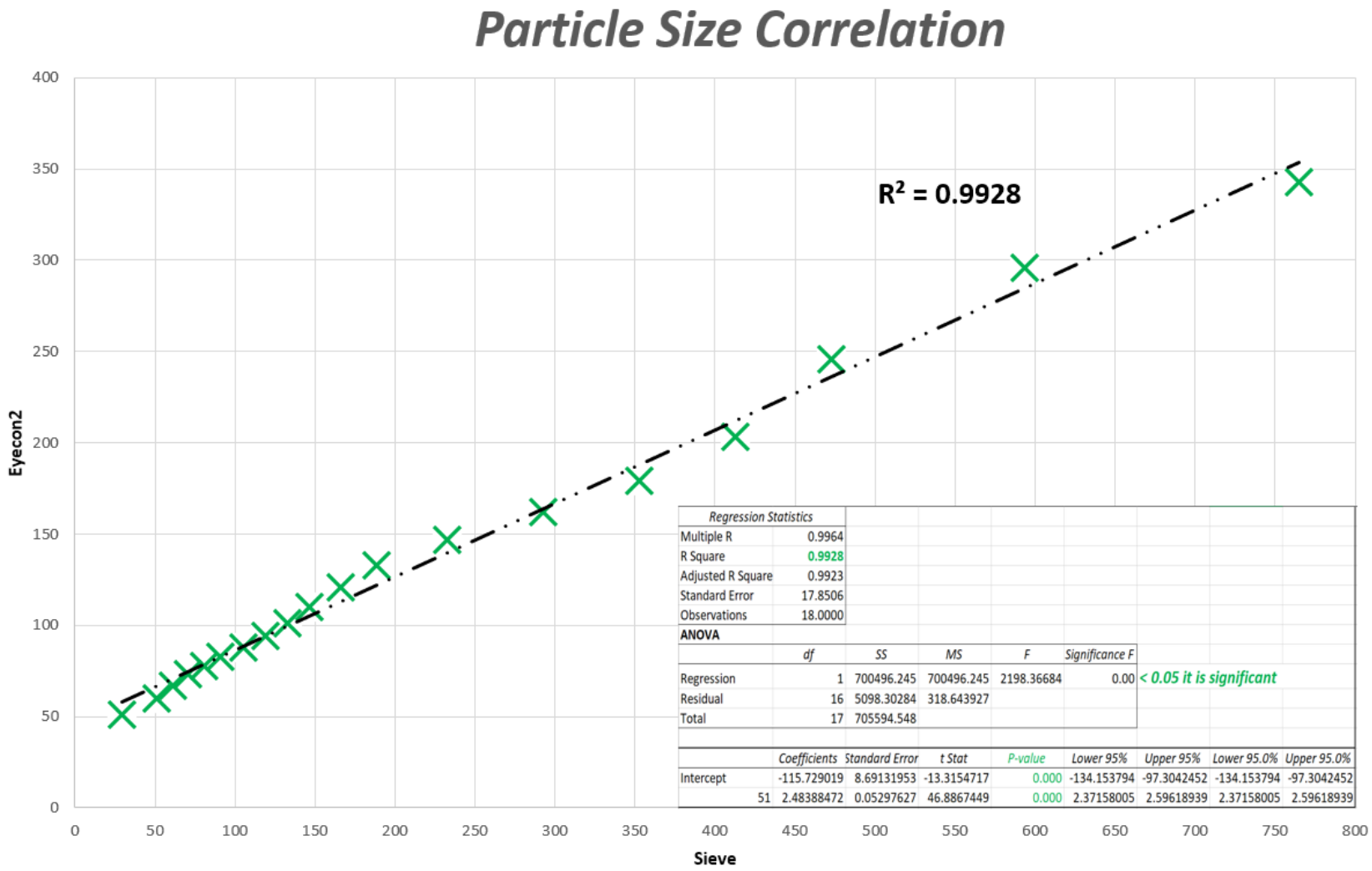
Analysis & the FDA

"New technologies may allow for greater understanding and/or confidence when ensuring product quality. Applicants should periodically evaluate the appropriateness of a product's analytical methods and consider new or alternative methods."



Lab Tour

Correlation



Regression Statistics	
Multiple R	0.9964
R Square	0.9928
Adjusted R Square	0.9923
Standard Error	17.8506
Observations	18.0000

ANOVA

	df	SS	MS	F	Significance F	
Regression	1	700496.245	700496.245	2198.36684	0.00	< 0.05 it is significant
Residual	16	5098.30284	318.643927			
Total	17	705594.548				

	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Upper 95%	Lower 95.0%	Upper 95.0%
Intercept	-115.729019	8.69131953	-13.3154717	0.000	-134.153794	-97.3042452	-134.153794	-97.3042452
51	2.48388472	0.05297627	46.8867449	0.000	2.37158005	2.59618939	2.37158005	2.59618939

Correlation

App Notes

Innopharma technology

Real-Time Prediction of Polymer-Coated Multiparticulate Dissolution using Process Analytical Technology

Colorcon · Glatt · Innopharma technology

Authors: Piyush Patel[A], Edward Gode
[A] Colorcon, PA, USA
[B] Glatt Air Techniques, NJ, USA
[C] Innopharma Technology, Dublin, Ir
[D] Innopharma College of Applied Scie

Introduction

Process Analytical Technology, or "
measure certain attributes of produc
minimising the need for sampling fo
traditional off-line analysis methods
data which facilitates rapid decision
between sampling and off-line resul
performed and the analytical stru
measurement results enabling contr
also on the true critical quality attrib

Twin Screw Granulation – Enabling Greater Process Understanding with the Eyecon Particle Characteriser

UNIVERSITEIT GENT · Innopharma technology

Authors: Thomas De Beer[A], Fien De Leersnyder[A], Ian Jones[B], Chris O'Calla
nt, Belgium
Ireland

con™ Particle Characteriser was used to monitor wet
ulator on a GEA Consigma 25. An integration system w
ture and analyse images of the granules without inter
us drier. The measured material could therefore be fu
ther offline analysis.

Plan

Implementation of PAT for In-Line Monitoring of a Milling Process During DoE for Continuous Processing

Innopharma technology · SERVIER

Authors: David Lafargue[A], Y. Gut[A], H. D'Inca[A], F. Tharrault[A], Emmet
[A] Servier, Orleans, France
[B] Innopharma Technology, Dublin, Ireland
[C] Innopharma College of Applied Sciences, Dublin, Ireland

Introduction

The study presented here outlines some of the steps involved in d
a continuous manufacturing system using Design of Experiment (
requirement of continuous processing is continuous monitorir
attributes (CQAs) to gain a sufficient understanding to devise a dat
in-line Process Analytical Technology (PAT) sensor enables real ti

technology

Unique Advantages of Process Analytical Technology in Twin-Screw Granulation

ThermoFisher SCIENTIFIC

Authors: Dr.-Ing. Margarethe Richter[A], Chris O'Callaghan[B]
[A] Thermo Fisher Scientific, Karlsruhe, Germany
[B] Innopharma Technology, Dublin, Ireland

Introduction

Monitoring Fluid Bed Granulation Processes In-Line with Real Time Imaging

Glatt · In

Authors: P. Cruise[A], C Cortazzo[B], Joachim Fröhlich[B], Lilia Sprich[B], Raoul Pila[B], Ian Jones[B]
[A] Innopharma Labs, Ireland
[B] Glatt GmbH Process Technology, Binzen, Germany

Introduction

The pharmaceutical manufacturing platforms of fluid bed granulation is widely used to modify particle size. However the adoption of PAT to monitor and control this process is difficult, due to its dynamic nature. This study examines the efficacy of a particle characterising technology to capture particle images under dynamic conditions and to calculate particle size distribution data during fluid bed granulation.

Experimental Plan

Alkermes Pharma Ireland Ltd collaborate with Innopharma Labs to enable enhanced control of granulation, milling and spheronisation of a manufacturing process

Alkermes Patient inspired

I. Jones[a*], James Burke[b].
[a] *Innopharma Labs, Ireland* [b] *Alkermes Pharma Ireland Limited, Ireland*

thermoscientific

WHITE PAPER

Continuous twin-screw granulation – What to consider in process design, development and scale-up

No. WP03

Author
Margarethe Richter
Thermo Fisher Scientific, Karlsruhe, Germany

Abstract
Twin-screw granulation (TSG) offers a significant advantage over traditional granulation methods: the possibility of continuous manufacturing. Due to the recognized advantages

Introduction
Continuous manufacturing of pharmaceuticals has grown more popular in recent years [1]–[6]. There are several advantages of continuous processes over traditional batch processes:
1. The "batch size" is not a fixed value in CM. Therefore, especially in the R&D phase of a drug, the amount of product can be reduced to the minimum needed for analysis and clinical trials. Furthermore, once the

The use of Real-Time At-Line Particle Size Measurement on a Pelletization Process for Accurate End-Point Prediction

Authors: Emmet Hogan[A], Mike Mulcahy[A], Dr. Ian Jones[B], Dr. Norbert Pöllinger[C], Mirko Nowak[C], Dr Orapin Rubino[D], Greg Jayne[D]
[A] Innopharma Technology, Dublin, Ireland
[B] Innopharma College of Applied Sciences, Dublin, Ireland
[C] Glatt GmbH, Binzen, Germany
[D] Glatt Air Techniques, Ramsey, NJ, USA

Real-Time In-Line Monitoring of the Impact of Process Parameter Changes on Critical Quality Attributes in Fluid Bed Granulation using Process Analytical Technology

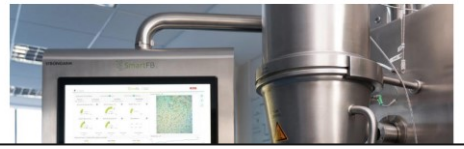
Authors: L. Kiernan[A], E. Hogan[A], V. Todaro[B], A-M. Healy[B], A. Greene[C], I. Jones[D],
[A] Innopharma Technology, Dublin, Ireland
[B] Trinity College Dublin, Dublin, Ireland
[C] Dublin Institute of Technology, Dublin, Ireland
[D] Innopharma College of Applied Sciences, Dublin, Ireland

Abstract

There is an increasing trend within the pharmaceutical industry to utilise all available sources of analytical data to support more rapid formulation development and subsequently introduce further

Self-Guided Control of a Fluid Bed Granulation Process

Authors: Caroline McCormack[A], Chris O'Callaghan[A], Gareth Clarke[A], Prof. Ian Jones[B], Luke Kiernan[C], Prof. Gavin Walker[D].
[A] Innopharma Technology, Dublin, Ireland
[B] Innopharma College of Applied Sciences, Dublin, Ireland
[C] Technological University Dublin (TUD), Dublin, Ireland
[D] University of Limerick, Limerick, Ireland



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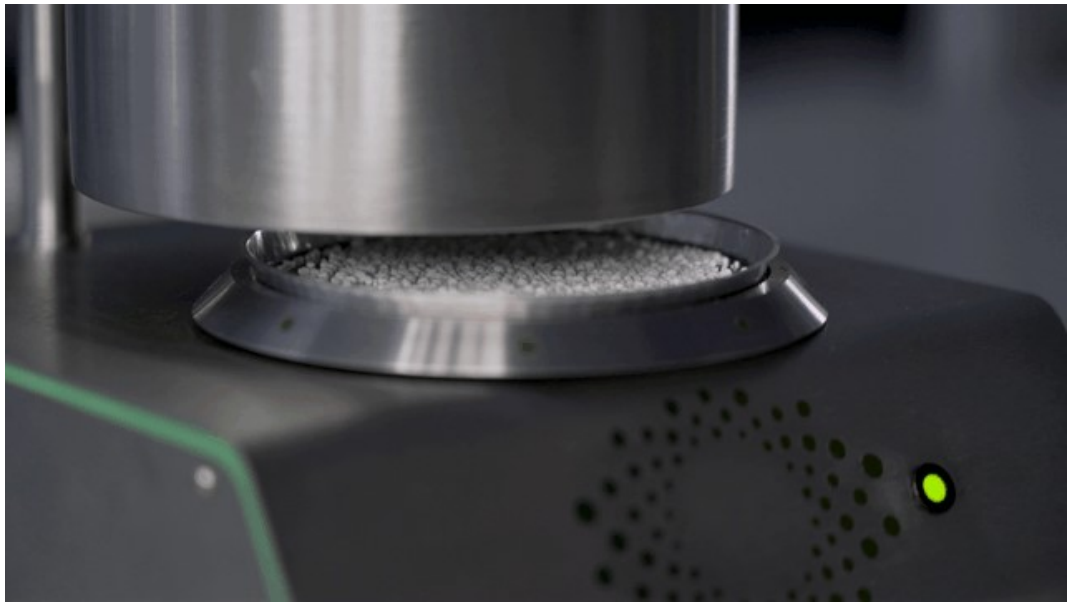
eyecon™ 2

Particle Size Analysis

Interpretation of results and correlation with orthogonal methods

- ✓ The importance of Particle size
- ✓ All particle size results are not created equally so correlate.
- ✓ How to correlate with orthogonal method
- ✓ FDA Guidance - Alternative analytical procedures



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Product Manager
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Thank you!