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Inline Particle Sizing for Process Control of Fluid Bed and High Shear Mixing Processes

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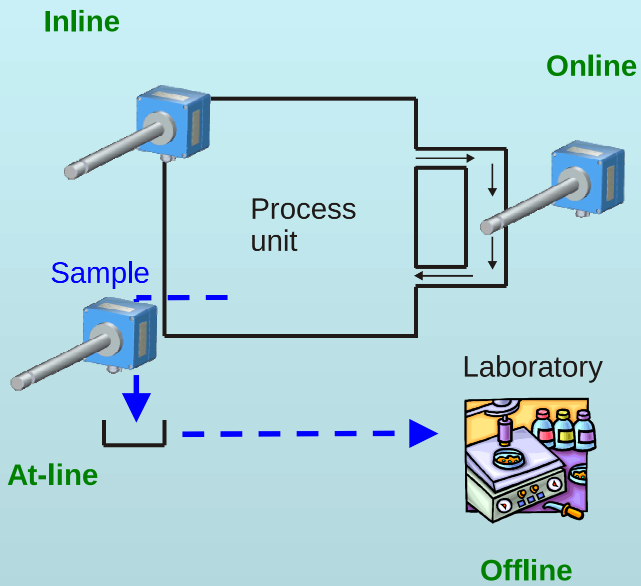
Presentation Outline

- In-line particle size analysis
- PAT (Process Analytical Technology)
- Requirements and Measuring Methods
- Presentation of Particle sizing results and comparability
- PARSUM's measurement principle
- Case Study Fluid Bed Processes
- Case Study High shear granulation processes
- Conclusion

In-line Particle Size Analysis
Definition of Terms

- **Online** – Measurement with "real time" output of the results (e.g. by continuous or quasi-continuous sampling or bypass)
- **Inline** – Measurement and analysis performed directly inside the process
- **Offline** – All laboratory methods with sampling (analysis is separated from process in respect to time and space)
- **AT-line** – Measurement of a sample near the process in production environment



- Further terms: In- process, In- situ …

Why Inline Particle Size Analysis ?

- Monitors the particle size continuously
- Gives more representative results
- Enables more stringent higher and lower limits
- Increases efficiency and throughput.
- Higher quality product (by tighter control set points)
- Improves batch to batch consistency
- Reduces the potential exposure to operator
- better control minimizes wastage
- Reduce costs of production

PAT (Process Analytical Technology)

- Improve process understanding and transparency
- Control critical process parameters
- Generate and verify process models
- Identify process endpoint in granulation processes
- Improve processes
- Shorter time for process development and up scaling

Inline Particle analysis can open a window to your process

Requirements for use in Industry

- Low hardware efforts for installation
- Wide measuring range … 50 µm – … mm
- True inline capability
- Robust industrial design
- Long term stability
- Independent of process conditions and product properties

Different Inline principles / devices for different applications
2 groups of instruments:

- Field scanning = Measurement of properties of a particle collective
- Stream scanning = Measurement of properties of single particles

Field Scanning Methods

Laser Diffraction

- Light scattering
- High accuracy
- Low particle concentration (Bypass mostly needed)
- 0.5….1000µm (different optics needed)

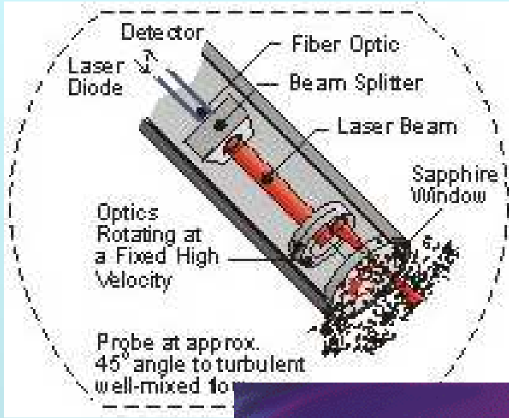
NIR-Systems

- Detecting of reflected Spectra
- fast measurement, quick response,
- model generation necessary

Stream Scanning Methods

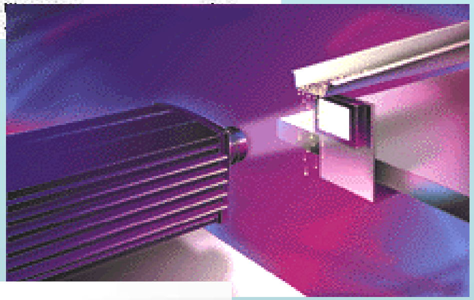
Laser scanning

- Rotating focused laser beam
- Cord length measurement
- About 2 … 1000 µm



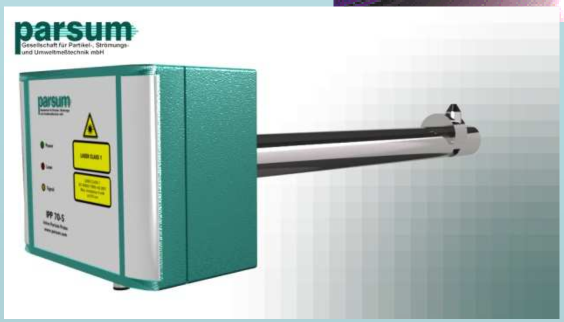
Camera systems

- Bypass needed,
- preparation of particle stream
- 30µm …. 30 mm



Modified spatial filtering

- No moving parts
- True inline (probe)
- Cord length measurement
- About 50µm … 6 mm



Particle Sizing

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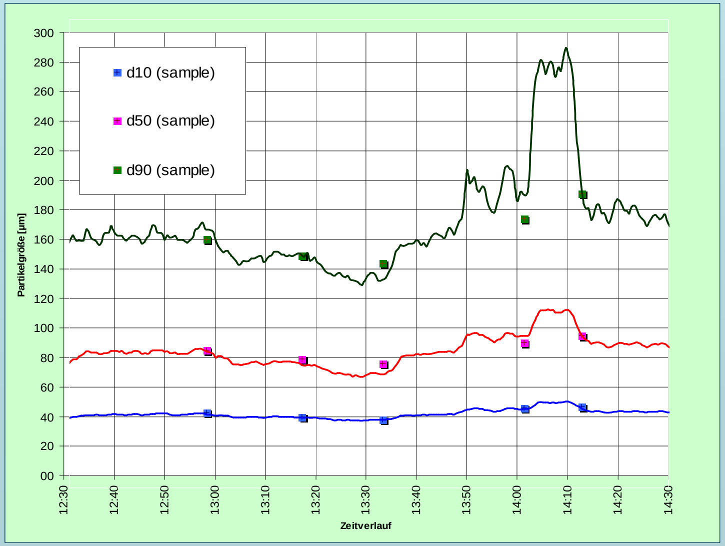
Presentation of Particle Sizing Results

Inline:

- Progress of PSD over time
- Concentrated information for process control e.g. X_{10},X_{50},X_{90}
- Dynamic of measurement is adjustable to process dynamic
- Averaged PSD at any interval

Off-line:

- PSD only at sample time
- No information about the progress of particle size



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Comparability of Inline and Off-line Results

- Comparing Inline and Off-line Measurements is the same as comparing Off-line measurements from different measuring methods

More important:

- Same place / Same time of inline measurement and sample taking
- Influence of process conditions to sample / Inline measurement

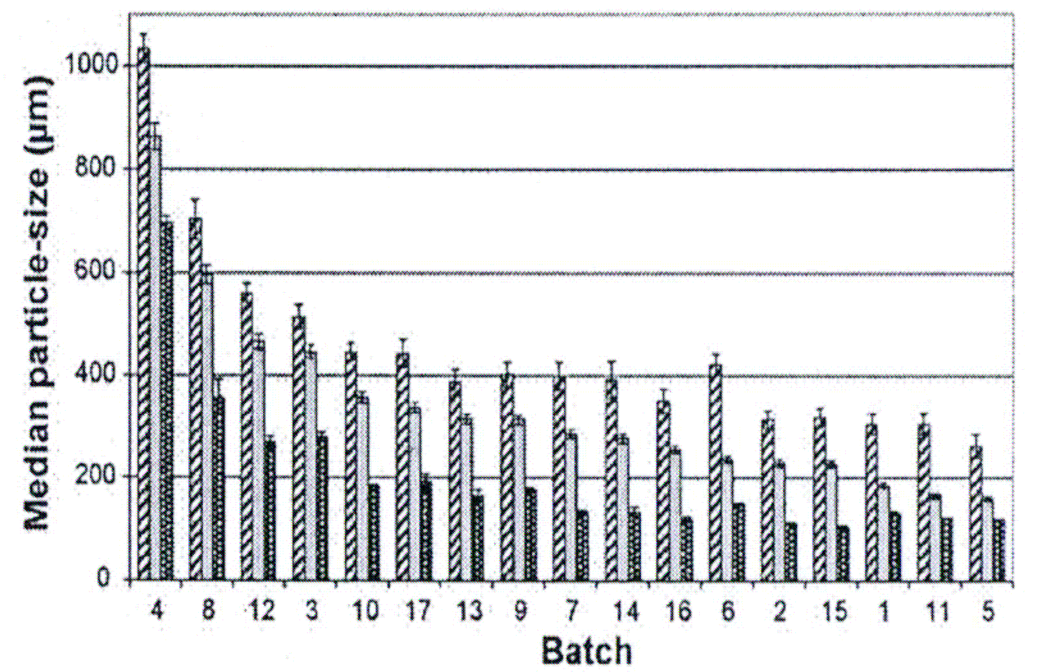
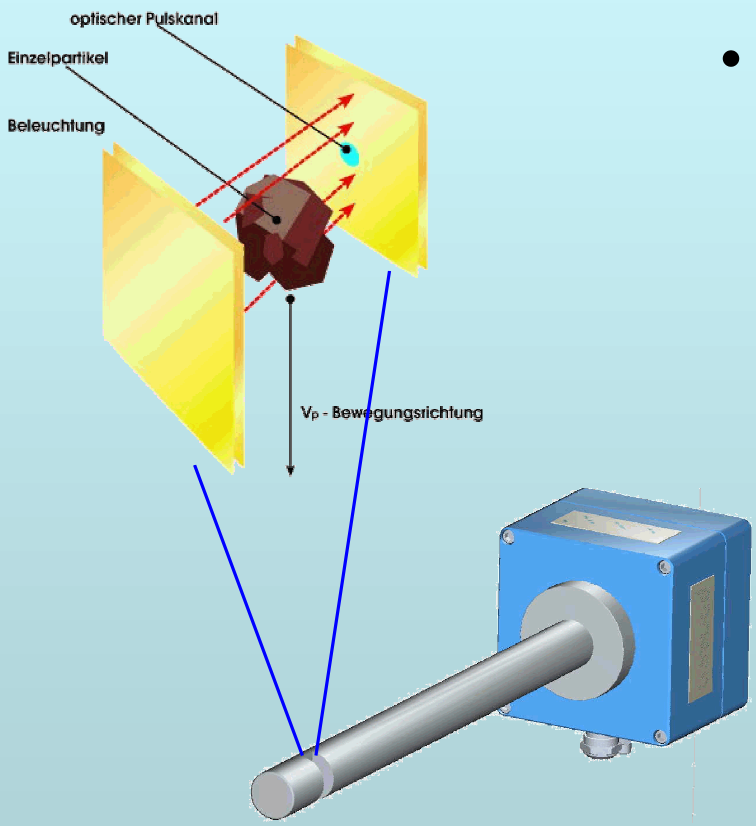


Fig. 1. Median granule size results ($n = 3$) of the batches, measured by sieve analysis (left column), SFT (middle column) and laser diffraction (right column) in descending order.

T. Närvänen et al. / International Journal of Pharmaceutics 357 (2008) 132–138

Parsum measuring principle



- Modified spatial filter method
- Measuring principle is based on evaluation of the shadows of a laser beam which are created by moving particles

Properties:

- Measuring range approx. 50µm to 6mm
- Velocity range up to 50 m/s
- Recording of particle velocity and particle size
- Method especially for online use
- Chord length measurement
- Single particle measurement
- Probe with no moving parts

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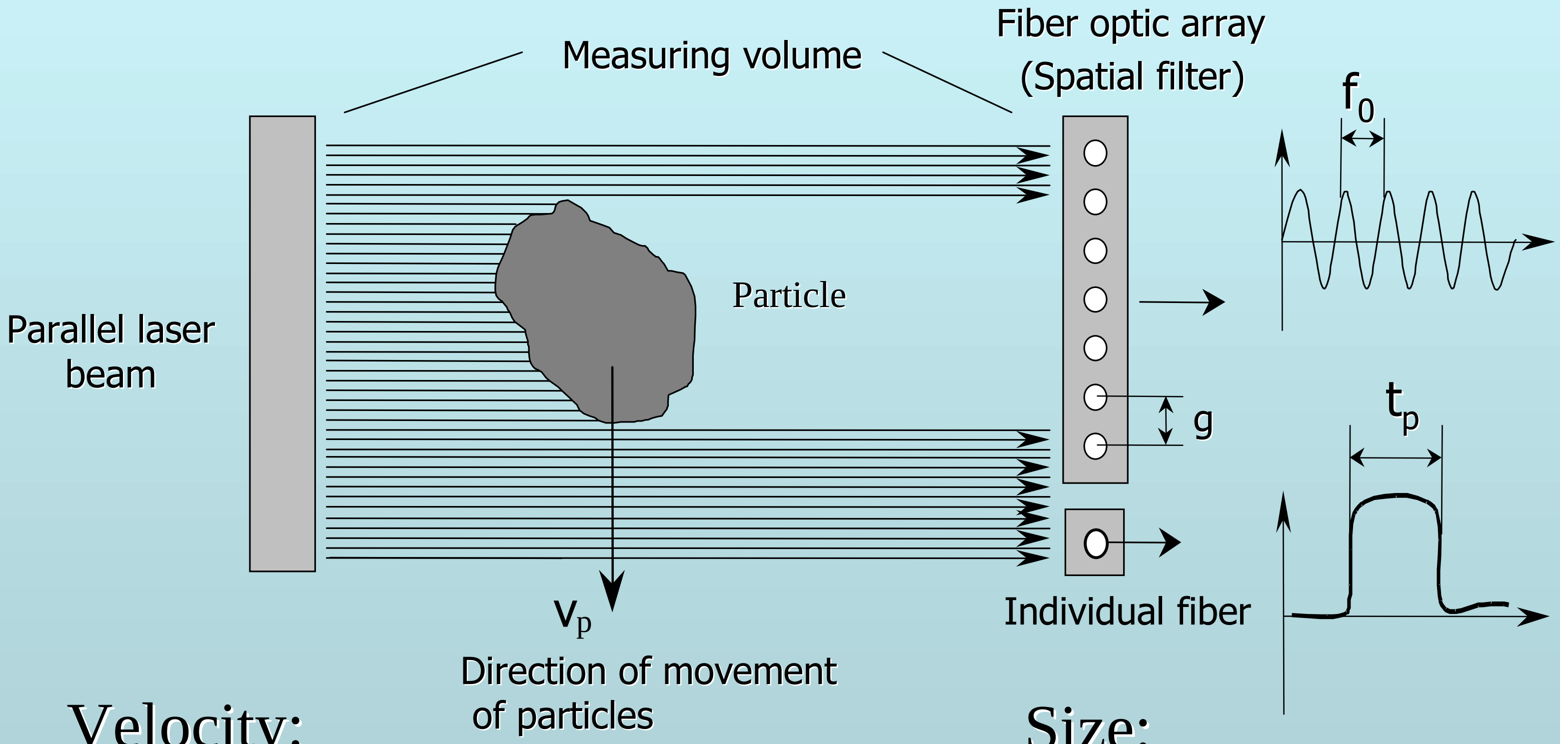
Modified Spatial Filter Method



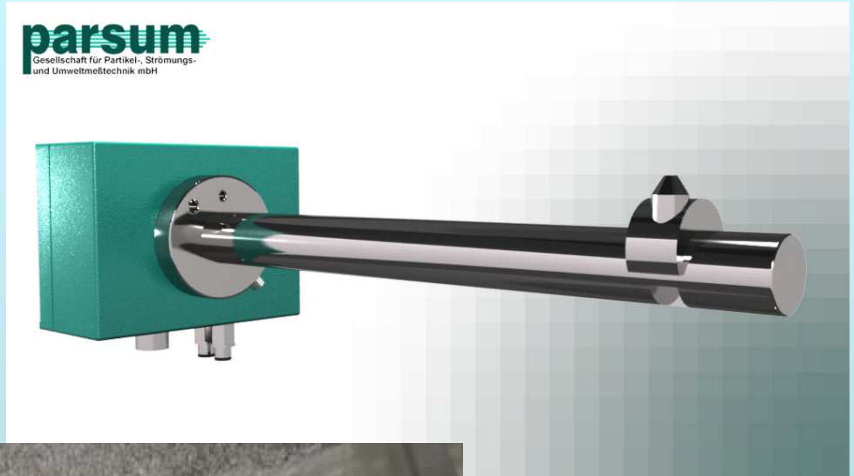
Velocity:

$$v_p = f_o * g$$

Size:

$$x_p = t_p * v_p - d$$

Process Interface – Inline Eductor

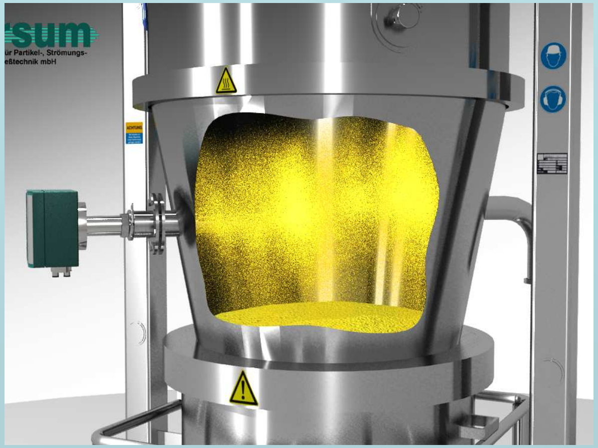


- For high loaded particle streams
- For particles with irregular movement (Fluid Bed, High Shear Granulation)
- Air purge to hold optics free
- Ring-nozzle causes sucking effect and accelerates particles
- Particles are moving on straight Lines,
- separation effect is minimized
- Installation with Tri Clamp DN50
- Periodic back purge function

Fluid Bed Batch Granulation

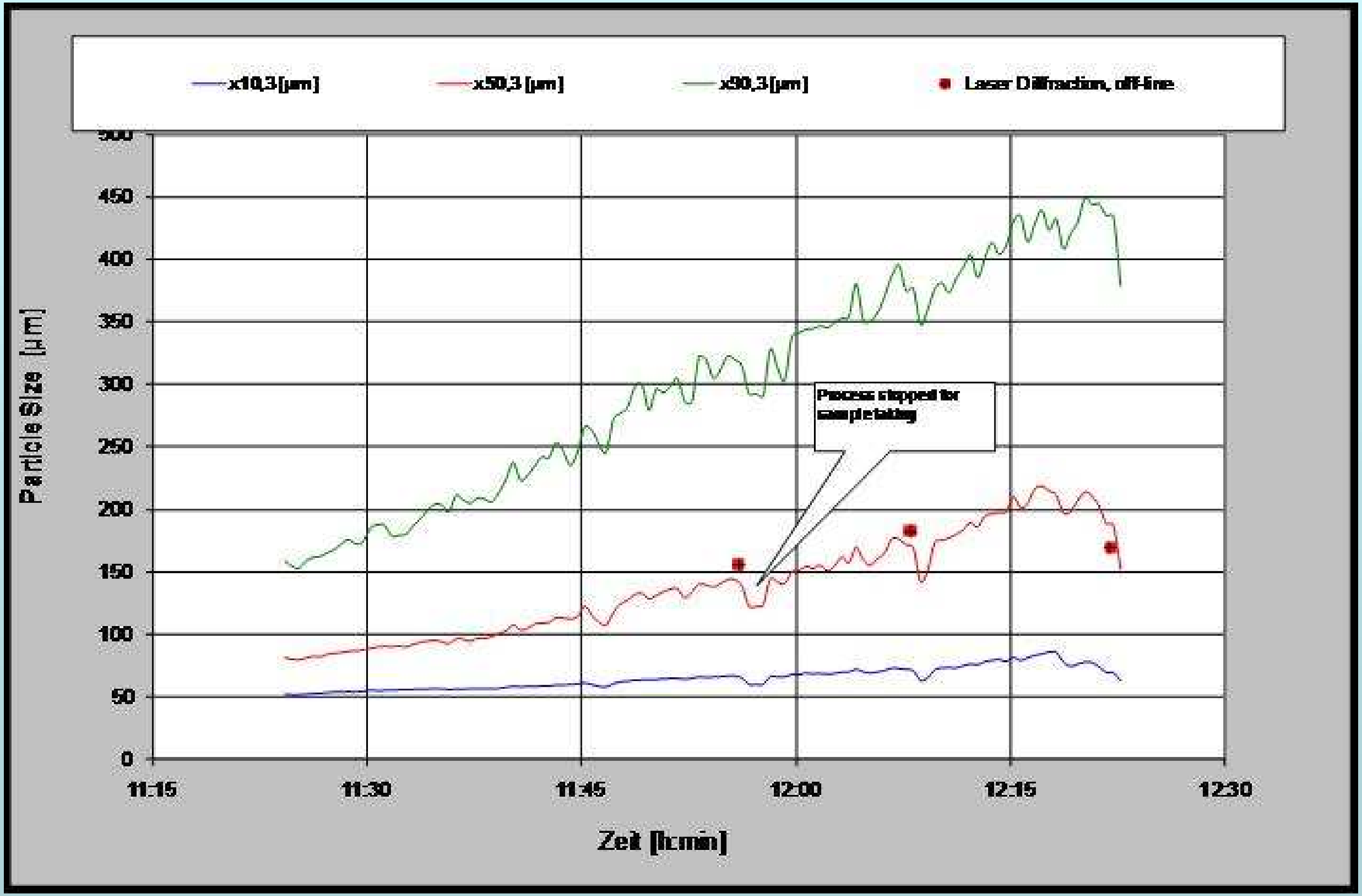
Objective:

- To see trends in granulation,
- To find end-point of granulation,
- To see any defect (blocked nozzles, break down of fluidized bed ...) and
- To demo the suitability of IPP-70 for direct measurement within fluidized beds.

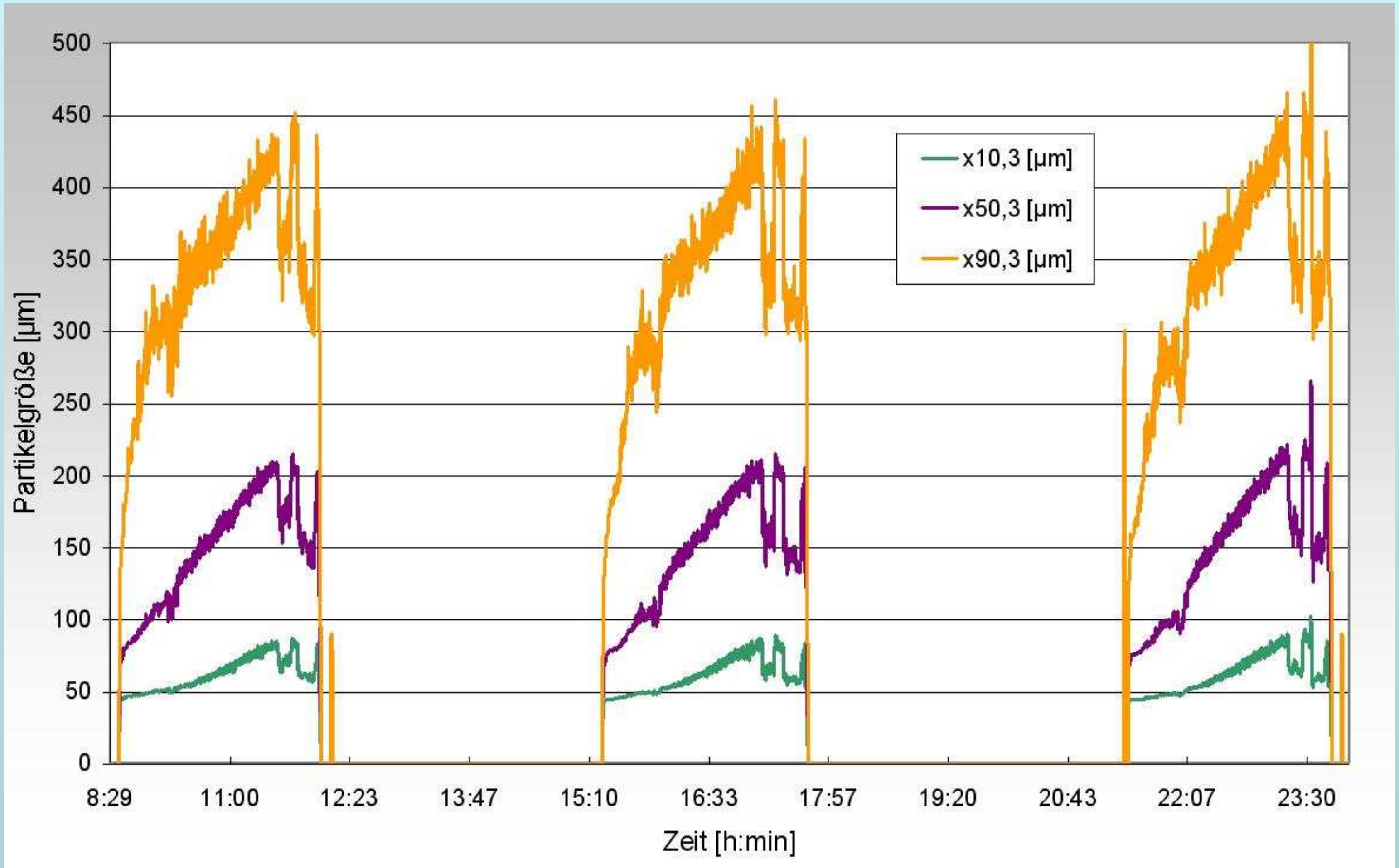


➢ Product: Lactose Powder,
➢ Equipment: 5 Kg lab scale FB Granulator, Top Spray
➢ Installation: IPP70-S with D23

Batch-Fluid Bed Granulation: Agglomeration of Lactose



Fluid Bed Granulation of 3 Batches (300 Kg) at a pharmaceutical Production Site



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Wurster Coating

Objective: Measurement of thickness of sprayed layer Detection of Agglomerates (Twins)

Product: Sugar pellets, spherical, 300µm,

Process-Equipment: Lab-scale FB-Granulator, 3Kg with Wurster-Tube and Bottom-Spray

Installation: IPP70-S with Inline-eductor D23

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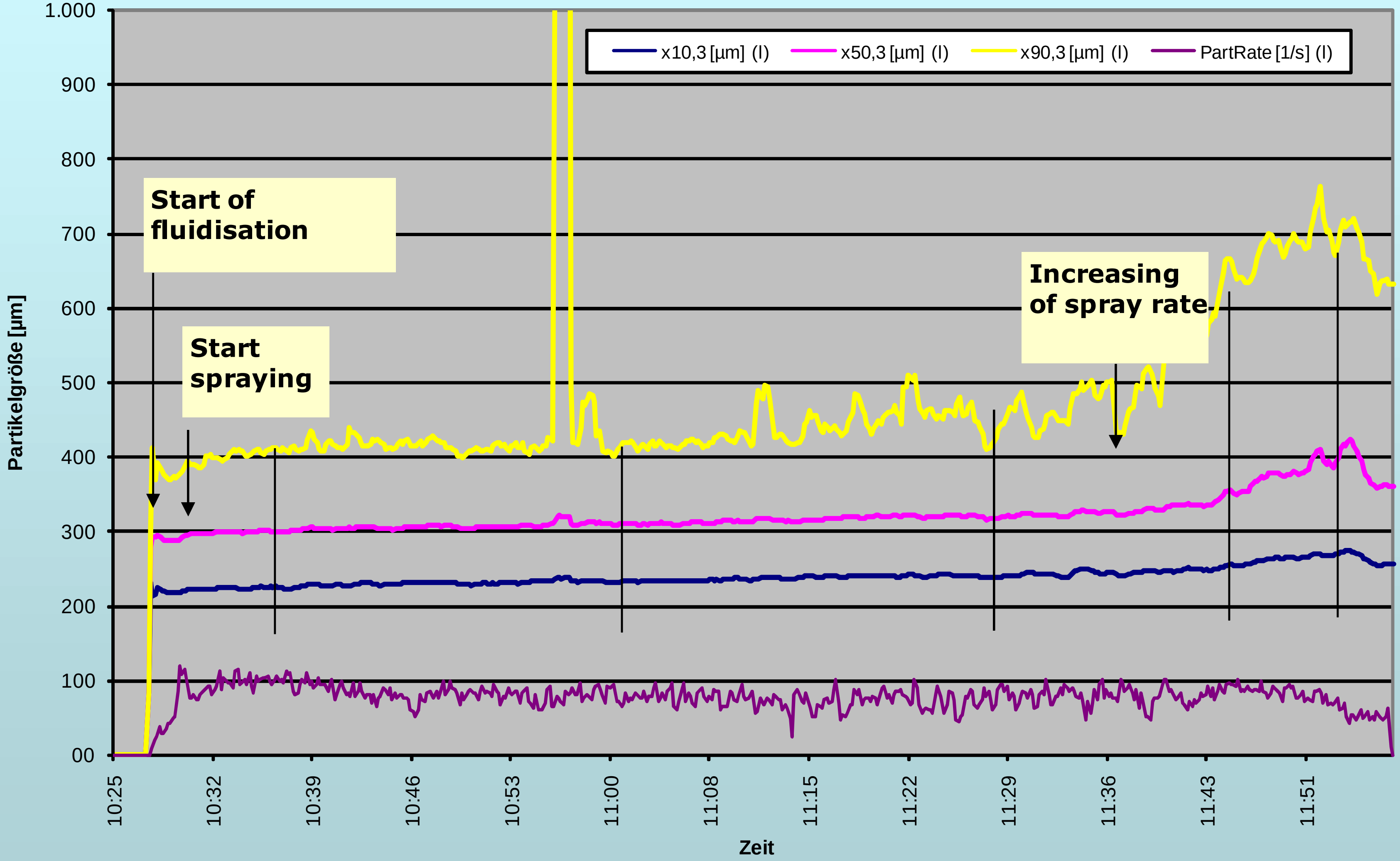
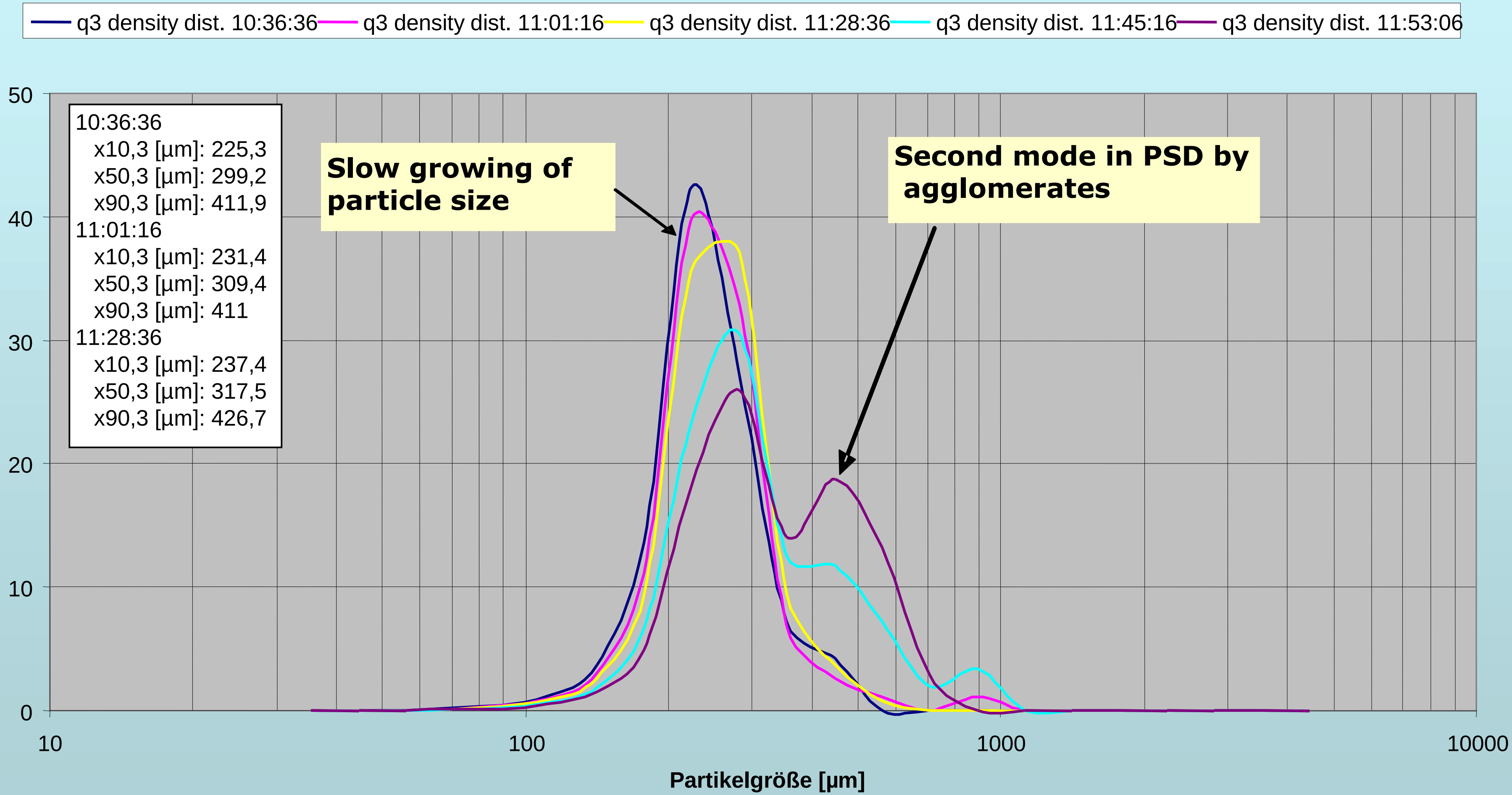
Wurster Coating



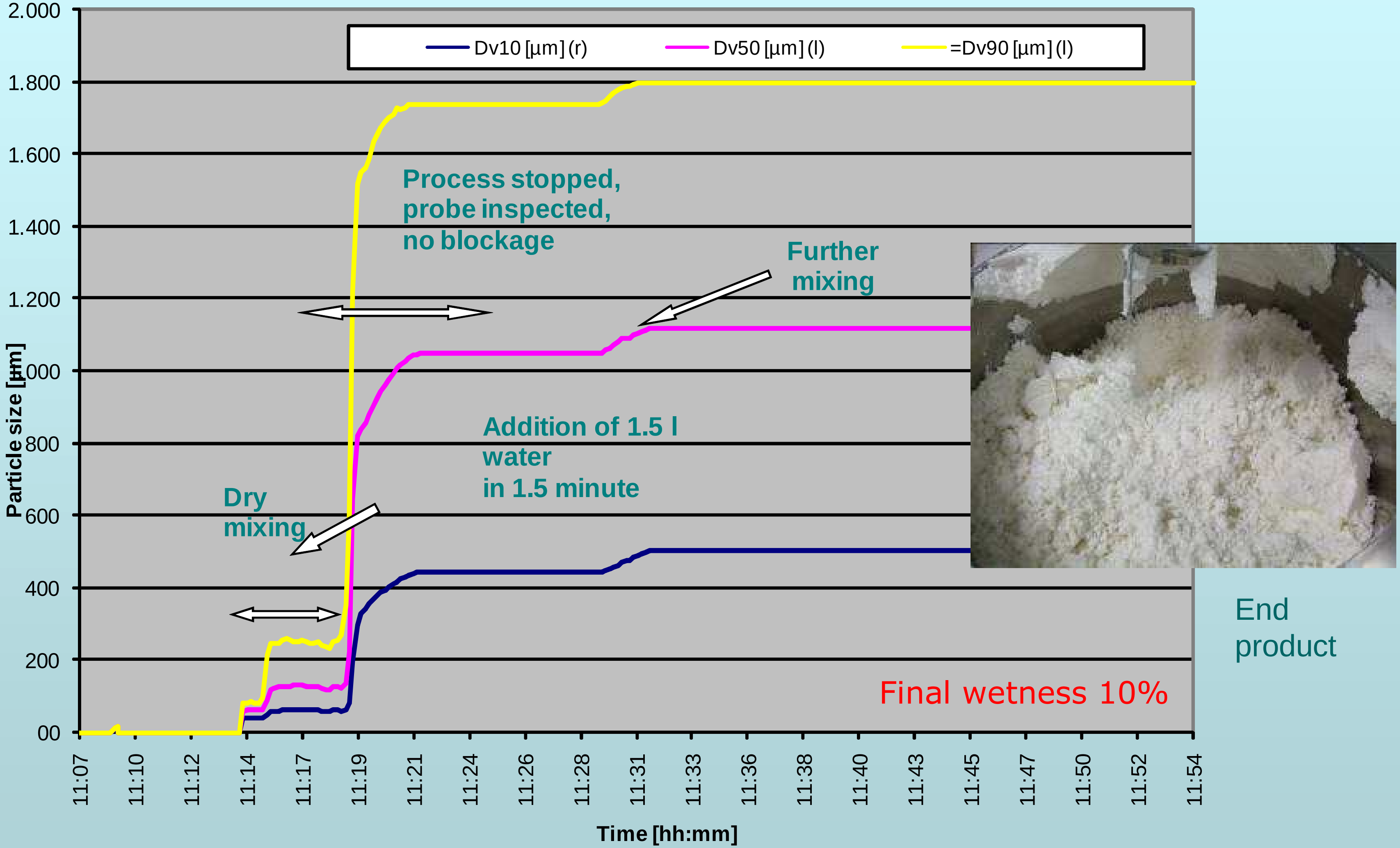
Wurster Coating



High Shear Granulation

- Diosna Dierks & Söhne GmbH (Osnabrück)
- Objective: To demo the suitability of IPP-70-s in smaller mixers 15 Kg, Lactose, MCC …
- Pilot Processer System P/VAC 10 - 60

High Shear Granulation



End product

High Shear Granulation, production scale

Objective: To demo suitability of IPP 70-SL in larger mixers.

To follow fast particle size changing

flexible depth of probe

Product:

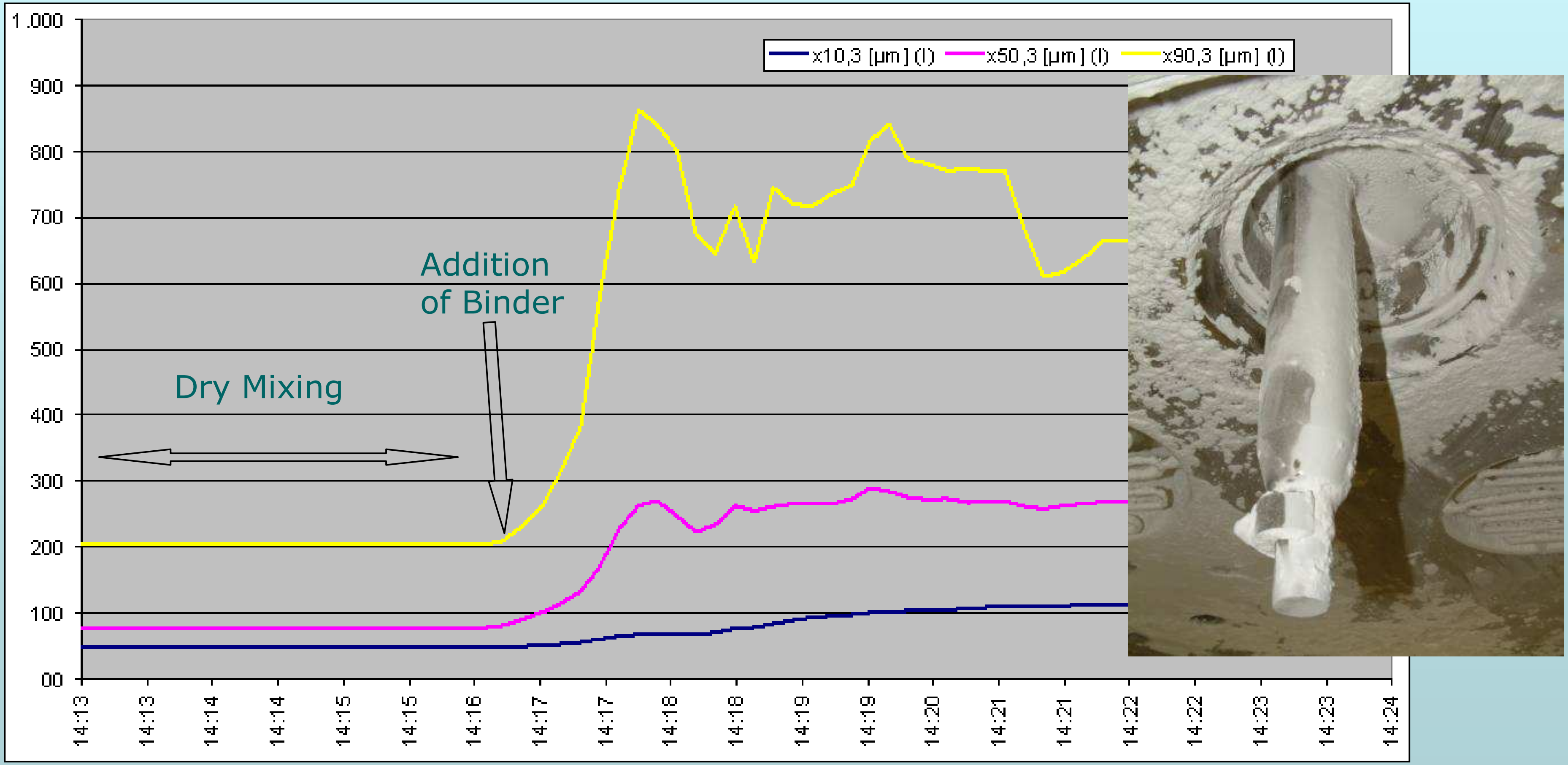
Lactose with API

Installation:

IPP 70-SL (60 cm)

with inline-eductor D23

High Shear Granulation, production scale



Inline Particle Sizing

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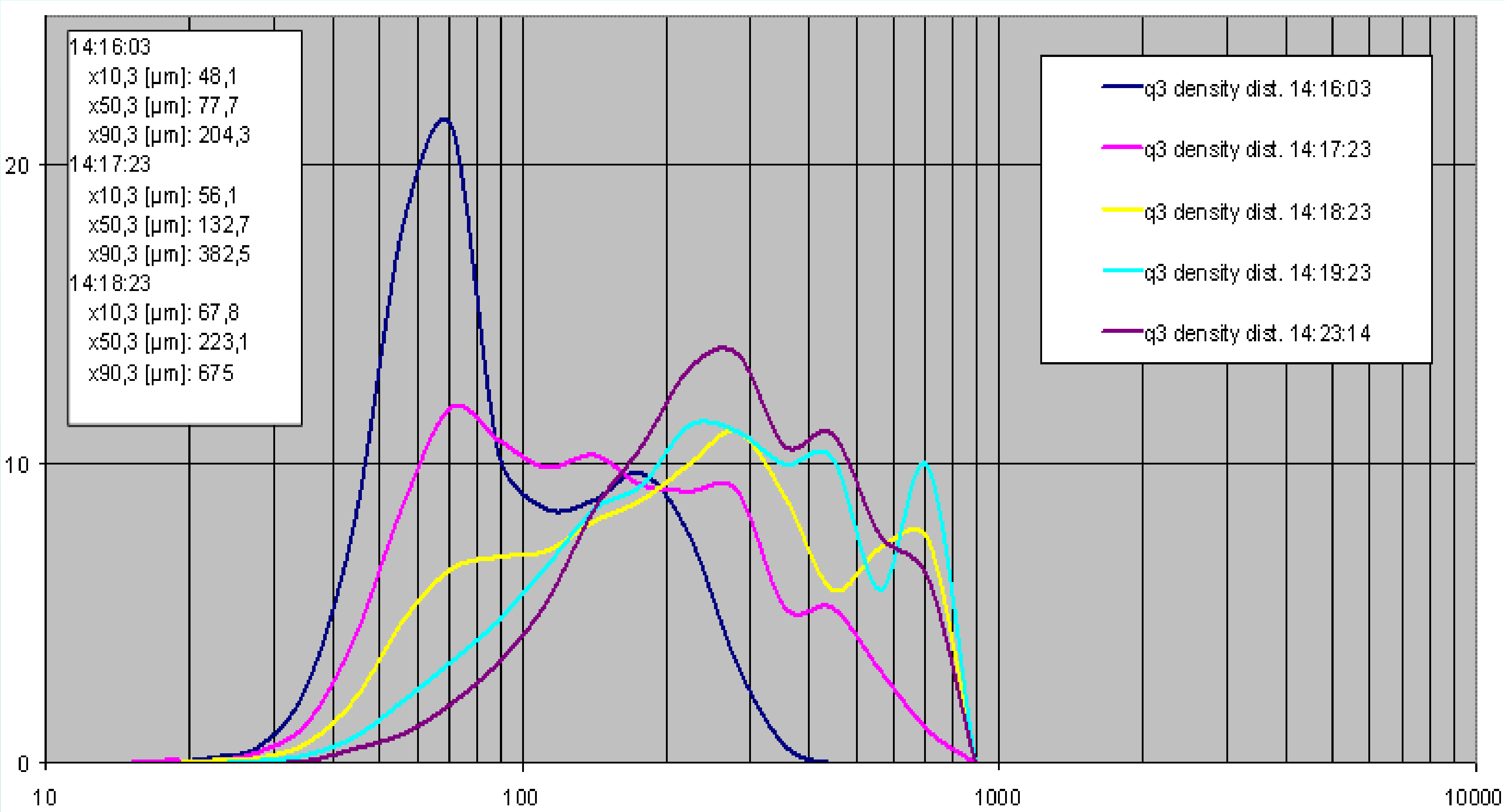
High Shear Granulation, production scale



Conclusion

IPP70 probe is a turnkey solution to gain on-line PSD information for most fluid bed processes

- Data correlate to standard off-line PSD methods
- Modeling of impact of granulation parameters on the final PSD is possible
- Designing the process to a pre-defined PSD
- Detect process failures

IPP 70 probe can monitor high shear granulation processes

- Help defining process endpoint

Thank you for your attention!

Questions?

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