8th Central European Symposium on Pharmaceutical Technology
September 16th–18th 2010, Graz, Austria

Spatial filtering technique as powerful tool for real-time particle size measurement for fluid bed applications in pharmaceutical industry

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parsum
Gesellschaft für Partikel-, Strömungs- und Umweltmeßtechnik mbH

Presentation Outline

- Introduction

- Measuring principle
  – spot scanning
  – spatial filtering velocimetry

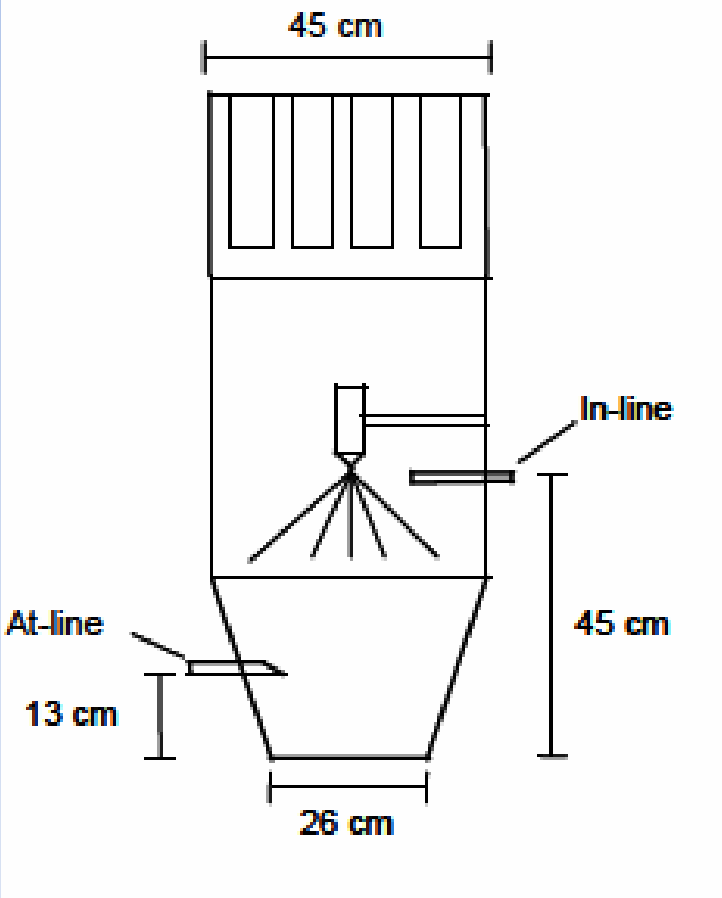
- Measuring system
  – Parsum IPP 70

- Examples of application to
  – fluid bed processes
  – high shear granulation processes

- Conclusions

Introduction

Results of Dissertation Tero Närvänen, University of Helsinki, Faculty of Pharmacy, 2009: „Particle Size Determination during Fluid Bed Granulation“

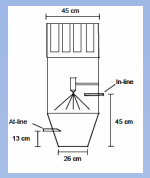


17 batches each 2kg theophylline anhydrate, 2 kg α-lactose monohydrate, 2 kg 7.5% aqueous binder solution

Fluid-bed granulator WSG 5, Glatt GmbH
41 process parameters

In-line particle size measurement by a Parsum Probe IPP 70 based on spatial filtering

Real-time particle size prediction based on spraying phase and drying phase model
Method: partial least squares regression

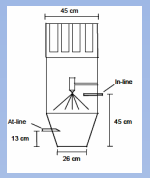


Results of modelling

Second-order polynomial fitting

Variables of modelling: median granule size, relative width of size distribution, humidity inlet air, liquid feed rate, pauses of liquid feed

Granule size measurement: sieve analysis, laser diffraction, spatial filtering



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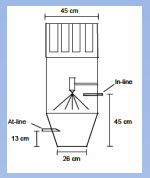
x50	Spatial filtering	Sieve analysis	Laser diffraction
Goodness of fit	0.94	0.89	0.90
Goodness of prediction	0.90	0.68	0.76



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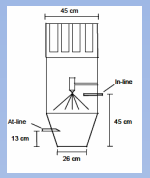
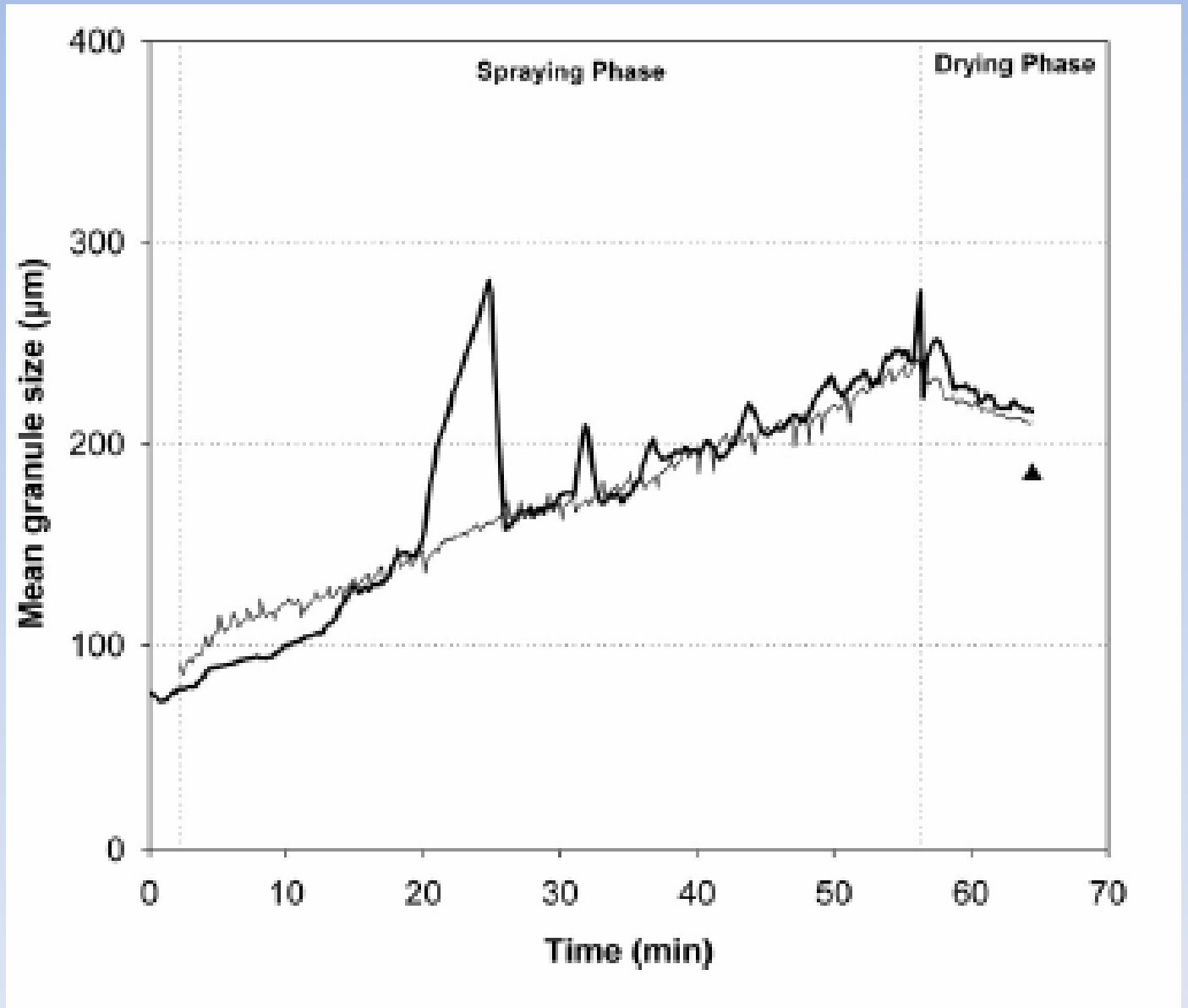
(x90-x10)/x50	Spatial filtering	Sieve analysis	Laser diffraction
Goodness of fit	0.71		
Goodness of prediction	0.31		



Real-time particle size prediction



x50 /µm
for one batch

Thick line: in-line spatial filtering

Thin line: predicted

Triangle: off-line spatial filtering

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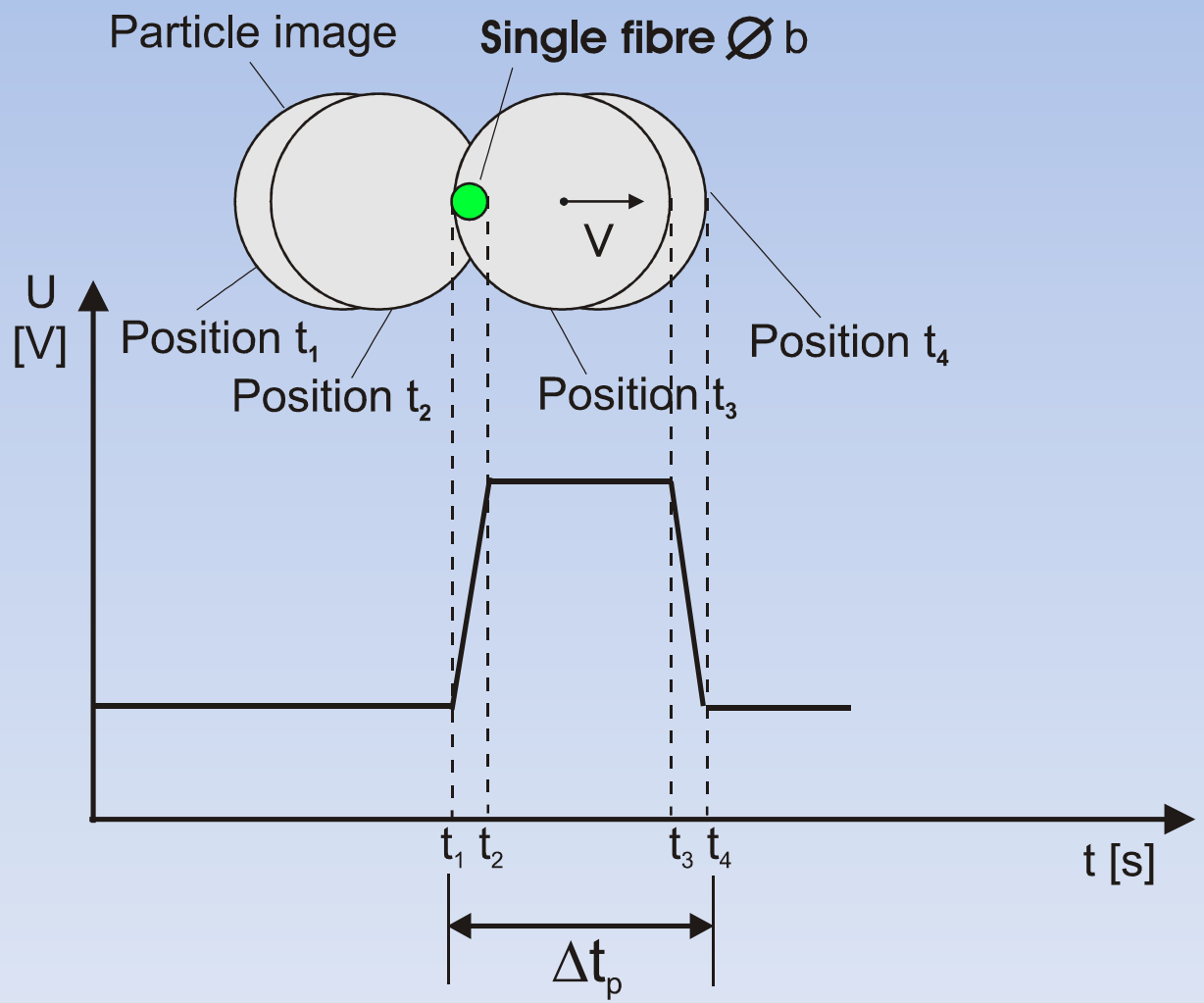
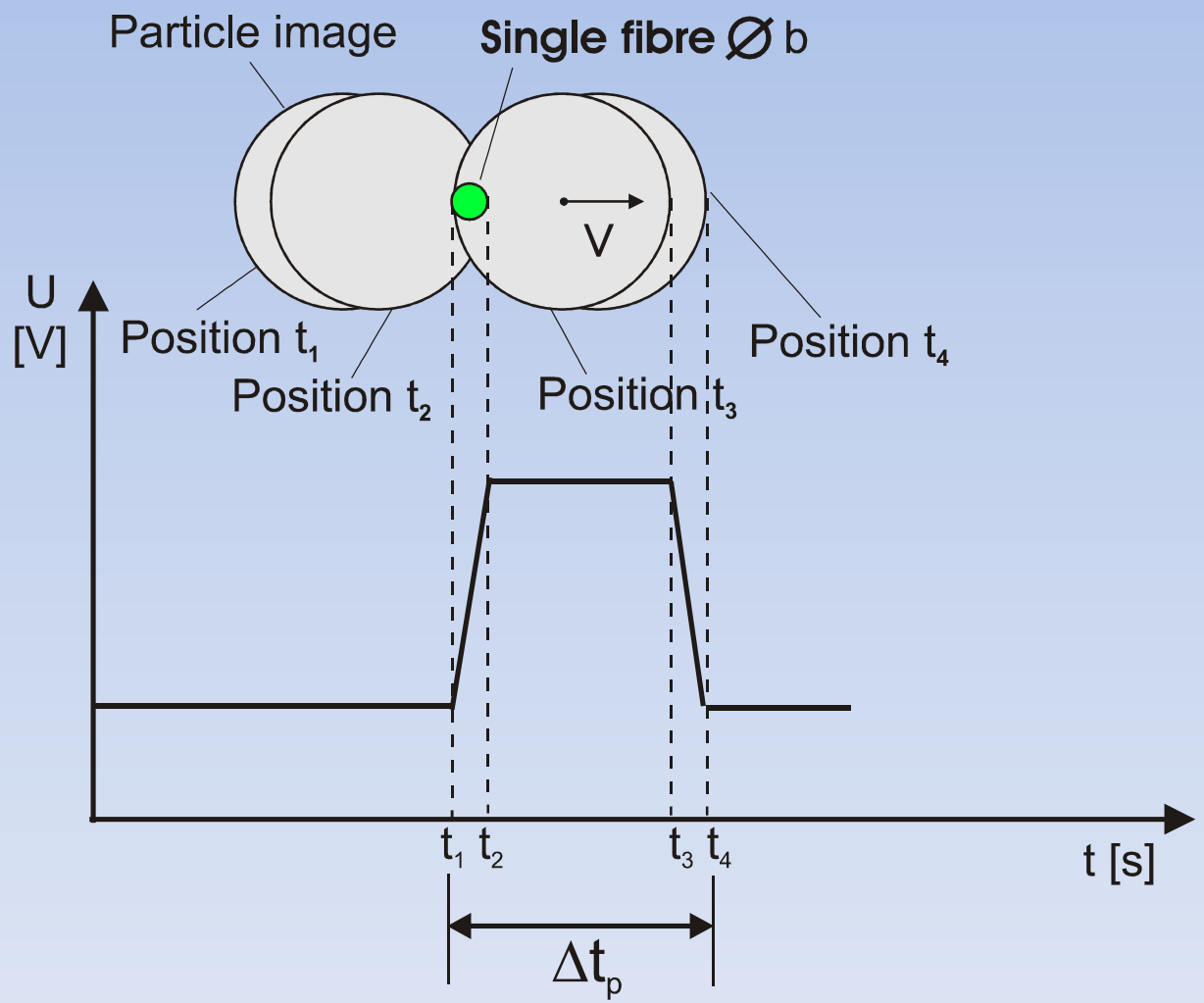
Real-time particle size measurement with spatial filtering technique (SFT)



First measuring principle:
Fibre-optical spot scanning

Real-time particle size measurement with spatial filtering technique (SFT)



First measuring principle:
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Measured quantity:
Chord length x

$x = v \cdot \Delta t_p - b$; $v = ?$

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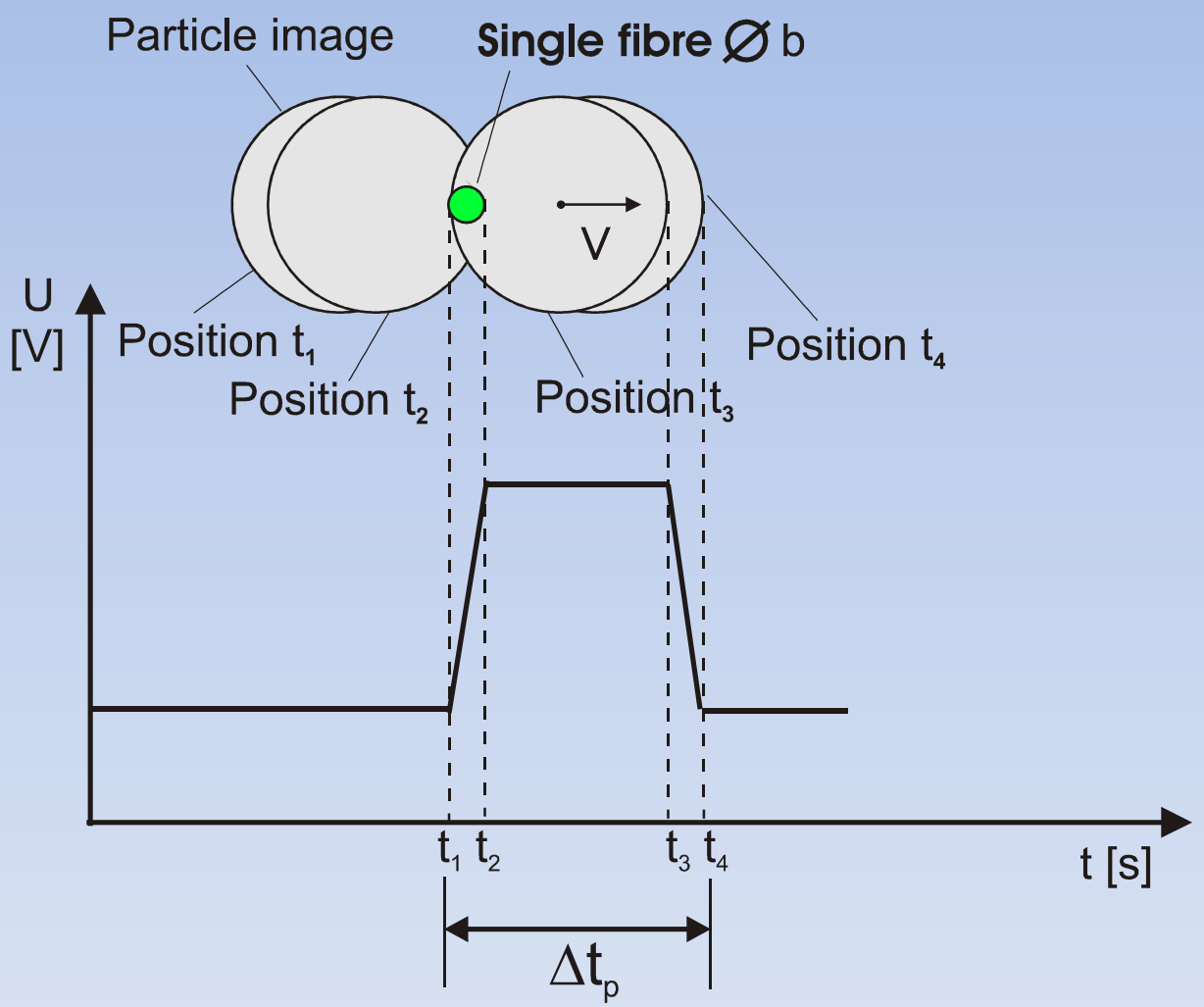

First measuring principle:
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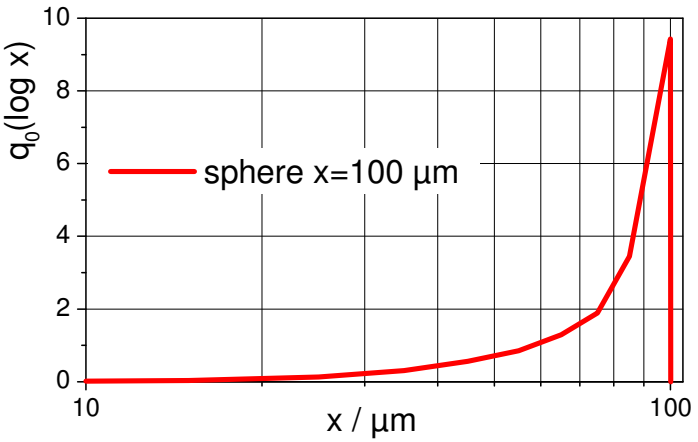
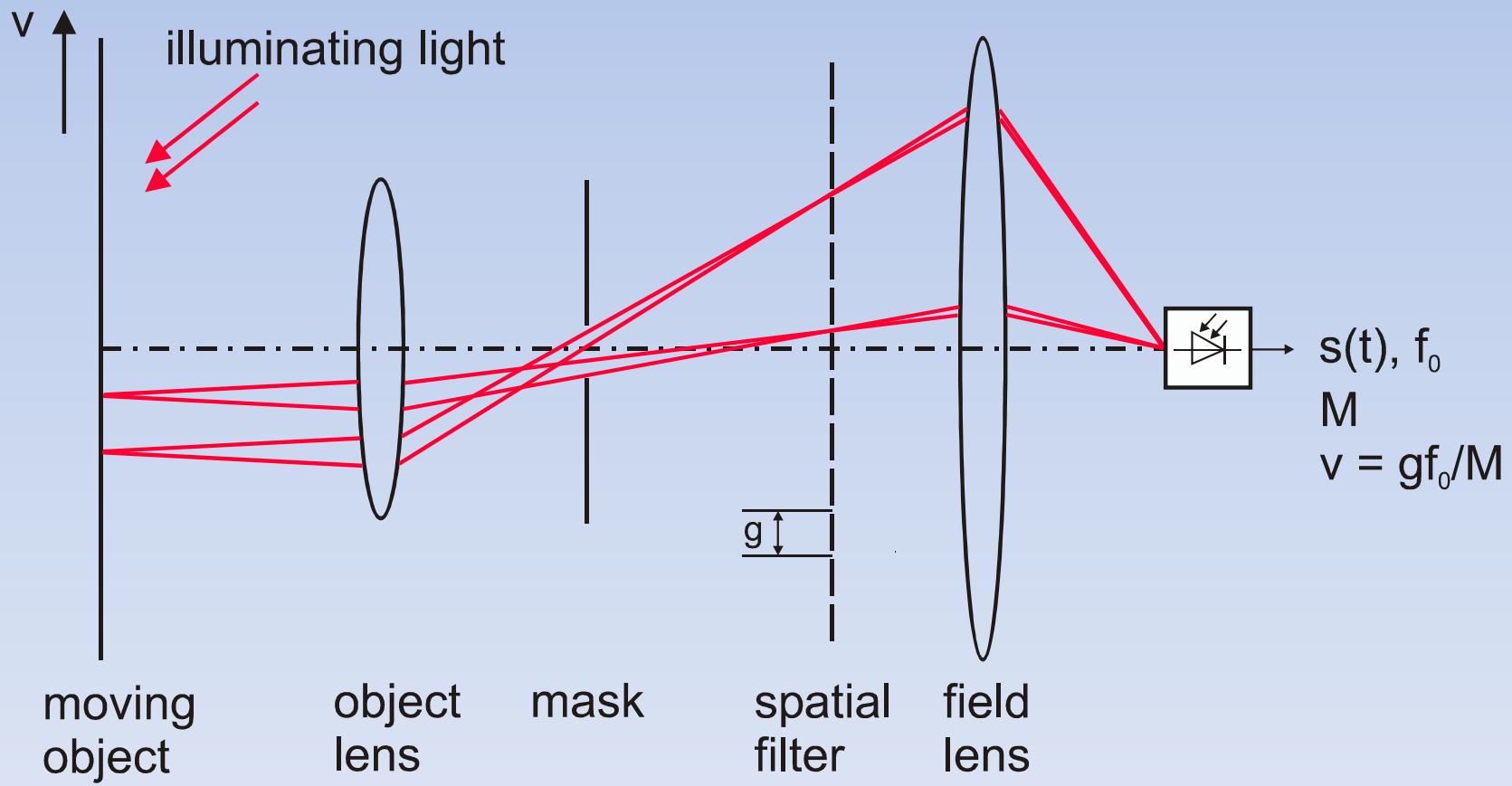
Chord length distribution



Real-time particle size measurement with spatial filtering technique (SFT)

Second measuring principle: SFT



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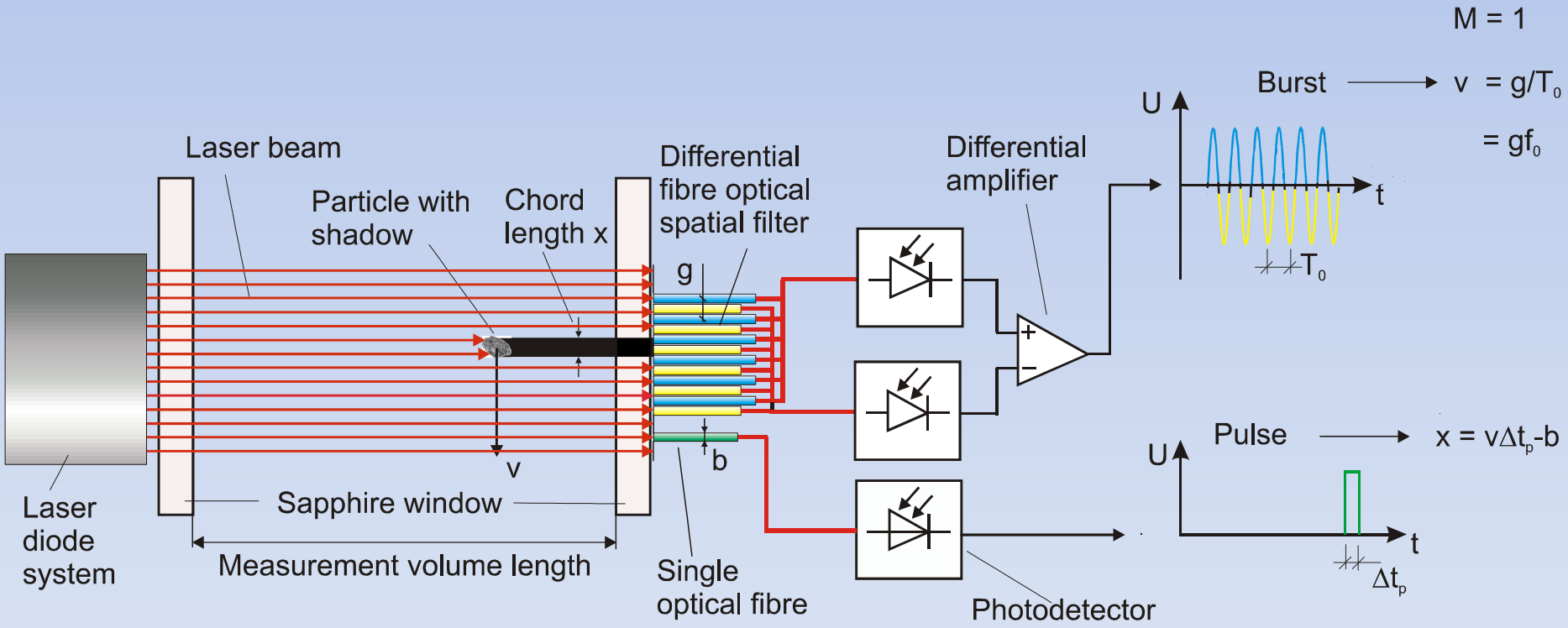
Probe system IPP 70 of Parsum GmbH



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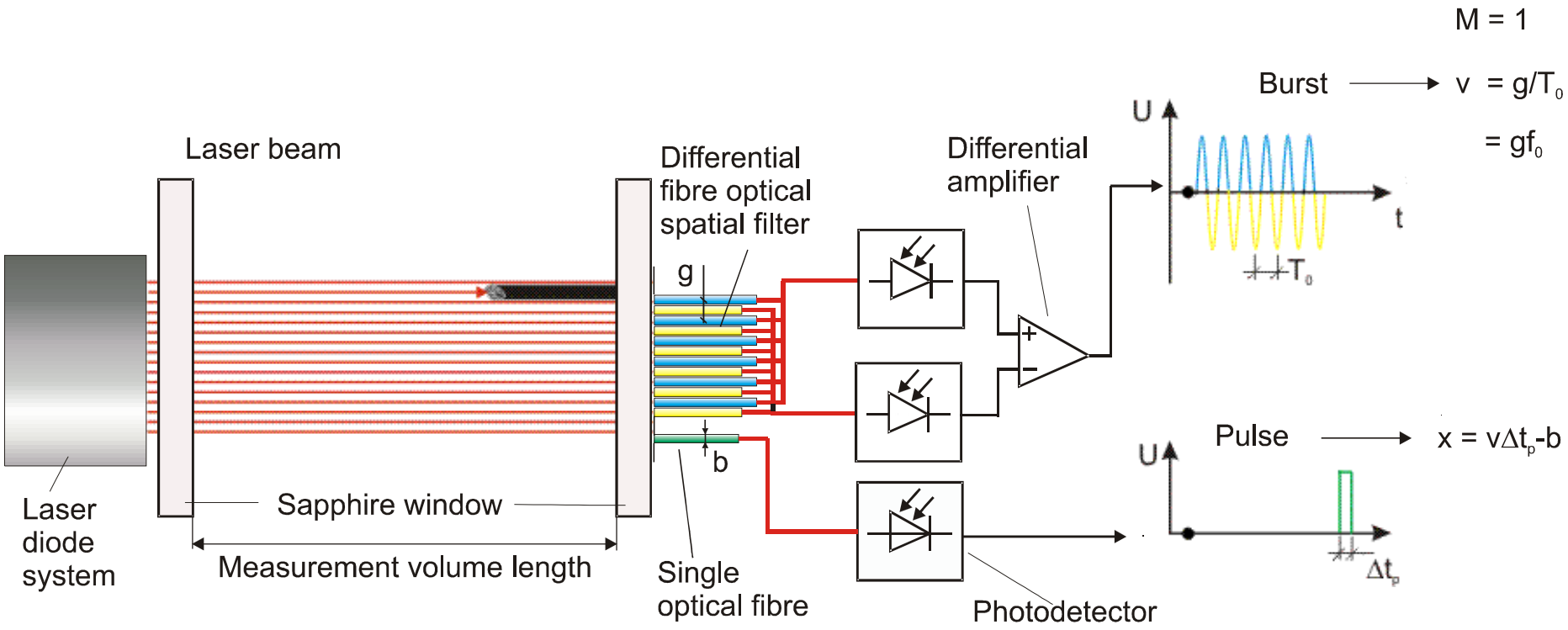

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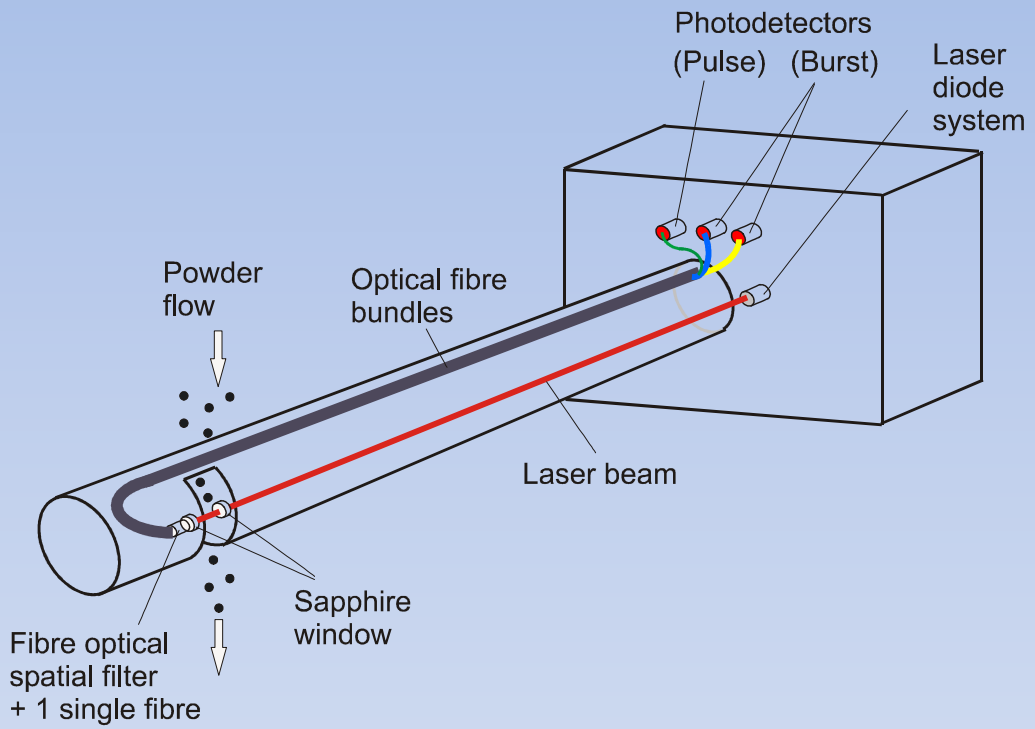

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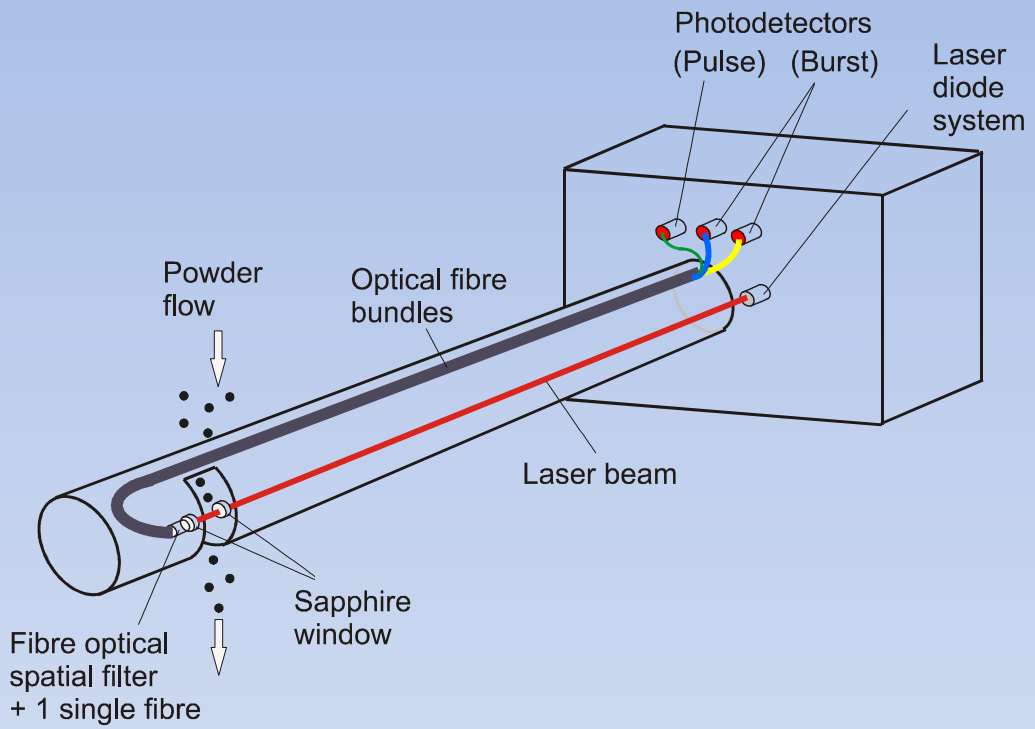

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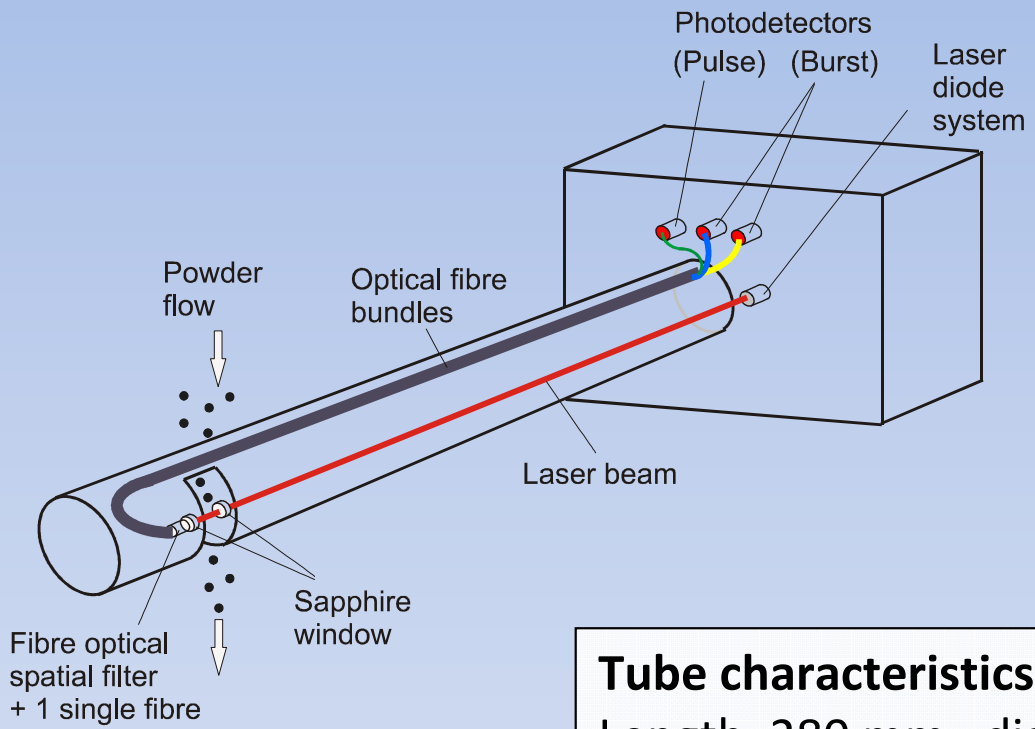

Tube characteristics:
Length 280 mm, diameter 25 mm (Standard)

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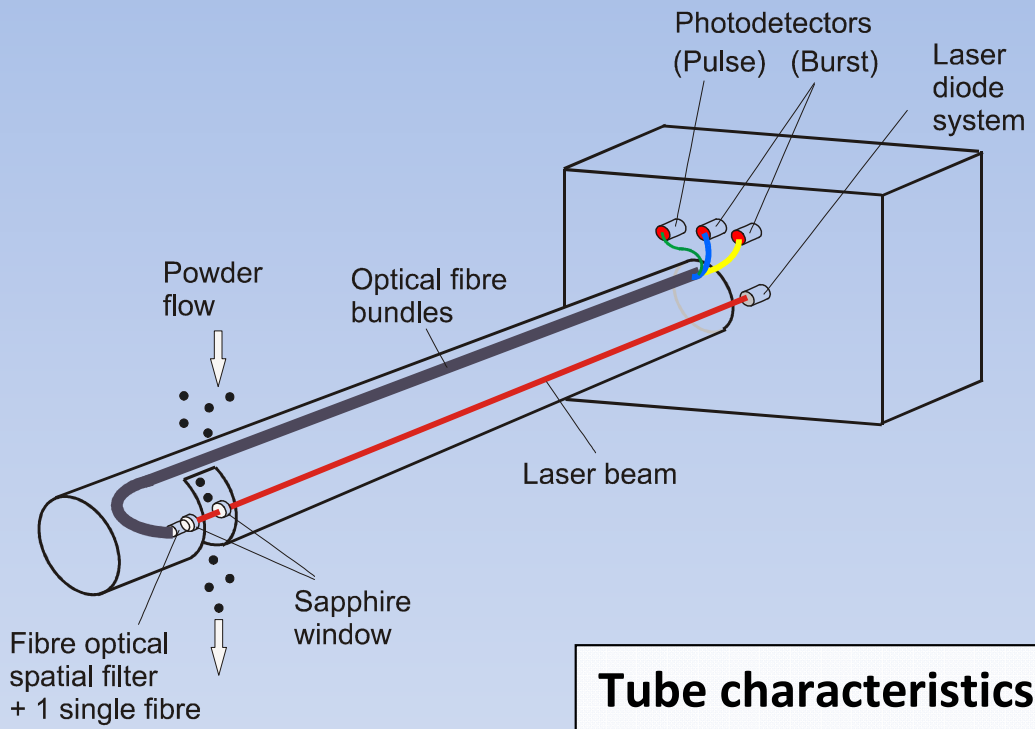
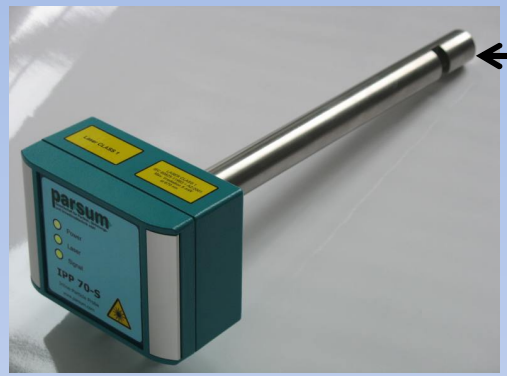


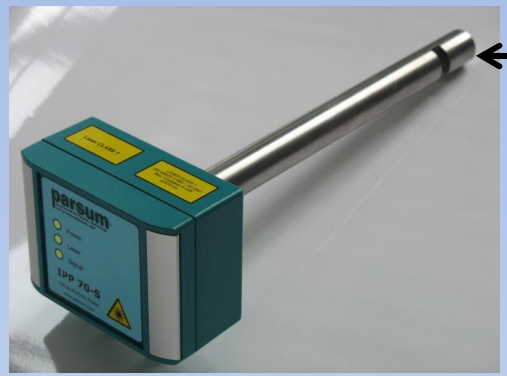
Tube characteristics:
Length 280 mm, diameter 25 mm (Standard)
Length up to 4000 mm, diameter 50 mm

Probe system IPP 70 of Parsum GmbH



- Flushing cells protect the sapphire windows

Probe system IPP 70 of Parsum GmbH



- Flushing cells protect the sapphire windows

- In-line disperser for high particle loading

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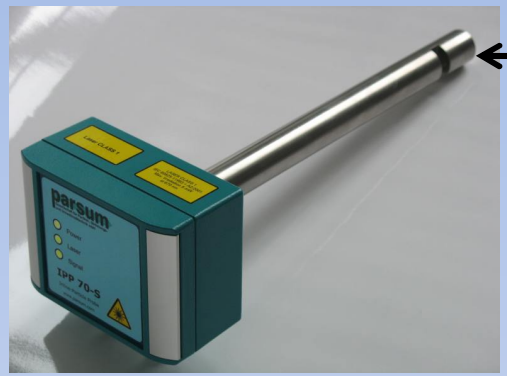

- Flushing cells protect the sapphire windows

- In-line disperser for high particle loading

- Barrier housing and special air valves allow applications for Ex environments

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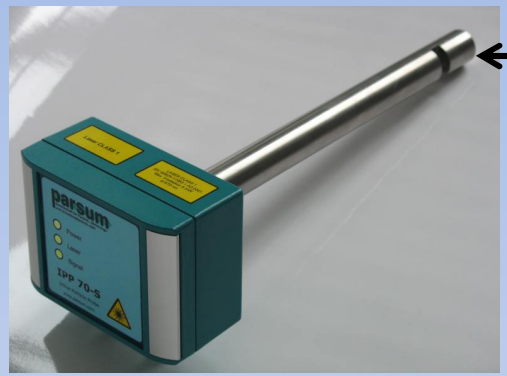

- Flushing cells protect the sapphire windows

- In-line disperser for high particle loading

- Barrier housing and special air valves allow applications for Ex environments

- 3 Pharma options: a verification kit with documents for installation and operational qualification, polished surfaces, software Parsum View

Probe system IPP 70 of Parsum GmbH

Main probe data:

- Particle size range: 50 µm...6 mm
- Particle velocity range: 0.01 m/s...50 m/s
- Data rate up to 20,000 particles/s
- Interface 4...20 mA or Web-Server

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Process conditions:

- -20°C...100°C at measuring point
- up to 4 bar
- 30 % particle volume concentration

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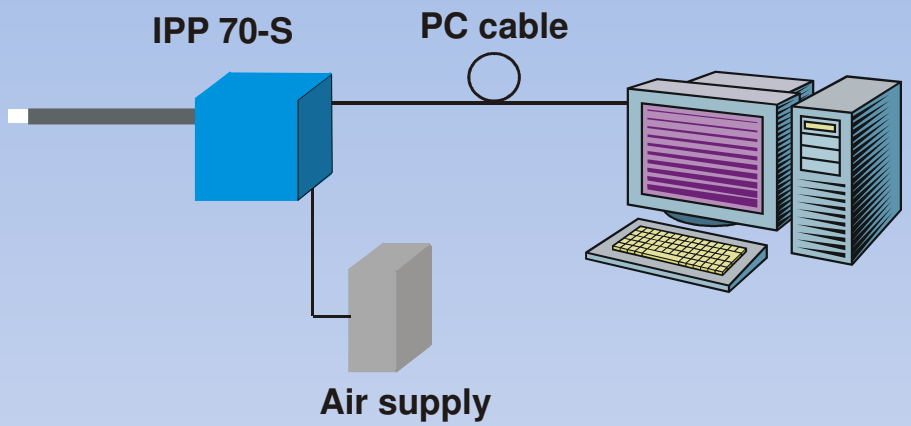
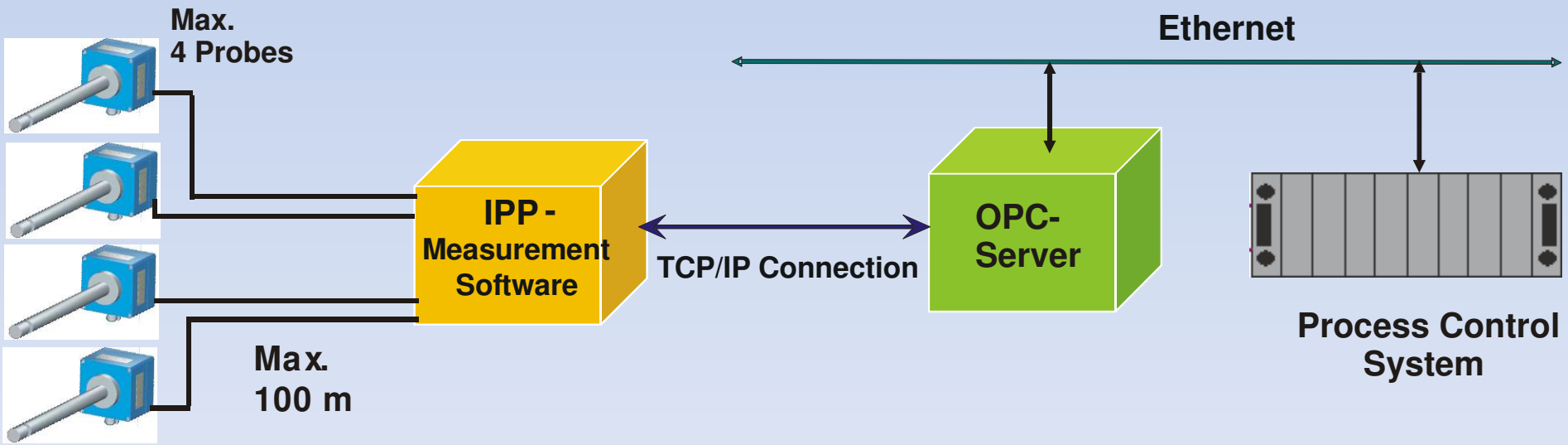
Data representation:

- Cumulative and density distributions
- Number and volume distributions
- Percentages x10, x50, x90
- Progress of the data over the measuring time by using a variable buffer size ⟶ **real-time measurement**

Probe system IPP 70 of Parsum GmbH





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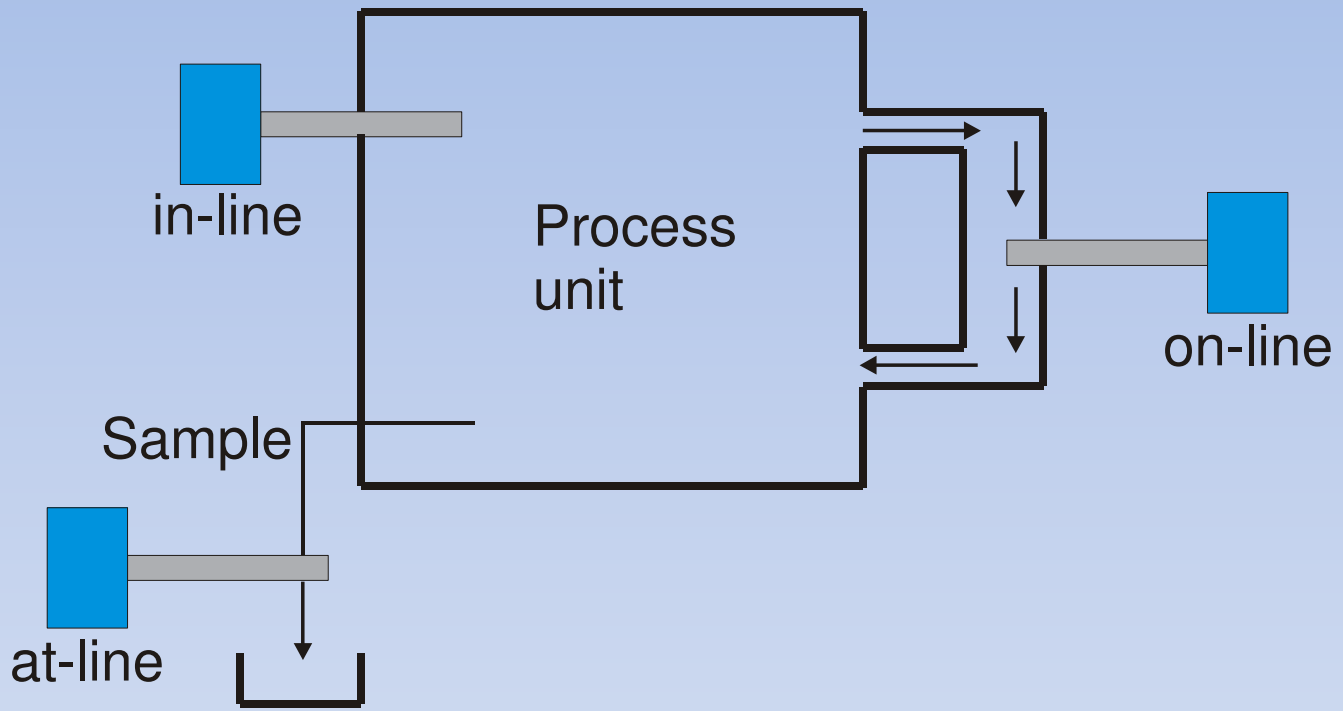
Application of IPP 70



<u>Focus:</u> Examples of in-line particle sizing

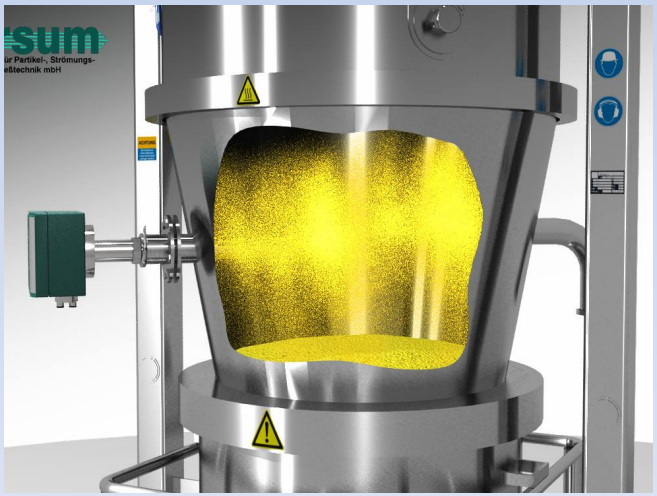
Fluid bed processes

1. Fluid Bed Batch Granulation

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

Objective:

Trends, end-point, defects



Fluid bed processes

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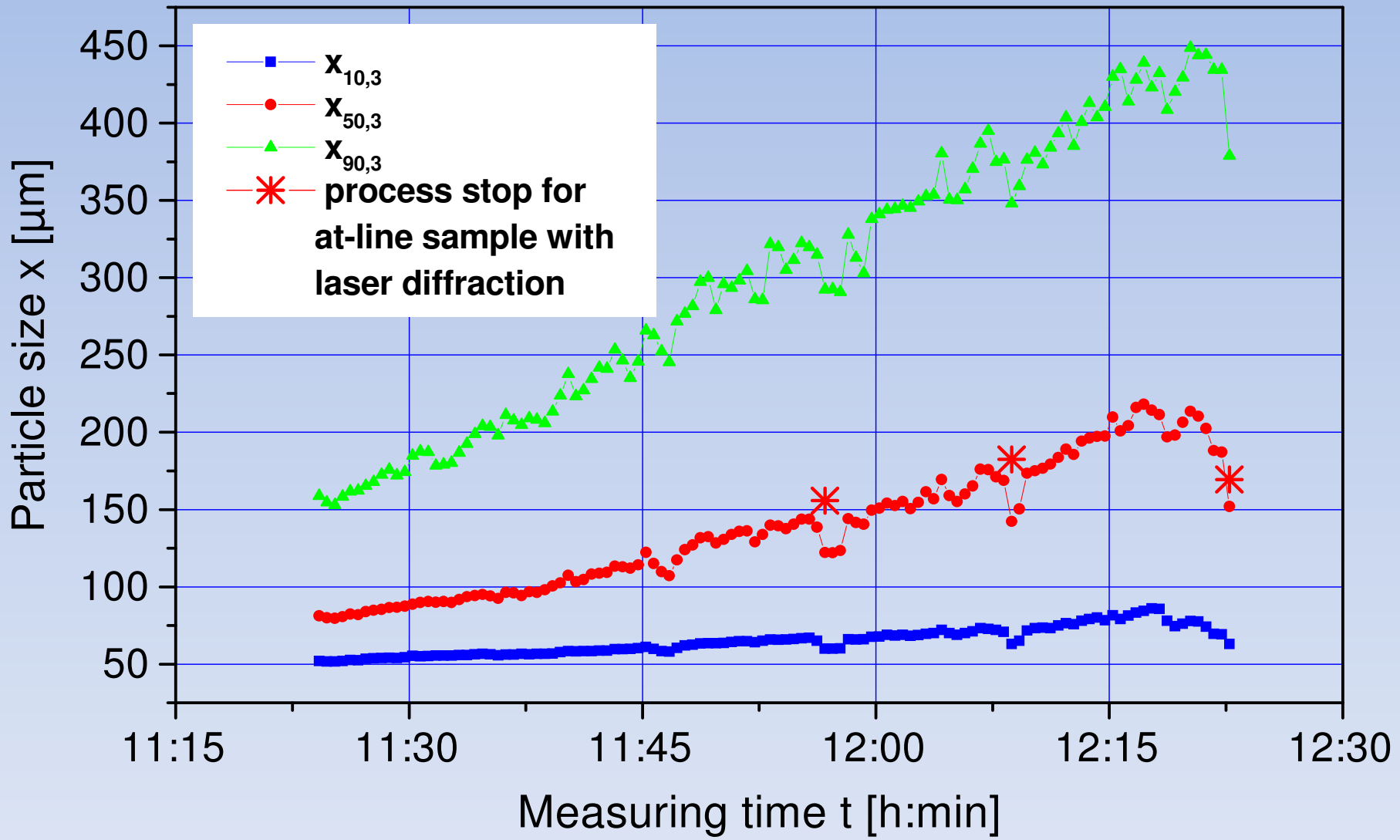


Fluid bed processes

2. Wurster Coating

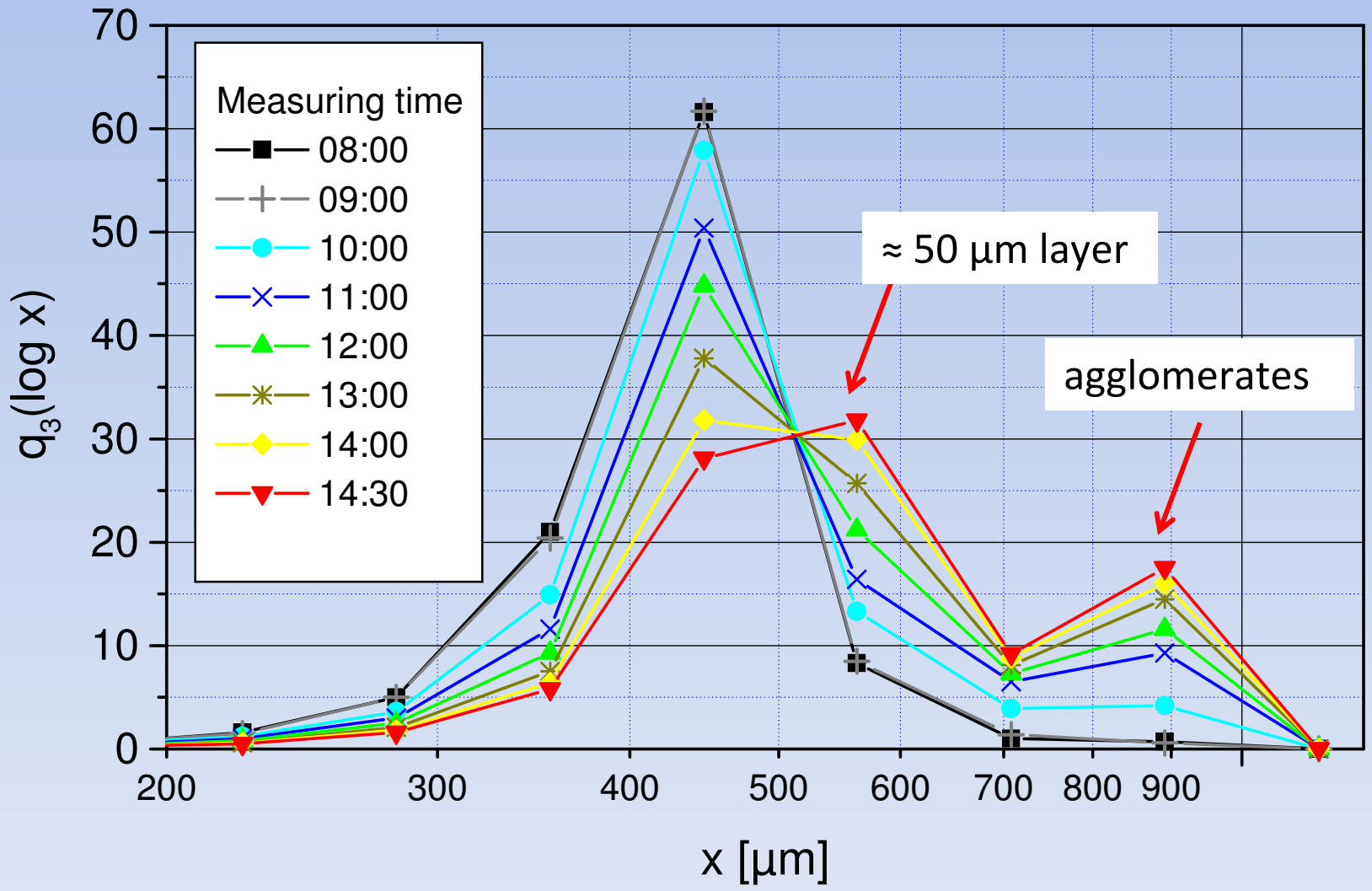
- Product: Sugar pellets, spherical, 200…700 µm
- Equipment: Lab-scale FB-Granulator, 3Kg with Wurster-Tube and Bottom-Spray
- Installation: IPP70-S with In-line-eductor D23

Objective:

- Measurement of thickness of sprayed layer
- Detection of agglomerates

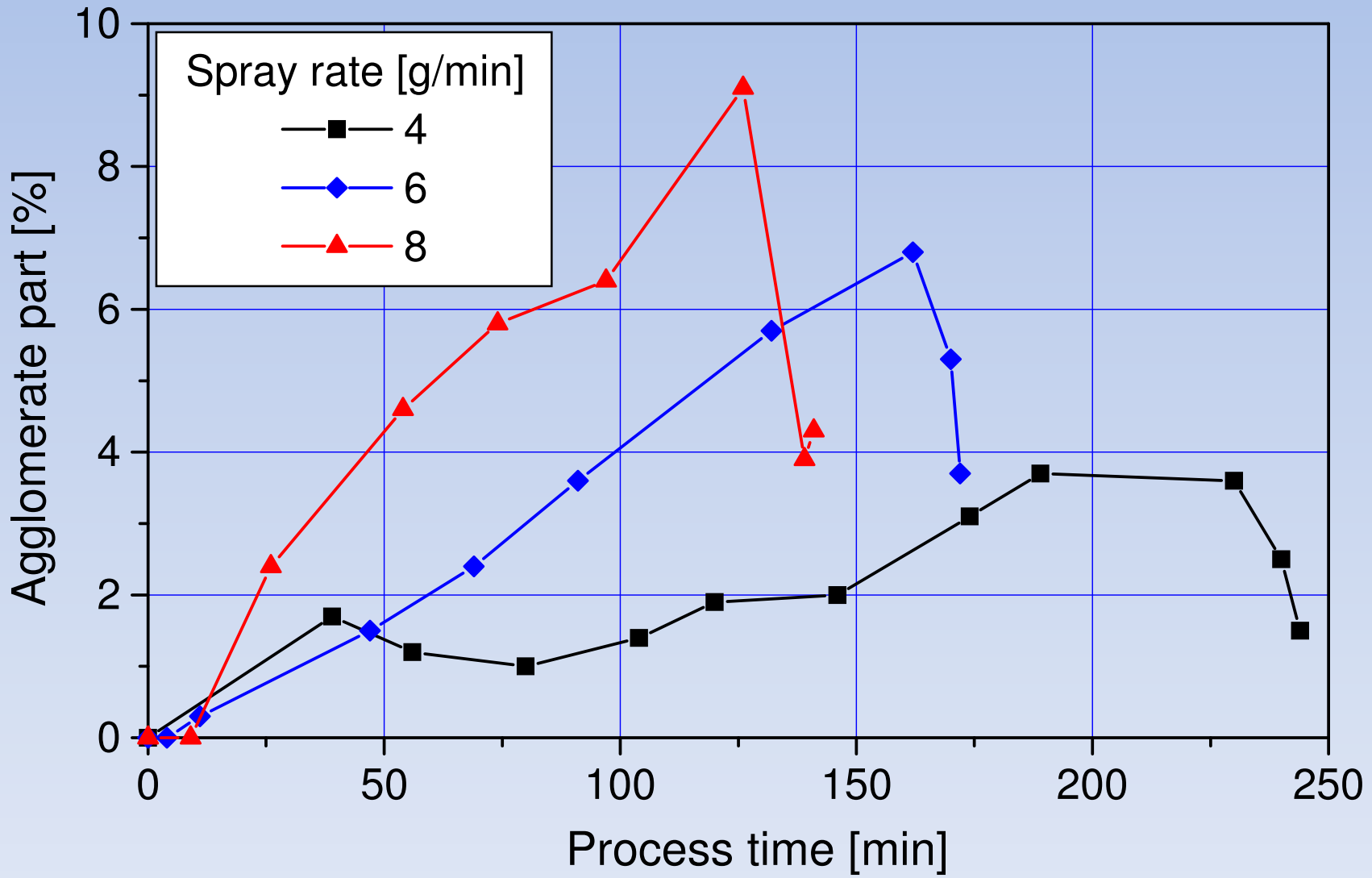
Fluid bed processes

2. Wurster Coating



Fluid bed processes

2. Wurster Coating (1,5 kg Cellets 200...355 µm, Pharmacoat-606-solution)
Agglomerates > 400 µm

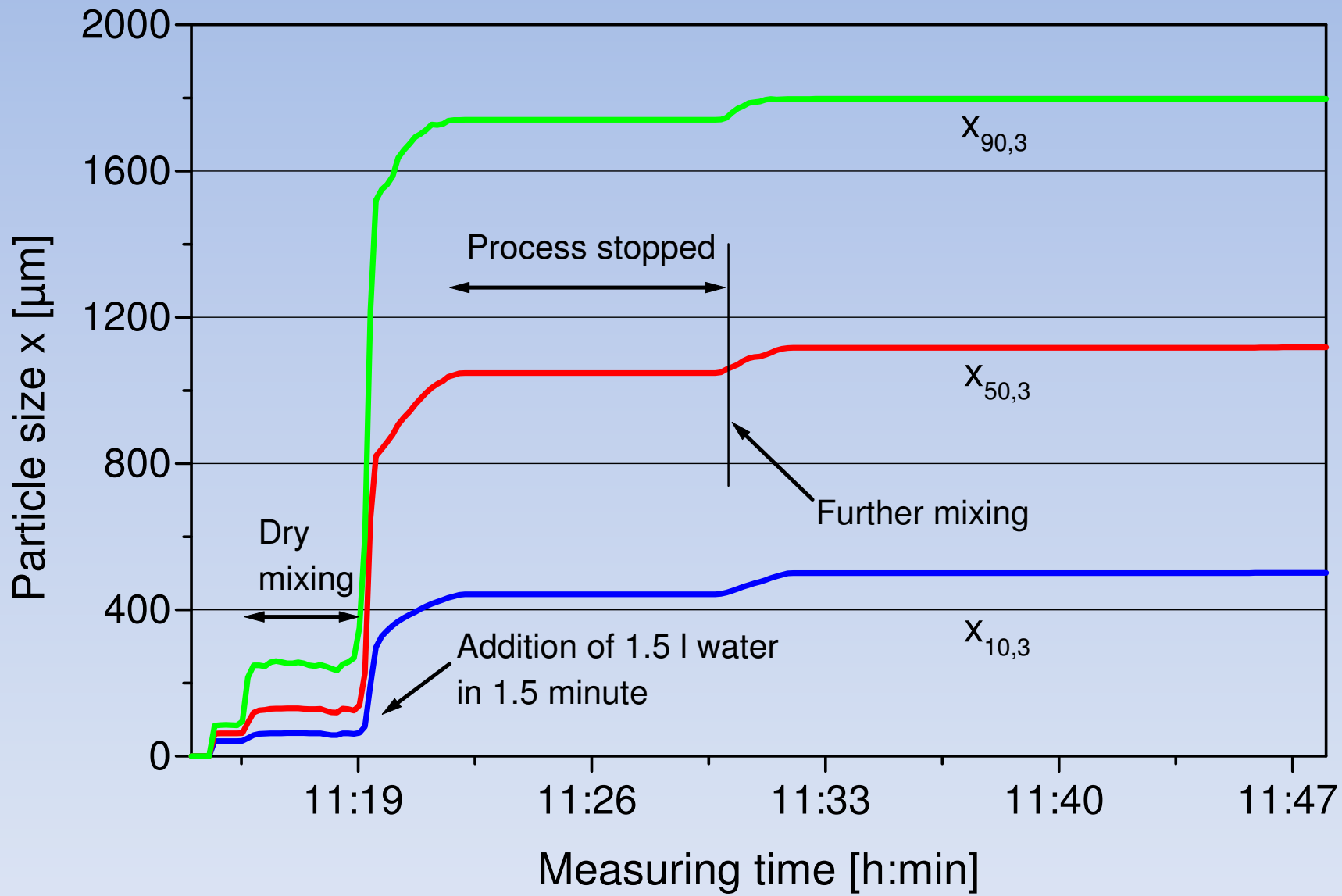


High shear granulation

- Diosna Dierks & Söhne GmbH (Osnabrück)
- Objective: Suitability of IPP 70-S, SL in mixers of different size, determination of endpoint
- 15 Kg, Lactose with API
- Pilot Processer System P/VAC 10 - 60

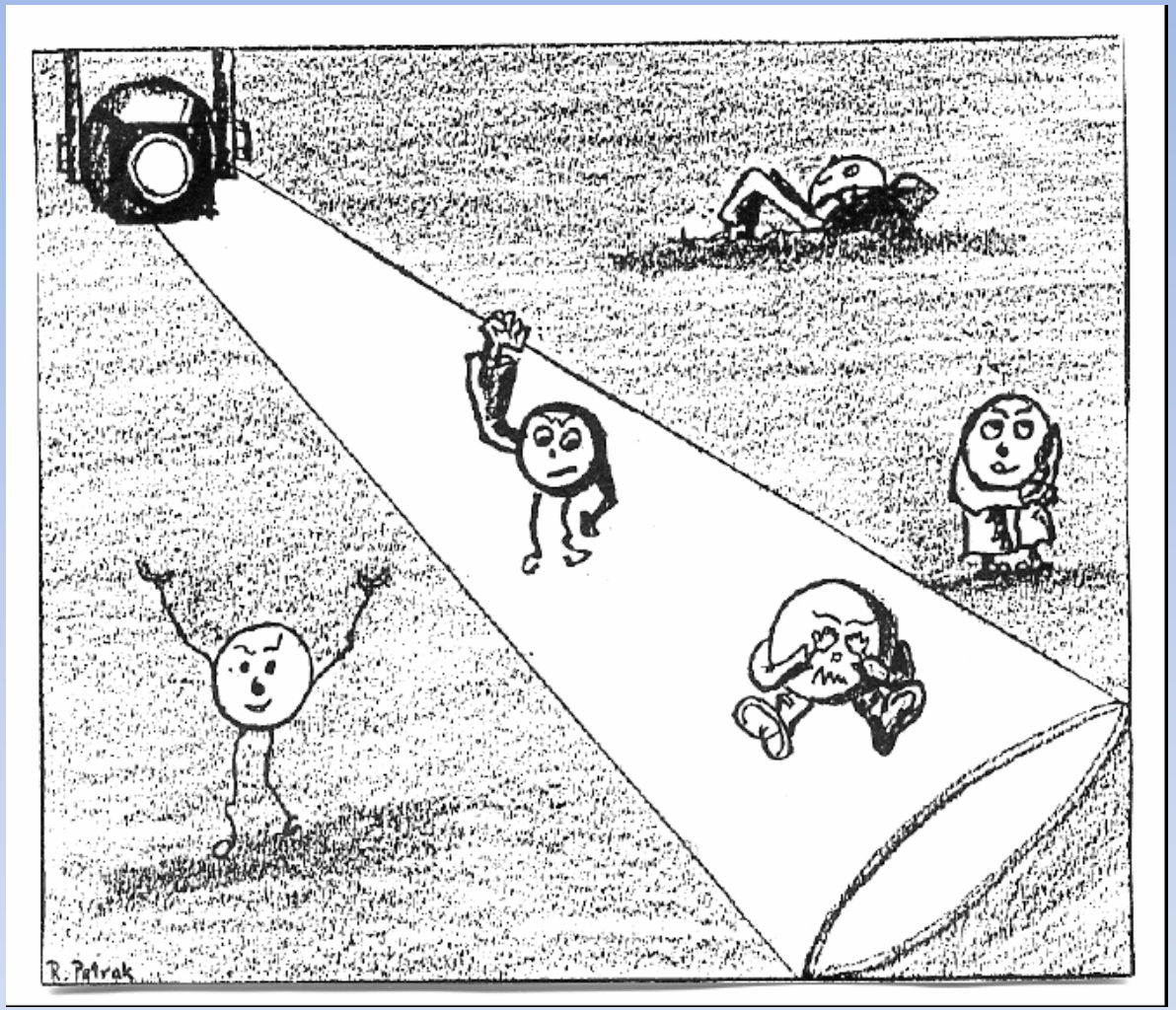
- Diosna P 600
- IPP 70-SL (60 cm)

High shear granulation



Conclusions

- IPP 70 probe is a powerful PAT tool for real-time PSD in-line measurement of most fluid bed processes
  - IPP 70-Data correlate to standard off-line PSD methods
  - IPP 70-Data support the prediction of particle size growth
  - IPP 70 Data detect process failures: entrapment in filter bags, blocking of distributor plate, segregation in granulator,…
- IPP 70 probe can monitor high shear granulation processes
  - Control of the process endpoint



Thank you for your attention

References

D. Petrak, Simultaneous Measurement of Particle Size and Particle Velocity by the Spatial Filtering Technique, *Part. Part. Syst. Charact*., 19, 391-400 (2002).

S. Schmidt-Lehr, H.-U. Moritz and K. C. Jürgens, Online Control of Particle Size during Fluidised Bed Granulation, *Pharm. Ind*., 69, 478-484 (2007).

T. Närvänen, T. Lipsanen, O. Antikainen, H. Räikkönen and J. Yliruusi, Controlling granule size by granulation liquid feed pulsing, *Int J Pharm.,* 357, 132-138 (2008).

A. Burggraeve, T. Van Den Kerkhof, M. Hellings, J. P. Remon, C. Vervaet and T. De Beer, Evaluation of in-line spatial filter velocimetry as pat monitoring tool for particle growth during fluid bed granulation, *Eur. J. Pharm. Biopharm.,*doi: 10.1016/j. ejpb. 2010.06.001.

J. Huang, C. Goolcharran, J. Utz, P. Hernandez-Abad, K. Ghosh and A. Nagi, A PAT Approach to Enhance Process Understanding of Fluid Bed Granulation Using In-line Particle Size Characterization and Multivariate Analysis, *J Pharm Innov,* 5, 58-68 (2010) DOI 10.1007/s12247-010-9079-x.

Jarvis Jeejing Ng, In-line particle size analysis for high shear granulation processes, APACT 10, 28.04.2010 – 30.04.2010, Manchester

D. Petrak, S. Dietrich, G. Eckardt and M. Köhler, In-line particle sizing for process control by an optical probe based on the spatial filtering technique (SFT), in: CD Proc. 6nd World Congress Particle Technol., H H 1 0 00613, Nuremberg (2010).

C. Fischer, A. Bück, M. Peglow and E. Tsotsas, Fiber-optical measurement of particle size distributions in fluidized bed processes,), in: CD Proc. 6nd World Congress Particle Technol., H H 1 0 00096.pdf, Nuremberg (2010).