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

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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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Second-order polynomial fitting

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<td>0.90</td>
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Real-time particle size prediction

Thick line: in-line spatial filtering

Thin line: predicted

Triangle: off-line spatial filtering

x50 /µm for one batch
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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: Fibre-optical spot scanning

Measured quantity: Chord length \( x \)

\[ x = v \cdot \Delta t_p - b ; \quad v = ? \]
Real-time particle size measurement with spatial filtering technique (SFT)

First measuring principle: Fibre-optical spot scanning

Measured quantity: Chord length $x$

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

Chord length distribution

Graph showing chord length distribution with a log-log plot for a sphere with a diameter of 100 µm.

Fibre image
Single fibre $\varnothing b$

Position $t_1$, Position $t_2$, Position $t_3$, Position $t_4$

U [V] vs. $t$ [s] graph with voltage pulses at positions $t_1$, $t_2$, $t_3$, $t_4$ and time interval $\Delta t_p$.
Real-time particle size measurement with spatial filtering technique (SFT)

Second measuring principle: SFT

\[ s(t), f_0 \]
\[ M \]
\[ v = g f_0 / M \]
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Probe system IPP 70 of Parsum GmbH

M = 1
v = g/T₀
= gΔt₀

Burst

Pulse

x = vΔt₀ - b
Probe system IPP 70 of Parsum GmbH

Laser beam

Differential fibre optical spatial filter

Measurement volume length

Sapphire window

Single optical fibre

Differential amplifier

Photodetector

M = 1

Burst $v = \frac{g}{T_0}$

Pulse $x = v \Delta t_p - b$

$\Delta t_p$
Probe system IPP 70 of Parsum GmbH

- Powder flow
- Optical fibre bundles
- Laser beam
- Sapphire window
- Fibre optical spatial filter + 1 single fibre

Photodetectors (Pulse) (Burst)
Laser diode system
Probe system IPP 70 of Parsum GmbH

- Laser beam
- Optical fibre bundles
- Photodetectors (Pulse) (Burst)
- Laser diode system
- Stainless steel
- Powder flow
- Sapphire window
- Fibre optical spatial filter + 1 single fibre
Probe system IPP 70 of Parsum GmbH

Tube characteristics:
Length 280 mm, diameter 25 mm (Standard)
Probe system IPP 70 of Parsum GmbH

Stainless steel

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
Probe system IPP 70 of Parsum GmbH

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- Barrier housing and special air valves allow applications for Ex environments
Probe system IPP 70 of Parsum GmbH

- 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
Probe system IPP 70 of Parsum GmbH

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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

IPP 70-S

PC cable

Air supply

IPP – Measurement Software

Max. 4 Probes

Max. 100 m

TCP/IP Connection

Ethernet

OPC-Server

Process Control System
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Application of IPP 70

Focus: 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
1. Fluid Bed Batch Granulation

- $x_{10,3}$
- $x_{50,3}$
- $x_{90,3}$
- Process stop for at-line sample with laser diffraction

**Graph:**
- X-axis: Measuring time $t$ [h:min]
- Y-axis: Particle size $x$ [µm]

**Legend:**
- Blue squares: $x_{10,3}$
- Red circles: $x_{50,3}$
- Green triangles: $x_{90,3}$
- Red asterisks: Process stop for at-line sample with laser diffraction
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

![Graph showing measuring times and particle size distribution.]

- Measuring times: 08:00, 09:00, 10:00, 11:00, 12:00, 13:00, 14:00, 14:30
- Particle size distribution
  - Approximately 50 µm layer
  - Agglomerates
2. **Wurster Coating** (1,5 kg Cellets 200...355 µm, Pharmacoat-606-solution)

Agglomerates > 400 µm

![Graph showing agglomerate parts over process time for different spray rates.](image-url)
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

Particle size $x$ [µm]

Process stopped
Further mixing
Dry mixing
Addition of 1.5 l water in 1.5 minute

Measuring time [h:min]

$X_{90.3}$
$X_{50.3}$
$X_{10.3}$
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


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).