Implementation of an online particle size distribution measurement instrumentation within a jet mill system as a PAT tool

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INTRODUCTION

The Quality by Design (QbD) and Process Analytical Technology (PAT) initiatives from the FDA published in 2002 requires a better understanding of pharmaceutical manufacturing processes [1-4].
The key Critical Quality Attribute (CQA) of micronised materials is their particle size distribution. The standard test method is sampling and later analysis the finished product. A suitable PAT tool for a micronisation process should detect particle size variations over the run time of the process. This would allow the adjustment of key parameters (i.e. milling pressure and feed rate) in real-time. The MYTOS/TWISTER® system (Sympatec GmbH, Clausthal-Zellerfeld, Germany) is designed to determine particle size online.
We describe the implementation of this system within a spiral jet mill with the goal of showing equivalence between the online and the standard offline reference method.

EXPERIMENTS AND METHODS

Experimental design:

- Model substance: Lactose monohydrate 200M
- Central composite face-centered (CCF) design of experiments (DoE) with 8 corner, 6 axial and 3 replicated center-point experiments
- Factors:
  - milling pressure (3 / 5 / 7 bar)
  - feeding rate (1 / 3 / 5 kg/h)
  - nozzle diameter (1.3 / 1.5 / 1.7 mm)

The experiments were performed in two blocks:
1) *Online trials:*

- Three trial series (each series -> constant nozzle diameter)
- Milling parameter change while micronisation system running
- Online determination of resulting particle size distribution (sampling frequency: 1/min)
- Next milling parameter combination set after five consecutive determinations

2) *Offline trials:*

- 17 separate trials of one factor combination each
- After finishing each trial sampling of the micronised product for offline standard particle size determination

Experimental set up:
The milling system consists of:

- Pilot plant AS100 Spiral jet mill (milling chamber diameter 100 mm, 4 nozzles with angle 50°)
- Double screw feeder BA 1496/5D combined with a automated gravimetric dose weighing system
- Filter unit (all equipment by Hosokawa Alpine AG, Augsburg, Germany)
- TWISTER RC 50 sampling module (pipe diameter 50 mm; sampling principle: Figure 1 and 2) placed behind the product outlet of jet mill

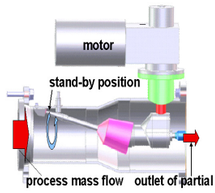

Figure 1: TWISTER cross-section showing the process pipe and the spinning sampling pipe in the parking position [5]

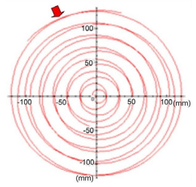

Figure 2: Spiral path of the sampling pipe over the cross-section of the process pipe. The sampling pipe scans the pipe diameter on a spiral line with constant path velocity to obtain a representative powder sample. The arrow indicates the parking position [5]. The sampled material is transferred to the MYTOS particle analysis system by negative pressure. The figure shows the dimensions of a TWISTER 250 module.

Table 1: Comparison of online and offline particle size determination units

	Online system	Offline reference system
Sampling unit	TWISTER RC 50	Not applicable
Analysis system	MYTOS® (0.25 µm - 3500 µm)	RODOS/M® (0.1 µm - 3500 µm)
Dispersion principle	RODOS®-aerosol jet (particle-particle collisions, particle-wall collisions, velocity gradients)	
Analysis principle	HELOS® laser diffraction, λ = 632.8 nm	
Measurement	31 channel Multi element detector / measuring frequency 2000/s	
Evaluation	Fraunhofer, Software: Windox (Version 5.2.0.0)	
Lens	R2 (focal distance 50 mm)	

RESULTS AND DISCUSSION

Resulting x_{50} values (median particle sizes):

- online trials from 1.3 to 8.8 µm
- offline trials from 1.7 to 9.7 µm

Graphical comparison:
The data from the online and offline trials including x_{10}, x_{50} and x_{90} values (x_{10} / x_{90} percentiles represent the particle size in relation to which 10 % / 90 % of the distribution is smaller [6]) were analyzed and evaluated using the DoE software package MODDE® (Version 7.0.0.1, Umetrics, Kinnelon, NJ, USA) in order to construct response surface diagrams (Figure 3) after optimization of the statistical model.

=> The graphical comparison of the online and offline data plots showed a high similarity.

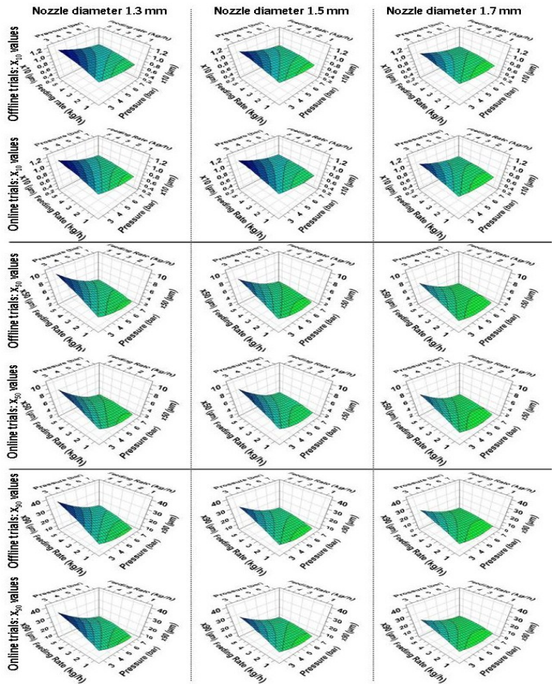

Figure 3: Response surface plots with x-axis feeding rate (kg/h), y-axis milling pressure (bar) and z-axis resulting x_{10} / x_{50} / x_{90} value (µm)

Mathematical comparison:
Set of acceptance criteria: The acceptance criteria given in Table 2 were derived from pre-trials performed before the start of the reported study. The software package nQuery Advisor® (Version 6.01; Statcon, Witzenhausen, Germany) was used to calculate the probability of successfully conducting a DoE model for the acceptance criteria. The criteria were considered finalized when they reached the 90 % level.

Statistical evaluation: The differences between the x_{10} / x_{50} / x_{90} mean values and the standard deviations of the differences were calculated for each online and offline trial with the same factor combination. A Schuirman test of equivalence [7] (two one-sided t-test procedure, TOST) was performed to calculate 90 % confidence intervals for the mean values of the differences. The resulting intervals were compared with the acceptance criteria. The results were shown in Table 2.

=> For the x_{10} / x_{50} / x_{90} values the confidence intervals were within the acceptance criteria.

Table 2: Results of calculation of 90 % confidence intervals

	Mean difference online vs. offline method	Lower / upper 90% confidence intervall limit	Lower / upper acceptance criterion limit
x_{10} value [µm]	0.01	0.00 / 0.02	+ / - 0.3
x_{50} value [µm]	0.12	-0.10 / 0.34	+ / - 1.0
x_{90} value [µm]	0.84	0.01 / 1,67	+ / - 2.0

CONCLUSION

The implementation of the online particle size determination tool MYTOS/ TWISTER into the pilot plant spiral jet mill system AS100 was successful. The equivalence between the determined online and offline reference values was confirmed by applying the two independent test methods with lactose monohydrate 200M as the test substance.

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