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Real time process control during wet granulation in a high-shear mixer using Spatial Filter Velocimetry – Influence of different formulations

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1. Introduction

The intention of pharmaceutical manufacturers to create more robust and controlled processes in production and development increased since the FDA advised the implementation of PAT-Tools instead of process validation [1].
By applying PAT-Tools, e.g. real time control of critical process parameters, the results of the manufacturing processes will always be in accordance with the defined specifications as long as the process can be controlled statistically. This approach is called „Quality by Design“.

2. Aims and objectives

In-line particle measurements are well established in fluid bed granulation to control the progress of the process [2].
The aim of this work was the caracterisation of a wet granulation process in a high-shear mixer using an unique in-line particle measurement probe.

First, detailed investigations of analytical parameters have to be performed necessarily. Second, experiments regarding process monitoring during wet granulation could be conducted.

3. Experimental method

3.1 Formulation type

For the experiments different prototype formulation have been investigated. The batch size of the powder mixture has been set to 672 g.

Table 1: Powder mixture

	[%]
Microcrystalline cellulose (MCC)	8,11 - 20,27
Potato Starch	2,68
Polyvinylpyrrolidone (PVP), type Kollidon® K-30	3,41 - 7,24
Lactose monohydrate	ad 100,0

Table 2: Granulation liquid

	[%]
Water, purified	5,88 – 27,12*

* Related to the total mass of moist powder mixture

3.2 High-shear mixer

All granulation experiments have been carried out in a high-shear mixer DIOSNA P1-6 (Diosna, Dierks und Söhne GmbH, Osnabrück, Germany). A 4 L bowl with an impeller and chopper was used. The granulation liquid was fed by a peristaltic pump.

Table 3: Process parameters (mixing of powder bed)

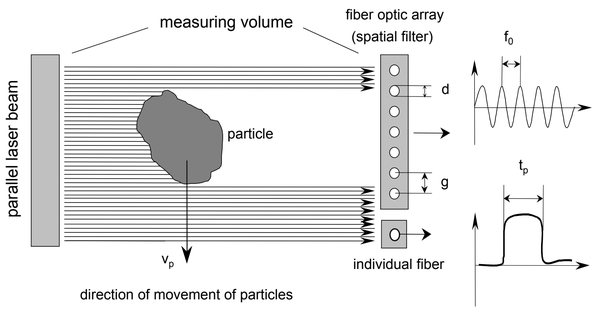
	unit	value
Impeller speed	rpm	150
Chopper speed	rpm	250
Mixing time	s	15

Table 4: Process parameters (wet granulation)

	unit	value
Impeller speed	rpm	300
Chopper speed	rpm	1500
Mixing time	s	240

3.3 In-line sensor

For in-line measurement a PARSUM IPP 70-S probe (Parsum GmbH, Chemnitz, Germany) based on the established technique of spatial filter velocimetry [3] was used. An incorporated pneumatic system ensures defined sample-flow and proper window cleaning of the array automatically. Data collection and evaluation was performed with specific software.



velocity: $v_p = f_0 \cdot g$ **particle size: $x_p = t_p \cdot v_p - d$**

Fig. 1: Measurement method of spatial filter velocimetry

4. Results

4.1 Investigation of analytical parameter: Coincidence factor

Coincidence is the occurrence of unrelated events in close proximity of space or time. It may happen, that two in principal isolated particles occupy the same place in space, the same point or period in time, or the same relative position when they pass the measuring volume. The resulting measurement artefact can be eliminated by a software tool, called “coincidence factor”. It ranges between “0” and and “1”.
For the investigation of the coincidence factor a prototype formulation with 16,22% of MCC, 2,68% of Potato Starch, 5,41% of PVP and 62,2% of Lactose monohydrate was used. The amount of granulation liquid was set to 13,49% in relation to the powder mass.

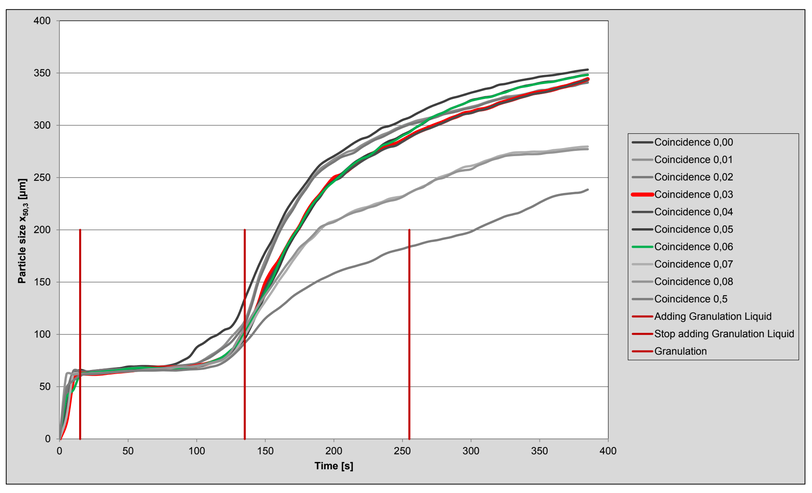


Fig. 2: Influence of different coincidence factors during wet granulation

Fig. 2 shows the results of different settings of the coincidence factor. The effect of coincidence factors between 0,0 and 0,06 on the measured particle size is nearly the same. It could be seen that higher coincidence factors have a significant impact on the determination of the particle size.

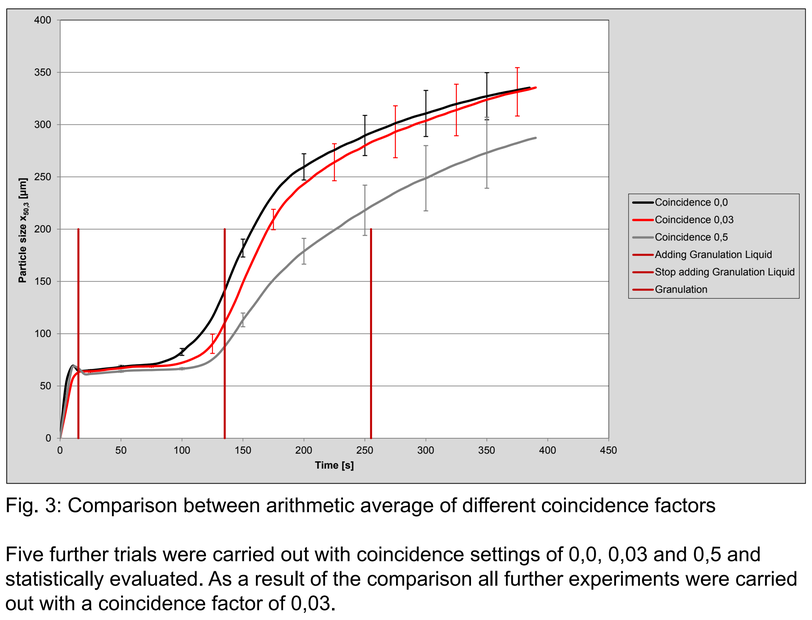


Fig. 3: Comparison between arithmetic average of different coincidence factors

Five further trials were carried out with coincidence settings of 0,0, 0,03 and 0,5 and statistically evaluated. As a result of the comparison all further experiments were carried out with a coincidence factor of 0,03.

4.2 Investigation of formulation parameter: Microcrystalline cellulose (MCC)

The influence of different amounts of Microcrystalline cellulose on the particle size of two formulations is illustrated in the figure below.

In this investigation a prototype formulation consisting of 2,68% Potato Starch. 5,41% of PVP, 8,11% up to 20,27% of MCC and Lactose monohydrate ad. 100% was used. The amount of granulation liquid was set to 13,49% in relation to the powder mass.

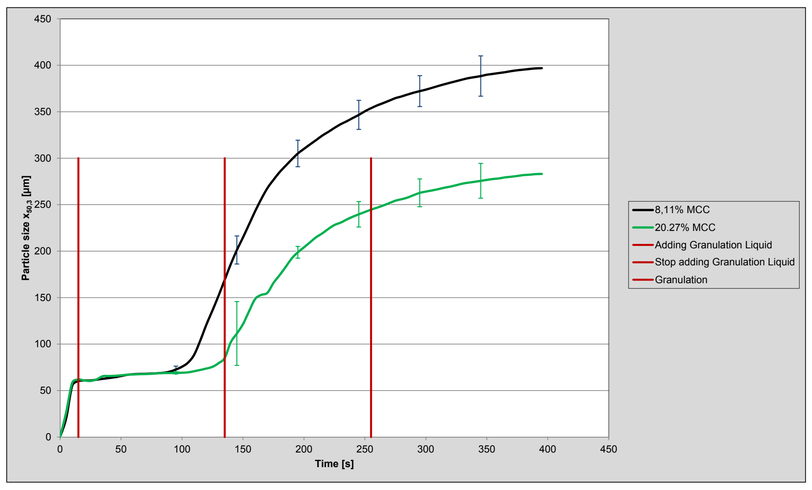


Fig. 4: Influence of different content of Microcrystalline cellulose on particle size

The results prove that an increase in concentration of MCC leads to a smaller particle size of the resulting granulate.

The impact of different amounts of MCC can also be shown in the power consumption of the impeller.

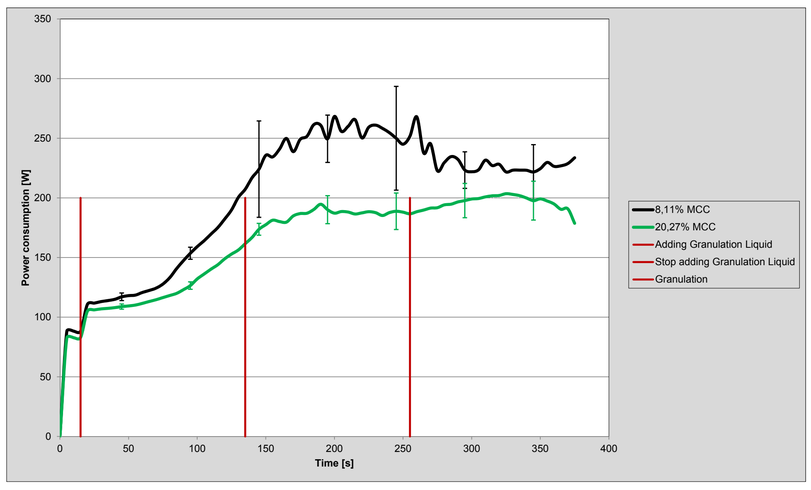


Fig. 5: Power consumption during granulation processes using different MCC quantities

Using a lower MCC quantity the power consumption increased due to the fact that the granule growth is not suppresed by MCC.

4.3 Investigation of formulation parameter: Polyvinylpyrolidone (PVP)

To verify the influence of the binder quantity the concentration of PVP was varied in a wide range. Additionally 16,22% of MCC, 2,68% of Potato Starch and Lactose monohydrate ad. 100% was added. The amount of granulation liquid was set to 13,49% in relation to the powder mass.

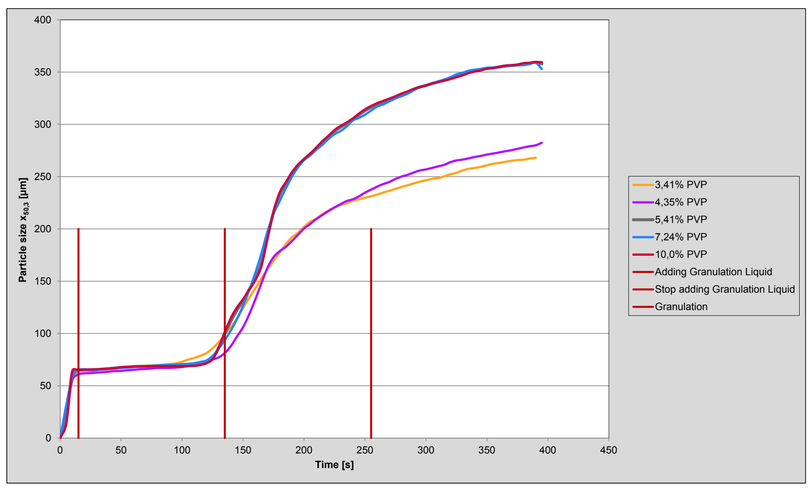


Fig. 6: Influence of different quantities of PVP

Experiments with different amounts of PVP showed that the particle size increases with higher concentrations of PVP. The in maximum reachable particle size was about 380 µm for the given formulation.

4.4 Investigation of formulation parameter: Granulation liquid

The influence of the quantity of granulation liquid is shown in the figure below. This investigation was performed with a prototype formulation consisting of 16,22% of MCC, 2,68% of Potato Starch, 5,41% of PVP and 62,2% of Lactose monohydrate.

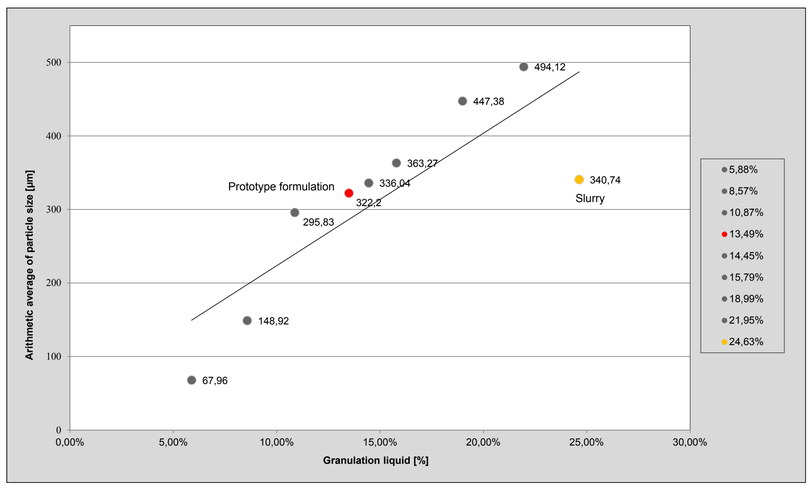


Fig. 7: Influence of different quantities of granulation liquid

There was an increase in particle size by increasing the amount of granulation liquid. The granulate growth was detected in real time.

5. Conclusion

In this work, the particle size distribution during the whole wet granulation process could be monitored.
The impact of different auxiliary substances on the granulation characteristics has been studied. To that purpose the content of these substances have been varied within a wide range. A strong influence of the different formulations on the resulting particle size distribution could be shown in real time. It was possible to correlate the results of the real time particle size characterisation with data generated by power consumption measurements. In addition, it was also possible to detect the different phases during granulate formation. The results were in full accordance with theoretical expectations. The endpoint of the granulation process could be fixed precisely.

6. References

[1] Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance, htttp://www.fda.gov/downloads/Drugs/Guidances/ucm070305.pdf (10. Nov. 2013, 17 pm)

[2] Schmidt-Lehr, S., Moritz, H.-U., Jürgens, K.C., Onlinekontrolle der Partikelgröße während einer Wirbelschichtgranulation. Pharm. Ind. 69, Nr. 4. S. 478-484, (2007)

[3] Dietrich, S., Günter, E., Köhler, M., Petrak, D., In-Line particle sizing for real time process control by fibre-optical spatial filtering technique (SFT). Advanced Powder Technology, Vol. 22, Issues 2, Pages 203-208 (2011)