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 validations [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]

2. Aims and objectives
In-line particle measurements are well established in fluid bed granulation to control fine progress of the process [3]. The aim of this work was the characterization 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. [2]

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.

3.2 High-shear mixer
All granulation experiments have been carried out in a high-shear mixer (DCPAP 10/6) (Diona, Dieterich und Söhne GmbH, Danzica, Germany) A 4 L bowl with an impeller and chopper was used. The granulation liquid was led by a peristaltic pump. [1]

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 point. The probability for this to happen is mathematically formulated by a software tool, called “coincidence factor”. It ranges between “0” 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 ad. 100% was used. The amount of granulation liquid was set to 13,49% in relation to the powder mass. [2]

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. This investigation a prototype formulation consisting of 2,68% Potato Starch, 5,41% of PVP and 62,2% of Lactose monohydrate ad. 100% was used. The amount of granulation liquid was set to 13,49% in relation to the powder mass. [1]

5. Conclusion
In this work, the particle size distribution during the whole wet granulation process could be monitored. The influence of different substances on the granulation characteristics has been studied. To that purpose the content of these substances have been varied within a wide range. Among 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 all the different phases during granulation formation. The results were in full accordance with theoretical expectations. The end point of the granulation process could be fixed precisely. [1]

6. References