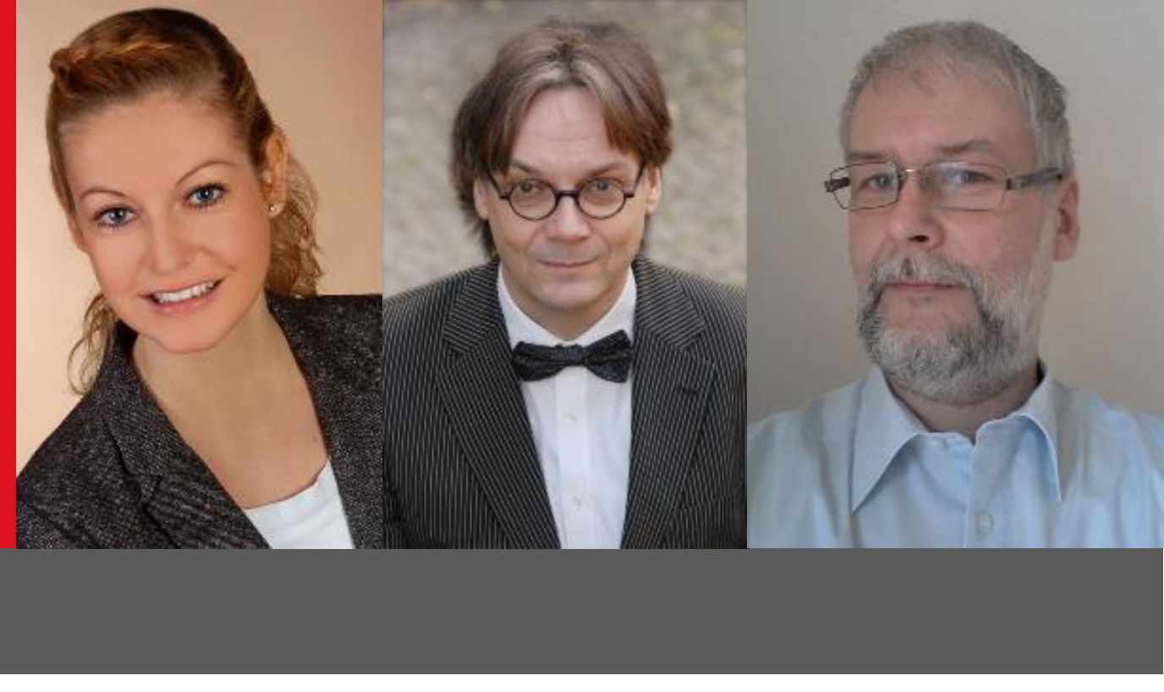
Hochschule Ostwestfalen-Lippe
University of Applied Sciences



PAT in High-Shear Granulation Processes using In-line Particle Size Measurements

C. Hüttner, G. Kutz, S. Dietrich[1]
Pharmaceutical Engineering, Hochschule Ostwestfalen-Lippe, University of Applied Sciences, Georg-Weerth-Straße 20, 32756 Detmold, Germany, Tel: +49 5231 45800 26,
Fax: +49 5231 45800 60, e-mail: gerd.kutz@hs-owl.de
[1]Parsum, Gesellschaft für Partikel-, Strömungs- und Umweltmesstechnik mbH, Reichenhainer Straße 34-36, 09126 Chemnitz, Germany, Tel: +49 371 267586 90,
Fax: + 49 371 267586 99, e-mail: die@parsum.de

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].
Applying PAT-Tools can provide valuable insight and understanding in R&D, for process optimization, scale-up and technology transfer as well as for routine production. The aim of the investigations is to clarify the influence of the critical process parameters (CPP) on the quality attributes of the pharmaceutical products and especially on the critical quality attributes (CQA). This scientific procedure is described as quality by design (QbD). The size distribution of granules is an important critical quality attribute of multiparticulate systems.

2. Aims and objectives

In-line particle measurements are well established in different pharmaceutical processes like fluid bed granulation, fluid bed drying, spray drying, milling, mixing and other. It can be used for batch as well as for continuous production to control the progress of the process [2].

For high shear granulation, real-time particle sizing has many advantages because the particle size of the final granule is often a defining characteristic. This work covers two case studies exploring the capabilities of an in-line particle measurement probe to characterize wet granulation processes in high shear mixers with various dimensions.

3. SFT In-line Particle Probe

For in-line measurement a PAT solution for continuous process monitoring, the PARSUM IPP 70-S probe based on the established spatial filter technique SFT [3] was used.

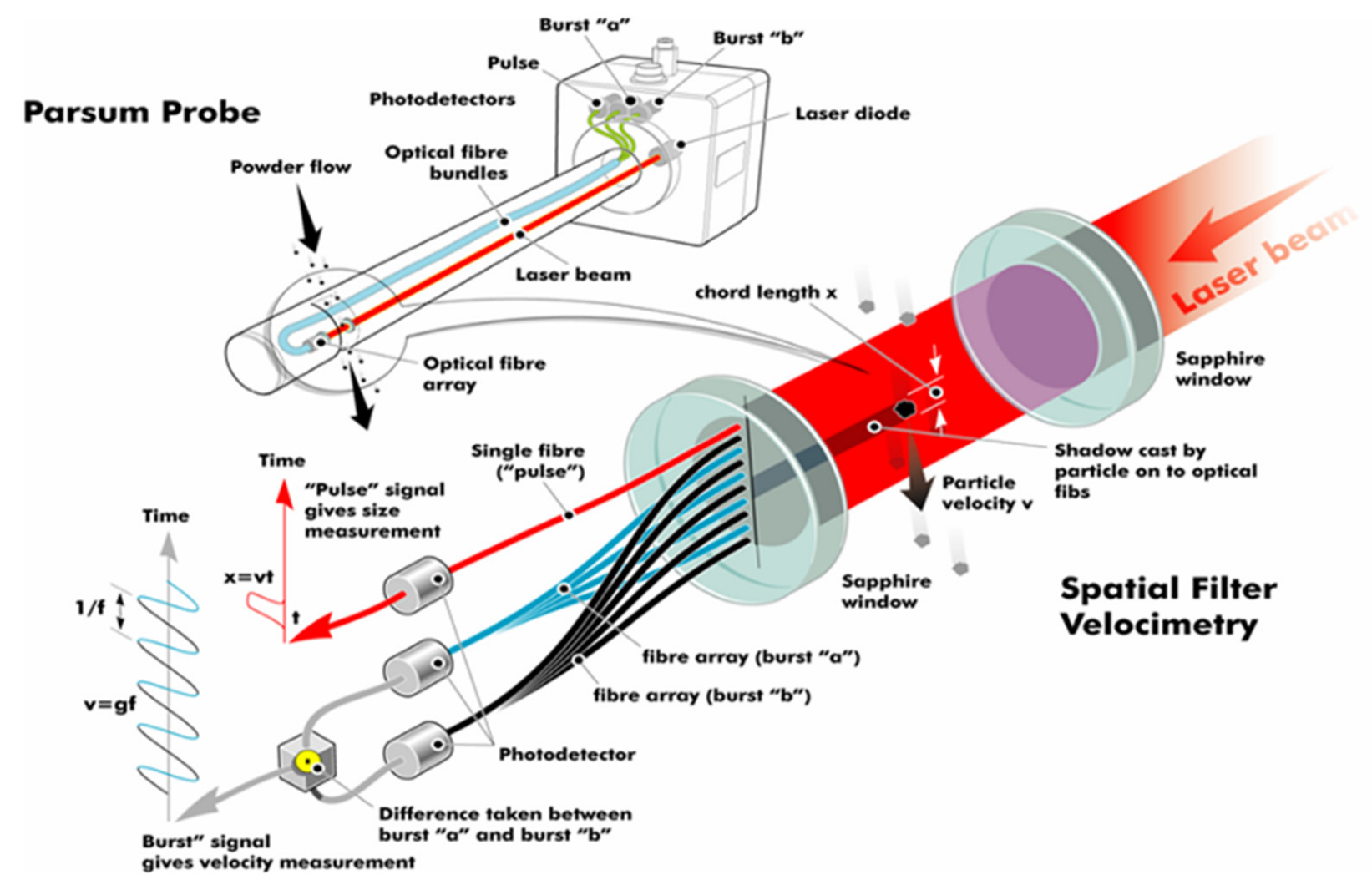


Fig. 1: Measurement principle of spatial filter velocimetry and design of the Parsum Probe

The Spatial Filtering Technique (SFT) provides on-line information about the chord length and velocity of a population of particles in fluids. Spatial filtering velocimetry (SFV) was modified by spot scanning in order to determine the chord length of a particle cross section. SFT involves both spatial filtering velocimetry and spot scanning.
Particles passing through the measuring volume, interrupting the light to a linear array of optical fibres. The individual velocity can be calculated from the sequential interruption of light received by the fibres of the spatial filter detector. The frequency of the resulting Burst-signal is proportional to the particle velocity. Particle size is determined using a the pulse signal, which is a measure of the time for which the particle blocks a single optical fibre. Measuring a large number of particles generates statistically valid results from which number- and volume-based distributions are calculated.

For measurements in highly concentrated particle systems like in a high-shear process it is necessary to use an in-line eductor D23 (Parsum GmbH, Chemnitz Germany) to ensure the dispersion of the sample-flow and a proper window cleaning of the optical windows.
Data collection and evaluation was performed with the Parsum standard measuring software IPP Ver. 7.14.

Fig. 2: In-line Particle Probe IPP 70-S with In-line Eductor D23

4. High-shear Mixers

4.1 Pilot Scale Mixer

At the Diosna P/VAC 10–60 the probe was installed vertically, using an existing port of the lid (Tri-Clamp DN 32) The measurement volume of the probe was below the powder level and approx. 80 mm over the impeller to reduce possible disturbances by the rotating mixer blade.
A placebo mixture was filled up to a height of 15 cm below the lid. It consists of Povidon 30 (1,5Kg), MCC (1 Kg), Lactose, Mesh 200 (15 kg). Water was used as granulation liquid.

Fig. 3: In-line particle probe IPP 70-Se with eductor D23 (Parsum GmbH, Chemnitz, Germany) installed in a high shear mixer Diosna P/VAC 10–60 with Bowl P60, (Diosna, Dierks und Söhne GmbH, Osnabrück, Germany).

4.2 Lab Scale Mixer (Diosna P1-6 with a 4 L bowl)

.

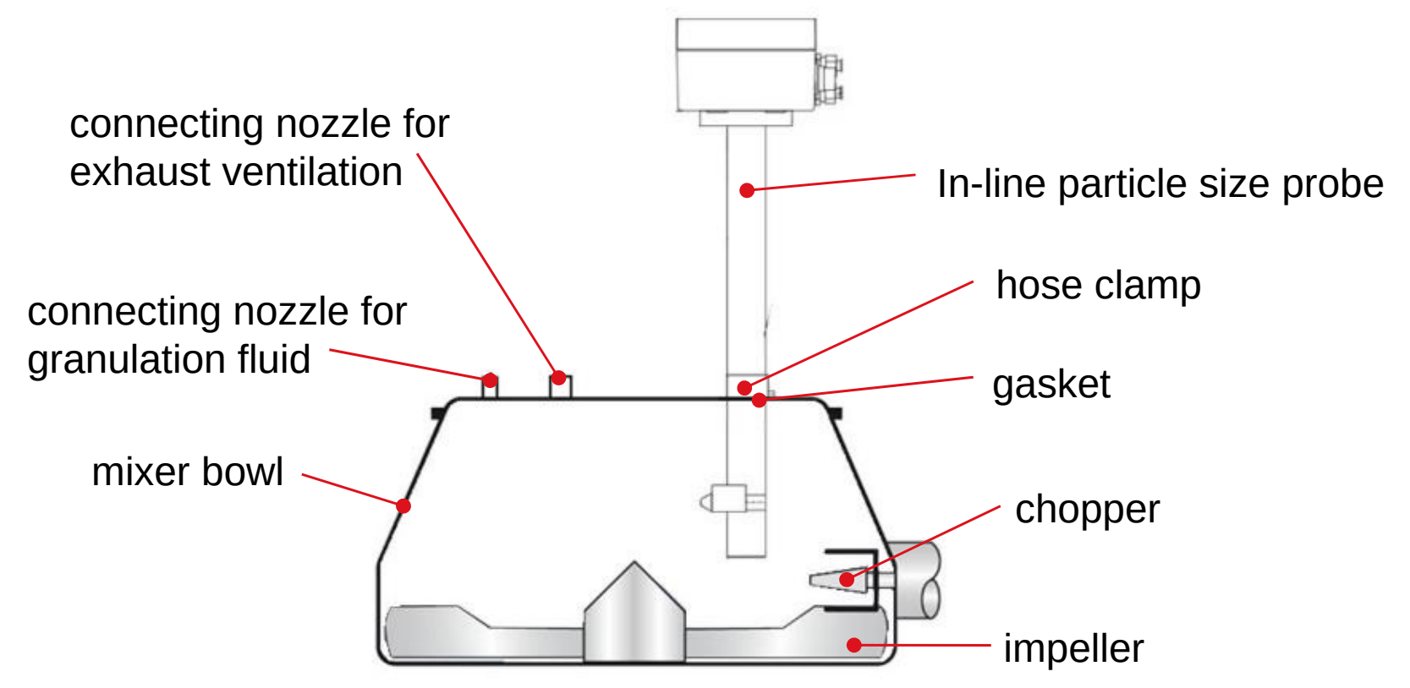


Fig. 4: Experimental Lab Scale set up (Diosna P1-6 with a 4 L bowl)

5. Results

5.1 Finding the Right Probe Settings

In the first case study the influence of basic parameter settings has been investigated to find optimal adjustment to the measurement conditions of a high shear granulation process in a pilot scale mixer.
It can be assumed a very good uniformity of the particle size distribution inside the mixer. Nevertheless at different measurement positions may different measurement conditions influencing the results. A good measurement position is characterised by a high data rate (measured particles per second) and a small "Loading" (optical concentration of particles). Especially in a short batch process a high data rate is very important in order to obtain statistically reliable results in short time. The following parameters have been found to be important:

- Depth of immersion
The inlet of the disperser must be covered in all process stages with material.
2 positions have been considered: 240 mm and 190 mm. To secure freedom from collisions with the mixing tool, a distance of 190 mm was chosen for all experiments.

- Angle
A rotation angle of 0 ° (between powder flow direction and orientation of the probe) is given when the opening of the disperser is directed against the flow of material. CCW rotation leads to negative angles, CW rotation to positive angles (Fig. 5).

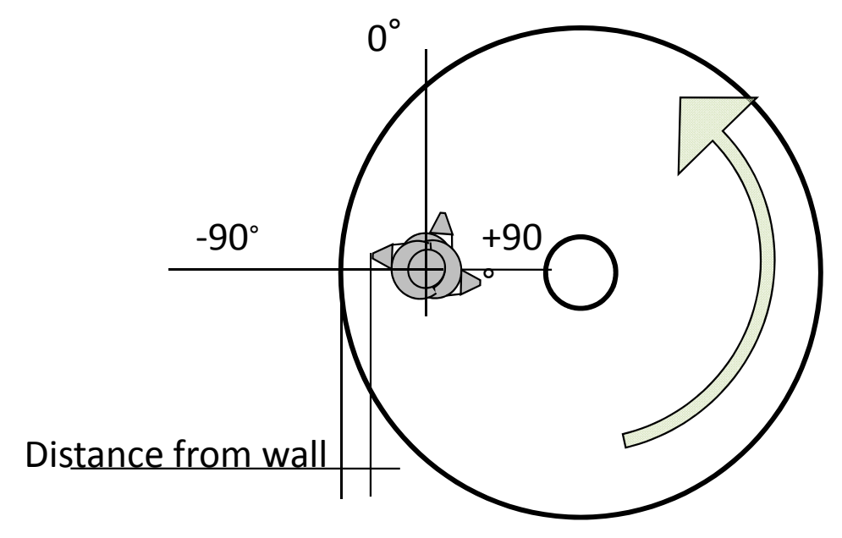


Fig. 5:
Rotation angle and distance from outer wall of the process vessel (view from above)

- Distance from wall
Possible installation places for the probe are usually very limited because of only little available openings. A wall distance of min. 50 mm to 150 mm has been found as optimal (Fig. 5), since it can come to a material jam between the wall and probe, which may lead to blockage of the probe.

- Air settings
An eductor D23 was used to disperse the particle stream and to hold the optical windows free from pollution. For the experiments, an eductor with a modified purge air flow was tested. The air outflow was not parallel to the surface of the optical window (Fig. 6, blue arrow) but at a certain angle away from optical windows (green arrows).

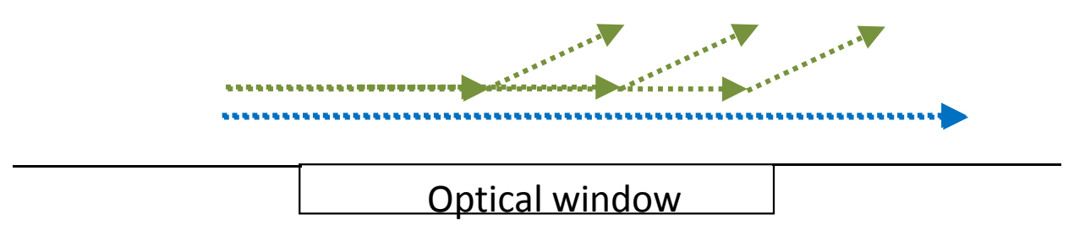


Fig. 6:
Outflow of purge air: standard (blue) and modified (green)

The contact of particles with the optical windows could be reduced and a growing contamination (to be seen in Fig. 8 as a decreasing of signal amplitudes) was prevented. An additional advantage of this configuration is that the cyclic purging pulse achieves a more intensive cleaning effect.

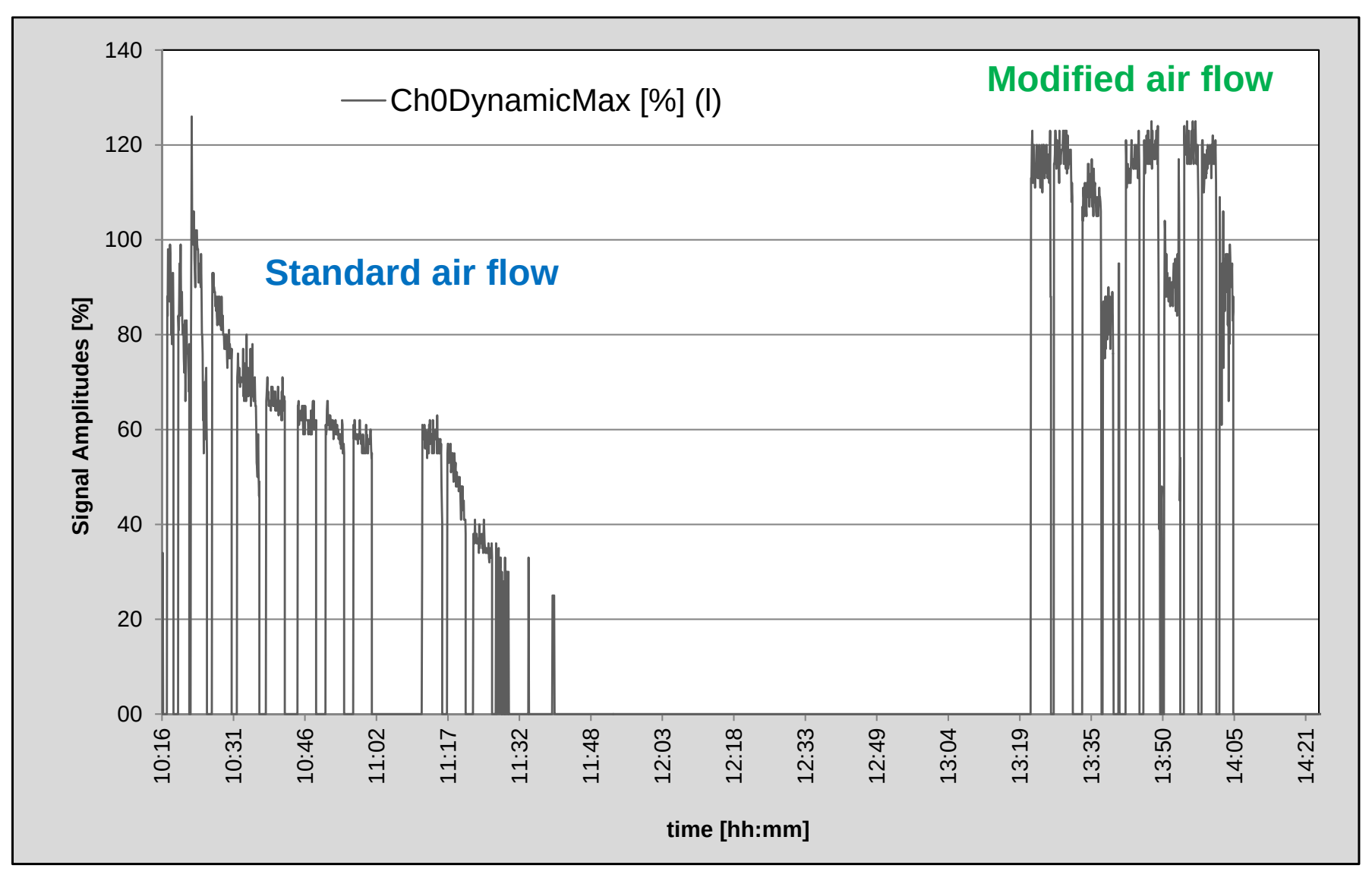


Fig. 7:
Influence of different air flows to pollution of the optical windows (to be seen on decreasing of signal amplitudes)

- Particle Buffer Size
The software parameter "Particle buffer" specifies the number of individual particles used for calculation of the distribution. This makes it possible to adapt the measurement dynamics to the process dynamics.
In high shear processes with high dynamics, the first approach was to use the smallest possible buffer. However, these led to very noisy histories of the results, especially after adding binder and begin of granulation very large single agglomerates are dominating the volume distribution. It has been found, that with respect to data rate a buffer size of 50,000 is a good balance between statistical certainty and fast reaction to process changing.

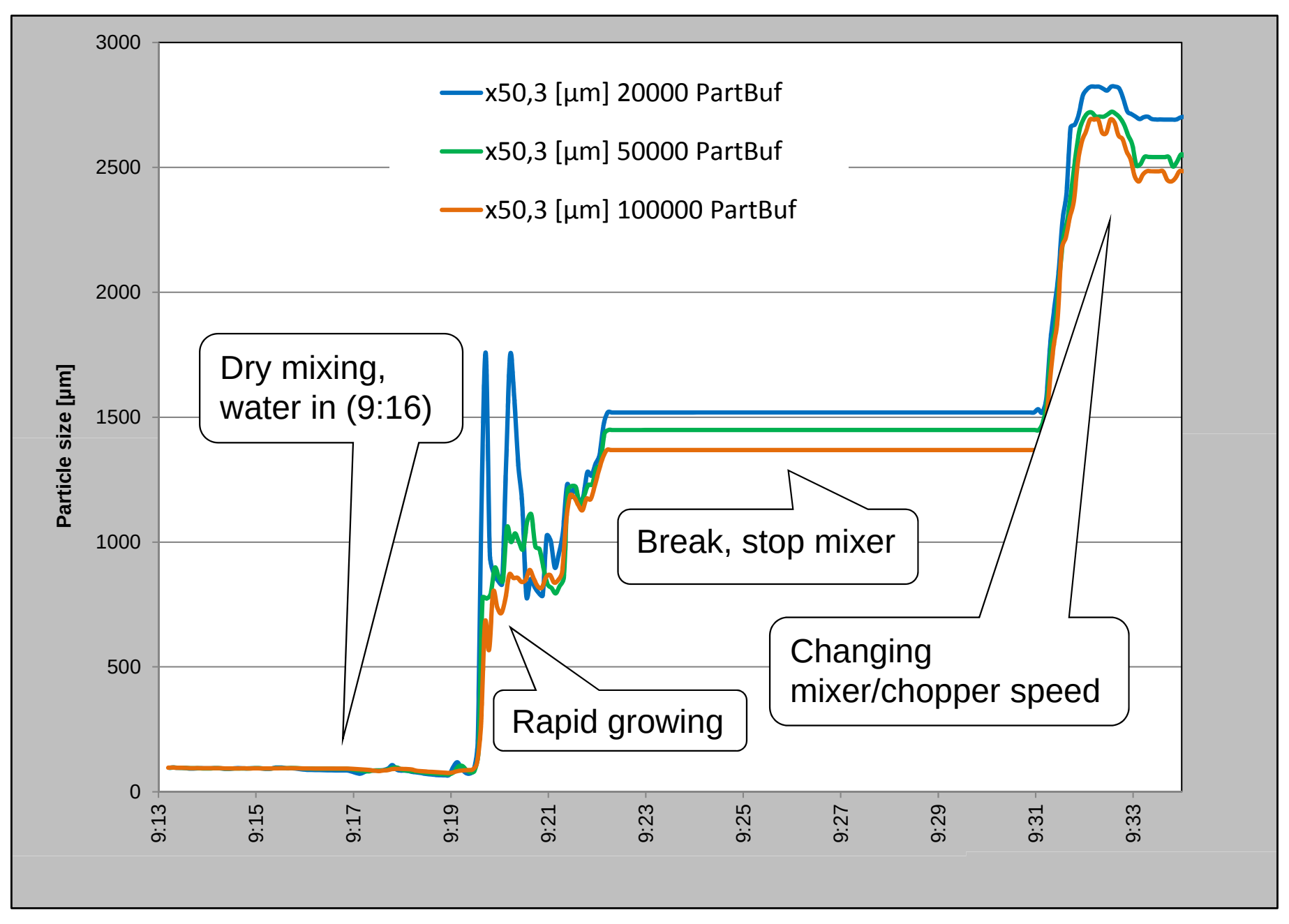


Fig. 8:
X50,3 (volume based) over the process time, with 3 different particle buffers sizes showing different dynamical behaviour of the measurement.

5.2 Investigation of formulation parameter: Microcrystalline cellulose (MCC)

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

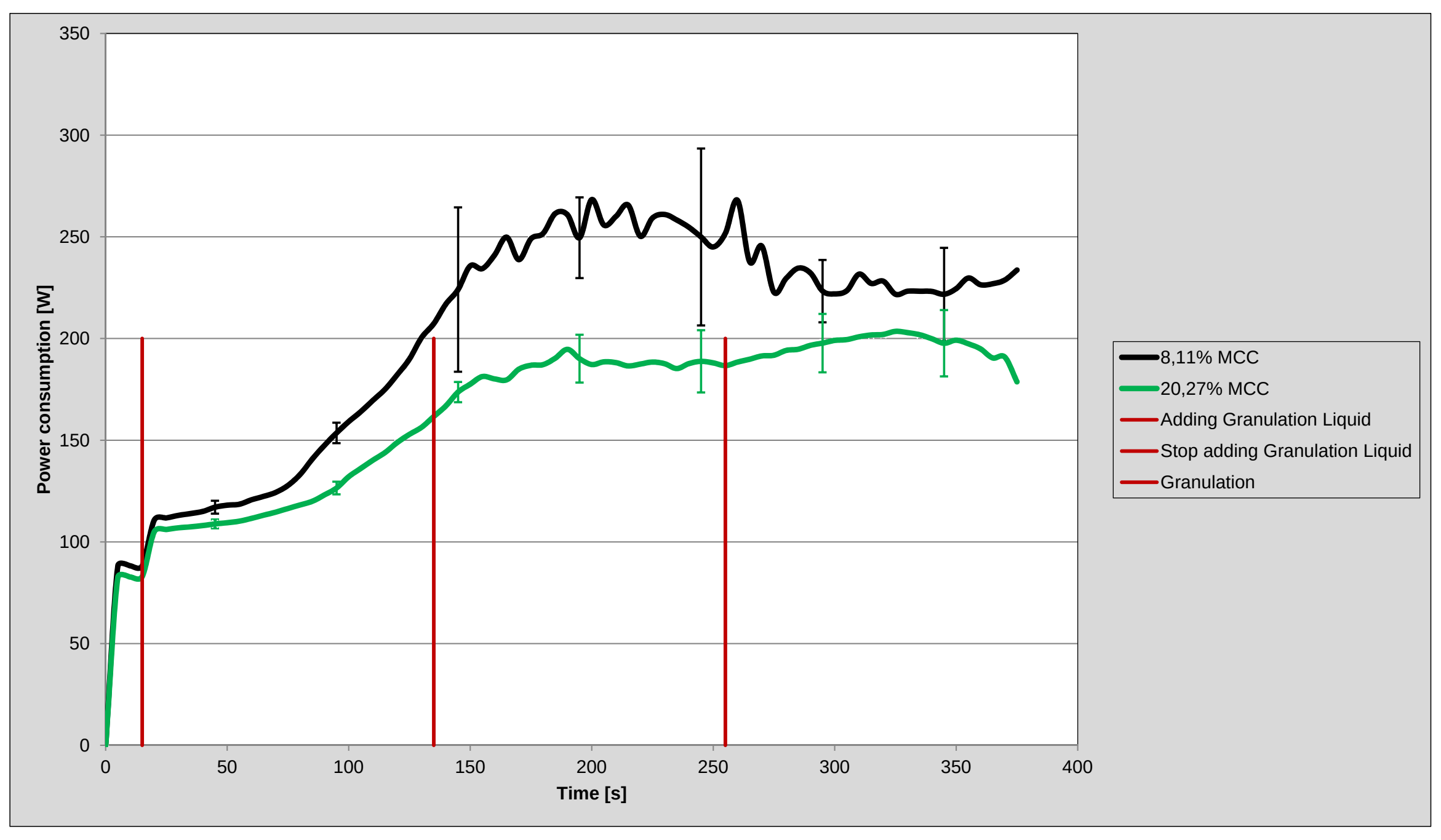


Fig. 9: Power consumption during granulation processes using different MCC quantities in a high-shear mixer type Diosna P1-6 with a 4 L bowl (batch size: 672g)

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.
The impact of different amounts of MCC can also be shown in the power consumption of the impeller.
Using a lower MCC quantity the power consumption increased due to the fact that the granule growth is not suppresed by MCC.

5.3 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.

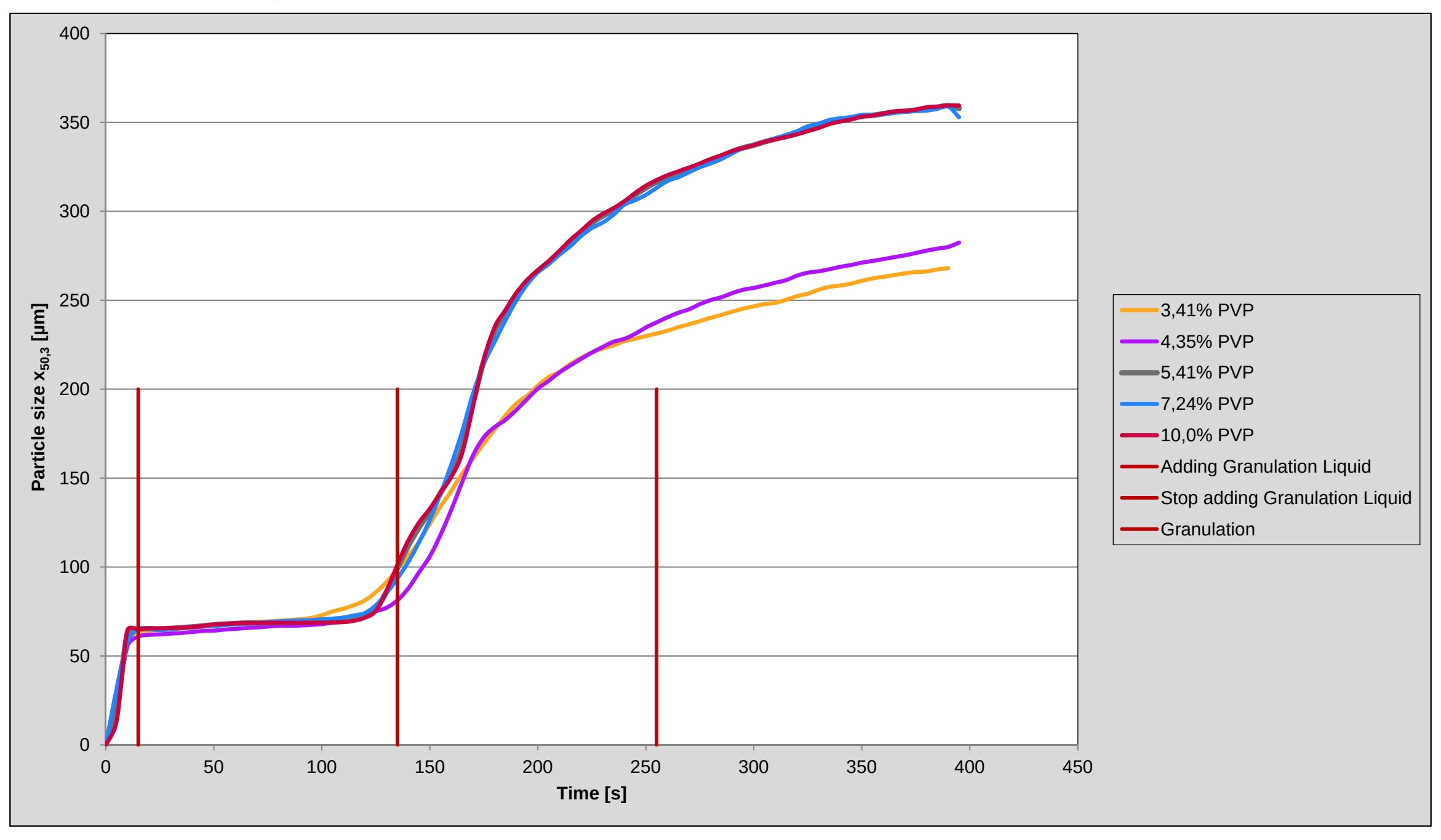


Fig. 10: Influence of different quantities of PVP in a high-shear mixer type Diosna P1-6 with a 4 L bowl (batch size: 672g)

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.

5.4 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.

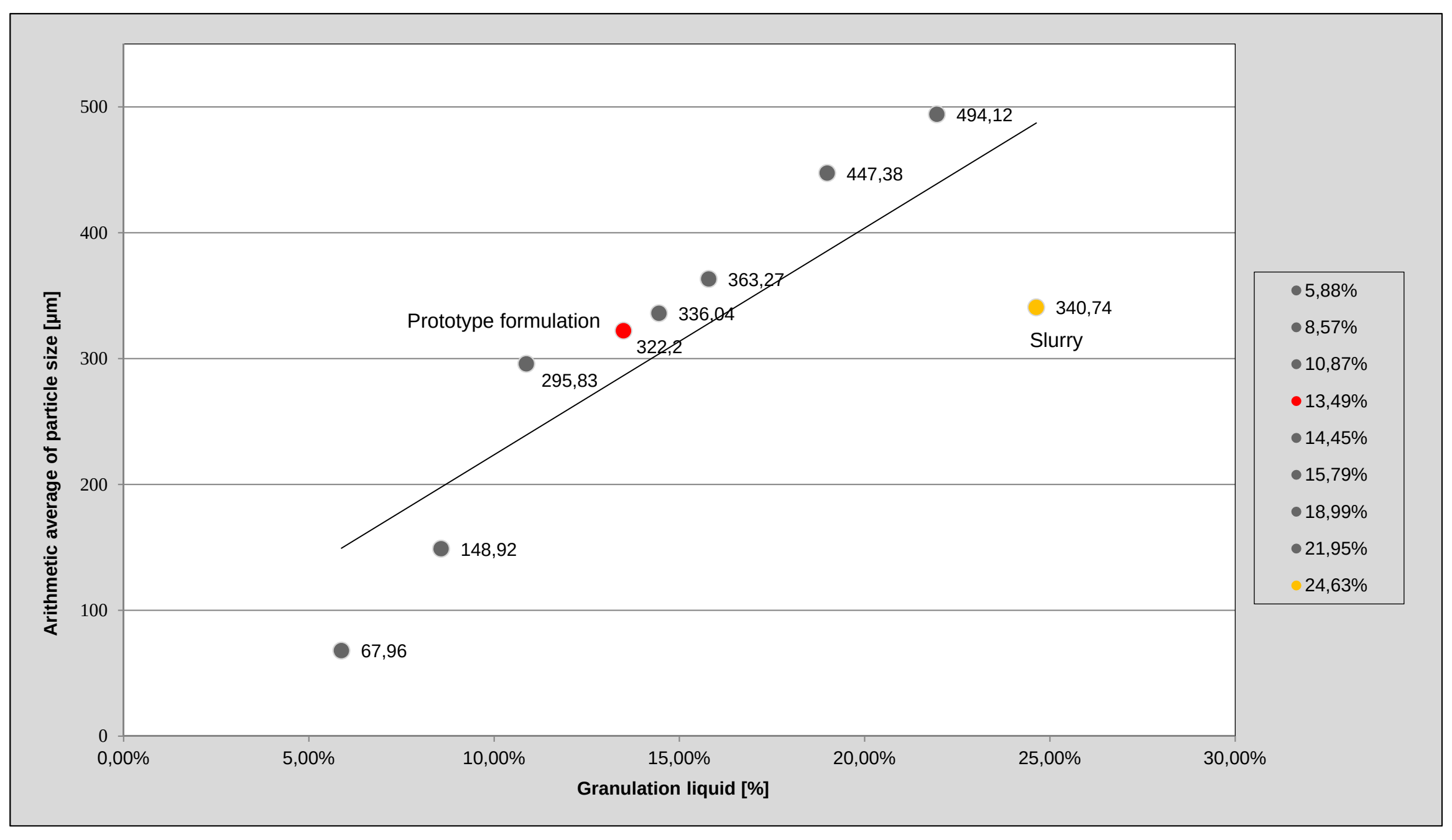


Fig. 11: Influence of different quantities of granulation liquid in a high-shear mixer type Diosna P1-6 with a 4 L bowl (batch size: 672g)

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

6. Conclusion

In this work, the particle size distribution during the whole high shear granulation process could be monitored. In both lab scale and pilot scale high shear mixer.
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.

7. 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. June. 2014, 18 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)