



# Real time particle size measurement during high-shear melt granulation

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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 implementation of a real time in-line particle measurement probe in a high-shear mixer.

First a feasibility study to measure particle size distributions during melt granulation processes with a unique sensor, the Parsum IPP 70-S, has been performed. Investigations regarding different prototype formulations in melt granulation processes followed.

## 3. Experimental method

### 3.1 Formulation type

Different prototype formulations have been chosen for the experiments.

Table 1: Prototype formulation, Type „A“

	[%]
Paracetamol	2,0
Polyethylene glycol 4000 (PEG 4000)	17,0
Lactose monohydrate	ad 100,0

Table 2: Prototype formulation, Type „B“

	[%]
Paracetamol	2,0
Polyethylene glycol 4000 (PEG 4000)	10,0 - 17,0
Microcrystalline cellulose (MCC)	0,0 - 20,0
Lactose monohydrate	ad 100,0

During feasibility study prototype formulation type „A“ was used. The second series of experiments included investigations regarding different amounts of Polyethylene glycol and different quantities of Microcrystalline cellulose in formulation type „B“.

### 3.2 High-shear mixer

All granulation experiments were 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 binder was added as a melt manually within 120 seconds using a syringe. The amount of powder bed was set to 800 g.

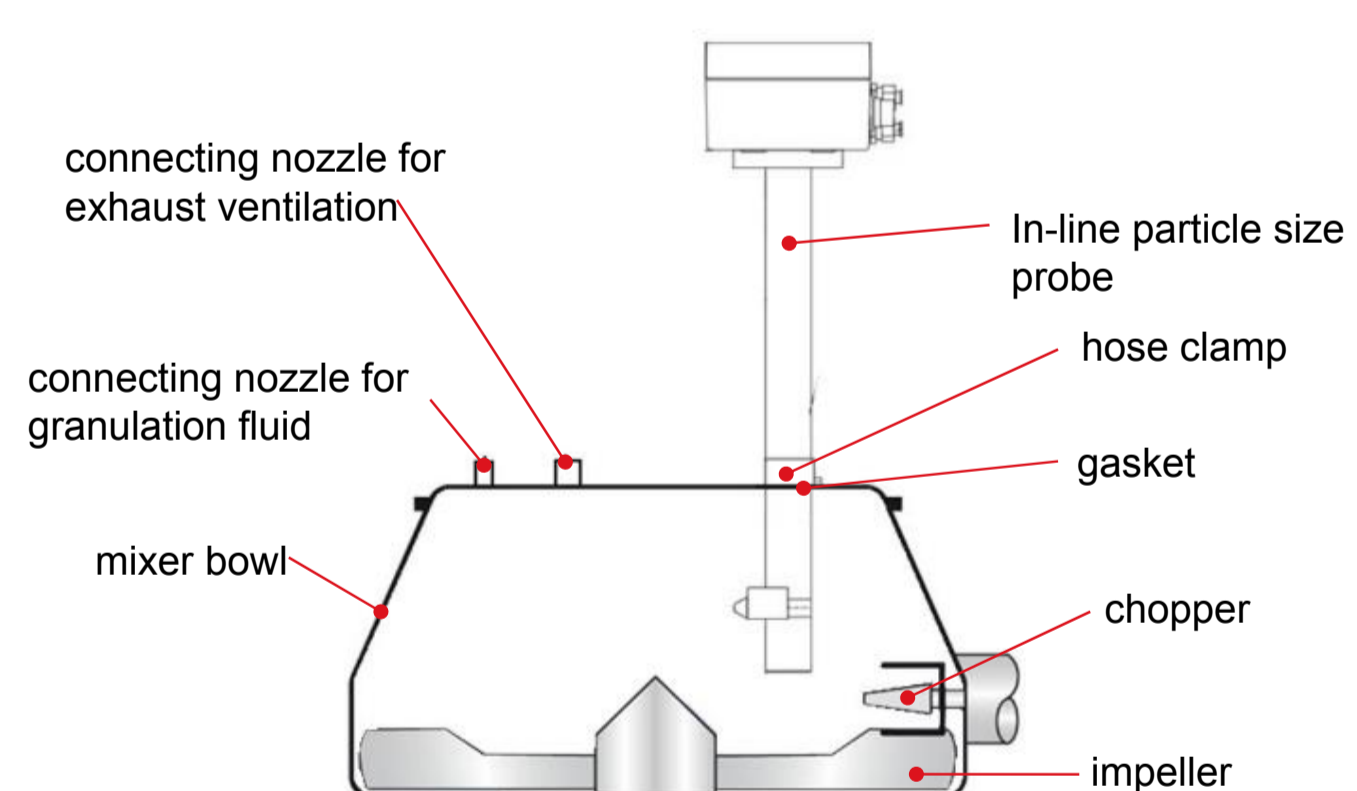


Fig. 1: Experimental set up

Table 3: Process parameters (heating phase)

	unit	value
Impeller speed	rpm	1500
Chopper speed	rpm	200

Heating phase was stopped as the powder bed reaches a temperature of about 75° C.

Table 4: Process parameters (granulation phase)

	unit	value
Impeller speed	rpm	550
Chopper speed	rpm	1800
Mixing time	s	300

### 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.

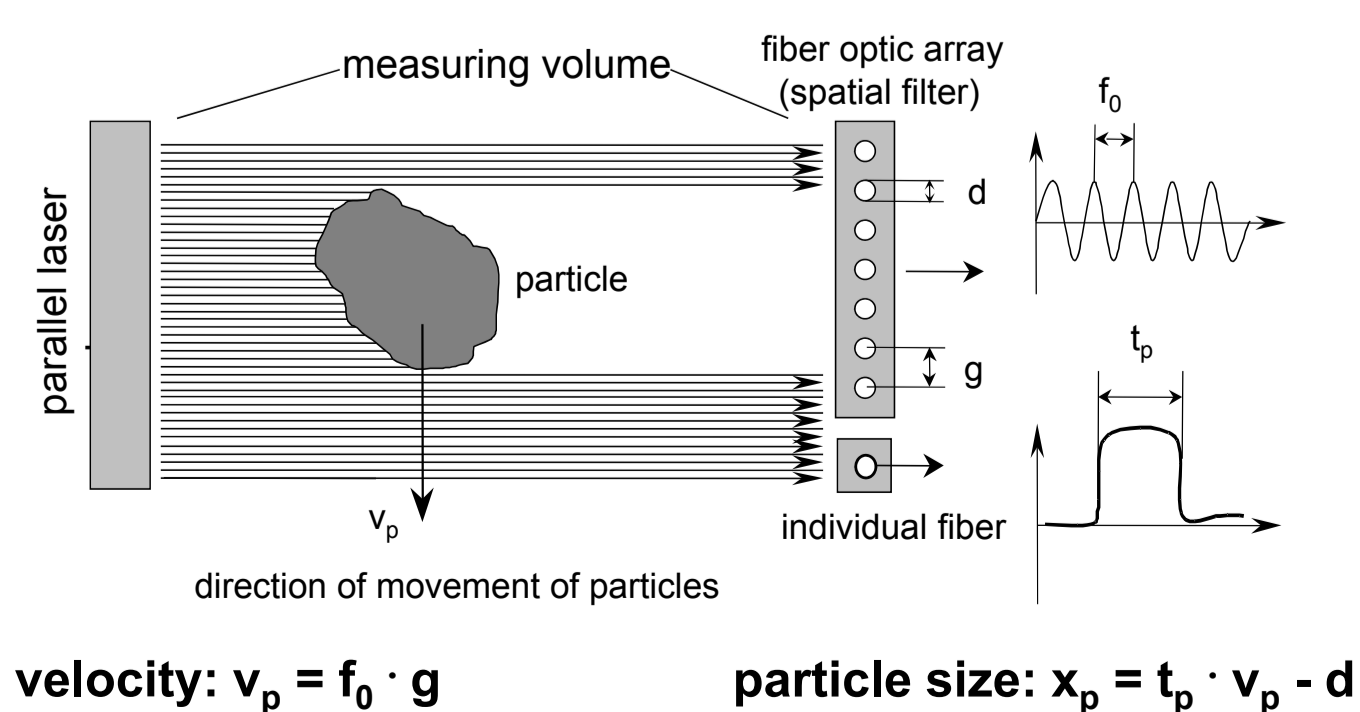


Fig. 2: Measurement method of spatial filter velocimetry

## 4. Results

### 4.1 Characterisation of prototype formulation type „A“

The reproducibility of a standard melt granulation process can be shown by three consecutive granulation experiments. Prototype formulation type „A“ was used.

The results are shown in Figure 3.

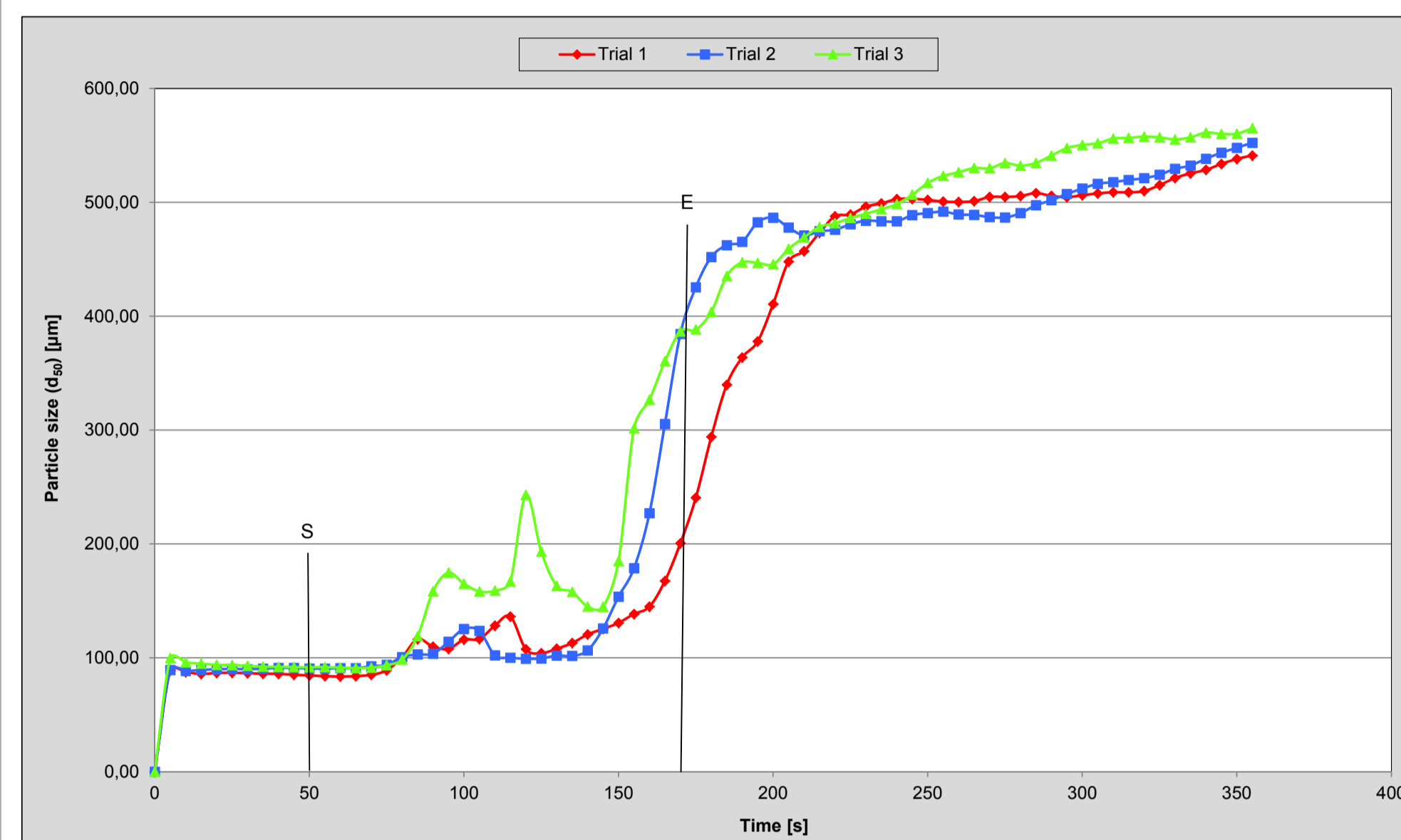


Fig. 3: Reproducibility of prototype formulation type „A“

Three phases of the granulation process could be seen. First phase - till 50 s - showed the mixing of the powder bed. In the second phase a growth in particle size could be detected. It started after adding the binder at „S“. The binder was added until „E“. In the third phase - beginning at 300 s - no further growth of particle size could be found. The final particle size was about 550 µm.

Further investigations will be necessary, because of an unknown signal shortly after adding the molded binder.

Fig. 4 shows a granulation experiment which was monitored by four different channels of the in-line particle size probe. Each channel was set to a different ring buffer size.

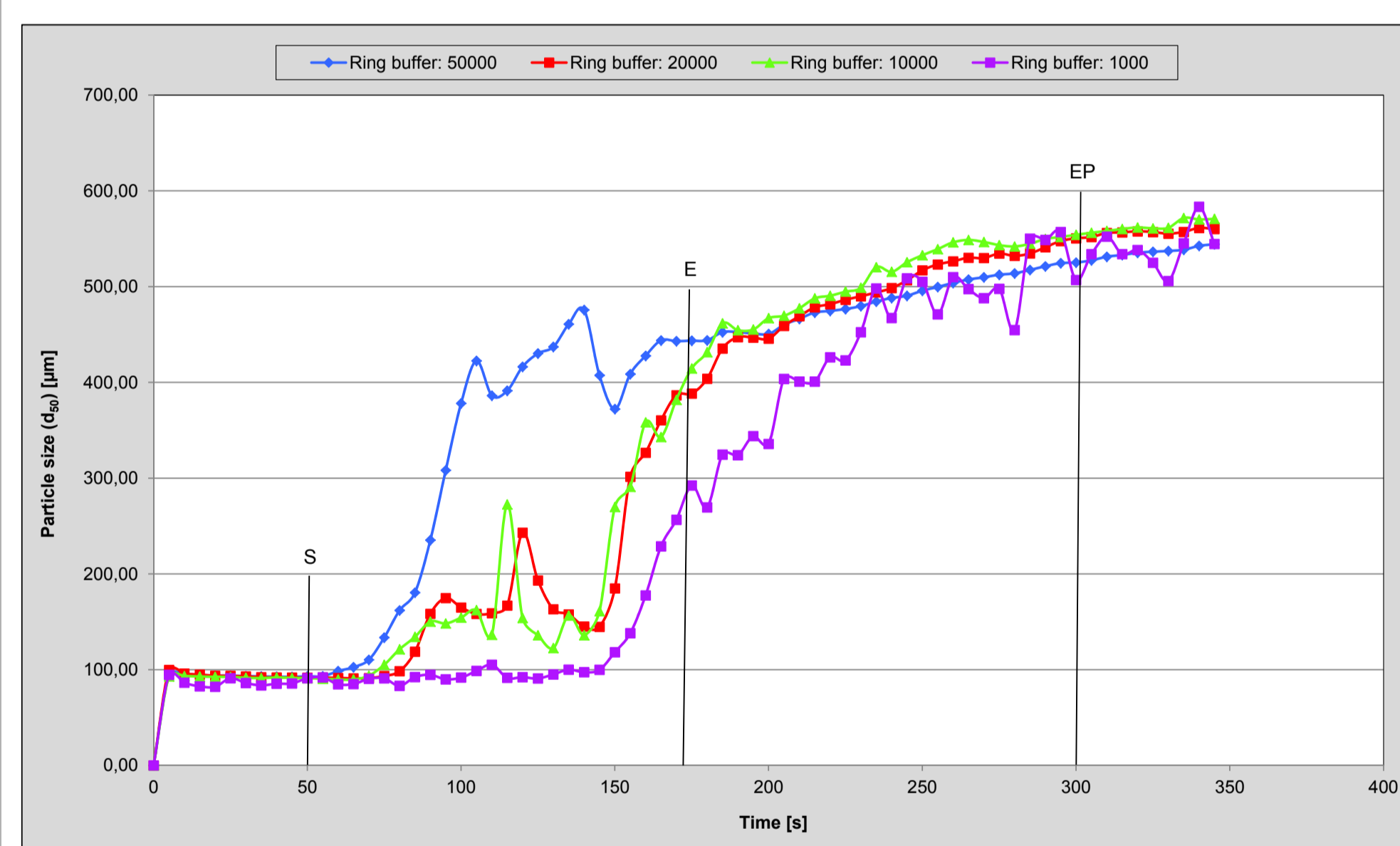


Fig. 4: Investigation of different ring buffer sizes

The process dynamic is different between 50 s and 300 s for each curve. In the second phase remarkable differences can be observed. Especially a ring buffer size of 50.000 leads to delayed process recording, while a ring buffer size of only 1.000 data fulfills the requirements in respect to an in-line process control.

The statement can be drawn, that the software settings have an important impact on the particle size detection.

In addition to in-line particle size measurement power consumption of the impeller was monitored during all three granulation processes.

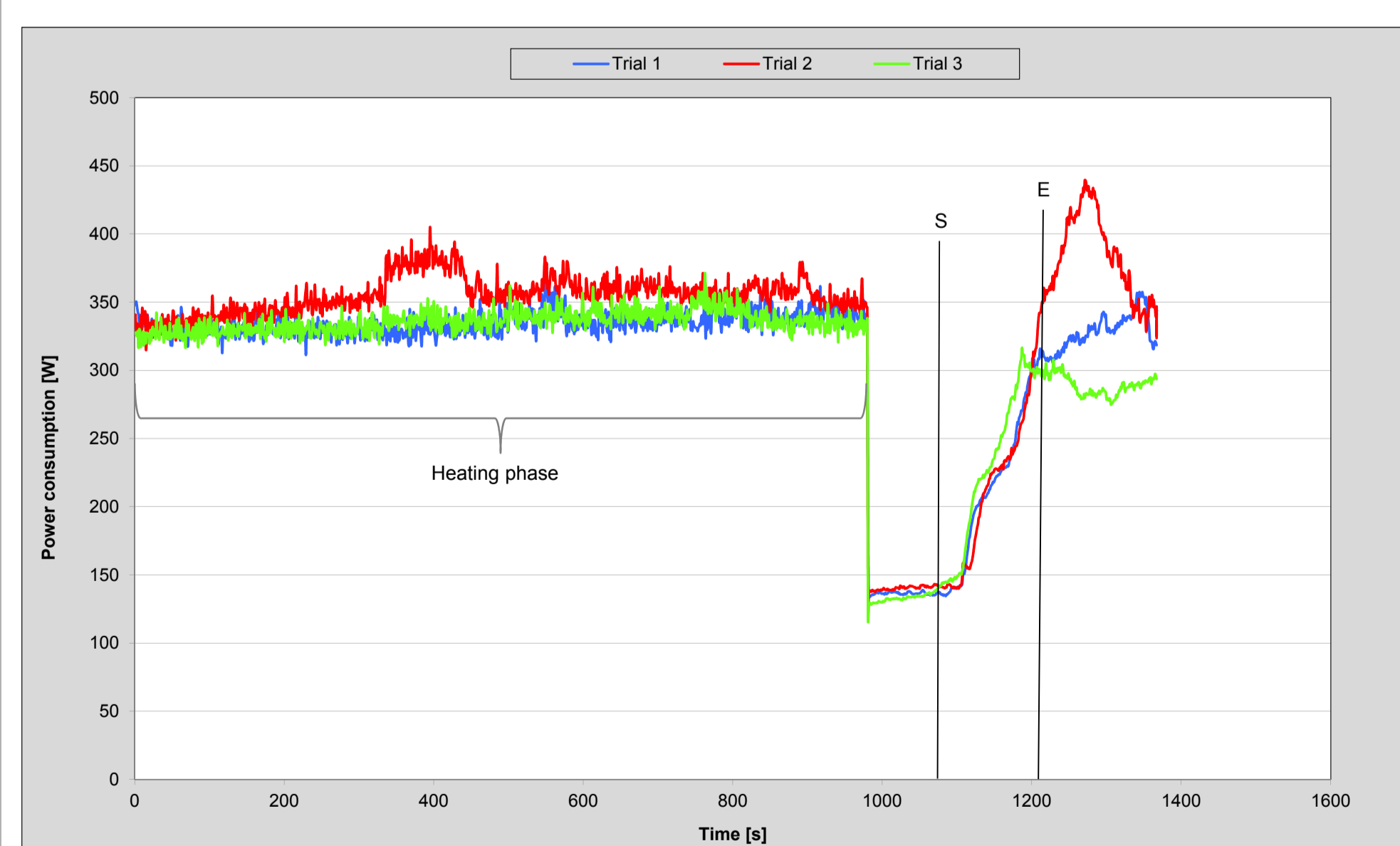


Fig. 5: Power consumption of the impeller during granulation of prototype formulation type „A“

The curves of power consumption can be divided into three phases. The first one is the „heating phase“ until 950 s. At this time the powder bed has a temperature of approx. 75° C. During the second phase the parameters for the granulation process were entered manually and the process was started. This phase takes 60 s to generate a smooth baseline. With the beginning of the third phase at point „S“ the injection of the binder has been started, granulate growth begins.

Phase one and two have nearly identical characteristics. In phase three different power consumptions have been detected. These different values may be caused by sticking melt in the mixer bowl especially at the bottom and the wall close to the impeller.

### 4.2 Influence of binder quantity

The aim of this investigation is the evaluation of the maximum binder quantity to be used for the given formulation type „B“.

Table 5: Prototype formulation, Type „B“

	[%]
Paracetamol	2,0
Polyethylene glycol 4000 (PEG 4000)	10,0 - 17,0
Lactose monohydrate	ad 100,0

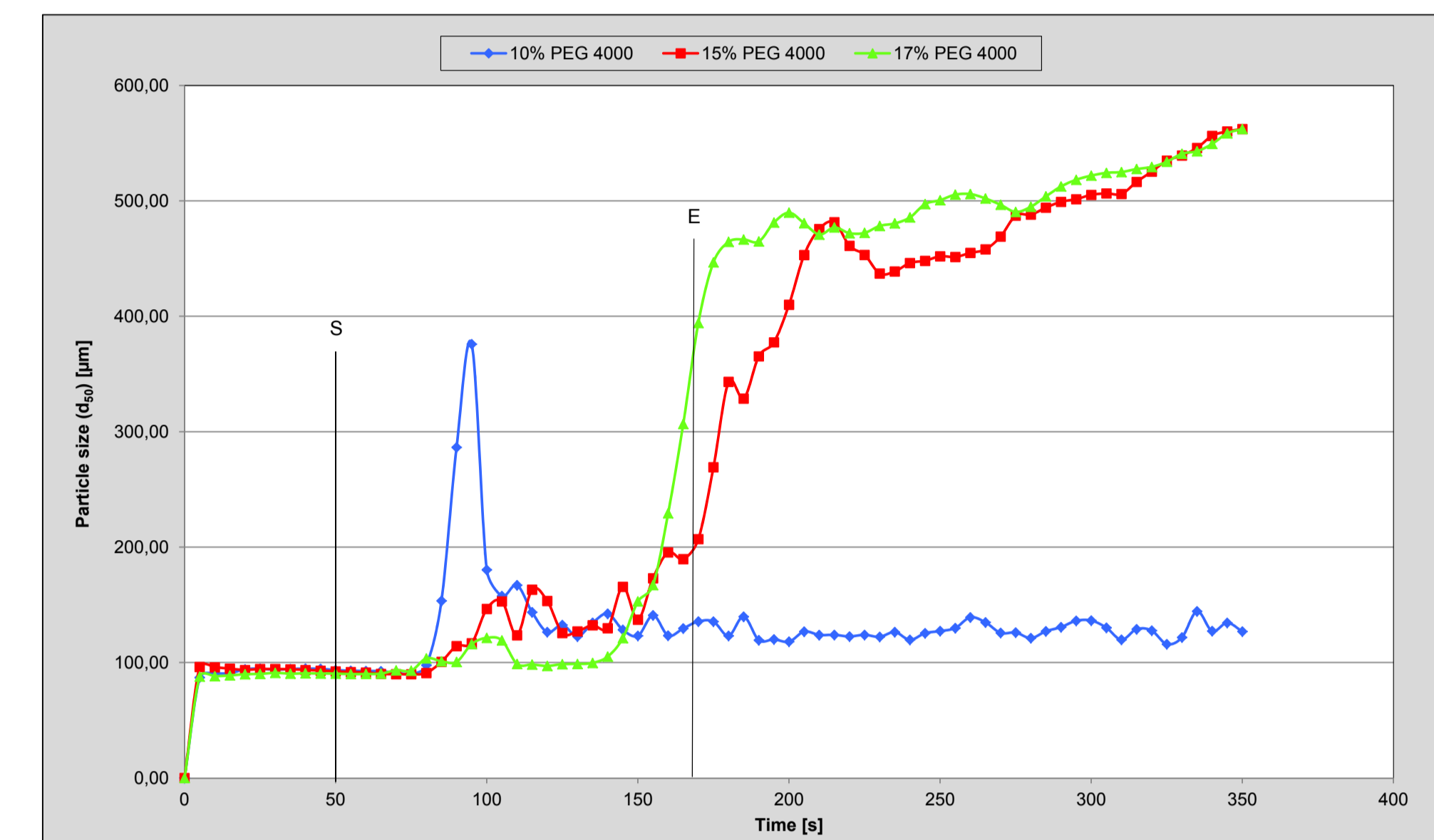


Fig. 6: Influence of PEG concentration in formulation type „B“

Primarily it was intended to evaluate binder quantity in the range of 10-30%. Orientating tests addicted that the melt granulation process is not possible for binder concentrations higher than 20%. Higher binder concentrations led to abortive attempts.

It could be clearly shown that the particle size increased with higher binder quantity.

### 4.3 Influence of Microcrystalline cellulose (MCC) quantity

The suitability of Microcrystalline cellulose as component of melt granulates as well as its impact on the particle size should be investigated. These examinations were carried out with a modified formulation type „B“.

Table 6: Prototype formulation, Type „B“

	[%]
Paracetamol	2,0
Polyethylene glycol 4000 (PEG 4000)	17,0
Microcrystalline cellulose (MCC)	0,0 - 20,0
Lactose monohydrate	ad 100,0

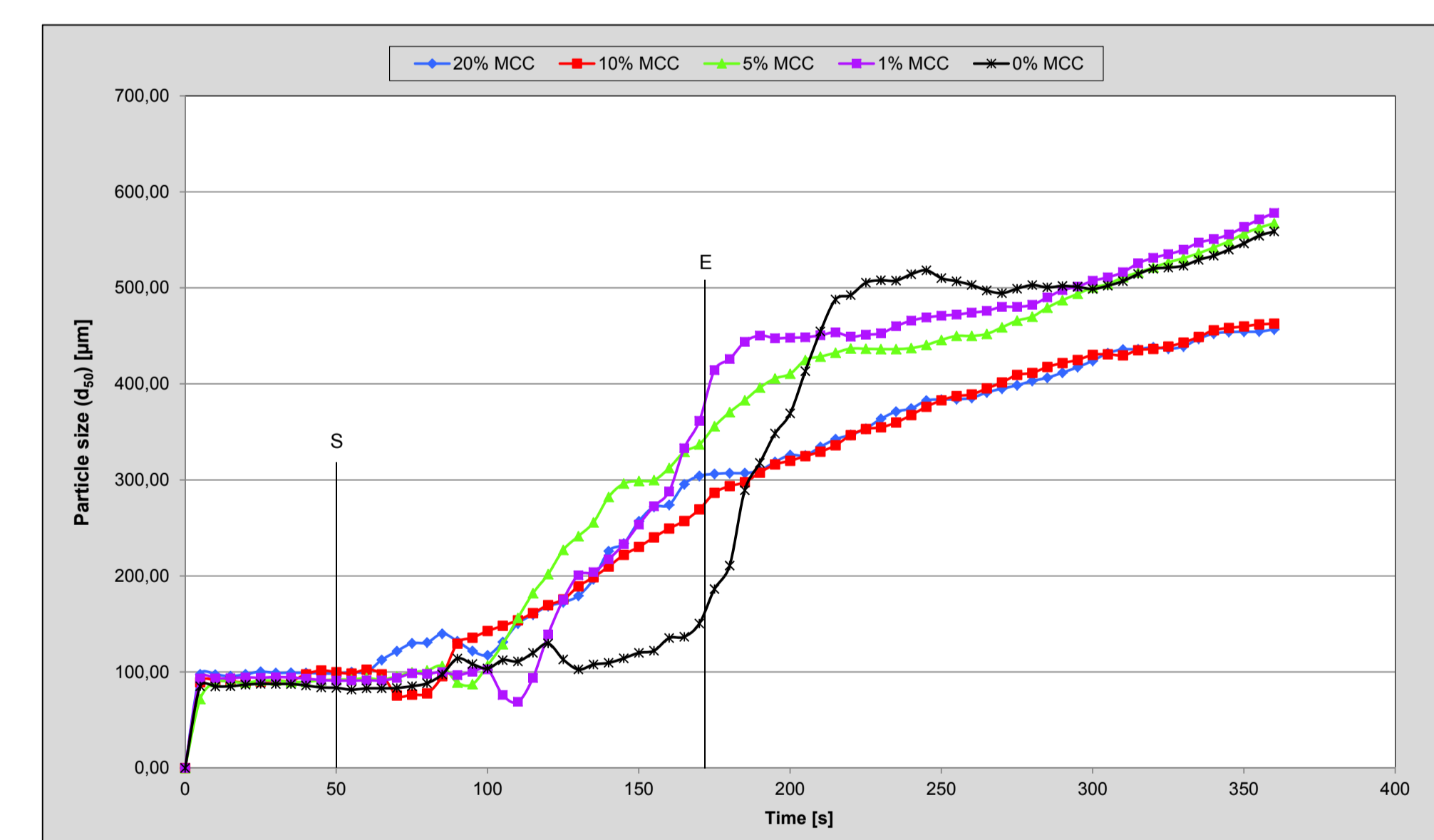


Fig. 7: Influence of MCC concentration in formulation type „B“

As a result it could be seen, that Microcrystalline cellulose in higher quantities decreases the particle size. Thus it is possible to attenuate the unwanted effects of high binder concentrations by adding MCC.

## 5. Conclusion

In this work, the particle size distribution during melt granulation processes could be detected. It was possible to differ between different phases of granulate formation over the whole process time. The results were in full accordance with theoretical expectations. The endpoint of the granulation process could be fixed precisely. So it could be shown that the used in-line particle size measurement sensor is in principle able to monitor melt granulation processes in high-shear mixers. 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 wide ranges.

## 6. References

- [1] Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance, <http://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)