Online Control of Particle Size during Fluidised Bed Granulation

Examination of a new type of laser probe for better control of particle size growth in fluidised bed granulation

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Summary

Online-control of the Particle Size during Fluid-bed Granulation / Evaluation of a novel Laser probe for better control of particle size in fluid-bed granulation

Good control over the particle size distribution during granulation is useful to obtain material that exhibits good compressability and hence good tableting properties. Time and resources can be saved using an on-line method capable of determining the particle size in real time thus ensuring the quality of the product and enabling the operator to react to deviations during the manufacturing process. Such a method based a novel laser probe will be introduced. It will be demonstrated in this article that the granular size up can be followed with high resolution and in real time. Based on the results obtained with the new probe it was possible to establish a model describing the correlation between the fluid-bed parameters like inlet air temperature, inlet air flow and spray rate and the final particle size in the granulation. With this model it is possible to calculate the parameters settings necessary to obtain a target particle size.

Zusammenfassung

Online-Kontrolle der Partikelgröße während einer Wirbelschichtgranulation / Untersuchung einer neuartigen Lasersonde zur besseren Kontrolle des Partikelgrößenwachstums in der Wirbelschichtgranulation

Die Kontrolle der Partikelgrößenverteilung während des Granulierprozesses führt zu gut verarbeitbaren Pressmassen. Eine Online-Methode zur schnellen Bestimmung der Partikelgröße kann Zeit und Ressourcen sparen, indem sie prozessbegleitend die Qualität des Produktes sicherstellt und die Möglichkeit eröffnet, rechtzeitig einzugreifen, sollten während des Prozesses Abweichungen auftreten. Eine solche Methode, basierend auf einer neuartigen Lasersonde, wird vorgestellt. Es wird gezeigt, dass die Verfolgung des Partikelaufbaus anhand der Partikelgröße mit sehr hoher zeitlicher Auflösung und Geschwindigkeit möglich ist. Basierend auf den mit der Sonde erhaltenen Ergebnissen war es möglich, ein Modell zu erstellen, das den Zusammenhang zwischen Parametern des Wirbelschichtprozesses wie Zulufttemperatur, Zuluftstrom und Sprührate der Granulierflüssigkeit sowie der erzielten Partikelgröße im Granulat beschreibt. Mit diesem Modell können die für das Erreichen einer bestimmten Partikelgröße nötigen Parametereinstellungen berechnet werden.

Key words

- **Particle size, size measurement, online control, growth**
- **Fluidised bed granulation**

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1. Introduction

In the pharmaceutical industry, the tablet still remains the most widespread of all drug forms. However, very few active ingredients can be tabletted directly. For this reason, in an initial production stage often a granulate suited for tabletting is produced. An important granulate parameter – in addition to factors such as moisture and active ingredient concentration – is the particle size as it influences many physical properties [1–3].

The median particle size x_{50} provides an indication of the quality of the granulate – particularly its suitability for tabletting. Consequently the particle size is a significant parameter for the control of granulation processes.

2. PAT

PAT is an initiative to develop and implement process analytical technology [4–8]. The basic idea behind the PAT initiative is for the pharmaceutical industry to completely understand the processes used in the manufacture of drugs. Critical process variables are monitored online and the process is controlled in feed-back loop so the result is always a product conforming to specification. This enables the method of parametric release without end product control. In contrast to the conventional validation strategy, which considers the successful production of three consecutive batches to be proof of a reproducible process, a PAT based approach may be based on the continuous analysis of the process enabling the product to be released as soon as the process ends. The release is dependent on compliance with the defined process parameter limits. At the same time, new knowledge is generated about the process from the data enabling the process to be continually optimised.

3. Particle size measurement with spatial filter velocimetry

There are numerous methods for determining particle size. However, very few meet the requirements demanded of an online measuring technique. Two methods had been given particular consideration: NIR spectroscopy and new inline particle probes based on laser techniques. As complicated chemometric models have to be used in NIR methods and these often lack flexibility, a laser probe from the Parsum Company (Chemnitz, Germany) is used for this work [9].

The measurement principle is based on an extended spatial filter which can convert light obscuration signals from individual particles into size information for analysis. In addition, the individual speeds and flight times of the particles are measured by a fibre optic array. At the same time, the movement of the particles is projected on the light collector, the spatial frequency filter (Fig. 1).

The fibre optic array is formed from a series of photodetectors. A particle passing these detectors produces a set of time-limited impulses: light obscuration data. Each photodetector produces an impulse whose length depends on the blockage time, which is correlated to the particle size, particle speed and flight path of the particle through the measurement cell. Summarizing the signals of the photodetectors in groups of the even and uneven detector numbers and subsequently subtracting these two sums, yields over time a characteristic frequency, f_0, for the analysed particle (Fig. 1). The particle speed, v, can be determined from this frequency:

$$v = f_0 \cdot g$$

g is the spatial filter interval corresponding to the distance between two laser light barriers in the same group. If the particle speed, v, is known then by analysing one single additional channel (Fig. 2), the particle size, x, can be determined as a chord length from the length of the impulse, t:

$$x = v \cdot t - d$$

d is the diameter of the optical fibre.

Due to the unknown flight path of the analysed particle, the chord length can be any line of intersection through the 2D projection surface of the particle. The size statistics determined are, therefore, based on the particle chord length. The measurement method is suitable for particle sizes from 50 to 2500 µm.

The measurement cell itself is equipped with sapphire windows kept free from fine dust or sticky particles by a permanent purge air flow. The laser light required for analysis is directed to the measurement cell by special fibre optics. The measurement volume illuminated by laser light in this way is placed directly in the particle flow.

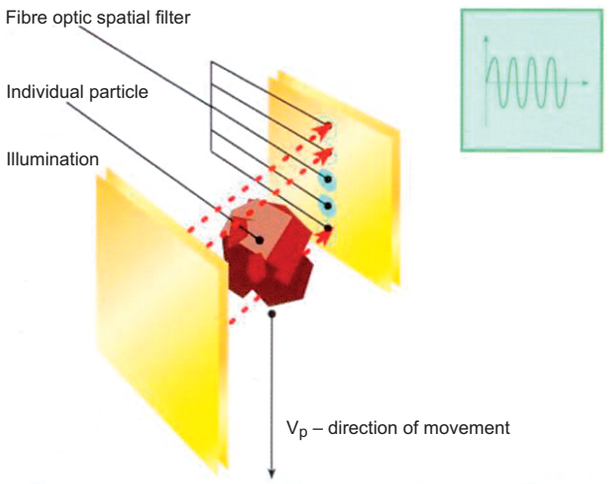

Fig. 1: Principle of the spatial filter to determine particle speed.

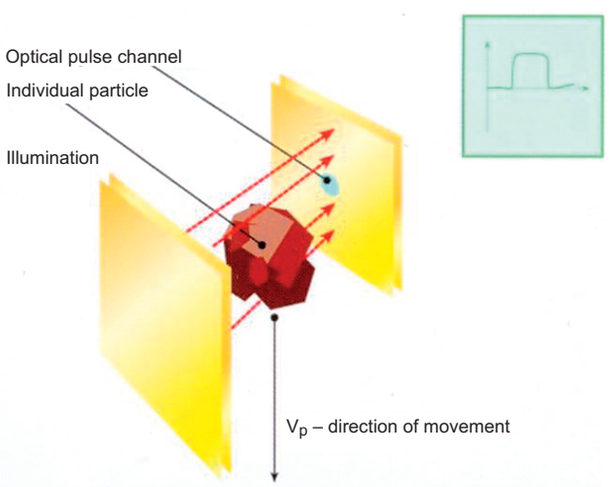

Fig. 2: Principle of a single optical channel to determine particle flight time.

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By installing a disperser unit into the measurement cell, the probe can also be used in systems with a high particle concentration. The disperser unit continuously supplies the measurement cell with an air flow of 10 to 20 l/min, which firstly disperses the particles – i.e. dilute to a measurable range – and secondly optimizes the flight path into the centre of the measurement cell and into the exact measuring direction. This enables measurements to be taken even in the case of irregular particle movement, e.g. as in the case of a fluidised bed. Well-directed dispersing makes it much easier to record individual particles. At the same time, the measuring conditions are strongly improved by adjusting the various flight paths and flight speeds of the individual particles to an optimized flight path for the measurement.

The individual particles are recorded at a measurement rate of up to several thousand particles per second. The raw data is transferred from the probe to a computer where the particle size is calculated. The result is presented in the form of a particle size distribution or a discrete particle size, e.g. x_{50}. Different calculation models such as q_0 or q_3 distribution can be obtained. x_{50} indicates an average value for the particle size and means the 50^{th} percentile or in other words: 50 % of the values are smaller. x_{10} (only 10 % of all particles are smaller) or x_{90} (only 10 % are bigger) can also be indicated accordingly. The total number of graded particles is permanently held in a circular buffer providing a sliding, constantly updated particle size distribution. In contrast to laser light scattering or the NIR method, no mathematical particle model is used as a basis, instead each particle is characterised immediately by means of its chord length.

4. Subject under examination

The granulation process examined in this article is fluidised bed granulation. The experiments were performed on a fluidised bed granulator from the Glatt Company (Binzen, Germany) with a capacity of 5 kg. Laser light scattering was chosen as reference method to be compared against particle size determination using the Parsum probe due to its widespread use and its acceptance as the standard method [10, 11].

5. Installing the probe

In a first set of experiments the general operational capability of the probe was tested in the fluidised bed. As a result the basic parameters could be fixed. A measuring interval of five seconds is required for online observation. Furthermore, the internal buffer of the measuring instrument was adapted to the measuring interval with 5000 to 10 000 particles to ensure the values provided were up to date.

In order to find the optimum measuring position for the probe, tests were performed for the vertical installation height in the fluidised bed, for the horizontal immersion depth in the fluidised bed and for the angular dependence of the probe.

The influence of the immersion depth and adjustment angle were examined in two tests with a spray dried granulate which was largely stable in the fluid bed as far as particle size was concerned.

The installation height of the probe in the direction of the air flow depends on how high the minimum particle concentration has to be for a representative measurement and how high the maximum particle concentration can be so the probe is not overloaded. The possible variations for the vertical installation height were predetermined, in this case, by the number of available installation ports.

The horizontal immersion depth was chosen so that, on the one hand, a relatively high particle concentration on the edge of the fluid bed was avoided and, on the other, direct contact of the probe with the granulating fluid sprayed on the fluidised bed was prevented. The measured results were consistent within these limits.

As the probe has a defined measuring direction, the angle of the probe can also be varied in relation to the direction of the air flow in the fluidised bed. Adjustment angle here means the rotation around the longitudinal axis of the probe rod. In the tests for angle dependency, a strong dependency of the measured results was demonstrated at angles over approx. 90°. For this reason, these large angles were avoided and the probe was always operated at an adjustment angle of 0° relative to the preferred direction of flow.

6. Test plan

The fluidised bed granulation process is affected by several factors and it is necessary to determine which of these have a significant influence on the process. The following parameters are examined: inlet air temperature, inlet air flow and the spray rate of the granulation fluid. The formulation is kept the same for all tests so that it was not an influencing factor. The particle size measured by the probe is stipulated as the target size.

Using the Design-Expert software of Stat-Ease Company (Minneapolis, USA), a D-optimal test plan is created for the above mentioned parameters, i.e. inlet air temperature, inlet air flow and spray rate of the granulating fluid.

The test plan is composed of ten experiments to determine relationships, four experiments to test the model and one experiment to document reproducibility – i.e. a total of 15 sets of parameters (Table 1). For the test environment, the limiting ranges are defined: spray rate: 30 to 50 g/min, air flow: 120 to 200 m^3/h and temperature: 60 to 70 °C, within which all test points are located.

Table 1: Statistical test plan. CentEdge: test point at the centre of an edge; PlaneCent: test point at the centre of a plane; Vertex: test point at a corner; Interior: test point at the centre of the cubic test environment.

Standard sequence	Randomised sequence	Design points	Spray rate (g/min)	Air flow (m^3/h)	Temperature (°C)
10	1	CentEdge	40	200	70
6	2	PlaneCent	50	160	65
8	3	Vertex	30	200	60
7	4	PlaneCent	40	160	60
12	5	Vertex	30	120	70
15	6	Vertex	50	120	70
2	7	Vertex	30	120	60
1	8	Vertex	50	200	60
11	9	Interior	35	180	65
9	A	CentEdge	30	160	70
3	B	Vertex	50	120	60
13	C	Vertex	30	200	70
14	D	Vertex	50	200	70
4	E	Vertex	50	120	70
5	F	PlaneCent	40	120	65

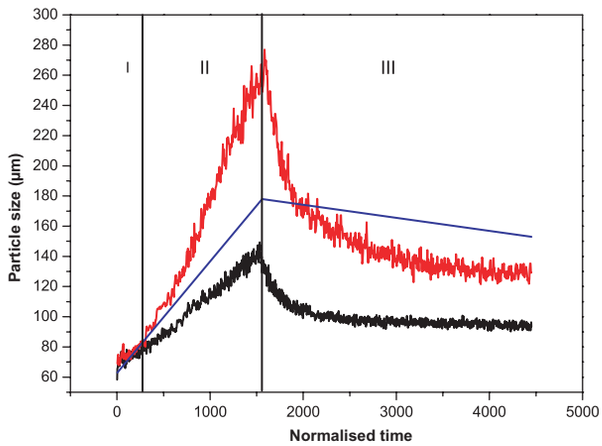

Fig. 3: Comparison between the expected course of granulation (blue) and the detected (black, red) I = Initiation phase; II = Phase of particle size growth; III = Disagglomeration process. I and II: Spray phase; III: Drying phase.

7. Materials and methods

In the tests, a placebo mixture is granulated. The mixture consists of:

– 3200 g lactose monohydrate
– 900 g maize starch
– 600 g starch 1500
– 50 g magnesium stearate

The granulating solution consists of:

– 250 g polyvinylpyrrolidon
– 1312.5 g water

Taking into account a production factor of 1.25, 312.5 g PVP is slowly stirred and dissolved into 1640.6 g water at approx. 700 rpm.

The fluidised bed granulator is loaded with excipients and prepared for granulation. Just before starting, the probe measurement record is started.

The interval between tests was every two minutes – after ten minutes the tests were performed every five minutes – the air flow, air temperature and the quantity of the already sprayed PVP solution are noted.

When the spray quantity planned for the test was reached, the spraying was ended and the product was dried until the product temperature had increased by 0.5 °C. Immediately after this, samples are taken to measure particle size using the reference method and the product moisture is determined by means of a rod probe.

Finally a lubricant (magnesium stearate) is added. The magnesium stearate is blended with the granulate for a period of 45 seconds.

8. Results and discussion

In the tests, the system gave an unexpectedly detailed picture of the granulation. Instead of the expected linear growth of the particles over the total duration of the spray phrase, an initiation phase could be noted and its length and course under test conditions were independent of the fluidised bed parameters (Fig. 3, Phase I). This was followed by the phase of particle size growth which was heavily dependent on the fluidised bed parameters (Fig. 3, Phase II). Finally, as a third phase after spraying ended, the drying phase was identified, in which a granule disagglomeration process occurred (Fig. 3, Phase III).

Moreover, periodic fluctuations in the particle size ("waves") were observed in the curves which could be correlated with the periodic shaking of the fine dust filters. Against initial considerations, it could be shown that the shaking parameters had a pronounced effect on the granulation process by continuously extracting the fine fraction from the fluidised bed and then periodically releasing this into the fluidised bed again.

As seen in Fig. 3, various particle sizes distributions can be produced with the same substance simply by varying the fluidised bed parameters. The analysis of the statistical test plan showed that the air flow, spray rate of the granulating fluid and the temperature can be used to control the particle size (x_{50}) in a linear relationship over a wide range (Fig. 4 and 5).

The model relationship found for the test granulation in the range tested is given by:

$$x_{50} = -26.1 + 3.0 \cdot (\text{spray rate in g/min}) + 1.2 \cdot (\text{air flow in } m^3/h) - 0.8 \cdot (\text{temperature in °C})$$

The influence of the individual parameters on the target size (x_{50}), therefore, differs significantly. The effects of the parameters obtained from the statistical test plan provide information on this. The spray rate and air flow were found to have a great influence. The influence of the temperature is, in contrast, rather small and its significance is also much less. This may possibly be due to the very small temperature range examined (ranging only from 60 to 70 °C). Further tests are required to demonstrate the validity of a linear relationship, especially beyond the current set limits of the test environment

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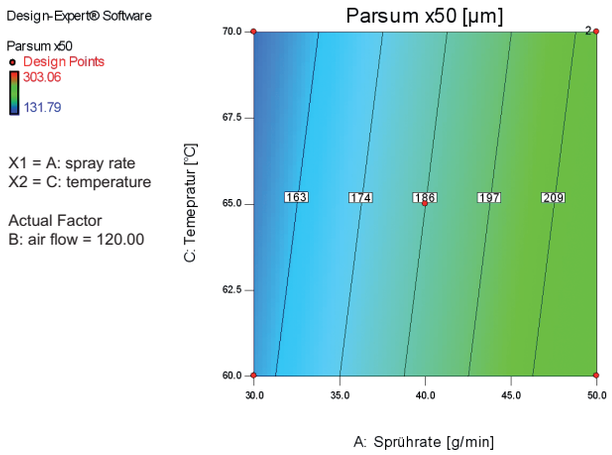

Fig. 4: Parsum x_{50} air flow 120 m^3/h.

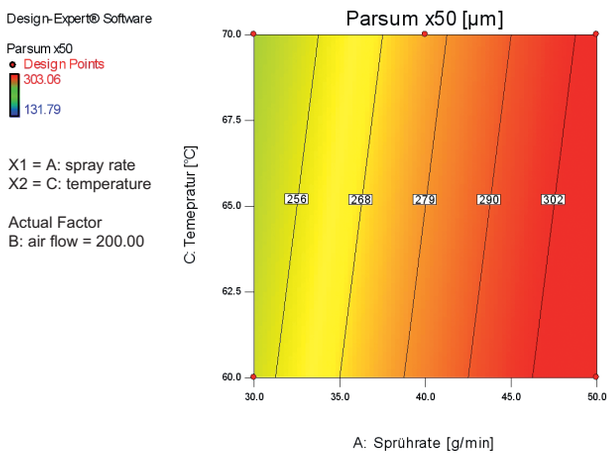

Fig. 5: Parsum x_{50} air flow 200 m^3/h.

(spray rate of 30 to 50 g/min and air flow of 120 to 200 m^3/h).

9. Comparison with laser diffraction data

To compare the values measured by the probe with values measured by laser diffraction, the fluidised bed was briefly switched off during granulation a total of three times at 1300, 2000 and 2700 seconds to take samples. In addition, the finished product was examined and compared with the last value from the granulation record of the probe.

A tendential consistency with the values measured by laser light scattering can be observed (Fig. 6). The 1st sample at 1300 seconds could not, however, be examined as agglomerates had formed which could not be disintegrated by the disperser unit of the laser diffractometer. The 2nd and 3rd samples examined by laser light scattering are approx. 8 % over the value measured by the probe. The last sample examined demonstrates with

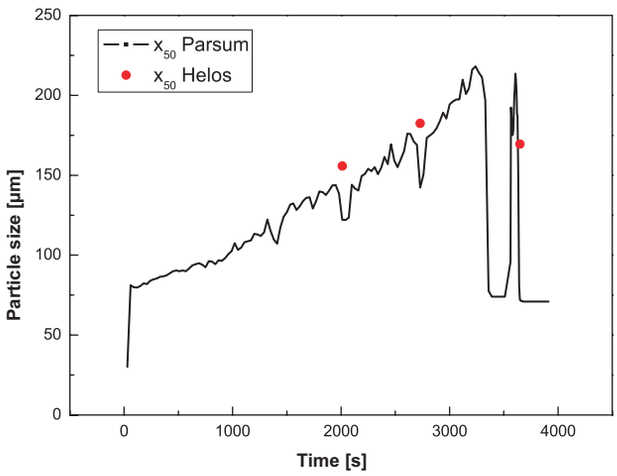

Fig. 6: Comparison of laser diffraction measurements (Helos) and Parsum x_{50}.

a greater negative deviation of more than 10 %. It is assumed that this is reasoned in the composition of the sample, as it is inhomogeneous, The reason is that after the spray phase ends, there is a short pause in which 50 g magnesium stearate is added to the fluidised bed container. Then the fluidised bed is switched on again for 45 seconds. This time is too short for the probe to produce a stable measurement (Fig. 6) as the circular buffer cannot be completely filled. Therefore, the finished granulate including the magnesium stearate fraction can be analysed by laser diffraction without any problems whereas the probe gives the last measurement for analysis as the value at the end of granulation without the addition of magnesium stearate.

10. Further tests

In addition to the statistical test plan, some further tests were performed to respond to specific questions concerning probe use. Firstly, these include testing reproducibility and the use of the probe in a second fluidised bed granulator. Moreover, tests were performed to increase understanding of the process and to examine the probe's reaction to failures and malfunctions during the granulation process.

11. Reproducibility

At the same time as the tests to examine the reproducibility of the measurement results, the reliability of the probe was ensured during the granulation of a mixture containing active ingredients. Placebo mixtures are generally easy to granulate. However, mixtures containing active ingredients are often poorly suited to granulation and can only be granulated with a great deal of experience due to the high proportion of active ingredients.

For the test, a formulation comprising 40 % of a micronised active ingredient was granulated twice under

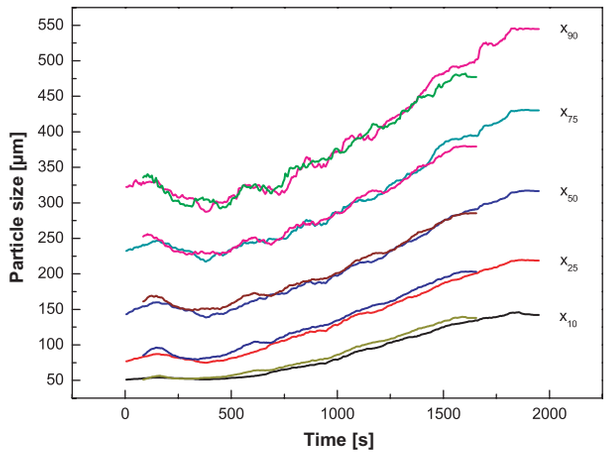

Fig. 7: Comparison of two identical tests on particle sizes x_{10}, x_{25}, x_{50}, $x_{75}$and x_{90} (Parsum).

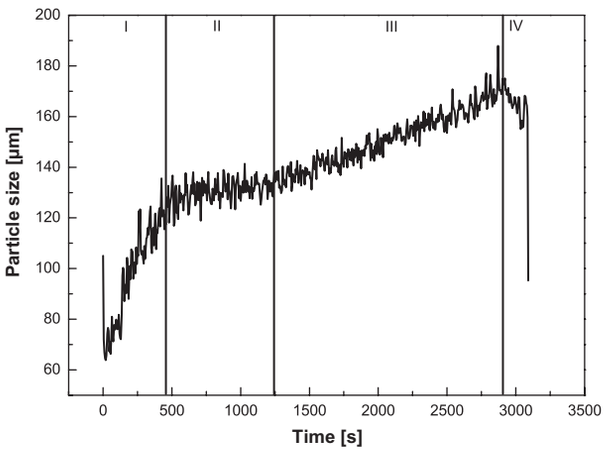

Fig. 8: Test on the WSG 15 with four distinguishable stages of granulation (Phase I to IV).

identical conditions. The results of both tests show high similarity. The difference between the measured PSD curves is on average 5 to 8 µm (Fig. 7). In the case of x_{10}, the difference is a maximum of 10 %, in the case of x_{90}, only a maximum of 3 %, referring in each case to the smallest value assumed by x_{10} and x_{90} in the course of the tests. It can, therefore, be deduced that the measurement results are reproducible.

12. Transferability

To examine transferability to other fluidised bed granulators, in addition to the tests on WSG 5, four tests were performed on a WSG 15. As with WSG 5, this is a fluidised bed granulator from Glatt featuring a capacity of 15 kg. As the first two tests were required to establish the minimum immersion depth – 10 instead of 6 cm with WSG 5 – the next two tests could record the granulation process. The different stages of granulation can be clearly seen (Fig. 8).

At the start, an air flow of 400 m^3/h is used. Here the particle size growth is 9.7 µm/min in the range from 50 to 350 seconds (Phase I). When the air flow was changed to 500 m^3/h at time point 450 seconds, the particle size growth decreased to 0.3 µm/min in the range from 600 to 1200 seconds (Phase II). For this reason, at timepoint 1250 seconds, the spray rate was adjusted from 140 to 145 g/min. The particle size growth then changed to 1.3 µm/min in the range from 1300 to 2800 seconds (Phase III). After 2900 seconds, spraying ended. Subsequent drying in the range from 2900 to 3000 seconds led to a partial disagglomeration and a resultant reduction in the average particle size by --5.5 µm/min (Phase IV). Any change to an influencing factor is, therefore, directly reflected in the granulation process shown by the probe. Consequently, the transfer of the method from WSG 5 to WSG 15 was successful.

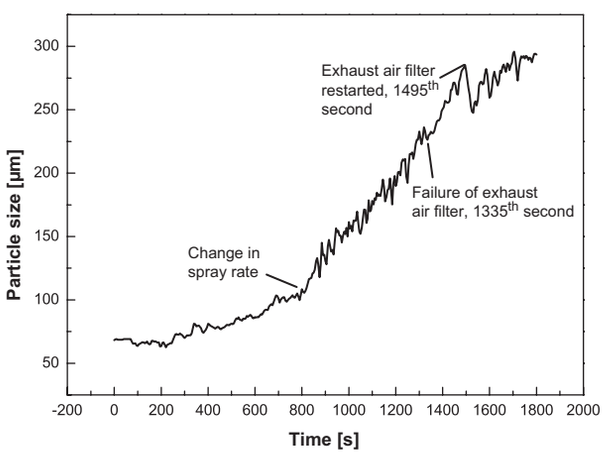

Fig. 9: Particle size development (x_{50}) with probe reactions to faults in the granulation process.

13. Reactions to anomalies in the process

During another test, several process failures and system malfunctions were simulated during granulation to test their influence on the measurement (Fig. 9). After starting the granulation under standard conditions, at 750 seconds, the spray rate was changed. Subsequently an increase in the particle growth rate could clearly be seen. The particle size growth rate increased from 3.6 µm/min to 12.9 µm/min. After 1335 seconds, the exhaust air filter failed. However, within the next 160 seconds, the fine fraction was still being continuously taken from the fluidised bed and collected in the filter bags. After 160 seconds, at 1495 seconds, the exhaust air filter restarted again and shook the fine fraction back into the fluidised bed. Whilst shaking was interrupted, the growth of the particles in the fluidised bed accelerated to 21.6 µm/min, due to the continuous withdrawal of the fine fraction. By restarting the shaking process, within 30 seconds, the complete fine fraction collected

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in the filters over the last 160 seconds was returned to the fluidised bed leading to a strong reduction in the average particle size which was in clear contrast to the fluctuations in the granulation process to that point.

However, the failure of the exhaust air filters revealed additional aspects. Both before and after the failure, the fluctuations in the granulation process are much more evident than during the 160-second pause. This proves the fluctuations to be caused by the filters shaking. These fluctuations can be observed in all tests and always with an interval of 20 seconds, as this is the default interval for the shaking sequence.

Fig. 10 shows an enlarged section from the development of particle size during granulation.

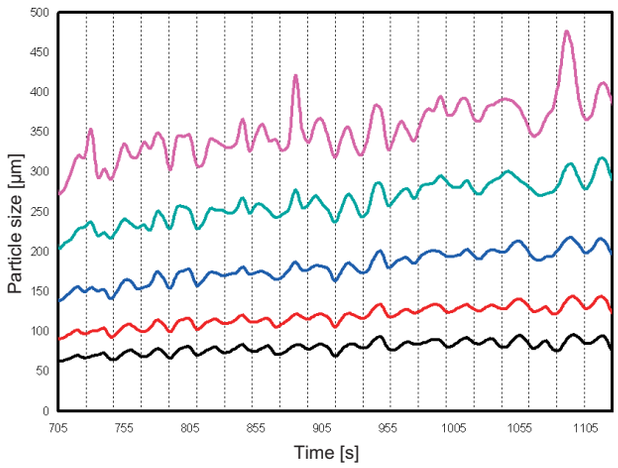

Fig. 10: Influence of the shake timing on the particle sizes (x_{10}, x_{25}, x_{50}, $x_{75}$and x_{90}).

14. Conclusion

Within the scope of this work, a detailed insight into the granulation process could be provided by the measuring system into particle size growth during fluidised bed granulation. By performing the tests, initially the optimum installation parameters could be determined and the software settings could be adjusted. The first analyses of the recorded granulation processes provided a conclusive picture. A surprising observation was that the shaking intervals led to an oscillation in the course of particle growth. Just as unexpected was the initial lag phase at the start of granulation, during which, in spite of spraying binder solution, no particle size growth could be recorded.

Using a statistically based design of experiment approach containing the variation of the factors spray rate, temperature and air flow, the granulation behaviour could be examined closely, using the probe under various conditions. The model derived from the tests showed statistical significance and made precise predictions about the properties of granulates to be produced.

In further tests, both the transferability of the measuring method to another unit and the reproducibility of the measurement results could be ensured. The comparison of the probe data with the results from laser light scattering reference method was successful.

In conclusion, the probe has proven to be a suitable instrument for the online control of particle size. Additionally, it features easy handling – both with regard to installation in the unit and software. Moreover, it is robust, easy to clean and shows demonstrably no influence on the process.

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