# INFLUENCE OF THE INSTALLED IN-LINE SPATIAL FILTER VELOCIMETRY (SFV) PROBE ON THE FLUIDIZED BED STABILITY

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## ABSTRACT

Fluid bed granulation is a primary process used in pharmaceutical industry to improve flowability, compressibility and homogeneity of powders for tablet compression. Granulates of high quality can be obtained by in process measurement and control of the critical process parameters. In this study, an in-line probe for particle size measurement was installed directly into the centre of the fluid bed below the spraying nozzle in a batch laboratory fluid bed granulator, and stability and homogeneity of the fluid bed process, yield losses due to material precipitation and reproducibility of the product parameters were investigated. The optimum fluid bed process parameters were evaluated in earlier investigations.

The model formulation consists of lactose monohydrate (Tablettose 70, Meggle-Pharma, D-Wasserburg) and microcrystalline cellulose (MCC 101 L, Sanaq AG, CH-Basel) in relation 1:1, aqueous hydroxypropylmethyl cellulose solution 7.5% (w/w) (Pharmacoat 606, Shin Etsu, D-Mühlheim) was used for agglomeration. The process was performed in a fluid bed granulator (GPCG 1.1, Glatt, D-Binzen) without and with installed in-line spatial filter velocimetry probe (IPP 70-S, Parsum, D-Chemnitz). Spray rate was varied from 8-16 g/min, the other process parameters were kept constant (process air temperature 60°C, atomization air pressure 2 bar, nozzle diameter 1 mm, batch size 150 g). Increasing agglomerate weight was compensated by adjusting process air volume (45-70 $m^3/h$). With installed probe particle size was measured continuously during the whole agglomeration process. Product quality was evaluated by particle size (sieve analysis, Retsch, D-Haan), bulk and tap density (tap volumeter, Erweka, D-Heusenstamm) and angle of slope (flow tester PTG S3, Pharma Test, D-Hainburg).

Independent of spray rate the fluid bed was stable over the whole process. The batches with installed as well as without probe yielded more than 90% at different spray rates. Product precipitation was negligible. Also injected air of the probe responsible for dilution and homogenisation of the specimen did not disturb the stability of the fluid bed. Product particle size, bulk and tap density and angle of slope gave similar values independent of probe presence or not, only at a spray rate of 12 g/min the $d_{50}$ values deviate about 40 µm. The in-line Spatial Filter Velocimetry (SFV) can be used as a process analytical technology (PAT) tool.

## KEYWORDS

Fluid bed granulation, in-line Spatial Filter Velocimetry probe

## 1. INTRODUCTION AND AIM

Fluid bed granulation is used in pharmaceutical industry to produce free-flowing and homogeneous powders for successful tablet compression or reproducible hard capsule filling. Various in-process control methods of the critical fluid bed process parameters are in use, e.g. measurement of particle size by the in-line probe IPP 70-S [1-5], to observe the agglomeration process and to guarantee a high quality of the granulates, especially reproducible particle size and particle size distribution. Therefore, the probe was installed directly into the centre of the fluid bed below the spray nozzle in a batch laboratory fluid bed granulator. The particle growth was observed online during the whole process. Although the installed probe occupies only a small area (15 $cm^2$) in the sectional area of the process chamber (363 $cm^2$, relation probe to sectional area 1:24) a risk arises for fluid bed process continuity and material precipitation. The aim of the investigation was to find out whether the installed probe has an influence on the stability and reproducibility of the fluid bed process and the yield on one hand and on the other hand on the product properties of the granulates. Therefore, analogous batches were prepared with installed probe and in absence of the probe.

## 2. THE MAIN PRINCIPLE OF FLUID BED GRANULATION

At the beginning of the fluid bed granulation process the primary powder particles are transferred by process air in a fluidized bed and sprayed with binder solution ("Spraying", Figure 1). Small droplets precipitate onto the particle surface forming a sticky film ("Moistening"). The powder particles agglomerate by liquid bridges under the influence of capillary forces. Simultaneously, the solvent (in most cases water) evaporates under the supply of hot process air. Saturation concentration of the binder and other dissolved components in the liquid is exceeded, precipitation takes place and at the end the material solidifies to solid bridges between the primary particles ("Solidifying"). Large agglomerates may break to pieces under the influence of shear forces, mutual friction in the fluid bed and abrasion at the process chamber wall. The agglomeration process tends to a stationary state of granule formation and disintegration. After final drying of the agglomerates the granules are received as irregular and polydisperse particles ("Blackberry structure").

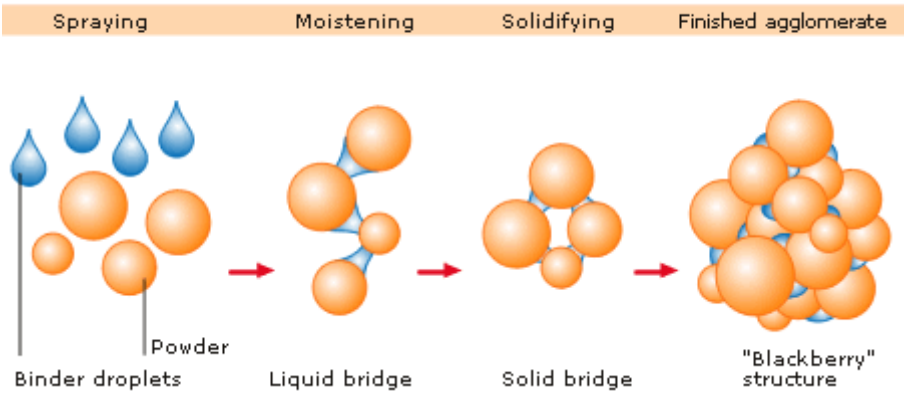


Figure 1: Main principle of the wet agglomeration process (www.glatt.com)

## 3. EXPERIMENTAL

The model powder formulation consists of lactose monohydrate (Tablettose® 70, Meggle-Pharma, D-Wasserburg) and microcrystalline cellulose (MCC Sanaq 101, Sanaq, CH-Basel) in relation 1:1, binder solution of hydroxypropylmethyl cellulose (Pharmacoat 606, Harke, D-Mülheim) 7.5% (w/w) in purified water was used. All substances were of pharmaceutical grade [6].

The batch laboratory fluid bed granulator GPCG 1.1 (Figure 2) consists of a conical 24" expansion chamber high 600 mm, 300 mm upper diameter and 140 mm lower diameter. The expansion chamber is equipped with control windows, sample slide 150 mm above the bottom and temperature sensor. A ring (inner diameter 140 mm, outer diameter 210 mm, height 65 mm) at the lower end of the chamber carries a narrow wire-gauze. The filter housing at the upper end of the expansion chamber contains a textile filter to prevent loss of fine particles and to remove them to the process chamber. The tower of bottom equipment, process chamber, expansion chamber and filter housing with exhaust air tube are vertically positioned on a table and tightly fitted by a hydraulic clamping system. The separate control unit is mounted on the right side of the table. The binary spray nozzle (Düsen-Schlick, D-Untersiemau/Coburg) of diameter 1.0 mm is used in the top spray modus and located in the centre of the process chamber and also in the centre of the fluid bed, respectively. Process air is generated by a ventilator situated in the exhaust air channel, heated and sucked through the wire-gauze at the bottom into the process chamber generating a fluid bed of the primary powder particles. The humidity of the process air is influenced by the actual room climate (temperature and humidity).

Before process start the apparatus was preheated. The spray rate was varied from 6-18 g/min, and the process was run on the one hand with installed probe and on the other hand without probe. Two identical batches were produced for each constellation. The other process parameters were kept constant: process air temperature 60°C, atomization air pressure 2 bar, upper position of the spray nozzle at the process chamber, nozzle cup position 2.5 scale for constant spray angle, amount of primary powder 150 g, consumption of binder solution 300 g and filter shaking for 5 s with 10 s pause. Increasing agglomerate weight during agglomeration process was compensated by adjusting the process air volume in the range of 45-70 m³/h with the exhaust air flap. With installed probe particle size was measured during the whole process. Furthermore, in intervals of 4 min probes were taken by the sample slide to evaluate agglomerate growth and humidity.

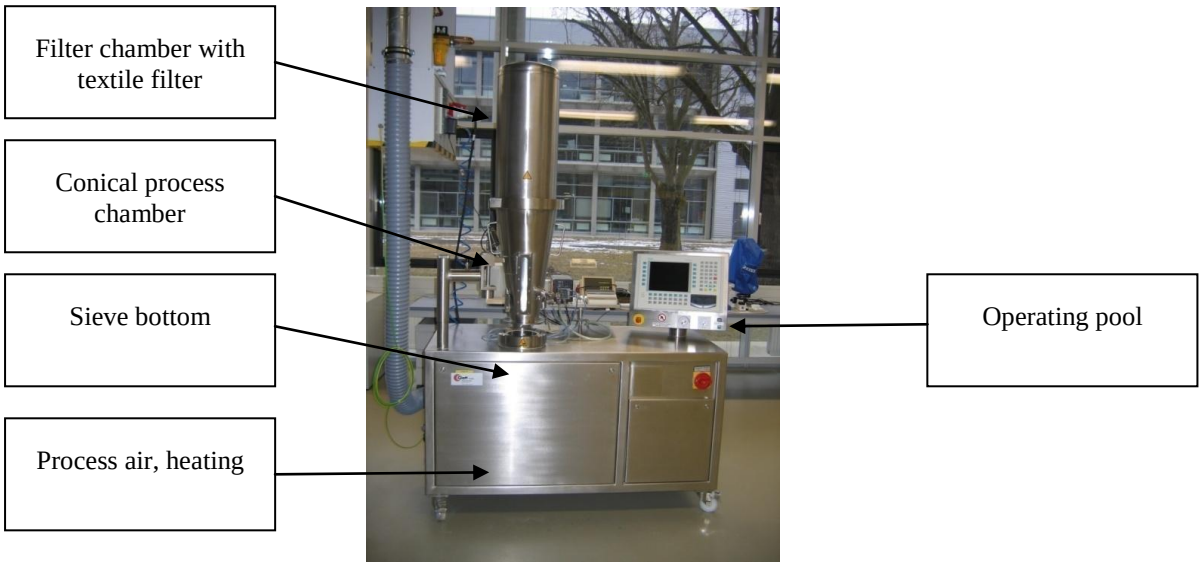


Figure 2: Batch laboratory fluid bed granulator GPCG 1.1

The in-line probe IPP 70-S is constructed from stainless steel and has sapphire windows (Figure 3). The probe consists of an electronic housing with photodetectors and laser diode, a probe tube (tube length L=280 mm, tube diameter D=25 mm), a probe head with optical components (optical fibre array) and a disperser D23 for dilution and dispersion of the particle flow if particle loading is too high. The probe system is suitable for size measurements in the range 50-6000 µm and for velocity measurements between 0.01 m/s and 50 m/s. The allowed temperature range at the measuring point reaches from -20°C to 100°C. With reference to the measurement principle, alignment and field calibration are not required. The probe is connected to a measurement computer at process level [4].


Figure 3: Particle probe IPP 70-S with disperser D23 (www.parsum.de)

The probe uses the technique of SFV to measure the particle size. The sensor works on a patented fibre optic measurement principle and measures simultaneously the size and the velocity of individual particles. Statistical techniques associated with the technique allow calculation of chord length distributions. Using SFV, size and velocity of particles can be separated from each other when they pass through a laser beam and cast shadows onto a linear array of optical fibres. The generated signal is transported to the photodetectors and amplified. The frequency of this signal is measured by photodetectors. It is proportional to the particle velocity. Knowing the spatial filter constant, the velocity can be calculated. As the particle passes through the laser beam, a secondary "pulse" signal is generated by a single optical fibre. Knowing the time of the pulse signal and the velocity of the moving particle, the chord length of the particle can be calculated [5].

The granulate quality was evaluated by particle size analysis (analytical sieve machine AS 200 basic, Retsch, D-Haan, amplitude 50%, duration 10 min, sieves 1000, 710, 500, 355, 250, 180, 125 and 90 µm), bulk and tap density (tap volumeter SVM 102, Erweka, D-Heusenstamm), angle of slope (flow tester PTG S3, Pharma Test, D-Hainburg) [6] and granule shape with stereo light microscope (Stemi 2000-C, Carl Zeiss, D-Oberkochen, ocular W-PI, 10x/23, magnification 5x).

## 4. RESULTS AND DISCUSSION

The granulate batches manufactured with spray rates between 8 and 16 g/min without installed probe as well as with installed probe (Table 1) yielded more than 90%. The agglomeration process was stable and super-wetting of the material in the fluid bed during the process or inacceptable material precipitation was not observed. Process time reduces with increasing spray rate due to availability of higher amounts of binder solution in the same time. At a spray rate of 18 g/min and above the agglomerates were too wet and the fluid bed collapsed. Contrary there was a deficient formation of agglomerates at spray rate 6 g/min and below. Suspected influences of the cylinder of the probe support of one side and the compressed air inside of the probe on the stability of the agglomeration process and larger amounts of precipitate and last not least on granulate properties on the other side were not detectable. The process parameters and the product parameters differ slightly in an acceptable range and not significant.

| *Spray rate [g/min]* | *8* | *10* | *12* | *14* | *16* |
|---|---|---|---|---|---|
| Yield [%] without probe | 92 | 97 | 94 | 97 | 96 |
| Yield [%] with probe | 92 | 97 | 91 | 97 | 91 |
| Process time [min] without probe | 41 | 31 | 30 | 27 | 23 |
| Process time [min] with probe | 39 | 31 | 29 | 25 | 23 |
| Bulk density [g/ml] without probe | 0,21 | 0,18 | 0,17 | 0,16 | 0,15 |
| Bulk density [g/ml] with probe | 0.21 | 0.19 | 0.20 | 0.17 | 0.16 |
| Tap density [g/ml] without probe | 0.25 | 0.22 | 0.21 | 0.19 | 0.17 |
| Tap density [g/ml] with probe | 0.26 | 0.23 | 0.23 | 0.20 | 0.19 |
| Angle of slope [°] without probe | 34.3 | 34.9 | 34.9 | 35.1 | 36.0 |
| Angle of slope [°] with probe | 33.5 | 34.2 | 34.5 | 34.8 | 35.5 |

Table 1: Granulate properties produced without and with installed probe

Mean particle size of the dry granulates measured with sieve analysis (Figure 4) ascends with increasing spray rate due to accelerated formation of agglomerates. There is no significant difference between the $d_{50}$ values for the process without and that with installed probe. The highest difference occurs for spray rate 12 g/min (390 µm without probe versus 350 µm with probe), but considering the polydispersity of granulates prepared by wet granulation and corresponding high values of standard deviation of particle size the differences are not significant. Both methods of particle size measurement (probe and sieve analysis) show the same trend regarding particle size and spray rate in the case of processing with installed probe (Figure 5) and also without installed probe (results not shown). Despite of the experience that the results of different particle size methods can deviate significantly from each other the results of sieve analysis and probe measurement are corresponding in a satisfying manner. The increase of particle size with increasing spray rate was confirmed qualitatively also by investigation with the microscope.

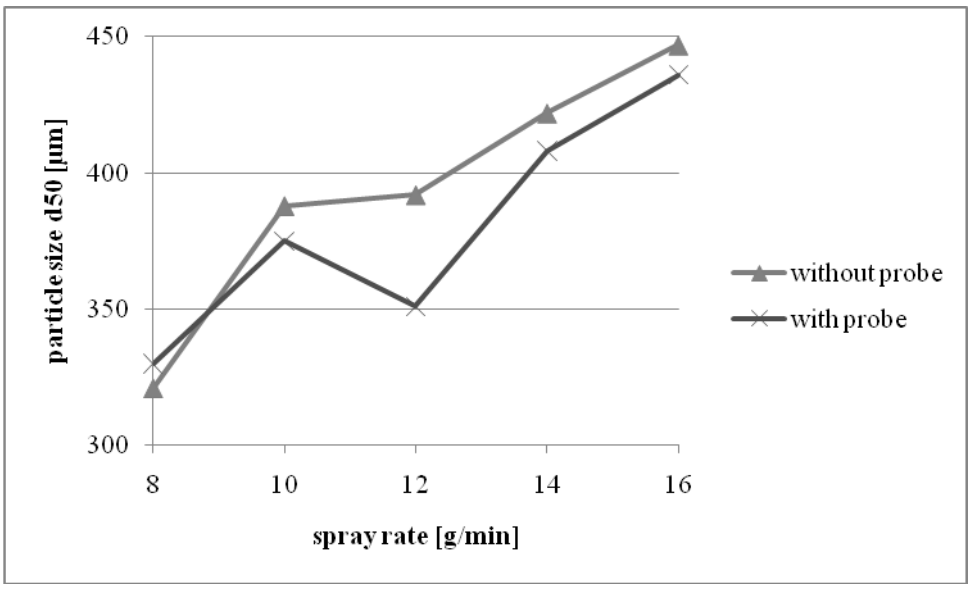


Figure 4: Mean particle size $d_{50}$ of granulates without and with installed probe in dependence of spray rate (sieve analysis)

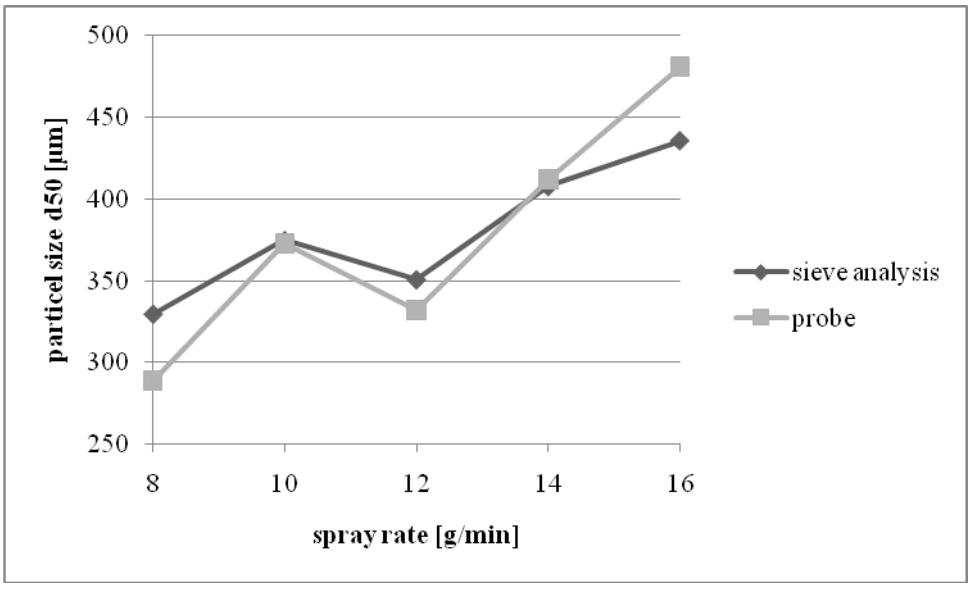


Figure 5: Mean particle size $d_{50}$ of granulates produced with installed probe: sieve analysis versus probe

Under the microscope an irregular shape of granules is visible, consisting of agglomerates of the primary particles. There is no difference in the shape between granulates produced without and with installed probe. Bulk and tap density of granulates (Table 1) decrease with increasing spray rate and increasing particle size. Obviously voluminous granules lead to large inter-particulate hollow space and therefore to relatively low apparent density. On the other side in the case of fine granulates the smaller particles may be incorporated into the hollow space between the large granules leading to higher density. The angle of slope rises slightly with increasing particle size what indicates flow deterioration. In general, coarse granulates flow better than fine ones leading to lower angle of slope values. The opposite tendency in the present case may derive from the irregular and unwieldy shape of the coarser granules in relation to the smaller ones observed under the microscope (Figure 6). Comparing bulk and tap density as well as angle of slope there is only insignificant difference between the batches without and with installed probe at one and the same spray rate.

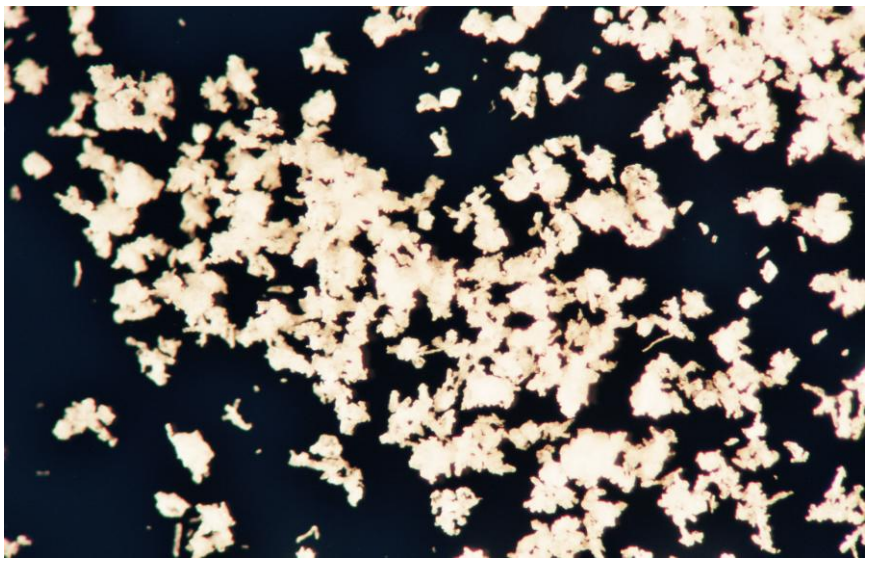

Figure 6: Microphotograph of placebo granulate, produced with probe, spray rate 10 g/min

## 5. CONCLUSION

Changes of geometry of through-flow spaces or additional installations imply a risk for flow conditions and may cause process disturbances. It was important to clarify the question whether the installation of a spatial filter velocimetry probe into the process chamber of a batch laboratory fluid bed granulator and practical directly into the centre of the fluid bed has an influence on the granulation process and possibly on the final granulate properties. The influences in consideration concern the additional object in the through-flow chamber and the atomization air for the dilution of particle dispersion inside of the probe. A model formulation was granulated under defined fluid bed conditions, namely without and with installed probe. Concerning homogeneity and reproducibility of the process there were no differences between both constellations, also the yield of the processes was comparable and acceptable with more than 90%. An apprehended material precipitation at the installed probe did not appear, and the comparatively low atomization air pressure inside of the probe in comparison to the strong process air flow rate revealed no effect. In dependence upon the spray rate granulates with different characteristics (particle size, bulk and tap density and angle of slope) were received, but there were no significant differences estimating analogous batches.

The in-line particle probe can be used as a process analytical technology (PAT) tool for monitoring and control of the particle growth during the granulation process. There is no risk of the probe installation on the process and the product. A medium-term aim is an automatically process control of the wet agglomeration process, especially of important process parameters like spray rate, spray time, process air temperature and process air volume by the SFV probe and the agglomerate particle size measurement.

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