

In-line measurement of layer thickness, agglomerate fraction and spray drying during pellet coating in the fluidized bed

Use of an in-line particle probe as PAT instrument for real-time monitoring

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ABSTRACT

The layer thickness in the fluidized bed pellet coating process represents an important process variable for the plant operator. The measurement in real time may be applied to monitor the influence of spray drying, layer thickness growth during the process time and to determine the end of the process. In-line measurements of the film thickness by a Parsum particle probe IPP 70-S are presented in this work. Directions for use of percentiles $x_{50,3}$ and $x_{90,0}$ to the determination of film thickness are given by application of model calculations and coating runs in fluidized bed Wurster coaters GPCG 1.1 and GF3. Undesirable generation of agglomerates in the coating process becomes visible by means of the cumulative distribution by volume $Q_3(x)$ and the density distribution by volume $q_3(x)$. The formation of fine particles by spray drying and abrasion is visible by means of the percentile $x_{10,0}$.

KEY WORDS

- Fluidized bed pellet coating
- Wurster coating
- In-line particle probe
- Layer thickness
- Agglomeration
- Spray drying
- PAT
- Particle measurement

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ZUSAMMENFASSUNG

Inline-Messung von Schichtdicke, Agglomeratanteil und Sprühtrocknung beim Pelletcoating in der Wirbelschicht: Einsatz einer Inline-Partikelsonde als PAT-Instrument zur Echtzeit-Überwachung

Die Schichtdicke im Wirbelschicht-Pellet-Coatingprozess stellt für den Anlagenbediener eine wichtige Prozessgröße dar. Anhand ihrer Messung in Echtzeit kann der Einfluss des Prozessparameters Sprühtrocknung während des Coatingprozesses überwacht, das Wachstum der Schichtdicke verfolgt und das Ende des Coatingprozesses festgestellt werden. Im vorliegenden Beitrag werden Inline-Messungen der Schichtdicke mit einer Parsum-Partikelsonde IPP 70-S vorgestellt. Ausgehend von Modellrechnungen werden anhand von Coatingversuchen in den Wirbelschichtapparaten GPCG 1.1 bzw. GF3 mit Wurster-Einsatz Hinweise zur Verwendung der Feinheitsmerkmale $x_{50,3}$ und $x_{90,0}$ bei der Schichtdickenbestimmung angegeben. Unerwünschte Agglomeratbildung während der Coatingprozesse wird mit Volumensummen- und Dichteverteilungen $Q_3(x)$, $q_3(x)$ dargestellt ebenso wie die Entstehung von Feinkorn infolge von Sprühtrocknung und Abrieb mit dem Feinheitsmerkmal $x_{10,0}$.

1. Introduction

With the Process Analytical Technology (PAT) Initiative of the United States FDA [1] and the Quality by Design (QbD) approach of the ICH [2, 3], new process applications are increasingly being integrated into pharmaceutical manufacturing processes, e.g. drug layering processes in coating. The coating of pellets is an important pharmaceutical-technological process in which the

product properties can be specifically adjusted by modifying the pellet surface. During coating in the fluidized bed and in the blasting bed as a batch or continuous system, the coating fluid is sprayed onto the pellets and dried off. For the system operator, the coating thickness in the coating process is an important parameter for process control. Measuring the coating thickness in real time makes it possible to monitor the influence of the process parameter spray rate during the coating process and detect malfunctions (e.g. irregularly nozzle spraying, spray rate too high, nozzle failure) in time. The dynamic measurement of the coating thickness allows the system operator to finish the coating process when the desired coating thickness is achieved.

Different PAT instruments have been investigated with respect to their suitability for determining the average film layer thickness and the uniformity of the film application. These include the sophisticated Raman and NIR spectroscopy [4] as well as the less complex dynamic image analysis and the fibre-optical spatial filtering method. For a fluidized bed pellet coating process, Foltmann et al. [6] determined the pellet size from in-line measurement with an in-line particle probe IPP 70-S (Parsum GmbH, Chemnitz). For comparison, at-line measurement of the minimum chord length (x_{\min}) was made with the dynamic image analysis system Camsizer[®]XT (Retsch Technology GmbH, Haan). The layer thickness was determined from the differences of the fineness characteristics $x_{50,3}$ or $x_{\min,50,3}$ respectively. On average, absolute layer thickness deviations of 4 μm (approx. 12 %) were found between the two measuring methods [6]. Investigations by Hudovornik et al. [7] resulted in a satisfactory correspondence of layer thicknesses from measurements with the in-line particle probe and a NIR probe.

During the coating of the pellets in the fluidized bed with functional polymers, if the moisture content is too high, larger agglomerates can be formed during the process because of the stickiness of the polymer coating solution in particular; this leads to defects in the layer as well as undesirable changes in the release behaviour of the active ingredients. As it is often not possible to completely prevent the formation of agglomerates, it is necessary to specify the agglomerate content in real time during the running process. By change of the process state variables, the coating process can be adjusted in such a way that only small tolerable agglomerate fractions occur. During the process, spray drying occurs because of excessively high gas temperature and spray pressure. The fine dust resulting from the dried atomised coating fluid can lead to clogging of the filters, resulting in reduced cleaning intervals and, in extreme cases, process interruption. In functional coating, some of the fine dust is integrated into the film layer leading to altered porosity and impaired release behaviour. The real time detection of fine grains with the aid of a suit-

able PAT instrument is necessary in order to be able to influence the course of the process in acceptable time.

The aim of this work was to investigate the PAT instrument fibre-optical spatial filter with regard to the suitability of different fineness characteristics for determining the layer thickness and for determining the agglomerate and fines fractions during pellet fluidized bed coating. The use of the in-line particle probe as a PAT instrument allows the particle size to be measured simultaneously with the process in real time. The measuring principle consists of a fibre-optical spatial filter for measuring the particle velocity and a fibre-optical spot scanning for measuring the particle size [8, 9]. In spot scanning, a chord length is determined as a measure of the particle size. An overview of the applications of the spatial filter technology is presented in Dietrich and Petrak [10].

2. Materials and Methods

The aim of the model calculations is to find suitable fineness parameters for determining the layer thickness with as little uncertainty as possible. For this purpose, spherical pellets with a modal particle size distribution are assumed in approximation to real coating processes. The pellets have the same layer thickness at the end of the coating process regardless of the pellet size and agglomeration is ignored.

With the spot scanning in the vertical direction, the result is a chord for which the length x_1 depends on the random local position of the pellet and the spatially fixed point sensor, where y_1 is the vertical distance of the chord to a line parallel to the chord through the spherical centre.

$$x_1(y_1) = 2\sqrt{r^2 - y_1^2} \quad (1)$$

The chord length distribution at a random pellet position can then be calculated from

$$P(x_1, x_2) = \frac{\sqrt{4r^2 - x_1^2} - \sqrt{4r^2 - x_2^2}}{2r} \quad (2)$$

P indicates the probability that the chord length according to fig. 1 lies between the chord lengths x_1 and x_2 in the case of a random cut.

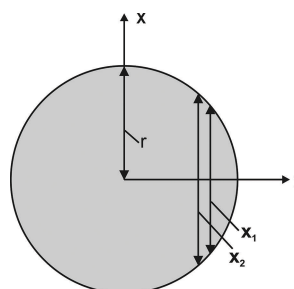


Figure 1: Circle with radius r and two chord lengths x_1 and x_2 in the scanning direction (source of all figures: the authors).

The number distributions for the density q_0 and the sum Q_0 are obtained from P for given values of x_i and x_2 , and the volume distributions q_3 and Q_3 are obtained by conversion.

First, the corresponding start chord length distribution in the form $q_0(x_m)$, $Q_0(x_o)$, $q_3(x_m)$ and $Q_3(x_o)$ is calculated for the present pellet start distribution using equation (2) (x_m = interval centre, x_o = interval upper size). The same procedure is performed at the end of the coating process. To avoid the time-consuming process of comparing the start and end distribution of chord lengths, variables derived from the cumulative distributions, e.g. the fineness characteristics $x_{50,0}$, $x_{90,0}$, $x_{50,3}$ and $x_{90,3}$, are determined. These values are used to determine the coating thickness and thus to control the coating process and the characterisation of product quality. Figure 2 shows an example for the coating of a pellet batch (spherical fraction 250–450 μm) with modal start distribution. The uniform layer thickness is 10 μm .

The calculation of the layer thickness from the half differences of the characteristic values from the cumulative distributions $Q_0(x_o)$ and $Q_3(x_o)$ yields acceptable results with low uncertainty for the characteristic values $x_{90,0}$, $x_{50,3}$ and $x_{90,3}$ (Table 1). Higher uncertainties arise for small fineness parameters.

For relatively narrow pellet size distributions found in standard commercial pellet grades such as Cellets® (made of microcrystalline cellulose) and homogeneous coating processes, the fineness param-

eters $x_{90,0}$ and $x_{90,3}$ with an uncertainty $< 1\%$ can be used for determining the layer thickness.

The aim of further investigations was to check the results of the model calculations using real coating processes, whereby the use of different fineness characteristics as well as the influence of agglomeration and fine grain formation from spray drying and abrasion were clarified.

3. Results and Discussion

The coating tests were carried out in a GPCG 1.1 fluidized bed apparatus (Glatt GmbH, Binzen) with Wurster insert. Cellets®200 (median 300 μm) were coated with an aqueous solution of sodium benzoate (30 % m/m) and polyvinylpyrrolidone (1.5 % m/m). An IPP 70-S particle probe with disperser D23 was used for the in-line measurement of particle size (fig. 3). The measuring point of the probe is located in the process vessel above the product layer in the downbed zone.

■ Table 1

Uncertainty of the layer thickness determination from the characteristic values $x_{50,0}$, $x_{90,0}$, $x_{50,3}$ and $x_{90,3}$ of the chord cumulative distributions Q_0 and Q_3 for a modal start distribution of the pellets.

Uncertainty of the layer thickness from $x_{50,0}$ [%]	Uncertainty of the layer thickness from $x_{90,0}$ [%]	Uncertainty of the layer thickness from $x_{50,3}$ [%]	Uncertainty from the layer thickness from $x_{90,3}$ [%]
10.9	1.8	5.3	3.7

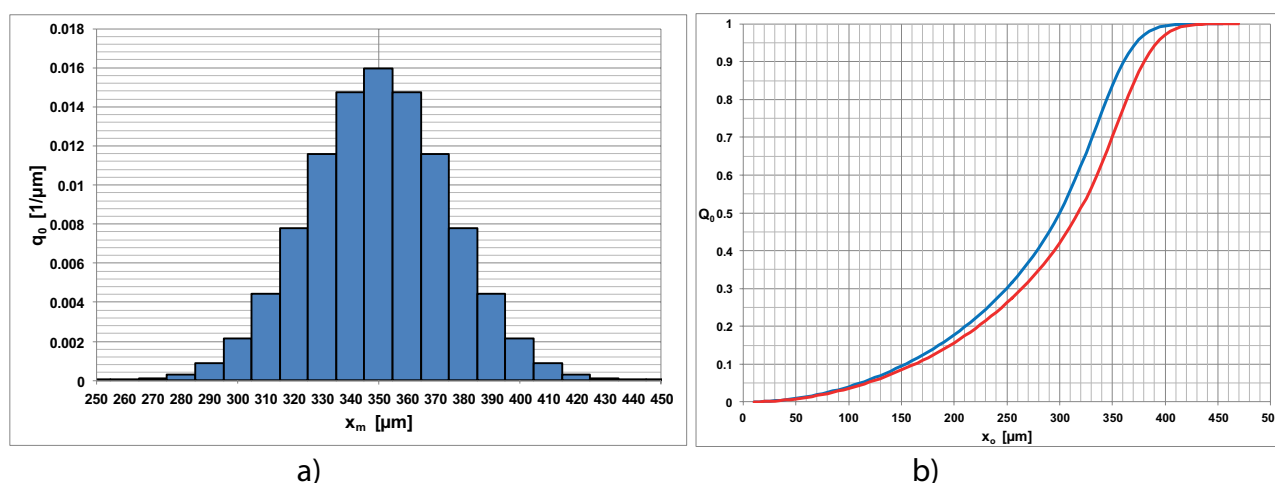


Figure 2: a) modal start distribution of the pellets, b) calculated chord length distributions $Q_0(x_o)$ of the start distribution (blue line) and the coated start distribution (red line) at the end of the process.

The relationship between spray rate (fig. 4, black line), fineness characteristics, layer thickness, and process time was investigated for the coating of Cellets®200 with sodium benzoate/polyvinylpyrrolidone using the IPP 70-S in-line particle probe. After 10 min of process time (fig. 4), the spraying phase was started and after 30 min the spray rate was gradually increased and ended after 50 min. With constant spray rate, the fineness characteristics increase continuously (spray phase 10–30 min process time). With an increase in the spray rate, super-humidification and increasing agglomerate formation occur in the process chamber; in particular, $x_{50,3}$ and $x_{90,3}$

increase disproportionately. A corresponding increase is observed for the layer thickness. At the end of the process the layer thickness was determined (45 μm) from the $x_{cmin,50,3}$ values with the Camsizer. Correspondence with the result of the particle probe (48 μm) is found here.

The time interval of the evaluated measuring points was selected such that the circular buffer (2000) was completely rewritten in each case. For process times between 0 and 40 min, the respective layer thicknesses as well as the agglomerate and fines fractions were determined. In the density distributions by volume, the height of the product peak at 300 μm decreases with increasing process time (fig. 5). Peaks above 600 μm also occur indicating agglomeration.

The total cumulative distribution by volume (fig. 6) remains practically unchanged for particle size below 200 μm . With increasing process time, it is shifted to higher particle size intervals because of agglomeration.

According to the authors' theoretical investigations for a polydisperse modal particle size distribution (spheres), the coating thickness can be determined from half the difference of the investigated fineness characteristics of final and starting cumulative distribution with accuracy of 2–10 %. The fineness characteristics determined tend to produce an increase in layer thickness with increasing process time (fig. 7), whereas the cumulative distribution by volume (curve $x_{90,3}$) increasingly



Figure 3: GPCG 1.1 with Wurster insert and in-line particle probe IPP 70-S.

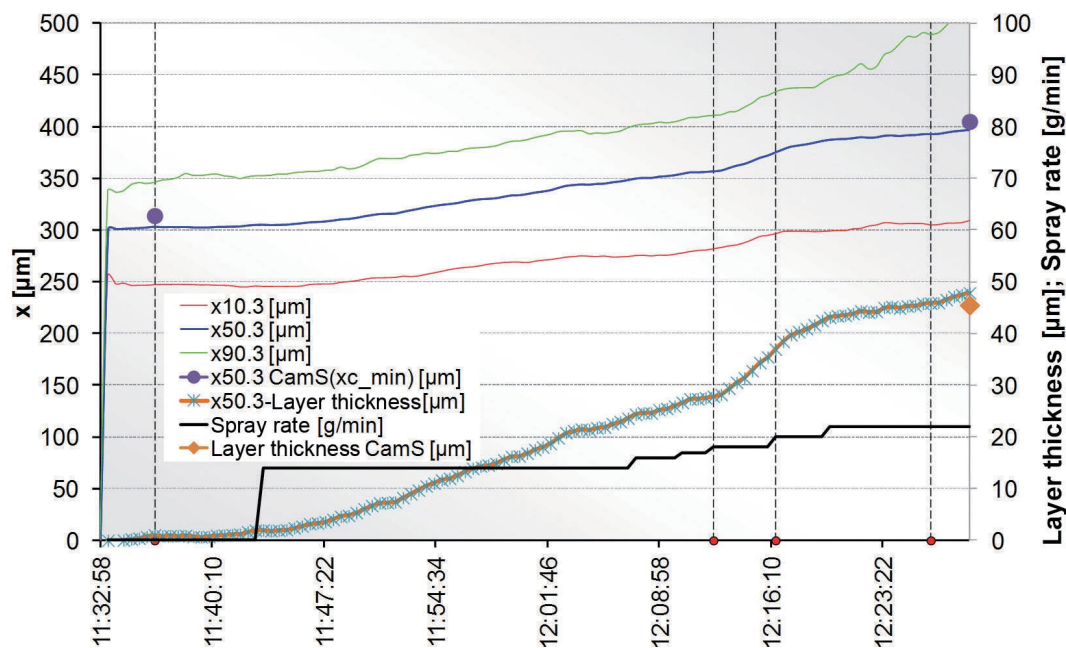


Figure 4 Fineness characteristics $x_{10,3}$, $x_{50,3}$ and $x_{90,3}$ spray rate, and layer thickness versus process time for coating of Cellets200 in laboratory apparatus GPCG 1.1, coating with aqueous solution of sodium benzoate (30 %) and polyvinyl pyrrolidone (1.5 %), spray start after 10 min, incremental increase in spray rate between 20 and 40 min spray time.

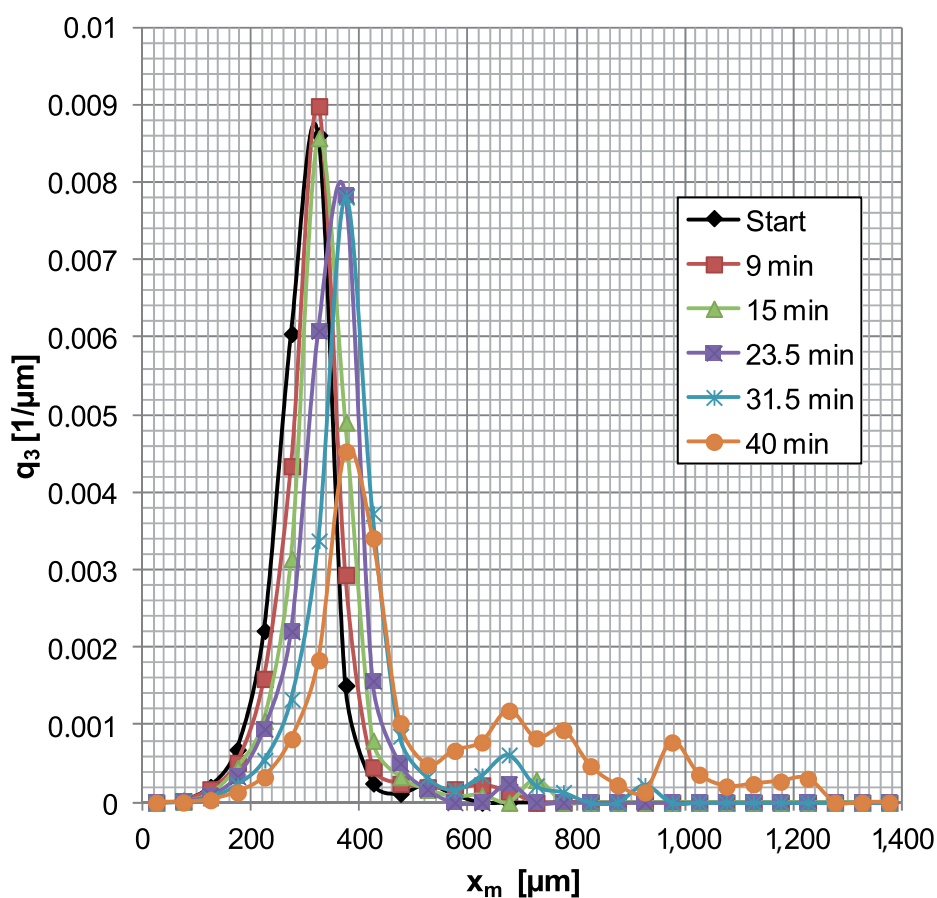


Figure 5: Density distribution by volume $q_3(x_m)$ with increasing process times.

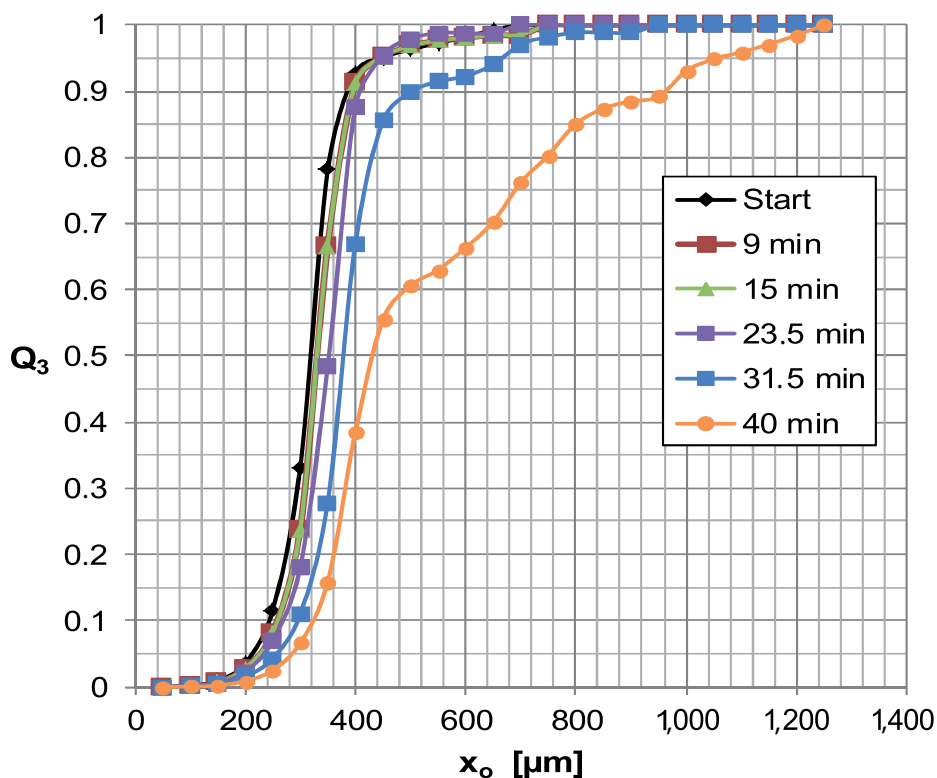


Figure 6: Cumulative distribution by volume $Q_3(x_o)$ with increasing process times.

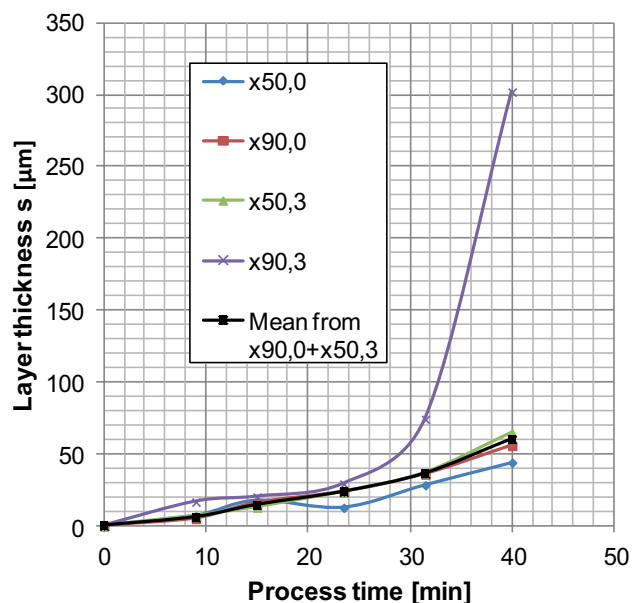


Figure 7: Curve of the layer thickness s as a function of the process time (parameter: fineness characteristics).

produces a layer thickness that appears larger than it really is due to the strong weighting of single large particles (agglomerates) after 30 min process time. The values

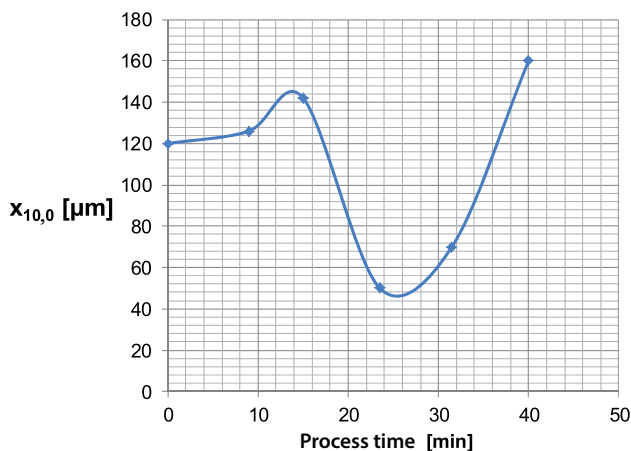


Figure 8: Fineness characteristic $x_{10,0}$ versus process time.

of the layer thickness using $x_{90,0}$ and $x_{50,3}$ correspond relatively well.

The fineness characteristic $x_{10,0}$ is significantly reduced after the start of the spray phase (fig. 8, from a process time of 15 min) indicating the formation of fine grains from spray drying. The induced increase in spray rate after 30 min counteracts spray drying with the increased supply of liquid, whereby $x_{10,0}$ increases again. This trend also affects the fineness characteristic $x_{50,0}$, albeit to a lesser extent. The formation of fines at pro-

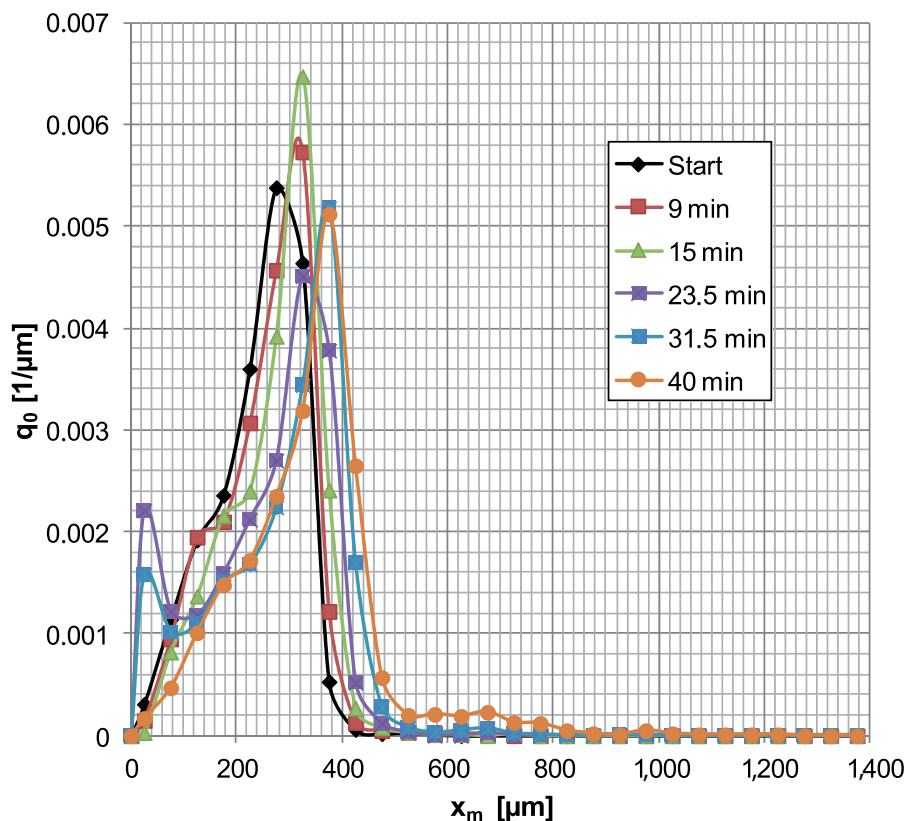


Figure 9: Density distribution by number $q_0(x_m)$ with increasing process times.

cess times of 23.5 min and 31.5 min can also be clearly seen in the density distribution by number q_0 (fig. 9, increase in the quantity proportions for pellets below 100 μm), while the fines below 100 μm in the density distribution by volume q_3 in fig. 5 become rather small in quantity because of the conversion. Another characteristic for the formation of fines is the increase in the pellet rate, which represents the number of pellets measured per unit of time.

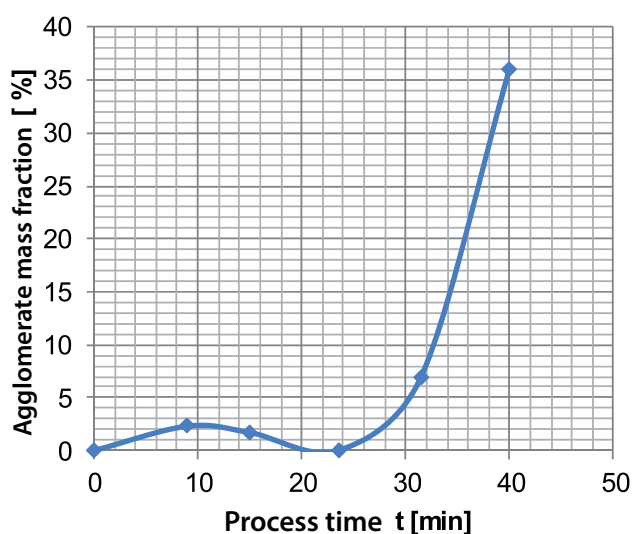


Figure 10 Agglomerate mass fraction versus process time, experiment fig. 4.

The formation of agglomerates becomes visible by a significant increase of the $x_{50,3}$ fineness characteristic against the process time [11]. It makes sense to use the cumulative distributions by volume when determining the mass fraction of agglomerates. It can be assumed that the agglomerate fraction will only become effective starting from a certain pellet size because of the volume fractions. This threshold value should be determined by considering the respective layer thick-



Figure 11: Fluid bed unit GF3 with Wurster insert and particle probe IPP 70-S.

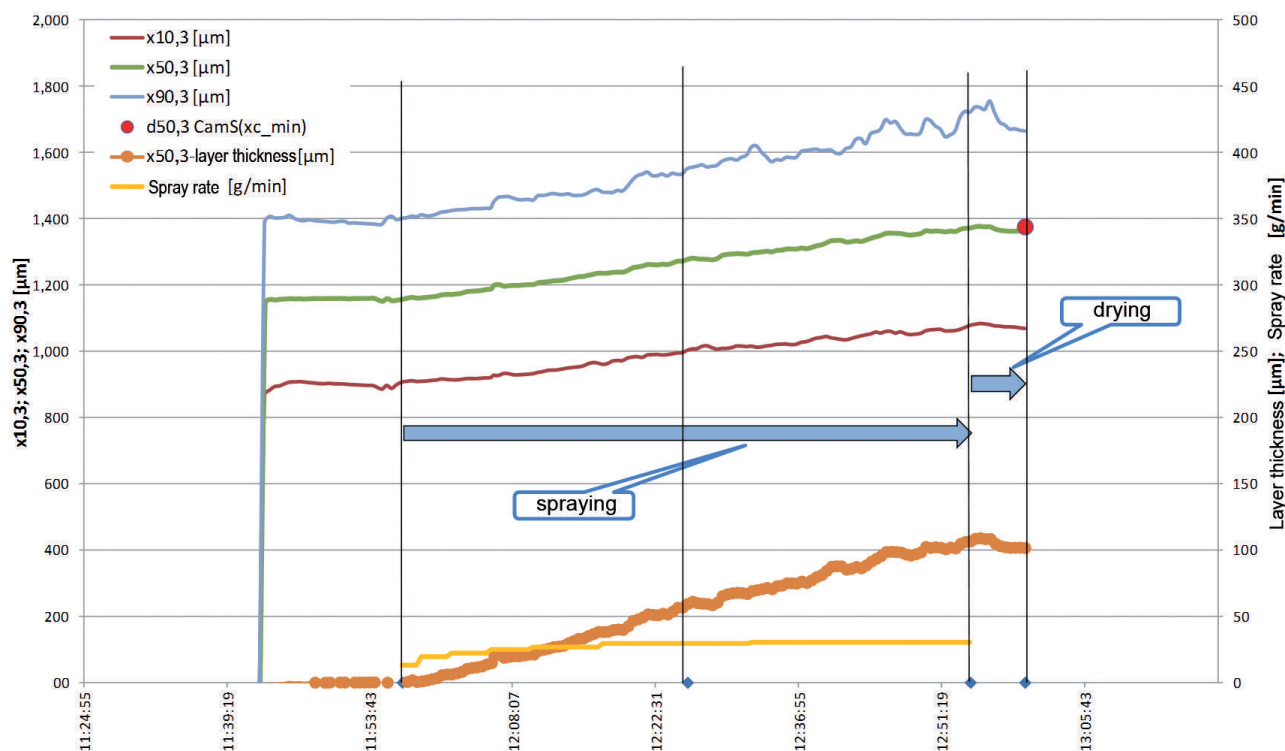


Figure 12: Fineness characteristics, spray rates and layer thickness versus process time for coating Cellets® 1000 with sodium benzoate solution (25%) in the GF3 fluidized bed apparatus.

ness and the form of the density distribution by volume. With the beginning of the spraying phase after 10 min, few agglomerates are formed which are disintegrated soon. A clear formation of agglomerates starts after a process time of 25 min with the increase of the spray rate as provoked process disturbance in the experiment (fig. 4–6). From the position of the median of the pellet size distribution at 300 μm and the position of the agglomeration peaks at 600–800 μm and 1,000 μm in the density distribution by volume (fig. 5), it becomes clear that as the process time progresses, the coated pellets predominantly combine into double and triple agglomerates.

The agglomerate mass fraction shown as a percentage in fig. 10 can be determined from the associated total cumulative distribution by volume (fig. 6).

Another example for in-line layer thickness measurement concerns batch processes for coating in a fluidized bed apparatus GF3 (Glatt Ingenieurtechnik GmbH, Weimar; fig. 11). Cellets®1000 were coated with an aqueous solution of sodium benzoate (25 %). All process parameters were kept constant. The measuring point of the probe was again located in the process vessel in the downbed zone. The relation between spray rate, fineness characteristics and layer thickness and the process time is shown in fig. 12. With the end of the spraying phase and the beginning of drying, the growth of the layer thickness comes to a standstill. At the end of the process, for comparison, the $x_{\text{cmin},50,3}$ value was measured with the Camsizer. It agrees well with the $x_{50,3}$ value of the in-line measurement (340 μm).

Using the IPP 70-S particle probe installed in-line as a PAT instrument for a pellet coating process made it possible to achieve a more uniform layer thickness than with gravimetric adjustment and to avoid inter-batch fluctuations.

Conclusion

The inline particle probe IPP 70/80 can be successfully used as a PAT instrument for in-line measurement of layer thickness as well as agglomerate and spray drying formation during pellet coating in the fluidized bed. The monitoring and control of the coating process made possible by the probe leads to a significant improvement in the quality of pharmaceutical products as well as an increase in the effectiveness of the processes.

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