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Implementation of real-time and in-line feedback control for a fluid bed granulation process

Theresa Reimers[a,b], Jochen Thies[b], Peter Stöckel[c], Stefan Dietrich[d], Miriam Pein-Hackelbusch[e], Julian Quodbach[a,*]

[a] Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University Düsseldorf, Universitätsstraße 1, 40225 Düsseldorf, Germany
[b] Glatt GmbH, Werner-Glatt-Straße 1, 79589 Binzen, Germany
[c] Boehringer Ingelheim Pharma GmbH & Co. KG, Binger Straße 173, 55216 Ingelheim am Rhein, Germany
[d] Parsum Gesellschaft für Partikel-, Strömungs- und Umweltmesstechnik mbH, Reichenhainer Straße 34-36, 09126 Chemnitz, Germany
[e] Life Science Technologies, Ostwestfalen-Lippe University of Applied Sciences and Arts, Georg-Weerth-Straße 20, 32756 Detmold, Germany

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ABSTRACT

The application of process analytical technologies (PAT) to monitor critical quality attributes (CQAs) provides an important approach to enhance process understanding and improve the reliability of pharmaceutical production processes. The present study focuses on the first PAT based feedback control system for a fluid bed granulation batch process. Real-time particle size measurement by in-line spatial filtering technique (SFT) using a modified time-based buffer system was applied to define a target particle size after spraying a specific amount of binder solution. After identifying an appropriate control variable, a suitable strategy for feedback control was established, followed by tuning of the control loop to obtain best performance of the integrated system. By adapting the final target particle size within a specified range good functionality of the system could be demonstrated. Investigations of the robustness further showed that the implemented system enables the production of a predefined target particle size also by varying process and formulation parameters. The effect of increasing spray rates and binder concentrations on the particle size could be compensated in a given range by feedback control ensuring a predefined product quality. The study provides an advanced approach for quality assurance of fluid bed granulation.

1. Introduction

Fluid bed granulation is a widely used and common process in the pharmaceutical industry (Faure et al., 2001). Hereby, a polymer solution is sprayed onto primary powder particles and permanent agglomerates are created. The particle enlargement improves several product characteristics for further production steps (Serno et al., 2016; Uhlemann and Mörl, 2000), such as the flowability, which is described as a key element in the production of solid pharmaceuticals (Mangal and Kleinebudde, 2018). Fluid bed granulation is susceptible to random variations in process and formulation variables that can cause significant variations between single batches. It is therefore characterized as a highly complex process (Burggraeve et al., 2011). Conventionally, the process is controlled by monitoring predefined process parameters and the final product quality is examined after manufacturing by time consuming off-line measurement methods (Burggraeve et al., 2013). Products that do not fulfil the predefined quality requirements are either rejected or reprocessed, leading to product waste and increased personnel costs. Nowadays, a more efficient and innovative solution for pharmaceutical manufacturing processes is provided by real-time monitoring of critical quality attributes (CQAs) using process analytical technology tools (PAT) (FDA, 2004) applying the so-called 'quality by design approach' (ICH, 2009, 2005).

Over the last decade various PAT tools for monitoring fluid bed granulation processes have already been evaluated and extensively discussed (Burggraeve et al., 2013; Da Silva et al., 2014). So far, the

Abbreviations: AAP, Atomization Air Pressure; CPP, Critical Process Parameter; CQA, Critical Quality Attributes; CV, Control Variable; DoE, Design of Experiments; FDA, Food and Drug Administration; FIFO, First in first out; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; MV, Manipulated Variable; PAT, Process analytical technology; PI control, Proportional Integral control; PV, Process Variable; PVP, Polyvinylpyrrolidone; QbD, Quality by Design; SFT, Spatial Filtering Technique; SP, Set Point; SR, Spray Rate; SSE, Steady State Error

* Corresponding author.
E-mail address: julian.quodbach@hhu.de (J. Quodbach).

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implementation of PAT led to an increased in-depth process understanding and consequently enabled the identification of important relationships between CQAs and critical process parameters. Thinking a step forward, real-time measurement by PAT can be regarded as initial step to further realise a fully automated process control system. Feedback control, which is most widely used due to its simplicity (Svrcek et al., 2000), presents a potential control strategy. Hereby, a process variable (PV) is compared to a predefined set value and an error value is determined as deviation between both values, which leads to the calculation of a response by a controller. By adapting the control variable (CV) using pre-programmed algorithms, the controller maintains the controlled process variable (PV) at the predefined set point. Nagy et al. (2017) recently implemented feedback control based on in-line Raman spectroscopy for a continuous twin-screw powder blending and tableting process. A further application, based on image analysis, was reported for twin-screw wet granulation (Madarász et al., 2018). Watano et al. (2001) used image processing to control particle growth during high shear granulation by integration of fuzzy control. The particle size as one of the key elements in pharmaceutical production steps presents an ideal PV for feedback control of fluid bed granulation. Real-time particle size measurement by spatial filtering technique (SFT) is well-known (Burggraeve et al., 2010; Närvänen et al., 2009a, 2009b, 2008), and thus, provides a promising initial step for process control. The theory of spatial filtering velocity has been introduced by Aizu and Asakura (1987), who named the simplicity and stability of the optical and mechanical systems as important advantages. Further modification by the fibre-optical spot scanning technique and the demonstration of the accuracy of the velocity and size measurement has been described by Petrak (2001). Generally, the chord length of the particle shadow image is calculated by simultaneously determining the individual velocity of the moving particle and the time of flight while passing a fibre-optical array (Petrak et al., 2011). A *number-based* particle buffer continuously stores and processes the measured data using the first in first out principle (FIFO-principle) (Folttmann, 2015); depending on the buffer size, response delays have been discussed (Fischer et al., 2011). In the context of fluid bed granulation, a consistently decreasing particle rate is due to agglomeration apparent with on-going process time. This in turn leads to an increased time to refill the buffer resulting in an increased time delay of the real-time measurement. Authors therefore introduced and evaluated a modified *time-based* buffer, which was found to be beneficial for process automation (Reimers et al., 2019).

The aim of the present study was to integrate a feedback control strategy based on real-time particle size measurement for a fluid bed granulation batch process using in-line SFT analysis featured with the modified time-based particle buffer system as initial step. A simple proportional plus integral (PI) controller should be applied providing a compensation of a determined deviation generated from the cumulative error value over time. After a first tuning step of the control parameters to attain best performance of the control system, functionality and robustness needed to be tested to further demonstrate the applicability of the integrated control system based on a placebo formulation as proof of concept.

2. Experimental methods

2.1. Materials

Granulation trials were performed using a placebo formulation containing an aqueous solution (5.5% as standard formulation) of polyvinylpyrrolidone (Kollidone 90F, BTC Europe GmbH, Monheim am Rhein, Germany). For each trial, a mixture (2:1 w/w) of lactose (GranuLac 200, Meggle Group Wasserburg BG Excipients & Technology, Wasserburg, Germany) and microcrystalline cellulose (MCC, Avicel pH 101, FMC Corporation, Philadelphia, USA) was granulated.

Table 1
Process values for granulation trials.

Process parameter	Standard process values
Inlet air temperature [°C]	65
Inlet Air Volume [m^3/h]	35–65
Spray rate [g/min]	13
Atomization air pressure [bar]	1.5

2.2. Fluid bed processing

All trials were performed using the lab scale system GPCG2 (Glatt GmbH, Binzen, Germany). The exact assembly of a granulator has been described in detail by Burggraeve et al. (2013). The nozzle was installed 37 cm above the distributor plate and a batch size of 1500 g/trial was granulated. For each granulation trial, a target PVP amount of 60 g was sprayed. Using a PVP concentration of 5.5%, a total spraying volume of 1091 g was calculated. The process air was preconditioned by dehumidification. The adjusted process parameters are presented in Table 1. Changes of the inlet air volume have been derived from preliminary experiments. For all trials performed by applying feedback control an initial atomization air pressure of 2 bar was set for the beginning of spraying. The process parameters were recorded by an external control unit, which was previously programmed using LabVIEW 2015 (National Instruments, Austin, USA). The endpoint of drying step was set to a predefined target product temperature (42 °C), which is commonly used as surrogate parameter. To achieve nearly identical process conditions, preheating of the used equipment was performed prior to granulation (30 min). Based on the following process set up, an inlet air volume of 100 m^3/h and an inlet air temperature of 65 °C was adjusted. Afterwards, a maximum of 3 min was necessary to achieve a predefined product temperature of 37 °C while heating and mixing.

2.3. Real-time particle size measurement by in-line SFT

In-line particle size measurement by SFT was performed using an IPP 80-P probe (Parsum GmbH, Chemnitz, Germany). For the pneumatic system the recommended settings (for internal air: 20 L/min and external air: 3 L/min) were adjusted. To ensure in-line particle size measurements also in dense material beds, the probe was equipped with a D 24 in-line disperser with an opening of 3.8 mm. Pressurized air from an air supply unit was used to disperse the incoming particle stream and to centre the particle flight path (Schmidt-Lehr et al., 2007). For all trials, the volume-based PSD was determined by using the new time-based buffer approach (Reimers et al., 2019). A time interval of 5 s was adjusted to provide a maximum data rate leading to a constant time delay of the control system. The measured data were additional processed by a Savitzky-Golay filter (Savitzky and Golay, 1964), where a moving set of points, also called smoothing window, is fitted to a polynomial curve. The smoothing window is defined by the number of window points (WPs) including one centre point and a variable number of side points, equal on each side of the centre point. The fitting procedure is continuously repeated for each set of WPs by dropping one previous value and adding a new one. In the present study 25 WPs with 12 side points on each side of the centre point were fitted by using a first degree polynomial function to minimize fluctuations in the generated data resulting in a constant time delay of 1 min. The constant time delay is calculated by multiplying the number of side points on one side of the centre point by the adjusted time interval. A more detailed explanation of the applied smoothing can be found in Reimers et al. (2019).

2.4. Probe position

The in-line SFT probe was implemented at an installation height of

Table 2
Design space of the performed DoE.

Factors	(–)	0	(+)
AAP [bar]	1.0	1.5	2.0
SR [g/min]	11	13	15

19 cm above the distributor plate. An insertion depth of 6.5 cm was used to avoid spraying on the probe. According to literature, the sensor was further rotated 45° to the right (Roßteuscher-Carl et al., 2014). This position has already been proven to generate reproducible results (Reimers et al., 2019).

2.5. Identification of an applicable process parameter as CV for feedback control

To study the influence of the atomization air pressure (AAP) and the spray rate (SR) on the particle size of granules and identify an applicable CV for feedback control, a 2^2 full factorial screening design of experiments (DoE) was performed including three repetitions at the centre point. In a binary nozzle system, the AAP describes the amount of air that is used to disperse the spraying solution, which is transported by a peristaltic pump and sprayed onto the fluidized particles by using a defined speed. The amount of liquid in a given time is the SR. The design space including factors and levels of the DoE is presented in Table 2. Seven experimental runs were performed. The described process range was identified based on previous experiments.

Response variable was the measured median particle size at the end of spraying (spraying amount of 1091 g). For analysing the generated data, Modde 12® software (Sartorius Stedim Data Analytics AB, Umeå, Sweden) and Microsoft Excel® 2016 (Microsoft Corporation, Redmond, USA) were used. The resulting models were first fitted by multiple linear regressions. Therefore, the resulting coefficients were scaled, centred and displayed with a confidence level of 95% (significance level of 0.05). Furthermore, based on the concept of backward regression, non-significant terms were eliminated in order to optimise Q^2 and generate best prediction precision. Hereby, terms were eliminated until either a maximum Q^2 has been generated, or no non-significant term has been existed.

2.6. Functionality of the feedback control system

For testing the functionality of the implemented feedback control system, the target particle size after spraying was increased to 613 or 590 µm and decreased down to 513 µm, while process parameters were kept constant. Experiments of each adjustment were replicated at least once.

2.7. Limitation of the integrated control system

To evaluate the upper and lower limit of the particle size, realisable by the implemented feedback control system, fluid bed granulation was performed twice. First by adjusting the AAP to the minimum of the predefined range (1.0 bar) and second by using an AAP of 2.0 bar as maximum level. Except of the AAP, process parameters were kept constant.

2.8. Robustness of the feedback control system

2.8.1. Increase of the spray rate

The robustness of the integrated control feedback system was evaluated by increasing the SR to 15 g/min and 17 g/min. The amount of applied PVP (60 g) was kept constant and the time of spraying decreased. The target particle size curve was adapted based on the amount of PVP sprayed at a certain point of time based on a SR of 13 g/min as presented in Table 3. Hereby, the final target particle size was equal for all processes (563 µm), so that only the slope of the curve increased. The adjustment of the inlet air volume was adapted in the same way as the target particle size curve, based on a defined amount of PVP sprayed at a certain point of time (Table 4). For each setting at least one replicate experiment was conducted.

2.8.2. Increase of the PVP concentration

As second step, the PVP concentration of the spraying solution was increased from 5.5% as standard concentration up to 7.0% and 8.5%. Due to a constant amount of PVP (60 g) the amount of spraying solution was reduced, so that the spraying time decreased. The target particle size curve was adapted in dependency of the sprayed amount of PVP at a certain point of time as described above. The exact target particle size values for PVP concentrations of 5.5%, 7.0% and 8.5% are represented in Table 3. Due to the reduced spraying time the inlet air volume settings had to be adapted as described above (Section 2.8.1) and presented in Table 4. For each variation at least one replicate was performed.

2.8.3. Evaluation of the viscosity of the spraying solution for differing PVP concentrations

The viscosity of the three investigated PVP concentrations (5.5%, 7.0% and 8.5%) as binder solution expressed in percentage by weight of binder in the solution was evaluated by using a rotational viscometer, Kinexus pro® (Malvern Panalytical GmbH, Kassel, Germany). A cone-plate geometry with a cone angle of 1° and a diameter of 60 mm was applied. For each measurement, the shear rate was increased from 100 s^{-1} up to 1000 s^{-1}. A gap width of 0.053 mm and a temperature of 25 °C was set.

3. Results and discussion

3.1. Identification of an applicable process parameter as CV for feedback control

The effect of AAP and SR as variable factors on the particle size was studied in a 2^2 full factorial DoE to identify an applicable process parameter for process automation. The resulting median particle sizes measured for all processes in dependency of the spraying quantity as well as the related fits are depicted in Fig. 1. Since particle growth seemed to be linear in between a spraying quantity of 400 g and 1091 g, a linear fit could be conducted to minimize random fluctuations in the obtained data and generate optimal comparable results. The resulting

Table 3
Adapted target particle size curve in dependency of the sprayed amount of binder solution for varying SRs/PVP concentrations.

Target particle size [µm]		Sprayed amount of binder solution/PVP [g]	Adjusted SR			PVP concentration		
			13 g/min	15 g/min	17 g/min	5.5%	7.0%	8.5%
t_0	100	0	0 s	0 s	0 s	0 s	0 s	0 s
t_1	363	195/10.7	900 s	780 s	688 s	900 s	706 s	582 s
t_2	563	1014/55. 8	4680 s	4056 s	3579 s	4680 s	3677 s	3028 s
t_3	563	1091/60	4680 s	4056 s	3579 s	4680 s	3677 s	3028 s

Table 4
Adapted inlet air volume settings in dependency of the sprayed amount of binder solution for varying SRs/PVP concentrations.

Inlet air volume [m^3/h]	Process phase	Adjusted SR			PVP concentration		
		13 g/min	15 g/min	17 g/min	5.5%	7.0%	8.5%
35	Heating and mixing						
45	Spraying	Start spraying					
55		400 g binder solution sprayed				314 g binder solution sprayed	259 g binder solution sprayed
65		650 g binder solution sprayed				511 g binder solution sprayed	421 g binder solution sprayed
65	Drying						

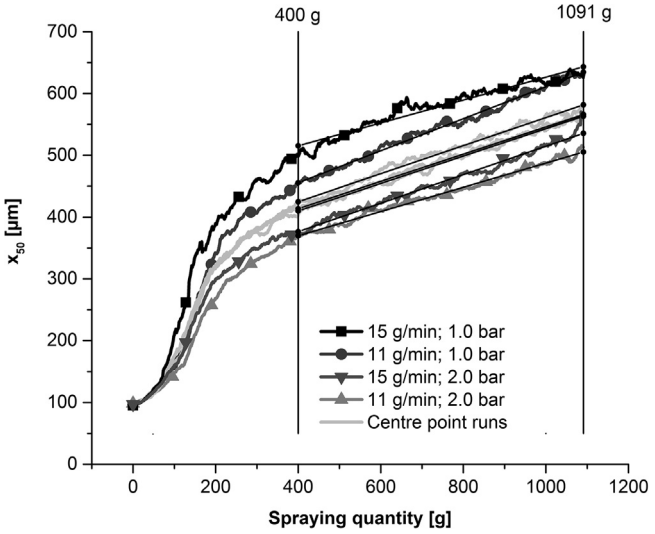

Fig. 1. Results generated by varying AAP and SR measured as x_{50} values [µm] plotted against the spraying quantity [g] plus linear fits for the market section from 400 g to 1091 g spraying quantity.

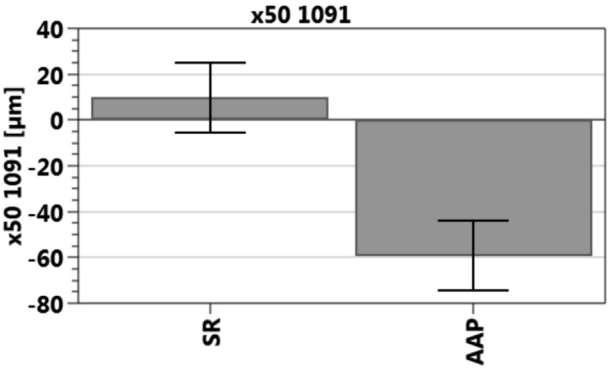

Fig. 2. Coefficient plots for x50_ 1091.

equations were used to calculate the median particle sizes at the target spraying quantity of 1091 g, which was defined as response parameter. The generated model describes the data well (R^2 = 0.967; Q^2 = 0.874 (Predictability)). The coefficient plot depicted in Fig. 2 shows a negative effect of the AAP on the in-line measured median particle size with statistical significance ($p < 0.05$), whilst no effect was presented for the SR. The obtained results imply that an increasing AAP results in the production of smaller granules. Adjusting the AAP causes a change of the air to liquid mass ratio at constant SRs and thus leads to the production of smaller or larger droplets. This finding is in line with the described effect of the AAP on granule growth in literature. With larger droplets larger and denser granules are produced (Yamamoto and Shao, 2016). Schæfer and Wørts (1978a) further demonstrated a linear correlation between droplet size and granule size and therefore, named varying the air flow rate as most suitable way for controlling granule size of the final granules. Surprisingly, the SR did not have an influence on the particle size in this study. This might be explained by two possible reasons. On the one hand, the chosen SR range might not have been broad enough to obtain strong differentiating particle sizes. On the other hand, it is also feasible that the formulation used might be highly robust particularly against changes in moisture content.

To successfully control the particle size by feedback control it is essential to identify the right PV as well as the right CV (Svrcek et al., 2000). The results generated for the design space of the current study indicate that the AAP could be a valid approach to control the particle size during fluid bed granulation based on the used formulation and therefore, this parameter was further defined as CV for feedback control.

3.2. Integration of a PI- controller for feedback control

For feedback control of a fluid bed granulation batch process a combined proportional plus integral controller was integrated into the SIMATIC S7-300 (Siemens AG, München, Deutschland) PLC (Programmable Logical Control) called ProcessView (Glatt version 2) of the GPCG2 unit. The operating principle of the control system is that a predefined target particle size should be achieved after spraying a specific amount of spraying solution by following a target particle size curve. The x_{50} value as common parameter for characterization of granule size therefore is set as PV. The data is measured by in-line SFT analysis and recorded by an external LabVIEW control system. After Savitzky-Golay smoothing the generated data is transferred from LabVIEW to the integrated control system and used as actual measured particle size value. The integrated feedback control system continuously compares the target particle size as desired set-point (SP = sp (t)) to the actual measured value (PV = $x_{50measured}$ (t)) and calculates the difference between both (SP–PV) as error value e(t). To minimize the calculated deviation the controller response is generated by adjusting the CV. Therefore, the AAP is adapted based on the sum of the control terms, the proportional and integral term (Eq. (1)). The proportional term provides an output value proportional to the calculated error value. Due to the fact that a non-zero error is needed to generate proportional gain, a pure proportional controller is generally accompanied by a so-called steady state-error (SSE), which is typically eliminated or reduced by an integral term. The integral term is provided by integration of the past SP-PV values over time and describes the accumulated error over the time, which is multiplied by the integral gain $\frac{K_P}{K_I}$.

$$MV = K_P e(t) + \frac{K_P}{K_I} \int e(\tau) d\tau \quad (1)$$

MV = Manipulated Variable
K_P = Proportional gain
K_I = Integral gain
τ = Time variable

The integral term accelerates the movement of the process towards the target point. Subsequently, the P- and I- term are summed up to maintain the control signal (Smith and Corripio, 2015; Svrcek et al., 2000). Generally, a granulation process can be divided into three parts

including the heating and mixing step as initial step to create a homogeneous mixture and heat the product. Secondly, the spraying step, which is commonly defined by spraying a specific amount of binder solution. After completing spraying, a drying step is performed in order to reduce the moisture content of the product until a predefined residual moisture content is achieved (Serno et al., 2016). Since process control can be provided only while spraying based on the defined CV the present study mainly focuses on the spraying step. Contrary to common control approaches, the target particle size as desired target parameter has to be increased continuously and does not present a constant value over time. As a compromise between a minimized fluctuation level and a maximized data rate to further ensure highly effective process control in-line measured particle size values could be provided only in 5 s time intervals. Consequently, the target particle size value, which is coupled to the in-line measured particle size, was generated in an equal time interval of 5 s. To avoid potential process collapses the AAP as controller respond was fixed in a predefined range from 1.0 to 2.0 bar. The described range is only valid for the used lab system and has to be reconsidered when scaling up the control system to pilot and production scale.

3.3. Target particle size curve and accepted deviation range

For process control, a time-based target particle size curve was created based on previous results of real-time particle size measurement during granulation. Three specific x_{50} values related to a certain point of time (t_0, t_1 and t_2) were connected building two single straight lines. Due to the limited spray rate control provided by the granulation unit minimal variations regarding the spraying time were observed. Therefore, a fourth time-point (t_3) was added to prevent t_2 from being the final value and allowing for compensation of differing spraying times. By achieving t_2 the target particle size is not increased but a horizontal line is constructed as connection to t_3, which represents the endpoint of spraying and thus the endpoint of process control. Consequently, the target particle size curve consists of three parts: a rapidly increase at the beginning followed by a slowed growth and ending with a short section of no change, which is meant to hold the particle size at the target value until spraying is completed and process control is finished. To keep the system as simple as possible, the target particle size curve was created manually based on the results generated by the centre point replicates represented in Section 3.1. Hereby, in particular the slope of the measured curves as well as the initial measured x_{50} value (approximately 100 µm) was focussed on resulting in a target particle size curve, which did not exactly match the measured particle size in t_1. The exact target particle size curve containing t_0– t_3 is presented in Fig. 3.

To define the maximum acceptable deviation from the target particle size ($x_{50target}$ in t_3), different aspects were considered. In literature, a variation coefficient of 1 to 2% is frequently accepted for analytical techniques (Kromidas, 2008). With ~1%, this was proven to be true for in-line SFT measurements in a fluid bed (Reimers et al., 2019). However, regarding the feedback control of the particle size during fluid bed granulation, varying results are not only induced by factors affecting SFT analysis. Defining the precision of fluid bed processes is more complex, as the setting of many parameters can significantly influence the outcome. By assigning a variation coefficient of 5% as overall acceptable deviation from the median, analytical precision and factors influencing the process are taken into account. For large scale processes, i.e. clinical or manufacturing scale, observed fluctuations may be smaller due to the increased mass. In these cases, the acceptable range should be adapted.

As the maximum relative deviation from the target particle size was set to ± 5%, values between 535 and 591 µm are accepted with a target particle size of 563 µm. Table S2 gives an overview of the deviation range accepted in dependency of the target particle size and lists the results for process control generated in this study.

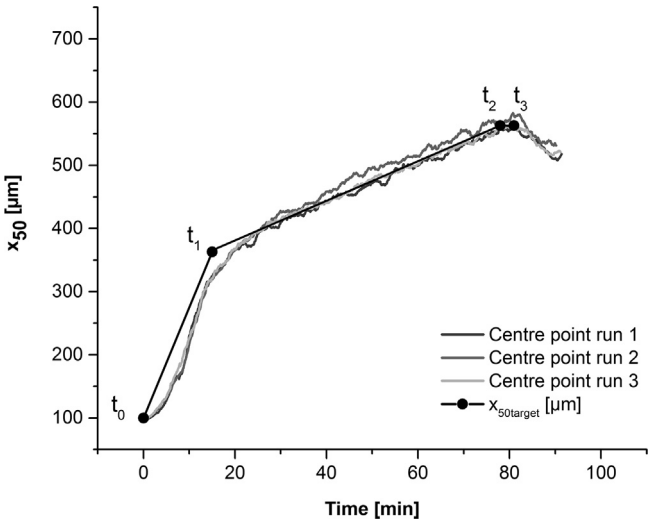

Fig. 3. Target particle size curve including t_0; t_1; t_2 and t_3 based on the centre point run 1–3 (according to Section 3.1).

3.4. Tuning of the feedback control

The tuning of the control loop is an optimisation process in order to achieve best performance of the control system. For this purpose, several methods have been described in literature. While no ideal way exists, the method of Ziegler and Nicholas (Ziegler and Nichols, 1942), also called closed-loop tuning, and the method of Cohen and Coon, open-loop tuning, as well as the methods based on the time integral of the error are most commonly used in industry (Cotabarren et al., 2015). Since the control system in the present study is modified from a common proportional plus integral control system by continuously increasing the target particle size as desired set point, rules given in literature for optimisation were considered, but could not be fully applied. Loop tuning was thus performed manually in orientation to those methods, applying the so-called 'Trial and error tuning method' (Svrcek et al., 2000). Hereby, the proportional action is set as main control element, while the integral control is applied later on to trim the proportional response. The tuning typically starts with the proportional gain only, by keeping the integral term to zero. For the first experiment using the integrated feedback control system K_P was set to 10 and the integral term to zero. Following, decreasing K_P values down to 0.5 (by progressively halving the K_P value) were tested while the integral term was kept at zero. The controller gain defines the change of the output for a given change in error: high proportional gain results in a large output response, while a small gain leads to a small output response and thus a reduced sensitivity of the controller in respond to the determined error. The larger the value of K_P is, the smaller the generated offset becomes. But there is a maximum value of K_P beyond which high process oscillations occur and the process becomes unstable (Smith and Corripio, 2015). Fig. 4A represents the results generated for $K_P = 10$ and $K_I = 0$ compared to the results measured by using a much lower setting for K_P in Fig. 4B ($K_P = 0.5$ and $K_I = 0$). A good correlation between the final target particle size (563 µm) and the final measured particle size (x_{50}_A: 569 µm; x_{50}_B: 577 µm) at the end of spraying was observed for both trials. The results represented a clear overshoot of the actual measured particle size right after achieving t_1. Even by adjusting the CV (AAP) to the maximum value the target particle size could not be matched until minute 40. The results demonstrated that minimizing the calculated error value by the control response is limited to the predefined range of the CV. In addition, the used placebo formulation showed a relatively high robustness against AAP variations. Higher frequencies of the oscillations of the output response were observed for the first experiment using a high K_P value. For both tuning settings the

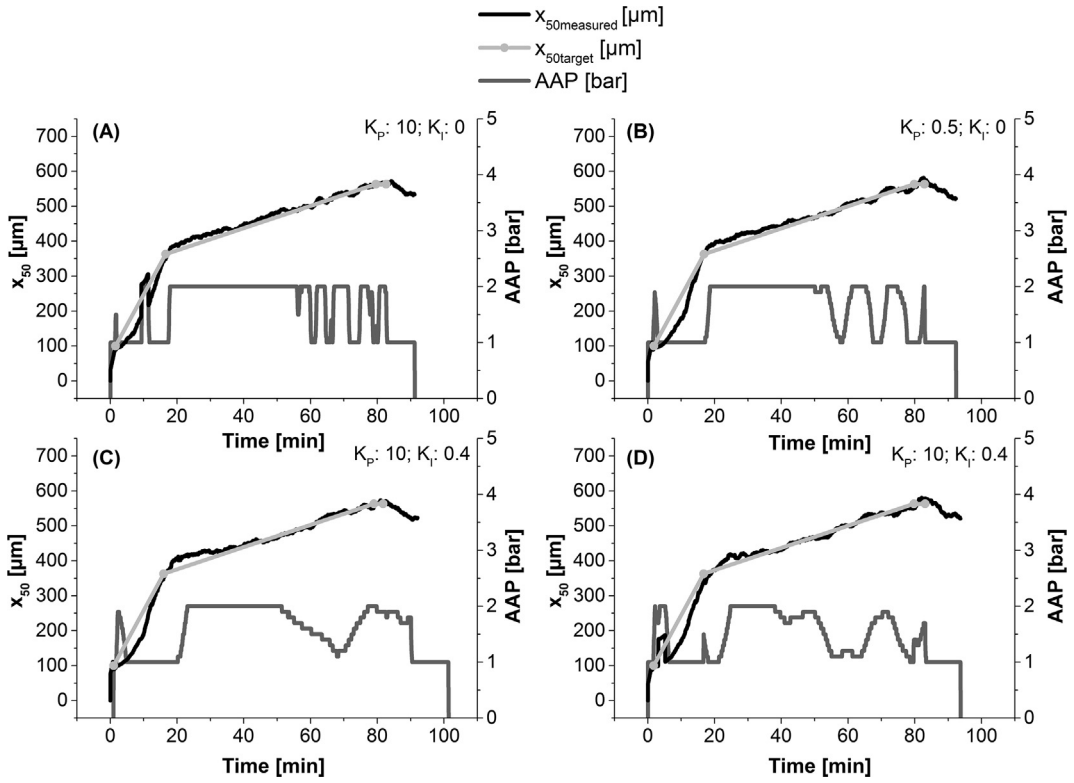

Fig. 4. Process control by applying differing tuning parameter settings (A + B) and for the final tuning parameter setting (C + D).

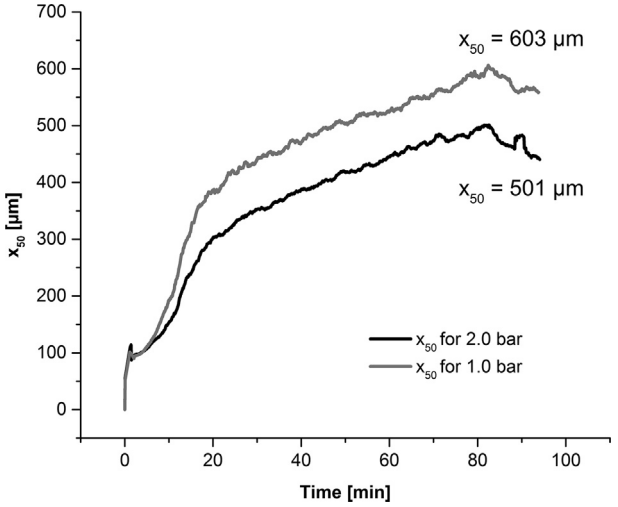

Fig. 5. Limitation of the integrated feedback control system based on the prefixed range of the control parameter (1.0–2.0 bar).

controlled particle size seemed to be uncontrollable during the first minutes of spraying. Additionally, one or several large particle(s) measured in the beginning of spraying for process A caused a clearly visible fluctuation (Fig. 4A), which led to an increase of the AAP up to 2.0 bar as maximum value.

By adding increasing K_I values from 0.2 up to 0.8 process control became more precise. The AAP as controllers' respond was not switched only from minimum to maximum but also in between. As it is described for a PI controller, a response period that is longer than for a P-only controller could be observed (Svrcek et al., 2000). Fig. 4C and D demonstrate the results for the final parameter settings of $K_P = 10$ and $K_I = 0.4$. These parameters were selected to provide relatively high responsive and sensitive feedback control by compensating a determined error accumulated over time and to further avoid high frequency oscillations of the output response. The observed overshoot of the actual measured particle size after t_1 could be slightly reduced, while the first spraying part remains similar for all trials. Since these values presented the final tuning settings for process control, following evaluated in this study, experiments were repeated twice. The results of a second replicate are presented in the Supplements (Figure S2). Regarding the final particle size measured after completing spraying the predefined range from 535 to 591 µm was matched for all processes (x_{50}_A: 557 µm; x_{50}_B: 579 µm; x_{50}_C: 579 µm). Additionally, a high repeatability (1.82%) was found applying the selected tuning parameters. During drying, a frequently described particle size reduction occurred due to loss of liquid, attrition or fracture (Iveson et al., 2001). Based on the CV of the integrated feedback control system, the particle size can be controlled only during spraying.

3.5. Limitation of the integrated control system

To identify the minimum and maximum particle size realisable in dependency of the prefixed CV, granulation was performed at an adjusted AAP of 1.0 bar and 2.0 bar. A minimum x_{50} value of approximately 501 µm and a maximum x_{50} value of approximately 603 µm was found as presented in Fig. 5. Since the trials were performed only once, results cannot be seen as absolute values but rather serve as orientation. Nevertheless, it can be said that process control using the integrated feedback system is limited to a specific range that is dependent on the selected process settings such as the prefixed range of the CV.

3.6. Evaluation of the functionality

To evaluate the functionality, it was investigated whether the implemented control system is able to respond to differing target particle size values, while process parameters were kept constant. By adapting t_2 and t_3 by adding and subtracting 50 µm, the final target particle size was varied while all process parameters except the CV were kept

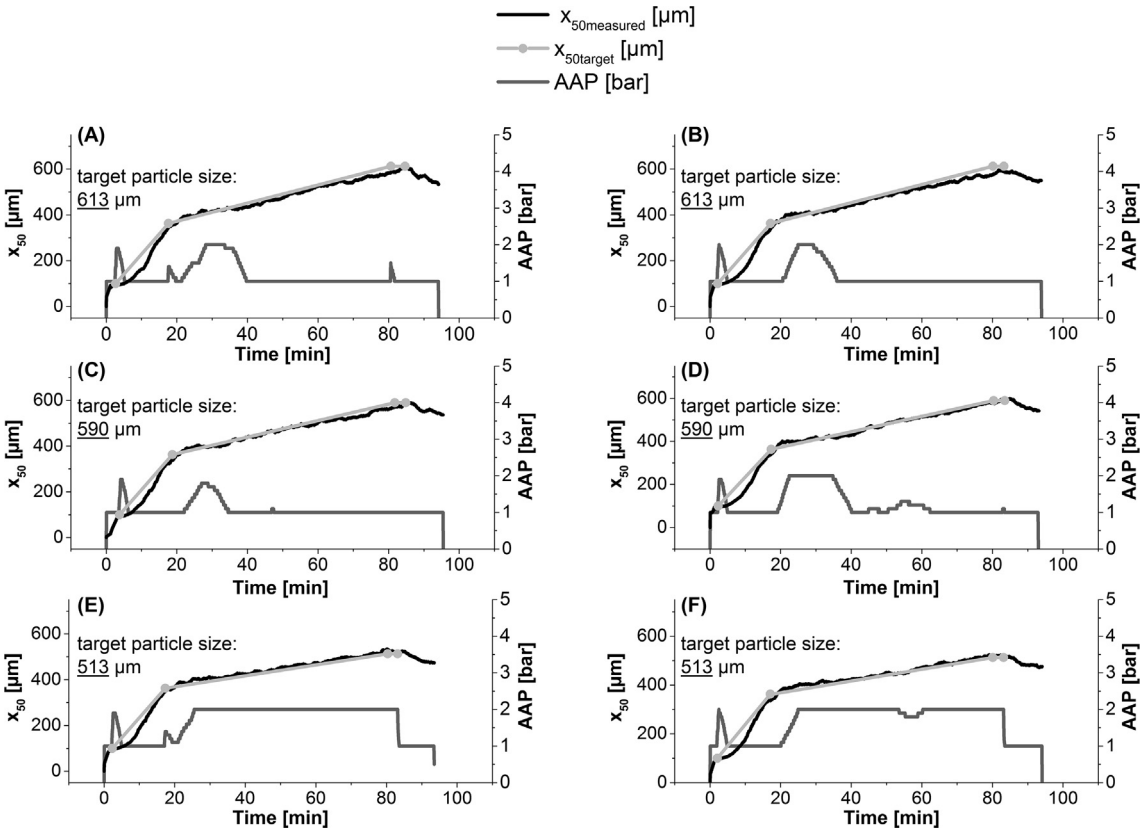

Fig. 6. Functionality of the integrated control system based on varying final target particle sizes of: x_{50}: 613 µm (A + B); x_{50}: 590 µm (B + C) and x_{50} 513 µm (E + F).

constant. The target particle size of 613 µm was investigated as critical value outside of the previously described process range to investigate how the control system behaves in such a case and repeated twice. Regarding the results, a fast increase for the first part followed by a short overshoot of the measured particle size after achieving t_1 was observed for all processes. After the target particle size curve was matched by the measured x_{50} values (approximately after minute 30) it was closely followed as presented in Fig. 6A and B. In the end of spraying a growing deviation between the target particle size curve and the actual measured x_{50} values was observed. Process A almost matched the final target particle size of 613 µm (x_{50}_A = 606 µm) at the very end of spraying. The deviation could not be fully compensated by the control system for process B. Consequently, a visible difference between the final measured x_{50} values (x_{50}_B = 588 µm) and the final target particle size (613 µm) was apparent after completing spraying. A second replicate presented in Figure S3 confirmed the results observed for process B (x_{50} final: 582 µm) and from Section 3.5. In both experiments, the final particle size still met the predefined range from 582 to 644 µm around the target particle size of 613 µm. As this value was out of the predefined working range of the control system, this was not expected. Furthermore, results showed a good repeatability (1.72%). The final target particle size was decreased to 590 µm and the experiment was conducted twice. Regarding the results (Fig. 6C and D), the target particle size could be followed closely by the in-line measured data. For both trials the measured x_{50} values (final x_{50}_C: 583 µm; x_{50}_D: 593 µm) almost matched the final target particle size (590 µm) after completed spraying. Decreasing the final target particle size to 513 µm, results showed a good correlation between the target particle size curve and the in-line measured x_{50} values, as presented in Fig. 6E and F. Moreover, a high conformity between the target particle size (513 µm) and the final measured particle size was found for process E and F (final x_{50}_E: 520 µm; x_{50}_F: 517 µm). For the second replicate a visible deviation was observed (537 µm) as presented in Figure S4. Nevertheless, the result still met the accepted deviation range (487–539 µm). Induced by the reduction of the AAP at the end of spraying, a delayed particle growth led to an increase of the particle size. A visible deviation resulted, which at this time could not be corrected by the control system. Nonetheless, a good repeatability was achieved (1.68%) also for a decreased target particle size.

In summary, good results were generated for target particle sizes of 513 µm and 590 µm and, therefore, an adequate functionality was found within the described particle size range. It was demonstrated that the implemented feedback system is able to achieve differing target particle size values. The results also support the assumption that the functionality of the control system is limited to the prescribed range of the CV. Results generated for a target particle size of 613 µm therefore could not fully fit the target particle size after completing spraying.

3.7. Evaluation of the robustness of the control system

It is known for fluid bed granulation that variations in several parameters can influence the final product quality (Yamamoto and Shao, 2016). These parameters can be divided into equipment, formulation and process related variables. To improve the reproducibility of fluid bed granulation processes by process control, a high robustness of the integrated feedback control system is essential. Consequently, the effect of increasing SRs as important process parameter and the effect of increasing PVP concentrations as important formulation parameter were evaluated to further examine the ability to manufacture products with suitable CQAs also by varying conditions and thus, demonstrate the potential benefits of the integrated feedback control system for fluid bed granulation.

3.7.1. Increase of the spray rate

To evaluate the robustness, it was first investigated whether the integrated control system is able to compensate increasing SRs to

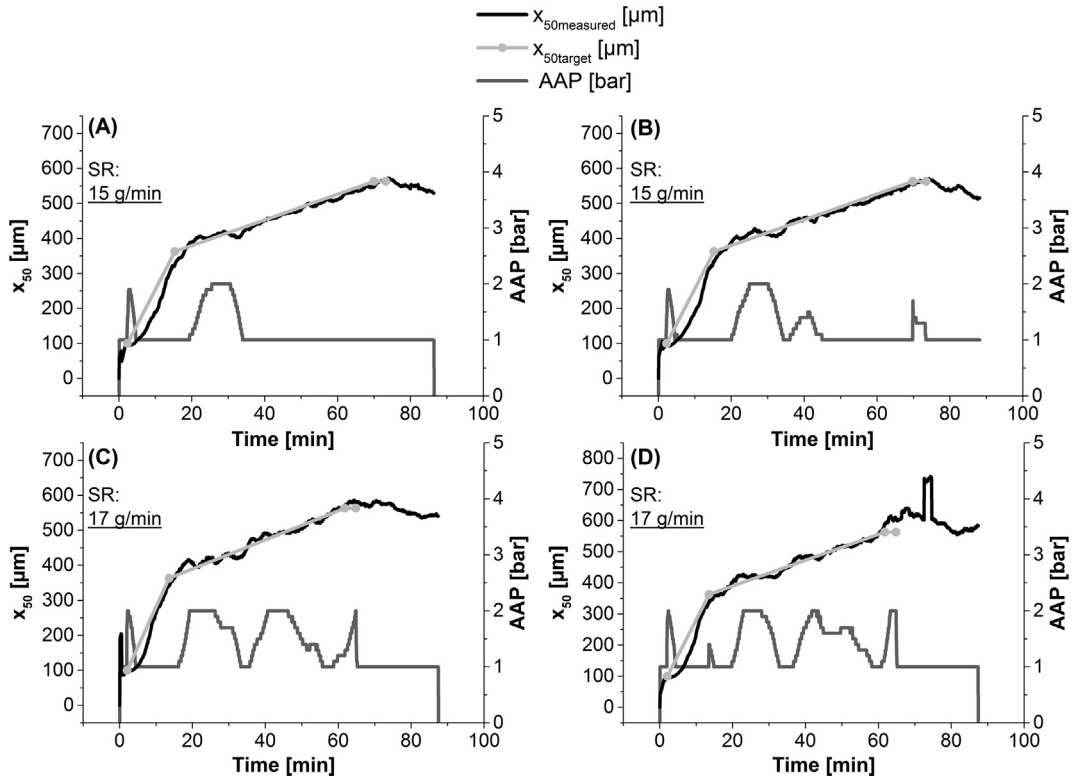

Fig. 7. Results for feedback control by increasing SRs of 15 g/min (A + B) and 17 g/min (C + D).

ensure a controlled particle size also by varying decisive process parameters.

In literature, two effects of increasing SR are described, which simultaneously affect the size of granules. When moisture content is accumulated in wet granulation processes, more liquid bridges are formed increasing the surface area between particles resulting in higher bonding capability of wet particles (Yamamoto and Shao, 2016). Secondly, by raising the SR at constant AAP, a change in the air to liquid mass ratio leads to a positive effect on the particle size due to the production of larger droplets. Schæfer and Wørts (1978b) found the particle size of granules to be directly proportional to the liquid flow rate.

However, a non-significant influence of varying SRs from 11 g/min up to 15 g/min has been already described in Section 3.1. But it still had to be tested, whether the integrated control system is able to adequately control the particle size by increasing SRs and thus decreasing spraying time. The results generated for a SR of 15 g/min presented in Fig. 7A and B showed a good conformity between the target particle size and the in-line measured x_{50} values. The measured particle size closely followed the target particle size curve and visibly matched the final target particle size of 563 µm after completing spraying (final x_{50}_A: 568 µm; final x_{50}_B: 562 µm). The results were found to be within the accepted deviation range of 535–591 µm. By further increasing the SR up to 17 g/min slightly higher fluctuations in the measured x_{50} values were apparent and thus, higher deviations from the target particle size curve were observed (Fig. 7C and D). Nevertheless, still a good correlation between the final target particle size and the measured final particle size (577 µm) was obtained for process C. Results for process D in turn showed a clear deviation from the final target particle size (final x_{50} measured: 608 µm). High SRs might have caused the production of large agglomerates during granulation, which were clearly apparent in the measured x_{50} values (Fig. 7D) and could also be observed in the product bowl after discharging. While the target particle size was closely followed during spraying, these agglomerates were not detected until achieving t_2. Typically, the mass of the granules is decreased while drying not only due to the reduction of moisture content but also induced by attrition and breakage resulting in the transport of initially heavy agglomerates to the upper part of the unit and enabling the detection by the probe. Performing a second replicate, an adequate conformity between target particle size and measured final particle size (final x_{50} measured: 579 µm) confirmed the results presented for process C (Figure S5). Additionally, results generated for a spray rate of 17 g/min showed a good repeatability (2.4%). Summarised, a good fit between target particle size and final measured particle size was observed for SRs of 15 g/min, while slightly higher deviations but still adequate results were generated for SRs of 17 g/min. It is known that the ability to compensate increasing SRs by feedback control systems is limited to the maximum value of the SR above which fluidized bed granulation is not possible (Ormós et al., 1973) and the predefined range of the controllers' respond. In this context, the current study confirmed that the integrated feedback control system is able to compensate varying SRs within a specified range to guarantee a predefined product quality.

Interestingly, drying time was prolonged in all processes, so that even though the spraying time was decreased, nearly a similar process time compared to a SR of 13 g/min was achieved.

3.7.2. Increase of the PVP concentration

The robustness of the integrated feedback control system was further evaluated by increasing the binder concentration to investigate whether process control is able to compensate changes of such a formulation variable. Binder concentrations in a range of 2–5% (w/w) are commonly used in industry for fluid bed granulation processes (Schæfer and Wørts, 1977). In the present study, the PVP concentration was increased from the defined standard of 5.5–7.0% and to 8.5%. Higher binder concentrations lead to a higher viscosity, resulting in the production of larger droplets and thus larger agglomerates. Schaefer et al. found the granule size to be directly proportional to the binder concentration for a given binder (Schæfer and Wørts, 1978a). Ennis et al. (1990) described an extreme influence of the liquid phase viscosity on

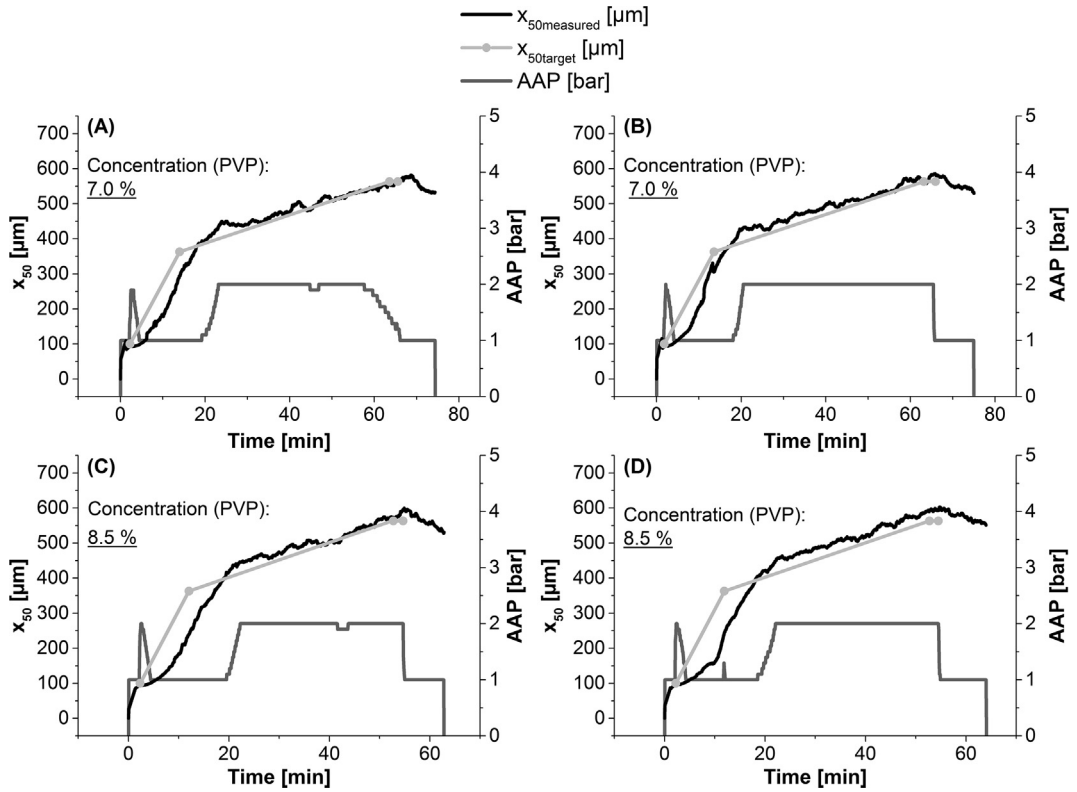

Fig. 8. Results for feedback control by increasing PVP concentrations of 7.0% (A + B) and 8.5% (C + D).

the inter-particle force between two relatively moving particles, which are bound by a pendular bridge. Measurements of the viscosity showed the increase in viscosity for the used PVP concentrations (5.5%: 0.054 ± 0.003 Pa s; 7.0%: 0.098 ± 0.0015 Pa s and 8.5%: 0.161 ± 0.0097 Pa s). Additionally, in-line SFT measurements during granulation using a PVP concentration of 7.0% for a constant total amount of PVP (60 g) and a constant adjusted AAP of 1.5 bar confirmed the described effect. Results presented a visibly faster particle growth and a clear increase of the final particle size (x_{50} = 666 µm and 661 µm) even though the process time was reduced compared to granulation performed using a lower PVP concentration of 5.5% (Figure S6).

For a PVP concentration of 7.0%, applying feedback control resulted in a reduction of the particle size increase and thus, a decreased deviation from the target particle size, as presented in Fig. 8A + B. A good correlation between the final measured particle size and the final target particle size within the accepted range was observed for process A (target: 563 µm, final x_{50}_A = 558 µm). For process B a larger deviation from the target particle size was observed, but the result was still within the accepted deviation range (x_{50}_B = 583 µm). The target particle size curve could be closely followed after a clear overshoot apparent for both processes. The AAP as the controller's response was set to the maximum of 2.0 bar for nearly the entire second process part, indicating the limit of the feedback control system. By further increase of the PVP concentration up to 8.5% process control was not able to compensate the change in viscosity and droplet size. A higher deviation of the final measured particle size to the final target particle size was apparent as presented in Fig. 8C and 8D (final x_{50}_C: 595 µm; final x_{50}_D: 594 µm). While the target particle size was more closely followed for process C, a clearly visible deviation between the target and the measured particle size curve was observed for process D. Nevertheless, results showed a nearly similar final particle size for both trials. In summary, an increasing viscosity almost by the factor two could be compensated by the integrated feedback control system implying that feedback control can be beneficial to ensure high product quality. Even though compensation of increasing PVP concentrations is limited because of the predefined settings of the feedback control system in this study, a clear effect of the control system on the final particle size could be observed by comparing the results for the experiments with a PVP concentration of 7.0%.

4. Conclusion

This study presents the first implementation of feedback control based on real-time particle size measurement for fluid bed granulation in the field of pharmaceutics. A combined proportional plus integral controller could be successfully implemented using in-line SFT particle size analysis coupled with a modified time-based buffer system.

The AAP was identified as potential CV and presented an appropriate parameter after tuning of the control loop. Results showed an adequate functionality within a specified range for the integrated control system. Additionally, evaluation of the robustness regarding varying formulation and process parameters presented valid results demonstrating that process variations within a certain range can be compensated by appropriate process control. In summary, the application of feedback control could be identified as advanced approach for quality assurance ensuring the production of high quality products in order to match predefined critical quality attributes also for further production steps and minimize the possibilities for unfulfilled quality requirements. One process, which also presented an insufficient product quality after manufacturing, did not match the predefined limits. Therefore, 5% as acceptable deviation from the mean target particle size was found to be a valid range for particle size control during fluid bed granulation. Consequently, feedback control provides an innovative solution to establish more efficient and saver manufacturing processes in the pharmaceutical industry. Nonetheless, the results presented in this study are limited to the used formulation and granulation unit. Further studies are needed to investigate whether the integrated control system is applicable for fluid bed granulation using less robust formulations containing varying types of binder as well as differing APIs as model drug substances.

Declaration of Competing Interest

None.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2019.118452.

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