Continuous Direct Compression of a High-dose Drug Evaluation of Process and Quality Attributes

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Summary

Continuous production has now been adopted even in the pharmaceutical industry and is indispensable in current product developments. This study focuses on the process of continuous direct compression, with the aim of guaranteeing constant product quality over the whole production run. A production run over eight hours was carried out to manufacture a high-dose acetylsalicylic acid tablet. In-line, at-line and off-line analyses of the intermediate and final product were performed. Process and quality data were used to detect and analyze errors in the process and eliminate them from future processes. Specific instances when the product quality was out of specification could be fully explained with the aid of the recorded data.

Keywords

Continuous production, continuous direct compression, QbCon, PAT, NIR

Introduction

The continuous manufacturing of medicinal products is now an indispensable, innovative process in the pharmaceutical industry. Many publications in this field describe and claim a slow development from batch-based production to continuous production, but reality is very different. Alongside conferences taking place across the whole world on an almost monthly basis dealing with this subject area closely, as well as research consortia dedicated to this topic, there are now five products which are manufactured continuously and which are approved by the FDA (Food and Drug Administration) and EMA (European Medicines Agency).

Some companies which are highly active in the field and have placed several plants for continuous production in their production facilities around the world, now even follow the maxim of producing each new product with a QbD (Quality by Design) approach over continuous processes. This shows that even the slow-to-modernize pharmaceutical industry is embracing these new, better and safer methods of production.

Compared to batch-based manufacturing, the benefits of continuous production are diverse, and not every pharmaceutical production considers the same benefits as a top priority. In a nutshell, benefits range from the possibility of manufacturing higher quality and therefore safer products, to the possibility of substantial savings through smaller GMP areas with less transport and storage, all the way up to greater production flexibility in the life cycle of a product, to name just a few [1].

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Similar to various manufacturing processes in the “batch-based world”, the continuous manufacturing of solid medicinal forms also provides various manufacturing methods. The most prominent routes are the manufacture of (film-coated) tablets based on continuous dry granulation, continuous wet granulation and drying or continuous direct compression. Two of the products continuously manufactured and approved so far are produced via continuous direct compression, which provides the same benefits as batch production, i.e. lower costs through great savings, shorter process times and smaller required machine and therefore GmP areas. The formulation must naturally be suitable for this purpose and have sufficient flowability and compactibility.

Due to the significant nature of the subject, this study presents the results of a continuous direct tabletting process which was performed over a production period of eight hours (one working shift). Alongside the simplicity of implementing a new formulation, it shows that a long process runtime is possible without significant problems. In-line and at-line process and product analyses measure the product quality in real time and allow a high degree of process control and adjustability. Off-line analyses performed later should confirm the consistent quality of manufactured medicinal forms. To understand this study, it is also important that this is a pure feasibility study without a product-relevant background. The formulation and the API (active pharmaceutical ingredient) concentration were chosen arbitrarily, and no discovery study for possible process parameters or even a design space was performed beforehand.

Materials

Acetylsalicylic acid was used as API in a direct compressible quality. It is a free-flowing powder, which contains 90% acetylsalicylic acid and 10% corn starch (abbreviation: ASS, Shandong Xinhua Pharmaceutical Co., Ltd, China). This was kindly provided in large quantities and had a total 78% ratio in the formulation. Microcrystalline cellulose (abbreviation: MCC, Vivapur 102, JRS, Germany) was used as a dry binder (21%) and sodium stearyl fumarate (PRUV, JRS, Germany) with 1% concentration was used as a lubricant for tabletting.

Methods

The continuous direct compression was executed on the QbCon®dc (direct compression) line at L.B. Bohle Maschinen + Verfahren GmbH (figure 1). This line consists of the following unit operations for a pure direct compression setup:

Material supply

The containers with raw ingredients are connected via normal hose lines to vacuum conveyors (Volkmann, Germany) which carry the materials to the dosing station. The vacuum conveyors are responsible for the first filling and later cyclical refilling of the gravimetric powder feeders.

Powder dosing and mixture

The materials are supplied by means of gravimetric powder feeders of a twin screw type (GZD 100.12 and GZD 200.12, Gericke AG, Switzerland) to the continuous blender (GCM 450, Gericke AG, Switzerland), which generates a consistently high mixing quality and should eliminate any feeder fluctuations.

In-line quality control of the powder blend

The powder leaves the continuous blender and is transported over a surface which has a near-infrared probe underneath (abbreviation: NIR, SentroPAT and SentroProbe, Sentronic, Germany). This is able to detect ASS concentration in real time through prior multivariate PLS (partial least squares regression) modelling.

The calibration of the PLS model was performed with fresh API-excipient mixes of known concentration, which were passed over the NIR measuring station. The adopted PLS model was used after calibration in the entire wavelength range of 1100-2100 nm. The integration time per spectrum was 9ms, and 100 measurements were averaged for an output spectrum.

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***Figure 1**: Production facility (QbCon® dc) used for the continuous direct tabletting in this study.*

Tabletting and at-line quality control

The powder subsequently flows into the filling hopper of the tablet press (XL 200, Korsch AG, Germany), which produced tablets with a target weight of 240 mg. The rotor consisted of 25 punch stations fitted with a set of round, biconvex 8 mm punches. A tablet tester (UTS 4.1, Kraemer Elektronik, Germany) was attached to the tablet press and connected to the entire control system. Measurements of the weight, breaking force and height of the tablets in regular intervals were sent back to the tablet press for feedback control in order to maintain consistent product quality.

Other:

The automation platform (L.B. Bohle, Germany) guarantees strict process monitoring and control of the entire process. Data recording and visualisation operates via this system. Since the material flows of the blender and tablet press can never be 100% the same, the rotor speed of the press was readjusted manually by the operator at irregular intervals to preserve a consistent filling level in the powder hopper of the press (manually, because in this study an automated fill-level sensor was not attached to the press). Off-line samples of the tablets were taken at regular intervals to test these for friability and disintegration time according to the pharmacopoeia.

The disintegration time of the tablet was respectively assessed, which disintegrated in the slowest time of six test specimens. Ten tablets were respectively taken at the start and towards the end of the process, which had to be tested regarding their ASS-content off-line via UV spectroscopy at a maximum absorption of 229 nm.

The QbCon®dc line was operated with a throughput of 27.5 kg/h, which resulted in dosing rates of 18.975 kg/h for ASS/corn starch, 8.25 kg/h for MCC and 0.275 kg/h for PRUV. The blender was operated with a constant rotational speed of 120 rpm, and the rotor speed of the tablet press could be changed in the 70-80 rpm range.

The required minimum tablet breaking force had to be > 50 N. With short pretests, the precompression force was set to 8 kN and the main compression force to 21 kN as a start value. Changing process parameters over time are permitted through the automation system if the need for readjustment is detected and initiated downstream of the tablet press by means of a testing system.

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Results and discussion

Gravimetric powder feeders replace the initial weighing and dispensing step of batch production and are an integral part of practically every continuous production technology. A uniformity of the finished dosage form can only be guaranteed by well-adjusted dosing systems [2]. A gravimetric powder feeder works (simplified) by recording the dispensed weight over time at a high frequency via the integrated load cell. The differential over time indicates the present dosing rate. In case of deviations from the target value, the control system reacts by adjusting the screw speed to maintain the target dosing rate. This control concept can be refined even more with preset dosing profiles. Figure 2 shows the behavior of the feeder for the MCC. In the top part of the figure, three curves are shown which represent the current dosing rate (blue), the screw speed (black) and the current weight of powder in the feeder (red).

Since material is constantly dispensed, the absolute weight of the powder decreases over time. Procedures running automatically refill the feeder via vacuum conveyors, which explains the cyclically decreasing and further increasing value for the powder weight in the feeder. The feeder scales have to be switched off during this refilling period, since feeder control would not work reliably due to the quick change in weight. In this time, the feeder therefore dispenses in a way which is not comparably reliable, like in the gravimetric status [3]. This can be detected in light fluctuations in the dosing rate, which occur especially when the feeder is refilled.

Another characteristic of many powders is the higher rotational speed which is necessary when the feeder reservoir becomes emptier over time (bottom right in figure 2 - red border). This behavior is due to the compressibility of a powder. If the compressibility is high, mass-pressure from above causes a compaction of the powder in the lower layers of freshly filled-up reservoir and therefore an increase of the bulk density. More material is moved into the screws and simultaneously carried away per rotation. To maintain the target dosing rate, the rotational speed must decrease. During the gradual emptyruptly. To a great extent, the feeder dispensed the MCC correctly in this production process.

The fluctuations of the dosing rate at the start of the production process

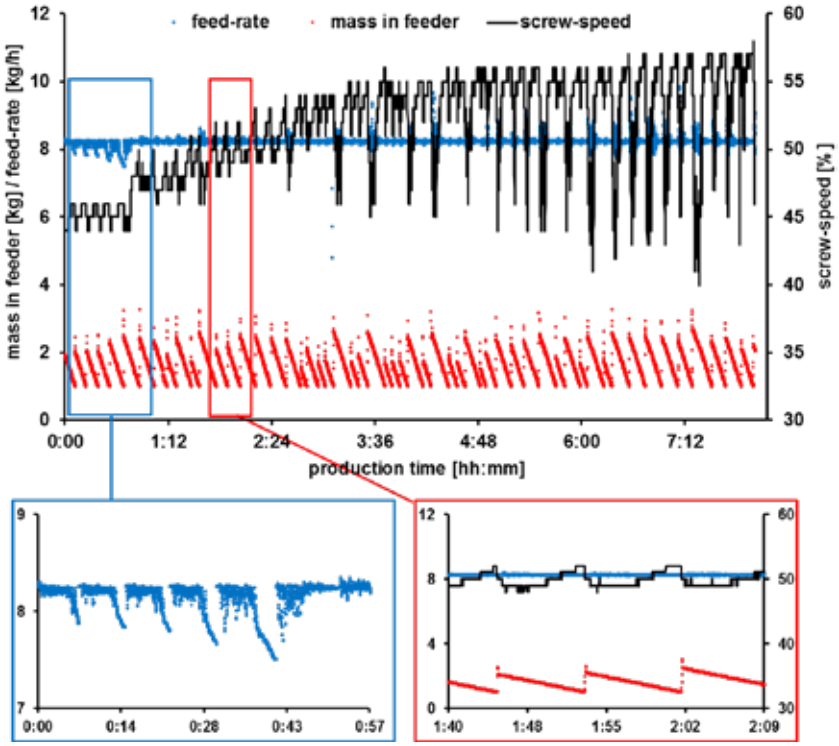

***Figure 2**: Dosing rates, screw speed and static weight of the MCC feeder in the production time; bottom left: Extract of the dosing rates in the initial period; bottom right: Extract of all three process parameters within a short period.*

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(blue border) will be discussed later on. Figure 3 shows the dispensing of the ASS and the PRUV, which show completely opposing behavior. The dosing rate of the ASS is constant over time and shows no anomalies, except for the discussed short fluctuations occurring during refilling routines. The constant rotational speed of the ASS feeder (yellow curve) even indicates that the direct compressible quality of the ASS has a powder bed consolidation during the refilling process that is hardly noteworthy but is beneficial to the stability of the dosing process.

The dispensing of the PRUV was considered difficult for two reasons. The powder is quite cohesive, adheres to surfaces, and does not have good flowability. Combined with the lower dosing rate of 275 g/h, difficult dispensing is to be expected. In relative terms, greater fluctuations appear in the dosing rate (red curve) compared with MCC and ASS, but the performance of the feeder is satisfactory, which is not in the least due to the strong control of the screw speed. This increases from an initial value of approx. 15% to values of 27% on average, showing the typical, discussed fluctuations in this area after the refilling stages. Starting from four hours into the production time, the rotational speed settles at approx. 22%. This behavior can be explained by strong bridging in the dosing container where less powder has gone into the screws.

The bridge had to be destroyed at a later stage so that the feeder continued working in a narrow rotational speed range. Since the dispensing of the lubricant can be critical for the subsequent tabletting stage, problems resulting from bad feeder performance would be evident through high ejection forces, etc. in the tabletting process. As this was not the case, satisfactory dispensing and sufficient blending in the continuous blender could be presumed.

After continuous blending, there is the possibility of automatically discharging the product which does not meet the previously defined specifications. These previously defined specifications could be API concentration limits, over or under which further processing would certainly lead to tablets with an incorrect potency. This measurement was carried out via NIR spectroscopy. Details on the measurement can be found in the methods section. Since this trial is purely a feasibility study, an automated discharging of non-conforming material was not in use. The NIR signal was simply used to monitor the API concentration over the the entire production time.

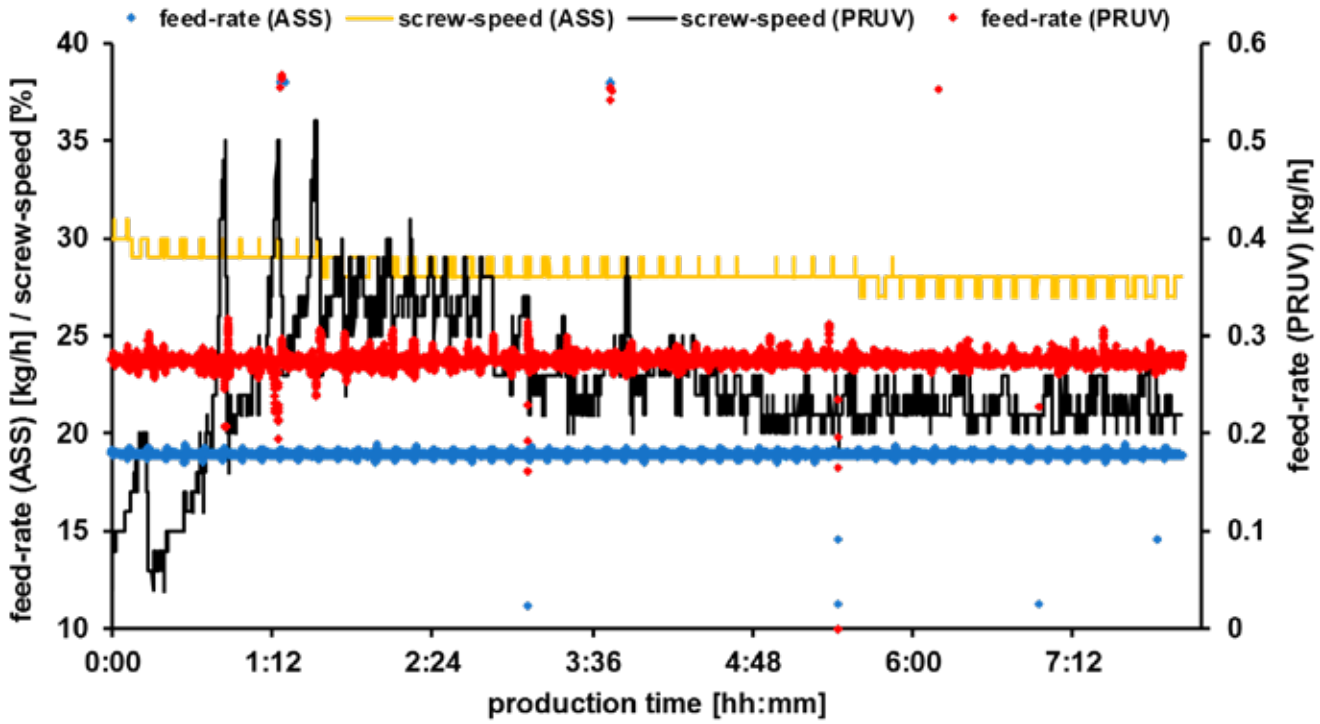

***Figure 3**: Dosing rates and screw speeds of the feeders for ASS and PRUV in the production time.*

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Figure 4 shows the relative progress of API concentration over the entire production time. The target content of the tablets and therefore also of the powder was at 70.2% ASS.

Two things are apparent. On the one hand, the excessive ASS concentration decreases in the first 40 minutes. After this period, the measured values remain at a constant level under normal fluctuations. On the other hand, the ASS content remains on average at 68.2 ± 1.2% and therefore under the envisioned 70.2%. For the case of the decreasing ASS concentration in the first 40 minutes, the blue-bordered part of figure 2 can be consulted.

This image shows an extract of the dosing rates curve of the MCC. It can be noted that the MCC was initially under-dispensed over long periods. The under-dispensing of the MCC is responsible for the temporarily excessive concentration of ASS in the entire mixture.

A continuous blender is capable of eliminating higher-frequency feeder-errors up to a certain cut-off frequency, which, roughly speaking, is in the range of the powder's mean residence time in the blender. However, the feeder-errors, which occurred in this case, lasted over several minutes and were combined with a such a high incorrectly dispensed MCC amounts that the continuous blender was no longer capable of eliminating these errors.

In comparison, fluctuations repeatedly appear in the average dosing rate in the later stage of the MCC dosing process. But these fluctuations are always limited to very small time-periods and fluctuate towards too little as well as towards too much dispensed powder. These errors can be eliminated by a continuous blender. From the moment the highly inaccurate dispensing of MCC stops, the ASS concentration measured via NIR spectroscopy settles on a constantly maintained value.

In the case of the insufficient concentration of ASS over the remaining production period, there is certainly the possibility that the PLS model for the NIR method was not calibrated with sufficient data or in a sufficiently robust manner. However, off-line measured tablet content shows something different at the start and at the end of the production run. Both values are in the range of the in-line measured ASS concentration, which suggests that the PLS model for this application was sufficient-

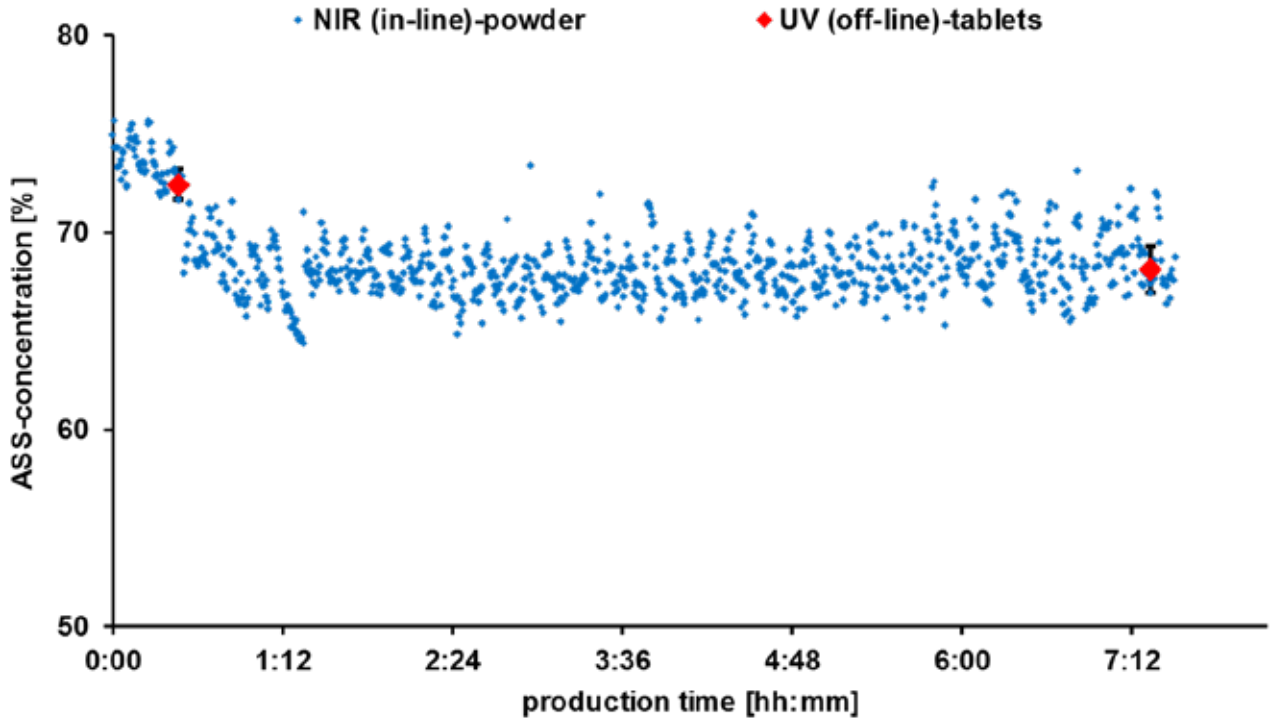

***Figure 4**: In-line measured ASS concentration after the continuous powder blender and ASS concentration in the tablets at the start and around the end of the production period; for tablets n= 10, average ± standard deviation.*

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ly precise. An evaluation of the raw ASS/starch powder and the UV-spectroscopic measurement, however, allowed to draw the conclusion that the directly compressible ASS no longer corresponded to the specified content after its shelf-life, but amounted to approx. 87%, explaining an API concentration which was consistently too low.

The continuous tabletting process proceeded without any issues during the whole production time and constantly delivered (except for content variations at the start) tablets consistent with the specified quality criteria. Particular attention has to be given to figure 5, in which the process parameters pre-compression and main-compression force as well as rotor speed are illustrated over the whole production period. Start-up and shut-down processes of the tablet press - where the filling shoe is filled or runs empty are visible at the beginning and at the end of the diagram. These two stages can be recognised by the increasing or decreasing compression forces. Apparently, the various concentrations of ASS at the start of the process have no huge influence on the compressibility and on the measured compression forces, which, on the one hand, could be due to the similar bulk densities of the materials and, on the other hand, to the fairly small differences in the concentration measured via NIR.

The rotor speed was adjusted by the operator manually, since the material flows from the blender and the tablet press are never completely synchronised, i.e. at the same level. Tablet compression is a volumetrically controlled process. Through a previous evaluation of the dependence of tablet breaking force from the dwell time of the main compression, it was identified that a range between a 70 and 80 rpm rotor speed creates a design space where tablets of the same quality are formed. In fact, during the process it was merely necessary to alter the rotor speed between 73 and 76 rpm to maintain a constant fill-level of the tablet press hopper. The quality attributes of the tablets were measured at-line, with the tablet-press conveying a quantity of 10 tablets to the tablet testing device automatically via the product diverter at the outlet approx. every 5 minutes.

As a result of these findings, the process parameters were automatically adjusted to maintain constant values for the tablet weight and breaking force. For instance, a slightly falling pre-compression force over the entire process run can be identified in figure 5. The results of the measured tablet weights, heights

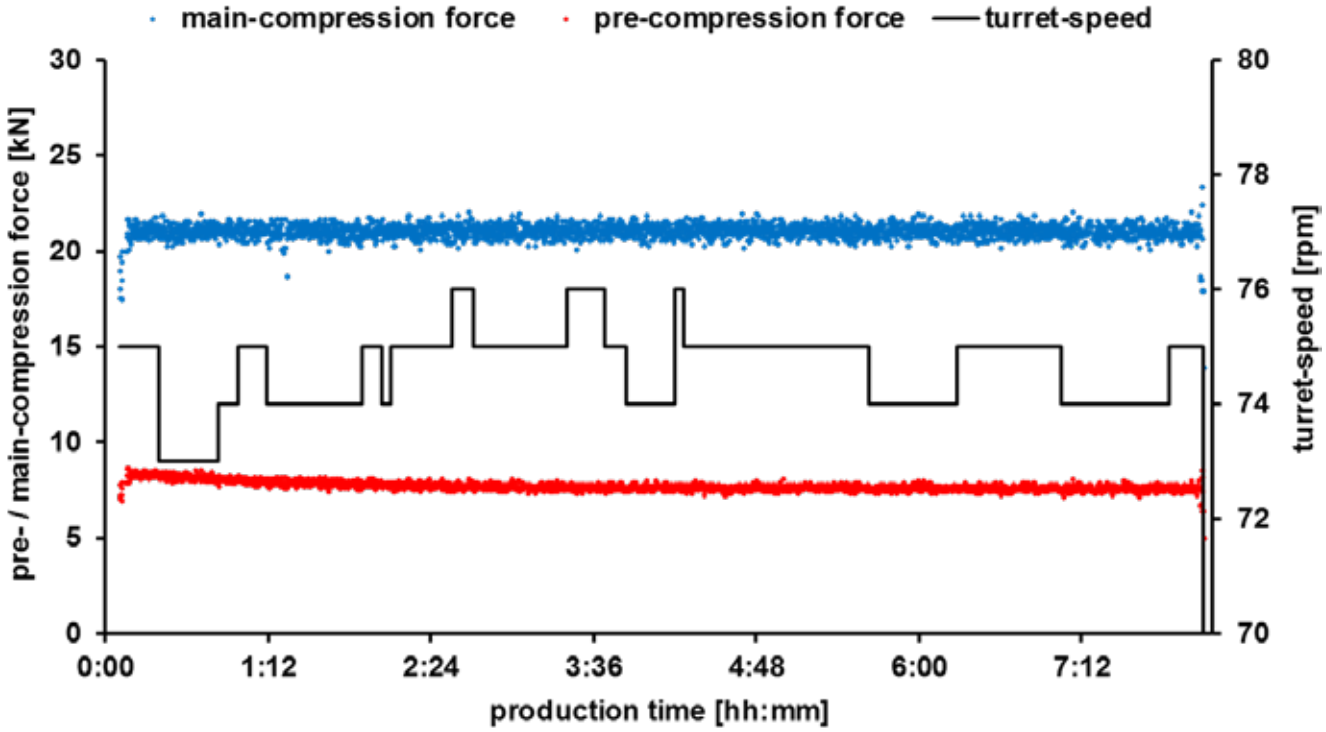

***Figure 5**: Important process parameters of the tabletting process in the production time.*

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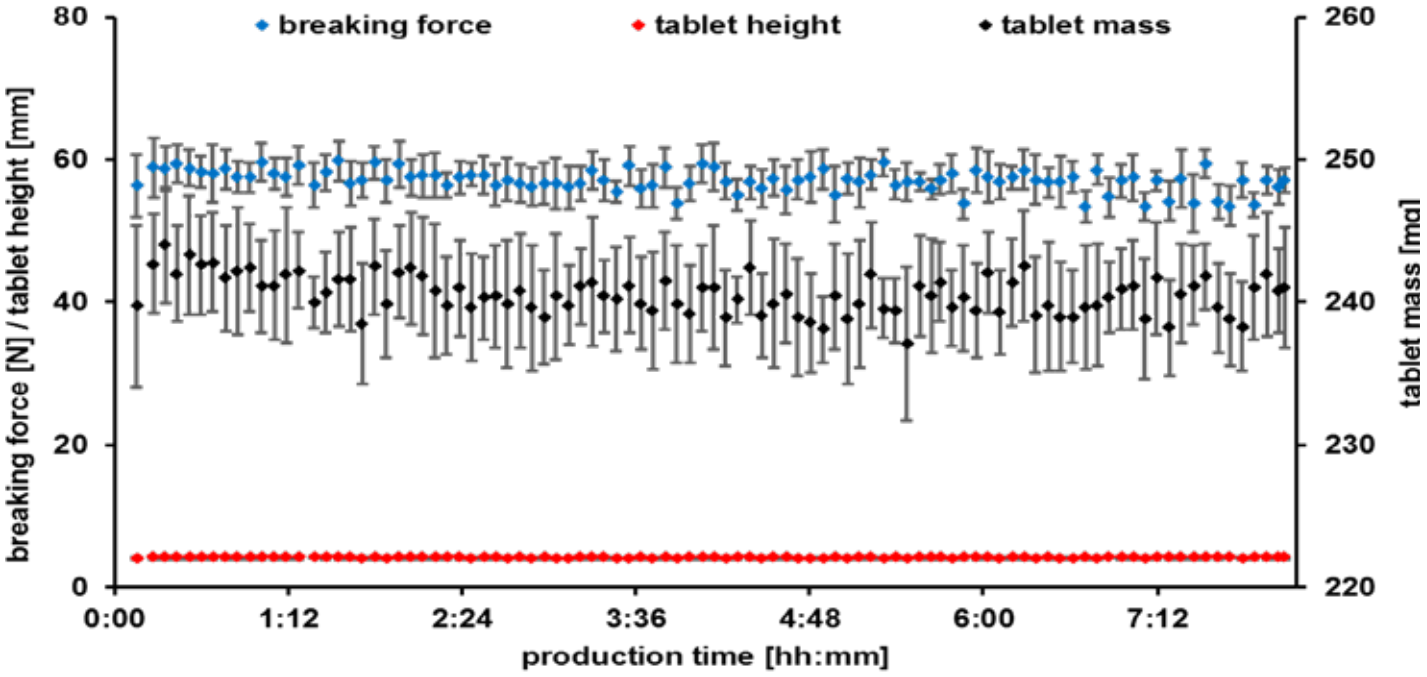

***Figure 6**: At-line measured critical quality attributes of the tablets; n= 10, average ± standard deviation.*

and breaking forces are displayed in figure 6.

The average weight of the measured tablets in that period amounted to 240.5 ± 1.3 mg, which corresponds to the required weight. The highest deviation of a series of measurements was 1.6%, which repeatedly shows that the tabletting process guarantees a constant tablet quality except for the initial deviations discussed. There were no previous requirements for the tablet height, except for the fact that it had to be as consistent as possible over time, which could be confirmed based on the data. An average height of 4.21 ± 0.02 mm was obtained over time, which corresponds to a relative standard deviation of 0.45%. This is a value which is absolutely satisfactory.

The same is true for the breaking force of the tablets, which needed to be > 50 N; this was found to be a sufficient strength for a later coating process.

The required breaking force was obtained in each case in the 8h production time, in which no individual measurement from which the average values were calculated was under 50 N. Other quality attributes of the tablets were examined off-line after the end of production. Figure 7 shows the average measured values for friability and the highest measured values for the disintegration time (slowest disintegration of n=6 tablets). In each case, the friability coincided with the value of < 1% required by the Ph. Eur., which is also very important for a downstream coating process. Since the aim was to obtain fast disintegrating tablets, which meet the requirements of the Ph. Eur. for non-coated tablets and disintegrate in < 15 min, the obtained values of < 60 s in almost each case are more than sufficient to fulfil this quality requirement.

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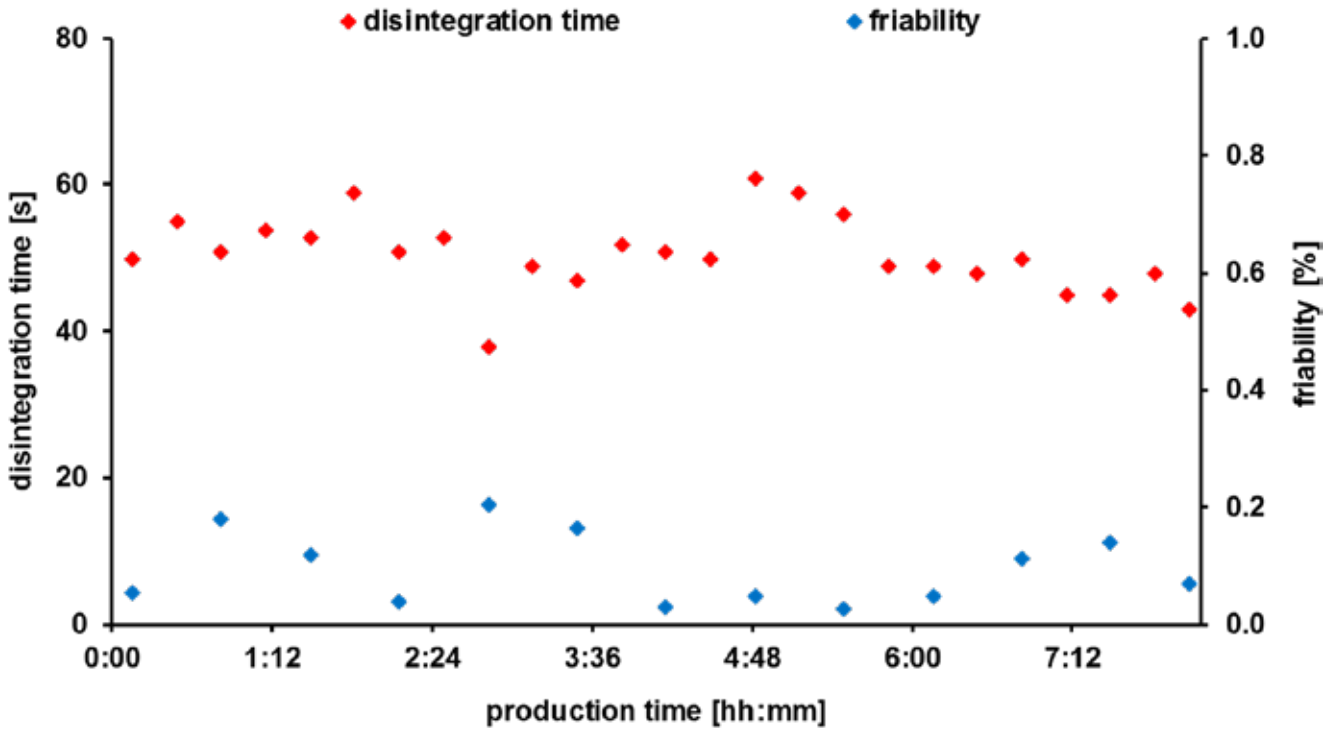

***Figure 7**: Off-line measured critical quality attributes of the tablets; n= 1 for friability and n= 6 for disintegration time (value of the last disintegrated tablet shown).*

Conclusion

The discussed data shows a successful continuous production by means of direct tabletting over eight hours. Not only were all the critical quality attributes maintained within their specifications over almost the entire production time, but it was also possible to detect inaccurate intermediate and final products via process-analytical technologies and process parameters. Even initial products with a concentration that was too low could be detected via the NIR method. The present results show that continuous direct tabletting for suitable formulations can represent easy access to the world of continuous production.

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