Seamless Integration of a Semi-Continuous Coating Process into Existing Solid Dosage Production

Abstract

A study was conducted using the KOCO 25 in conjunction with the ROB 50, in order to provide insight on the operation concept and process quality. In total, eight coating cycles were accomplished, focusing on the maximum throughput considering the capabilities of the process machine.

1. Introduction

Throughout the past years, continuous manufacturing has become an important topic for both pharmaceutical companies and regulatory agencies around the world. As a technology-driven machine supplier, L.B. Bohle has engaged into this subject from the beginning, today offering continuously operating process solutions from single unit operations to a full production line to their customers.

A highlight within the product portfolio is the KOCO 25, a semi-continuously operating film coater. Together with the ROB 50, a fully automatic tablet container hoist, these two jointly operating machines provide an integrated solution for an efficient and fully automated coating process in pharmaceutical production environments. With its automation concept, the combination of ROB 50 and KOCO 25 is designed to connect to a tablet press, either for existing batch-oriented production environments or to extend a continuous manufacturing line. A 3D illustration of this setup is provided in Figure 1. It is the ideal solution for customers already involved in continuous manufacturing and those in process of entering the field.

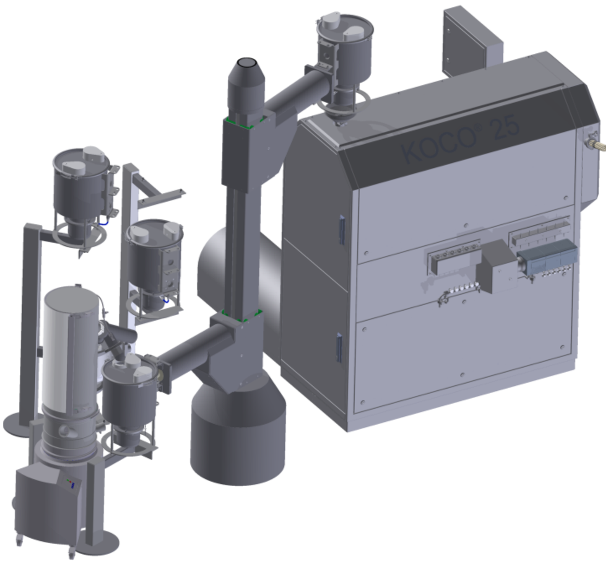

Figure 1 Machine setup of ROB50 and KOCO25. In the lower left, the tablet deduster presents the tablet source from the upstream process.

This case report provides an overview about the technology of the semi-continuous coater and the ROB 50, followed by a study investigating a representative coating process in a continuous manufacturing layout.

2. Process concept: ROB 50 + KOCO 25

The machine combination of ROB 50 and KOCO 25 provides a turn-key solution to fluently integrate a semi-continuous coating process downstream of a tableting process. The main application is for tableting processes, operating for several hours at constant throughput. Examples are high volume products in batch manufacturing, or continuous production lines.

2.1. Process Concept: ROB 50

In current batch environments, each unit operation is considered independent, with the product at the process outlet collected in a container and moved to a GMP warehouse, for further processing. Consequently, after the tableting process, typically followed by a tablet deduster, the produced tablet cores are accumulated into large tablet containers, to be stored manually in the warehouse and scheduled for coating at a later time point. However, this workflow implies both costs for storage and increased lead time.

In order to provide a fluent transfer from the tableting process to the coating, the ROB 50 has been developed by L.B. Bohle as an automated post hoist. This handling robot is interfaced with both the tablet press and the downstream coating process, implementing an

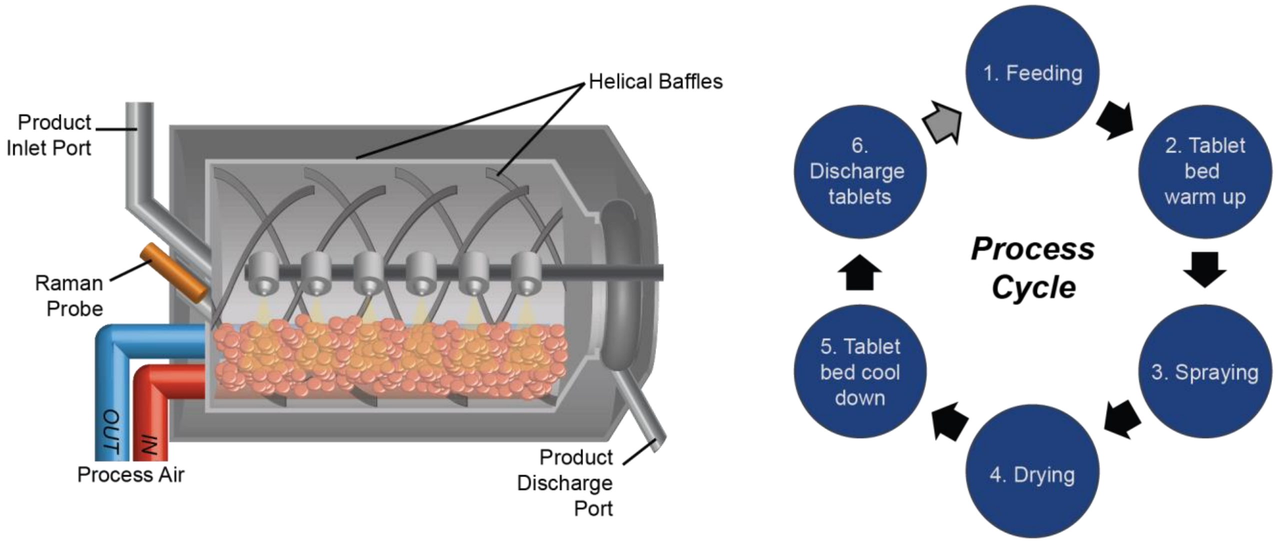

Figure 2 On the left, the mechanical design of the KOCO25 is provided. The right chart illustrates the cyclic operation with in total six phases.

autonomous transfer system with integrated container storage and inventory system.

During operation, a status signal from the tablet press is sent, if one of the two containers after the deduster has been completed with a new filling of tablets for the coater. This signal triggers the ROB 50 to pick up the full container, move it into the container storage and replace it by an empty container. On the one hand, the container storage serves as a buffer between tablet compression and coating, but on the other hand is used to allow the recently compressed tablets in the containers to cure, according to the product specific time for elastic recovery. Therefore, the configuration of the container storage, especially in terms of capacity, is built customer and product specific.

On the other side of the production chain, the coater can request a container with tablet cores, to be fed into the coater for a new coating cycle. Based on the data in the inventory system, the ROB 50 picks the container next in line, moves it to the coater and discharges the tablet cores into the coating pan. Of course, the integrated inventory system ensures that the tablet cores are kept in the container storage at minimum for the required tablet core relaxation time.

2.2. Machine design: KOCO 25

The KOCO 25 is designed as a semi-continuous coater, featuring a reliable throughput while ensuring a constant residence time for all cores.

The process machine, as illustrated in Figure 2 (left), is built on the industry proven, patented Bohle design for drum coaters[1]. That is, the coating pan is elongated in comparison to the diameter, with two helical mixing spirals, which ensure a homogeneous distribution and mixing of the tablets throughout the spray zone. Additionally, the process air both enters and exits the process chamber through the tablet bed, which in comparison to a typical, diagonal air flow reduces spray drying to a minimum.

The spray arm features an automatic adjustment of the spray angle and distance, carrying a total of six, two-substance spray nozzles (Schlick). Furthermore, the spray system includes recirculation and single supply of the spray nozzles, to ensure a homogeneous and reliable application of the coating suspension.

In contrast to common batch coaters, the KOCO 25 uses a feeding of tablet cores through a product inlet port on top of the machine, leading to an opening in the rear of the coating pan (see Figure 2 and Figure 3). This port is normally closed and the product valve is only opened to fill the drum for a new coating cycle. The discharging of the coated tablets is through a corresponding port at the front of the coater.

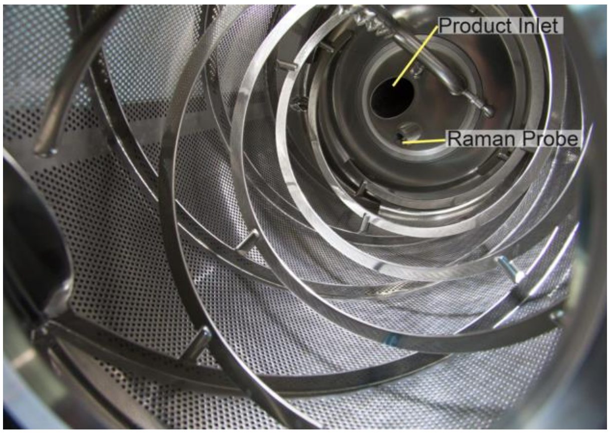

Figure 3 Picture of the inside coating pan, with the product inlet port and Raman probe position highlighted.

[1] US6547882 B1

The process control is designed to operate in a cyclic manner, to repetitively execute the defined recipe, each execution further denoted as cycle. The process cycle is presented in Figure 2 (right), with the following phases:

1. Feeding of the coating pan with a given amount of tablet cores through the inlet port.
2. Tablet bed warm up, commonly using the exhaust temperature as target parameter.
3. Spraying of the suspension with drying air active, if necessary following a spray profile with different spray rates.
4. Drying of the coated tablets.
5. Tablet bed cool down.
6. Discharging of the coated tablets through the outlet in the front door.

Due to the design advantages of the coating pan, air duct and spray system, the KOCO 25 can repetitively execute the coating cycle, without affecting the process and product quality. In order to allow for a fast continuation of the next process cycle after discharging and filling new tablet cores, the coater features a bypass valve to keep the process air active.

The choice for a semi-continuous process was taken in order to comply with the requirements and expectations of the pharmaceutical industry: A truly continuous coating process is defined by tablets being provided to the process at a constant flow rate, passing through the actual process, and coated tablets continuously leaving the process on the other end. However, as the behavior of the tablet cores to pass through the process cannot be controlled sufficiently, this will lead to wide residence time distributions and consequently varying exposure times of the tablet cores to the spraying process. Especially for functional coatings, this will result in insufficient coating uniformity. Instead, the KOCO 25 as a semi-continuous coater has equal residence times for all tablet cores, in combination with the advantages of the patented helical mixing spirals.

Table 1: Recipe parameters of the tablet cores

API:	5 %	Acetaminophen USP 90%, Code 0090 (Mallinckrodt)
Lubricant:	0.7 %	MgSt LIGAMED MF-2-V (Peter Greven NL)
Excipient (Filler):	94.3 %	Tablettose® 80 (Meggle)

Table 2 Targeted characteristics of the tablet core

Shape:	Round, bi-convex
Diameter:	8 mm
Weight:	192 mg
Hardness:	>50 N

Table 3 Tablet press compression parameters

Turret speed:	84 rpm
Main compression force	13 kN
Pre compression force	1.4 kN
Min. tablet relaxation time:	20 min

Finally, the integration of a Raman spectroscopy probe head into the rear of the coating pan (see Figure 3) can be used for in-line monitoring of the process. Hence, the KOCO 25 is ready for PAT and improved process control, using Raman spectroscopy to determine the process end point.

3. Coating study using the KOCO 25

A case study has been conducted to provide reference data on the KOCO 25 in terms of efficiency and quality. The process design was chosen similar to customer trials as regularly performed in the Service Center, allowing to transfer the results to other customer projects. The study design and results are provided in the following.

3.1. Materials

All tablet cores for this study were produced using the continuous direct compression line by L.B. Bohle, with Gericke loss-in-weight feeders and a continuous paddle blender, supplying a KORSCH XL 200 rotary tablet press with a downstream Kraemer KD7010 tablet deduster.

The continuous feeding, blending and tableting process operated with a constant output of tablet cores set at 25 kg/h. The details of the tablet core recipe are provided in Table 1, representing a low-dosage product with in total three raw components. Acetaminophen as surrogate API was chosen to have a tracer for the integrated PAT measurements of the direct compression line. The targeted tablet core characteristics are provided in Table 2, for which the tablet press was operated with the compression parameters as listed in Table 3. Through the production time, the compression parameters were adjusted minimally for turret speed and compression forces around the given set points.

In total 120 kg of tablet cores were produced, in parallel to the actual coating study, thereby representing an actual continuous manufacturing scenario. The outlet of the deduster was the interface to the ROB 50 post hoist, followed by the KOCO 25, as

Table 4: Recipe parameters of the coating suspension

Coating:	Opadry II beige HPMC-based (Colorcon)
Solids level:	17 % w/w
Solvent:	Purified Water

Table 5 Overview of coating parameters for the first eight cycles (A, B, …, H) at maximum throughput.

Phase ID:	1	2	3	4	5	6
Phase:	**Filling**	**Warm Up**	**Spraying**	**Drying**	**Cool Down**	**Discharging**
End of phase criterion:	Container fully discharged (from ROB50)	Exhaust air temperature: 45 °C	Cum. suspension applied: 2700 g	Fixed phase length: 1 Min	Fixed phase length: 1 Min	
Inlet air flow:	*fixed fan speed*	600 nm³/h	600 nm³/h	600 nm³/h	600 nm³/h	*fixed fan speed*
Inlet air temp.:	75 °C	85 °C	85 °C	60 °C		
Drum speed	3 rpm	3 rpm	15 rpm	5 rpm	5 rpm	
Spray rate:	-	-	120 g/min	-	-	-

described in section 2.

The minimal tablet relaxation time was chosen to 20 minutes, following an initial assessment on the tablet expansion characteristics, where no significant tablet expansion was observed.

As coating suspension, a HPMC-based color coat was prepared according to Table 4, following the supplier's recommendation for the solid fraction. The suspension required for the entire study was prepared in a single suspension container and continuously stirred, to avoid agglomeration and sedimentation of solids.

3.2. Study design

In total, eight coating cycles were executed, each with a loading of 15 kg of uncoated tablet cores. For a targeted weight gain of 3%, this led to a cumulative suspension mass of 2.647 kg, therefore 2.7 kg were chosen to account for minor spray losses.

The eight cycles (identified as A, B, …, H) focused on achieving a maximum throughput and documenting the effects on the equipment and especially spray system. Therefore, the recipe parameters were identified to operate with the maximum spray rate of 120 g/min. The summary of the most important process parameters is provided in Table 5. The entire cycle duration was less than 36 minutes, including filling and discharging. In fact, this implies that every 36 minutes a new cycle can be started. With the repetitive operation, this results in an overall productivity of 25 kg/h of uncoated tablets processed.

During the study, short interruptions between each cycle occurred, which were required to assess the coating pan and spray guns after each cycle. Accumulations of coating suspension were documented with a photo camera and video, to allow for an objective, qualitative assessment.

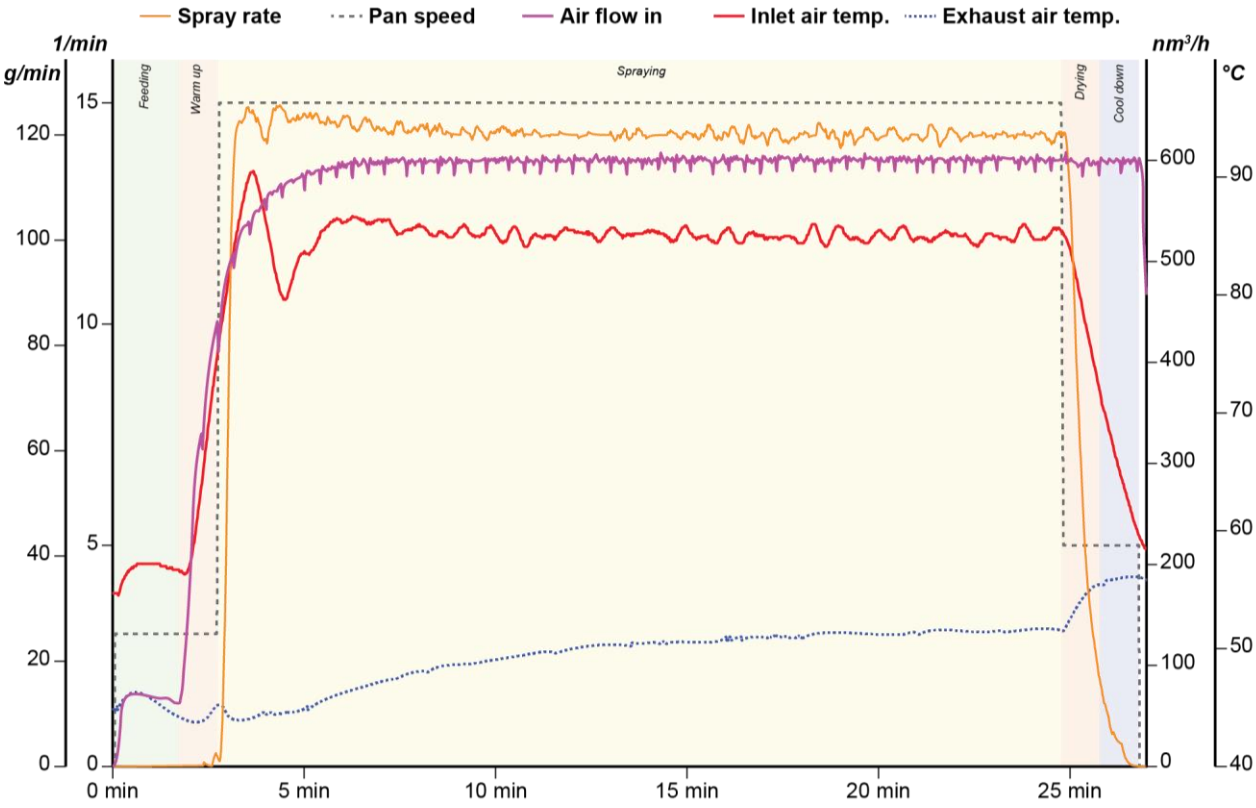

Figure 4 Exemplary process data set for coating cycle H at 120g/min. The background colors denote the phase.

3.3. Results

For the eight repetitive coating cycles (A to H), the targeted throughput of 25 kg/h was achieved. The process time for each cycle varied between 29 and 32 minutes, whereas the variation were due to the filling and warm up phases. The spray time for all cycles was 22 minutes, as the spray system delivered a homogeneous spray rate.

An exemplary dataset for cycle H is presented in Figure 4. For all process parameters, the corresponding set points were kept within the given limits by the control system. The overshoot of the inlet temperature during the first two minutes of spraying was due to the response of the control loop for the electrical heating.

Although foreseen in the recipe management, no variation of the spraying parameters was used during the study. This functionality is a benefit for products where, depending on the tablet core properties, it is required to change temperatures or spray rates along the process.

A qualitative view of the coated tablets for cycles A through H is further provided in Figure 5. As indicated before, all parameters were tuned towards maximum throughput, that is the solid level of the suspension was at the upper limits of the supplier's recommendations, the spray rate was chosen at 120 g/min and the targeted weight gain was at 3% w/w.

Still, from the qualitative assessment of Figure 5 it is apparent that a homogenous result within each coating cycle was achieved (intra-cycle), but also between the different cycles A through H (inter-cycle) for the color coat.

For more critical applications, such as API or modified release film coatings, both the fill level of the coater and the actual process and spray parameters can be adapted, providing sufficient margin to increase the quality of the coating process even more.

Considering long term stability of the coating process, the above mentioned results for cycles A through H already underline the repeatability of the quality. However, further qualitative assessments were conducted to document deposits of coating suspensions, which might call for a regular cleaning of the coating pan or spray system. As this would reduce the overall productivity of the machine, the design of the coater during engineering was optimized towards resistance against soiling.

The results of this documentation are provided in Figure 7 and Figure 8. The first picture provides a wide angle view into the coating pan after cycle H, that is after a total of eight coating cycles. Although minor depositions of coating suspension on the spirals and the pan itself occurred, these are only marginal and do not impair operation.

This is even more obvious in Figure 8, which provides detailed views for the coating pan, the spray nozzles and the air duct for the initial condition and after four,

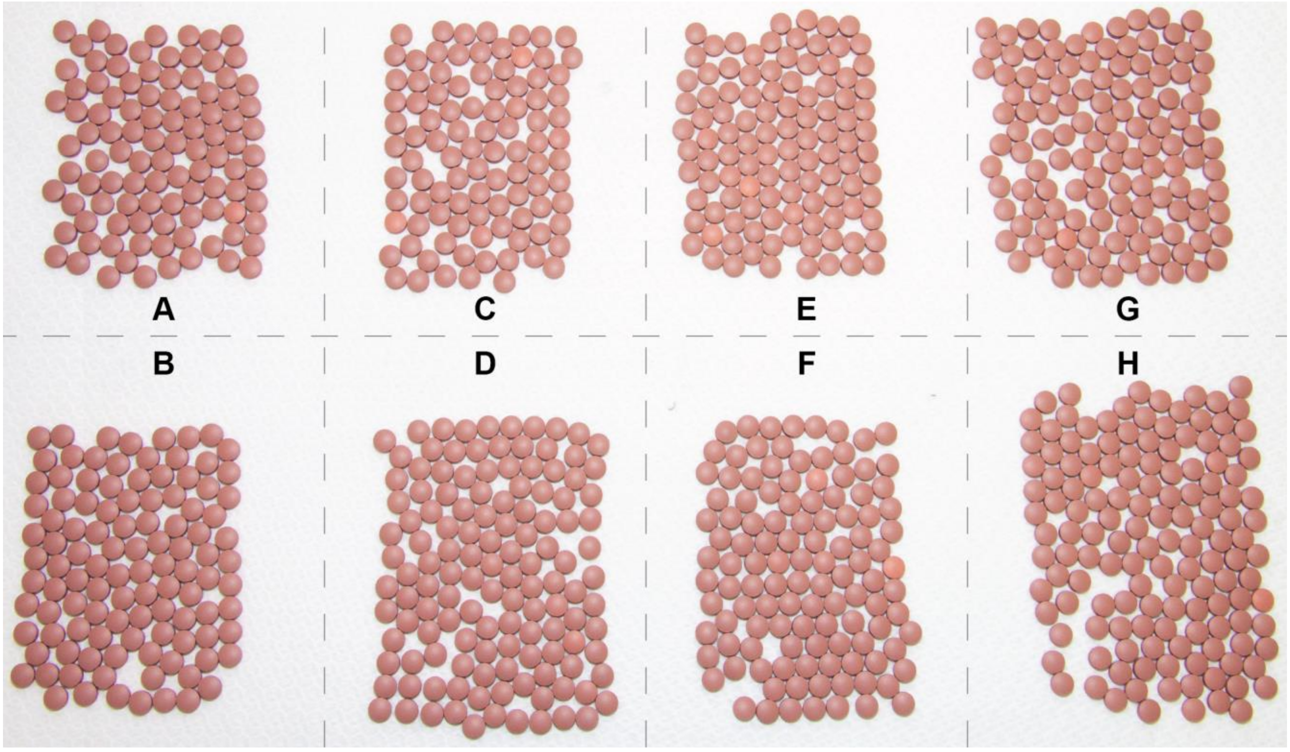

Figure 5 Visual, qualitative comparison of the coated tablets.

respectively eight coating cycles.

Although for the coating pan minor deposits on the spirals and the pan itself are present, there is no visible difference between the situation after cycle four and cycle eight.

Similarly, the soiling of the spray guns did not impair the operation of the coater. This was as expected, as the spray system uses anti clogging nozzles, with regular purging of the nozzle tips in the process by configurable air purge intervals. It should be noted that no manual cleaning between the cycles was conducted.

Finally, likewise the air duct system does not have deposits of particles, which might cause implications for the air flow. A major reason for this minimal soiling is the air flow with the process air entering and exiting the process chamber through the tablet bed, thereby minimizing the risk of spray drying. Otherwise, the spray dried suspension particles might accumulate in the air ducts.

4. Summary

In this study it was shown, that the KOCO 25 design provides the ability to continuously coat tablets at a throughput of 25 kg/h. A constant, homogenous quality was achieved, both within each cycle and along multiple cycles.

Figure 6 View into the coating pan after eight coating cycles. As can be seen, no major deposits are visible.

Furthermore, it was shown that the design allows for a repetitive operation without affecting the quality. This was especially due to the resistance to deposits and minimal spray drying.

As such, the KOCO 25, in conjunction with the ROB 50, provides the ideal solution for pharmaceutical manufacturers to extend an existing tableting process or a continuous manufacturing line with a qualitative outstanding and reliable semi-continuous coating process.

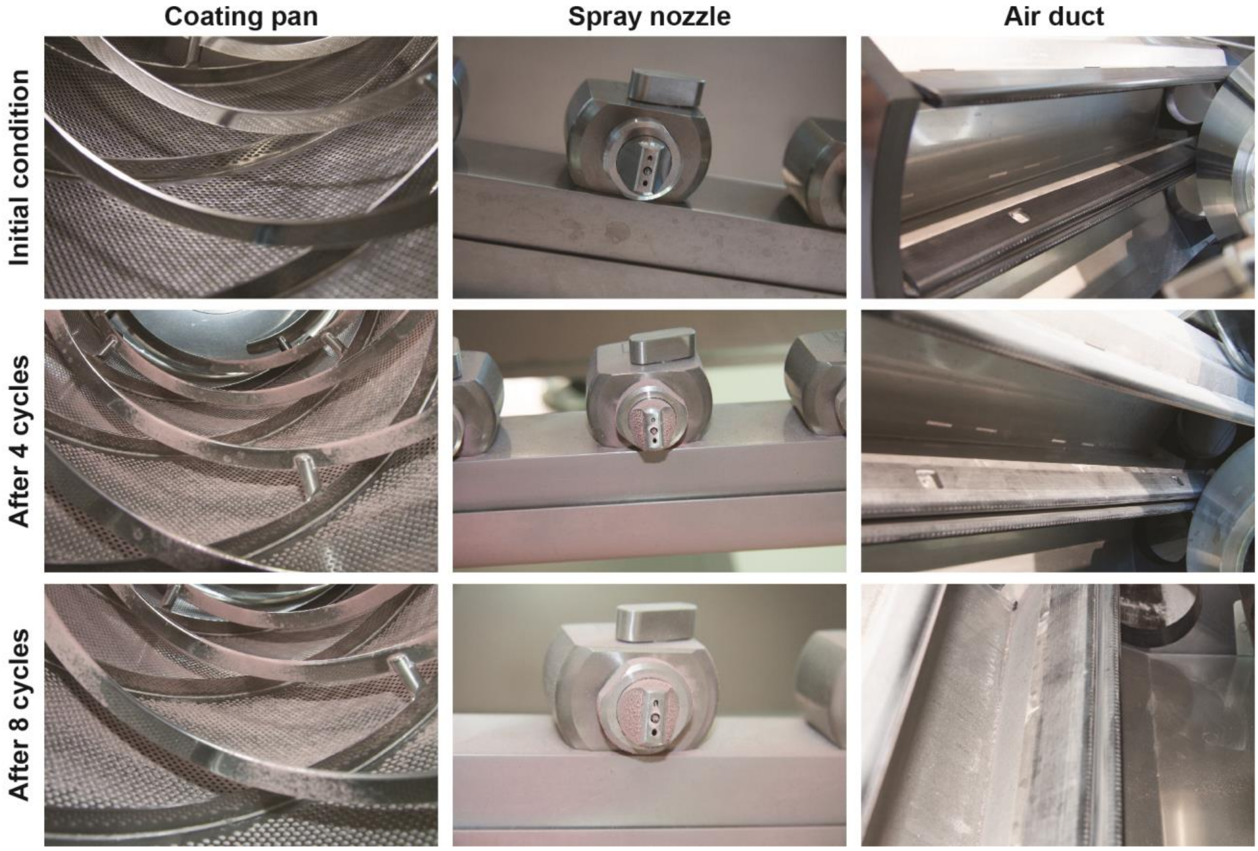

Figure 7 Photo documentation of the process area over repetitive cycles, specifically the coating pan, spray nozzles and air duct.

