

KORSCH: MAGAZINE

The KORSCH AG Customer Magazine

P. 04

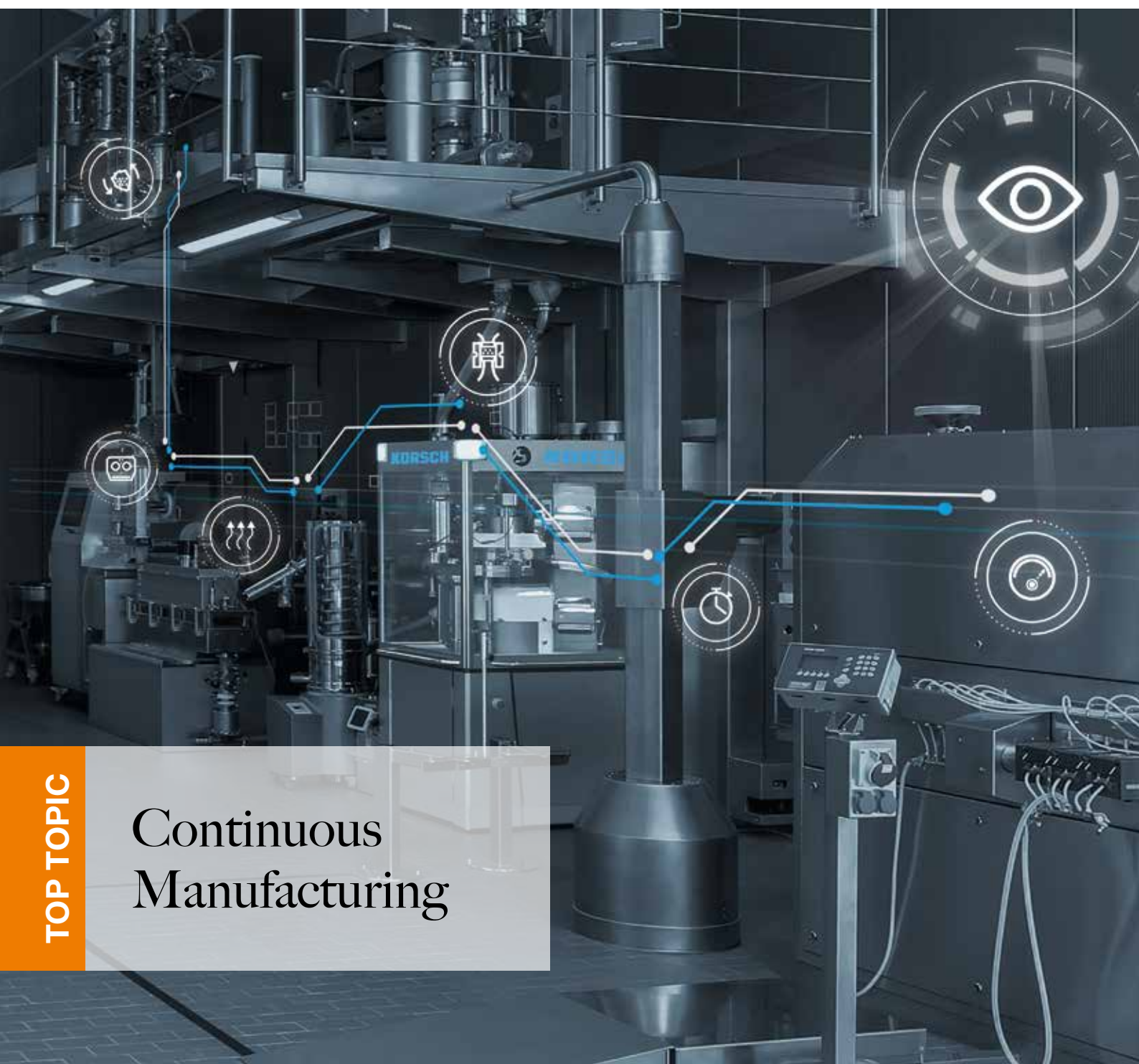
Production with a Bright Future:
Continuous Manufacturing

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Wet or Dry Granulation: As
Appropriate for Each Product



TOP TOPIC

Continuous Manufacturing

Stronger Together

Dear Readers,

Everything in this issue revolves around continuous production. We would also like to introduce you to our partners, because we believe that continuous production is all about teamwork. The reason for this lies in the process itself. Individual process steps in a continuous, automated process are mutually dependent. Analyzing the relevant process parameters and rolling them out at interfaces is therefore crucial. Technology partnerships enable us as a team to guarantee optimum processes and optimum, reproducible quality as a result.

That is why this issue of our magazine is going beyond tabletting – we take a bird's eye view and show you how our machines are integrated into continuous production processes, how they communicate with other units and share information. To make this happen, we have recruited skilled backup and conducted in-depth conversations with a large number of partners. Their expertise and experience help us to action our projects and provide you with first-hand information.

We regularly learn new things and develop a deeper understanding of the overall process during the course of a continuous manufacturing project. That is why we would like to take you on a production journey: from feeding and mixing via tabletting to final coating. Find out more about common analytical methods and their importance for the process.

A fascinating topic harboring huge potential – be inspired!

Yours sincerely
Stephan Mies
CEO of KORSCH AG



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08 Products & Processes

*Fast and Effective:
Direct Compression*

10 Products & Processes

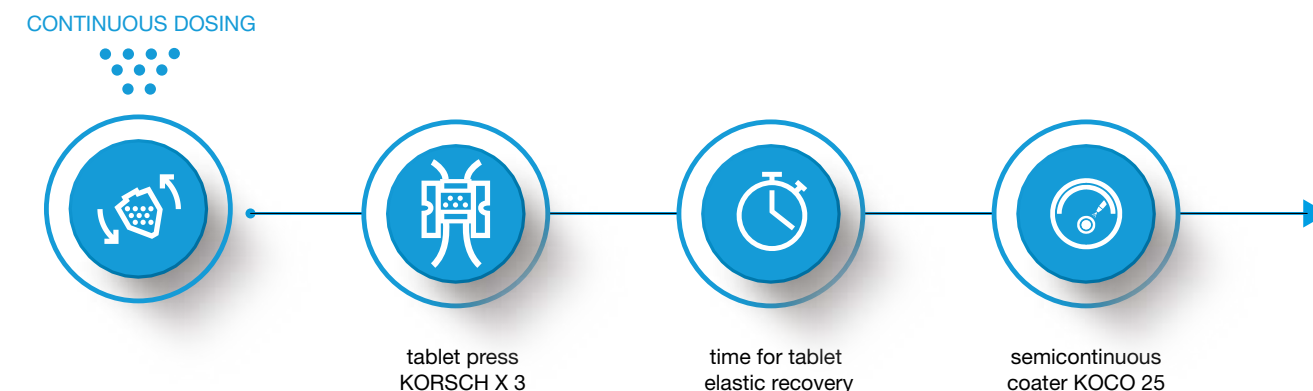
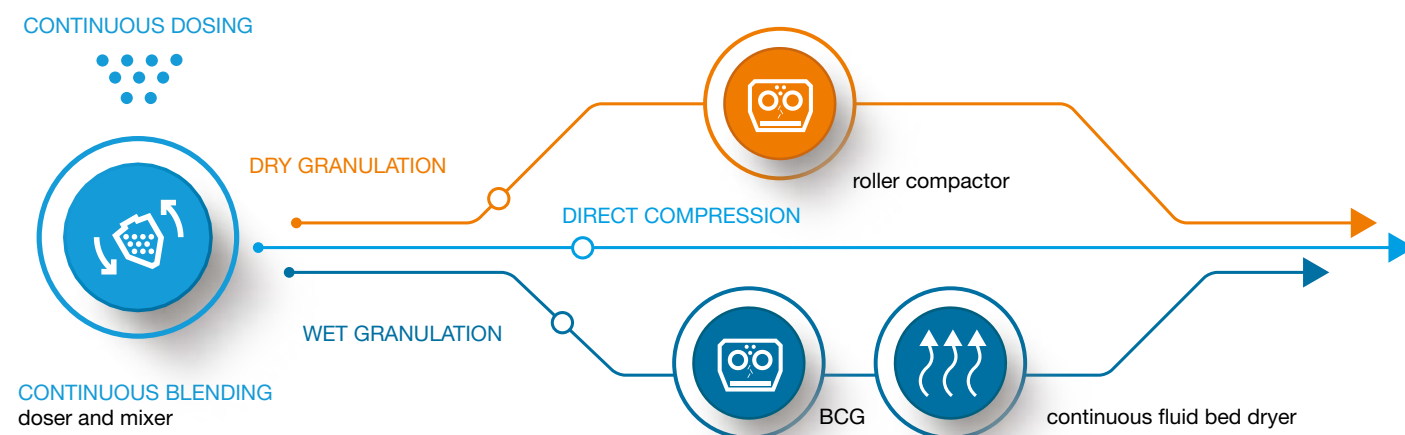
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TOP TOPIC

Production with a Bright Future: Continuous Manufacturing

Continuous production is increasingly gaining traction in the pharmaceutical industry – its advantages are obvious.

Batch production remains the default mode of operation in the pharmaceutical industry. Today, there is an increasing trend to consider continuous production technologies, however, to date, the FDA has approved only 10 products to date. In contrast, continuous process technology has been in use in other sectors like the food industry for years. Thorsten Wesselmann, Managing Director of L.B. Bohle, sees a strong case for the pharmaceutical industry changing its mindset: "Here the FDA is demanding – understand your process! And you should be demanding realtime acceptance."

That is impossible in a conventional batch process, as he explains further. "Here, one completed production stage follows the next. This results in a major disadvantage: you can only check quality retrospectively by taking samples and then testing them in the laboratory. During this time the batch is in quarantine until the lab releases it. That wastes a lot of time. The entire batch may also have to be discarded if errors occur. In contrast, quality can be tracked and checked inline at every stage in the continuous process." That is why a technology partnership led by KORSCH and L.B. Bohle has designed a continuous production system that features inspection

stations at the key process stages – mixing, feeding, granulation, drying, tableting, and coating.

Testing and understanding relationships

The development phase of a continuous process initially involves a great deal of product tests that are conducted on a real production line. "We then create a design space, for example, we monitor tablet hardness," is how Thorsten Wesselmann describes the approach. "If that varies slightly and is a bit too soft, for example, lactose needs to be added to increase bulk. But this needs to be controlled by the feeding and mixing unit at the start of the process. A higher lactose content requires more granulation liquid, which in turn impacts on moisture and therefore the drying process. Ultimately, we want maximum quality during the realtime acceptance procedure. To achieve this, we need process analysis tools along the entire line." (Read more about PAT starting on page 12.)

Continuous production therefore leads to a deeper understanding of the process as well, which in turn impacts on formulations. That is why scientific partners, like universities, are also involved in product development. For example, they can create mathematical models that help with modeling and parameterization.

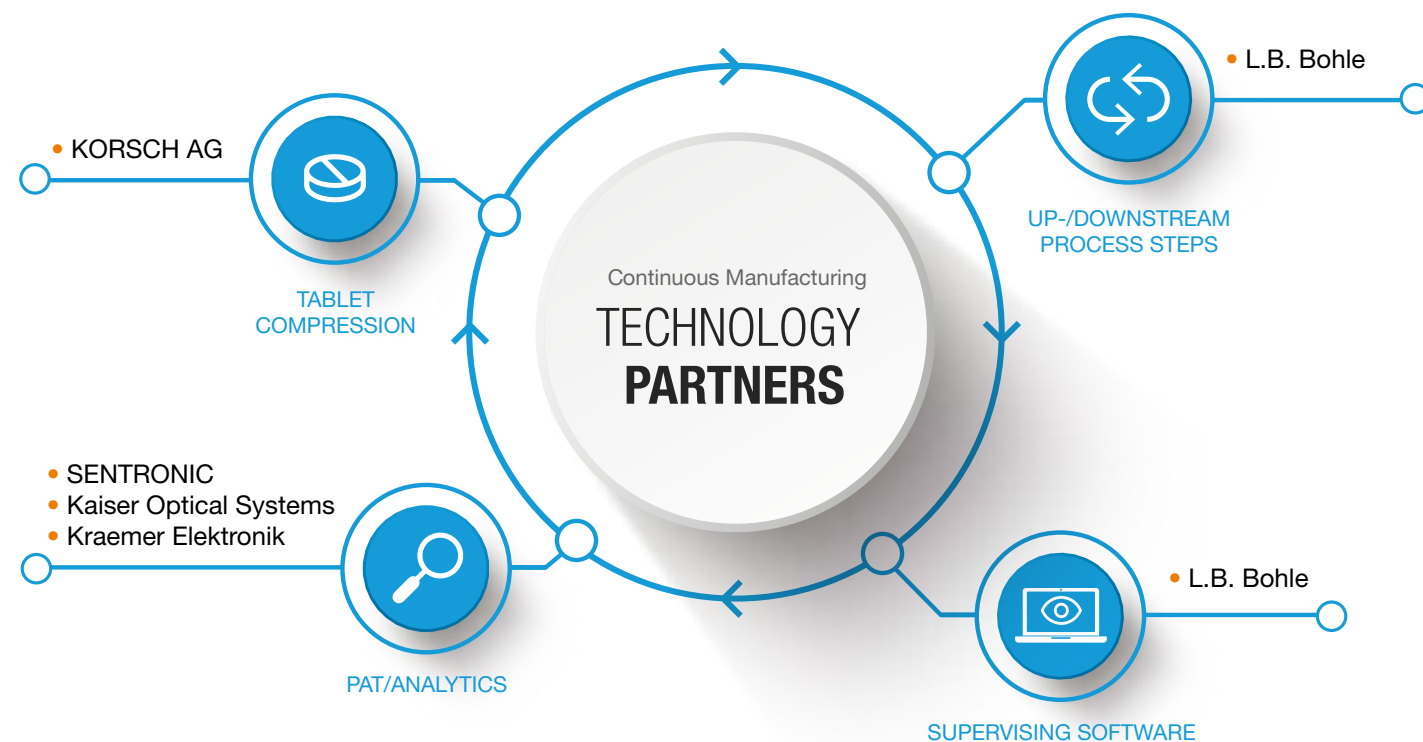
Applying batch process experience

Tablet presses are by nature continuous-production machines and therefore do not require major hardware

modifications to enable them to be incorporated into a continuous production line. Quality control automation, delivered by the PharmaControl press force control system augmented by the PharmaCheck tablet tester, which has been proven in a batch production environment, is also ideal for continuous production. When it comes to plant design, the manufacturer's wealth of experience also comes into play. "Some of the features that we originally developed for batch campaigns are also very useful in a continuous context," Fred Murray, the Global Sales Director for KORSCH, points out. He gives an example: "We have plants that run one batch process after another during large-scale production. Here, the machines have to run for long periods without cleaning. That is why we have developed an advanced automatic punch lubrication and dust extraction system that enable these near-continuous run capabilities."

All processes can be mapped

Customers can map all three production processes in their continuous production lines. "The simplest and least complex is direct compression," Thorsten Wesselmann explains. "In this process we need the compound to be directly compressed. To achieve that, we require raw materials that can be compacted without granulation." Dry granulation is a more demanding process. "Here, we use our BRC roller compactor, which compacts powder into ribbons that are then ground down to the right granule size. The advantage here is that roller compacting,



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„Our technology partners have a significant knowledge base about all unit operations as well as the integrated process.“

Fred Murray

Paradigm shift in manufacturing

The operators are key to the management of any continuous production plant. After all, it is no longer just a question of operating a machine but about managing the entire tablet production process. The technology partnership provides customers with specific support to meet their training needs. “Without training, the switch to continuous production is just not feasible, because operators have to be guided away from thinking purely in machine terms towards a process mindset,” Mr. Wessselmann explains. To achieve that, they require a much wider spectrum of knowledge and need to know how machines influence one another and change outcomes. Controlling instead of operating, this is the paradigm shift that our technology partnership is mentoring. However, not every customer wants the full engineering program. The technology partnership can also assist them by providing individual services. ■

PERFECT FOR CONTINUOUS MANUFACTURING: KORSCH X 3

Mr. Murray recommends the X 3 tablet press for continuous manufacturing. “The X 3 is very well aligned with the output requirements of continuous production. The X 3 offers a wide range of turret configurations and high containment-flexibility, and the control system permits seamless integration,” is how he summarizes the benefits of this machine. With an advanced production control system: the X 3 is pre-configured to dovetail with the smart factory. “It is a plug-and-play machine for a continuous process, but appropriate for batch as well,” the US expert says.

Benefits:

- smart sensors and PAT technology (PharmaControl and NIR)
- robust dual-column design
- exchangeable turret
- press force control
- installation flexibility
- superior accessibility (no corner columns)
- easy to clean
- quiet and low-vibration
- two machine models: the X 3 SFP for single-layer or the X 3 MFP for single- or bi-layer production
- various OEB options: OEB 3 or OB 4/5 with WipCon® system



like tableting, is by nature a continuous process in which we are highly proficient.”

Wet granulation is the most complex of the continuous manufacturing processes. Granulation liquids are used in this process. “Sometimes this results in a very complicated mixture ratio involving high shear forces on the screws. Therefore, we require a large number of tests to achieve the perfect setting.” (Find out more about direct compression, starting on page 8 and about the various granulation processes starting on page 10.)

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“We are the only manufacturer that enables the customer to test an entire continuous production line.”

Thorsten Wessselmann

End-to-end engineering is feasible

Customers can acquire a complete turnkey system, including upfront testing and user training. This is where Fred Murray sees the biggest benefit: “Our customers benefit from our process development experience and our testing capacities in Germany and the USA. Our technology partners have a significant knowledge base about all unit operations as well as the integrated process. And most importantly, we have validation expertise.”

The continuous process testing facilities at L.B. Bohle in Ennigerloh are unrivaled. “We are the only manufacturer that enables the customer to test an entire continuous production line,” Mr. Wessselmann points out. “I don’t know of any place other than in our Technology Center where this is possible. Furthermore, we can offer all three process scenarios: direct compression, dry granulation and wet granulation. We provide everything from a single source, thus eliminating interfaces between different sets of equipment. That is a key benefit for the customer.”



Fast and Effective: Direct Compression

Achieving the desired tablet in just a few steps

“Direct compression is the fastest continuous production method – but it only works under certain conditions,” KORSCH direct compression specialist Ingo Stammnitz explains. “Direct pressing procedures are only feasible if materials exhibiting good adhesive and flow properties are used. In that case, a seamless sequence of process steps including weighing, feeding, mixing, and compression, as well as coating, where applicable, are all that’s needed to get the job done.”

First benefit: closed process

This process of direct compression offers a number of benefits. For example, it saves a great deal of space and requires little in the way of material logistics. Furthermore, the operator does not need to be permanently attaching and detaching items of equipment. That means that less air enters the process. “Hygroscopic substances can be processed better,” Ingo Stammnitz explains. “That is because less air also means less moisture in the process. The materials used in direct compression and dry granulation in particular are often moisture-sensitive.”

Second benefit: no material segregation

Continuous processing offers another bonus, when mixtures with differing particles sizes are involved, as the KORSCH expert states. “A mixture containing very small and very large particles is subject to a sieve action – the small particles fall through the large ones and both materials separate. However, there are no downtimes in processes involving gravimetric feeders and continuous mixers. As the material is constantly in motion, this segregation effect does not occur at all.”

Third benefit: continuous control

In order to ensure the mixture has the right concentration of active ingredients, continuous direct compression plants use near-infrared measurements (NIR – you can read more about this topic in our article about process monitoring on page 12). The weight, height, and hardness of the tablets are checked after the tablet pressing stage using the PharmaCheck® tablet tester.

Batch numbers of the materials are crucial for documentation. In batch processes that is simple, but continuous production requires exact knowledge of particle dwell times in the system. This was previously an impediment. “To enable us to monitor this issue, we can dispatch tracers into the process,” the expert explains. “We can undertake batch tracing this way or using NIR technologies. After all, this is a key tablet quality parameter.”

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“Less air also means
less moisture
in the process.”

Ingo Stammnitz

Fourth benefit: no scale-up

As development and validation occur directly on the production line, no scale-up is required, which in turn reduces the time to market and ensures a smooth start to production. ■



L.B. Bohle's twin-screw granulation has been established for almost 20 years.

Wet or Dry Granulation: As Appropriate for Each Product

When direct compression is not feasible, wet or dry granulation is the answer.

Like the tablet press, dry granulation using a roller compactor is a continuous process per se and particularly suitable for high-volume, moisture and/or temperature-sensitive products. The process functions as follows: the roller compactor compresses powder to form ribbons. These are ground down to form granules with the desired particle size distribution – all in a single production step. An integrated PAT (Process Analytical Technology) tool, like continuous measurement of granule size distribution, can prevent entire batches from having to be rejected and ensures consistently high quality.

Dr. Robin Meier, Scientific Operations Manager at L.B. Bohle, explains the advantages and disadvantages of the process: "Dry granulation is a less complex process and therefore requires both less energy and less space. But processing using a roller compactor requires significantly more excipients than the wet granulation process. To achieve good particle size distribution and firm consistency, granules require a binder, which in dry methods can account for up to 40 percent of the content. In the wet granulation process, we sometimes achieve under five percent in terms of excipients."

Wet granulation: a complex process

Very effective binders are used in the wet granulation process. The product characteristics of disaggregation, consistency, compressibility, and particle size distribution can be controlled very effectively using the right excipients. But traditional methods such as fluidized bed or high-shear granulation are typical batch methods. In 2017, L.B. Bohle developed the twin-screw granulator for continuous production purposes and the QbCon® 1 continuous dryer for laboratory-scale applications, which can feed, granulate, and dry simultaneously. Featuring short dwell times and narrow dwell time distribution in the dryer, it ensures that defective products are specifically removed. At the same time, that can make material traceability easier.

Process Analytical Technology provides smart controls: QbCon® 1 can be equipped with NIR (near-infrared spectroscopy) for inline content ascertainment and continuous particle size analysis purposes or with Raman spectroscopy, in order to maintain consistent granule quality. (You can obtain details about PAT tools on subsequent pages.)

Drying is the crucial issue after wet granulation

Robin Meier reveals where the plant design challenges lie: "Dedusting and cleaning the filters play a key role alongside drying times. Both must occur in parallel to machine operation. We are currently the only company in the market that has found a solution to this problem and can guarantee extremely long filter service lifetimes." The material is returned to the process from the filters. That has one other advantage: "It is necessary to prevent operators coming into contact with particulate matter, especially when containment processes are involved. We can eliminate this risk."

„Dry granulation is a less complex process.“

Robin Meier

L.B. Bohle has conceptually designed these systems both for laboratory-scale applications as well as for production involving containment solutions. "Our initial experience tells us that the continuous process can be implemented very quickly. An OEB 5 plant can already start producing for the market seven months after its FAT. This lead time can only be achieved if we are able to evaluate and enhance the continuous process within a minimum timeframe, without having to pass entire batches through the plant," is the conclusion reached by the Scientific Operations Manager.



The complete plant (dry granulation in the picture) is available for testing at L.B. Bohle's Technology Center in Ennigerloh.

Everything Under Control

PAT tools are able to monitor individual process steps and deliver key control information.

One of the major benefits of continuous production is permanent quality control. Uninterrupted testing enables production staff to react directly to divergences, remove reject products and readjust parameters.

Process Analytical Technology (PAT) enables production sequences to be monitored. Andreas Teske, process engineer at L.B. Bohle, is familiar with the established tools for continuous production: "We generally use near-infrared spectroscopy, NIRS for short, in tablet presses. The light source generates a fingerprint, which reveals substances moisture content and active ingredient concentration. These quality attributes are then reported to the system, which reacts to any divergences accordingly." Defective tablets are then rejected and the composition in the mixer is recalibrated. Monitoring is inline and permanent, and enables an immediate response to unexpected measurement results. Andreas Teske views this as a distinct advantage over batch production: "In this system we do not have to reject an entire batch, but only have to remove the poor-quality output. We increase product quality and are able to respond much faster."

Wet granulation requires major use of PAT

Furthermore, this technology is also used to measure dehumidification following wet granulation. The use of particle size measuring instruments is also feasible before, during, and after granulation, as this parameter impacts on the flowability of the material and the hardness of the tablets.

Another PAT tool is Raman spectroscopy. Here, a light beam penetrates the product, meaning that this technology is ideal for checking the coating procedure, for example. "We are able to track the increase in mass during the coating procedure," Andreas Teske explains.

Another PAT tool used by KORSCH after tablets have been compressed is the PharmaCheck® tablet tester. Arno Rathmann, Head of Automation at KORSCH, explains what its function is: "Our PharmaCheck® can measure the three attributes of weight, hardness and height. The tablet press records the data and can immediately correct any divergences – especially when these divergences are still within the norm, meaning that no

rejects occur." This case therefore involves a closed loop system with closed loop feedback to press force control system.

Sophisticated control technology

All test results are relayed to the SCADA (Supervisory Control and Data Acquisition) system. This higher-level software links all machines and manages communication between the individual plant units as well as with the customer system. Single product lines are displayed separately by the SCADA system in pharmaceutical manufacturing operations. This means that all individual plant components can be actuated and controlled within the SCADA system. The operator has to decide whether the measurement results should trigger user intervention or an automatic mechanism. "We are installing a PAT data management system," Andreas Teske explains. "This software handles the processing of raw data, as well as the evaluation and analysis of all PAT measurement sites. A target value control procedure can also be incorporated, if required."

The SCADA system controls the interfaces between the machines and ensures the flow of information, but at the same time it functions as an interface for the operator. "This is often key to the success of the plant," the process engineer is talking from experience here. "Whereas

users previously had to be familiar with just one machine, they now require knowledge of the entire process. It is therefore vitally important to integrate and train all those involved at an early stage."

Simple R&D process

The process software reveals interrelationships that previously did not attract attention. While that is of R&D benefit, it is significantly more challenging for human resources. Talking of R&D: continuous production is superior in this respect too. Given that all measurements are taken within the production plant right from the start and individual machines are not scaled up, all measurement values are portable and all monitoring processes are identical. The only difference between a short test and continuous production is that production time is increased. Arno Rathmann can envisage further automation of other inspection scenarios: "The visual batch inspection undertaken by the user could, for example, be performed by means of a camera check. There are already appropriate final inspection devices on the market." Their incorporation in these processes appears to be just a matter of time. ■





Continuously Safe

Entire facilities need to pass the leak-proof test, if high-containment production is involved.

Removable connections and joints are always critical sites, when highly active or toxic products are being manufactured, as these are the exact locations where particles can escape. They are reduced to a minimum in continuous production, which is why this method is particularly suitable for containment purposes.

“As with the overall process design of continuous production facilities, the challenge in meeting containment requirements lies in the consistent linkage of individual

plant sections,” Johannes Nitzsche states. The KORSCH project manager quotes an example. “Instead of the double dump valves used in batch production, material flows in the machine are usually continuous. For OEB 4 and 5 products, however, we utilize a vacuum to seal the tablet press, which has an upward suction effect and impacts on material flow.”

Particular complexity results from these interdependencies in such projects. Users should therefore seek advice from a specialist to en-

sure the right outcome: a convenient containment process involving zero transfer between different process stages.

Integration is the challenge

In this respect, the same thing applies to containment as to an entire continuous production plant: a higher degree of integration of individual plant sections and better communication between those sections are required. The data to make that happen is provided by process analysis tools (PAT – you can also read more about this topic on pages

12 and 13). “The actual challenge therefore lies in linking the processes and in the configuration of the higher-level SCADA software,” is how Johannes Nietzsche encapsulates the issue.

Within the tablet press itself, the differences between batch and continuous tend to be minor. A “barrier isolator” closes the inside of the press off from the circulating air, while wash-in-place (WIP) nozzles are used for cleaning. If the mixing unit is also cleaned using fluids, then these can also be conducted through the tablet press.

“Every continuous production facility is unique. But our tablet presses are basically the same machines,” Ingo Klaer, Head of Product Development at KORSCH, explains. “In the pharmaceutical industry, smaller machines like the X 3 tend to be used for continuous production purposes. This tends to involve long duration runs. Larger presses are often used for batch processes, to enable processing to be as fast as possible.” Smaller machines, in particular, are ideal for production involving containment processes, as the volumes to be produced for highly active products are usually smaller.

Experience gained from other applications

KORSCH has already gained extensive experience of continuous processes in the chemical industry. However, Ingo Klaer sees clear differences compared to pharmaceutical applications. “Continuous processing saves money, because large quantities can be produced non-stop. In the chemical industry, for example, we supplied a customer with several XT 600 tablet presses for manufacturing catalysts in a cluster. This too is an OEB 4 case, as materials like nickel, lead and cadmium are also toxic. But large presses

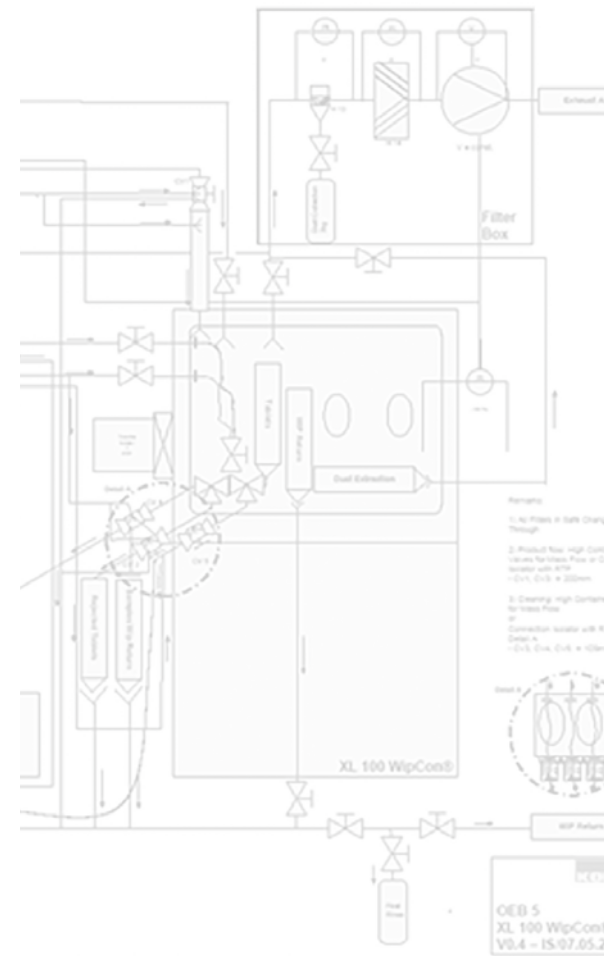
are used, because the issue here is bulk.” Containment is therefore not uncharted territory in continuous production.

Customized plants

A containment plant needs to be customized, and the same applies to a continuous production plant. If you combine the two, the need for a specific configuration or design is even greater. Furthermore, the three possible processes (direct compression, dry granulation, and wet granulation) each require a very different quantity of machines and therefore differing WIP cleaning inputs. This diversity makes a general appraisal of whether it is more cost-effective and/or simpler to action a containment process in continuous or in batch mode more difficult.

Lower costs and less complexity in the case of continuous production could be attributed to the fact that less footprint is required, and no special systems and receptacles are needed for transferring between process stages. Conversely, there are factors in the continuous process, however, which can increase both costs and complexity. That applies in particular to expensive PAT tools (especially NIR spectroscopy), system validation, and sophisticated monitoring systems for the facility.

Ingo Klaer points out: “Such plants are never off-the-shelf; each one is custom-designed and complex. Containment needs to be factored in to the engineering at plant level.” Specialists like KORSCH or L.B. Bohle are the ideal partners in this regard. ■



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Publisher:
KORSCH AG
Breitenbachstraße 1
13509 Berlin
Germany

E-mail: berlin@korsch.de
Phone: +49 30 43576-0
Fax: +49 30 43576-350
CEO: Dipl.-Ing. Stephan Mies

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Charlottenburg District Court
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Editorial team:
KORSCH AG
C&G: Strategische Kommunikation GmbH

Design, layout, text and production:
C&G: Strategische Kommunikation GmbH
Hoffnungsthaler Straße 1, 51491 Overath,
Germany
Phone: +49 2204 9756-0
E-mail: info@c-g-gmbh.de
www.wir-verstehen-technik.de



KORSCH
The Specialist.



L.B. BOHLE

NEW JOINT LOCATION IN INDIA

Due to the ever-increasing demand from the Indian pharma industry, KORSCH and L.B. BOHLE have decided to join forces by setting up beginning of 2022 a common sales, service and spare parts center in Hyderabad. The building would be the new KORSCH headquarter for India and will include an INNOVATION CENTER for product formulation and optimization, training certification, tablet compression trials, as well as factory acceptance testing. This partnership will make possible for our local customers to test a broad range of equipment for OSD production.

www.korsch.com

KORSCH

KORSCH AG – Berlin
Breitenbachstraße 1
13509 Berlin
Germany
Phone: +49 30 43576-373
E-mail: berlin@korsch.de

KORSCH America Inc.
18 Bristol Drive
South Easton, MA 02375
USA
Phone: +1 508 238-9080
E-mail: sales@korschamerica.com

KORSCH Asia Pacific
Hong Kong
China
Phone: +49 30 43576-175
E-mail: service.asia@korsch.de

KORSCH India Private Limited
Unit 709-711, B Wing, Atrium 215
Andheri Kurla Road, Andheri East
Mumbai, MH-400059, India
Phone: +91 98 6716 8123
E-mail: info@korschindia.com

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