Issue 1 | 2022

KORSCH: MAGAZINE

The KORSCH AG Customer Magazine

TOP TOPIC

Research & Development

Our customers respond

Focus on Innovation

Dear readers,

A huge amount of time and effort is invested in the extensive process of research and product development before a drug in tablet form obtains regulatory approval. As technological leader in tableting for R&D purposes, we have made it our mission to provide pharmaceutical companies with optimum support.

We therefore took the logical step of entering into strategic partnerships that enable us to provide our customers with even more comprehensive, integrated solutions. We have established an extremely effective partnership with MEDELPHARM, the world compaction simulator market leader. We are able to cover all tablet product development requirements through our joint universal R&D product line, and have also established several productive partnerships with universities to action topic-related knowledge transfer and synergy effects.

KORSCH INNOVATION CENTERS in Berlin, Boston and Hyderabad (India) as well as the MEDELPHARM Science Laboratory in Lyon are of particular importance. Some also possess expertise in and equipment for key upstream and downstream tableting processes, thanks to our strategic partnership with L.B. Bohle.

In this issue, we conduct revealing interviews with customers, provide you with a detailed insight into the processes and challenges involved in successful product development, including a look over the shoulders of our experts at the INNOVATION CENTER in Berlin.

I wish you a stimulating read,

Yours sincerely
Stephan Mies
CEO of KORSCH AG

TOP TOPIC

The Signs are Pointing to Change on the Product Development Stage

New tools and new stakeholders are getting involved in the development of new products.

New vaccines usually take around ten years to develop. The new Covid vaccines, which were available after just one year, showed that this process really can be fast-tracked. In the past, pharmaceutical corporations dominated the market. Today, they are joined by an increasing number of small startups that are driving innovation and the development of new active ingredients. These "inventors" receive valuable assistance from CDMOs (contract development and manufacturing organizations), which provide them with the support they need to develop innovative drugs and bring them to market. We spoke with Dr. Sanjay Konagurthu, Senior Director Science & Innovation at Thermo Fisher Scientific, a leading provider of end-to-end pharmaceutical services, about the changes in drug development.

Sanjay Konagurthu, PhD
Senior Director
Science & Innovation,
Thermo Fisher Scientific

KORSCH:MAGAZINE: How long does the development process for a new drug take?
Sanjay Konagurthu: This is a complex process. It often takes at least ten years from the discovery of the active ingredient to its market launch. However, in certain cases, such as the development of drugs with orphan drug status, the process can also be fast-tracked.

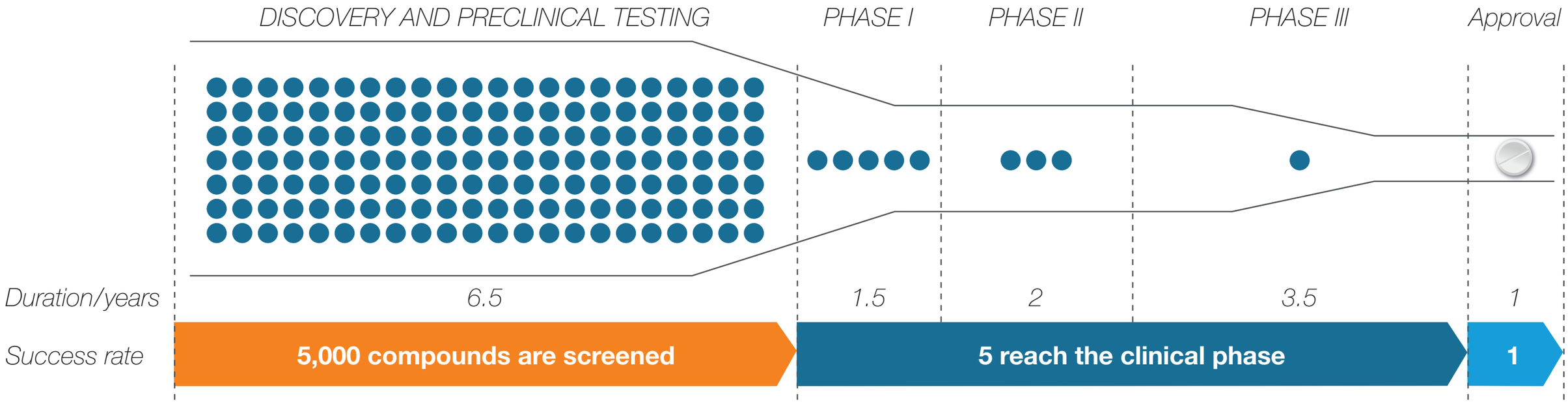
KORSCH:MAGAZINE: And what are the success rates involved in bringing a product to market?
Sanjay Konagurthu: These are very low. To start with, out of 10,000 to 15,000 new compounds identified with the aid of high-throughput screening during the discovery phase, typically less than 10 of these reach the clinical phase. Subsequently, one of these is typically approved and reaches the market. The biggest challenges the industry faces with small molecules relate to solubility and bioavailability.

KORSCH:MAGAZINE: At what stage of development is a patent application filed?
Sanjay Konagurthu: This happens very early on, and an umbrella of patents is filed to cover the molecule, formulation and the process.

KORSCH:MAGAZINE: Is time to market the key influencing factor in the development process?
Sanjay Konagurthu: Most revenue is generated prior to patent expiration while the innovator companies have exclusivity. After that, competitors quickly follow with similar molecules, and once the patents have expired, the product is manufactured by third parties as a generic. It is the huge increase in generics over the last 30 years that is making the difference. Therefore, the time factor plays an essential role in product development.

Even though the different phases of product development follow a logical process, there are many interactions between them. Some steps can also be performed in parallel to shorten the time to market.

Top Topic



It usually takes 15 years from the discovery of a molecule to the mass production of a tablet ready for the market, and only one in 5,000 molecular compounds is suitable for series production.

KORSCH:MAGAZINE: How exactly can time to market be shortened?
Sanjay Konagurthu: We take a very systematic product development approach. Nowadays, development can be speeded up by leveraging predictive modeling tools for process, pharmacokinetics (the totality of all processes a drug undergoes in the body) and stability issues. Methods such as compaction simulation, DEM (discrete element method) or CFD (computational fluid dynamics) are also used. These enable critical material properties and process parameters to be understood, each of which impacts on the critical quality attributes of the product. To develop a robust drug product, you need to have a really good handle on performance, process – i.e. manufacturability – and stability. All three must be considered holistically.

> ***"The tablet is the most widely used form of administration and will remain so in my opinion."***
>
> Dr. Sanjay Konagurthu

KORSCH:MAGAZINE: What do you regard as upcoming product development trends?
Sanjay Konagurthu: An important issue is solubility, in order to be able to exploit the potential of new APIs, improve their efficacy or enable their use in the first place. The use of technologies such as amorphous dispersions through spray drying, hot melt extrusion or lipid-based approaches can help overcome the solubility and bioavailability challenges. Continuous manufacturing will also be an important aspect. However, it is not suitable for all drugs and requires a certain production volume. Other current topics that will play an increasingly important role are "targeted medicine" or "precision medicine".

KORSCH:MAGAZINE: Dr. Konagurthu, the development of pharmaceutical products is currently undergoing change. Who is driving these innovations?
Sanjay Konagurthu: These are often small startups or even universities that conduct research and innovate. They discover new molecules and carry out initial tests, sometimes even initial animal testing. Such startups with promising approaches are occasionally taken over by large corporations, which then partner with them to complete the development and market launch processes. This happened, for example, with messenger RNA (mRNA) technology for vaccines. In other cases, the startups turn to CDMOs.

KORSCH:MAGAZINE: What does a CDMO like Thermo Fisher offer these new, innovative startups?
Sanjay Konagurthu: Around 80 percent of our customers are now smaller and emerging pharma businesses. We offer them everything from a single source – from API production, testing and screening, formulation, production for clinical phases, scale-up and commercialization through support with packaging and distribution. We therefore service the entire development, production and value chain.

KORSCH:MAGAZINE: What are the advantages for these businesses?
Sanjay Konagurthu: They don't have to deal with a wide range of different suppliers and service providers, because procurement and supply chains can be very complex. We have created our own programs to systematically accelerate product development for our customers, so that they can get to market as quickly as possible.

KORSCH:MAGAZINE: How do you see the future of the tablet?
Sanjay Konagurthu: I think the tablet has outstanding properties in terms of performance, production capabilities, and stability. It is the most widely used form of administration and will remain so in my opinion. After all, who would reach for a syringe, if they could take a tablet instead? Vaccines in tablet form will also be a major topic of interest.

KORSCH:MAGAZINE: Let's talk about your laboratory: what equipment and machinery do you use?
Sanjay Konagurthu: We have equipment from the well-known manufacturers in our network – and therefore, of course, various tablet presses and simulators from KORSCH-MEDELPHARM too. We perform a lot of compaction simulations; this is part of our toolbox, along with predictive modeling and other engineered solutions.

KORSCH:MAGAZINE: We are delighted to hear that! Thank you very much for the informative interview!

Everything Starts with an Understanding of the Materials

Simulators and software solutions provide valuable product development support when appropriate raw materials need to be selected.

Sound knowledge of the active pharmaceutical ingredient (API) to be formulated and the required excipients is a basic prerequisite for the successful development of any pharmaceutical dosage form. This applies in particular to direct tableting. This is because the variety of different materials is vast: suppliers offer the full range from fillers to disintegrants and flow agents to flavor maskers. Communication with raw material and equipment suppliers is therefore important for ensuring resilient formulations and secure supply chains that have any potential product variability covered. Coprocessed excipients may also provide a solution. These are a combination of different materials that are given different functionalities through physical coprocessing manufacturing rather than through simple blending.

Step by step to the optimum solution

First of all, the API is extensively characterized, to enable the required excipients to be selected. The second step involves defining the most suitable production process, based on an interpretation of the API characterization data. Is direct compression feasible or is a preceding dry or wet granulation process necessary? Consideration must also be given to anticipated production volumes and to the issue of which tablet press can or should be used for serial production purposes. “If continuous production is being considered, this should also be factored in right at the beginning,” Thorsten Cech, European Application Lab Manager at BASF, advises, because subsequent changeovers are rarely feasible without problems occurring. Potential downstream processes, such as coating, should also be considered. Last but not least, storage time and therefore requisite stability must be included. It is also advisable to consider more than one production process in the formulation phase, in case problems arise at a later stage of product development. The required excipients can be selected as part of the third step, based on the API characterization and the production parameter outcomes.

Database and software support

The aim is to develop a stable formulation as quickly as possible in order to shorten the time to market. There is a wide range of support available: compaction simulator and tablet press software databases help to determine the individual fingerprint of both the API and excipients at constant process parameters. This includes various properties such as compactibility, tabletability, compressibility, elasticity, elastic recovery, and others.

Thorsten Cech
Manager European Application Lab,
BASF

Simulators, such as KORSCH-MEDELPHARM’s STYL’One Evo, enable accurate functional characterization of tableting behavior. This is a valuable add-on to pharmacopoeia-based characterization, which is primarily concerned with mechanical product properties (such as flowability). Another advantage is that know-how remains within the company, as the measurement data is stored as a knowledge database in the tablet press’ software.

The algorithm of BASF’s ZoomLab™ software solution provides an opportunity that builds on and complements this capability. This free, web-based tool guides the user through the API characterization process by means of easy-to-follow tests and questions, and therefore specifies a choice of possible excipients for the formulation. To do this, the software draws on an extensive database that includes raw materials from both BASF and other suppliers. “Our ZoomLab™ virtual pharmaceutical assistant helps the product developer avoid a time-consuming and costly series of tests. The active ingredient itself does not need to be disclosed here in order to meet confidentiality requirements,” Thorsten Cech explains.

Compacting simulators are ideal for characterizing small material quantities. They allow testing of numerous different compaction profiles, for example sawtooth profiles at constant punch speed. “This is an immense advantage when the active ingredient is only available in small quantities or is very expensive,” Bruno Leclercq, Business Development Manager at MEDELPHARM, explains.

Quality by Design significantly improves the development process

In recent years, Quality by Design has been the “game changer” in terms of raw material selection and the search for the optimum formulation, says Thorsten Cech. “Manufacturing a product with as little variability as possible is of the utmost importance,” he emphasizes. It is therefore necessary to define which process parameters and excipient properties have an impact on the quality attributes of the finished tablet. These describe the design space within which drug quality remains constant and is not subject to any major fluctuations, meaning that consistently high quality is guaranteed over the long term. So-called Design of Experiments is used to investigate any variability. The individual process- and product-relevant factors are examined during this process, and varied independently of one another in order to determine their effect on the target variable and to derive a comprehensive cause-effect model. From this, it is possible to determine whether the intended targets are achievable or whether certain targets are contradictory. It is also important to minimize potential problems in advance, for example through a change of supplier, a change of production location or similar.

ABOUT BASF

BASF is one of the world’s leading manufacturers of excipients for the pharmaceutical industry. A comprehensive portfolio addresses the needs of oral, dermal and parenteral applications. Solubilizers are also provided to improve the solubility and bioavailability of active ingredients. The portfolio is complemented by products specifically for biopharma applications. For tablet formulation purposes, BASF provides binders, fillers, disintegrants, lubricants and coprocessed all-in-one products like Kollitab™ DC 87 L, which was launched in 2021.

The European Application Lab in Ludwigshafen is well equipped and features, for example, KORSCH-MEDELPHARM R&D equipment, XP 1 and XL 100 tablet presses and the STYL’One Evo compaction simulator. It is used both for the company’s own trials and for customer consultancy purposes.

BASF-developed ZoomLab™ software with its algorithm actively assists pharmaceutical companies with selection of excipients and starting formulations.

Active Formulation Support

Dr. Friederike Gütter is a pharmacist and process expert at the KORSCH INNOVATION CENTER in Berlin, and she explains the conditions that need to be met to enable KORSCH to provide effective formulation development support. “The customer needs to know exactly what their starting point and objective are – we find the path in between for them. Either the entire process or in the form of assistance with specific challenges.” This means that the customer not only needs to know the relevant data for the active ingredients, but also all the parameters of the desired tablet.

Process parameters impact on formulation

It is important to keep an eye on all process parameters during the formulation phase at all times – especially those relating to scalability, as material properties and behavior can easily change at larger production volumes. In particular, the powder blend’s flow pattern in the tablet press to be used for subsequent production must be assessed, as different presses offer many different configurations and geometries. Any processes before or after actual tableting, such as, preceding dry or wet granulation or the subsequent final coating, are equally important. For example, the insertion of a granulation step prior to tableting can improve the powder flow properties significantly. However, that requires a large number of process steps, resulting in a more costly and complex process. A strategic partnership with L.B. Bohle enables KORSCH experts to access equipment covering the entire pharmaceutical tablet production process. KORSCH’s innovative tableting technology dovetails with L.B. Bohle’s upstream and downstream processes.
Customers can test their formulations at the L.B. Bohle Technology Center in both batch and continuous process modes and select the best process strategy.

Represented worldwide

If the active pharmaceutical ingredient and excipient properties, the required production process, and the desired product quality attributes do not fit together perfectly, the specialists at the INNOVATION CENTER will find the right compromise to deliver the optimum result. Customers benefit in particular from our experts’ extensive, cross-sector experience. INNOVATION CENTERS can be found worldwide in Germany, France, the United States and India, and they offer a wide range of services: From full formulation and assistance with any problems that arise to just rental of the simulators and R&D presses, a specific solution is always found for each customer.

On the Trail of Solubility

Korbinian Löbmann (left), Chief Scientific Officer & Co-founder and **Søren Vinter Søgaard** (right), Scientific Director, **Zerion Pharma**

Innovative, Copenhagen-based startup Zerion Pharma utilizes the equipment and know-how of the MEDELPHARM INNOVATION CENTER (called “Science Lab” in France) for product development purposes. KORSCH:MAGAZINE spoke with Zerion Pharma’s scientific director, Søren Vinter Søgaard, and the company’s co-founder and CSO, Korbinian Löbmann.

KORSCH:MAGAZINE: What is Zerion Pharma, and why was it established?
Korbinian Löbmann: Zerion Pharma is a startup founded in early 2019 based on a decade of research at the University of Copenhagen to solve one of the most important problems in the pharmaceutical industry: Poor drug solubility. The screening of new drug molecules targets specific binding sites in receptors that are lipophilic or hydrophobic. The result is that more than 80 to 90 percent of new drugs have poor solubility. However, solubility is a prerequisite for being absorbed by the body when given orally. There is great potential and opportunity here. Whilst there are some technologies available to address poor drug solubility, many APIs are still facing challenges and potentially do not reach the market because they were insoluble. Here Zerion Pharma has pioneered a technology to deal with this problem.

KORSCH:MAGAZINE: And what is your approach to solving the problem?
Søren Vinter Søgaard: We have developed a new formulation approach called the Dispersome® technology. This is an amorphous mixture of API with the protein beta-lactoglobulin, a purified protein obtained from the whey by-product during cheesemaking. We are developing this technology including an innovative class of highly effective excipients for poorly soluble small molecules in stable amorphous formulations with high API content. Here, we achieve up to 50 times higher solubility than conventional approaches involving crystalline materials.

KORSCH:MAGAZINE: How do you go about it?
Korbinian Löbmann: The objective is to come to market with a product as quickly as possible. We are currently developing an improved generic product in which one unit replaces what used to be four tablets in the originator product. This is achieved by the solubility enhancing effect of the Dispersome® technology, which allows a reduction of the amount of API while keeping the formulation bioequivalent. This is a clear benefit for the patient and shows the potential behind Zerion Pharma’s technology.

KORSCH:MAGAZINE: How do you go about developing the tablet?
Søren Vinter Søgaard: As we don’t have all the needed equipment on site, we perform tests on the simulator at the Science Lab in Lyon on a regular basis. I was already familiar with the STYL’One Evo, so I was able to create the test protocols, send the material to the lab, and then evaluate the results without being on site myself.

KORSCH:MAGAZINE: Why did you use a simulator?
Søren Vinter Søgaard: The advantage of the simulator is that we only need small amounts of the API for the tests, while testing at real production speed. It also offers extensive data acquisition and valuable analysis tools for evaluation purposes.

KORSCH:MAGAZINE: How is your working relationship with the staff in the Science Lab?
Søren Vinter Søgaard: Very good! They not only execute our protocols, but also provide additional constructive feedback and helpful comments. This has resulted in productive dialog.

KORSCH:MAGAZINE: What happens next?
Korbinian Löbmann: In order to test flowability and material behavior under production conditions, further trials may be conducted on the rotary presses at the KORSCH INNOVATION CENTER in Berlin. With our first product we are planning to enter the market in 2026.

KORSCH:MAGAZINE: Thank you very much for the interesting interview and good luck!

From Development Phase to Serial Production

Scale-up is the last step on the way to commercial tablet production.

Once formulation and clinical trial phases have been successfully completed, this final phase involves scaling up to serial production. “When moving from R&D tableting machines to full-scale production machinery, all the relevant parameters that may impact the performance of the developed formulation need to be carefully considered,” explains Johny Bertels, Senior Scientist, Oral Solids Development, Janssen Research & Development within the Janssen Pharmaceutical Companies of Johnson & Johnson. For example, flow behavior can change if larger quantities of material are involved, a fact that only becomes apparent when switching to large rotary presses. Segregation of ingredients is also a common problem that can only be foreseen within a certain range, the expert stresses. What is critical is that changes associated with high-speed production are factored directly into the formulation. This applies, for example, to uniform filling of the die, despite high speeds and centrifugal forces, or a possible change in material behavior as a result of heat generation during high-speed production. The latter can lead to material sticking to the punch.

Johny Bertels
Senior Scientist,
Janssen Research & Development within the **Janssen Pharmaceutical Companies of Johnson & Johnson**

UPSCALING THROUGH “RESCALING”?

When developing new products, it is essential to take account in the design space and anticipate that the products may be manufactured on a different production machine in the future. A study on a simulator helps here: it can specify some process parameters in extensive detail and include factors that vary greatly from machine to machine.

Even if a product was initially developed without such a study, a simulator can still provide valuable services at the time when product transfer is to be actioned. It can determine the necessary settings on the new production machine within a very short time, using little material. This significantly increases the chances that the three validation batches will be handled smoothly and successfully on the new production machine.

Tablets are also subjected to greater mechanical stress during serial production, e.g. during transport between the press and the dedusting system or even in the tablet collection device. This is an important factor to consider, especially for orodispersible (non-coated) tablets. Last but not least, there may also be changes in the API itself. Only a very small amount of the API is produced at the start of the product development phase; later, as API production is increased, the morphology of the API may also change as the synthesis process is enhanced, and this in turn may change its ratios. All this requires special consideration: if necessary, the production process must be adapted or the equipment modified. At worst, the product has to revert back to the development phase, in order for minor modifications to be made to the formulation.

Scale-up phases

Scaling up is a three-phase process: the initial, small-scale formulation development phase involves single punch presses and material volumes of just a few grams. Then – during the pilot phase – a switch is made to rotary presses, and larger material volumes of up to 20 kilograms are processed. Actual production presses are only used during the third phase – with volumes of up to 300 kilograms per batch. “The Oral Solids Development team at the Janssen R&D Beerse site handles all phases up to pilot stage. For commercial manufacturing, we shift pilot processes to production facilities via technical transfer,” Johny Bertels explains. But even during commercial production, quality attributes are continuously monitored in the early years. “We never stop learning new things about the product and processes, even during the production phase,” is how he explains this philosophy. Integrating equipment variability into the design space during formulation is a big help in this regard, Johny Bertels says. If continuous manufacturing is planned instead of batch production, the last scale-up phase after the pilot phase is omitted. Final product development steps are actioned on the production machinery. Here, however, it is particularly important that the formulation retains its stability in the face of speed changes, Johny Bertels emphasizes, as the production speed of the tablet press varies depending on material inflow.

Simulators mean fewer test runs

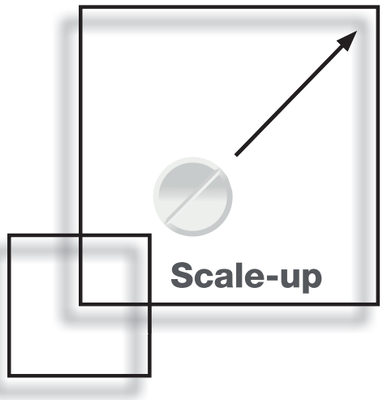
A wide range of compression behavior tests, including precompression force and production speed, can be carried out very early in the development process with the aid of compaction simulators. These tests provide accurate results that are representative of large tablet presses. “Although simulators cannot replace the pilot phase with a rotary tablet press, they do reduce the number of test runs required for the pilot and production phases,” Bruno Leclercq, Business Development Manager at MEDELPHARM, explains. The benefits include significant savings of time and materials during the development process. Multilayer and core-coated tablets are also easier to develop using simulators. This represents an enhancement, because in the past this

Final product development steps are actioned on the production machinery.

was time-consuming and only feasible in production sized machines. “In the past,” Johny Bertels recounts, “tableting was considered an art, where experience and intuition were the key factors. Nowadays it is a high-precision, scientifically-based process, thanks to state-of-the-art software and tableting equipment.”

Faster product development in the future

Comprehensive characterization of the API is becoming increasingly important. Its mechanical properties are investigated and defined even more systematically, leading to a more precise formulation. Improved computing power, the use of artificial intelligence or computer simulations such as FEM (Finite Element Modeling) also help to include and interlink more data. This minimizes trial-and-error testing and enables specific formulations to be developed more quickly. “But it will always be necessary to manufacture tablets in order to analyze them,” is how Johny Bertels sums up the product development future.



KORSCH-MEDELPHARM offers the right equipment for every phase of the product development process.

Commercial production on the XL 400[4]

capacity up to 1,000 kg

Technology transfer to planned production press X 3

capacity up to 300 kg

Pilot phase on a laboratory rotary press XL 100

capacity up to 20 kg

capacity up to 300 g

Formulation development on a small scale on the XP 1 eccentric press or the STYL’One Evo simulator

R&D Meets Production

Product development of solid dosage forms involves two phases, during which R&D and production go hand in hand.

Firstly, when preparing clinical batches, i.e. the first GMP-compliant production (Good Manufacturing Practice) of a new product which can help with final product development optimization. Secondly, when troubleshooting problems that arise either during the preparation of clinical batches or during industrial production. This often requires a return to the R&D level to analyze and solve any errors.

The right GMP tablet press for every clinical production phase

In order to be approved, pharmaceuticals undergo various test phases. Once the actual active ingredient has been developed and tested in vitro – under laboratory conditions – for its effects and possible toxicity, this is followed by in-vivo tests in living organisms. During phase 1 of the clinical trials, the active ingredient is formulated for the first time and tested for tolerability in a small group of healthy volunteers. During phase 2, the group of test subjects increases to as many as 1,000 sick patients, in whom the effects and correct dosage of the drug is researched over a short period of time. Finally, the effects and any adverse drug reactions are tested on a larger group of patients over a longer period of time during phase 3.

“It should be emphasized that all KORSCH R&D presses meet GMP standards,” says Dr. Friederike Gütter, pharmacist and process expert at the KORSCH INNOVATION CENTER. This applies to both machine design

X 3 – single and double layer tablet press for medium-sized batches.

Production overview in the operating menu of the KORSCH X 3

and data integrity. Complete, secure and non-manipulable data recording is fundamental to the development of new pharmaceutical products and to their production for clinical samples. All measured data as well as any machine adjustments and events are logged in a complete audit trail. The customer can select, analyze and utilize the data relevant to them or to the inspection authorities from the extensive quantity of data available.

Even the smallest press, the XP 1, on which settings can also be changed manually, enables every process parameter to be automatically logged and stored, the expert explains. This small eccentric press is particularly suitable for phase 1, as it can be equipped not only for research involving measurements of displacement and press force data, but also for small-scale production under GMP conditions. It can also be used for early sample tablet production for marketing purposes.

The XL 100, as the smallest KORSCH rotary press with press force control and optional single sorting, is ideal for phase 2 operations. The X 3 is suitable for the larger production quantities (of bi-layer tablets as well) required in phase 3. Should an advanced tablet form (tab-in-tab) be used for a double-blind study, the STYL'One Evo for small quantities or an XL 400[4] MFP with core inserter for larger quantities are the appropriate solutions.

Troubleshooting and first aid

The production of clinical batches can also serve as a first step towards scale-up and process optimization. The INNOVATION CENTER experts assist with active troubleshooting when problems arise during clinical production as well as in the scale-up phase. "The fact that difficulties can arise here is normal and has nothing to do with formulation failures or errors during the development of clinical batches," Lennart Vedder, pharmaceutical engineer at KORSCH, explains. The most complex issue is certainly material flow, says the expert, because the flow behavior of the APIs and excipients or dwell time in the feeder, for example, can change depending on production volume or production speed. Temperature changes also have an effect on material behavior and therefore on outcomes. It is therefore often helpful to reproduce and analyze problems that occur on production machinery on smaller R&D machines. In view of high material costs, troubleshooting and rectification involving the use of simulators saves valuable time and money.

INNOVATION CENTER – KNOW-HOW AND SUPPORT FOR TABLET MANUFACTURERS

The specialists at the INNOVATION CENTER offer tablet manufacturers valuable product development and process optimization assistance. Not only do they have extensive and, above all, cross-industry expertise, but they can also draw on all tablet presses from the KORSCH-MEDELPHARM R&D product portfolio. Given this concentrated know-how, they provide pharmaceutical companies with an excellent level of development support, both when optimizing their formulations and in the event of problems occurring during production. This is because even minor changes to the parameters on the machines often have a major impact. Compared to in-house development, outsourcing to the INNOVATION CENTER not only frees up capacity, but also saves valuable time – and time to market is significantly reduced.

Troubleshooting with the simulator

The STYL'One Evo compaction simulator is ideal for simulating and eliminating a wide range of problems. Given its precise measurements and convenient evaluation options using the integrated analysis software, it is not only user-friendly but also highly efficient. An actual practical example, according to Lennart Vedder, was a bi-layer tablet, the halves of which keep on splitting apart after the pressing process. With the help of the simulator, the expert found out that a formulation component of the tablet exhibited plastic behavior. He therefore had to reduce the press force, as the bond was already formed at low force – and became unstable again, if the force was too high.

New solutions for more accurate process simulation are also being constantly developed. For example, in order to simulate the rising temperatures of a rotary press operating for hours at a time, KORSCH's collaborative partner MEDELPHARM is now developing heatable parts to be incorporated in its STYL'One Evo production simulator.

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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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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

Information is Based on Data and Knowledge is Based on Information

The software for KORSCH-MEDELPHARM simulators and R&D tablet presses collects and analyzes extensive quantities of data.

Software developers, process engineers, and customers jointly determine in advance what information is relevant for developing and manufacturing a specific product and what should be recorded.

Data plays an important role throughout the life cycle of a pharmaceutical product. All product properties must be determined and backed up with reliable figures, even at the first stage of product development – active ingredient characterization. “Formulation is also based on data: compression force, breaking strength and ejection force are just some of the parameters used to determine the design space for the formulation,” Adrien Pelloux, Application Lab Manager at MEDELPHARM, explains. And even for products that are already on the market, a database is useful for identifying divergences to ensure batch consistency. Data also proves how changes, e.g. a new production facility or a change of supplier, impact on processes.

Measurements and data acquisition

“We specify the appropriate sensors and their optimum positioning together with the machine designers, in order to avoid the mechanical malfunctions that can occur as a result of high-speed compression, for example,” is how Guillaume Tardy, System Project Manager at MEDELPHARM, explains next steps in the software development procedure. The sensors need to provide appropriate signals for the acquisition and processing of high-frequency data. This can involve different types of signals: digital process signals, for example, show which process is currently being executed. Analog signals typically provide information on force, displacement or torque, and communication signals provide information on the position of a drive mechanism, for example. The objective is to take extensive and extremely accurate measurements that are not distorted or altered by external influences, such as electrical noise or mechanical vibrations.

“The signal’s waveform itself can also provide information,” Adrien Pelloux relates from practical experience. For example, the waveform of the ejection signal can be used to identify faults in the process, such as when the tablet sticks to the die and the formulation requires additional lubricants.

Data analysis at the user’s location

The R&D software provides an extensive database that allows the user to determine the design space of a formulation, including parameters such as the main and precompression forces, the compression zone in the die and machine output. This enables the issue of whether the tablets exhibit the properties specified in the marketing authorization to be ascertained. Arno Rathmann, head of automation at KORSCH, elaborates: “Our software enables the scientists to convert this data into usable information, on which the right formulation or process execution decisions are based. “ In terms of safety, quality and legal compliance, the R&D software naturally meets the necessary requirements in all areas, software developer Guillaume Tardy affirms, citing standards such as GMP, ALCOA, ICH or FDA 21 CFR Part 11, among others. (More details on this in the info box.)

Continuous enhancement

The machine software is being continuously enhanced and expanded in order to adapt it to increasing requirements. For example, work is currently underway to expand communication capability to include additional devices. “Our main focus is also on constantly improving user benefits and usability,” says Guillaume Tardy. This ensures that the customer can also fully evaluate and use the data collected. The user learns what extensive capabilities the software offers during an intensive training course that comes with every machine sold. New data is also constantly being collected to meet specific needs on the customer side – such as analysis of the impact of temperature on product behavior. “Here, feedback from our customers and from users in the scientific community is very important for our work,” says Arno Rathmann, emphasizing the importance of feedback from the field.

The R&D software offers extensive data material such as compression curves for comparing different products.

CONFORMITY AND STANDARDS

The software for KORSCH-MEDELPHARM’s simulators and R&D tablet presses is developed in accordance with the GAMP 5 standard (Good Automated Manufacturing Practice). Using the R&D software complies with International Conference on Harmonization (ICH) guidelines for Quality by Design, Quality Risk Management and Lifecycle Management: during product development trials, users can easily determine the quality target profile of their products (QTPP) and the critical process parameters (CPP) for tableting.

Furthermore, the software complies with 21 CFR Part 11 for the USA and EU Annex 11 for Europe. The specifications of the ALCOA principle are complied with in relation to the processing of critical information and data integrity. ALCOA stands for Attributable (who generated the data?), Legible (data can be read and stored correctly at any time during the software life cycle), Contemporaneous (time recording of the data), Original (work with original source or certified copy) and Accurate (data corresponds to reality and is processed correctly).

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KORSCH

KORSCH AG – Berlin
Breitenbachstraße 1
13509 Berlin
Germany
Phone: +49 30 43576-0
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 Singapore Pte. Ltd.
1 Scotts Road, 21-10 Shaw Center
228208 Singapore
Singapore
Phone: +49 30 43576-300
E-mail: info@korschsingapore.com

KORSCH India Private Limited
Plot No: M24, TSIIC, Medical Device Park
Adjacent to ORR Exit No.4, Industrial Area Bollarum,
Sultanpur, Hyderabad, 502319, Telangana State, India
Phone: +91 80 0899 7035
E-mail: info@korschindia.com

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