The Customer Magazine by Harro Höfliger Edition 1 |October 2015

Processing of RackPacks[®]

Roche Diagnostics relies on turnkey equipment



Taking medication made easy!

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ear Sir or Madam, Dear business associates, I am delighted that you have opened our new customer magazine. Be "Harro's" guest once again - this time not as a visitor to our company, but as a reader. Because not everyone can stop by in person on a regular basis, we will present useful and interesting facts twice a year in our customer magazine HARRO.

In a thoughtful and hopefully attractive fashion, we introduce to you some of our most interesting machine systems in their practical applications. We also want to inform you about upcoming events and presentation series, and provide news from our company and country. Keeping in touch with you in this way is a matter close to my heart. If you are already somewhat familiar with us, you know that listening is one of our recipes for success. This also applies to our magazine. Therefore, if you have any suggestions, criticism or questions, we look forward to receiving your message at harro.magazine@hoefliger.com.

Incidentally, there is a good reason to explain how we chose to name our magazine. In all of the international language areas, only very few individuals can pronounce the name "Höfliger" without a problem. When I introduce myself in person, often I am asked "Harro ... who?". Therefore, our editorial team made a virtue out of necessity, and the magazine received the short and concise name HARRO.

I hope you find this an interesting read!

Warm regards, Harro Höfliger

HARRO Edition 1

Driven by Knowledge

With our own training center, the Harro Höfliger Academy is now an ideal platform for in-house training and continuing education at our company headquarters in Allmersbach im Tal. The modern facility offers the best conditions for instruction in metalworking, electrical as well as control technology skills for mechanical engineering. Since 1981, intensive training has been offered at Harro Höfliger. A total of 300 trainees have successfully completed their vocational training. Today, around 60 percent of former trainees continue to work as professionals in our company.



Service for the Swiss

What began as a joint project on January 3, 2005 between Harro Höfliger and Uhlmann Pac-Systeme, is today the successful Swiss branch office located in Arlesheim. On the ten-year anniversary, Managing Director Roberto Zürcher and Office Manager Manuela Hummel are still on board and have been there since day one. A total of eight team members tend to 110 Uhlmann machines and 60 Harro Höfliger lines in Switzerland – this includes consulting, technical customer service and retrofitting. The experts of the Swiss team support the local pharmaceutical companies in all matters relating to the packaging process.



nn Höfliger Schweiz team from left to right: Jörg Gentner Roberto Zürcher, Udo Lorenz, Manuela Hummel, Marc Hartzer, Jan Paetzold, Markus Haener, Marco Specker and Dr. Sven Borchert



On site in the MENA region

In the Middle East as well as in North Africa, the pharmaceutical industry is on a growth trajectory, which was an excellent foundation for the launch of Harro Höfliger Mena S.a.r.l in Tunis. Besides installation and production support, the company's task is the development of an efficient sales and after-sales service program in the MENA region (Middle East & North Africa). The team has already recorded sales success in Egypt, Saudi Arabia, Algeria, Tunisia and Iran. The Modu-C capsule filling machine is a success story. But first orders for winding machines and projects for the inhalation, assembly and adhesive bandage areas are also on record.

"We set the standard in Remote Service"

Once production is up and running, it has to be efficient. In order to keep downtime to a minimum, Harro Höfliger developed a Service Portal together with the partner companies of Excellence United. Jackson Heslop, Customer Service Director at Harro Höfliger, discusses the benefits of this system, and how it works.

Mr. Heslop, what was the reason for the development of the Excellence **United Service Portal?**

Jackson Heslop: Our customers' desire for faster assistance when service is required. Together with our customers, we identified the need in a workshop and laid the foundation for a new standard in Remote Service.

Can you clarify this with an example?

Imagine a line that produces several thousands of packages daily, and it stops. Our Service Portal can then be directly activated via the operator panel of the machine and provides a multi-media "Conference Center". The operator or maintenance technician connects directly with the machine manufacturer. There are several tools available. For example, a "Chat Board" where messages can be exchanged, a "White Board" for the transfer of photos and drawings, and a webcam, which transmits detailed pictures of the fault location. In real-time communication via headset, possible solutions can be found quickly. In most cases, sending a service technician is unnecessary. This saves the customer time and money.

Does the Service Portal also provide preventive support?

Yes, we wanted a tool that can be used prior to a malfunction. A maintenance manager provides instructions for preventive maintenance and supports the planning of maintenance intervals. In addition, with a few clicks the operator can access the machine documentation or open the integrated spare parts catalog.



"The Service Portal simplifies many processes."

Jackson Heslop, Customer Service Director. Harro Höfliger

Does the operator need special training for the Service Portal? The user interface is intuitive, so extensive training is not necessary. The service request is supposed to be a quick and easy way to contact the service specialists of the machine manufacturer.

What about security when transmitting data?

The connection to the line manufacturer is a reverse link, which means the machine supplier can connect only after an operator-side service request. This connection can be terminated at any time by the operator. The system is based on an SSL-encrypted client-server connection similar to online banking.

Where is the service portal already in use?

Today, roughly 80 of our lines are in operation worldwide with the Excellence United Service Portal. We have already answered numerous service requests, and gathered experience to further improve the Portal.

More information is available in video about the Excellence United Service Portal www.hoefliger.com



Ten plus points

High performance in design, application, versatility and usability: The continuous motion cartoning machine MKC celebrated a very strong premiere at the FachPack 2015 as a part of Harro Höfliger's standard portfolio. Here are the ten most important highlights of the new versatile cartoner.

Accuracy

The cartons are transported carefully with a carrier chain system. The 4-finger support guarantees precise and fixed positioning of the carton during the packaging process. Surface damage is strictly avoided, even when processing refined, glossy, matt or sensitive cartons.

Best accessibility

The operator has all critical functions within easy reach, and under control: The continuous product insertion from behind, the folding carton magazine positioned at an ergonomic height, the pivoting folding unit and extendable drawer and pre-insertion. All these features offer the best operating comfort and efficiency.

Patented

The patented rotary carton-withdrawal system with a 4-fold rotor and active carton opening provides for reliable removal of the carton from the magazine and transfer into the chain.



Wide range of applications

The cartoner can be equipped with different feeding systems. Customer specific solutions can be added to the standard modules. This enables the packaging of bottles, bags, tubes, blisters, vials, patches and more. All standard carton closure types and special closures are possible. Labeling systems, leaflet folding and insertion equipment, booklet and brochure dispensers complete the machine's broad versatility.



The continuous motion of the 5-inch version achieves 250 cartons per minute. At 7.5 inches, it achieves 200 — smoothly and safely.

Fast change-over

The machine's design and configuration provide for fast format changeovers. This applies to both the mechanical as well as the electronic level. The format parameters are centrally administered and position indicators ensure reproducible format changeovers. There are very few format parts, and changeovers can be carried out with almost no tools.

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Intriguing design

The cartoner is designed in modern balcony construction — in accordance with GMP and applicable safety regulations. The ergonomic machine design with smooth surfaces sets new standards.



Thanks to the modular design in the product feed area with separate components for product chain, product insertion and folding carton closure, the machine has a very flexible configuration and can be easily integrated into a wide variety of packaging lines.



Total control

On the newly designed, movable 17.3" color display with touch function, the operator can constantly observe and monitor all parameters. A standard industrial PC allows for easy integration of marking and inspection systems into the user interface.



Best materials

The guarding completely consists of single pane safety glass. This ensures an optimal view of the work process and GMP-compliant cleaning. In addition, the material does not build up static charges and is scratch resistant.



started right away"

Ten different machines on 650 square meters under one central control system combined and handed over turnkey ready by Harro Höfliger: Two years of intensive development and cooperation were required for this enormous line for the processing of RackPacks® at Roche Diagnostics in Mannheim. Rainer Wäsch, Qualification Director Site Engineering at Roche in a dialogue about the challenges and experiences of this project.

> Rainer Wäsch, Qualification **Director Site** Engineering Mannheim as well as project leader for this assembly and packaging line



What do you consider special about this line?

Rainer Wäsch: First, the impressive size. It covers an area of about 650 square meters. Then, of course the outstanding packaging concept, which we implemented in this line. It is capable of processing a total of 65 products with four different formats. The line's output is also rather impressive: 150 cycles in the finishing area and up to 100 cycles per minute in the cartoning section.

Were there any particular challenges during implementation? Yes, sure! We had already been using two older lines for this product. It was necessary to analyze the weak points of these machines and of the production process, and to develop

solutions for a better performance. The line consists of standard and specialty machines from Harro Höfliger as well as machines from other manufacturers. All these machines had to be connected to work together. In addition, we wanted to combine two different inserts with two different RackPacks on this new line - naturally at the highest possible output. Plus, after installation, we immediately wanted to go into production without extensive adjustment and training activities.

How was the turnkey handover achieved?

Harro Höfliger installed the complete line in its technology center in Satteldorf and reproduced our infrastructure. This ensured a reliable operation right from the beginning under real conditions at our premises. In doing so, the qualification phase of our operating staff could be extremely shortened - and unpleasant surprises avoided. Two of our teams travelled to Satteldorf in order to qualify the line on site, to document its disassembly and to provide guidance and support later during installation at our premises.

"I particularly value the open and clear communication with Harro Höfliger – and I am always astonished about Harro Höfliger's high level of technical problem solving expertise."

> Rainer Wäsch. **Qualification Director Site Engineering** at Roche in Mannheim

How was the cooperation with Harro Höfliger?

We have been cooperating on this project for a total of two Despite the line's high complexity we are on target. Of course, years. Of course there are points of friction when developing critical moments occurred again and again in our given time and implementing such a huge packaging line. This is why frame. But the milestones have been reached and we could we initiated a so-called steering committee already at the start up the line on schedule in July this year. beginning of the project. This committee meets once a month and develops solutions for issues. All members have What do you value most about the company Harro Höfliger? always been well-prepared and the discussions were con-This is easy to answer: the open and clear communication. structive, goal-oriented and open.

What specifications do you follow when developing such a project?

We follow the project management approach, which is specified by Roche. Milestones are the developed design of the line with the final detailed design review, the pre-Factory Acceptance Test (pre-FAT), the FAT and SAT (Site Acceptance Test) as well as qualification with IQ (Installation Qualification) and OQ (Operational Qualification). This is followed by the documented dismantling and installation, an acceptance run and finally the validation.



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Are you satisfied with the course of the project?

Nothing was withheld or sugarcoated. All stumbling blocks were put on the table and discussed. Moreover, I am always astonished about Harro Höfliger's high level of technical problem solving expertise. Even when faced with difficult tasks, the engineers find ways to reach the goal. Areas needing improvement were quickly addressed and resolved. All project members have been very flexible and open to our wishes.



Four different folding cartons with up to 65 combinations of RackPacks

XStraw[®] is the name of a new dosage form using a drinking straw. The straw, which is pre-filled with a drug, enables a more comfortable intake for children and for patients having difficulty swallowing. The image illustrates the benefits and how it works.

Taking medication made easy!

Patient

This new drug dosage form has been particularly developed for application in pediatrics and geriatrics and guarantees simple and intuitive intake. This method is especially well accepted by children, since "playful" drinking ensures safe administration.

Straw with protective cap

The drinking straw enables comfortable intake of the drug with water, fruit juice, tea or other beverages. A closing cap and the packing protect the drug during transport and storage. This new drug dosage form has been developed for one-time use: There is no cleaning required and hygienic application is guaranteed.

Pellets

The filling technology developed by Harro Höfliger ensures precise dosing of the drug. For active ingredients with a bitter or unpleasant taste, pellet coating provides taste-masking properties.



In the straw, the pellets are dispersed in the liquid and transported that way

Filter

The filter is located at the lower end of the drinking straw and prevents leakage or loss of the medication. However it is permeable for the liquid. It moves upward when suction is applied and remains in the upper position, indicating complete drug consumption to the user or caregiver — a practical control function.

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Cross-sectional view of a pellet with multi-layer coating

DS Technology GmbH

This entity markets the new oral drug dosage form XStraw[®]. In the background are the cooperating partners Glatt, Raumedic and Harro Höfliger. Experienced experts who offer support in the laboratory and the clinical stage, give helpful tips during product launch and are system partners during installation and implementation of the entire production line on-site at the customer's location. All services and more details can be found at www.d-s.technology

The three XStraw® partners

Glatt: Development and production of pellets and granules, pharmaceutical contract manufacturing, development and production of granulation and fluid bed systems.

Raumedic: Extrusion of drinking straws, injection molding of caps, customized development, production and delivery of individual components for filling in cleanrooms.

Harro Höfliger: Delivery of filling and packaging lines, development of new technologies, competence in dosing and packaging technology, especially in the pharmaceutical industry, worldwide service. The dry-powder inhaler "Dreamboat" with cartridges for individual application

Inhaling insulin instead of injecting

Powder inhalers help diabetics: Harro Höfliger designed and built two filling and assembly systems for dry-powder inhalation systems for the US based MannKind Corporation. MannKind is a biopharmaceutical company, focusing on the development of therapeutic products for the treatment of diabetes and cancer, with technologies that allow pulmonary absorption of drugs (through the lungs).

Harro Höfliger (right) and Al Mann (centre) during the visit to the production facility aunch in the US

insulin. In about 60 clinical trials involving more than 5,300 volunteers, MannKind was able to show that AFREZZA[®] can be used to control high blood sugar in adults with type 1 and type 2 diabetes. After approval by the U.S. Food and Drug Administration in 2014, the drug has been introduced to the market in 2015. The therapeutic system consists of a dry powder inhaler called "Dreamboat" and a powder filled cartridge. This cartridge is inserted into the inhaler for a singledose application, and discarded by the patient after the inhalation process. The inhaler is re-used over a 15 day period. Various amounts of insulin can be dosed using cartridges containing different amounts of powder. The cartridge lids are color coded according to strength, in blue, green and vellow.

The cartridges contain powder particles loaded with insulin. By inhaling the powder, the insulin passes into the bloodstream through the patient's lungs. MannKind utilizes a Technosphere® powder formulation which is based on an organic molecule called Fumaryl Diketopiperazine (FDKP). The unique features of FDKP is its ability to form Technosphere® particles, its rapid dissolution in the lung and its elimination from the body without undergoing metabolism.



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FREZZA® is a new, fast-acting, inhaled

"Especially for development projects like our production lines, in which countless influencing factors have to be considered, the solid project management provided by Harro Höfliger is indispensable."

Jürgen A. Martens, **Corporate Vice President of Operations** and Chief Operating Officer of MannKind Corporation

The MannKind Powder Filling and Assembly Machine is based on the Harro Höfliger FLP-200 machine platform (Filling machine, Lengthwise transport, Pallet, 200 mm pitch). In this machine platform, a tray

serves as the transport medium. At the end of the machine, after cleaning and complete product removal, the tray is returned to the start of the process.

Vibrating conveyors feed the cartridges and corresponding lids into the line. A Pick & Place system positions each cartridge in the trays. A socalled 'walking beam' transports the trays from station to station. Two vacuum drum filler systems provide high-precision dosing of the powder into the cartridges.

Every dosing system is equipped with an AMV-sensor (Advanced Mass Verification), for one hundred percent weight verification of the powder dosing. That means the AMV-sensor verifies 400 individual doses of powder per minute. In the event of under-dosing or over-dosing, the machine sorts out the affected cartridge and moves it to the fail part ejection area.

The filled cartridges are sealed with color-specific lids and subsequently coded with laser markings. Every machine work step is followed by a control step, which checks the previous operation. Correctly filled cartridges that have been fully closed with the proper colored lid and have received a legible LOT-coding, are moved to the pass part discharge of the machine.

From there, the cartridges are transported into an intermediate storage. From there into an automatic blister machine. Fifteen (3x5) Cartridges per blister

"The courage to explore new avenues, combined with the Swabian perseverance to see things through to the end, distinguishes Harro Höfliger and makes them stand out."

Jürgen A. Martens, Corporate Vice President of Operations and Chief Operating Officer of MannKind Corporation

are packaged at a time. Already three machines were delivered and are running smoothly. The first machine was used in the production of the required sample quantities during clinical development phase then converted to supply commercial product.



The commissioned production line meets the following requirements:

- Powder dosing in 400 cartridges/min.
- Filling weights: 3 15 mg per cartridge
- Filling tolerance max. +/-5%
- 100% verification of each powder dose
- Fitting the lid on 400 cartridges/min.
- Cartridge color verification (green, blue, yellow according to strength)
- Laser marking of cartridges and crosscheck of markings
- Intermediate storage of at least 3,200 filled and assembled cartridges for approximately 8 minutes of accumulation
- Filling machine under laminar flow





Patch with a Holiday fragrance heals abdominal pain

Harro Höfliger manufactures traditional patches for the Shanxi Yabao Pharmaceutical Group

Even the unopened folding carton entices with a scent of cinnamon and anise. Then there is the content, which carries an aroma of spicy gingerbread. This product enjoys great popularity in China. The patch is coated with a herbal paste and helps infants and small children who suffer from abdominal pain and diarrhea. It is produced and distributed by the Shanxi Yabao Pharmaceutical Group Co., Ltd., headquartered in the Chinese Shanxi province, and is manufactured on a Packing and Four-Side Sealing Machine from Harro Höfliger.

The so-called "gingerbread" patch has been available in China since 1992. The Yabao patch is readily available in pharmacies and costs about 1 Euro each. At first it was handmade. Today, about 150 million pieces are sold per year -a magnitude that can no longer be manufactured by hand but requires automated machine processing.



A look at patch production at the Shanxi Yabao Pharmaceutical Group in China



Re-use without waste: The remaining punched-out grid is returned to the extruder

Non-slip: Application of protective film

Properly shaped: Processing by means of a rotary die-cutter

Flashback: In 2007, Harro Höfliger received a development contract from Yabao. For two years, possible ways to process active ingredient paste were tested. The first attempt was the vertical slicing of an active ingredient strand of paste with a hot blade. However, this method failed at high speeds, due to the tough and sticky texture. Not until 2009, were the developers able to find a stable process: The paste was rolled out flat and the appropriate quantity applied to the patch carrier film using a punching process. This method was presented to the decision makers at Yabao who then ordered a PMK Patch and Pouch Packaging Machine. In 2010 it passed the Factory Acceptance Test with the customer present.

Technology in detail. The line's centerpiece is the continuous packing process with the integrated four-side sealing machine PMK 300. It receives the flattened active ingredient mass from the upstream extruder. The paste is processed on a carrier material in three adjoining webs, with a width of about five centimeters each.

Using a method specifically developed by Harro Höfliger, the machine punches out round active ingredient slices. The punch and compressed air shape the sticky paste properly. A cooled climate area, which is kept at a constant temperature, prevents the punch from becoming contaminated. Thanks to the cooled

"The excellent service and prompt support by the Chinese as well as the German Harro Höfliger team on site in China has convinced us, and led us to order additional machines."

> Ren Wuxian, President, Shanxi Yabao Pharmaceutical Group Co., Ltd.

air, the paste is easily removed from the punches and sticking of active ingredient particles is prevented. The remaining active ingredient grid is returned to the extruder for re-use.

The punched out active ingredient slices are placed on two films. The first film prevents moisture, the second film serves as a carrier for the glue which adheres to the skin later. Another protective film is pre-printed and encloses the paste including the adhesive side. Now the patch is packed in a

four-side sealed pouch. The finished patch is applied to a in a light-proof and air-tight pouch – ready for transport to the pre-printed aluminum film and closed by another film from pharmacies. above. An inkjet printing unit applies batch numbers and Since Yabao is very pleased with the automated packaging expiration dates before the completed pouch is conveyed toprocess, another PMK machine was ordered in 2011. To date, wards the cartoner. The cartoning machine processes 200 downstream cartoning has been a manual process, but in cartons per minute. Each carton will contain three patches and 2015 these operations will also be automated. Two more an instruction leaflet. The option with two patches per carton complete lines will follow so that the patches can be will be processed at an output of 250 folding cartons per minproduced on a total of four packaging lines – with automatic cartoners from Harro Höfliger and full wrapping machines ute. Prior to the onward transport, a camera controls the quality and contents of the imprint. Now the patch is sealed from a third party supplier.

The gingerbread patch in TCM

Traditional Chinese Medicine (TCM) relies on alternative healing methods, which have proven effective in the Far East for several thousand years. TCM considers the abdominal region as the vitality and well-being center of the entire body, the navel as one of the most important acupuncture points. It is on the navel, where the so-called "gingerbread patch" is placed. The patch contains a paste made from pure

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Well packed: The pouches on their way to the cartoning machine



"Never change a winning team"

The enterprise Pfizer is investing more than 7 billion US dollars in the research and development of new drugs. The core element of this business model is focusing on human health. In Germany, Pfizer employs more than 2,000 employees at three sites. At the Freiburg plant, Pfizer produces and packages innovative drugs for the global market, now also as contract manufacturers for the filling of hard capsules. Harro Höfliger's contribution is explained in the following interview with Dr. Clemens Stief, Teamleader at Pfizer in Freiburg.



Dr. Stief, what made you decide in favor of the technologies from Harro Höfliger?

Pfizer's main requirements were the devel-

opment and production of highly potent drugs and consequently the application and use of containment systems. Guaranteeing the highest level of quality and safety for our employees, and the environment during production, was and is important to us. We knew that the use of a new principle for exposure prevention in the production process involves a certain degree of risk. This is why we decided for a dependable and trustworthy partner who is not afraid to implement new concepts. With Harro Höfliger, we can look back on a long-standing partnership. Together we already implemented several successful projects. In addition to the experience already gained with Harro Höfliger, we were convinced by their innovative technology and pragmatic approach to the containment topic. Especially the patented trolley system which enables the use of a variety of filling media, particularly in the Research and Development area. This concept was well received and contributed to our decision in favor of Harro Höfliger.

Were there any other decision criteria? Of course. Worth mentioning is certainly the trust already gained, the target-oriented cooperation and the fast, simple and uncomplicated communication during the projects. In addition, proximity played a role. This is especially advantageous during the project planning phase.

Production has already started. Does the system meet your requirements?

By entering into contract manufacturing, a strategic move to better utilize our systems, we not only serve Pfizer's requirements but also have to meet the demands of our customers. The containment version of the Modu-C is the first system of its kind, where flexibility, cleaning or batch sizes often play an important role. The capsule filling system Modu-C thus offers exactly the right solution for our production and development requirements. The capability to handle small quantities as well as medium-sized lots at an adequate speed, in addition to high flexibility, makes the Modu-C MS stand out. This system provides safe production, minimized exposure and offers flexible retrofitting. The patented trolley system allows for fast and simple changeovers of the dosing systems. This is a building block for the high degree of flexibility, which we in turn owe our customers.

What, if a service technician is needed?

Our experience has been very positive so far. We can rely on short-term availability, fast response times and an uncomplicated and constructive cooperation. If the worst comes to the worst, the Harro Höfliger technicians provide quick and straightforward support on site and work closely with our employees. Often, a minor problem can guickly be resolved over the phone.

Dr. Stief, you have been working with machines from Harro Höfliger for many years now. Would you decide again for this company?

Before I answer your question I would like to go back a bit: As an advanced development unit with routine production tasks, reliability combined with flexibility (e.g. filling a variety of media into one capsule) is of great interest to us, particularly in the high containment sector. With Harro Höfliger we have found a dependable partner, also for the development of new processes. Each machine supplied to us to date has been further developed on a joint basis. The basic reguirements are always the same: high quality, safety and flexibility, Coming back to your question: Yes, we would again collaborate with Harro Höfliger in keeping with the motto: "Never change a winning team."

Inventing according to plan

The term "innovation" is like a currency: If used carelessly, it becomes worthless. In specialty machine engineering, actual innovations are priceless, since every customer inquiry requires highly individual solutions, which can rarely be pre-engineered. This emphasizes the importance of systematically utilizing this innovative capacity to reliably meet current customer requirements, and to implement future developments, for example, in the pharmaceutical industry.

The award given to Harro Hofliger as the most innovative medium-sized company in 2009 in the TOP-100 competition provided further motivation to introduce innovation management as a staff function. Thus, the research and development process has been geared towards the strengths of Harro Höfliger. The result: ideas from employees, suppliers and customers lead to clear processes, and experts are included based on their specific knowledge.

Our innovation process passes through four phases:

Phase 0: Testing the idea for innovative potential Phase 1: Testing the concept for functional viability Phase 2: Further development of the technology through pilot systems

Phase 3: Implementation of the machine technology in the market



Form meets function: Scetching the disc-filler

HARRO Edition

How does innovation management in specialty machine engineering work?



Asthma patients expect their portable powder inhalers to be as small as possible, but at the same time contain medication for an entire month. One solution is to place the pre-dosed powder portions in small chambers, which are circular or spiral shaped and located on a plastic ring, the so-called disc. The difficulty is often filling all 30 to 60 chambers of the disk as precisely and effectively as possible. The handling and dosing of such powders is an extremely demanding task due to poor flow properties and very small dosing quantities. For this reason, Harro Höfliger has developed the Discfiller in a targeted innovation project. The approach was to minimize the impact of the dosing process on the sensitive powder. First, the relevant market developments were analyzed, followed by brainstorming sessions, which led to the first preliminary tests and construction of a prototype. This culminated in a patent application. Subsequently, consistent development continued with a focus on target customers.

Result: A dosing technology that can be scaled-up and is ready for production. The new Disc-dosing system can accurately fill up to 60 cavities with the desired dose of the inhalation powder within a dosing cycle. The filling level can be adjusted as desired, thus giving pharmaceutical companies more flexibility in formulating their products.

It melts on your tongue!

Oral and buccal film strips offer a great potential for the growing pharmaceutical market, which is expected to grow from 182 billion dollars (in 2013) to 218 billion dollars in the year 2018. For more than 20 years, Harro Höfliger has been known in the market for their well-established machine program for the processing of web materials containing active ingredients.

> Oral (ODF) and buccal (MBF) film strips represent one of the highly promising alternatives to medication intake: once placed on your tongue or inside your cheek, they dissolve quickly and distribute the active ingredient. This offers great advantages. The patient's fear of swallowing pills is eliminated. Also, gastro-intestinal side effects can be reduced. Finally, the drug's effectiveness is increased. Once in contact with saliva, the active incredient is released and transferred via the oral mucosa to the body within a very short time - entirely without chewing or the addition of water. MBF are suitable for higher doses and release of the active ingredient is time delayed.

Tablets, capsules and the like have been the established oral drug dosage forms for many years. However, the efficiency to release the active ingredient may be negatively affected. Patients may find haptics, taste or tablet size unpleasant, or have difficulty swallowing. Even fast dissolving tablets don't completely eliminate these disadvantages, and they are difficult to handle.

Dosing sizes

A typical ODF is rectangular and between 2 and 10 square centimeters in size. If necessary, the thickness of the carrier material can be increased. MBFs normally have round shapes in order to improve comfort of the MBF within the mouth. The drug quantity for film strips is limited by its polymer matrix and the strip thickness. As a rule, the upper limit of the drug concentration typically corresponds to 30 percent of the total

weight. The dimensions of the film strip can be adapted to the desired dosage.

As with tablets and capsules, the ODF packaging must generally ensure both safe usage of the product as well as protection until consumption. Ambient environment, conversion and packaging must be controlled in one work step. Since all materials must be protected against moisture and oxygen, the integrity of the seal must be ensured. Also, package design, lengthy storage periods, good printability and economic costs must be taken into account. Opening and use of the pouches should be intuitive, and the dose itself must be clearly recognizable.

The production of ODF and MBF is based on transdermal patch technology for which the typical casting production principle for films is applied. The aqueous polymer formulation is printed or sprayed onto a substrate, then dried. It is also possible to apply a taste-masking coating. The finished film polymer matrix is converted into strips and packed into individual pouches. Optional production methods are melt extrusion, extrusion of an amorphous solid dispersion, and rolling or printing methods.

During **development** of new products on a laboratory scale, factors such as production, conversion and packaging procedures must be considered up front to enable a smooth scale-up to production level. During high machine speeds, effects can occur which cannot be foreseen during the laboratory stage. This is why the Proof-of-Principle testing is often required in order to identify the impact of different film types and process steps. After analysis and gualification of the aqueous polymer formulation, further questions have to be clarified. For example, how surface and dissolution speed of the film strip influence release of the active ingredient, or which layer application process complies with the exact requirements for thickness, surface properties or weight of the film strip.



Precise and fixed transfer of the ODF to the packaging material



Precision during Iongitudinal cutting and spreading

Conclusion

ODF and MBF offer huge potential for the pharmaceutical market. In order to demonstrate their superior ease of handling and effectiveness, the therapeutic benefit as well as production and packaging costs must be considered carefully.



Eventful. Informative. Competent. The open-design booth drew visitors almost like magic



Visitors were able to experience Harro Höfliger "with all senses"



The Excellence United partners appeared together in Hall 3. Three of the five Excellence United Partners participated at the ACHEMA: Siegfried Drost (Managing Director, Uhlmann), Siegfried Bullinger (Managing Partner, Bausch+Ströbel) and Harro Höfliger (Managing Director and Company Founder, Harro Höfliger), from left to right, were all visibly pleased with the results of the exhibition

Success at the world's leading trade show

Once again, Frankfurt was the center of the process industry for five days. From June 15-19, 2015, the world's leading trade show, ACHEMA, attracted 3,813 exhibitors from the chemical, pharmaceutical and food industries and around 167,000 trade visitors to the Main metropolis. Right in the middle of the action was the team from Harro Höfliger and our Excellence United partners. The exhibition team from Allmersbach im Tal completely agrees with the organizer's conclusion of the trade show as having been "from satisfaction to excitement". Thomas Weller, CEO of Harro Höfliger, summarizes: "Highly qualified prospective customers spent a considerable amount of time to learn more about our innovations."

The sharp increase of international trade visitors was remarkable, and several contracts were finalized directly at the show." For an "experience with all senses" Harro Höfliger presented exciting live shows. Robot-Show-Acts and 3-D animation on touch screens inspired the trade show visitors.

A professional focus where new technologies for the production of oral and inhalable pharmaceutical dosage forms were on display. \blacksquare



Innovations at a glance: The powder laboratory



Listening. Understanding. Inspiring. High-level discussions with experts!

7 EXHIBITION TRENDS*

- The trend is shifting from batch to continuous processes
- Biopharmaceutical drugs are experiencing significant growth
- Aseptic filling is becoming increasingly important
- Modern formulation technologies are increasingly in demand
- Batch sizes continue to decrease and demand high system flexibility
- Trend towards modular standardized system solutions
- Demand for a dust-free environment when handling powder and granules
- and granate

HARRO Edition 1

*Compiled by specialized journalists of PROCESS magazine



Team Harro Höfliger thanks you for your visit and is looking forward to the next trade show

Visit us:

Pack Expo/Pharma Expo Las Vegas, USA, September 28 – 30, 2015

Maghreb Pharma Expo Algiers, Algeria, September 29 – October 01, 2015

FachPack Nürnberg, Germany, September 29 – October 01, 2015

BIOTECHNICA Hannover, Germany, October 06 – 08, 2015

World of Energy Solutions Stuttgart, Germany, October 12 – 14, 2015

CPhI/P-MEC Madrid, Spain, October 13 – 15, 2015

SCANPACK Göteburg, Sweden, October 20 – 23, 2015

AAPS Orlando, USA, October 25 – 29, 2015

COMPAMED Düsseldorf, Germany, November 16 – 19, 2015

CHINA-PHARM Shanghai, China, November 17 – 20, 2015

Pharmtech Moskau, Russia, November 24 – 27, 2015

P-Mec India Mumbai, India, December 01 – 03, 2015

Arab Health Dubai, United Arab Emirates, January 25 – 28, 2016

Pharmapack Paris, France, February 10 – 11, 2016

Open Days 2016 Inhouse Show Harro Höfliger Almersbach i.T., Germany, April 19 – 20, 2016

Interphex New York City, USA, April 26 – 28, 2016

KoreaPharm Kintex, South Korea, April 26 – 29, 2016

Powtech Nürnberg, Germany, April 19 – 21, 2016

Analytica München, Germany, May 10 – 13, 2016

Inventive. Qualified. Reliable.



Driven by Innovation Strength and Knowledge

At Harro Höfliger we foster a culture of understanding. This contributes to the success of our business partners. We are engineering system partners for individual production processes, as well as standard machines and platforms. This combination allows us to tailor processes to precisely suit the customer product. From the planning stage to implementation, our market specialists, creative designers and experts work handin-hand with you — the innovators of new products. We provide support every step of the way, from laboratory phase through completion of your production line.



