JULY 2019 # 01

the Small Molecule Manufacturer™

Scaling the Tableting Peak

Has tablet manufacturing equipment reached its full potential – or are there greater heights ahead?

SERVICE

BOSCH
Invented for life

CONGRATULATIONS

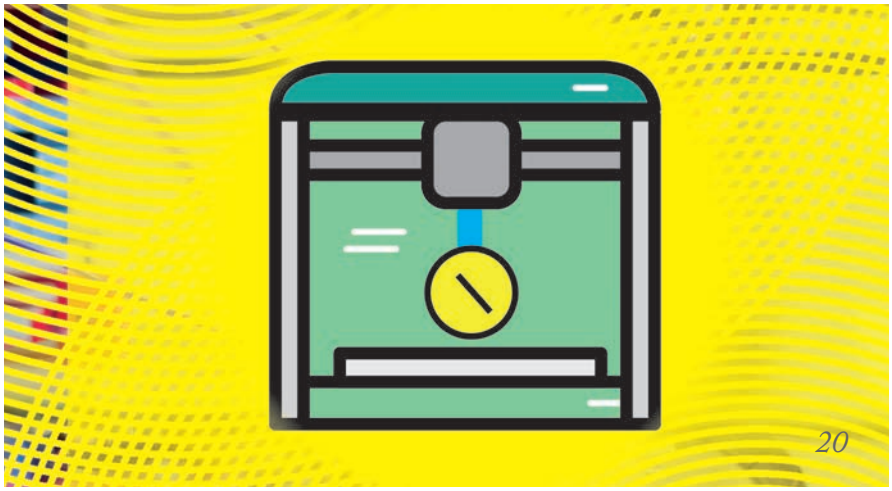
on the launch of the new magazine

Pharma
i 4.0
Starter Edition

www.boschpackaging.com

Follow us on

Contents



the Small Molecule Manufacturer
ISSUE 01 - JULY 2019

Editor - Stephanie Sutton
stephanie.sutton@texerepublishing.com
Deputy Editor - James Strachan
james.strachan@texerepublishing.com
Deputy Editor - Roisin McGuigan
roisin.mcguigan@texerepublishing.com
Assistant Editor - Maryam Mahdi
maryam.mahdi@texerepublishing.com
Content Director - Rich Whitworth
rich.whitworth@texerepublishing.com
Publisher - Richard Hodson
richard.hodson@texerepublishing.com
Associate Publisher - Helen Conyngham
helen.conyngham@texerepublishing.com
Business Development Manager - Helen Johnson
helen.johnson@texerepublishing.com
Business Development Executive, Americas - Kevin Vlad kevin.vlad@texerepublishing.com
Business Development Executive, Americas - Sarah Griffith sarah.griffith@texerepublishing.com
Head of Design - Marc Bird
marc.bird@texerepublishing.com
Designer - Hannah Ennis
hannah.ennis@texerepublishing.com
Designer - Charlotte Brittain
charlotte.brittain@texerepublishing.com
Digital Team Lead - David Roberts
david.roberts@texerepublishing.com
Digital Producer Web/Email - Peter Bartley
peter.bartley@texerepublishing.com
Digital Producer Web/App - Abygail Bradley
abygail.bradley@texerepublishing.com
Audience Insight Manager DPO - Tracey Nicholls
tracey.nicholls@texerepublishing.com
Traffic & Audience Database Coordinator - Hayley Atiz hayley.atiz@texerepublishing.com
Project Manager - Webinars - Lindsey Vickers
lindsey.vickers@texerepublishing.com
Traffic and Audience Manager - Jody Fryett
jody.fryett@texerepublishing.com
Traffic Assistant - Dan Marr
dan.marr@texerepublishing.com
Events Manager - Alice Daniels-Wright
alice.danielswright@texerepublishing.com
Event Coordinator - Jessica Lines
jessica.lines@texerepublishing.com
Marketing Manager - Katy Pearson
katy.pearson@texerepublishing.com
Marketing Executive - Sarah Botha
sarah.botha@texerepublishing.com
Marketing and Events Executive - Kevin O'Donnell
kevin.odonnell@texerepublishing.c
Social Media Manager - Joey Relton
joey.relton@texerepublishing.com
Financial Controller - Phil Dale
phil.dale@texerepublishing.com
Accounts Assistant - Kerri Benson
kerri.benson@texerepublishing.com
Chief Executive Officer - Andy Davies
andy.davies@texerepublishing.com
Chief Operating Officer - Tracey Peers
tracey.peers@texerepublishing.com
Senior Vice President, North America - Fedra Pavlou
fedra.pavlou@texerepublishing.com

Change of address:
info@themedicinemaker.com
Hayley Atiz, The Small Molecule Manufacturer, Texere Publishing Limited, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK

General enquiries:
www.texerepublishing.com
info@themedicinemaker.com
+44 (0) 1565 745200 sales@texerepublishing.com

Distribution:
The Small Molecule Manufacturer, is published monthly by Texere Publishing Limited, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK.
Single copy sales £15 (plus postage, cost available on request info@themedicinemaker.com)
Non-qualified annual subscription cost is £110 plus postage

Cambrex

Your molecule
Our mission

Drug substance | Drug product | Analytical services

www.cambrex.com

Why launch a new publication dedicated to small molecule drug development and manufacture? Right now, the wider pharmaceutical community are most excited by cell and gene therapies. Certainly, such "advanced" medicines are compelling – but, in many cases, they apply only to niche groups of patients. And because of the challenges of developing, manufacturing, and delivering these complex therapies, it's hard to know the overall impact that these amazing – and often amazingly expensive – therapies will have across the world. Novartis, for example, plans to sell its new gene therapy for spinal muscular atrophy for more than $2 million – putting it out of reach for many patients.

But small molecules reach everyone. Ibuprofen, acetaminophen, diazepam, hydrocortisone, ivermectin and amoxicillin represent just a fraction of the common small-molecule drugs on the WHO's list of essential medicines. Small molecule drugs address countless therapeutic areas from over-the-counter painkillers to sophisticated chemotherapeutics to the groundbreaking medicine sofosbuvir for Hepatitis C. Though some are expensive (sofosbuvir costs around $84,000 for a full course of treatment), most of them come nowhere near the price tags of biopharmaceuticals or advanced medicines.

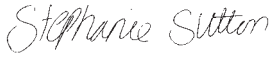
Small molecule medicines – and the people who develop and manufacture them – deserve to be recognized and applauded for their continued role in an ongoing success story. Yes, biopharmaceuticals and advanced medicines offer incredible benefits for (some) patients, but small molecules are typically easier and cheaper to manufacture, transport and deliver to patients. The humble tablet – the most common small-molecule dosage form – can be taken almost anywhere, allowing patients in the most remote regions to access their therapeutic potential.

To all of you involved in the development, manufacture and commercialization of small molecule medicines: The Small Molecule Manufacturer is your magazine. We will report on the trends and technologies shaping the industry – and introduce you to the people behind them.

In this issue, we focus on tableting, granulation and 3D printing. But we'd love to hear what you would like to read about in the future. Please get in touch: stephanie.sutton@texerepublishing.com.

In the meantime, please enjoy the first issue of The Small Molecule Manufacturer!

Stephanie Sutton
Editor



Upfront

Reporting on the trends, personalities and industry announcements that are shaping small molecule manufacturing.

We welcome information on any developments in the field concerning small molecules that caught your eye, in a good or bad way. Email: stephanie.sutton@texerepublishing.com

Wet, Wet, Wet

Continuous wet granulation will be the star of a new UK facility, which stems from a collaboration between CPI, GSK and AstraZeneca

In the UK, CPI is collaborating with GlaxoSmithKline and AstraZeneca to establish a small-scale continuous wet granulation manufacturing facility for oral solid dosage forms. The facility is due to be completed in Q3 2020 and will be available as a national, open-access centre for contract development. The facility is part of a project called PROSPECT CP (Proving Real-world Scalable Predictive Tools/Technologies for Complex Particles).

"One of CPI's strategic themes is predictive design and manufacturability, which includes exploring the use of PAT-enabled, model-based process control to help accelerate the adoption of digital manufacturing technologies across the whole formulation industry," says Jacquin Wilford-Brown, Principal Scientist at CPI. "PROSPECT CP is one component of this, seeking to create a facility to remove risks and barriers, and speed up development of new solid products. The initial demonstrator is in the pharmaceutical space, building on our previous work and linking forward to the Medicines Manufacturing Innovation Centre."

Tablets remain the most prevalent drug delivery method and wet granulation is often used for APIs with challenging processing properties, as some molecules are simply not amenable to direct compression approaches. In recent years, CPI has noted that more and more pharma companies are expressing interest in continuous technologies. Given that the UK Medicines Manufacturing Innovation Centre is running a project focused on direct compression, it made sense for CPI and its partners to look at twin-screw wet granulation.

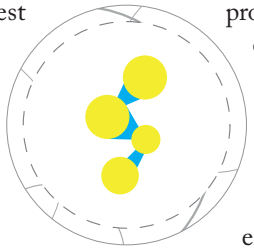
"We aim to create, test and validate a national open-access contract development facility for process development and optimization of oral solid dosage forms, based on twin-screw wet granulation interfaced with a range of real-time measurements," says Wilford-Brown. "Broadly speaking, we want to generate process understanding to support the development of new products and processes and establish control strategies for commercial manufacturing processes for drug products approaching registration. This will also allow us to understand and demonstrate the value of novel materials or excipients, and assess new and existing process analytical tools in real-life manufacturing scenarios."

De-risk and improve production

Despite more companies showing interest in continuous manufacturing, Wilford-Brown believes that we are only part way along the technology adoption curve. Many pharma companies have existing assets based on batch manufacture. Although many agree that continuous processing offers advantages, new capital investment for continuous technologies may be difficult to justify. Similar considerations also apply to the adoption of PAT. "Integration of PAT is fantastic once it works, but it can be difficult to get to that point. Possession of the right PAT probe without the correct presentation method does not enable appropriate process control, so capital expenditure on PAT alone doesn't guarantee success," says Wilford-Brown.

To monitor a continuous process, manufacturers need to be able to access a representative portion of samples from the process with appropriate resolution. As a continuous process is, by its nature, continuous, it can be difficult to "break"

into discrete portions that would enable real-time monitoring of the critical quality attributes of a product at the right point in the process. "There are a number of hurdles to effective implementation, but the prize is massive! Tighter quality specifications and more robust medicines manufactured at a lower cost, with the future potential of real-time release. On top of that, modeling approaches can be used to highlight the best points for PAT monitoring. By combining novel technologies, it is possible to effectively de-risk production," says Wilford-Brown.



The pharma sand pit

One of the big roles of the new facility will be to act as a "sand pit" where companies can test new ideas without impacting their current manufacturing lines – particularly new PAT technologies. For continuous wet granulation to get a foothold in pharma, in-line PAT will be essential in giving manufacturers immediate feedback on a process and control in real time. "Specifically, PAT enables the Model Based Controller (MBC) to predict the necessary process changes before the product goes out of specification, driving less waste. Without the pertinent chemical and physical information, linking the critical process to product parameters, we would not be able to effectively do this," explains Wilford-Brown. "Ultimately, we want to reduce or even remove the need for end-of-manufacture testing, so that product release is faster and the therapies reach patients much more quickly. PAT is also a major focus of the UK's Medicines Manufacturing Innovation Centre."

The facility will include a range of different PAT techniques, such as NIR spectroscopy, Raman spectroscopy and particle sizing technology. But the real intention is for the facility to be a platform for the evaluation of emerging PAT tools.

GSK and AstraZeneca will bring their technical knowledge and strategic guidance to the project. Both companies have significant experience in the use of various PAT tools, advanced process control and continuous manufacturing. They will also be ensuring that the focus is kept on developing a capability and a service that will be appropriate and relevant for the pharmaceutical industry.

What's Going On?

New products, facility expansions, and acquisitions from across the small-molecule drug development space

Products & services

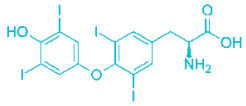
- StarTab (Colorcon) is a starch-based excipient designed for direct compression that, according to the company, provides excellent flow, and superior compressibility and hardness to help simplify formulation and manufacturing. It can be used at high tableting speeds, and can also reduce the overall number of excipients required for a formulation and avoid the use of superdisintegrants.
- The Quartic Platform (Quartic.ai) is a smart manufacturing platform powered by artificial intelligence that aims to help manufacturers make their legacy processes and facilities smarter. The system has two main components: Quartic Illuminator creates context for data from the Internet of Things, OT, MES and ERP systems and helps users unlock value from the intelligence; Quartic eXponence combines automated machine learning with complex event processing to create asset intelligence. The company believes that the use of AI should increase the productivity of manufacturing while reducing costs.
- The SimpliFiH Service (Lonza) is an integrated first-in-human service package for poorly soluble small molecules. The service encompasses the key drug substance and drug product components required for first-in-human studies for small molecules: drug substance development and supply, solid-state characterization/bioavailability enhancement, and phase-appropriate drug product in powder-in-capsule, powder-in-bottle, liquid-filled hard capsule or tablet format.

Facilities & expansions

- Eli Lilly is selling the rights in China for two legacy antibiotics, Ceclor and Vancocin, as well as a manufacturing facility in Suzhou, China, that produces Ceclor. The buyer is the Chinese pharma company Eddingpharm. Lilly will receive a deposit of $75 million and a payment of $300 million upon closing of the transaction, and will provide ongoing services for a time to ensure the continuity of product supply and support the smooth transition of the facility.
- Catalent is investing in several different facilities across its business; around $25 million will go to Catalent's Swindon site in the UK to bolster the production of Zydis and Zydis Ultra tablets; $14 million will be pumped into expanding softgel capabilities in Eberbach, Germany, which includes the creation of two new softgel encapsulation lines for the company's Vegicaps technology; and $5 million is being invested at the company's drug development center of excellence in Somerset, New Jersey, to expand the site's hot-melt extrusion capabilities.
- Thermo Fisher Scientific is acquiring an API manufacturing site in Cork, Ireland, from GlaxoSmithKline. The site mainly manufactures complex and specialized APIs. Thermo will continue to produce APIs for GSK under a multi-year supply agreement, but also plans to expand use of the site to develop and produce complex APIs for other customers too. The site contains 270 m^2 of reactor capacity, 10 production buildings, an R&D pilot plant and lab infrastructure.
- Cambrex has expanded its liquid packaging capacity and weekly output at its Mirabel, Québec site in Canada with the addition of a cGMP packaging line and a new filler on the existing packaging line. The new cGMP liquid packaging line allows the use of two fillers (XP and non-XP) working in parallel from process development through to cGMP commercial production, and offers the flexibility to accommodate ethanol and isopropanol-based solutions, aqueous solutions, lotions or suspensions. A new vision system has also been installed for online serialization.
- C2 PHARMA has acquired the Digoxin API product portfolio of Polish company, Nobilus Ent. Under the agreement, C2 PHARMA will be the product owner, and Nobilus the manufacturing partner and releasing entity for the API. Since 2014, Digoxin API availability has been frequently and severely disrupted due to high levels of impurities and an unreliable supply chain. To mitigate the expected future impact of those Digoxin API shortages, C2 PHARMA hopes the acquisition will help mitigate the future impact of those Digoxin API shortages. The company is also investing in a new, dedicated manufacturing facility with Laurus Labs in India for parallel manufacturing to add redundancy.

Small Molecules; Big Numbers

A snapshot of the small molecule market



Most commonly prescribed medicines in 2016:

Levothyroxine

Lisinopril

Atorvastatin

Metformin Hydrochloride

Amlodipine Besylate

THE GLOBAL MARKET

The global small molecule drug discovery market was valued at **$ 29.36 billion in 2018**

By 2024, it is projected to reach **$ 46.88 billion**, representing a CAGR of **8.11%**

The global small molecule API market is expected to reach **$279.7 billion by 2027**

Synthetic/chemical APIs make up **81.4%** of the global small molecule API market

North America

currently dominates the market for small molecule drug discovery. The country also holds the largest market share of the global small molecule API market: 38%

It is anticipated to reach $106.3 billion by the end of 2027

However, Asia-Pacific is the fastest growing region

Significant players:

Albemarle Corp, Allergan, Aurobindo Pharma, Boehringer Ingelheim, Bristol-Myers Squibb, Cambrex, Dr Reddy's, GlaxoSmithKline, Merck Sharp & Dohme, Mylan, Novartis, Lonza, Pfizer, Sun Pharmaceuticals, and Teva

In 2018, 64% of FDA drug approvals were for small molecule drugs

Sources
ResearchandMarkets, "Small Molecule Drug Discovery Market – Growth, Trends, and Forecast (2019 – 2024)", (2019); Market research Future, "Global Small Molecule API Market Research Report– Forecast to 2027", (2019).

HAS TABLET MANUFACTURE REACHED ITS PEAK?

The tablet press is a pharma manufacturing facility staple, but today's systems need to be faster, more reliable and more flexible than ever before; after all, companies are now manufacturing mini-tablets, bilayered pills and experimenting with continuous processing. Here, we ask three leading tablet machine makers for their thoughts on the trends driving innovation.

Some would say that the tableting process hasn't changed significantly over the years. What are your thoughts?

Robert Sedlock (Natoli Engineering): I would say that the overall tableting process has remained the same; the core principles of compression and the basics of how tablet presses operate are largely unchanged. However, significant improvements have been made in the control systems and safety features of tablet presses. Adjustments to tablet weight or thickness are no longer made by mechanical handwheels but are now controlled through touchscreen human-machine interfaces (HMIs) and servo motors, for example.

Scott Koehler (Elizabeth Companies): I believe that is a fair comment from a fundamental perspective. It is both testimony to the longevity of a stable process technology, and the cost-effective nature of compressing solid dose products. It is also compelling that similar technology can apply across a wide variety of products and industries beyond pharmaceuticals. Though the basic process is common, the nuances are significant, which challenges both tablet manufacturers, who need to ensure their formulations have the right properties to work well in the equipment, and equipment manufacturers who are designing machines to be as flexible as possible.

Matt Bundenthal (Fette Compacting): Although the core process has not changed all that much, manufacturers are using increasingly creative approaches in terms of the form taken by finished tablets. This, in some cases, is prompted by marketing-driven initiatives, but can also be based on requirements for optimized bio-availability, or making a controlled substance more resistant to abuse, for example.

Like virtually everything else today, speed has become a driving force in tableting. While not every formulation lends itself to being compressed at high speeds, most end users would like their presses to compress their products as quickly as possible. And given the increasing prevalence of potent compounds, modern presses have to run quickly and maintain control more tightly than ever before.

Another significant change to the compression process is the degree to which electronic and computer controls have facilitated the attainment of this balance between speed and control. Results must be validatable, and repeatable, to the highest degree – something not practically attainable with the "manual" presses of old.

FEATURING

Robert Sedlock is the Director of Technical Training & Development at Natoli Engineering. Natoli offers a full line of products and services to assist at all stages of the tablet and encapsulation production process.

Scott Koehler is Vice President, Sales & Marketing at Elizabeth Companies. Elizabeth started as a six-man machine shop in 1954 and has grown into a global provider of punches and dies, tablet presses, parts and services.

Matt Bundenthal is Director Sales and Marketing at Fette Compacting America. Fette has installed more than 5000 machines across the globe and specializes in tableting and capsule machinery.

What new innovations and trends are emerging?

Robert: I am excited by the advances in materials science and coating technology – there are now a variety of different steel types and coatings available to help address tableting issues, such as sticking and picking, abrasion and corrosion control, or any combination of common tableting issues. Frequently, a change of material or application of a specialized coating can resolve tablet defects and/or significantly improve tooling service life.

Scott: For me, industry adoption of continuous manufacturing techniques – although still in its infancy – portends powerful shifts in terms of factory processes and the wider business landscape of the pharma industry. Overall, continuous manufacturing should lead to more cost-effective and efficient processes. For continuous processing, the basic tableting process is not so different, but the compression department must adapt to more agile and fluid production flow. Apparatus within the compression activity, consequently, must compliment the new paradigm and be robust from short to long product runs.

Matt: Over the last 5–10 years, I've seen an increasing focus on potent compounds. Technologies specific to high-containment applications (for example, wash-in-place features, glove ports, door interlocks, and rapid transfer ports) have been developed to greatly mitigate the risk of operator exposure, mostly in the form of accidental inhalation. High-containment presses are therefore increasingly popular in the pharmaceutical realm. High-containment applications necessitate not only effective means for ensuring that potent products remain inside the tablet press, but they also must allow an operator to periodically gain access to the interior of the machine during a campaign (to check a suspect punch, for example, or to change a fill cam) without breaching containment. Hence, the use of rapid transfer port technology, glove ports and integrated spray and vacuum wands within the compression zone.

More recently, there is a trend towards continuous manufacturing, as Scott mentioned. The tablet press is only one component in an integrated equipment train that allows the user to avoid the "hold" phases between conventional manufacturing steps, and thus streamline their overall process. Given the need for the different pieces of equipment, such as mixers, blenders and presses, to communicate in an unencumbered fashion, these applications have also driven improvements in controls integration and ease of use.

What kind of requests are you receiving from the industry?

Scott: Often we are asked about transitioning tablet production to multi-tip tooling in support of cost reduction initiatives or efficient scaling of factory output. Another cost-motivated trend is the adoption of direct compression powder batches in lieu of wet granulation. Direct compression powder blends are often less forgiving within the tableting process than wet granulation and require intelligent press and tooling choices to reach reliable volume production.

Also, there are many opportunities in pediatric medicines, which are accelerating the need for smaller, low-dose tablets. Production of such small tablets is often being considered with multi-tip tooling; the design of such tooling and the tablet press set-up become critical to robust production.

Robert: Mini-tablets are a growing market for our customers. This dosage form is compelling because it can address many compliance issues – certainly in the pediatric space, but also geriatric patient

populations who may have trouble swallowing conventional tablets. As well as being easier to swallow, mini-tablets are able to deliver precise dosages with ease; delivering an exact dose to children is far more difficult than the average adult, as weight and height can vary significantly even within the same age range.

Matt: As Scott and Robert say, mini- and micro-tablets have become more common, as some manufacturers are essentially combining the compression and encapsulation processes (in other words, mini- or micro-tabs can be fed into empty capsules after being compressed). An advantage of mini-tabs is the fact that, if any surface defect exists on an individual small tablet, there is a very low risk of compromising the product's therapeutic band. A surface defect on a more conventional, larger tablet, like an unseen crack, however, can lead to all of the API being released too soon in the intestinal tract, thereby potentially ruining the intended therapeutic effect.

Double-layer tablets remain the most common of the "uncommon" tablet dosage forms, though some of the technologies involved in their processing – such as mechanisms for higher-speed, more accurate first-layer sampling – have improved by leaps and bounds.

Another infrequently used but interesting tablet type meters, or "pumps" its active product at a controlled rate through a tiny aperture – typically created with a laser-based drill.

How are these trends affecting innovation in tableting equipment?

Scott: These trends require more thoughtful consideration of the dynamics between tablet press and tooling as compared with traditional single-tip, heavier tablets. Optimization of press cam tracks and tooling head forms enable volume production at acceptable compression forces. As tips are added to punches, there is a corresponding increase in the tablet press compression forces needed to generate the higher volume of acceptable tablets. As compression tooling multi-tip assemblies become more complex, a more critical view is necessary to ensure reliable operation within the tablet press, while avoiding large escalation in tooling cost.

Robert: The size of mini-tablets and the rather delicate nature of the tooling pose a different set of challenges compared with typical tablets. When you have 20 or more tips on a single punch, downstream equipment must be able to process the drastically increased number of tablets; for quick and efficient removal, air-assisted tablet take-offs can be helpful. Other press features, such as lower punch retainers and shallow fill cams can also help maintain the mechanical integrity of the tooling.

The flow properties and particle size distribution of a formulation intended for mini-tablets is also incredibly important. Not only do you need to achieve equal and consistent fill in all the die bores, but you must also have a product that flows well into the smaller, more restrictive die openings. As noted, mini-tablet punch tips are delicate – and, therefore, more prone to bending or experiencing other forms of damage if over-compressed. Presses with finite controls and instrumentation that is sensitive enough for the collection of compression analytics enable tablet manufacturers to report on data that is precise and accurate in order to alleviate the chances of tooling damage.

Matt: In the past, double-layer tablets presented challenges (typically running much slower than mono-layer tablets, with high loss and low yields). Today, their increasing popularity has driven a host of new features that i) prevent cross-contamination between layers, ii) decrease the likelihood of transitional rejected tablets, and iii) allow for compression force control of each individual layer, rather than just the final, complete tablet. It is also far easier with modern presses to rapidly change from mono-layer to bi-layer mode – and back again – than it was in the past.

It is also common nowadays to hear of tablet manufacturers moving from larger, sustained runs to more numerous, smaller ones. To remain commercially viable, such companies require tablet presses that allow transition from "Product A" to "Product B" in the shortest possible changeover time. To that end, removal of parts has to be as easy as possible – as does re-assembly – and the fewer tools needed the better. Easily removable turret assemblies, and now "segmented" turrets, which dramatically reduce changeover times by eliminating the need for individual dies, have revolutionized changeover procedures and led to greatly increased press utilization levels.

What aspects of formulation should companies be considering?

Scott: Fundamentally, the granulation or powder must be compressible. Sometimes the mix simply is not – regardless of what tableting equipment is used. You must also consider the ratio of fine granules (< 0.2 microns) within the formulation. A formulation with a high percentage of "fines" can cause segregation, which leads to an inability to form a cohesive bonding of particles. A high percentage of fine granules can result in low yields due to product flow-by, imperfections on the tablet (such as flashing), and capping issues.

Matt: The two primary product characteristics that will affect how well a product may behave on a tablet press are flow and, unsurprisingly, compressibility. All high-speed tablet presses use some form of hopper to bring product to the feeder, and once in

the feeder the product must flow well enough to make its way into individual die cavities. The smaller the cavities, the greater the challenge.

Filling the cavities efficaciously is half the battle. If you can't form a tablet that holds together under compression, with the target weight, thickness and hardness, then you're back to square one. Improving flow and compressibility is a topic that warrants its own article! In brief, improving flow generally takes one of two early paths: a more effective flowing agent or the selection of a main filler with a higher degree of coarse particles – silicon dioxide, for example. A good first step for improving compressibility is to check the deformation profile of the product. There should be a high enough degree of plastic deformation under compression, without damaging particles. If the profile is too low, it can often be improved by increasing the concentration of an excipient with a profile more conducive to compression, such as microcrystalline cellulose.

Robert: As Matt and Scott say, there are a number of formulation factors that must be taken into account. I also believe that being able to simulate the compression behavior of a formulation on a small-scale R&D press can be invaluable, as it helps you predict and resolve potential issues prior to full-scale production. Additional tooling features, such as reduced head flats, can simulate the dwell times of large production presses to better anticipate any issues that might arise during scale-up.

TOP TIPS!

Comprehensive training on using and maintaining equipment is a must.

Establish a preventative maintenance program.

Clean and lubricate the machine properly.

Keep compression pressure as low as possible.

Don't ignore problems – once damage occurs, it accumulates.

In what ways can companies improve efficiency and production in their tableting operations?

Scott: As with most mechanical devices, proper care and maintenance make a huge difference in asset life and the quality of products produced. Properly maintained tablet tooling and rotary presses can last for decades. A simple adage to determine end-of-life of tablet tooling is: "Does the tooling still make good tablets?" If not, it is likely time to replace. By nature, tablet tooling does wear, so when it comes to some aspects of maintenance, especially polishing, "less is more." It's disappointing to see short-lived tooling because of over and improper polishing of the cup face. In the case of rotary tablet presses, most damage often starts in transients during start-up or shut-down of the press. When a press stops under load and is restarted without first relieving the pressure rolls, it causes the highest stress and wear on press and tooling (and can sometimes be catastrophic to the tooling). Thoroughly documented start-up/shut-down procedures, and well-trained personnel are the lifeblood of tableting equipment longevity.

Robert: One of the most prevalent causes of tablet press failure comes as a result of inadequate or irregular tooling and press maintenance. Here, training is key. With proper and frequent training of press set-up technicians, operators, and tooling technicians, costly mistakes can be avoided, which increases productivity and reduces downtime. Some companies cross-train and frequently move their personnel around to different areas of production. However, because of the high-level of technical expertise that is required for each process, it is more beneficial to keep them well-trained (and well-paid) on one process to ensure your operation runs more efficiently. It is also important to establish performance indicators that can be used to compare productivity over time. Without a baseline on which to measure success, you will be unable to effectively evaluate areas of potential improvement.

Matt: Comprehensive training should precede all else. It represents the cornerstone of protecting one's operators and the tablet press itself (a huge capital investment for any company) – and it ensures that the press always operates and performs at the levels for which it was designed. Training can take many forms, but if an equipment manufacturer offers any type of certification program, the opportunity should be seized with gusto. There is no better way to ensure maximal production results than to learn the ropes from those who designed the press in the first place. It is astounding how small deviations from the original equipment manufacturer's recommended practices can quickly lead to a loss of efficiency.

Though most vendors would like to sell new equipment as frequently as possible, the truth is many of the leading companies manufacture presses that can easily offer useful lives of two decades or more. Having said that, there are some signs that a press may require refurbishment or, in more terminal cases, replacement. Some of the warning signals can include:

- erratic compression forces
- poor or inconsistent weight control caused by various issues, such as bad punch seals, worn dosing station gearboxes, worn/damaged cams
- low yields
- noisy compression stations
- product found in places where it should not be; worn seals are a common culprit
- excessive wear on parts that should not ordinarily wear out (for example, compression rolls, feeder tables)
- excessive vibration

One of the most common drivers for replacing a press with a new unit, if it is not purely capacity-driven, is the phenomenon of electronic and control obsolescence. There does come a time when certain components – often computer-related – simply become unavailable and, in those cases, an end user may find their hand forced.

Can you share your top tips for maintaining tableting machinery?

Scott: Properly functioning lubrication throughout the tablet press, as well as cam track and pressure roll inspections for irregular fit and wear. Once damage occurs, it only snowballs. It is imperative to monitor the turret condition. Punch guides, die table surface and seals should be checked regularly for cleanliness and wear. Improper turret maintenance leads to a host of downstream issues, such as improper tool alignment, excessive cam wear, yield loss, and poor tablet quality.

Finally, properly set-up tooling with good alignment. Three basic tips that should cover all tableting machinery are:

- keep compression pressure as low as possible
- clean and lubricate the machine properly
- keep punches and dies in good condition

Matt: The number one tip is to establish a preventive maintenance program; make it an official part of your internal standard operating procedures, and enforce its consistent implementation without fail.

The more critical items to regularly keep an eye on with a modern tablet press include the following:

- compression rolls
- cams (fill, ejection, dosing)
- punch seals and restraining mechanisms
- scrapers
- turret assemblies
- lubricant levels
- gearboxes
- force feeders

Ask your OEM press vendor for all documentation to augment your own procedures.

Robert: Establishing a standard operating procedure for regular inspection helps keep the tooling and equipment in good working order. Also, the operator should be reminded when it is time to replace tooling or a wear part – before press downtime and productivity loss can ever occur. Prevention is always the best approach!

Born to Be Manufactured

Tablets are the preferred dosage form for both patients and drug manufacturers; the tableting process is well established and cost-effective, but the science and engineering go deeper than you expect. A number of aspects must be considered to design a tablet that is well suited for commercial manufacture.

By Jim Calvin and Andy Lapinsky

The manufacturability of an oral solid dose tablet can sometimes be an afterthought, given that most formulation conversations revolve around therapeutic efficacy (dose requirements and tablet format, such as conventional or bilayer tablet), the patient (swallowability and ease of use), and marketing (brand awareness and differentiation). But to make consistently good tablets, early design choices are often more meaningful than choosing good tooling and machinery. Different tablet designs require different engineering considerations and there are many factors that dictate how well a formulation will run in a given tablet press, and if the design a company has in mind for their product is actually practical from a manufacturing perspective. Certain designs used with the wrong punch, for example, create stresses that lead punches to wear out quickly, or result in tablet defects. Choosing in incompatible steel to the formulation compound being compressed can lead to abrasion of tool faces and die walls.

Tablets come in a very wide range of geometrical formations. There will always be a certain amount of weight that is needed in the tablet and from there you must consider the tablet's length, width, band thickness and cup depth.

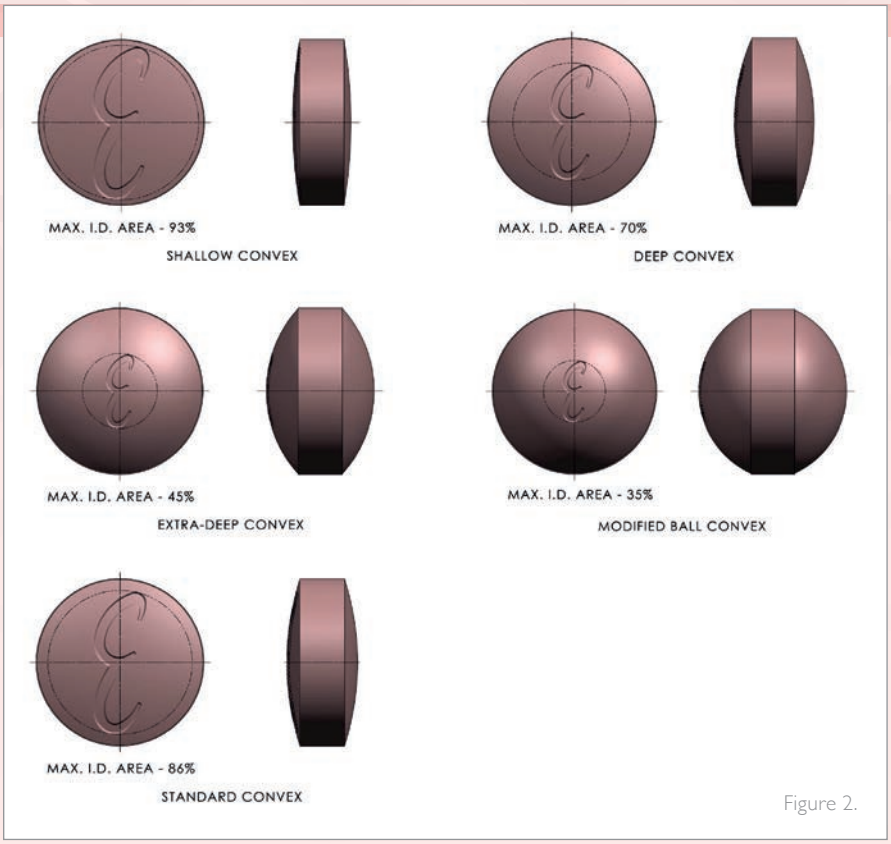


Figure 2.

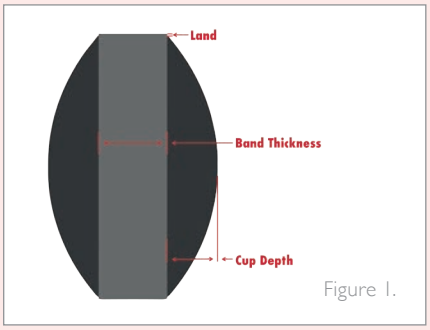


Figure 1.

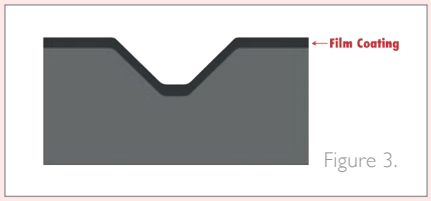


Figure 3.

If the length and width are chosen incorrectly and the tablet ends up too small, the thickness has to grow to accommodate the necessary weight. This is actually one of the most common mistakes we see; as the tablet thickness grows, manufacturers often run into compression issues, as well as high ejection forces, capping and friability problems. Another common mistake is for companies to produce a small-sized tablet successfully, only to find it is then too small to add desired logos or other identifying text on the tablet surface.

The building blocks of good design

In our tooling design process, we use software to create a solid model to evaluate the stresses and strains that a given tablet shape will create on the punch tip. The computer simulations promote collaboration with product designers and timely iterations when changes to tablet geometries are still possible. This type of software can also be used to transfer an existing product to another geometrical shape through reverse engineering. Broadly speaking, there are a variety of tablet geometry aspects that need to be considered.

- Cup depth. A tablet's cup depth is the distance from the cup's lowest point (usually the center point of the tablet) to its highest point of the land. Some tablets will have a shallow depth and others will be concave. As the cup depth increases, the compression force that can be used on that tool to achieve tablet

hardness decreases. Too much cup height increases the distance for the compression forces to travel from the perimeter of the punch to the apex, or the punch's cup apex, and can lead to premature punch wear and tear, and even breakage.

- Land. The land is a narrow plain perpendicular to the tablet's band, creating a junction between the band and cup radius. Although the punch is made out of steel, the area at the perimeter of the tip is very weak so a land should be incorporated into the tablet to strengthen the punch and prevent nicks on the punch edge, which could cause compression issues (see figure 1).
- Band thickness. Too wide of a tablet band can cause high tablet ejection force, and issues with coating and non-uniform density. For all compression tooling, the two closest points are compacted first and this can create a dense area that locks air into the cup, leading to capping issues. If the band is too narrow, it can create high compression forces that may affect tablet hardness, density and cause friability problems, with tablets that are too thin being susceptible to chipping or tablet edge erosion in particular.
- Identification. The area available for identification on a tablet, such as the addition of a logo, depends on the cup radius and the style of cup, as well as the geometrical shape of the debossing, including the depth and angle needed. The flatter the geometry of the tablet's cup, the larger the available area for identification. If the debossing is placed too close to the perimeter of the tablet, you'll lose clarity of the debossing (see figure 2).
- Film coating. It is important to decide if the tablet will be coated at the very start of the design process because it can affect other aspects, such as debossing. For example, it is important to ensure the debossing is deep and wide enough that the film coating doesn't fill in the areas and make the identification unreadable. With certain shapes, film coating can also lead to twinning (see figure 3).

In addition to considering the tablet's geometry, we also advise paying careful attention to granulation. Where possible, try to ensure you have free-flowing granules that aren't abrasive – otherwise you'll be wearing down the tooling. Maintenance is important too – take care of your tools! Your operators need to understand how to set-up the machine and identify irregular operation. Once something starts wearing it needs to be addressed before there is a domino effect on other parts of the process.

The early bird

There are many aspects to good tablet design and it's fair to say that it is a very unique science. You need to understand your formulation, additional components, such as binders and other excipients, and your tools and machinery, especially when considering more complex layer tablets or core-tablets. Chemists and engineers should work together to answer the questions and ensure the final formulation will suit both sides. It is also important to consider the differences between the R&D phase – where you'll be working at low speeds and volumes – and the production phase where the pressures on the system may be different and possibly more challenging to maintain tablet quality at increased production volumes.

Many in the industry advise drug developers to consider their formulation strategy and impact upon manufacturing as early as possible. We also urge companies to give early thought to manufacturing process to avoid common issues such as picking, sticking, flashing, and high compaction and ejection forces (tips available at https://catalog.eliz.com/toolingtroubleshooting/). There are some "tricks of the trade" that can help compensate for bad tablet design and formulation, such as altering the press feeder speed to affect the hardness and weight of the tablet, but overall it is difficult to effect major change. In the case of multi-layer tablets, tooling design decisions complimentary to tablet press configuration are essential to robust layer definition. Regulatory authorities are strict and once performance qualification has been completed and the line is validated there isn't much that operators can do. Instead, it pays to get it right early on by considering the options before your design causes manufacturing issues.

Meet the Experts

Andy Lapinsky has been working for Elizabeth Carbide since 1989, taking on roles of increasing responsibility over the years. Today, he is the manager of engineering and CNC programming where he oversees the design of compression tooling and technical services for Elizabeth tooling customers.

Jim Calvin joined Elizabeth in the 1980s making tooling. Early in his career, Jim transitioned to Elizabeth-Hata International (press division) designing and building press control systems, working as a service technician and service manager, servicing and installing equipment, validating, troubleshooting and training. Today, he is General Manager of Elizabeth-Hata International.

Inside the Medicine Machine

Getting into Granulation

Dry granulation offers several advantages to manufacturers – cost for one – and it's now attracting more attention as the push towards continuous manufacturing ramps up. Here, machine maker Tobias Borgers highlights granulation machinery that's suitable for both batch and continuous processing.

How does the machine work?

The goal of granulation is to take fine, non-compactable powders and turn them into coarser agglomerates that can be pressed into tablets. Agglomerates can be composed of dry, solid granules, where each granule represents an agglomerate of primary particles with sufficient solidity. In the dry granulation process, agglomerates are created through mechanical pressure alone.

With our BRC series, powders are processed to free-flowing granules with a defined density or porosity that allows for immediate pelletizing after compacting. We wanted to offer better performance than the existing products on the market so we designed the BRC to offer a high level of product capacity with minimum material loss. Force is generated by purely electromechanical means to ensure consistent ribbon properties and it can evenly compact material over a production range of 1-400 kg/h (product dependent).

The powder is compacted between two rollers with specified gap widths. The impact on the rollers, as well as the gap width, is monitored via sensors and there is also the option to install process analytical technology (PAT). All data are integrated into a control circuit to ensure continuous process quality, while an electro-mechanical drive provides precise and fast control. The chopper unit below the compacting rollers processes flakes into a granule at a defined granular size, and the unit is equipped with a conical sieve with replaceable inserts for different particle sizes. Even at high material throughputs, the cone-shaped sieve and its inserts gently crush the ribbons into granules with the desired particle size distribution. Each BRC can be mounted with a different rotary sieve within minutes to adjust to new process and ribbon requirements.

During the development of the series, engineers paid particular attention to make scale-up from the BRC 25 to BRC 100 as easy as possible by using identical roller geometry and control in both machines.

Of course, ease-of-use, targeted control, cleaning and hygienic design were all considered; when developing equipment for the pharma market, getting these aspects right is essential!

What is your advice in terms of care and maintenance?

When developing systems and equipment,

I think it is important to ensure they are robustly manufactured and can be used for many years. Some Bohle products have been used in production for over 20 years and in several shifts daily! The BRC requires extremely low maintenance as hydraulic technology was abandoned entirely. Cleaning and inspection are essential to ensure long-term reliability, and we also advise a regular service.

Why do companies prefer to use dry granulation over wet granulation, where possible?

Roller compaction, or dry granulation, is receiving a lot of attention from pharma manufacturers because roller compaction is a continuous process by design – and many companies are considering a move to continuous manufacturing. Dry granulation is an established procedure for producing pharmaceutical solids. It is employed not only for products that are sensitive to moisture or temperature, but also for its cost advantages. In comparison to wet granulation, no energy-intensive drying processes are necessary. Without a drying step, it becomes superfluous to stock up on, distill and dispose of industrial solvents.

What's your advice for choosing the right granulation system?

Today, a wide range of different granulation systems are available on the market. Wet granulation systems are divided into fluid bed granulation, high-shear granulation, single-pot granulation and twin-screw granulation. The units for dry granulation/roller compaction can be classified by roll assembly and layouts, sealing systems and roll surface conditions. Dry granulators are differentiated on the basis of their roller configuration; there are granulators with rollers configured horizontally, vertically and diagonally. We've seen a lot of demand for horizontally-configured rollers; advantages of this configuration include improved deaeration of the screws and a shorter discharge route for the slugs. In addition, dry granulators vary in terms of the width, diameter and surface characteristics of the rollers.

The system you choose will depend on the needs of your API and your business. I advise considering:

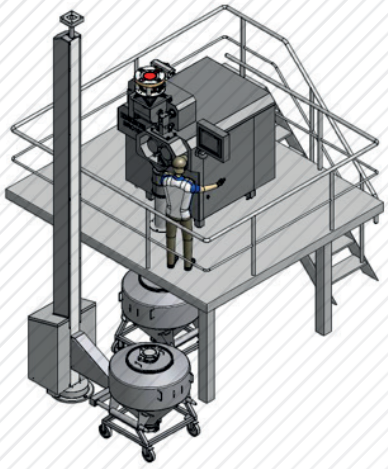
- Product capacity, capacity for each batch, and throughput
- Process robustness
- Scale up
- Process and product understanding
- Flexibility (including batch sizes, integration of different set up processes and the ability to react to market demands)
- Service and maintenance costs and requirements
- Footprint of the unit and requirements for the GMP area

What industry trends are likely to shape the development of future granulation machines?

Continuous manufacturing processes will determine the future of the pharmaceutical industry. Changing frameworks in the healthcare systems of the large pharma markets, such as the US and Western Europe, have been accompanied by budget reductions and economization processes in recent years – with many manufacturers changing their mindsets in terms of how they produce medicinal products. Today, there is a huge emphasis on the cost of drugs.

Continuous processing has great potential for more efficient and cost-effective manufacturing of tablets and meeting regulators' – specifically the FDA's – calls for improved safety and product quality (the FDA has also been vocal about PAT and continuous manufacturing).

For L.B. Bohle, continuous production is shaping the future of pharmaceutical solid dosage production machines.



More Innovation

Another system offered by L.B. Bohle for continuous processing is QbCon, a modular processing line that produces coated tablets out of raw powders within a single production stream. QbCon is produced in partnership with Korsch (tablet presses) and Gericke (continuous feeding and blending), and allows for the flexible arrangement of different unit operations, depending on the requirements of the customer. Several routes of manufacturing tablets from powders are feasible in the setup; for example, continuous direct compression for suitable powder mixtures or continuous wet granulation to improve the bulk properties of the powder before tableting can be conducted. The line also includes roll-compaction/dry granulation in a continuously working process, which is much more economic and less energy intensive than a wet granulation process.

The Next Big Thing?

Additive Benefits

Will 3D inkjet printing enable the manufacture of personalized tablets?

By Hatim Cader

Additive manufacturing or 3D printing refers to processes where products are made layer-by-layer. One of these technologies, inkjet printing, has shown potential in the manufacture of pharmaceutical products, including solid oral dosage forms. Rather than using typical powder compression methods, tablets could be made by the deposition of micro-sized droplets, selectively jetted onto a substrate. Instead of containing a colored ink, as in most inkjet systems, these droplets contain a drug – and can be repeatedly deposited until a 3D product is created.

The conventional route for tablet manufacture is a long and multi-step process that is well-suited for the mass manufacture of tablets, but offers limited avenues for personalized medicine. For the latter, inkjet printing could have a major impact as it would be possible to offer complex therapies customized to individual patients with consideration to their age, gender, weight and medical condition. Personalization can come in the form of multiple drugs in a single tablet, patient-specific dosing and/or multiple or multifunctional materials for controlling drug release. The highly programmable nature of inkjet printing would make it easy to meet the personalized demands of custom therapies.

I recently completed my doctoral research at the UK's Centre for Additive Manufacturing (part of the University of Nottingham) where I investigated inkjet printing for oral pharmaceutical tablets. Previously, solvent-based inkjet printing had been used to create oral formulations with the use of an edible substrate – meaning the printing technique was used as a dosing technology, rather than an individual manufacturing process. There have also been hot-melt inkjet and UV-curable inkjet formulations, but they have been limited to a single material for the tablet. My research focused on using solvent-based formulations to create wholly inkjet printed freestanding tablets (i.e., without the use of an edible substrate). Using multiple materials, I was able to illustrate a highly controlled drug release. To achieve this control, I designed and printed reservoir devices, which consisted of a polymer-drug internal core, an impermeable shell and a release-controlling membrane allowing for one-directional drug release.

The first stage of my research involved developing the internal core

"By varying the ink formulation, printing parameters and geometry of the device, I was able to create tablets capable of delivering sustained and controlled release."

of the device. Recently published in the International Journal of Pharmaceutics (1), one unique aspect of this work is the use of a water-based formulation to create freestanding tablets for the core. With this formulation, the risk of toxic solvents or hazardous uncured materials was removed and no extreme conditions were required to create the printed tablets. We were able to show the consequences of printing drug-containing materials layer-by-layer and, more importantly, to conclusively prove that the drug was distributed homogenously throughout the tablet and in its desired polymorphic form. Drug release studies showed that complete drug release was rapid (approximately seven minutes) and the formulation developed could potentially be used for any water-soluble drug.

My next research focus was to introduce a degree of control into the system. By formulating (with an organic solvent) a hydrophobic and hydrophilic polymer blend, I was able to print a release-controlling membrane. By varying the ink formulation, printing parameters and geometry of the device, I was able to create tablets capable of delivering sustained and controlled release (from seven minutes to over seven hours) with significant consistency. In addition to simply extending release, I created specific release profiles, such as a delayed and a bimodal (initially fast and transitions to a slower release) drug release.

Even though much has been achieved with additive techniques for pharmaceutical products, there are shortcomings that need addressing, including the low output of most 3D printers and the relatively high costs of printers that offer high accuracy and reliability. Although this is a significant issue in the academic research setting, these problems can be resolved by greater cooperation between pharmaceutical companies and large 3D printer manufacturers through the optimization of printer specifications and parameters. Another significant factor holding back 3D printing from

"The conventional route for tablet manufacture is a long and multi-step process that is well-suited for the mass manufacture of tablets, but offers limited avenues for personalized medicine."

being adopted by the pharmaceutical industry is the lack of knowledge of the technology, particularly in regulatory agencies.

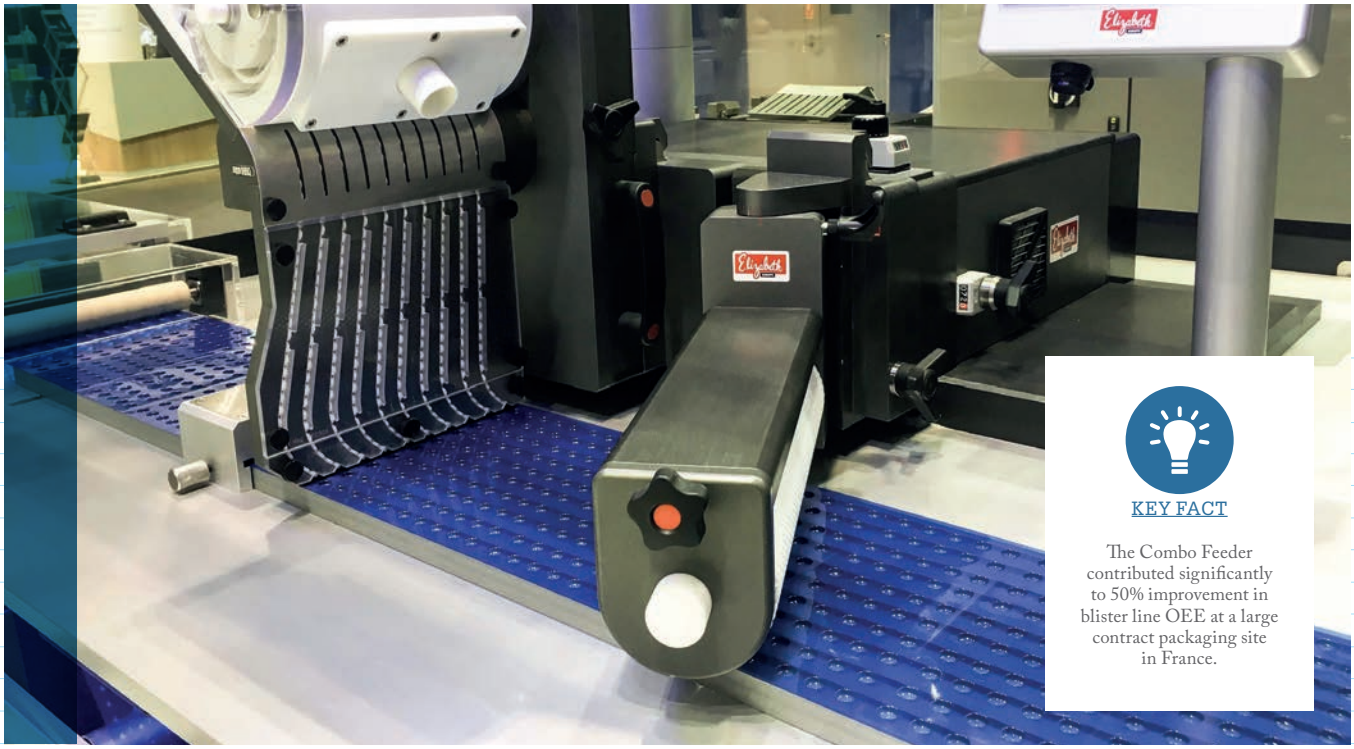
Despite these drawbacks, interest from pharmaceutical companies in additive manufacturing for tablet production is growing. Major companies, including GlaxoSmithKline, AstraZeneca and Pfizer, have all worked with leading academic institutions in the UK to further understand the technology's feasibility, advantages and constraints for pharmaceutical production. A company called FabRx, created by academics at University College London, has also been set up to create personalized medicines using a variety of different 3D printing technologies. More recently, a collaboration between AstraZeneca, Xaar, an inkjet technology company, and Added Scientific, an additive manufacturing research company, finished their investigation into the feasibility of using inkjet printing for the manufacture of personalized dosages on an industrial scale. To date, only Aprecia Pharmaceuticals in the US has produced an FDA approved oral pharmaceutical product made using 3D printing (Spritam uses a binder jetting technology). But it highlights that there are ways to overcome the drawbacks of 3D printing and allow it to be used by the pharmaceutical industry for commercial medicines.

The majority of inkjet printing research for pharmaceuticals has been from academia, but as industry gets involved, so must the regulatory agencies. Only together can we drive such technologies into more routine use.

Hatim Cader completed his doctoral research at the University of Nottingham. As part of the Centre for Additive Manufacturing, his research focused on the additive manufacturing of oral pharmaceuticals.

Reference

1. *HK Cader et al., "Water-based 3D inkjet printing of an oral pharmaceutical dosage form," Int. J. Pharm., 10, 359–368 (2019).*



KEY FACT

The Combo Feeder contributed significantly to 50% improvement in blister line OEE at a large contract packaging site in France.

Elizabeth Companies

Blister Line Combo Feeder

The Combo Feeder integrates most popular blister feeding techniques into one flexible platform easily configured for small to large batches.

Blister packaging of solid dose products presents many obstacles. When implementing a new blister layout, a good strategy to first consider is a brush box feeder. It is easy to install and efficient, but it is incompatible with flat tablets or capsules. Therefore, a steady ramp feeder is a better option, except if the tablet is a caplet that shingles into the steady track groove. Fortunately, the versatility of a vibrating ramp provides a viable solution, but it has speed limitations. Lastly, a tube feeder provides higher speed and is also appropriate for alu/alu packaging.

In conclusion, the ideal feeder does not exist. The maximum OEE with the minimum CAPEX requires a combination of several feeders. But there is insufficient space in the blister line to accommodate different feed frames, and it is inconvenient to frequently replace a feeder with another.

Elizabeth's patented Combo Frame is the ultimate solution! The Combo Frame overcomes these challenges. It offers a compact, standardized platform that can be adapted to the feeding formats discussed above by the rapid exchange of precision format parts. The result is a versatile system that escalates the OEE and the capability to confidently package an increasing range of products.

CONTACT: *Vincent Jollivet*
vincent.jollivet @elizeurope.com
WEB: *www.elizeurope.com*
www.eliz.com

Bosch Packaging Technology

Xelum: A New Approach to Continuous Manufacturing

The Xelum platform, based on proven fluid bed technology, doses APIs and excipients as discrete masses, so APIs of less than 1% can be dosed precisely. Individual packages, so-called X-keys, continuously run through the process chain and are discharged successively.

Xelum ensures lower production costs and high flexibility. The same is true for the Xelum R&D and pilot unit: process parameters are identical and scale-up becomes obsolete. This significantly reduces development time, as well as API usage.

CONTACT: *fritzmartin.scholz@bosch.com*
WEB: *www.boschpackaging.com*

Frewitt

Case Closed: An Elegant, Yet Simple Solution

When used as a twin system, Frewitt's ConiWitt-150 conical sieve mill docked to the FreDrive provides the perfect solution for preparing API products in a closed system. How? While one system is in operation, the second can be prepared.

Each of the twin systems include a large selection of sieves, eight cleaning nozzles, infinitely variable rotor regulation, with either a rectangular profile for grinding dry products or a round profile for grinding moist products.

CONTACT: *Mr. Notker Kling*
Regional Sales Manager – Germany
n.kling@frewitt.com
WEB: *www.frewitt.com*

Charles Ischi AG – Testing Technology

UTS-S20: Dust-Proof Tablet Testing Technology

The new dust-proof automatic tablet testing system, the UTS-S20 has various modifications including a two-way sorter features for tested tablets, special cover design and enhanced sealing system.

Easily connected it offers better operator protection and frequent quality control statistics. Use the UTS-S20 as an online monitoring device connected to your tablet press. Sampling can be initiated either from the production machine or via our Ph21 software and sampling gate. Attachable to any tablet press.

CONTACT: *+41 32 621 49 23*
WEB: *www.ischi.com*

L.B. Bohle Maschinen + Verfahren GmbH

Fluid Bed Granulator and Dryer BFS

L.B. Bohle developed the BFS with tangentially mounted spray nozzles and the Bohle Uni Cone BUC®. With the innovative and patented BUC® process a complete fluidization is assured which leads to high coating uniformities and high yields in the final product due to the absence of particle twinning.

Clear benefits with regards to process optimization, ergonomics and cleaning make the BFS stand out significally from other systems.

BFS batch sizes: 1 to 960 litres

CONTACT: *info@lbbohle.de*
WEB: *www.lbbohle.com*

The Master of Small Molecule Design

Sitting Down With… Brian Henry, Vice President of Drug Product Design, Pharmaceutical Sciences Department at Pfizer.

Why is the small molecule space still so exciting?

Pfizer is fortunate to be going through a very rich vein of filings, and I'd estimate that about 50 percent of our portfolio is made up of small molecules. We filed five new small molecules last year alone, which I think is exceptional and showcases how much can still be done in the small molecule world.

But certainly, drug development is becoming more difficult. There is significant chemical diversity and the molecules are becoming larger and more complex. They are harder to synthesize, formulate and manufacture on a commercial scale. As one example, we are currently working on a product where the lead time to make the API is three years. Having to make decisions three years before anyone else is ready requires a great deal of scientific knowledge – as well as nerves of steel!

And patients are waiting, so we have to move as fast as we can. If you wait for clinical trial results then you'll lengthen development times considerably, so it is important to invest early. We have a serious push in Pfizer to reduce our development timelines, wherever possible, all while still ensuring safety and high quality. A few years ago, we completed the development of an HIV medicine in seven years, which at the time was fast. More recently, we managed to file a medicine for a rare type of cancer in just four and a half years, so that is now our new target to beat. It's really exciting when you see a new medicine benefit patients in a clinical trial and you just want to develop new ways to get it to patients as quickly as possible.

You take a patient-centric approach to drug development...

Putting patients first is at the core of everything we do at Pfizer. We've worked really hard to understand the patient's journey, and we always keep them in focus when developing new medicines. However, some older medicines aren't as patient friendly as they could be; for example, some have limitations in how they can be taken with food. In some of those cases, we must make the effort to reformulate them. Why? Because it's important for patients.

We also have a big focus on pediatric medicines. We find that many of our oncology medicines have the potential to be applied to other cancers, including rare child cancers. Among other approaches, we have invested £5 million in a highly-specialized novel manufacturing technology, based at the Sandwich site, that will enable scientists to explore innovative ways to make medicines more palatable with flexible dosing for children. After all, if a medicine tastes bad, then parents will struggle to get their child to take it – and that can be frustrating for all concerned! When developing medicines, you need to consider all of your patients, no matter the age.

What new technologies or approaches could enhance drug development?

I think a lot more could be done in terms of making development more flexible through adaptable clinical trials design, for example. There is also the potential for using real-world evidence but, as innovators, we need to figure out what we can validate and how we can demonstrate the patient and societal benefits to regulators and payers.

I'm also interested in predictive science within pharmaceutical sciences. It's just better, faster and more efficient to design in silico first and then make and test second. Although there are quite a few predictive technologies and approaches available and in development, we could be hindered by the skills gaps the industry currently faces in this field.

In manufacturing, there is a move towards continuous manufacturing technologies for both API and drug products, which can resolve scale up challenges, development risks, and speed up medicine development more efficiently.

What exactly does your role at Pfizer involve?

There are a few different elements to my role. Firstly, I'm the Global Head of the Drug Product Design group, which designs all the tablets, capsules, creams and other products. We need to ensure we've designed the right molecule, that the product is stable and can be delivered correctly, and that the manufacturing team can make it at the right volumes. My other role is a site role at Sandwich in the UK, where I lead the Medicinal Sciences group and strive to ensure we have the right environment in terms of our collaborations and life sciences strategies.

I am fortunate in that I get to work with highly motivated and brilliant scientists from numerous different departments, including regulatory, commercial, manufacturing, chemists, biologists, and clinicians. Medicine development is only successful when those different skills and repositories come together.

What gives you most pride at the Sandwich site?

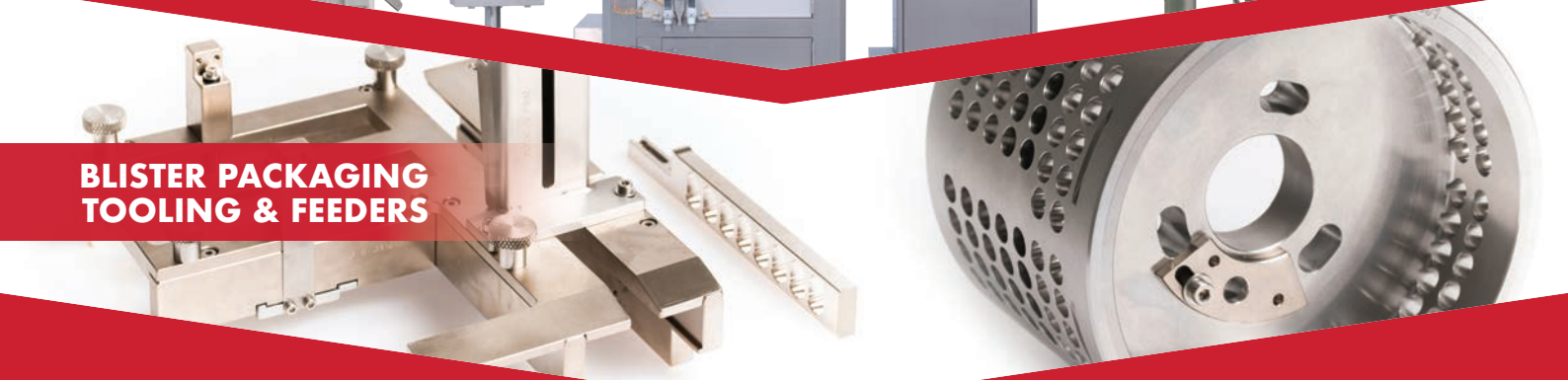
The way in which Pfizer is inspiring and helping to train the next generation of scientists gives me great pride. Not only do we have a selection of graduate and PhD training on site, but we also go out to schools with our award-winning "Science in a Box" interactive program, which teaches children about science and the medicine development process. The concept originated in Sandwich, and has now been rolled out across the UK reaching more than 20,000 students in 2017/2018 alone.

Pfizer has been in Sandwich since the 1950s. Last year, we had a celebration on site because we've been making clinical trial supplies at the facility for 20 years. We currently have about 700 people on site – mainly doing research and development. We also have a regulatory submissions hub that handles half of the company's filings on a global basis, and a pilot chemical plant that makes our small molecule APIs for use in clinical trials around the world. For Pfizer, the Sandwich site is unique and all small molecules come to us at some point in their lives!

COMPRESSION TOOLING

PRESS PARTS & TURRETS

ROTARY TABLET PRESSES



BLISTER PACKAGING TOOLING & FEEDERS

We understand that your products depend on the reliability of your equipment. Consumers must trust your products every day, and you demand consistent quality of your tablet. For over 60 years, generations of Elizabeth employees have put a personal guarantee on customer satisfaction and taken pride in innovative solutions. We promise our customers unequaled level of customer service, product performance, prompt and courteous communication, and trust. Experience the difference, the Elizabeth difference.

Elizabeth

ELIZ.COM | 1-412-751-3000

ELIZEUROPE.COM | +33 (0) 254 902 120