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# Solid Dosage Drug Development and Manufacturing 2020

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# Oral Dosage Form Innovation in OTC Pharmaceuticals

**Gerry McNally**

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**A quick look at the history of OTC dosage form development shows the importance of patient-centered innovation.**



Although both share a preference for use of oral solid-dosage forms, the business model for consumer pharmaceutical manufacturers—often called over-the-counter (OTC) manufacturers in the United States—differs significantly from that of prescription drug manufacturers. However, both types of companies have been responding to market changes by focusing on formulation and delivery changes that increase convenience to the patient/consumer. **Figure 1** summarizes recent trends in consumer-directed innovation in the OTC pharmaceutical market.

Differences between prescription and OTC products first became pronounced in the mid-1980s, when OTC manufacturers began to introduce increasingly diverse consumer-oriented products, and to change their approach to marketing, promotion, and packaging. The OTC marketing approach became more like that used in other fast-moving consumer packaged goods (FMCG) industries (e.g., foods, beverages, and personal care products). Packaging and advertising were increasingly directed to the consumer, rather than the health-care provider or pharmacist.

## Emphasis on form and sensory attributes

During the 1990s, the marketing of dosage formats and features such as form and sensory attributes (e.g.,colors, appearance, and flavors) became part of the product promotion mix. Recently, a major growth driver for OTC pharmaceuticals, particularly in the US, has been new products that resulted from prescription-to-OTC switches. These products were predominantly standard tablets or capsules with relatively few new delivery formats other than some modified-release products, the most unique being a slow-release nicotine chewing gum.

Introduction of more competitive and higher quality private-label or store-brand products in the 1990s underscored the need for branded OTC manufacturers to differentiate their offerings. The pressure to innovate with dosage form and packaging design has remained constant, driven by competing OTC brands as well as generic-pharmaceutical companies that supply drug stores and supermarkets with copies of branded products. Retailer consolidation has also driven increased competition, and dosage form innovation has become a crucial way for companies to differentiate products (1).

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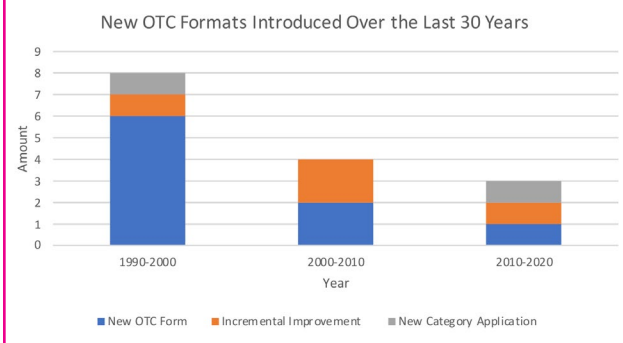
**Figure 1. Innovation in over-the-counter oral solid dosage delivery forms (1990 - 2020)**




## Greater consumer focus in OTC products

Both product packaging and delivery form have become key differentiators for OTC products. Traditional syrup, tablet, and capsule formats have made way for a diverse array of forms such as softgels, gelcaps, chewing gums, powders, effervescent tablets for hot and cold drinks, as well as orally disintegrating tablets and confectionery-derived forms.

A number of considerations go into the consumer's buying decision (2). Delivery format may often reflect patient compliance issues, especially for pediatric formulas, but perceptions of efficacy and consumer preference are also crucial. More complex OTC formulations and delivery systems often require unique manufacturing technology and almost always involve complex analytical methodologies due to the additional excipients used in the formulations.

Most orally administered products that switched from prescription to OTC did not introduce new delivery formats. However, many brought significant consumer benefits (e.g., less frequent dosing) to existing categories such as longer-acting analgesics. An example would be Bayer's longer lasting Aleve.

They also created new paradigms for consumers (e.g., once daily dosing for heartburn and seasonal allergy treatments). These product introductions greatly increased the consumer's awareness and understanding of the benefits of longer-acting remedies and less-frequent dosing. As a result, consumers expect more from OTC treatments. Continuous innovation in packaging and drug delivery formats is required if a new OTC franchise is to remain successful (3).

## More convenient dosing

Around 30 years ago, several sustained-release cough cold brands that had dosing of 12 hours, were developed and marketed, such as Drixoral (originally Schering-Plough's trade name), and Delsym (Fison's brand in the 1980s, but now Reckitt Benckiser's [RB's]). These products may have been ahead of their time because most OTC products in the mid-1980s were dosed at a 4–6-hour frequency. It was not until the 1990s, after several longer-acting drugs switched from prescription to OTC, that consumers became familiar with once- or twice-daily dosing. Thus, Delsym and other legacy long-acting brands experienced something of a renaissance in the late 1990s and early 2000s.

Johnson & Johnson's Tylenol analgesic brand maintained a strong market presence over several decades, due to continuous form innovation, which included introducing novel gelatin-coated, capsule-shaped tablets called gelcaps, with a later addition of gelatin-coated round tablets called geltabs. In the mid 2000s, Tylenol gelcaps were replaced by rapid-release gels, gelatin-coated caplets with laser-drilled holes that enabled faster disintegration and dissolution. Other innovations included improving the taste of pediatric analgesics by replacing liquid formulations with suspensions, thus improving patient compliance.

For solid-dose formulations, taste-masked drug particles were incorporated into chewable tablets, which offered a convenient dosage form for both children and adults. Taste-masked drug particles also enabled the convenient powder pack dosage format introduced in 2019 as Children's Tylenol dissolve packs. Another innovation in the cough/cold category was the hot-drink format first introduced in the UK under the Lemsip brand(now owned by RB) and later in the US as Theraflu (Sandoz's brand in the 1990s but GlaxoSmithKline's today).

## Technology licensing and development partnerships

Increasing competition in consumer pharmaceuticals and limited resources for developing innovative forms inhouse paved the way for partnerships between drug delivery specialists and contract development and manufacturing organizations (CDMOs). Examples of successful partnerships within the OTC space included the RP Sherer Company (now Catalent), which owns and offers Liqui-Gel softgel technology for license (using its OptiGel technology in-house) and Zydis, the first orally disintegrating tablet (ODT) to use freeze drying technology. One of the first commercially significant branded OTC Liqui-Gel introductions was for the cough and cold treatment, Vicks' Nyquil/Dayquil (Proctor and Gamble), and was followed by Advil (now GSK's, but originally Wyeth's and later Pfizer's) Liqui-Gel for pain relief.

ALZA Corporation was another notable drug delivery company to supply the OTC industry with novel oral and transdermal drug delivery technologies. The oral technology was the osmotic-controlled release oral delivery system (OROS), which was used to produce long-acting formulations of several antihistamines and decongestants. The decongestant product is still on the market today under the Sudafed 24-Hour brand (Warner Lambert's technology when launched, but now Johnson & Johnson's).

Other unique forms introduced by third-party collaborations included fast orally dissolving films (ODFs), which enjoyed a level of market success following the launch of Listerine pocketpaks (originally Warner Lambert's trade name but now J&J's) in 2001. However, since then, this format has all but disappeared from the OTC market. The German firm Hermes Pharma has recently been promoting consumer/patient-friendly dosage formats (4).

FIGURE COURTESY OF THE AUTHOR.

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A recent trend has been the development and manufacture of various confectionery pharmaceutical forms such as soft chews and gummies; the United States Pharmacopeial nomenclature is "chewable gel." The gummy form was first introduced in the pediatric vitamin category but soon became a favorite with adult OTC formulations, and is currently used in vitamin and supplement, as well as antacid, laxative, and probiotic treatments.

The pharmacy chain CVS recently introduced a Keurig (K-Cup) formulation of the traditional hot drink cold relief products, using technology invented and produced by Raritan Pharmaceuticals (5). GlaxoSmithKline later leveraged the technology in its Theraflu PowerPods product line.

## The unique importance of dose format

The history of OTC pharmaceuticals clearly shows the importance of dosage form to the consumer. Several OTC brands have been created based on a core drug-delivery platform, including RB's Lemsip and GlaxoSmithKline's (GSK's) (formerly Sandoz's) Theraflu cough and cold brands (powders for dissolution in hot water) and RB's (formerly Adams') Mucinex (12- and 24-hour guaifenesin and guaifenesin combination products).

The importance of dosage-form and value-added innovation in OTC lifecycle management cannot be overstated. Generic manufacturers have noticeably improved the quality of products supplied to store brands and have matched most new formats introduced by the national brands. Innovative technology developed for branded OTCs is being copied, in ever shorter development timeframes, by fiercely competitive generic drug suppliers.

Based on the broad acceptance of generic drug products and the slowing pace of innovation from the national brands, it is likely that the share of store brands will continue to grow. Considering the decrease in major new prescription-to-OTC switch candidates, it is more important now than ever that consumer healthcare companies innovate in new delivery formats.

This has long been the challenge for older molecules particularly those that have been on the market for 30 years or more. The significant innovation in formats driven by the consumer healthcare companies in the analgesic, upper respiratory, and gastrointestinal categories was one of the key strategies to drive growth and protect market share of older drugs. At the same time, developing proprietary forms that appeal to consumers has become more difficult and requires a depth of cross-functional technical expertise and capability that many firms may no longer possess inhouse.

The economics of OTC pharmaceuticals depend on optimized manufacturing processes, and it is clear that efficiencies gained from scale allow leading players to be cost competitive with both base products and new technology platforms. OTC companies have leveraged pharmaceutical processes and scaled them for large volume, lower-cost OTC drug products. Examples exist across all unit operations. Innovations such as gelatin-coated dosage forms saw the utilization of capsule-manufacturing technology being applied in a new way to make a novel solid dosage form that has gained wide acceptance. In the future, continuous processing, already a standard in food and beverage categories, may be crucial for sustained success in OTC.

The OTC industry has also leveraged technology from outside of oral solid dose manufacturing, as evident in the softgel form. Borrowing from transdermal drug delivery technology gave rise to oral film strips, while a growing number of confectionery formats have appeared across various consumer healthcare categories, taking innovations in candy manufacturing and applying them to pharmaceuticals. Novel excipients and new grades of existing excipients have also enabled the expedient formulation and commercialization of several dosage forms (e.g., directly compressed ODTs). Development of many directly compressible grades of active ingredients have helped OTC manufacturers innovate less expensively.

Meanwhile, advances in coating polymers have enhanced the ability to taste mask bitter active ingredients more effectively while at the same time lowering production costs. There have also been major advances in sensorially important ingredients such as flavors, sensates, high-potency sweeteners, and elegant tablet coating polymer systems, all of which must comply with increasingly stringent regulatory requirements. Without the significant advances in many areas of analytical and stability science, many innovations might never have been commercialized, or would have been cost prohibitive.

## Understanding the consumer

Consumer benefits associated with various dosage formats such as ease of swallowing, appearance, convenience, portability, and taste have been shown to be important (4,6,7). When considering OTC innovations, it is important to assess areas of opportunity. This may involve looking at gaps in the marketplace, how important a particular dosage form is to the end user, and how satisfied they are with the existing formats. In gathering such insights, it is important to keep in mind that the average consumer is most likely to provide feedback that will drive incremental innovations based on his or her understanding of what is already available. To be successful, the OTC development scientist and formulator should, ideally, have a good understanding of current consumer trends, not only in healthcare but in the FMCG category overall. Factors such as convenience, customization, and the role and impact of on-line marketing and selling are all broad trends that should inform product development.

Changes in demographics such as the aging population may also present opportunities for new insights into consumer behavior. When consumers have a clear need, their preferences will lead dosage form development, as they have with gummy and soft chew formats in certain supplement categories.

Although it may be time consuming and expensive, consumer testing and validation is critical to ensuring success. This may require conducting test markets or pilot launches in several cities to uncover product flaws or aspects that can be optimized. This approach can offer valuable insights to improve products and avoid costly product failures down the road. Ultimately, consumers are looking for value and for

new products that satisfy an unmet need. New technologies entering the OTC market must offer a cost-effective alternative and must be positioned appropriately which requires deep consumer understanding and market knowledge. Core value-added benefits offer consumers something distinctive such as faster onset or longer duration of action. Other benefits may include reduced side effects, improved taste/sensory performance for pediatric medicines, and easier dosing/convenience. Differentiating value-added benefits may be designed into products. They reinforce the product experience and emphasize a "reason to believe." A good example is liquid-filled capsules or softgels that connote faster acting (6,7,8). Overall, sensory signals enhance the consumer experience. This is evident in the cough and cold category, where forms such as cooling liquids, hot soothing drinks, and well-flavored lozenges all enhance the medicating experience and give consumers confidence in the product.

In short, dosage format is critically important to the success of branded OTC pharmaceuticals. It is one of the deciding factors in consumer's minds when they purchase a non-prescription drug product. To ensure continued growth of both mature and newly switched OTC brands, innovator companies must diligently pursue an aggressive life cycle management strategy encompassing patent-protected dosage forms in conjunction with protectable claims and packaging innovation.

In recent years, innovation in OTC oral delivery formats has slowed (**Figure 1**), due in part to increased pressure on profit margins. Many parent pharmaceutical companies are focusing on a limited number of standardized manufacturing platforms. At the same time, many of the drug delivery companies and CDMOs that partnered with companies on OTC product development are now focusing on more profitable niches in the prescription drug business, and on biologics and innovative treatments such as cell-and gene-based therapies. It is clear that consumers will continue to select and purchase what they see as the more user friendly dosage formats. What remains to be seen is whether innovation will continue to be seen in nationally branded products, or whether it will be taken over by disruptive innovators such as new brands or store brands, a trend that has already begun in some product categories.

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# Considering Excipient Regulations

Jennifer Markarian

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**Understanding European GMPs and new rules from China are crucial for formulating solid-dosage drugs.**



Understanding the regulatory requirements in the countries in which a drug will be manufactured or sold is crucial. *Pharmaceutical Technology* interviewed Yuwei Heinzel, head of Pharma Registration with Merck KGaA, in Darmstadt, Germany and Cloris Tian, senior regulatory manager for Merck KGaA in Asia-Pacific and China, about regulations of excipients for solid-dosage drugs.

## EU regulations

**PharmTech:** What do you see as the most significant regulatory changes related to excipients used in solid-dosage drugs?

**Heinzel (Merck):** Regulatory authorities are increasingly demanding stricter quality management in excipient production and use, which affects both excipient suppliers and pharmaceutical manufacturers. Since March 2016, excipient users in the European Union must define and implement good manufacturing practice (GMP) requirements for excipients, including comprehensive risk assessments for each excipient. The EU excipient risk assessment guidelines (1) capture both the intended use and source of the excipients. Its main topics cover the determination of appropriate GMP based on type and use of excipient, the determination of an excipient manufacturer's risk profile, as well as confirmation of application of appropriate GMP.

However, while regulations regarding GMP for APIs clearly define what is needed for compliance, the EU excipient risk assessment guidelines are—as their name suggests—not more than guidelines that offer tools and a framework but do not prescribe how to implement them. They neither provide detailed instructions nor a clear definition of appropriate GMP for excipients. This is the responsibility of the manufacturing authorization holder.

In China, regulatory authorities have gone a decisive step further: regulatory compliance is required not only for APIs, but also for excipients used in drug manufacturing. In fact, it is mandatory to register all excipients used in drugs sold on the Chinese market, including those used in imported drugs—a globally unique situation.

## Chinese regulations

**PharmTech:** Can you summarize China's co-review procedure and explain how this affects excipients?

**Tian (Merck):** Excipients came into regulatory focus in China in 2001 when article 11 of the Pharmaceutical Administration Law (2) stipulated that excipients used for pharmaceutical production should meet the requirements for medicinal use. This very general wording led to quite inconsistent approaches. In 2005, the China FDA (CFDA) proposed that excipient registration be done according to the same process as APIs. This included a stand-alone review by the Centre of Drug Evaluation (CDE) for import and novel excipients, and by the local FDA for excipients described in the *Chinese Pharmacopeia*.

The reforms were triggered by a substantial backlog in drug review. China's pharmaceutical industry had developed rapidly in the interim, resulting in a broad range of new, improved medical products. However, the approval process couldn't keep pace with these rapid innovations. In 2015, the Chinese State Council initiated substantial reforms aiming at establishing a more transparent and more efficient process for drug approval and, as a result, also for excipient approval. The number of reviewers was increased from the previous 100 to approximately 800 and a 'co-review' process was established.

As of December 2017, according to CFDA announcement No. 146 (3), all pharmaceutical excipient manufacturers or owners, domestic or foreign, must submit their dossiers to the CDE. After a successful completeness check, a registration number is created on the CDE registration platform. Then the registrant can issue a Letter of Authorization (LOA) to its customers (i.e., the drug manufacturers) for their respective drug application. In fact, the drug manufacturer or owner can only submit an application if it provides valid registration numbers for all excipients used.

After successful submission by the drug manufacturer, the CDE commences the assessment process. The applicant must answer questions regarding the product and is informed if there is a deficiency letter for the API, excipient, or packaging material. If so, the CDE contacts the respective excipient registration owner. Once this assessment has been finalized, the drug approval is issued to the drug manufacturer. At the same time, the status of the co-reviewed excipients is changed to 'A' for 'Active' on the CDE platform.

In the first quarter of each year, pharmaceutical excipient manufacturers must submit annual reports to the CDE to keep their registration number active. If certain excipients have already been successfully registered in the context of previous drug reviews and have maintained their registration number, there may be no need for a new review and the National Medical Products Administration (NMPA) (formerly the CFDA) can use the excipient registration data directly. However, another technical review may be necessary if the CDE decides that the use of the excipient has changed.

**PharmTech:** Have there been any regulatory changes for other ingredients, such as colorants?

**Tian (Merck):** In China, the classification of excipients as listed in the Chinese Pharmacopeia (ChP) was proposed in 2018 (4), which has since then served as the basis for the dossier requirements for excipients. The revised dossier requirements were published in a recent announcement in July 2019 (5). The amendments also include changes to the exemption list for low-risk excipients.

Apart from corrigents, flavors, spices, pH adjusters, and inorganic salts, the exemption list for low-risk excipients also includes pigments (colorants) and inks, more precisely iron oxide, plant carbon black, and cochineal, as well as benzene-free inks for capsule inscription. Generally, the exempted excipients can be used without going through the complex review and registration process. However, the final registration exemption of an excipient needs to be confirmed by the CDE and depends on how the excipient is used in the drug formulation.

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## Mitigating risk in formulating with excipients

New tools for formulators of oral solid-dosage (OSD) drugs are being developed to improve understanding of the properties and variability of excipients and, thus, reduce risk. These tools include guidelines from the International Pharmaceutical Excipients Council Federation (IPEC), databases of excipient properties, and a new software program.

IPEC, in collaboration with the Parenteral Drug Association (PDA), published a joint technical report in December 2019 that formalizes a risk assessment for excipients (1). The report discusses the types of supply chains, and risks from these, and presents options for evaluating and mitigating risk. IPEC is also preparing to publish a guideline on quality by design (QbD) that will, among other topics, provide guidance on incorporating excipient variability into QbD formulation projects and assist users in addressing the impact of excipient variability on finished product quality in development and control strategy, explained Brian Carlin, director of QbD and Regulatory at DFE Pharma, in a presentation at IFPAC (2). "A certificate of analysis (CoA) is not enough," said Carlin. "A CoA might not specify attributes that are crucial for your particular process, for example, the water binding capacity of microcrystalline cellulose when used in wet granulation." He also noted the importance of working collaboratively with suppliers to set specifications for critical material attributes and recommended having a range rather than a fixed level of excipient with a CMA to ensure consistent finished product critical quality attributes. Continuous multivariate monitoring of the process can help identify "drift" caused by the inevitable cumulative changes in product, process, or excipient, he added. Drift may cause an otherwise innocuous excipient variability to interact with a finished product criticality, causing special cause variation.

**Continuous multivariate monitoring of the process can help identify "drift" caused by the inevitable cumulative changes in product, process, or excipient.**

***—Brian Carlin, DFE Pharma***

Considering the role of excipients in a formulation is particularly important in continuous manufacturing, noted Chris Moreton, vice-president of Pharmaceutical Sciences at FinnBrit Consulting and a member of the *Pharmaceutical Technology* editorial advisory board, at the conference (3). He emphasized designing more robust formulations using QbD and the benefit of using process analytical technology (PAT), possibly with feedforward control, to make process adjustments to cope with variability.

Researchers at Rutgers, The State University of New Jersey, are developing a database of excipient properties for direct compression as part of their work on continuous manufacturing with the C-SOPS industry consortium, said Doug Hausner, associate director at C-SOPS (4). The team has set up a digitized system for collecting material characterization data, so that the material data can be analyzed in conjunction with process data and used for process modeling.

Researchers with the National Institute for Pharmaceutical Technology & Education (NIPTE) at the University of Maryland are developing an excipient database as a risk determination tool. The goal is to create an information management system using failure modes and effects analysis to identify risk, explained Steve Hoag, professor at the University of Maryland (5). The initial database, with a limited number of excipients, was developed using a grant from FDA to NIPTE and is publicly available, said Hoag. The group hopes to obtain funding to add more excipients to the database.

**Considering the role of excipients is important in continuous manufacturing.**

***—Chris Moreton, FinnBrit Consulting***

BASF has introduced a "virtual pharma assistant" web-based tool for aiding excipient selection that considers excipients and their interactions with APIs (6). ZoomLab, which is available on BASF Pharma Solutions' website, is intended to eliminate pre-formulation trial and error by predicting potential tablet formulations for API parameters that are input by the user. The database used by the tool includes a range of excipients, fillers, and binders and combinations of these. In the initial version, data are included for processability in direct compression, but the company intends to expand the tool to consider other critical properties and other processes. The first version can be used for APIs in BCS Class I and III.

A new digital tool from BASF named RegXcellence aims to simplify the compliance process. The regulatory and quality portal gives customers the ability to instantly download documents, find audit information, and have a compliance overview of the customer's portfolio, says the company (6). The virtual assistant provides a faster way to maintain documentation.



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# A Little Thought Goes a Long Way in Tableting

Felicity Thomas

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**Understanding formulation properties early in development can prevent some costly issues later on.**



Oral solid dosage forms remain the most popular within the pharmaceutical industry as a result of convenience of administration and general acceptance with patient populations. With speed-to-market becoming an ever more pressing matter for drug developers, a more complete understanding of material properties as early in the development cycle as possible can avoid potentially costly tableting pitfalls.

"Tableting has been around for more than 100 years, and at its core it seems quite easy, but if you don't really understand the material properties, there is a chance that you could reach commercialization and end up with a formulation that is not suitable for tableting," explained Elaine Stone, Merlin Powder Characterisation, during an event sponsored by Catalent in Nottingham, UK in December 2019 (1). "A little bit of thought about what properties a formulation needs to have at the beginning can really help the tableting process."

## Tablet basics

"For those that don't know so much about tablets, they are quite complex little things, so when they are popped out of the wrappers from the pharmacy they appear simple, but there are a lot of different ingredients that have gone into them," Stone said. "Some of these ingredients are really good for tableting, and some are really bad for tableting but good for other things. So, we've got a combination of all sorts of different ingredients in there, and to get a really good formulation for tablets we need a suitable balance of these ingredients."

In terms of tablet strength, Stone explained that it is necessary to have a formulation that will be strong enough to form the tablets and be transportable without breaking, yet also break up fast enough so that the drug is bioavailable once swallowed. "There are these two competing properties within a tablet formulation that we need to balance, which can be achieved through understanding both mechanisms," she added.

Some of the issues that can arise from poor tablet compression understanding include a formulation that cannot run on a tableting machine, tablet sticking, tablet capping, and reduced press speed, which are all costly, Stone emphasized.

## Compression factors

"There are two main factors involved in tablet compression," Stone continued. "The first is deformation and the second part of it is persuading all of those particles to bond back again with each other to form a solid compact."

**Particle deformation.** There are three main ways for a particle to undergo deformation—elastic deformation, plastic deformation, or brittle fracture. "The first one, elastic deformation, means that when the formulation is compressed, it changes shape, but as soon as you release the compression force the substance reverts back," Stone confirmed. "This type of deformation is a challenge to deal with from a pharmaceutical point of view because we want permanent change. Therefore, elastic particles, such as starches, can be problematic for tableting."

If a particle exhibits plastic deformation, there will be a permanent change of the particle's shape; Stone noted that these particles tend to be quite soft and pliable and can deform at low compaction forces. "For brittle fracture, stresses during compression include crack propagation along the particle or granule, and the end result is fragmentation," she said.

**In addition to compression speed, yield pressure can be impacted by … materials that are polymorphs or salt forms, the moisture content of the material, particle size, or particle shape.**

However, many materials do not precisely match these categories, which means a way of investigating how a particle may behave when compressed is required. "We can investigate a little bit more by performing the Heckel test," Stone added.

The Heckel analysis was originally created for metallurgy but was adopted by the pharma industry to assess compression properties of materials (2). The analysis basically involves compressing material and then plotting the relative density of the material against punch pressure (2). "We take a small amount of material—it takes less than three grams to do a Heckel test—we compress it at a constant speed, and then we calculate the yield pressure," Stone said.

"Lots of materials can be sensitive to speed of compression," Stone added. "If you have assessed the material in a lab setting on a small piece of equipment, it is possible that the material will behave differently once you scale-up onto a larger piece of equipment that has a faster running speed."

A way to combat this potential discrepancy is to perform the same test at production relevant compression speed and compare the changes in yield pressure to determine the strain rate sensitivity (3). Once plotted, in a graph of strain rate sensitivity versus yield pressure, it is possible to categorize materials and determine whether you need to balance out the formulation to improve tabletability.

"If you have identified a material and it has properties that are not necessarily ideal for tableting, you can decide to add in different ingredients to balance it out," Stone said. "So, if you have a material that is too soft and plastic you might want to add in some brittle materials, or vice-versa, to balance the formulation and make it more suitable for tableting, for example. Therefore, through identifying the material characteristics you have a good idea of where to start with the formulation design."

In addition to compression speed, yield pressure can be impacted by a few other things, such as materials that are polymorphs or salt forms, the moisture content of the material, particle size, or particle shape. "Moisture is a plasticizer, so it can lower the yield pressures, and particle size can be quite important, particularly if micronization is involved, because really small particles behave completely differently sometimes to the larger particles from which they originated," Stone confirmed.

**Bonding and tablet strength.** During compaction, when the particles have deformed and fragmented and moved closer to each other, with the compression forces being applied, bonds are formed between the particles. As the number of inter-particulate bonds increase, then so too does the strength of the tablet.

"What we are trying to do during tableting is reduce the volume of the formulation blend and promote bonding between the different ingredients," Stone said. "The success of tableting—deformation and bonding—can be measured by looking at the tensile strength."

In essence, when plotting the tensile strength as a function of compaction pressure, it becomes apparent that on increasing the compression forces, the compact thickness decreases and there is a region where the material has tablet-like properties, which is desirable for tableting. If there is insufficient force applied, the tablets will not be formed, and if there is over-compression, then capping and lamination can occur. "If the process is in the over-compression region, then it is on the edge of failure all the time," stressed Stone. "This can lead to tablets that look ok but perhaps have cracks and deformities within that cause capping and lamination."

## Formulation design

It is possible to use various data from compaction simulators to help determine whether the formulation design will be viable for a tableting process. Tabletability is an assessment of the tensile strength versus punch pressure; compactability is solid fraction versus tensile strength; and compressibility is punch pressure versus solid fraction.

When assessing tabletability, small batches of formulation are needed and it is possible to make the tablets at different speeds and see whether or not an appropriate tensile strength is achievable. "Although it is recommended for a formulation to be able to achieve a tensile strength of at least 1.7 MPa, it doesn't necessarily mean that the production target needs to be the same," Stone said. "However, if the formulation cannot achieve good strength then there will probably be issues during production."

Compactability, which is independent of the speed of manufacture, can be used to explain the impact of density on tablet hardness. "It is possible to perform a roller compaction simulation to show how the blend will perform," added Stone. "This performance can then be compared against all the different solid fractions, and all the various options that are available for the formulation blend will be apparent." As an example, a potential roller compaction blend with a low tensile strength would be indicative of a blend that will not provide robust roller compaction ribbons—the ribbons will mill to very fine powders—so it may be worthwhile to use different binders or fillers in the formulation to improve the tensile strength.

"Compressibility is really good for our understanding of press process and understanding of the settings that may be required when scaling up," explained Stone. By looking at compressibility, material wastage can be avoided during process set-up as it is possible to work out what might be required to achieve the desired solid fraction.

## Useful tool

"Compaction simulation can be used in early development and only requires small amounts of material," said Stone. "It's really useful to understand the drug properties that you have before you start formulating, but compaction simulation can also help you to predict what is going to happen with those formulations at early stages, when there is a chance to alter the blend."

"Additionally, compaction simulation can be used to predict scale-up behavior and optimize the properties of new molecules in production," she added. "Furthermore, compaction simulation is pretty fast and saves on materials."

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## Suppliers plan for chloroquine capacity

Following reports that hydroxychloroquine and chloroquine are under evaluation in clinical trials as a potential treatment of COVID-19, drug companies are donating doses and planning for ramping up supply.

Bayer announced in a March 19, 2020 press release that it will donate 3 million tablets of the drug Resochin (chloroquine phosphate). It is currently not approved for use in the United States, but Bayer said it is working with appropriate agencies on an Emergency Use Authorization for the drug's use in the US (1).

Novartis announced in a March 20, 2020 press release that it will donate up to 130 million doses of generic hydroxychloroquine and that it is supporting ongoing clinical trials. The company also noted in the release that it would aim to ensure that patients currently depending on this medicine are not impacted by the donation, and that it is exploring scaling of capacity to increase supply. Novartis Sandoz division currently only holds a registration for hydroxychloroquine in the US, and it will pursue appropriate regulatory authorizations from FDA and the European Medicines Agency, the company reported (2).

Mylan said in a March 19, 2020 press release that it has restarted production of hydroxychloroquine sulfate tablets at its West Virginia manufacturing facility in the US to meet the potential for increased demand resulting from potential effectiveness of the product in treating COVID-19. Mylan's drug is approved by FDA for the treatment of malaria, lupus erythematosus, and rheumatoid arthritis. The company said it is also taking steps to initiate production of this product outside the US in the coming weeks. The press release noted that Mylan expects to be in a position to begin supplying product by mid-April, and with currently available API, will be able to ramp up manufacturing to provide 50 million tablets (3).

Teva said in a March 20, 2020 press release that it would donate more than six million doses of hydroxychloroquine sulfate tablets, which are approved by FDA for malaria, lupus erythematosus, and rheumatoid arthritis, to US hospitals as an investigational target to treat COVID-19. "Additional production of hydroxychloroquine sulfate tablets is also being assessed and subsequently ramped up with materials that are being sent to Teva from our ingredient supplier. Teva will ship six million tablets through wholesalers to hospitals by March 31, and more than 10 million within a month," the company said in the press release (4).

FDA noted in a March 19, 2020 press release that it would ensure the drug would remain available for patients who take it to treat severe and life-threatening illnesses, such as lupus (5). While cautioning that first the efficacy of the drug in treating COVID-19 must be ensured, FDA Commissioner Stephen Hahn, MD, said in the press release, "At the same time, we will engage with domestic manufacturers to ramp up production of this product to mitigate any potential supply chain pressures. If clinical data suggests this product may be promising in treating COVID-19, we know there will be increased demand for it."

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—*The editors of* Pharmaceutical Technology

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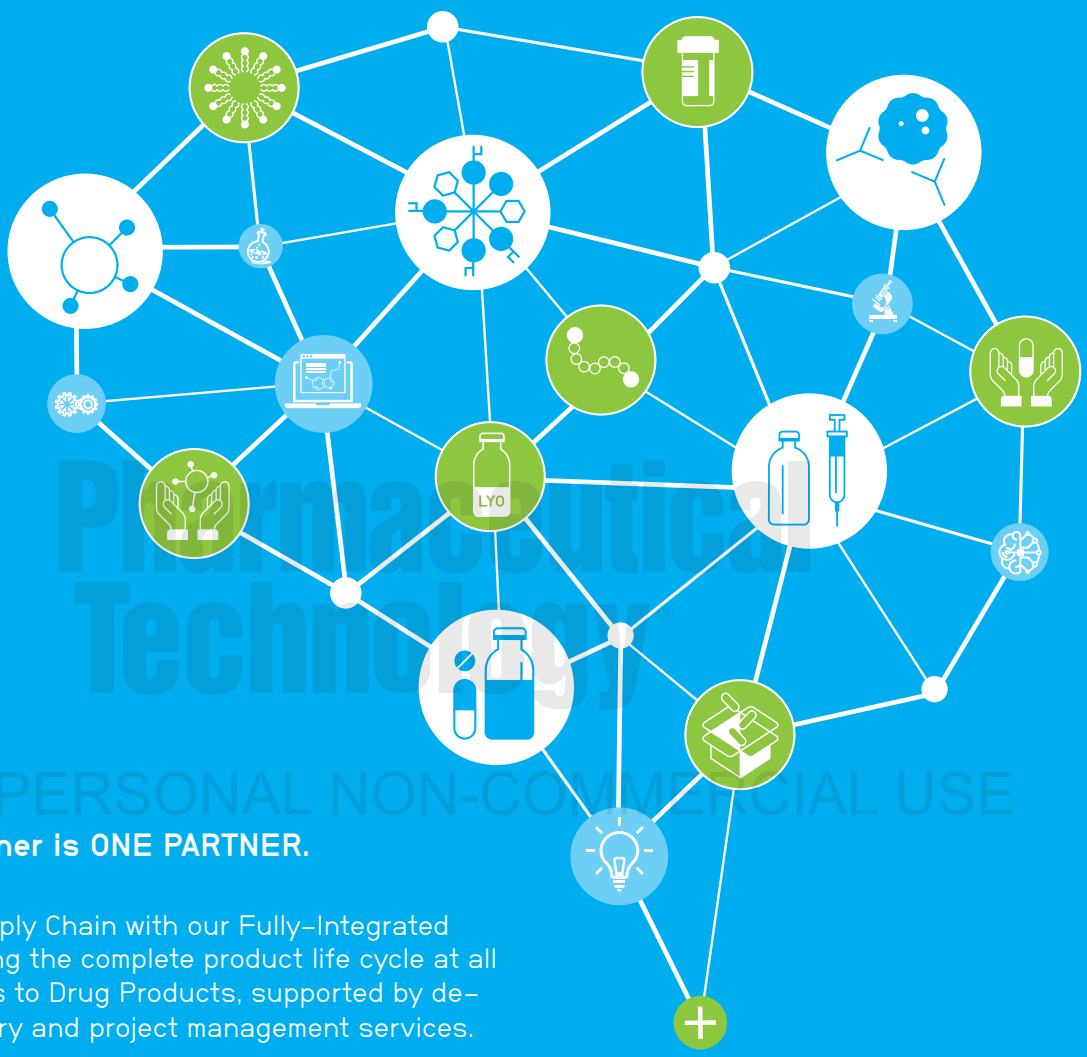




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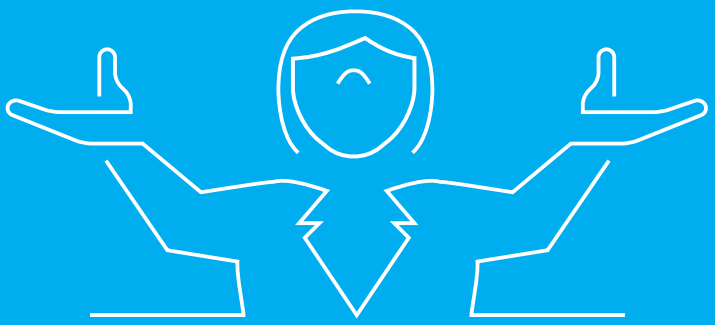

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# Considerations for Tablet Compression with Multi-Tip Tooling

Frederick Murray

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**The prospect of using multi-tip tools to increase production output on a single tablet press has long been considered by process engineers who seek additional capacity with minimal capital investment. The math is simple: a press tool design with two or three tips will produce two or three times the output of a press running with single-tip tools. There are technical and validation challenges, however, that are often difficult to navigate.This article examines multi-tip tool technology and the process control and validation issues that must be carefully evaluated to assess the potential for success.**



**Frederick Murray** is president of KORSCH America Inc, fred.murray@korschamerica.com.

Rotary tablet presses are configured with press tools consisting of an upper punch, lower punch, and die. For most applications, the upper punch has a single tip, which is configured to match the geometry of the tablet being produced. Tablet press tooling geometry is governed by the US standard in the American Pharmacists Association's Tableting Specification Manual (TSM) (1) and the European Euronorm standard (2). These standards define the tooling length, tool head geometry, and related tolerances. Most modern tablet presses offer an exchangeable turret capability that permit tablets of different sizes (using different tool standards) to be produced on the same press. **Table I** lists typical turret configurations for a single and double-sided press.

For all tablet press designs, the pitch circle of the die table for a given press is fixed, and the number of punches is different to meet varying tooling standards; this set-up allows, for example, an increased number of punch stations when the die size is smaller. For a single-sided tablet press, which produces one tablet per revolution, at any given press speed, the output is calculated by **Equation 1:**

Output (tablets/hour) = Press speed (revolutions/min) x Number of punch stations x 60 min/h. **[Eq. 1]**

## Options to increase output

Many customers leverage exchangeable turret technology to maximize output based on tablet size. For example, for an 8-mm tablet running on a standard 35-station B turret at 80 RPM, the output is calculated as follows using **Equation 1**:

Output = 80 rev/min x 35 x 60 min/hour = 168,000 tablets/h.

For the same tablet on a 47-station BBS turret at the same press speed, the output would be:

Output = 80 rev/min x 47 x 60 min/hour = 225,600 tablets/h.

The use of the BBS turret, with identical processing parameters including press speed, compression dwell time, and feeder dwell time, has resulted in an output improvement of 34.3%.

For double-sided rotary presses, which produce two tablets per revolution and are designed for high volume pro-

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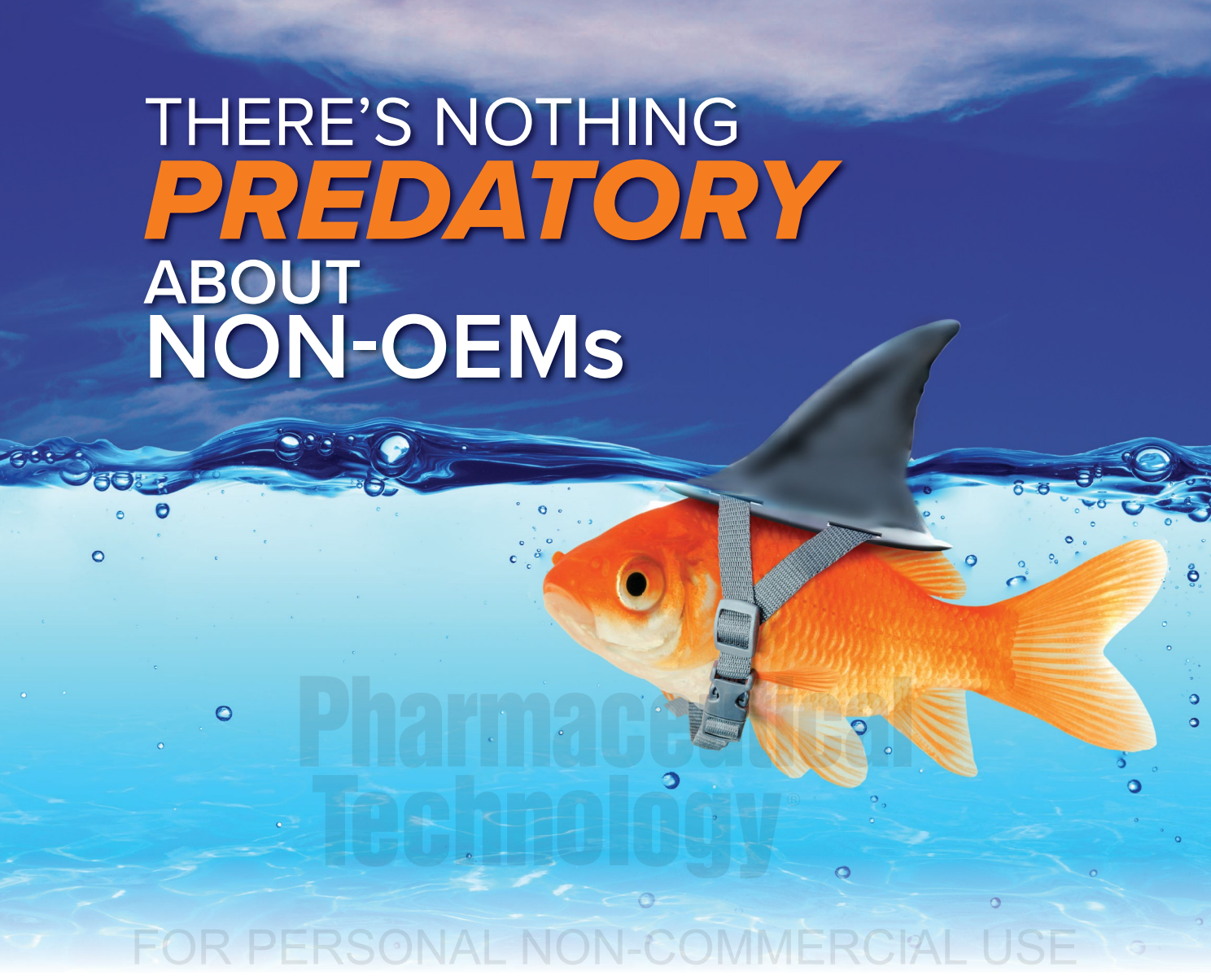



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**Table I: Tablet press turret configurations. TSM is Tableting Specification Manual and EU is Euronorm.**

| Turret specification | Maximum tablet diameter | Nominal punch barrel diameter | Nominal die diameter | Number of punch stations (single-sided press) | Number of punch stations (double-sided press) |
|---|---|---|---|---|---|
| TSM or EU D | 25 mm | 25 mm | 38.10 mm | 29 | 59 |
| TSM or EU B | 16 mm | 19 mm | 30.16 mm | 35 | 71 |
| TSM or EU BB | 13 mm | 19 mm | 24.00 mm | 44 | 87 |
| TSM or EU BBS | 11 mm | 19 mm | 21.00 mm | 47 | 95 |

duction, the number of punch stations and nominal turret sizes are listed in **Table I**.

At any given press speed, the output is then calculated using **Equation 2**:

Output (tablets/hour) = Press speed (rev/min) x Number of punch stations x 2 x 60 min/h. **[Eq. 2]**

For the same 8-mm tablet running on a standard 71-station B turret at 60 RPM, the output is calculated as follows:

Output = 60 rev/min x 71 x 2 X 60 min/h = 511,200 tablets/h.

For the same tablet on a 95-station BBS turret at the same press speed, the output becomes:

Output = 60 rev/min x 95 x 2 x 60 min/h = 684,000 tablets/h.

The use of the BBS turret, with identical processing parameters including press speed, compression dwell time, and feeder dwell time, has resulted in an output improvement of 33.8%.

Running a product on a turret that maximizes production output is an excellent strategy for maximizing tablet compression capacity. However, whenever a significant increase in tablet production capacity is required, the issue of multi-tip tools (see **Figure 1**, for example) is often at the center of the discussion.

Based on the tablet size and tool specification, it is often possible to configure the upper and lower punches with multiple tips that will compress and eject multiple tablets at each punch station. In theory, the use of multi-tip tools can dramatically increase production capacity by the multiple of the tips that can fit on the press tool. In general, the number of tips that can be incorporated on a single punch is a function of the tablet size and the turret being utilized, as listed in **Table II**.

Returning to the example of the 8-mm tablet, using a 5-tip tool configuration on the 59-station turret would achieve an output as follows:

Output = 60 rev/min x 59 x 5 x 60 min/h = 1,062,000 tablets/h.

This represents an improvement of 107% of the nominal output achieved with single-tip tools on the 71-station B turret, and an improvement of 55% over the nominal output achieved with the 95-station BBS turret. This appears to be an easy decision for a good return on investment (ROI), as outputs can be doubled and only a single set of multi-tip tools is required. Unfortunately, there are constraints and challenges that make this seemingly simple calculation complicated to implement. Understanding these constraints requires a fundamental understanding of press force control theory and tablet rejection systems on modern tablet presses.

## Press force control theory

Tablet weight is the critical quality attribute for virtually all tablet compression applications. Precision tablet weight control ensures that each tablet delivers the prescribed dosage of active ingredient. Even with the most advanced tablet testing technology, tablet presses can still produce tablets faster than the tablet weight can be measured. Periodic samples and statistical control methods are fine, and there is a secondary parameter—the press force required to produce each tablet—that can be measured in real-time as the basis for automatic tablet weight control. This system permits the real-time, in-process measurement of tablet weight and the ability to reject individual tablets that exceed indicated quality control limits.

In general, press force control theory can be explained as follows:

- If a die is filled with a certain volume of material, and then the volume is reduced by bringing the upper and lower punch tips closer together during compression, there will be a resulting press force.

**Table II: Single-sided rotary press with multi-tip tooling. TSM is Tableting Specification Manual and EU is Euronorm.**

| Turret specification | Maximum tablet diameter (single-tip) | Tablet diameter (multi-tip) | Number of punch tips |
|---|---|---|---|
| TSM or EU D | 25 mm | 6 mm | 7 |
| TSM or EU D | 25 mm | 8 mm | 5 |
| TSM or EU D | 25 mm | 10 mm | 3 |

**Figure 1.** Multi-tip tools, such as this tool from Wilson Tool, can be used to increase capacity.

- If the volume of material in the die is constant, and the final thickness at compression (distance between the upper and lower punch tips) is constant, then the compression force also will be constant.
- If the volume of the material in the die is constant, and the final thickness at compression (distance between the upper and lower punch tips) is reduced, then the compression force will increase.
- If the volume of the material in the die is constant, and the final thickness at compression (distance between the upper and lower punch tips) is increased, then the compression force will decrease.
- Correspondingly, if the final thickness at compression is fixed, and the amount of material in the die is increased, then the compression force will increase; if the final thickness at compression is fixed, and the amount of material in the die is decreased, then the compression force will decrease.
- With the vast majority of tablet presses, compression rollers are fixed during compression. That is, the upper and lower punches are driven to the same position by the upper and lower compression rollers. At a constant thickness during compression, the press force is thus determined by the amount of material in the die, which is the tablet weight.

Along with a high-speed encoder, press force instrumentation, which is generally mounted on the compression roller shaft, permits the peak compression force of each tablet to be measured. This allows the real-time inspection of each and every tablet that is produced. Once the tablet press has been set up to achieve the specified tablet weight, thickness, and hardness, the resulting press force is measured and established as the press force setpoint. To set up press force limits, the tablet weight is adjusted to the high average limit, and the resulting compression force is then established as the high average limit. For the high single-value press force limit, the tablet weight is adjusted once again to the maximum individual tablet weight, and the resulting compression force is then established as the upper reject limit. The same procedure is then utilized to establish the lower average and lower reject limit.

The press force control loop will then measure the press force associated with each and every tablet produced. An average force will be calculated (usually using a moving average algorithm) and compared to the press force setpoint. A low average compression force would indicate that the weight is slightly low, and the tablet press makes a closed loop correction to the dosing cam to increase the amount of material in the dies. A high average force would indicate that weight is slightly high, and the tablet press makes a closed loop correction to the dosing cam to decrease the amount of material in the dies. The adjustments are very precise and configured such that the system is tuned to return to the desired press force without hunting or overshooting the adjustment. If the average compression force violates the upper and lower limits, then the press is stopped instantaneously. This general press force control algorithm has been in use for more than 30 years.

The measurement of individual press forces permits the detection of out-of-spec tablets, which present as a high or low force and which violate the upper and lower tablet rejection limits of the force control system. Most modern rotary tablet presses offer a single-tablet rejection system, which will reliably remove a single tablet from the product stream. A mechanical gate, or more commonly, a very short burst of compressed air, will remove an individual tablet across the full operating speed range of the machine.

## Constraints of multi-tip tools

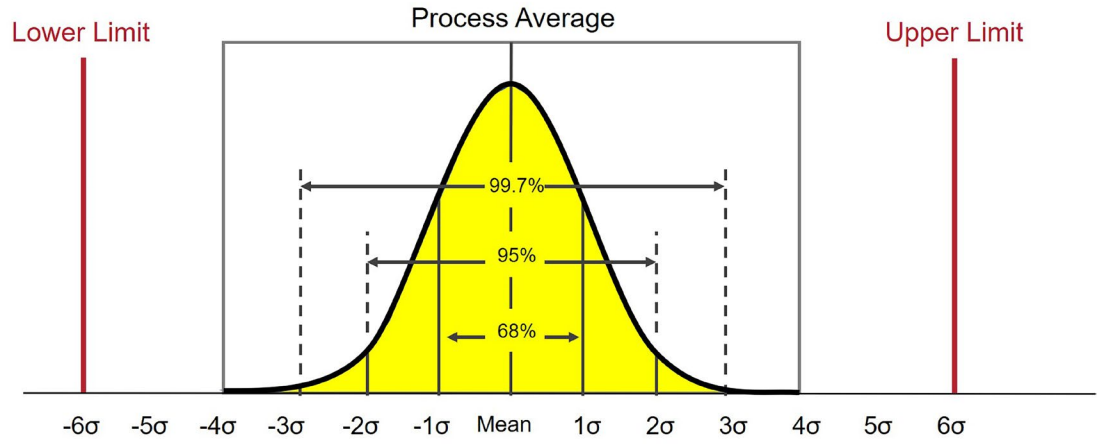
The key constraint in the use of multi-tip tooling is the validation question pertaining to press force measurement and the ability to reject individual tablets that may be out of specification. Press force control theory, which matches an individual press force measurement to a corresponding tablet weight, encounters significant challenges when multi-tip tools are used. In essence, multiple tablets are being produced, but only a single force is being measured.

In theory, a press force associated with multiple perfect tablets may be the same as the press force associated with a combination of overweight and underweight tablets. As such, the use of multi-tip tools does not permit the measurement of the individual press force for each tablet, which eliminates the ability to reject individual tablets. In most cases, this limitation is enough to derail any consideration of the use of multi-tip tools.

There are also additional process constraints that must be considered. When a punch is configured with multiple tips, the force exerted by the head of the punch on the compression roller is cumulative. That is, if one 8-mm tablet

FIGURE 1 IS COURTESY OF WILSON TOOL.

**Figure 2.** The process capability index is the ratio of the upper and lower specification limits, divided by six sigma.




requires a 10 kN compression force, then a press tool with 5 tips will measure 50 kN. In general, products that required higher compression forces will run at a slower press speed than products that require low compression forces. Indeed, in many cases, whatever output gain may be realized with multi-tip tools is quickly offset by the speed reduction associated with the comparably high cumulative compression force requirement.

There is also the matter of die fill. Producing a single, 8-mm tablet of a specific tablet weight will permit a higher press speed than a process where it is necessary to fill five die holes for every punch station. For products that have less than robust flow properties, again, any output gain associated with multi-tip tooling can be offset by the speed reduction required to achieve consistent die fill.

Multi-tip tools are best when the tablet weight control is not critical. Outside of the pharmaceutical industry, for example, producing small mints and sweeteners at rates that exceed 1,000,000 tablets per hour is quite common with the use of multi-tip tooling.

For those who seek to utilize multi-tip tools for pharmaceutical and nutraceutical products, the only way to overcome the press force control/tablet rejection validation constraint is to develop a statistical case that demonstrates consistent and superior process capability—one in which all tablets are well within the specification limits at all times. This requires the calculation of process capability for tablet weight, thickness, and hardness, as described in **Equation 3**.

$$Cp = (USL - LSL) / 6 \times \Sigma \quad [\textbf{Eq. 3}]$$

where Cp = process capability index, USL = upper specification limit, LSL = lower specification limit, and Σ = standard deviation.

The process capability index is the ratio of the upper and lower specification limit, divided by six sigma, which comprehends 99.7% of the process samples, as shown in **Figure 2**. A process capability index of 1.67 or higher is generally considered to be good, but the final determination is a question for the quality control group. In general, the process capability index must be evaluated for all critical process quality attributes, including tablet weight, thickness, hardness, dissolution, and content uniformity.

## Conclusion

The use of multi-tip tools does seem to present a compelling opportunity to significantly increase production output on a tablet press. However, critical and technically valid constraints surrounding product quality and process validation have significantly limited the application of this technology in pharmaceutical manufacturing. The inability to reject an individual tablet, or even to recognize a high or lower individual force associated with a tablet reject, remains the key barrier.

For small tablet formats with low compression forces and superior material flow properties, including mini-tablets, it is possible to leverage the use of multi-tip tools based on a substantial statistical analysis of process capability in the context of specification limits. For larger tablets and higher compression forces, any potential gain with multi-tip tools is usually offset by the need to slow the machine down based on the cumulative press force, and/or the dwell time required to fill multiple die holes on each station. And again, the inability to reject an individual tablet, or even to recognize a high or lower individual force associated with a tablet reject, remains the primary obstacle to successful implementation.

Multi-tip tooling does offer an opportunity for significant capacity increases. However, the high-cost of multi-tip tools as compared to conventional, single-tips must be considered in determining the true ROI.

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FIGURE 2 IS COURTESY OF THE AUTHOR.

# In Top Tablet Form

Felicity Thomas

AJISAI13 - STOCK.ADOBE.COM

**OSD forms are popular within the industry due to the various advantages they offer, but there are specific considerations required to get the best OSD form possible.**



According to market research, the global oral solid dosage (OSD) formulation market is projected to experience growth, potentially reaching $926.3 billion by the end of 2027 (1). As the most common form of pharmaceutical dose used in the world, not only do OSDs offer a cost-effective option for manufacture but they also provide advantages in terms of ease of packaging and transportation, compared with other dosage forms.

To discuss some of the key considerations, potential issues, available techniques and solutions, and best practices that formulators and manufacturers should keep in mind when approaching OSDs and tableting, *Pharmaceutical Technology* spoke with Rob Blanchard, research, development and quality systems manager, I Holland; John McQuaid, vice-president of technical operations, Almac Pharma Services; and Michael Wilkins, head of formulation and process development, Almac Pharma Services.

## Key formulation considerations

**PharmTech:** What are some of the key considerations for formulating a robust OSD drug?

**Wilkins (Almac):** For formulators and developers, it is essential to have information about a compound's solubility and permeability. Knowing the position of the drug in the Developability Classification System (DCS) helps determine an appropriate formulation strategy for an OSD form. In addition, understanding the compounds' degradation pathway and sensitivities to environmental conditions maintains focus on the stability of the drug product. Together, these considerations direct the formulator to develop a robust drug product with optimal release profile and shelf-life.

Standard functional excipients are incorporated into OSD forms. These can include diluents, disintegrants, binders, glidants, preservatives, and lubricants to name a few. They should be biologically inert, but they play a role in the performance of the drug product and impact on the robustness of the manufacturing process. They should not negatively impact the stability of the product, and so selection of different materials and grades is important to produce the ideal formulation.

## Techniques for improvements

**PharmTech:** Are there techniques that can be used to improve the solid dosage formulation for specific patient populations?

**McQuaid (Almac):** It is imperative that dosages are designed with the particular patient population in mind—for example, specific formulations for pediatrics or other patient populations who may have difficulty swallowing conventional solid dosage forms such as capsules or tablets. Common techniques that are employed to help with the challenges of these specific patient requirements include modifying release formulations to improve patient convenience/compliance, taste masking, and changes to the dosage form itself.

In particular, age-appropriate formulations, especially for pediatrics, is an area that requires much consideration. Industry is witnessing significant growth in multi-particulate formulations, such as mini-tablets that are filled into unit dose stick packs or proprietary dispensing devices where the dose can be adjusted at the point of pharmacy dispensing to suit the bodyweight of the patient. An alternative approach is powder-in-bottle or powder-in-sachet formulations, which are also growing strongly.

## Potential problems during tableting

**PharmTech:** From your experience, what are some of the main aspects of a pharmaceutical formulation that could cause issues when compacting/compressing into an OSD form?

**Blanchard (I Holland):** Sticking is one of the most common problems to affect tablet production and occurs when granule builds-up on the punch tip face. Sticking has huge implications on production, causing tablet press downtime and reduced tablet output. Pinpointing the root cause of sticking is very challenging, but the main causes include:

- **Undesirable moisture within the formulation.** Moisture can enter into the process either in wet granulation or due to excess humidity in the compression chamber in a non-environmentally controlled area. Effective solutions include the use of hydrophobic, anti-stick coatings applied to the tooling, which repel rather than attract moisture, and utilizing the optimum dwell time.
- **Abrasive formulation.** Compressing ingredients containing high quantities of hard, sharp-edged elements can scrape away or penetrate the surface of the tool when repeatedly compressed. Eventually the wear can create traps, which lead to sticking. To help with abrasive formulations, consider wear-resistant tool steel, coatings, and treatments.
- **Poor tool maintenance.** Tablet tooling should have an appropriate surface finish. If this is left to deteriorate, over a period of time, due to the continuous compaction of granules, it will lead to tableting defects, such as sticking, owing to the worn, uneven finish. It is important to implement a planned maintenance process to keep tooling in optimum condition. The most effective process should include the seven steps of clean, assess, repair, measure, polish, lubricate, and store.

## Solutions to tableting issues

**Pharm Tech:** What process solutions are available to help overcome challenging formulations in tableting?

**Blanchard (I Holland):** There are a number of solutions, and it is really dependent on the problem; however, tool coating selection can have a fundamental impact. With the correct specialized coating or treatment applied, some of the biggest challenges that can delay production, such as corrosion, wear, and sticking issues, can be avoided. What is crucial, when it comes to choosing a tool coating, is understanding the product being compressed. Match the properties of the formulation to the coating, so for example, if the formulation is particularly abrasive, use an anti-wear coating that will improve the hardness of the tooling.

Correctly matched coatings allow for better tableting efficiency and output by reducing the requirement for tools to be taken out of production for additional cleaning and maintenance work to remove problematic residue. There is a tool coating to suit every requirement, whether that is preventing sticking, reducing wear, or withstanding corrosive properties.

## Best production practices

**Pharm Tech:** Are there any best practices you could share with drug formulators to achieve optimal tablet production?

**Blanchard (I Holland):** For optimal tablet production, improve workplace skills. It's all very well investing in the latest high-speed tablet press and innovative tooling, but this can be compromised without a trained and knowledgeable team in place who understands how to use and maintain the equipment correctly. Improving and recording levels of workplace skills is critical to the success of efficient modern manufacturing.

Investing in learning and development provides several benefits, such as reduced downtime, increased productivity, and increased profit. Effective, planned training will not only save on labor by anticipating problems that could halt production before they occur, but ultimately, will also create a better educated workforce.

Another best practice to optimize production is through a tool management system (TMS). The efficient and accurate management of punches and dies is vital to optimize output and profitability. Through computer-based monitoring systems, productivity per punch can be maximized more effectively to meet with high-capacity manufacturing requirements. Any problems within tool inventory management can have serious implications on the bottom line. Crucially, manufacturers should have a complete audit trail covering tooling usage and maintenance, which a TMS can fulfill. This is not only good practice, but an important regulatory requirement in the majority of pharmaceutical environments.

## Trends for the future

**Pharm Tech:** What trends do you foresee happening in the field of solid dosage formulations and tableting over the coming 5–10 years?

## Advances in oral solid dose drug development

**Emergent BioSolutions to Develop Oral Vaccine**

Emergent BioSolutions has announced a development and clinical materials agreement to develop an oral vaccine candidate to fight the COVID-19 coronavirus. Under the agreement with Vaxart, a clinical-stage biotechnology company, Emergent develop and manufacture Vaxart's experimental oral vaccine candidate for COVID-19.

Development services will begin immediately, and, upon Vaxart's election, Emergent will produce clinical material to initiate a Phase I clinical study, which is anticipated for early in the second half of 2020. Vaxart's oral recombinant vaccine candidate is based on its proprietary variant annotation analysis and search tool (VAAST) platform.

Emergent will provide development services out of its Gaithersburg, MD, location and manufacture drug substance at its Bayview facility in Baltimore, MD, which is a designated Center for Innovation in Advanced Development and Manufacturing (CIADM) by the United States Department of Health and Human Services. This facility has the capacity to produce tens to hundreds of millions of doses of vaccine annually. Additionally, it is capable of producing at clinical scale and in parallel, allowing scale-up to produce commercial volumes.

"Emergent is pleased to deploy our nimble [contract development and manufacturing organization] CDMO expertise to support fellow innovators, like Vaxart, and advance an experimental COVID-19 vaccine candidate," said Syed T. Husain, senior vice-president and CDMO business unit head at Emergent BioSolutions, in a company press statement (1).

"I'm pleased that we are joining forces with an experienced manufacturer such as Emergent to help advance our oral COVID-19 vaccine to the clinic," said Wouter Latour, MD, CEO of Vaxart, in the press release. "We believe an oral vaccine administered using a room temperature-stable tablet may offer enormous logistical advantages in the roll-out of a large vaccination campaign, and Emergent is a great partner to help in this endeavor."

**Aprecia, Purdue University Partner for 3-D Printing Projects**

Aprecia Pharmaceuticals, a pharmaceutical company headquartered in Blue Ash, OH, and Purdue University's College of Pharmacy announced on Feb. 20, 2020 that they are partnering on future 3DP pharmaceutical equipment and medications. Aprecia was the first company to receive FDA approval, in 2015, for a 3D-printed medication.

"Aprecia's mission is to maximize and expand its 3DP technology platform through global partnerships that will provide pharmaceutical solutions for unmet patient needs," said Chris Gilmore, Aprecia CEO, in the press release (2). "Purdue University is an esteemed institution, and we are confident that this partnership will advance our future in 3DP pharmaceutical research and development."

"Purdue University is committed to its investment in drug discovery and development as well as student and faculty enrichment that will continue to yield global advancement in medicine and healthcare," added Eric Barker, dean of Purdue's College of Pharmacy, in the press release. "As a College, our mission is to prepare the next generation of leaders in pharmacy. Partnering with Aprecia aligns perfectly with that mission. We are excited to combine our talented students and faculty with the successful researchers at Aprecia to work together to accelerate discoveries in this emerging field."

**References**


1. Emergent Biosolutions, "Emergent BioSolutions Signs Development and Manufacturing Agreement with Vaxart for their Experimental Oral Vaccine Candidate for Coronavirus Disease," Press Release, March 18, 2020.
2. Aprecia Pharmaceuticals, "3D Pharmaceutical Printing is the Focus of Aprecia-Purdue Partnership," Press Release, Feb. 20, 2020.


—*The editors of* Pharmaceutical Technology



**McQuaid (Almac):** As well as an increasing use of appropriate technologies to address issues related to poorly soluble drugs, we also foresee an increase in the requirement or technologies to safely handle the development and manufacture of more potent drugs. We also see a trend of batch sizes decreasing as medicines are targeted towards smaller patient population in line with the growing trend in orphan and ultra-orphan indications.

**Blanchard (I Holland):** The mass appeal of tablets and rising competition from emerging markets is pushing manufacturers to find quick, efficient, and cost-effective methods of producing high-quality tablets. To accomplish this goal, the implementation of continuous manufacturing (CM) will be an important trend in the future of tablet manufacture.

For CM to be successful, manufacturers must utilize innovative solutions and technology, including the correct tool steel and coating choices, for example, or appropriate tablet design. The use of specialized tooling that helps to achieve higher press speeds with challenging products and formulations will also be highly important to minimize manual intervention such as tool cleaning or replacement and maximize the benefits of CM.

To take these different elements of CM into account and lead the way to cost-effective and efficient processes, manufacturers should seek expert advice from tooling manufacturers so the appropriate adaption and updates can be made to current production processes and designs.

## Reference


1. Future Market Insights, "Oral Solid Dosage Formulation Market," futuremarketinsights.com, Market Report, July 18, 2017. **PT**


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## Sanofi to Create European API Giant

Sanofi has announced plans to create what potentially would be the world's second largest API manufacturing company to serve the pharmaceutical market, with €1 billion (S1.1 billion) in expected sales by 2022, the company reported in a Feb. 24, 2020 press statement (1).

Citing increasing medicine shortages and a reliance on API supplies from Asia, Sanofi noted in the statement that "the new entity would contribute to supporting and securing API manufacturing as well as supply capacities for Europe and beyond."

The new company would combine Sanofi's API commercial and development activities with six of its European API production sites in Brindisi, Italy; Frankfurt Chemistry, Germany; Haverhill, UK; St. Aubin les Elbeuf, France; Újpest, Hungary; and Vertolaye, France.

Plans to launch an initial public offering will be evaluated for an anticipated decision by 2022, the company reported. In addition, Sanofi said it plans to establish a long-term customer relationship with the new API supplier and will hold a minority stake in the new company.

"Based on the expertise and experience built over decades within our industrial network, this new entity would help ensure a greater stability in supplying drugs to millions of patients in Europe and beyond," said Philippe Luscan, executive vice-president, global industrial affairs at Sanofi in the press statement.

*Source: Sanofi, "Sanofi to Create New Industry Leading European Company to Provide Active Pharmaceutical Ingredients," Press Release, Feb. 24, 2020.*

## USP Offers Support for COVID-19 Drug Developers

The US Pharmacopeia (USP) is offering free technical assistance to developers of antiviral drugs and vaccines and experts from regulatory authorities to combat the COVID-19 pandemic. The organization's scientific teams are available to help drug developers ensure the quality of materials during scale up and to design tests to ensure the quality of materials, according to a March 18, 2020 statement.

USP also will offer support for manufacturers of treatments for secondary implications of the outbreak, such as bacterial infections.

Available assistance includes test methods to meet regulatory expectations, qualification of excipients and raw materials to be used in manufacturing; USP Reference Standards, which can be used to demonstrate the suitability of methods and for the development and validation of analytical methods; and technical assistance to those interested in following USP processes and use USP standards.

In addition, USP is making select published monographs and General Chapters available for free.

*Source: USP, "US Pharmacopeia (USP) Offers Support for Developers of COVID-19 Antiviral Drugs and Vaccines," Press Release, March 18, 2020.*

## Migraine Therapy Approved in ODT Format

FDA has approved NURTEC ODT (rimegepant), an orally disintegrating tablet developed for the acute treatment of migraine in adults from Biohaven Pharmaceutical Holding Company. The drug was developed using the proprietary Zydis technology from Catalent; the freeze-dried tablet disperses almost instantly in the mouth without water, providing patients with a convenient dosing option, Catalent reported in a March 17, 2020 press statement.

NURTEC ODT, the first calcitonin gene-related peptide receptor antagonist available in a fast-acting ODT, is the first FDA-approved product for Biohaven.

"Since rapid onset of relief is consistently ranked among the most important attributes of acute migraine medications, along with the benefits of easier administration without water, Zydis is an ideal platform for the delivery of acute migraine treatments," said Jonathan Arnold, president, oral and specialty delivery, Catalent, in the press statement.

Catalent's Swindon, UK facility develops and manufactures more than one billion ODTs annually.

*Source: Catalent, "Catalent Partners with Biohaven on New Fast-Dissolve Migraine Treatment," Press Release, March 16, 2020.*

## CMOs Report No Pandemic-Related Interruptions

The Pharma & Biopharma Outsourcing Association (PBOA), a trade group representing contract manufacturing organizations (CMOs) and service providers in the bio/pharmaceutical sector, issued a press release on March 17, 2020, stating member companies report "no material disruptions to their operations" during the ongoing coronavirus pandemic.

"Our member companies stand ready at full capacity to produce the drugs, vaccines and other therapeutics their customers supply to patients in the US and abroad. As the COVID-19 pandemic unfolded, we surveyed our members regularly about potential supply disruptions due to supply chain issues; they continue to report no material shortages of ingredients or key components," said Gil Roth, PBOA president in the statement.

"Our members are diligent about the health of their employees, taking internal steps to minimize the number, size and frequency of in-person meetings, as well as restricting visits from customers and consultants, and staggering shifts to reduce potential for contact," Roth continued. "As the virus spreads in the US, they presently report no material operational or staffing issues related to personnel or their families becoming ill."

"PBOA's member companies have significant capacity and technical resources that can be further deployed to bring important drugs and vaccines to patients as this crisis continues to develop," said PBOA Chairman Peter Bigelow in the statement. "Some are already involved in the manufacture of investigational compounds to be used in clinical trials against COVID-19."

*Source: PBOA, "PBOA Members Committed to Continuing to Reliably Manufacture Drug and Vaccine Products," Press Release, March 17, 2020.*

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