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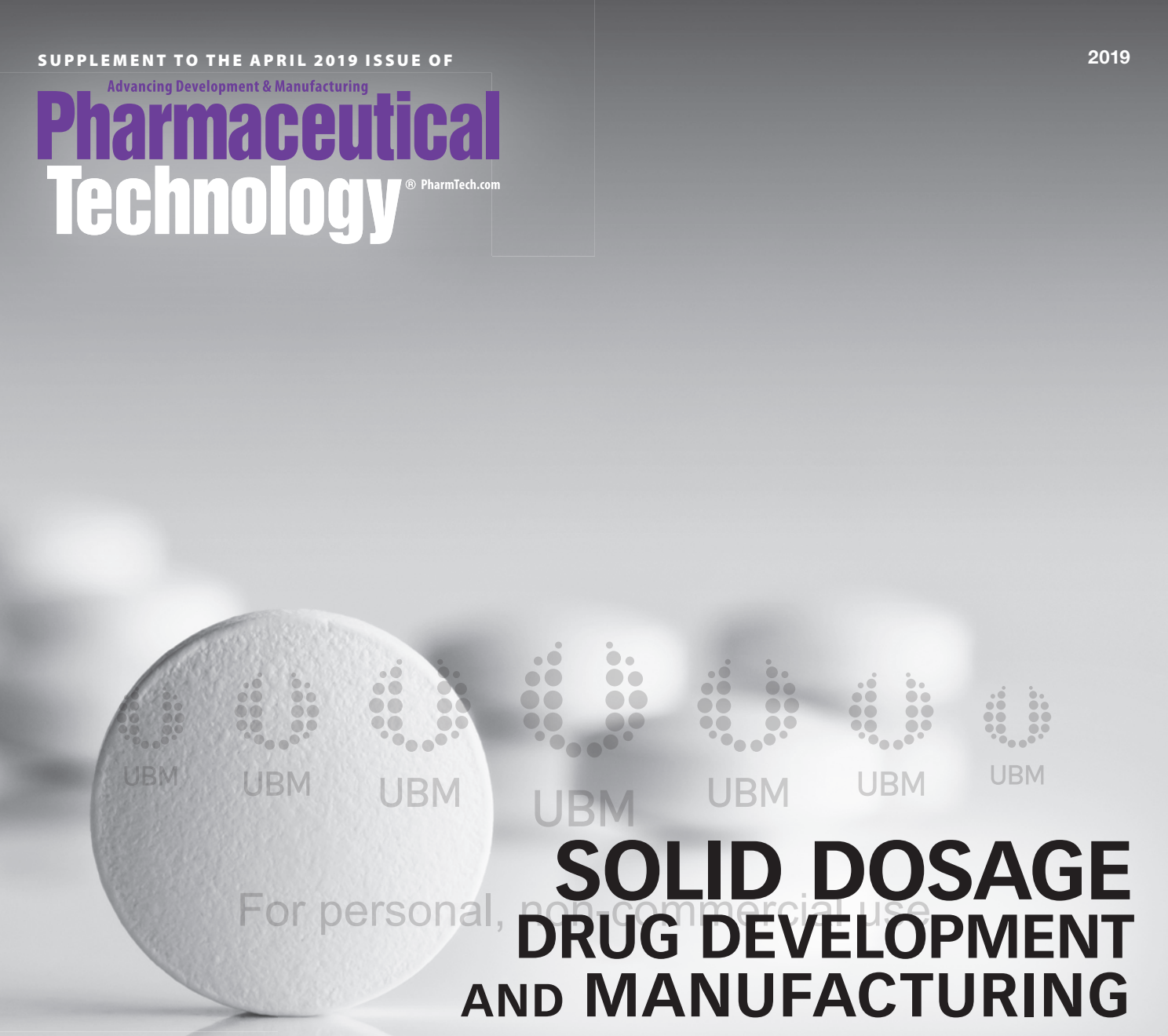

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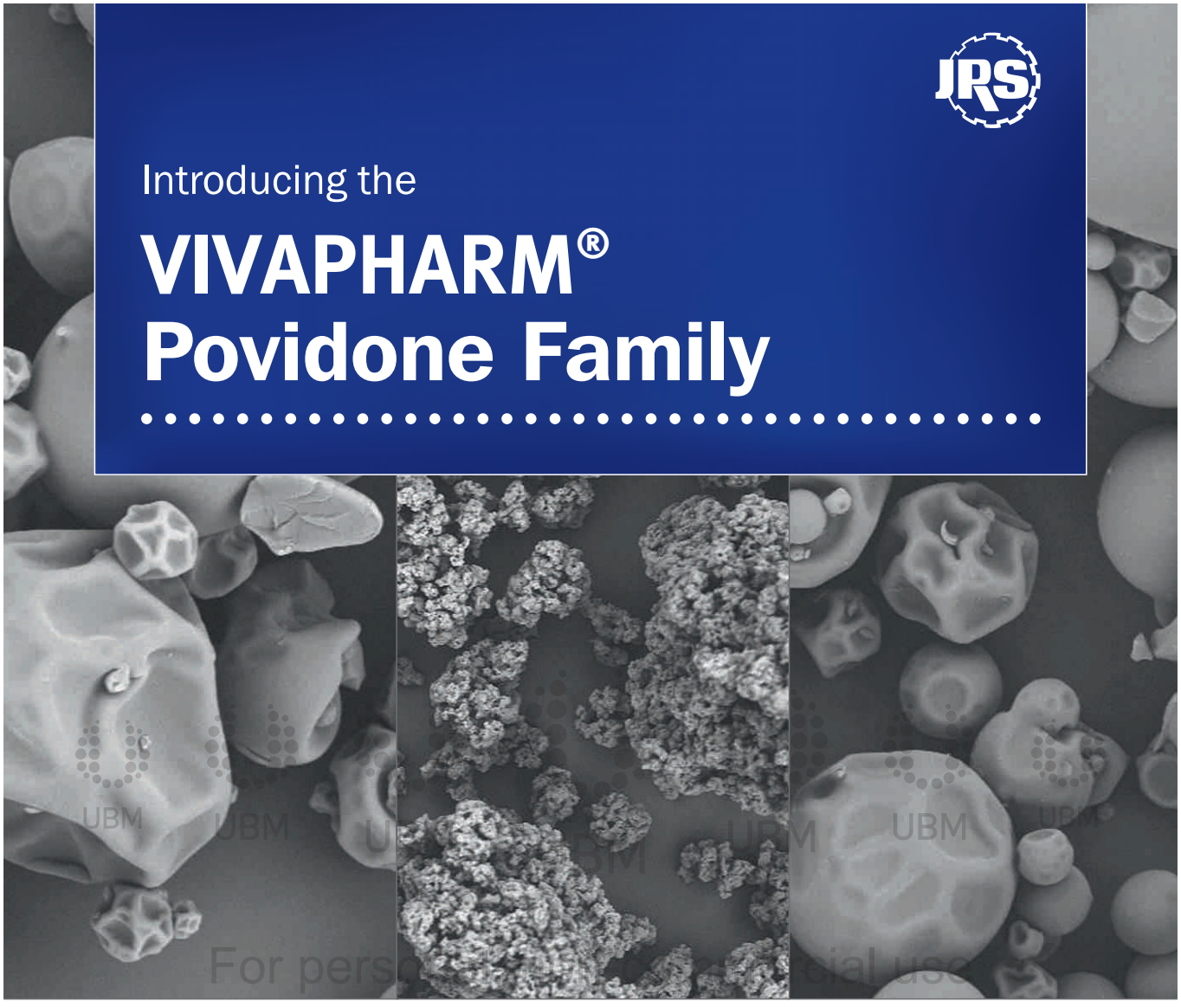

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Modified-Release Formulations: Improving Efficacy and Patient Compliance

Philippe Gorria and Jérôme Revel

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Modified-release oral dosage forms can offer benefits to both formulation scientists and patients.

Modified-release (MR) drug delivery systems are developed to control the rate and/or the site of release of drugs to achieve specific clinical objectives that cannot be attained with conventional dosage forms. There are clear advantages of using MR oral dosage forms, such as improved efficacy, reduced adverse events, increased convenience, patient compliance, and performance.

The use of MR pellet technology offers even more advantages to manufacturers. For example, it is easy to modify the drug dosage by using different filling mass when filling capsules with pellets. It is also possible to combine two or more drug products in a single carrier (i.e., capsules) to obtain a fixed-dose combination (FDC).

In this article, Jérôme Revel, senior development engineer, and Philippe Gorria, Pharmaceutical Development senior director at Recipharm, discuss why more drug developers and manufacturers are exploring the use of MR oral dosage forms and the benefits it can offer both formulation scientists and patients. They also outline the challenges companies need to overcome in order to successfully produce these products.

Market demand for MR systems

There are a number of trends contributing to increased interest in MR. Commercially, the interest in developing new products with improved properties based on existing molecules is increasing. The revenues from such products are usually lower than those of new chemical entities (NCEs), but lower development costs and reduced risks make these projects attractive.

Over the past 15 years, a number of medicines, including several blockbuster products, have arrived at the end of their patent protection and have been opened to the generics market. To extend patent protection, reformulation with extended release properties is a lifecycle management opportunity. Similarly, the MR development of an immediate-release (IR) formulation that is already on the market allows an intellectual property owner to take advantage of an extended market authorization.

Philippe Gorria is senior director of Pharmaceutical Development, and **Jérôme Revel** is senior development engineer, both at Recipharm.

From a therapeutic perspective, MR products offer several potential benefits. The typical advantages that can be achieved could be described as extended release and delayed release. Benefits of these type of formulations include:

- **Sustained blood levels.** Extended-release pellets are useful for all drugs with a shorter than optimal half-life, as they can maintain therapeutic blood level concentrations over prolonged periods with once daily administration.
- **Attenuation of adverse effects.** MR negates the high-peak blood concentrations that may be reached soon after administration with conventional dosage forms. Consequently, adverse effects as a result of the transiently high concentration can be avoided.
- **Improved convenience and patient compliance.** Drugs with short half-lives often need to be given at frequent intervals throughout the day (at least twice daily) to maintain blood concentrations within the desired therapeutic range. The potential reduction of daily doses (to once a day) offered by extended-release products can improve patient compliance and help to avoid missed doses.
- **Protecting acid-sensitive drugs.** With delayed release, an enteric coating is usually used to protect the product until it has passed the gastric bladder and reached the gut. This serves to protect acid-sensitive drugs from gastric acid, and it may reduce the likelihood of certain drugs irritating the stomach.

MR pellet technology and its therapeutic advantages

MR dosage forms can be divided into monolithic and multiple unit formulations. Monolithic forms are often simple to manufacture, as they can usually be produced with conventional tableting processes. Multiple unit preparations, such as pellets, require a more complex manufacturing process, but offer less variable progression in the gastrointestinal (GI) tract and make it easier to combine components with different drugs or varying release profiles.

Because of their spheroidal shape, uniform size, and smooth surface, pellets are of particular interest for the manufacturing of MR drug delivery systems and offer a number of benefits to patients as well.

With pellets in a capsule, it is easy to modify the dose without any formulation modification, as the mass of pellets can be adjusted to obtain the right dosage based on the API assay of the pellets. Pellet materials are also incredibly diverse and are ready to be filled into capsules or sachets, compressed into tablets, or dispersed into liquid suspension—making them suitable for patients that cannot swallow whole tablets or capsules.

For patients, pellet formulations may be provided with pH-sensitive or time-controlled polymer coatings when intended for enteric delivery, (e.g., delivery to the intestine without release in the gastric bladder). This makes the progression of pellets in the GI track less sensitive to variation than with monolithic forms after meals. The risk of dose dumping due to a bad coating is also less prominent than with monolithic forms.

Benefits of FDCs

FDCs have advantages when there is a patient population for whom treatment with a particular combination of APIs in a fixed ratio of doses has been shown to be safe, effective, and contribute to the overall therapeutic effect.

The development of FDCs is being driven by a number of public health concerns as they continue to be increasingly used in the management of HIV/AIDS, malaria, and tuberculosis, which are considered to be some of the foremost infectious disease threats in the world today. They also help to improve patient compliance and convenience of administration because they decrease the number of doses required each day.

For manufacturers, it's simple to combine several types of pellets and demonstrate the stability in a final dosage form for registration after developing the MR formulation and obtaining regulatory approval of each API pellet separately. These combinations create advantages, including lower costs of manufacture compared to the costs of producing separate products to be administered concurrently. It can also reduce the amount packaging and simplifies the logistics of distribution.

Pellet manufacturing processes

The process for manufacturing MR pellets consists of two or more steps depending on the extended-release properties required. The first one is the layering process, which consists of coating the drug substance onto neutral spheres (from 90µm to 1.5mm) to obtain immediate-release (IR) pellets. This step is followed by coating with a functional polymer to obtain MR pellets. Depending on the compatibility between drugs and excipients, a seal-coat can be performed between IR and MR pellets.

The quantity of film coating may be expressed as a percentage coating level. The aim is to find a good ratio between polymer and possible water-soluble pore-forming agent, which is added to modify the permeability characteristic of the coating. The percentage coating level then has to be chosen to reach the target product profile, which will depend on pellet size. A batch of smaller pellets contains a greater total pellet surface area and will require a greater percentage coating level to achieve a controlled-release film of a suitable thickness.

When using aqueous polymer dispersions, it is necessary to ensure the good coalescence of the coating to eliminate membrane porosity. This can be achieved by a curing step at the end of coating either in a fluidized bed or an oven at a temperature above the minimum film-forming temperature. Wurster Fluid Bed Coating (FBC) technology is widely used in the manufacture of MR pellets due to its ability to apply high-quality films. FBC technology is characterized by the

location of a spray nozzle at the bottom of a fluidized bed of solid particles. The particles are moved through a central column, with a fluidizing air stream that is designed to induce a cyclic particle flow upward past the spray nozzle. The nozzle sprays coating solution or suspension concurrently with particle flow. Passing particles move upward into an expansion chamber as droplets deposit on their surfaces. The expansion chamber reduces air velocity to allow particles to circulate back to the coating chamber. It also allows particles to further separate from one another temporarily and minimize the potential for particle agglomeration.

Film-coating processes require evaporative removal of an organic solvent or aqueous vehicle as the film coat is deposited. When organic solvents have to be removed, nitrogen is used and is also recycled within the system. The evaporated solvents are recovered in condensers. When water has to be removed, atmospheric air is used in a once-through system.

Using QbD and DoE to take products from laboratory to commercial scale

Development of a MR dosage form starts with the definition of the target product profile based on clinical needs. In addition to the pharmacokinetic (PK) profile, it is important to define the strength and capsule size to evaluate the right drug-assay target for MR pellets.

Then it is necessary to conduct pre-formulation investigations, for example, to assess the compatibility between the active substance and the chosen excipients (binder, lubricant, stabilizer, plasticizer, rate-modifying component, etc.). This can be performed by mixing API and excipients and following the potential degradation during six weeks at 40 °C/75% relative humidity (RH) in open and closed flasks.

Next, the MR dosage form development needs to be performed by selecting the right excipients and process parameters to achieve robust products. Even if the development is performed at laboratory scale, it is important to keep in mind the future scale-up, robustness, and manufacturability of the product.

In the laboratory, formulation development is performed with a batch size around 1 kg. Successful scale-up in Wurster processing depends on a number of factors, such as batch size, spray rate, atomization pressure, fluidization flow rate, and product temperature.

A quality-by-design (QbD) approach can be used to develop the coated pellets manufacturing process and ensure the quality of the product. The QbD concept is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control as defined by the International Council for Harmonization (ICH) Q8(R2) *Pharmaceutical Development*, effective August 2009 for Europe (1). The process for manufacturing MR pellets is influenced by a complicated matrix of input and output parameters, including critical process parameters (CPPs) and critical quality attributes (CQAs).

Other sources of variability involve changes in equipment, raw materials, and operators—and it is not easy to understand the effect these have on the quality of the product. Managing and controlling CPPs is crucial to product quality and providing flexibility in future processes. After the formulation development is done at laboratory scale, the manufacturing at pre-pilot scale is performed.

A parametric study based on design of experiment (DoE) is then performed. The statistical design of experiments can be applied in the coating process design to help understand the effects of multi-dimensional combinations and interactions of different parameters, including both FBC and solutions/suspensions preparations, on the product quality. This work helps to define the CPPs—that is to say, parameters which have an impact on CQA such as dissolution profiles for MR pellets. The application of the DoE strategy leads to the establishment of a "design space" and manufacturing control strategy. This approach can then be applied from lab-scale activities to industrial scale. Finally, industrial scale-up is undertaken followed by a robustness study, which aims to provide confidence in the fluid bed process and support claims for parameter limits in commercial coating processes. This is the ability of the process to tolerate variability without negatively impacting product quality.

Challenges in MR development

Over the past decade, progress has been made in the development of high-performance polymers and aqueous-based polymeric dispersions, which are suitable for the manufacture of MR dosage forms. However, developing MR formulations with alcohol-resistant properties remains a challenge. Sometimes when a MR product is consumed with alcohol, the MR mechanism could be adversely affected, which could lead to dose dumping (alcohol dose dumping or ADD). In the case of some compounds such as opioids, the dose dumping could result in serious adverse events. Both the United States and European Union have guidelines in place that require manufacturers to assess ADD when developing MR formulations, for example, the guideline on the PK and clinical evaluation of MR dosage forms (2,3).

MR formulation development requires highly specialized equipment and regulatory knowledge. Many pharmaceutical companies simply neither have a sufficient number of MR projects nor the in-house expertise to justify an investment in these capabilities.

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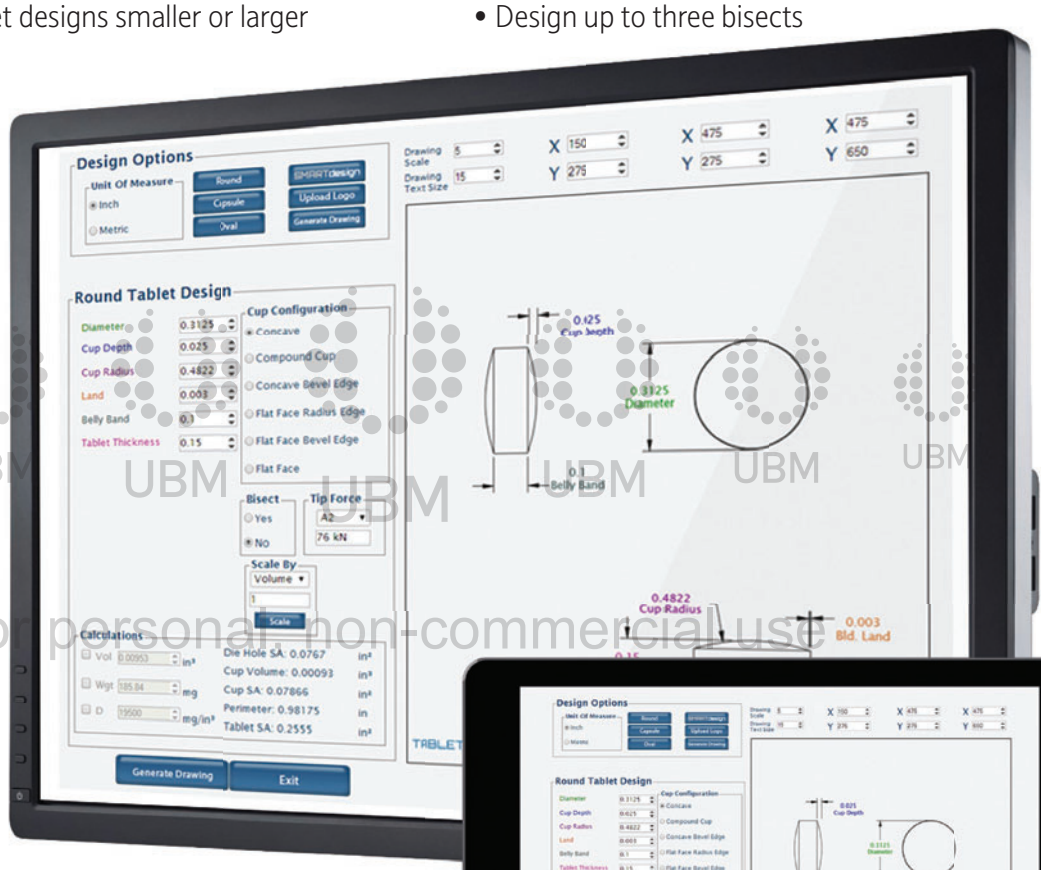

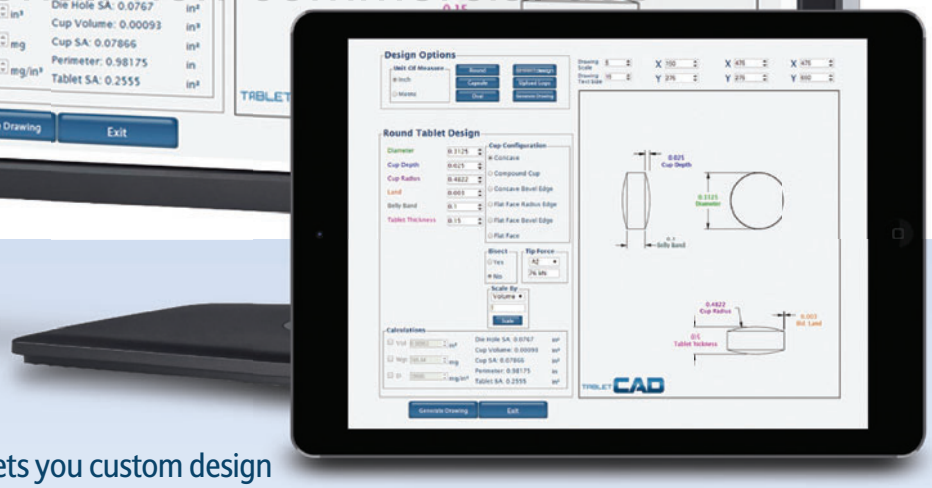

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Gilding the Pill

Kelly Boyer

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Market demand and regulatory guidance continues to promote improved medication design.

Patient acceptability of a drug is a key issue during the development process. With almost four in 10 adults reporting difficulty in swallowing tablets, medication design continues to be a topic of concern for the pharmaceutical industry.

In the case of children, the elderly, and psychiatric patients, their physiological and cognitive responses may be different from those of the general population. Individuals may also experience specific problems associated with health conditions, disease status, and drug therapy-associated factors. Perception of medicines and a willingness to take tablets may be as important as physical difficulties in swallowing or dysphagia.

If a tablet is difficult to swallow, patients may delay taking a dose, choose to skip a dose, or may stop taking a course of tablets. This has an impact on patient safety, therapeutic outcomes, and can also contribute to antimicrobial resistance—if the full dosage regime is not completed.

As the number and variety of medicines available increases and people are living longer, patients are often taking multiple medications and supplements. While taste, smell, and palatability are of importance in developing pediatric formulations, factors to support safe swallowing are crucial for elderly patients, especially to prevent the risk of choking.

Companies are increasingly using innovative approaches to improve patient experience and patient outcomes. They recognize that drugs must meet the needs of target populations. Focusing on the specific needs of patients ensures 'safety-by-design' and has an impact on the drug's success in the marketplace. This may include formulating drugs with extended release profiles to reduce dosing frequency or using combination drugs. However, this approach can lead to larger tablets, which can negatively impact the ability to swallow.

Regulatory guidance

In the past few years, FDA in the United States and the European Medicines Agency (EMA) have issued guidance documents encouraging pharmaceutical companies to design products that promote patient compliance and reduce medication errors. In practice, this means that tablets should be of an appropriate size and shape to enhance swallowability and palatability of the drug. Tablet weight, surface area, disintegration time, and propensity for swelling should all be considered when designing products.

Kelly Boyer is general manager, Film Coatings at Colorcon Inc.

EMA has issued a comprehensive guide on minimizing risk for patients, which considers particular concerns for elderly patients who are prone to esophageal retention and risk of aspiration, and are more likely to experience conditions that lead to impaired swallowing, such as stroke or Parkinson's disease. Both the pediatric and geriatric populations will gain a huge advantage from the advances in pharmaceutical technology, which offers bespoke formulations to meet their specific needs.

One important advance, recognized by regulatory agencies around the world, is the contribution of film coatings applied to tablets and multi-particulate dosage forms; bringing benefits that include:

- Achieving the desired immediate- (IR) or modified-release (MR) profile
- Easing swallowability by increasing mobility compared to an uncoated tablet of the same size and shape
- Improving the palatability of tablets by masking unpleasant tastes and odors
- Improving the esthetic appeal of tablets
- Allowing easy identification, thereby minimizing the risk of medication errors, which are currently reported to harm 1.5 million people each year
- Enhancing the performance of the drug, protecting it from the environment, reducing friability and dusting issues, and ensuring better stability of the overall formulations.

In the past few years, [regulatory bodies] have issued guidance documents encouraging pharmaceutical companies to design products that promote patient compliance and reduce medication errors.

From the point of view of the patient and the regulator, the crucial advantages of film coating are enhanced swallowability, improved visual appeal, and easier identification, which leads to greater patient safety and compliance, as well as fewer medication errors. For the drug company, film coating also improves process efficiency, provides an effective moisture barrier, achieves better core protection, and enhances the mechanical properties of the tablets for their handling during packaging and transport.

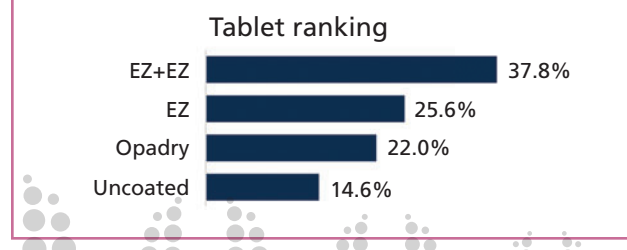
Evaluating film coatings: Study overview

Film coating specialist, Colorcon, has performed many studies to assess potential solutions to the problem of swallowability. It has conducted research into a wide range of associated factors: tablet size, coating, weight, shape, surface area, disintegration time, palatability, and propensity for swelling.

Table I: Study tablet specifications.

#	Tablet specification	Short name
1.	Uncoated placebo tablet	Uncoated
2.	Opadry (Complete Film Coating System) 03F white coated placebo tablet	Opadry
3.	Opadry EZ (Easy Swallow Film Coating System) white coated placebo tablet	EZ
4.	Opadry EZ (Easy Swallow Film Coating System) white and clear top-coated placebo tablet	EZ+EZ

Figure 1: Study participant preference ranking of tablets.



Most recently, the company set up a study, in conjunction with the University of Birmingham, United Kingdom, that evaluated the impact of various film coatings on the ease of swallowing and 'mouthfeel' of tablets for 86 healthy adult volunteers, to determine which factors were most associated with improving the swallowing experience (1). Mouthfeel was found to be more important than taste for patient acceptability.

A single center cross-over study was used to measure the mouthfeel and swallowing experience of four 19mm placebo tablets. One tablet was uncoated, and the other three were coated as detailed in **Table I**.

All participants completed a background questionnaire and then received the same four samples in a randomized order. Participants were asked to score the mouthfeel after holding the tablet in their mouth for 10 seconds based on the following parameters: smoothness, stickiness, slipperiness, and palatability, using visual analog scales (VAS). They were asked to rank the tablets in order of preference for ease of swallowing. The time taken to swallow the tablet and the volume of water used to aid swallowing were also recorded.

Wilcoxon's test was used to determine specific differences between samples; this was used to look at differences between the three coated tablets and significant differences were reported when $p<0.0167$ (derived from $p=0.05$ divided by the three samples; 0.05/3).

FIGURE COURTESY OF COLORCON.

In the analysis of the mouthfeel parameters, the uncoated tablet was always statistically significantly worse compared to the three coated tablets based on the VAS scores, $p<0.01$ from the Wilcoxon's test. Pairwise comparisons between the coated tablets showed significant differences (2).

When the tablets were ranked in order of preference based on overall swallowing experience, the favorite sample was EZ+EZ, which was the first choice for 37.8% of participants, followed by EZ. Opadry ranked third, and the least popular was the uncoated tablet (**Figure 1**).

All coated tablets had a better mouthfeel (in terms of being smooth, non-sticky, and pleasant), required less volume of water to swallow, and were swallowed more quickly than uncoated tablets. Palatable samples were reported to have smooth and slippery textures with no pronounced taste. The slipperiness of the tablet was found to be the best predictor of the ease-of-swallowing.

The tablet finish that was preferred by volunteers was the Opadry EZ film coating—either pigmented or with additional top-coat for extra gloss. This reportedly increased mobility during the swallowing process, according to the study participant responses (3).

Compared with other coating formulations, the slip provided by this coating, once wet, significantly reduced the probability of sticking in the throat or esophagus during the swallowing process. The improved tablet flow, combined with a glossy finish, encourages better patient compliance and consumer appeal (4).

The ability to detect differences in tablet coatings was influenced by age and gender, with younger females showing the greatest ability to distinguish between the samples. Although the study did not include any children or geriatric volunteers, it is hoped that the findings may be used in future studies to understand how the work translates into these patient populations.

Patient benefits

Colorcon will now incorporate the results of this study to reinforce the patient benefits for tablet coating. The company anticipates that this approach will support the pharmaceutical industry to create products that satisfy both the perception and reality of ease of swallowing for all ages, mitigating adverse events such as pain, gagging and choking, and allowing clear differentiation between drugs.

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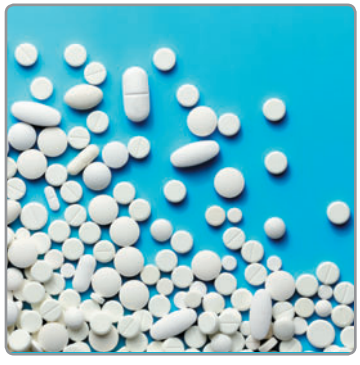

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Flexibility and well considered manufacturing approaches could help tablet manufacturers face the increasing pressure resulting from the shifting bio/pharma development landscape.

Broadly speaking, oral solid dosage forms remain the most popular choice for drug developers and patients, offering convenience, simplicity, cost-effectiveness, and higher rates of compliance. Tablets have maintained the top position in terms of dosage form popularity for some time, yet according to certain reports, the rising trend of more complex, specialized medicines in development is leading to the necessity of more flexible and sophisticated manufacturing approaches (1).

Additionally, growth in emerging markets has placed pressure on solid dose manufacturers to accelerate production while also managing to keep costs at an efficient level. To learn more about the challenges associated with tableting and these industry trends, *Pharmaceutical Technology* spoke with Michael Oxford, research & design engineer at I Holland.

Challenges facing manufacturers

PharmTech: Could you highlight the main challenges drug manufacturers face when trying to quickly and cost-efficiently process oral solid-dosage forms/tablets while also maintaining high quality?

Oxford (I Holland): In order to efficiently manufacture a quality tablet, design is key. Details including shape, profile, and features such as a blended land are just some of the factors that must be considered.

Let's initially look at the shape. A round shape is the most common as it is the easiest to produce. Non-round shapes are more complex and can require specialized tool manufacturing capability. Once the basic shape has been decided, take time to look at the size. Look at the type of press available for tablet manufacture as this can limit the size of the tablet. Also, if production has to be fast, consider using multi-tip tooling, which can also affect the size of the tablet.

An important element of successful tablet design is ensuring that the blended land works. If a blended land is applied incorrectly, a range of issues can ensue during compression. For example, the tablet land can chip during take-off, and coating can build up on the edge of the tablet and eventually chip.

Finding the correct blended land will increase tablet strength and performance, therefore resulting in higher volumes. It's important to remember that a correctly selected and applied blended land provides benefits in terms

of handling, loading, setting, tooling strength, and the visual appearance of the tablet.

Also consider the tablet profile. The profile is affected by several aspects including the granule, embossing requirements, coating process, packaging, and the branding required. Additionally, think about the volume of the tablet and if it will be coated as this can present challenges for the tablet designer. Successful coating is dependent on the tablet profile. Because the core of a tablet has reduced hardness compared to the peripheral of a tablet, core erosion can occur during the coating process. Erosion is caused when the tablet comes into contact with the coating pan and other tablets, leading to wear. This weakness can be reduced by avoiding very deep concaves.

An expert tooling designer will be able to design and add appropriate strengthening features, such as blended lands and profile changes, resulting in a robust tablet that can be quickly and cost-effectively produced.

Dwell time and its impact

PharmTech: What about dwell time and its impact on the tableting process?

Oxford (I Holland): In a nutshell, dwell time is the amount of time that the punch head remains under full load when in contact with the compression roller. It will have a huge impact on production as some tablet formulations are dwell-sensitive, therefore they require longer compression.

It is important that the correct amount of force is used for the right amount of time. Too much or too little of either can result in tableting problems. Excessive force or over-pressuring of the punch can cause failure of the tool and will damage the press. For this reason, it is vital to understand how to optimize dwell time correctly.

Influences that can affect dwell time include the punch head flat diameter and shape, use of precompression, and revolutions per minute used during production. It is important to remember that dwell time plays a significant part in determining if a tablet can be produced successfully, especially those incorporating formulations that are challenging to compress. Not all formulations are dwell sensitive, as some will compress effectively at any speed; the majority, however, are very susceptible to even the slightest change.

When understanding the dwell time required for a formulation, research of the characteristics of the formulation is essential—is it plastic or elastic? Does it have a high moisture content? All these elements will affect the dwell time.

Dwell time can also play a part in stopping common problems like sticking, capping, or friability during manufacture, for example, using specific tooling that can be used without slowing the press, so production runs satisfactorily. Innovative new punches on the market allow tablet manufacturers to achieve higher press speeds with challenging products and formulations without the significant capital expenditure of a new press.

All formulation factors must be considered

PharmTech: You mentioned that the drug formulation can affect dwell time; does it have other implications in other aspects of the tableting process?

Oxford (I Holland): The formulation can have a huge impact on the quality of the tablet and the overall process. You must look at every element of the formulation; for example, does the formulation have a high moisture content or does it have abrasive or corrosive ingredients? There are a whole host of factors to consider. The overall formulation composition has to be studied so the correct tooling can be used to reflect the formulation being compressed and ensure a quality fault-free end product.

"The overall formulation composition has to be studied so the correct tooling can be used to reflect the formulation being compressed and ensure a quality fault-free end product."

—Michael Oxford

One of the main problems encountered is that of a sticky or abrasive formulation. Looking at the latter problem, some formulations contain unrefined, hard, abrasive ingredients, which makes production a challenge. Formulations with this composition, when repeatedly compressed, can scrape away or penetrate the surface of the tool. The abrasion can lead to the erosion of punch tip detail such as logo embossing and other identification specifications. Eventually this wear can lead to weight variation, sticking, and other issues, resulting in the scrapping of the punch.

Abrasion can be resolved through the use of wear-resistant premium steel. It is important to fully understand the differences between the selection of steels as they have a variety of advantages and disadvantages. One example is that some wear-resistant steel can be less resilient to fracture in some applications due to reduced toughness and tensile strength. If the changeover to a premium steel does not offer the extra wear resistance required, then a powder metallurgy steel will provide greater wear resistance.

If the selection of a wear-resistant steel is not enough, then a wear-resistant coating can be applied to the tooling to offer more strength and prolong its life. The correct coating will not only add wear resistance, but will also offer benefits in terms of corrosion protection and anti-stick properties. There are coatings on the market that

are around five times harder than normal tablet-tooling steels. These coatings can increase wear resistance to tooling in comparison to uncoated tooling and can extend tool life by over 900%, following research and working examples from I Holland.

"Multi-tip tooling has transformed the way tablets are produced, and it is now considered one of the most productive forms of tablet manufacture."

—Michael Oxford

Tablet sticking

PharmTech: As you have highlighted earlier, tablet sticking can be a common problem; what options are available to help overcome this issue?

Oxford (I Holland): Sticking is the most common problem and one we come across daily. Because it is such a dominant issue in tablet production, I Holland investigated the cause of formulation sticking and developed 'TSAR Predict'. It is an algorithmic predictive model that calculates the optimal anti-stick coating to apply to compression tooling based on the properties and characteristics of the formulation. We can identify the most appropriate punch or die coating for sticky formulations, which can eliminate the need to conduct in-the-field testing.

There can be many reasons for the cause of sticking, from Van der Waals forces to capillary action associated with high moisture content, or conversely, sticking due to static electricity generated in very dry conditions. Because the physical properties of any sticky formulation are unique, there is no one-size-fits-all anti-stick solution. Applying a predictive tool specifically developed to recognize the correct punch or die coating solution for a sticky formulation is the answer and one that will save a lot of time and money.

Tool selection

PharmTech: What are some of your key tips and tricks for the best tool selection?

Oxford (I Holland): The correct choice of tool steel can make a huge impact on production and is one of the most important considerations. The tool material must be balanced to give optimum tooling performance and durability. Good steel selection will achieve the best possible balance of a number of properties including abrasion and corrosion resistance, compressive strength, hardness and resistance to chipping and cracking, a clean structure, and good machinability and formability. Tablet punches and dies are the main components to interface with the powders and granules, so they must be metallurgically robust. If the wrong choice of tooling steel is used, the compression of, for example, abrasive formulations, will result in numerous problems.

To select the right tool, consult with a tablet tooling expert and provide as much information as possible. With years of experience, they can offer advice on the most suitable tooling for the job.

Tableting trends

PharmTech: Have you witnessed any significant trends in tableting over the past decade that have had a positive/negative impact on the industry, and what are your predictions for the coming decade?

Oxford (I Holland): Perhaps one of the most significant trends in the past 10 years is the use of multi-tips. Oral solid-dose drug manufacturing is increasing. To keep up with demand, manufacturers need to implement production process improvements to efficiently manufacture tablets. Multi-tip tooling has transformed the way tablets are produced, and it is now considered one of the most productive forms of tablet manufacture.

Successful implementation of multi-tipped tooling can reduce the need to invest in additional tablet presses, therefore reducing the overall capital spend. The number of tool set-ups required per production batch can also be reduced and product batches are completed quickly, decreasing the overall production time. It also benefits tablets that need to be compressed within a very short time of the formulation being prepared.

Over the coming decade, shorter lead times and cost implications will put pressure on manufacturers to invest in new technologies and processes. There are also stringent quality requirements that the pharmaceutical industry must apply. These requirements are leading to the need to improve production through durable tablet tooling and the associated maintenance equipment.

The implementation of continuous manufacturing to increase volume will be an important trend in the future and one which will help reduce reaction time and time to market. At I Holland, we have recently designed a product that aims to maximize uptime. The XDF (eXtended Dwell Flat), a novel patented elliptical head form, has been created to increase dwell time on existing presses without the need for modifications. As the importance of increased productivity continues to grow, accommodative solutions, such as XDF, will afford tablet manufacturers the ability to meet future industry demands and trends.

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Best Practices for Vacuum Conveying of Pharmaceutical Powders

Jennifer Markarian

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Automated material handling can eliminate risks associated with operators manually carrying and pouring bags of powder into feeder hoppers. When specifying an automated powder transfer system, consider material properties, facility constraints, and designs to mitigate explosion.

Pharmaceutical Technology spoke with David Kennedy, business development manager at equipment supplier VAC-U-MAX, about best practices in the use of vacuum conveying for transferring powders in a pharmaceutical manufacturing facility.

Considering automation

PharmTech: What are some of the situations where an automated vacuum conveying system could be used instead of manual transfer of powders?

Kennedy (VAC-U-MAX): The first factor to consider is the type of process that the vacuum conveyor is feeding. For example, a high-speed packaging machine, such as an auger-filler, will be well-served by an automated conveying system so that the filler never runs out of material. Automated transfer (i.e., a permanent installation) also reduces the ladder-climbing and lifting that accompanies a manual operation. This benefit would also apply to tablet press loaders or capsule fillers.

Even small-rate applications, however, can still involve repetitive motions that will fatigue the operator or put them at risk for musculo-skeletal disorders. Loading V-blenders or double-cone blenders, feeders, and mixers can be a labor-intensive operation that can be improved by using a bag dump station with vacuum conveyor or direct-charge blender loading to transfer powders from ground level up to a mezzanine instead of the intensive manual lifting and climbing activities. Some low-rate applications can still be 'automated' with an operator who manages a suction wand to draw powders from drums to a vacuum conveyor that lifts the powder to a process that is 10 or 20 ft. in the air. Other applications include high-rate gel-cap inspection systems that are typical fed by a specialized vacuum conveyor.

Benefits of automated systems include reduced fugitive dust (i.e., escaping out of the process), improved product quality due to the enclosed system, improved ergonomics for workers, and increased throughput over manual operations, which is particularly important in times of qualified labor shortages.

In addition, automated systems aid in compliance with United States (US) Occupational Safety and Health Administration (OSHA) safety regulations for preventing falls by eliminating the

Jennifer Markarian is manufacturing editor of *Pharmaceutical Technology*.

need to climb ladders or stairs with containers of raw materials. Some features of vacuum conveying systems, such as mobile lift frames or column lifts, can bring the conveying equipment down to ground level for maintenance or sanitation to eliminate the need for performing those duties as higher elevations. Vacuum conveying systems also keep walking/working surfaces clean of debris. For example, it not unusual to see a pallet of bags forklifted up to a mixer mezzanine for manual dumping into a mixer. As each bag is emptied, product can fall on the walking surface. A properly-designed vacuum conveying system leaves the bag-dumping operation at ground level.

Specifying a system

PharmTech: What are the factors in sizing a system?

Kennedy (VAC-U-MAX): Several factors to consider include:

- Bulk density (weight of powder in a common volume, lb/ft^3 or g/cc^3)
- Convey rate (expressed in lbs or ft^3/hour)
- Duty factor (one small batch per minute, or one large batch per hour)
- Conveying distance (longer distance requires more horsepower)
- Number of elbows in the conveying route (more elbows converts to longer convey distance)
- Particle size and characteristics (e.g., fine particles need more filter area in the conveyor, sticky powders need good techniques for discharge from the conveyor, abrasive materials need special consideration)
- Combustibility (requires explosion protection techniques)
- Available headroom over the process being filled
- Equipment construction (materials, sanitation and polish requirements, chemical compatibility)
- Ingredient accuracy (batch weighing and/or loss-in-weight feeding).

PharmTech: Do you need to characterize the powder when setting up the system?

Kennedy (VAC-U-MAX): Materials must be characterized for particle shape, size, percentage of fines, flowability, discharge friendliness, aeration or de-aeration characteristics, friability (breakage factors), moisture absorption, sensitivity to temperature, and so on. After characterization, even when you think you know everything about the powder, a responsible supplier will run a test in their lab to prove out all of their hypotheses.

PharmTech: What precautions are needed to mitigate explosive risks?

Kennedy (VAC-U-MAX): First the customer must have the material tested for explosivity by a qualified lab. There are several types of explosion protection techniques standardized by the US National Fire Protection Association (NFPA) that have advantages and trade-offs for a customer, which include:

- Explosion venting (allows the explosion to take place and directs it out a certain vented direction, but the process vessel must be located near an exterior wall, requires equipment rebuild, and has higher downtime)
- Chemical suppression (prevents the thermal event from occurring by injecting dry chemical powder into the vessel before deflagration; process vessel can be located anywhere inside or outside the plant, has less equipment damage and reduced downtime)
- Explosion venting with flameless venting (also allows explosion to take place, but flameless vent allows process equipment location anywhere within the plant, but still have internal equipment damage and rebuild time)
- Reduced oxygen concentration (uses an inert gas, such as nitrogen or argon, as the conveying medium instead of plant air that contains oxygen, which is a fuel for combustion; more costly than ambient plant air; more controls and monitoring for oxygen concentration levels; respiratory concerns for plant workers; no special requirements to relocate the equipment; no explosions results in no downtime)
- Explosion containment (build the equipment to withstand the pressure and contain the energy of the explosion inside the vessel, high up-front costs, equipment rebuilding and re-certification).

Handling of combustible powders requires equipment bonding and grounding per NFPA standards, and all electrical components must comply with the hazardous area designations (class, division, and groups) (1,2). To further improve explosion protection, all equipment should be manufactured in anti-sparking stainless steel. All controls need to be classified for the area.

Best practices for poorly flowing or potent powders

PharmTech: What are some best practices for transferring powders that don't flow easily?

Kennedy (VAC-U-MAX): Some powders may have improved flow characteristics with the use of bin vibrators, bin activators (i.e., live-bottom bins), or pulse-air devices in the hopper section. Other materials require hopper designs with offset cones (e.g., straight on one side and a 60–70 degree slope on the other) or flared-tube hoppers (e.g., straight-sided tube hoppers and full-opening valves) that will handle materials with high fat or moisture content. It is also critical to understand the process conditions for the equipment being fed by the conveyor: are moisture or vapors generated when the process is filled or is there a high-temperature condition in the vessel being filled?

PharmTech: What are the considerations for containment for highly potent powders?

Kennedy (VAC-U-MAX): Use vacuum technology for conveying because if it develops a leak, it will only leak inward, not outward. Dust-tight designs on the powder supply end and the discharge end are crucial. Maintenance that can be performed without entering the equipment itself (i.e., confined spaces) is desirable. Some high-risk or high-potency applications will call for bag-in, bag-out filter changing designs to reduce operator exposure.

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Solving Sticking and Picking Through Tablet Design

Bill Turner and Kevin Queensen

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Sticking and picking are common problems in tablet manufacturing. Considering tablet compression issues before tablet designs are finalized can prevent unanticipated problems during scale-up and full-scale production.

Sticking is one of the most common problems of tablet manufacturers. It occurs when granules or particles from the formulation attach and stick to the face of a punch cup, resulting in defective tablets. Picking is a specific type of sticking that refers to material becoming stuck on the faces of the compression tooling due to embossed designs, such as the letter or numerals of the tablet logo or identifier. Sticking or picking issues are often not detected until transferring the product from research and development to production.

Possible causes

Although sticking and picking are frequently related to deficiencies in tablet design, remediation does not always require changing the design (and thus the tools used for tablet manufacturing). When powder sticks in the punch cup or embossed characters, one of the first things to check is the moisture level of the formulation. Excess formulation moisture or excessive humidity in the compression suite can initiate sticking or picking.

Insufficient compression force is also a potential source of sticking/picking because the compaction of the powder is not complete. When this occurs, the adhesive forces of the punch are stronger than the cohesive forces of the inadequately compressed tablet.

Another potential cause of sticking and picking is a deficiency in the amount of lubricant within the formulation. An increase of lubricant will impart greater release of the compressed tablet from the punch cup surface.

Careful inspection of the punch cups is also essential to ensure there are no surface scratches to capture small particles of formulation. Scratches will lead to filming, which is an initial slow form of sticking, often due to fines and excess moisture in the granulation. If surface scratches are identified, punches should be polished. Additionally, a specialized polishing compound can be used to impart greater lubricity and better product release properties.

When simple or environmental fixes are not enough, a full tablet design review may be necessary. Tablet design plays a pivotal role in oral solid dosage manufacturing, although it's often overlooked. Typically, a pharmaceutical company's marketing department pushes for certain tablet shapes and logos with the end goal of promoting brand recognition. However, those

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designs may not be optimal for manufacturing requirements and demands. Compression tooling suppliers, who are often highly-experienced tablet design experts, can identify potential sticking and picking issues before tablet designs have been finalized, thus reducing production challenges.

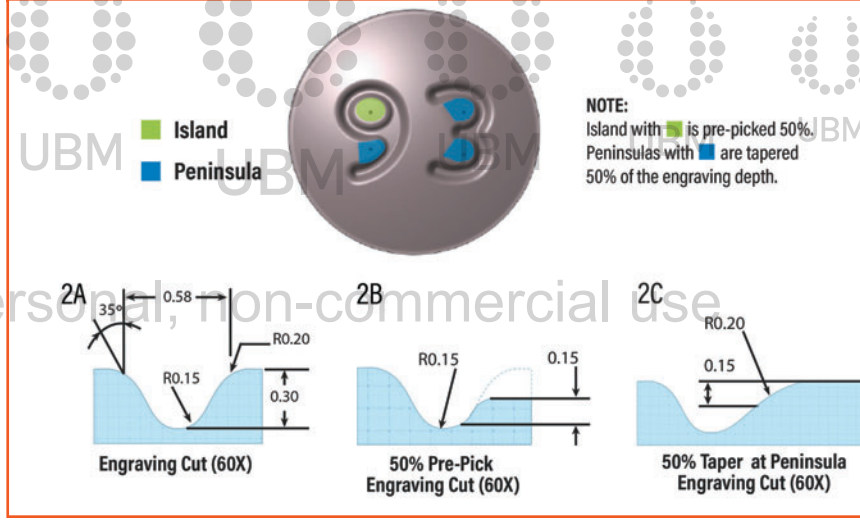
Tablet design solutions

Font selection: serif vs. sans serif. Font selection is often a battle of form versus function. As illustrated in **Figure 1**, an ornate or decorative serif font will be more prone to picking problems compared to a more simplistic, sans serif font. The same embossing using a practical, simplified sans-serif font uses increased engraving and corner radii. This font modification minimizes picking opportunities, increases the likelihood for consistent powder compaction, and yields the best over all possible cohesive forces for the tablet.

Picking problems can best be addressed during the tablet design process by making modifications to the embossed letters or using compound cup configurations to improve compression in the deepest areas of the punch cup. The compound cup configuration allows for greater control over the curvature of the cup surface, thus allowing for optimization of the surfaces directly around the logo.

Figure 1. Decorative or serif fonts are more prone to picking problems than simple, sans serif fonts.

Figure 2. The risk of picking in an island or peninsula in a typical engraving cut (shown in 2A) can be reduced by decreasing the island depth using a pre-pick cut (2B) or by tapering (2C).



Adjusting the engraving cut. Although it is important to first consider the font or typeface for the design, attention should also be given to the design of the engraving cut. Pre-picking letter or numeral islands as well as tapering the peninsulas for some letters will often alleviate picking problems.

Figure 2 highlights where a peninsula (i.e., a partially enclosed area) and an island (i.e., a fully enclosed area) are formed within a typeface on a typical round tablet. The variation in engraving width, as well as the isolated peninsulas of the serif font letters, are impediments to even powder compaction. This variation often leads to powder picking away from the compressed tablet core and remaining in the punch cup. The engraving of the "93" cut into the tablet is shown in **Figure 2A** with typical engraving width, depth, and an angle of 35 degrees. Most product formulations can readily be compressed into tablets using tools with this style of engraving design. However, many formulations are not typical, and problems can still occur.

To reduce or eliminate problems with material picking in the center island of the "9," pre-picking can be incorporated in the design. Pre-picking decreases the height of the resulting island or pad on the tablet by intentionally adjusting the depth of the engraving cut on the cup face. For example, as shown in **Figure 2B**, the depth for the island is reduced from 0.30 mm to 0.15 mm. This reduction is defined as a 50% pre-pick. The amount of reduction can range between 10 and 100%, depending on the extent of the picking problem. For branding or aesthetic purposes, consideration must be given to tablets that will be coated post-compression, as excessive pre-pick will significantly reduce the clarity of the logo. The partial pre-pick concept is applicable to any letter or numeral with fully enclosed areas (i.e., islands or pads).

FIGURES COURTESY OF THE AUTHORS.

Many other somewhat complex characters that do not have fully enclosed areas are also prone to picking. Letters such as E, S, K, and M and numerals such as 2, 3, and 5 all contain these partially enclosed areas (i.e., peninsulas). For these areas, a feature called "tapering" or "ramping" is employed to reduce the likelihood of picking. Starting on the tablet surface at the open end of the peninsula, this feature tapers downward toward the enclosed end of the peninsula by a percentage of the engraving depth. Peninsulas usually are tapered between 10 and 50% of engraving depth, with 30% as the most common. An example of a 50% taper is illustrated in **Figure 2C**.

Logo/identifier placement. Although font selection and design of the engraving cut are two crucial aspects of tablet design, attention should also be paid to the placement of the identifier. The size and spacing of the characters can be modified to reduce the occurrence of picking. Additionally, moving the placement of the characters out of center can also be an effective option as illustrated in **Figure 3**.

Exploring tooling material

If sticking and picking have been discovered during the research and development stage, or if it is time to order the next set of punches for a product with known sticking and picking challenges, another consideration is to have the punches made from a specialty steel. The steel type used will vary based on the product's formulation.

It is widely accepted that punch steel with a high concentration of chromium in the alloy, usually between 16 and 18%, enhances release of the compressed product. For example, M340 or 440C are beneficial for sticky products because the high chrome content yields improved product-release characteristics. Steels with higher levels of carbon (D2) and vanadium (PM-3V, 9V, 10V) provide better wear resistance for abrasive formulations common in nutraceuticals, as sticking can occasionally be caused by a degradation in cup surface finish caused by these types of abrasive products. Other specialty steels are available to enhance the performance and the service life of the punches and dies for compression strength, wear resistance, and corrosion resistance. A reputable tool vendor will have multiple grades of high-chrome steel available and should help their tablet manufacturing customers to make the best selection for a particular formulation. The finish of the tooling, whether it be mirror or matte, is an additional aspect that should be discussed with the tooling vendor when working with a difficult product.

As an alternative to using a specialty steel, a specialized coating can enhance the release characteristics of the punch faces and reduce or eliminate sticking and picking. The most common coatings are hard chrome (Cr) and chromium nitride (CrN). Several other coatings are available as well, depending on the unique characteristics of the formulation to be compressed. It should be noted that due to the abrasion of some formulations and polishing, coating layers can wear off over time, reducing their effectiveness. A tooling vendor should be able to explain the unique properties and advantages of the tool steels and coatings available for a formulation.

Figure 3. Out-of-center placement of text can reduce picking.

A proactive approach

Consulting with a qualified tooling vendor and discussing sticking and picking issues early in the development process will help reduce potential production issues and costs associated with purchasing redesigned tooling. There are several remedies that can help eliminate sticking and picking, ranging from slight formulation changes to tablet design and tooling modifications. It is important to discuss all product properties with the tool vendor during the tablet design phase to help eliminate sticking and picking issues before they occur. **PT**

Speeding Sample Preparation and API Extraction from Solid Oral Dosage Formulations

Carlos Lee, Anster Charles, Beverly Nickerson, Gail Johnson, and John Warzeka

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Laboratory testing found that a novel approach reduced the time required for sample preparation from hours to minutes. This article summarizes test methods and results.

Questions often arise about the completeness and robustness of assay and content uniformity procedures in oral solid dosage formulations. Although FDA allows up to ± 10% API loading variability for brand-name formulations (and ± 20% for generics), low and/or highly variable results often trigger debate about their source. Analysts sometimes trace them to the formulation, while formulators may blame the analytical methods used to study them.

A semi-automated sample preparation and extraction device was introduced to the market in 2015, with the goal of speeding up, simplifying, and providing more robust and complete extraction of APIs (and impurities) from solid oral dosage formulations. This article summarizes results of comprehensive equipment testing.

Issues with sample preparation

Over the past 25 years, significant strides have been made in liquid chromatography. The advent of ultra-high pressure liquid chromatography (UHPLC) and the resurgence of supercritical fluid chromatography (SFC) have led to significant reductions in chromatographic run times. It is now standard for potency and purity testing based on liquid chromatography and SFC methods for pharmaceutical dosage formulations to take 2–30 minutes. Ten to 15 years ago, this testing required more than an hour.

However, before content uniformity and assay/purity testing samples can be injected into chromatography equipment, they must be prepared, and API and impurities extracted. Typical sample preparation and extraction times are on the order of 30 minutes or more for immediate release (IR) type solid oral dosage formulations and can run between 4 and 24 hours for controlled release (CR) type formulations.

A 1991 survey in *LCGC* (1) found that sample preparation and extraction accounted for two-thirds of the time that analytical scientists spent on testing and analyzing samples, and not much has changed in 25 years (2). Automated and semi-automated sample preparation and extraction techniques such as microwave assisted extraction (MAE) and accelerated solvent extraction (ASE), applicable

Carlos Lee, Beverly Nickerson, Gail Johnson, and John Warzeka all worked for Pfizer Worldwide Research and Development in Groton, CT during the performance of the study. **Anster Charles** was a graduate student at the University of Missouri's Chemistry Department, Columbia, MO. **Carlos Lee*** (clee@lyndra.com) currently works for Lyndra Therapeutics, Watertown, MA.

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to IR formulations, have helped reduce sample preparation and extraction times (3,4). However, most sample preparation for content uniformity and assay/purity testing is still done manually, and requires such steps as sonication, stirring, and mechanical shaking. In addition, results continue to reflect inefficient, lengthy, and incomplete extraction of APIs and impurities/degradation products from drug product matrices (5).

Based on extensive testing, the PrepEngine (Distek, USA) allowed preparation of samples and API extraction from solid oral dosage formulations to be accomplished in less than 10 minutes. Testing evaluated variables such as processing speeds, extraction times, extraction volumes, and extraction solvents and their impact on the extent of recovery of APIs and impurities/degradation products. It also compared these values with results achieved via manual preparation and extraction procedures for the same formulations.

Low and/or highly variable [content uniformity] results often trigger debate about their source. Analysts sometimes trace them to the formulation, while formulators may blame the analytical methods used to study them.

Key steps in sample preparation and API extraction

Three critical steps are required for effective and efficient sample preparation and extraction in pharmaceutical solid oral dosage formulations (6). First, the formulation undergoes dispersion or disintegration to produce small granules. Following the matrix's increase in surface area, the API is solubilized in the dissolving solvent, then the undissolved excipients that remain in the resulting solution are removed by either centrifugation or filtration, providing a solution free of particles for chromatographic analysis.

The PrepEngine was designed to focus on the two most critical and rate-limiting steps in the procedure: particle size reduction and solubilization of the API. Stainless steel or polypropylene blades within the device's tall, cylindrically shaped PrepTubes serve as a homogenizer and allow for dispersion of solid oral dosage formulations. Simultaneously, the blades create intense vortexes within the tubes, which facilitates interaction between the API and the dissolving solvent.

Table I: Solid oral dosage formulations studied. IR is immediate release; CR is controlled release.

Compound	Formulation type
Compound A	100 mg IR Tablet
Compound B	11 mg CR Tablet - extrudable core system (ECS)
Compound C	20 mg CR Tablet - swellable core technology (SCT)
Compound D	10 mg CR Tablet - swellable core technology (SCT)
Compound E	20 mg IR softgel capsule

Materials and methods

Solid oral dosage formulations: One IR tablet dosage formulation, three CR tablet dosage formulations, and one softgel IR capsule solid oral dosage formulation were obtained from Pfizer Inc. (Groton, CT) and evaluated using the PrepEngine. Results were then compared with results from the manual validated sample preparation and extraction procedures that had been developed for these formulations. Apart from the IR tablet, the formulations that were tested were chosen for the complexity of their manual sample preparation and extraction procedures. Information about the various formulations is provided in **Table I**. Samples were manually prepared as described in **Table II** and analyzed using the validated high-performance liquid chromatography (HPLC) methods developed for the compounds involved in this study.

Sample preparation and extraction procedure

In all but a few of the studies conducted, the extraction solvents that were developed for and used in the manual sample preparation and extraction procedures were retained. In cases where a sequential addition of diluents was called for, such as aqueous followed by organic, extraction was simplified by pre-mixing the diluents and using the mixture to extract the API and impurities/degradation products from the formulation. Extractions were performed on single, intact tablets as well as on a composite of tablets (typically five tablets were used per composite).

The general procedure employed for sample preparation and extraction using the PrepEngine involved accurately transferring a specified volume of pre-mixed extraction solvent to the polypropylene PrepTubes. A Dosimat Plus titrator (Metrohm, USA) was used to deliver the dissolving solvent to the PrepTubes. After addition of the extraction solvent to the PrepTubes, a single intact tablet/capsule was weighed and transferred to the tubes. The tubes were then capped, and the samples were processed for specified times and speeds.

With the PrepEngine, samples can be processed for up to four hours, with speeds ranging from 500 rpm to 6000 rpm. Following development work on single replicates to optimize conditions for extraction of the actives and impurities/degradation products from the various formulations, 10 replicates were evaluated in parallel under the

Table II: Manual sample preparation and extraction conditions.

Compound	Manual sample preparation and extraction procedure
Compound A	1. Transfer tablet to a 100-mL volumetric flask.
	2. Half-fill the flask with diluent (75/25, v/v, water/acetonitrile, with 0.1% phosphoric acid).
	3. Shake on reciprocating shaker for approximately 30 minutes.
	4. Bring to volume with diluent and invert to mix.
	5. Centrifuge solution for approximately 5 minutes.
	6. Transfer 5 mL of supernatant to a 50-mL volumetric flask and dilute to volume with diluent.
Compound B	1. Transfer 5.0 mL of 0.1% perchloric acid ($HClO_4$) to a 100-mL volumetric flask.
	2. Transfer tablet to the flask and shake on a reciprocating shaker for 30 minutes.
	3. Add 15.0 mL of acetonitrile to the flask and shake for 40 minutes.
	4. Add 50 mL of 0.1% $HClO_4$ to the flask and shake for 4 hours.
	5. Dilute to volume with 0.1% $HClO_4$.
	6. Filter with 0.45-µm nylon filter.
Compound C	1. Transfer tablet into a 100-mL volumetric flask.
	2. Add 20.0 mL of acetonitrile to the flask.
	3. Shake for 2 hours on a flatbed shaker.
	4. Add 30.0 mL of 25/75, v/v, water/methanol to the flask and shake for 4 hours.
	5. Add 30.0 mL of 25/75, v/v, water/methanol to the flask and store on bench overnight.
	6. Resume shaking the following morning for 6 hours.
	7. Add 10 mL of 25/75, v/v, water/methanol to the flask and mix by inversion.
	8. Allow the solution to equilibrate to room temperature and dilute to volume.
	9. Transfer two grams of silica gel into a 20-mL scintillation vial and add 10 mL of sample solution. Vortex for 2–3 minutes.
	10. Allow silica to settle, then filter supernatant with polytetrafluoroethylene (PTFE) filter.
Compound D	1. Cut one tablet in half and quantitatively transfer to a 50-mL volumetric flask.
	2. Use 35 mL acetonitrile to ensure quantitative results.
	3. Shake flask for 4 hours on a reciprocating shaker.
	4. Dilute to volume with acetonitrile and invert to mix.
	5. Decant 30 mL to a sealable bottle or flask leaving the undissolved sweller layer behind.
	6. Filter the decanted solution and analyze by liquid chromatography.
Compound E	1. Set up a shaking water bath at 45 °C.
	2. Transfer a single capsule into a 100-mL volumetric flask.
	3. Add 50 mL of diluent (50/50, v/v, potassium phosphate buffer, pH 6.8/methanol) and place flask in the water bath.
	4. Shake the flask at 150 strokes/minute for 75 minutes (shake longer if capsule shell residue is still observed, but no longer than 4 hours at 45 °C).
	5. Remove the flask from the shaker and allow to equilibrate to room temperature (approximately 1 hour).
	6. Dilute to volume with diluent and invert several times to mix.
	7. Filter solution with a 0.45-µm nylon filter.
	8. Transfer 5.0 mL of the filtrate to a 50-mL volumetric flask and bring to volume with diluent.

optimized conditions. Composite samples involving up to five tablets were also evaluated.

Results and discussion

Initial studies with the PrepEngine were performed on Compound A, a 100-mgA (milligram active) immediate release tablet formulation. IR formulations are designed to rapidly disintegrate when exposed to aqueous conditions. Results following extraction of the active component of Compound A using the PrepEngine are shown in **Table III**. Extractions were performed at 3000 rpm for two minutes, and provided potency results essentially identical to that

Table III: Potency (% label claim) of compounds A, B, C, D, and E. IR is immediate release; CR is controlled release; SCT is swellable core technology; RSD is relative standard deviation.

Sample no.	Compounds—potency (% label claim)				
	A[1] (IR tablet)	B[2] (CR–ECS tablet)	C[3] (CR–SCT tablet)	D[4] (CR–SCT tablet)	E[5] (Soft gel capsule)
1	101.6	100.5	102.9	100.0	100.3
2	101.6	98.8	103.6	102.1	99.9
3	99.1	99.8	103.8	101.7	98.9
4	101.0	98.9	102.2	100.5	100.6
5	99.7	99.8	102.0	106.3	99.7
6	99.7	98.4	105.5	109.5	98.7
7	99.0	97.4	103.3	101.1	99.0
8	101.7	97.5	104.0	98.0	99.0
9	102.6	96.8	103.2	95.3	99.8
10	102.6	96.5	106.7	101.5	98.8
Mean	100.9	98.4	103.7	101.5	99.5
%RSD	1.4	1.4	1.4	3.9	0.7

[1]PrepEngine conditions: 3000 rpms; 2 minutes; Potency (manual method, n=10) mean = 101.3% LC; %RSD = 1.3.
[2]PrepEngine conditions: 5000 rpms; 5 minutes; Potency (manual method, n=10) mean = 98.7% LC; %RSD = 1.28.
[3]PrepEngine conditions: 3000; 6 minutes; Potency (manual method, n=10) mean = 103.6% LC, %RSD = 1.7.
[4]PrepEngine conditions: 3000; 6 minutes; Potency (manual method, n=10) mean = 100.9% LC, %RSD = 5.3.
[5]PrepEngine conditions: 3000; 6 minutes; Potency (manual method, n=10) mean = 99.0% LC.

Table IV: Exploratory work—dispersion of 20-mgA compound C SCT tablets in various diluents. SCT is swellable core technology.

Sample #	Diluent	Processing speed (rpm)	Processing time (mins)	Observations*
S1	50/50, v/v, methanol/ ethanol	3000	6	Tablet completely dispersed. No viscosity issues.
S2	50/50, v/v, THF/ ethanol	3000	6	Tablet completely dispersed. No viscosity issues.
S3	Methanol	3000	6	Tablet completely dispersed. Slightly viscous
S4	60/20/2, v/v/v, methanol/ ACN/water	3000	6	Did not completely disperse. Viscous
S5	50/25/25, v/v/v, methanol/ ACN/ ethanol	3000	6	Did not completely disperse. No viscosity issues
S6	75/25, v/v, methanol/ ACN	3000	6	Did not completely disperse. Slightly Viscous

* Viscosity assessments were visual in nature

obtained by the manual validated method. While the manual method, which used a reciprocal shaker to disperse and extract the active from Compound A, can provide complete extraction of the active, the PrepEngine was capable of performing the extraction in two minutes compared to the 30 minutes required by the manual method. The above corresponds to savings of nearly 93% in extraction time for the 100-mgA Compound A IR tablet. Furthermore, with the ability to perform extractions on up to 10 samples in parallel, the PrepEngine device has the potential to increase throughput in the laboratory, when compared to semi-automated approaches such as ASE and the tablet processing workstation (TPW). Additionally, no new degradation products and/or impurities were observed in the PrepEngine prepared samples, and no carryover issues were evident after cleaning and drying the PrepTubes.

Compound B - CR (ECS tablet technology): Compound B is an 11-mgA CR tablet formulation based on the extrudable core system (ECS) technology developed in 2009 (7). ECS tablets are single layer core tablets with a semi-permeable coating. The active is delivered osmotically through a hole in the coating.

The primary components in the 11-mgA tablet formulation include the API, and excipients such as copovidone, sorbitol, hydroxyethylcellulose, magnesium stearate, and cellulose acetate. As indicated in **Table II**, the 5.5-hour manual sample preparation procedure for Compound B involved the sequential addition of aqueous and organic solvents, followed by filtration of the final solution through a 0.45 µm nylon filter. Using the pre-mixed manual method final diluent composition (85/15, v/v, 0.1% $HClO_4$/acetonitrile), the PrepEngine extracted the active and degradants/impurities from Compound B tablets completely within 5 minutes, with processing speeds of 5000 rpm (**Table III**).

Compound C and D (SCT technology): The most challenging controlled release formulation investigated in this study involved those based on the swellable core technology (SCT) (8,9). SCTs are osmotic pump bilayer

Table V: Potency of 20-mgA compound D SCT tablets following sample clean-up. SCT is swellable core technology; RSD is relative standard deviation; HPLC is high pressure liquid chromatography.

Sample	Potency % LC
S11	103.2
S12	102.6
S13	104.8
S14	101.2
S15	104.3
Mean	**103.2**
%RSD	**1.37**

Initial diluent: 50/50 methanol/ethanol
Initial diluent volume: 50.0 mL
Final diluent (after clean-up): 40/40/20 methanol/ethanol/water, with 1 g silica gel
Final diluent volume: 10.0 mL

Table VI: Potency of 10-mgA Compound D SCT Tablets following sample preparation with 50 mL of 100% ethanol and the PrepEngine. SCT is swellable core technology. LC is liquid chromatography; HPLC is high pressure liquid chromatography. RSD is relative standard deviation.

Sample	Potency % LC
S1	100.0
S2	102.1
S3	101.7
S4	100.5
S5	106.3
S6	109.5
S7	101.1
S8	98.0
S9	95.3
S10	101.5
Mean	**101.5**
RSD	**3.92**

- Diluent = 100% ethanol (50 mL)
- Content uniformity results—manual method: 100.9 % LC; range = 94.6–109.3 % LC; %RSD = 5.3
- Processing speed = 3000 rpm
- Processing time = 6 minutes
- An aliquot of each sample was centrifuged for 10 minutes prior to HPLC analysis

tablets in which the active layer and osmotic or sweller layer is surrounded by a thick, hard, semi-permeable, polymer membrane. Once exposed to an aqueous environment, the osmotic layer absorbs water and swells. As the osmotic layers swells, it pushes onto the active layer, forcing the hydrogel suspension of active and excipients to exit through a small laser drilled hole in the coating. This osmotic pump mechanism provides drug delivery at a constant rate.

As indicated in the sample preparation and extraction procedure described in **Table II**, manual extraction of the active from Compound C, a 20-mgA SCT formulation, was extremely challenging and time-consuming. The 24 or more hours required to extract the active from the formulation is due primarily to the thick and hard polymer coating, and the polymer in the core of the tablet. Both serve to impact tablet wettability, thus decreasing the rate at which water penetrates the coating to initiate swelling and dispersion of the formulation. Additionally, the presence of polyethylene oxide (PEO) in the osmotic and drug layers facilitates gelling of the formulation, leading to the formation of a highly viscous suspension.

The results obtained for the two … formulations suggest that the use of alcoholic solvents ... in combination with the PrepEngine might allow for a universal sample preparation and extraction approach for swellable core technology formulations.

Initial sample preparation and extraction studies on the 20-mgA Compound C SCT tablet focused on identifying more suitable dissolving solvents capable of facilitating rapid dispersion of the tablets while having no negative impact on the viscosity of the extraction solution. Results from exploratory work on Compound C are shown in **Table IV**. As shown, all extraction solvent systems containing acetonitrile and/or water did not facilitate complete dispersion of the SCT tablet. Increasing the processing speed or processing time did not have any appreciable impact on the dispersion rate when acetonitrile and/or water were present in the extraction solvent. The presence of acetonitrile (ACN) and/or water in the diluent system caused the bilayer tablets to swell and made them rubbery. The above made it difficult for the rapidly moving stainless steel blades to fully disperse the intact tablet. In sharp contrast, diluent systems containing alcoholic solvents such as methanol or ethanol and/or tetrahydrofuran (THF) facilitated complete dispersion of the SCT tablets. While solvent systems containing THF allowed for complete dispersion of the SCT tablets within single digit timeframes,

they were not studied further because the presence of THF in the dissolving solvent led to chromatographic peak splitting issues due to the differences between the highly organic dissolving solvent and the highly aqueous initial mobile phase chromatographic conditions. Reducing the injection volume did not minimize the observed peak splitting issues.

Methanol, when used alone, facilitated complete dispersion of the SCT tablets; however, the viscosity of the solution tended to slowly increase with time, likely due to the slow solubilization of PEO in the diluent. In contrast to methanol alone or THF-based solvent systems, ethanol by itself or in combination with methanol proved to be ideally suited for the 20-mgA Compound C SCT tablets.

Not only did ethanol or ethanol/methanol mixtures provide rapid and complete dispersion of the SCT tablets, the viscosity of the resulting solutions remained visually unchanged (when compared to the viscosity of the sample diluent in the absence of the drug product matrix). The only noteworthy drawback with use of the above alcoholic solvent systems was the observation of peak splitting during chromatographic analysis when the injection volume was at or above 4 µL. The observed peak splitting issues were, however, easily overcome by reducing the injection volume to 2 µL. The nominal concentration was increased by a factor of two to maintain the same nominal on-column concentration.

Following developmental work to optimize the processing speed and processing time, the 20 mgA Compound C SCT tablets were analyzed in replicates of 10 via the PrepEngine. As shown in **Table III**, the PrepEngine quantitatively extracted the active ingredients from the 20 mgA Compound C SCT tablets within six minutes, when processed at 3000 rpm. The resulting chromatograms of the PrepEngine extracted samples were identical to those obtained via the manual method. Essentially identical results were obtained using ethanol or 50/50, v/v, ethanol/methanol extraction solvents.

Sample solutions containing 100% organic solvents can sometimes lead to chromatographic peak splitting due to incompatibility between the sample solution and the mobile phase. Additionally, the presence of high levels of PEO and other high molecular weight excipients in the sample solution can affect HPLC column lifetime and compromise HPLC systems. Attempts were made to reduce this impact by assessing and introducing sample clean-up procedures following extraction with 50/50 ethanol/methanol. The sample clean-up step evaluated involved diluting the ethanol/methanol extracted solution (either pre- or post-centrifugation) with water to obtain a 40/40/20 (v/v/v) ethanol/methanol/water mixture, followed by the addition of 1 g of silica gel.

The solution was vortexed and centrifuged, and a sample of the clear non-viscous supernatant was analyzed by HPLC. The purpose of adding approximately 20% water to the 50/50 ethanol/methanol extract was to make the solution more compatible with the initial mobile phase composition. Additionally, silica gel was added to the final solution mixture in order to remove (by adsorption) PEO and other high molecular weight excipients from the solution matrix, thereby reducing the viscosity of the solution and minimizing its potential impact on column lifetime.

Assay results following sample clean-up of the initial 50/50 ethanol/methanol extraction solvent are captured

Figure 1: Universal sample preparation and extraction approach for swellable core technology (SCT) formulations.

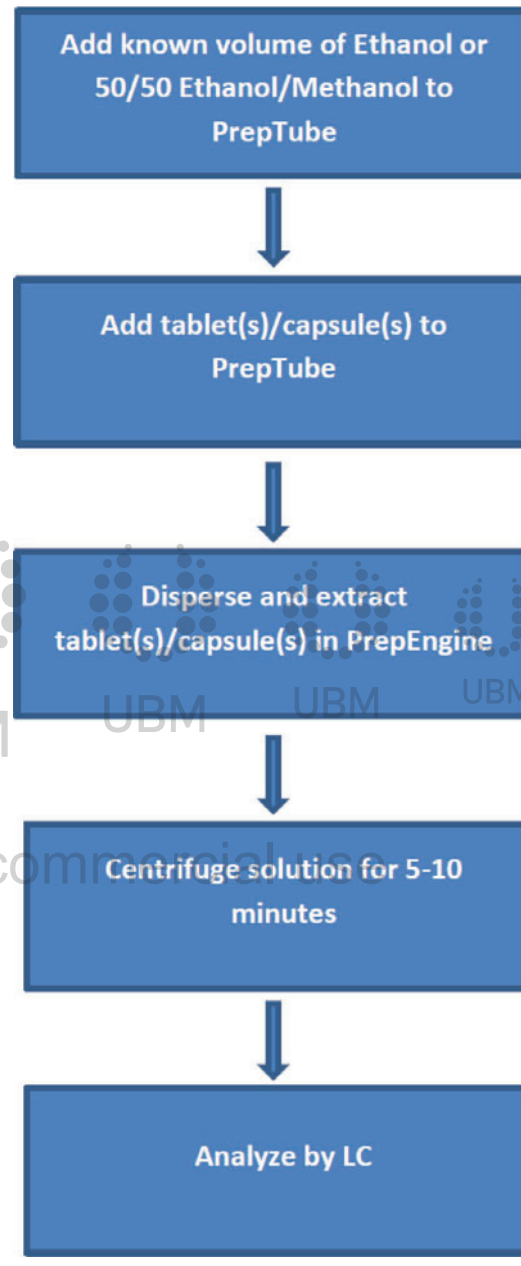

FIGURE COURTESY OF THE AUTHORS.

in **Table V**. Results were essentially identical to that obtained when directly injecting the 50/50 ethanol/methanol based extraction solution at 2 µL, suggesting that the sample clean-up step had no impact on the overall extraction efficiency.

Challenging manual sample preparation for SCT

Results of tests on the 20-mgA Compound C SCT formulation were subsequently applied to Compound D, another SCT formulation. As indicated in **Table II**, the manual sample preparation procedure for the 10-mgA Compound D SCT formulation was quite challenging, involving cutting the tablets in half to expose the inner core, followed by shaking on a reciprocal shaker for 4-hours using 100% ACN as the extraction diluent. A near 40-fold improvement in the rate of extraction was realized when the 10-mgA Compound D SCT formulation was extracted with the PrepEngine and 50/50 ethanol/methanol (**Table III**) or 100% ethanol (**Table VI**).

The results following sample clean-up were also unchanged from those obtained with no sample clean-up. The results obtained for the two SCT formulations suggest that the use of alcoholic solvents such as 50/50 ethanol/methanol or 100% ethanol in combination with the PrepEngine might allow for a universal sample preparation and extraction approach for SCT formulations. The schematic representation of such an approach is captured in **Figure 1**. The universality of the proposed approach is, however, highly dependent on the solubility of the API of interest in alcoholic solvents.

Compound E—softgel capsule: An interesting formulation evaluated with the PrepEngine was Compound E, a 20-mgA softgel capsule formulation. The primary excipients in this formulation included polyethylene glycol (PEG) and polysorbate 80. The manual sample preparation and extraction condition for this formulation was a bit atypical for a pharmaceutical dosage formulation. The procedure entailed shaking the sample in a water bath at elevated temperatures (45 °C), for up to four hours.

The capsule formulation was extracted in 50/50 potassium phosphate buffer, pH 6.8/methanol using 100-mL volumetric flasks. Initial exploratory work on the PrepEngine showed that Compound E could be extracted from the softgel capsule within three minutes at 3000 rpm with potency values between 97.8–98.7%. Within this timeframe, the softgel capsules were easily ruptured, allowing the active and excipients to be released from the capsule shell and interact with the diluent.

Extending the process time pulverized the capsule shell

Additional development work showed that extending the processing time from three to six minutes allowed for the capsule shell to be totally pulverized rather than simply ruptured, thereby providing for a more quantitative and more robust extraction procedure (**Table III**). Under the optimized PrepEngine condition, and utilizing the same diluent as that used in the manual sample preparation and extraction procedure, the PrepEngine was able to quantitatively extract the API and impurities/degradation products from Compound E within six minutes (as compared to the two to four hours required by the manual sample preparation procedure). No new degradation products and/or impurities were observed when Compound E was extracted with the PrepEngine.

Conclusion

Testing showed that the PrepEngine facilitated rapid and quantitative extraction of APIs and degradation products/impurities from IR and CR pharmaceutical solid oral dosage formulations. Extraction efficiencies and precision were comparable to levels obtained with often more time-consuming and cumbersome manual sample preparation and extraction procedures.

With the capability to process up to 10 samples in parallel, throughput is excellent when compared to that of most semi-automated procedures such as accelerated solvent extraction and the tablet processing workstation. The device is simple and user friendly, and, when coupled with alcoholic solvents such as mixtures of ethanol and methanol or 100% ethanol, allows for the development of a universal sample preparation and extraction approach for SCT formulations.

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CPhI north america

2019 PLANNING GUIDE

bioLIVE informEx P-mec iCSE InnoPack FDF

CPhI North America Heads to Chicago

CPhI North America offers educational, networking, and exhibition opportunities for bio/pharma professionals engaged in drug formulation, development, and manufacturing.

Event Overview

CPhI has a 30-year record for organizing worldwide pharmaceutical events. Now in its third year, CPhI North America has become an important event for bio/pharmaceutical developers, manufacturers, and suppliers. CPhI North America 2019 will be held at McCormick Place, Lakeside Center in Chicago, IL, from April 30–May 2.

Comprehensive Exhibition

The CPhI North America 2019 exhibition is organized into seven zones:

- bioLIVE: Bioprocessing Zone
- CPhI: Manufacturing Ingredients Zone
- FDF: Finished Drug Products Zone
- iCSE: The Drug Development Zone
- InformEx: Fine and Specialty Chemicals Zone
- InnoPack: The Packaging Zone
- P-MEC: The Machinery Zone

Educational Sessions

More than 110 hours of educational content include the following:

- A three-track conference program covering drug development, drug manufacturing, and bioprocessing.
- Insight Briefings and Exhibitor Showcases that are free to attend for exhibition visitors.
- Keynote sessions on pressing industry topics.

Networking

Daily networking events and opportunities to build new connections and solidify existing ones. The free Bond Meeting Service allows registered attendees and exhibitors to search, connect, and book meetings with key contacts at the show.

Registration

CPhI North America offers registration options to fit visitor schedules and goals. See www.cphinorthamerica.com/packages-pricing for details. Use Promo Code PHARMTECH to receive $100 off any Conference or VIP Pass.

Travel

The Lakeside Center of McCormick Place is located at 2301 South Lake Shore Drive, Chicago IL 60616-1490. Shuttle buses will provide transportation from official event hotels. See cphinorthamerica.com/travel-info for official hotel and travel arrangements, parking information, and shuttle bus routes.

Women in Leadership Forum

Thursday, May 2, 8:00–11 am

The CPhI Women in Leadership Forum brings together female executives from across the global pharma network to share experiences, trade knowledge, and build a community of like-minded individuals. Hear strategies for leadership and advice on overcoming workplace challenges from industry speakers, while also making new contacts and networking.

8–8:30 am
Breakfast and Networking

8:30–8:35 am
Welcome and Introduction from the Chair

8:35–9:25 am
From Manager to Leader
Pharma leaders share lessons learned in their journey From Manager to Leader including:

- Effective communication
- Authentic leadership
- Building a future fit workforce
- Creating allies, acknowledging privilege, and advocating others
- Preparing yourself to be in a male-dominated environment.

9:30–10:15 am
Campfire Session with Alise Cortez
Join speakers for a discussion with Alise Cortez, a Purpose/Engagement Catalyst, to delve deeper into their stories; ask questions about your own career challenges.

10:15–11 am
Build Your Personal Brand
In this speed networking session, participants will share three things they need to build their personal brand and share 10 intentions to help others achieve theirs.

Schedule is subject to change. Passes for this event can be purchased via the Register link on www.cphinorthamerica.com.

CPhI North America Events as of March 6, 2019. Visit cphinorthamerica.com for schedule updates.		
Monday, April 29, 2019		
Time	**Event**	**Location**
2 pm–6 pm	Registration Open	Lakeside Center (Located Across from Hall D Entrance)
Tuesday, April 30, 2019		
Time	**Event**	**Location**
7:30 am–6 pm	Registration Open	Lakeside Center (Across from Hall D Entrance)
9:30 am–12:30 pm	Morning Conference Sessions	Rooms E535a, E353b, and E353c
10 am–5 pm	Show Floor Open	Hall D
10:30 am–3:30 pm	Insight Briefings	Hall D, Insight Briefings Theater, 1400/1500 Aisle
10:30 am–4:30 pm	Exhibitor Showcases	Hall D, Showcase Theater, 200/400/500 Aisle
11 am–3 pm	CPhI Café	Hall D
12 pm–2 pm	Lunch	Hall D, Back of 100/200 Aisles and 2500/2600 Aisles
1:30 pm–2:15 pm	Keynote Address, former US Sen. Jeff Flake	Room E353c
2:15 pm–4:45 pm	Afternoon Conference Sessions	Rooms E353b, E353c
6 pm–8 pm	Welcome Reception, sponsored by Biophore Pharma Inc. *Additional fee required.*	Lakeside Fountain Terrace, Adjacent to Registration
Wednesday, May 1, 2019		
Time	**Event**	**Location**
8 am–5 pm	Registration Open	Lakeside Center (Across from Hall D Entrance)
9:30 am–12:30 pm	Morning Conference Sessions	Rooms E535a, E353b, and E353c
10 am–5 pm	Show Floor Open	Hall D
10:30 am–3:30 pm	Insight Briefings	Hall D, Insight Briefings Theater, 1400/1500 Aisle
10:30 am–4:30 pm	Exhibitor Showcases	Hall D, Showcase Theater, 200/400/500 Aisle
11 am–3 pm	CPhI Café	Hall D
12 pm–2 pm	Lunch	Hall D, Back of 100/200 Aisles and 2500/2600 Aisles
1:30 pm–2:15 pm	Keynote Address	Room E353c
2:15 pm–4:45 pm	Afternoon Conference Sessions	Rooms E353b, E353c
5 pm–6 pm	VIP Reception Odyssey Cruise Yacht on Lake Michigan *Invitation only*	Lakeside Fountain Terrace, Adjacent to Registration
6 pm–8 pm	Cruise on Lake Michigan *Invitation only*	
Thursday, May 2, 2019		
Time	**Event**	**Location**
8 am–3 pm	Registration Open	Lakeside Center (Across from Hall D Entrance)
8 am–11:30 am	Women in Leadership Forum *Additional fee required*	Room E353a
10 am–3 pm	Show Floor Open	Hall D
11 am–3 pm	CPhI Café	Hall D
12 pm–2 pm	Lunch	Hall D, Back of 100/200 Aisles and 2500/2600 Aisles
1 pm–3 pm	PharmaQue – *Open to all attendees*	Back of 100 Aisle

Conference Covers Multiple Tracks

Education tracks examine strategies and technologies for drug development, drug manufacturing, and bioprocessing.

Education tracks, scheduled for Tuesday, April 30, 2019 and Wednesday, May 1, 2019 explore the latest trends in drug development, drug manufacturing, and bioprocessing.

For registration information, see www.cphinorthamerica.com/packages-pricing. Use Promo Code PHARMTECH to receive $100 off any Conference or VIP Pass.

Drug Development Track

Tuesday, April 30, 2019, 9:45 am–10:30 am
Building a Better Drug: Strategies to Enhance Patient Drug Regimen Adherence
Moderator: Rita Peters, editorial director, *Pharmaceutical Technology*

Tuesday, April 30, 2019, 10:30 am–11:15 am
Development and Manufacturing Considerations of High Potent Drug Products–a CDMO's Perspective
Anil Kane, PhD, MBA, executive director, global head of technical and scientific affairs, Patheon Inc., part of Thermo Fisher Scientific

Tuesday, April 30, 2019, 11:45 am–12:30 pm
Outsourcing of NDA Approvals and CMO Performance in 2018 and Future Outlook
Peter Shapiro, PhD, editor-in-chief and director of the Drugs Business Fundamentals Databases, PharmSource and Pharma Intelligence Center

Tuesday, April 30, 2019, 2:15 pm–3 pm
Chemical Facilities Outreach Exchange
Lisa Parnpichate, supervisory special agent, FBI, Weapons of Mass Destruction Directorate, Chemical Countermeasures Unit

Tuesday, April 30, 2019, 3 pm–3:45 pm
Miniaturization Pharmaceutical Technology (MPTech)—An API Manufacturing Process to Increase the Operational Efficiency and Its Impact and Benefits on Patients
José Ángel Marañón, PhD, executive-vice president, Tradichem Industrial Services

Tuesday, April 30, 2019, 4 pm–4:45 pm
High Potency API (HPAPI) Best Practices—Controlling Quality
Speakers to be announced

Keynote Address

Tuesday, April 30, 2019
1:30 pm–2:15 pm
Former US Sen. Jeff Flake (R-AZ) (2013–2018) will share opinions on pharma manufacturing, healthcare innovation, and the direction of healthcare as he sees it under the current structure of divided government, as well as scenarios beyond 2020.

Sen. Flake served nearly two decades on Capitol Hill in both the Senate and House of Representatives.

Wednesday May 1, 2019, 9:45 am–10:30 am
Formulation Trends Spotlight: Semi-Solid, Topical, and Transdermal
Speakers to be announced

Wednesday, May 1, 2019, 10:30 am–11:15 am
Quality by Design: Methods for Optimizing Spray-Dried Dispersions for Bioavailability Enhancement
David Lyon, PhD, director, research, Lonza Pharma and Biotech

Wednesday, May 1, 2019, 11:45 am–12:30 pm
Is a Geographically Integrated CMC Supply Chain the Next Evolution of the CDMO Model?
Jingling Chen, PhD, vice president pharmaceutical development services, STA Pharmaceutical, a WuXi AppTec Company
Xiaoyong Fu, PhD, senior vice-president API development and commercialization, STA Pharmaceutical, a WuXi AppTec Company

Wednesday, May 1, 2019, 2:15 pm–3 pm
Continuous, On-Demand Dehydration of Solvents in Flow Chemistry Manufacturing Processes
Hannah Murren, chief technical officer, Compact Membrane Systems

Drug Manufacturing Track

Tuesday, April 30, 2019, 9:45 am–10:30 am
API Part I—Advances in API Synthesis and Manufacturing
American Chemical Society

Tuesday, April 30, 2019, 10:30 am–11:15 am
API Part II—Advances in API Synthesis and Manufacturing
American Chemical Society

Tuesday, April 30, 2019, 11:45 am–12:30 pm
When Science and Politics Collide: A Political Forecast Into 2019 and Issues That Will Impact Chemical Processing
Moderator: Michael Kennedy, principal attorney, Kennedy Law and Policy
Panelists: Caitlin Filippi, management and program analyst, FBI

Tuesday, April 30, 2019, 2:15 pm–3 pm
Quality Risk Assessment in Pharmaceutical Industry
Muhammad Naeem, chief operating officer, Indus Pharma Pvt. Limited

Tuesday, April 30, 2019, 3 pm–3:45 pm
Challenges in Extractables and Leachables Studies of Plastic Process Materials
Dujuan Lu, PhD, global E&L leader, SGS Life Sciences

Tuesday, April 30, 2019, 4 pm–4:45 pm
AI, IoT, and the Road to Pharma 4.0
Bikash Chatterjee, president and CSO, Pharmatech Associates

Wednesday, May 1, 2019, 9:45 am–10:30 am
Pharma's Problem with Data Integrity
Brian Nadel, independent consultant, EAS Consulting

Wednesday, May 1, 2019, 10:30 am–11:15 am
Extrusion Applications in Manufacturing Pharmaceutical Oral Drug Products
Bei Chen, PhD, operations science and technology, AbbVie

Wednesday, May 1, 2019, 11:45 am–12:30 pm
Innovation without Imitation: Utilizing U.S. FDA Drug Master Files
Dr. Uma Kale, Regulatory Compliance Manager, DuPont
Melissa Sayers, senior regulatory specialist, drug division, Registrar Corp.

Wednesday, May 1, 2019, 2:15 pm–3 pm
The System Development Lifecycle and Computer System Validation in Drug Manufacturing
Tony Pezzolo, practice manager, compliance and validation services/global CSV SME, PerkinElmer

Wednesday, May 1, 2019, 3 pm–3:45 pm
The Critical Approach to the Design of a HPAPI Suite in a Multi-use Facility
Speakers to be announced

Bio-Processing Symposium

Wednesday, May 1, 2019, 9:45 am–10:30 am
Upstream Processing: A New Approach for Scalability and Transfer
Guillaume Plane, global development and marketing manager, End-To-End BioReliance Solutions, MilliporeSigma

Wednesday, May 1, 2019, 10:30 am–11:15 am
Extractables and Leachable Case Study for Biopharma
Mary Lynne Bercik, PMP, PMI-RMP, CPSM, Executive Director, Merck Pharmaceuticals

Wednesday, May 1, 2019, 11:45 am–12:30 pm
Filling the Gap in Skilled Workforce Shortage in Biomanufacturing
Parviz A. Shamlou, PhD, executive director and head, Jefferson Institute for Bioprocessing

Wednesday, May 1, 2019, 2:15 pm–3 pm
The Role of Bacteria in Drug Metabolism
Abhinav Bhushan, PhD, assistant professor, department of biomedical engineering, Illinois Institute of Technology

Keynote Address

Wednesday, May 1, 2019
1:30 pm–2:15 pm
Topic and speaker to be announced

Conference information is as of March 6, 2019. For updates, visit www.cphinorthamerica.com.

Exhibit Hall Serves as Meeting Hub

The CPhI North America Exhibition Hall will feature more than 670 companies.

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Location

McCormick Place, Lakeside Center
Chicago, IL, USA

Exhibit Hours

Tuesday, April 30, 2019: 10 am–5 pm
Wednesday, May 1, 2019: 10 am–5 pm
Thursday, May 2, 2019: 10 am–3pm

Pharma Value-Chain Zones

The CPhI North America exhibition floor features more than 670 exhibitors covering all aspects of the pharmaceutical value chain. Attendees can source solutions across seven zones:

- **bioLIVE**: A new addition to CPhI North Amercia in 2019, this bioprocessing zone will feature suppliers for biopharma processing and manufacturing.
- **CPhI**: The manufacturing ingredients zone will showcase suppliers of APIs and excipients and in addition to their intersection with sustainability.
- **FDF**: The finished drug products zone will feature suppliers and contract service providers for small and large-molecule finished dosage formulations.
- **iCSE**: The drug development zone will highlight contract service providers specializing in pre-clinical and clinical drug development research and analytical and lab services.
- **InformEx**: The specialty chemicals zone will showcase custom chemical development.
- **InnoPack**: The packaging zone will present pharmaceutical packaging highlighting sustainable, user-friendly, and cost-effective solutions.
- **P-MEC**: The machinery zone will present innovations in pharmaceutical equipment and machinery.

Find solution providers

Exhibiting companies offer a range of equipment, materials, and services for bio/pharmaceutical development, formulation, and manufacturing, including the following:

- Analytical and lab services
- Aseptic processing equipment and supplies
- Automation and robotics
- Bio/pharmaceutical manufacturing services
- Capsules and tablets
- Cleaning systems
- Cleanroom technologies
- Clinical trial services
- Coatings
- Color and dispersions
- Consumables
- Contract development services
- Contract manufacturing
- Custom API manufacturing
- Custom drug product manufacturing
- Drug delivery systems
- Excipients
- Filtration/separation/purification
- Formulation services
- Generic API manufacturing
- Intermediates, fine and specialty chemicals
- Laboratory and analytical instruments
- Lyophilization
- Packaging equipment
- Packaging services
- Pharmaceutical manufacturing equipment
- Process automation and controls
- Purification and separation techniques
- Specialty chemicals
- Syringes, vials, and injectable drug supplies.

Meet the PharmTech team

Visit Booth 2446 to learn more about *Pharmaceutical Technology* and *BioPharm International*.

Meet the editors, publisher, and marketing representatives of *Pharmaceutical Technology* and *BioPharm International* during CPhI North America.

Stop by booth 2446 to meet the staff, review recent issues, start or renew a subscription, discuss writing and contributing opportunities, or discover marketing options for print and digital media.

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Covering all dosage forms

Exhibitors offer development and manufacturing solutions for a range of drug dosage forms including the following:

- Aerosols
- Capsules
- Creams
- Drops
- Injectables
- Lotions
- Ointments
- Parenterals
- Powders
- Softgels
- Sprays
- Suppositories
- Tablets
- Transdermal patches.

Global bio/pharma supplier market

Companies from more than 30 countries will exhibit at CPhI North America. Nations represented include:

- Canada
- China
- France
- Germany
- India
- Italy
- Japan
- Switzerland
- United Kingdom
- United States

CPhI North America Exhibit Hall

Floor plan as of March 26, 2019. For updates, visit www.cphinorthamerica.

Explore Potential Bio/Pharma Solutions

The CPhI North America Exhibition Hall will host presentations, briefings, and showcases on a range of bio/pharma development and manufacturing topics.

Exhibitor Showcases

Exhibitor Showcases are a platform for pharma industry suppliers to present forward-thinking perspectives on key products, innovations, and services. These 25-minute, free-to-attend presentations provide an open platform to interact face-to-face with equipment, product, and material suppliers, as well as contract service providers.

Insight Briefings

Insight Briefings, in-depth seminars on technical and business topics on the CPhI North America exhibition floor, are accessible to all exhibition visitors. Topics include accelerated drug approval programs, the digital transformation of the pharmaceutical industry, and supply chain security advancements.

Exhibitor Showcase Schedule

Tuesday, April 30, 2019

Time	Event
10:30 am	Nitto Avecia Pharma Services
11 am	Grantek Systems Integration
11:30 am	Lacamas Laboratories
12:30 pm	SafeBridge Consultants, Inc.
1 pm	J-Star Research
1:30 pm	Kodak Specialty Chemicals
2 pm	Flow Sciences Inc.
2:30 pm	Recro Gainesville
3 pm	SGS North America Inc.

Wednesday, May 1, 2019

Time	Event
10:30 am	Mastermelt
11 am	Albemarle
11:30 am	Optima Chemical
1 pm	UPM Raflatac
1:30 pm	USP
2 pm	USP
2:30 pm	USP
3 pm	Seqens

Information listed is as of March 7, 2019.
For updates, visit www.cphinorthamerica.com.

Insight Briefings Schedule

Tuesday, April 30, 2019

Time	Event
10:30 am	DSM
12:30 pm	Sterigenics/Nelson Labs
1:30 pm	Arcinova
2:30 pm	Cambrex

Wednesday, May 1, 2019

Time	Event
10:30 am	Sharp
11:30 am	Systech
1:30 pm	Catalent

Ad Index

Jeff spent all day searching for a pharma supplier.

He should have visited Pharma Marketplace instead.

Pharma Marketplace is an online directory that connects you with 2,000 bio/pharmaceutical suppliers around the world.

Don't be like Jeff.

pharmtech.com/marketplace

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