ORAL DRUG DELIVERY

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This edition is one in the ONdrugDelivery series of publications. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

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STRATEGIES FOR STREAMLINING THE DEVELOPMENT OF COMPLEX ORAL DRUG PRODUCTS

Here, Aruna Railkar, PhD, Senior Drug Development Consultant at Quotient Sciences, presents three case studies to illustrate the formulation challenges in complex drug programmes.

Drug development programmes, regardless of dosage form or molecule type, are challenging, given the many stages a lead drug candidate or new chemical entity (NCE) must progress through to achieve regulatory approval and demonstrate efficacy in patients. For complex drug programmes requiring specialised formulation development expertise – such as solubility enhancement, modified release or paediatric dosage forms – the challenges in achieving both clinical and commercial success are even greater.

For drug developers with challenging molecules, establishing a suitable formulation and technology strategy early in the development process will help to decide whether or not the desired target product profile (TPP) can be achieved and reduce time to clinic. Overall, an integrated approach to drug development that combines drug substance, drug product and clinical testing activities can remove white space, minimise risks and accelerate development timelines.

For formulation design, an integrated approach offers the ability to screen a range of technologies and dosage forms using biorelevant *in vitro* screening tools and physiologically based *in silico* models, providing a significant advantage for flagging early developability problems before transitioning drug candidates into human pharmacokinetic (PK) studies to understand a molecule's full potential.

This article presents three case studies that explore how Quotient Sciences' integrated drug development platform, Translational Pharmaceutics® – which incorporates drug substance, drug product and clinical testing – has been applied to overcome formulation challenges in complex drug programmes, helping to reduce timelines and, ultimately, get new treatments to patients faster.

SOLUBILITY-ENHANCEMENT CASE STUDY

Formulation Development and Screening of Solubility-Enhancing Formulations Using an Integrated Drug Development Approach

Poor aqueous solubility, leading to solubility-limited exposure, has been recognised as a major challenge in the development and evaluation of NCEs during early discovery, preclinical and clinical development stages (Phase I and II). There are various formulation strategies to improve solubility, all with the primary goal of improving oral bioavailability.

Quotient Sciences' approach to solubility enhancement is based on understanding a molecule's physicochemical properties, using the Developability Classification System (DCS) to choose the most appropriate formulation approach and technology for each molecule. By understanding the drivers of poor exposure

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"Solubility enhancement can be addressed early in the drug substance stage or downstream in the drug product stage."

for a drug, formulation efforts can be focused on appropriate techniques to provide meaningful improvements for *in vivo* performance.

The company has the capability to evaluate chemical modifications, such as salt and polymorph screening, and physical modifications, such as particle size reduction, complexation, solubilisation using a lipid-based approach and stabilisation using amorphous forms. With its integrated Translational Pharmaceutics platform, from drug substance to clinic, solubility enhancement can be addressed early in the drug substance stage or downstream in the drug product stage.

In this case study, a poorly soluble NCE facing challenges of low oral exposure, non-linear PK, high variability and a large positive food effect was assessed.[1] These issues, which were observed in the first-in-human (FIH) study, were preventing the customer advancing their programme into patient clinical studies.

To overcome these challenges, a two-part Translational Pharmaceutics study was conducted for the client. Drug products based on three solubility-enhancing formulation platforms were developed:

- A micronised formulation using particle-size reduction of the API
- A self-emulsifying drug delivery system using a lipid-based formulation
- An amorphous formulation using a spray-dried dispersion (SDD).

Drug products were produced on a small scale for fast clinical assessment in human subjects without the need to conduct larger-scale, cost-prohibitive process development and lengthy stability programmes for multiple technologies.

In part one, the Translational Pharmaceutics platform enabled integration of real-time adaptive clinical manufacturing and dosing of drug product in healthy volunteers using a six-period crossover design to obtain comparative human PK data from the three enabling formulations. In part two, higher doses were administered to healthy volunteers to establish safety margins for patient clinical studies and dose linearity was determined based on the area under the curve (AUC).

Ultimately, a new lead formulation was identified for the client in a condensed timeframe of about six months. Overcoming solubility barriers in a short period of time allowed the client to progress the compound into patient clinical studies.

MODIFIED-RELEASE CASE STUDY

Employing an Integrated Approach to Formulation Development and Optimisation of a Modified-Release Dosage Form to Achieve the TPP

There are numerous formulation strategies available for designing modified-release (MR) dosage forms. However, one of the key challenges when developing an MR formulation is to identify the *in vivo* release rate and the dose required to achieve the TPP. While *in vitro* dissolution data are generated to describe drug release, the assumption that this will represent *in vivo* performance is unproven until *in vivo* clinical data are available.

Often, with MR formulations, an overall reduction in exposure is observed when delivering to lower regions in the gastrointestinal (GI) tract, due to reduced absorption. Contributing factors include reduced fluid volumes (for dissolution and solubilisation) and surface area, and differing permeability. Similarly, there are recognised challenges and risks associated with using preclinical animal models to design MR formulations due to significant inter-species anatomical and physiological differences. The use of Translational Pharmaceutics, which combines formulation development, real-time clinical manufacturing and clinical testing in humans, can help identify the optimal platform, dose and release rate to meet the TPP of interest.

In this case study, an NCE in development for the treatment of inflammatory diseases was being dosed twice a day (BID) or three times a day (TID) during early clinical trials due to a short half-life and a slower terminal phase.[2] The customer ideally wanted to develop a once-a-day (QD) product to increase patient compliance and therapeutic outcomes. The TPP was a lower peak-to-trough ratio compared with the immediate-release (IR) product and coverage of the lowest efficacious concentration over the desired duration. A matrix-based MR dosage form was proposed to reduce the dosing regimen frequency.

Quotient Sciences carried out two clinical studies in healthy volunteers to achieve these objectives. In the first study, matrix minitablets in capsules or monolithic matrix tablets were developed and evaluated using *in vitro* dissolution rates of 80% release over eight and 12 hours. While a QD PK profile was achieved in the fasted state with the slower *in vitro* dissolution rate with both types of matrix-based drug products, the formulation was susceptible to a food effect when administered with a high-fat meal. This resulted in most of the exposure occurring within the first 12 hours of dosing, which is not optimal for QD dosing.

The second clinical study was built on the results of the first study and was designed to evaluate a proprietary technology platform, DiffCORE™, from the client, with the overall goal of overcoming the food effect issue. The use of the Translational Pharmaceutics platform enabled evaluation of multiple variables in this two-part adaptive clinical study, including formulation modifications, food effect and dose levels/tablet strengths.

Flexibility was maximised by inclusion of a two-dimensional formulation design space in the regulatory submission, which allowed quantitative changes in the release rate and dosing during the clinical study to achieve the desired PK profile. This integrated Translational Pharmaceutics approach allowed for multiple formulation iterations to be tested in the same healthy volunteers in both the fed and fasted state within a short timeframe, resulting in rapid identification of the optimal formulation to enable QD dosing.

"The use of Translational Pharmaceutics, which combines formulation development, real-time clinical manufacturing and clinical testing in humans, can help identify the optimal platform, dose and release rate to meet the TPP of interest."

"Developing a suitable and palatable formulation is a critical requirement for drug development programmes targeting potential paediatric indications."

PEDIATRIC DEVELOPMENT CASE STUDY

An Integrated Paediatric Formulation Development, Taste Assessment and Relative Bioavailability Evaluation Programme

Developing a suitable and palatable formulation is a critical requirement for drug development programmes targeting potential paediatric indications. As young children may have difficulty swallowing tablets and capsules, special dosage forms – for example, liquid formulations such as solutions or suspensions, multiparticulates such as granules (dispersible, dissolvable powders) or mini tablets – may need to be developed, depending on the age of the target population. However, the taste masking of these formulations must be considered to ensure patient compliance.

Developing formulations for a paediatric population requires special consideration of the excipients because certain excipients that are acceptable in adult dosage forms may not be acceptable in paediatric dosage forms. Depending on the age and indication, some patients, such as neonates, may require enteral feeding by tube, so compatibility with the dosing units is also an important consideration. When a medication is designed to be administered with or sprinkled on food/juices, compatibility and stability with food and taste masking becomes critical, and suitable flavours and sweeteners may need to be a key component of the dosage form strategy.

In this case study, the client wanted to develop an oral paediatric formulation for patients aged three months to 12 years.[3] The goal was to select and identify a suitable novel oral suspension formulation, with an optimal flavour and/or sweetener combination to improve palatability in the target population. Using its Translational Pharmaceutics drug development platform, Quotient Sciences carried out a two-part study to achieve these objectives.

Part one of the study was designed to profile the taste characteristics of the API and identify a suitable flavour system. Five formulations with different flavour and sweetener combinations were compared with the reference drug suspension in healthy volunteers. Taste assessments were performed by administering formulations using the sip-and-spit technique 30 minutes apart, with palate cleansing in between. The clinical trial subjects filled out a questionnaire (immediately after each sip-and-spit part) to rate the overall acceptability and seven key taste characteristics (smell, sweetness, bitterness, flavour, mouth feel/texture, grittiness and aftertaste) on a nine-point Likert scale. Statistical analysis of the data enabled selection of the optimal formulation.

Part two of the clinical study enabled a relative bioavailability assessment of the suspension formulation identified in part one, compared with the reference adult formulation, which was an oral tablet.

The integration of formulation development with taste-masking strategies, real-time adaptive GMP manufacturing, taste assessment and PK studies allowed the client to meet the expectations of both regulators and patients. As a result, the client was able to seamlessly enter paediatric patient clinical trials with a palatable drug product in a timely and cost-effective manner.

CONCLUSION

In summary, by integrating drug substance, drug product and clinical testing activities, Translational Pharmaceutics has been proven to accelerate complex molecules through the development pathway. This streamlined approach seamlessly supports Quotient Sciences' customers' programmes across the full development lifecycle, from candidate development to commercial product launch.

Key applications of the integrated approach include:

- Fast-tracking molecules from FIH to proof of concept
- Development and optimisation of clinical formulations, including solubility enhancement, modified release and paediatric drug products
- Lifecycle management of late-stage and commercial products
- Evaluation of novel drug delivery technologies for all routes of administration.

The major benefit of using Translational Pharmaceutics was quantified in a published study by the Tufts Center for the Study of Drug Development (CSDD) as significant time and cost savings in reaching key regulatory and clinical milestones as quickly and efficiently as possible. On average, development timelines are reduced by over a year, delivering financial gains of more than US$200 million (£159 million) per approved new drug through a combination of reduced research and development costs and earlier access to commercial sales. This enables better decision making early on, based on human data, and a more streamlined outsourcing model.

Quotient Sciences offers its clients the ability to develop, manufacture, release and dose drug products within one organisation. This maximises the probability of success and significantly reduces development time and costs for its customers, getting new medicines to patients faster.[4]

ABOUT THE COMPANY

Quotient Sciences is a drug development and manufacturing accelerator, providing integrated programmes and tailored services across the entire development pathway. Cutting through silos across a range of drug development capabilities, the company aims to save precious time and money in getting drugs to patients. Everything it does for its customers is driven by an unswerving belief that ideas need to become solutions, and molecules need to become cures, fast. Because humanity needs solutions, fast.

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ABOUT THE AUTHOR

Aruna Railkar, PhD, has over 25 years of experience in the pharmaceutical industry, working at the discovery–development interface, providing critical input for progressing compounds into clinical development, prodrug evaluation, understanding challenges in absorption/exposure of lead molecules and development of formulation strategies (conventional or enabling) based on compound properties. During her career at Hoffmann-La Roche, Dr Railkar led the group characterising compounds' physicochemical and biopharmaceutic properties to inform NCE selection and provided stage-appropriate formulation development for preclinical and clinical studies, collaborating with discovery and development teams in multiple therapeutic areas. Her area of interest is the development of novel dosage forms for existing drugs. She joined Quotient Sciences in 2019.

MODIFIED-RELEASE MICROSPHERES: MAXIMISING COATING INTEGRITY AND OPTIMISING RELEASE

In this article, Jonathan Cape, PhD, Head of Multiparticulates at Lonza Small Molecules, discusses development considerations and workflows to select optimal enteric coat weights for modified release microspheres – balancing performance considerations with API stability and the excipient burden to patients.

Modified-release (MR) microspheres are widely used intermediates for dosing compounds that require protection from the gastric environment. They can also deliver drugs to the site of action in the upper and middle gastrointestinal tract, such as the duodenum or jejunum. Polymeric enteric coatings are often used on top of an immediate-release or MR inner core particle to give MR microspheres this type of additional functional performance.

Manufacturing technologies to make these microspheres are well established. For making the inner drug-containing cores, these include spray layering, melt-congeal and granulation methods. Fluid bed techniques are commonly used to apply the enteric coatings. However, developing new enteric- coated microspheres requires the correct selection of polymeric coating, plasticisers and anti-tacking agents, along with an appropriate inner core matrix material. Moreover, the weight of coating applied affects both manufacturability and enteric functionality, and these need to be balanced. Other excipient considerations include minimising the impacts on API stability in the drug product formulation and level of impurities in the excipients.

Managing performance versus excipient burden considerations can be a primary driver for formulation decisions, as MR microspheres often require heavy coat weights to achieve strictly enteric functionality. It can be above 50% in some cases, representing a significant amount of the excipient burden to a patient. This burden can be critical for vulnerable patient populations, such as paediatrics.

COATING PROCESSES

Fluid bed coating is the most commonly used unit operation to apply enteric coatings to small microsphere intermediates with diameters ranging from about 0.1 to 0.5 mm. This unit operation consists of partially entraining particles in a vertically directed airflow from a fluidised bed charged with microspheres through a central vertical column (a Wurster column).

In the bottom spray configuration, a spray nozzle located within the Wurster column coats the particles as they pass through the spray plume emerging from the nozzle. Particles de-entrain and fall back to the fluidised bed and are then repeatedly passed through the column, gradually building up the coat on the uncoated particles. The batch will finally reach an endpoint based on a target that has been set for the average applied coat weight.

Excipient impacts on API stability and patient toxicity are generally assessed early on in a programme. This allows the formulation approach to be aligned with the quality target product profile. Both stability and toxicity determine the maximum tolerable coat weight in a formulation, providing upper limits to the amounts of impurities that may be present in the excipients used to coat. For example, enteric polymers may contain trace impurities such as peroxides, aldehydes and free acids that can impact API stability. Minimising the source of these impurities through coat weight control is one way in which the stability of the drug product can be ensured.

"Upper limits to certain excipients may also be dictated by the acceptable daily intake of the target patient population."

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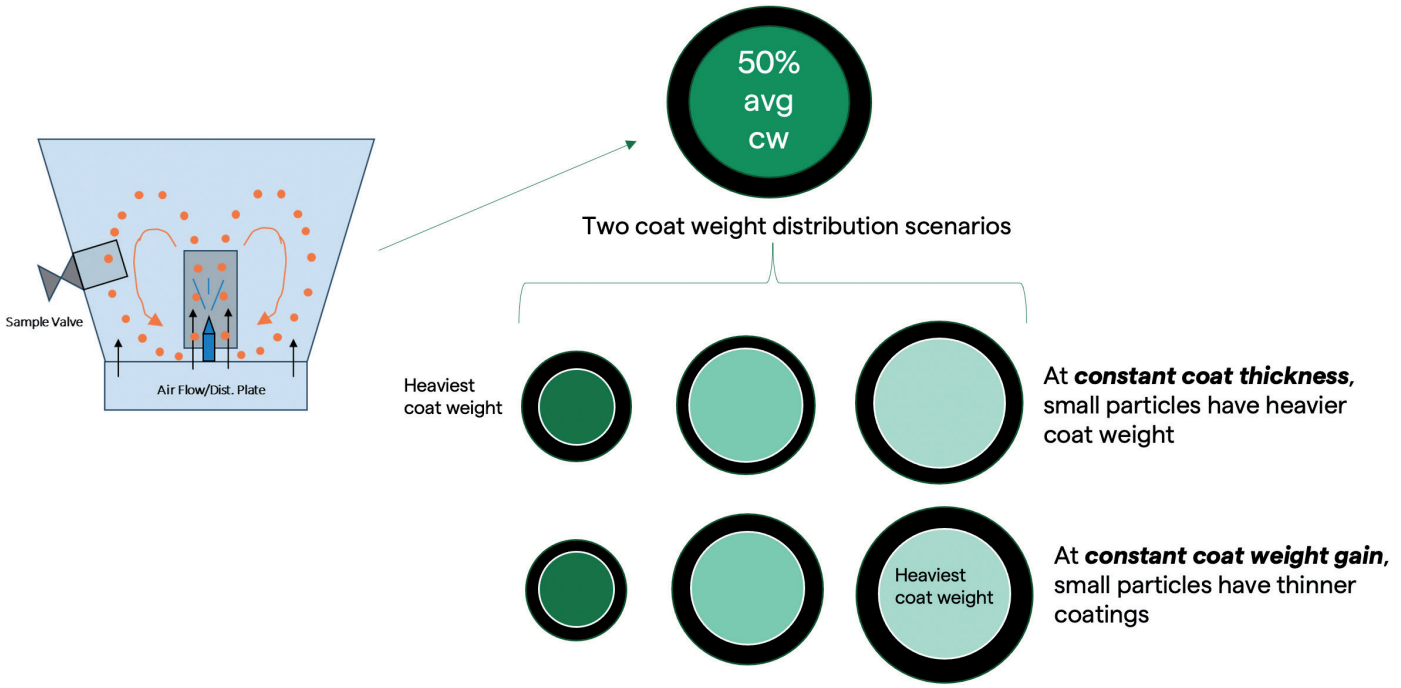

Figure 1: Coat weight distribution and impact on performance.

Upper limits to certain excipients may also be dictated by the acceptable daily intake of the target patient population. This applies to enteric coatings and additives within them, including plasticisers and anti-tacking agents. As an example, toxicology data is often lacking in paediatric populations for novel coating formulations, and therefore upper dosing limits are often inferred from animal studies or demonstrated safety in adult formulations. One general strategy is to maintain excipient doses well below demonstrated safe levels for adults when used in indications for sensitive populations.

Formulators must also ensure that the coating itself performs its intended function and achieves the target specifications for enteric dissolution. Two main factors are relevant when selecting the target applied coat weight for the enteric coating. First, enteric performance is generally only achieved if a sufficiently high threshold average coat thickness is applied to the particles. This threshold varies considerably between coating formulations and is often empirically determined by making a performance assessment of intermediate coat weight samples from an initial fluid bed survey run. Sufficient coat thickness ensures that, on average, the coating completely covers the texture of the underlying core particle, and that coating defects are buried under additional coating material to achieve optimal integrity of the coat.

Second, the average applied coat weight needs to be sufficiently high so that it accounts for the coat weight variations that will inevitably occur across the range of the core particles' size distribution. In other words, the applied coat weight is generally not equal for all sizes of core particle; this variation is referred to as the coat weight distribution. This coating heterogeneity can have critical implications for early burst release in coated microsphere formulations.

COAT WEIGHT DISTRIBUTION

To understand how coat weight distributions arise, consider a general case where particles traversing the spray plume each have an equal probability of being hit by coating droplets. These particles may be prone to pick up equal coat thicknesses across the core population. This situation is commonly encountered in fluid bed coating and will result in larger particles having a lower relative coat weight than smaller particles. These larger, less-coated particles may exhibit early release if an osmotic potential exists in the core particle.

Alternatively, under other fluid bed coating conditions, particles may accumulate coating in a manner proportional to their cross-sectional area. In this case, each particle within the core population may pick up an equivalent coat weight, but the coat thickness may be vastly different between large and small particles on account of the nature of the surface area to volume. This limiting case leads to the opposite behaviour. Here, small particles will have thinner coatings, and larger particles will have thicker coatings. Both these limiting case examples implicate insufficient coat weight or coat thickness as root causes of early release in enteric-coated microsphere populations. This is illustrated in Figure 1.

> "A sharp transition in early-release behaviour will often be observed as the coat weight rises above a critical level."

It is worth considering the overall workflow for enteric coat optimisation, as shown in Figure 2. Fortunately, several tools in development workflows are available that allow formulators to pinpoint the threshold for sufficient coat weight in prototype formulations, and then understand dissolution failure modes and sensitivity in terms of the formulation and process space. Drawing intermediate coat weight samples during an initial prototype coating run is commonly performed to test the sensitivity of overall release to the average coat weight.

This experiment is essential to determine the initial ballpark target for the coat weight required to achieve the enteric-release target. A sharp transition in early-release behaviour will often be observed as the coat weight rises above a critical level, which may vary with core and coating formulations. Early release may still be observed, even at coat weights approaching or exceeding the upper limits established by the stability and toxicology considerations. If this occurs,

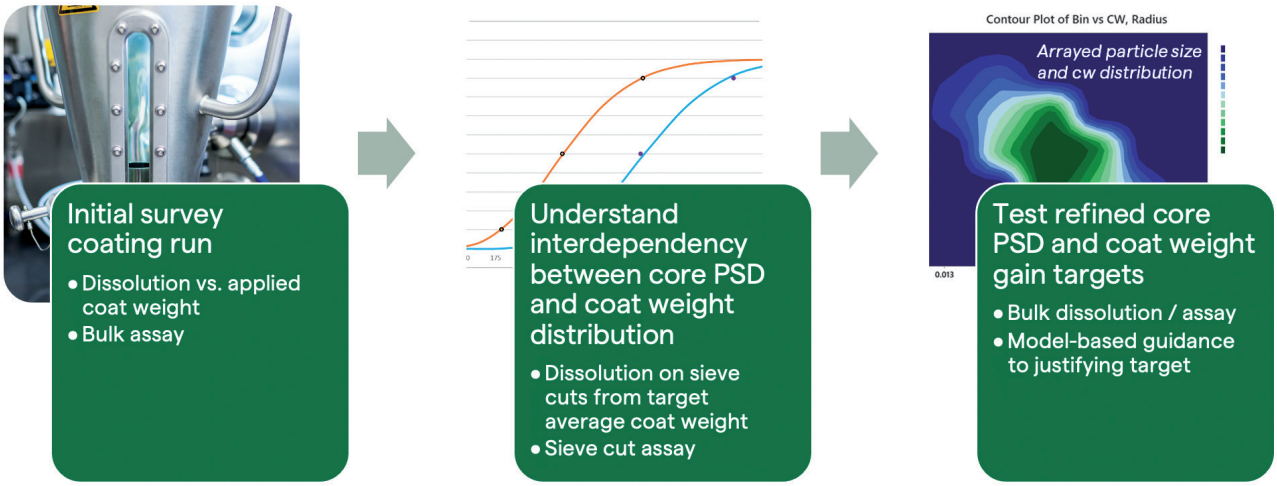

Figure 2: Workflow for enteric coat optimisation.

a deeper dive is required to gain a better understanding of the nature of early release and then explore mitigation strategies.

Further experimentation may involve separating the target coat weight population by sieving it into sub-populations with different particle sizes. If the enteric dissolution performance of these sub-populations is measured, it should reveal the mechanism driving early release.

It should also make it possible to determine whether the fluid bed coating process is taking place on a constant coat thickness or a constant coat weight basis. For example, if increasing assay is observed with increasing overall particle size, then the coat weight distribution is consistent with a constant coat thickness model. In this case, the larger particles will be under-coated relative to the average target coat weight established using bulk measurements, making this part of the population more prone to either passive permeation or osmotic burst mechanisms.

> "If increasing assay is observed with increasing overall particle size, then the coat weight distribution is consistent with a constant coat thickness model."

PASSIVE PERMEATION OR OSMOTIC BURST?

Simulation and further experimentation can distinguish between passive permeation and osmotic burst mechanisms, which, in turn, can lead formulators to a viable control strategy for dissolution performance. Simple micrographic evidence is often sufficient to demonstrate an osmotic burst mechanism, in which particles can be seen to swell and then burst after a lag phase. This behaviour is observed only in a subset of particles, thus providing strong evidence for the under-coating of a specific sub-population of particles within the core population. Further, this data can be quantitatively modelled according to osmotic flux and passive permeation models for early release. One such model is shown in Figure 3.

Many core particle formulations incorporate water-soluble components. These include the drug itself, of course, but also excipients such as functional polymers, binders and fillers. While specific formulations are beyond the scope of this discussion, microsphere core formulations will nearly always have some propensity for water uptake.

Polymeric enteric coatings have a propensity for water uptake, too, making them permeable upon soaking, and allowing

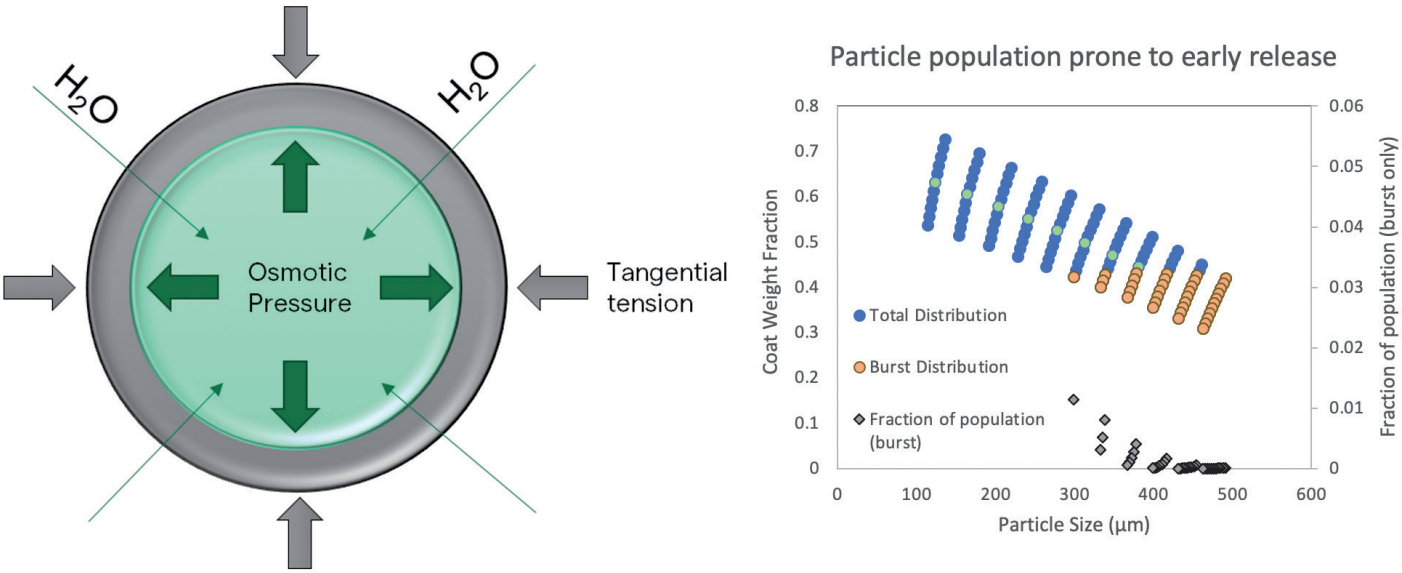

Figure 3: Predictive model of coat weight distribution and dissolution impact.

a limited influx of water or media into the inner core particle. This influx is governed by the osmotic potential of the core, which can be modelled with equations of state or mixing functions, such as the Flory–Huggins solution theory. The inner core necessarily swells, but the coating around it tends to resist swelling. When the osmotic force within the particle and the effective modulus of the outer coating are equal, the particle is in mechanical equilibrium and will maintain its swollen size. However, if the inner osmotic potential exceeds the outer coating's ability to contain it, the particle will burst. This mechanism appears to explain early burst release in many cases.

Passive permeation differs, as it will not result in particle swelling, and neither will early bursting be observed in micrographic soak test studies. This mechanism of early release is strongly impacted by both the coating formulation and coat weight. As with osmotic bursting particles, the passive permeation mechanism is also subject to coat weight distribution impacts. Particles with thinner coatings will exhibit reduced lag times to early release, and faster permeation once release begins. However, in contrast to the osmotic burst mechanism, early release resulting from passive permeation can be expected to occur throughout the entire particle population.

MITIGATION STRATEGIES

Once these mechanisms have been identified and understood, mitigation strategies may be developed around the formulation and coating process. For example, if a thinly coated sub-population with a high particle size is found to be responsible for early release, a control strategy around ingoing core particle size may be implemented to mitigate it. Modifications to the average target coat weight may also be employed to bump the formulation into a better performance space.

"If the inner osmotic potential exceeds the outer coating's ability to contain it, the particle will burst."

Alternatively, strengthening the coating by incorporating high-molecular-weight polymers may enable the formulation to resist osmotic swelling. Passive permeation may be mitigated by similar approaches: targeting and eliminating thinly coated sub-populations, modifying the overall coat weight target and altering the coating's formulation. Reducing the levels of, or even eliminating, plasticisers or water-soluble additives in the formulation may also help.

Designing enteric-coated microspheres can be a nuanced process, but this can be made easier if target product profile constraints are carefully considered at the outset and appropriate workflow tools are in place. Establishing upper limits to coat weight based on API stability and patient excipient burden considerations should be the first step in designing an enteric-coated microsphere product design.

Using simple experimental tools alongside modelling can help to establish acceptable performance based on target coat weight, whereas fine-tuning the coat weight distribution allows performance, stability and other aspects of the target product profile to be optimised. These workflows allow the empiricism to be taken out of enteric-coating optimisation, leading to robust and scalable products.

ABOUT THE COMPANY

Lonza is a global partner to the pharmaceutical, biotech and nutrition markets. The company works to enable a healthier world by supporting its customers to deliver innovative medicines that help treat a wide range of diseases. It achieves this by combining technological insight with world-class manufacturing, scientific expertise and process excellence. At Lonza Small Molecules, connected experts provide contract development and manufacturing services, helping pharma and small biotech companies deliver their medicines to patients in need. From the earliest stages of discovery to the final drug product, Lonza is a CDMO partner that simplifies the outsourcing experience with its reliable, timely service, anticipating risks and solving problems.

ABOUT THE AUTHOR

Jonathan Cape, PhD, started his journey in pharmaceuticals with Bend Research in 2011 as a Senior Research Chemist and Principal Scientist after postdoctoral research focusing on redox catalysis at both Washington State Department of Chemistry and Los Alamos National Laboratory, Materials Chemistry Group (US). From 2013 to 2019 he worked in the Lonza Global R&D group, supporting innovations in spray-dried dispersions, multiparticulates and capsules. From 2019 to 2021, he was the analytical development manager for Lonza Capsules & Health Ingredients R&D. Starting in 2021, he served as a Principal Investigator and then Lonza's Multiparticulate Technology Head, leading a portfolio of early and late-stage programmes involving modified release.

INCREASE PRODUCTION SUCCESS THROUGH TABLET DESIGN TECHNIQUES

In this article, Richard Ball, Design Office Manager at I Holland, considers the important features of tablet design and discusses its importance to the mass production of tablets.

Tablets are the most widely used pharmaceutical dosage form. Manufacturers choose tablets for many reasons, such as cost-effectiveness, ease of use, portability, administration and dosing accuracy. With the need to produce tablets quickly and efficiently, one of the primary considerations for tablet manufacturers is design specification.

Good tablet design is critical to producing a robust mass-produced oral solid dose. Without it, anti-counterfeiting, tool strength, tablet coating, functionality and compressibility can all be affected. Good design also helps to prevent common tablet compression problems, such as sticking, picking, capping and premature tool failure. Therefore, planning design early in the development process is important to ensure a consistent and high-quality final product is produced.

> "Understanding how a tablet's design will impact the production and delivery of the final product is critical to profitable manufacturing and market success."

IS YOUR TABLET IN GOOD SHAPE?

Understanding how a tablet's design will impact the production and delivery of the final product is critical to profitable manufacturing and market success. The first thing that should be considered when designing a tablet is the shape.

Although unusual and intricate shapes can be used, most manufacturers stick to the basic round or oval-shaped tablets for manufacturing ease and consistency. These shapes are preferred because they are more streamlined and are typically easier to swallow than other designs (Figure 1). Markings used for brand identity are also simpler to apply. Importantly, these shapes are robust – an important factor when mass-producing tablets.

Designer shapes may look aesthetically pleasing, but they present a challenge during production and require specialised tool manufacturing capability. Selecting an

Figure 1: Designer shapes may look aesthetically pleasing, but they present a challenge during production and require specialised tool manufacturing capability.

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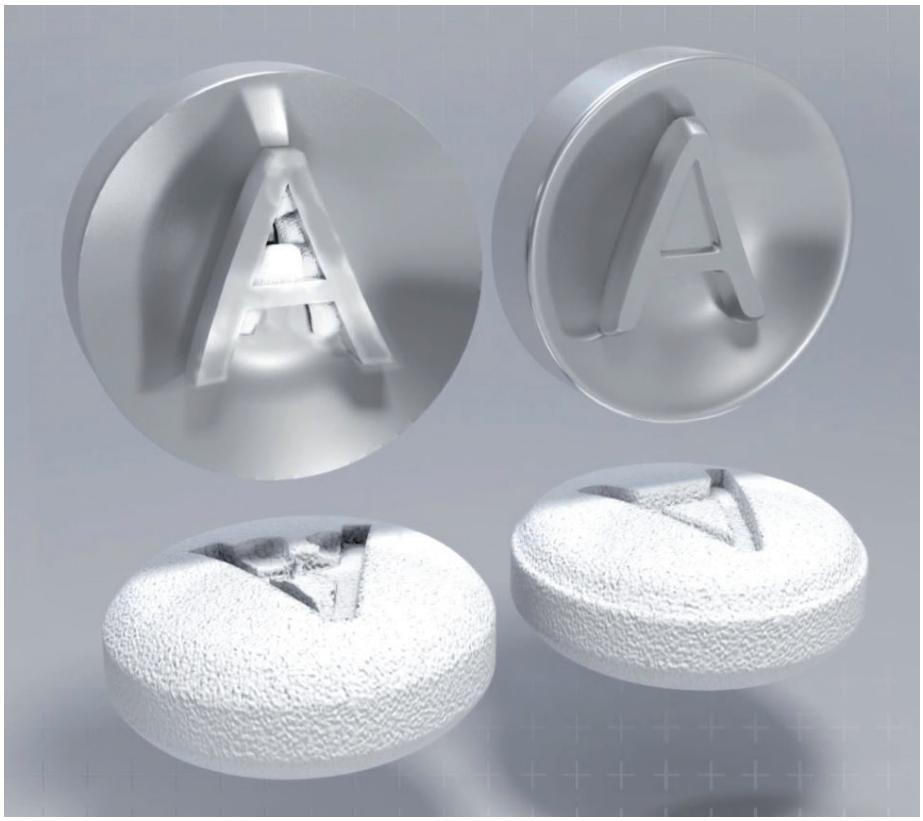

Figure 2: Good tablet design prevents common tablet compression problems, such as picking, where the compressed granule adheres to the detail on the punch face making any embossing detail indecipherable.

"If the tablet is to be coated, the profile must be correct for the manufacturing process to be successful."

incorrect shape, or one that has been badly designed, can have a huge impact on the bottom line, as manufacturing problems will inevitably delay production.

When designing the shape, thought must also be given to the tablet size and volume. Too big and it is difficult to swallow, too small and important identification, such as embossing, cannot be added. Consideration should also be given to the type of press available for tablet manufacture, as this can limit the size of the tablet.

THE RIGHT PROFILE

Once a shape has been decided on, the next design consideration should be the tablet's profile. There are different profile designs to accommodate specific requirements, including flat-faced, bevelled edge, single or double radius, ball and pill. The final decision is influenced by several factors including, but not limited to, the formulation, coating process, tablet thickness, friability, tablet hardness, packaging, swallowability and functionality. Embossing and branding requirements can also affect what profile is chosen.

If the design is to be heavily embossed, it is important to avoid tablet profiles with a deep cup, such as a ball or pill. Deep cup profiles can cause a softer core in the tablet, which, in turn, can lead to picking and erosion (Figure 2). It will also reduce the available space for the embossing itself. Using a shallower profile with a reduced cup depth is recommended, as it will allow for a larger embossing area.

If a tablet design specifies the profile to have a deep curve, it can often cause wear on the areas of tooling with the steepest gradient. In addition, the action of compression abrades the punch tip face, removing material over time, which can lead to problems such as delamination, resulting in the tablet splitting apart. By designing in a flatter tablet profile or a double radius, formulators can help reduce the granule's frictional action across the punch surface.

If the tablet is to be coated, the profile must be correct for the manufacturing process to be successful. The coating should be uniform and should not crack under stress. The coating solution is usually sprayed onto the uncoated tablets as they are agitated in a pan or fluid bed. As the solution is applied, a thin film is formed, which sticks to each tablet. The liquid portion of the coating solution is then evaporated by passing air over the surface of the tumbling pans. A single application may be enough to form the coating or it may develop in layers through multiple spraying cycles. This puts stress on the softer centre. Typically, the centre of a tablet is softer than the outer diameter, so when the tablet comes into contact with the coating pan and other tablets, core erosion can occur. This weakness, caused by mechanical stress during coating, can be reduced by using double-radius profiles and avoiding shallow concaves or flat profiles.

If a tablet design includes a shallow profile with hard, sharp edges, the coating process can damage the exposed perimeter of the tablet. Because the tablet cannot roll effectively in the coating pan, chipped edges and cracks within the coating are commonplace. By choosing a double radius with a balanced profile, the tablet edge will be stronger and it will roll with ease to ensure a uniform coating is achieved.

BRIDGING THE GAP

Inadequate design of branding or markings on the tablet can cause bridging. Here, the coating builds up in the embossing detail on the tablet surface, due to it not flowing easily into the contours of the design, and making the embossing indistinct. The effect of this can bridge over and create a void underneath, or in-fills the design and leaves too much coating material in the marking, resulting in poor definition.

Bridging happens for a number of reasons, but the most common causes are inadequate adhesion of the film coating, poor marking design and inappropriate coating procedure. The spray rate and drying time can also have an influence. If all these factors are not carefully considered, the adhesion characteristics of the coating will be affected. Additionally, bridging is likely if the angle of the marking design is too acute or deep. If the stroke or section of the embossing is too wide or too shallow, in-filling may occur.

"The scoring or breaklines enable a tablet to be split evenly; therefore, it must be appropriately functional, as unequal breaking can result in variations in the administered dose."

TAKE A BREAK

An important consideration when designing a tablet is the breakline. The scoring or breaklines enable a tablet to be split evenly; therefore, it must be appropriately functional, as unequal breaking can result in variations in the administered dose. The level of inaccuracy can be related to the breakline design, formulation and tablet hardness (Figure 3).

If a breakline must be included in the tablet's design, there are several factors to consider. First, is the tablet big enough to be easily separated? The breakline may need to penetrate the tablet wall while maintaining optimised radii and angles. If the radius at the bottom of the breakline is too large, it can negatively affect breakability.

Will the identification design and embossing work with the breakline? Maximising the tablet face area will help to avoid picking when the compressed granule adheres to the detail on the punch face, making any embossing detail indecipherable. Additionally, it is important to ensure that any embossing is not too close to the land edge or exceeds the cup depth, as this can cause problems during the tableting process.

If a breakline is designed on both sides of the tablet, alignment is crucial, particularly when using round tooling. An anti-turn key should be installed on the upper and lower punches and the press should include key guides in the upper and lower turret. A breakline feature can protrude above the punch tip edge, so the upper and lower punches must be set correctly for effective tablet ejection and take-off, as well as avoiding press components.

The upper and lower tip gap should also be considered, if adding a protruding breakline, to prevent the upper and lower punch from coming into contact. Where the breakline protrudes more than the gap setting, it will be necessary to manufacture the nominal length of the tooling to the top of the protruding breakline. This should be carefully considered during the design stage, as it can result in failure and damage to the upper and lower punches.

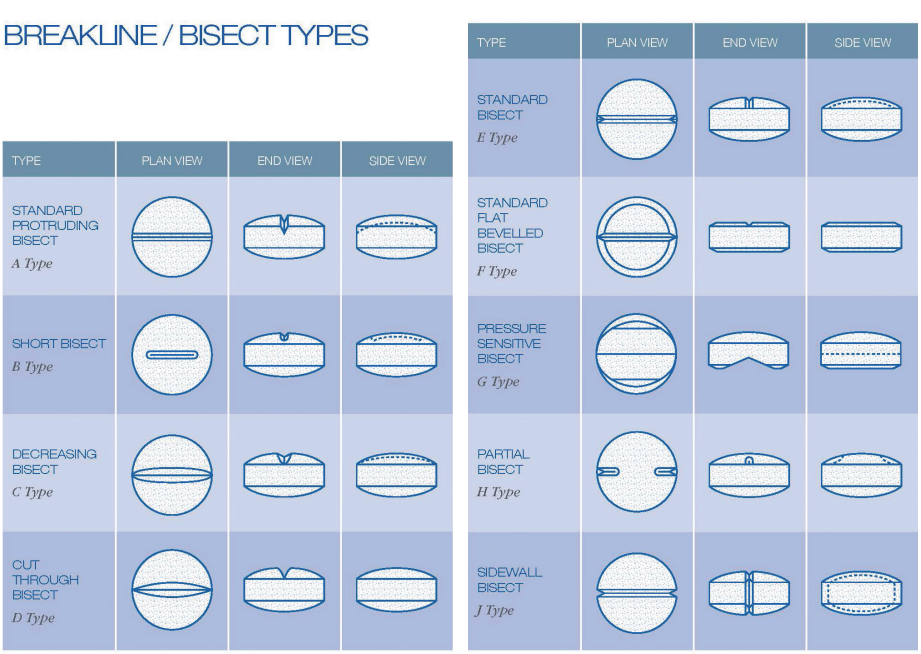

Figure 3: Scoring or breaklines enable a tablet to be split evenly; therefore, it must be appropriately functional as unequal breaking can result in variations of the administered dose.

Figure 4: Tooling must have the strength, durability and performance to stand up to the high demands of tablet compression.

USE THE CORRECT TOOLING

Tooling must have the strength, durability and performance to stand up to the high demands of tablet compression (Figure 4). An important factor to consider is a blended land (Figure 5).

The land on a tablet is the flat lip or ridge around the perimeter of the tablet face perpendicular to the tablet's edge. If a blended land is applied incorrectly, a range of issues can ensue during compression, including chipping of the tablet land during take-off, capping, the build-up of coating on the tablet's edge and, in extreme cases, punch tool breakage.

Applying the correct blended land will increase tablet strength and performance, resulting in higher production yields. To correctly blend the land, a reputable tool manufacturer will ensure that the flat area on the tip edge is maintained while applying a radius (blend) to the intersection between the flat perimeter of the punch tip and the concave cup that forms the tablet profile. It is important to remember that

"Applying the correct blended land will increase tablet strength and performance, resulting in higher production yields."

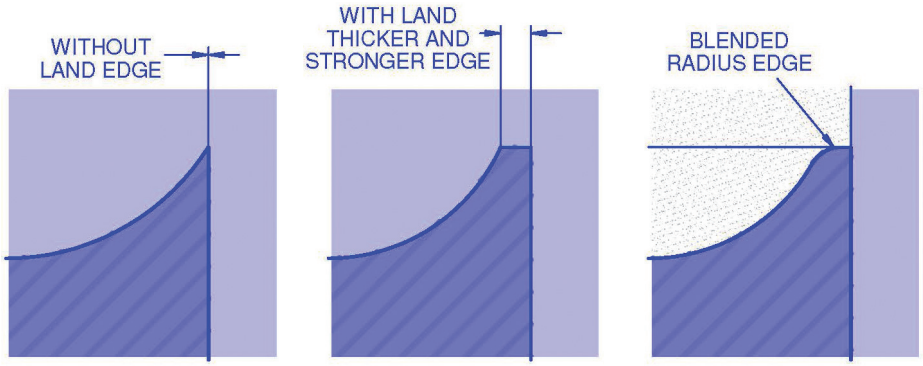

Figure 5: If a blended land is applied incorrectly a range of issues can ensue during compression, including chipping of the tablet land during take-off, capping, the build-up of coating on the tablets edge and, in extreme cases, punch tool breakage.

a correctly selected and applied blended land provides benefits in handling, loading, setting, tooling strength and the visual appearance of the tablet.

DESIGN WITH CARE

Tablet design is crucial and should not be underestimated; get it wrong and it will have a huge impact on tablet production. To work successfully, the tablet manufacturer must consider important design factors, such as tablet shape, profile and breakline style.

There are many other elements to consider when designing a tablet, including factors not discussed here. Everything, from tooling material and coating to branding typefaces and anti-counterfeiting techniques, must be considered. The list is long; therefore, consulting with an expert tablet designer and tool manufacturer should be done early in the design process. This ensures that the tablet design is robust and can be cost-effectively and efficiently mass-produced.

ABOUT THE COMPANY

I Holland is a leading manufacturer of punches and dies and supplier of tablet tooling maintenance equipment. The company has been established for over 75 years and uses these decades of experience, research and engineering know-how to provide expert solutions to its customers around the world. I Holland's commitment to research and development, and understanding the science behind tablet tooling, allows the company to help its customers with innovative solutions, no matter what the problem is and no matter what industry.

ABOUT THE AUTHOR

Richard Ball graduated from University of Derby (UK) with a Bachelor's degree in Mechanical Engineering. He started at I Holland in 2011 and is now the Design Office Manager. His main responsibilities are overseeing the creation of tablet and tool drawings and troubleshooting customer technical problems related to all aspects of tablets and tooling. Mr Ball also maintains I Holland's product lifecycle management system and seeks to continuously improve its processes.

POWDER CHARACTERISATION FOR PHARMACEUTICALS: BEYOND STANDARDS

Here, Aurélien Neveu, PhD, Head of Laboratory and Applications, Marco Lupo, PhD, Particle Scientist, and Filip Francqui, Managing Director, all at Granutools, discuss the limitations of current standardised procedures for assessing the properties of pharmaceutical powders and how Granutools' instruments – GranuPack and GranuHeap – offer a significant improvement over these existing standards, enabling keener insights and more repeatable analyses.

INTRODUCTION

Powders are one of the most commonly used material forms in the pharmaceutical industry. In particular, powdered materials are core to the manufacturing process of pharmaceuticals for solid oral and dry powder inhaler (DPI) applications. The processes involving powders are usually constituted by different steps, such as the feeding of the material into the production line, the blending of several constituents (excipients, API, additives) and the actual manufacturing of the product (tablets, capsules or inhalation devices).

Each of these production stages is influenced by the properties of the powder. For example, the homogeneity of the blends will be reduced if working with strongly segregating powders. Furthermore, the flowability has a drastic impact on the consistency of the mass flow at the output of the feeders, which can lead to variability in the mix.

In applications such as the production of tablets, the powder has to fill a small die prior to the compression stage. This critical step has to be fully controlled, as it will directly influence the weight consistency of the final tablets. In particular, the rheology of the powder has been identified as an essential property to predict and control the mass variability in tableting processes.[1]

The properties of a powder can also play an important role during administration to the patient. Particularly with DPI applications, the small API particles have to reach targeted spots in the lungs. A common way to proceed is to attach the small API particles to the surface of a carrier made of larger particles. The API particles can then be carried through the throat and released into the lungs. The electrostatic properties of the particles play a fundamental role in this process.

Therefore, it is essential to precisely evaluate the powder properties to better optimise the formulations as well as develop

> "It is essential to precisely evaluate the powder properties to better optimise the formulations as well as develop materials with improved processability."

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materials with improved processability. Powder properties can be evaluated in numerous different ways – a consequence of the lack of theoretical knowledge due to the complexity of the material. Contrary to classical fluids, for which the evaluation of the viscosity is usually sufficient to get a global picture of the flowing behaviour, there is no such universal metric for granular materials and powders up to now.

Over the decades, different methods for evaluating these material properties under specific solicitations have been developed. The most common ones consist of evaluating the angle of repose, the tapped density, the flowability and the response to shear. However, in these characterisation methods, the material is tested in a wide range of stress states, ranging from quasi-static to dynamic. Therefore, despite relying on the same micro-properties and interactions at the scale of the particles, each of these methods produces different information. Furthermore, a change in the characterisation protocol can lead to different results.

As an example, consider a very simple angle of repose (AOR) evaluation. A heap of powder is built and the angle of the heap that the powder naturally forms is measured. This angle depends on the properties of the particles, mainly their shape, and the particle–particle interactions, such as friction and cohesive forces. Measuring the AOR therefore gives an indirect evaluation of these properties. However, depending on the protocol that is followed to form the heap, different angles can be observed for the same powder. As a consequence, the results are influenced by the method protocol and the operator that performs the measurement. The necessity to define standardised procedures is thus unavoidable.

The most common characterisation methods used to evaluate pharmaceutical powder properties have been standardised by modern pharmacopeias and standardisation organisations. These standards are designed to provide well-established and easy-to-follow procedures. As everyone follows the same protocol, the results can be directly compared. These standardised procedures are especially useful when defining production criteria to guarantee that the material meets the expected quality. In fact, most of the regulations applied to pharmaceutical products rely on the evaluation of the powder properties according to standardised protocols.

However, the existing standards for powder property analysis are based on old and simple techniques, which can suffer from a lack of accuracy and repeatability. Moreover, the information gathered from these techniques is limited and is no longer sufficient for the current needs of high-end product development. This article focuses on two commonly used characterisation methods: tapped density analysis and the AOR.

TAPPED DENSITY ANALYSIS

Tapped density analysis is a very popular method for powder characterisation because of both the simplicity and the rapidity of the measurement. Evaluating the packing properties gives useful insights into the powder properties. Indeed, the way the particles rearrange during packing is influenced by the micro-properties of the material. In essence, the measurement is performed by first evaluating the apparent bulk density – the density obtained after pouring the powder into the measurement cell. Then, taps are applied to reach the tapped density corresponding to the maximum bulk density. A common metric extracted from this method is the Hausner ratio – the ratio of the tapped to the apparent density. The Hausner ratio is used as a flowability metric; the higher the Hausner ratio, the higher the cohesiveness of the powder and thus the lower its flowability.

Current Standards – Advantages and Drawbacks

The standardised tapped density protocol is fully defined in multiple pharmacopeias. A brief outline of the USP <616> protocol is discussed here. First, approximately 100 g of powder is poured inside a 250 mL graduated cylinder. Then, a predefined sequence of taps from a height of 3 mm is applied to pack the powder. The bulk density is evaluated after 10, 500 and 1,250 taps, and then followed by subsequent 1,250 taps sequences if the volume difference between two consecutive sequences is greater than 2 mL. For each bulk density evaluation, a naked-eye measurement of the powder volume is performed by the operator and, as the total mass is known, the bulk density is computed. Despite its long-term use, the tapped density standardised method still suffers from several limitations:

1. Initial powder bed levelling

After the pouring of the powder by the operator, USP <616> asks the operator to "carefully level the powder without compacting". This powder levelling can induce variability in the apparent density measurement and may lead to unwanted initial packing of the material and an incorrect apparent density estimation. Moreover, the operator has a strong influence on this step, leading to operator-dependent results and reducing the advantages of using standardised procedures.

2. Visual assessment of the powder volume

The standardised tapped density measurement requires a visual evaluation of the powder volume. Therefore, the measurement accuracy will depend on the graduated cylinder precision (2 mL) but also on the operator performing the volume reading. Indeed, for moderate to highly cohesive powders, the powder-air interface is very irregular (Figure 1) and the operator will usually determine an average interface position to estimate the volume of powder. Moreover, if the graduated cylinder is not perfectly levelled during taps, a slope can appear in the powder bed. In this case, the measurement accuracy and operator dependency are even worse.

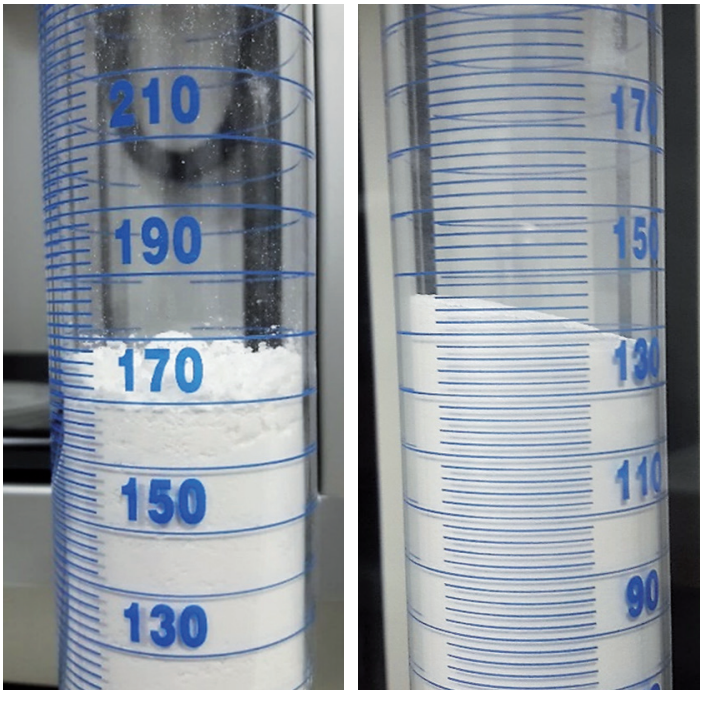

Figure 1: Measurement variability induced by visual reading in standardised tapped density protocols.

3. Large amount of powder required

The standardised measurement requires a large amount of powder – approximately 100 g. However, this amount of powder may not be available due to production or cost constraints, especially in the formulation development process.

Improved Method – GranuPack

Due to the lack of accuracy inherent in the standardised method, the insights gathered from this measurement can have limited applicability – it is difficult to highlight small differences in properties. In particular, when performing batch-to-batch evaluation to detect drifts in production, small changes in powder properties have to be evidenced, as they can lead to large variations in final product quality.

To tackle these limitations, an improved tapped density instrument has been developed by GranuTools based on the most recent fundamental research.[2] The GranuPack provides high accuracy and guarantees low operator dependency. With the GranuPack, only 35 mL of powder is required to perform a tapped density measurement.

To obviate user dependency on the initial pouring, a special initialisation protocol has been designed for the GranuPack. First, an initialisation tube is placed into the measurement cell (Figure 2), into which the operator pours the powder. Then, the tube is automatically moved upwards to pour the sample into the measurement cell in a user-independent and repeatable way. A light, diabolo-shaped piece is placed on top of the powder to ensure a flat powder surface. Finally, taps are applied and a sensor precisely measures the height of the powder after each tap.

The GranuPack assesses the complete packing curve, enabling a level of investigation into the packing dynamics that is not possible with the standard protocol. This allows for gathering useful new insights into the powder properties. Figure 3 shows a comparison between the procedure laid out in USP <616> and the GranuPack protocols for two lactose powders. In both cases, the obtained Hausner ratio is similar, but the repeatability is drastically improved with the GranuPack protocol.

ANGLE OF REPOSE

Another commonly used powder characterisation method is measuring the AOR. The AOR directly depends on the internal friction of the material and the strength of its cohesive forces. The higher the AOR, the higher the cohesiveness and thus the lower the flowability. Unfortunately, the protocols defined in USP <1174> and EP 2.9.36 do not give a strict procedure to measure this angle, which can induce operator-to-operator variability. Therefore, the standardised AOR evaluation does not provide the precision required to perform a fine evaluation of drifts in powder properties.

The AOR protocol has been improved upon by the GranuHeap instrument[2] – an automated heap shape measurement method based on image processing and analysis (Figure 4). The operator pours

> "The AOR protocol has been improved upon by the GranuHeap instrument – an automated heap shape measurement method based on image processing and analysis."

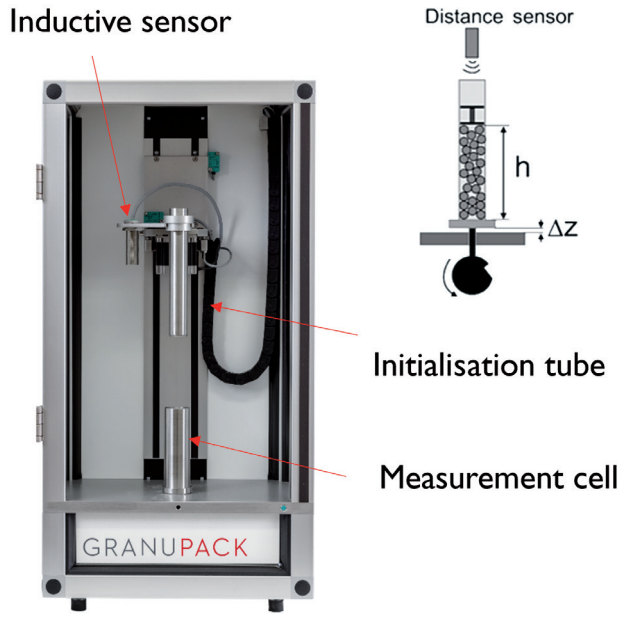

Figure 2: GranuPack – an improved tapped density analyser.

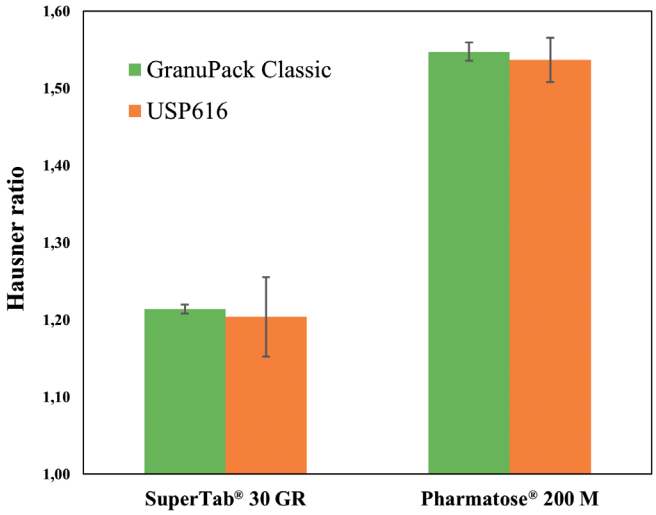

Figure 3: Hausner ratio measured with the GranuPack Classic and the USP <616> procedure for both powders. Error bars are ± the standard deviation on three independent tests.

Figure 4: GranuHeap – an automated AOR measurement device.

the powder into an initialisation tube, which then moves upward at a constant speed of 5 mm/s, allowing the powder to form a heap on a cylindrical support in a repeatable way. Then, the base slowly rotates and pictures of the heap at different angles are taken and analysed by a custom image recognition algorithm to determine the position of the powder-air interface and compute the AOR.

This protocol removes the user dependency of the AOR evaluation, which is particularly important when evaluating cohesive powders. Therefore, the GranuHeap provides an accurate and repeatable way to measure the AOR and constitutes a major improvement over the standardised procedure.

CONCLUSION

Defining standardised characterisation protocols is essential to guarantee the quality of the products and to ensure that they meet the strict regulation criteria. However, the characterisation protocols on which the current standards rely are based on old and overly simple methodologies that do not allow for fine evaluation of the material properties. With the constant development of high-end pharmaceutical products and processes, such as the transition from batch-to-batch to continuous manufacturing production, there is an increasing need for more refined characterisation methods.

Fortunately, new and improved powder characterisation tools have been developed during the last decade. In particular, the GranuPack and GranuHeap devices presented in this article provide a major improvement to tackle the limitations of the standardised protocols. The industry must now move forwards and upgrade the current standards to use these high-precision, state-of-the-art powder characterisation methods.

ABOUT THE COMPANY

Granutools combines decades of experience in scientific instrumentation with fundamental research on powder characterisation to develop and manufacture instruments that measure physical powder characteristics, such as flow, static cohesion, dynamic cohesion, tapped density and tribo-electric charge.

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2. *Lumay G et al, "Measuring the flowing properties of powders and grains". Powder Technol, 2012, Vol 224, pp 19–27.*

ABOUT THE AUTHORS

Aurelien Neveu, PhD, primarily focuses his research activitiess on the understanding of granular materials at different scales. During his PhD, he developed discrete numerical models to describe the fragmentation mechanics of cohesive granular materials by taking the complex micro-properties of the grains into account. He then moved to a larger scale to study segregation in gravity-driven rapid flows and the aeolian transport of granular materials, with huge implications for natural disasters. Dr Neveu is now working as a particle scientist at Granutools, performing research into powder characterisation.

Marco Lupo, PhD, graduated with a master's degree in Chemical Engineering from the University of Salerno (Italy) in 2016 and achieved a PhD in Chemical Engineering from the same university in 2021. In his PhD thesis, he studied how to quantitatively characterise the quality of the powder layers in selective laser sintering processes, both from an experimental and a modelling point of view. Dr Lupo now works as a Particle Scientist at Granutools.

Filip Francqui is the Managing Director of Granutools and has over 20 years of experience in the precision instruments business. Mr Francqui's experience covers the semiconductor, electronic microscopy and nanotechnology fields. Before founding Granutools, he was successively managing the Belgian, Dutch and Indian business for the electronic microscopy subsidiary of Thermo Fisher Scientific, which was famous for high-resolution and low-voltage imaging. Mr Francqui holds a master's degree in Applied Physics from the Free University of Brussels (Belgium) and an MBA from INSEAD (Singapore). He has authored numerous publications in scientific journals and holds two patents.

PRODUCT SHOWCASE: Optimising Gastric Resistance in Complex Oral Drug Products with Novel, Functional, Ready-To-Fill Capsules

Hard capsules are one of the most common solid dosage forms used for oral administration of active ingredients. Capsules are relatively simple to use compared with tablets, which require more formulation development and quality control and therefore take longer to produce. Capsules can be manufactured in different sizes and using different materials, depending on their main purpose and content. Hydroxypropyl methylcellulose (HPMC)-based capsules are the most common non-animal-derived alternative. Although they are a good substitute for gelatin, they have limitations, particularly when intended for enteric formulations because they are not resistant to gastric acid.

Coating capsules with functional polymers is a potential solution to this challenge. However, for the growing number of active molecules that are sensitive to acid, moisture and temperature, such as nucleotides, peptides and live biotherapeutics, the coating process conditions are unsuitable because these processes can cause damage or degradation.

Therefore, a new approach is necessary for the oral delivery of sensitive actives that enables reliable protection and provides an efficient and accelerated drug development timeline. Developing a delayed-release formulation of acid-sensitive actives that can be used in solid dosage forms, such as tablets, pellets and capsules, can be costly. Typically, this involves several stages, starting from R&D to scale-up and validation, all of which require significant investments of time and money. Sourcing a ready-to-fill functional capsule is an effective way of saving costs, reducing time to market and boosting the performance of oral drug delivery products.

> "Capsules are relatively simple to use compared with tablets, which require more formulation development and quality control and therefore take longer to produce."

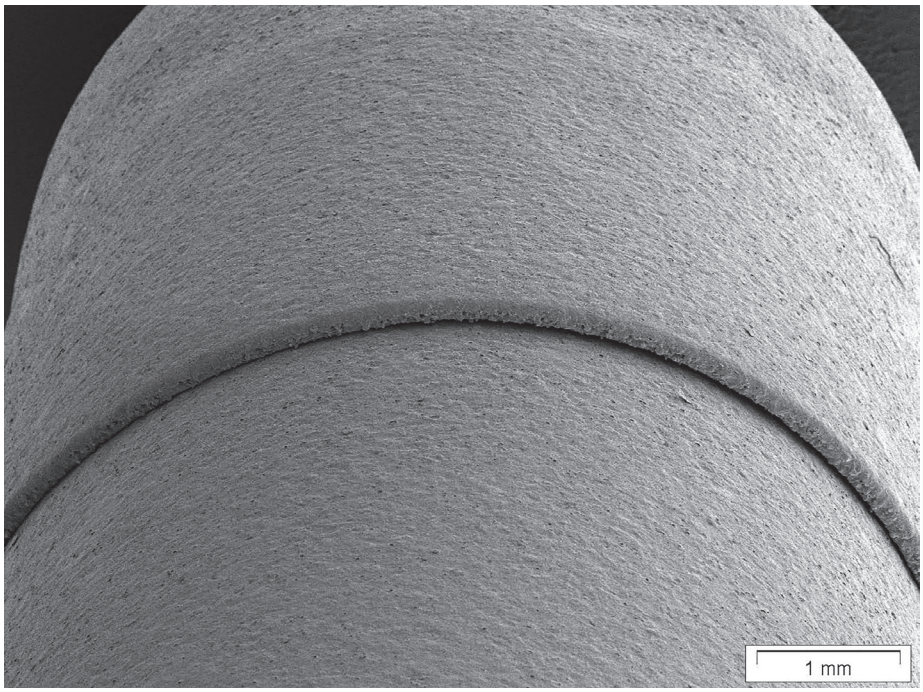

Figure 1: SEM image of final locked capsule at 20x magnification.

> "Developing a delayed-release formulation of acid-sensitive actives that can be used in solid dosage forms, such as tablets, pellets and capsules, can be costly."

EUDRACAP® is a non-animal-derived platform of functional, ready-to-fill capsules for fast-track development of sensitive drugs. The HPMC capsules are functionalised with a coating based on EUDRAGIT® polymers and can be easily opened and closed on standard manual and automatic capsule filling systems.

AN EFFECTIVE SOLUTION FOR ENTERIC DRUG DELIVERY

EUDRACAP® capsules allow targeted drug delivery (also of sensitive actives), reduce clinical risk and accelerate time to market. One type of capsule in the EUDRACAP® portfolio is EUDRACAP® enteric, which is designed to optimise gastric resistance and improve absorption of drug products targeted for release in the upper small

intestine. The high-quality HPMC capsules feature a precisely tailored functional coating that is well accepted by many key regulatory bodies around the world.

EASY TO OPEN AND CLOSE ON STANDARD EQUIPMENT

EUDRACAP® enteric capsules can be easily opened and closed on standard manual and automatic capsule filling systems. Various forms can be efficiently filled, including powders, pellets, granules and selected liquids (Figure 1).

RELIABLE PROTECTION AND PRECISE, RAPID RELEASE

Dissolution testing confirms that no drug release occurs during the acid stage (HCl 0.1N). After conversion to the buffer stage at pH 6.8, rapid release begins immediately, with excellent reproducibility across all tested batches (Figure 2).

Using EUDRACAP® enteric ready-to-fill capsules can accelerate the product development process, reduce complexity and risks during formulation development, and simplify scale-up and validation by replacing several complex process activities with just a single capsule-filling step.

In addition to EUDRACAP® enteric capsules, the EUDRACAP® portfolio also includes a customisable product, EUDRACAP® Select, which allows a capsule to be tailored to the specific needs of the pharmaceutical product.

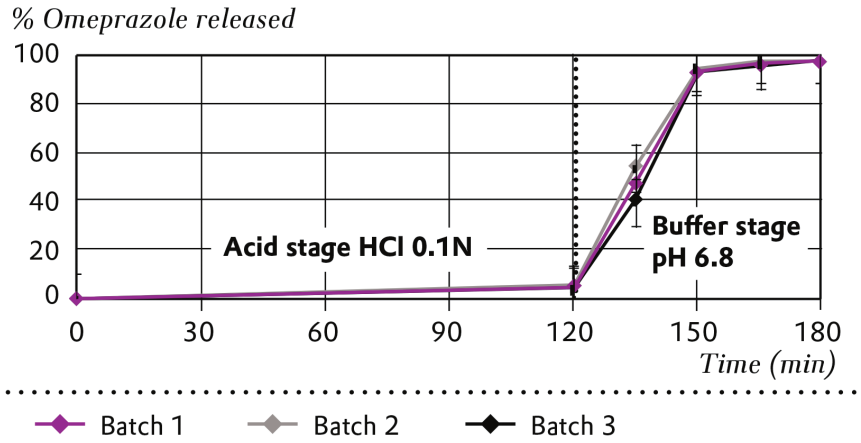

Figure 2: Dissolution profile using omeprazole as an acid labile model compound.

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CHALLENGES AND ACHIEVEMENTS OF TiO_2 REPLACEMENT IN HARD CAPSULES

In this article, Susana Ecenarro Probst, Vice-President R&D & Regulatory, Qualicaps EMEA & South Asia, looks at the issues arising in replacing TiO_2 in hard capsules and introduces the company's alternative hard capsule formulation.

Titanium dioxide (TiO_2) – also known as E-171 – is widely used in the pharmaceutical industry for solid oral dosage forms, such as tablets, hard capsules and soft capsules, as an opacifier and white colourant. The worldwide use of this excipient and food additive began to be threatened due to some concerns raised by the French consumer healthcare community in 2018, which drew special attention to the so-called nanomaterial risk that this ingredient could have inherently present. In April 2019, an official communication from the French authorities finally announced the prohibition of TiO_2 as a food additive in the first country in Europe. The ban started on January 1, 2020, and the first one-year period was extended until December 2021.

Nevertheless, by 2015, the European Commission had already requested the European Food Safety Authority (EFSA) to review the safety of E-171 as a food additive, to which an EFSA panel concluded in June 2016 that no real concerns existed about the continued safe use of E-171. Despite this, the EFSA recommended that more testing should be performed to complete the toxicological studies.

Finally, in May 2020 EFSA published an updated scientific opinion regarding E-171 toxicity after assessing the latest toxicological information and studies available.[1] It concluded that, based on all currently available evidence, genotoxicity concerns could not be ruled out and the E-171 TiO_2 food additive could no longer be considered safe.

Because TiO_2 is extensively used in medicinal products as a colourant and opacifying agent (mainly tablet film coating and hard-shell capsule formulation), Commission Regulation (EU) 2022/63 announced in January 2022 that, for the time being, TiO_2 remained on the list of authorised additives to allow its use in medicinal products to avoid any shortage of medicinal products that may impact public and animal health. A review clause stated that, after three years, an updated assessment would be issued by the EMA and provided to the European Commission by April 2024 for further decisions.

The EMA published a Q&A paper on relevant technical aspects related to the pharmaceutical quality of TiO_2 replacement in medicinal products, encouraging the pharmaceutical industry to make all possible efforts to speed up the investigation of new alternatives for replacing E-171 in drug products.

> "The EMA published a Q&A paper on relevant technical aspects related to the pharmaceutical quality of TiO_2 replacement in medicinal products, encouraging the pharmaceutical industry to make all possible efforts to speed up the investigation of new alternatives for replacing E-171 in drug products."

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In response to questions from the QWP Expert/EMA, an interesting survey conducted by the three European associations representing human medicines manufacturers (AESGP, EFPIA and Medicines for Europe) revealed that out of all the marketing authorisations for products containing TiO_2 in European Economic Area (EEA) countries (June 2021), the EV Codes (unique codes assigned to any entity (e.g. substance, product, etc.)) representing oral pharmaceutical forms containing TiO_2, accounted for 63% of tablets and 95% of capsules.[2]

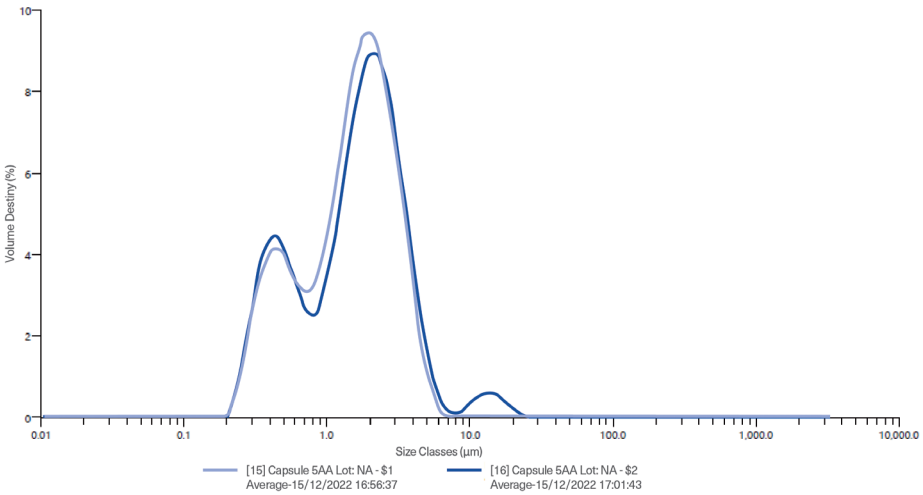
Derived from the last EMA published document, the following relevant considerations and concerns have been raised and discussed for marketed medicinal products by the pharmaceutical industry in different conferences, held in Europe during the last year:

- A review of the risks related to business, regulatory and technical matters needs to be performed by pharma industries as many products are impacted.
- The EMA's strong recommendation communicated to the pharma industry to accelerate the research and development of alternatives is crucial to evaluate the feasibility of the replacement and be able to present a consolidated review in April 2024 based on "objective verifiable" scientific information.
- Detailed safety and quality technical information, including stability data, should be provided in a short timeframe in the case of tablets and capsule suppliers for the complete evaluation of new alternative candidates, to initiate the manufacturing of medicinal products and pilot stability studies, where appropriate.
- The new tablet and capsule alternatives should have no manufacturing capacity constraints and become commercial at a reasonable cost.
- The possible 1–1 replacement of calcium carbonate for TiO_2 may not be an adequate solution as studies have shown that the final appearance did not achieve the same colour result in several marketed products.
- The handling and decision-making position on new variation submissions of existing worldwide marketed medicinal products could become country- or region-dependent due to a possible discrepancy between a potential suspension of TiO_2 by the European Commission in 2025 (decision based on the EMA review) and some important countries, such as the US, Canada and the UK, which have already expressed and published their arguments against the prohibition of this excipient.
- The EMA Regulatory Authority would have to be able to assume all these new dossier variations submissions and be able to respond within an acceptable timeframe to the pharma companies.

Over the last few years, hard capsule manufacturers have undergone some important challenges in investigating and developing a new alternative expected to reproduce or emulate the TiO_2 properties of what has been considered for decades as a well-established white pigment, opacifier and protector of UV light. The following action items have been, therefore, thoroughly revised:

"Hard capsule manufacturers have undergone some important challenges in investigating and developing a new replacement alternative expected to reproduce or emulate the TiO_2 properties."

- Assessment of the regulatory framework (per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use regions) for the new TiO_2 alternative and subsequent viable hard capsule drug product dossier variation submissions.
- A review of safety risks as heavy metals and the content of nanomaterial, the latter associated with potential toxicity as indicated by the EFSA; the determination of the particle size distribution and subsequently the assurance of nanoparticles content absence (1–100 nm) or the compliance with the content percentage stated by the current and latest recommendation of a nanomaterial definition as per the European Commission (Commission Recommendation of 10.6.2022 on the definition of Nanomaterial):
  "'Nanomaterial' means a natural, incidental, or manufactured material consisting of solid particles that are present, either on their own or as identifiable constituent particles in aggregates or agglomerates, and where 50% or more of these particles in the number-based size distribution fulfil at least one of the following conditions:
  (a) one or more external dimensions of the particle are in size range of 1 nm to 100 nm.
  (b) the particle has an elongated shape, such as a rod, fibre or tube, where two external dimensions are smaller than 1 nm, and the other dimension is larger than 100 nm.
  (c) the particle has a plate-like shape, where one external dimension is smaller than 1 nm, and the other dimensions are larger than 100 nm."
- The quality verification referred to:
  - Opacity (contrast index) and transmittance (UV protection) suitable results for an acceptable appearance of a white and coloured opaque capsule that will represent stable UV protection for photosensitive formulation ingredients.
  - Critical quality attributes within the specification of stability study capsule batches (disintegration, dissolution test, brittleness, weight and dimensional parameter).
- The control of the colourant replacement effectiveness related to the TiO_2 functional properties as a colourant, opacifier, UV protector and not generally reactive substance implies:
  - The achievement of colour suitability for existing marketed drug products (minimising the patient impact due to appearance changes) for new hard capsule developments, with an adequate match to a Pantone colour reference.
  - The selection of not generally reactive alternative component(s) within the hard capsule composition.
  - Good mechanical properties, including:
    - Absence of brittleness or the same performance as with TiO_2-containing hard capsules.
    - Surface smoothness with results according to TiO_2 capsule shells.
    - Machinability/runnability with several filling machines at different speeds.
  - Capsule shell UV laser imprinting/ marking suitability.



Trend	Record Number	Sample Number	Dx (10) (µm)	Dx (50) (µm)	Dx (90) (µm)	Laser Obscuration (%)	Residual (%)	Result Below (0.1) µm (%)
	15	Capsule 5AA Lot: NA - $1 Average	0.414	1.56	3.21	6.93	0.89	0.00
	16	Capsule 5AA Lot: NA - $2 Average	0.399	1.70	3.74	6.51	0.88	0.00
Mean			0.406	1.63	3.48	6.72	0.88	0.00
1xStd Dev			0.0103	0.0973	0.373	0.30	0.007	0.00
1xRSD (%)			2.53	5.97	10.7	4.42	0.78	

Figure 1: PSD for HPMC capsule. Note: Analytical Instrument: Mastersizer 3000 apparatus (Laser Diffraction).

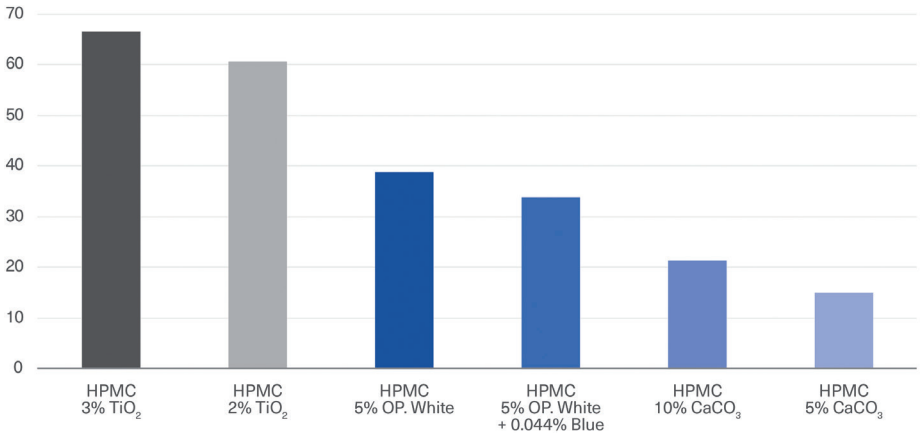


Figure 2: Comparison of Quali-V® containing TiO_2 versus different Quali-V® TiO_2-free capsules with different opacifying agents in the composition.

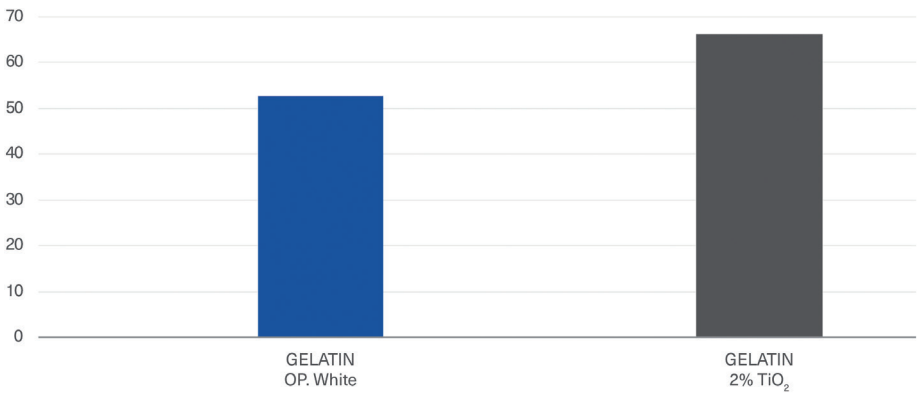


Figure 3: Comparison of Quali-G™ containing 2% TiO_2 versus Quali-G™ TiO_2-free capsule with opacifying agent in the composition (Gelatin OP. White).

"The final capsule product testing results with the new opacifying agent have shown an absence of nanoparticles."

As mentioned, one of the critical challenges has been the achievement of an acceptable colour opacity and whiteness and the certainty to match different existing colours by changing the opacifying agent amount depending on the desired final colour. Calcium carbonate, as a unique direct substitution for titanium dioxide, cannot fully achieve this purpose for all product colour requirements of pharma companies.

Qualicaps Europe has been developing a new hard capsule formulation by carefully evaluating different opacifying agents in recent years. After conducting a comprehensive evaluation of existing available excipients regarding safety, regulatory and quality considerations, the company decided to focus on the most suitable options based on the previously mentioned aspects. The incorporation of selected new opacifying agents, together with a consistent and robust manufacturing process, have been successfully validated for hydroxypropyl methylcellulose (HPMC) and gelatin TiO_2-free hard capsules.

Some relevant scientific evidence data, compiled under a capsule product technical dossier, are presented here as an example:

1. Safety-standard-related results for empty capsule evaluation: particle size distribution (PSD) for HPMC capsule (Figure 1). The final capsule product testing results with the new opacifying agent have shown an absence of nanoparticles.
2. Quality-standard-related results for empty capsule evaluation:
   a. **Opacity results**: The opacity or contrast index for Quali-V® with TiO_2 was compared with different Quali-V® TiO_2-free capsules with different opacifying agents in the composition (Figure 2). The opacity for Quali-G™ TiO_2-free with an opacifying agent was compared with Quali-G™ containing 2% TiO_2 (Figure 3).
   b. **Transmittance results**: Transmittance results are presented in Figures 4 (HPMC capsules) and 5 (gelatin capsules), comparing different colour formulations.

c. **Disintegration and dissolution results:** The empty Quali-V® TiO_2-free capsules comply with a final disintegration time acceptance criteria of NMT 15 minutes tested as per the Ph Eur Test (chapter 2.9.1. "Disintegration of tablet and capsule" of European Pharmacopoeia 11th Edition).

The dissolution profiles of TiO_2-free capsules are like standard Quali-V® TiO_2 capsules complying with EP Ed 11.0th monograph, 2.9.3. "Dissolution Testing for oral dosage forms monograph" and Chapter 5.17.1 "Recommendations on Dissolution Testing for immediate release-dosage forms", in which the acceptance criteria is stated as no less than 80% of dissolved API amount in less than 45 minutes.

Figures 6 and 7 show the results of three batches without TiO_2 versus one with TiO_2 as a reference analysed with buffer solutions at pH 1.2 and pH 6.8.

FINAL REMARKS

Since the European Commission announced a potential ban on using TiO_2 as an excipient, the pharma industry has been actively searching for a replacement for this component extensively used in different oral dosage forms for marketed human medicinal products. The estimated proportion of medications including TiO_2 as an excipient is vast, representing – in the case of ingested pharmaceutical capsules – more than 90% of the total number of marketing authorisations containing TiO_2 in EEA countries (April 2021).

The efforts behind finding an alternative for this well-established excipient as an opacifier, whitening colourant and other functional properties have been a priority in the last few years for hard capsule manufacturers. Qualicaps has developed a suitable alternative with TiO_2-free HPMC and gelatin hard capsules fulfilling the expected safety, quality and

"The estimated proportion of medications including TiO_2 as an excipient is vast."

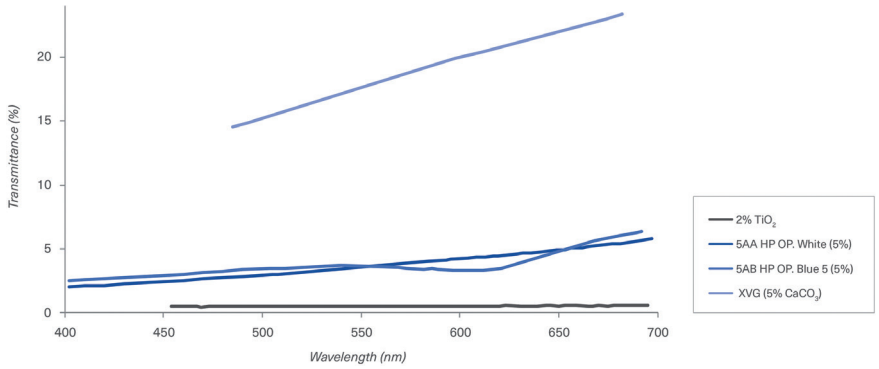


Figure 4: Comparison of different colour formulations of HPMC capsules containing TiO_2, $CaCO_3$ and opacifying agent in the composition.

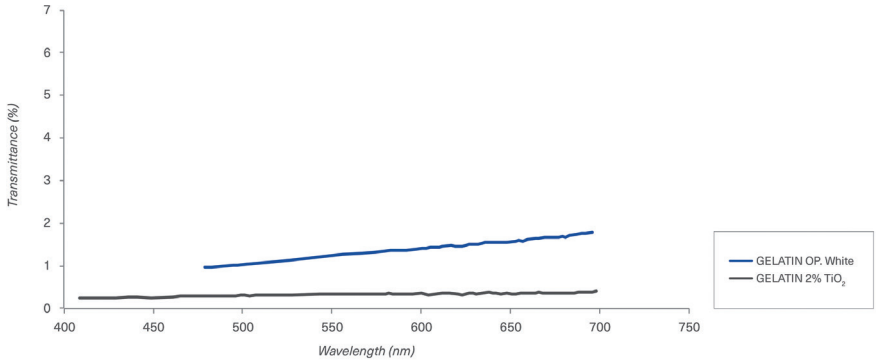


Figure 5: Comparison of different colour formulations of gelatin capsules containing TiO_2 and opacifying agent in the composition.

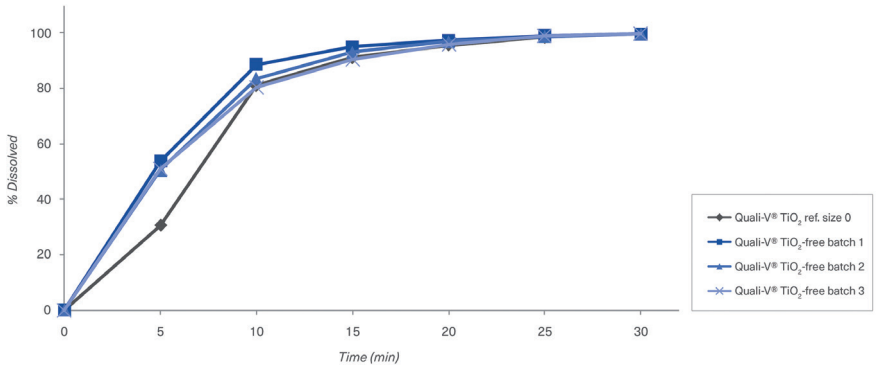


Figure 6: Dissolution profiles of three different batches of Quali-V® containing TiO_2 and opacifying agent with buffer solutions at pH 1.2 (Capsule fill formulation: acetaminophen 20% and lactose 80%. Dissolution test method: paddle at 50 rpm).

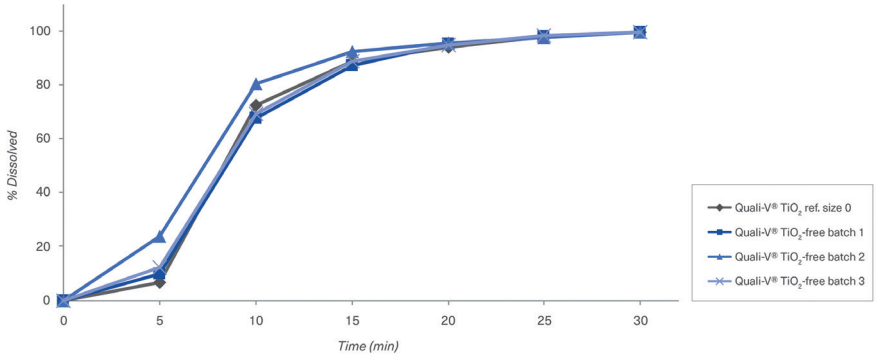


Figure 7: Dissolution profiles of three different batches of Quali-V® without TiO_2 and one of Quali-V® containing TiO_2 with buffer solutions at pH 6.8 (Capsule fill formulation: acetaminophen 20% and lactose 80%. Dissolution test method: paddle at 50 rpm).

effectiveness standards required, and providing excellent appearance and performance compared with existing TiO_2-containing capsules.

ABOUT THE COMPANY

Qualicaps has more than 125 years of experience as a company dedicated to manufacturing capsules. As such, it has a unique perspective on how to contribute to health for the benefit of patients.

Qualicaps delivers pharmaceutical-grade, hard, two-piece capsules to the pharmaceutical industry, together with a comprehensive service along the product lifecycle through its global team of commercial, scientific and technical experts. Qualicaps is a responsible company that takes pride in producing each capsule to offer specific and optimal solutions for drug delivery and overall health and wellbeing challenges.

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ABOUT THE AUTHOR

Susana Ecenarro is Vice-President of R&D and Regulatory Affairs for Qualicaps EMEA and South Asia. She holds an MBA, Green Belt Six Sigma certification and a bachelor's degree in pharmacy. Her professional career started in the German pharma company Schering AG where, for almost 20 years, she led different quality teams with several responsibilities, including validations and technology transfers, US FDA audits, GMPs, analytical development, operational excellence projects, etc. Before joining Qualicaps, Ms Ecenarro was responsible for the Analytical Development R&D unit at the Bayer Healthcare facility in Spain for five years. The R&D department established within the Qualicaps EMEA company enforces innovative new capsule product launches through new product development, industrial scaling up and a customer added-value services centre. The aim is to strengthen the customer-specific Rx and Gx capsule projects with the company's capabilities for the customisation of the capsules and with yearly academia/third-party collaborations linked to important, valuable scientific content generation.


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HARD CAPSULES: A HOLISTIC APPROACH FOR ORAL DRUG DELIVERY AND FORMULATION

In this article, Jnanadeva Bhat, PhD, Vice-President R&D (Pharma & Nutra), and Manali Dalvi, White Papers & Publications Lead (Pharma & Nutra), both at ACG Capsules, discuss how advances in capsule technology as an oral drug delivery method have opened up new avenues for the development of more effective and patient-friendly drugs.

In recent years, the pharmaceutical industry has seen a surge in innovation. The convergence of existing trends involving the need for complex delivery systems, together with significant growth in comprehensive product development, has modified the landscape of drug discovery on a global scale. In parallel, the industry is witnessing numerous emerging technologies such as genomics, nanoscience and biotechnology.

The industry is constantly striving to improve drug delivery systems to enhance the therapeutic efficacy of drugs, reduce side effects and improve patient compliance. Driven by increased investment in R&D, expiring patents in the pipeline and consistent regulatory support, the pharmaceutical industry is undergoing a dramatic shift away from many of its conventional processes.

Researchers are now focusing on continuous and incremental innovation in pharmaceutical formulations to develop new products with minimal side effects, while also providing targeted and specific therapeutic breakthroughs. The industry is exploring various dosage forms and carrier systems to accelerate development and tailor development to evolving trends in delivery methods, such as tablets, capsules, injections, transdermal patches, inhalers and implants. Each of these delivery methods has its own set of challenges and benefits, depending on the drug and target delivery site. Therefore, the delivery system should be selected on a case-by-case basis, taking into account factors such as drug solubility, stability and bioavailability.

An oral drug delivery system (ODDS) is considered the most attractive delivery format due to its convenience, patient preference and cost effectiveness. According to global estimates, approximately 60% of commercially available small-molecule drug products are administered orally.[1] The oral route of drug delivery has higher patient compliance than parenteral routes, such as intravenous, subcutaneous and intramuscular injections. It allows for the delivery of a wide range of therapeutic ingredients. However, some of these may cause challenges due to their physicochemical properties, such as poor water solubility and membrane permeability, as well as gastric irritation – making it difficult to develop effective oral dosage forms. However, advancements in oral drug delivery have overcome many of the challenges once associated with it.

> "Advancements in oral drug delivery have overcome many of the challenges once associated with it."

HARD CAPSULES AS A GO-TO OPTION FOR DRUG DELIVERY

Lately, there have been numerous innovations in oral drug delivery. The sector is expanding to encompass areas including smart drug delivery, 3D printing technology and nanotechnology-based drug delivery – which all align with the trend towards customised healthcare. ODDS options include tablets, capsules, powders, oral films and liquid orals.

Tablets and capsules are two popular dosage forms, with hard capsules catering more to the industry's needs. Owing to their simplicity, ease of manufacturing and patient acceptance, they are the preferred dosage form over tablets. Unlike tablets, capsules do not require binders or further complex granulation processing, which can increase the cost of production and require

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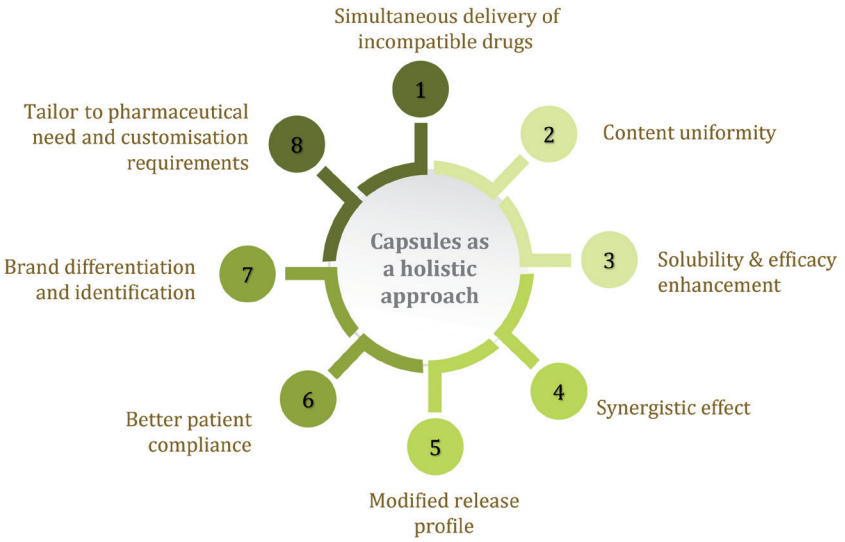

Figure 1: Capsules as a holistic approach for an oral drug delivery.

stricter quality control. They can be filled with a variety of formulations, including powders, pellets and liquids, making them a versatile dosage form. They also have the advantage of being able to deliver a variety of doses without the need for specialised equipment. This versatility facilitates easier development and customisation of formulations – essential for meeting the diverse needs of patients.

BEYOND HARD CAPSULES

The use of capsules in drug development is emerging as a promising area of exploration for the industry. There is a shift away from the traditional powder-filling technique and new possibilities using capsule shells as delivery containers are opening up. This is becoming an all-encompassing solution for all forms of delivery, such as solids, liquids and semi-solids, and where factors such as flowability, content uniformity, customised drug product development, patient compliance, efficacy and stability enhancement need to be considered.

Capsules have revolutionised drug delivery by allowing multiple APIs to be delivered together without compatibility challenges. This is achieved by encapsulating the various actives in different ways in a single or dual capsule shell. The dynamic nature of hard capsules enables them to server as a carrier for various modified release APIs. Additionally, it allows for the delivery of multi-particulate dosage forms, such as pellets and granules, coated with functional polymers to achieve modified-release properties. It also facilitates the combined encapsulation of mini tablets or multi-unit pellet systems, thereby controlling the release of the API(s).

Furthermore, advances in capsule technology have enabled the encapsulation of liquids, along with a tablet, pellet or capsule, inside. This not only improves the bioavailability of APIs but also enables customised release – either at specific times or targeted to an exact area of the body – to enhance the therapeutic effect of different molecules.

> "There is a shift away from the traditional powder-filling technique and new possibilities using capsule shells as delivery containers are opening up."

CAPSULES AS A ONE-WAY SOLUTION

The pharmaceutical industry is constantly evolving and exploring new ODDS possibilities. However, there are some limitations in the process. Oral delivery may present challenges relating to bioavailability, stability and efficacy. Advancements in capsule development are now addressing factors such as incompatibility, solubility, efficacy enhancement and content uniformity (Figure 1).

Solid–Solid Combination	Conceptual Examples
Powder in capsule (conventional)	Amoxicillin/Rifampicin/Gabapentin
Pellets in capsule	Omeprazole DR/Lansoprazole DR
Pellets of multiple APIs in capsule	Carvedilol phosphate IR + Carvedilol phosphate DR
Pellets and tablet in capsule	Domperidone tablet + Omeprazole pellets/ Levosulpride SR tablets + Rabeprazole ER pellets
Powder and tablets in capsule	Trospium IR as powder + Trospium SR as tablet
Powder and pellets in capsule	Carbidopa IR as powder + carbidopa DR as pellets
Micro-tablets in capsule	Venlafaxine tablet
Capsule in capsule	Pre and probiotic + alpha lipoic acid & vitamins
Solid–Liquid Combination	**Conceptual Examples**
Liquid fill capsule	Ibuprofen/ peppermint + spearmint oil
Tablet in liquid fill capsule	Atorvastatin + Aspirin enteric-coated tablet
Capsule in liquid fill capsule	Domperidone Maleate + Rabeprazole DR pellets in tiny capsule
Pellets in capsule in liquid fill capsule	Domperidone Maleate + Omeprazole DR pellets
Single API pellets in liquid fill capsule	Artemether + Lumefantrine pellets

Table 1: Combinations for hard-capsule filling.

The novel capsule delivery format enables the distribution of the APIs in two major formats:

- Solid–solid combination
- Solid–liquid combination.

SOLID–SOLID COMBINATION

Combination Drug Delivery and Synergism

Combination drug delivery is a growing trend, especially with the expiration of patents and the increase in generic products. It has demonstrated its effectiveness when it comes to treating diseases such as cancer, diabetes and cardiovascular disease. This strategy of combining different drugs with different mechanisms of action can lead to a synergistic effect with better treatment outcomes. It enables the constituent drugs to function together to target multiple pathways that contribute to the disease, offering an overall enhancement to the therapeutic effect.

With the advancement in capsule-filling technology, it is now possible to encapsulate multiple APIs in various forms, including powder, pellets, tablets and mini-tablets. (Table 1). This assists in a quick changeover to alternative combinations. This approach to drug development increases patient adherence, reduces multi-drug resistance with single-capsule administration and minimises the chance of taking the incorrect combination or an improper dose of the API. Moreover, it also improves the content uniformity of the product.

Overruling the Incompatibility Challenge

Incompatibility between pharmaceutical ingredients is a significant challenge encountered during the development of drug products. Reactive impurities produced by drug–drug interactions may cause product instability due to the production of toxic degradants, which can limit the scope of product development. Capsules provide a solution to this problem by allowing the delivery of multiple APIs without causing compatibility issues. By using a protective coating, the formulator can encapsulate multiple compatible or incompatible APIs in a single capsule.

Figure 2: Solid–solid capsule combinations.

Aside from that, a capsule-in-capsule approach is the best solution for resolving compatibility issues. This technique allows the encapsulation of APIs in two separate capsules. Physical separation of the two APIs by the inner capsule decreases the risk of interaction, providing a protective barrier (Figure 2). This separation helps maintain the stability and integrity of the individual APIs until they are released and reach their target site.

Modified-Release Patterns

Combination ODDSs that incorporate different release profiles in a single capsule can offer several advantages in terms of treatment customisation, patient compliance, convenience and therapeutic outcomes. Various release profiles, such as immediate release (IR), delayed release (DR) and sustained release (SR), can all be achieved in a single capsule by using pellets with modified-release properties within the coating processes.[2]

> "Combination ODDSs that incorporate different release profiles in a single capsule can offer several advantages in terms of treatment customisation, patient compliance, convenience and therapeutic outcomes."

Moreover, coating pellets with different polymers is a crucial step in this type of ODDS. This involves applying a polymer layer onto the surface of the drug pellets, which provides a barrier that controls the release of the drug. Coating can be achieved via several methods, such as fluidised bed coating, pan coating or spray coating. These techniques ensure precise control over the thickness and composition of the coating layer, which ultimately determines the drug-release characteristics. However, selecting the correct polymer and coating technique is essential for controlling release kinetics in the pellets.

The combination ODDS can provide multiple release profiles in a single dosage form, by encapsulating the coated pellets within a capsule shell. These profiles include immediate release with rapid onset, delayed release allowing the release of the drug after a predetermined lag time, and sustained release providing a prolonged release over an extended period. Mini- or micro-tablets in capsules provide another approach for release profile modification, allowing for a higher variation in the release profile compared with the pellets due to the surface area of the inner dosage form. Although not a conventional drug delivery method, this strategy opens up customised dosing regimens, with increased therapeutic efficacy and decreased dosing frequency to improve patient convenience.

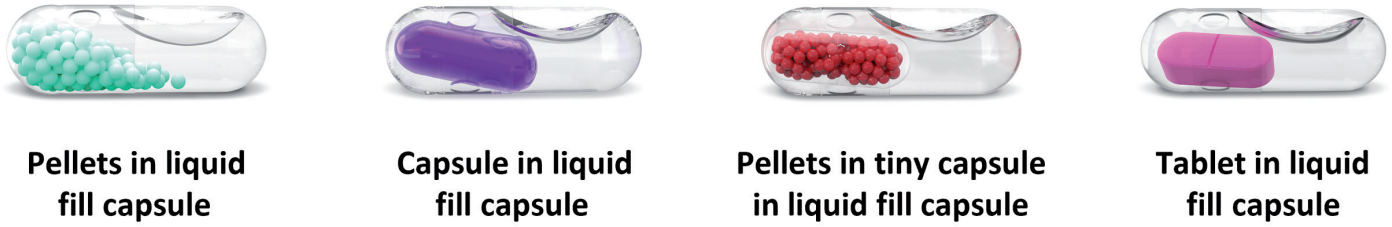

Figure 3: Solid–liquid capsule combinations.

SOLID–LIQUID COMBINATION

Encapsulation technology is no longer restricted to solid formats but now also can include liquid formulations.[3] Capsules are now widely used for the delivery of various non-solid formulations, such as non-aqueous liquids, suspensions, self-emulsifying drug delivery systems, thixotropic gels, semisolids and hot melts. After filling, the capsules are sealed with an appropriate sealing technique to prevent leaking.

There are four major combinations possible with this technique – tablet in liquid, capsule in liquid, pellets in capsule in liquid and pellets in liquid (Figure 3). These combinations allow the formulator to develop their product with a multiple-release profile without changing the original form of the API (solid or liquid) (Table 1). For example, a single API in a liquid form (IR) and another API in a tablet or capsule form inside the outer capsule (DR/SR). This delivery format enables the delivery of hygroscopic APIs.

As these materials are very sensitive to moisture, their delivery can be facilitated by encapsulating the material with molten excipients, such as polyethylene glycol or wax up to a temperature of 70°C. These formats are emerging as an effective way to deliver highly potent drug formulations, such as anti-cancer treatments, steroids, hormonal therapies and immunosuppressants. This technology has also made it easier to administer an exact amount of potent drugs by suspending or solubilising it in the carrier liquid, thereby avoiding any loss of the potent formulation. Moreover, given the flexibility in dose adjustment between the inner solid component and the outer liquid, this technique facilitates customised treatment and dose titration based on patient needs.

CONCLUSION

Overall, advances in capsule technology as an oral drug delivery method have opened up new avenues for the development of more effective and patient-friendly therapeutics. Techniques such as capsule-in-capsule, combination filling, modified release, functional coating and 3D printing of capsules are gaining momentum in the market. These advancements have provided numerous benefits in terms of combating stability and compatibility issues, as well as helping to manage delivery challenges. They have also enabled brand differentiation, helping to support increased patient compliance. Continued research will likely progress towards myriad future advancements in oral drug delivery.

ABOUT THE COMPANY

ACG has been serving the pharmaceutical industry for more than five decades. It is one of the largest manufacturers of empty hard capsules in the world. Its integrated pharmaceutical manufacturing solutions encompass a varied portfolio of not only capsules but also packaging films and foils – and extend further to tablet manufacturing, encapsulation, end-to-end packaging and inspection machines, all of which operate with the synergy of delivering the "One ACG" experience. ACG has a presence in over 100 countries and a strong team of nearly 3,200 associates who collaborate to provide world-class technologies across multiple domains.

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ABOUT THE AUTHORS

Jnanadeva Bhat, PhD, has been associated with the pharmaceutical industry for more than two and a half decades. As a product formulator, he has worked on various dosage forms, including tablets, soft gelatin and hard capsules, injectables and lyophilised formulations. At ACG, Dr Bhat heads the formulation R&D laboratory, where he primarily leads new product development projects, new promotions and acts as the customer interface. He has published several technical white papers and articles.

Manali Dalvi is part of the capsules R&D team at ACG. Her primary responsibilities include writing and publishing scientific research articles, as well as developing segmented solutions and technical content as part of thought leadership programmes. Ms Dalvi is also involved in all the company's industry and institute-related collaborations and research activities. She also leads all industry-institute collaborative projects and research activities to support ACG branding initiatives.

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TREATING THE NEXT GENERATION: THE UNTAPPED POTENTIAL OF ORALLY DISPERSIBLE FILMS

In this article, Keat Theng Chow, PhD, Head of Applied Sciences Pharma, Greater Asia, at Roquette, explores the latest scientific thinking on orally dispersible film formulation, and how these advancements could open a new chapter in paediatric patient compliance.

"Children are not just small adults."[1] First coined by the EU's 2007 Paediatric Regulation, this phrase increasingly reflects the pharmaceutical industry's approach to children's medicine. Gone are the days when young patients were forced to make do with smaller doses of drugs authorised for adult use.

Now, regulators and brands alike are allocating significant research and development budgets to find the ideal formulations and dosage forms for paediatric medications. Despite this shift, however, there is a particular delivery method that is yet to receive the attention it deserves as a solution to the challenge of making medications, safer, easier and generally more fun for kids to take.

Orally dispersible films (ODFs) have long been recognised as valuable assets in the ongoing medication compliance conversation. Portable, palatable, easy to administer and offering functional benefits such as reduced first-pass metabolism, faster onset of action and improved bioavailability, these convenient dosage forms are ideally suited to the needs of paediatric patients. But, despite these obvious advantages, recent research suggests just 1% of children favour ODFs compared with more traditional delivery methods such as tablets and capsules.[2]

This disconnect could be related to issues such as awareness, accessibility, efficacy – or a combination of all three. Besides, manufacturers of ODFs face a range of challenges – from ensuring drug solubility and stability to improving production efficiencies to get drugs to market faster. Fortunately, new technologies, excipients and production strategies are emerging to open up the true potential of ODFs and give children the fun and functional treatment options they actually need.

CHANGING PERCEPTIONS OF CHILDREN'S MEDICATIONS

The debate over whether the benefits of specialised paediatric treatments outweigh the ethical concerns of involving children in clinical trials has raged for decades.[3] Until the 1980s, there were few standardised protocols for administering drugs to children, meaning healthcare providers were often forced to adapt medicines only authorised for adults by amending dosages or delivery forms according to their own experience.[3] This "off-label" approach was standard practice for paediatricians across Europe and North America, despite the increased risks of delivering ineffective or even harmful treatments.

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Figure 1: Healthcare professionals increasingly agree that the unique treatment needs of children require the development of specialised medications.

"The consensus today is that the unique physiology and healthcare needs of children require and deserve specialised treatments."

Around the mid-2000s, we began to see this picture shift towards the modern conception of paediatric pharmaceuticals – namely, that there was a clear need for drugs tested and approved for use by children.[3] The EU's 2006 investigation into the availability and efficacy of medicines for patients aged 0–17 years reflected this change in attitude, concluding that there was a serious lack of consistency and knowledge surrounding children's pharmaceutical provision. Across the Atlantic, US lawmakers recognised a similar issue, passing the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) in an attempt to improve healthcare outcomes for young patients.[4]

The consensus today is that the unique physiology and healthcare needs of children require and deserve specialised treatments (Figure 1). Incredible progress has been made in this area over the last 15 years – with more than 260 new medicines for use by children authorised in Europe between 2007 and 2016,[3] and a further 700 products adding specific paediatric use information to their labels across Europe and the US.[5] But much work remains in several key areas, notably the development of more convenient, patient-centric dosage forms. The evolving science behind ODF production provides a useful case study, demonstrating both the challenges drug manufacturers must overcome to better serve young patients, and the incredible potential these treatments represent.

THE BASICS OF ODF FORMULATION

The vast range of biocompatible polymers available and advancements in thin-film technologies has made it possible to develop a variety of ODF formats since the first prescribed ODF in 2010 – fuelling their acceptance and popularity as a novel drug delivery system. Although ODFs can take many different forms, in the pharmaceutical industry, they typically appear in a 2 x 3 cm strip, weighing 30–40 mg and loaded with 20–30 mg of API. Buccal and sublingual mucosa applications have gained the most interest in recent years, but ODFs can be delivered via ocular and transdermal routes too.

When it comes to suitable actives, ODF formats are most compatible with relatively potent, water-soluble and ethanol-soluble APIs that can be dosed at less than 30 mg/day. Relevant applications include prescription and over-the-counter product groups, including cough, cold, sore throat, allergic reactions, gastrointestinal, pain and sleep medications. ODF forms are also an ideal choice for the delivery of substances susceptible to first-pass metabolism. Nano/micronised Biopharmaceutics Classification System (BCS) class II and IV drugs and biomolecules have recently been identified as suitable candidates for ODF formulation too, enabling a more patient-friendly alternative for some APIs that are traditionally delivered via parenteral delivery routes.

At base-line level, ODF formulations require a film-forming polymer or combination of polymers, such as maltodextrin, hydroxypropylated starch, hydroxypropyl methylcellulose (HPMC), gelatin or hydroxypropyl-beta-cyclodextrin (HPβCD), a plasticiser such as sorbitol or glycerol, a surfactant, a sweetening and flavouring agent, and – depending on the specific application – a saliva-stimulating agent.

There are a number of viable manufacturing options for ODFs, but the most commonly used processes include solvent and semi-solid casting, hot-melt extrusion, solid dispersion and rolling. And the mechanical strength, muco-adhesive properties and drug-release rate of the formulation can be adjusted by using different combinations of polymers in different amounts. All this apparent flexibility makes it difficult to understand why ODFs remain relatively uncommon in paediatric healthcare (Figure 2) but, as with all pharmaceutical dosage forms, there are caveats that put a damper on their mainstream viability.

"Manufacturers must consider disintegration time, textural properties, API stability, taste and mouthfeel – all while keeping the number of ingredients to a minimum to reduce production complexity."

Figure 2: ODFs have immense potential to improve paediatric drug delivery but are currently uncommon in paediatric healthcare.

A QUESTION OF STABILITY

In ODF formulations, balance is critical. To create a successful end product, manufacturers must consider disintegration time, textural properties, API stability, taste and mouthfeel – all while keeping the number of ingredients to a minimum to reduce production complexity. Drug producers can call upon several pre-processing strategies to help increase API solubility and bioavailability in ODFs, the most common of which are API treatments, including micronisation or nanonisation. However, even with these steps, preserving the physical stability of poorly soluble APIs in ODFs remains a ubiquitous challenge.

Research conducted by scientists at Roquette Pharma Solutions set out to explore this issue and evaluate whether the excipient HPβCD could support the formulation stability of an ODF featuring the poorly water-soluble model drug loratadine.[6] In the trial, ODFs were prepared using HβCD as the bulk filler excipient and the long-chain polymer HPMC 60HD50 was included to further enhance the film's mechanical properties. Suitable plasticisers were also included. HPβCD was not included in the control ODF formulation. The ODFs were prepared via two different production methods; an ethanol/aqueous (60:40) co-solvent system; or a solvent-free process involving heat-cool-heat cycling (121°C, 1 atm).

The chemical stability of the loratadine ingredient was evaluated following its heat-cool-heat production cycle via reversed-phase high-performance liquid chromatography (RP-HPLC) with ultraviolet (UV) light and charged aerosol detectors (CADs). The final ODF formulation was assessed according to critical quality attributes, including disintegration time, mechanical properties, moisture content and taste masking. Solid-state characterisation was conducted via polarising light microscopy (PLM), X-ray diffraction (XRD) and differential scanning calorimetry (DSC).

When comparing the two formulations, researchers found that the HPMC-only loratadine films initially presented as amorphous solid dispersions but underwent significant drug recrystallisation after one week of storage in a closed polyethylene bag at ambient conditions. In contrast, minimal drug recrystallisation was detected in the loratadine films formulated with HPβCD. The study also found that inclusion of HPβCD in the formulation increased the aqueous solubility of loratadine and helped suppress the bitter taste of the drug in a concentration-dependent manner.

Based on these findings, the Roquette research team concluded that using HPβCD as the primary excipient in an ODF formulation successfully conferred the properties of solubility enhancement and taste masking, while helping to assure the physical and chemical stability of the drug. These results represent a positive development for manufacturers of paediatric medications, providing a useful starting point for further investigation.

"Market commentators speculate that 3D printing could unlock "build-your-own" medications for patients."

THE POTENTIAL OF 3D PRINTED ODFS

As we have seen, smart excipient selection, complexation and formulation strategies already exist for maximising the effectiveness of ODFs. Looking ahead, however, the world of alternative paediatric dosage forms is taking on a new dimension. Having simmered close to the surface for almost 20 years, the pharma industry is seriously considering 3D printing as a valuable tool for increasing access to more convenient dosage formats. There is still work to be done here regarding standardised protocols for processing safety, but the future generally seems bright for 3D-printed pharmaceuticals – particularly for paediatrics.

The benefits offered by this technology fall into two main categories: patient centred and manufacturing centred. In the case of the former, market commentators speculate that 3D printing could unlock "build-your-own" medications for patients, similar to the 3D printed, customisable supplements already popular in the nutraceuticals sector.[7,8,9] On the manufacturing side, the key advantages are speed and flexibility. 3D printing has the potential to significantly reduce time to prototype, empowering manufacturers to accelerate the path to clinical testing while keeping development costs low.[10] These features are especially relevant in the context of devising specific treatments for children, the lower demand for which made them an unattractive candidate for time- and cost-intensive traditional manufacturing methods.

"3D printing has the potential to significantly reduce time to prototype, empowering manufacturers to accelerate the path to clinical testing while keeping development costs low."

SOLUBILITY IMPROVEMENT ENTERS A NEW DIMENSION

3D printing could represent the next great leap in solubility improvement for ODF formulations, too. In a recent study, researchers at Roquette explored the viability of a 3D-printed ODF formulation containing loratadine as the API and HPβCD as a solubilising and filler excipient.[11] The specific objective of this study was to optimise an ODF formulation of a poorly soluble drug for 3D printing, using the pressure-assisted microsyringe technology, also known as bioprinting.

Building on the previous research presented at AAPS PharmSci360 in 2020, an HPβCD-HPMC-loratadine formulation was selected for the study. The prepared hydrogel demonstrated shear thinning properties with slight thixotropy, which allowed it to be successfully extruded from the syringe tip and recover its shape immediately after printing. Researchers were able to achieve the required amorphous state for the loratadine API through complexation with HPβCD. This complexation step was critical to ensuring the poorly soluble active could be incorporated into the ODF in a sufficiently high concentration to be effective.

Upon its conclusion, the study successfully demonstrated that a hydrogel formulation consisting of HPβCD, sorbitol and HPMC was suitable for the fabrication of ODFs via 3D printing by the pressure-assisted microsyringe technology. In addition, it provided further evidence of HPβCD's value as a solubility enhancer in ODF formulations and established a workable set of printing parameters for optimised ODF formulation through 3D printing. The implications of having a fast, effective and cost-efficient method for producing patient-centric dosage forms are extremely significant, not just for children's medicine, but for treatment of any patient group with specialised dosage requirements.

FILMS OF THE FUTURE

ODFs are an undeniably powerful weapon in the fight for better paediatric pharmaceuticals. The studies mentioned in this article, and many more besides, have produced some incredibly positive results that will begin to turn the tide on the industry's acceptance of ODFs as a mainstream dosage form – but the conversation cannot end here. More work is needed to tackle the API solubility and stability issues associated with ODF production, and increase awareness among producers, paediatricians and patients alike of the game-changing potential these flexible films represent. With these goals at the forefront, pharma producers can build a brighter future where every patient has access to the specialised care they need – whether young, old or anything in between.

ABOUT THE COMPANY

Roquette is a family-owned global leader in plant-based ingredients, a pioneer of plant proteins and a leading provider of pharmaceutical excipients. Founded in 1933, the company currently operates in more than 100 countries, has a turnover of about €5 billion (£4.3 billion) and employs more than 8,000 people worldwide. Life and nature have been its sources of inspiration for decades. All its raw materials are of natural origin. From them, the company enables a whole new plant protein cuisine; it offers pharmaceutical solutions that play a key role in medical treatments; and it develops innovative ingredients for food, nutrition and health markets. Roquette aims to unlock the potential of nature to improve and save lives. Thanks to a constant drive for innovation and a long-term vision, the company is committed to improving the wellbeing of people all over the world. It puts sustainable development at the heart of its concerns, while taking care of resources and territories. The company is determined to create a better and healthier future for all generations.

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