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ON drugDELIVERY

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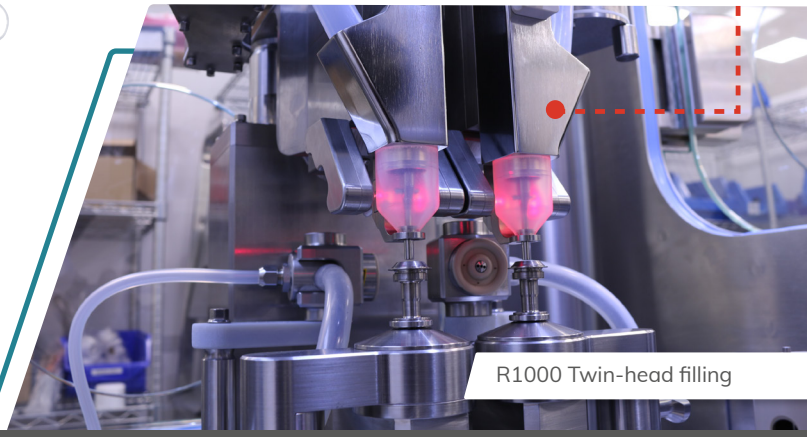

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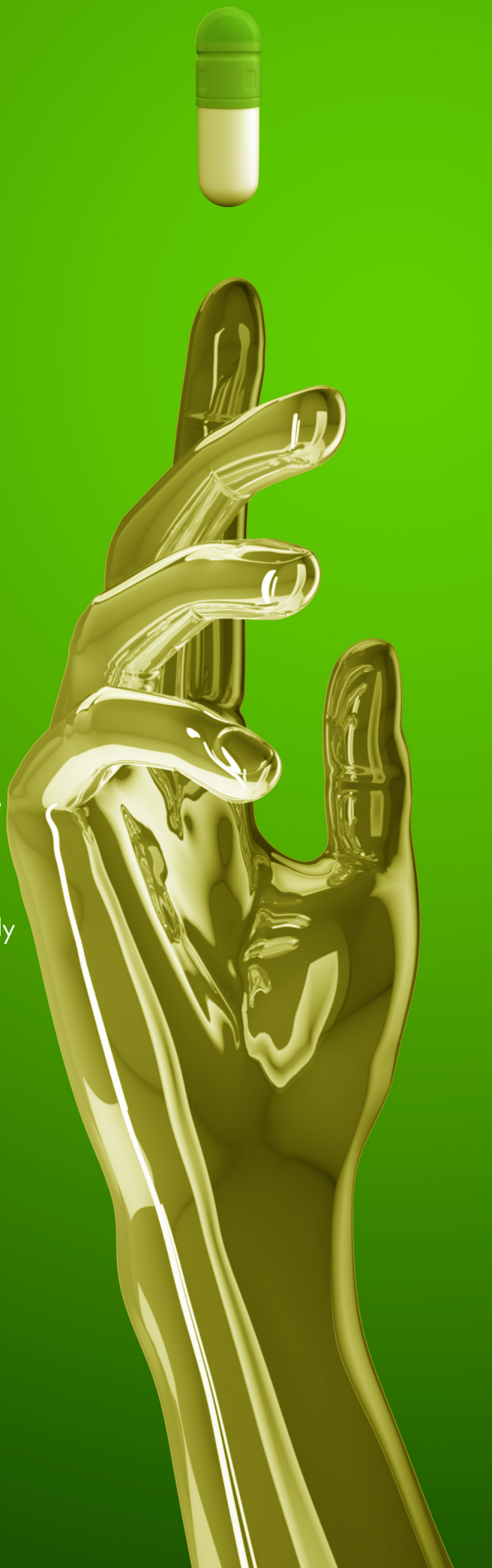

Qualicaps

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ONdrugDelivery Issue N° 109, July 30th, 2020

NOVEL ORAL DELIVERY SYSTEMS

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

EDITORIAL CALENDAR

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Sep	Wearable Injectors
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ONdrugDELIVERY®

SPI Pharma™
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Mannogem® XL Ruby & Opal

Enhanced Performance
Better Patient Experience

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MAKING MEDICINE EASIER TO TAKE

In this article, Graeme Macleod, PhD, Head of Global Research and Development, and Wayne Camarco, Global Head of Technical Development, both of SPI Pharma, discuss the rational design of excipients to meet the needs of patient-centric formulations.

Regulators are increasingly insisting that formulators consider patient centricity in the dose form they are developing. This means, in addition to normal factors such as stability, efficacy, content uniformity, robustness and manufacturability, the organoleptics of the dose form must be considered from the start of any project.

In solid dose form design, there has been a significant increase in the number of patient-centric dose forms coming onto the market to help meet these requirements. Orally disintegrating tablets (ODTs), chewable tablets, granules, resuspendable tablets or granules and orally dispersible powders are all examples of dose forms that help to improve patient adherence, particularly in patient groups – such as paediatrics and elderly patients – where this can be particularly challenging. Patient adherence can be enhanced with dosages that are easier and/or more pleasurable to take – e.g. orally disintegrating or chewable dosages with favourable taste and texture.

Despite the evolving requirements of patients and regulators alike, the introduction of excipients enabling formulators to meet these objectives has been minimal. Development of new excipients – or existing excipients with enhanced functionality – is time consuming and can be costly to excipient companies. Often the rewards do not meet the efforts expended. This conundrum requires excipient suppliers to think rationally about what the ideal "universal excipient" might look like to address these challenges.

> "In an ideal world, the formulator would have a monograph excipient with all the benefits of a co-processed system. With this in mind, SPI Pharma set about development of a universal excipient."

UNIQUE COMBINATION OF MATERIAL SCIENCE AND APPLICATION KNOW-HOW

SPI Pharma was the first company to launch a co-processed excipient specifically aimed at rational design of ODTs. Our Pharmaburst® platform, for the first time, enabled the formulation of a directly compressible blend of API, excipient and lubricant that could meet the competing requirements of ODT development.

An ODT formulation needs to be sufficiently robust to withstand downstream processing, such as packaging, but at the same time disintegrate within 30 seconds in the mouth and impart a positive patient experience. SPI Pharma used its knowledge of key excipients, such as mannitol, and its co-processing expertise to design a system that met these needs. Since then, many other companies have launched similar products that were designed with ODT in mind.

Despite the success of these types of products, there remained some limitations in that the multi-component nature of co-processed systems meant they were not suitable across the board for a range of development projects. In an ideal world, the formulator would have a monograph excipient with all the benefits of a co-processed system. With this in mind, SPI Pharma began development of a universal excipient.

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ENHANCED PERFORMANCE IN A FAMILIAR PACKAGE

Mannitol is widely used as an excipient in oral dose form development due to its low hygroscopicity and high stability or inertness. It does not undergo the Maillard reaction with amine APIs (unlike lactose) and has successfully been used to formulate some difficult actives in swallow tablets, such as levothyroxine. It has extremely pleasant organoleptics, with a mild sweetness and a minor cooling effect as it solubilises in saliva. This has made it the preferred excipient in ODT formulations and the base for most ODT platforms.

As more and more drugs are converted to patient-centric dose forms, it was clear that mannitol had many of the attributes required to fit the needs of a universal excipient, with all the requirements set out in Table 1. The main barrier to its ubiquitous use was its relatively low tabletability.

For a formulator, the ability of an excipient to form a robust compact is critical, particularly in ODTs which generally have higher porosity or superior solubility to enable rapid disintegration. Formulators measure the tabletability of a given formulation by producing tablets over a range of compression forces and measuring the strength of the resultant tablet using standard equipment, such as a hardness tester, and converting the result into a tensile strength which considers the tablet thickness and diameter (Figure 1).

Features	Requirement
Tabletability	medium to high; resultant tablets robust and low friability
Stability	inert, low hygroscopicity;
Organoleptics	sweet and cooling to the mouth; non gritty texture
Solubility	high
Disintegration	fast inherent, with minimal need for disintegrant
Flowability	high; suitable for direct compresion tableting processes

Table 1: What properties would a universal excipient possess?

By taking the slope of the tensile strength versus compression force (Figure 2), the formulator can compare different formulations or excipients to understand the relative tabletability. The greater the tabletability, the more robust the resultant tablet will be and the lower the friability it will have. These are critical quality attributes (CQAs) that are key to rational drug design. If one could combine a high tabletability with the inherent stability, inertness and pleasant organoleptics, one would be close to having the universal excipient desired for rational dose form design.

Knowing this, SPI Pharma scientists set about trying to design this universal excipient. The result of more than 18 months of development work is the Mannogem® XL technology. In March 2020, SPI Pharma launched the Precious Gem Collection, which includes two new grades of Mannogem XL mannitol – "Ruby" and "Opal" – that we believe offers formulators an excipient that meets existing monograph needs and has universal applicability.

- Tensile strength equation: $\sigma_x = (2 \cdot F) / (\pi \cdot t \cdot D)$

Where s_x is the tensile strength (MPa)
F is the crushing force (N), measured by diametral compression
t is the compact thickness (mm)
D is the compact diameter (mm)

- The linear region of the tensile strength versus pressure graph is known as the compactibility slope
- The compactibility slope describes the inter-particular cohesion in the compact or the tabletability

Figure 1: Calculation of tablet tensile strength and its use in determining tablet robustness.

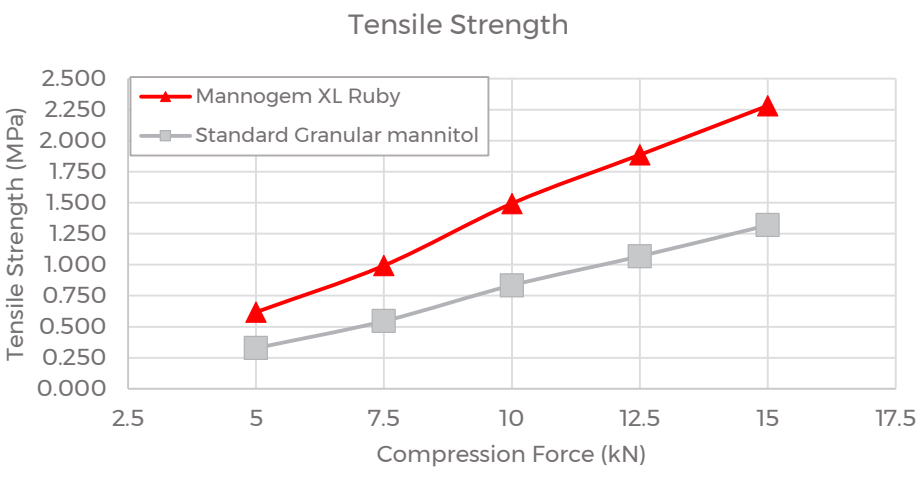

Figure 2: Comparing the tabletability of Mannogem XL Ruby to standard granular mannitol.

MANNOGEM XL RUBY

Earlier, we explained the challenges in developing a chewable tablet or ODT. These challenges are amplified when formulators are required to develop a formula that requires taste masking. Taste masking is an absolute must for certain APIs that can be bitter or astringent in nature. These attributes can be particularly off-putting for children, who already need encouragement to take their medicines.

Fortunately, taste-masking approaches exist, such as SPI Pharma's Actimask® technology, to help reduce the bad taste of a given API. In the majority of cases, the taste-masking approach requires application of a polymeric membrane to granules of the drug to help mask the bad taste. As a result of these taste-masking techniques, the resultant drug particles can be quite large (in pharmaceutical terms), easily greater than 300 microns.

Unfortunately, this causes another problem for the formulator. Blending a larger particle size API with a smaller particle excipient causes segregation of the active particles from the rest of the blend. A simple example of segregation is to think of granola. Anyone familiar with granola will know that the small particles – raisins and nuts – tend to settle at the bottom of

> "Segregation of a powder blend containing API will lead to content uniformity issues, which is unacceptable because the patient would receive either higher or lower amounts of the drug, leading to possible side effects or subtherapeutic doses."

the box, meaning the last few bowls are lacking in the larger particles. The same type of phenomenon occurs with direct compression blends with much more serious consequences.

Segregation of a powder blend containing APIs will lead to content uniformity issues, which is unacceptable because the patient would receive either higher or lower amounts of the drug, leading to possible side effects or subtherapeutic doses. Neither is acceptable. To overcome this issue, there are currently granular grades of mannitol on the market that have a larger particle size than the more common spray-dried grades.

By matching the taste-masked API particle with the larger particle size, it is possible to overcome the segregation described. However, until now, these grades of mannitol had even lower tabletability than the smaller particle size spray-dried grades. SPI Pharma's Mannogem XL Ruby, for the first time, combines the large particle size of a granular mannitol with tabletability approaching that of spray-dried material.

Mannogem XL Ruby is a uniquely designed excipient that enables formulators to do things they were unable to contemplate previously. They can now formulate an ODT with all the benefits of mannitol that make it patient centric, but with the added benefit of incorporating taste-masked APIs that can be blended with confidence that drug segregation will not be an issue. Additionally, Ruby's superior tabletability means there is less compaction force required, reducing the stress applied to pressure-sensitive formulation components, such as taste-masked APIs or multi-unit pellets systems (MUPS).

MANNOGEM XL OPAL

By extending this same functionality to a spray-dried product – Mannogem XL Opal – SPI Pharma can further extend the use of mannitol as a universal excipient, giving the most compressible grade of mannitol. As already described, the target for the formulation scientist is to have a rationally designed formulation that optimises the combination of high tabletability, low friability and rapid disintegration.

The superior tabletability of Opal enables the formulator to develop products that have high drug loading to a level that was not previously possible with mannitol. It also enables simplicity of formulation, negating the need to use other binders – such as microcrystalline cellulose and hydroxypropyl cellulose – which can undermine the organoleptics and accelerating development.

Additionally, smaller tablets are possible with Opal to enhance patient adherence by improving swallowability. An example of a simplified chewable tablet formulation is given in Table 2.

As formulations are transferred from development to manufacturing scale, the robustness of the formulation is key. The principles of quality by design require formulations to have a wide design space to minimise development time, particularly when it comes to technical transfers from development to production.

Mannogem XL Opal has been uniquely designed to optimise the key attributes described above to give this robustness and wide design space. Such formulations will transfer to production quickly and enable high yields and fast production speeds to be achieved. Table 3 compares the performance

Material	Quantity (mg)
Actimask® APAP 92M*	172.5
Mannogem XL Opal	989.1
Crospovidone	49.8
Magnesium Stearate	24.9
Colour	2.5
Flavour	6.2
Total	**1245.0**

Table 2: Typical direct compression Mannogem XL Ruby APAP (acetaminophen) chewable tablet formulation. *Actimask APAP 92M is SPI Pharma's taste-masked APAP, 172.5mg equivalent to 160mg of APAP

Mannogem XL Opal					
Compression Force (kN)	5	7.5	10	12.5	15
Tensile strength	0.63	1.06	1.64	2.15	2.43
Friability	0.9%	0.6%	0.0%	0.3%	0.2%
Disintegration time	33.4	54.6	102.2	141.2	182.2
Ejection force	100	140	180	210	250

Larger Design Space

Competitor 1					
Compression Force (kN)	5	7.5	10	12.5	15
Tensile strength	0.42	0.75	1.16	1.55	1.86
Friability	2.6%	1.3%	0.2%	0.8%	1.2%
Disintegration time	50	77.2	99.4	137.8	163.4
Ejection force	100	150	200	230	260

Failure Borderline Fail Success

Smaller Design Space

Table 3: Extending design space using Mannogem XL Opal.

"Regulatory requirements and patient demands have pushed dose design earlier in the drug development process."

of an Opal-based formulation with the same formulation that uses standard mannitol. As seen below, the Opal formulation is much more robust in terms of all the key CQAs.

CONCLUSION

Increasingly, the recent advances in regulatory expectations with respect to dose form patient centricity add to this challenge. With its Precious Gem Collection, SPI Pharma has taken the rational design approach and extended it to designing excipients that can significantly enhance patient-centric dose form functionality and formulation robustness.

Regulatory requirements and patient demands have pushed dose design earlier in the drug development process. Requirements for patient centricity in new drug development, and the need to match doses with consumer preferences in OTC development, have increased the importance of functional excipients that provide convenience and ease of administration. Mannitol is understood to be one of the best excipients to create easy-to-administer and aesthetically pleasing doses.

Simultaneously, drug delivery has become more sophisticated and dose development has become more complicated, requiring rational application of specifically functional excipients. In this respect, SPI Pharma has developed a collection of mannitol excipients that match targeted functionality, with the ability to make drugs easier to administer.

Product	Main Application	d50 (µm)	Bulk Density (g/mL)	Tapped Density (g/mL)
Mannogem XL Opal	Direct compression ODTs, swallow and chewable tablets	160	0.52	0.45
Mannogem XL Ruby	Direct compression ODTs and chewables with larger MUPS or taste-masked APIs where segregation is an issue	300	0.65	0.57

Table 4: Typical physical properties and applications for Mannogem XL Ruby and Opal grades

Excipients can no longer be generally applicable – they must provide specific functionality that can be applied to a rational design concept. Typical physical properties and applications of Mannogem XL Ruby and Opal grades are summarised in Table 4.

Mannogem XL Ruby addresses the emerging need to create orally dispersible doses with large-particle, multicomponent ingredients. Mannogem XL Opal can help make tablets more robust with fewer ingredients. These new grades are a demonstration of excipients that are developed with drug development and patient needs in mind. Rationally designed excipients from SPI Pharma match the rational approach of the industry and meet the increasing demands of developing safe and efficacious medicines.

ABOUT THE COMPANY

SPI Pharma provides the innovative solutions global pharmaceutical and nutritional customers need to succeed. The company helps solve the most challenging formulation problems efficiently, cost effectively and with a focus on service. Serving over 55 countries in the manufacture and marketing of antacid actives, excipients, drug delivery systems for tablets and powders, taste-masked actives and vaccine adjuvants, SPI Pharma employs more than 300 people globally and is backed by parent company Associated British Foods. It also specialises in drug development services, having participated in over 60 commercially launched and marketed drugs globally.

ABOUT THE AUTHORS

Graeme Macleod attained his PhD in pharmaceutical technology from the University of Manchester (UK). He has 25 years of industrial experience in the fields of formulation development, drug delivery, pharmaceutical solid form equipment and excipients. Dr Macleod joined SPI Pharma in June 2017. His areas of experience include oral dose form technologies and processes, novel soft capsule technologies and drug formulation.

Wayne Camarco joined SPI Pharma in 2019 as Global Head of Technical Development. He has broad-based excipient and API experience in the areas of formulation development and technical service. Mr Camarco has worked in a variety of technical, sales and business development roles at ACG Capsules in the US, Juniper Pharma (Catalent, UK), Ashland Specialty Ingredients (US) and Rhodia (US and France).

MARIA FLYNN, ADARE PHARMACEUTICALS

As President and Chief Executive Officer of Orbis Biosciences, Maria Flynn led a company that provides innovative technology that improves the delivery, efficacy, and safety of pharmaceuticals. Under her leadership, the Convention on Pharmaceutical Ingredients awarded Orbis the Excellence in Formulation Award and, in 2020, Adare Pharmaceuticals acquired the company. Previously, Ms Flynn was a Director at Cerner Corporation (North Kansas City, MO, US) and, before that, an engineer with Camp Dresser & McKee (now CDM Smith, Boston, MA, US).

Ms Flynn has been named in *Entrepreneur Magazine's* "Entrepreneurial Women to Watch", *Kansas City Business Journal*'s "Women Who Mean Business", and *Ingram*'s "Business Magazine's 40 Under 40", and she received the Central Exchange's "STEMMy Award for Enterprising Innovator". She serves on the Board of Directors of BioNexus KC (DBA Kansas City Area Life Sciences Institute), and she is a member of Pipeline Entrepreneurs, the region's premier entrepreneurial leadership organisation.

Ms Flynn holds an MBA from the University of Chicago Booth School of Business, where she was a Herman Family Fellow for Women in Entrepreneurship, an MS in engineering from Stanford University, and a BS in engineering from Kansas State University.

In this exclusive interview, Maria Flynn talks with ONdrugDelivery about trends in the oral drug development and delivery space, completing the Orbis acquisition during a global pandemic, and how the excellent technology portfolio and strategic fit between Orbis and Adare form part of the combined organisation's unique story.

Q We're picking up an increase in activity, innovation, energy and optimism around the oral drug delivery segment at present. What do you think are the causes/drivers?

A With our clients – pharma and OTC companies that invest behind innovation – we have seen increased attention on product lifecycle management. For example, we see pharmaceutical companies applying innovative technologies and creating difficult-to-replicate formulations, within their product portfolios. In addition, there is a marked increase in attention to medication compliance.

The difference between today and 10 years ago is, before, the industry talked a lot about addressing the needs of paediatric and dysphagic patients, whereas today we are doing it. We are now starting to address problems such as bad taste and swallowing challenges.

> "The difference between today and 10 years ago is, before, the industry talked a lot about addressing the needs of paediatric and dysphagic patients, whereas today we are doing it. We are now starting to address problems such as bad taste and swallowing challenges."

This has to be done very cost-effectively, in part due to the pricing pressures that pharma companies face. That is where many of Adare's solutions are well-positioned – technologies that can be scaled and offer a rapid speed to market.

Q How is Adare Pharmaceuticals positioned to capitalise on this upswing in activity?

A Flexible manufacturing solutions are another key industry requirement. As a technology-driven specialty CDMO, Adare provides exactly those turnkey CDMO solutions. Indeed, a top driver for Orbis to integrate into Adare was to be able to provide our customers with that turnkey flow from development all the way to commercial production (see Figure 1).

In terms of technology offering, we have a number of solutions that address the increased industry focus on specific patient populations with particular needs.

Figure 1: Adare's turnkey CDMO solutions, from development through to commercialisation.

Figure 2: Selection of Adare's key technology brands.

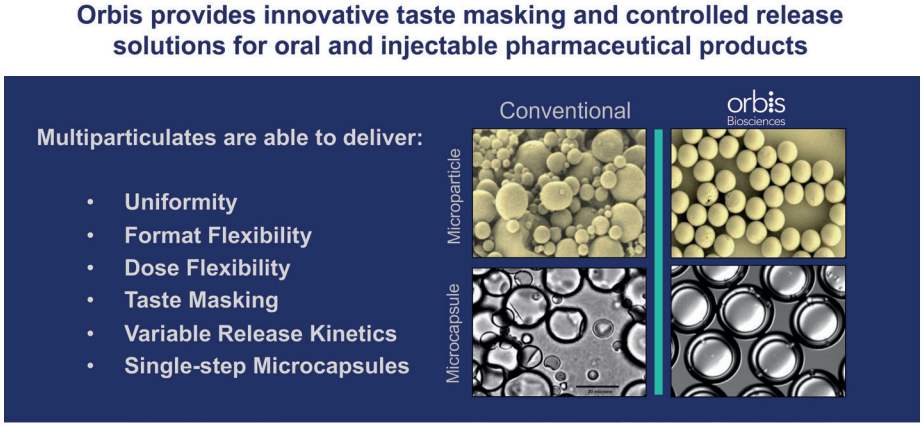

Figure 3: Superior particle uniformity from the Precision Particle Fabrication technology.

They include taste-masking, novel dosage formats, easy-to-titrate formats, and easy-to-swallow solutions. These technologies, combined with our expertise and intellectual property, provide our customers with protectable products, including next-generation treatments.

Some of Adare's key technologies (Figure 2) include: Microcaps for taste-masking via a solvent or aqueous-based coacervation process; Diffucaps, which incorporates release-controlling polymers or protective coatings into drug layer cores, granules, or crystals; and MMTS, the Multi Mini Tablet System, in which functional membranes are applied to one- or two-millimetre cylindrical tablets to control release rates.

Another interesting technology from Adare is Parvulet®, which enables pharmaceutical products to be presented as a solid powder or a tablet that converts into a semi-solid in the presence of water. It has great potential for addressing special swallowing considerations for paediatric, geriatric, and dysphagic populations with applications on both the prescription and OTC side.

To the Adare portfolio, Orbis adds the Precision Particle Fabrication® technology, the only technology on the market that can meet that need for uniform particles, and offer true control over variability in particle size that is so important for oral and injectable drugs (see Figure 3).

"Flexible manufacturing solutions are another key industry requirement. As a technology-driven specialty CDMO, Adare provides exactly those turnkey CDMO solutions."

"The Orbis technologies compliment Adare's existing offering and capabilities well, enabling us to offer our customers a broader range of innovative tools and solutions to create new successful products."

This technology offers format flexibility, dose flexibility, taste-masking, variable release kinetics, and a single-step microcapsule process, via a flexible, reproducible and scalable technology that accommodates a wide range of APIs.

Our Precision Particle Fabrication technology has given rise to three different platforms: Optimμm®, for oral delivery (Figure 4); Stratμm™, for injectable delivery; and Unison®, for otic treatments. The Orbis technologies compliment Adare's existing offering and capabilities well (Figure 5), enabling us to offer our customers a broader range of innovative tools and solutions to create new successful products.

Q How has the Covid-19 pandemic affected the company, and did it have an impact on the Adare/Orbis acquisition process?

A In many ways Orbis was very lucky to join Adare during this time. Adare has facilities in Milan, Italy, which was at an epicentre of the pandemic. Seeing how these sites kept working was remarkable. My perception was that the Adare executive leadership team was on the ball and saw the Covid-19 implications coming before most

Figure 4: Orbis's Optimμm platform for oral delivery is based on its Precision Particle Fabrication technology.

Figure 5: The combined Adare / Orbis delivery technology portfolio offers an impressive range of solutions.

people did. They put in place the necessary processes and procedures early, securing PPE, and doing the right things to take care of their people. It was impressive to watch and, once the acquisition was completed, to join the organisation. Orbis incorporated these best practices into our site in Lenexa, Kansas.

Completing the acquisition during a global pandemic was definitely a test of flexibility. Throughout the due diligence, deal, and integration, we were able to keep going by adjusting our processes. Things you might normally do in person, we did virtually. It shows Adare's commitment because it would have been very easy to delay and say, "Let's table this for a better time". However, we completed the deal, and it is a great success story.

Beyond the Orbis integration, the pandemic continues to present challenges, and we continue to overcome them. For example, Adare completes technology transfer from its Ohio, US site to the Milan, Italy site, and managed to work out how to do this virtually. In business development, we cannot be at conferences, so we find other ways to meet customers virtually as well. Our customers' programmes continue, and there is the same need to get their products to market, so these are very busy times. There is a lot of learning that we would not have had if we were not going through this Covid-19 experience.

Q **Adare acquired Orbis in May 2020 and this was a major event for both companies. Could you describe how the acquisition came about, why the two companies represent a good fit?**

A We built Orbis with a vision to integrate it into a larger company after making the necessary progress and maturing the technology.

"We developed the relationship over a long period. The two companies kept in touch, meeting at conferences for example, and kept building the relationship until we reached a point where Adare's strategy had a focus to bring in additional technologies and Orbis's technologies had matured to a point that we met the criteria for Adare."

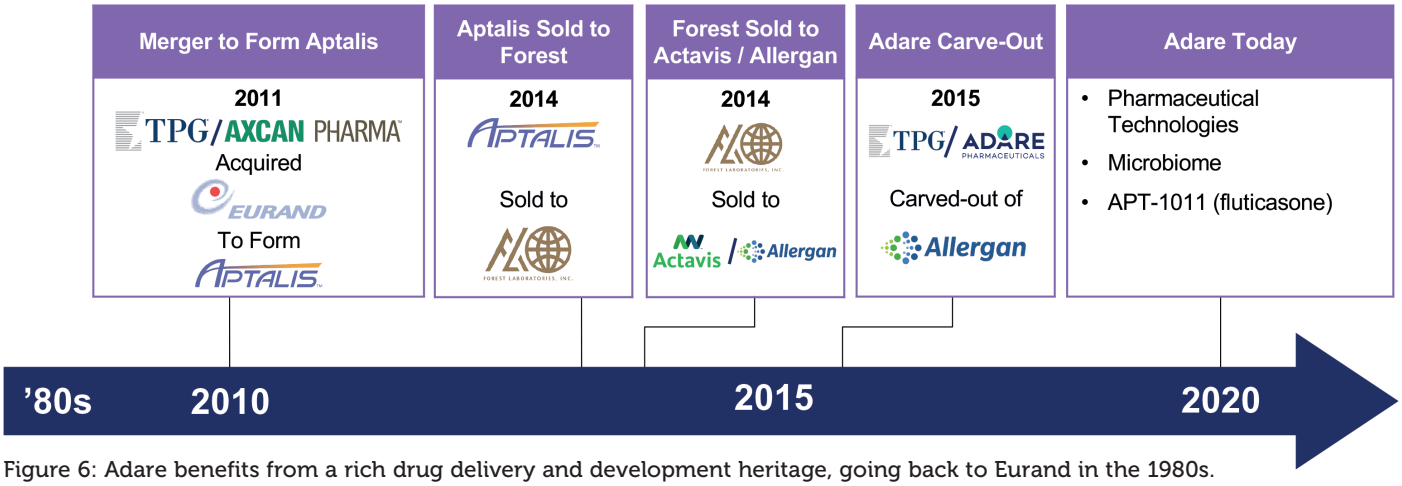

Figure 6: Adare benefits from a rich drug delivery and development heritage, going back to Eurand in the 1980s.

Adare has a rich drug delivery and development heritage, going right back to Eurand in the 1980s. Orbis has known Adare for about eight years, when what is now Adare was called Aptalis (see Figure 6). Even in those early days, the fit between the companies' missions was clear. Both Orbis and Adare had been able to achieve best-in-class drug delivery technologies in the solutions that they brought to the market.

We developed the relationship over a long period. The two companies kept in touch, meeting at conferences for example, and kept building the relationship until we reached a point where Adare's strategy had a focus to bring in additional technologies and Orbis's technologies had matured to a point that we met the criteria for Adare.

In terms of the strategic fit from a technology portfolio perspective, we looked at how we could present our clients with the most robust offering. Across taste masking, extended release, enteric release, and novel formats for oral drugs, the companies saw an opportunity to build on Adare's technology portfolio.

One clear point of differentiation is Orbis's Stratμm technology, which is for injectable products. This represents an exciting expansion of Adare's offering beyond oral products and into injectable products for the first time.

What is fascinating about Adare is the mindset and ability to evolve continuously. Rather than remaining the same company for 40 years, it has expanded and grown. The recent innovations such as the Parvulet™ technology and the addition of Orbis's technologies, including the new expansion into injectable products, show how the organisation really understands how to keep continually moving to the next level. That is what characterises our unique and ongoing story.

ABOUT THE COMPANY

Adare Pharmaceuticals is a global technology-driven specialty CDMO providing turnkey product development through commercial manufacturing expertise focused on oral dosage forms for the pharmaceutical, animal health and OTC markets. Adare's proprietary technology platforms specialise in ODT's, taste masking and customised drug release.

With more than 30 years of proven legacy, Adare has successfully developed and manufactured more than 40 products sold by partners in more than 100 countries globally.

ADARE™ PHARMACEUTICALS

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AN EASY PILL TO SWALLOW

In this article, Kelly Boyer, Vice-President, Film Coating, and Ali Rajabi-Siahboomi, PhD, Chief Scientific Officer, both of Colorcon, explore the role of different tablet coating materials in improving the patient experience and adherence to prescription regimens.

Around four in 10 adults report difficulty in swallowing tablets.[1] Recent guidance documents published by the US FDA and the EMA recognise that size, shape and coating are all contributory factors in the swallowing process and can impact adherence to prescription regimens.[2]

If a person has trouble swallowing, they may delay taking a tablet, skip a dose or discontinue the medication. Any of these actions can pose a serious health threat and, in the case of antibiotics, may contribute to antimicrobial resistance. Poor swallowability also leads to unnecessary medical costs and lost revenue for the drug manufacturer. Medical costs associated with skipping or discontinuing a medication are estimated at US$269 billion (£215 billion) in the US alone.[3]

Colorcon, a leader in the development and supply of specialty excipients, is incorporating the results of recent patient studies on swallowability to reinforce the benefits of tablet coating. The company anticipates that this approach will support the pharmaceutical industry in the creation of products that overcome both the perceived and real problems associated with swallowability, for all ages, mitigating adverse events such as pain, gagging and choking, whilst also providing a means of clear drug product differentiation.

> "Perception of medicines and a willingness to take tablets may be as important as physical difficulties in swallowing or dysphagia."

FACTORS THAT AFFECT SWALLOWABILITY

Perception of medicines and a willingness to take tablets may be as important as physical difficulties in swallowing or dysphagia. If the medicine is crucial to the health and well-being of the patient, they will be much more likely to take it. If the medication is discretionary and taken only to support lifestyle or general health, the patient may choose to skip a dose or stop taking the tablets altogether.

A patient's experience and ability to swallow medications may be impacted by age and whether they have underlying health issues such as stroke, Parkinson's disease or other neurological disorders that can lead to dysphagia. In the case of children, the elderly and psychiatric patients, their physiological and cognitive responses may be different from those of the general population.

There are essentially four phases of swallowing, the first two of which are the most important when it comes to the patient deciding to take the dose. Firstly, factors around the appearance of the tablet are important. If the visual perception of the tablet is large and rough, it will be perceived as difficult to swallow and the patient will be less likely to put it in their mouth. Next is how the tablet feels in the mouth/on the tongue – does it have an unpleasant taste, what is the texture like? The last two phases of swallowing revolve around avoiding choking and the tablet sticking in the oesophagus.

Each of these phases constitutes the patient's perception of whether a tablet is easy or hard to swallow. In all cases, taking water with the tablet is important

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"Tablet weight, surface area, disintegration time and propensity for swelling should all be considered when designing products."

as this provides lubrication to improve transit times to the stomach and aids the disintegration process of the tablet itself.

REGULATORY GUIDANCE

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

Regulatory agencies around the world have acknowledged the advantages of film coatings applied to tablets and multiparticulate dosage forms. Benefits include:

- Easing swallowability by increasing mobility compared with an uncoated tablet of the same size and shape
- Improving the palatability of tablets by masking unpleasant tastes and odours
- Improving the aesthetic appeal of tablets
- Achieving the desired immediate- or modified-release profile
- Allowing easy identification, thereby minimising the risk of medication errors
- Enhancing the performance of the drug, protecting it from the environment, reducing friability and dusting issues, and ensuring better stability of the overall formulations.

SAFETY BY DESIGN

As the number and variety of medicines available increases and people are living longer, many patients are taking multiple medications and supplements. Pharmaceutical companies recognise that their products must meet the needs of target populations. While managing taste, smell and palatability are especially important for paediatric formulations, in the case of elderly patients it is crucial to support safe swallowing and reduce the risk of choking.

Focusing on the specific needs of patients ensures 'safety by design' and has an impact on a drug's success in the marketplace. This may include formulating drugs with extended-release profiles to reduce dosing frequency or using combination drugs. However, this approach can lead to larger tablets, which can negatively impact the ability to swallow.

Colorcon has conducted research into swallowability in order to improve the patient experience and safety. Studies have considered the impact of tablet size, weight, shape, surface area, disintegration time, palatability and propensity for swelling. Recent research focused on the development and application of film coatings to provide enhanced formulations that can positively impact the swallowing experience for patients.

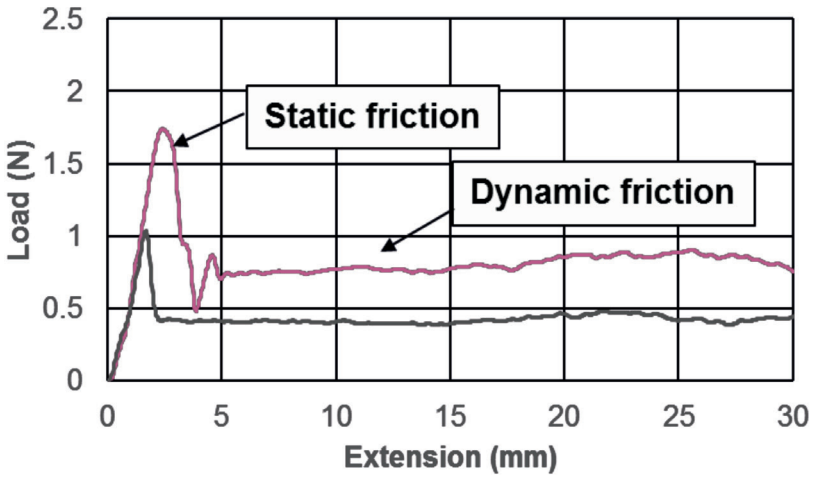

Figure 1: *In vitro* measurement of slip behaviour. Red line: hydroxypropyl methycellulose (HPMC)-based film coating. Black line: developmental slippery coating.

"In the case of oral dosage forms, the frictional interaction between surfaces and how fluids can act as a lubricant are important."

SWALLOWABILITY AND UNDERSTANDING SLIP

Tribology is the field of science that describes how surfaces interact with each other at a microscopic scale. In the case of oral dosage forms, the frictional interaction between surfaces and how fluids can act as a lubricant are important. Mixed lubrication is where there is still some physical contact between the surfaces, but a liquid is helping to reduce the overall friction. Hydrodynamic lubrication is achieved by increasing the amount of liquid between the surfaces, so they are separated and glide over each other more easily, with minimal friction.

Uncoated tablets can take 10 minutes or longer to move from the mouth to the stomach. Early research used gamma scintigraphy to measure the influence of film coatings on reducing transit times and demonstrated that the most effective coatings can reduce transit times to around 20–30 seconds.[4]

To investigate the incorporation of hydrophilic polymers into film coatings to lubricate the tablet surface when wet – either by contact with saliva or through taking a glass of water with the tablet – Colorcon developed a single test to characterise how different coating materials behave and to rank their slip performance. Slip was determined by measuring the force necessary to move tablets held in a weighted sled across a wet surface. The force necessary to start the sled moving (static friction) and the load necessary to keep the sled in motion (dynamic friction) were measured.

Using this test, different materials and film coating formulations were evaluated to identify good slip behaviour. The red line in Figure 1 represents a traditional hydroxypropyl methycellulose (HPMC)-based film coating, while the black line represents a developmental slippery coating, later launched as Opadry EZ, easy-swallow coating. Both the static friction and dynamic friction of the developmental coating are significantly lower than the traditional coating, indicating enhanced slip.

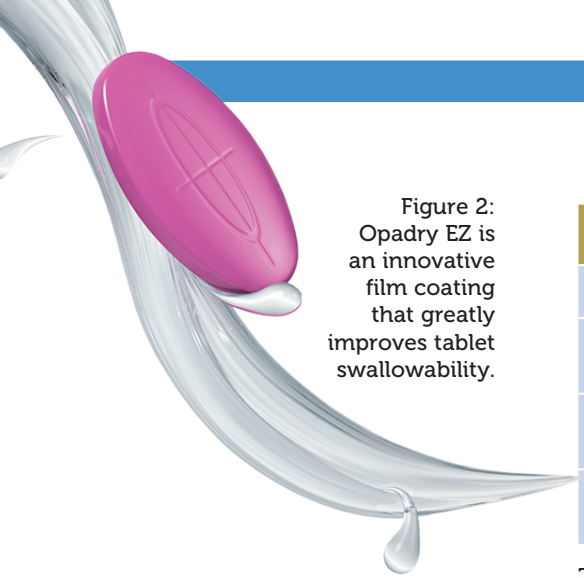

Figure 2: Opadry EZ is an innovative film coating that greatly improves tablet swallowability.

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

Table 1: Four variations of tablets used in the study.

As a result of this work, Opadry EZ easy swallow film coating was launched in February 2018. This innovative film coating greatly improves the swallowability of any tablet to which the coating is applied (Figure 2). Once wet, the slip performance is enhanced, significantly reducing the probability of the tablet sticking in the throat or oesophagus.

HUMAN SWALLOWABILITY STUDY

To test whether the enhanced slip of Opadry EZ, as shown by this *in vitro* method, resulted in a better swallowing experience for patients, an investigation was carried out in association with the University of Birmingham in the UK.[5] The study involved 84 healthy volunteers with a wide age and gender distribution. A single centre crossover study was used to measure the mouthfeel and swallowing experience of four 19 mm placebo tablets, taken in randomised order. One tablet was uncoated and the other three were coated as detailed in Table 1. Each participant was given four tablets in a randomised order.

Participants were asked to score the mouthfeel after holding the tablet in their mouth for 10 seconds based on the following parameters: smoothness, stickiness, slipperiness and palatability, using visual analogue scales (VAS). They were asked to rank the tablets in order of preference for ease of swallowing. The time taken to swallow the tablet and the volume of water used to aid swallowing were also recorded.

When the tablets were ranked in order of preference based on overall swallowing experience, the favoured sample was Opadry EZ-EZ, which was the first choice for 37.8% of participants (Figure 3). The tablet finish that was preferred by volunteers was the Opadry EZ film coating, either pigmented or with additional top coat for extra gloss. This reportedly increased mobility during the swallowing process.

The slipperiness of the tablet was found to be the best predictor of the ease of swallowing. VAS results for slipperiness were converted to a numerical score (Figure 4). Most participants gave the uncoated tablet a low score, indicating that the tablet stayed in place or stuck in the mouth. The Opadry EZ tablets had a higher proportion of people reporting high levels of slipperiness, with EZ-EZ showing the highest number of participants scoring easy slip.

In addition, participants provided three words to describe their experience of swallowing each of the tablets in order to explore their perception of the tablet in their mouth. The results are shown in Figure 5 using word clouds – responses with the highest occurrence appearing in large font and those with only a few occurrences in small or very small font. Colour is used to differentiate, with orange words depicting undesirable characteristics and green showing desirable characteristics.

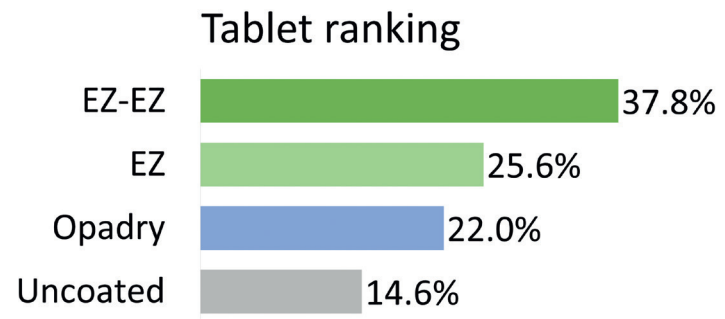

Figure 3: Study participant preference ranking of tablets.

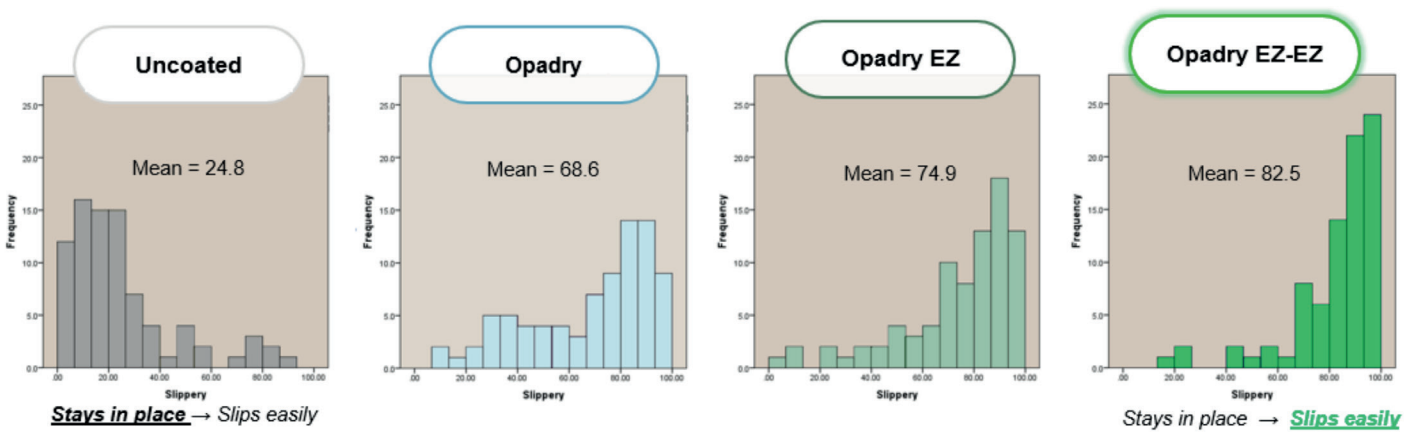

Figure 4: Scores of slipperiness versus frequency of score used.

Figure 5: Positive patient experience with Opadry EZ-EZ.

The results show that coated tablets are preferred to uncoated and demonstrate differentiated performance for swallowability depending on coating type. The Opadry EZ-EZ coating is preferred for mouthfeel, palatability and overall tablet acceptance, thereby providing the most positive patient experience.

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

BENEFITS FOR PATIENTS

Compared with other formulations, the slip provided by the Opadry EZ-EZ tablet coating, once wet, significantly reduces the probability of sticking in the throat or oesophagus during the swallowing process. The improved tablet flow, combined with a glossy finish, also encourages better patient adherence and consumer appeal. Adopting this approach to tablet design supports the pharmaceutical industry to create products that satisfy both the perception and reality of ease of swallowing for all ages, mitigating adverse events such as pain, gagging and choking – and allowing clear differentiation between drugs.

ABOUT THE COMPANY

Colorcon is a world leader in the development, supply and technical support of formulated film-coating systems, modified-release technologies and functional excipients for the pharmaceutical and nutritional industries. Its products and technologies are complemented by value-added services, supporting all phases of solid dose design, development, and manufacture.

REFERENCES

1. *"Pill-Swallowing Problems in America: A National Survey of Adults". Survey, Harris Interactive, 2003.*
2. *Steffenino R, "Is Your Tablet Hard to Swallow? Guidance Addresses Drug Tablet Design". Pharmaceutical Technology, 2017, Vol 41(10), p 408.*
3. *"Responsible Use of Medicine". IQVIA Institute, 2012.*
4. *"Modern Tablet Film Coatings and Influence on Ease of Swallowing". AAPS poster, Colorcon, 2003.*
5. *Hofmanová JK Rajabi-Siahboomi A, Haque S, Mason J, Teckoe J, To D, Batchelor HK, "Developing Methodology to Evaluate the Oral Sensory Features of Pharmaceutical Tablet Coatings". Int J Pharm, 2019, Vol 562, pp 212–217.*

ABOUT THE AUTHORS

Kelly Boyer is Vice-President, Film Coatings at Colorcon, where she heads the Global Business Development team responsible for the design, supply and technical support of formulated film coating systems for the pharmaceutical and nutritional markets. Ms Boyer has a degree in Chemical Engineering and over 30 years of experience in delivering innovative technology solutions around the world.

Ali Rajabi-Siahboomi is Vice-President and Chief Scientific Officer at Colorcon in the US. He obtained a bachelor's and a doctorate degree in pharmacy from University of Nottingham (UK). Dr Rajabi-Siahboomi has been with Colorcon for 20 years after a successful academic career in the UK. His main research interest and experiences are in the areas of solid dosage pharmaceutics, technology, and drug release modulation. He has published extensively in the field of oral drug delivery systems and is a regular contributor to pharmaceutical industry events around the world.

TECHNOLOGY SHOWCASE: Röchling Medical's Sympfiny®

Röchling

Multiparticulates for direct oral delivery are an emerging technology with many advantages over traditional dosage forms, including extended shelf life, no refrigeration requirements in storage and transport and tasteless formulations. Yet widespread use of multiparticulate drugs has been limited due to the lack of an accurate and easy-to-use dosing and dispensing device.

In collaboration with HS Design, Röchling Medical has developed Sympfiny®, an innovative system for dosing and delivering multiparticulate, dry powder, and microsphere drug formulations for oral delivery.

Benefits in Paediatrics

Multiparticulates are particularly suited for use in paediatric medicine. Commonly, drugs for paediatric patients are administered orally as liquids, rapid-dissolve tablets or chewable tablets. The problem:

- Children do not like the taste – a major cause of incomplete dosing in children
- Masking bitter tastes requires large amounts of sugar and flavourings
- There are significant inaccuracies in dosing with liquid syringes.

Formulating to solve taste, storage, and dosing issues results in high development costs, extended research time and trade-offs with other drug features.

Multiparticulates are bead-like drug formulations akin to microspheres with coated and/or matrix architecture (Figure 1), which offer a wide range of drug release profile flexibility for single or multiple drug combinations. Multiparticulates do not have an inherent taste, eliminating the need to reformulate for various tastes. They are shelf-stable without refrigeration, allow for high dose flexibility and may be dosed with or without water.

Multiparticulate Drug Delivery Challenges

The control of multiparticulate drugs is not easy. They are complex microspheres of solid medication surrounded by a coating that prevents them from dissolving until they reach the stomach. These spheres behave like tiny ball-bearings, flow more readily than water and pour out of small openings. Compressed as solid particles they "lock" together. Multi-particulates can also stick together if they become damp or statically charged. This presents a range of challenges:

- Multiparticulates display the properties of both liquids and solids
- Solutions for liquid dosing are poorly suited for multiparticulates
- Existing delivery systems (e.g. sachets, stick packs, straws, break-open capsules) are limited to single dose or require complex preparation steps by caregivers.

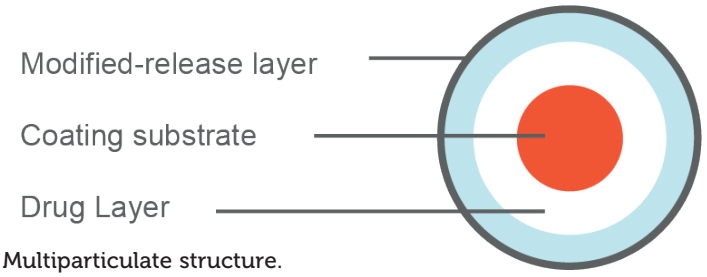

Figure 1: Multiparticulate structure.

Sympfiny®: Accurate Dosing & Delivery

The Sympfiny® system is a first-of-its-kind innovation in the delivery of multiparticulates. The system, comprising oral syringe and container, enables caregivers to store, extract, and deliver dry drugs with the same, familiar technique used with liquid oral drugs. The patent pending design allows controlled and precise dosage and ensures that an untrained caregiver can dispense the medication directly and accurately into the patient's mouth.

The Sympfiny® syringe, available in 1 and 2 mL, has an innovative dose-setting capability for dosing with multiparticulates. A dose-setting clip is fixed to the syringe that slides along the plunger rod and locks into place at the required dose amount.

To deliver a dose, users simply set the dose clip, insert the plunger into the barrel and pull out the plunger until it stops at the pre-set dosing volume. Then the syringe is inserted into the bottle until it engages, locking the syringe into place. With the dose setting clip in place users are guaranteed consistently accurate delivery volume.

With the bottle vertical, multiparticulates will freely flow into the syringe. When the syringe is removed by pulling downwards, the valves on the bottle and syringe seal automatically and no multiparticulate leaks.

This convenient and reliable system allows parents to deliver taste-masked medication to their children without the emotional or physical strain currently felt with bad-tasting liquid drugs.

The Sympfiny® system fits standard bottle sizes but can also be customised to accommodate different dosing volumes or container sizes and forms.

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UNIQUE MINITABLET DISPENSER MEETS FLEXIBLE ORAL DOSING NEED

Bjørn Knud Andersen, Director, Front-End Innovation & Head of Technology Accelerators and IPR at Phillips-Medisize, discusses how an innovative minitablet dispenser that mounts on a standard medication container simply and effectively meets the growing needs of patients in paediatrics, geriatrics, oncology and other areas who require reliable customised oral dosing.

Meeting the varied and customised oral dosing needs of patients in areas such as paediatrics, geriatrics and oncology can be challenging. First, patients often require highly flexible oral dosing based on their age, weight, body surface area or other variables – but relatively small patient populations can make the cost prohibitive when it comes to offering multiple, finely adjusted, fixed oral doses. Second, patients may find it difficult or impossible to swallow normal-sized tablets and/or capsules.

Whilst liquid dosing may present an alternative to tablets, it comes with its own drawbacks – including poor taste (often a deterrent for young patients); the need to refrigerate reconstituted suspensions to ensure their stability over the course of treatment; potential to spill and overall annoyance of accurately dispensing a liquid formulation; and the possibility of microbial contamination.

For these and other reasons, minitablets may offer a more viable option to syrups for these patient populations as they can be flexibly combined to create the proper incremental dose and the tiny pellets can be easily swallowed. However, the need to depend on the patient or caregiver's ability to accurately handle and count the minitablets for the correct dose presents its own set of challenges.

> "The need to depend on the patient's or caregiver's ability to accurately handle and count the minitablets for the correct dose presents its own set of challenges."

The systems currently available predominantly rely on volumetric measuring principles. For example, if it is determined that a patient-required dose of 10 minitablets would occupy approximately one-tenth of a millilitre, the patient sets a syringe plunger to that amount and then fills the cavity with minitablets. But with this imprecise approach, it's unclear exactly how many minitablets are included in each dose and the number is also likely to vary.

BUILT-IN FLEXIBILITY, RELIABILITY AND ACCURACY

Phillips-Medisize has developed an innovative, easy-to-use minitablet dispenser (Figure 1) which removes this guesswork from the equation, enabling patients and caregivers to accurately and reliably dispense the exact number of minitablets needed per dose. The patented, low-cost dispenser mounts directly on a standard Ø38 mm tablet bottle neck and can be used with minitablets ranging from ~2.0–2.5 mm diameter (i.e. the initial

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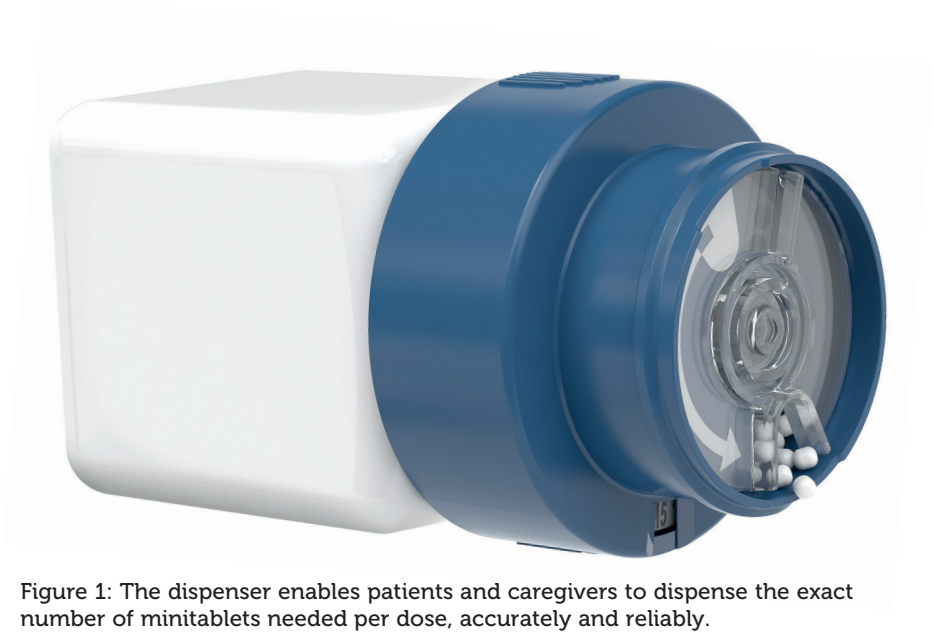

Figure 1: The dispenser enables patients and caregivers to dispense the exact number of minitablets needed per dose, accurately and reliably.

"With the novel integrated minitablet dispenser, tablets are protected until the time they are dispensed."

generic variant). It can be co-packaged with the medication bottle or supplied separately.

With the dispenser permanently positioned directly on the bottle (Figure 2), only counted and dispensed minitablets come into contact with the outside environment. This helps to avoid currently existing situations where the use of a dosing spoon is required to reach into the primary container or the need to pour a large amount of minitablets out of the bottle for counting and then return excess tablets afterwards. With the novel integrated minitablet dispenser, tablets are protected until the time they are dispensed. Here's how the dispensing solution works:

- The user adjusts the dispenser to the desired minitablet count between one and 20. The "set and forget" approach requires the user to pre-set the dispenser dosing disc only once. However, the setting can easily be changed if the medication dosage needs to be adjusted at any point during treatment.
- Next, the user unscrews the child-resistant bottle cap, mounts the dispenser onto the bottle and repositions the cap.

Figure 2: The user adjusts the dispenser to the desired minitablet count between one and 20.

- When it's time to dispense medication, the user unscrews the cap and inverts the bottle to shake the minitablets into the dispenser metering chamber, which has a transparent lid. Then the user turns the bottle back upright and shakes it gently. The correct number of minitablets will automatically fall into the indentations on the dosage disc (one per indentation) and the rest will shake off and fall back into the bottle.
- After visually confirming that there's a minitablet in each hole and therefore the count is correct, the user rotates the transparent metering chamber lid and pours the minitablets onto a spoon, food or other option. The device has been optimised to carefully avoid damaging or crushing the minitablets during dispensing. In addition, it prevents any potential contamination that could occur if patients poured out minitablets into their hand, counted out the ones needed, and poured the rest back into the bottle.
- If more than 20 minitablets are required per dose, the sequence can be repeated as necessary (e.g. reaching doses up to 60 minitablets).
- Once the minitablets have been dispensed, the user closes the transparent lid and puts the bottle cap back on.

ADDING VALUE THROUGH CONNECTED HEALTH

Phillips-Medisize has the capability to design adaptations to the standard product, such as accommodating different minitablet dimensions, preset count ranges and bottle interface designs. In the future, the device could potentially be part of the growing connected health ecosystem. By integrating a low-cost connectivity electronics module into the dispenser, it could be possible to detect tablet metering, dispensing activity and other patient behaviours, thereby helping to monitor, measure and support medication adherence.

"It prevents any potential contamination that could occur if patients poured out minitablets into their hand, counted out the ones needed, and poured the rest back into the bottle."

Phillips-Medisize's ability to manufacture the electronics internally makes connectivity much more affordable. As a Molex company, Phillips-Medisize can take advantage of its vast global electronics design expertise, manufacturing capability and purchasing power to minimise the cost of connectivity, as well as total manufacturing costs.

PREPARED TO SCALE UP PRODUCTION

Initially, Phillips-Medisize began developing the device with a global pharmaceutical company to deliver a medication which the customer had already formulated into minitablets. Rather than filling capsules with the minitablets, the company was looking for a way to dispense them directly to paediatric patients (Figure 3), and the flexible dispenser concept generated enthusiasm at paediatric conferences.

The customer has assigned its intellectual property rights supporting the innovative dispenser to Phillips-Medisize. In turn, Phillips-Medisize has validated the device's child resistance and senior friendliness, as well as validated its usability through five formative and one summative human factors engineering (HFE) studies. With final industrialisation compete, Phillips-Medisize now aims to make the dispenser available to an array of pharmaceutical companies globally.

The Phillips-Medisize minitablet dispenser is a Class I medical device in the EU and Class I 510(k) exempt in the US. It carries the CE mark and is ready for clinical trials or co-packaging for commercial launch.

While the initial generic variant has been designed for use with a standard Ø38 mm tablet bottle neck and to be used with minitablets ranging from ~2.0–2.5 mm in diameter, the platform can easily be adjusted to accommodate other tablet dimensions and bottle formats. Furthermore, customisation is possible for other functional parameters, such as tablet preset range.

CONCLUSION

For special patient populations with customised oral dosing needs where minitablets are the best option, Phillips-Medisize's innovative dispenser offers a promising solution. Its patented design enables patients and caregivers alike to experience improved accuracy in counting the tiny pills without requiring a new or different bottle. At the same time, the container minimises the risk of contamination. The ability to add connectivity in the future will help encourage medication adherence.

Figure 3: The innovative minitablet dispenser meets a growing need for paediatric patients who require reliable customised oral dosing.

"For special patient populations with customised oral dosing needs where minitablets are the best option, Phillips-Medisize's innovative dispenser offers a promising solution."

ABOUT THE COMPANY

Phillips-Medisize, LLC, a Molex company, is an end-to-end provider of innovation, development, manufacturing and post-launch services to the pharmaceutical, diagnostics, medical device and speciality commercial markets. Post-launch services include a connected health app and data services. Backed by the combined global resources of Molex and its parent company Koch Industries, Phillips-Medisize's core advantage is the knowledge of its employees to integrate design, moulding, electronics and automation, providing innovative high-quality manufacturing solutions.

ABOUT THE AUTHOR

Bjørn Knud Andersen has been with Phillips-Medisize since 1997 and is part of the Front-end Innovation team responsible for innovation to translate pharmaceutical drug delivery needs into competitive, patient-centric device solutions. As part of that role, he also heads activities related to developing the Phillips-Medisize Technology Accelerators. Mr Andersen is an industry expert with more than 20 years of experience within medical diagnostics, electronic drug delivery devices and connected health systems.

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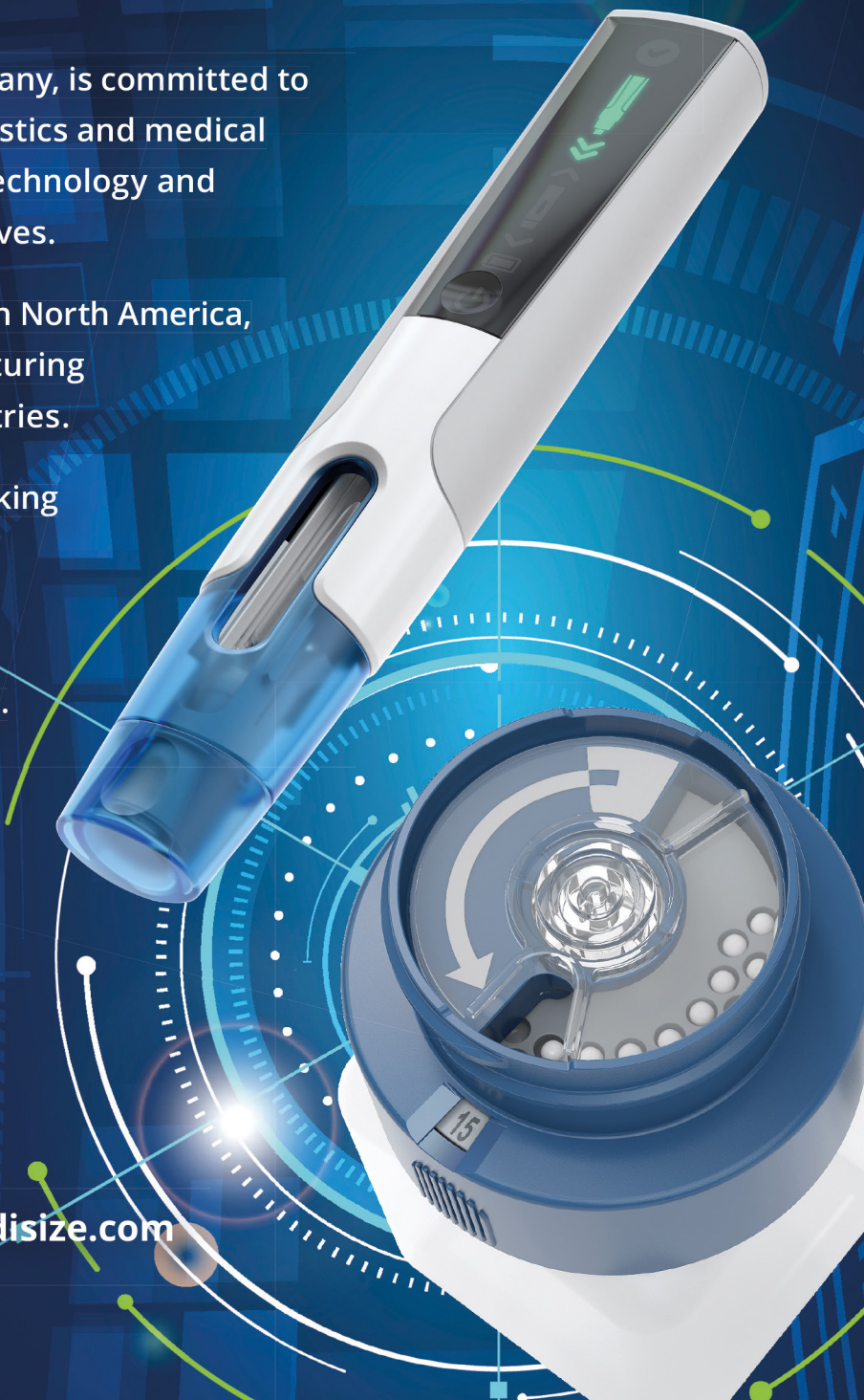

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NANOPARTICLE ENGINEERING: REVOLUTIONISING ORAL DRUG DEVELOPMENT & DELIVERY

In this article, Satu Lakio, PhD, Pharmaceutical Development Manager, and Niklas Sandler, PhD, Chief Technology Officer, both of Nanoform, discuss the benefits of nanoparticle engineering technology as a means of improving the bioavailability and solubility of drug compounds.

It is an established fact that the failure rate of drugs entering Phase I trials is over 90%.[1] This is a staggering figure, considering the huge expense and the many years of hard work across the drug discovery and development pipeline that lie behind every investigational drug. As healthcare systems around the world continue to be challenged to create more efficient and effective therapies, there is increasing interest in methods for improving this low success rate.

A significant obstacle to the release of new medicines is the increasing complexity of drug molecules, which contributes to increased hydrophobicity and poorer water solubility. This is clear from the contrast between the solubility of drugs within the development pipeline and those that reach the market: 70–90% of pipeline drugs fall into the low solubility categories of the Biopharmaceutical Classification System (BCS). Meanwhile, fewer than 40% of drugs on the market fall under the same classification.[2] With this in mind, it is apparent that technologies which can enhance drug solubility and bioavailability have great potential to improve efficiency within the drug development pipeline. Nanoparticle engineering – the process of shrinking down the size of drug particles – has emerged as a promising solution to this problem.

> "... it is apparent that technologies which can enhance drug solubility and bioavailability have great potential to improve efficiency within the drug development pipeline."

ENHANCING SOLUBILITY AND BIOAVAILABILITY

Poor solubility and bioavailability are major causes of attrition in the drug development pipeline. Solubility, defined as the ability of a solute to dissolve in a solvent and give a homogenous system, is an important parameter for drug developers.[3] It is one of the factors influencing whether a drug can achieve the desired concentration in systemic circulation for optimal therapeutic effect. This characteristic is often linked to bioavailability, which refers to the extent and rate at which a drug enters systemic circulation in an unchanged form, thereby reaching its target area.[4]

A significant proportion of drugs delivered through the oral route are absorbed into the body through the gastrointestinal tract. Poor water solubility will result in decreased drug absorption through the intestinal wall, consequently reducing bioavailability. The trend for larger, more complex drug molecules that do not naturally fit Lipinski's

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'Rule of Five' exacerbates this issue, as molecules of this nature often exhibit poor aqueous bioavailability. Consequently, with 70–90% of new chemical entities displaying poor solubility or permeability, the race is on to create technological innovations that can address the issue and create a pathway for novel treatments to reach patients.[2]

NANOPARTICLE ENGINEERING AS A SOLUTION

Various nanoparticle engineering techniques have received attention for their ability to improve the solubility and bioavailability of drug compounds, thereby addressing a leading cause of drug development failure. Engineering APIs down to the nanoscale has a dramatic impact on specific surface area – a phenomenon directly correlated with dissolution behaviour. The relationship between surface area and solubility was developed from the Ostwald-Freundlich theoretical model, which is specific to nanoscale particles.[5]

$$pv\frac{RT}{M}\ln\frac{S_r}{S_\infty}=\frac{2\lambda_{sl}}{r}$$

where p= density of the solid, v= number of moles of ions formed from one mole of electrolyte, R= gas constant, T= temperature, M= molar mass, S_r= the solubility of particles of radius r, S_∞= the solubility of the solid of a plane surface, λ_{sl}= interfacial tension.

Greater surface area enables more interaction between the solute and solvent, which leads to improved solubility. Indeed, reducing particle size below 100 nm increases surface area by 30- to 40-fold. Extrapolating this further, a particle size reduction of around 50–100 nm can increase the surface area by up to 1000-fold.

Different nanoparticle engineering approaches that exploit this relationship can, in general terms, be split into 'top down' mechanical attrition-based approaches and 'bottom up' solution-to-particle formation processes. Nanomilling is a popular example of the former, and can successfully produce nanoparticles as small as 150 nm. By raising the surface free energy, however, nanomilling can introduce amorphous domains on crystalline particles, making it unsuitable for some sensitive APIs. Moreover, the need for surfactants to stabilise milled material in suspension can create challenges with respect to stability and shelf life down the line.

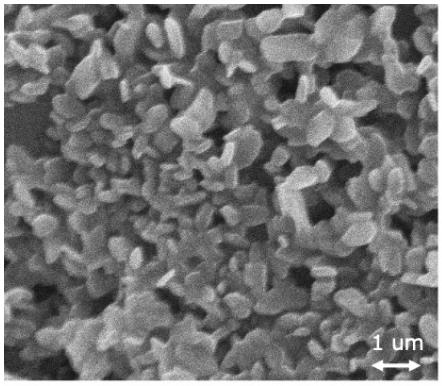
> "Improving the bioavailability and solubility of drug compounds also confers another advantage: lowering the dose required for therapeutic effect."

Spray-drying is an example of a bottom up, solution-to-particle process which has already been widely adopted within the pharmaceutical industry. This technique is particularly useful for creating API particles for respiratory delivery in the low micron range, and can be used to increase bioavailability by producing API particles in spray-dried amorphous solid dispersions. These dispersions are produced by spray-drying the API with a polymer, which acts to stop the API particles from interacting. One disadvantage of this is that the polymer can add a lot of weight to the resultant preformulated material, which can make it impossible to create some formulations at the intended dose and in the desired format. While these techniques have their merits, and are useful in certain situations, it is clear that there is a need for a technology that can reduce particle size to the low nanoscale range, in a controlled and uniform manner, without necessitating the use of surfactants. Nanoform's propriety Controlled Expansion of Supercritical Solutions (CESS®) technology provides precisely this.

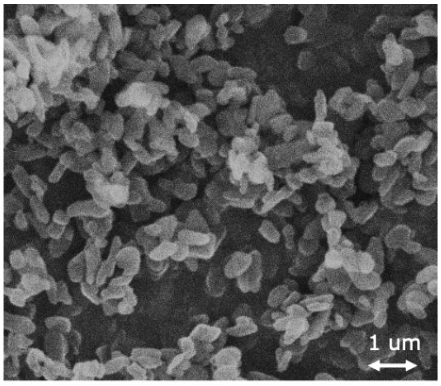
RECENT BREAKTHROUGHS IN NANOPARTICLE ENGINEERING TECHNOLOGY

Recent advances have led to the development of Nanoform's proprietary CESS® nanoforming™ technology, which reduces the size of API particles while maintaining tight control of system thermodynamics and, consequently, surface properties. The technique involves dissolving and extracting API particles from supercritical carbon dioxide ($scCO_2$). As the process does not require excipients, the need for extended compatibility studies is significantly reduced, accelerating the initiation of clinical trials. This patented technique is the only existing technology to successfully and uniformly reduce drug particle size down to 50 nm, and on occasion as small as 10 nm. This is a major breakthrough, as increasing surface area to this extent means that many novel drugs written off as unviable can be revisited. By significantly improving dissolution rates, intrinsic solubility, and bioavailability, Nanoform's technology has the potential to double the number of compounds reaching clinical trial.

Improving the bioavailability and solubility of drug compounds also confers another advantage: lowering the dose required for therapeutic effect. By reducing the quantity of API that needs to be administered, this feature helps to reduce manufacturing costs and limit waste, as well as reducing side-effects for patients. In addition, as the CESS® nanoforming™ process does not require the use of organic solvents and possesses a small manufacturing footprint, there is also a substantial environmental benefit associated with its use. As the industry works towards incorporating more sustainable practices, this feature is expected to become ever more important.



Nano API suspension



Nano API bulk dry powder

Figure 1: SEM images show that nanoformed™ piroxicam remains as individual primary particles in suspension and does not agglomerate.

NANOFORMING™ IN ACTION

The extraordinary capabilities of the CESS® nanoforming™ process were demonstrated in a study on piroxicam, a nonsteroidal anti-inflammatory drug. The research assessed the different pharmacokinetic behaviour between d50: 236 nm piroxicam particles produced using Nanoform's CESS® technology, and d50: ~2 µm piroxicam particles.

Both the nanoformed™ d50: 236 nm piroxicam and d50: ~2 µm particles produced suspensions that were easily re-dispersible. Scanning electron microscope (SEM) images of the material showed that the piroxicam nanoparticles produced using Nanoform's CESS® nanoforming™ process remained as individual primary particles in suspension, and did not agglomerate (Figure 1). In addition, it was observed that the nanoformed™ piroxicam showed improved dissolution *in vitro* compared with the micron-sized particles (Figure 2).

Interestingly, the nanoformed™ suspension had significantly increased piroxicam plasma concentrations over the micron-sized suspension form (Figure 3). The increase was most pronounced within the first 80 minutes. Up to 480 minutes, the Area Under the Curve (AUC) was 85–87% higher and T_{max} was reached two- to six-fold faster in the nanoformed™ suspension group compared with the micron-sized suspension reference group. In addition, the C_{max} was 55–89% higher in the nanoformed™ suspension group within the 480 minutes follow-up time. The results suggest a potential 54% reduction in the dose required for therapeutic effect, which could be even more pronounced with a smaller particle size. This exciting dose reduction capability is highly relevant for BSC II and possibly BSC IV compounds – categories into which 70–90% of all drug development pipeline drugs fall.[2]

The results of the study also demonstrated that a 20 mg/kg oral dose of nanoformed™ piroxicam possessed superior pharmacokinetic properties compared with piroxicam microparticles, with a p-value of less than 0.01 at 80 minutes, faster T_{max}, higher Cmax and larger AUC. When tested at 5 mg/kg, both the suspension and powder blend of nanoformed™ material in capsule performed similarly and to good effect. This provides strong evidence for the efficacy of both formulations, from which researchers can draw confidence for moving forward with human trials (Figure 3). Altogether, the superior properties of nanoformed™ piroxicam formulations demonstrated in the study highlight the immense potential of the technology, and lay the groundwork for human trials.

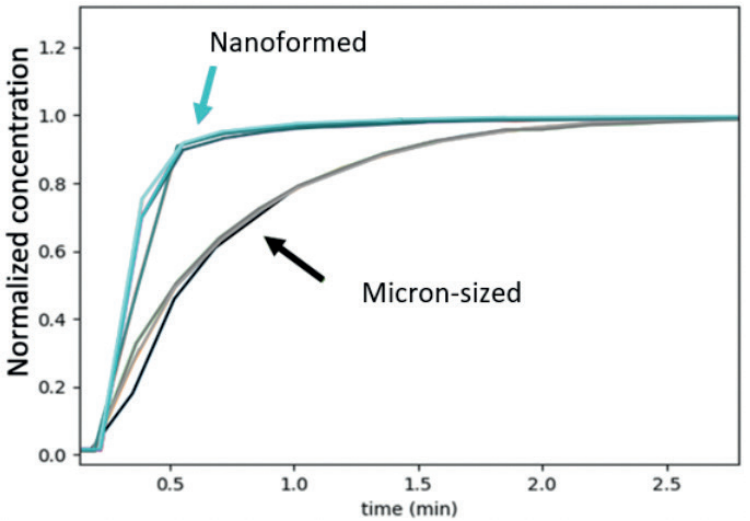


Figure 2: Nanoformed™ piroxicam shows improved *in vitro* dissolution compared with its micron-sized counterparts.

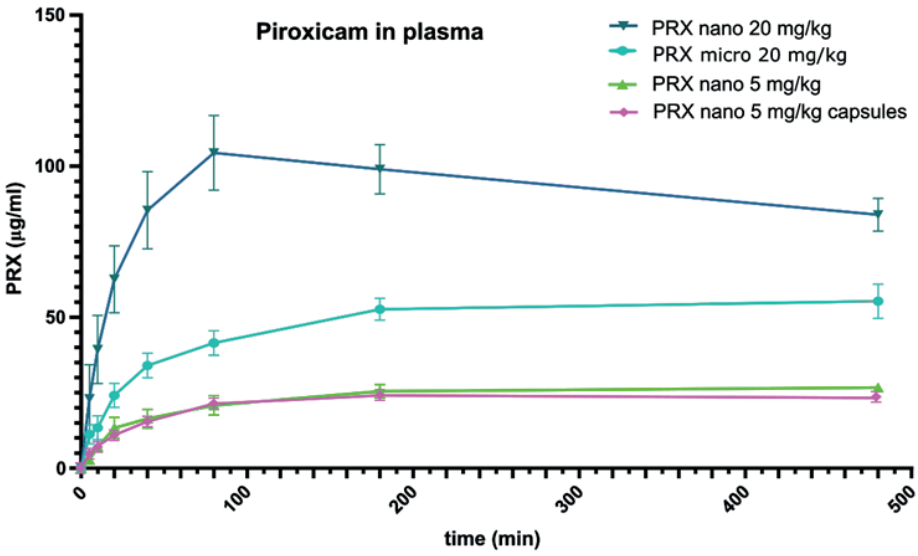


Figure 3: Piroxicam plasma levels in rats after 20 mg/kg and 5 mg/kg PRX administration. Nanoformed™ piroxicam shows improved concentration relative to other dosage forms. Suspension and powder in capsule show similar release profiles.

FUTURE OUTLOOK

Building on the success of the initial studies on piroxicam, Nanoform has progressed to developing a compressed tablet formulation in preparation for human clinical trials (Figure 4). The tablet is easily manufactured using direct compression. With 85% of the most sold drugs in the US and Europe being orally administered, this drug delivery route remains one of the most common in the world.[3] Armed with recent advances, Nanoform is now well positioned to access this route and begin dosing nanoformed™ piroxicam in humans in 2021.

> "Building on the success of the initial studies on piroxicam, Nanoform has progressed to developing a compressed tablet formulation in preparation for human clinical trials."

Figure 4: Nanoform is developing a tablet formulation in preparation for human trials.

It is clear that as a solution to the recurring problem of poor bioavailability and solubility of novel drugs in the discovery and development pipeline, the power of nanoparticle engineering technology promises to pave the way forward. By reducing the size of drug particles to increase their surface area in a controlled manner, and without the use of excipients, the latest CESS® technology in particular has shown its enormous potential for improving efficiency within the pharmaceutical industry. This exciting development has implications not only for new drug candidates, but also for previously developed therapies that were discarded due to problems with solubility and bioavailability.

ABOUT THE COMPANY

Nanoform is a nanoparticle medicine enabling company. Nanoform works together with pharma and biotech partners globally to reduce attrition in clinical trials and enhance the formulation performance of molecules through its nanoforming™ services. The company's patented and scalable CESS® technology produces nanoformed™ API particles as small as 10 nm. This enables poorly soluble molecules in the drug development pipeline to progress into clinical development by increasing their rate of dissolution , intrinsic solubility, and improving their bioavailability. Nanoform's unique technology provides novel opportunities in many value-enhancing drug delivery applications.

REFERENCES

1. *Lowe, D, "The Latest on Drug Failure and Approval Rates". In the Pipeline Blog, May 9, 2019.*
2. *Kalepu S, Nekkanti V, "Insoluble drug delivery strategies: review of recent advances and business prospects". Acta Pharm Sinica B, 2015 Vol 5 (5), pp442–453.*
3. *Savjani KT, Gajjar AK, Savjani JK, "Drug solubility: importance and enhancement techniques". Int Scholarly Res Notices, 2012, Article ID 195727.*
4. *Polin, RA et al, "Fetal and Neonatal Physiology" (Fifth Edition), Elsevier, 2017.*
5. *Sun J et al, "Effect of particle size on solubility, dissolution rate, and oral bioavailability: evaluation using coenzyme Q_{10} as naked nanocrystals". Int J Nanomedicine, 2012, Vol 7, pp5733–5744.*

ABOUT THE AUTHORS

Satu Lakio, PhD, is the Pharmaceutical Development Manager at Nanoform. She earned her PhD at the University of Helsinki, Finland, focusing on enhancing the understanding of pharmaceutical powder processing. Dr Lakio completed her postdoctoral research at Monash University in Melbourne, Australia, studying inhalation powder. She has previously worked in several positions within academia and as an Associate Principal Scientist at AstraZeneca and Senior Development Manager at Orion Pharma. Dr Lakio holds an adjunct professorship at the University of Helsinki and University of Eastern Finland (Pharmaceutical technology). Currently, her research focuses on the pharmaceutical development of nanoformed™ particles.

Niklas Sandler, PhD, is Chief Technology Officer at Nanoform. He has extensive experience in academia and industry, specialising in pharmaceutical product development and material science. His research in pharmaceutical technology has been published in over 100 papers in major international journals. Professor Sandler's earlier work focused on novel pharmaceutical manufacturing technologies, process analytics, formulations for additive manufacturing and material characterisation.

MILENA BATALLA, PHD, PANARUM

Milena Batalla is the Chief Executive Officer and Co-Founder of Panarum Corporation. She obtained a PhD in Pharmacy and Biochemistry from the University of Buenos Aires, Argentina, in 2017. She is a successful entrepreneur and executive leader, experienced in the creation and approval of innovative pharmaceutical technologies and successful patents such as Proteoral®. She has excellent public speaking and communication skills and engages stakeholders worldwide with her company.

In this interview, Dr Batalla introduces the company and describes its Proteoral® technology for the oral delivery of proteins to the bloodstream, therapeutic applications, and products to date. Panarum is an Argentine company and this interview is presented here in Spanish and English, an exciting first for ONdrugDelivery!

Milena Batalla es una exitosa CEO y cofundadora de Panarum Corporation. Obtuvo un doctorado en Farmacia y Bioquímica de la Universidad de Buenos Aires en 2017. Es una exitosa empresaria y líder ejecutiva, virtuosa en la creación y aprobación de tecnologías farmacéuticas innovadoras y patentes exitosas como Proteoral®. Tiene excelentes habilidades para hablar en público y comunicarse, y logra la contribución de todas las partes interesadas del mundo en su empresa.

En esta entrevista, Dr Batalla presenta la compañía y describe su tecnología Proteoral® de delivery oral de proteínas terapéuticas al torrente sanguíneo, aplicaciones terapéuticas y productos hasta la fecha. Panarum es una empresa argentina y esta entrevista se presenta en español e inglés, ¡una emocionante primera vez para ONdrugDelivery!

Q The history of oral protein and peptide delivery has been difficult at times, although recently more breakthroughs are being made, with promising results. How does Proteoral® differ from previous oral protein/peptide delivery technologies? What is the mechanism of action?

A Yes, that is precisely why we regard Proteoral® as the Holy Grail of oral protein delivery. Proteoral® is the universal oral delivery device that successfully transports therapeutic polypeptides into the bloodstream. The therapeutic proteins and Proteoral® encapsulated in gastro-protected nanoparticles (Figure 1) remain 100% intact, protected from the stomach fluids.

In the intestine by the changing pH of the intestinal fluids, 100% of the therapeutic proteins and the Proteoral® recombinant protein are released from the polymeric nanoparticles. With Proteoral®, 75% of the oral dose of the administered protein is absorbed into the bloodstream. Proteoral® triggers an innocuous temporary opening of the intestinal wall's intercellular junctions and successfully accomplishes paracellular transepithelial passage of therapeutic polypeptides into the blood vessels (Figures 2 and 3). The proteins absorbed into the bloodstream successfully and consistently perform their biological action in patients receiving these therapies.

"Proteoral® triggers an innocuous temporary opening of the intestinal wall's intercellular junctions and successfully accomplishes paracellular transepithelial passage of therapeutic polypeptides into the blood vessels.

Proteoral® desencadena la apertura temporal inocua de las uniones intercelulares de la pared intestinal y logra con éxito el paso transepitelial paracelular de los polipéptidos terapéuticos en los vasos sanguíneos."

P ***La historia de la administración de proteínas y péptidos por vía oral ha sido complicada por momentos, si bien últimamente se están logrando más avances con resultados prometedores. ¿En qué se diferencia Proteoral® de las tecnologías anteriores de administración oral de proteínas y péptidos? ¿Cuál es el mecanismo de acción?***

R *Sí, precisamente por eso consideramos que Proteoral® es el Santo Grial de las proteínas orales. Proteoral® es el dispositivo de administración oral universal que transporta con éxito polipéptidos terapéuticos al torrente sanguíneo. Las proteínas terapéuticas y Proteoral® encapsuladas en nanopartículas (Imagen 1) gastroprotegidas mantienen el 100% de las proteínas terapéuticas intactas de los fluidos estomacales.*

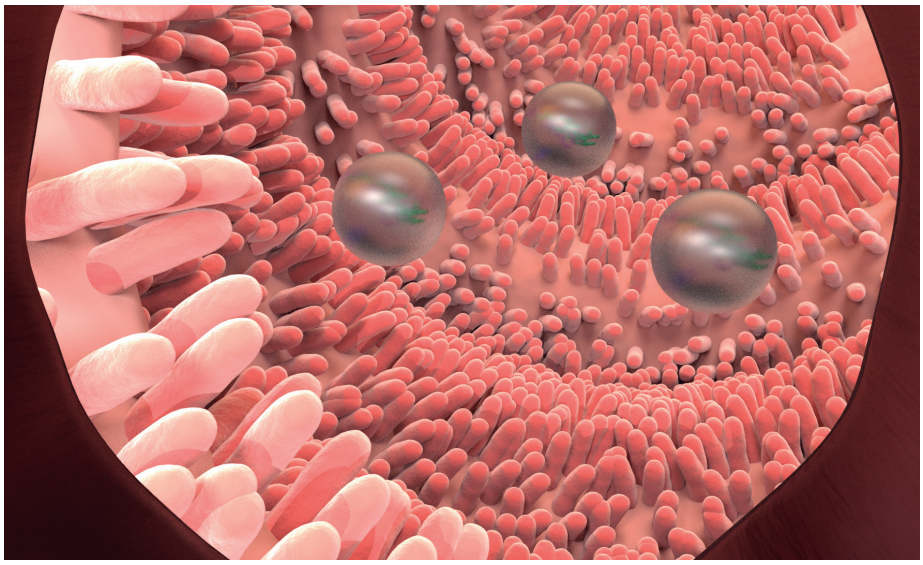


Figure 1: Hermetic polymer – therapeutic proteins and Proteoral® encapsulated in gastro-protected nanoparticles. *Imagen 1: Las proteínas terapéuticas y Proteoral® encapsuladas en nanopartículas gastro protegidas.*

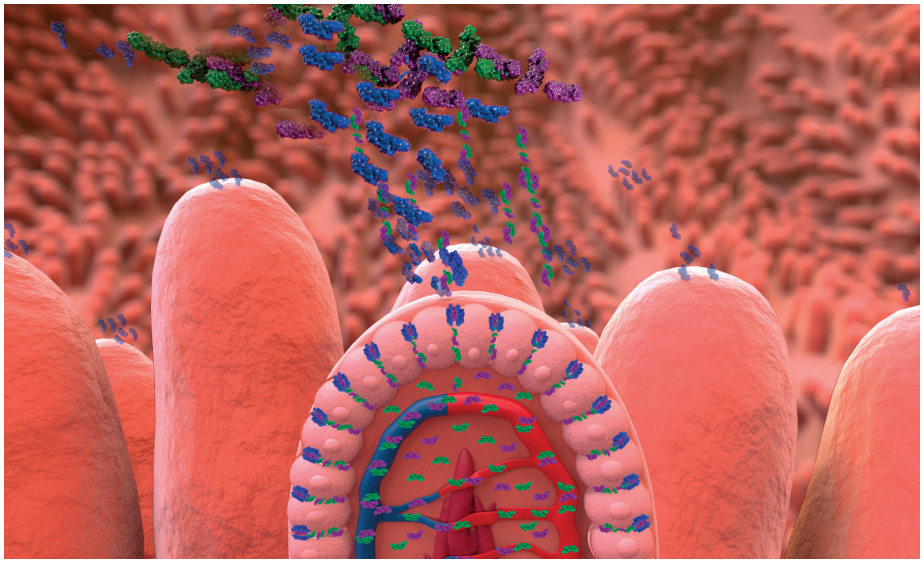


Figure 2: Proteoral® triggers an innocuous temporary opening of the intestinal wall's intercellular junctions. *Imagen 2: Proteoral® desencadena la apertura temporal inocua de las uniones intercelulares de la pared intestinal.*

En el intestino por la acción del pH de los fluidos intestinales, el 100% de las proteínas terapéuticas y la proteína recombinante Proteoral® se liberan de las nanopartículas poliméricas. Con Proteoral®, el 75% de la dosis oral de la proteína administrada se absorbe en el torrente sanguíneo. Proteoral® desencadena la apertura temporal inocua de las uniones intercelulares de la pared intestinal y logra con éxito el paso transepitelial paracelular de los polipéptidos terapéuticos en los vasos sanguíneos (Imágenes 2 y 3). Las proteínas absorbidas en el torrente sanguíneo realizan con éxito y consistentemente su acción biológica en pacientes que reciben estas terapias.

Q What is the current stage of development of Proteoral®? Can you share details of studies that have been completed, or planned in the future?

A With the Proteoral® technology, we have carried out *in vitro* and *in vivo* studies with successful results. The results of *in vivo* studies of the pharmacokinetics and pharmacodynamics of therapeutic proteins (hormones) administered with Proteoral® confirm a 75% absorption of the therapeutic proteins into the bloodstream, with successful and consistent therapeutic action.

In our pipeline, we have achieved successful oral absorption into the bloodstream of oral monoclonal antibodies and used Proteoral® in numerous therapeutic polypeptides. Proteoral® is a successful device for delivering oral therapeutic proteins into the bloodstream in patients who receive these therapies.

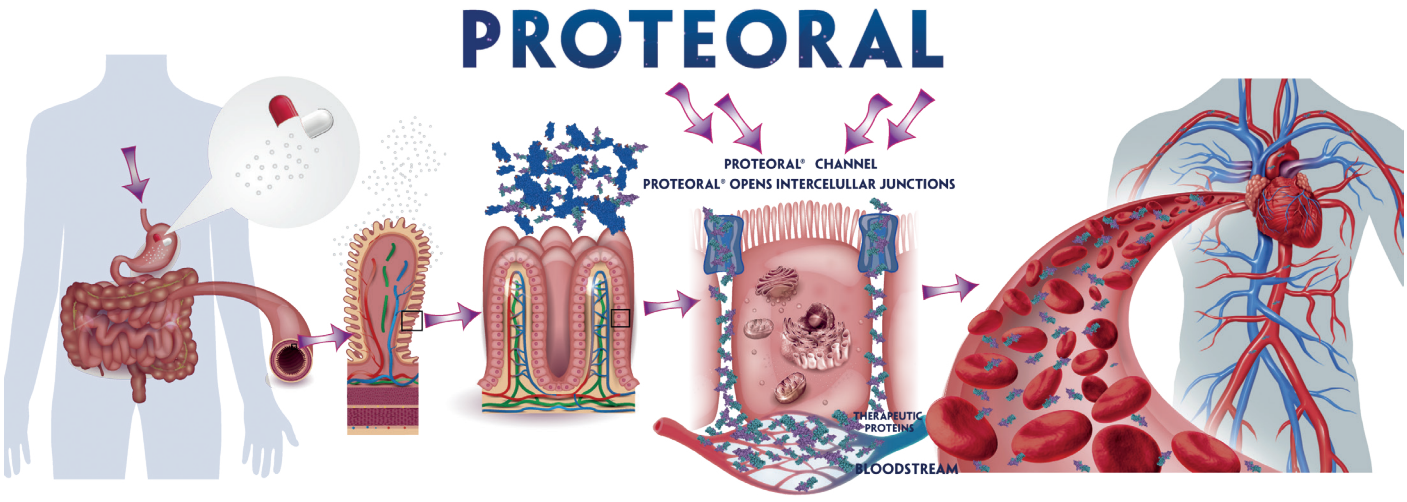


Figure 3: Proteoral's mechanism of action. *Imagen 3: Mecanismo de acción de Proteoral®.*

P ¿En qué fase de desarrollo está Proteoral® actualmente? ¿Puede contarnos detalles de los estudios que se han llevado a cabo y los que están en curso o se planean a futuro?

R Con la tecnología Proteoral®, hemos realizado estudios in vitro e in vivo con resultados exitosos. Los resultados de los estudios in vivo sobre la farmacocinética y farmacodinámia de las proteínas terapéuticas (hormonas) administradas con Proteoral® confirman una absorción del 75% de las proteínas terapéuticas en el torrente sanguíneo, con acción terapéutica exitosa y consistente.

En nuestra cartera, hemos logrado una absorción oral exitosa en el torrente sanguíneo de anticuerpos monoclonales orales y hemos utilizado Proteoral® en numerosos polipéptidos terapéuticos. Proteoral® es un exitoso dispositivo de administración de fármacos de proteínas terapéuticas orales en el torrente sanguíneo en pacientes que reciben estas terapias.

Q Which therapeutic markets and disease indications is Proteoral® most suitable for and why? Can you say which indication or therapeutic class is, or will be, the first target for development?

A We consider Proteoral® to be beneficial for patients with chronic diseases requiring therapy with polypeptides with systemic therapeutic action. The therapeutic markets we target with Proteoral® are those of oral gonadotropins. Our success means providing couples with successful and beneficial fertility treatments.

Other potential target markets for Proteoral® are those of insulin and other hormone therapies, monoclonal antibody therapies for diseases of the immune system, and therapies for patients with cancer and osteoporosis, among other applications (Figure 4).

> "*In vivo* studies of the pharmacokinetics and pharmacodynamics of therapeutic proteins (hormones) administered with Proteoral® confirm a 75% absorption of the therapeutic proteins into the bloodstream, with successful and consistent therapeutic action.
>
> *Los estudios in vivo sobre la farmacocinética y farmacodinámia de las proteínas terapéuticas (hormonas) administradas con Proteoral® confirman una absorción del 75% de las proteínas terapéuticas en el torrente sanguíneo, con acción terapéutica exitosa y consistente."*

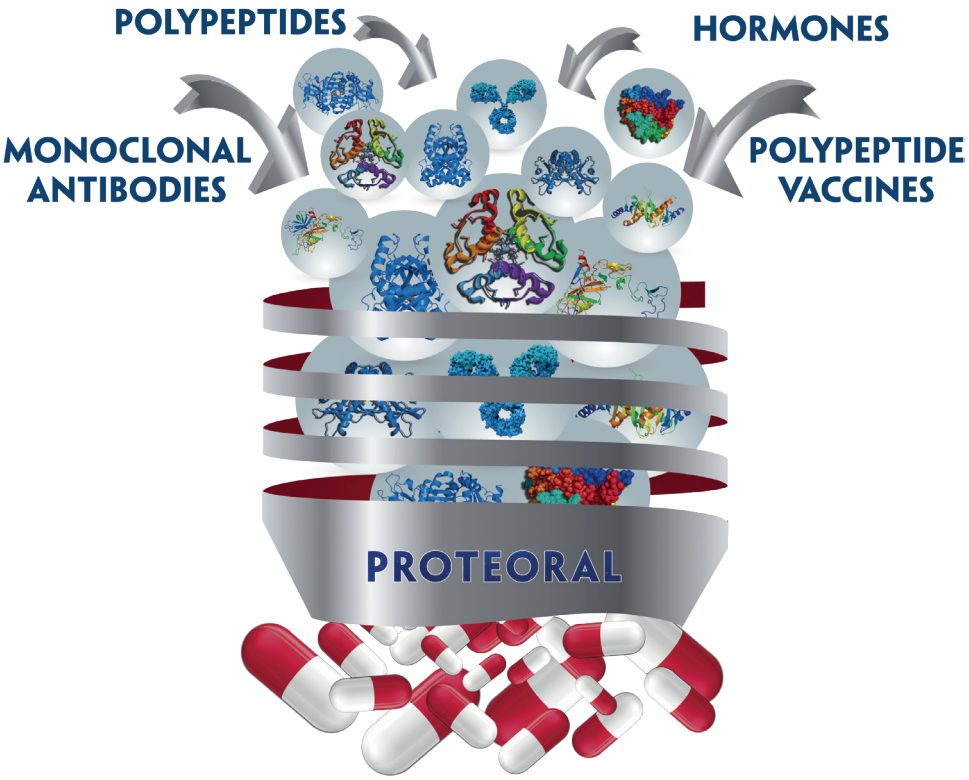


Figure 4: Proteoral® is the universal oral delivery device that successfully transports therapeutic polypeptides. *Imagen 4: Proteoral® es el dispositivo de administración oral universal que transporta con éxito polipéptidos terapéuticos.*

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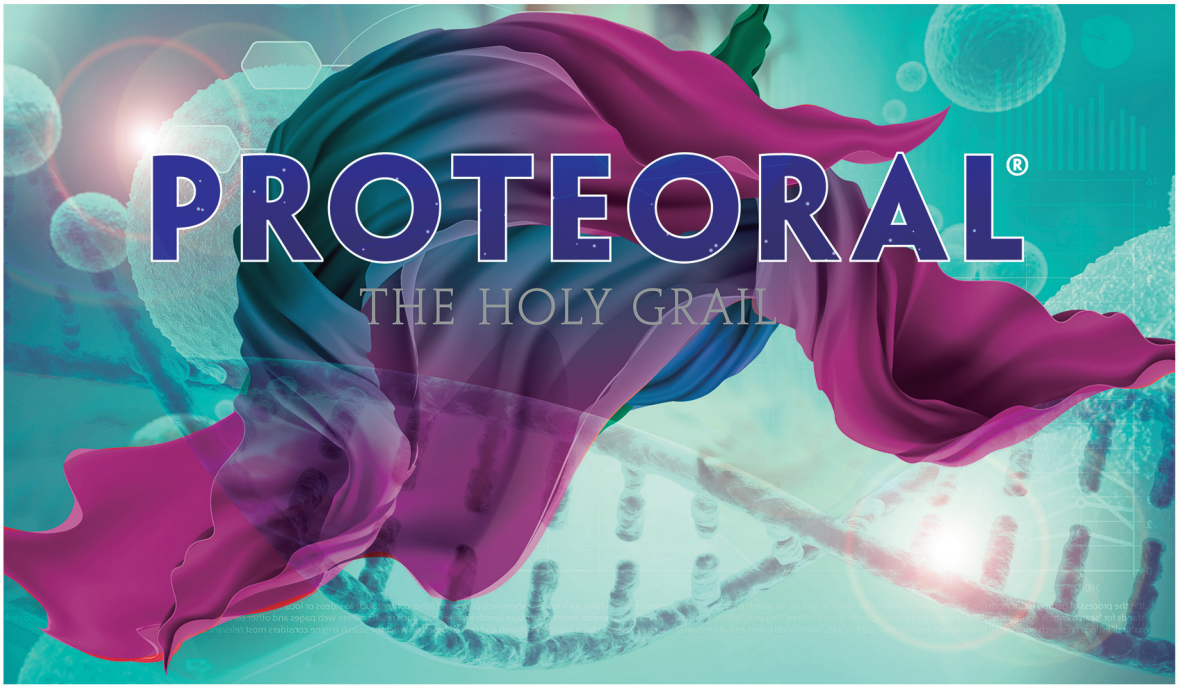

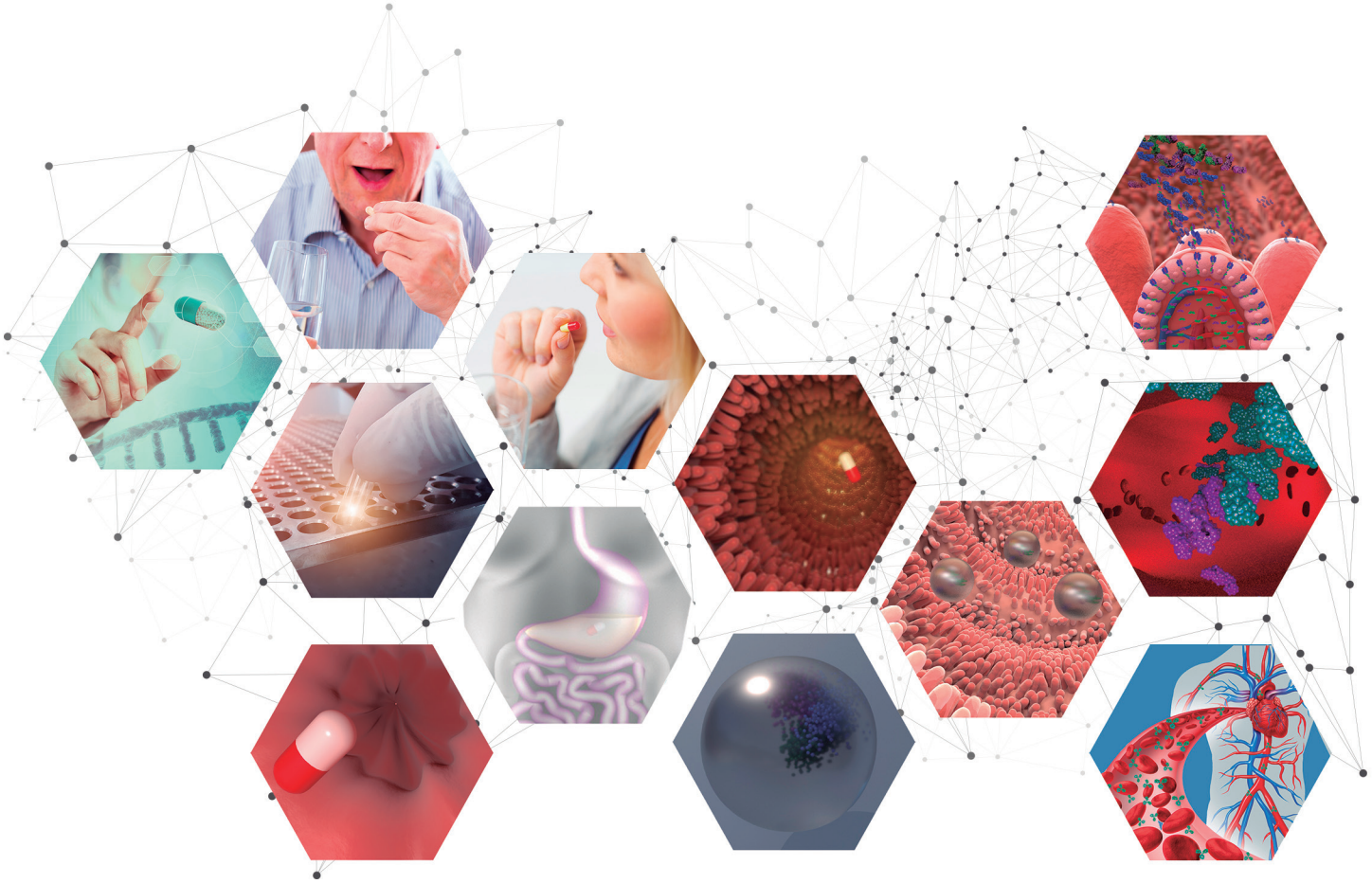

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P ***¿Para qué mercados terapéuticos e indicaciones es más adecuado Proteoral®? ¿Por qué? ¿Puede contarnos qué indicación o clase terapéutica es, o será, la primera diana para el desarrollo?***

R Consideramos que Proteoral® es exacto para pacientes con enfermedades crónicas que requieren terapia con polipéptidos con acción terapéutica sistémica. Los mercados terapéuticos a los que nos dirigimos con Proteoral® son los de las gonadotropinas orales. Nuestro éxito significa proporcionar a las parejas tratamientos de fertilidad exitosos y beneficiosos.

Otros mercados que abarcan Proteoral® son los de la insulina y otras terapias hormonales, las terapias con anticuerpos monoclonales para enfermedades del sistema inmunitario y las terapias para pacientes con cáncer y osteoporosis, entre otras aplicaciones (Imagen 4).

Q Can you describe Panarum as a business?

A Our business is Proteoral® and the pharmaceutical drugs successfully manufactured and sold. Panarum started in 2017 with investments from angel investors; and we quickly accomplished the internationalisation of our company. This year, we signed an agreement for the first international venture capital investment in Panarum.

Our successfully signed and executed strategic alliance agreements with innovative pharmaceutical laboratories include regulatory milestones, the oral proteins obtained, the sales of the Proteoral® recombinant protein to our clients, and the royalties from the sales of the oral proteins. Our next steps include building Panarum's strategic alliances with global distribution channels for the marketing of Proteoral®. Our goal is to be a public offering.

"Panarum started in 2017 with investments from angel investors; and we quickly accomplished the internationalisation of our company. This year, we signed an agreement for the first international venture capital investment in Panarum.

Panarum comenzó en 2017 con inversiones de inversionistas ángeles; y rápidamente logramos la internacionalización de nuestra empresa. Este año, firmamos un acuerdo para la primera inversión internacional de capital de riesgo en Panarum."

P ***¿Puede describir a Panarum como empresa?***

R Nuestro negocio es Proteoral® y los medicamentos farmacéuticos fabricados y vendidos con éxito. Panarum comenzó en 2017 con inversiones de inversionistas ángeles; y rápidamente logramos la internacionalización de nuestra empresa. Este año, firmamos un acuerdo para la primera inversión internacional de capital de riesgo en Panarum.

Nuestros acuerdos de alianza estratégica firmados y ejecutados con éxito con laboratorios farmacéuticos innovadores incluyen hitos regulatorios, las proteínas orales obtenidas, las ventas de la proteína recombinante Proteoral® a nuestros clientes y las regalías de las ventas de las proteínas orales. Nuestros próximos pasos incluyen la construcción de alianzas estratégicas de Panarum con canales de distribución global para la comercialización de Proteoral®. Nuestro objetivo es ser una oferta pública.

Q Finally, COVID-19 is of course something that people and businesses across the world are thinking about at present. I wondered if you could tell us how the virus has affected your business, and how you have been able to overcome the effects of the virus and associated restrictions? Would there be potential application of Proteoral® in the development of oral COVID-19 vaccines?

A In the current context of COVID-19, we have adapted and focused on continuing the company's growth. We escalated the Proteoral® technology, restructured the company, and hired senior staff in the Human Resources and Technology departments. We insourced certain activities that used to be outsourced, achieved new strategic alliances with suppliers from the biopharmaceutical industry, and achieved the certification of the company's quality system.

We consider that the oral administration of polypeptide-based vaccines is a viable therapy and, as such, comes within our field of study of Proteoral®.

P ***Por último, el COVID-19 es, lógicamente, algo que está en cabeza de la gente y las empresas de todo el mundo en la actualidad. Me preguntaba si podría contarnos cómo ha afectado el virus a su empresa, y cómo ha conseguido superar los efectos del virus y las restricciones relacionadas. En relación con esto, ¿podría haber una aplicación de Proteoral® para el desarrollo de vacunas orales contra el COVID-19?***

R En el contexto actual de COVID-19, nos hemos adaptado y enfocado en continuar el crecimiento de la compañía: escalamos la tecnología Proteoral®, reestructuramos la compañía y contratamos personal sénior en los departamentos de Recursos Humanos y Tecnología. Contratamos actividades que solían subcontratarse, conseguimos nuevas alianzas estratégicas con proveedores de la industria biofarmacéutica y obtuvimos la certificación del sistema de calidad de la empresa.

Consideramos que la administración oral de vacunas basadas en polipéptidos es una terapia viable y, como tal, entra en nuestro campo de estudio de Proteoral®.

PANARUM

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THE RISE OF COMPLEX ORAL DELIVERY SYSTEMS

In this article, María Fernández-Martos Balson, Biomedical Engineer, and Bastiaan De Leeuw, Head of Business Development, Drug Delivery, both of Cambridge Design Partnership, explore the oral delivery of biologics and the challenges that must be overcome in order to enhance bioavailability. The authors also take a look at some recently developed drug-device combinations.

After a series of failed experiments in November 1923, pathologist Geoffrey Harrison concluded that the "oral administration [of insulin] in alcohol would be so uncertain and so expensive as to be of little or no therapeutic value in diabetes mellitus in man". He published his results – and encouraged other researchers to join him in publishing their own data – with a mind to "prevent the raising of false hopes in [...] those suffering from diabetes".[1] This was a mere two years after the discovery of insulin.

Since then, peptide- and protein-based therapies have risen in prominence, representing approximately 12% of the pharmaceutical market as of 2018, and with the potential to grow substantially over the next 5-10 years.[2,3] Hundreds of biologics are now approved to treat a variety of ailments, from cancer to rheumatoid arthritis. And, since Harrison, many attempts have been made to administer such drugs in non-invasive manners, from inhalation to transdermal patches. The oral route is of particular interest for its convenience and tolerability for patients, and many recent efforts have been focused on this area.

Of course, not all therapeutic peptides would benefit from oral administration, even when achievable from a technical perspective. Robustness of delivery, patient compliance, dosing regimen and bioavailability must all be weighed up, along with the economic considerations.

From a patient perspective, it is a no-brainer: who would choose an injection if they could take a pill instead? From a business perspective, drugs may be well suited to this approach if the projected market expansion for an oral formulation outweighs the development costs and risks, as well as the projected increased cost due to any additional API that may be required to compensate for unavoidable reduced oral bioavailability.[4] To date, predominantly diabetes-associated drugs have been considered, as the mechanism is well understood and the opportunity to avoid the need for multiple daily injections is attractive.

> "The oral delivery of biologics remains a "holy grail" – a tantalising vision and a worthy goal."

Yet, despite the obvious appeal and after nearly a hundred years, needles are still required. The oral delivery of biologics remains a "holy grail" – a tantalising vision and a worthy goal. In this article we will explore the challenges faced by a protein on its journey from the gastrointestinal (GI) lumen to the bloodstream and explain how ingestible devices can be used to increase oral bioavailability. The reward is self-evident. The challenge, not trivial.

THE API'S PERILOUS JOURNEY

For a therapy to be effective, the API must reach the target delivery site (in this case, systemic circulation) in sufficient concentrations. A key measure of success, then, is bioavailability: the fraction of the administered dose that reaches the bloodstream, typically expressed as a percentage. When delivered orally, proteins have extremely low bioavailability, usually less than 1%.[5] This is because their half-life in the GI lumen is short and their ability to permeate through the GI walls is limited.

The human digestive system has evolved over millions of years to break down nutrients, to eliminate waste and to protect itself. It is not a friendly environment, especially for proteins (i.e. food). To reach the bloodstream, a drug must first survive the acidic environment of the stomach, elude

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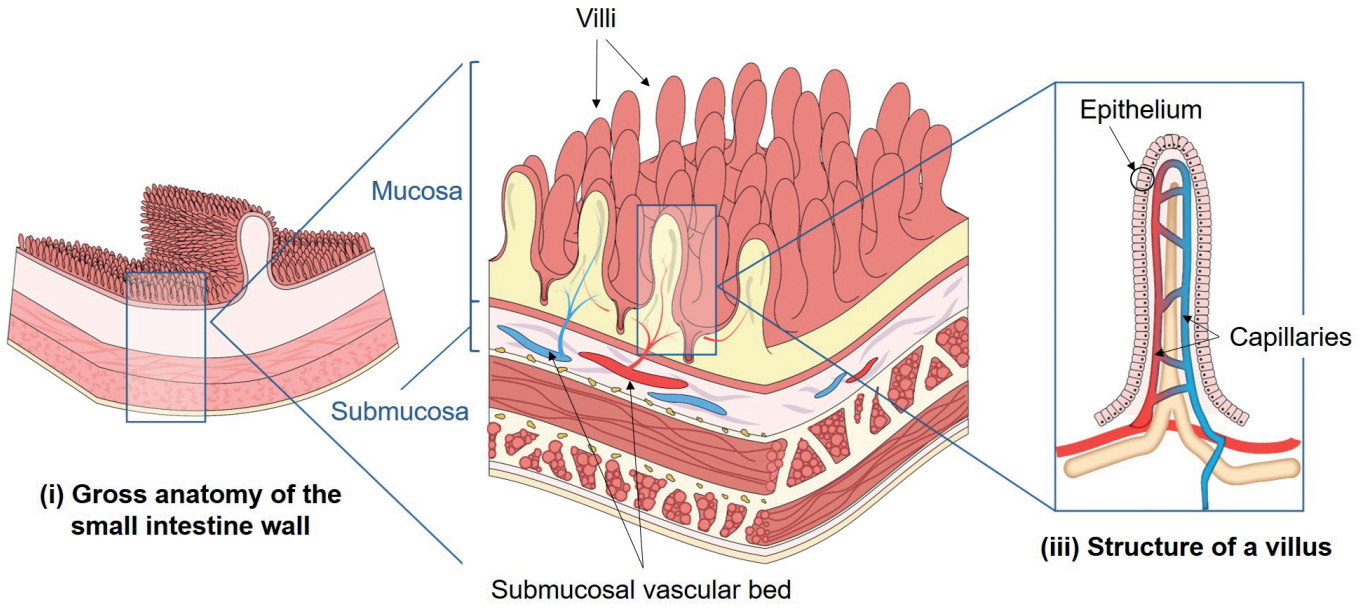

Figure 1: A cross section of the small intestine wall, highlighting the location of the submucosal vascular bed and the capillary network within the villi.

enzymatic degradation and get as far as the GI wall. Once there, the drug faces a coating of mucus and several layers of densely packed cells.

The mucus alone presents a formidable barrier. Constantly shed and secreted, it flows from wall to lumen, and from stomach to colon; drugs must diffuse upstream to reach the epithelium. It is viscous, prone to forming intermolecular bonds, and consists of a fine mesh of mucin filaments – in summary, it is very effective at preventing the passage of large, interactive molecules.[6]

For any API that makes it past the mucus the final hurdle is in the wall itself. To reach the capillaries in the villi or the vascular bed within the submucosal layer (Figure 1), the API must cross the epithelium. Epithelial cells are tightly packed and connected to one another by the aptly named tight junctions (multiprotein complexes that seal the gaps between adjacent cells). There are two main paths across this barrier (Figure 2), neither of which is easy for therapeutic peptides, as they are typically too hydrophilic to permeate through the cellular membrane and across the cells themselves (transcellular transport), and too large to pass between tight junctions (paracellular transport).[7] Overall permeability is therefore very low.

ENHANCING BIOAVALABILITY

In order to reach the bloodstream intact and in sufficient quantities, an API must successfully navigate the aforementioned obstacles. That is, the delivery system must achieve the following high-level functions:

- Protection: protect the API from chemical and enzymatic degradation in the GI lumen
- Localisation: enable the API to reach the GI wall
- Absorption: ensure transport of the API through the GI wall.

Attempts to fulfil these functions – and thus improve bioavailability – fall into two broad categories: pharmaceutical strategies (relying on reformulation and use of excipients) and mechanical strategies (relying on physical parts and mechanisms).

The pharmaceutical approach typically involves the use of enzyme inhibitors to decrease the rate of protein breakdown in the lumen (protection) and the use of permeation enhancers to improve diffusion of the drug through the epithelium (absorption), while relying on regular diffusion/advection and the increased drug half-life in the lumen for

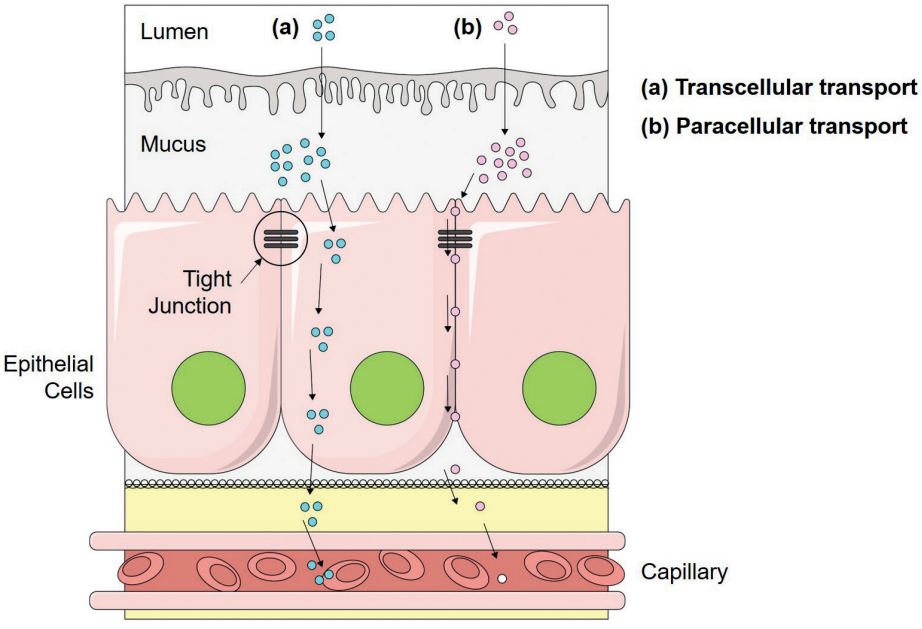

Figure 2: Two paths across the epithelium to reach systemic circulation: through the cells themselves, or between them.

"The challenge, of course, is to obtain a useful improvement in bioavailability (increasing it to 30-50%)[5] while mitigating the safety risks."

localisation. Other formulation techniques include direct chemical modification of the peptide or protein to increase permeability (e.g. PEGylation) and the use of carrier systems such as nanoemulsions and nanoparticles.[8,5]

Chemical strategies such as these have demonstrated marginal improvements in the oral bioavailability of therapeutic macromolecules, with some formulations achieving 1–2% bioavailability in clinical studies.[9] This only provides an incremental change, rather than truly enabling a shift in the attractiveness of oral administration. Moreover, the technologies deployed can carry undesirable side effects, for example some permeation enhancers may cause inflammation or allow pathogens to breach the epithelial layer, potentially leading to infections. The challenge, of course, is to obtain a useful improvement in bioavailability (increasing it to 30–50%)[5] while mitigating the safety risks. Many specific drug formulations (and some platform technologies) that aim to strike this balance are currently in development.[10]

In contrast to the purely pharmaceutical approach, device-enabled oral delivery aims to fulfil the three key functions by mechanical means. In principle, the concept is simple: the patient swallows a small device, as they would a pill. The device becomes activated once it reaches the desired location (typically the stomach or small intestine) and then, by some means, the device creates a high and localised concentration of API adjacent to the epithelium – or else it penetrates the mucosa in order to bypass the epithelium entirely and thus achieve greater bioavailability.

Physical concepts for enhanced wall penetration include the use of microneedles, ultrasound and electroporation, while a common motif to address both protection and localisation is the use of enteric materials.[9] Enteric coatings or components allow a device to pass through the acidic environment of the stomach in a dormant state, dissolving only upon reaching the higher pH of the small intestine (which then triggers the device's active state). This targeted deployment serves a double purpose: protecting the API from chemical degradation in the stomach, and bringing the drug closer to the epithelium (simply because the small intestine is much narrower than the stomach).

IN THE PIPELINE

Over the past 10 years, development efforts in this space have been shifting towards drug-device combinations. This section describes some of the more mature designs (note that this is not a comprehensive list and does not reflect the full breadth of technologies currently in development).

In an ongoing collaboration, a team of engineers from Massachusetts Institute of Technology (MIT) (US) and Novo Nordisk (Denmark) has developed several devices that show promise in preclinical studies. The self-orienting millimetre-scale applicator (SOMA) delivers a solid drug needle into the gastric mucosa. The device's shape, inspired by the leopard tortoise, ensures that the device always lands and remains on the bottom of the stomach in the upright position. Within minutes, a sugar trigger dissolves, releasing a spring that inserts the needle into the mucosa. The needle, made of up to 80% compressed insulin, dissolves over the course of one hour, releasing the API.[11]

The luminal unfolding microneedle injector (LUMI), another MIT/Novo Nordisk device, targets the small intestine instead. It consists of three legs, joined at the centre, and tipped with solid drug-loaded microneedles. Once it reaches the higher pH of the intestine, the device – initially constrained within a capsule – is deployed by a spring. The tripod unfolds in the small intestine lumen, pressing the needles into the wall, where they dissolve.[12] Proof of principle studies in pigs achieved a bioavailability of 10% and demonstrated that non-biodegradable device components were safely excreted and that there was minimal damage to the epithelium at the injection site, although long-term safety remains to be demonstrated.[13]

"Promising preclinical results, such as those of the LUMI system, demonstrate concept feasibility."

Rani Therapeutics (San Jose, CA, US) is developing a similar device. Upon reaching the small intestine, the RaniPill™ is activated. A partition between two compartments (containing dry citric acid and sodium bicarbonate respectively) dissolves, allowing the reagents to mix and produce CO_2. The gas fills a balloon, which in turn pushes a solid drug needle into the mucosa. The needle dissolves and the rest of the device is passed.[14,15] Rani's technology has attracted interest from a number of pharmaceutical companies, including Novartis (Switzerland) and Shire (now Takeda) (Japan), and they recently announced a successful Phase I study with octreotide in humans with a bioavailability claim of >70%,[16] although their data have not yet been formally published in a peer-reviewed journal.

Progenity (San Diego, CA, US) and Baywind Bioventures (San Diego, CA, US), two relatively new companies, are developing devices that aim to deliver high-velocity jets of drug solution directly through the epithelium. Both are in early development phases currently.

THE REAL CHALLENGE: SCALING UP

Promising preclinical results, such as those of the LUMI system, demonstrate concept feasibility. The next challenge is ensuring device safety and robust delivery at scale.

Typical candidate peptides for oral delivery require frequent dosing (weekly to daily) and have large target patient populations. Assuming, for example, that a once-weekly device was adopted by 5% of diabetics in the US, 80–90 million units would be required per year.[17] To be a viable therapy, the device would have to deliver the drug safely and reliably every time. It would have to be manufacturable and fillable, and fulfil its functions in tolerance cases. This is the puzzle that must be solved if oral delivery of biologics is to succeed where other non-invasive approaches have failed. Some of the key pieces are:

Miniaturisation

There is a trade-off between device size and potential payload. Drug loading should be maximised, but size is ultimately constrained by patient tolerability and the risk of intestinal obstruction. For frequently dosed

devices, the device envelope should ideally fit within a size 0 capsule (L = 21.7 mm, ø = 7.34 mm), a requirement that places a significant burden on the manufacturing process. Component features require micrometre accuracy, and manufacturers may need to develop specialist processes and equipment to handle and assemble millimetre-sized components, to fill the primary container (if delivering a liquid) or to manufacture components out of solid drug (e.g. microneedles).

Anatomy and Physiology

Not only do device tolerances matter, the device must also work reliably in spite of inter- and intra-patient variability. Human anatomy is not subject to drawing tolerances; patient's GI tracts vary significantly in shape, size and motility patterns. There are also differences between the fed and fasted states, and differences due to disease states and co-morbidities. Ensuing variations in the chemical and enzymatic makeup of the gastric and intestinal fluids, the presence or absence of chyme, peristalsis, gastric emptying times, etc, must all be taken into account.

To succeed here, device engineers must gain a deep understanding of anatomical and physiological variability in the GI tract, and of how its extremes affect each of the device functions, from localisation, though delivery, to eventual dissolution or passing.

Material Selection

Choosing the right materials can prove challenging too, as there are often conflicting requirements. There may be a need for components that store energy (e.g. springs), dissolve at certain times (e.g. triggers) and/or act as impermeable membranes (e.g. to prevent dry reagents from mixing prematurely). These requirements must all be balanced alongside manufacturability, sterilisability and patient safety.

For example, from a safety perspective, it is preferable for sharp components, such as hollow needles, to be able to dissolve in the GI tract, in order to mitigate the risk of damage to the epithelium as the device is passed. However, soluble materials can rarely hold an edge for very long in the moist environment of the GI tract. Engineers must weigh such considerations and choose wisely to ensure reliable delivery while mitigating the associated risks (and while operating in a regulatory environment that is not yet set up for this new class of devices).

> "Basic feasibility of device-enabled delivery has been demonstrated in preclinical studies, with data supporting the potential to obtain much improved bioavailability."

LOOKING AHEAD

Compared with 1923, we are surely closer to being able to solve the oral delivery puzzle. Basic feasibility of device-enabled delivery has been demonstrated in preclinical studies, with data supporting the potential to obtain much improved bioavailability. Whether this promise will become a commercial reality remains to be seen, but the goal is certainly worth the journey.

To get there, companies should focus on turning the technical advances that have been made so far into robust and scalable technologies, through a deep understanding of physiology, manufacturing and material selection.

ABOUT THE COMPANY

Cambridge Design Partnership is an employee-owned technology and product design partner, located in Cambridge (UK) and Raleigh, North Carolina (US). CDP provide an integrated and holistic product development capability through a highly qualified team, well equipped development labs and ISO 13485/9001 approved methods. This encompasses research and strategy, design, technology and digital innovation, product development and regulatory and manufacturing support. CDP experts are able to take combination products through a full design cycle and submission, enabling customers to launch products that are user-centric and commercially effective.

With broad experience developing devices across all forms of drug delivery, our team builds upon technological advances from various industries and sectors to develop reliable devices that can be manufactured at scale. We are well positioned to address the technical challenges posed by miniaturisation, material selection and physiological variability, critical to deliver upon the promise of oral biologics delivery.

REFERENCES

1. *Harrison GA, "Insulin in alcoholic solution by the mouth". Br Med J, 1923, Vol 22;2 (3286), pp 1204–1205.*
2. *https://www.medgadget.com/2019/12/protein-therapeutics-market-2020-global-analysis-opportunities-and-forecast-to-2025.html, accessed on July 9, 2020.*
3. *Aitken M, Kleinrock M, Simorellis A, Nass D, "The Global Use of Medicine in 2019 and Outlook to 2023". IQVIA Institute Report, 2019.*
4. *Shields P, "Oral Peptide Therapeutics - A Holy Grail or Quixotic Quest?". Drug Discovery World, 2017.*
5. *Shaji J, Patole V, "Protein and Peptide Drug Delivery: Oral Approaches". Indian J Pharm Sci, 2008, Vol 70(3), pp 269–277.*
6. *Boegh M, Nielsen HM, "Mucus as a Barrier to Drug Delivery – Understanding and Mimicking the Barrier Properties". Basic Clinl Pharmacol Toxic, 2015, Vol 116(3), pp 179–186.*
7. *Renukuntla J, Vadlapudi AD, Patel A, Boddu SH, Mitra AK, "Approaches for Enhancing Oral Bioavailability of Peptides and Proteins". Int J Pharm, 2013, Vol 447 (1–2), pp 75-93.*
8. *Bruno BJ, Miller GD, Lim CS, "Basics and recent advances in peptide and protein drug delivery". Ther Deliv, 2013, Vol 4(11), pp 1443–1467.*
9. *Caffarel-Salvador E, Abramson A, Langer R, Traverso G, "Oral delivery of biologics using drug-device combinations". Curr Opin Pharmacol, 2017, Vol 36, pp 8–13.*
10. *Muheem A et al, "A review on the strategies for oral delivery of proteins and peptides and their clinical perspectives". Saudi Pharm J, 2016, Vol 24(4), pp 413–428.*
11. *Abramson A et al, "An ingestible self-orienting system for oral delivery of macromolecules". Science, 2019, Vol 363 (6427), pp 611–615.*
12. *Abramson A et al, "A luminal unfolding microneedle injector for oral delivery of macromolecules". Nat Med, 2019, Vol 25 (10), pp 1512–1518.*

13. *Brayden DJ et al, "Systemic delivery of peptides by the oral route: Formulation and medicinal chemistry approaches". Adv Drug Delivery Rev, 2020.*
14. *https://www.ranitherapeutics.com/technology/. Accessed July 9, 2020.*
15. *Imran M, "Device, system and methods for the oral delivery of therapeutic compounds". International Patent No WO2013003487, Issued 2013.*
16. *"Rani Therapeutics Announces Positive Phase I Study Results of Oral Octreotide using RaniPill™". Press Release, Rani Therapeutics, January 30, 2020.*
17. *Centers for Disease Control and Prevention. "National Diabetes Statistics Report, 2020". Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services, 2020.*

ABOUT THE AUTHORS

María Fernández-Martos Balson has a Masters degree in Bioengineering and Mechanical Engineering from the University of Cambridge, where she focused on the computational modelling of dynamic cell tissues, with a view to understand how tumour metastasis begins. Prior to joining CDP, Ms Fernández-Martos Balson worked in the innovation department of a leading drug delivery device manufacturer, where she contributed to a range of development projects, including the early-stage design of an intraocular injection device and the late-stage development of a gas-powered autoinjector. Since joining CDP, she has been involved in the design of subcutaneous, intratumoural and oral drug delivery devices.

Bastiaan De Leeuw has been active in the field of drug delivery for the last 20 years. Mr De Leeuw has led projects covering dry-powder formulation development, inhaler design and development, and autoinjector design and development, as well as the associated stages of clinical and regulatory evaluations. In addition, he led the initial clinical evaluation of urologic diagnostic tests at NovioGendix (the Netherlands) (now MDxHealth, Irvine, CA, US) and has worked at Focus Inhalation (Turku, Finland), Akela Pharma (Austin, TX, US), Oval Medical (Cambridge, UK) and Bespak (Norfolk, UK). Mr De Leeuw obtained his MSc Biopharmaceutical sciences at Leiden University (the Netherlands), focusing on polymeric drug delivery systems for formulation of proteins and peptides. His research there combined pharmaceutical technology and pharmacology in industry-sponsored projects.

ONdrugDELIVERY

EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
Aug 2020	Industrialising Drug Delivery	PASSED
Sept 2020	Wearable Injectors	Aug 21, 2020
Sept/Oct 2020	**NEW TOPIC – INAUGURAL ISSUE!** Drug Delivery & Enviromental Sustainability	Sep 10, 2020
Oct 2020	Prefilled Syringes & Injection Devices	Sep 24, 2020
Nov 2020	Pulmonary & Nasal Drug Delivery	Oct 8, 2020
Dec 2020	Connecting Drug Delivery	Nov 5, 2020
Jan 2021	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 3, 2020
Jan/Feb 2021	Prefilled Syringes & Injection Devices	Dec 17, 2020
Feb 2021	Novel Oral Delivery Systems	Jan 7, 2021
Mar 2021	Ophthalmic Drug Delivery	Feb 4, 2021
Apr 2021	Pulmonary & Nasal Drug Delivery	Mar 4, 2021
May 2021	Delivering Injectables: Devices & Formulations	Apr 1, 2021
Jun 2021	Connecting Drug Delivery	May 6, 2021
Jul 2021	Novel Oral Delivery Systems	Jun 3, 2021

OPTICORE™: A FIRST-IN-CLASS COLONIC TARGETING TECHNOLOGY

In this article, Felipe Varum, PhD, Senior Project Lead, Pharmaceutical Development, and Roberto Bravo, PhD, Head Pharmaceutical Development – both of Tillotts – and Abdul Basit, PhD, Professor of Pharmaceutics at UCL School of Pharmacy, discuss the use of colonic targeting coating technology OPTICORE™ to deliver APIs in the treatment of ulcerative colitis (UC) patients.

The large intestine remains a relatively unexplored part of the gastro-intestinal (GI) tract in terms of drug delivery. Despite several physiological challenges that need to be overcome, it offers significant and attractive possibilities for drug product manufacturers. Delaying drug release serves multiple purposes, including protection of acid-labile drugs and protection of the stomach from irritating compounds.

Moreover, colonic targeting opens new avenues for delivery and systemic absorption of molecules that undergo degradation and/or are poorly absorbed in the upper GI tract.[1] This is due to the low levels of luminal and mucosal metabolic enzymes found in the colon, in comparison with the small intestine,[2,3] and drugs which are substrates for intestinal cytochrome P450 enzymes (CYPs) and efflux transporters.[4,5]

Targeting the distal part of the gut relies almost exclusively on enteric coatings (pH-sensitive polymers) based on Eudragit® S100, Eudragit® L100 (Evonik) or mixtures thereof. A range of successful drug products employing enteric coatings are available as first-line treatments for mild-to-moderate inflammatory bowel disease conditions such as UC, Crohn's disease and microscopic colitis. They include: Asacol™/Octasa®/Asacolon™/Fivasa™ (mesalazine; Tillotts Pharma/Allergan), Mezavant®/Lialda® (mesalazine; Cosmo Pharmaceuticals) and Entocort™ (budesonide, Tillotts Pharma).

> "To allow complete drug release in the colon, accurate targeting and rapid coating dissolution is paramount to ensure effective delivery."

THE CHALLENGE

Dissolution of oral dosage forms coated with enteric polymers relies on pH gradients along the GI tract, which, along with other physiological characteristics, exhibit significant inter- and intra-individual variability. GI pH sharply increases from the stomach to the duodenum and

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then gradually increases until the distal small intestine.

However, a luminal pH drop occurs at the ileocaecal junction due to the production of short chain fatty acids by colonic microbiota. This halts the pH increases observed in the small bowel, and results in challenges to the triggering of pH-sensitive dissolution systems in the colon. To allow complete drug release in the colon, accurate targeting and rapid coating dissolution is paramount to ensure effective delivery, even under challenging conditions of rapid transit time and significant pH drop in the colon – as often seen in patients with UC.[6]

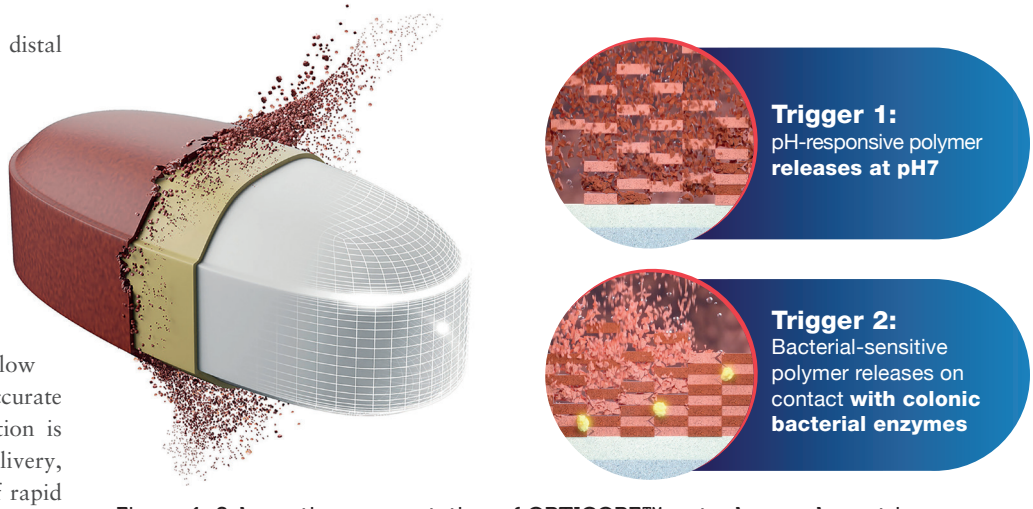

Figure 1: Schematic representation of OPTICORE™ outer layer release triggers.

A NOVEL SOLUTION

OPTICORE™ is a first-in-class validated colonic targeting coating technology.[7] It comprises two trigger systems (pH and bacterial enzymes) enabled by the incorporation of Intract Pharma's Phloral® in the outer layer (Figure 1). There is also an inner layer promoting release acceleration.

The inner layer of OPTICORE™ builds on the benefits of the Duocoat® technology (Evonik) in accelerating drug release from enteric coated dosage forms.[8,9] This layer is composed of a partially neutralised enteric polymer with a buffer salt (Figure 2). The high pH, buffer capacity and ionic strength promotes an active acceleration of the dissolution of the enteric polymer in the outer layer as soon as one of the release triggers is initiated (fail-safe feature).

> "The versatility of the OPTICORE™ technology makes it suitable for use in any type of oral solid dosage forms such as tablets, capsules or pellets."

The presence of the inner layer beneath the outer layer promotes a faster drug release from OPTICORE™ coated tablets (Figure 3) in buffer simulating the luminal composition of the terminal ileum (pH 7.4 Krebs buffer) in comparison with state-of-the art enteric coatings designed for colonic targeting (Eudragit® S, (Evonik) dissolves above pH 7).

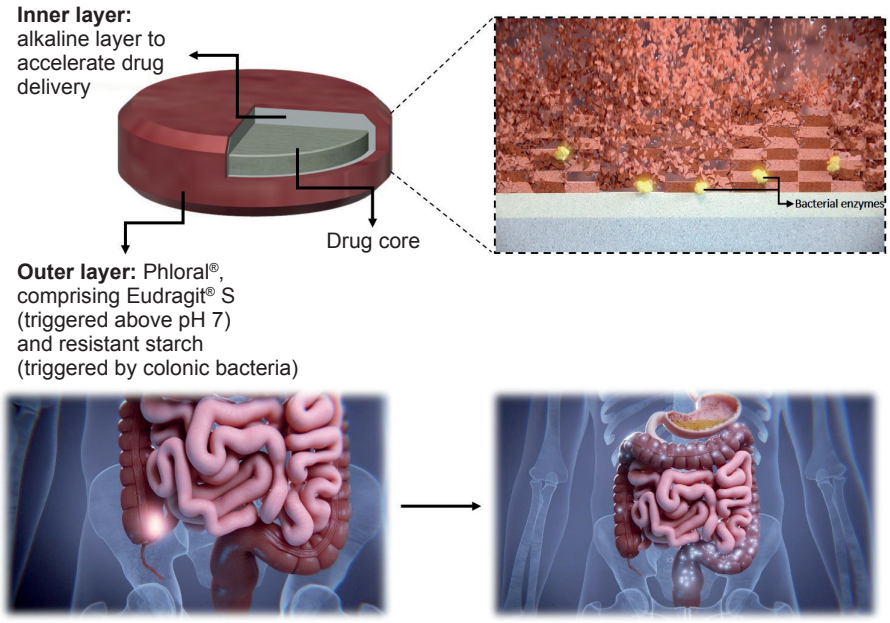

Figure 2: Schematic representation of the OPTICORE™ coating structure and tablet disintegration in the colon.[7]

The outer layer of OPTICORE™ comprises the two-trigger release technology Phloral®.[10,11,12] This combines an enteric polymer, such as Eudragit® S, which is responsible for the pH-driven dissolution, and resistant starch (Figure 2). When embedded into the outer layer coating, this polysaccharide does not dissolve or swell during transit in the upper gut and resists digestion by salivary and pancreatic enzymes.

In the large intestine, where bacterial numbers are several orders of magnitude higher than in the upper gut, resistant starch can serve as a source of energy for colonic microbiota. This allows for weakening of the coating structure, acting as a second drug release trigger, even in conditions of lower luminal colonic pH and fast transit time, as often seen in UC patients.

Below the pH trigger (pH = 7) of the enteric polymer in the outer coating, drug release from OPTICORE™ coated tablets can be initiated due to the action of bacterial enzymes (Figure 3) as shown in a model of the human colon (human faecal slurry).[7]

The combination of these features provided by the outer and inner layer allows an accurate and timely release of the API in the ileo-colonic region, making it available throughout the colon (Figure 2). The versatility of the OPTICORE™ technology makes it suitable for use in any type of oral solid dosage forms such as tablets, capsules or pellets.

Optionally, an isolation layer between the drug-containing core and the inner layer may be used, particularly if the drug is acidic, which may limit the features of the inner layer in terms of enteric polymer dissolution acceleration.

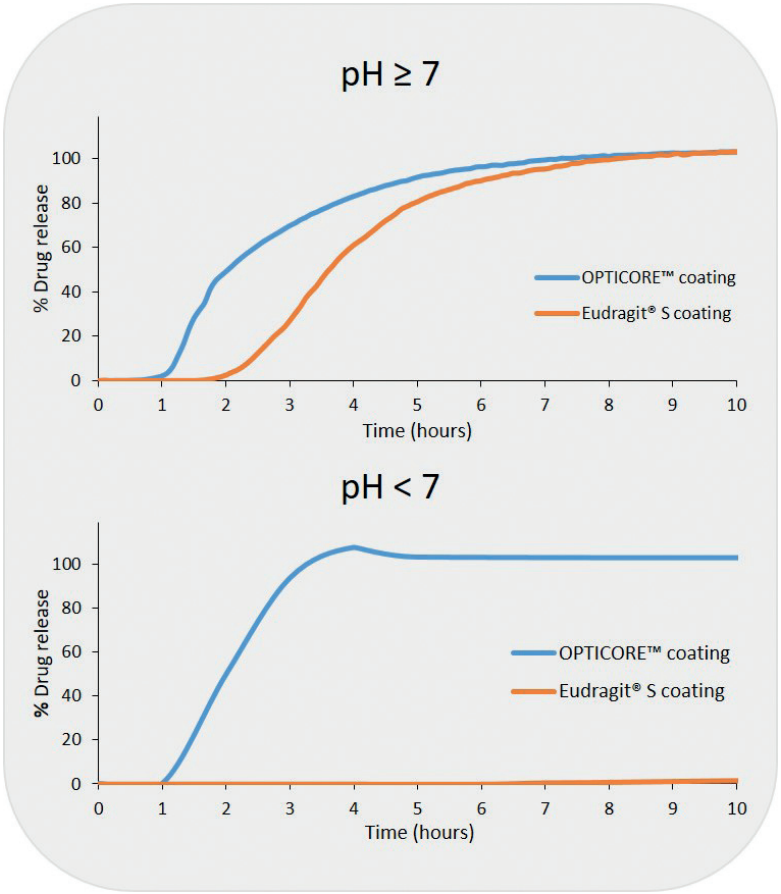

Figure 3: Drug release from OPTICORE™ coated tablets mediated by pH and by bacterial enzymes.

CLINICAL PROOF OF CONCEPT AND BENEFITS

The benefits of the dual-trigger system (Phloral®) to ensure accurate colonic targeting have been demonstrated in healthy human subjects by means of gamma-scintigraphy[10] and in *Clostridium difficile* patients who received a faecal material transplantation delivered in capsules coated with this technology.[11]

The OPTICORE™ technology has been successfully implemented in a novel mesalazine 1600 mg drug product. Gamma-scintigraphy investigations showed accurate colonic targeting in all subjects enrolled in the study (Figure 4), allowing for a distribution of the drug along the colon to ensure sufficient local concentrations, both in healthy subjects and in mild-to-moderate UC patients.

OPTICORE™ coated 1600 mg tablets successfully met the primary clinical endpoints (clinical and endoscopic remission) of the largest mesalazine induction therapy Phase III study incorporating central reading.[13] The first drug product developed based on the OPTICORE™ technology is now available from Tillotts Pharma for treating UC patients in multiple markets under the brands Asacol™ 1600, Octasa™ 1600, Yaldigo™ 1600 and Asacolon™ 1600.

> "OPTICORE™ coating technology offers significant advantages, particularly for accurate drug delivery in the colon of UC patients, even when using single-unit dosage forms, such as tablets."

CONCLUSIONS

OPTICORE™ coating technology was successfully developed by combining an alkaline inner layer with an outer enteric layer embedded with pH and enzymatic triggers. The inclusion of resistant starch to the Eudragit® S coating formulation does not impact coating robustness and the enteric properties, but is designed to allow an accelerated drug release when the pH of the luminal fluid is above seven (as in Krebs buffer pH 7.4) or below seven (as in pH 6.8 human faecal slurry). Therefore, OPTICORE™ coating technology offers significant advantages, particularly for accurate drug delivery in the colon of UC patients, even when using single-unit dosage forms, such as tablets.

ABOUT THE COMPANY

Tillotts Pharma is an international specialty pharmaceutical company with more than 300 employees in Switzerland and around the world. It markets its own products – such as Asacol™ and Entocort™ – as well as in-licensed products in around 65 countries through its affiliates within Europe and a network of gastroenterology-focused partners throughout the world. Tillotts has been part of the Japanese Zeria Group since 2009.

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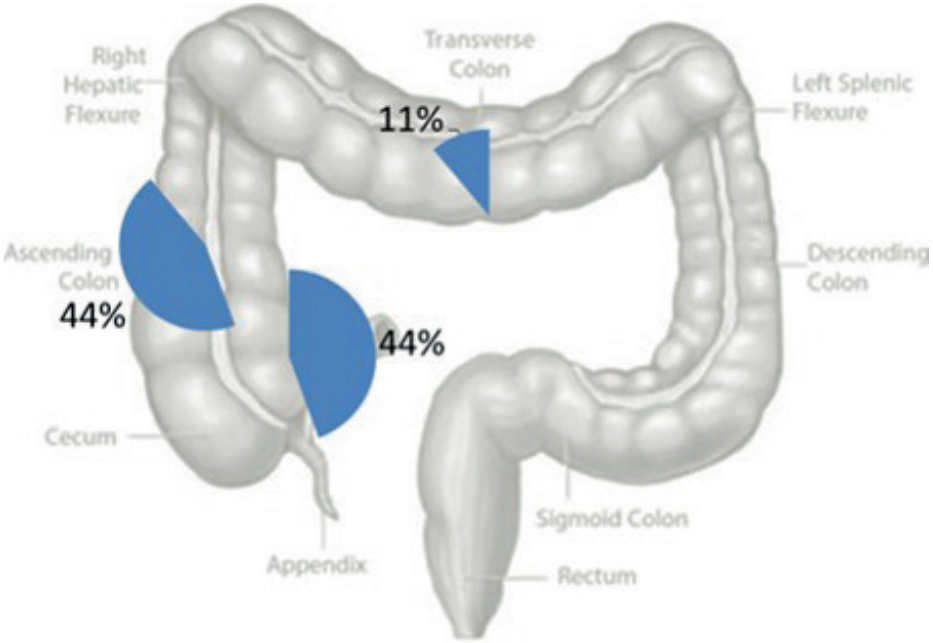

Figure 4: Representation of OPTICORE coated tablets' disintegration locations within the large intestine in human volunteers (followed by gamma-scintigraphy).

The **UCL School of Pharmacy** is one of the most highly rated pharmacy schools in the UK. It has more than 175 years of experience and tradition, throughout which it has retained its identity as a specialist institution dedicated to teaching and research in pharmacy and the pharmaceutical sciences. The UCL School of Pharmacy is currently rated fifth in the world by QS Rankings (Pharmacy and Pharmacology) as well as 10th in the Shanghai Ranking (Pharmacy and Pharmaceutical Science).

REFERENCES

1. *Lee SH et al, "Strategic approaches for colon targeted drug delivery". Pharmaceutics, 2020, Vol 12(1), pp 68.*
2. *Yadav V et al, "Gastrointestinal stability of therapeutic anti-TNF α IgG1 monoclonal antibodies". Int J Pharm, 2016, Vol 502 (1–2), pp 181–187.*
3. *Bak A et al, "Local delivery of macromolecules to treat diseases associated with the colon". Adv Drug Deliv Rev, 2018, Vol 136–137, pp 2–27.*
4. *Tubic-Grozdanis M et al, "Pharmacokinetics of the CYP 3A substrate simvastatin following administration of delayed versus immediate release oral dosage forms". Pharm Res, 2008, Vol 25 (7), pp 1591–1600.*
5. *McConnell EL et al, "Colonic treatments and targets: issues and opportunities". J Drug Target, 2009, Vol 17 (5), pp 335–363.*
6. *Fallingborg J et al, "Very low intraluminal colonic pH in patients with active ulcerative colitis". Dig Dis Sci, 1993, Vol 38 (11), pp 1989–1993.*
7. *Varum F et al, "OPTICORE™, an innovative and accurate colonic targeting technology". Int J Pharm, 2020, Vol 583, pp 119372.*
8. *Liu F et al, "A novel double-coating approach for improved pH-triggered delivery to the ileo-colonic region of the gastrointestinal tract". Eur J Pharm Biopharm, 2010, Vol 74 (2), pp 311–315.*
9. *Varum F et al, "A novel coating concept for ileo-colonic drug targeting: proof of concept in humans using scintigraphy". Eur J Pharm Biopharm, 2013, Vol 84 (3), pp 573–577.*
10. *Ibekwe VC et al, "A new concept in colonic drug targeting: a combined pH-responsive and bacterially-triggered drug delivery technology". Aliment Pharmacol Ther, 2008, Vol 28 (7), 911–916.*
11. *Allegretti JR et al, "Fecal microbiota transplantation capsules with targeted colonic versus gastric delivery in recurrent Clostridium difficile Infection: A comparative cohort analysis of high and low dose". Dig Dis Sci, 2019, Vol 64 (6), pp 1672-1678.*
12. *Varum F et al, "A dual pH and microbiota-triggered coating (PhloralTM) for fail-safe colonic drug release". Int J Pharm, 2020, Vol 583, pp 119379.*
13. *D'Haens GR et al, "Randomised non-inferiority trial: 1600 mg versus 400 mg tablets of mesalazine for the treatment of mild-to-moderate ulcerative colitis". Aliment Pharmacol Ther, 2017, Vol 46 (3), pp 292–302.*

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Roberto Bravo, PhD, is Head of Pharmaceutical Development at Tillotts Pharma. He leads a team of project leaders and scientists responsible for the development of new drug products for the effective treatment of inflammatory bowel diseases. Prior to Tillotts Pharma, Dr Bravo's career started 20 years ago, when he joined F Hoffmann-La Roche and thereafter Actelion Pharmaceuticals, engaged in the physicochemical characterisation of new active compounds and in formulations to improve their oral bioavailability.

Abdul Basit, PhD, holds the position of Professor of Pharmaceutics at the UCL School of Pharmacy. He is a leading authority on oral drug delivery, digital health and innovative pharmaceutical technologies, including 3D printing. Professor Basit is a world authority on translational research; he has founded two spin-out companies (FabRx and Intract Pharma) and has invented several drug products that have entered the clinic.

INNOVATIONS IN 3D PRINTED PHARMACEUTICALS

In this article, Sarah Trenfield, PhD Researcher at University College London (UCL); Abdul Basit, PhD, Professor of Pharmaceutics at UCL and Co-Founder of FabRx; and Alvaro Goyanes, PhD, Co-Founder and Director of Development at FabRx, discuss the latest innovations in 3D printed pharmaceuticals.

Three-dimensional (3D) printing is causing a paradigm shift in the way medicines are designed, manufactured and administered. Conventional pharmaceutical manufacturing processes were first introduced around 200 years ago and, despite the significant technological advancements made so far during the 21st century, many of these are still in use today.

Although these methods are cost-effective for large-scale production, they can be inherently time-consuming, labour intensive and dose inflexible. This poses significant challenges for those patient groups that require tailored dosing (such as within paediatrics and geriatrics) or for certain medicines that require frequent dose adjustments based on blood levels (e.g. narrow therapeutic index drugs).

This often requires patients to split or crush and weigh formulations or pharmacists to extemporaneously prepare the formulations in hospitals, to achieve the correct dose – increasing the risk of medication error and inconsistency. To overcome these challenges, in recent years there has been a considerable push to move away from treating patients via a "one-size-fits-all" approach. Crucially, a report from NHS England (UK) showed that up to 70% of patients do not gain efficacy from the traditional mass manufacturing approaches.[1]

To achieve greater efficacy, the use of innovative technologies is required within pharmaceuticals to facilitate the production of small-scale, dose-flexible formulations. One technology which has great potential here is 3D printing – an additive manufacturing process enabling the design of

> "The use of innovative technologies is required within pharmaceuticals to facilitate the production of small-scale, dose-flexible formulations."

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Figure 1: FabRx's M3DIMAKER™ 3D printing technology for personalised medicine production.

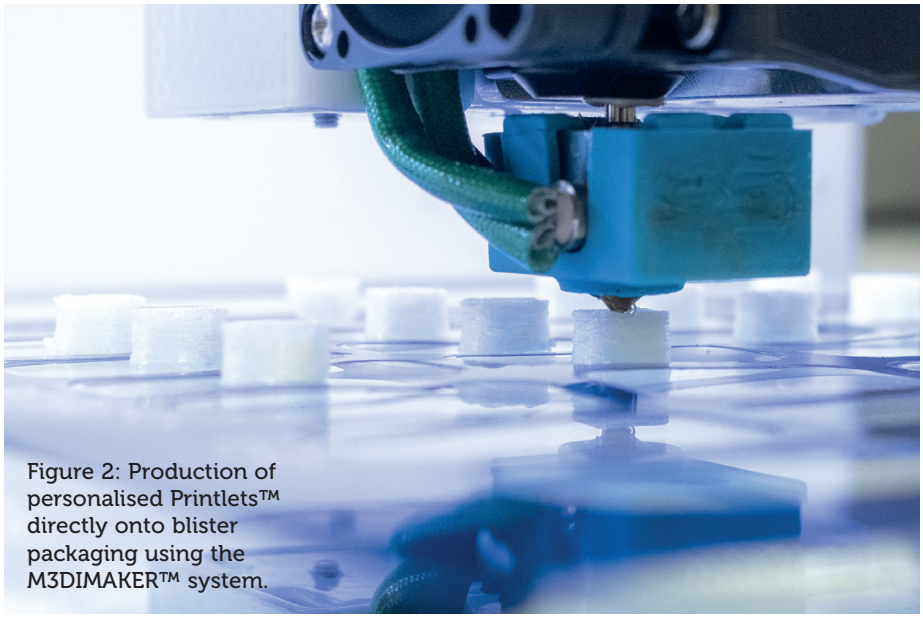


Figure 2: Production of personalised Printlets™ directly onto blister packaging using the M3DIMAKER™ system.

oral dosage forms using computer-aided design (CAD) software for the on-demand, layer-by-layer production of Printlets™ (3D printed tablets).[2,3]

Over the last seven years, FabRx has pioneered the use of 3D printing technologies for the production of personalised pharmaceuticals and medical devices, with a vision to revolutionise the way tablets are manufactured – moving away from a one-size-fits-all approach towards the production of personalised medicines at the point of care.

In 2020, FabRx launched the world's first 3D printer for personalised medicines (M3DIMAKER™) which is designed for the small-batch production of highly flexible drug products (tailored dosages, drug release, geometries and multiple drugs) to provide a truly personalised approach for patient care. Indeed, the M3DIMAKER™ platform could be used throughout the drug development timeline, ranging from research and development, preclinical studies, and first-in-human (FIH) clinical trials all the way through to front-line medical care.

M3DIMAKER™: FABRX'S PHARMACEUTICAL 3D PRINTER

FabRx's breakthrough 3D printer, the M3DIMAKER™, aims to deliver unique personalised medicines with appearance and dosages that can be tailored directly to the patient on demand (Figure 1).[4] The groundbreaking additive manufacturing technology can produce Printlets™ with a precise dose and tailored drug release – and can even combine multiple medications into a single "polypill" for patients with complicated medication regimens.

The M3DIMAKER™ consists of a sleek hardware system that is controlled by specialised user-friendly software, enabling the required dose to be easily selected by the pharmacist or user to achieve the needs of the patient or research outcome (Figure 2).

The key features of FabRx's M3DIMAKER™ technology include:

- User-friendly software – FabRx's specialised software enables the required dose to be easily printed by the pharmacist or user according to the needs of the patient or research aims.
- Multi-nozzle printing system – the M3DIMAKER™ is an alternating nozzle system, giving users the choice between three different extrusion printing nozzles and so allowing the user to easily adapt the system to their manufacturing needs.
- Able to be validated to GMP – the M3DIMAKER™ has been developed in close communication with regulatory agencies (e.g. the UK MHRA, the Spanish AEMPS, the US FDA and the EU EMA) and hospital end users in order to create a system that is fit for purpose.[5] Due to the hardware design and materials used in production, the M3DIMAKER™ is able to be validated to GMP requirements for research and clinical manufacture.
- Assured quality control and security – the system is fitted with advanced in-line quality control and security measures, alongside camera monitoring of the printing process, to track the progress and detect any faults during manufacture. Incorporation of a modern fingerprint access control alongside a data matrix reader ensures manufacturing reliability, enabling only qualified personnel to have access to the technology's features.
- High throughput and low wastage – the preparation of one-month's medication (28 Printlets™) can be carried out in approximately eight minutes, revolutionising the drug manufacture timeline.
- Compact and versatile – as the printer is compact (bench-top size) and easily portable, an on-demand manufacture of pharmaceuticals in a wide variety of settings (research, clinical trials and within clinical settings) can be achieved.
- Affordable cost – the M3DIMAKER™ has been designed with the budgets of the end users in mind, providing a cost-effective approach to small-batch manufacture.

The M3DIMAKER™ system can formulate a wide variety of drugs, ranging from small molecule compounds through to large molecules and biologics, including antibodies. These advantages could benefit clinical practice, specials manufacturing companies and pharmaceutical companies seeking to deliver their active in a personalised and more cost-effective manner. Using the FabRx M3DIMAKER™, the drug products produced may generate increased revenue due to enhanced medication adherence and improved efficacy and safety profiles, as well as increased product margins via premium pricing.

"The M3DIMAKER™ system can formulate a wide variety of drugs, ranging from small molecule compounds through to large molecules and biologics, including antibodies."

WORLD FIRST CLINICAL STUDY

As a world first, FabRx's personalised medicine 3D printer was integrated into a hospital setting to treat children (3–16 years) with a severe metabolic disorder – maple syrup urine disease (MSUD).[6] The first-line therapy for MSUD involves the personalised oral supplementation of isoleucine; the dose of which is tailored according to blood levels. In current clinical practice, however, practitioners are required to extemporaneously prepare formulations (via weighing powder and manually filling capsules) due to the lack of commercially available oral treatments for MSUD.

To overcome these challenges, FabRx's 3D printer was integrated into the pharmacy department of the University Clinical Hospital in Santiago de Compostela (Spain). This innovation enabled the production of chewable and palatable Printlets™ containing isoleucine in a variety of dosages, colours and flavours (Figure 3), which were evaluated for patient acceptability and therapy control. The researchers found that 3D printing enabled tighter control over target blood concentrations compared with the standard therapy (capsules) – and that the flavours and colours of the 3D printed dosage forms were well accepted amongst all patients.

This study was a significant milestone in 3D printing history and demonstrated the true benefits of such technology in the pharmaceutical arena.

OTHER FABRX 3D PRINTING TECHNOLOGIES

Alongside the M3DIMAKER™, FabRx has extensive experience in formulation development and a wide range of 3D printing technologies, including fused deposition modelling (FDM), selective laser sintering (SLS) and stereolithography (SLA). FDM is an extrusion-based technology which has the capability to manufacture multiple-drug combinations (polypills) as well as sustained- or delayed-release tablets. SLS incorporates a laser which is used to create drug-loaded Printlets™ with various characteristics, ranging from orodispersible to controlled-release dosage forms.[7] To manufacture sustained-release medical devices and drug-loaded Printlets™, FabRx can use SLA 3D printing, which is capable of using a light to transform a liquid into solid parts.

Furthermore, in 2019, FabRx developed a revolutionary new 3D printing system for the production of pharmaceuticals. The novel printing system, known as direct powder extrusion (DPE), enables the production of drug products in a single-step process directly from powdered materials – avoiding the time-consuming steps usually required to produce 3D printer filament feedstock used in FDM printing.[8] This technology enables flexible and tailored dosing with minimal development times, showing promise in the field of preclinical studies or early phase clinical trials.

"The benefits of 3D printing could also have a wide-reaching impact on global health."

LATEST INNOVATIONS IN 3D PRINTED MEDICINES

Due to the highly flexible nature of 3D printing processes, this technology enables the generation of drug products that would be impossible to produce using conventional manufacturing processes. For example, using SLS, the University College London (UCL) and FabRx team was able to produce orodispersible Printlets™ that were designed to have Braille and Moon patterns on the surface, providing an innovative and practical medicine strategy for patients with visual impairment (Table 1).[9]

In particular, Printlets™ with different shapes were fabricated to offer additional information, such as the medication indication or its dosing regimen. Despite the presence of the patterns, the Printlets™ were found to retain their original mechanical properties and dissolution characteristics and disintegrated within approximately five seconds, avoiding the need for water and facilitating self-administration of medications. Such a concept could revolutionise medicine taking for patients with visual impairment, e.g. by reducing medication errors and supporting increased independence.

The benefits of 3D printing could also have a wide-reaching impact on global health, tackling the challenges arising from opioid abuse. The UCL and FabRx team, in collaboration with Nisso Chemical Europe (Düsseldorf, Germany), devised a

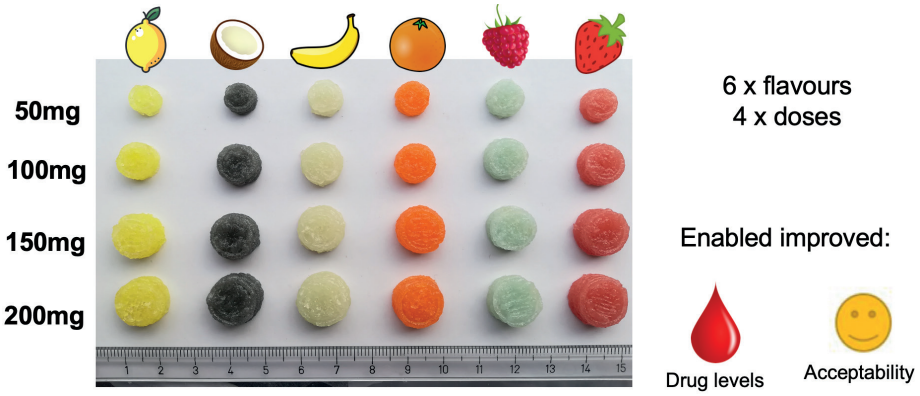


Figure 3: FabRx formulations used in a clinical study for the treatment of children with a severe metabolic disease – MSUD.

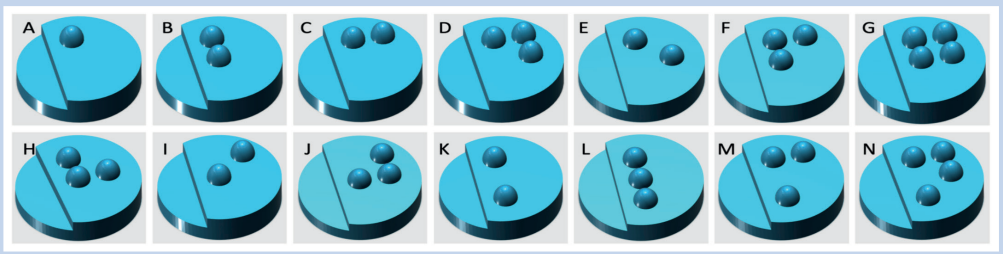
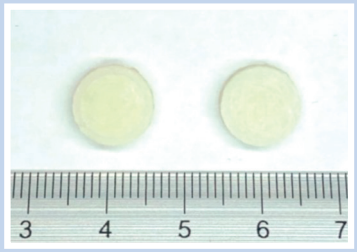
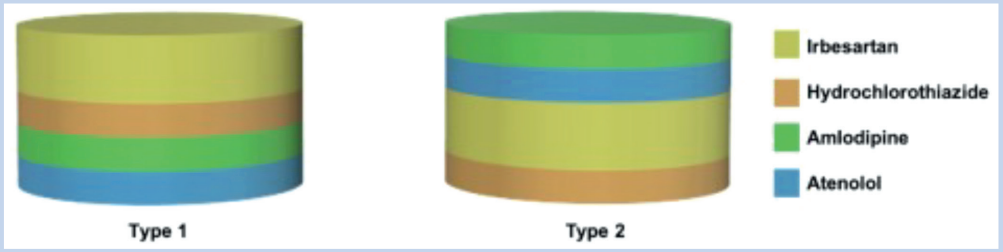
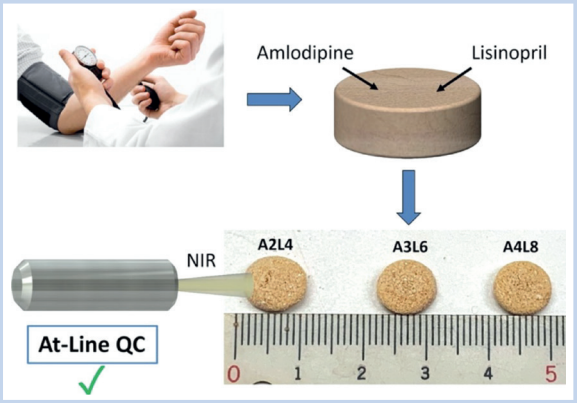
Description	Image	Reference
3D printed tablets with Braille and Moon patterns for visual impairment		9
3D printed tablets with opioid abuse-deterrent properties		10
Four layered polypill in two conformations		12
Dose verification of 3D printed antihypertensive polypills		13

Table 1: Novel applications of 3D printing using FabRx 3D printing technologies.

novel formulation strategy whereby abuse-deterrent 3D printed formulations were produced using DPE, a technology devised by FabRx (Table 1). In this study, DPE enabled the production of modified-release drug products containing tramadol in a single-step process directly from powdered materials.[10] This technology was capable of preparing drug products with both alcohol-resistant and abuse-deterrent properties, offering a novel approach for the safe and effective use of opioids.

3D printing could also be useful for patients who are prescribed complex medication regimes, such as in the case of polypharmacy – the administration of more than one medicine – which can lead to confusion and errors in medication management. FabRx has used SLA to print multiple drugs into the same dosage form to create 3D printed polypills (aka polyPrintlets™).[11]

As an example, four different drugs were printed in two multi-layered configurations, reducing the number of tablets from four a day to just one (Table 1).[12] In another study, the team produced antihypertensive polyPrintlets™ using SLS containing personalised dosages of two drugs (amlodipine and lisinopril) which then underwent a real-time quality control process using spectroscopic methods to confirm the dosage of the APIs within the formulation.[13] Such a concept revolutionises the capability for on-demand quality control and dispensing of 3D printed dosage forms at the point of care.

CONCLUSION

The potential for 3D printing to transform pharmaceutical practice is evident. Indeed, 3D printing systems can revolutionise formulation production to move away from mass manufacture to the production of highly flexible and personalised dosage forms on demand, providing benefits from research and development through to clinical care. The April 2020 launch of the world's first personalised medicine 3D printer, FabRx M3DIMAKER™, is a significant milestone in

the history of this technology, and is driving forward the use of 3D printing technologies in pharmaceuticals to make treatments safer and more effective for patients around the world.

ABOUT THE COMPANY

FabRx was established in 2014 by leading academics from UCL and is experienced in the application of 3D printing technology for medicines and medical devices. Since its initiation, FabRx has developed more than seven different types of pharmaceutical 3D printers and, in 2017, won the TCT Best Start Up Award. In 2018, FabRx was awarded a grant totalling nearly £1 million from Innovate UK to develop the world's first personalised medicine 3D printer (M3DIMAKER™) and conducted a world first clinical study using its Printlets™ technology in 2019.

REFERENCES

1. *"Improving Outcomes Through Personalised Medicine". NHS, September 7, 2016.*
2. *Trenfield SJ, Awad A, Madla CM, Hatton GB, Firth J, Goyanes A, Gaisford S, Basit AW, "Shaping the future: recent advances of 3D printing in drug delivery and healthcare". Expert Opin Drug Deliv, 2019, Vol 16, pp 1081-1094.*
3. *Basit A, Gaisford S, "3D Printing of Pharmaceuticals". Springer International Publishing, 2018.*
4. *"FabRx's pharmaceutical 3D printer for personalised medicines, M3DIMAKER™, is now available!". Press Release, FabRx, April 6, 2020.*
5. *"FabRx meet with the MHRA and AEMPS to discuss 3D printing for personalised medicines". Press Release, FabRx, April 11, 2019.*
6. *Goyanes A, Madla CM, Umerji A, Duran Piñeiro G, Giraldez Montero JM, Lamas Diaz MJ, Gonzalez Barcia M, Taherali F, Sánchez-Pintos P, Couce ML, Gaisford S, Basit AW, "Automated therapy preparation of isoleucine formulations using 3D printing for the treatment of MSUD: First single-centre, prospective, crossover study in patients". Int J Pharm, 2019, Vol 567, 118497.*
7. *Allahham N, Fina F, Marcuta C, Kraschew L, Mohr W, Gaisford S, Basit WA, Goyanes A, "Selective Laser Sintering 3D Printing of Orally Disintegrating Printlets™ Containing Ondansetron". Pharmaceutics, 2020, Vol 12 (2), pp 110.*
8. *Goyanes A, Allahham N, Trenfield SJ, Stoyanov E, Gaisford S, Basit AW, "Direct powder extrusion 3D printing: Fabrication of drug products using a novel single-step process". Int J Pharm, 2019, Vol 567, 118471.*
9. *Awad A, Yao A, Trenfield SJ, Goyanes A, Gaisford S, Basit WA, "3D Printed Tablets (Printlets™) with Braille and Moon Patterns for Visually Impaired Patients". Pharmaceutics, 2020, Vol 12, pp 172.*
10. *Ong JJ, Awad A, Martorana A, Gaisford S, Stoyanov E, Basit AW, Goyanes A, "3D printed opioid medicines with alcohol-resistant and abuse-deterrent properties". Int J Pharm, 2020, Vol 579, 119169.*
11. *Robles-Martinez P, Xu X, Trenfield JS, Awad A, Goyanes A, Telford R, Basit WA, Gaisford S, "3D Printing of a Multi-Layered Polypill Containing Six Drugs Using a Novel Stereolithographic Method". Pharmaceutics, 2019, Vol 11 (6), pp 274.*
12. *Xu X, Robles-Martinez P, Madla CM, Joubert F, Goyanes A, Basit AW, Gaisford S, "Stereolithography (SLA) 3D printing of an antihypertensive polyprintlet: Case study of an unexpected photopolymer-drug reaction." Additive Manufacturing, 2020, Vol 33, 101071.*
13. *Trenfield SJ, Tan HX, Goyanes A, Wilsdon D, Rowland M, Gaisford S, Basit AW, "Non-destructive dose verification of two drugs within 3D printed polyprintlets". Int J Pharm, 2020, Vol 577, 119066.*

ABOUT THE AUTHORS

Sarah Trenfield is a PhD Researcher at UCL specialising in developing 3D printed technology for pharmaceuticals. She qualified with a first-class Pharmacy degree from Cardiff University in 2015 and undertook her pre-registration year at Merck Sharpe and Dohme. In 2016, Ms Trenfield successfully registered as a Pharmacist and began studying for her PhD on 3D printed medicines. Since then, she has authored more than 21 publications on the topic and has received a number of prestigious awards.

Abdul Basit holds the position of Professor of Pharmaceutics at the UCL School of Pharmacy. He is a leading authority on oral drug delivery, digital health and innovative pharmaceutical technologies including 3D printing. Professor Basit is also a world authority on translational research; he has founded two spin-out companies (FabRx and Intract Pharma) and has invented several drug products that have entered the clinic.

Alvaro Goyanes is the Co-Founder and Development Director at FabRx, as well as an honorary lecturer at UCL and a lecturer at the University of Santiago de Compostela (Spain). He was one of the first researchers assessing opportunities of 3D printing to manufacture personalised oral dosage forms and medical devices. Dr Goyanes is a recognised world expert in the 3D printing of medicines and has worked as a Registered Pharmacist so has first-hand knowledge of pharmaceutical needs in clinical settings.

RECENT DEVELOPMENT IN COMPLEX TABLET FORMULATION DESIGN FOR VERSATILE APPLICATIONS

In this article, Mathieu Degomme, PharmD, Pharmaceutical Development Project Manager, and Aline Moulin, PhD, Pharmaceutical Development Director, both of Skyepharma, outline three case studies from recent early-stage development programmes to illustrate what kind of complex tablets can be developed to meet specific target dissolution profiles for versatile applications.

Recent research in pharmaceutical science has mainly been concentrated on improving the administration of drugs that are already recognised as offering therapeutic advantages rather than on developing new pharmacologically active molecules – because such an approach requires less investment, reduces the time to market and produces results that are nearly always valuable.[1]

Indeed, to have the targeted therapeutic impact, a drug must be biologically available and reach the circulatory system in effective concentrations. Such concentrations must be maintained – if possible, without excessive fluctuation – for long enough to allow the drug to be distributed to all target tissues and organs before it is eliminated.[2,3]

Modified-release (MR) drug delivery systems are developed to modulate the apparent absorption and/or alter the site of release of drugs, in order to achieve specific clinical objectives that cannot be attained with conventional dosage forms.[4,5] Possible therapeutic benefits of a properly designed MR dosage form include improved efficacy and reduced adverse events, increased convenience and patient compliance, optimised performance, and a greater selectivity of activity or new indications. A clinically successful MR product with enhanced medical benefits also offers commercial advantages, such as product differentiation and/or line extension, maximised drug potential and market expansion, and increased cost effectiveness.

> "The bioavailability of a drug depends on the quantity and the rate at which it reaches the systemic circulation."

The bioavailability of a drug depends on the quantity and the rate at which it reaches the systemic circulation. If there are no problems with its absorption – or if there is no accumulation of the drug – then its bioavailability can be regulated by controlling the release kinetics from the dosage form.

With the use of drug delivery systems, it is possible to modulate the drug release rate so as to control the following factors:

- The rate of uptake through the gastro-intestinal (GI) tract into the bloodstream
- The plasma concentration
- The maintenance of plasma concentration levels, hence efficacy and duration of action.

Thus, depending on the duration of action required, controlled drug delivery systems can convey greater quantities of drugs than conventional pharmaceutical dosage forms for prolonged therapeutic efficacy.

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"Depending on the duration of action required, controlled drug delivery systems can convey greater quantities of drugs than conventional pharmaceutical dosage forms for prolonged therapeutic efficacy."

Different case studies from recent early-stage development programmes will be reported in this section to illustrate what kind of complex tablets can be developed to meet specific target dissolution profiles for versatile applications.

CASE STUDY ONE

The target product profile defined with our partner for this first case study was to maintain the plasmatic concentration of the API above a defined target over a 12-hour period, to limit the tablet intake to two per day.

We used Geomatrix® tablet technology. The tablets are made of three layers that have specific functionalities:

- The fast-release layer will behave similarly to an immediate-release tablet
- The slow-release layer will delay the release of the amount of API it contains through a swelling effect
- The dissolution profile of the slow-release layer is also controlled by a third layer – the inactive layer which reduces slow-release layer exposure to the dissolution media.

This technology allows us to target a wide range of drug-release profiles and plasmatic concentration to be maintained as needed. For this project, the targeted *in vitro* dissolution profile – Geomatrix® sustained release – was defined as shown in Figure 1.

As slow-release layer behaviour is impacted by the tablet design (size, shape), excipients (type, amounts, viscosity grades) and process parameter, a wide range of parameters have been studied as well as their impact on dissolution profiles. Different profiles were obtained, thus demonstrating the versatility of the Geomatrix® technology for the obtention

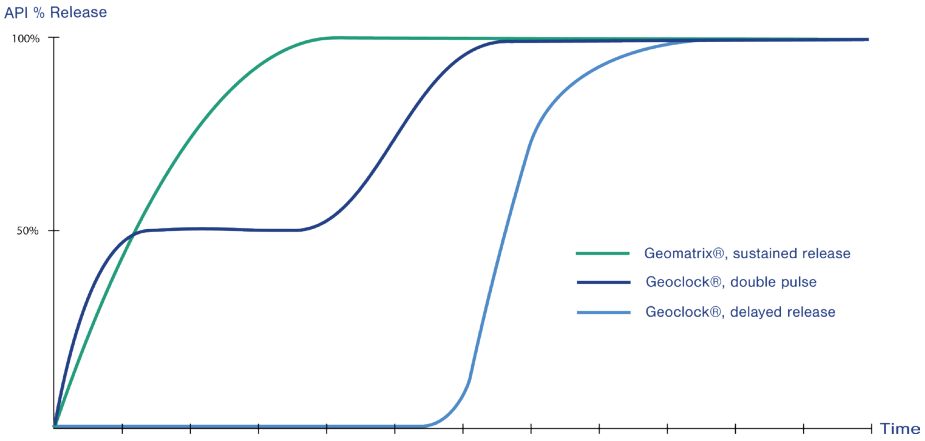

Figure 1: Examples of dissolution profiles obtained with Geomatrix® and Geoclock® technologies.

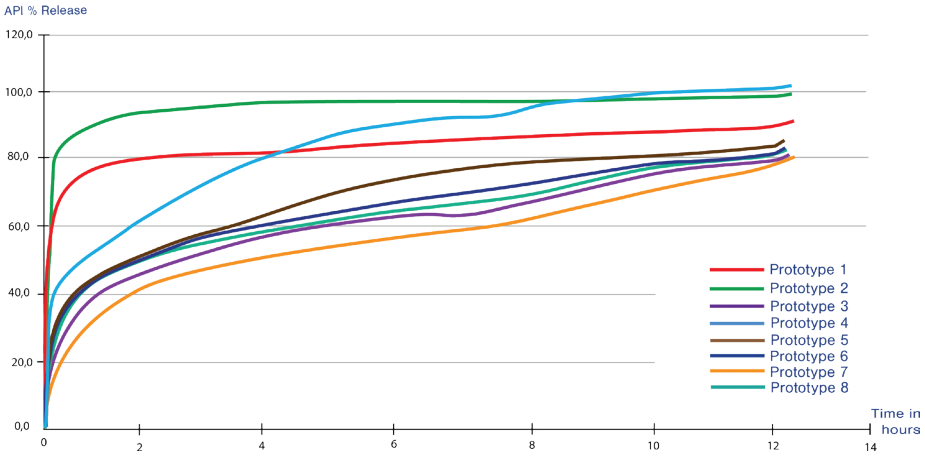

Figure 2: Dissolution profiles obtained for the different Geomatrix® prototypes.

of sustained-release profiles, as illustrated in Figure 2. In this particular case study, our partner chose three prototypes with significantly different profiles for further preliminary clinical evaluation.

Slow-release layer behaviour can also be impacted by pH conditions. Specific pH dependent excipients can thus be chosen to reduce pH impact on drug-release profiles, and Geomatrix® tablets can, at the end, be film coated to target a specific GI area and enable potential API absorption.

CASE STUDY TWO

The target product profile defined for this project was to block the API release during three hours after the tablet intake, and release the API as fast as possible after this lag time (dissolution profile similar to an immediate-release tablet as soon as the API release begins). For this project, we decided to use Geoclock® simple pulse tablets.

Geoclock® simple pulse tablets are made from a core tablet containing the API, and an inactive layer applied by press coating. The inactive surrounding layer will provide a delayed-release effect by delaying the core water intake and the drug release during an appropriate time (from one to 10 hours). Once the water reaches the core, the swelling of this core induces outer shell breaks and the core acts as an immediate-release tablet. This phenomenon is independent from pH conditions (location in the GI tract and fed/fasted conditions). This technology is particularly appropriate for the development of tablets with APIs used in chronotherapy approaches.

As the outer shell layer behaviour – responsible for the lag time – is impacted by the tablet design (size, outer shell thickness), excipients (type, amounts, hydrophobic power) and process parameter, a wide range of parameters have been studied and their impact on dissolution profiles studied. From the different dissolution profiles obtained during the development, one was chosen as it matched the target product profile (Figure 3).

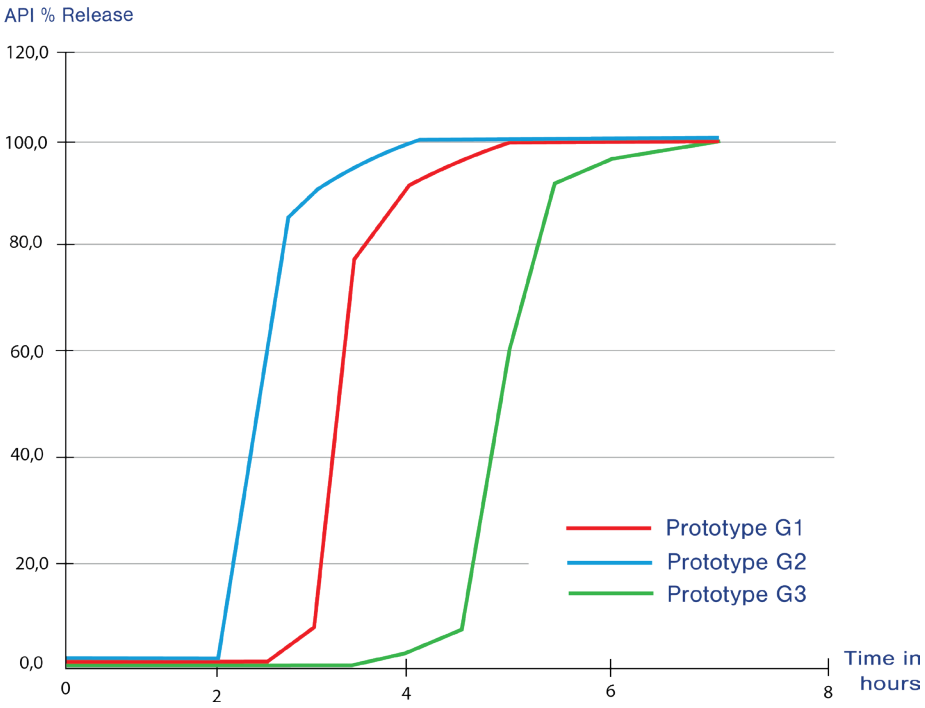

Figure 3: Dissolution profiles obtained for the different Geoclock® prototypes.

Three prototypes which allowed us to obtain the above-described dissolution profiles were selected and registered in the product NDA. Further development led to product industrial development and commercialisation in the US market.

CASE STUDY THREE

The target product profile for the third case study consisted of providing two different behaviours to a single API in one tablet. One fraction of the API needed to be released quickly, as for an immediate-release tablet. The release of the second fraction of the API needed to be delayed. This would lead to a plasmatic concentration above a defined target during 12 hours. One approach for this development was to use the Geoclock® double pulse tablets.

Geoclock® double pulse tablets are made of one core containing one API, an inactive layer applied by press coating and an immediate-release layer containing another, or the same, API, applied at the top of the press-coated tablet. This technology is appropriate in cases where the plasmatic concentration has to be maintained over time above a target by a single administration.

In vitro dissolution profiles obtained demonstrate that two pulses of API release are obtained (Figure 4). The lag time between the two pulses of release and the ratio of API between the immediate-release part and the delayed-release part can be adjusted to bring the dissolution profile to the target product profile.

Another application can be the management of two APIs in the same tablet with two different drug-release profiles. A recent development consisted of adding natural plant extracts (immediate-release profile) to a Geoclock® tablet containing another API in the core to be delayed released.

> "We were able, by playing with different types of complex tablets, to target with success a wide range of target product profiles."

CONCLUSION

The case studies presented above demonstrate that it was possible, by playing with different types of complex tablets, to target with success a wide range of target product profiles. Note that the multilayer tablets and press-coated tablets presented here are technologies that are already industrialised and manufactured currently at large scale on Skyepharma's GMP site for the European, Brazilian and US markets.

ABOUT THE COMPANY

Skyepharma is a centre of excellence for complex oral solid dosage forms. It provides solutions bringing value to its clients at any stage of a product development lifecycle, from early-stage development up to commercial manufacturing and packaging activities. Skyepharma's value proposition includes services tailored to clients' requirements, supporting them up to market for their solid dosage form projects.

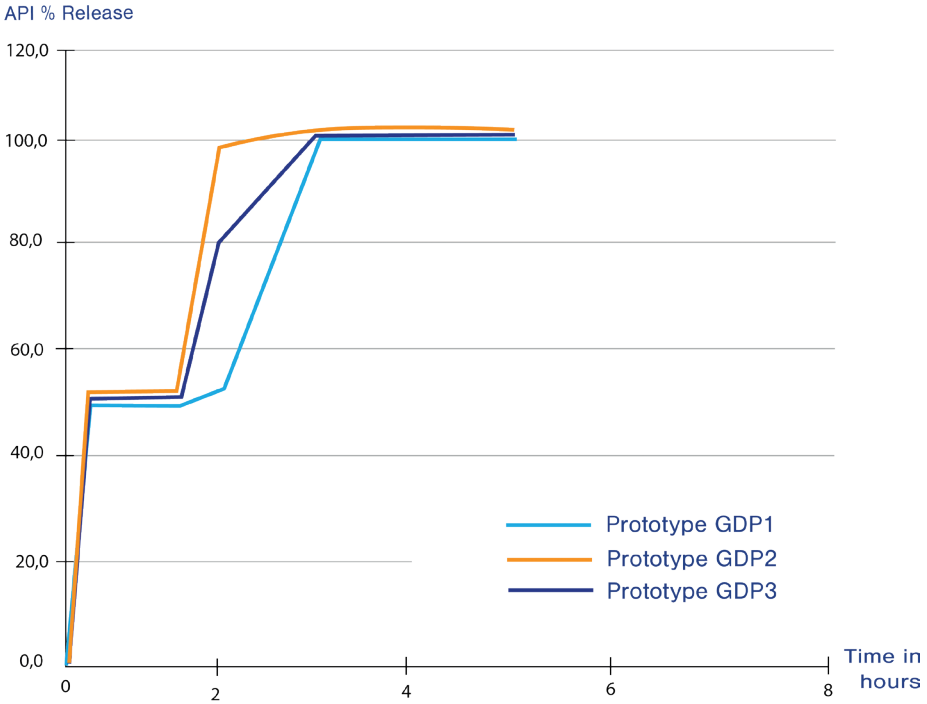

Figure 4: Dissolution profiles obtained for the different Geoclock® double pulse prototypes.

REFERENCES

1. *Qiu Y, Zhang G, "Research and Development Aspects of Oral Controlled-Release Systems" (Wise D, ed). Handbook of Pharmaceutical Controlled Release Technology, CRC Press, August 2000.*
2. *Lin S, Kawashima Y, "Current status and approaches to developing press-coated chronodelivery drug systems". J Controlled Release, 2012, Vol 157, pp 331–353.*
3. *Satani RR, Chotaliya MB, Raval MK, Sheth NR, "Review on recent trends in press-coated pulse drug delivery system". Int Bull Drug Res, 2014, Vol 4(6), pp 60–91.*
4. *Arunachalam A, Karthikeyan M, Konam K, Prasad PH, Sethuraman S, Ashutoshkumar S, Manidipa S, "Floating drug delivery systems: A review". Int J Res Pharm Sci, 2011, Vol 2(1), pp 76–83.*
5. *Abdul S, Poddar SS, "A flexible technology for modified release of drugs: multi layered tablets". J Control Release, 2004, Vol 97(3), pp 393–405.*

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Mathieu Degomme graduated from the University of Limoges (France) in 2009 and, the same year, received his MSc in Development and Production of Pharmaceutical Products from the University of Lyon (France). He then achieved his PharmD, also in 2009, as an apprentice in the validation department at Boiron (France). Again, in 2009, Dr Degomme joined Advanced Accelerator Applications and worked in the production, control and release of radiopharmaceutical sterile products. He joined Skyepharma in 2013 as Quality Assurance Manager and Qualified Person, and was appointed Project Manager at the New Product Introduction Department in 2017.

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POLYMER CHEMISTRY'S INFLUENCE ON CONTROLLED-RELEASE TABLETS MANUFACTURED VIA DIRECT COMPRESSION

In this case study, Nasrin Mahmoudi, PhD, PharmD, Technical Service Manager, Pharmaceutical Application and Innovation; Kevin McIntyre, Pharmaceutical Applications Supervisor; Joseph Lee, Research Associate; Holly Bertrand, Research Chemist; Yeli Zhang, PhD, Technical Service Manager; Fernanda Onofre, PhD, Americas Regional Applications Leader; and Amina Faham, PhD, Global Director, Applications Development and Innovation, all at DuPont Nutrition and Biosciences, investigate the effect of a simple direct compression method on controlled-release matrix tablet formulations.

It is common industry practice to produce hydrophilic matrix tablets using a wet or dry granulation process. Either method will help achieve the required powder flow properties for a successful compression and a robust formulation, but compared with those relatively complicated processes, simple direct compression manufacturing is preferred. In a controlled-release matrix tablet formulation, hydroxypropyl methylcellulose (hypromellose) and polyethylene oxide are often used as key polymer excipients to control drug release. The chemical, physical and mechanical properties of these polymers have significant influence on manufacturing processes and product attributes.

In the case study that follows, we will examine discoveries made by the research team at DuPont Nutrition and Biosciences (DuPont) on the influence of polymer chemistry in matrix tablet performance manufactured through a simple direct compression method. A particle-engineered grade of DuPont's proprietary form of hypromellose (METHOCEL™ K100M DC2) and a high-molecular-weight grade of its polyethylene oxide with inherently good flow properties (POLYOX™ WSR-301) were selected for the evaluation as rate-controlling polymers. Propranolol hydrochloride was used as a soluble model drug.

> "The chemical, physical and mechanical properties of these polymers have significant influence on manufacturing processes and product attributes."

A Look at Composition

Matrix tablet formulations consisted of 20% w/w propranolol HCl as a model drug, 30% w/w hypromellose (METHOCEL™ Premium K100M DC2) or polyethylene oxide (POLYOX™ WSR-301) as a release-rate-controlling polymer, 40% w/w microcrystalline cellulose (Avicel® PH102) and 9% lactose monohydrate (Fast Flo®) as filler, 0.5% w/w colloidal silica (SiO_2, Cab-O-Sil®) as anti-adherent and 0.5% w/w sodium stearyl fumarate (Alubra®) as lubricant.

Preparing the Powder Blend

The research team began by incorporating the ingredients into 1 kg batches. They preblended silicon dioxide with Avicel®, passing the subsequent mixture through

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a 20-mesh screen. The preblend silicon dioxide mixture, propranolol HCl and fillers were then passed through a conical mill (Quadro® Comil® Scalable Lab System) at 2,500 rpm for de-lumping and to ensure uniform distribution of the drug. The final mix was blended with the rate-controlling polymer and lubricant in a 4-qt V-blender (with no intensifier bar) at 25 rpm for 15 minutes.

Powder Blend Testing

Particle size distribution of the rate-controlling polymers – METHOCEL™ Premium K100M DC2 and POLYOX™ WSR-301 – were measured using a laser diffraction technique.

The bulk and tapped densities of each blend were measured to obtain Carr's Compressibility Index (Equation 1), an indication of the flowability of a powder in which lower values indicate better flow properties; and the Hausner ratio (Equation 2), a number correlated to the flowability of granular material where Vt is the tapped density of powder (g) and Vb is the bulk density (mL).

Equation 1

$$Compressibility\ Index = 100 \times \left(\frac{Vt-Vb}{Vt}\right)$$

Equation 2

$$Hausner\ Ratio = \frac{Vt}{Vb}$$

Time for Compression

Each blend was compressed into 400 mg tablets on a four-station Korsch rotary tablet press, using a 13/32 SRC tooling at a turret speed of 20 rpm. A compression profile was generated at five compression forces (4, 6, 8, 10 and 12 kN). The resulting matrix tablets were evaluated for physical properties, assay and content uniformity, hydration and gel properties, drug release and stability. Tablet properties, including weight and dimensions (n=5), were measured manually. Crushing strength was measured using a Dr Schleuniger 8M Pharmatron tablet hardness tester. Friability of tablets (n=16) was performed at 100 drops using a VanKel 45-2000 friability tester, according to USP. Tensile strength (TS) of tablets was calculated, and tablets with TS of 2 MPa were selected for further comparison studies.

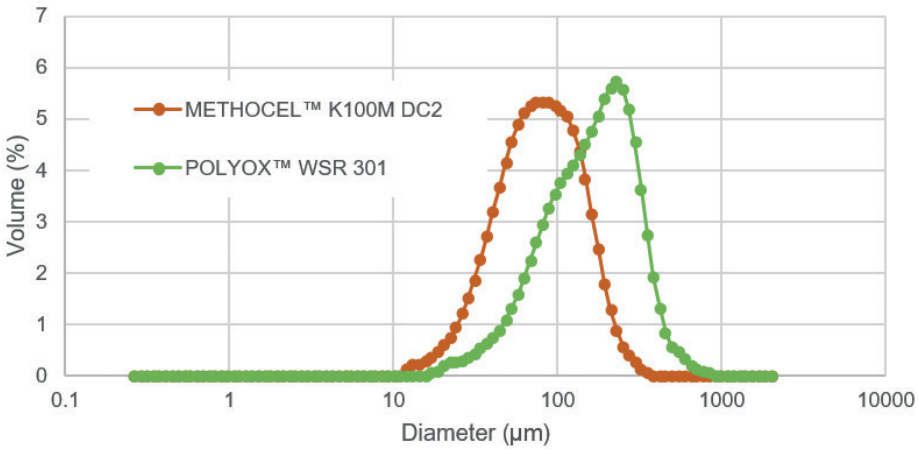

Figure 1: Particle size distribution of METHOCEL™ Premium K100M DC2 and POLYOX™ WSR-301.

ID	Description	Bulk Density g/cc	Tapped Density g/cc	Carr's Compressibility Index (%)	Hausner ratio
F1	Propranolol/METHOCEL™ K100M DC2	0.44	0.54	17.8	1.2
F2	Propranolol/POLYOX™ WSR-301	0.46	0.50	7.3	1.1

Table 1: Formulation blends properties.

The uniformity of each tablet was assessed by dissolving them one by one (n=10) into 100 g of methanol, followed by centrifugation and dilution of 2.5 g of supernatant with 50 g methanol. Drug concentration was measured by UV spectroscopy at 290 nm in a 1 cm cell with a methanol blank.

Biorelevant dissolution testing was carried out using USP Apparatus 2 at 100 rpm with a buffer of 0.1N HCl for 90 minutes, followed by media replacement with 900 mL pH 6.8 phosphate buffer.

Hydration Properties and Gel Strength

The DuPont team measured polymeric hydration and gel strength from the prepared matrix tablets using a Stable Micro System TA-XT2 Plus texture analyser set to "compression test mode". The instrument was equipped with a flat-end, cylindrical acrylic probe with a half-inch (1.27 cm) diameter to measure force while travelling downwards onto the hydrogel formed by polymer hydration. To prepare samples for texture analysis, placebo tablets of METHOCEL™ K100M DC2 and POLYOX™ WSR-301 were manufactured using a compaction simulator targeting a TS of 2 MPa. The active tablets with the same TS were also tested for gel strength. The tablet samples were hydrated in 0.1N HCl (2h) and transferred into deionised (DI) water (25 mL) followed by testing at one, three, five and 24 hours after DI water hydration. All samples were tested in triplicate at each time interval.

Results

Figure 1 shows particle size distribution of the release-rate-controlling polymers, METHOCEL™ Premium K100M DC2 and POLYOX™ WSR-301. Densities and flow indices of both formulation blends are shown in Table 1. Clear differences in particle size distribution, densities and flow properties were found. The METHOCEL™ powder with smaller mean particle size (85 µm) contributed to the higher density of the blend and the higher Carr index (18). As expected, the POLYOX™ with a larger mean particle size (177 µm) contributed to the lower Carr index (7.3), lower tapped density and improved flow properties of the POLYOX™ formulation blend.

Regardless of the differences in blend flow properties, both tablet formulations demonstrated low weight variation with an RSD of less than 0.5%, which indicates satisfactory flow properties of the blends.

Tabletability of the propranolol tablet

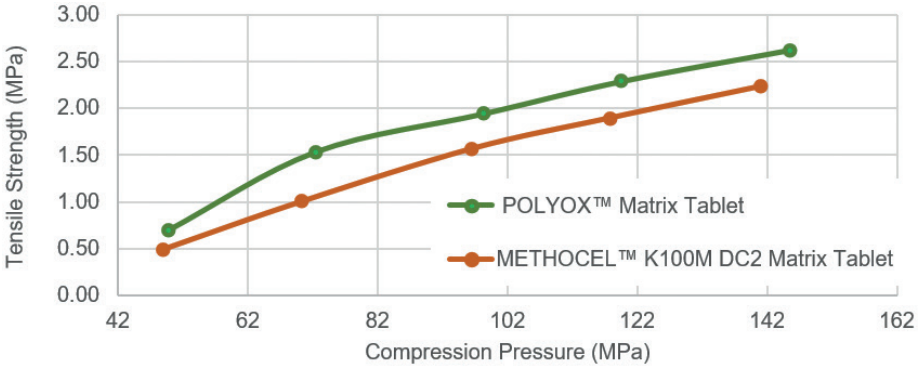

Figure 2: Tabletability of the propranolol formulation.

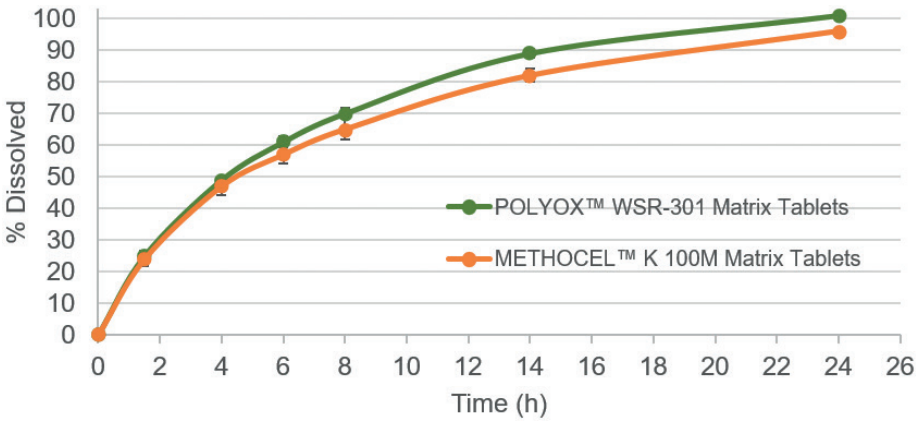

Figure 3: Comparative dissolution profiles of propranolol tablets.

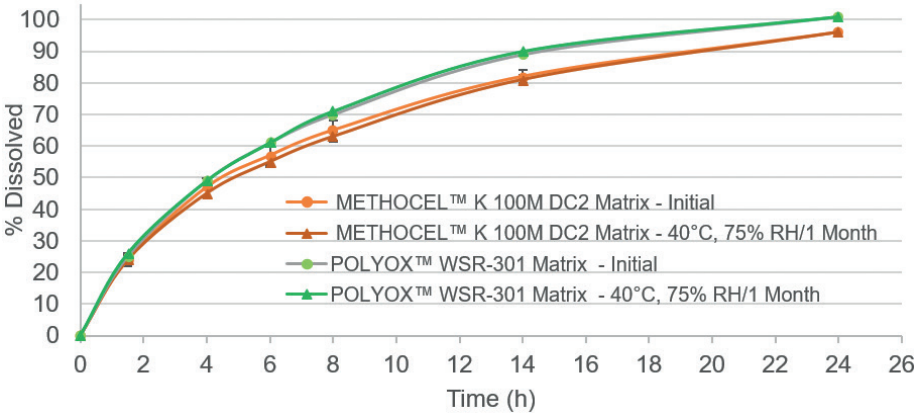

Figure 4. Comparative dissolution profiles of propranolol tablets - stability evaluation.

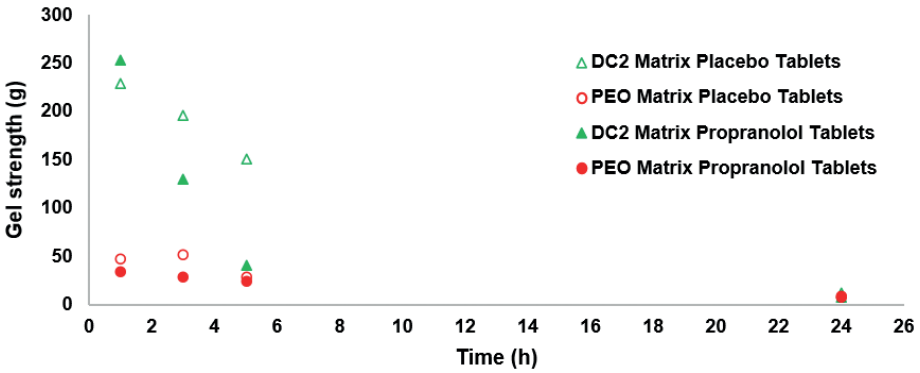

Figure 5. Comparative gel strength of METHOCEL™ K100M DC2 tablets and POLYOX™ WSR-301 tablets.

formulations are shown in Figure 2. POLYOX™ tablet formulations demonstrated higher tablet hardness and tensile strength, which indicates higher compactability of the POLYOX™ polymer with no influence on performance demonstrated by comparable dissolution (Figure 3).

Friability of both tablets was low, 0.1% (TS, 2.24 MPa) and 0.06% (TS, 2.63 MPa) for the METHOCEL™ and the POLYOX™ formulations, respectively.

Uniformity of dosage-unit testing for the METHOCEL™ K100M DC2 matrix tablet samples displayed a mean weight of propranolol HCl of 80.8 ±1.5 mg/tablet (n=10) or 101.0 ±1.9% of the 80 mg label claim. The calculated USP acceptance value (AV) of 4.5 satisfied the USP requirement of less than or equal to the maximum allowed acceptance value (L1) of 15.0. For the POLYOX™ WSR-301 matrix tablets, the mean weight of propranolol HCl was 81.6 ±0.8 mg/tablet (n=10) or 102.0 ±1.1% of the 80 mg label claim. The calculated USP AV of 2.5 satisfied the USP requirement of less than or equal to the maximum allowed acceptance value (L1) of 15.0.

The extended drug-release profiles of both tablet formulations were shown to be robust, as shown in Figure 3. While the propranolol HCl release from POLYOX™-based tablets was slightly faster, the difference was not significant and both profiles were similar with an f2 similarity factor – a measure of the closeness between two dissolution profiles – greater than 71.

The stability study of both tablet formulations indicated no significant changes in drug release after storage for one month under conditions of accelerated stability. The comparative dissolution profiles of the tablets are shown in Figure 4.

Studying hydration showed that POLYOX™ hydrates faster and becomes softer than METHOCEL™ K100M DC2, an observation found in gel strength studies as well. As shown in Figure 5, less force is needed for the probe to travel into the POLYOX™ gel layer as compared with the METHOCEL™ gel layer surrounding the tablets.

Direct Compression Success

DuPont successfully employed METHOCEL™ K100M DC2 and POLYOX™ WSR-301 to manufacture matrix tablets using a simple direct compression method. The two robust matrix tablet formulations for propranolol HCl,

> "Both formulations demonstrated high tablet tensile strength, low tablet friability, good content uniformity and great blend flow properties."

a soluble model drug, were studied in parallel. Both formulations demonstrated high tablet tensile strength, low tablet friability, good content uniformity and great blend flow properties. The propranolol HCl release profiles from both matrix tablets were similar and remained stable after one month of storage under accelerated stability conditions. The investigation demonstrated that both polymers may be successfully used in matrix tablet manufacturing via a direct compression process, which is more cost-effective than dry or wet granulation methods. This has lasting implications for an industry in which simplicity can greatly increase the speed to market of potentially life-saving drugs.

ABOUT THE COMPANY

DuPont (NYSE: DD) is a global company with technology-based materials, ingredients and solutions that help transform industries and everyday life. DuPont's employees apply diverse science and expertise to help customers advance their best ideas and deliver essential innovations in key markets including electronics, transportation, construction, water, health and wellness, food and worker safety.

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Nasrin Mahmoudi, PhD, PharmD, is a member of the Application Development and Innovation (AD&I) scientists' team at DuPont Nutrition & Biosciences. She manages customer technical service requests in North America, develops applications for DuPont excipients, contributes to innovation projects and presents related information to customers, enabling them to troubleshoot and facilitate their formulations development process. Dr Mahmoudi earned her PharmD and PhD degrees from Tehran University of Medical Sciences (Iran) and completed post-doctoral research at Rutgers University (NJ, US) and Pfizer (NY, US). She has more than 17 years of experience in the pharmaceutical industry, particularly in solubility enhancement, and immediate- and controlled-release dosage forms.

Kevin McIntyre is Pharmaceutical Applications Research Laboratory Supervisor at DuPont Nutrition and Biosciences. His career spans 20+ years in the industry, including over 10 years in R&D / Process Engineering at Teva Pharmaceuticals (Israel). His expertise is used to optimise trial design and execution within the laboratory, and ensures DuPont standards are being met.

Joseph T Lee Jr is a Research Associate in the Pharmaceutical Solutions division of DuPont Nutrition & Biosciences. He is a graduate of the University of Scranton (PA, US) with a career spanning 40 years in the industry. Formerly, Mr Lee provided three decades of vital analytical support in the Health and Nutrition division of FMC Corporation (PA, US). He held previous positions in the Metals department at NMS Labs (PA, US), the Dissolution laboratory at Wyeth Pharmaceuticals (PA, US) and the Analytical department at Microbiological Associates (MD, US) providing testing for the National Institutes of Health. Analytical techniques include dissolution testing, spectroscopy, microscopy and chromatography.

Holly P Bertrand is a Principal Scientist at DuPont Nutrition and Biosciences. She is a graduate of Rutgers University (NJ, US) with over 25 years of analytical experience in rheology (suspension and powder), thermal (DSC, TMA, TGA), texture analysis, particle size analysis, Brunauer-Emmett-Teller (BET) surface area and microscopy. In her current role, she provides analytical support for both food and pharmaceutical project teams in new product development, as well as critical support work for manufacturing, sales and marketing.

Yeli Zhang, PhD, is a technical service manager in the pharma solutions division of DuPont Nutrition and Biosciences. Prior to her current role, Dr Zhang worked at FMC in the health and nutrition business, where she began as a senior scientist in excipient product development and support. She would later become North America Health Technical Manager, responsible for providing technical support on FMC's excipients to North American pharmaceutical companies. Before joining FMC, Dr Zhang worked at National Starch and Chemical Company (now Ingredion) (IL, US) as a senior scientist in areas of starch excipient and delivery system development.

Fernanda Onofre, PhD, is Americas Regional Applications Leader at DuPont Nutrition and Bioscience. Dr Onofre joined FMC in 2010, transferring to DuPont in 2017, taking on the role of Americas Regional Applications Leader for Pharma Solutions, heading the Technical Teams and Applications Labs in both North and Latin America. During her career, Dr Onofre led the customer Technical Support and all Technical-related activities in the EMEA and LATAM regions. She holds a PhD and a MSc in Food Science from the University of Arkansas (US), where she worked with food ingredients in pharmaceutical applications. She is a licensed pharmacist, graduated from the Universidade Federal do Ceará (Brazil).

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THE FLOWABILITY OF LACTOSE POWDERS TO OPTIMISE TABLETING PROCESSES

In this article, Aurélien Neveu, PhD, Particle Scientist at Granutools; Pauline Janssen, Product Application Specialist at DFE Pharma; and Geoffroy Lumay, PhD, Associate Professor at the University of Liege and Co-Founder of Granutools, discuss how new measurement methods can help gain a better understanding of the flowability of lactose powders – a necessary step for future improvement of oral delivery systems.

The processability of pharmaceutical powder plays a key role in the design and improvement of production processes for oral delivery systems (e.g. tableting, capsule filling). To control and optimise processing methods, material properties and the behaviour of bulk powder should be characterised.

Blending is one of the first steps in a direct compression process and is critical to achieve a homogeneous blend with uniform API loading. Good flow combined with density supports de-agglomeration of an API during blending (Figure 1).

Free-flowing powder has a relatively flat powder bed in a blender and tends to set up a "rolling" motion inside the powder bed. This results in ball milling of the API agglomerates, which is beneficial for the uniform spread of the API particles over the blend. Poor-flowing powder has a higher dynamic angle of repose and tends to avalanche. This results in less motion inside the powder bed and less ball milling of agglomerates. De-agglomeration of the API is beneficial to achieve good content uniformity in a pharmaceutical formulation, and this becomes more critical with a lower API dose.

Moreover, good flowing properties of a powder are also required for flow through the tableting system, resulting in uniform flow into the die cavities. Insufficient flow can lead to uneven filling of the dies, resulting in large weight and dosage variations of the final tablets. At high tableting speeds, the time to fill dies is reduced, making flow properties of the blend even more important. The particle properties, mainly size and shape, strongly influence the flowability of the powder and thus the critical filling velocity achievable in die filling.[1]

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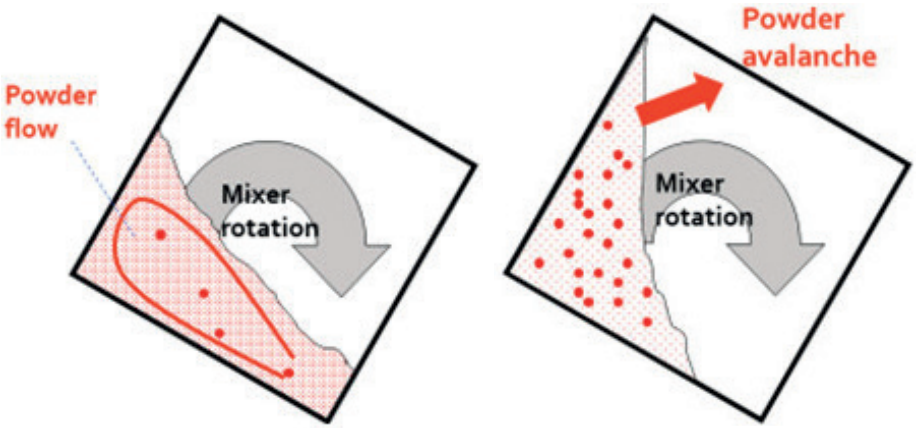


Figure 1: Free-flowing powders tend to set up a rolling motion inside the powder bed, resulting in ball milling of the API agglomerates. Poor-flowing powder tends to avalanche and results in less motion inside the powder bed and less ball milling of API agglomerates.

"Good flow of a pharmaceutical formulation is critical to produce uniform dosage forms."

Consistent flow is also important for continuous manufacturing processes, which are gaining more and more interest from the pharmaceutical industry. Raw material feeding is usually one of the first units of operation in a continuous manufacturing line. The ability to feed powder consistently and continuously is regarded as one of the critical requirements for finished product quality and therefore stringent control on feeding is required.

Lactose is one of the most widely used excipients in the pharmaceutical industry. There are many reasons for its popularity, the fact that lactose is largely inert, relatively inexpensive, safe, many different grades are available and it has a long history of usage in successful formulations worldwide. For direct compression processes such as tableting, lactose excipients can be used as a filler-binder to provide bulk density, compaction and flow to the formulation. Good flow of a pharmaceutical formulation is critical to produce uniform dosage forms.

In this article, we present how new measurement methods can help to gain a better understanding of the flowability of lactose powders, which is a necessary step for future improvement of oral delivery systems. Firstly, the well-known angle of repose is estimated to get a first screening of the cohesiveness of the powders. These results are then compared and extended to a vertical flow through an aperture, in a geometry closer to those encountered in die filling. Then, the effect of the process speed on the flowability – i.e. the rheological behaviour – is investigated with the rotating drum measurement method.

EXPERIMENTAL METHOD

Repose Angle (GranuHeap)

The GranuHeap instrument is an automated heap shape measurement method based on image processing and analysis. To create the powder heap, an initialisation tube with an internal diameter equal to that of the circular support (40 mm) is filled with 100 mL of powder. The tube then moves upward at a constant speed of 5 mm/s, allowing the powder to form a heap on the cylindrical support in a repeatable way. In the present study, 16 pictures of the heap, separated by a rotation of 11.25°, are taken and analysed by a custom image recognition algorithm to determine the position of the powder/air interface and compute the repose angle.

Flow through an aperture (GranuFlow)

The GranuFlow instrument is a laboratory hopper allowing the aperture size to be easily modified with a rotating device. The flow rate as a function of the aperture sizes D is measured with an electronic balance connected to a computer to obtain a complete flow curve. This flow curve is fitted with a theoretical model to extract the main parameters: the minimum aperture size (D_{min}) and the Beverloo parameter (C_b) related to the flowability of the sample.

Mass flow rate (F in g/s) was investigated for different hole size D (from 2–28 mm). The Beverloo parameter (C_b in g/mm^3) and the minimum aperture size to obtain a flow D_{min} are deduced from the regression with Beverloo law:

$$F = C_b \sqrt{g}\,(D - D_{min})^{2,5}$$

Dynamic Cohesive Index (GranuDrum)

The rheology of powders is investigated with the GranuDrum, an automated powder flowability measurement method based on the rotating drum principle. A small amount of powder (50 mL in this study) is placed in a horizontal drum with transparent sidewalls. The drum rotates around its axis at an angular velocity ranging from 2–60 rpm. Snapshots (40 images separated by 1s) are taken by a charge-coupled device (CCD) camera for each angular velocity. The air/powder interface is detected on each picture with an edge detection algorithm. Afterwards, the average interface position and the fluctuations around this average position are computed.

For each rotation rate, the dynamic cohesive index is measured from the interface fluctuations, which are solely due to the cohesive forces acting between the grains. The dynamic cohesive index is thus close to zero for non-cohesive powders and increases when the cohesive forces intensify. Furthermore, by varying the rotation rate, complex rheological properties of powders (shear thinning, shear thickening and thixotropic behaviour) can be investigated.

MATERIALS

Five lactose powders provided by DFE Pharma have been selected for this study, mainly differing in their production methods:

- Pharmatose® 450M: a fine-milled alpha lactose monohydrate
- SuperTab® 24AN: a granulated anhydrous lactose
- SuperTab® 30GR: a granulated lactose
- SuperTab® 21AN: an anhydrous lactose
- SuperTab® 11SD (EU): a spray-dried lactose.

Pharmatose® 450M is a milled lactose grade which is commonly used in wet and dry granulation processes. SuperTab® grades are high-end lactose grades specifically designed for direct compression processes and provide additional functionality in terms of flow and compression.

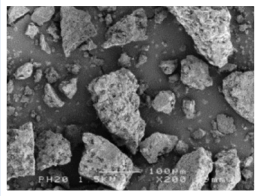
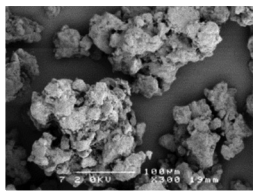
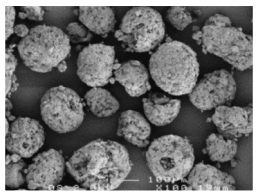
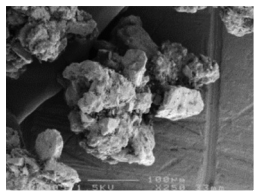
SuperTab® 21AN	SuperTab® 24AN	SuperTab® 11SD	SuperTab® 30GR	Pharmatose® 450M
				

Table 1: SEM images of the particles making up the powders.

	SuperTab® 21AN	SuperTab® 24AN	SuperTab® 11SD	SuperTab® 30GR	Pharmatose® 450M
Type	Anhydrous	Anhydrous granulated	Spray dried	Granulated	Milled
x10 (µm)	24	40	44	38	3
x50 (µm)	180	121	119	126	18
x90 (µm)	387	298	223	297	49

Table 2: Type and size distribution of the particles making up the five powders.

Table 1 provides scanning electron microscope (SEM) images of the powder's particles, revealing the shapes of the grains. Particle size distributions are summarised in Table 2.

RESULTS AND DISCUSSION

Repose Angle

Figure 2 presents the measured angle of repose for all powders. It appears that the Pharmatose® 450M and SuperTab® 21AN exhibit a similar angle of repose, higher than the other ones. Powders can then be classified in two categories with a threshold angle of repose around 55°, above which they are expected to have higher bridging propensity. Moreover, based on its lower angle of repose, the SuperTab® 11SD is expected to have the lowest bridging propensity, closely followed by SuperTab® 30GR and SuperTab® 24AN.

Pharmatose® 450M has the lowest particle size and thus it is not surprising it exhibits a higher cohesiveness and thus a higher angle of repose.[2] However, particle size is not the only parameter affecting flow, as it also depends heavily on powder morphology, as can be observed for SuperTab® 11SD which has a spherical shape.

Vertical flow

Figure 3 presents the mass flow rate versus the silo aperture for the three powders able to flow through the maximum tested aperture size (28 mm). First of all, only the SuperTab® 24AN, SuperTab® 30GR and SuperTab® 11SD were able to flow through the larger aperture size (28 mm) tested in this study, in coherence with the lower repose angle measured with the GranuHeap.

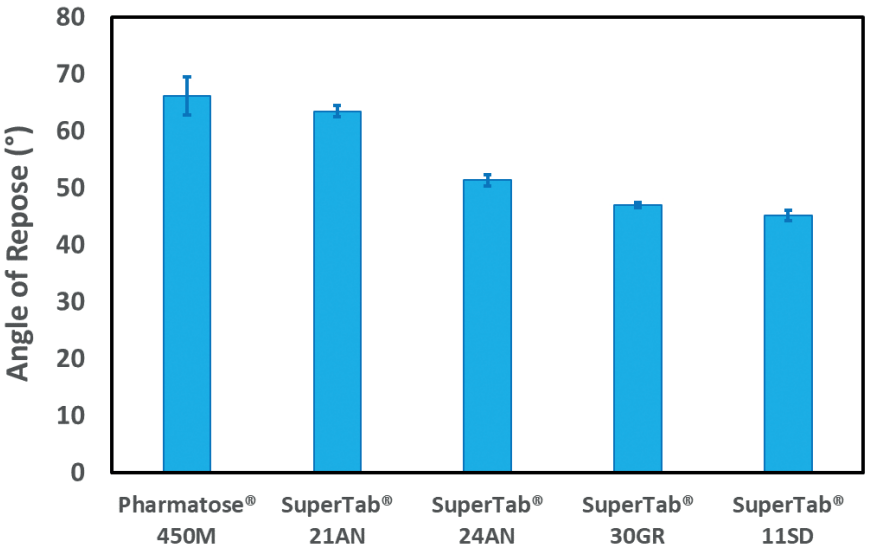


Figure 2: Mass flow-rate versus aperture for the three powders able to flow through the larger aperture (28mm).

> "The cohesiveness of a powder depends on the size of the particles that make up the powder: the smaller the particle, the higher the cohesion."

The SuperTab® 11SD has the highest Beverloo parameter and thus exhibits the best flowability through the silo aperture. This powder has also the lowest D_{min} and is thus able to flow though a smaller aperture than the other ones. It is then followed by SuperTab® 30GR and SuperTab® 24AN, in this order, in total accordance with the angle of repose measurements obtained with the GranuHeap.

The cohesiveness of a powder depends on the size of the particles that make up the powder: the smaller the particle, the higher the cohesion. However, other characteristics of the grains can play a role – such as the shape, the surface roughness or the chemical properties. For the powders we considered,

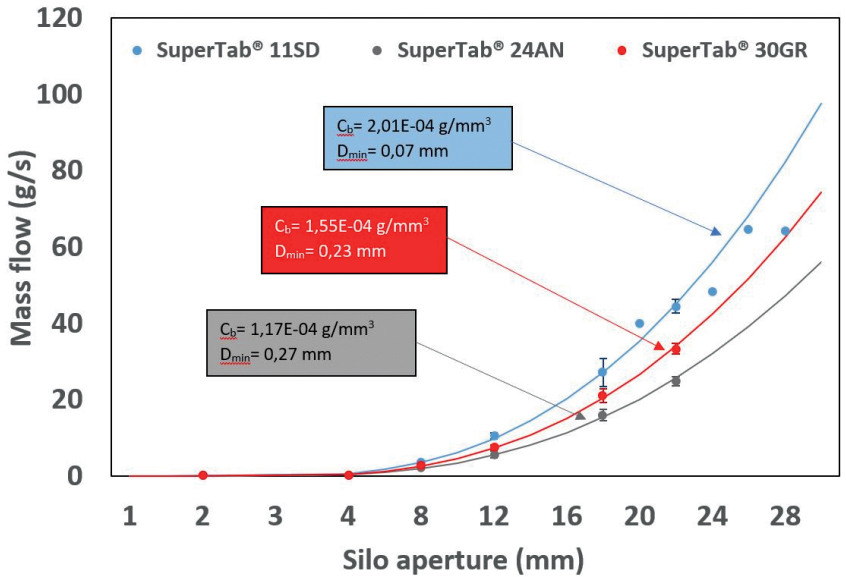


Figure 3: Mass flow rate versus aperture for powders.

it appears that the SuperTab® 21AN has the higher median particle size (x50=180 µm) but also a high bridging propensity, as it was not able to flow through the 28 mm aperture.

Considering the three powders that did flow through the 28 mm aperture (SuperTab® 11SD, SuperTab® 30GR, SuperTab® 24AN), the SuperTab® 11SD has the lowest particle size but also the lowest D_{min} and highest C_b. Therefore, the shape of the particles seems to be a more relevant characteristic to explain the flowability performance of these powders. Indeed, although the SuperTab® 11SD particles are smaller, they have a regular spherical shape which promotes the flow. The SuperTab® 30GR and the SuperTab® 24AN are granulated powders composed of agglomerates of slightly round shapes, explaining why they also exhibit a good flowability.

The more irregular shape of particles of the SuperTab® 21AN leads to increased bridging propensity due to interlocking effects. Pharmatose® 450M combines irregular particle shapes with the smallest particle size (x50=18 µm) – this powder is thus expected to have the lowest flowability.

The obtained results indicate the same ranking of hopper diameters for these lactose grades as shear cell measurements did before (SuperTab® 24AN was not considered in this experiment). With the previous shear cell measurements, the minimal required hopper dimensions in a conical hopper were predicted. Hopper outlet diameters were predicted to be the lowest for SuperTab® 11SD (15 mm), followed by SuperTab® 30GR (17 mm). SuperTab® 21AN was predicted to require a higher minimum hopper outlet of 96 mm, due to its relatively high wall friction. For Pharmatose® 450M, the predicted hopper diameter was 210 mm.[3]

Dynamic cohesive index

Cohesive index values as a function of the increasing rotating speed are presented in Figure 4. The observations and the classification obtained with GranuHeap and GranuFlow are consistent with the GranuDrum for equivalent stress state, i.e. at low rotating speeds. Moreover, the cohesive index gives another level of description as it allows us to distinguish the SuperTab® 21AN and the Pharmatose® 450M. It is evident that the Pharmatose® 450M exhibits the most cohesive behaviour, with a cohesive index much higher for the whole speed range. This is consistent with the significantly lower particle size of this powder (x50=18 µm).

Pharmatose® 450M, SuperTab® 11SD, SuperTab® 24AN and SuperTab® 30GR show shear-thickening behaviour, meaning that their cohesiveness increases with process speed. This decrease of flowability may limit the critical filling velocity achievable in oral delivery production processes. On the contrary, SuperTab® 21AN shows strong shear-thinning behaviour, leading to a cohesive index at high speed equivalent to those of the best flowing powders at low speed. Therefore, this powder is expected to perform the best at higher processing speeds. The larger particle size and irregular

> "The proper characterisation of powder flowability is a key step in understanding and improving manufacturing processes of oral delivery systems."

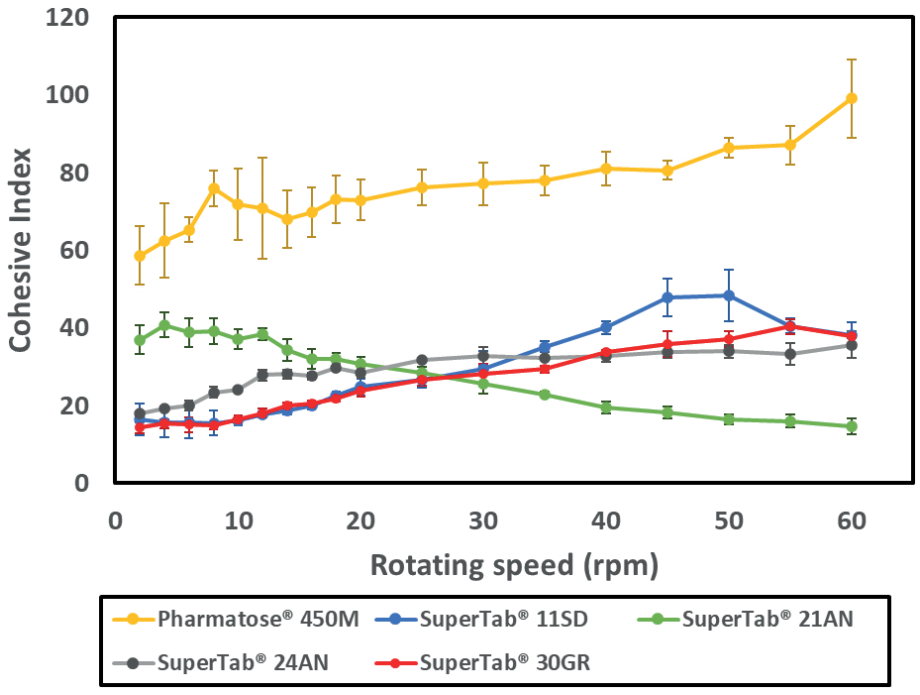


Figure 4: Cohesive index versus rotating drum speed. Shear-thickening behaviours are observed, except for powder SuperTab® 21AN, which exhibits strong shear-thinning behaviour.

particle shapes may explain why this powder differs strongly from the others.

CONCLUSIONS

The proper characterisation of powder flowability is a key step in understanding and improving manufacturing processes of oral delivery systems. For this reason, the flowability of five lactose powder grades was investigated. The SuperTab® 11SD, SuperTab® 24AN and SuperTab® 30GR showed the best flowability with GranuHeap, GranuFlow and GranuDrum instruments.

It appeared that SuperTab® 21AN did not exhibit the best flowability despite the large particle size of this lactose grade, explained by the irregular shape of the grains. The small particle size of Pharmatose® 450M led to a much higher cohesiveness and poor flowability compared with the other studied powders. Moreover, shear thickening is observed except for the SuperTab® 21AN which showed strong shear-thinning behaviour.

For inherently dynamic processes, especially in continuous manufacturing lines, this improved knowledge of rheological behaviour provides indispensable information to develop and select the most suitable powder.

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.

ABOUT THE AUTHORS

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

Pauline Janssen is a Product Application Specialist in oral solid dosage (OSD) at DFE Pharma. She has been working on application development of excipients based on fundamental knowledge of excipients and powder physics. Ms Janssen joined DFE Pharma at the beginning of 2017 and worked as a product developer on multiple OSD and DPI projects. As an analytical expert, she supported the design of experiments to understand products and their usage.

Geoffroy Lumay is Associate Professor and Soft Matter Physics Chair at the University of Liege in Belgium. Dr Lumay is leading research projects in the field of soft matter physics at the intersection between fundamental sciences and industrial applications. He teaches both basic and advanced physics to students in pharmaceutical sciences, engineering and agronomy. Dr Lumay co-founded the company Granutools, which is developing, producing and commercialising a range of laboratory instruments dedicated to powder characterisation.

REFERENCES

1. *Zakhvatayevaa A, Zhonga W, Makrooa HA, Harea C, Wu CY, "An experimental study of die filling of pharmaceutical powders using a rotary die filling system". Int J Pharm, 2018, Vol 553, pp 84–96.*
2. *Boschini F, Delaval V, Traina K, Vandewalle N, Lumay G, "Linking flowability and granulometry of lactose powders". Int J Pharm, 2015, Vol 494, pp 312–320.*
3. *"Understanding the differences between lactose grades in terms of powder flow". Technical Paper, DFE Pharma.*

FORMULATION FLEXIBILITY WITH NEW ERA HPMC CAPSULES

In this article, Sanjay Powale, Head – Research & Development; Anita Solanki, Lead – White Papers and Publications; and Dorene Almeida, Lead – Application Lab, all of ACG, discuss the benefits of HPMC capsules in overcoming challenges faced by traditional gelatin capsules.

The two-piece hard capsule has evolved significantly since its inception around 170 years ago.[1] One of the most versatile dosage forms used for formulating pharmaceutical products, today's hard capsules have opened avenues for innovation by offering a high degree of flexibility in terms of what they can contain – from powders and pellets to semisolids and even liquids. Additionally, capsules can also be used to deliver more than one active ingredient with the added advantage of masking unpleasant taste and odour.

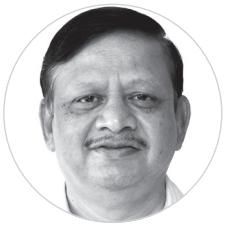
Traditionally, capsules have been made from gelatin which is obtained from animal sources. Owing to the high suitability of gelatin capsules in pharmaceutical formulations, they achieved significant success quickly. They are non-toxic, robust and easy to handle on high speed machines. Gelatin capsules disintegrate within 5–10 minutes in biological media. They also show rapid *in vitro* dissolution of immediate-release (IR) solid oral dosage forms which is desirable and is also an indication of satisfactory *in vivo* performance. Therefore, gelatin capsules are preferred by pharmaceutical manufacturers for producing IR formulations. Gelatin, due to its excellent gelling properties, forms robust films and has remained a popular choice among empty capsule manufacturers.

However, although nearly ideal, gelatin capsules are associated with challenges such as high inherent moisture content, which often leads to incompatibility issues when filled with moisture-sensitive ingredients; high susceptibility to adverse interactions with ingredients containing aldehydic functional group; and transmissible spongiform encephalopathies (TSE) and bovine spongiform encephalopathy (BSE) related concerns. These limitations have necessitated the introduction of newer polymers to advance into more sophisticated materials for manufacturing capsule shells.

> "HPMC capsules have inherently low moisture content which allows for the encapsulation of ingredients that are sensitive to moisture and are hygroscopic in nature."

HYDROXYPROPYL METHYLCELLULOSE (HPMC)

Hydroxypropyl methylcellulose (HPMC), a cellulose-based polymer (derived from plant sources), which has been used in pharmaceutical products for many years as an excipient in various formulations and coating applications, successfully addresses most of the limitations of gelatin when used as capsule shell material.[2] HPMC complies with global pharmaceutical regulatory norms and it is acceptable as an additive for human consumption in accordance with



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US Code of Federal Regulations Title 21 Section 172.874 and EU Regulation (EC) No. 1333/2008. It is also listed in the US FDA Inactive Ingredient Database.[3]

HPMC CAPSULES

Two-piece HPMC capsules were first developed in 1989 as a vegetarian alternative to hard gelatin capsules. HPMC capsules is certified by Vegan USA, and the UK Vegetarian Society. It is also certified by various Kosher and Halal certifying bodies.

HPMC capsules have inherently low moisture content which allows for the encapsulation of ingredients that are sensitive to moisture and are hygroscopic in nature. This has greatly broadened the scope of capsules in drug delivery. Due to their manifold advantages, HPMC capsules are gradually gaining popularity among pharmaceutical and nutraceutical manufacturers.

HPMC CAPSULE MANUFACTURING PROCESS

The method used for manufacturing HPMC capsules conventionally has been adapted from the gelatin capsule making process. The process involves dipping cold pin moulds into a hot solution of HPMC followed by gelation at low temperature and then drying to obtain the capsules. This method is perfectly suitable for gelatin because it gels on its own at cold temperatures, unlike HPMC. So, to manufacture HPMC capsules by this method, the incorporation of a gelling system is required. The gelling system usually includes a gelling agent such as carrageenan,[4] gellan gum, pectin and gel promoters such as potassium ions, calcium ions and sodium ions, which help in forming the capsule shell.

Dissolution testing is a very important parameter for predicting a product's efficacy. Achieving the desired dissolution criterion with regular HPMC capsules can sometimes be challenging. To address this lacuna, ACG Capsules has specially formulated ACGcaps™ H+ and ACGcaps™ HA. These newer variants of HPMC capsules not only exhibit gelatin-like dissolution performance but also possess several other additional advantages. The *in vivo* and *in vitro* performances of HPMC capsules largely depend on the capsule shell composition and manufacturing process. Hence, by employing a novel technology that eliminates or limits the use of gelling system, ACG Capsules has been able to produce HPMC capsules that are capable of superior dissolution. The advanced technology used to manufacture ACGcaps™ H+ is called thermo-gelation. This process is ideal for polymers such as HPMC which exhibit gelling capabilities at high temperatures. HPMC is liquid at lower temperatures and completely soluble in water. This procedure of manufacturing capsules involves dipping hot pin moulds in a cold solution of HPMC and achieving gelling under hot conditions. This does not require the use of any gelling system due to the temperature-dependent rheological behaviour of the HPMC polymer.

> "ACG is the first and only capsule manufacturer in the world to be certified by the Clean Label Project for ACGcaps™ H+. This certification confirms that ACGcaps™ H+ capsules are clean, safe, healthy and contaminant-free."

ACGcaps™ H+

Since there are no gelling agents or promoter, ACGcaps™ H+ only contains HPMC as the film forming polymer of the capsule. It shows superior dissolution performance compared with regular HPMC capsules, releasing its contents independently of pH and ionic strength of the dissolution media that is comparable to gelatin capsules. These capsules are suitable for filling ingredients that are hygroscopic and/or sensitive to moisture. Additionally, the absence of gelling agents eliminates the chance of any possible interaction with the dissolution media. Due to its vegetarian source, this capsule supports the claims of Vegan society and meets global dietary needs and preferences. ACG is the first and only capsule manufacturer in the world to be certified by the Clean Label Project for ACGcaps™ H+. This certification confirms that ACGcaps™ H+ capsules are clean, safe, healthy and contaminant-free.

> "Regular HPMC capsules made using carrageenan as a gelling agent show variable drug release patterns in certain dissolution media. However, this does not hold true for ACG's ACGcaps™ HA."

DISSOLUTION PROFILE: PH INDEPENDENT DRUG RELEASE

Regular HPMC capsules exhibit differences in dissolution at different pH levels. At certain pH levels, the dissolution profile may not meet the desired criteria. However, ACGcaps H+ does not show a pH-dependent dissolution profile. This has been further demonstrated with a study conducted using ACGcaps™ H+. An *in vitro* dissolution study of ACGcaps™ H+ containing acetaminophen was conducted in five different dissolution media of varying pH and ionic strengths. The capsules showed pH independent release. The result of this dissolution study is represented in Figure 1.

The dissolution study that was conducted on ACGcaps™ H+ confirms its pH-independent drug release profile in all five dissolution media.

KEY BENEFITS OF ACGcaps™ H+

- Dissolution is independent of pH and ionic strengths
- Consistent dissolution performance across all biological pHs
- Possesses disintegration characteristics that are comparable to gelatin capsules
- Made primarily with HPMC and water, without processing aids such as gelling agents
- Clean, inert and robust capsules for pharmaceutical and nutraceutical applications
- Remain stable and robust on storage across a broad temperature range.

ACGcaps™ HA

Regular HPMC capsules made using carrageenan as a gelling agent show variable drug release patterns in certain dissolution media. However, this does not hold true for

ACGcaps™ HA, which contain carrageenan as a gelling agent and employs a modified manufacturing process. It is an inert and high performing HPMC capsule that is intended for pharmaceutical applications. These capsules are suitable for molecules that need to meet the required dissolution criterion in 0.01N HCl. They are also suitable for hygroscopic and moisture sensitive ingredients.

ACGcaps™ HA is specially designed for molecules such as dabigatran etexilate mesylate whose dissolution medium assigned by the FDA's Office of Generic Drugs is 0.01N HCl.

In order to examine the dissolution performance of these capsules, a study was performed with dabigatran etexilate mesylate capsules. The innovator product contained the drug in the form of pellets that were filled into capsules. Dissolution of ACGcaps™ HA (containing dabigatran etexilate mesylate pellets) and the innovator product was carried out using the method described in Table 1.

CHALLENGES WITH OTHER CAPSULES

Inconsistent dissolution profile and variation in drug release in 0.01N HCl was observed. However, with ACGcaps™ HA capsules, desired dissolution performance in 0.01N HCl was observed which was in-line with the innovator product. The results have been presented graphically in Figure 2.

This dissolution of ACGcaps™ HA confirms its desirable dissolution properties for dabigatran.

KEY BENEFITS OF ACGcaps™ HA

- Suitability for molecules that need to achieve the desired dissolution performance in 0.01N HCl (pH 2.0)
- Modified capsule shell composition for better dissolution performance
- Less susceptible to cross linking
- Consistent quality and machine performance

CONCLUSION

HPMC capsules are now being extensively used by many leading pharmaceutical manufacturers globally. In 2019, five new capsule products were launched in different HPMC capsule variants by prominent pharmaceutical companies. Today, the commercially available HPMC capsules range from conventional powder-fill to liquid-fill capsules, sprinkle capsules, dry powder inhalation capsules and much more, offering greater formulation flexibility for product development.

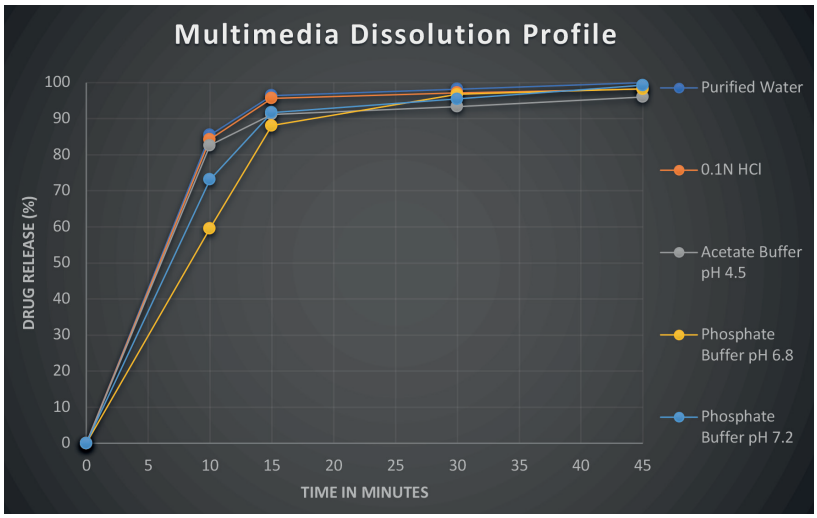


Figure 1: Dissolution profile of acetaminophen in ACGcaps™ H+. (Apparatus used: USP Type 2; Volume: 900 mL; Speed: 50 rpm; Time interval: 10, 15, 30 and 45 minutes.)

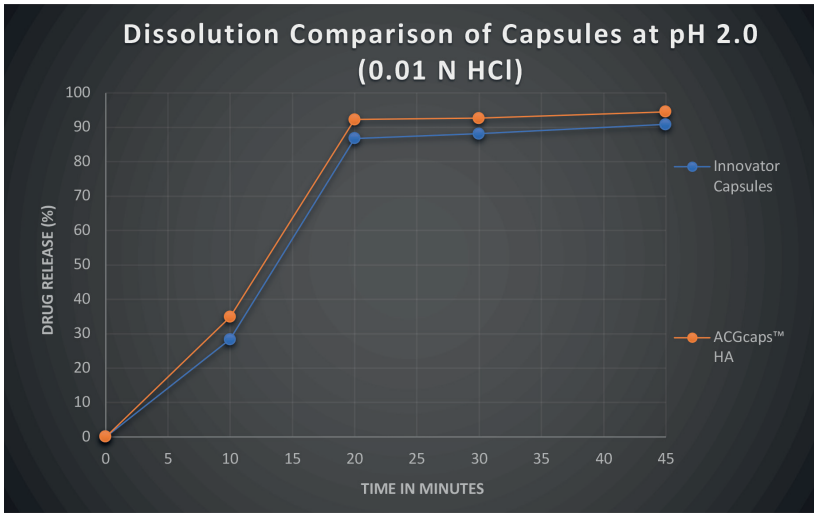


Figure 2: Dissolution profile of ACGcaps™ HA versus innovator capsules containing dabigatran etexilate mesylate pellets. (Apparatus: Modified Basket; Capsule size: 0; Speed: 100 rpm.)

USP Apparatus	Speed (RPM)	Medium	Volume (mL)	Sampling Time Points (minutes)
I (Basket) for 75 mg I (Basket with modified diameter of 24.5 mm) for 150 mg	100	0.01N HCl (pH 2.0)	900	10, 20, 30 & 45

Table 1: FDA-recommended dissolution method for dabigatran etexilate mesylate.

"...the commercially available HPMC capsules range from conventional powder-fill to liquid-fill capsules, sprinkle capsules, dry powder inhalation capsules and much more, offering greater formulation flexibility for product development."

With a strong focus centred around innovative therapy, ACG Capsules has been able to devise new era products to provide pharmaceutical manufacturers with

better drug delivery. The thermally gelled capsule, ACGcaps™ H+, not only delivers the clean label promise but also significantly aids the achievement of desired dissolution characteristics across all biological media and helps formulate stable products. This variant can be used for pharmaceutical and nutraceutical products. For specific pharmaceutical products faced with dissolution hurdles, ACGcaps™ HA is the optimal choice.

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. The company's integrated pharmaceutical manufacturing solutions encompass a varied portfolio of not only capsules, but also packaging films and foils and extends 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 that collaborate to provide world-class technologies across multiple domains.

REFERENCES

1. *Kendall RA, Basit AW, "The Role of Polymers in Solid Oral Dosage Forms". Polymers in Drug Delivery, 2006, Edition 1, pp 35–48.*
2. *Moawia MA, "HPMC Capsules: Current Status and Future Prospects". J Pharm Pharm Sci, 2010, Vol 13(3), pp 428–442.*
3. *Majee SB, Avlani D, Biswas GR, "HPMC as Capsule Shell Material: Physicochemical, Pharmaceutical and Biopharmaceutical Properties". Int J Pharm Pharm Sci, 2017, Vol 9(10), pp 1–12.*
4. *Patil D, Kalafat J, Bhat J, Powale S, Giripunje A, Diez F, HPMC Capsules in DPIs: Evaluation of the Puncturing Force using Capsules Prepared by Different Manufacturing Methods and having Different Compositions. Drug Delivery to Lungs, 2018.*

ABOUT THE AUTHORS

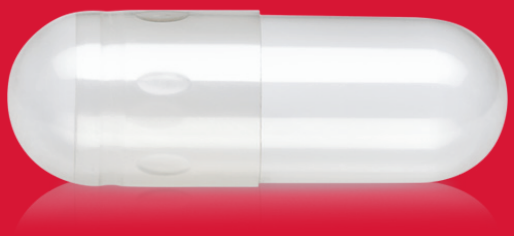
Sanjay Powale is Head of Research & Development at ACG Capsules. He leads the innovation teams and is responsible for building a pipeline of new products, for the material sciences division and for formulation, which ensures parity or differentiation with competition. Mr Powale keeps a close watch on emerging technologies and science to be incorporated to build cutting edge technology for manufacturing of hard capsules. For protection of business interest, he also drives publications of white papers, application notes and patents.

Anita Solanki, Lead – White Paper & Publications, team of ACG Capsules for over two years. She had been involved in the Research & Development department with a cumulative experience of about four years. Her primary responsibility includes creating, writing and publishing scientific literature, involvement in segmented solutions for customers and preparing research articles. Ms Solanki also leads all the industry-institute collaborative projects and research activities to support ACG branding initiatives.

Dorene Almeida, Lead – Application Lab, is a key member of the Research & Development department at ACG Capsules with a total experience of five years. Ms Almeida is involved in all activities in the Application Lab (Pharma), where her primary responsibility is to help customers resolve their capsule formulation challenges. Along with this, she is also a lead in performing scientific studies on capsules which provide solutions for numerous capsule-based formulations. She also works closely with new polymer development laboratories and the scientific business development team for new products.

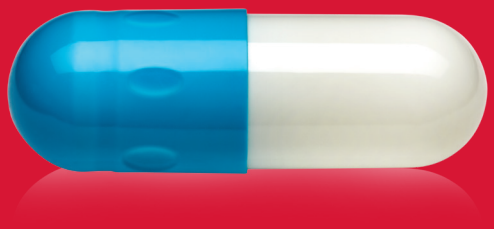
IS MEETING THE DESIRED DISSOLUTION CRITERION GETTING INCREASINGLY CHALLENGING?

Not anymore! ACGcaps™ H+ and ACGcaps™ HA are here to make it easy



ACGcaps™ H+
HPMC Plus Capsules

Made with HPMC and water, these capsules are ideal for immediate-release products. They exhibit excellent dissolution performance releasing all contents independent of pH and ionic strength.



ACGcaps™ HA
Platinum Standard in HPMC Capsules

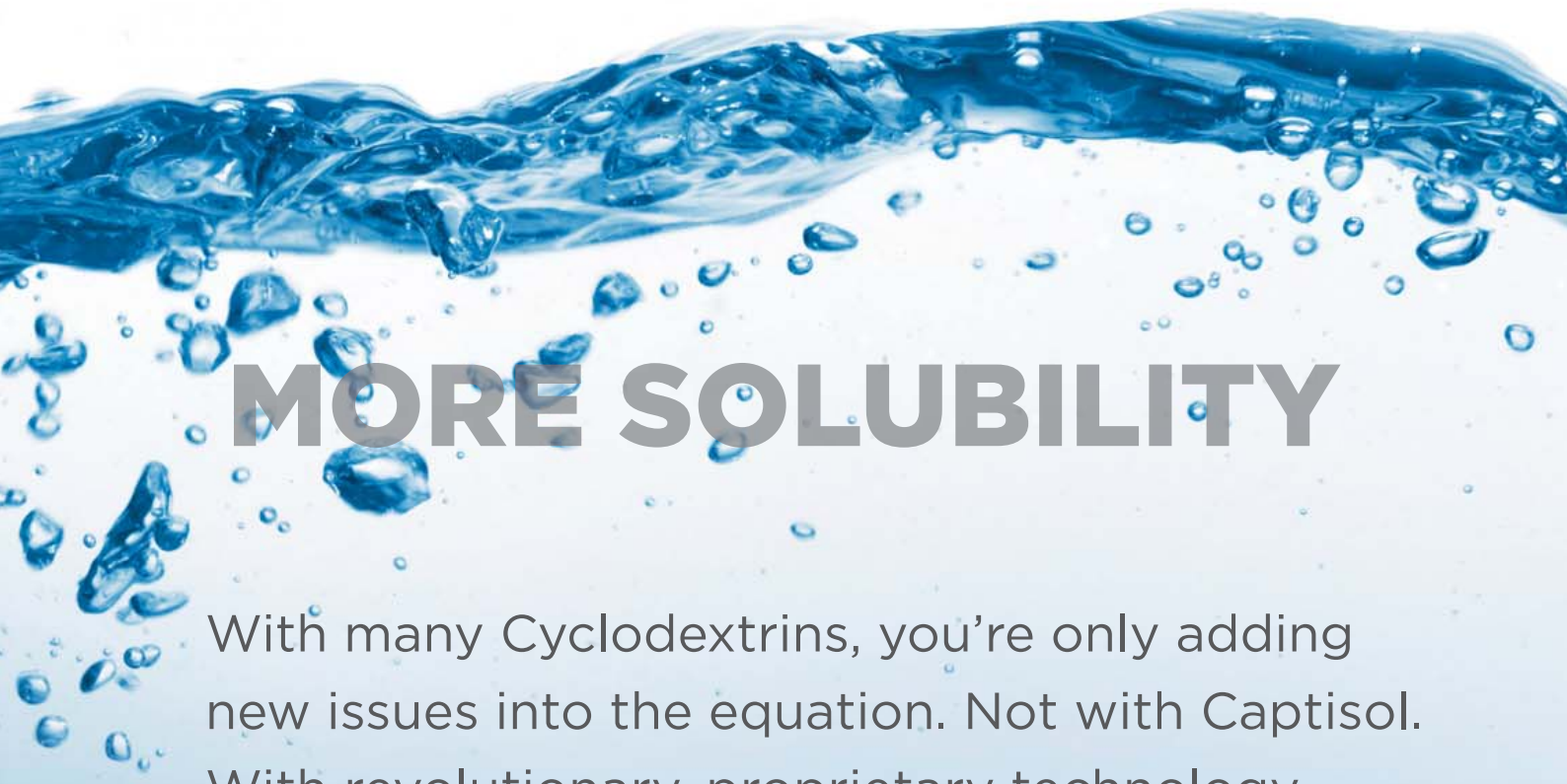
These capsules possess superior dissolution characteristics and are a perfect fit for drugs which need to meet the dissolution criterion in 0.01N HCl. They are suitable for moisture-sensitive ingredients.

Making the world healthier, together.

Scan the code to get in touch with us and know more about our new age HPMC capsules

ACG CAPSULES

MORE TECHNOLOGY.



MORE SOLUBILITY

With many Cyclodextrins, you're only adding new issues into the equation. Not with Captisol. With revolutionary, proprietary technology, Captisol is rationally engineered to significantly improve solubility, stability, bioavailability and dosing of active pharmaceutical ingredients.

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