NOVEL ORAL DELIVERY SYSTEMS

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NOVEL ORAL DELIVERY SYSTEMS

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REMOVING CLINICAL TRIAL BIAS WITH OVER-ENCAPSULATION

Here, Frédérique Bordes-Picard, Business Development Manager for Innovative Products, Julien Lamps, Product Manager, and Stephen Rode, Manager of Business Development, of Lonza's Capsules and Health Ingredients segment discuss the considerations to take into account when using over-encapsulation to blind clinical trials, including the advantages of hydroxypropyl methylcellulose over gelatin as a material.

During the preparation of clinical studies, best practice calls for identifying the method used to blind the dose form visually as early as possible in the drug development process. While there are many blinding options available, over-encapsulation remains the most popular method adopted by sponsors to meet regulatory requirements due to its relative simplicity.[1]

Double-blinding is the key to pharmaceutical trial robustness and study integrity.[2] Beyond formulation and form, visually blinding trial doses becomes a critical factor in determining efficacy and therapeutic performance. A properly blinded study removes both investigator and patient bias caused by awareness of the drug's source and suppresses potential placebo effects as well.

"Though simple in practical terms, over-encapsulating pharmaceuticals and blinding them for a study involves several unique operations that can introduce complexities that may be tough to manage effectively without support."

SIMPLE, YET COMPLEX IN PRACTICAL TERMS

Though simple in practical terms, over-encapsulating pharmaceuticals and blinding them for a study involves several unique operations that can introduce complexities that may be tough to manage effectively without support. Both the European Commission's Volume 4 Good Manufacturing Practices Annex 13 and the US FDA's 21 CFR Part 211 provide the regulatory framework for the use and qualification of comparative agents in clinical trials. Good manufacturing practice compliance requires:

- Provision of data to show that product quality has not been altered
- Justification of expiry dating
- Blinding that resists tampering and clearly reveals when tampering has occurred
- Rapid unblinding to identify the product in case of emergency.

Despite the relative simplicity of over-encapsulation, proper planning and careful

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execution are still fundamental to success – full consideration must be given to every detail from capsule colour and size selection, as well as engaging a well-trained team dedicated to the process.

PRIMARY OVER-ENCAPSULATION CONSIDERATIONS

It is important to select the appropriate components to support over-encapsulation of the trial tablet or capsule dose, as well as provide the means to prevent patients from discerning between investigational and control doses after receiving their clinical supply.

When the bioavailability of the investigational new drug is critical to determining efficacy, it is important that both the investigational and reference drug be encapsulated with the same capsule material so clear and appropriate comparisons and conclusions can be drawn. This is essential, for example, when similar *in vitro* dissolution profiles are called for in the clinical trial design.

SIZE MATTERS MORE THAN EVER

Once the trial dose form and formulation have been identified, determining what size of capsule shell is needed to properly blind each unit comes next. However, there are nuances to this. For example, although not completely necessary, Lonza Capsules and Health Ingredients (CHI) recommends from experience that efficiencies can be made if the dose being encapsulated does not protrude above the body of the shell when inserted (Figure 1). If the unit does not "sit" properly inside the body shell, issues can occur during the backfill process, which can increase waste, cause unnecessary downtime and, ultimately, raise cost.

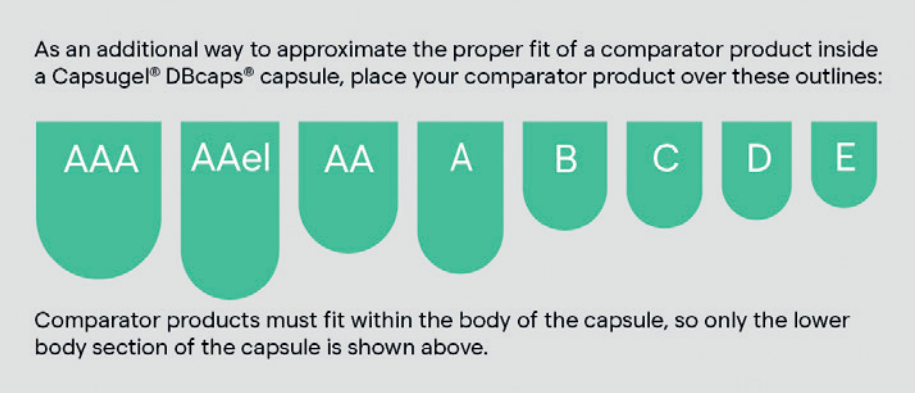

Figure 1: Over-encapsulation works best when the entirety of the dose fits inside the body of the capsule.

Patient-Centric Flexibility Required

A study design might call for splitting tablets to fit them into the smaller capsule sizes to suit patient group requirements. However, splitting doses by physically breaking tablets is not a precise process and introduces variation. Regulators saw fit to mitigate this by prompting drug developers to address these issues during filling. However, that adds to the complexity and leads to greater demand for more flexible over-encapsulation solutions to fit more clinical supply dose forms.

It is clear that capsule size is an extremely important detail to help assure trial supply dose compliance and blinding performance. Correctly specifying size requires data and input from all corners of drug development, trial design and administration.This includes input from critical supply, equipment and fill-finish partners.

"It is clear that capsule size is an extremely important detail to help assure trial supply dose compliance and blinding performance. Correctly specifying size requires data and input from all corners of drug development, trial design and administration."

ELIMINATING TRIAL BIAS WITH COLOUR

First and foremost, the encapsulating capsule's colour must completely obscure the enclosed dose form regardless of its colour. Ideally the colour and opacity of the capsule will hide any and all attributes that might give away the true identity of the contents. Anything that reveals which dose is which could impact patient compliance and trial data. For most applications, that means capsules for over-encapsulation are opaque and usually a different colour or colour combination to that of the dose being blinded.

It is certainly vital to select a capsule colour that blinds the dose and adds extra control to the study, but it is also important to assure the colour's ingredients are accepted by regulators and meet dietary restrictions and source standards wherever the study is being conducted. Several countries have restrictions on particular colours or the total number of capsules.

MOTION CONTROL EQUALS BLIND CONTROL

Over-encapsulation ensures blind control and study integrity because it completely hides which dose is being controlled (Figure 2). That extends to the "feel" and weight of blinded clinical supplies. For example, blinding a single small solid dose effectively usually requires a backfill of excipients to stop it from rattling around in the encapsulating capsule.

Of course, other control doses and placebos have to maintain the exact look and feel of every other dose being prescribed in the trial. If the rattle is not eliminated, the patient might possibly be able to identify if they are in the test or control group.

Backfill can be avoided in certain cases, but only if a similar rattle between the doses can be maintained. Lastly, when selecting backfill excipients, it is preferable to choose one that is present in the dose form being blinded.

DO NOT FORGET TO CONSIDER DISSOLUTION AND STABILITY

Probably one of the more critical issues to consider when specifying an over-encapsulation capsule is its general compatibility with the trial and control doses, as well as any excipients. Considering the low solubility issues associated with today's highly potent APIs, evaluating these factors is becoming more important than ever.

Among the most commonly used excipients for backfilling are microcrystalline cellulose and lactose monohydrate. While both are often used independently of one another and combined in blends, research has shown that combinations of the two can impact dissolution results. Depending on the grade of the material chosen, a lubricant, usually magnesium stearate, is added as part of the backfill formulation (usually less than 0.5%). However, not all grades of these two materials require lubrication, and adding the magnesium stearate is usually based on its presence in the formulation of the unit being encapsulated in the first place.

It is imperative to conduct dissolution profile and stability analyses early in development to verify that the material selected does not interfere with or create any bioavailability issues in the over-encapsulated dose form.

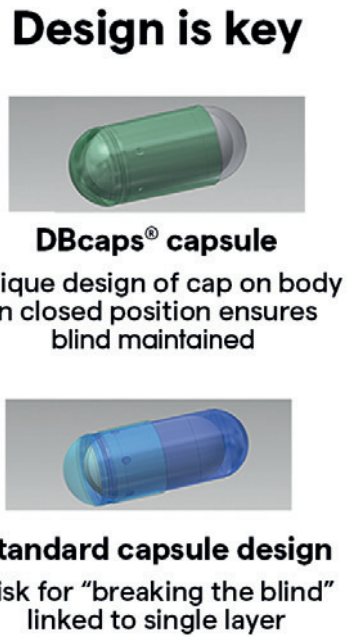

Figure 2: Lonza CHI's DBcaps capsules double-layer the cap over the body which, combined with appropriate use of capsule colouring, ensures that the dose inside cannot be visually identified.

STORAGE AND SHELF-LIFE CONSIDERATIONS

Trial dose supply fill-finishers, among others, should also carefully consider the shelf life of encapsulating shells, along with similar storage-related concerns. For many sensitive potent formulations, storage and inventory control are extremely important to maintain the integrity of trial supplies during long trial cycles.

Extended periods of storage in dry conditions can turn capsules brittle and leave them prone to breaking, filling and quality issues. This is a quality assurance priority that should not be overlooked; close consultation with suppliers may reveal better-performing gelatin capsule materials or alternatives that deliver best-in-class performance and meet the industry's increasing desire for cleaner-label ingredients.

Gelatin or HPMC? A Material Choice

While gelatin-based capsules offer traditional benefits and are backed up with data to prove compatibility, they do not meet clean-label requirements – i.e. being free from animal proteins or with colourings derived from natural sources.

ABOUT THE AUTHORS

Frederique Bordes-Picard is Business Development Manager for Innovative Products at Lonza CHI. Ms Bordes-Picard is a biochemical engineer by training (Bordeaux Polytechnic Institute), she also holds a Master of Business Administration from KEDGE Business School (France). Ms Bordes-Picard has been working in the pharmaceutical industry for more than 20 years, first at AstraZeneca UK working on analytical development of therapeutic proteins and antibodies within Bertin Pharma (now Eurofins), mainly on generic product development and licensing out. Ms Bordes-Picard joined Lonza Capsules and Health Ingredients in 2010 as Pharmaceutical Business Development Manager providing technical and regulatory support for new capsule-based product developments. She has developed specific expertise around cDPI product development and filing, supporting multiple companies working on innovative or generic DPI projects.

Julien Lamps is Product Manager at Lonza CHI, focusing primarily on inhalation and HPMC portfolios. Mr Lamps graduated from École Nationale Supérieure de Chimie de Lille, France with an engineering degree in chemistry in 2004. He later joined Capsugel as a Quality Assurance Engineer in the Colmar plant in 2011. In this role he worked at the interphase of operations and customers, specialising in co-ordinating new product introductions to develop innovative offers around modified-release profiles.

Stephen Rode is Manager of Business Development at Lonza CHI. He received his BSc in Agronomy from Pennsylvania State University, US, and a GBA in Executive Management from The Wharton School at the University of Pennsylvania in 1988. With more than 31 years of industry experience, Mr Rode has worked with many top pharmaceutical and consumer healthcare companies. In addition to sales and business development responsibilities, he has actively participated on various internal capsule development teams.

Capsules based on hydroxypropyl methylcellulose (HPMC) show great potential for becoming the best-practice alternative to gelatin-based formulations, not only because of their provenance but their performance as well. Further benefits include circumventing the regulatory burden of working with animal derivatives and their global market acceptance for multi-centre studies.

HPMC-based capsules are widely preferred in clinical trials, and for many investigational new molecular entities (NMEs), because they have the added flexibility to accommodate a vast array of drug products and formulations. With many potent NMEs in development, the challenges related to deploying APIs in gelatin-based capsules are contributing to a shift towards the use of HPMC-based capsules. Issues with cross-linking reactions and difficulty containing hydroscopic APIs top the list of these challenges.

Benefits of HPMC-Based Capsules

HPMC-based capsules offer a higher moisture tolerance compared with their gelatin-based counterparts, which helps to stabilise formulations and to mitigate the challenges associated with APIs and excipients that are incompatible with gelatin. Furthermore, HPMC-based capsules can boast a wider range of moisture tolerance and can withstand a wider range of temperature variation and fluctuation in storage and transit, meaning there is less chance of the capsule becoming brittle or breaking.

CONCLUSION

Over-encapsulation is one of the simplest solutions for blinding solid oral dosages in comparative clinical trials. Compatibility with the trial API must be the highest priority when investigating options for over-encapsulation. Dissolution, diffusion and stability studies are essential elements of selection and therapeutic performance. Furthermore, patient-centricity is increasingly informing selection and specifying criteria, leading to the development of innovative clean-label HPMC-based capsules compatible with vegetarian and vegan lifestyles.

Of the many blinding options available, the over-encapsulation method using products such as DBcaps from Lonza CHI is one of the most commonly applied options for efficiently controlling and blinding oral solid doses in clinical trials today.

ABOUT THE COMPANY

Lonza's Capsules and Health Ingredients segment is a global capsule and equipment developer and manufacturer, which designs and produces products for a range of oral dosage forms. The company provides customised solutions that optimise formulations to more than 4,000 customers in 100 countries.

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PODD

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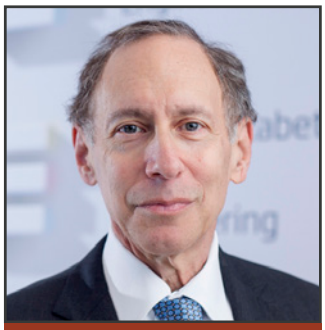

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NANOPARTICLE ENGINEERING AND 3DP DELIVERY FOR GAME-CHANGING ORAL THERAPEUTICS

In this article, Niklas Sandler, PhD, Chief Technology Officer of Nanoform, and Thomas West, Vice-President, Pharmaceutical Development, of Aprecia, consider the technological advances in nanoparticle engineering that can improve the bioavailability and delivery of oral therapeutics.

A total of 85% of the most-sold drugs in the US and Europe are orally administered.[1] With this in mind, technological advances that can improve the efficacy of orally administered therapeutics are vital. Nanoparticle engineering approaches can offer an effective means of improving the solubility, and thus bioavailability, of oral medications. This is significant because poor solubility leads to poor absorption in the gastrointestinal tract, meaning that drugs cannot reach their therapeutic target. For this reason, poor aqueous solubility is a major cause of failure for drug candidates in development.

While technologies such as nanoparticle engineering may be highly effective on their own for solving the challenge of poor solubility and bioavailability, collaboration within the industry is essential to fully optimise the power of new technologies. For example, 3D printing can facilitate therapies with rapid disintegration that are easier to swallow. By combining it with nanoparticle engineering, new opportunities can be created for enhanced patient-centric therapeutics (Figure 1). This article will look at the potential of nanoparticle engineering combined with industry collaboration to benefit patients worldwide.

Figure 1: Nanoform-branded tablet.

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"Innovations that can improve the bioavailability and solubility of small-molecule drug candidates could allow novel small-molecule therapies that would ordinarily have failed to achieve drug development success."

ENHANCING THE PHARMACOKINETICS OF SMALL-MOLECULE DRUGS

Technologies that improve the pharmacokinetic properties of a drug candidate have the potential to set the stage for a new wave of game-changing oral small-molecule and biological drugs. The solubility of a compound is defined as its ability to dissolve in a solvent to produce a homogeneous solution.[2] On the other hand, a drug's bioavailability refers to the extent and rate at which the drug enters the systemic circulation in an unchanged form, thereby reaching its target area.[3] These two variables are linked, with poor solubility being a factor that leads to poor bioavailability and makes it harder for new drug candidates to succeed. This is exacerbated by the present trend towards larger and more complex small-molecule drugs with greater molecular weights and hydrophobicity and, consequently, poor aqueous solubility.

The challenge this creates is evidenced by the difference between the solubility of drugs in development compared with those on the market. In total, 70–90% of in-development drugs fall into the low solubility categories of the Biopharmaceuticals Classification System (BCS).[4] Meanwhile, fewer than 40% of drugs on the market fall under the same classification.[1] Innovations that can improve the bioavailability and solubility of small-molecule drug candidates could allow novel small-molecule therapies that would ordinarily have failed to achieve drug development success.

OPENING UP NEW POSSIBILITIES FOR BIOLOGICS

Improving the pharmacokinetic properties of biologics also opens up new possibilities for drug delivery innovation in a rapidly growing market. Biologics, encompassing therapeutic proteins and other large biomolecules, as well as nucleic acid (DNA and RNA)-based therapies, have exploded in popularity in recent years. In 2020, seven of the top 10 best-selling drugs were biologics.[5] The growth of the biologics market has been impressive and can be attributed in part to their high specificity, potency and safety profiles.

However, despite their success, bringing a biological drug to market comes with a number of challenges. Among these is that the cost of biologic production is high. Biologics can also have stability issues, which can cause loss of activity. Depending on several factors, including the administration route, biologics can also suffer from poor bioavailability. Improvements in technology that can allow the industry to access their potential are vital to help patients unlock the unique benefits of biologics. For example, enhancing the properties of biologics could pave the way for innovations such as an oral insulin formulation. This would remove the need for invasive injections for diabetics and could greatly improve their quality of life.

In light of this, nanoparticle engineering approaches that can improve bioavailability and drug delivery could lay the groundwork for more life-changing drugs to reach the patients who need them.

NANOPARTICLE ENGINEERING PRINCIPLES AND APPROACHES

Reducing the size of API particles increases their specific surface area. This leads to a proportional increase in dissolution rate that is especially noticeable at the nanometre scale, resulting in better absorption of poorly soluble drugs. For example, reducing particle size to 100 nm can result in a 30–40-fold increase in surface area from a 10 µm particle. Meanwhile, a particle of 50 nm can achieve a 1000-fold increase in specific surface area to a 10 µm particle. It is this principle that nanoparticle engineering approaches apply to improve the pharmacokinetic properties of drug candidates (Figure 2).

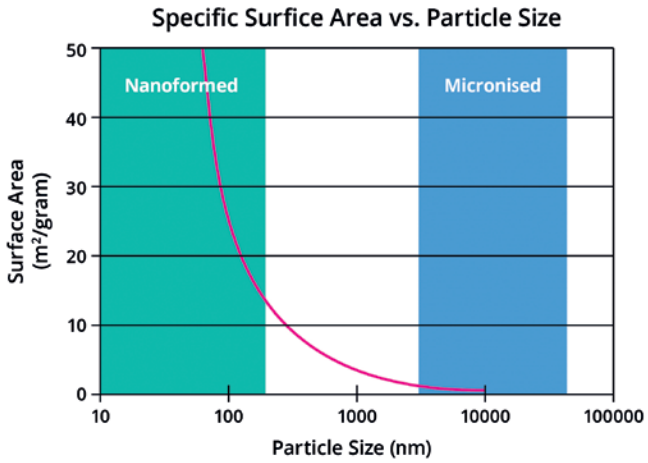

Figure 2: Graph illustrating the relationship between size and surface area for particles.

There are a number of nanoparticle engineering approaches on the market. For example, nanomilling is a technique that can successfully reduce drug particle size by milling in a wet medium. However, the use of mechanical energy to break up the nanocrystals raises surface free energy. This can result in amorphous domains on the crystalline material, introducing inherent instability which can make the API challenging to process further. The end product also requires excipients such as surfactants.

Spray-drying is an example of a popular micron-sized particle engineering method used for overcoming solubility issues in drug development. As the name implies, it works by spray-drying APIs with a polymer to create an amorphous solid and is effective for certain applications. Unfortunately, the technique can produce amorphous material that can create stability issues and make it more challenging to form tablets or capsules.

NANOFORMING DRUG PARTICLES WITH ENHANCED PERFORMANCE

Nanoform's Controlled Expansion of Supercritical Solutions (CESS®) technology is a recrystallisation technique that dissolves and then crystallises small-molecule API particles from a solution of supercritical carbon dioxide ($scCO_2$) without necessitating the use of excipients or changing the API's inherent chemical properties. It is a controlled process, creating uniform particles that are tuneable in size, shape and polymorphic form. $scCO_2$ is also a highly environmentally friendly solvent and offers excellent scalability. Using this technique, it is possible to create nanoparticles below 200 nm in size and, in some cases, as small as 10 nm. This is small enough to cross the blood-

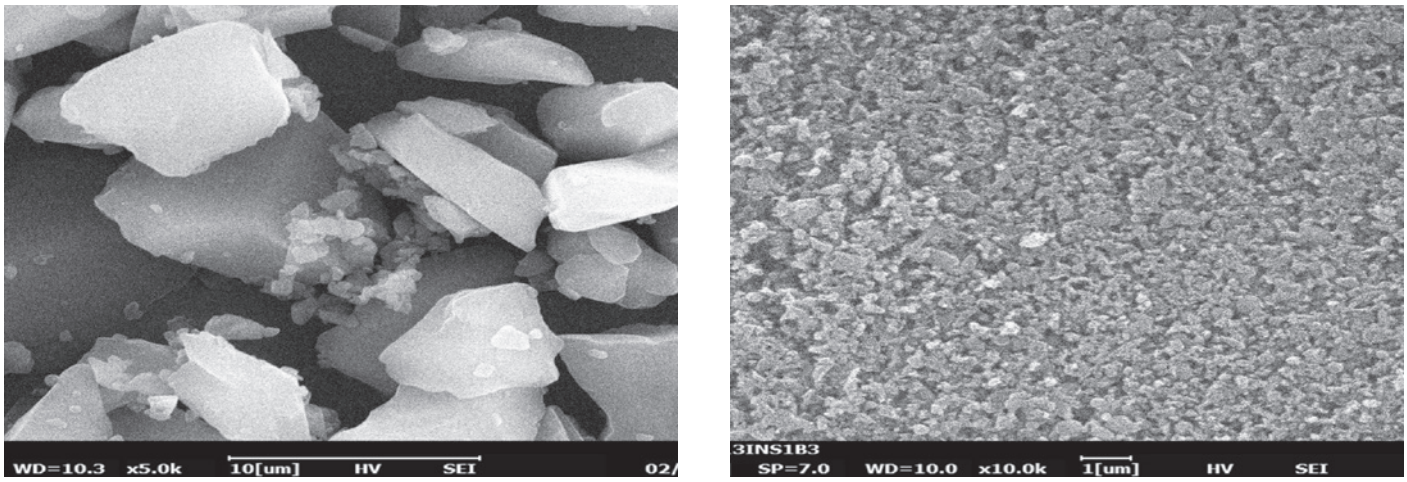

Figure 3: Microscopy images showing insulin particles before (left) and after (right) nanoforming.

> "Nanoform's bio-nanoparticle technology is designed specifically for biologics, and can create stable biological nanoparticles as small as 50 nm. This is a break away from traditional methods that involve attaching the biologic to a drug delivery device, and holds the potential to significantly improve drug delivery of biologics by improving pharmacodynamic properties."

brain barrier, opening up exciting new possibilities for treating central nervous system (CNS) disorders, such as Alzheimer's disease. In addition to creating opportunities for new therapies, this technology could also allow drugs that were previously discarded due to bioavailability issues to be revisited. In this way, CESS could double the number of drugs that reach clinical trials and, ultimately, the market.

Meanwhile, Nanoform's bio-nanoparticle technology is designed specifically for biologics, and can create stable biological nanoparticles as small as 50 nm. This is a break away from traditional methods that involve attaching the biologic to a drug delivery device, and holds the potential to significantly improve drug delivery of biologics by improving their pharmacokinetic properties (Figure 3).

COLLABORATING TO PROVIDE ANSWERS

Collaboration in the industry is essential to bring new innovations to life. The capabilities of CESS have been highlighted by experimental results obtained through a collaboration with Pharmorphix® (acquired by Johnson Matthey) (Cambridge, UK) solid state services. The comparative *in vitro* dissolution study was carried out on piroxicam, an anti-inflammatory drug, and CESS-nanoformed piroxicam particles set a new benchmark in the industry. The release time for CESS-nanoformed particles was more rapid than those created using other industry-standard techniques, including spray-dried amorphous dispersion, micron-sized, co-crystal, milled, and salt and hot-melt extrusion.

The rapid absorption of nanoformed piroxicam was demonstrated in a first-in-human trial of CESS-nanoformed piroxicam, carried out in collaboration with Quotient Sciences (Nottingham UK). The trial investigated the behaviour of single 20 mg nanoformed piroxicam immediate-release (IR) tablets in healthy volunteers, compared with 20 mg tablets of reference products, Feldene (Pfizer) and Brexidol (Chiesi).

Nanoformed tablets had a time of maximum plasma concentration T_{max} of 1.75 h, earlier than both Felden and Brexidol (2.75 h and 2.25 h, respectively). The nanoformed piroxicam tablets exhibited an increased area under the curve (AUC) during the first hour after dosing. Achieved without the use of excipients, the faster absorption observed for nanoformed piroxicam compared with Brexidol provides strong evidence that nanoforming can enable simpler formulation strategies and higher drug loads in final products. This feature is of particular interest for therapies where rapid action is required, such as epilepsy.

Taken together, the results provide compelling evidence that nanoforming can facilitate simpler, faster-acting drug formulations with high drug loads. Further collaborations, however, continue to reveal new possibilities for nanoforming in the industry.

A 3D-PRINTED NANOMEDICINE REVOLUTION

A partnership between Nanoform and Aprecia, a three-dimensional printing (3DP) pharmaceutical company, is set to explore how their respective technologies can be combined to create nanoparticle-enabled 3DP dosage forms (Figure 4).

Figure 4: Tablets created using Aprecia's ZipDose technology showing size progression.

"3DP is an entirely new way of making therapeutic dosage forms, and it can create novel structures that possess different functionality to those made using traditional manufacturing techniques. For example, Aprecia's ZipDose® formulations enable dose loading of up to and beyond 1000 mg that disintegrate in the mouth in seconds when taken with a small sip of liquid."

Figure 5: ZipDose technology enables rapid disintegration in seconds.

3DP is an entirely new way of making therapeutic dosage forms, and it can create novel structures that possess different functionality to those made using traditional manufacturing techniques. For example, Aprecia's ZipDose® formulations enable dose loading of up to and beyond 1000 mg that disintegrate in the mouth in seconds when taken with a small sip of liquid. So, for patients, it is swallowed like an oral solution or suspension. Moreover, ZipDose formulations are also efficient on a mass basis, often incorporating drug (or desired payload) as 40–60% of the total tablet weight (Figure 5).

The unique physical structure of ZipDose units is responsible for this differentiated capability. They are porous and uncompressed, created through selective binding of powder with liquid using the binder jetting style of 3DP. As a result, they resemble a powder that has been carefully "stitched together" using designed patterns of liquid droplets. This structure rapidly wicks liquid into the pores, which disconnects or dissolves the bridges between particles, leading to disintegration in the mouth within seconds. In this way, even very high dose medicines can be provided in an easy-to-swallow format using a small sip of liquid.

By combining ZipDose and CESS to create 3DP dosage forms containing nanoformed API particles, it may be possible to make high-dose medicines easier to take. CESS can improve the effective bioavailability of certain APIs, reducing the total dose of a drug required for the therapeutic effect. Meanwhile, ZipDose technology can be used to provide an easy-to-swallow formulation at any size, including reducing the pill count for medicines that require multiple tablets or capsules at each instance of dosing. The simple case above is of particular benefit to paediatric and geriatric patients, as these populations often have difficulty swallowing large, intact tablets and capsules. This phenomenon, known as dysphagia, affects over 16 million people in the US alone[6] and could occur non-clinically in as many as 40% of Americans.

These improvements in dosage form efficiency, ease of administration and drug absorption could also enable combination therapies that would not have been possible before. For example, 3DP could facilitate a modular dosage form approach, building tablets up in sections with tailored release profiles, or APIs that are separated for stability reasons. The list goes on, with the potential applications of 3DP in combination with nanoparticle engineering promising to open up a new world of novel therapeutics for patients.

SMALL IS POWERFUL

Whether for small-molecule drugs or biologics, methods that can enhance oral drug delivery and bring novel therapies to market hold the potential to significantly improve patient outcomes. The latest nanoparticle engineering approaches offer a tidy solution to the poor

ABOUT THE AUTHORS

Prof 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. Prof Sandler's earlier work focused on novel pharmaceutical manufacturing technologies, process analytics, formulations for additive manufacturing and material characterisation.

Thomas West is the Vice-President of Pharmaceutical Development at Aprecia Pharmaceuticals, focusing on internal pipeline and partnership/licensing opportunities. For over 20 years he has held positions of escalating responsibility, applying 3D printing to the life sciences in start-up to development-stage companies. His experience includes diverse aspects of novel product and process development, regulatory strategy, intellectual property and market assessment. Example applications include rapidly disintegrating oral dosage forms, controlled-release oral and implantable dosage forms and synthetic bone graft substitutes. He is a co-inventor on numerous patents related to 3D printing and co-authored a book chapter outlining the development context for SPRITAM, the first 3D printed pharmaceutical product to receive US FDA approval. Mr West received his BSc and MSc degrees in Chemical Engineering from Rutgers University (NJ, US), and is a registered patent agent.

solubility and bioavailability of new drug candidates, and could significantly improve patients' quality of life through rapid-onset pills with potentially reduced adverse side-effects. Collaboration within the industry is essential to fully realise the potential of new technologies. Combined with 3DP, new possibilities are created that can give hope to patients in all walks of life.

ABOUT THE COMPANIES

Nanoform is an innovative nanoparticle medicine enabling company. Nanoform works together with pharma and biotech partners globally to provide hope for patients in developing new and improved medicines using Nanoform's platform technologies. The company focuses on reducing clinical attrition and on enhancing drug molecules' performance through its nanoforming technologies and formulation services. Nanoform's capabilities include GMP manufacturing, and its services span the small to large molecule development space with a focus on solving key issues in drug solubility and bioavailability, and on enabling novel drug delivery applications. Nanoform's shares are listed on the Premier-segment of Nasdaq First North Growth Market in Helsinki (ticker: NANOFH) and Stockholm (ticker: NANOFS).

Founded in 2003, **Aprecia** received the first and only FDA-approved 3DP pharmaceutical product approval in 2015 and is a global leader in using 3DP technology for commercial-scale, pharmaceutical manufacturing. Aprecia's proprietary 3DP technology includes a multi-patented, binder-jetting, manufacturing system, allowing for both open-bed and in-cavity printing, as well as their advanced formulation and rapid-prototyping platforms. Aprecia uses its ZipDose technology platform to create rapidly disintegrating oral dosage forms that are easy to take and easy to administer. Aprecia licenses its exclusive technology platform to pharmaceutical partners as a means to extend product lines, improve patient reach and experience, and address FDA requirements as a paediatric delivery form.

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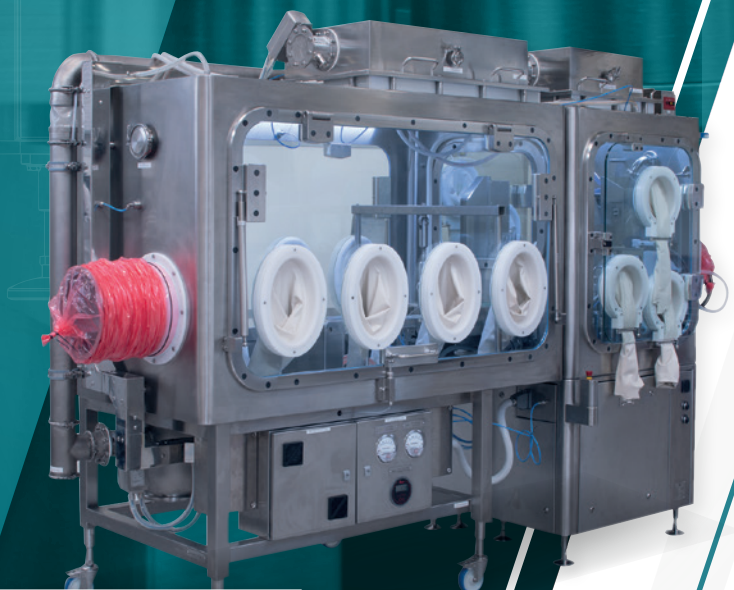

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GASTRIC FLOATING MICROCAPSULES FOR THE MANAGEMENT OF PARKINSON'S DISEASE

In this article, Kaarunya Sampathkumar, PhD, Research Fellow at Nanyang Technological University, Joachim Loo, PhD, Associate Professor and Founder, LiberaTx, and Sashi Kesavapany, PhD, Chief Executive Officer and Co-Founder, LiberaTx, discuss current treatments for Parkinson's disease and explore the benefits of extended-releasing polypharmacy oral formulations.

Parkinson's disease (PD) is a degenerative disorder of the central nervous system and is the second most common neurological disorder after Alzheimer's disease, with an estimated 10 million people being affected.[1] The disease is characterised by an asymmetric onset of bradykinesia, resting tremor, rigidity and postural instability. Symptoms of this motor-degenerative disease stem from the death of dopamine-generating cells in the substantia nigra. The most common treatment for PD is with levodopa (LD), which can help to alleviate the symptoms of the disease by converting to dopamine in the brain. Levodopa improves disability and capacity to perform important activities of daily living. Approximately 85% of patients have some degree of benefit with this therapy.

ISSUES WITH LEVODOPA TREATMENT

LD is not without its issues, however, as chronic administration leads to a pharmacological problem – levodopa induced dyskinesia (LID). It is widely accepted that LID is due, at least in part, to the short half-life of LD. Dyskinesia most commonly occurs at the time of peak LD plasma concentrations during intermittent or pulsatile LD stimulation – peak-dose dyskinesia.[2]

> "On average, LID affects 40% of PD patients after five years of treatment, and 90% of patients by 9–15 years of treatment."

Reviews of observational studies and clinical trials agree that, on average, LID affects 40% of PD patients after five years of treatment, and 90% of patients by 9–15 years of treatment.[3] LID has been associated with exhaustion, fatigue and weight loss due to the excessive involuntary movement in patients, and it is said to limit the PD patient's social life, causing feelings of isolation, frustration and depression.[4]

A study on the direct healthcare costs and predictors of treatment costs associated with LID in the US found that the presence of LID resulted in an increase in total treatment costs of 29% and in PD-related treatment costs of 78% when compared with costs incurred among those patients without LID.[5] Other factors influencing treatment costs were the use of other PD medications and the presence of select comorbidities (psychiatric, cardiovascular, chronic renal disease, injury and fracture). To mitigate LID, a continuous and non-fluctuating provision of LD to the brain is therefore essential.

> "A study on the direct healthcare costs and predictors of treatment costs associated with LID in the US found that the presence of LID resulted in an increase in total treatment costs of 29% and of PD-related treatment costs of 78% when compared with costs incurred among those patients without LID."

Current oral formulations of LD in the market fail to address the issue of fluctuating LD levels, whereby most patients are known to take up to five tablets a day,[6] resulting in a

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rapid sinusoidal rise and decline of LD – the cause of LID. To provide a continuous delivery of LD, other pharmacological strategies, including intestinal infusion, administered through an external device, have since been explored.[7] Intestinal infusion of LD, although effective, has been associated with procedural- and device-related technical problems in 20% to 70% of patients.[8] As oral tablets remain the simplest and most convenient form of drug administration, designing oral formulations that can provide a continuous delivery of LD to the brain is therefore the most feasible approach to mitigate LID in PD patients.

The innovation of an economical, convenient oral formulation that does not disrupt or alter the daily lives of PD patients, while mitigating LID, would therefore provide huge benefits to these patients, whether from a cost or quality-of-life perspective. Along these lines, LiberaTx's technology aims to reduce the requirements and cost of current treatment.

THE TECHNOLOGY

In view of the current clinical problems, the LiberaTx team sought to design a floatable, extended-releasing formulation that permits the sustained release of polypharmacy (i.e. multiple drugs) to mitigate LID. This strategy exploits the stomach as a drug reservoir for the slow release of levodopa into the upper intestinal tract, where levodopa is mainly absorbed by the body.

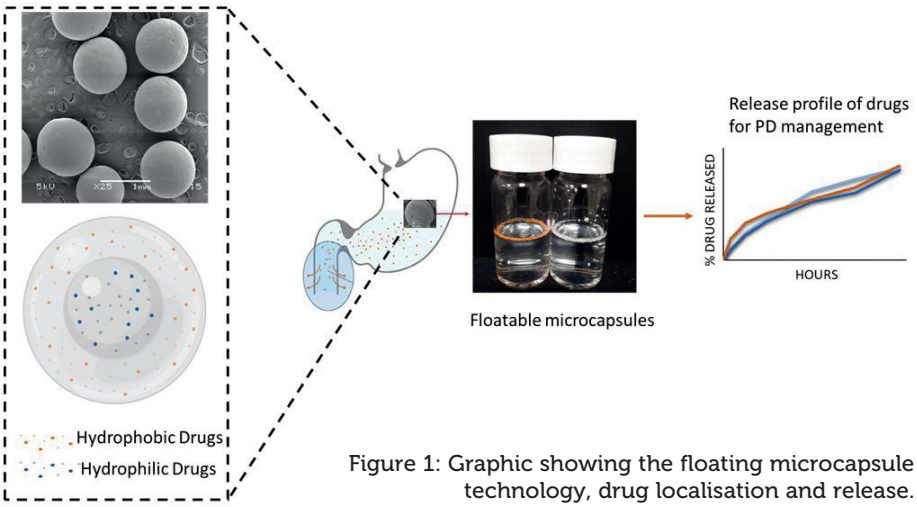

Figure 1: Graphic showing the floating microcapsule technology, drug localisation and release.

This strategy prolongs the gastric retention time of the drugs, and allows for the drugs to be slowly absorbed in the upper gastrointestinal tract (Figure 1). Such a strategy is therefore similar to the levodopa intestinal infusion device but miniaturised into the form of an oral capsule. This avoids the technical problems and undesirable issues of the external infusion device, while avoiding the LID that comes with commercial oral PD tablets. Based on this, LiberaTx has patented a floatable microencapsulation technology that allows for the controlled, sustained release of multiple drugs (polypharmacy) from microcapsules, while avoiding drug-drug interactions.[9,10]

A preliminary pharmacokinetics study of LiberaTx's patented extended-release polypharmacy oral PD formulations to deliver LD in mice has shown highly promising results. If successful, this platform formulation, besides its intended use for PD, can also be exploited for sustained release of polypharmacy in the management of other chronic diseases where patients face a high pill burden.

A simple, economical, scalable and versatile encapsulation process was devised for the production of these multidrug-loaded, sustained-release gastric floating microcapsules.[11,12] Microcapsules co-loaded with LD, carbidopa (CD) and entacapone (ENT) were fabricated through a scalable emulsion technique. In order to attain prolonged gastric residence time, these capsules were designed to be hollow – i.e. of lower density – to attain better floating capabilities.

To achieve different drug release kinetics, several formulations were fabricated. For comparison purposes, an equal amount of PD drugs was encapsulated in these samples at a ratio of 4:1:8 (LD:CD:ENT), so as to replicate an equal drug ratio as commercially available PD tablets – i.e. Stalevo-100 (Novartis, Basel, Switzerland).

> "A preliminary pharmacokinetics study of LiberaTx's patented extended-releasing polypharmacy oral PD formulations to deliver levodopa in mice has shown highly promising results."

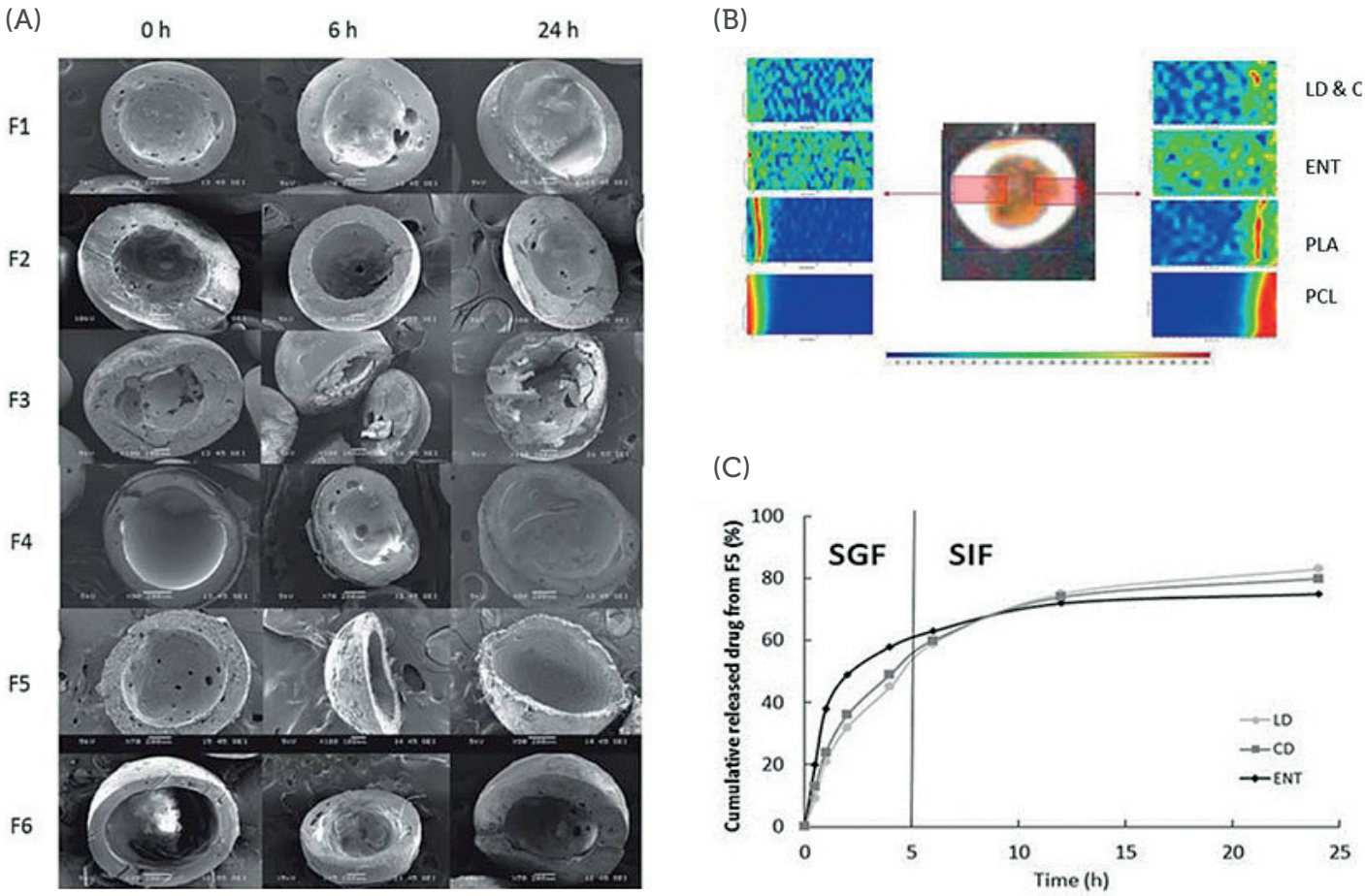

Figure 2: (A) Cross-sectional SEM images of different formulations of spray-coated microcapsules (SC-MC) loaded with LD, CD and ENT in SGF at different time points; (B) Raman mapping of a SC-MC showing the localisation of LD, CD and ENT in different compartments within the particle; (C) *in vitro* release profiles of LD, CD and ENT from optimised formulation in SGF and SIF (simulated gastric/intestinal fluids).

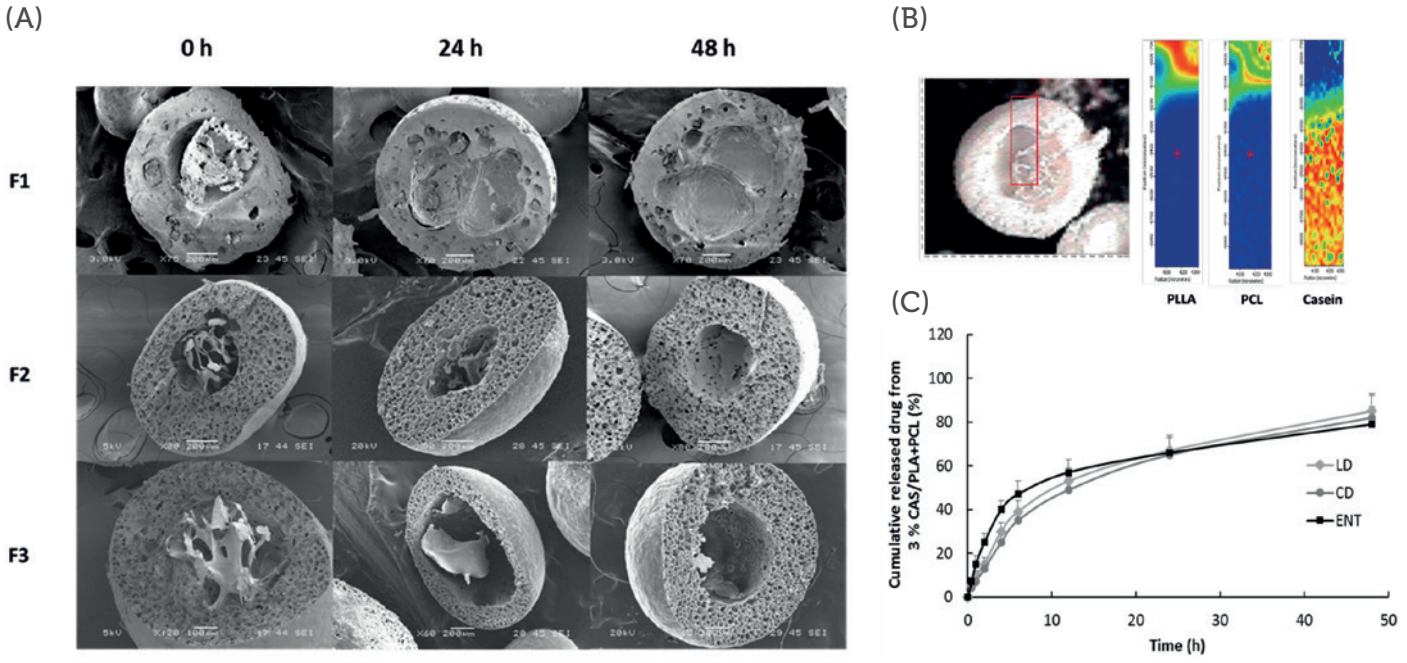

Figure 3: (A) Cross-sectional SEM images of different formulations of casein microcapsules (C-MC) loaded with LD, CD and ENT in SGF at different time points (B) Raman mapping of a C-MC showing the localisation of LD, CD and ENT in different compartments within the particle; (C) *in vitro* release profiles of LD, CD and ENT from optimised formulation in SGF and SIF (simulated gastric/intestinal fluids).

Figures 2(A) and 3(A) show the cross-sectional scanning electron microscopy (SEM) images of the formulations (from top to bottom) with increasing drug release time (left to right). Figures 2(B) and 3(B) show the localisation of the drugs in different compartments of the particle. To test the hypothesis that this advanced polypharmacy drug delivery system can achieve sustained and controlled release of three PD drugs, as opposed to commercially available tablets, the release profiles of the drugs were investigated.

As shown in Figures 2(C) and 3(C), a sustained release of LD, CD and ENT was obtained from LiberaTx's formulations. Pharmacokinetics studies of these formulations in mice showed promising results when compared with commercial formulations (i.e. Stalevo). LiberaTx's extended-release polypharmacy formulations (SC-MC and C-MC) have a superior absorption profile of LD compared with the control at the same drug dosages. Similarly, LiberaTx's formulation showed better bioavailability of LD, and a raised and stable dopamine level in the brain (Figure 4).

The floating microcapsules, as a platform technology, also aim to improve patient medication compliance by providing sustained release of polypharmacy for the management of chronic diseases. In a research paper by HealthPrize Technologies and consulting company Capgemini, medication noncompliance was described as "one of the most serious problems in healthcare", affecting all parties and causing more than just financial drawbacks.[13] According to a recent report, medication non-adherence is costing the global pharmaceutical industry in excess of US$1 trillion (£720 billion) annually.[14] This platform technology is expected to address this colossal issue by reducing the pill burden and improving patient medication compliance.

CURRENT MEDICATIONS AND THEIR LIMITATIONS

Currently there are several commercially available tablets for PD on the market – including Stalevo, Sinemet (Merck Sharp & Dohm, Kenilworth, US), Rytary (Impax Pharmaceuticals, Hayward, US) and Madopar-HBS (Roche, Basel, Switzerland). LD is the main active ingredient in all these formulations. However, administering LD alone results in poor bioavailability.

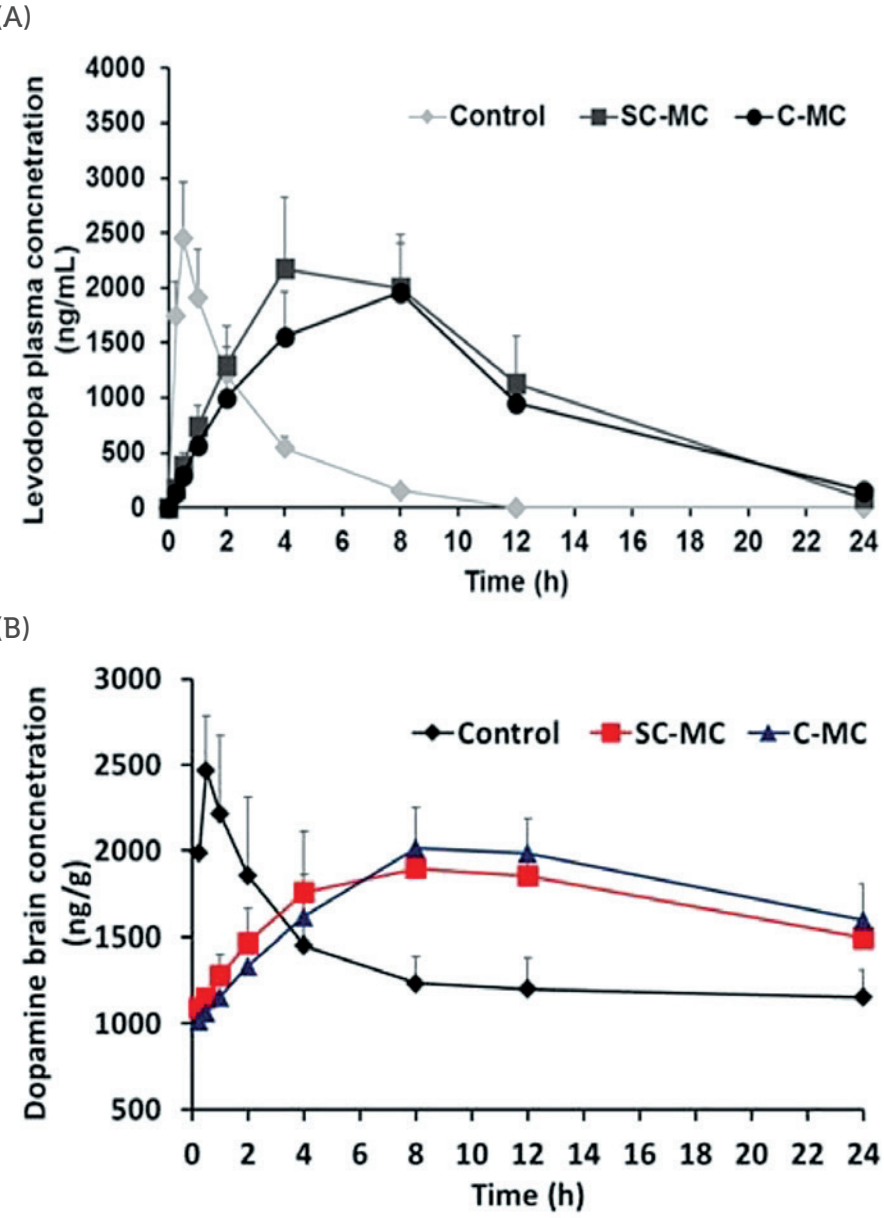

Figure 4: (A) Plasma concentrations of LD and (B) brain dopamine concentrations from control (i.e. commercial formulation) and LiberaTx's two patented formulations (SC-MC and C-MC).

> "LiberaTx's extended-release polypharmacy formulations have a superior absorption profile of LD compared with the control at the same drug dosages. Similarly, LiberaTx's formulation showed better bioavailability of LD,and a raised and stable dopamine level in the brain."

To increase bioavailability, some formulations include other drugs, such as CD and/or ENT. For example, Sinemet (a two-drug formulation) is a combination of CD and LD, and Stalevo (a three-drug formulation) contains LD, CD and ENT. CD is an inhibitor of aromatic amino acid decarboxylation. ENT, a catechol-O-methyltransferase (COMT) inhibitor, is a nitro-catechol-structured compound. These drugs work synergistically to increase bioavailability of LD in the brain for conversion to dopamine. Table 1 summarises these marketed tablets and the issues associated with them. While there have been a number of

Marketed Technology	Issues with Marketed Tablets
Sinemet (*Merck Sharp & Dohme*) and Stalevo (*Novartis*)	• Lack the capabilities of providing controlled and sustained release of multiple drugs. • Do not possess prolonged gastric retention time. • Although controlled release versions of these are available, their pharmacokinetics are still less than desirable. • Require multiple dosing daily, thus reduce patient compliance and cause LID.
Madopar-HBS (*Roche*)	• A levodopa and benserazide releasing floating system, which is used in PD. The controlled release is based on the dissipation of hydrated boundary layers upon the dissolution of gelatin capsules. • A single-unit floating system, which is unreliable in prolonging the gastric retention time owing to its "all-or-nothing" emptying process. • Results in high variability in bioavailability and local irritation due to a large amount of drug delivered at a particular site of GI tract. • Although Madopar-HBS showed improvement over standard Madopar, the bioavailability is reduced as compared with standard Madopar (60–70%), due to incomplete absorption.

Table 1: Issues with current marketed tablets for Parkinson's disease.

extended-release formulations for LD/CD combinations, there have not been any such products for the LD/CD/ENT combination, until LiberaTx's formulation.

A secondary clinical problem that presents in PD patients is medication non-compliance. Adherence to medication is critical for the management of chronic conditions. In fact, for neurologically incapacitated patients (i.e. stroke, Alzheimer's disease, PD, mental disorders, etc.), poor adherence to prescribed drugs remains the key reason for sub-optimal clinical outcomes. Medication non-adherence is observed among 50% of patients with chronic illnesses, and the common reasons are forgetfulness and complex medication regimens,[15] and is one of the most common causes of therapeutic failure, costing $290 billion per year in the US alone.[16] Extended-releasing polypharmacy oral formulations therefore address the issue of medication non-compliance by lowering the pill burden, while enhancing recovery or managing chronic diseases.

"Medication non-adherence is observed among 50% of patients with chronic illnesses, and the common reasons are forgetfulness and complex medication regimens, and is one of the most common causes of therapeutic failure, costing $290 billion per year in the US alone."

ABOUT THE COMPANY

LiberaTx is a spin-out company forged from the material sciences research expertise of Dr Joachim Loo at Nanyang Technological University (Singapore) and Dr Sashi Kesavapany, who has pharma experience in neurodegeneration. LiberaTx seeks to address the unmet medical need of enhancing oral bioavailability of medications for various diseases. Using its proprietary technology, LiberaTx reformulates existing marketed pharmaceuticals to improve treatment outcomes, while reducing the pill burden on patients. In addition, LiberaTx is working with partners to formulate novel biopharmaceuticals and nutraceuticals to promote general health and well-being. The first therapeutic assets are being positioned for alleviating LID in Parkinson's disease.

ABOUT THE AUTHORS

Joachim Loo, PhD, is an Associate Professor at Nanyang Technological University (Singapore) and Founder of LiberaTx, with close to 20 years of experience and expertise in designing and developing drug delivery technologies for controlled release. He is Principal Investigator of several grants that led to this patented floating microcapsule technology and has published more than 200 papers and filed 16 patents, with seven of these granted in various countries. Has also developed a radioactive drug delivery system in collaboration with the International Atomic Energy Agency (IAEA), United Nations, and is co-convenor of the ISO-TC229 – Nanotechnology (Health and Safety) Committee.

Sashi Kesavapany, PhD, is Chief Executive Officer and Co-Founder of LiberaTx, and has 20 years' post-PhD experience in target and disease biology. After two postdoctoral stints in KCL and at the NIH, he moved his neurodegenerative R&D into translational models of Alzheimer's disease and neuroinflammation. He was an Assistant Professor in NUS until 2009. He then headed *in vitro*, *in vivo* and pharmacological teams in GlaxoSmithKline R&D, working on a number of programmes in the R&D portfolio, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease and spinal muscular atrophy. He has routinely managed hitID and *in vivo* PK/PD experiments that progress molecules through the drug discovery pipeline.

Kaarunya Sampathkumar, PhD, is a Research Fellow in the research team led by Dr Joachim Loo in the School of Materials Science and Engineering at Nanyang Technological University (Singapore). She has a master's degree in Medical Nanotechnology from SASTRA University (India) and received her PhD from Nanyang Technological University. Her main research interest is the encapsulation and controlled delivery of active ingredients using micro/nanoparticles using both synthetic and natural polymers for oral delivery and her expertise lies in the gastro retentive drug delivery system for Parkinson's disease and other indications.

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ANALYTICAL TECHNIQUES FOR THE FORMULATION OF GASTRORETENTIVE TABLETS

In this article, Jamie Clayton, Operations Director, Freeman Technology, Phil Bone, PhD, Technical Service and Applications Specialist, Micromeritics, and Kyu Mok Hwang, PhD, Postdoctoral Researcher, Sungkyunkwan University, discuss the value of analyses such as mercury porosimetry and powder rheology in characterising excipients for gastroretentive tablet formulation, and go on to detail a case study investigating polymer excipients for a novel bilayer floating tablet.

For certain drugs, formulation into a gastroretentive (GR) oral solid dosage (OSD) form can be a successful strategy for improving bioavailability and therapeutic efficacy. Such drugs include those in Biopharmaceutics Classification System (BCS) Class IV, which covers actives with low solubility and low permeability, and as such present some of the toughest formulation challenges. Prime targets for GR OSD forms are drugs for local action in the stomach, with a narrow absorption window (NAW) or with poor solubility or stability under alkaline conditions. Improving the gastroretention of such drugs can boost efficacy, and at the same time enable a streamlined dosing regime via sustained or controlled release. Expandable, swelling, floating, mucoadhesive and high-density systems are all routinely deployed depending on the properties of the drug and the required delivery profile.[1]

This article considers the specific challenge of developing floating GR OSD forms and the analytical techniques that can be deployed to support their formulation. Experimental work by researchers at the School of Pharmacy, Sungkyunkwan University[2] highlights the value and relevance of porosity and powder flowability measurements in the development of novel, bilayer GR tablets.

FORMULATING TABLETS THAT FLOAT IN THE STOMACH

In both the fed and fasting states, the stomach empties on a regular basis, which can be problematic when it comes to the efficacy of OSD forms. Short periods of intense, regular contractions sweep undigested food from the stomach to the small intestine, potentially removing drugs from their preferred location of activity. For drugs that have a NAW in the first part of the gastrointestinal tract (GIT), that are prescribed for local action or that only dissolve or absorb effectively under acidic conditions, this action effectively brings drug delivery to a halt, limiting bioavailability.[3]

> "Prime targets for GR OSD forms are drugs for local action in the stomach, with a NAW or with poor solubility or stability under alkaline conditions. Improving the gastroretention of such drugs can boost efficacy, and at the same time enable a streamlined dosing regime via sustained or controlled release."

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"Sustained release formulations are associated with high patient compliance and provide lower, more consistent drug concentrations, reducing the risk of undesirable systemic effects. Technologies that enhance gastroretention increase the viability of sustained release, with floating tablets being the most practical and widely studied approach."

A range of different formulation strategies have been deployed to increase gastroretention, notably for sustained release products. Sustained release formulations are associated with high patient compliance and provide lower, more consistent drug concentrations, reducing the risk of undesirable systemic effects. Technologies that enhance gastroretention increase the viability of sustained release, with floating tablets being the most practical and widely studied approach.[1] Formulated to have lower density than the gastric juices (density of approximately 1.0 g/cc), such tablets rise to the top of the stomach to reduce the risk of removal. Examples of commercial floating tablets can be classified on the basis of whether they deploy effervescent or non-effervescent systems, and include products such as Cifran OD® (Ranbaxy, India), an antibiotic, and Madopar NBS® and Prolopa HBS® (both Roche, UK), which are both prescribed for Parkinson's disease.

The successful formulation of floating GR products relies on controlling the properties of the tablet to achieve the required retention time and drug release profile *in vivo*, under the specified conditions of use. Tablet size, shape and density can all be optimised to meet these goals, with polymers frequently incorporated to impart buoyancy via swelling or the incorporation of air. However, formulation is complicated by the need to:

- Achieve immediate buoyancy – delayed buoyancy, such as that imparted by slowly swelling polymers, risks premature product loss
- Ensure that the tablet is sufficiently mechanically robust to withstand gastric action for the duration of drug delivery
- Simultaneously control both the drug release profile and tablet residence time – often parameters that are manipulated to improve strength or buoyancy simultaneously impact drug release.

Measurement of the physicochemical properties of excipients and the finished product provides a foundation for the development of a successful product.

WHICH ANALYTICAL TECHNIQUES CAN HELP?

While the formulation of floating GR OSD products has much in common with that of conventional tablets, the need to understand and control buoyancy is distinct. Furthermore, excipients, such as sublimating agents, that can be used to impart porosity (and by extension buoyancy) can increase the cohesiveness of tableting blends, making them harder to process.[2] Against this backdrop, the following analytical techniques are noteworthy in terms of their ability to provide valuable insight.

Mercury Porosimetry – Detailed, Comprehensive Pore Size Characterisation

Mercury porosimetry quantifies median pore size, pore size distribution and other porosity parameters, from measurements of the amount of mercury that penetrates a sample as a function of pressure (Figure 1). Washburn's equation describes the direct correlation between pore size and the pressure required for pore filling. Relative to other techniques for porosity characterisation, mercury porosimetry is fast and accurate, offers a very wide dynamic range – from a pore size of 3 nm to 0.36 mm – and generates more detailed results. For example, it can be used to determine tortuosity within a tablet and information about pore shape.

Using mercury porosimetry on tablets generates data that can inform on mechanical strength and fluid transfer within the tablet. Pore structure governs fluid transfer and quantifies the resistance to fluid penetration of the tablet, elucidating its wetting characteristics.[4] If a tablet exhibits any elastic behaviour due to the incorporation of polymeric additives, then this would also be observable in a comparison of mercury intrusion and extrusion profiles. Such data can elucidate disintegration behaviour and provide fundamental insights into dissolution performance. For GR OSDs, detailed porosity measurements can make it easier to understand how to simultaneously engineer tablet robustness and buoyancy.

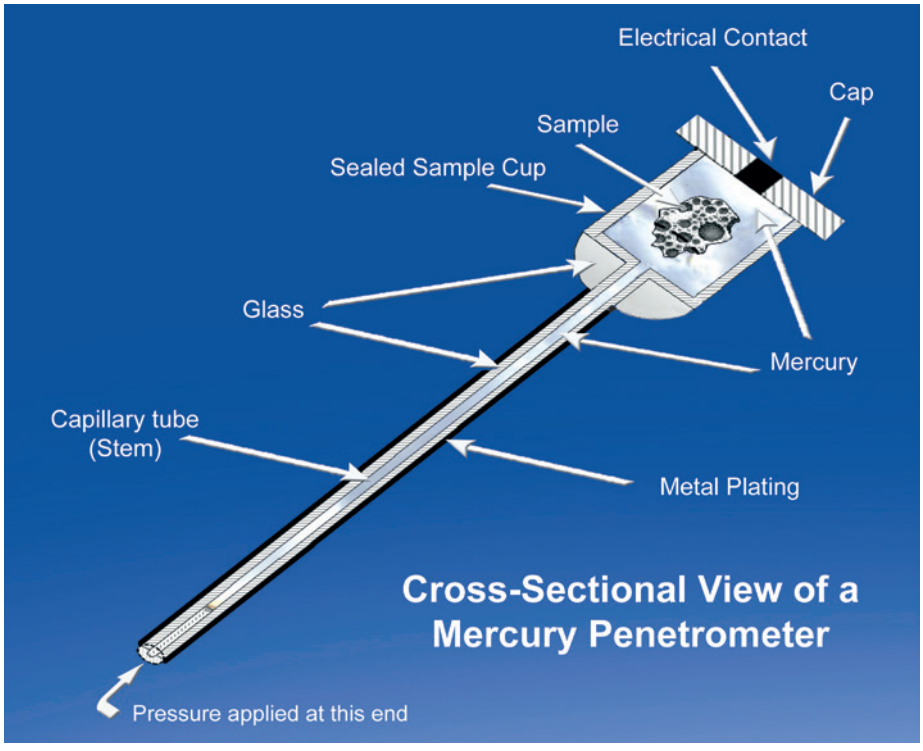

Figure 1: Mercury porosimetry involves measurement of the amount of mercury forced into the pores of a sample as a function of pressure.

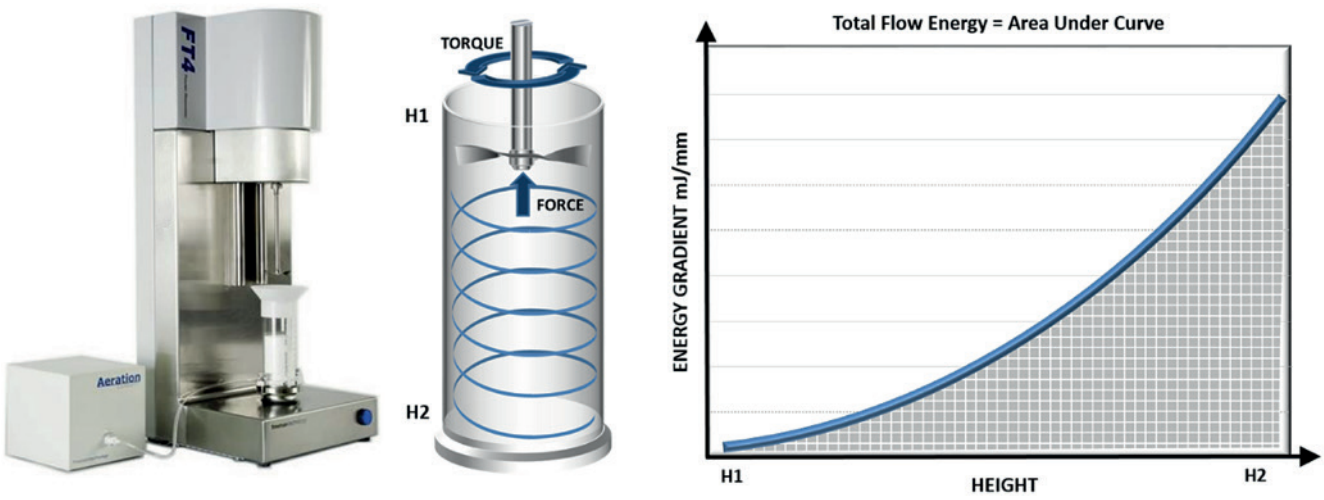

Figure 2: Dynamic testing can quantify the flow behaviour of powders in a consolidated, moderate stress, aerated or fluidised state.

Dynamic Powder Testing – Sensitive, Relevant Powder Flowability Measurement

Powder flowability can be assessed using a range of techniques, including those specified in United States Pharmacopeia (USP) 1174 – shear cell testing, flow through an orifice, angle of repose and tapped density methods. However, experience underlines the superior sensitivity and relevance of dynamic powder testing for many pharmaceutical applications, including tableting.[5] Dynamic testing involves the generation of flow energy values from measurements of the axial and rotational forces acting on a precision-engineered blade as it rotates through a powder sample. Powders can be tested in a consolidated, moderate stress, aerated or fluidised state to simulate the process of interest, a capability which sets dynamic testing apart from other methods (Figure 2).

Dynamic properties are measured using well-defined, largely automated protocols, including basic flowability energy (BFE) and specific energy (SE), which respectively quantify the confined (forced flow) and unconfined (gravity flow) flow properties of a powder in a low stress state. Dynamic measurements are highly repeatable and reproducible, and the technique is associated with exemplary sensitivity, with the ability to differentiate powders that other test methods classify as identical.

Flowability is a critical characteristic for tableting blends that impacts the efficiency of die filling and, more generally, the ease and consistency of powder movement through a tableting press. Indeed, flow additives are routinely incorporated into tableting blends to enhance flowability and facilitate the production of high-quality tablets of uniform weight at an economically attractive rate. With dynamic testing it is possible to quantify flow behaviour under different conditions to directly simulate specific steps of the tableting process. Furthermore, since instrumentation for dynamic testing also enables shear and bulk property measurement, it is also possible to generate highly relevant data for hopper discharge (shear cell and permeability) and tablet compression (bulk density, permeability and compressibility).

CASE STUDY: DEVELOPING A BILAYER GR TABLET WITH HYDROPHOBIC POLYMERS

A recent study by researchers at Sungkyunkwan University illustrates the challenges of GR formulation and the insights provided by the aforementioned analytical techniques.[2] The goal of the study was to develop a strong bilayer floating GR tablet for the sustained release of rebamipide (RBM). A BCS IV drug used to treat gastric ulcers and gastritis, RBM has low oral bioavailability, due to poor, regionally variable permeation. A GR sustained release formulation has the potential to significantly enhance the therapeutic potential of RBM, which currently relies on high-frequency dosing. In contrast to conventional practice, the researchers chose to investigate the use of a hydrophobic, rather than hydrophilic, polymer to create a strong, inert matrix capable of withstanding gastric action, post-hydration.

Tablets were prepared using two discrete powder blends, one to form the GR layer, the other to form the drug release layer. The GR layer was a blend of polymer – either Kollidon® SR (BASF, Ludwigshafen, Germany) or polyethylene oxide (PEO) 7M (Polyox® WSR 303 – DuPont, Wilmington, DE, US) – and varying levels of camphor (Junsei Chemical, Tokyo, Japan), a sublimating agent. The drug layer was a wet granulated blend of RBM (Estech Pharma, Seoul, South Korea) and dicalcium phosphate (DCP) (Calipharm A®, Innophos, NJ, US) mixed with colourant and polymers to control erosion and the rate of drug release. MgSt (Daejung Chemical, Siheung, Korea) and Aerosil® R972 (Evonik, Essen, Germany) were added to both blends ahead of compaction to improve flowability and tableting performance.

Complete tablets were produced using a two-step process. The first step involved manual filling of the die with the GR layer, followed by pre-compression. The drug layer was then added, and the entire tablet was subject to a compression force in the range 0.5–1.5 tons. Tablets were then dried at 60°C for 12 hours in a vacuum oven to ensure complete sublimation of the camphor prior to stabilisation and subsequent analysis. Single GR layer tablets were also produced for further analysis.

A range of analytical tests was applied to rationalise and optimise the performance of the tablets, including:

- Gas pycnometry (AccuPyc 1340 – Micromeritics) to determine the volume fraction of the polymeric drug release agent in the drug layer
- Scanning electron microscopy (SEM) (JSM-6010 plus LA model scanning microscope – Jeol, Tokyo, Japan) to investigate particle morphology
- Tests to assess tablet performance – hardness, hydrated drug layer strength, buoyancy and dissolution performance.

Porosity Measurements

Mercury porosimetry measurements (AutoPore IV 9500 V1.09 – Micromeritics) were carried out in accordance with the standard protocols for the instrument to investigate the structure of the GR layer.

	Kollidon® SR	PEO 7M
Median Pore Diameter (V) (nm)	1981.5	6888.8
Median Pore Diameter (Area) (nm)	4.1	12.7
Average Pore Diameter (4V/A) (nm)	40.7	295.9
Bulk Density (g/mL)	0.7852	0.7653
Apparent (Skeletal) Density (g/mL)	1.1388	1.1215
Porosity (%)	31.0491	31.7625

Table 1: Porosity metrics and pore size distribution data for GR single layer tablets produced using 20% camphor and a 1 ton compression force.

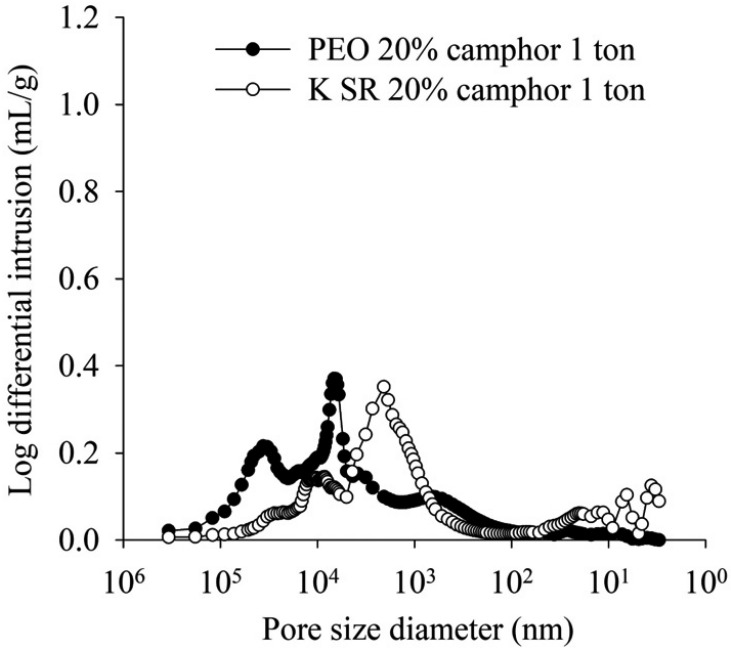

Figure 3: Fluid intrusion for two tablets with differing pore diameters.

The data shown in Table 1 and Figure 3 show the impact of polymer choice on developed porosity. Although average porosity and density are similar in each case, the Kollidon® SR formulation has much smaller pores. This difference may be attributable to the differing morphology of the two polymers; the Kollidon® SR particles are finer – a volume-weighted average particle diameter of around 60 µm compared with 157 µm for the PEO 7M – with a more regular, spherical shape and smoother particle surface (SEM data – not shown). The hollow structure of the Kollidon® SR and small cavities in the particles might also be a contributing factor. In contrast, the PEO 7M particles are larger, denser and more irregular in shape.

Figure 4 shows data illustrating the impact of camphor concentration and compression pressure on the porosity of Kollidon® SR samples. These results show that total porosity can be increased either by reducing compression force or increasing camphor concentration. The only two formulations that produced floating bilayer tablets were those with the highest total porosity, those produced with 20% camphor at 0.75 tons and 0% camphor at 0.5 tons. The data also suggest that the inclusion of camphor results in an appreciable population of relatively large pores, relative to those produced by the compaction process. These results are again consistent with the SEM data, which show that, after sublimation, the Kollidon® SR matrix, though quite coherent, includes many pores that are substantially bigger than neighbouring particles.

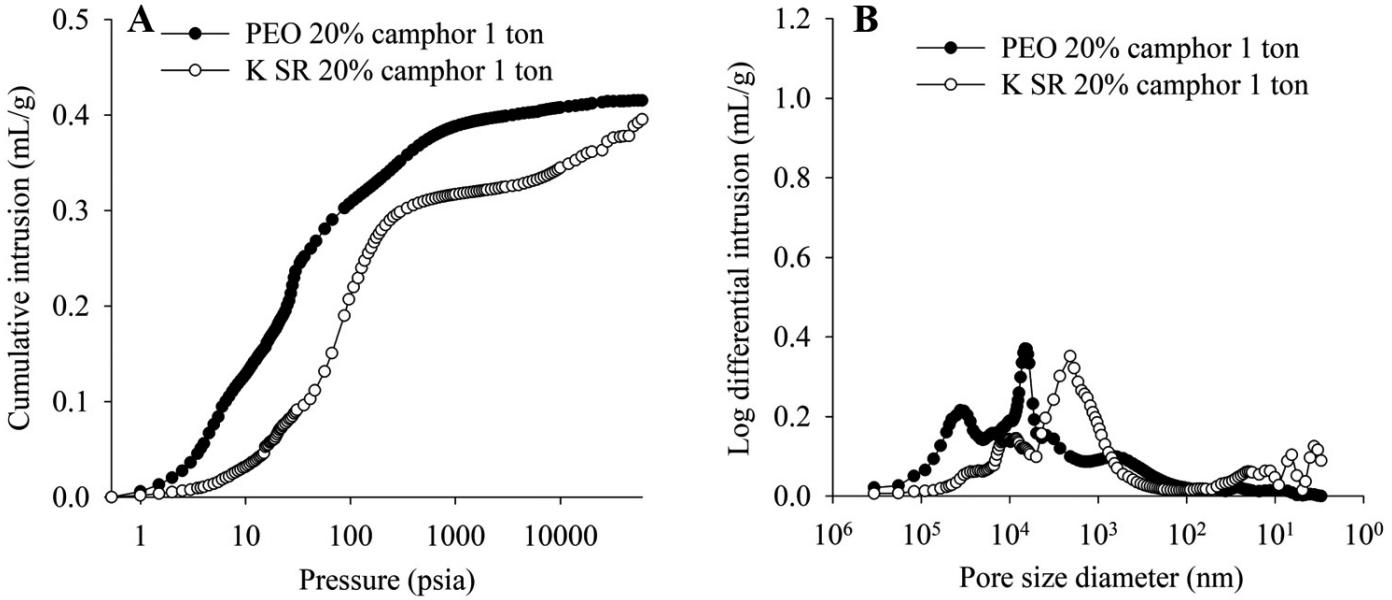

Figure 4: Porosimetry data showing the impact of camphor concentration and compression force.

	Parameters	Kollidon® SR	PEO 7M
Convential Methods	Angle of Repose (°)	29 ± 1	33 ± 2
	Carr's Index (%)	8 ± 1	12 ± 3
FT4 Powder Rheometer	Bacis Flowability Energy (mJ)	55.30 ± 0.89	295.37 ± 12.21
	Specific Energy (mJ)	2.33 ± 0.14	8.40 ± 0.18
	Flow Rate Index	1.53 ± 0.04	2.75 ± 0.47
	Conditioned Bulk Density (g/mL)	0.487 ± 0.006	0.406 ± 0.002

Table 2: Flow property data for GR blends incorporating 20% camphor.

These results illustrate the importance of measuring pore size distribution rather than averaged porosity metrics, which failed to detect differences between the two polymers. They also show how camphor and compression force can be manipulated to achieve highly porous tablets that also have the strength and hardness required; tablets produced with excessive levels of camphor or at low compression were shown to lack viable hardness. Such insights are critical when developing tablets that combine the required mechanical characteristics with *in vivo* buoyancy.

Flowability

The flow behaviour of GR blends incorporating optimised levels of camphor was characterised using traditional techniques (angle of repose and Carr's index) and by dynamic testing (FT4 Powder Rheometer® – Freeman Technology) using standard testing protocols for the instrument (Table 2).[6] The dynamic parameters measured include BFE, SE and flow rate index (FRI), which is determined by measuring BFE as a function of blade-tip speed (FRI is defined as BFE at 10 mm/s divided by BFE at 100 mm/s).

Both traditional powder testing methods classify the Kollidon® SR as having 'excellent' flow properties compared with the 'good' classification of the PEO 7M. However, the variability of these data is such that the two powders are barely differentiated, particularly by Carr's Index. Furthermore, the results are contrary to expectations on the basis of particle size, since finer particles typically exhibit relatively poor flowability. In contrast, the dynamic and bulk property values exhibit greater repeatability and more robust differentiation. In addition, since dynamic testing enables the simulation of process conditions, these properties can be used to investigate which formulations are likely to perform well in the various steps of a tableting process.

BFE data reflect flow behaviour under forced conditions, such as in the feed frame of a tablet press. BFE values for PEO 7M are substantially higher than for Kollidon® SR, indicating that it presents greater resistance to flow under these conditions and is more likely to perform poorly in this type of unit operation. This result may be attributed to the smooth, regular morphology of the Kollidon® SR particles, which is typically more conducive to good flow characteristics.

SE data are more relevant to gravitational powder flow, but similarly highlight the greater flowability of the Kollidon® SR. SE values are strongly influenced by inter-particle friction and mechanical inter-locking. These results again suggest that the PEO 7M is the more cohesive powder and further underline the impact of the morphology of the Kollidon® SR, which is likely to reduce mechanical and frictional forces within the powder.

FRI data similarly indicate the greater cohesiveness of the PEO 7M, since more cohesive powders are generally more sensitive to changes in flow rate because of their greater tendency to entrain and trap air. Bulk density data for the two polymers supports the hypothesis that the Kollidon® SR is more efficiently packed and contains less air. From a practical perspective, these data suggest that the PEO 7M is likely to be more sensitive to changes in processing rate.

> "The development of GR tablets, and more specifically floating tablets, is a promising strategy for active ingredients that are not easily delivered via more conventional OSD forms."

In summary, the flow data provide consistent evidence that the Kollidon® SR blend is likely to perform better at every stage of the tableting process, compared with an equivalent PEO 7M blend, with dynamic testing providing more sensitive and relevant insight than can be accessed via traditional methods.

CONCLUSION

The development of GR tablets, and more specifically floating tablets, is a promising strategy for active ingredients that are not easily delivered via more conventional OSD forms. However, formulating such tablets is a demanding task, complicated by the need to engineer both buoyancy and the mechanical strength required to withstand gastric action for an appreciable residence time.

The study presented here shows how mercury porosimetry and powder rheology can be applied to generate data to support excipient choice and successful product development. Both techniques played a role in helping researchers to develop a successful bilayer tablet with a highly porous, hydrophobic GR layer with superior mechanical strength and tableting properties, compared with conventional hydrophilic alternatives.

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ABOUT THE COMPANIES

Freeman Technology, a Micromeritics company, specialises in systems for measuring the flow properties of powders and has more than 15 years' experience in powder characterisation. It invests significantly in R&D and applications development, and provides full support alongside its range of products.

Micromeritics is a leading supplier of high-performance systems to characterise particles, powders and porous materials with a focus on physical properties, chemical activity and flow properties. The company's technology portfolio includes: pycnometry, adsorption, dynamic chemisorption, intrusion porosimetry, powder rheology, activity testing of catalysts, and particle size. Micromeritics has R&D and manufacturing sites in the US, UK and Spain, and direct sales and service operations throughout the Americas, Europe and Asia. Micromeritics systems are the instruments of choice in more than 10,000 laboratories of the world's most prestigious government and academic institutions and most innovative companies. The company's world-class scientists and responsive support teams enable customer success by applying Micromeritics technology to the most demanding applications.

Sungkyunkwan University is a national university with 622 years of history and tradition. The university has led the development of higher education in Korea by challenging and innovating with a mind for sharing and coexistence. Sungkyunkwan University intends to make a leap forward to become a globally leading university and contribute to the prosperity and development of humanity along with other prestigious universities in the world.

ABOUT THE AUTHORS

Jamie Clayton is Operations Director at Freeman Technology. He graduated from the University of Sheffield (UK) with a degree in Control Engineering and is responsible for overall management of company activities, including the R&D, production, sales and customer support teams. During his time with the company, Mr Clayton has worked as a mentor with several academic groups and is an active member of ASTM F42. He is also a regular contributor to conferences and workshops on the topic of powder rheology and works closely with clients on the application of the company's technology.

Dr Phil Bone is a Technical Service and Applications Specialist at Micromeritics, and studied Medicinal Chemistry at the University of Leeds. This and an industrial placement during his degree have created a lifelong interest in pharmaceuticals. A PhD on the computational design and synthesis of analogues of a glycopeptide antibiotic further strengthened that interest. Following his PhD, Dr Bone worked at a CRO that specialised in sono-crystallisation and particle engineering, before becoming a service engineer covering laser diffraction and image analysis systems. He joined Micromeritics as a service engineer in 2015, and last year moved into a hybrid role to offer greater support to the company's pharma customers. He now covers service and application support for the UK.

Dr Kyu-Mok Hwang is a research scientist working in JW Pharmaceutical, South Korea. Kyu-Mok received his BSc degree in Pharmacy in 2012 from Sungkyunkwan University. Afterward, he received his PhD in manufacturing pharmacy from the same university, where he also finished his postdoctoral study. His thesis project focused on the development of a solid dosage form for gastroretentive drug delivery, including multiparticulates and bilayer tablets, which are amenable to scale up. His postdoctoral project focused on understanding the role of formulation and roller compaction on granule and tablet properties, including tabletability, granule flow and tablet dissolution.

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FORMULATION SOLUTION FOR MOISTURE-SENSITIVE DRUGS

In this article, Laura Canalejas, Scientific Business Development Manager at Qualicaps Europe, outlines the benefits of Quali-V® Extra Dry – a hypromellose capsule designed for moisture-sensitive formulations.

It is well known that moisture affects the performance of some drug products, presenting a fierce challenge in the formulation of oral dosage forms. Moisture may have a significant impact on a wide range of chemical, physical and microbial properties of the finished pharmaceutical product, leading to a degradation of the API and a subsequent loss of potency and reduced shelf life.

The interaction of moisture with pharmaceutical solids is essential to an understanding of water-based processes, for example, manufacturing processes or prediction of the stability of solid dosage forms. Furthermore, both the API and excipients have different moisture sorption properties that can result in unexpected processing-induced phase transitions.[1]

Dosage forms are exposed to moisture from many sources – including bulk drug, excipients, manufacturing processes, environmental conditions, etc.[2] In terms of excipients, using hard capsules could contribute to minimising the potential moisture effect on the formulation since they act as a container and therefore as a physical barrier to protect the filling content.

Back in the 1990s, Qualicaps introduced the first vegetal capsule based on hypromellose (HPMC) into the pharmaceutical market, branded as Quali-V®. This plant-based capsule made it possible to overcome stability issues that had emerged in gelatin capsules and were prevailing in the two-piece capsules market from the 19th century.

Despite the low moisture content present in HPMC capsules (three times reduced versus gelatin capsules), there are still some APIs (e.g. pancreatin, omeprazole, ranitidine, dabigatran and tiotropium) and excipients (polyethylene glycols, acid glycerol esters and acid triglycerides) whose hygroscopicity and sensitivity to moisture may alter the properties of the product.

Such hygroscopic and moisture-sensitive compounds could be challenging for formulators and may involve extra investment due to the need to apply different pathways to protect the API – i.e. galenic forms such as pellets or capsule-in-capsule technology, a final additional drying process after filling or the use of moisture-protective packaging materials. The possibility of drying the filled capsule to reduce the water content as much as possible exposes the whole filling to harsh drying conditions. Furthermore, adding an additional step in the process after the filling involves extra resources in terms of capabilities (with dedicated equipment, room, human resources and conditions) and timing, extending the process up to 12–14 hours and thus decreasing the overall yield.

Quali-V® Extra Dry, the HPMC Capsule Designed for Moisture-Sensitive Formulations

Qualicaps, the pioneer hard capsule manufacturer, which developed the

> "The production process for Quali-V® Extra Dry was adapted to incorporate an extra drying phase by using unique equipment developed by Qualicaps Europe."

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"In HPMC capsules, water does not act as a plasticiser – hence the moisture content can be decreased whilst the mechanical strength remains."

first HPMC capsule, has launched a novel HPMC capsule that resolves the aforementioned undesirable effects and additional costly countermeasures caused by moisture. Quali-V® Extra Dry is a capsule with an extremely reduced moisture content (2.0%–3.5%), half that of the standard HPMC capsules on the market.

In order to obtain such a low moisture value, the production process for Quali-V® Extra Dry was adapted to incorporate an extra drying phase by using unique equipment developed by Qualicaps Europe, with funding awarded by the European Union through the Centre for the Development of Industrial Technology.

HPMC Extra Dry Capsule				
Parameter	Description			
Moisture content	2.0%–3.5%			
Dissolution	USP and Eur.Ph dissolution profile at pH 1.2 and pH 6.8			
Brittleness	Minimal			
Runnability	Tested in automatic high-speed filling machines:			
	MG2 Planeta 100	Bosch GKF-1400	IMA MATIC-120	IMA Adapta 100
Storage conditions	15°C–30°C in heat-sealed aluminium liners			
Handling conditions	Temperature: 20°C–30°C (set point 25°C ± 2) RH: 15%–25% (set point 20% ± 2)			
Shelf Life	Capsule: 18–24* months Final drug product: 2–3 years			

* Stability studies carried out at ICH accelerated and long-term conditions meeting the specifications after 6 months. Shelf life depends on the size of the capsule.

Table 1: Description of the Quali-V® Extra Dry capsule properties.

Nevertheless, this special drying process does not compromise the capsule's physical or mechanical properties. The innovative capsule maintains the advantages of the standard Quali-V® – i.e. without preservatives, pharmaceutical grade, plant-based suitability for certain dietary and religious restrictions and chemically inert with the absence of crosslinking phenomena. Some Quali-V® Extra Dry properties are described hereafter and listed in Table 1.

Brittleness is a critical aspect when capsules come into play. Water in gelatin capsules functions as a plasticiser and, when this level falls below the specification limits, the capsules become brittle and crack on handling. However, in HPMC capsules, water does not act as a plasticiser – hence the moisture content can be decreased whilst the mechanical strength remains.[3,4,5]

An impact test, by dropping a weight of 50 g from 10 cm above the capsule, was performed to evaluate how fragile Quali-V® Extra Dry could be at low relative humidity environmental conditions: minimal brittleness has been observed, as shown in Figure 1.

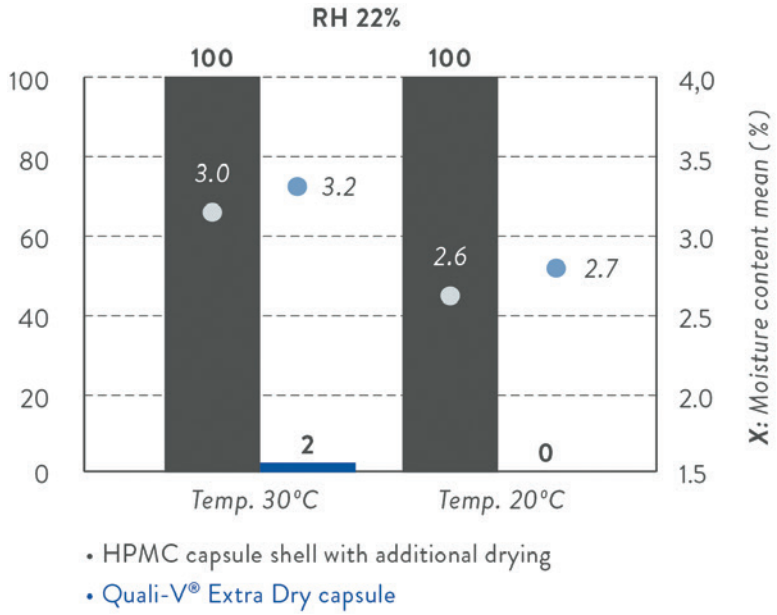


Figure 1: Capsule brittleness/impact test (empty capsule; n=50) (Qualicaps Japan).

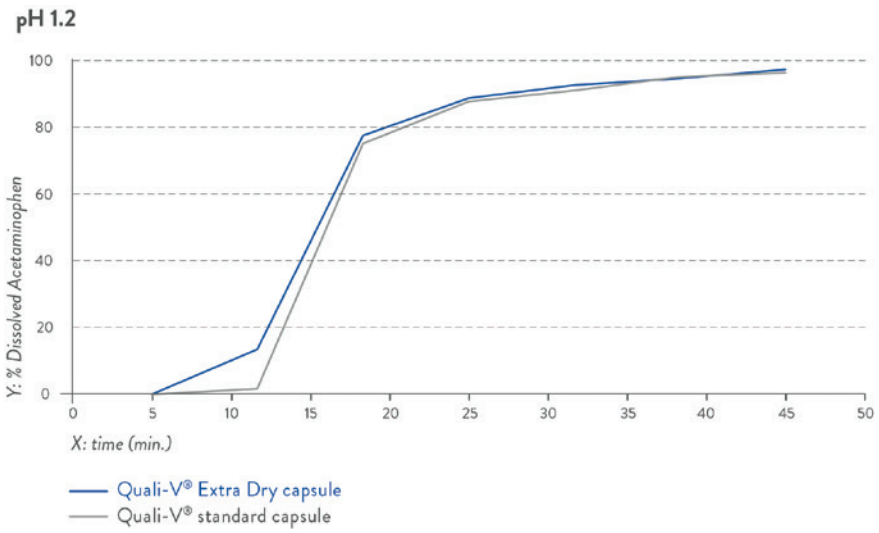


Figure 2: Dissolution profile for pH 2.1 capsule fill formulation – acetaminophen.

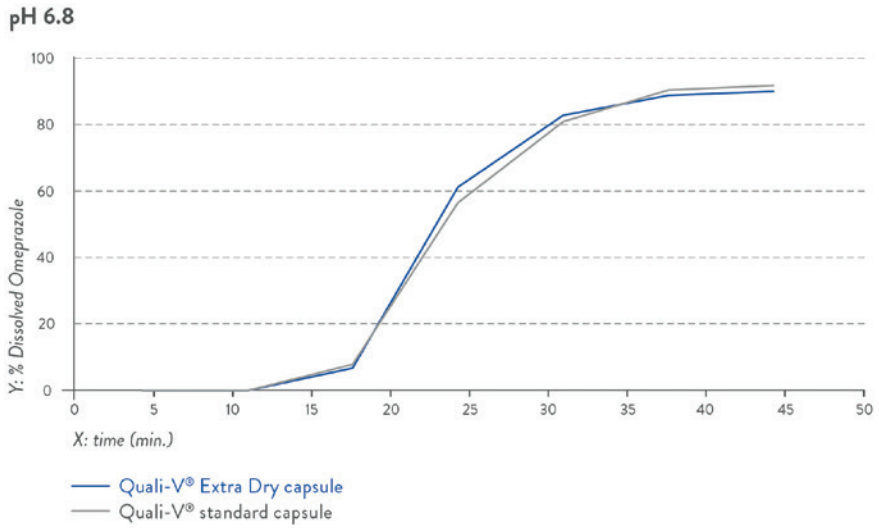


Figure 3: Dissolution profile for pH 6.8 capsule fill formulation – omeprazole pellets.

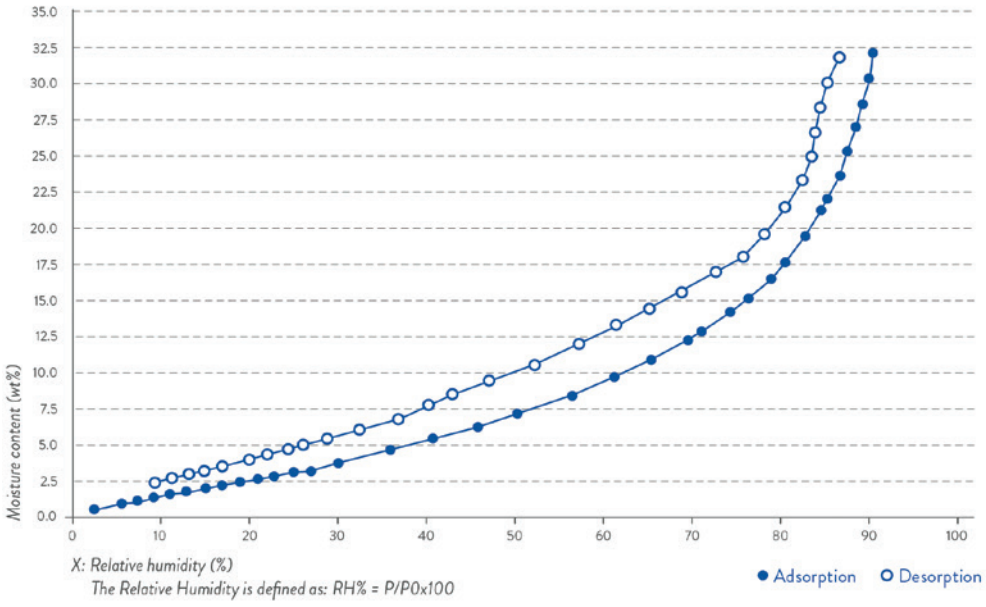
The dissolution profile of this novel capsule is equivalent to the one of standard HPMC capsules, complying with both USP and Eur Ph dissolution profiles at either pH 1.2 or pH 6.8 (Figures 2 and 3).

It is important to highlight that Quali-V® Extra Dry requires specific handling and storage conditions in order to retain the moisture content within the specification and thus secure its quality properties. Since Quali-V® Extra Dry is provided in heat-sealed and moisture-proof aluminium liners, only the temperature needs to be controlled between 15°C and 30°C when storing these capsules.

Once the bag is opened, the following handling and filling conditions are highly recommended: a temperature between 20°C and 30°C as well as a relative humidity in the range of 15%–25%. Such handling conditions have been defined by performing an absorption and desorption study with a volumetric method (Figure 4).

The present data are obtained by means of a volumetric method, as per USP41<1241>, EP9.02.9.39.

"The Quali-V® Extra Dry capsule, with a guaranteed extremely low moisture content, provides enormous benefits when formulating moisture-sensitive drugs."



RH (%)	wt/%
14.94	1.9771
16.90	2.1951
18.92	2.4111
20.95	2.6282
22.96	2.8464
24.91	3.067
26.74	3.286
30.11	3.7131
36.02	4.5543

The present data are obtained by means of a volumetric method as per USP41<1241>, EP9.0 2.9.39.

Figure 4: Water vapour absorption/desorption isotherm curve (25°C) (Qualicaps Japan).

CONCLUSION

In summary, the Quali-V® Extra Dry capsule, with a guaranteed extremely low moisture content, provides enormous benefits when formulating moisture-sensitive drugs. It has a number of advantages over standard HPMC capsules – such as superior chemical inertness, stability results by avoiding compatibility issues and brittleness when environmental conditions are out of the standard range – and the Extra Dry capsule makes it possible to maximise those benefits even when formulating moisture-sensitive drugs. Furthermore, the Quali-V® Extra Dry capsule may limit or even avoid the need for other measures to control moisture, such as adding a drying step in the filling process, thus improving the manufacturing yield.

ABOUT THE COMPANY

Qualicaps, a Mitsubishi Chemical Holding Corporation company, has more than 120 years of experience as a company dedicated to manufacturing capsules. It delivers pharmaceutical-grade, hard, two-piece capsules to the pharmaceutical and consumer healthcare industries, together with a comprehensive service along the product life cycle through a global team of commercial, scientific and technical experts. Qualicaps is a responsible company that takes pride in producing each capsule with the aim of offering specific and optimal solutions for drug delivery and overall health and wellbeing challenges.

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Laura Canalejas is Scientific Business Development Manager at Qualicaps Europe. She holds a bachelor's degree in Biotechnology and an MSc in Pharmaceutical Industry. Her main work mission in Qualicaps is to continuously assess and provide formulation support throughout the whole life cycle of products in hard capsule dosage form, especially during the development of NMEs. Ms Canalejas also takes an active role in promoting collaborations with third parties, focusing on the application of state-of-the-art capsule technologies.

SMARTER MEDICINES TO SECURE PRODUCTS AND PROMOTE PATIENT ENGAGEMENT

In this article, Gary Pond, Global Program Manager – Authentication at Colorcon, looks at digital authentication and discusses how on-dose microtaggants can provide a high level of security in authenticating tablets and capsules in the fight against counterfeit products.

COLORCON'S ON-DOSE AUTHENTICATION SYSTEM PROVIDES A DIGITAL SECURITY LAYER TO SAFEGUARD PATIENTS AND UPHOLD BRAND INTEGRITY

Take Control with SoteriaRx® Digital Authentication

Pharmaceutical companies are accountable for ensuring that their medicine is safe when it arrives in the hands of patients. The covid-19 pandemic has led to a dramatic increase in the number of online pharmacies and the supply of counterfeit drugs. As criminal gangs employ more sophisticated methods, sometimes re-using real packaging, smarter medicines, which protect patients, are of paramount importance for brand integrity and trust.

On-dose authentication solutions are difficult to replicate or reverse engineer and provide a robust and reliable means of deterring and identifying counterfeiting and verifying product identity. Perhaps the most significant benefit of on-dose authentication is to increase the speed of decision making in the supply chain for suspected counterfeit or illegally diverted drugs. When a suspect event occurs, pharma companies will be able to react faster to determine if the product is real or fake, regardless of whether they have access to the packaging. Sometimes this process can take days or weeks but, with on-dose authentication, it is possible to authenticate a product in real time.

"Perhaps the most significant benefit of on-dose authentication is to increase the speed of decision making in the supply chain for suspected counterfeit or illegally diverted drugs."

Colorcon, a world leader in the development and supply of film-coating systems and excipients for the pharmaceutical industry, now provides on-dose authentication technologies to meet client needs. The SoteriaRx® on-dose authentication platform provides the most robust technology currently available for instant verification of drugs at the dosage level.

In addition to desktop and mobile readers, proof of concept shows that it is now possible to identify the on-dose microtaggants using a smartphone app. This will enable the ability to improve patient outcomes by reminding patients to take their medication, scan the tablet to verify that the right medicine is being taken at the right time, provide patient support materials and alert carers if vulnerable patients fail to take their medicines. This technology can also play an important role in supporting virtual clinical trials.

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THE THREAT OF ILLEGAL ONLINE PHARMACIES

Globalisation and outsourcing have led to complex supply chains for many pharmaceutical products. This increases the risk of counterfeiting and diversion, which can result in health risks and loss of trust for the consumer, impact revenues and cause reputational damage to the brand owner.

Many countries have introduced serialisation legislation that requires product identifiers to be used on each package to provide traceability throughout the distribution supply chain. However, traceability and security measures focused on the packaging level may still not be enough to protect patients. Even if a package is authentic, it is impossible to verify whether the medicine inside is real, fake or has been diverted.

With the growth in online sales, virtual pharmacies are a major contributor to the supply of counterfeit medicines. When looking to buy medicine online, it has been found that 100% of searches return links for illegal pharmacies,[1] over 90% of online pharmacies operate illegally, around 62% of medicines purchased online are fake or substandard[2] and over 90% of incidents are in the highest risk category, potentially endangering life.[3] In 2018, the Pharmaceutical Security Institute reported that counterfeit medicine incidents increased by 33% in a single year and 138 countries were impacted.[4]

Since the start of the covid-19 pandemic, there has been a massive increase in online drug sales. A record number of fake online pharmacies were shut down in May 2020 as criminals sought to take advantage of the crisis. Interpol led a global crackdown that saw more than 100,000 online marketplaces offering illicit drugs removed. Between 18 and 25 May, there were 277 arrests in 92 countries.[5] In the UK, fake medicines worth more than US$13 million (£9.17 million) were seized as part of the operation.

In 2020, the WHO identified the issue of counterfeit drugs as one of the urgent health challenges for the next decade.[6] Writing in the American Journal of Tropical Medicine and Hygiene in 2019, doctors from the US government, universities, hospitals and the pharmaceutical company Pfizer warned that the rise in "falsified and substandard medicines" had become a "public health emergency" and that poor quality drugs exact an annual economic toll of up to $200 billion.[7] In addition to the direct harm that they cause, the supply of counterfeit antibiotics is a major driver of antimicrobial resistance.

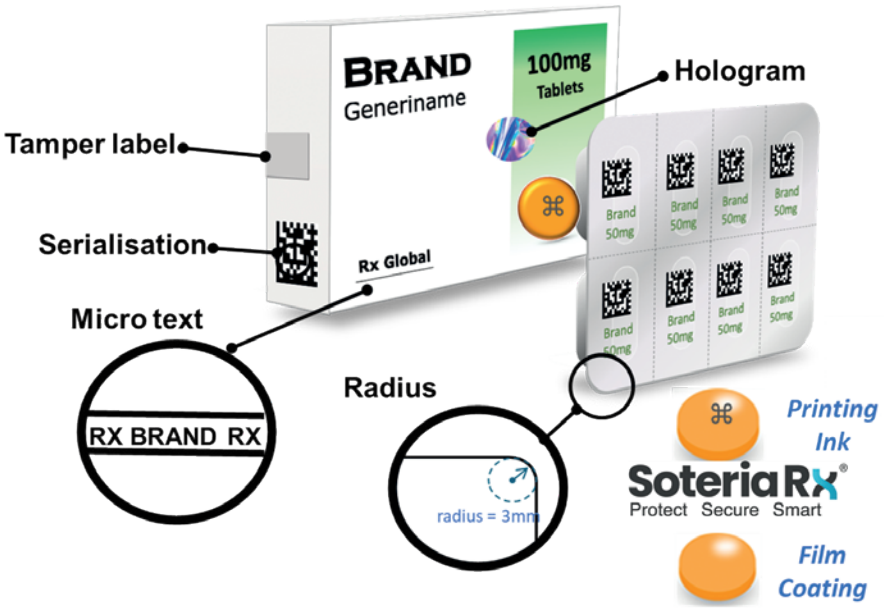

Figure 1: Multi-layered security approach for pharmaceutical products.

HOW THE INDUSTRY CAN FIGHT BACK – MAKING MEDICINES SMARTER WITH ON-DOSE MICROTAGGANTS

There is growing recognition that packaging and serialisation will not solve the problem of counterfeit medicines. As serialisation matures, it will provide a valuable tool for track and trace but, for the highest risk products, on-dose microtaggants provide a much higher level of security, allowing individual tablets and capsules to be authenticated. Instant verification at the dosage level reduces the risk of counterfeiting and product diversion while facilitating quality control and returns monitoring. Figure 1 shows a range of security measures that are now available.

Appropriate security measures will be determined by the risks associated with each product for different stakeholders (Figure 2). For low-risk products, serialisation on the secondary packaging may provide adequate protection but, for high-risk drugs, on-dose authentication using microtaggants is required to better protect patients and brands.

Microtaggants are uniquely encoded materials that are virtually impossible to replicate or reverse engineer. They can be incorporated in tablet coatings or in the

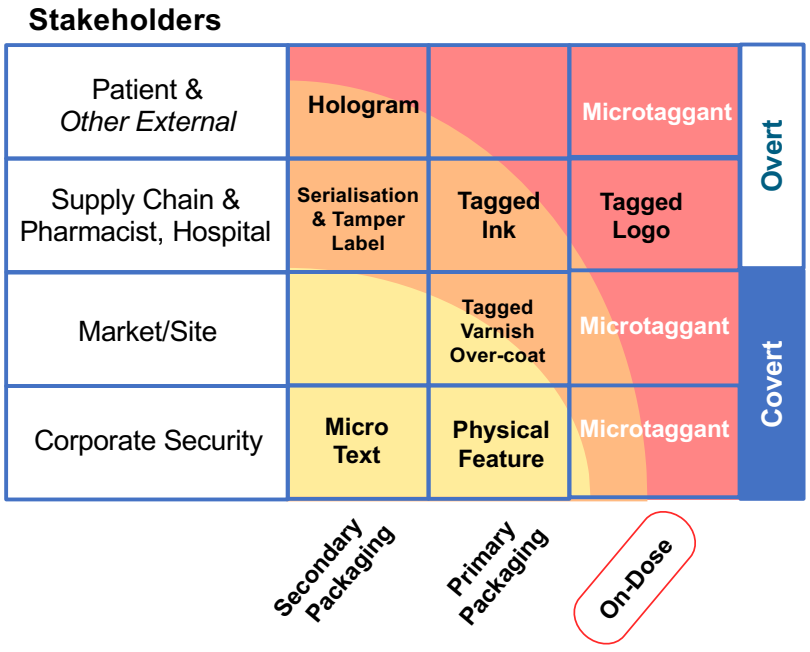

Figure 2: Stakeholder security measures for pharmaceutical products.

"Microtaggants are uniquely encoded materials that are virtually impossible to replicate or reverse engineer. They can be incorporated in tablet coatings or in the inks used on tablets or capsules and detected in the lab or the field using handheld devices."

inks used on tablets or capsules and detected in the lab or the field using handheld devices. The technology requires no additional manufacturing equipment or capital investments, and the US FDA has stated that, when microtaggants are pharmaceutically inactive and incorporated into new or existing drugs, they can be treated as excipients without the need for further clinical trials. This means that manufacturers of an approved product in the US would only need to incorporate the microtaggants as a Level 1 post-approval change in the Annual Report. For NDAs, inclusion would be part of the standard submission process.

The quantities of microtaggants added to film coatings or inks are so small their use has no impact on how coatings are applied, and they will not affect the product's stability, disintegration or dissolution. The cost per tablet of incorporating the microtaggants is negligible relative to other manufacturing costs as the microtaggants are simply included in the standard film coating or tablet printing process.

Colorcon has the exclusive worldwide rights to molecular taggants from Applied DNA Sciences (Stony Brook, NY, US) and TruTag Technologies' (Emeryville, CA, US) silica technology for on-dosage use, and both are marketed under the SoteriaRx solution platform.

These different types of microtaggants are now commercially available and can be customised with unique information for product verification and traceability.

DNA Microtaggants

Non-biologic molecular DNA is robust and easy to detect and, because it is possible to produce different versions of the same DNA molecule, it can be made regional-, product- or company-specific. The microtaggants are simply added to the standard tablet film coating or capsule printing process and can then be detected using appropriate reagents (such as an antigen and antibody). The microtaggants are not damaged by exposure to heat and pressure during the coating process, and the integrity of the DNA remains consistent throughout the shelf life of the product.

Silica Microtaggants

Spectrally encoded silica microtaggants can be detected by how they reflect light. Like DNA, the microtaggants are incorporated into the film coating or printing ink and applied during the manufacturing process. Silica is already widely used as a pharmaceutical excipient within tablet and capsule formulations, making it an easy material to include.

Recent work has concentrated on developing convenient readers to scan information carried on the microtaggants. Proof of concept demonstrates that tablets or capsules with silica microtaggants can be identified using a smartphone app, providing instant verification by internal and external quality assurance teams, including enforcement agencies.

SMARTPHONE AUTHENTICATION APPS ENABLE DIRECT PATIENT ENGAGEMENT

The introduction of a smartphone app (Figure 3) means that patients can play a part in verifying their medication, and that interaction could be leveraged to add value through patient engagement and brand loyalty. Through software development kits, this type of app can easily be customised for individual companies and specific medications to help:

- **Improve adherence and achieve better outcomes for patients**
  It is easy for someone who is sick or confused to take the wrong drugs or miss doses. The app can remind patients when it is time to take their medication and which tablets to take. For many conditions, for example, following an organ transplant or for the treatment of certain cancers, adherence to the correct medication regime is vital. Scanning each tablet before it is taken would reassure the patient, and results could also be relayed to a caregiver or medical team, alerting them if the patient has failed to scan the medication at the correct time.

"The introduction of a smartphone app means that patients can play a part in verifying their medication, and that interaction could be leveraged to add value through patient engagement and brand loyalty."

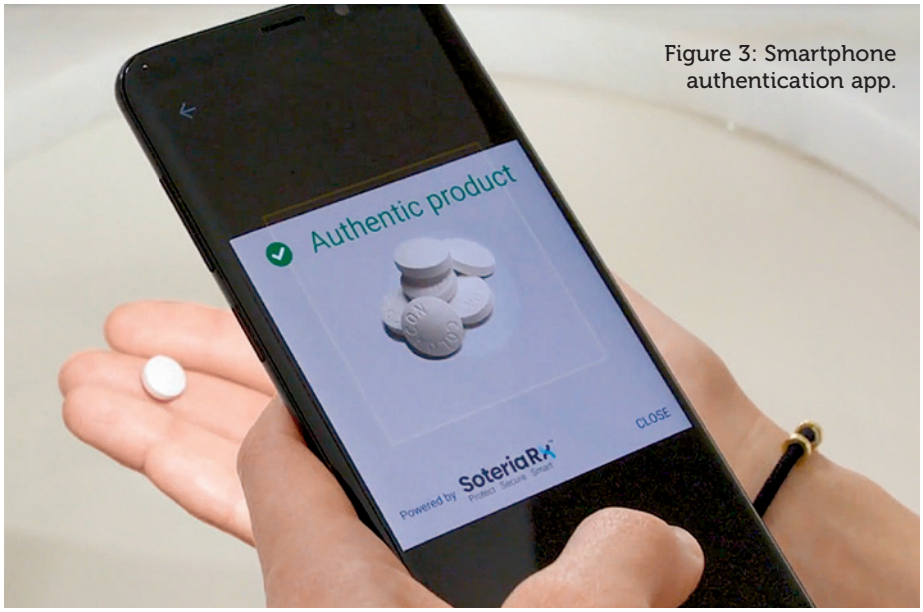

Figure 3: Smartphone authentication app.

"No new investment is needed to incorporate the microtaggants; they are simply added to a standard tablet film coating process."

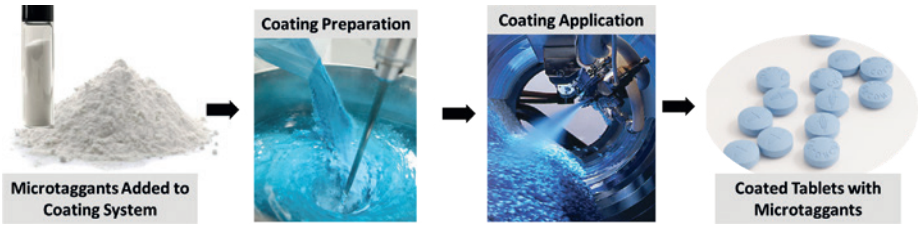

Figure 4. Simple to apply directly on-dose via the tablet coating system.

- **Promote patient trust and brand loyalty**
  Cases have been reported of patients with extremely serious conditions failing to take their medication due to concerns over side effects. The app could remind and actively assist patients to recognise certain side effects, provide reassurance that they are not unusual, and help manage these initial challenges to ensure they stay compliant with their regimen. There could also be reminders for repeat prescriptions and updates as new information becomes available. This type of engagement could give the patient a sense that the drug manufacturer is doing all it can to support them.

- **Make virtual clinical trials more robust and reduce costs**
  On-dose microtaggants can also be incorporated in clinical supply programmes, to reduce the opportunity for error in the allocation and administration of these expensive trials. Introducing on-dose authentication into clinical trials allows for validated patient engagement at any stage in the trial, ensuring the right patients are taking the right drugs at the right dosage. This validation is all done without impacting the blinding process. Soon it may be possible for patients to film themselves scanning and taking a drug as required for the trial, thus improving visibility and compliance and providing real-time patient support.

CHOOSING THE BEST SOLUTION

It is important to understand how effective and reliable an authentication process will be, and the benefits that may be gained as a trade-off for the time and resources required to implement advanced technology. By leveraging current tablet coatings and print technologies, no new investment is needed to incorporate the microtaggants into standard manufacturing procedures; they are simply added to a standard tablet film coating or capsule printing process. The film-coating process does not change, there is no impact on the final tablet finish and the cost is negligible (Figure 4).

Machine reading of security features is faster and more reliable than manual inspections and will be suitable for high-volume applications. SoteriaRx technology equips product quality teams with a faster way to identify rogue batches and make more informed decisions as to whether a batch needs to be held pending further investigation or immediately recalled.

Multinational Companies are now Implementing Customised On-Dose Authentication for High-Risk or High-Value Products

Incorporating microtaggants directly into the product and using the smartphone app provides a unique opportunity for brands to secure their products and expand this technology to interact with patients for the best possible outcomes. Through real-time data collection and analysis, patient-focused product teams will be able to provide more personalised support resources when needed.

Following extensive R&D by in-house scientists and its technology partners, Colorcon is now working with leading pharmaceutical companies to help them consider how SoteriaRx integrates with their current product security strategies to provide an optimal solution. We do not need to look to the future for smart medicines to become a reality. Innovative technology is available today that enables digital authentication of the patient's medicine using their smartphone and a secure cloud application to provide real-time support.

ABOUT THE COMPANY

Colorcon is a world leader in the development, supply and support of formulated film-coating systems, modified-release technologies and functional excipients for the pharmaceutical industry. Colorcon also provides innovative digital on-dose technologies and detection services for the authentication of medications. The company's best-in-class innovative products are complemented by extensive application data and value-added services to support solid oral dose design and development. Colorcon's focus on market issues and technology development has earned the company an international reputation as a pharmaceutical supplier of choice. That reputation is based on superior product quality, unparalleled support, extensive regulatory assistance and reliable supply from multiple locations.

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ABOUT THE AUTHOR

Gary Pond has over 25 years of life science expertise and eight years in healthcare technology. He has held sales and marketing leadership positions at Sanofi, Merck and Abraxis Bioscience. Immediately prior to joining Colorcon, Mr Pond led the Brand & Marketing Center of Excellence at IQVIA (NC, US). He currently leads the commercialisation efforts for authentication solutions at Colorcon.

SoteriaRx®

Protect Secure Smart

Take Control with On-dose Digital Authentication

SoteriaRx® provides a level of authenticity, transparency and brand protection not previously available to the Pharma industry.

Protect
company reputation and brand integrity

Secure
product and improve patient safety

Smart
medicines to connect with your patients

Brands and patients at risk

The rise in counterfeit and diverted drugs is a major problem for the pharmaceutical industry. Added to this is the significant growth of illegal online pharmacies, exposing patients to even more counterfeit products.

The solution: Smart Medicines

SoteriaRx on-dose authentication provides the industry with a unique, covert, powerful solution. Medicines are made smart with on-dose taggants that can be authenticated at any stage of the supply chain.

Linking physical product with a digital experience

A novel mobile app enables patients to verify their medicine, giving them peace of mind and the opportunity to engage directly with the brand.

Secure and elegant solution

Simple to adopt and scale

Easy to authenticate

Cost effective

Find out more at www.colorcon.com

Supported by Colorcon - Trusted Global Leader in Pharmaceutical Film Coatings and Specialty Excipients

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ADDRESSING ONGOING AND NEW BIOAVAILABILITY CHALLENGES

Here, Stephanie Emory, PhD, Associate Director of Pharmaceutical Development at Metrics Contract Services, explores the pros and cons of various technologies for enhancing solubility and bioavailability for oral drug formulations. Further, Dr Emory draws on her experience as a reviewer at the US FDA to discuss how developers can view the FDA as a partner to aid success when leveraging innovative approaches.

As drug discovery continues to rely heavily on high-throughput screening techniques to identify drug candidates based on receptor binding affinity, it is increasingly common that potential candidates suffer from low solubility and bioavailability. In turn, the challenge of dealing with this issue is faced by an ever-growing number of projects.

It is reported that the majority of new chemical entities (NCEs) currently in development have bioavailability challenges due to low solubility, low permeability or both. While low permeability is a more complex problem to solve, there is an increasing number of technological solutions to address the two main culprits of low solubility: high crystalline lattice energy and greater lipophilicity.

Enhanced dissolution, solubility and bioavailability of poorly soluble APIs can be achieved using a variety of approaches. For oral solid dosage forms, which continue to be the most desirable finished dosage forms, common approaches include solubilisers, micro/nanoparticles, salts, co-crystals and amorphous solids dispersions (ASDs).

SOLUBILISERS

Simple approaches to mild solubility limitations include co-mixing of solubilisers or self-emulsifying excipient systems into traditional solid oral dosage formulations or dissolving the API in a liquid-filled capsule formulation. These techniques can be effective for some APIs, particularly those that are highly lipophilic, and the time and cost required to determine their effectiveness is relatively low. This technique is often combined with particle size reduction to further enhance solubilisation. However, for more significant solubility challenges, these approaches often fall short of achieving sufficient increases in bioavailability and, for liquid-filled capsules, can present additional stability challenges for APIs that are unstable in solution.

> "While traditional milling and homogenisation techniques are widely available for particle size reduction, these high-energy processes are not ideal for heat-sensitive APIs. An array of alternative, lower-energy techniques are becoming increasingly common, using both top-down and bottom-up approaches."

MICRO/NANOPARTICLES

Particle size reduction technologies are now routinely used to increase bioavailability in poorly soluble drugs. The principle is relatively simple; reducing particle size increases the relative surface area and consequently the rate of solvation. Overall, the degree of crystallinity is significantly reduced and, particularly at the nano-scale, an increase in apparent solubility results in faster and more complete dissolution.

While traditional milling and homogenisation techniques are widely available for particle size reduction, these high-energy processes are not ideal for heat-sensitive APIs. An array of alternative, lower-energy techniques are becoming increasingly common, using both top-down (cryo-milling) and bottom-up (nanocrystals) approaches. While bottom-up techniques typically result in a smaller and more uniform particle size distribution compared with top-down methods, they require appreciable

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solubility in appropriate solvents, which limits their use for extremely insoluble compounds.

AMORPHOUS SOLID DISPERSIONS

Creating ASDs offers better dissolution profiles and enhanced bioavailability by completely eliminating the crystal structure, making this technique ideal for APIs where high lattice energy is the main reason for low solubility. High lipophilicity can also be addressed by choosing a more hydrophobic carrier.

Both spray drying and hot melt extrusion (HME) can be used to produce ASDs. Several factors come into play when deciding whether to progress with an ASD and which technology to use. These include performance, projected dose, stability and manufacturability. When choosing which technology to employ for optimising the ASD's performance, two key factors should be considered: the physicochemical properties of the API and the phase of development, which influences the amount of API available for formulation development.

Important physicochemical properties for creating an ASD include the solubility of the API in a solvent suitable for spray drying, as this is crucial to ensuring a readily scalable and viable process. HME is sometimes preferable as it does not rely on solvents. The heat and shear forces exerted during HME can be critical for overcoming really tough solubility challenges but pose significant barriers for heat-sensitive APIs.

In early-stage or discovery-support activities, API availability is limited, which often makes spray drying the preferable approach because its feasibility can be determined with much less API than with HME. For APIs that are amenable to HME, which is typically identified after proof-of-concept clinical studies, an initial spray-drying process can sometimes be converted to HME where necessary.

"Regardless of whether it is produced by spray-drying or HME, residual crystallinity and re-crystallisation of the API in ASDs can pose further challenges to drug development. Stability studies are required to ensure a viable product is developed; however, *in vivo* performance is often overlooked once the ASD has been optimised for its solid state."

ASDs present several challenges to downstream formulation. Poor flow is a particular concern, especially for spray-dried dispersions. Dry granulation is often employed to improve flow, although this also reduces compressibility, creating challenges for tablet compression. Due to the ratio of polymer to drug required to create a stable ASD, additional excipients must be included judiciously to produce a reasonably-sized finished dosage form. Ideally this is balanced by an increase in bioavailability, which allows for a lower dose, although this is not always the case. Given the increased focus on patient-centricity and compliance in today's drug delivery industry, size and swallowability are imperative considerations, and excipient use must be finely balanced.

Regardless of whether it is produced by spray drying or HME, residual crystallinity and re-crystallisation of the API in ASDs can pose further challenges to drug development. Stability studies are required to ensure a viable product is developed; however, *in vivo* performance is often overlooked once the ASD has been optimised for its solid state.

ASDs are subject to what is commonly referred to as the "spring and parachute" effect; in the gastrointestinal (GI) tract, compared with pure crystalline API, ASDs exhibit more rapid and complete dissolution (the "spring") resulting in a metastable supersaturated solution of API which, if not maintained or slowed by crystallisation inhibitors (the "parachute"), can result in precipitation of the API to its most thermodynamically stable (i.e. low solubility) form, reducing or even eliminating any increase in bioavailability using an ASD enabled in the first place. While polymers used for ASDs often have additive effects, such as crystallisation inhibition or influence on the polymorph formed during re-crystallisation, their use levels and the need for additional crystallisation inhibitors should be examined during formulation optimisation to maximise both *in vivo* performance and stability to fully capture the benefits of ASDs.

SALTS

Salt formation and selection is one of the most frequently used approaches to increase the bioavailability of poorly soluble ionisable APIs. However, while solubility is increased, permeability may be negatively impacted, as passive diffusion across the GI membrane is significantly reduced when the drug is in its charged form. This affects the location and extent of absorption *in vivo* as the changing pH along the GI tract creates "windows" where more of the drug molecule is in its neutral form and can be more easily absorbed. In addition to effects on permeability, the *in vivo* dissolution of some salts, especially hydrochloride salts, can be limited by the common ion effect of chloride in the GI tract. The overall benefit of salt formation depends on the balance of its impact on solubility and permeability.

CO-CRYSTALS

Unlike salt formation, co-crystal technology can be applied to non-ionisable APIs. Co-crystallisation is a more contemporary approach to improving bioavailability that involves co-precipitation of an API with a soluble co-former, using non-covalent

"Improvement of physicochemical properties, such as solubility, dissolution rate, stability and melting point, makes co-crystals an attractive option for poorly soluble APIs. However, it is important to note that co-crystals are more stable than ASDs but suffer the same 'spring and parachute' phenomenon without the additive effects on crystallisation inhibition afforded by many ASD polymers."

intermolecular forces (primarily hydrogen bonds) between the two compounds to form a single-phase crystalline material with a lower lattice energy and higher apparent solubility compared with pure crystalline API.

Improvement of physicochemical properties, such as solubility, dissolution rate, stability and melting point, makes co-crystals an attractive option for poorly soluble APIs. However, it is important to note that co-crystals are more stable than ASDs but suffer the same "spring and parachute" phenomenon without the additive effects on crystallisation inhibition afforded by many ASD polymers. Therefore, additional formulation development is needed to optimise *in vivo* performance.

There is also evidence that co-crystals can impact membrane permeability, although this is not yet fully understood, and both positive and negative effects have been observed. Further, the potential for co-crystals to interrupt cellular integrity has raised concerns about their toxicity, as well as the physiological effects on the GI tract exerted by some co-formers leading to changes in absorption.

FDA AS A "PARTNER"

With the pharma industry continuing to churn out increasingly complex and challenging molecules, novel formulation and processing strategies continually emerge to support these efforts. With limited official guidance available for these new technologies, developers are often hesitant to fully embrace them for fear of significant regulatory hurdles.

The US FDA's response in recent years has been to publicise its intent to make regulatory decisions based on scientific reasoning rather than stoic adherence to guidelines that are often not fully applicable to newer technologies. Evidence of this can be seen in the FDA's Emerging Technology Program, which invites drug sponsors to meet with the agency to proactively explore new technologies and discuss potential issues before these novel processes and formulations are included in new drug applications (NDAs). Ultimately, the FDA's mission is to advance new therapies to market that are safe and effective.

Regardless of whether well-established or innovative approaches are employed, sponsors would be wise to communicate and be transparent during their investigational new drug (IND) and pre-NDA phases, openly discussing challenges and potential solutions. This allows the agency to fully understand and provide guidance well before the NDA review clock starts.

Addressing issues ahead of time helps ensure a smoother and more favourable review process, whereas downplaying significant challenges rather than addressing them directly is a high-risk strategy. A major amendment or complete response letter can lead to significant delays in approval and loss of first-to-market advantages.

CONCLUSION

With so many options for bioavailability enhancement currently available, developers who invest in thorough API characterisation are well-poised to swiftly overcome these challenges by identifying the technologies best suited to their product. Conversely, when API characterisation is limited, exploring multiple pathways in parallel can save considerable time.

"Addressing issues ahead of time helps ensure a smoother and more favourable review process, whereas downplaying significant challenges rather than addressing them directly is a high-risk strategy."

Although relying on new technology and complex formulation carries inherent risks to the drug development cost and timeline, careful development strategies and transparent collaboration with regulators is the best strategy to avoid delays in getting new therapies on the market.

ABOUT THE COMPANY

Metric Contract Services, founded in 1994, now a division of Mayne Pharma, is an oral solid dosage form CDMO providing formulation development, analytical testing and commercial manufacturing services to support drug development from concept to global commercialisation.

ABOUT THE AUTHOR

Stephanie Emory is Associate Director of Pharmaceutical Development at Metrics Contract Services. Dr Emory has 12 years of pharmaceutical industry experience and a strong background in product development, specifically in the field of bioavailability enhancement of small molecule formulations. She joined Metrics from the FDA where she reviewed the CMC/Drug Product portions of INDs, NDAs and industry meeting packages for CDER's Office of Pharmaceutical Quality. Prior to the FDA, she spent seven years at UPM Pharmaceuticals, a then Baltimore-based CDMO, serving as both technical lead and project manager for the development of pre-clinical through Phase III clinical supplies. She has experience with a wide range of solid oral dosage forms and manufacturing processes, including solubility-enhancing formulations, as well as scale-up, tech transfer and process validation activities. Dr Emory holds a Bachelor of Science in Pharmaceutical Sciences and a doctorate in Industrial & Physical Pharmacy from Purdue University (West Lafayette, IN, US).

Evonik's Newly Launched EUDRACAP™ Functional, Ready-To-Fill Capsules

Evonik introduces EUDRACAP™, its newly launched platform of functional ready-to-fill HPMC capsules, which helps optimise release profile, protects sensitive active ingredients, and speeds time to market.

Functional capsules can improve a targeted drug delivery strategy and allow the use of more sensitive active molecules. EUDRACAP™ (Figure 1) is Evonik's newly launched platform of functional ready-to-fill HPMC capsules. Completely free from animal-derived products, EUDRACAP™ helps optimise release profile, protects even the most sensitive active ingredients, and speeds up time to market.

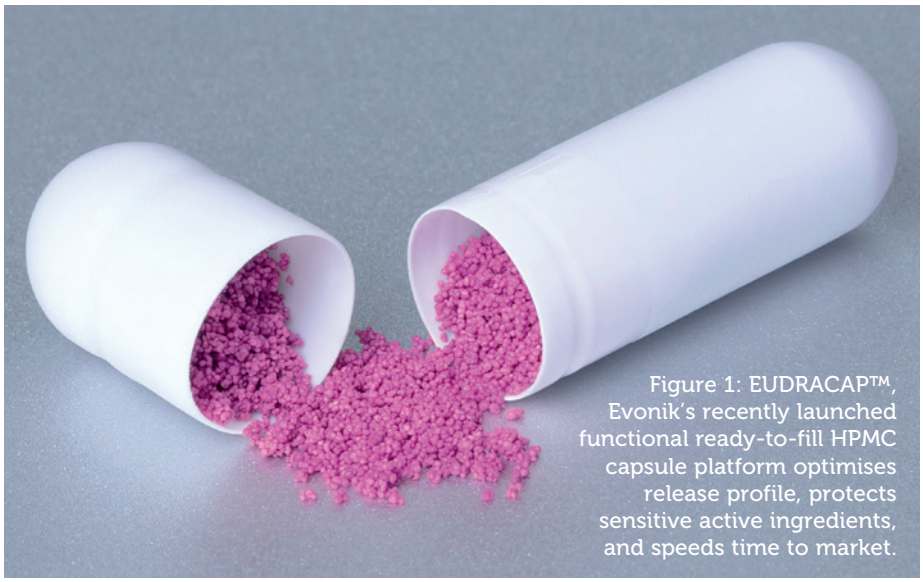

Figure 1: EUDRACAP™, Evonik's recently launched functional ready-to-fill HPMC capsule platform optimises release profile, protects sensitive active ingredients, and speeds time to market.

Targeted Drug Delivery from pH 4.0 to 7.2

Challenges in targeted drug delivery can be overcome with EUDRACAP™. Evonik's established functional coatings EUDRAGIT® can be applied to EUDRACAP™ to match the specific release profile for effective pH targeting of sites including the mid-to-upper small intestine and colon.

Active Ingredients – Effective Acid Resistance for up to Four Hours

Active ingredients that are sensitive to heat, moisture or gastric acid can also present a challenge. EUDRACAP™ can help optimise absorption and avoid premature dissolution, therefore supporting the delivery of molecules such as nucleotides and peptides as well as live biotherapeutics.

Speed to Market – Fully USP and EP Compliant to Reduce Regulatory Risk

Reducing clinical risk and speeding up time to market is key for early-stage drug development. EUDRCAP™ reduces complexity, time and risk, and accelerates clinical trials. The EUDRCAP™ platform of catalog and customisable coating options has a strong regulatory track record, extensive formulation and cGMP services. With EUDRAGIT® Evonik has more than 60 years of safety and reliability.

Easy to Use and Suitable for a Range of Fillings

EUDRACAP™ capsules are easy to open, fill and close on manual or high-speed automated capsule filling lines. Functional coatings of EUDRAGIT® polymers are homogeneously applied across the entire surface of the pre-locked capsule including part of the surface area covered by the capsule cap in the final-locked stage. The capsules are suitable for a range of fillings including powders, pellets and granules.

Leveraging the Versatility of EUDRAGIT®

The EUDRACAP™ platform provides a flexible range of custom options such as a choice of size, colour and release profile. Many EUDRAGIT® drug delivery and process technology options are available to match specific immediate, delayed, sustained or modulated release profiles or solubility enhancement requirements.

EVONIK EXPERTISE

Evonik is one of the world's leading formulation development and scale-up partners for oral drug delivery solutions. Areas of formulation expertise include colonic delivery, microbiome delivery, bioavailability enhancement, and personalised dosage forms for patient groups including children and the elderly.

ABOUT THE COMPANY

Evonik Health Care is a CDMO for advanced oral and parenteral drug delivery solutions covering early development to commercial manufacturing. Evonik Health Care is also one of the world's largest CMOs for APIs, intermediates, amino acids, cell culture ingredients and medical device excipients.

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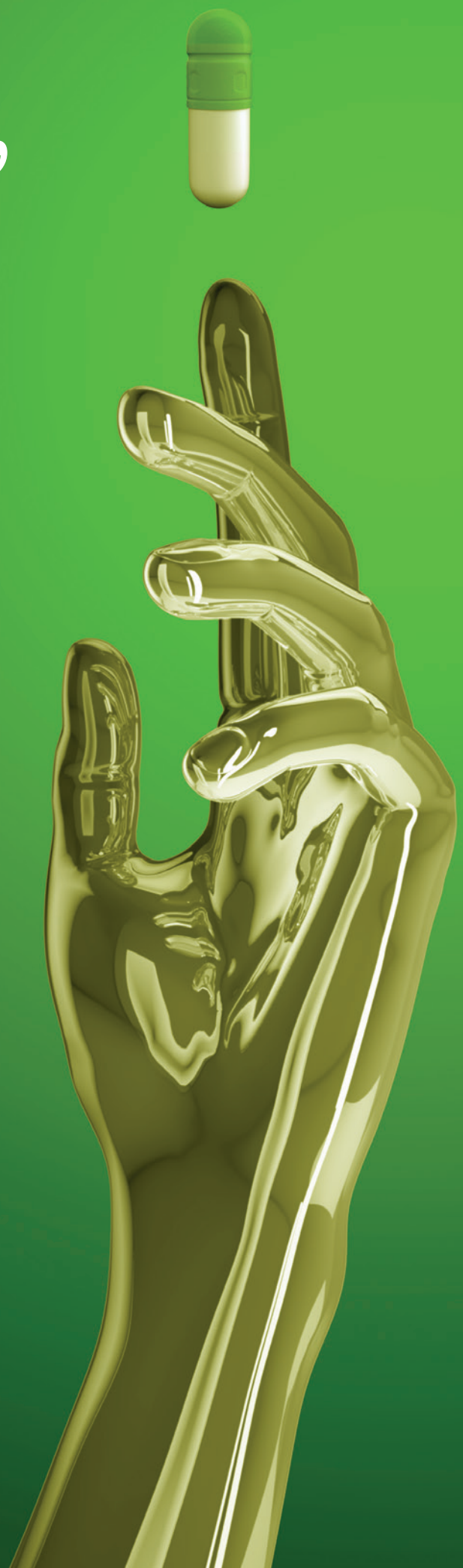

A novel capsule for delivering hygroscopic pharmaceutical drugs

Qualicaps®, the company responsible for several milestones in the history of hard capsule development within the pharmaceutical industry, continues to innovate by presenting an extra dry cellulose capsule that will enable the development and production of moisture-sensitive and hygroscopic drugs.

Quali-V® Extra Dry, the cellulose capsule with an extremely low moisture content ideal for moisture-sensitive and hygroscopic pharmaceutical drugs.

- *Pharmaceutical Grade*
- *100% Vegetal Origin*
- *Preservative Free*
- *Standard HPMC Equivalent Dissolution Profile*
- *Minimal Brittleness*
- *Lower Moisture Content (2.0%-3.5%)*

Qualicaps