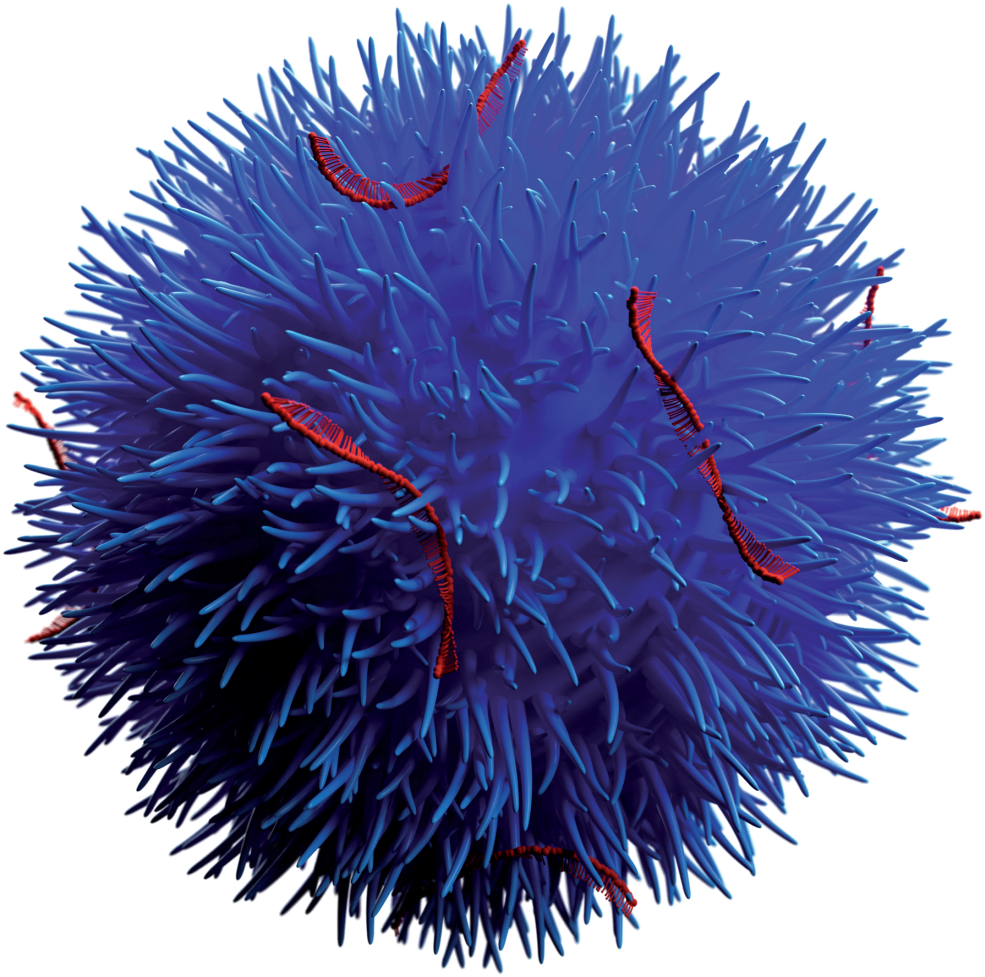
ORAL DRUG DELIVERY

ON drugDELIVERY



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ORAL DRUG DELIVERY

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

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EDITORIAL:

James Arnold, Managing Editor
E: james.arnold@ondrugdelivery.com

CREATIVE DESIGN:

Simon Smith, Head of Creative
E: simon.smith@ondrugdelivery.com

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Guy Furness (guy.furness@ondrugdelivery.com)

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Front cover image, "A Nuvec® mesoporous silica nanoparticle" courtesy N4 Pharma (see this issue, Page 3). Reproduced with kind permission.

ARE ORAL FORMULATIONS OF OLIGONUCLEOTIDE THERAPEUTICS WITHIN REACH?

Here, Nigel Theobald, Chief Executive Officer at N4 Pharma, discusses key issues and strategies for formulation scientists aiming to unlock the potential of oral delivery for small interfering ribonucleic acid drugs targeted against gastrointestinal diseases and cancers.

Oral delivery has long been the preferred route for administering medication. It is the most common and convenient dosage form for the majority of the world's population – it can be easily self-administered and is non-invasive, resulting in increased treatment compliance and greater population coverage. Oral delivery has always been considered most suitable for small molecule drugs; in fact, 60% of small molecules, which make up to 90% of the total commercial drug products, are administered orally.[1]

> "For siRNA therapeutics in particular, there is a high level of consensus that they hold significant promise as improved therapeutic options for certain conditions, and offer a new tool against hard-to-treat diseases."

Naturally, as various classes of biologic therapeutics have emerged in recent years, oral delivery has been investigated for administering these drugs too. For small interfering ribonucleic acid (siRNA) therapeutics in particular, there is a high level of consensus that they hold significant promise as improved therapeutic options for certain conditions, and offer a new tool against hard-to-treat diseases, due to their ability to selectively downregulate or silence disease-causing genes.

However, siRNA therapeutics require novel delivery systems to achieve their clinical effectiveness, as they are susceptible to rapid elimination by gastrointestinal (GI) processes if administered without protection and are poorly absorbed into systemic circulation. So far, the six siRNA drugs approved by regulators are injectables and there are, as of yet, no large-scale clinical trials for any other dosage forms.[2]

TARGETING THE GI TRACT

In recent years, significant advancements have been made in understanding the genetic roots of many diseases and how undesirable gene expression can be downregulated, augmented or corrected with therapeutic success.

In particular, the specific advantages of siRNA therapeutics over alternative small molecule and monoclonal antibody (mAb) drugs that have been demonstrated are:[3]

- **Simplicity**: siRNA executes its function by complete Watson–Crick base pairing with messenger RNA (mRNA), whereas small molecule and mAb drugs need to recognise the complicated spatial conformation of proteins.
- **Specificity**: siRNA has a more distinct, specific mechanism of action with reduced side effects.
- **Broad application**: Theoretically, any gene of interest can be targeted by siRNA – only the correct nucleotide sequence is needed to match the targeted mRNA.
- **Rapid development**: High-throughput screening methods can identify effective siRNA sequences against disease targets, accelerating the drug development process, which means that siRNA is potentially faster to market over a wider therapeutic area.

In addition, the complexities of delivering drugs via the GI tract have been extensively studied. From the mouth to the lower intestines and colon, it is clear that each segment presents

Nigel Theobald
Chief Executive Officer
E: nigel@n4pharma.co.uk

N4 Pharma PLC
Weston house
Bradgate Park View
Chellaston
Derbyshire
DE73 5UJ
United Kingdom

www.n4pharma.com

"Well-known factors, such as pH, enzymatic activity and the surface area and structure of the intestine wall, dictate the extent and rate of drug absorption, making it essential for drug developers to tailor formulations accordingly."

formidable barriers and various absorption mechanisms that influence drug bioavailability. Well-known factors, such as pH, enzymatic activity and the surface area and structure of the intestine wall, dictate the extent and rate of drug absorption, making it essential for drug developers to tailor formulations accordingly, driving the development of novel strategies to enhance efficacy.

In parallel, dissatisfaction with current therapies for immune-mediated GI inflammatory diseases, such as inflammatory bowel disease (IBD) and Crohn's disease, have stimulated research into siRNA. It holds promise as a targeted, precise therapy that could be used to treat intestinal diseases associated with the upregulation of specific proteins found in, for example, gut epithelial cells.

Common current treatments for IBD include amino salicylates, corticosteroids and immunosuppressives – interventions that often cause side effects such as hypertension, osteoporosis, depression and increased susceptibility to infections. These side effects are due, in large part, to the non-specificity of drug action and could be mitigated by the use of siRNA therapeutics, whether as a stand-alone or concurrent therapy. GI cancers, such as colorectal cancer, are also being targeted for new treatment approaches using siRNA.

UNDERSTANDING THE CHALLENGES

Looking to the current literature for guidance, it is striking to note that, in all reports on oral siRNA, there is a strong consensus around the common challenges over and above those faced for small molecules. Furthermore, there is a wide range of innovative formulation strategies being explored in an effort to overcome these key issues. These include controlled release formulations, enteric-coated lipid-based nanoparticles (LNPs) and polymeric carriers.[4]

A recent review article[5] highlights the preclinical data for IBD and colorectal cancer, presenting a clear assessment of some of the barriers to oral delivery. Another group hypothesises that oral administration facilitates the direct delivery of siRNA to lesions within the small intestines and colon, making it the ideal approach for treating patients with IBD.[5] In addition, scientists from the University of Texas[6] and, separately, a team from a consortium of European researchers,[5] completed comprehensive reviews that summarise the formulation challenges and delivery strategies for oral delivery of siRNA, reporting on recent advancements from basic research towards the preclinical stage of drug development.

In summary, their findings indicate that, in order to translate oral formulations of siRNA from research in animal models to human clinical trials for specific diseases, drug developers must overcome a threefold challenge:

- Protect the siRNA as it travels through the GI tract
- Develop a formulation to deliver the siRNA to the targeted part of the GI tract and the correct cell type (e.g. macrophage)
- Selectively release the siRNA at the site of action.

NOVEL ORAL sIRNA DELIVERY SYSTEMS

A comprehensive exploration of all available options is beyond the scope of this article; however, the following is a sample of example strategies for oral siRNA delivery that are currently in preclinical research.

Lipid Nanoparticles

Given the well-established use of liposomes and LNPs in both small molecule and gene therapy applications, the first approved siRNA drugs have been intravenous (IV) formulations using LNPs. As such, a number of researchers have used LNPs as a starting point for oral siRNA delivery studies. However, LNPs are not without significant challenges; the literature describes a wide range of critical factors for successful development, namely:

- Particle size and formulation options
- Compatibility and safety
- Protection and targeting
- Uptake and efficacy
- Metabolism and clearance
- Cost and scale-up potential.

One study, conducted by a group experienced with LNP formulation,[7] concentrated on efficacy and metabolism, using a combination of *in vitro* and mouse models to better understand the fate of LNPs in the GI tract. They studied LNP delivery under deconstructed stomach and intestinal conditions to assess stability over the expected pH range found in the GI tract, as well as looking at biodistribution and potency in mouse studies.

In summary, the authors noted that the LNP formulation was stable under varying pH levels and that LNPs entered the cells of the small intestine and colon and remained in the gut for up to eight hours following administration. They also saw, however, that enzyme degradation significantly reduced LNP efficacy and prevented gene-silencing activity *in vivo*. They suggest that orally delivered LNPs need to be protected in the stomach and upper intestine in order to achieve siRNA delivery to intestinal epithelial cells.

Milk-Derived Exosomes

In recent work, a group from the Korea Institute of Science and Technology (KIST) in Seoul investigated oral tumour necrosis factor alpha (TNF-α) siRNA delivery via milk-derived exosomes (M-Exos) for effective treatment of IBD.[8] The study highlighted that M-Exos offer superior structural stability compared with other LNPs and that, in the group's experiments, they were an efficient siRNA carrier.

M-Exos were loaded with TNF-α siRNA and efficacy in treating colitis was assessed in a dextran sulphate sodium (DSS)-induced inflammatory bowel disease murine model. The results demonstrate that M-Exos loaded with TNF-α siRNA effectively inhibited the expression of TNF-α-related inflammatory cytokines. Moreover, given that M-Exos are composed of unique lipids with high bioavailability, orally administered M-Exo/siRNA effectively reached colonic tissues, leading to decreased TNF-α expression and successful alleviation of colitis symptoms.

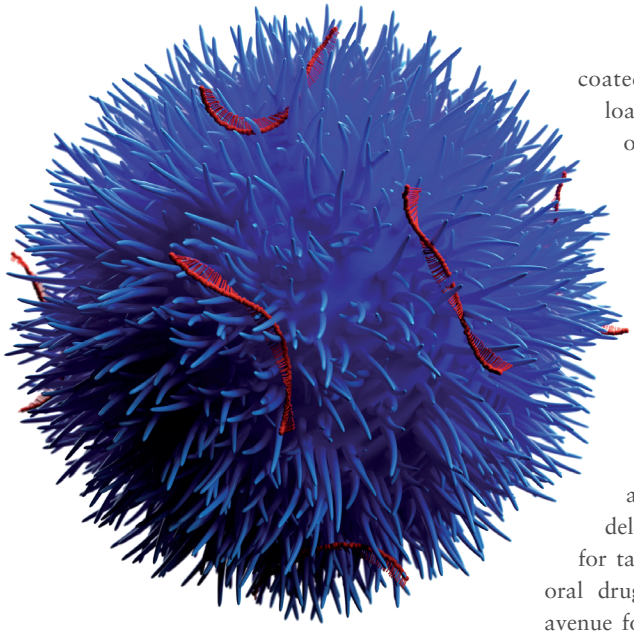

Figure 1: Visualisation of a Nuvec particle.

Engineered Silica Nanoparticles

Mesoporous silica nanoparticles (MSNs) have been identified as a suitable route for drug delivery due to their size, relatively inert nature and extremely large specific surfaces that can be functionalised by therapeutic and targeting entities. A series of preclinical studies using Nuvec®, a novel silica nanoparticle (Figure 1), have shown that the surface structure provides the siRNA with protection from enzyme attack as the siRNA cargo is held within the spikes on the particles.

With regard to oral delivery, further processing can provide a lyophilised, powdered form that allows loading of the siRNA/Nuvec intermediate into enteric-protected capsules (and potentially to be compressed into tablets) for targeting particular GI locations. At the site of action, the particle enters the target cell where the siRNAs detect and degrade a homologous mRNA sequence in the cell, resulting in reduction of the relevant protein and consequent inhibition of cell growth. This mode of action allows for precise targeting and the inhibition of identified signalling pathways with reduced toxicity, immune system response and potential side effects.

Experiments have confirmed the successful *in vivo* oral administration of Nuvec® loaded with a deoxyribonucleic acid (DNA) plasmid for ovalbumin. The therapeutic was administered by enteric-coated capsule and the contents, having been released in the intestinal lumen, were taken up by intestinal cells, with successful transfection and release of the newly synthesised ovalbumin. In a study conducted earlier this year, an enterically coated capsule containing Nuvec loaded with a DNA plasmid for ovalbumin was administered to mice and both protein/antigen and immunoglobulin G (IgG) antibody expression was observed. This research is ongoing.

LOOKING AHEAD

Moving through 2024, the increased research activity around siRNA looks set to deliver on the long-heralded potential for targeted gene therapy. Importantly, oral drug delivery remains the preferred avenue for siRNA administration, offering convenience and patient compliance, especially for long-term conditions such as IBD and Crohn's disease. This places the work of formulation scientists at the leading edge of drug development and, whilst challenges persist, ongoing research efforts and technological innovations are driving the field forward, opening new possibilities for improved drug efficacy and patient outcomes.

By harnessing the power of innovative formulation strategies and advanced drug delivery technologies, many believe the potential of oral oligonucleotide drug delivery can be unlocked. This is arguably the most cost-effective route for drug developers due to lower sterility constraints, more flexibility in design of dosage form and ease of production, compared with current IV formulations.

ABOUT THE COMPANY

N4 Pharma is a specialist pharmaceutical company developing novel delivery systems for oncology, gene therapy and vaccines. N4 Pharma's business model is to partner with companies developing novel antigens in these fields to use its novel Nuvec technology as the delivery vehicle and to develop its own product for post glaucoma surgery. As these products progress through preclinical and clinical programmes, N4 Pharma will seek to receive upfront payments and, ultimately, royalty payments once products reach the market.

REFERENCES

1. *Kumari N et al, "Oral Delivery of Nucleic Acid Therapies for Local and Systemic Action". Pharm Res, 2023, Vol 40(1), pp 107–122.*
2. *Sehgal I, Eells K, Hudson I, "Oral Delivery of Nucleic Acid Therapies for Local and Systemic Action". Pharmacy (Basel), 2024, Vol 12(2), Article 58.*
3. *Hu B et al, "Therapeutic siRNA: state of the art". Signal Transduct Target Ther, 2020, Vol 5(1), Article 101.*
4. *Lou J et al, "Advances in Oral Drug Delivery Systems: Challenges and Opportunities". Pharmaceutics, Vol 15(2), Article 484.*
5. *O'Driscoll CM et al, "Oral delivery of non-viral nucleic acid-based therapeutics - do we have the guts for this?". Eur J Pharm Sci, 2019, vol 133, pp 190–204.*
6. *Afrin H et al, "Oral delivery of RNAi for cancer therapy". Cancer Metastasis Rev, 2023, Vol 42(3), pp 699–724.*
7. *Ball RL, Bajaj P, Whitehead KA, "Oral delivery of siRNA lipid nanoparticles: Fate in the GI tract". Sci Rep, 2018, Vol 8(1), Article 2178.*
8. *Han G et al, "Oral TNF-α siRNA delivery via milk-derived exosomes for effective treatment of inflammatory bowel disease". Bioact Mater, 2023, Vol 34, pp 138–149.*

ABOUT THE AUTHOR

Nigel Theobald, Chief Executive Officer at N4 Pharma, has over 25 years' experience in healthcare, building businesses and strategy development and implementation, with a strong network covering all aspects of pharmaceutical product development and commercialisation. He was the head of healthcare brands at Boots Group in 2002 before leaving to set up a series of successful businesses, including Oxford Pharmascience Group, which he grew over five years into an AIM-quoted company with a market capitalisation of £40 million upon departure. Mr Theobald formed N4 Pharma in 2014.

NAVIGATING THE TRANSITION: EXPLORING ALTERNATIVES TO TiO_2 IN PHARMACEUTICAL FORMULATIONS

In this article, Lucía Gurruchaga, Scientific Business Development Leader & Pharma Rx Business Leader at Qualicaps, discusses the push to develop an alternative opacifier and white colourant to titanium dioxide in the wake of the European Commission's announcement that the additive may be banned in medicinal products, presenting data from recent testing on Qualicaps' own novel alternative.

Titanium dioxide (TiO_2), also known as E-171, is an inert, naturally occurring material that is produced in two main different forms. The primary form, which represents over 98% of total production, is the pigment grade. The pigmentary form is used in applications that require white opacity and brightness, which TiO_2 is ideal for due to its excellent light scattering properties. Some of these applications are paints, coatings, plastics, inks, foods, medicines and toothpastes. The other form is an ultrafine nanomaterial product. This form is selected when different properties, such as transparency and maximum UV light absorption, are required – for example, in cosmetic sunscreens.[1]

TiO_2 stops light transmission through a film by acting as an opacifier. This property has been widely used in the pharmaceutical and consumer healthcare industries as a white pigment and opacifier for oral solid dosage forms, such as tablets and hard and soft capsules. Approximately 91,000 human medicinal products and 800 veterinary medicinal products contain TiO_2 in the EU, according to EU trade associations.[2] However, in recent years, the use of this excipient has been questioned due to safety concerns.

REGULATORY BACKGROUND AND CURRENT STATUS

In 2015, the European Commission (EC) requested that the European Food Safety Authority (EFSA) evaluate the safety of E-171 as a food additive. In 2016, the EFSA concluded that no real concerns existed about the continued safe use of E-171 but recommended that more tests be performed to complete the toxicological studies. In June 2018, the French National Assembly enacted a temporary suspension of the use of E-171 as a food additive. No other EC members supported this position, deciding rather to wait for all ongoing studies to be completed before taking further action.

In May 2021, the EFSA published a safety assessment of E-171 as a food additive based on scientific evidence considered by the panel to be reliable, including data obtained with TiO_2 nanoparticles and data from an extended one-generation

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Lucía Gurruchaga
Scientific Business Development Leader & Pharma Rx Business Leader
T: +34 686 367 155
E: lgurruchaga@qualicaps.com

Qualicaps Europe
de Av del Monte Valdelatas, 4,
28108 Alcobendas
Madrid
Spain 28108

www.qualicaps.com

reproductive toxicity study. Genotoxicity studies showed that TiO_2 particles have the potential to induce DNA strand breaks and cause chromosomal damage, but not gene mutations. No clear correlation was observed between the physicochemical properties of TiO_2 particles and the outcome of either *in vitro* or *in vivo* genotoxicity assays. Therefore, based on all the available evidence, a concern for genotoxicity could not be excluded and, given the many uncertainties, the panel concluded that E-171 can no longer be considered safe when used as a food additive.[3] The EFSA neither identified nor recommended any new studies to clarify the genotoxicity concern and other remaining uncertainties.

In September 2021, the EMA, in response to a request from the EC, provided a scientific analysis on the technical purpose of the use of TiO_2 in medicinal products, the feasibility of replacement and possible timeframes for alternatives. In its conclusions, the EMA stressed that, from a technical point of view, it should bepossible to find alternatives to replace TiO_2 both as a colourant and for other uses. The EMA highlighted the need to carefully assess alternatives to ensure their compatibility with the various components of individual pharmaceutical products. Furthermore, the EMA concluded that it was difficult to recommend a precise transition period timeframe for the replacement of TiO_2 in medicinal products, considering the time needed to reformulate each individual product.[2]

Based on the EMA scientific analysis, and in order to avoid shortages of medicinal products that could have impacts on public health, Commission Regulation (EU) 2022/63 stated that TiO_2 should remain provisionally on the list of authorised additives to allow its use in medicinal products as a colourant, pending the development of adequate alternatives to replace it, while ensuring the quality, safety and efficacy of the medicinal products concerned. However, the EC also encouraged the pharmaceutical industry to accelerate the research and development of alternatives to be used as a replacement for TiO_2 in medicinal products, and to submit the necessary variation to the terms of the marketing authorisations concerned.[4]

Finally, the EC has committed to review the necessity to maintain TiO_2 – or otherwise delete it from the list of food additives for exclusive use as a colourant in medicinal products – within three years from the date that the regulation entered into force. This review was set to be based on an updated assessment of the EMA, expected to be published in April/May 2024. It should account for the progress made during this period in developing alternatives for TiO_2 in medicinal products both for new and existing products. Possible impacts on quality, safety and efficacy have to be assessed and avoided. As of writing, there has not been any update either from the EMA or from the EC on this regard.

"The EC has committed to review the necessity to maintain TiO_2 – or otherwise delete it from the list of food additives for exclusive use as a colourant in medicinal products – within three years from the date that the regulation entered into force."

In May 2023, the US FDA submitted a Citizen Petition from the Environmental Defense Fund entitled "Request To Revoke Color Additive Listing for Use of Titanium Dioxide in Food", which is still open. In November 2024, the Joint Expert Committee on Food Additives (JEFCA), formed by the WHO and the Food and Agriculture Organization (FAO), issued an assessment of the health impacts of TiO_2 as a food additive. After reviewing the available scientific literature, the JEFCA determined that more research was needed to address the current uncertainty about the distribution of TiO_2 particle sizes.[5]

At present, there is still not enough data to issue a final conclusion on TiO_2. Countries such as China, the US and Brazil continue to carry out their evaluations.

MARKET SITUATION

During this period, the pharmaceutical industry has faced several challenges in the transition from TiO_2 to alternative opacifiers. As mentioned prior, TiO_2 has been a widely used excipient in the pharmaceutical industry for more than 50 years. It is present in the majority of pharmaceuticals, in the coating of tablet films for capsule shells, as well as packaging materials. Its extensive use is due to its critical functions, which result from the following properties:

- **Inert substance:** TiO_2 is of particular benefit because it does not impact the properties of APIs or excipients. Being an unreactive ingredient, it is a common substance for medicines because it is well tolerated.
- **Consistent homogeneous colouring:** TiO_2 enables a consistent colour scheme and plays an important role as an opacifier. Consistent colouring of medicines plays a significant role in the recognition of a medicine to allow for differentiation for the patient, who needs to be able to readily distinguish between multiple medicine types, which can have a direct impact on therapeutic adherence and patient safety. In addition, colour variations may give false indication to the user that the product has degraded or is not efficacious.

Overall, TiO_2 contributes to developing a robust dosage form, protecting APIs, ensuring shelf-life stability and, therefore, securing the safety and efficacy of pharmaceuticals for longer periods.[6]

As pointed out by the "*Use of titanium dioxide as excipient in human medicines. Industry feedback to QWP Experts/EMA Questions*" survey, investigations into alternatives should identify an excipient with comparable properties regarding opacity, transmittance, water solubility and particle size, leading to the same uniform film quality as TiO_2. The alternative excipient must be safe for the patient in all aspects and compatible with the medicinal products in question.

The replacement of TiO_2 presents an important multifactorial challenge. Besides demonstrating that the replacement will have the same or sufficient similar performance, a seamless supply in line with the required quality standards for pharmaceuticals has to be ensured.

One of the alternatives to TiO_2 that has been identified during this period is calcium carbonate ($CaCO_3$). However, it can't provide the same degree of opacity and whiteness as TiO_2. Additionally, as excipients, carbonates need to be included at a higher concentration than TiO_2, which can have a negative impact on the film coatings by reducing film strength or increasing capsule brittleness. For light-sensitive drugs, it may also cause a higher rate of degradation.

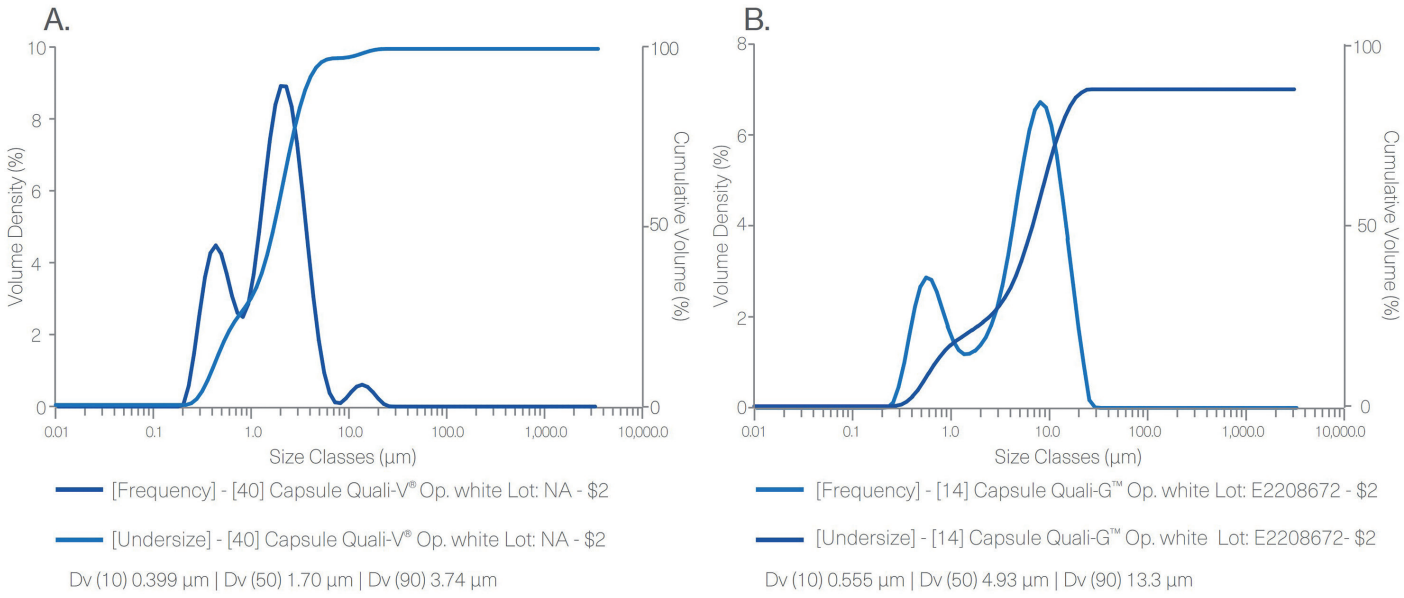

Figure 1: PSD result for Quali-V® TiO_2-free capsule (A) and Quali-G™ TiO_2-free (B) measured by laser diffraction in a Mastersizer 3000 (Malvern Panalytical, Malvern, UK) apparatus.

"Qualicaps has successfully validated a new alternative formulation with a new opacifying and whitening agent for TiO_2-free HPMC and gelatin hard capsules, which is now commercially available as Quali-V® TiO_2-free and Quali-G™ TiO_2-free."

QUALICAPS SOLUTION

Qualicaps Europe has played a pioneer role in recent years in developing a new TiO_2-free formulation that can overcome these challenges. The company's research and development work has been focused on developing a new alternative that complies with safety, quality and regulatory standards. As a result, Qualicaps has successfully validated a new alternative formulation with a new opacifying and whitening agent for TiO_2-free hydroxypropyl methylcellulose (HPMC) and gelatin hard capsules, which is now commercially available as Quali-V® TiO_2-free and Quali-G™ TiO_2-free. Some of the scientific data derived from the development work, compiled in the corresponding capsule product technical dossiers, are presented below.

Safety-Related Results

Particle Size Distribution

Figure 1 shows the results obtained from the particle size distribution (PSD) analysis performed with Quali-V® TiO_2-free and Quali-G™ TiO_2-free capsules. These results demonstrate the absence of nanomaterials in both formulations containing the new opacifier.

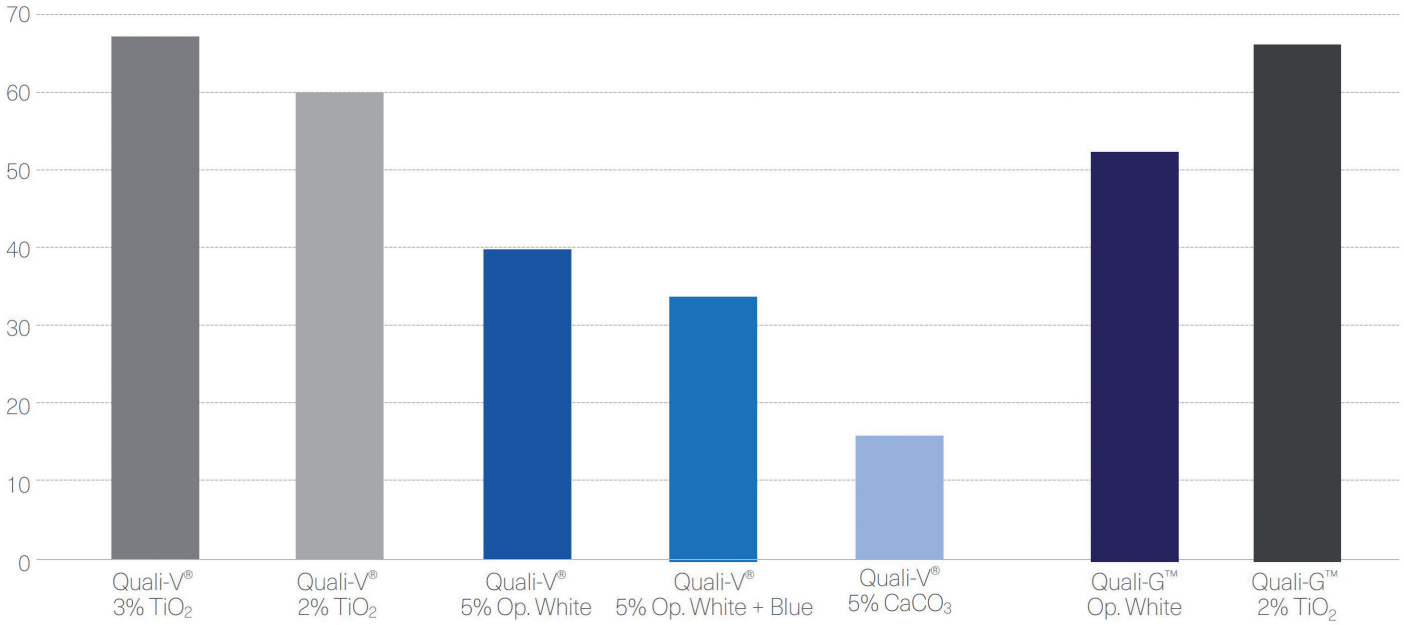

Figure 2: Opacity results of Quali-V® and Quali-G™ formulated with different opacifying agents, measured with a Lab Scan® XE (HunterLab, VA, US).

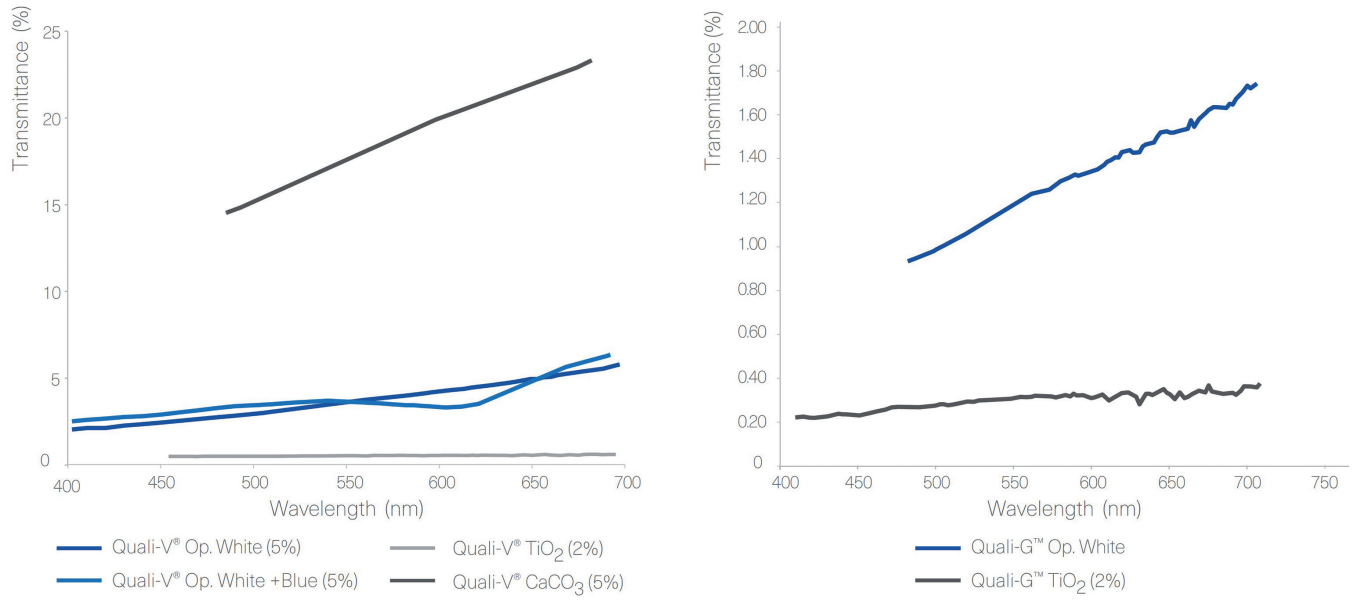

Figure 3: Transmittance results of Quali-V® and Quali-G™ formulated with different opacifying agents, analysed using a Cary 60 UV-Vis spectrophotometer (Agilent, CA, US).

Quality-Related Results

Opacity

For Quali-V® capsules, the opacity was analysed by comparing different formulations containing different types of opacifiers and concentrations. The results show that the highest opacity is obtained with the capsules formulated with TiO_2. Quali-V® capsules formulated with the new opacifying agent show the second highest opacity. The lowest opacity is obtained with the Quali-V® capsules formulated with $CaCO_3$ (Figure 2). For the Quali-G™ capsules, two formulations were compared – Quali-G™ containing 2% of TiO_2 and Quali-G™ formulated with the new opacifier (Figure 2).

Transmittance

Figure 3 shows the results obtained from the transmittance test performed with Quali-V®, using different opacifying agents. The results show that there is a big difference in transmittance between the Quali-V® formulated with $CaCO_3$ and the other formulations. For Quali-G™, transmittance is slightly higher when formulated with the new opacifier, but in line with the results obtained with HPMC.

Disintegration and Dissolution

Figure 4 shows a comparison between the dissolution profiles for Quali-V® TiO_2-free capsules and Quali-V® with TiO_2 at pH 1.2 and pH 6.8. All capsules tested complied with the specifications described in European Pharmacopoeia (EP) Ed 11.0, monograph 2.9.3, "Dissolution Testing for oral dosage forms", and Chapter 5.17.1, "Recommendations on

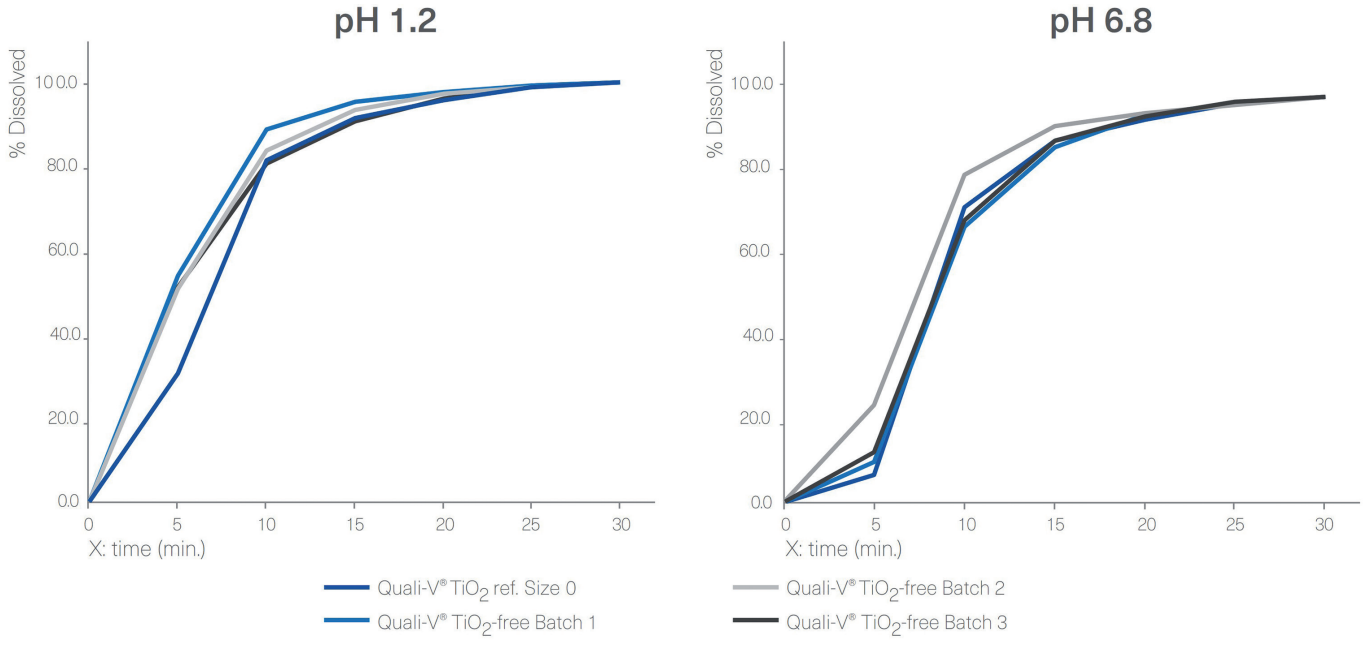

Figure 4: Dissolution profiles of four different batches of Quali-V® formulated with the new opacifier (Quali-V® TiO_2-free) compared with Quali-V® formulated with TiO_2 (Quali-V® TiO_2) at pH 1.2 and 6.8 (capsule fill formulation: acetaminophen 20%, lactose 80%; dissolution test method: paddle at 50 rpm).

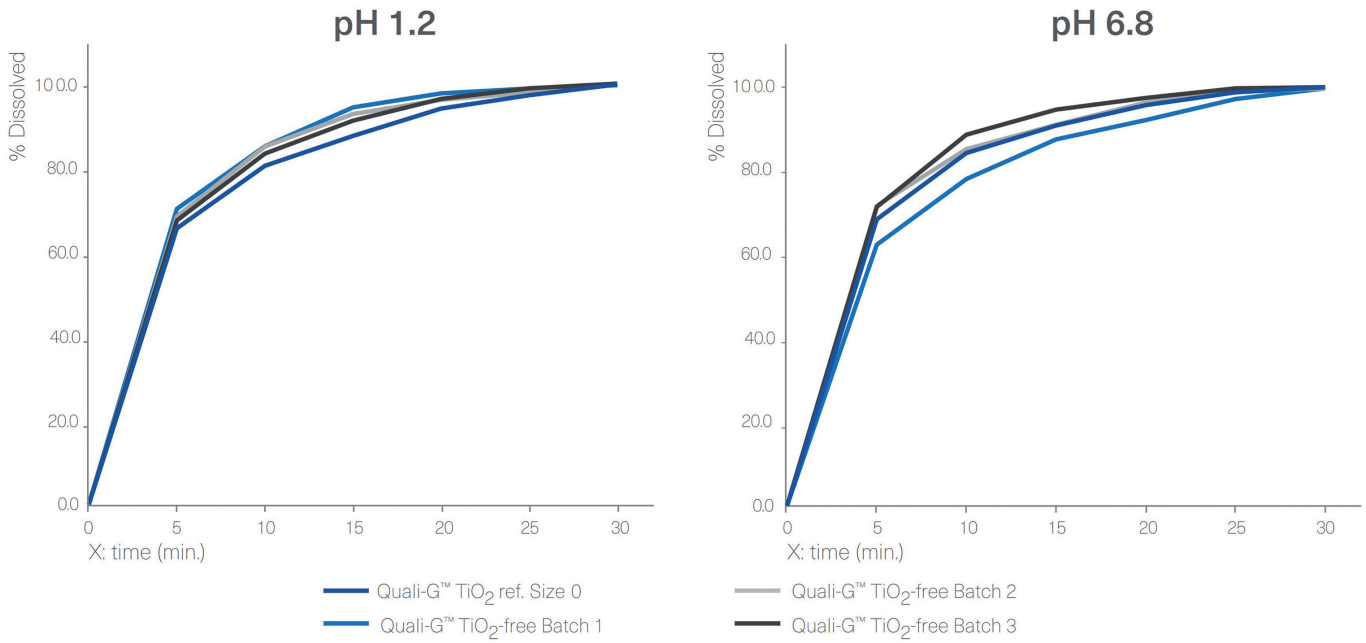

Figure 5: Dissolution profiles of four different batches of Quali-G™ formulated with the new opacifier (Quali-G™ TiO_2-free) compared with Quali-G™ formulated with TiO_2 (Quali-G™ TiO_2) at pH 1.2 and 6.8 (capsule fill formulation: acetaminophen 20%, lactose 80%; dissolution test method: paddle at 50 rpm).

Dissolution Testing for immediate release dosage forms", in which the acceptance criteria is stated as no less than 80% of the API dissolves in less than 45 minutes. Quali-V® TiO_2-free and Quali-V® with TiO_2 dissolution profiles are comparable at both pH levels.

Disintegration tests of empty Quali-V® TiO_2-free capsules were performed following the analytical method described in the chapter 2.9.1 "Disintegration of tablet and capsule" of the EP 11th Edition. All the batches analysed met the specification of no more than 15 minutes.

For the gelatin capsules, a dissolution profile comparison was performed between Quali-G™ TiO_2-free and Quali-G™ with TiO_2 at pH 1.2 and pH 6.8 (Figure 5). All dissolution profiles are comparable and comply with the specification of immediate release dosage forms described above, since more than 80% of the API is dissolved in less than 45 minutes.

The results obtained from the disintegration test of empty Quali-G™ TiO_2-free capsules showed a disintegration time of no more than 15 minutes, complying with the acceptance criteria. The analytical method applied was the same as described above for the HPMC disintegration tests.

Stability Studies

Stability studies were performed according to ICH Topic Q1A (R2), "Stability testing of new Drug Substances and Products", and ICH Q1E, "Evaluation of Stability Data", for both Quali-V® TiO_2-free and Quali-G™ TiO_2-free. Stability-indicating parameters, such us brittleness, dimensions, weight and loss on drying, were tested at every time point for long-term, intermediate and accelerated stability. All the results obtained to date have been satisfactory and compliant with the acceptance criteria. The current shelf life for both Quali-V® TiO_2-free and Quali-G™ TiO_2-free products is 24 months. The ongoing long-term stability study will continue up to 60 months.

CONCLUSION

The pharmaceutical industry is facing a big challenge due to the EC's announcement of a potential ban on using TiO_2 as an excipient in medicinal products. As encouraged by the EC, hard capsule manufacturers have been working for the last few years to offer an alternative solution to this widely used opacifier and white colourant. As of writing, the EMA has not announced any official decision derived from the assessment expected by April/May 2024, on which the EC will base its final decision on regulating TiO_2 for medications.

Qualicaps has developed and launched a new alternative solution that complies with safety and quality standards, providing excellent appearance and performance, for both HPMC and gelatin capsules.

ABOUT THE COMPANY

Qualicaps is a global player in the manufacturing and commercialisation of hard capsules and pharmaceutical processing equipment for the oral dosage market. With over 125 years of capsule manufacturing experience and the introduction of several capsule innovations to the pharmaceutical market, Qualicaps is uniquely positioned to provide an integral service to its customers through its global team of commercial, scientific and technical experts. Since October 2023, Qualicaps has been part of Roquette, a global leader in plant-based ingredients for the health and nutrition markets that operates in more than 100 countries, across more than 30 manufacturing sites, and employs around 10,000 people worldwide.

REFERENCES

1. *Beetsma J, "Transparent Inorganic Pigments: Titanium Dioxide and Iron Oxide". Ultrus Prospector, Aug 2022.*
2. *"Final feedback from European Medicine Agency (EMA) to the EU Commission request to evaluate the impact of the removal of titanium dioxide from the list of authorised food additives on medicinal products". EMA, Sep 2021.*
3. *"Safety assessment of titanium dioxide (E171) as a food additive". EFSA, May 2021.*
4. *"Commission Regulation (EU) 2022/63 of 14 January 2022 amending Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council as regards the food additive titanium dioxide (E 171) (Text with EEA relevance)". European Commission, Jan 2022.*
5. *"Joint FAO/WHO Expert Committee on Food Additives risk assessment of titanium dioxide risk released – background information". WHO, Nov 2023.*
6. *"Use Of Titanium Dioxide as Excipient in Human – Medicines Industry Feedback to QWP Experts/EMA Questions". EMA, Jul 2021.*

ABOUT THE AUTHOR

Lucía Gurruchaga, in her role as the Scientific Business Development Leader & Pharma Rx Business Leader at Qualicaps, brings a wealth of expertise and experience to her position. With a bachelor's degree in Biochemistry and an MSc in Research, Development and Innovation of Drugs, Ms Gurruchaga has accumulated several years of experience in pharmaceutical research and development (R&D), specialising in analytical and galenic development in pharmaceutical laboratories. Ms Gurruchaga plays an indispensable role within the scientific team at Qualicaps, her responsibilities spanning providing comprehensive R&D support, overseeing the selection process for the most suitable hard capsule for a formulation and offering steadfast assistance throughout the entire drug development journey. Ms Gurruchaga's commitment to excellence ensures seamless support across the entire drug product lifecycle. Furthermore, Ms Gurruchaga actively engages in collaborations with external research and development centres on various projects aimed at enhancing the properties and performance of hard capsules. Her significant contributions consistently drive innovation and foster a culture of excellence within the industry.

Aptar CSP Technologies

TARGETING NITROSAMINE PRECURSORS WITH NOVEL ACTIVE MATERIAL SCIENCE SCAVENGER TECHNOLOGIES

In this piece, Ivy Comer, Scientist III, Amanda Murph, Scientist II, and Jason Pratt, Director, Material Science, all at Aptar CSP Technologies, discuss the challenges in combatting N-nitrosamine formation in oral solid dosage forms, and present the company's 3-Phase Activ-Polymer technology as a novel packaging-based solution.

N-nitrosamine or nitrosamine drug substance-related impurities (NDSRIs) are a class of potentially carcinogenic compounds that have been wreaking havoc on the pharmaceutical industry, leading to product recalls and heightened regulatory scrutiny of both commercialised and in-development drugs. Nitrosamines are found as impurities in various drug products, and studies show that, over time, nitrosamine formation levels can grow beyond the US FDA's daily thresholds, potentially putting patients at risk.

Nitrosamines are substances that can form under certain conditions through a process known as nitrosation, especially in the presence of nitrosating agents such as nitrite salts, alkyl nitrites, nitrogen oxides (NO_x), nitrosyl halides, nitrosonium salts and nitro compounds, along with amines or amides. Nitrosating agents can arise from the use of recycled solvents or reusing catalysts across different processes or manufacturing lines with inadequate control and inappropriate monitoring. They can also be generated from impure starting materials or intermediates in the upstream step or from the carry-over of other manufacturing processes along the same production line.

> "Controlling the presence of nitrosating agents and their interaction with precursors is crucial in mitigating nitrosamine formation."

Another key variable in nitrosamine formation is the nitrite levels in many of the most commonly used excipients – for example, magnesium stearate and microcrystalline cellulose (MCC) can average 2,000–3,000 ppb levels of nitrites, aiding in nitrosamine-forming reactions.

Controlling the presence of nitrosating agents and their interaction with precursors is crucial in mitigating nitrosamine formation. Aptar CSP Technologies has conducted a series of studies[1] that explores the possibility of leveraging innovative active material science technologies to develop a novel nitrosamine-mitigating solution for oral solid dosage forms. The branch of the study presented here focuses on the role that nitrites in excipients play in nitrosamine formation (Box 1). It also investigates how Aptar CSP Technologies' proprietary Activ-Polymer™ platform technology can mitigate the risk associated with MCC. The data presented explore whether nitrite impurity levels contained in a sample lot of placebo MCC tablets can be meaningfully reduced when placed together with Aptar CSP's Activ-Film™ material in a sealed environment.

Ivy Comer
Scientist III
T: +1 334 740 0800
E: ivy.comer@aptar.com

Amanda Murph
Scientist II
T: +1 470 848 3716
E: amanda.murph@aptar.com

Jason Pratt
Director, Material Science
T: +1 334 750 0165
E: jason.pratt@aptar.com

Aptar CSP Technologies
960 West Veterans Blvd.
Auburn
AL 36832
United States

www.csptechnologies.com

BOX 1: THE IDEA IN BRIEF

The Problem

Pharma companies are facing increasing regulatory scrutiny and higher risk of product recalls due to N-nitrosamines and NDSRIs in drug products. The mechanism of reaction and root cause of nitrosamine formation is not always understood, which makes mitigating this risk difficult.

The Challenge

The current mitigation strategies employed by pharma developers, such as making changes to their formulation or manufacturing processes, can be costly. Additionally, it is difficult to control the variables associated with N-nitrosamine formation with any certainty. Additional or alternative mitigation strategies may need to be considered to fully address the risk.

The Solution

New innovations in active material science technologies can offer an active packaging-based solution that can react with NO_x gases in the packaging headspace to inhibit nitrosamine formation. Not only can these technologies stop nitrosamine formation, but they can serve as an additional "insurance policy" by adsorbing or scavenging N-nitrosamines post-formation, providing a holistic risk mitigation solution.

MITIGATING NITROSAMINE RISKS ASSOCIATED WITH EXCIPIENTS

Oral drug formulations typically involve a blend or granulation of their APIs with various excipients, many of which have been shown to include nitrite impurities at trace levels. According to Boetzel *et al*, the excipients, such as fillers and diluents, have the greatest influence over the nitrite concentration.[2] MCC is an extremely common diluent in oral solid dosage forms, particularly tablets and capsules, and has the highest number of results in Lhasa Limited's (Leeds, UK) "Nitrite in Excipients" database at 0.04–2.4 ppm. These nitrites can form nitrosating species, such as nitrous acid and various volatile NO_x compounds, especially under moderately acidic conditions. For APIs at risk of nitrosamine formation, the presence of nitrosating species in the excipients used in the formulation has been shown to directly increase the rate of formation of nitrosamines.

As pharmaceutical developers seek to assess and mitigate the risk of N-nitrosamine formation in their current drug products and in-development APIs, they have employed strategies such as using nitrocellulose-free packaging or choosing alternate or supplemental excipients, reagents or catalysts. However, these solutions are not infallible, as companies may not always be able to source low- or no-nitrite excipients, and these strategies can result in overformulation, which could potentially lead to new problems.

> "The mechanism of reaction and root cause of nitrosamine formation is not always fully understood, complicating the process of finding an adequate risk-mitigation strategy."

Additionally, the mechanism of reaction and root cause of nitrosamine formation is not always fully understood, complicating the process of finding an adequate risk-mitigation strategy. Aptar CSP's challenge as an active material science company is to provide pharma companies with an active packaging-based solution to prevent nitrosamine formation and/or remove nitrosamine impurities post-formation at the point of packaging, reducing the need for changes to formulation or manufacturing processes. The technology could be used as a primary solution or as an additional measure of protection to complement other strategies used to prevent N-nitrosamine formation.

INNOVATIONS IN ACTIVE MATERIAL SCIENCE TECHNOLOGIES

Nitrites are known to form volatile, gaseous NO_x components, especially through protonation under mildly acidic conditions.[3] In the absence of any additional reactions, such gases will come to an equilibrium in the environment. However, by removing the NO_x from the environment, the equilibrium reaction will drive the formation of additional NO_x gases that, if removed, will continue until the trace levels of nitrite are consumed.

New innovations in active material science technologies can offer an active packaging-based solution that can react with NO_x gases in the packaging headspace to inhibit nitrosamine formation. Leveraging over 20 years of material science expertise, Aptar CSP Technologies' 3-Phase Activ-Polymer™ platform technology is delivered in a unique formulation comprised of a base majority polymer that provides the structure, a channelling agent and active particles (Figure 1). The channelling agent coats and distributes active particles throughout the polymer matrix and allows targeted molecules to enter through the hydrophilic channels. Those molecules migrate to the active particles, where they are adsorbed and permanently removed from the headspace.

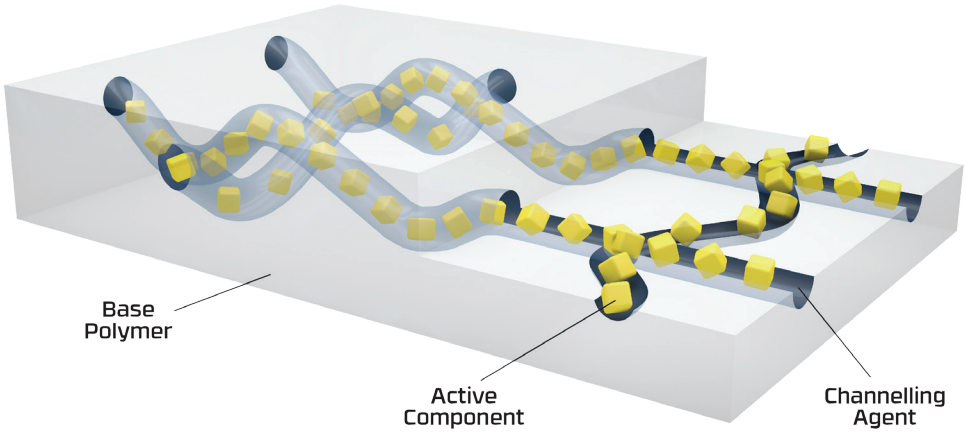

Figure 1: 3-Phase Activ-Polymer™ technology matrix.

For the purposes of this study, the technology, deployed as an Activ-Film™ material sealed together with MCC tablets, was engineered to quickly and efficiently capture and/or react away the volatile NO_x species, thus preventing the formation of nitrosamines by removing the nitrosating agent (Figure 2). This technology is called N-Sorb (Figure 3).

N-SORB STUDIES

In one study, four versions of N-Sorb mitigation films were exposed to MCC tablets in sealed foil bags during a six-day ageing period. The methodology[5] used for the experiment was based on a chemical derivative method that reacts with all available nitrites directly into a measurable compound. The compound was detected and quantified using a gas chromatography-mass spectroscopy headspace, with a detection ranging from 5 to 100 ppm. The instrumentation specifications for the experiment were:

- Agilent GC 8890, Model Number G3542A
- Agilent MSD 5977, Model Number G7077C
- Agilent Headspace 8697, Model Number G4511A.

All four versions of the N-Sorb mitigation film significantly reduced the average levels of nitrite present in the samples compared with the controls. None of the mitigant's range of concentration overlapped or extended into the control concentration, indicating that nitrite levels were significantly reduced after ageing. After six days of ageing at 60°C in an oven, the samples containing the MCC and either N-Sorb 20 or N-Sorb 23 mitigation film had the lowest level of nitrite concentration remaining in the headspace (Figure 4).

> "After six days of ageing at 60°C in an oven, the samples containing the MCC and either N-Sorb 20 or N-Sorb 23 mitigation film had the lowest level of nitrite concentration remaining in the headspace."

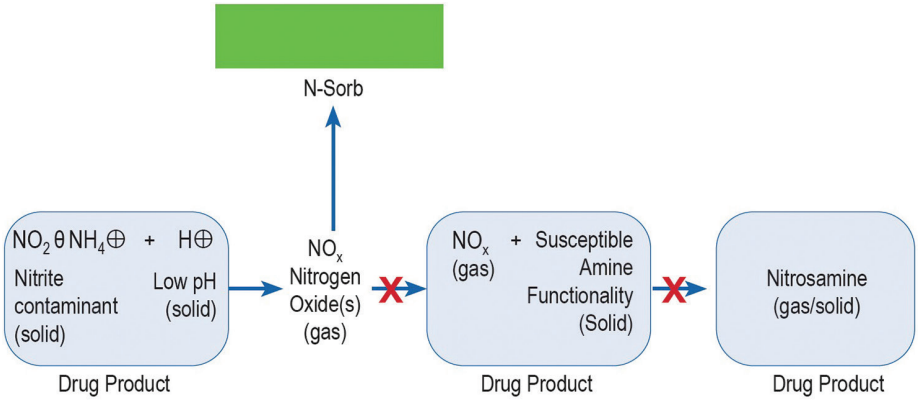

Figure 2: How N-Sorb can prevent nitrosamine formation.[4]

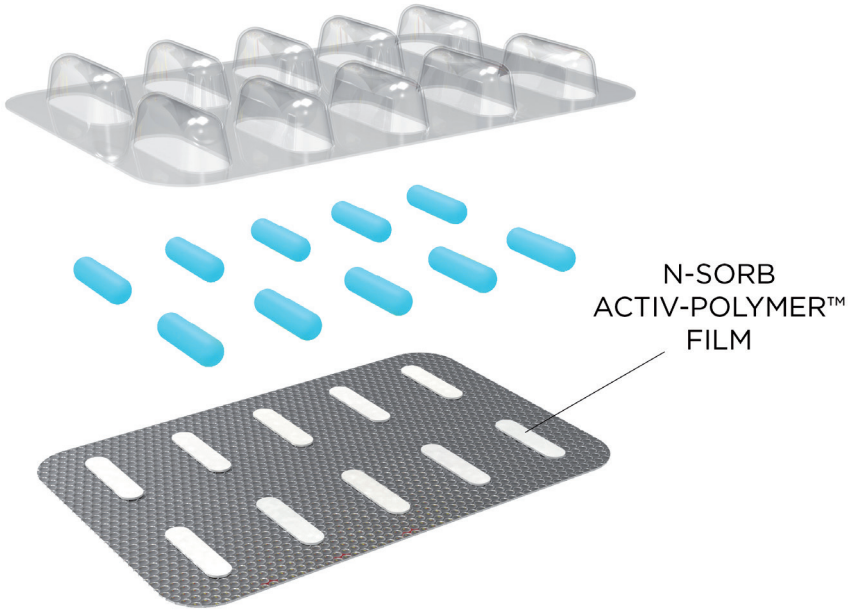

Figure 3: Example deployment of N-Sorb Activ-Polymer™ film sealed in an Activ-Blister™ configuration with tablets.

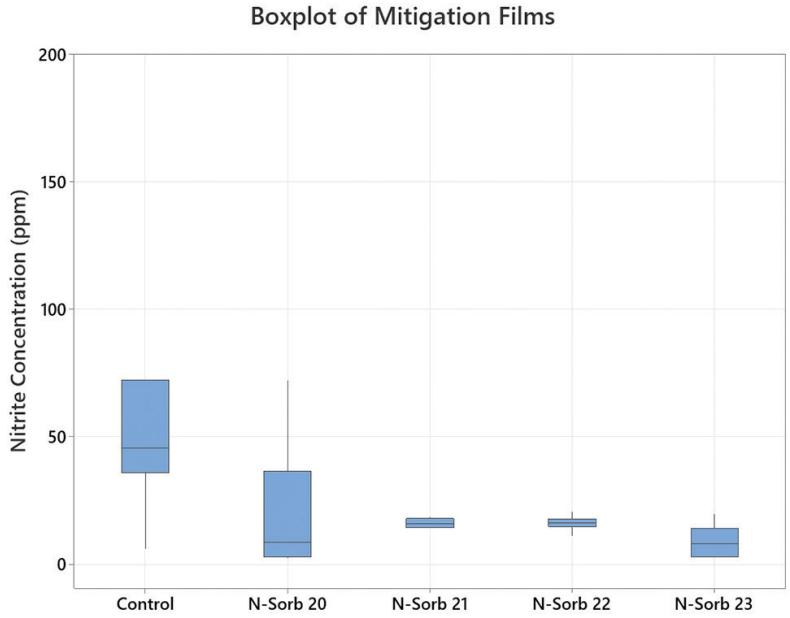

Figure 4: Nitrite concentration (ppm) versus N-Sorb mitigation films sealed with MCC tablets.

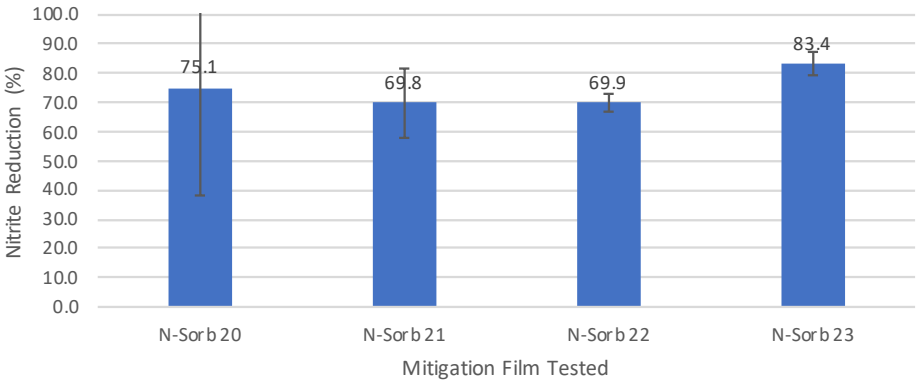

Figure 5: Percentage reduction of nitrites in MCC tablets sealed with N-Sorb mitigation films when compared with control sample.

"Aptar CSP Technologies' innovative Activ-Polymer™ platform with its N-Sorb technology offers pharmaceutical developers a promising alternative to current nitrosamine mitigation strategies."

Nitrite was reduced by all N-Sorb mitigation films tested with MCC tablet samples during the ageing period compared with the amount measured in the control samples (Figure 5). All the mitigation films exhibited a reduction of ~70% or more compared with the amount measured in the control sample. MCC tablet samples exposed to the N-Sorb 23 mitigation film during the test period resulted in the highest reduction of nitrite concentration, along with the lowest variation of the top two mitigation film performers, as illustrated by Figures 4 and 5.

CONCLUSION

Aptar CSP Technologies' innovative Activ-Polymer™ platform with its N-Sorb technology offers pharmaceutical developers a promising alternative to current nitrosamine mitigation strategies by actively removing nitrosamines from the headspace of sealed drug packaging. The key findings from this study demonstrate the potential of N-Sorb as a potent scavenger of nitrite precursors:

- **Significant Nitrite Reduction:** All tested N-Sorb mitigation films significantly reduced nitrite levels in the headspace compared with controls, with reductions exceeding 70% in some cases.
- **Efficient Capture:** N-Sorb 23 exhibited the highest nitrite reduction and lowest variation, demonstrating its efficacy in capturing and/or reacting with the volatile NO_x species responsible for nitrosamine formation.
- **Post-Formation Mitigation Potential:** While the study focused on preventing nitrosamine formation, the technology's ability to capture nitrite supports its potential efficacy for reducing existing NDSRIs in packaged drugs.

For drug formulation and analytical scientists, N-Sorb presents a compelling solution offering several advantages:

- **Targeted Intervention:** N-Sorb specifically addresses the root cause of nitrosamine formation – the presence of nitrosating agents, such as NO_x gases – without requiring extensive formulation changes.
- **Simplicity and Ease of Integration:** N-Sorb can be seamlessly integrated into existing packaging formats and processes, minimising disruption to manufacturing workflows.
- **Flexibility and Potential for Broad Applicability:** The modular design of Activ-Polymer™ technology allows for customisation to suit specific drug product requirements and target various nitrosating agents beyond NO_x gases.

While further research is warranted to fully validate the long-term effectiveness and compatibility of N-Sorb with diverse drug products, this study provides a strong foundation for its potential as a game changer in the fight against NDSRIs. By offering a targeted, efficient and easily implementable solution, N-Sorb can empower drug developers to ensure the safety and quality of their products while streamlining compliance with regulatory requirements.

ACKNOWLEDGEMENTS

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ABOUT THE COMPANY

Aptar CSP Technologies is part of AptarGroup Inc, a global leader in drug and consumer product dosing, dispensing and protection technologies. Aptar CSP Technologies leverages its active material science expertise to transform ideas into market opportunities, accelerate and de-risk the product development process and provide complete solutions that improve consumers' and patients' lives. The company offers a complete set of services from concept ideation and design and engineering to product development, global production, quality control and regulatory support that results in expedited speed-to-market.

REFERENCES

1. *Baertschi S, Daou J, Pratt J, "Mitigating N-Nitrosamine Risks with Novel Active Material Science Innovations". White Paper, Aptar CSP Technologies, May 2023.*
2. *Boetzel R et al, "A Nitrite Excipient Database: A Useful Tool to Support N-Nitrosamine Risk Assessments for Drug Products". J Pharm Sci, 2023, Vol 112(6), pp 1615–1624.*
3. *Sluggett GW, "Artifactual degradation of secondary amine-containing drugs during accelerated stability testing when saturated sodium nitrite solutions are used for humidity control". J Pharm Biomed Anal, 2018, Vol 149, pp 206–213.*
4. *Carloni L-E et al, "Solid State Kinetics of Nitrosation Using Native Sources of Nitrite". J Pharm Sci, 2023, Vol 112(5), pp 1324–1332.*
5. *Zhang S-X et al, "A high-throughput headspace gas chromatographic technique for the determination of nitrite content in water samples". J Chromatogr A, 2018, Vol 1538, pp 104–107.*

ABOUT THE AUTHORS

Ivy Comer is Scientist III in the Applications and Research Development Team at Aptar CSP Technologies. She joined the team with a BS in Biochemistry from Auburn University (AL, US), where her passion for science evolved into a deep commitment for innovation, analytical methodologies and meticulous active-applications problem-solving. Ms Comer's aptitude for strategic leadership, communication and collaborative problem-solving has led to impactful solutions within the medical and packaging industries.

Amanda Murph is Scientist II within the Research and Applications Development division at Aptar CSP Technologies. Leveraging her expertise in materials engineering, Ms Murph spearheads the Nitrosamines Mitigation project, where she assumes a leadership role in project planning and execution. Despite her relatively brief tenure in the industry, Ms Murph's commitment to innovation is evident as she continuously explores novel applications for various materials. Driven by a passion for collaborative problem-solving, Ms Murph remains steadfast in her pursuit of excellence, prioritising results and tangible outcomes.

Jason Pratt is Director of Material Science at Aptar CSP Technologies. An experienced scientist with a passion for innovative solutions to commercial opportunities, Mr Pratt is skilled at bringing together and mentoring high power teams to tackle impossible problems. He is a green chemist with over 40 patents across the food, cosmetics, pharma and construction industries.

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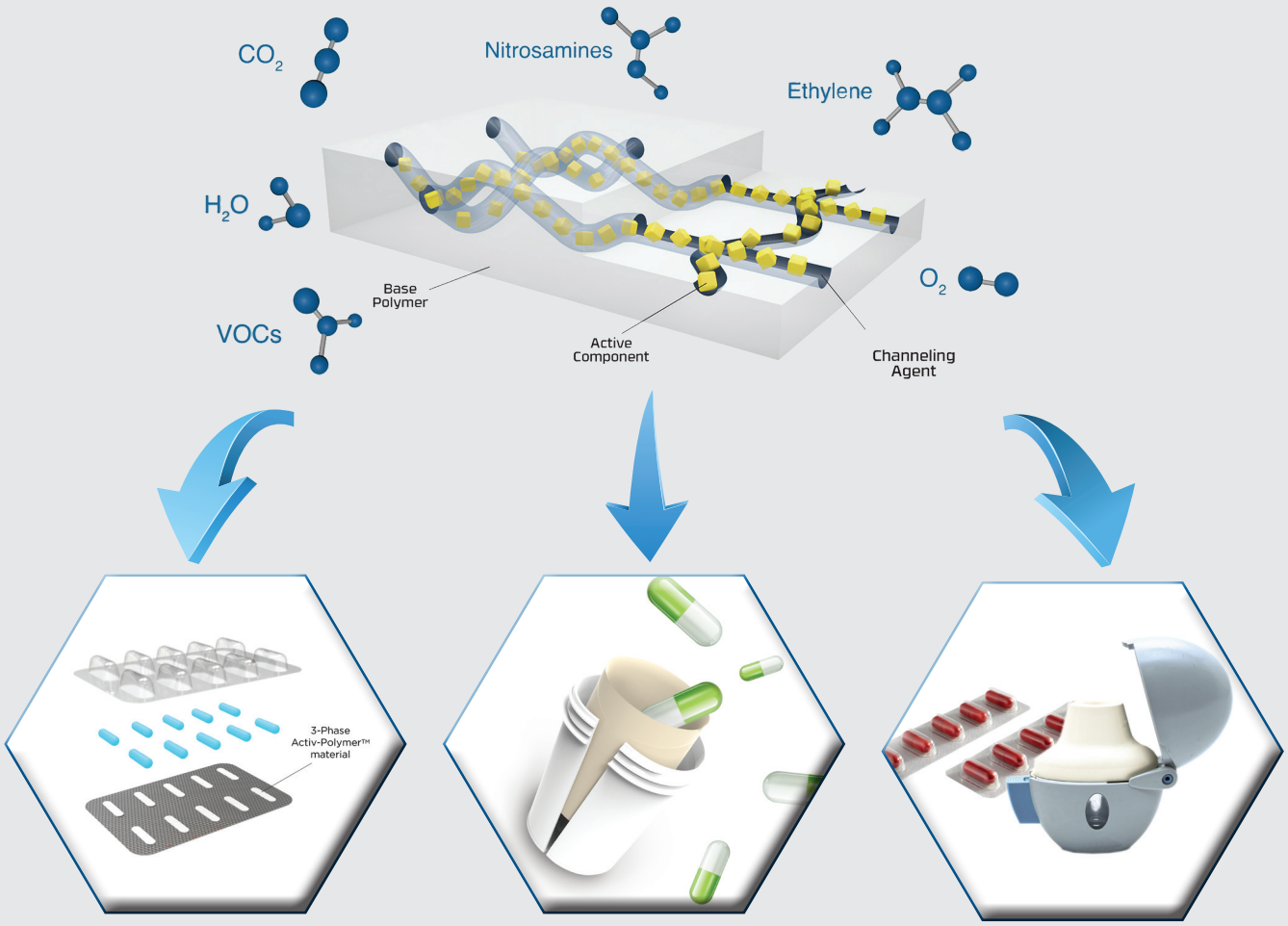

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Aptar CSP Technologies

DIFFERENTIATING ORAL SUSPENSIONS WITH VERSATILE EXCIPIENTS

In this article, Mariona Venceslao Molins, Marketing Manager for Europe and Global Market Manager for Oral Treatment, and Liliana Miinea, PhD, Technology Manager, both at Lubrizol, discuss how excipient-based approaches can facilitate patient-centric formulations and transform oral suspensions.

In today's crowded pharmaceutical market, drug developers increasingly need to consider how their products can align with patients' preferences and improve compliance. Certain patient populations – such as paediatric and geriatric, or those with neurodegenerative conditions – often struggle with taking oral solid dosages. One possible cause of this is difficulties with swallowing large tablets and capsules (dysphagia). In a large population-based survey, one in six adults in the US was found to struggle with dysphagia.[1] Furthermore, approximately 1% of children in the US experience swallowing difficulties,[2] and dysphagia can also be a common symptom of neurodegenerative disorders.[3] This challenge will only be further exacerbated by the global demographic shift to an ageing population, with the number of people aged 80 years or older expected to triple to 426 million by 2050.[4]

When it comes to improving patient compliance with medication, oral suspensions are a useful option. They are much easier to swallow than solid dosage forms, which is crucial for those who suffer from dysphagia. Using the right excipients, oral suspensions can also be developed in palatable, no-spill and shake-free formats, which are more convenient for patients suffering from the tremors symptomatic of conditions such as Parkinson's disease and multiple sclerosis.[5] These factors can be crucial for helping patients stick to their vital medication regimens.

However, the pharmaceutical landscape is complex and, alongside patient compliance, there are a host of other factors that drug developers need to consider. First and foremost, formulators are looking to create products that stand out in a crowded and competitive market. At the same time, pharmaceutical manufacturers are increasingly looking to streamline their processes to reduce complexity and cost. Developers need to balance these competing demands while delivering patient-friendly products. This is where pharmaceutical excipients shine.

> "Using the right excipients, oral suspensions can also be developed in palatable, no-spill and shake-free formats."

GIVING DRUGS A NEW LEASE OF LIFE

Over the years, the excipient market landscape has transformed. Drug developers are no longer looking for simple binders and fillers to package their APIs, but for functional excipients that can help them to bring highly differentiated products to market. This can be achieved by formulating an entirely new drug product with a novel API as part of an NDA or through the reformulation of a pre-existing API through the US FDA's 505(b)(2) approval pathway.

The 505(b)(2) pathway allows for the use of safety and efficacy data from previous studies to streamline approval.[6] It is possible to capitalise on the 505(b)(2) route by reformulating approved drugs using versatile excipients that facilitate more patient-centric dosage forms. Ultimately, this allows for the creation of differentiated products, including opportunities for over-the-counter (OTC) drugs that are more convenient and comfortable for patients, which can give them a competitive edge.

EXCIPIENT-BASED APPROACHES FOR TRANSFORMING ORAL SUSPENSIONS

Whether developing a new drug product or reformulating a pre-existing one, the choice of excipient is crucial. With oral suspensions, the key excipients are the suspending agents. These are a class of

Mariona Venceslao Molins
Marketing Manager for Europe and Global Market Manager for Oral Treatment
E: mariona.venceslao@lubrizol.com

Dr Liliana Miinea
Technology Manager
E: liliana.miinea@lubrizol.com

Lubrizol
29400 Lakeland Boulevard
Wickliffe
OH 44092
United States

www.lubrizol.com

"Whether developing a new drug product or reformulating a pre-existing one, the choice of excipient is crucial."

excipients added to dispersed systems to ensure that solid particles in the formulation are kept uniformly distributed within the continuous phase, thereby maintaining the physical stability of the product.

The importance of the suspending agent cannot be understated. When dispersing an API in the liquid phase, formulators need to overcome an array of challenges, including (but not limited to) creaming, sedimentation, caking, particle growth and adhesion to the container.[7] To counteract these processes and formulate a shelf-stable oral suspension, a high-quality suspending agent is critical. Suspending agents can bring other benefits too, such as helping manufacturers to optimise texture and mouthfeel, improving the patient experience.

Suspending agents come in many forms, and formulators must select the option that is right for their drug development project. One popular class of suspending agents is natural polysaccharides and their derivatives (such as starch, pectin and xanthan gum), which work by increasing the viscosity of the aqueous systems in which they are dispersed. Cellulose-based suspending agents are a subset of these natural polysaccharides and include water-soluble ethers, such as methylcellulose and hydroxyethyl-cellulose. Another alternative used in the market is hydrated silicates, which are naturally occurring siliceous clays that form colloids in water (e.g. bentonite and hectorite).[7]

Carbomers – synthetic high molecular weight cross-linked polyacrylic acid polymers that swell in water to form hydrogels – are another important class of suspending agents that can confer significant advantages to a formulation.

CARBOMERS IN ORAL SUSPENSIONS

Of the vast array of suspending agents, carbomers are emerging as a popular choice for creating differentiated oral suspensions, thanks to their unique chemistry. Carbomer particles swell when they are hydrated and neutralised, forming a colloidal dispersion. These swollen, close-packed microgels can hold the solid API particles permanently within the gel structure, helping to provide excellent suspending properties – even at very low inclusion levels.

The suspending ability of carbomers is due to their high yield value. This helps to prevent sedimentation and maintain uniformity. Carbomers also impart shear thinning properties, which means that they flow more easily when under stress,[8] allowing for easier filling and dosing and making them more amenable to cold processing during manufacture.

"Carbomers are unique in that they provide a wide range of viscosity profiles and have high yield values, even at low concentrations."

Carbomers are unique in that they provide a wide range of viscosity profiles and have high yield values, even at low concentrations. These combined features make carbomers more efficient as a suspending agent than cellulose-based excipients or natural gums such as xanthan.

Using these polymers, formulators can impart properties that make the final product easier to use for the consumer, such as improved pourability, ease-of-swallowing and no-spill properties. Carbomers can also impart mucoadhesive properties to a formulation. This mucoadhesion can improve the sensorial experience by providing a soothing effect for a cold and cough formulation, for example, while simultaneously enhancing bioavailability and tissue protection. Furthermore, due to their long history of use within the pharmaceutical industry, formulators can be confident that carbomers are safe and effective.

BRINGING IT ALL TOGETHER: A CASE STUDY OF CARBOMERS IN ACTION

Paracetamol is one of the most well-known and popular OTC analgesics in the world.[9] Using a popular carbomer available on the market,[10] formulators were able to take this common drug and reformulate it into a differentiated oral suspension with improved patient-centric and manufacturer-friendly properties.

Firstly, the inclusion of the carbomer polymer imparted no-spill properties to the oral suspension compared with a reference formulation, allowing for greater ease-of-use for patients who suffer from neurodegenerative disorders. Furthermore, the polymer imparted mucoadhesion, allowing for protective tissue coating and greater bioavailability. Lastly, by facilitating cold processing, the resulting oral suspension allowed for superior scalability and ease of manufacturing. This effectively illustrates how incorporating the right excipient can transform a drug formulation and facilitate crucial patient-centric properties while also addressing manufacturing needs.

FACTORS TO CONSIDER WHEN CHOOSING AN ORAL EXCIPIENT

Innovation in the excipient landscape means that there is a wide range of variables to consider when seeking out the right excipient for a drug development project beyond functional ability. Formulators should seek out multifunctional excipients, such as carbomers, that can simplify formulations and streamline manufacturing, as well as increase the potential for product differentiation.

Another aspect to consider is that natural thickeners and suspending agents are often derived from plants and, in recent years, crop shortages have led to challenges in sourcing these ingredients. These difficulties can hinder vital R&D work and disrupt commercial production, so using synthetically derived excipients, such as carbomers, from a provider that has a strong supply chain is critical. The chosen excipient supplier should also be able to provide comprehensive expertise and technical support, which will help to facilitate the development of effective and differentiated oral suspensions using their excipients.

> "Incorporating the right excipient can transform a drug formulation and facilitate crucial patient-centric properties while also addressing manufacturing needs."

THE POWER OF EXCIPIENTS

In a crowded and competitive market that needs to serve an increasingly ageing population, and with a significant proportion of patients struggling with dysphagia and neurodegenerative disorders, patient-centric oral suspensions will continue to be in demand. Whether for 505(b)(2) reformulations or NDA projects, excipient-based strategies are key to helping drug developers to bring enhanced oral suspension products to market.

In particular, carbomer-based suspending agents offer an array of advantages due to their unique chemistry. Ultimately, by incorporating effective excipients that facilitate patient-centric formulations and streamline manufacturing, pharma companies can bring differentiated products to market while driving improved quality of life for patients – a win for everyone.

ABOUT THE COMPANY

The Lubrizol Corporation, a Berkshire Hathaway company, is a specialty chemical company whose science delivers sustainable solutions to advance mobility, improve wellbeing and enhance modern life. Founded in 1928, Lubrizol owns and operates more than 100 manufacturing facilities, sales and technical offices around the world and has more than 8,000 employees.

REFERENCES

1. *Adkins C et al "Prevalence and Characteristics of Dysphagia Based on a Population-Based Survey". Clin Gastroenterol Hepatol, 2020, Vol 18(9), pp 1970–1979.e2*
2. *Bhattacharyya N, "The prevalence of pediatric voice and swallowing problems in the United States". Laryngoscope, 2015, Vol 125(3), pp746–750.*
3. *Ueha R et al, "Management and Treatment for Dysphagia in Neurodegenerative Disorders". J Clin Med, 2023, Vol 13(1), Article 156.*
4. *"Ageing and Health". WHO, Oct 1, 2022.*
5. *"Tremor". US National Institute of Neurological Disorders and Stroke, Jan 8, 2024.*
6. *"Abbreviated Approval Pathways for Drug Product: 505(b)(2) or ANDA?" US FDA, Sep 19, 2019.*
7. *"Pharmaceutical Suspending Agents: Overview, Types, and Selection Criteria". Pharma Central, Oct 23, 2021.*
8. *"Flow and Suspension Properties". Company Web page, Lubrizol, Pharmaceutical Bulletin 07, Oct 29, 2008.*
9. *Ayoub SS, "Paracetamol (acetaminophen): A familiar drug with an unexplained mechanism of action". Temperature (Austin). 2021, Vol 8(4), pp 351–371.*
10. *"Oral Suspensions". Company Web page, Lubrizol, Pharmaceutical Bulletin 22, May 31, 2011.*

ABOUT THE AUTHORS

Mariona Venceslao Molins is the Marketing Manager for Europe and Global Market Manager for Oral Treatment at Lubrizol Life Science Pharma. Her work focuses on developing and executing the strategy for pharmaceutical excipients in the European region as well as the global implementation for the oral treatment market. Prior to Lubrizol, she worked for SYNLAB as the Global Brand Manager. Ms Venceslao Molins holds a bachelor's and master's degree in Business Administration from ESADE Business School, Barcelona (Spain), and a master's in Pharmaceutical Marketing from Universitat Pompeu Fabra, Barcelona (Spain).

Liliana Miinea, PhD, is a Technology Manager with Lubrizol Life Science. Her work focuses on developing new technologies for pharmaceutical applications, mainly in the areas of controlled release, drug solubility enhancement and enhanced mucosal delivery. She has over 20 years of experience in developing and characterising ingredients, including nanomaterials, polymer/nanomaterials composites and novel excipients. Prior to Lubrizol, Dr Miinea worked at Avantor Inc, and conducted postdoctoral research at Washington University in St Louis (MO, US) and the Center for Nanomaterials Research at Dartmouth College (NH, US). Dr Miinea holds a PhD in Chemistry from the University of Houston (TX, US).

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ADAPTING TO AN AGEING WORLD: FORMULATION STRATEGIES TO BOOST PATIENT COMPLIANCE

In this article, Jason Hunt, Global Strategic Marketing Manager, and Yeli Zhang, PhD, Senior Application Development & Innovation Scientist, both at IFF Pharma Solutions, discuss the key factors undermining patient compliance in older adults and explore how the pharmaceutical industry can leverage excipients to enhance drug formulations and improve medication compliance among this critical demographic.

The ageing population is an undeniable global trend, with a profound influence on the world's demographic landscape. The number of people aged 65 years or older worldwide is projected to more than double by 2050, rising from 761 million in 2021 to 1.6 billion.[1] This naturally raises several challenges in healthcare; as we age, the risk of developing chronic diseases increases, meaning the number of people with healthcare needs is on the rise. In the US alone, an evidence-based model predicts that the number of adults aged 50 years and older with at least one chronic disease will double from 71.5 million in 2020 to 142.7 million by 2050, underscoring the difficulties posed by the ageing trajectory.[2]

This rapid population ageing and escalating chronic disease burden are putting unprecedented pressure on the pharmaceutical industry to address the medical needs of the expanding senior demographic more effectively. However, to make any meaningful impact, drug manufacturers must tackle a pivotal issue for this age group – poor patient compliance.

IMPLICATIONS OF AN AGEING POPULATION ON THE PHARMACEUTICAL INDUSTRY

The healthcare challenges presented by the world's ageing population have significant implications for the global economy and healthcare systems. In the UK, for instance, individuals over the age of 65 account for more than 40% of hospital admissions and occupy around 60% of inpatient beds, as well as being the most frequent users of health and social care services.[3] Alarmingly, the cost associated with the rising prevalence of ageing and chronic diseases is estimated to reach a staggering US$47 trillion (£37 trillion) globally by 2030.[4]

For the pharmaceutical industry, this translates to a surge in demand for certain medications. This trend will primarily impact drugs that address the most prevalent chronic conditions affecting senior individuals. These include:[5]

- Cardiovascular disease
- Hypertension
- High cholesterol
- Arthritis
- Coronary heart disease
- Diabetes
- Chronic kidney disease
- Heart failure
- Depression
- Alzheimer's disease
- Dementia
- Chronic obstructive pulmonary disease.

The increased prevalence of comorbidities in ageing populations – when individuals are affected by multiple conditions simultaneously – adds further pressure to the need for age-related disease medications. Notably, the prevalence of comorbidities in US adults aged 50 and older is projected to rise from 7.8 million in 2020 to 15 million by 2050.[2]

Beyond providing the necessary medications to seniors, healthcare providers also face the major issue of poor compliance among this demographic. But why is this the case – and how can it be addressed?

TACKLING THE PERVASIVE CHALLENGE OF POOR PATIENT COMPLIANCE IN SENIORS

Several factors contribute to poor patient compliance among older patients. For example, those suffering from comorbidities are more likely to have complicated treatment regimens that are more difficult to follow. The ageing process can also

Jason Hunt
Global Strategic Marketing Manager

Dr Yeli Zhang
Senior Application Development & Innovation Scientist

IFF Pharma Solutions
974 Centre Road
Wilmington
DE 19805
United States

www.iff.com

"The implications of poor medication adherence are profound, contributing to as much as 50% of treatment failures in the US, as well as 125,000 deaths and up to 25% of hospitalisations every year."

impact cognition and memory, leading to forgetfulness – meaning senior patients are at an increased risk of missing or incorrectly taking their medications.

Additionally, some older adults have difficulty swallowing oral medicines, a condition known as dysphagia, which can significantly compromise compliance. Many of these individuals resort to crushing tablets or opening capsules to overcome this issue, which can alter drug absorption and lead to serious consequences, such as under- or overdosing, or even fatality.[6]

The implications of poor medication adherence are profound, contributing to as much as 50% of treatment failures in the US, as well as 125,000 deaths and up to 25% of hospitalisations every year.[7] Addressing this is therefore crucial for improving health outcomes and quality of life among the ageing population. So, what formulation strategies can drug developers implement to make their medications more suitable and appealing to senior adults?

Optimise Dosing With Controlled-Release Formulations

The pharmaceutical industry experienced a pivotal breakthrough over 50 years ago with the development of oral and transdermal controlled-release (CR) drug formulations.[8] These innovative delivery systems allow for the gradual release of an API in the body, revolutionising medication administration and offering several advantages over conventional oral dosage forms. Among the many advantages of CR formulations is improved patient compliance.[9]

It is not just patients that benefit from CR systems, but formulators too. CR formulations enable drug manufacturers to modulate the pharmacokinetic profile of the API, leading to more predictable, consistent and sustained drug levels in the bloodstream.[9] This means that patients may not need to take as much medicine to reap the benefits, which has the potential to reduce pill burden, further improving compliance. Moreover, these specialised delivery formats can help to minimise drug level fluctuations, mitigating the risk of adverse reactions.[9]

In addition, some CR technologies can improve bioavailability. For example, certain cyclodextrins complexed with poorly water-soluble APIs can improve the solubility, and possibly the permeability, of the API, thereby enhancing the bioavailability while also providing controlled release.[10] Prodrugs are another method that can potentially improve bioavailability and, if so designed, can support controlled release.[11] CR matrices and barrier coatings may also provide added benefits in protecting the API within the formulation from enzymatic or pH degradation. However, these technologies do not protect APIs that have already been released from the formulation.

CR formulations can also address the unique needs of different patient populations. Drug manufacturers can customise CR delivery systems to achieve specific release profiles tailored to individual therapeutic outcomes. For example, CR transdermal patches have recently been developed for administering carvedilol, a beta-blocker drug used to treat hypertension and heart failure – a common disease among the elderly.[12] The matrix design of these innovative patches enables the slow, sustained release of the drug through the skin, reducing the frequency of administration for patients who have difficulty swallowing, are more forgetful or who already take several other pills.[12]

Overcome Swallowing Challenges With ODTs

Solid oral dosage forms are the default formulation for most drugs, due to their convenient administration, accurate dosing, manufacturing efficiency and widespread acceptance. However, as mentioned prior, pills and capsules can be difficult or unappealing to swallow for some senior patients.[13] To address this, innovators can consider strategies, such as smaller tablets or capsules, easy-to-swallow film coatings or novel oral delivery systems, including liquid formats or orally disintegrating tablets (ODTs).

Designed to rapidly disintegrate in the mouth without the need for water, ODTs enable easy administration for patients who struggle with conventional solid dosage forms.[14] One way to achieve this simple method of administration is through the incorporation of superdisintegrants, which facilitate rapid tablet breakdown upon contact with saliva. In some cases, the intent is for the API to be absorbed through the oral mucosa, bypassing first-pass metabolism in the gastrointestinal tract. ODTs can facilitate this, potentially offering superior bioavailability compared with traditional tablet and capsule formulations.[14]

The benefits of this patient-centric delivery method have been demonstrated in several clinical studies, including one investigating the efficacy and tolerability of mirtazapine ODTs in depressed elderly nursing home residents with complex medical and cognitive comorbidities.[15] The results of this specific trial revealed that the rapidly dissolving tablets provided effective antidepressant action and were also well-tolerated in these "difficult-to treat" patients.

By overcoming swallowing difficulties through innovative formulation strategies, ODTs present a simple yet impactful solution for improving medication adherence among the elderly. However, not all APIs are well-suited to this format, which is why palatability is a focus for some manufacturers.

Enhance Palatability to Boost Adherence

While palatability might seem like an obvious influencer of patient compliance, it is often overlooked in the pharmaceutical industry.[16] Implementing strategic taste-masking techniques to conceal the bitter or unpleasant taste of drugs can significantly improve medication acceptance for many

"By overcoming swallowing difficulties through innovative formulation strategies, ODTs present a simple yet impactful solution for improving medication adherence among the elderly."

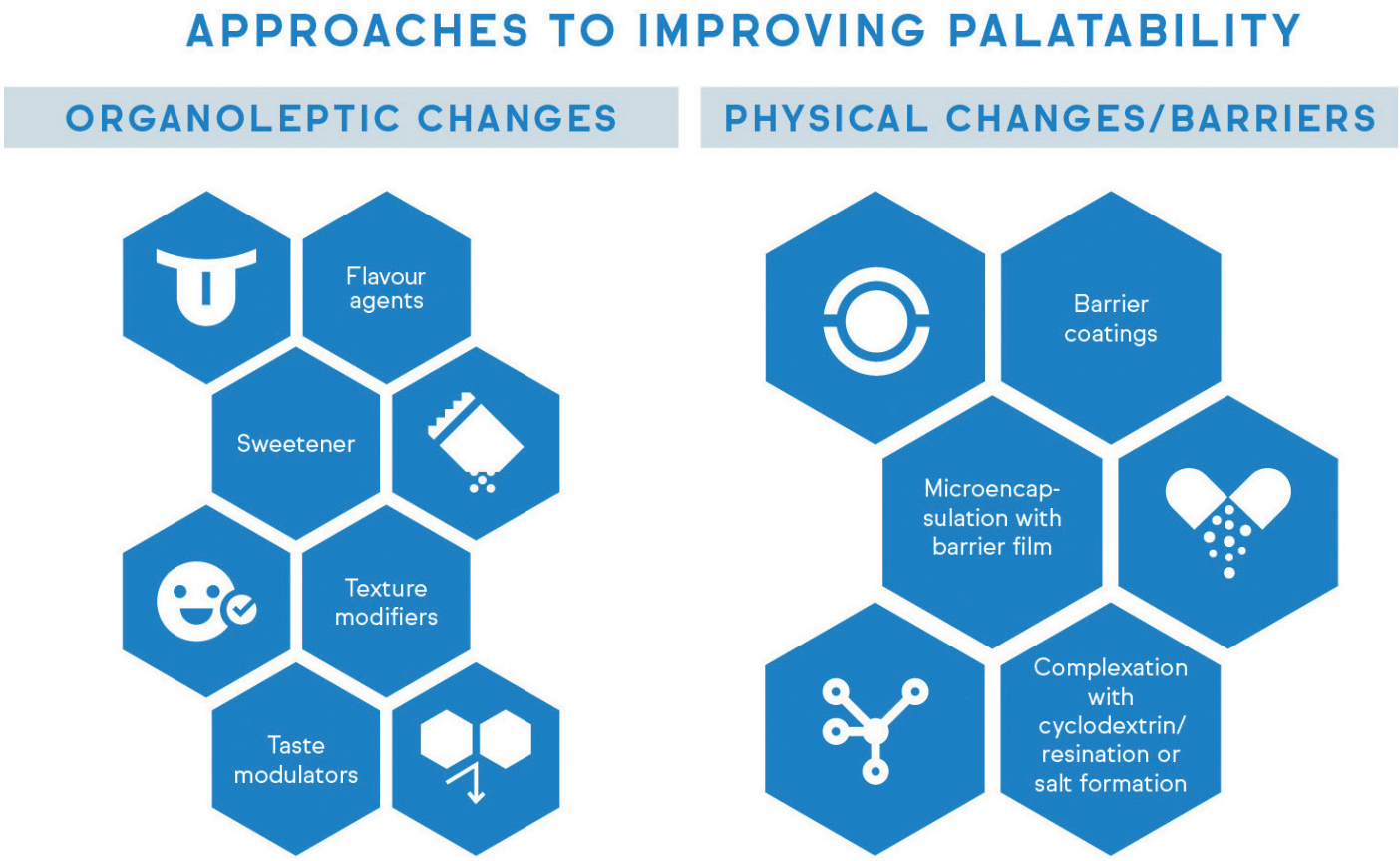

Figure 1: Taste-masking approaches typically fall into two major categories – organoleptic changes and physical alterations.

patients. Taste-masking approaches typically fall into two major categories, as shown in Figure 1. The first involves modifying the perception of unpleasant taste through the addition of more palatable ingredients, such as flavouring agents, sweeteners or bitterness inhibitors.[17] This method is suitable for APIs with low-to-moderate bitterness but can prove challenging for highly bitter drugs.

The alternative strategy is to physically or chemically alter the properties of the unpalatable API to prevent direct contact with the patient's taste receptors.[17] This can be achieved through complexation, encapsulation or other techniques that create a barrier between the bitter compound and the taste buds. For example, ethylcellulose can be used as a barrier membrane to prevent the tongue from experiencing the taste of bitter APIs, such as rupatadine fumarate and paracetamol.[18,19] Through taste-masking strategies, pharmaceutical manufacturers can develop drug products that are not only efficacious, but also more readily accepted by senior patients – a pivotal consideration for long-term medication compliance.

THE CRUCIAL ROLE OF EXCIPIENTS

All the solutions and strategies discussed in this article would not be possible without excipients. While excipients may not possess inherent therapeutic effects, they play an essential role in optimising drug formulations. The following are some examples of how these versatile pharmaceutical ingredients can make a meaningful impact on patient drug compliance.

> "Through taste-masking strategies, pharmaceutical manufacturers can develop drug products that are not only efficacious, but also more readily accepted by senior patients – a pivotal consideration for long-term medication compliance."

Facilitating CR Delivery

Functional excipients are crucial to the success of CR formulations, as their unique properties help modulate the release kinetics of APIs. Factors such as excipient chemistry, particle size and molecular weight can all influence CR performance.[20,21] For example, many innovative CR products leverage high-molecular weight, water-soluble cellulose ethers such as hypromellose (HPMC) to attain CR performance. Further fine-tuning can be achieved by adjusting excipient substitution levels – for HPMC, varying the degree of hydroxypropyl substitution may impact hydrophilicity and, in turn, CR performance.

Enabling ODT Formulation

Excipients are necessary components of ODTs, each serving a distinct purpose in the formulation. For example, croscarmellose acts as a superdisintegrant, promoting rapid disintegration of ODTs upon contact with saliva.[22] On the other hand, excipients such as mannitol provide excellent compactability and act as a bulking material to produce ODTs with robust physical properties.[22] Excipients can also be incorporated into ODTs to provide specific functions, such as flowability, compressibility, palatability and dissolution enhancement.

Masking Unpleasant Tastes

Excipients can be leveraged as physical barriers or solubility modifiers to improve the palatability of bitter or unpleasant-tasting drug products.[17] For example, polymer coating technologies can create a protective layer that prevents direct API-taste receptor interactions. Depending on the drug's bitterness profile and formulation properties, APIs can be coated with excipient polymers that have either a pH-dependent (e.g. hypromellose phthalate) or pH-independent (e.g. ethylcellulose) release profile. The coating level on the API or dosage form can be optimised to successfully achieve taste masking.

CONCLUSION

It is evident that addressing patient compliance among the ever-growing ageing population is an urgent need for global healthcare systems. By leveraging advanced drug delivery technologies and specialised excipients, pharmaceutical companies can develop more patient-centric formulations to improve outcomes for older patients. From CR systems and dissolvable tablets to effective taste-masking alternatives, these innovations can increase the odds that patients will take their medications as prescribed and improve their quality of life. This will, ultimately, have a ripple effect beyond individual patients, offering broader benefits for the global economy and healthcare systems.

ABOUT THE COMPANY

IFF Pharma Solutions is a global leader in food, beverage, health, biosciences and sensorial experiences. For more than 130 years, the company has been focused on finding the most innovative solutions to help bring "better for you" products to market. While it has grown over the years, IFF remains agile in its approach and puts its customers' needs at the forefront of the company's thinking. IFF's product portfolio includes the taste, texture, scent, nutrition, enzyme, culture, soy protein and probiotic categories.

REFERENCES

1. *"International Day of Older Persons 1 October". Web Page, United Nations, accessed May 2024.*
2. *Ansah JP, Chiu C-T, "Projecting the chronic disease burden among the adult population in the United States using a multi-state population model". Front Public Health, 2022, Vol 10, Article 1082183.*
3. *"Protecting the rights of older people to health and social care". British Geriatrics Society, Jan 2023.*
4. *"Methodological Appendix: The Global Economic Burden of Non-Communicable Diseases". World Economic Forum & Harvard School of Public Health, Sep 2011.*
5. *"The Top 10 Most Common Chronic Conditions in Older Adults". National Council on Aging, Apr 2024.*
6. *"Crushing tablets or opening capsules: many uncertainties, some established dangers". Prescrire Int, 2014, Vol 23(152), pp 209–211, 213–214.*
7. *Kim J et al, "Medication Adherence: The Elephant in the Room". US Pharm, 2018, Vol 43(1), pp 30–34.*
8. *Ezike TC et al, "Advances in drug delivery systems, challenges and future directions". Heliyon, 2023, Vol 9(6), Article e17488.*
9. *Adepu S, Ramakrishna S, "Controlled Drug Delivery Systems: Current Status and Future Directions". Molecules, 2021, Vol 26(19), Article 5905.*
10. *Real DA et al, "Cyclodextrin-Modified Nanomaterials for Drug Delivery: Classification and Advances in Controlled Release and Bioavailability". Pharmaceutics, 2021, Vol 13(12), Article 2131.*
11. *Zhang X et al, "Facile Fabrication of 10-Hydroxycamptothecin-Backboned Amphiphilic Polyprodrug with Precisely Tailored Drug Loading Content for Controlled Release". Bioconjug Chem, 2018, Vol 29(7), pp 2239–2247.*
12. *Mo L et al, "Formulation and development of novel control release transdermal patches of carvedilol to improve bioavailability for the treatment of heart failure". Saudi J Biol Sci, 2022, Vol 29(1), pp 266–272.*
13. *Forough AS et al, "A spoonful of sugar helps the medicine go down? A review of strategies for making pills easier to swallow". Patient Prefer Adherence, 2018, Vol 12, pp 1337–1346.*
14. *Hannan PA et al, "Oral Dispersible System: A New Approach in Drug Delivery System". Indian J Pharm Sci, 2016, Vol 78(1), pp 2–7.*
15. *Roose SP et al, "Open-label study of mirtazapine orally disintegrating tablets in depressed patients in the nursing home". Curr Med Res Opin, 2003, Vol 19(8), pp 737–746.*
16. *"The importance of taste in pharmaceutical development". Manufacturing Chemist, Oct 2017.*
17. *"Taste Masking 101: Optimize Taste And Improve Patient Outcomes". Webinar, Adare Pharma Solutions, Jun 2021.*
18. *Wasilewska K et al, "Ethylcellulose in Organic Solution or Aqueous Dispersion Form in Designing Taste-Masked Microparticles by the Spray Drying Technique with a Model Bitter Drug: Rupatadine Fumarate". Polymers (Basel), 2019, Vol 11(3), Article 522.*
19. *Alhamidi R, Ibrahim W, "Preparation and Evaluation of Taste Masked Paracetamol Microcapsules". Res J Pharm Technol, 2022, Vol 15(8), pp 3703–3708.*
20. *Heng PW et al, "Investigation of the influence of mean HPMC particle size and number of polymer particles on the release of aspirin from swellable hydrophilic*

matrix tablets". J Control Release, 2001, Vol 76(1–2), pp 39–49.

21. *Dahl TC et al, "Influence of physico-chemical properties of hydroxypropyl methylcellulose on naproxen release from sustained release matrix tablets". J Control Release, 1990, Vol 14(1), pp 1–10.*
22. *Ghourichay MP et al, "Formulation and Quality Control of Orally Disintegrating Tablets (ODTs): Recent Advances and Perspectives". Biomed Res Int, 2021, Vol 2021, Article 6618934.*

ABOUT THE AUTHORS

Jason Hunt is the Global Strategic Marketing Manager for IFF Pharma Solutions and has been working in the excipients industry for over 20 years. Mr Hunt started at Dow Chemical in 2014 as a Market Segment Leader in the Food and Pharma division; focused on managing various commercial aspects of the pharma business, his role expanded to include corporate key account management activities with strategic customers for the full Dow Chemical portfolio. When the Dow and FMC pharmaceutical businesses came together at Dupont, now IFF Pharma Solutions, he took on the responsibility of leading the North American direct sales team. Before joining IFF Pharma Solutions, Mr Hunt worked at Lubrizol and Croda as an Account Manager. With a strong focus on customers, he has strived to make IFF Pharma Solutions the predominate excipient supplier globally through his connection to the products and the people with whom he interacts. Mr Hunt holds a bachelor's degree in Biology from the University of Delaware (DE, US).

Yeli Zhang, PhD, is an Application and Innovation Technical Service Manager at IFF Pharma Solutions and has been working in the excipient industry for over 20 years. She started her Technical Service Manager role at FMC Health and Nutrition, where she was responsible for providing technical support to FMC's North America excipient market. Dr Zhang continued her Technical Service Manager role at DuPont Pharma Solutions and later IFF Pharma Solutions through multiple company mergers and acquisitions. Prior to her current Technical Service Manager role, Dr Zhang worked at FMC Health and Nutrition as a Senior Scientist in excipient product development and support. Before joining FMC, she worked at the National Starch and Chemical Company (an ICI company) as a Senior Scientist in the areas of starch excipient and delivery system development. Dr Zhang received her PhD at Cornell University (NY, US) in the field of Polymer Science and Biomaterials.

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TACKLING IRON-DEFICIENCY ANAEMIA: A LEAP FORWARD WITH A REVOLUTIONARY BUCCAL PATCH

In this Early Insight, Buddhadev P Chaudhuri, PhD, Co-founder and Chief Executive Officer, and Frederik Ceyssens, PhD, Co-founder and Chief Technology Officer, both at Keylika, discuss the challenges of iron-deficiency anaemia and introduce the company's new buccal patch for iron delivery.

There is currently a silent epidemic on a massive scale among us, with hardly anybody talking about it: iron-deficiency anaemia (IDA), by far the most prevalent nutritional disorder in the world. According to the WHO, the estimated prevalence of iron deficiency (ID) is 30% of the world's population.[1] Roughly 15%–25% of this can be categorised as moderate-to-severe ID. This condition, characterised by an insufficiency of red blood cells or haemoglobin in the blood, results in a diminished capacity to carry oxygen throughout the body, impairing both physical and cognitive performance. Individual sufferers complain of lack of energy, weakness and significant cognitive impairment, with devastating consequences in countries with limited healthcare capacity. IDA is more prevalent among women of childbearing age, with approximately half a billion sufferers worldwide.[2]

High doses of iron supplements have historically been the primary treatment for IDA, but this therapy has many disadvantages, for example, iron is incredibly inefficiently absorbed and not well tolerated most of the time, with chronic gastrointestinal (GI) side effects that few people manage to avoid. Iron supplementation became proverbial as a therapy in which the cure was often deemed worse than the disease. Intravenous (IV) iron infusion typically works better than supplements. However, it can still cause life-threatening hypersensitivity reactions and introduces its own set of complications – it is invasive and necessitates clinical administration, thus significantly increasing healthcare costs.

> "Innovation is imperative to combat the IDA epidemic effectively."

Innovation is imperative to combat the IDA epidemic effectively. Therefore, biotechnology startup Keylika is developing the world's first resorbable buccal patch for iron delivery. This wearable patch, along with the drug design itself, has the potential to redefine the paradigm of anaemia management and IDA drug delivery.

ANAEMIA

There are multiple reasons why IDA can develop, including nutritional deficiencies; chronic blood loss from medical conditions, such as GI ulcers or heavy menstrual bleeding; a need for extra iron from pregnancy or infancy; loss of iron from the gut or malabsorption of oral iron due to underlying medical conditions, such as chronic kidney disease or inflammatory bowel disorders; resection of parts of the GI system; or long-term use of drugs that block iron absorption.

IDA causes a reduction in haemoglobin, which reduces the capacity of the blood to transport oxygen. This impacts individuals across multiple dimensions, compromising their quality of life. In its early stages, the condition can result in subtle but noticeable symptoms, including fatigue, weakness and pallor, and can be accompanied by more dramatic symptoms, such as shortness of breath, dizziness and unusual food cravings.

Severe forms of the disease can significantly limit one's capacity to accomplish daily activities, reduce productivity at work and school, inhibit physical development in children and, eventually, lead to neurocognitive impairment. In addition to the effects on wellbeing, IDA can amplify the adverse effects of pre-existing illnesses, further compounding the cumulative health burden.

Prompt diagnosis and treatment of the condition are critical to lessen the negative impact on the lives of those afflicted.

Dr Buddhadev P Chaudhuri
Co-Founder and
Chief Executive Officer
E: buddha@keylika.com

Dr Frederik Ceyssens
Co-Founder and
Chief Technology Officer
E: frederik@keylika.com

Keylika
135 Mississippi St
San Francisco
CA 94107
United States

www.keylika.com

Sadly, it is severely underdiagnosed, and its symptoms are often dismissed as merely psychological in cause.

THE CURRENT STANDARD OF CARE

The current treatment options for IDA focus on replenishing the body's iron stores and addressing the underlying causes of anaemia. Treatments can be administered orally or intravenously, depending on the severity of the condition and the individual's specific health profile.

Oral Iron Supplements

Initially, clinical providers will prescribe an oral iron supplement for mild-to-moderate IDA, which is the most common treatment. These supplements are typically available in the form of ferrous sulfate, ferrous gluconate, ferrous fumarate, ferrous bis-glycinate or haem iron. The latter is a more efficient source but has been associated with colorectal cancer.[3] The oral route is preferred for its convenience, cost-effectiveness and generally good patient compliance at low doses. However, higher doses (50–120 mg/day of elemental iron) are typically accompanied by a range of GI side effects, such as bloating, nausea, constipation, upset stomach or diarrhoea, sometimes necessitating adjustments in dosage or the type of iron supplement. Additionally, the absorption of oral iron can be influenced by factors such as the presence of certain types of food (e.g. phytates), specific medications and the overall health of the GI tract, necessitating mindful timing and management of supplement intake for optimal effectiveness.

IV Iron Therapy

In cases where oral iron supplements are ineffective, poorly tolerated or in situations of severe IDA, IV iron therapy may be employed. IV iron is directly infused into the bloodstream, bypassing the GI tract and eliminating many of the side effects of oral supplements. This method is particularly beneficial for individuals with conditions that impair oral iron absorption, require rapid replenishment of iron stores or have acutely severe anaemia needing quick resolution.

Intravenous iron is also indicated in certain situations, such as chronic kidney disease or in the pre-operative setting, where it has been shown to improve outcomes. While IV iron therapy is highly effective, there is a risk of serious adverse effects due to the high payload of iron administered at once. These include the rare, but potentially fatal, risk of anaphylactic shock. Therefore, the treatment requires medical supervision in a hospital setting, making it less accessible and more financially burdensome to the patient and the healthcare system. Depending on the type of insurance coverage, clinic and prescribed iron drug, out-of-pocket patient costs can range from US$1,000 to US$5,000 (£800–£4,000) per infusion. Additionally, IV iron can only be prescribed by a specialist (not the primary care physician) and may involve long wait times at the infusion clinic.

> "Recent scientific advancements in the treatment of anaemia, particularly IDA, have led to the development of more sophisticated and targeted treatment options."

INCREMENTAL ADVANCEMENTS IN IV AND ORAL IRON SUPPLEMENTS

Recent scientific advancements in the treatment of anaemia, particularly IDA, have led to the development of more sophisticated and targeted treatment options, aiming to improve efficacy, reduce side effects and enhance patient compliance.

Newer oral iron supplements, such as iron amino acid chelates and polysaccharide-iron complexes, have been designed to enhance iron absorption and reduce the GI side effects associated with traditional iron supplements. Their increased bioavailability means that lower doses of iron can be effective, potentially minimising the unpleasant side effects that deter patient compliance.

Significant developments have been made in the composition and administration of products on the frontier of IV iron treatments. Newer-generation IV iron formulations, such as ferric carboxymaltose, iron sucrose and iron isomaltoside, offer the advantage of allowing larger doses of iron to be administered in a single visit without the need for a test dose due to their lower risk of allergic reactions. This advancement significantly reduces the treatment burden on patients, improving adherence and outcomes, particularly in chronic conditions requiring ongoing ID management. Still, this method remains within the limited boundaries of the current standard of care.

Nevertheless, much work remains to optimise efficacy and minimise side effects in managing anaemia. At this point, oral supplements and IV remain the two prevailing treatment classes despite their disadvantages.

NEW TECHNOLOGY ON THE HORIZON

Keylika is challenging this status quo and developing the world's first resorbable buccal patch (Rx) for treating IDA. This patch combines the efficacy of parenterals such as IV with the ease of orals, without the drawbacks of either, while still delivering iron systemically, bypassing the gut and the first-pass metabolism. The buccal route is promising, as the buccal mucosal membrane is four to 4,000 times more permeable than the stratum corneum of the skin,[4] which is a more commonly used transdermal delivery route.

Keylika's iron ligand complex KYLK01, combined with a resorbable transmucosal patch, has the potential to transform the standard of care for ID. The molecule has been optimised in size (<500 Da), solubility (water), ligand selection (antioxidant), stability across a wide pH range and oxidative state (ferric). This new chemical entity (NCE) is a mixed ligand iron complex tailored for a transdermal route of delivery.

The data from Keylika's latest *in vivo* pharmacokinetic (PK) study in iron-deficient hamsters demonstrates efficacious and safe systemic iron absorption with the resorbable buccal patch. The patch adheres to the inner cheek of the mouth and dissolves fully in under an hour, releasing the iron drug.

Keylika's technology aims to provide a highly productive, safe and economical solution for ID.

> "Keylika's iron ligand complex KYLK01, combined with a resorbable transmucosal patch, has the potential to transform the standard of care for ID."

The Iron Complex

The metallodrug complex KYLK01 embodies several differentiators to previous and existing iron drugs and delivery mechanisms:

1. The ligands are selected to enhance iron absorption and serve as an antioxidant specifically.
2. The complex is small (<500 Da), increasing the ease of skin permeation.
3. Its high solubility dramatically increases drug payload for a therapeutically relevant dosage.
4. The ferric ion (Fe^{3+}) form of iron aids in a seamless uptake by the iron protein transporter (transferrin) in blood plasma.
5. The iron transport occurs by passive diffusion driven by a concentration gradient with the resorption of the patch in an oral salivary environment, without the need for additional complex technology aids (such as microneedles, iontophoresis, etc) to permeabilise the skin.
6. The new drug complex does not contain a large-molecule carbohydrate moiety, minimising the chances of hypersensitivity reactions. Instead, it is composed of generally recognised as safe natural compounds that follow well-known metabolic pathways.

The result is an effective, safe and highly bioavailable iron form.

Patch Formulation

Keylika's patch (Figure 1) formulation is a proprietary microemulsion-based solution that combines water-soluble polymers (USP-grade), terpenes-based permeation enhancers, dissolution rate-determining components and the water-soluble iron compound KYLK01. This formulation was first synthesised in a solution form, which was used for the *In Vitro* Permeation Test in a Franz Diffusion Cell (IVPT FDC) study on porcine buccal skin. The solution was then poured into moulds and baked under a vacuum to produce resorbable patches encapsulated with iron. KYLK01's high water solubility allows for a maximum elemental iron payload of around 50 mg in the patches.

In vitro dissolution studies in diluted saliva have demonstrated the full release of the iron payload (tested patches containing 30 mg Fe) in under an hour, as confirmed by inductively coupled plasma atomic emission spectroscopy.

In Vivo PK Study

ID was induced in hamsters by feeding them an iron-deficient diet over an 8-week period. Baseline serum iron levels were measured, followed by the application of a resorbable patch in the buccal pouch of the animals. Hamsters were divided into two groups of four animals each: commercial ferric citrate (control) and test (KYLK01). Animals were under light isoflurane anaesthesia during this study.

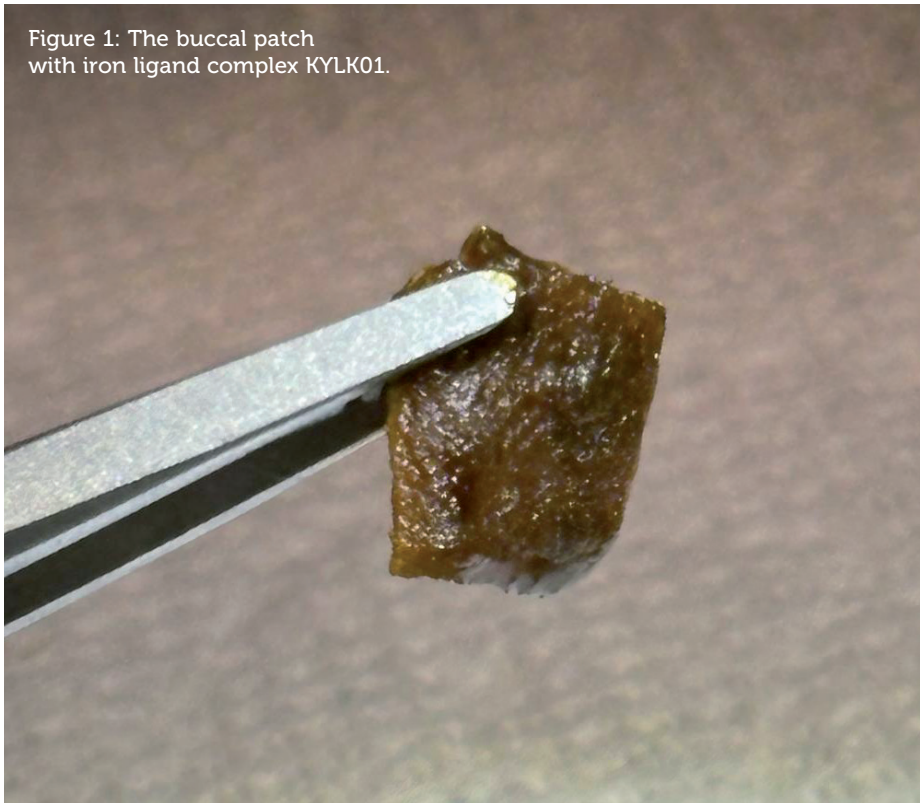


Figure 1: The buccal patch with iron ligand complex KYLK01.

> "The oral cavity minus the buccal pouch was also evident, demonstrating that the buccal patch remained in place, dissolved in the cheek pouch and was absorbed systemically via the transmucosal route only."

The control group was administered a commercially available iron supplement, ferric citrate, while the test group received KYLK01, both in resorbable patches. Blood was sampled at intervals of 30 minutes and analysed for serum iron. Serum iron levels increased significantly over time in the test group. In contrast, the control group showed almost no iron uptake, indicating that KYLK01 has a much better systemic absorption profile than iron (III) citrate (Figure 2). Each patch was loaded with 6 mg elemental Fe.

To investigate the chances of oral ingestion of the buccal patch, a necropsy was performed with a pathological examination of the entire GI tract. No evidence of the coloured patch or remnants was found throughout the whole tract, including the oesophagus, stomach and intestines. The oral cavity minus the buccal pouch was also evident, demonstrating that the buccal patch remained in place, dissolved in the cheek pouch and was absorbed systemically via the transmucosal route only. No signs of buccal irritation or systemic toxicity were observed.

The significantly superior PK profile with KYLK01 buccal patches is preliminary proof that:

1. KYLK01 is systemically absorbed via the transmucosal route
2. The resorbable patch formulation successfully dissolves in saliva, releasing the iron for buccal uptake
3 KYLK01's rational molecular design, tailored for a buccal delivery, is successful, as opposed to using iron (III) citrate.

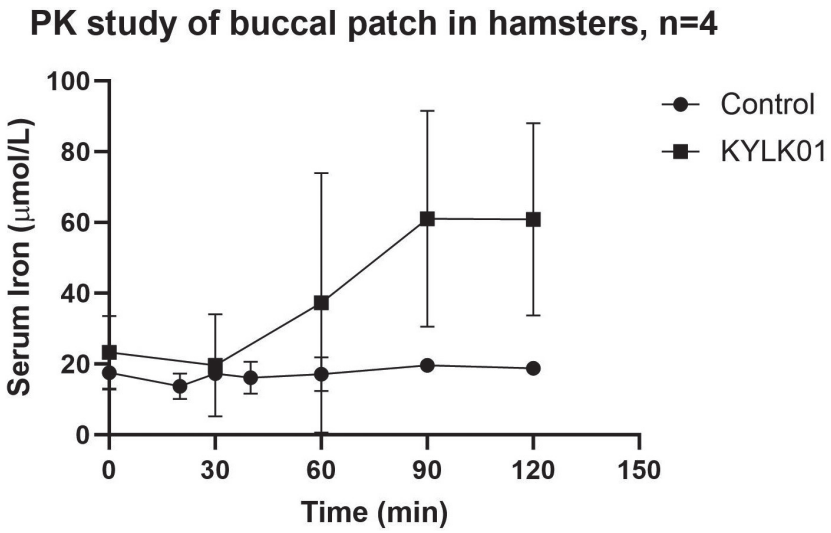


Figure 2: PK study of buccal patch in hamsters.

CONCLUSION

ID is a hugely underserved problem supported by a sub-par standard of care. The limitations of current treatments and the transformative potential of this innovation make it evident that Keylika is not merely introducing a new treatment option but instead changing the paradigm of IDA treatment with the first-ever buccal delivery of iron. The transport of this novel iron complex through the highly vascularised oral mucosa into systemic circulation circumvents the GI tract and associated adverse side effects. As a convenient point-of-care solution, the patch could potentially eliminate the compliance-limiting side effects of oral supplements while erasing the cost, stress, risk and time requirement of IV iron infusions, heralding a new era of convenience, efficacy and safety in ID treatment. The success of early animal studies boosts Keylika's confidence that it can also employ the buccal route for a multitude of hard-to-deliver drugs, from small to large molecules.

ABOUT THE COMPANY

Keylika is developing the world's first resorbable buccal patch (Rx) for iron administration to treat IDA, especially in women of childbearing age suffering from moderate-to-severe ID, as a potential best-in-class breakthrough therapy. The iron drug is an NCE developed in-house and tailored to the transbuccal route of administration.

Keylika develops small-to-large-molecule drugs and optimised drug delivery technologies to effect the best clinical outcomes across human and animal health. Keylika's platform lies at the unique intersection of *de novo* drug design and micro/nanotechnologies (semiconductor-based microsystems, devices and formulations) for non-oral, systemic drug delivery without molecular size constraints to generate best-in-class therapies.

Keylika is an early-stage biotech startup backed by Y Combinator (Summer 2022 batch) and other angel investors.

REFERENCES

1. *Kumar A et al, "Iron deficiency anemia: pathophysiology, assessment, practical management". BMJ Open Gastroenterol, 2022, Vol 9(1), Article e000759.*
2. *"Anaemia". WHO, May 1, 2023.*
3. *Aglago EK et al, "Dietary intake of total, heme and non-heme iron and the risk of colorectal cancer in a European prospective cohort study". Br J Cancer, 2023, Vol 128, pp 1529–1540.*
4. *Wanasathop A et al, "Permeability of Buccal Mucosa". Pharmaceutics, 2021, Vol 13(11), p 1814.*

ABOUT THE AUTHORS

Buddhadev "Buddha" Chaudhuri, PhD, is CEO and Co-Founder of Keylika. With over 15 years of R&D experience, Dr Chaudhuri is a subject-matter expert in drug delivery microtechnologies. He holds a PhD in transdermal drug delivery microsystems from Imec/KU Leuven, Belgium, and was a Post-Doctoral Fellow at the University of California, San Francisco (UCSF) and UC Berkeley. Dr Chaudhuri has successfully led the technology development at several medtech start-ups in Europe and the US. The most notable amongst them is Biolinq, where he spearheaded the microneedle technology development for dermal sensing of glucose.

Frederik Ceyssens, PhD, is CTO and Co-Founder of Keylika. He has over 15 years of R&D experience developing medical micro-implantable devices. One of his most notable inventions is a novel flexible neuro-prosthesis to treat blindness. Dr Ceyssens holds a PhD in microtechnology plus a bachelor's degree in medicine from KU Leuven, Belgium. He has published more than 150 research articles in peer-reviewed journals, earning over 1,800 citations.

CANNABIDIOL DELIVERY THAT IS ON THE "TIP OF THE TONGUE"

In this article, Zdravka Misic, PhD, Innovation Project Manager at dsm-firmenich, explores how formulation expertise can be applied to overcome the low bioavailability of cannabinoids and how innovation in orally disintegrating tablets is driving progress for cannabidiol-based therapeutics.

Cannabinoid-based early drug development – particularly the cannabidiol (CBD) category – is gaining increasing attention and investment due to its undeniable innovation potential. However, the low bioavailability of cannabinoids makes formulation challenging, especially when developing solid oral dosage forms, which are still preferred by patients. Consequently, to date, innovation in drug delivery in the CBD space has been limited, with most cannabinoid therapies reliant on oil-based oral solutions for administration.

This has prompted the question, "How can patient-centric CBD-based therapies with improved efficacy, compliance and patient acceptability be achieved?" The answer may be presented by orally disintegrating tablets (ODTs) – a promising dosage form for the delivery of a wide range of APIs – which hold significant potential for delivery of CBD-based therapies.

UNDERSTANDING CBD FORMULATION TO DATE

Cannabinoids have sparked intense interest among the scientific community thanks to their potential to offer wide-ranging therapeutic benefits for human health. Among these compounds, CBD stands out for its therapeutic benefits owing to its non-intoxicating nature. Progress in CBD research has revealed its capacity to potentially treat multiple medical conditions, with emerging evidence related to neurological disorders, such as central nervous system (CNS) diseases, mood disorders, cancers and even sleep disorders (e.g. insomnia). In view of this, CBD holds significant promise in addressing unmet patient needs.

Despite pioneering advancements, CBD-based drug development is still in its early stages and comes with some challenges. Enhancing the bioavailability of CBD and unlocking its complete therapeutic potential for patients is one noteworthy opportunity. The low bioavailability of the molecule – as little as 6% in humans[1] – may sometimes necessitate doses above 300–400 mg per day to achieve a substantial therapeutic effect.[2] Consequently, patients are required to administer large quantities of cannabinoid-based medications, typically in the form of oil-based oral solutions, to attain beneficial outcomes. However, this approach can be unpleasant and introduce potential complications, such as unwanted adverse effects like diarrhoea.

Enhancing the bioavailability of CBD would help to mitigate these challenges and, while progress is being made, much of the research in this field is still focused on oil-based oral solutions. This is fuelling the exploration of more patient-centric and convenient dosage forms for CBD-based therapies in clinical trials – one of those being ODTs.

> "Cannabinoids have sparked intense interest among the scientific community thanks to their potential to offer wide-ranging therapeutic benefits for human health."

ODTs: A POTENTIAL GAME CHANGER FOR CBD-BASED THERAPIES

ODTs represent an innovative dosage form for drug delivery, offering benefits that cater to varying patient needs and preferences due to their user-friendly and convenient form. Designed to dissolve quickly in the mouth without water, they are easy to administer on-the-go and, therefore, facilitate better patient compliance. This makes ODTs an appealing drug delivery system for patients who have difficulty swallowing pills or tablets, such as older adults, or those seeking more

Dr Zdravka Misic
Innovation Project Manager
E: zdravka.misic@dsm-firmenich.com

dsm-firmenich AG
Wurmisweg 576
4303 Kaiseraugst
Switzerland

www.dsm-firmenich.com

Figure 1: Sleep disorders are an underserved therapeutic area that could greatly benefit from an improved delivery method for CBD-based therapeutics.

> "ODTs are absorbed in the mouth, thereby bypassing the gastrointestinal tract and avoiding first-pass metabolism – the breakdown of the API in the gut or liver."

treatment flexibility. The swift dissolution and absorption of the API into the bloodstream makes ODTs particularly beneficial for health conditions requiring immediate effect, such as insomnia and other sleep disorders.

ODTs are absorbed in the mouth, thereby bypassing the gastrointestinal tract and avoiding first-pass metabolism – the breakdown of the API in the gut or liver. This allows for faster absorption of the API into the bloodstream and rapid onset of action. For this reason, they are an attractive option for drugs that do not absorb easily in the stomach and those with limited bioavailability due to first-pass metabolism, such as CBD. Cannabinoids, like CBD, can be affected by incomplete absorption in the gut and undergo extensive first-pass metabolism in the liver (up to 75% for CBD).[1]

The versatility and effectiveness of ODTs has led to their use across multiple therapeutic settings, from alleviating pain via analgesic medications to providing relief from allergies through antihistamines and facilitating fast-acting treatment during acute episodes in patients with psychiatric disorders. Given the persistent challenge of CBD bioavailability and delivery for drug developers, ODTs are emerging as an extremely promising avenue for cutting-edge CBD formulation.

ADVANCEMENTS IN CBD-BASED ODTs

One field where CBD-based ODTs hold promise is for the treatment of insomnia. Sleep disorders are a prevalent worldwide concern that can profoundly impact an individual's quality of life and overall wellbeing. Studies have indicated that insomnia affects somewhere between 10% and 30% of the global population, with some estimates reaching as high as 60%.[3] Despite its frequent occurrence and ease of diagnosis, the condition remains extremely challenging to treat. Many prescriptions and over-the-counter (OTC) medications for insomnia exhibit limited efficacy and are often accompanied by undesirable side effects and the potential for dependency or tolerance issues.

To tackle this prevalent yet largely unaddressed problem, CBD has garnered attention as a possible solution due to its promising therapeutic effects in conditions associated with insomnia, such as anxiety and pain. Subsequently, CBD has become a focal point of several sleep disorder trials and, although the science is still emerging, preliminary research is favourable (Figure 1).[4]

To help advance research further in this field, dsm-firmenich has teamed up with Oz Medicann Group Pharma (Sydney, Australia), an innovator in cannabinoid medicines, to investigate the possibilities of a CBD-based ODT for insomnia. In the next phase of clinical trials, the efficacy and dosage level of a Schedule 3 OTC ODT is to be explored. However, it is not just insomnia where these CBD-based ODTs have the potential to transform patient care.

A BRIGHT OUTLOOK AHEAD

There is a myriad of opportunities for groundbreaking CBD developments, presenting a chance to broaden treatment options for patients globally. Currently, over 220 clinical trials are underway to explore the therapeutic capacity of CBD, especially in the realms of CNS diseases, mood disorders and pain management. Despite affecting tens of millions of people worldwide annually, these conditions lack cannabinoid-based therapies for their treatment.

CBD science is particularly robust and established in CNS disorders, which encompass a broad category of neurological conditions, including epilepsy and Parkinson's disease. The molecule's favourable safety profile, along with its anti-convulsant effects and neuroprotective properties, have propelled research in this area, leading to the introduction of CBD-based treatments on the market.

Further research currently being initiated includes trials exploring the role of CBD as an immunomodulatory agent. The API's immunomodulatory and anti-inflammatory properties make it a compelling therapeutic compound for diseases characterised by excessive inflammation, such as chronic diseases or inflammatory conditions. Moreover, cannabinoid research does not stop at CBD. Investigations related to minor cannabinoids, such as those found in lower concentrations in the cannabis sativa plant, including cannabinol and cannabigerol, are also underway and anticipated to become a growing focus for innovation.

THE KEY TAKEAWAY

ODTs represent a patient-friendly dosage form that prioritises convenience, efficacy and ease-of-use, ultimately enhancing the overall treatment experience for patients across various healthcare settings. With this in mind, ODTs could revolutionise CBD delivery in a way that places patient centricity and elevated care at the forefront.

ABOUT THE COMPANY

As innovators in nutrition, health and beauty, dsm-firmenich reinvents, manufactures and combines vital nutrients, flavours and fragrances for the world's growing population to thrive. With its comprehensive range of solutions, including natural and renewable ingredients and renowned science and technology capabilities, dsm-firmenich works to create what is essential for life, desirable for consumers and more sustainable for the planet. As a purpose-led partner in the pharmaceutical industry, dsm-firmenich remains at the forefront of leading-edge cannabinoid research; driving forward the next frontier of medicine and helping drug developers realise the full therapeutic potential of these unique compounds. dsm-firmenich is a Swiss-Dutch company, listed on the Euronext Amsterdam, with operations in almost 60 countries and revenues of more than €12 billion (£10.3 billion) annually. With a diverse worldwide team of nearly 30,000 employees, the company brings progress to life for billions of people every day, everywhere.

REFERENCES

1. *Perucca E, Bialer M, "Critical Aspects Affecting Cannabidiol Oral Bioavailability and Metabolic Elimination, and Related Clinical Implications". CNS Drugs, 2020, Vol 34(8), pp 795–800.*
2. *Arnold JC et al, "The safety and efficacy of low oral doses of cannabidiol: An evaluation of the evidence". Clin Transl Sci, 2023, Vol 16(1), pp 10–30.*
3. *Bhaskar S, Hemavathy D, Prasad S, "Prevalence of chronic insomnia in adult patients and its correlation with medical comorbidities". J Family Med Prim Care, 2016, Vol 5(4), pp 780–784.*
4. *Ranum MR et al, "Use of Cannabidiol in the Management of Insomnia: A Systematic Review". Cannabis Cannabinoid Res, 2023, Vol 8(2), pp 213–229.*

ABOUT THE AUTHOR

Zdravka Misic, Innovation Project Manager at dsm-firmenich, holds a PhD in Pharmaceutical Sciences from the University of Basel (Switzerland). She started her career as a formulation scientist at Teva in 2004. In 2009, she moved to Switzerland to ETH Zürich as an ESKAS (Swiss Government Excellence Scholarships for Foreign Scholars) scholarship holder. Dr Misic joined dsm-firmenich in 2014 and, since then, has worked as a Principal Pharmaceutical Scientist on developing new delivery systems for dsm-firmenich's products and collaborated closely with marketing in presenting them to customers. She also leads external collaborations with academic partners (including the International University of Applied Sciences and ETH Zürich) and established CDMOs within the pharmaceutical industry. Since January 2024, Dr Misic has switched to the position of an Innovation Project Manager, dedicated to pharma innovation projects in the specific development of new oral solid CBD formulations with enhanced bioavailability.

STRATEGIES TO MITIGATE GELATIN CROSS-LINKING IN ORAL SOLID DRUG DELIVERY

Here, Jnanadeva Bhat, PhD, Vice-President R&D (Pharma & Nutra), and Manali Dalvi, Lead – White Papers & Publications, both at ACG Capsules, discuss the factors contributing to gelatin cross-linking in oral solid dose delivery – and strategies to tackle the resulting challenges.

The oral solid drug delivery system is a prominent mode of drug administration. It is recognised for being non-invasive, patient compliant and convenient; steadfastly catering to the multifaceted demands of the market through its pioneering methodologies.

Despite the emergence of cutting-edge techniques such as biologics, molecular delivery and parenteral administration, the prevalence of solid delivery systems continues to undergo ongoing innovation. From traditional pills and capsules to novel variations, such as gummies, soft chews, granules, lozenges and pastilles, the oral delivery mechanism has revolutionised pharmaceutical formulations, capturing the attention of both healthcare professionals and consumers. Its adaptability, accessibility and effectiveness have propelled it to the forefront, surpassing even the established parenteral and intravenous routes.

Irrespective of the product type, the fundamental goal of processing oral solid dosage (OSD) forms remains unwavering: to create formulations that guarantee consistent dosing, reliable distribution of ingredients, and uniform dissolution and bioavailability. However, achieving this objective is contingent upon the dosage forms, actives and excipients employed.

Gelatin often serves as a crucial excipient in OSD formulations. Whether encapsulating active ingredients within hard or soft shells or serving as a coating agent for tablets or a gelling agent in any other formulations, gelatin emerges as a fundamental ingredient across various oral delivery formats. Its versatility finds applications in a wide range of dosage formats.

However, despite its extensive use, OSD manufacturers grapple with a persistent challenge: gelatin cross-linking within formulations, initially observed in 1974 for hard capsules containing chloramphenicol. This phenomenon poses a threat to the dissolution of pharmaceutical products, underscoring the need for strategies to mitigate such barriers. As we navigate the complexities of drug formulations, addressing issues such as gelatin cross-linking becomes paramount in advancing the efficacy and reliability of oral drug delivery systems.

CROSS-LINKING IN THE GELATIN

Following the ingestion of gelatin capsules or gelatin-coated tablets, the primary objective of the formulation lies in releasing the inner content into the biological media. However, it is often observed that gelatin-based formulations tend to experience dissolution failures upon ageing, which is primarily attributed to cross-linking in stressed gelatin-containing products. It causes the formation of a swollen, thin, tough, rubbery, water-insoluble membrane, known as a pellicle (Figure 1).

This may act as a barrier to the drug release from the formulation, resulting in the slower release of the filled formulation, which consequently leads to a decrease in dissolution values or no release at all in *in vitro* studies. The degree of cross-linking can vary within and between capsules, making it difficult to predict the extent of the issue. Once formed, these pellicles are irreversible, rendering the gelatin insoluble. As a consequence, dissolution results will have higher variability when

"Despite its extensive use, OSD manufacturers grapple with a persistent challenge: gelatin cross-linking within formulations."

Dr Jnanadeva Bhat
Vice-President R&D (Pharma & Nutra)
T: +91 022 7194 8420
E: jnanadeva.bhat@acg-world.com

Manali Dalvi
Lead – White Papers & Publications
T: +91 022 7194 8419
E: manali.dalvi@acg-world.com

ACG Capsules
Plot 131, Kandivali Industrial Estate
Kandivali West
Mumbai 400067
India

www.acg-world.com

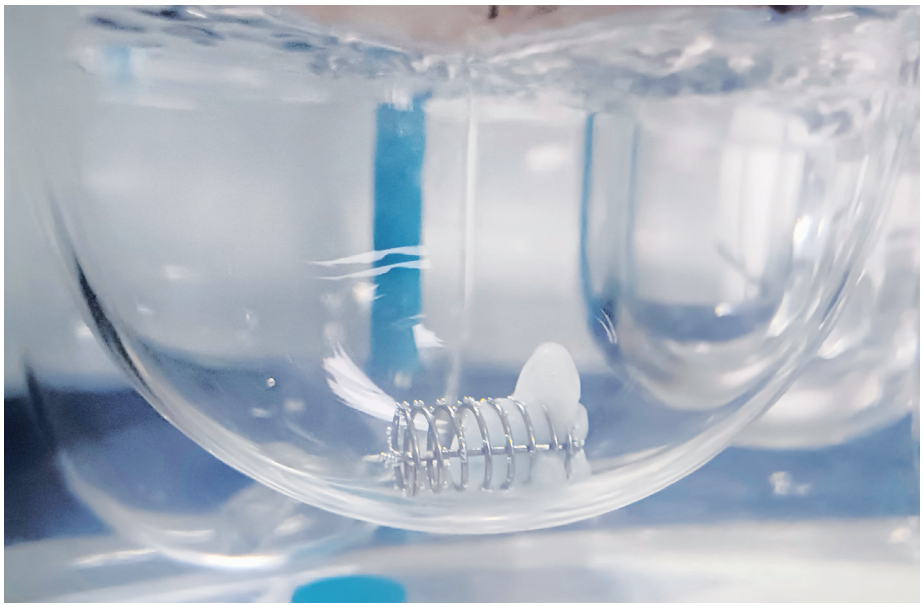


Figure 1: Cross-linked capsule.

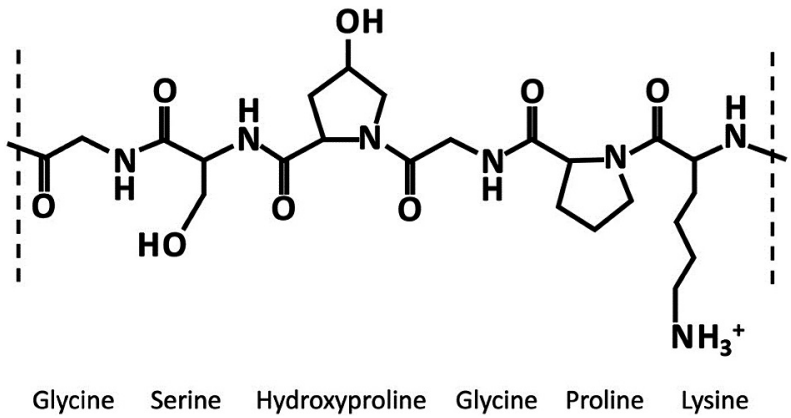


Figure 2: Gelatin structure.

gelatin capsule/coated tablets are cross-linked. This phenomenon – during the early stages of drug insertion into the market – often results in failure to meet regulatory guidelines for *in vitro* studies, prompting regulatory authorities to recall the product.

MECHANISM OF GELATIN CROSS-LINKING

Gelatin, derived from collagen via hydrolysis, is a soluble protein mixture primarily composed of amino acids (Figure 2). These amino acids, linked by amide bonds, form a linear polymer with molecular weights ranging from 15,000 to 250,000. Cross-linking in gelatin can arise from chemical interactions between its peptide chains or individual amino acids. These interactions can be triggered by small amounts of aldehydes, which are present in excipients or APIs. They may also occur from the breakdown of formulation components or packaging materials – or exposure to harsh conditions such as high temperatures and humidity.

> "There are two main types of cross-linking reactions observed in gelatin: internal and external."

There are two main types of cross-linking reactions observed in gelatin: internal and external. Internal cross-linking takes place when gelatin capsules are exposed to high temperatures and humidity, primarily affecting their inner surfaces. In contrast, external cross-linking occurs when gelatin-based formulations, such as hard or soft capsules and gelatin-coated tablets, interact with substances such as aldehydes, peroxides or sulfonic acids. These substances cause chemical changes in the gelatin molecules, transforming them from a random coil configuration to a collagen triple helix structure.

The mechanism of gelatin cross-linking involves three distinct pathways, each driven by specific molecular interactions and catalytic factors.

1. **Intrastrand and Interstrand Cross-Linking**: Gelatin's reactivity stems from interactions among amino acids within the same gelatin molecule (intrastrand) or between neighbouring molecules (interstrand). Key amino acids involved in this process (most notably lysine) exhibit trifunctional properties. Lysine residues in close proximity undergo oxidative deamination, yielding terminal aldehyde groups. These aldehyde groups can then react with neighbouring ε-amino groups of lysine, forming imine intermediates. Subsequent aldol condensation reactions lead to the formation of cross-linked products containing pyridinium rings. This cascade of reactions is catalysed by external factors such as heat and relative humidity or the presence of a chemical agent.
2. **Reaction with Carbonyl Groups**: Another mechanism involves the interaction between lysyl ε-amino groups and aldehydic impurities present as contaminants. This reaction generates hydroxymethylamino derivatives, which undergo dehydration to form imines. These imines then engage in further reactions with hydroxymethyl lysine residues, forming dimethyl ether bridges. Ultimately, rearrangement reactions result in methylene linkages between lysyl ε-amino groups, facilitating cross-link formation. Similar reactions can occur with aldose sugars commonly found in pharmaceutical formulations, wherein imine intermediates react with free amino groups to yield ketose sugars. Subsequent reactions between imines and sugars lead to cross-linking via carbonyl functionalities.
3. **Formation of Aminals**: Additionally, gelatin cross-linking can occur through the formation of aminals, which are amine derivatives of acetals. This process is influenced by the pH of the environment. Aminals formed between gelatin chains contribute to cross-linking, further enhancing the structural integrity of the gelatin network.

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Lopinavir/ Ritonavir	Capsulte (Soft-Gelatin)	II (Paddle)	50	Tier 1: 0.5 M Polyoxyethylene 10 Lauryl Ether with 10 mM Sodium Phosphate monobasic (pH 6.8) Tier II: same as above with NMT 1750 USP units/L of Pancreatin	900	10,15, 30 and 45	06/18/2007
Celecoxib	Capsule	II (Paddle)	50, 100 and 200 mg: 50 rpm; 400 mg: 75 rpm	Tier I Medium: 0.04 M tribasic sodium phosphate (pH 12) with 1% SLS. Tier II Initial Medium: 750 mL of simulated gastric fluid, USP (includes pepsin); At 20 minutes, while stirring, add 180 mL of appropriate concentrations of SLS solution (for a final concentration of 1% SLS). Add about 70 mL of 1.2 N NaOH to adjust the pH to 12.	Tier I: 1,000 mL Tier II: 750 mL (initial) 1,000 mL (final)	10, 20, 30, 45 and 60	07/01/2010

Table 1: Representative two-tier dissolution method.

FACTORS CONTRIBUTING TO GELATIN CROSS-LINKING

Cross-linking in gelatin formulations can stem from various environmental and chemical factors, significantly impacting their stability and performance (Table 1).

Environmental Factors

Elevated humidity, temperatures and intense light exposure can trigger cross-linking reactions within gelatin-based formulations, resulting in prolonged *in vitro* dissolution times. The presence of high humidity facilitates direct catalysis of imine formation, a crucial step in cross-linking reactions.

Additionally, certain excipients may produce byproducts in moist environments, further promoting cross-linking. For example, corn starch may contain hexamethyl tetramine, which decomposes in humidity, generating ammonia and formaldehyde, thus facilitating cross-linking in gelatin. Moreover, high humidity conditions can induce arginine-arginine cross-linking in gelatin. Elevated temperatures accelerate the rate of cross-linking reactions, hastening the formation of insoluble gelatin networks.

Light or ultraviolet (UV)-visible radiation exposure can influence dissolution properties. Intense light exposure correlates with reduced *in vitro* dissolution rates, adding complexity to the matter of gelatin cross-linking in pharmaceutical products.

> "Several chemical factors can exacerbate gelatin cross-linking in pharmaceutical formulations."

Chemical Factors

Several chemical factors can exacerbate gelatin cross-linking in pharmaceutical formulations (Table 2).

One prominent contributor is formaldehyde, which can be released from various sources commonly found in formulation excipients. These sources include plasticisers, preservatives and polyethylenated compounds, such as polyethylene glycol (PEG). Interestingly, ethers of PEG, aliphatic alcohols or phenols, polyethylenated glycerides and non-ionic surfactants can all contribute to formaldehyde release, thus promoting the cross-linking of gelatin. PEGs, frequently employed as solvents in pharmaceutical formulations, can release low-molecular-weight aldehydes when exposed to aerobic conditions, thereby further enhancing gelatin cross-linking. Additionally, aldehydes such as furfural, commonly found in bottles containing rayon coils, have been demonstrated to react with gelatin, resulting in the formation of insoluble cross-linked products.

Humidity
Heat
Light
Excipients or APIs with carbonyl functional group
Aldehydes (furfural, acrolein, formaldehyde, glyceryl aldehyde) and ketones
Imines
Sugars (glucose and aldose sugar)
Oxidising agent
PEGs (containing peroxide/aldehydes)
Metal ions (colorants/dyes)
Sulfated polysaccharides (chondroitin sulfate)

Table 2: Causative agents for cross-linking.

To confirm whether gelatin cross-linking has occurred, instrumental techniques such as various spectroscopies have been applied, including nuclear magnetic resonance (NMR), UV spectroscopy using 2, 4, 6-trinitrobenzene sulfonic acid (TNBS) assay, fluorescence spectrophotometry (FS), near infrared (NIR) and Fourier transform-infrared (FT-IR). However, it is important to note that these spectroscopic techniques may have limitations for identifying cross-linking in gelatin capsule shells when the formulations experience dissolution slowdown due to stress tests in stability studies or a long-time storage of marketed formulations.

STRATEGIES TO MITIGATE THE CHALLENGE POSED BY CROSS-LINKING IN GELATIN-BASED FORMULATIONS

Overcoming the challenge of cross-linking in a dissolution study is crucial for innovators facing hurdles in the *in vitro* evaluation of gelatin formulations. Fortunately, there are several ways to mitigate the issue of cross-linking within the formulation. One such approach involves leveraging different grades of gelatin, each exhibiting distinct behaviours regarding cross-linking. Notably, type B gelatin demonstrates reduced cross-linking compared with type A gelatin.

Another effective approach involves inhibiting the formation of aldehydes, which are crucial catalysts for cross-linking in capsules. Compounds such as lysine, phenylalanine, glutamine, p-aminobenzoic acid and glycine serve as potent scavengers for carbonyl compounds, obstructing aldehyde interaction with the gelatin shell and thereby significantly reducing cross-linking. Using glycine to scavenge aldehydes in the formulation effectively neutralises reactive aldehydic functional groups, preventing further cross-linking.

> "Combining glycine with citric acid proves highly effective, offering dual benefits by scavenging aldehydes and facilitating pH manipulation within the formulation."

Furthermore, combining glycine with citric acid proves highly effective, offering dual benefits by scavenging aldehydes and facilitating pH manipulation within the formulation.

Other inhibitors, such as semicarbazide, piperidine and hydrochloride, can also modify capsule properties, effectively inhibiting cross-linking. An alternative approach involves using aldehyde-free excipients, presenting a promising avenue for tackling the dissolution challenge. Importantly, safeguarding formulations against moisture, temperature fluctuations and light exposure will also play a pivotal role in maintaining stability and preventing undesirable cross-linking reactions.

A collaborative effort between the US FDA's CDER, the United States Pharmacopeia (USP) and academia in the early 1990s yielded valuable insights into gelatin capsule non-compliance during dissolution tests and its impact on bioavailability.[1] Notably, while cross-linking primarily occurs *in vitro*, the behaviour shifts markedly during *in vivo* testing. Cross-linked capsules face minimal hurdles *in vivo*, suggesting a divergence between laboratory and real-world outcomes. This is due to the presence of the enzymes in the gastrointestinal (GI) environment acting as biological scissors, effectively breaking down the cross-linked bonds in capsule shells.

This research led to the development of two-tier dissolution testing, which incorporates enzymes into the dissolution medium in some cases to account for potential *in vivo* enzyme activity, highlighting the importance of considering both *in vitro* and *in vivo* data when evaluating drug delivery systems. The USP two-tier dissolution method offers a standardised approach for handling formulations that fail initial dissolution assessments. This methodology aligns well with bioequivalence studies, streamlining processes and reducing associated time and costs.

The USP General Chapters Dissolution <711>and Disintegration and Dissolution of Dietary Supplements <2040> offer provisions for incorporating enzymes into dissolution media when dosage forms fail to meet dissolution acceptance criteria due to gelatin cross-linking. More than 25 pharmaceutical products have used two-tier dissolution methods, as per the FDA's dissolution database and USP standards (Table 1). In particular, GI enzymes such as pepsin and pancreatin have proven effective in breaking down cross-linked gelatin within the stomach, operating within specific pH ranges to optimise protease activity. By integrating these enzymes into dissolution studies, the observed slow drug release *in vitro* can be addressed effectively. This strategic inclusion ensures that dissolution assessments accurately reflect the intended performance of the formulation, aligning with regulatory standards and facilitating robust evaluation of product efficacy.

The implementation of two-tier dissolution testing – primarily introduced in the First Supplement of USP 24 – involves the strategic addition of enzymes to dissolution media. Pepsin, added to acidic mediums or water, aims for an activity level of 750,000 units per litre or less. However, it demonstrates optimal proteolytic activity up to pH 4 and diminishes above pH 5.5, rendering it unsuitable for two-tier dissolution testing when the medium exceeds pH 4.

On the other hand, pancreatin USP, included in mediums at or above pH 6.8, targets a protease activity level of not exceeding 1,750 units per litre. Pancreatin, renowned for its wide substrate specificity, boasts enzymes such as trypsin, α-chymotrypsin, carboxypeptidase, lipase and amylase, enabling it to hydrolyse proteins, fats and polysaccharides effectively. With a favourable proteolytic activity range around pH 6–8, pancreatin presents a versatile option for addressing gelatin cross-linking during dissolution testing.

While pepsin and pancreatin offer valuable solutions for *in vitro* dissolution challenges, it is important to acknowledge their limitations in mimicking *in vivo* conditions fully. Factors such as the presence of bile salts and gastric motility, crucial *in vivo* mechanisms, are challenging to replicate accurately in routine dissolution testing. At this point, enzymes such as papain and bromelain, derived from papaya and pineapple, respectively, could be considered. These enzymes, not naturally found in the human body, are primarily employed to digest cross-linked gelatin during dissolution tests. Papain, with an optimal pH range of 4–7, and bromelain, optimal at pH 4.5–7.5, both exhibit potent protease activity and can be evaluated using the case in digestive power test, as delineated in the USP monographs.

While these remedies offer promise in resolving the cross-linking challenge, careful consideration must be given to the cautionary note regarding the use of other additive media components when designing dissolution media. For example, the inclusion of surfactants such as sodium lauryl sulfate for solubility enhancement can compromise the activity of enzymes, introducing complexities in the two-tier dissolution study (Table 1). In such cases, a prudent approach involves pre-treating cross-linked gelatin capsules with enzyme-containing media devoid of surfactants. This ensures the maintenance of enzymatic activity, thus preserving the accuracy of dissolution testing. By navigating these intricacies thoughtfully, researchers could optimise dissolution protocols to emulate physiological conditions, thus enhancing the reliability of their findings more closely.

SUMMARY

While cross-linking in gelatin-based pharmaceuticals may pose challenges to dissolution during *in vitro* studies, it is important to note that *in vivo* dissolution is often unaffected. This is due to the enzymatic activity within the GI tract which digests cross-linking efficiently, aiding dissolution. Nonetheless, despite this natural process, several precautions should be taken to ensure regulatory acceptance of the product.

Various strategies exist to prevent cross-linking during the formulation stage. These include tailoring gelatin formulations to specific grades, incorporating cross-linking inhibitors, integrating stability enhancers or exploring alternative excipients less prone to cross-linking. These approaches effectively mitigate cross-linking issues.

> "If cross-linking does occur during formulation, strategic use of the USP two-tier dissolution method would be crucial, especially in capsule formulations."

However, if cross-linking does occur during formulation, strategic use of the USP two-tier dissolution method would be crucial, especially in capsule formulations. Optimising dissolution studies in this manner can enhance pharmaceutical evaluations, supporting the reliability and efficacy of drug development processes. Through these proactive measures, researchers can confidently and precisely navigate the complexities of cross-linking in gelatin-based pharmaceuticals.

ABOUT THE COMPANY

ACG has been delivering solutions to the global pharmaceutical and nutraceutical industry for more than 60 years, across six continents and in 100 countries. ACG is the world's only integrated pharma manufacturing solutions company with products ranging from capsules to films and foils, engineering equipment and inspection systems, all meeting international regulatory requirements. Collaboration is at the core of ACG's ethos of finding innovative solutions to the world's greatest health challenges.

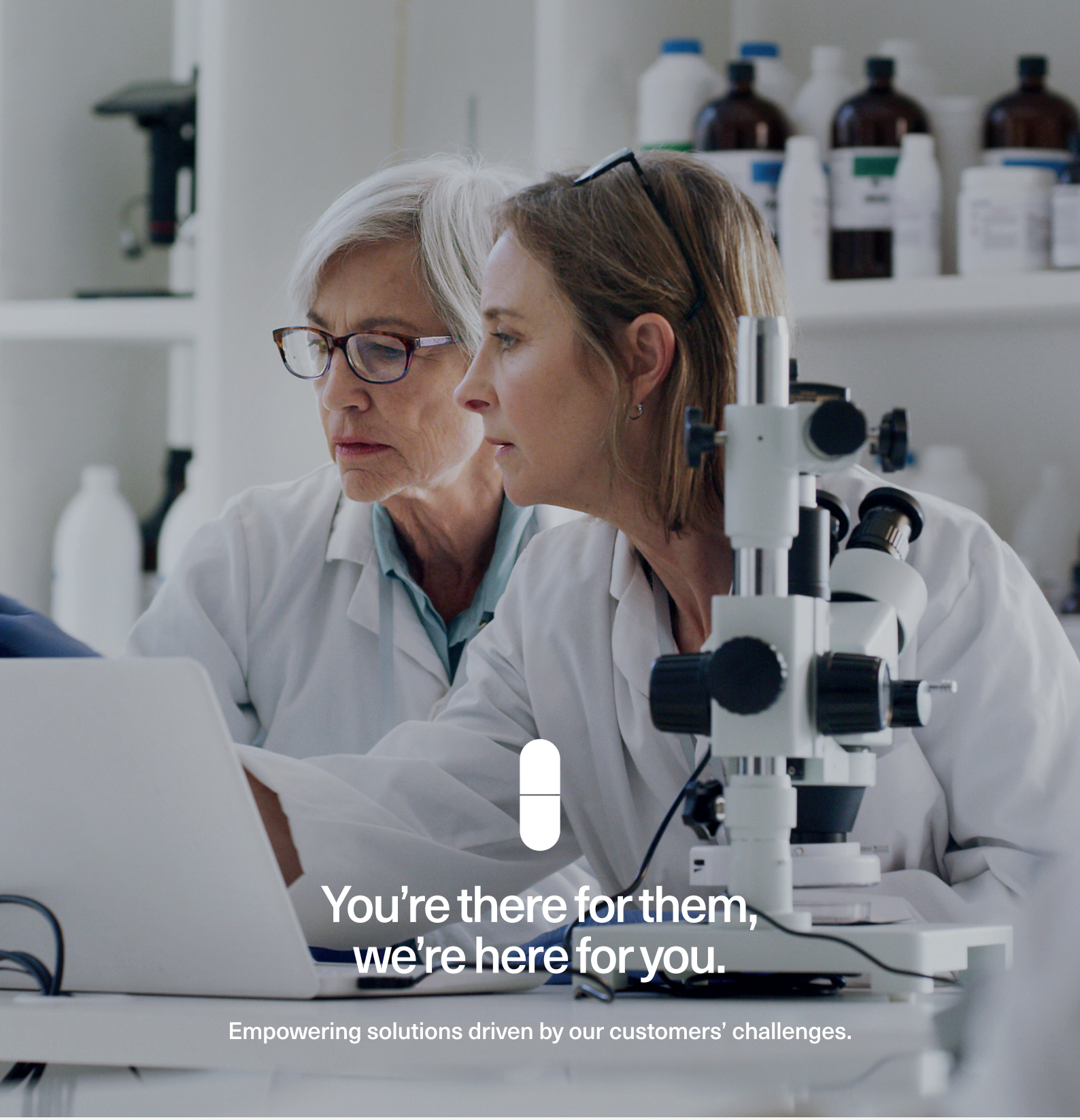
REFERENCE

1. *Aikman M et al, "Collaborative development of two-tier dissolution testing for gelatin capsules and gelatin-coated tablets using enzyme-containing media". Pharmacopeial Forum, Vol 24(5), Sep-Oct 1998.*

ABOUT THE AUTHORS

Jnanadeva Bhat, PhD, is Vice-President and Head of R&D (Pharma & Nutra) at ACG Group. He has been associated with the pharmaceutical industry for nearly three decades. As a product formulator, he has worked on various dosage forms, including tablets, soft gelatin and hard capsules, injectables and lyophilised formulations. At ACG, Dr Bhat heads the formulation R&D lab where he primarily leads new product development projects and customer interface.

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



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