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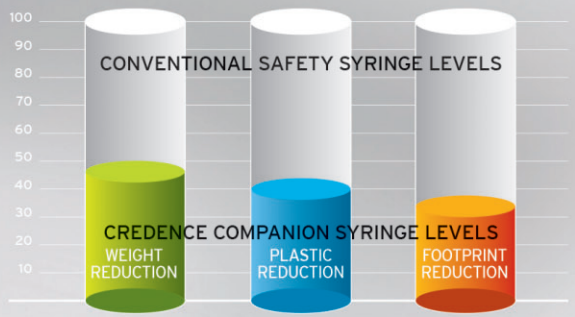

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Vaccine Technology

"Several new technologies have emerged that aim to address these critical areas. The challenge is how to deliver vaccines intact, at low cost, and with equal or better efficacy to populations around the world while avoiding or minimizing the requirements for cold-chain – making the "last mile" of vaccine delivery less burdensome."

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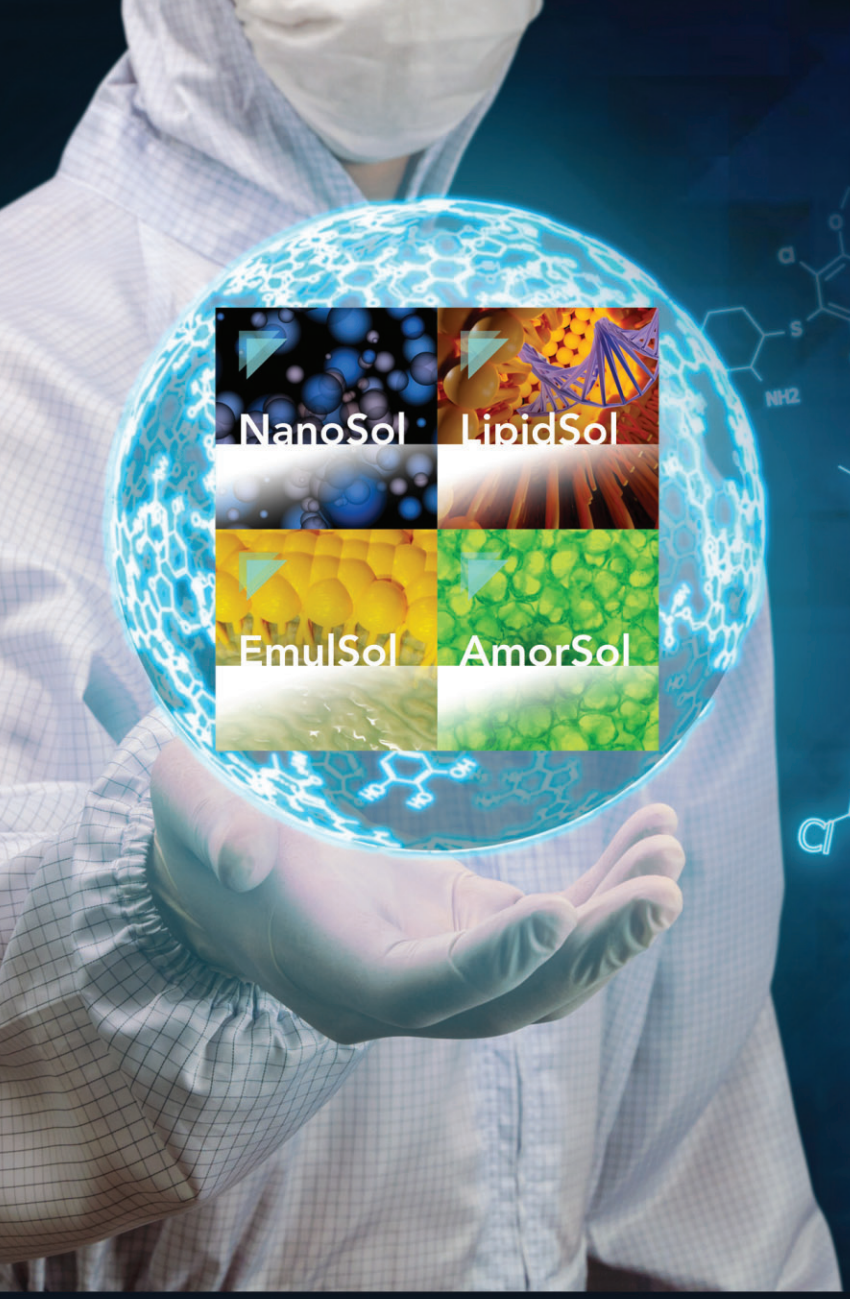

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"As more peptides and beyond-the-rule-5 compounds enter the pipeline, the need for versatile bioavailability enhancement approaches will only continue to grow. Lipid-based excipients provide a safe, proven mechanism to boost solubility and absorption across a wide range of liquid and solid dosage forms."

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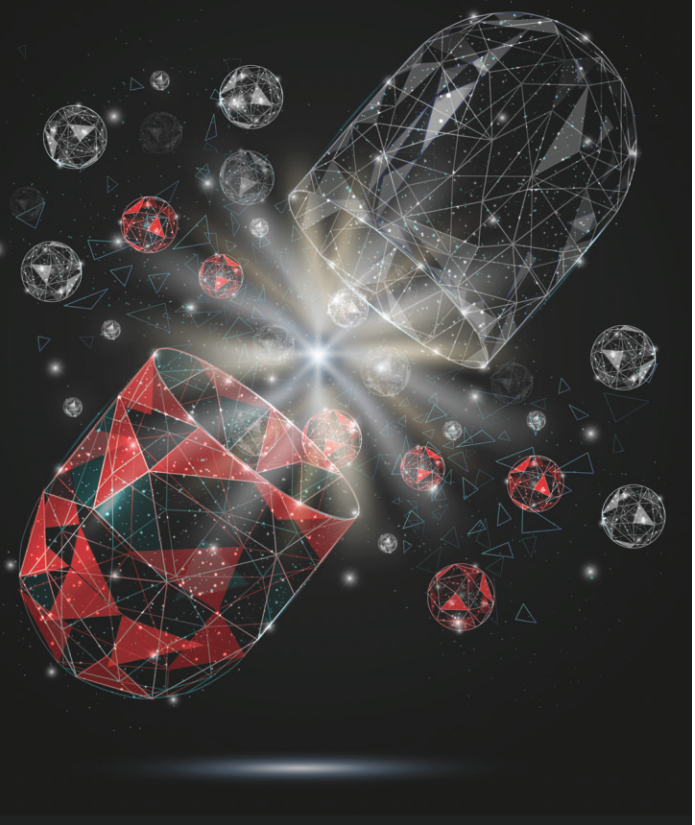

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Ginkgo Datapoints and Apheris Launch Industry Consortium to Advance AI-Powered Antibody Developability

Ginkgo Datapoints, an offering of Ginkgo Bioworks, and Apheris GmbH today announced that the Antibody Developability Consortium has kicked-off with its founding members. The Consortium is a new industry collaboration designed to help pharmaceutical and biotech companies predict manufacturability and developability risks earlierby building the field's largest standardized antibody developability dataset. The founding members of the consortium include AbbVie, argenx, Lundbeck, and Takeda, and it remains open to additional pharmaceutical and biotech companies.

"Pooling standardized developability data across the industry can create stronger predictive models than any one company could build alone" said Yves Fomekong Nanfack, Head of AI/ML Research at Takeda. "As we advance Takeda Research's ambition to become an AI-native discovery organization, this capability can help identify promising antibody candidates earlier, inform better development decisions and bring new therapies to patients faster."

Developability challenges can prevent otherwise promising antibody candidates from progressing efficiently toward patients. Antibody developability, encompass the biophysical properties that influence whether a candidate antibody can be manufactured, formulated, and successfully advanced into a clinical product. Predicting these barriers early could support more informed candidate selection and reduce avoidable development time and investment. However, existing predictive models have been limited by small, fragmented, and inconsistent datasets, while even large internal datasets are constrained in sequence diversity.

The Antibody Developability Consortium was created to address this gap by unifying efforts to produce a standardized, purpose-built, diverse dataset and corresponding AI models at scale.

Each founding member will contribute proprietary antibody sequences, with Ginkgo Datapoints filling any remaining capacity from publicly available sources to reach 10,000 antibodies in total. All members benefit from the rich diversity of antibody sequences sourced collectively from members and public sources. Using Apheris's infrastructure, members can train, benchmark, and refine AI models using the full consortium dataset, without raw proprietary sequences being exposed to other members.

Erwin Pannecoucke, Principal Scientist Discovery, argenx, says: "Predictive developability models can significantly accelerate discovery and development. The Consortium's extensive antibody dataset and federated design enable every partner to learn together and ultimately bring better medicines to patients faster."

The consortium is designed so that members can develop models trained on the full consortium dataset, and apply resulting models and their own fine-tuned derivatives internally while retaining ownership of the proprietary sequences and assay data they contribute.

Ginkgo Datapoints leads the scientific design and execution of the consortium: designing the sequence selection approach, overseeing antibody production, and conducting high-throughput wet-lab characterization across core developability endpoints. Ginkgo also trains a foundation antibody developability model on the resulting dataset within Apheris's secure environment. Apheris' federated infrastructure delivers the foundation model into each member's environment for fine-tuning on proprietary data, as the basis for developing new models. The same infrastructure runs Ginkgo's diversity algorithm for sequence selection, allows members to train their own models using consortium data, and protects confidentiality of proprietary sequences contributed by individual memebers. Charlotte Deane, Professor of Structural Bioinformatics at the University of Oxford and Peter Tessier, Professor of Pharmaceutical Sciences and Chemical Engineering at the University of Michigan, will provide independent scientific oversight. Together, the consortium provides pharmaceutical partners with a broader portfolio-level developability capability without having to build the data or infrastructure themselves.

The consortium's initial dataset is targeted for delivery to members by early 2027. The consortium will also explore the addition of more complex antibody formats over time to enable new drug classes and other key properties that enable early predictions of which drugs will succeed or fail.

"For AI to impact developability decisions in a drug program, it has to perform on a pharma's own molecules," says Robin Röhm, CEO and co-founder of Apheris. "The Antibody Developability Consortium delivers the largest standardized antibody dataset and the foundation model trained on it. Apheris' federated infrastructure brings that model to each member and lets them fine-tune it on their proprietary molecules inside their own environment."

"We are building the largest, most standardized antibody developability dataset the industry has ever seen, along with the predictive models trained on it," says Rich Cohen, Senior Director at Ginkgo Datapoints. "Ginkgo Datapoints brings the lab data generation scale, the diverse sequence selection expertise, and the published modelling track record needed to lead this initiative."

"At argenx, collaboration is central to how we innovate. Through our Immunology Innovation Program, we combine deep disease biology expertise with antibody engineering to advance new medicines for patients with high unmet need," said "This consortium represents an important step forward in building predictive models for antibody developability by creating datasets that are designed for machine learning, addressing limitations associated with convenience datasets," said Athena Hadjixenofontos, Director of Data Science, Head of AI in Biotherapeutics and Genetic Medicine at AbbVie. "Federated infrastructure enables participants to contribute data while keeping proprietary sequences private. These capabilities could meaningfully accelerate antibody discovery and help advance new medicines for patients."

For more information, visit https://datapoints.ginkgo.bio/.

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Aptar Pharma, Macquarie University Study High-Dose Dry Powder Delivery for Inhaled Biologics

Aptar Pharma and Macquarie University have launched a three-year research program aimed at addressing some of the formulation and delivery challenges associated with administering biologic medicines as high-dose dry powders to the lungs.

The project, supported through the Australian Research Council's Linkage Program, will examine how dry powder formulation characteristics affect aerosol performance and delivery through Aptar Pharma's Orbital dry powder inhaler platform.

The research program, titled "Unlocking the Potential of Dry Powder Carriers for Biologic Applications" (ARC LP250100089), brings together Macquarie University researchers with Aptar Pharma's expertise in inhalation science, pharmaceutical development, and drug delivery technology.

Pulmonary delivery has long been investigated as an alternative route for administering medicines that would otherwise require injection. For biologic therapies, the approach could potentially offer a more convenient method of administration for some treatments.

Developing an inhaled biologic, however, involves more than converting a liquid or injectable formulation into a dry powder. Biologic molecules can be sensitive to processing and environmental conditions, while the relatively large doses that may be required can create additional formulation and device challenges.

A dry powder formulation must maintain the integrity of the active molecule while also achieving the physical properties needed for efficient aerosolization. The resulting particles must then interact appropriately with the inhaler and respiratory tract to support consistent delivery. The Aptar Pharma and Macquarie University project is intended to investigate those relationships in greater detail.

Researchers will study several approaches to dry powder formulation, including engineered particles, blended formulations, and combined powder systems.

The work will examine how differences in formulation characteristics affect aerosol behavior when the powders are delivered using Aptar Pharma's Orbital platform. The inhaler is designed for high-payload dry powder applications, making it a platform for investigating formulations where the amount of material that must be delivered presents a particular challenge.

Understanding the relationship between the formulation and inhaler is important because aerosol performance does not depend solely on the properties of the powder. Particle characteristics, powder interactions, device design, airflow, and dispersion behavior can all influence how effectively a formulation becomes an inhalable aerosol.

The researchers intend to generate data that can help clarify those interactions and inform the design of future dry powder formulations for biologic applications.

The project will also incorporate computational fluid dynamics (CFD) modeling to investigate aerosol movement and particle transport. CFD approaches can be used to simulate how air and particles behave within inhalation systems, providing a way to examine aspects of aerosol performance that may be difficult to characterize experimentally on their own.

By combining experimental formulation studies with computational modeling, the research team expects to develop a more detailed understanding of how formulation and device variables influence powder dispersion and transport.

The resulting models could eventually help researchers evaluate formulation and inhaler configurations earlier in the development process.

The growing interest in inhaled biologics reflects the potential to deliver complex molecules directly to the respiratory system. But biologics can introduce formulation requirements that differ from those encountered with many conventional small-molecule inhaled drugs.

Stability is one consideration. A formulation must preserve the properties of the biological active ingredient during processing, storage, and administration. The powder must also have suitable aerodynamic and physical characteristics to produce an effective aerosol.

Excipients may play an important role in achieving those properties, particularly when developers are working with high drug loads or molecules that are sensitive to environmental or mechanical stresses. The Macquarie University program will examine different formulation strategies to better understand how these variables affect delivery through a dry powder inhaler.

Guillaume Brouet, Vice President, Scientific Affairs at Aptar Pharma, says the collaboration is intended to address some of the technical barriers that remain between the potential of biologic medicines and their delivery through inhalation. "By combining academic and industry expertise, this program will help advance scientific understanding of high-dose dry powder delivery and support the development of future inhaled biologic medicines."

For Macquarie University, the project provides an opportunity to connect fundamental research in respiratory science with an established inhalation technology platform.

"The ARC Linkage Program supports collaborations that translate scientific excellence into real-world impact," says Daniela Traini, PhD, Professor of Respiratory Science at Macquarie University. "This project brings together researchers and industry experts to investigate critical questions in dry powder biologic delivery."

The three-year program will generate formulation, aerosol-performance, and modeling data that could help guide future work on high-dose inhaled biologic therapies.

Rather than focusing solely on the inhaler or the formulation independently, the collaboration is examining the two as an integrated delivery system – an approach that could become increasingly important as developers explore dry powder formats for larger and more complex therapeutic molecules.

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ACG Develops High-Barrier Polypropylene Blister for Pharmaceutical Packaging

ACG has introduced a polypropylene-based blister packaging system designed to address two requirements that can be difficult to reconcile in pharmaceutical packaging: protecting sensitive medicines from moisture and oxygen while moving toward packaging structures that are more compatible with recycling.

The company's new RecycloPod PP Ultra uses a predominantly polypropylene construction with a thin ethylene vinyl alcohol (EVOH) barrier layer. ACG says the system is intended for pharmaceutical applications where maintaining product protection is essential while reducing the material complexity associated with conventional blister formats.

The development is part of ACG's RecycloPod portfolio of packaging solutions and was developed in collaboration with customers.

Blister packaging must protect pharmaceutical products from environmental conditions that can affect stability, shelf life, and performance. Moisture and oxygen are among the key factors that packaging developers must control, particularly for formulations with high sensitivity to either exposure. Polypropylene has gained attention as a potential material for more recyclable blister packaging, but achieving the necessary oxygen barrier can present a greater technical challenge than controlling moisture transmission.

ACG's approach combines polypropylene with EVOH to address that limitation. The RecycloPod PP Ultra forming structure consists of PP/EVOH/PP layers, with the EVOH serving as the high-barrier component within the predominantly polypropylene structure.

According to ACG, the material achieves a water vapor transmission rate below 0.60 g/m^2 per day and an oxygen transmission rate below 0.20 cm^3/m^2 per day. Those specifications are intended to provide the environmental protection needed for pharmaceutical products while allowing the packaging to retain a largely PP-based architecture.

The forming material is designed to be paired with a polypropylene lidding film, resulting in a blister format in which polypropylene is the primary packaging material.

For pharmaceutical manufacturers, the ability to introduce a new material structure without extensive changes to production equipment can be an important consideration. ACG says RecycloPod PP Ultra is designed to support thermoforming and sealing using established pharmaceutical packaging processes.

That compatibility could help reduce some of the manufacturing challenges associated with transitioning from conventional blister materials to alternative structures.

Rather than treating recyclability as a separate consideration from manufacturing performance, the development combines material selection, barrier protection, forming, and sealing requirements within a single packaging design.

Pharmaceutical blisters have traditionally used material combinations selected primarily for their ability to protect the drug product. Plastic and aluminum structures, for example, can provide strong barrier properties but may contain multiple materials that complicate recycling. The push toward more recyclable packaging is prompting manufacturers to reconsider those established constructions.

For pharmaceutical applications, however, simply reducing the number of materials is not sufficient. Any redesigned package must continue to protect the drug product throughout its intended shelf life and meet applicable manufacturing and regulatory requirements.

The use of EVOH in RecycloPod PP Ultra illustrates that challenge. Barrier layers can play an important role in maintaining product protection, but their presence also needs to be considered when evaluating the recycling characteristics of a multilayer package.

As a result, packaging development is increasingly focused on finding material combinations in which functional barrier components can coexist with the requirements of the targeted recycling system.

The development also comes as pharmaceutical packaging manufacturers assess the implications of the European Union's Packaging and Packaging Waste Regulation (PPWR).

The regulation is increasing industry attention on packaging waste, recyclability, and material efficiency. For pharmaceutical manufacturers, those objectives have to be balanced against the specific performance requirements of drug packaging.

That makes blister packaging a particularly interesting area for material innovation. The package must maintain the barrier properties necessary to protect the medicine, while its construction may need to evolve to address broader environmental objectives.

For packaging developers, the challenge extends beyond selecting a recyclable polymer. The complete package—including forming material, barrier layers, lidding, adhesives where applicable, manufacturing processes, and end-of-life considerations—can influence the overall environmental and technical profile of the system.

ACG is positioning RecycloPod PP Ultra as one component of a broader effort to develop pharmaceutical packaging with a reduced environmental footprint.

The underlying approach reflects a shift in blister development. Historically, optimization has centered heavily on achieving the barrier properties required by the drug product. Increasingly, developers are having to consider those requirements alongside material efficiency and end-of-life considerations.

High-barrier PP structures offer one potential route through that transition. By retaining polypropylene as the primary material while incorporating a thin functional barrier layer, ACG is seeking to balance pharmaceutical protection with a simpler packaging architecture.

The longer-term test for such systems will be whether they can deliver the required combination of drug-product protection, manufacturing performance, regulatory compliance, and compatibility with appropriate recycling pathways at commercial scale.

RecycloPod PP Ultra represents ACG's approach to that challenge, combining PP-based construction with EVOH barrier technology and processes intended to integrate with existing pharmaceutical blister manufacturing.

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Nanexa Licenses Long-Acting Injectable Technology to Novo Nordisk in Potential $1.3B Deal

Nanexa has entered into a global exclusive licensing and collaboration agreement with Novo Nordisk covering the use of its PharmaShell drug delivery technology in as many as five peptide-based development programs targeting obesity, type 2 diabetes, and other cardiometabolic diseases. The agreement could generate up to $1.3 billion for Nanexa, including a $700 million upfront payment and development and regulatory milestone payments. Additional payments are tied to product sales, while Nanexa will also receive low single-digit royalties on global net sales of products developed under the agreement.

The deal gives Novo access to Nanexa's PharmaShell platform for the development of long-acting injectable formulations. The programs will target different dosing schedules, with monthly and quarterly administration identified as development goals.

For Nanexa, the agreement represents a major commercial application of its drug delivery technology and follows a 2025 license and option agreement with Moderna.

PharmaShell is based on atomic layer deposition (ALD), a coating technology that Nanexa has developed for drug delivery applications.

The platform applies an ultrathin inorganic coating to individual drug particles. By modifying the properties of the coating, the technology is intended to control the release of the active pharmaceutical ingredient over an extended period.

In injectable formulations, the approach is being developed to create sustained-release products that could potentially reduce the frequency with which patients need to receive treatment.

That could be particularly relevant to chronic diseases such as obesity and type 2 diabetes, where patients may require long-term treatment and adherence to dosing schedules can be an important consideration.

Under the Novo agreement, the companies will investigate whether PharmaShell can be used to develop peptide-based medicines with substantially longer intervals between injections.

Novo will receive a worldwide license to use the PharmaShell platform in up to five development programs. The collaboration is structured around different target dosing frequencies rather than a single formulation approach. Monthly and quarterly administration profiles are among the targets specified in the agreement.

Long-acting drug delivery has become an increasingly important area of pharmaceutical development as companies seek to extend dosing intervals and improve the convenience of chronic therapies. In metabolic disease, the opportunity is particularly significant because treatments may need to be administered over many years. Extending the interval between injections could reduce the number of administration events required over the course of treatment, provided the formulation can maintain the necessary drug exposure and product performance. Peptide drugs can present specific formulation and delivery challenges, making drug delivery technology an important component of efforts to develop longer-acting versions of existing or emerging therapies.

Nanexa's agreement with Novo does not disclose the specific peptide assets that will be covered by the collaboration. Nanexa CEO David Westberg describes the Novo agreement as an important step in expanding the application of PharmaShell beyond the company's existing programs. "We are very excited about and proud of this license agreement with Novo and look forward to working with them to successfully develop products with less frequent dosing in obesity and type 2 diabetes indications. He also pointed to the agreement as additional external validation of the platform following Nanexa's 2025 collaboration with Moderna.

For Nanexa, the agreement could also change the company's development strategy. Rather than licensing the platform at an early stage in every case, the company says the financial resources from the Novo deal could allow it to advance selected internal programs further before entering into future partnerships.

Nanexa Chairman Göran Ando says the agreement provides the company with additional resources to expand the potential applications of its ALD technology. "With this agreement, Nanexa enters a new era of considerable financial strength, allowing us to significantly expand applications of our unique ALD technology to other therapeutic areas," Ando said.

The company has indicated that it intends to use the increased financial flexibility to pursue additional opportunities while continuing to develop its partnership with Novo.

For the broader drug-delivery field, the agreement highlights the interest in technologies capable of extending the duration of injectable therapies. The commercial opportunity will ultimately depend on whether PharmaShell-enabled formulations can demonstrate the required pharmacokinetic, manufacturing, stability, and clinical characteristics across the programs selected for development.

For now, the Novo collaboration gives Nanexa access to a large-scale development partner and places its PharmaShell platform into a set of programs targeting some of the fastest-growing areas of metabolic medicine.

For more information, visit https://nanexa.com/.

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SPECIAL REPORT

Excited About Excipients?

By: Kurt R. Sedo, Executive Editor, and Cindy H. Dubin, Senior Editor, PharmaCircle

Article originally published in *PharmaCircle Weekly Intelligence* newsletter

INTRODUCTION

They may be inactive, but excipients are the unsung heroes of today's complex formulations. Many development programs involve poorly water-soluble compounds, highly potent APIs, molecules with limited chemical or physical stability, or products that require specific release profiles. From a formulation scientist's perspective, excipient selection is increasingly driven by the specific challenge that a molecule presents, rather than by traditional functionality alone. In these cases, excipients are no longer selected solely for manufacturability; they are increasingly expected to actively contribute to product performance by improving solubility, enhancing bioavailability, stabilizing sensitive compounds, or enabling controlled drug release. "As a result, formulators are seeking excipients with more sophisticated and multifunctional properties than ever before," says Almudena Domniguez Fernández, group leader, Ardena, "The growing complexity of modern drug candidates is significantly changing what formulators are expecting from excipients,"

This trend is particularly evident in the development of amorphous solid dispersions, lipid-based systems, modified-release formulations, and other advanced drug delivery platforms. For poorly soluble molecules, excipients may play a critical role in maintaining supersaturation, preventing recrystallization, or enhancing wetting and dissolution. For highly potent compounds, they can help to ensure content uniformity and robust processing, despite very low drug loads. Similarly, for unstable molecules, carefully selected excipients can reduce degradation pathways and improve shelf-life. Then, there are biologics and advanced therapies, which require highly

specialized stabilizing excipients to protect sensitive molecules from degradation and aggregation.

"The overall industry trend points toward excipients that provide functionality beyond traditional filling, binding, or disintegration roles," says Fernández. "The focus has therefore shifted from simply which excipient can be used, to which excipient can best solve the specific development challenge."

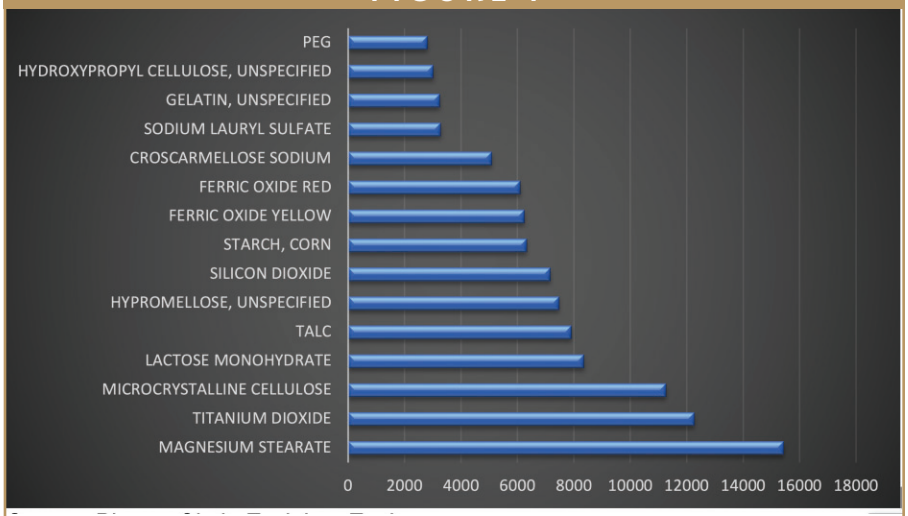
Unmesh Lal, vice president, Healthcare & Life Sciences, Frost & Sullivan agrees: "The conversation has shifted from excipients as inactive ingredients to excipients as formulation enablers. The industry is focused on solving drug solubility, bioavailability, stability, patient adherence, and delivery challenges, particularly for complex therapies and patient-centric formulations."

NEW EXCIPIENTS ENABLE ADVANCED DRUG PRODUCTS

The shift in drug products entering the market influences both the types of excipients selected and how they are used in formulations, making excipient functionality and performance increasingly critical to product development and delivery. While excipients are inactive ingredients in drug products, their chemical and functional characteristics often help enable formulation of advanced drug products.

"The past several years have brought important advances in new medicines that improve and save lives, powered by innovative drug delivery systems requiring increasingly complex formulations to create more patient-centric dosage forms than in the past, says Claire Chisolm, Senior Manager, Science & Standards

FIGURE 1



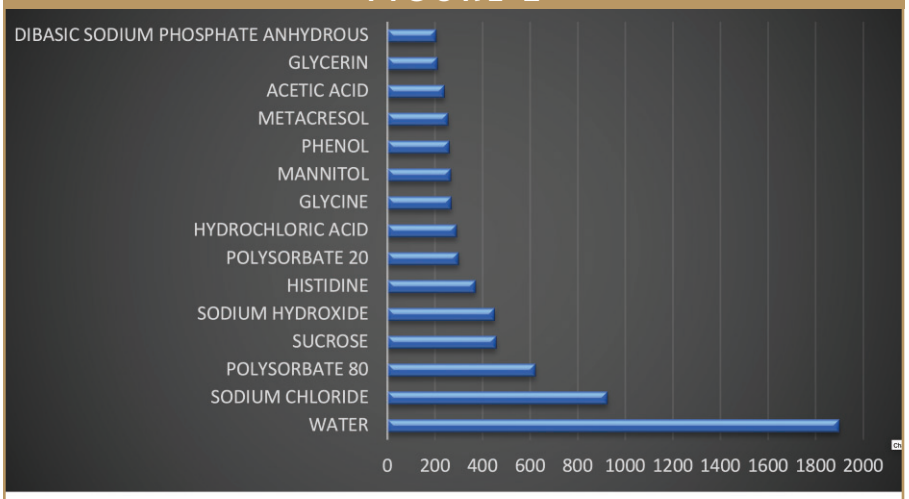
Excipients Used in Marketed OSDs
Source: PharmaCircle Excipient Explorer

Excipients, USP. "For example, lactic acid-glycolic acid and lactide-glycolide polymers (PLGAs and PLGs, collectively referred to as LG polymers) possess unique biodegradation characteristics that enable controlled-release formulations with drug release durations ranging from days to months; a game changer for patient convenience and compliance."

This year, several excipients have been introduced to solve a variety of development challenges, such as developing oral alternatives to injectable therapies. See Figure 1 for most commonly used excipients currently used in oral solid dosage forms (OSD). For example, Ashland just announced the commercial launch of permexa™ sodium caprate, an intestinal permeation enhancer designed to support oral delivery of peptides, biologics and low-permeability drugs, including GLP-1 agonists. The excipient targets challenges in permeability, formulation consistency, process robustness and scalability for oral drug products. Permexa™ sodium caprate combines established sodium caprate functionality with an IP protected process aimed at improving powder flow, compressibility and formulation consistency while maintaining permeability enhancement characteristics. The excipient is designed with an IP-protected process to support more robust tablet manufacturing through improved powder flow, enhanced compressibility and greater formulation consistency, while maintaining the permeability enhancement characteristics required for oral drug delivery applications. One cannot overlook the timeliness as the launch piggybacks off market momentum in oral peptide and biologics development. (Source: Ashland).

Earlier this year, RIBUS launched two plant-based excipients. Nu-FILL is an organic-certified alternative to microcrystalline cellulose. The rice hull and rice bran-based excipient designed to replace microcrystalline cellulose in tablets, capsules and stick packs, offering supplement manufacturers a clean label and certified organic-compatible filler with comparable flow and compressibility performance. The company says Nu-FILL matches the performance of traditional fillers while complying with clean-label and organic standards. Nu-MAG® is a rice bran extract for tablet and capsule

FIGURE 2



Excipients Used in Injectable Marketed Biologics
Source: PharmaCircle Excipient Explorer

manufacturing, replacing magnesium stearate. The company says it reduces powder adhesion to dosing equipment and improves fill consistency, best suited for compressed lonzenges, effervescent tablets, and chewable formats (Source: RIBUS).

Considered more of a taste modulation technology platform rather than a single excipient (though the individual ingredients it uses function as formulation excipients or additives), ModulaSENSE® Bitter aims to tackle patient adherence by removing API bitterness at the receptor level. Instead of relying on generic masking, ModulaSENSE® Bitter, developed by dsm-firmenich, combines blockers, maskers, and sweeteners with evidence-based insights to create targeted, formulation-specific bitterness masking solutions. The technology has been developed through a multi-step, scientifically-driven workflow and is applicable across a wide range of APIs and oral dosage forms (Source: dsm-firmenich).

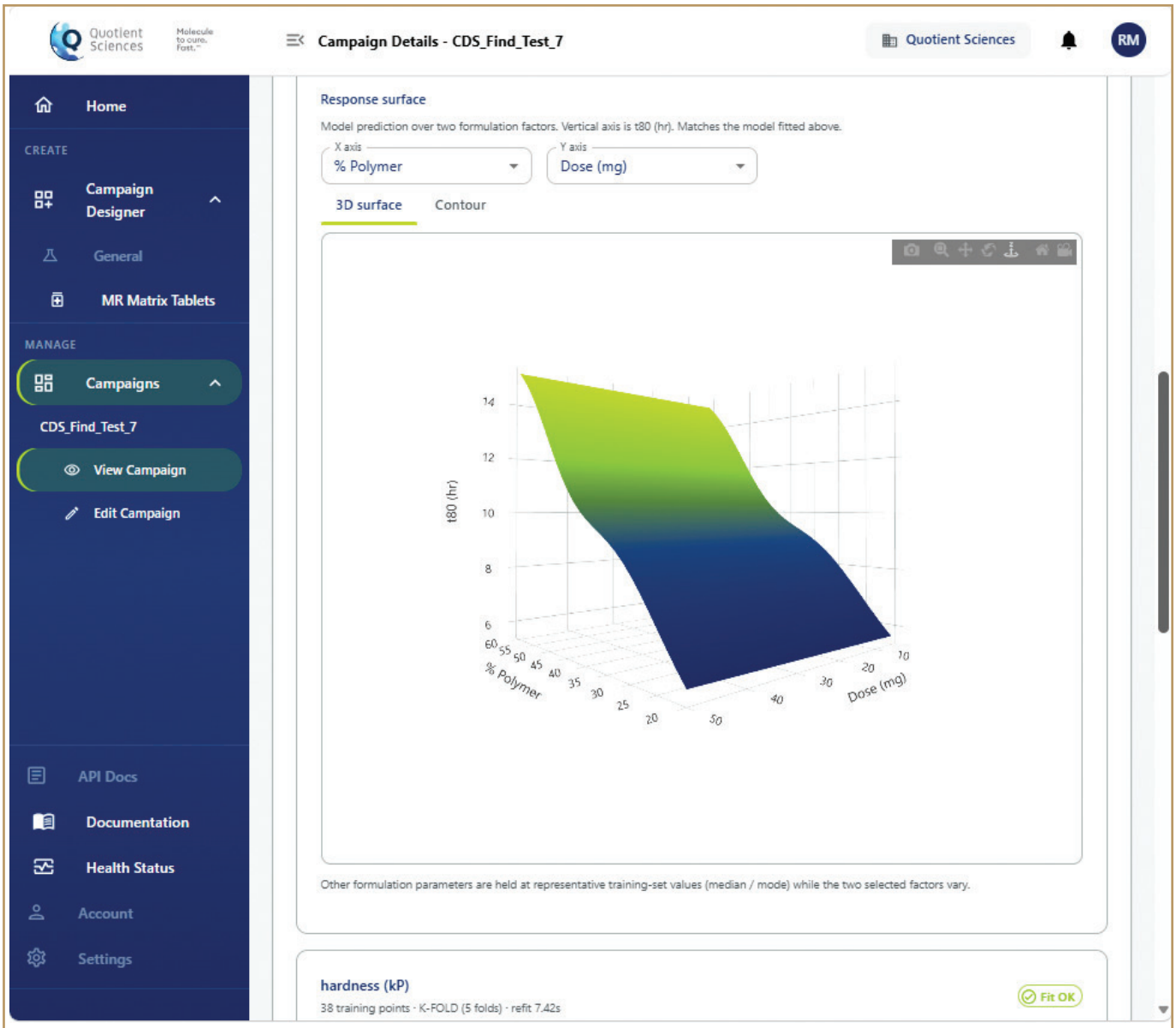
No matter the dosage form, stabilizing excipients play a critical role in maintaining molecular integrity and preserving the therapeutic performance of pharmaceuticals. In biopharmaceutical manufacturing, these excipients are increasingly employed to mitigate degradation, aggregation, and chemical instability, particularly in protein- and peptide-based therapeutics. Stabilizers can enhance product stability during processes such as lyophilization and aseptic processing, as well as under temperature-induced stress conditions. Consequently, their application has expanded significantly in the development of biologics, vaccines, and specialty injectable formulations (Figure 2).

GELITA, for instance, launched a gelatin excipient, featuring less than ten endotoxin units per gram, for vaccine stabilization and controlled and targeted drug delivery as well as 3D bioprinting of living tissue. Derived from collagen, MEDELLAPRO® closely mimics the natural extracellular matrix of the human body, providing a biocompatible and biodegradable solution that is safely absorbed by the body with time. The specialized gelatin can be processed into a wide range of forms, including hydrogels, films and nanoparticles, making it suitable for diverse applications (Source: GELITA).

AI & COMPUTATION TOOLS SEEK OUT THE BEST EXCIPIENTS

Many are extremely interested in the suitability of Artificial Intelligence as a valuable tool for excipient selection and formulation design. Traditionally, formulation development relied heavily on expert knowledge combined with extensive experimental screening. "While this approach remains essential, AI can help accelerate decision-making by identifying patterns across large formulation datasets, and predicting which excipients are most likely to meet predefined formulation objectives," says Fernández,

Recent analysis from Boston Consulting Group suggests that AI-enabled approaches could reduce time and cost in early development by 25-50%. The numbers bear out. In September, Quotient Sciences reported interim results of a clinical study in which a proprietary AI algorithm selected modified-release formulation compositions and doses during the trial. The algorithm reached the study's preset pharmacokinetic target within three dosing periods, meeting the program's interim objectives. The clinical work follows laboratory screening in which the same algorithm demonstrated that it could rapidly learn the relationship between tablet composition and in vitro drug release. The algorithm mapped the formulation design space after screening one-third fewer formulations than conventional methods. That finding prompted the hypothesis now being tested in the clinic: A model capable of learning that relationship in the laboratory could also learn how composition influences



Quotient's AI platform's learned relationship between formulation composition and product performance.

pharmacokinetics in humans.

Prior to the study, formulators identified a shortlist of excipients relevant for the desired formulation type, explains Andrew Lewis, Chief Scientific Officer at Quotient Sciences. The AI algorithm was provided with the excipient options, in vitro targets and constraints to work within (e.g. min/max levels of excipients). The AI then requested formulations which were manufactured and tested and the results used to train the model. The model was able to select excipients and identify formulations that met the *in vitro* Target Product Profile after screening up to 50% less formulations than conventional formulation development. These formulations were then optimized in a clinical study, where the same AI algorithm selected formulation compositions targeting a specific pharmacokinetic target. It managed to learn the relationship between composition and pharmacokinetics after evaluating only three prototypes.

"Generally speaking, the suite of excipients applied is governed by the physicochemical properties of the drug and the technology necessary to develop a particular formulation type," he says. "The AI platform we have developed starts with excipient selection by our expert formulators and provides them with a tool to rapidly identify compositions that meet pre-defined criteria, simultaneously creating a digital twin of the formulation/drug product as it learns."

This digital twin can synergize with other *in-silico* tools such as predictive stability and PBPK modelling to predict the impact of formulation and/or process changes on performance and product

Photo courtesy of Ardena

quality. "It's entirely feasible that in the future AI, if trained on the right, high-quality data, may be able to select excipients based on a drug's structure or limited characterization data and propose formulations and manufacturing routes that hit *in vitro* and *in vivo* targets," says Lewis.

Another promising AI application is the prediction of excipient impact on critical quality attributes such as stability, solubility, dissolution performance, and ultimately bioavailability. Pharmaceutical formulations are complex systems, and predictive models remain highly dependent on the quality and quantity of available data. Experimental verification, mechanistic understanding, and formulation experience continue to be essential. "AI-based tools can help identify promising formulation approaches by analyzing large datasets and learning from previous formulation outcomes," says Fernández. "This can reduce development timelines and allow scientists to focus experimental efforts on the most promising options. In the near future, the greatest value of AI will likely be its ability to support risk-based decision making, accelerate formulation screening, and help scientists navigate increasingly complex development challenges more efficiently."

Scientists at the University of Minnesota are also seeking answers to complex development challenges. They have developed a computational tool called CapSACIN (Capsid Surface Abstraction and Computationally-Induced Nanofragmentation) to seek out the best combination of excipients for protecting vaccines, gene therapies, and other virus-based medicines if/when they are not stored and/or transported under prime conditions as the products move through the supply chain. Rather than simulating an entire virus, CapSACIN focuses on specific regions of a virus's outer shell (the capsid). The research, published earlier this year in the Journal of Chemical Theory and Computation, used U.S. National Science Foundation (NSF) ACCESS allocations on the Expanse system at the San Diego Supercomputer Center (SDSC), located at the University of California San Diego Halıcıoğlu School of Data Science and Computing. The team tested CapSACIN using Porcine Parvovirus to determine which parts of the virus are most vulnerable to damage. Ultimately, CapSACIN also predicted the excipients sorbitol and trehalose would provide the greatest stability for the virus, while glycine would be less effective. These predictions closely matched results from wet-lab studies, providing strong evidence that the new tool works as intended and can significantly reduce the time and expense required to develop new vaccines, gene therapies and other biologic medicines (Source: U.S. National Science Foundation).

While both AI and computation science may help identify promising candidates and prioritize experiments, ultimately the suitability of an excipient still needs to be supported by appropriate experimental data and scientific evidence. "The use of AI, or any other technology, does not change the fundamental expectations the FDA has of applicants: all decisions must be grounded in sound pharmaceutical science and supported by adequate scientific evidence," says an FDA spokesperson. "Regulatory standards for the evaluation of inactive ingredients remain in full effect regardless of the methods used to select them, and applicants bear full responsibility for demonstrating that their products meet those standards."

A NEED FOR ALIGNED STANDARDS

Regarding standards and regulations, industry insiders agree there is a need for continued alignment among standards-setting bodies, regulators, industry, and other stakeholders as excipients play a significant role in formulation of advanced medicines. "To support this evolving landscape, USP has been working with regulators and industry to help solve challenges related to excipients," says Chisolm. "These include establishing standardized approaches to name, characterize, and define key functional properties for complex excipients such as PLGAs/PLGs (LG polymers), phospholipids, polyethylene glycols (PEGs), and polysorbates that are increasingly critical to long-acting injectables, lipid nanoparticles, and other advanced medicines."

Unlike drug substances and drug products, pharma excipients are not covered by the ICH Q1 stability guidelines. However, excipients play a critical role in ensuring the quality, performance and shelf life of pharma products. In March, the 2026 IPEC Excipient Stability Guide was released, providing a science- and risk-based framework for designing, implementing, and documenting stability programs specifically for pharma excipients. A recent AAPS PharmSci 360 webinar, Establishing Effective Stability Programs for Pharmaceutical Excipients, presented by IPEC Americas and IPEC Federation, highlighted key enhancements in this new version of the guide:

- Three risk-based stability study designs: use of historical data in lieu of formal studies, warehouse studies, and formal stability studies.

- Expanded best practice guidance covering bracketing/matrixing for compound families, stability considerations for different types of excipients (e.g. novel, CoPE) and classic excipients when used in non-traditional dosage forms (e.g. vaccines and biologicals); bulk storage, accelerated and ongoing stability, transportation studies, expiration/retest periods, and specifications for tested attributes. In addition, throughout the guide efforts were made to harmonize terminology, add clarification, reorganize information and remove redundancies.

- Differentiation between excipient and API requirements, where applicable.

The FDA also released a new final guidance for industry titled "Evaluation of Therapeutic Equivalence (TE). While little changed from the draft guidance of the same title issued in July 2022, a new process has been introduced for applicants of certain hybrid 505(b)(2) applications to request TE codes. The guidance now states that "in certain circumstances, a 505(b)(2) application holder may use the process described in section 505(j)(7)(A)(v)(I) to request that FDA make a therapeutic equivalence evaluation for a prescription drug in a 505(b)(2) application where the sole difference from a listed drug relied upon in the application is a difference in inactive ingredients not permitted under 21 CFR 314.94(a)(9)(iii)-(iv)," (Source: FDA).

"Some drug products reach the market through a 505(b)(2) application — a middle-ground approval pathway for drugs that are similar to a brand-name drug but have meaningful differences, sometimes due to differences in inactive ingredients (excipients)," an FDA spokesperson tells PharmaCircle. "Unlike standard generic drugs, 505(b)(2) drugs are not automatically evaluated for therapeutic equivalence by the FDA. However, if the only difference between a 505(b)(2) drug and the brand-name drug it references is a difference in excipients, that wouldn't be permitted under rules applying to generic drugs. The law provides a streamlined process under Section 505(j)(7)(A)(v)(I) for the applicant to request a TE evaluation directly."

Chisolm says that awareness of the impact of excipient quality specifications and critical material attributes (CMAs) on the performance and associated safety profile of drug products has grown increasingly complex. "As drug products have grown increasingly complex, so has awareness of the impact of excipient quality specifications and critical material attributes (CMAs) on the performance and associated safety profile of drug products," she says.

A FUTURE OF SMARTER EXCIPIENTS

As formulators consider excipient attributes, they are definitely moving away from a one-size-fits-all approach. Excipients are increasingly being engineered to address the unique stability, delivery, and performance requirements of specific modalities such as proteins, peptides, inhaled biologics, sustained-release injectables, ophthalmics, and targeted delivery systems.

"As the industry moves toward complex biologics, advanced drug delivery, and patient-centric formulations, the strategic importance of excipients is becoming more visible than ever," says Lal, who is excited about the future of excipients. "The excipient is becoming an integral part of the therapeutic platform rather than an afterthought. The future of excipients is not about replacing proven materials, but about engineering smarter, application-specific excipients that enable complex therapies, improve patient outcomes, and unlock new drug delivery possibilities." ◆

Formulation Forum

Oral Delivery of Nanocrystal Suspensions

By: Shaukat Ali, PhD, Sr. Director, Scientific Affairs & Technical Marketing, and Jim Huang, PhD, Founder & CEO, Ascendia Pharmaceutical Solutions

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INTRODUCTION

Oral delivery remains most widely route of administration of drugs over the decades, and this trend continues. It is truly a hallmark of patient convenience and acceptance, ease of administration, stability, and most specifically, cost effectiveness compared to non-oral administered therapeutics.[1] The molecules administered through other routes as well as oral (p.o) could have challenges stemmed from poor solubility and bioavailability, making formulation development more complex and time consuming. In fact, over 90% of new chemical entities are poorly soluble and over 40% marketed drugs below to either Biopharmaceutical Classification System (BCS) II or IV, making them less permeable and poorly absorbed, hence less bioavailable.[2] Taken collectively, many of marketed molecules across all modalities are formulated in a class of excipients provide an exceptional solubility, and permeability to overcome the mucous membrane barrier in gastrointestinal (GI) tract.

Oral absorption is often hampered by the food effect. For example, if the food uptake interferes with absorption in the gut, it is so-called the negative food effect. In contrast, if absorption is increased on food intake, it's so-called the positive feed effect.[3] The gastrointestinal environment conditions such as pH, fluid volume, viscosity, motility, and stomach residence time, all impact the effective absorption of drug molecules. Lipophilic molecules generally tend to show improved solubility and absorption, and the exposure in plasma as result of pH shift in the fed state. As a result of positive food effect in the fed state leading to higher bile secretion, and fluid volume, it results in lower pH shift (ca. 1-3) and increased gastric empty or T_{max}, which in turn helps improve drug solubilization with higher area under curve (AUC) than in the fasted state. As a result of negative food effect in the fed state, on the other hand, it leads to higher viscosity with higher pH shift (ca. 2-5) causing lower AUC as opposed to fasted state.[4] The absence of food effect demonstrates the equal or similar exposure of drugs or AUC in fed state or fasted state, resulting in an increased T_{max} with food due to delayed gastric emptying.

Huang and Ali have published a review on nanosuspensions for injectable formulations.[5] Shi et al., have published their work citing the approved nanocrystal drugs for intramuscular, subcutaneous drugs.[6] This article sheds light on the challenges and opportunities to improve solubility and enhance oral bioavailability of molecules in nanocrystals or crystalline suspensions.

STRATEGIES FOR INCREASING SOLUBILITY

Increasing solubility remains the primary objective to improve the bioavailability of NCEs possessing higher melting and higher log P.[7] Of the solubilization technologies used, the nanostructured drug delivery system, complexation with cyclodextrins, pH alternation, salt formation remained the most conventional methods. Others non-conventional approaches as amorphous solid dispersions (ASD) technologies like hot melt extrusion, spray drying, Kinetisol®, and co-crystals, and self-emulsifying drug delivery systems are all commonly used for most challenging molecules, leading to marketing of several commercially drugs. In nanostructured delivery system, the nanocrystals derived from micronization or micro- or nano-milling with particles 1-100 nm can help enhance the solubility and bioavailability of molecules. It can also increase drug loading and improve long term physical and chemical

stability. Often stabilized by surface active agents, e.g. solubilizer and polymers, these nanocrystals are suspended in aqueous and non-aqueous solutions and hence, preventing aggregation or flocculation by maintaining steric and electrostatic interactions.[8]

MANUFACTURING OF NANOCRYSTAL SUSPENSIONS

Drug nanocrystals are prepared by top-down and bottom approaches, or by combing the two. In top down or high shear with high energy input, the larger particles are broken into small particles, mostly irregular in shapes and sizes. In top-down approach, the milling process is accomplished by wet bead milling (WBM) and high-pressure homogenization (HPH). In WBM, for example, drug and stabilizers are milled together in a grinding medium container filled with wear-resistant beads derived from either yttria stabilized zirconia or cross-linked polystyrene. As a result, the particle size is reduced with high-speed rotor though shear friction and impact force between drug particles, grinding medium and wall of the milling chamber.[9] In HPH, on the other hand, the particle size is reduced by turbulence and shear stress, and cavitation forces as it forced through a narrow aperture under pressure.[10]

In bottom-up approach, the process involves precipitation or forming nanocrystals through nucleation and crystal growth via antisolvent in a supersaturation solution. It is accomplished by dissolving the drug in organic solvent and crashing the drug in an aqueous solution containing stabilizers (solubilizers and polymers) in an anti-solvent manner, leading the desired particles under rapid and efficient mixing or sonication.[11] Use of compatible stabilizers is important to increase the suspension-ability of particles without agglomeration, sedimentation and/or to prevent Oswald ripening. These stabilizers tend to separate the particles and keep suspended by maintaining the distance between each other through electrostatic interactions and/or steric interactions.

NANOCRYSTAL SUSPENSION MARKETED DRUGS

There are several nanocrystal drugs marketed over the years. First launched in 2000, sirolimus (Rapamune®) as tablets improved the oral bioavailability by 21% as compared to non-milled drug. Aprepitant nanocrystal launched as Emend® in 2003 showed 25-30% dose reduction due to its enhanced oral bioavailability. Fenofibrate as Tricor® and megestrol acetate as Megace ES® showed significant increase in oral bioavailability by reducing the food effect as nanocrystals.[4] Table 1 lists examples of few commercially available nanocrystal drugs showing the method of preparation, particle size, and pharmacokinetic performance.

As cited above in Table 1 the nanocrystal drugs when compared with commercial drugs showed much greater bioavailability than commercial products. It can be taken to suggest that the processes and ultimate the particle size and the morphology as a result, play an important role in absorption of drugs through gastrointestinal tract. Let's take a closer look into some important factors contributing to higher bioavailability.

NATURE OF PARTICLES: MORPHOLOGY & SIZE

As evident from Table 1, nearly all drugs have a wide distribution range of particles prepared by different processes, whether used top down, bottom up or the combination of the two, and also on the properties of drugs, concentrations and type of stabilizers used. Each method requires different conditions and setups. In wet bead milling process, for example, the bead size and speed and time determine the particle size. Thus, finding an ideal condition for achieving the critical material attributes is essential for a robust process. The quality by design (QbD) approach is used to identify and minimize the variabilities during manufacturing.

TABLE 1

Rx/name	Process method	Particle size	PK data	Reference
Cinacalcet	Anti-solvent precipitation	244 nm	1.9-fold increase in C_{max} and 1.6-fold increase in AUC fasted state *vs* Sensipar®, no food effect	12
Ritonavir	High pressure homogenizer	541 nm	2-fold increase in C_{max} and AUC in fed state *vs* commercial drug	13
Megestrol acetate	Wet ball milling	158 nm	2-fold increase in C_{max} and 3.6-fold increase in AUC *vs* commercial drug	14
Clindipine	Antisolvent precipitation	280 nm	3-fold increase in C_{max} and 1.8-fold increase in AUC vs commercial drug	15
Aprepitant	Wet bead milling	151 nm	1.3-fold increase in C_{max} and 1.5-fold increase in AUC *vs* commercial drug	16
Rebamipide	Antisolvent precipitation	148 nm	C_{max} and AUC same in Tablets	17
Gliclazide	Antisolvent precipitation	96 nm	3-fold increase in C_{max} and 1.7-fold increase in AUC *vs* commercial drug	18

Marketed oral nanocrystal suspensions

Cyclosporine A, a known immune suppressant, was first launched as soft gel capsules and is now available as nanocrystal suspension achieved by nano-milling with particles ranging from 280 nm to 2967 nm. For nano-milled cyclosporine with 280 nm particles in size, the oral bioavailability was about 1.5-fold higher than those larger cyclosporine particles. A further reduction in particles to < 280 nm, could lead to improvement in pharmacokinetic performance.[19] Ma et al. investigated the impact of particle size oral absorption of isoliquiritigenin nanocrystals varied between 46 nm and 555 nm. The C_{max} and T_{max} and AUC improved on nano-milled samples, with particles 277 nm showed a significant enhancement in pharmacokinetic performance as compared to 46 nm particles. *In vitro* release data is also consistent with the *in vivo* findings. Thus, achieving the optimal particle size is critical for each preparation to improve oral bioavailability. Predictive tools such simulation modeling could be used to further optimize the formulation to reduce particle size variability and to improve the bioavailability assessment.[20]

Like particle size, the morphology of particle also plays a critical role in mucus permeation and absorption. For example, lovastatin nanocrystal, is known to exhibit different bioavailability in rats depending upon the particle morphologies.[21] The authors have demonstrated that rod shaped particles have much deeper penetration than flaky or spherical particles, suggesting that these rod-shaped nanoparticles can easily be internalized by epithelial cells, whereas, the spherical shaped particles are trapped in the mucus layer networks, thus, causing the reduced permeability as compared to rod shaped particles. It is believed that longer rod-shaped particle can increase the contact within the intestinal membrane by rotating through mucus networks.[22]

DISSOLUTION RATE & EFFECT OF FOOD EFFECTS OF NANOCRYSTAL SUSPENSIONS ON BIOAVAILABILITY

The dissolution of nanocrystals depends upon particle size and morphology as well solubilizers. The larger surface area to volume ratio and short diffusion distance can enhance the dissolution rate according to Noyes and Whitney equation.[23] In the gut, the endogenous secretion of bile salts and phospholipids has drastic impact on dissolution rate. The particle curvature also affects the dissolution rate, which is due in part, by allowing more particles interact with intestinal membrane and blood vessels.[24] Junyapraser et al. observed that dissolution rate of gliclazide at pH 7.4 and at 30°C was about 2.3-fold higher in C_{max} and AUC as compared to pure drug.[18] When tested in rats, the *in vivo* data showed a remarkable reduction in blood glucose level as compared to commercial drug or pure drug, further demonstrating the particle size reduction, and nanocrystal suspension stability which helped achieve the rapid dissolution, absorption and improve efficacy of drug. Thus, dissolution rate and oral bioavailability of poorly soluble can also be affected by fed and fasted states, but the nanocrystals have the potential to eliminate fed/fasted state since the dissolution rates in both conditions are fast enough.[25] Other drugs like entrectinib, an anticancer drug with pKa of 2.5 (weak base) showed a poor solubility in the fasted state but higher solubility in gastric pH in the absence of food. The entrectinib nanocrystals with particle size 83 nm, on the other hand, dissolved >98% in 4 hours both in the fed and fasted states simulated intestinal fluids (FaSSIF and FeSSIF). *In vivo* data in rats showed nearly similar oral bioavailability (13949 ng.h/min vs. 11702 ng.h/min), with no food effects in the fed or fasted state. The C_{max} and AUC of nanocrystals showed 4-fold and 3-fold increase, respectively, as compared to pure entrectinib. In other case, nanocrystals may not have an impact on drug absorption in the fed and fasted states.

For example, antiviral drug ritonavir nanocrystals with particle size 541 nm, the dissolution was complete within 2 hours, but the *in vivo* data of commercial drug showed AUC 1.3-fold increase as compared to nanocrystals in the fasted group.[13] In the fed state, the AUC was 10-fold higher than fasted state (442 min.mg/ml vs 47 min. mg/ml). With taken together, these results suggest that nanocrystals may improve oral bioavailability, but they were sufficient to eliminate the food effect. It is evident that entrectinib nanocrystals, a BCS II drug with particle size of 83 nm were able to eliminate the food effects in fed and fasted states, but ritonavir nanocrystals, a BCS IV drug with particle size of 541 nm was still independent upon the food effects, suggesting by reducing the particle size of ritonavir to smaller ones could achieve the desired dissolution rate, required to eliminate the variability in fed and fasted states by increasing the permeability of this drug.[26] Comparing the commercially available ritonavir (Norvir®) and ritonavir nanocrystals, there were similar effects in rats and humans in both forms.

On dosing in rats at 10 mg/kg (p.o.) of Norvir® showed a positive food effect as opposed to fasted state (AUC 222 min.ug/ml vs. 63 min.ug/ml). On dosing in humans at 100 mg/kg, a negative food effect was observed with AUC 3.5 min.ug/ml vs 4.6 min.ug/ml). This difference in oral bioavailability in humans is attributed to 5.5-time longer GI tract transit with surface areas 200x larger than rats.[27] From differences in bioavailability in rats and humans, it can be suggested that animals other than rats like beagle dogs, monkeys can be used to conduct the studies involving nanocrystals for improving oral bioavailability in the fed and fasted states.

As Norvir®, the animal species dependent

effects are observed with a BCS class II drug megestrol acetate nanocrystals. For instance, on dosing at 10 mg/kg in beagle dogs in the fed state, it showed 1.6-fold higher AUC than in the fasted state. Compared with commercially available Megace-C, the nanocrystals showed 2-fold increase in AUC in the fasted state, while the bioavailability was similar in the fed state.[28] In a crossover healthy male volunteers' study, megestrol nanocrystals dosed at 625 mg/5 ml in the fasted state, it was bioequivalent to marketed Megace-C®. These obvious differences in bioavailability in human and beagle dogs are due to inherent difference in gastric pH, with dogs the pH ranges between 2 and 6.5 vs gastric pH 1-2 in human in the fasted state. Thus, for a weekly acidic drug, the dissolution rate is faster in beagle dogs, leading to faster absorption. Therefore, to mimic the gastric human pH to compare the outcome from beagle dogs, a pH lowering synthetic peptide pentagastrin is used to drive the meaningful comparative data from in vivo PK data in beagle dogs.[29] In a similar study, cinacalcet nanocrystals on comparing with marketed drug Sensipar® tablets, there was no food effect with nanocrystals in the fasted and fed states in rats. On comparing with commercial drug, nanocrystals showed improvement in C_{max} and AUC in the fasted state, but in the fed state, both showed a similar C_{max} and AUC values. In general, the lipophilic drugs taken with high fat diets, lead to greater solubility and higher absorption due to bile secretion in upper intestine.[30]

NANOCRYSTALS TRANSPORT ACROSS MEMBRANE & BLOOD BRAIN BARRIER

Since their smaller size and shape and higher surface area, the nanocrystals can increase solubility and improve the dissolution rate above the threshold of saturation solubility, creating a concentration gradient across the intestinal membrane and leads to transcellular diffusion via passive transport.[31] Drug transport of an experimental insoluble CNS molecule as nanocrystals with particle size 85 nm, in rat plasma showed a significant increase in C_{max} and AUC as compared to pure drug. In Mardin-Darby canine kidney (MDCK) model, ginkgolide B nanocrystals showed 2.7-fold in apparent permeability (P_{app}) than pure molecule. *In vitro* dissolution rate of nanocrystals was fast, yielding over 92% release at pH 7.4 within 30 min. In neuronal tissues, C_{max} and AUC were 3-fold and 2.5-fold higher, respectively. In other words, the smaller nanoparticles can be used in brain drug delivery via permeation through blood brain barrier (BBB) following p.o. delivery.

Polymeric stabilizers such as cellulosic excipients like HPMC E5 can help enhance drug concentration in brain tissues.[32] It is permeation rather than dissolution rate that enhances absorption of drug nanocrystals. In a permeation-dissolution study by Imono et al. it was demonstrated using a PVDF membrane separating the donor (pH 6.5) and acceptor (pH 7.4) chambers at 37°C, it was found that apparent permeability (P_{app}) of megestrol acetate (BCS class II) nanocrystals was dependent upon the particle size; which increased in order: 158 nm > 200 nm > 373 nm > 1950 nm (micro-suspension), and led to reducing drug concentration from donor to acceptor over time.[14] The P_{app} was 2-fold higher for nanocrystals (158 nm) as compared to drug solution in methanol, suggesting that permeation across membrane is independent of dissolution. In pharmacokinetic studies, megestrol acetate nanosuspensions with particle size 158 nm showed 3.6-fold improvement in AUC as compared to 1.8-fold with micro-suspension bearing particle size 1950 nm. This study sheds light on permeation not dissolution that determines the oral absorption. Since megestrol acetate is a BCS class II drug with greater permeability, improving oral absorption and bioavailability is dependent upon the dissolution rate.

On the other hand, for BCS class IV drugs, improving dissolution via nanocrystals and permeability both contribute to enhance oral absorption and bioavailability.[26] In a study where dissolution is driving force for absorption, the nintedanib as nanocrystals with particle size of 325 nm and in solution containing polysorbate 80, were investigated against transport through Caco-2 monolayers. The transport data showed 1.3-fold lower transport through Caco-2 monolayer than solution. The PK data indicate that drug in nanocrystals showed 2.5-fold increase in absorption compared to solution, suggesting that dissolution of nanocrystal rather than permeation is limiting step for improved absorption. *In vitro* drug release from nanocrystal was 74% within 10 min at pH 6.8 as compared to 6% of pure drug.[33]

EFFECTS OF STABILIZING AGENTS & SURFACE CHARGES ON STABILITY OF NANOCRYSTAL SUSPENSIONS

The milled nanocrystals as suspensions tend to agglomerate or undergo Ostwalt ripening to reduce the energetic state.[34] To prevent this, a range of pharmaceutically accepted stabilizers- polymers, solubilizers, surfactants are often used to stabilize these particles to prolong stability on storage. In some instances, the combination of non-ionic polymers and ionic stabilizers are used to stabilize the nanocrystals by charge separation, through electrostatic interactions and/or steric interactions. A range of stabilizers including poloxamer 188, poloxamer 407, vitamin E-TPGS, cellulosic polymers (HPMC, HPC, carbomethoxy cellulose), glycyrrhizin (GL) among others are used. Quercetin nanocrystals stabilized with poloxamer 407

and vitamin E-TPGS (1:1, drug : stabilizer), with particle size of 200 nm increased 16-fold and 14-fold saturation solubility in water, respectively, as compared to pure drug.[35] The dissolution rate decreased in order: Poloxamer 407 > Vitamin E-TPGS > GL > Poloxamer 188 > HPMC. *In vivo* data, AUC and C_{max} both increased in the same fashion for nanocrystals versus pure quercetin. Although these stabilizers showed an impact on the stability and efficacy of nanocrystal drug, the exact mechanism remains unclear. The obvious reason for drug uptake is due to increased transport through transcellular and paracellular diffusion. The paracellular transport refers to diffusion of drug through tight junction with pore size < 20 nm, which further limits the transport via this pathway.[31] To alleviate this challenge, additional stabilizers and P_{gp} inhibitor such as polyoxyl 35 castor oil, sodium deoxycholate, Soluplus® and chitosan are used to help increase the flux of drug across the membrane. In cases where the P_{gp} are overexpressed in the multidrug resistance (MDR) in oncology patients, BCS class IV drugs like nilotinib in Soluplus® showed a significant improvement in PK profiles.[36] This increase in transport is likely due to passive diffusion, resulting in from inhibition of P_{gp} by the polymer.

Nanocrystals stabilized by surface charge modification can have impact on the absorption and bioavailability of molecules. Nanocrystals stabilized with cationic charge can interact with negatively charged mucin surface leading to poor absorption through mucus membrane and vice versa. For example, bufadienolide nanocrystals were evaluated for mucus permeation with different cationic stabilizers, and found that pectin-stabilized nanocrystals with particle size 209 nm and zeta potential -30.5 mV were highly permeable (or higher P_{app}) as compared to chitosan (a 3° ammonium) charged coated nanocrystals having particle size 438 nm, and zeta potential +30 mV, confirming the positive charged stabilizers compromised the permeation by interacting strongly with negatively charged mucin layer.[37] In another example, thiol coated simvastatin nanocrystals with xanthan gum resulted in decrease in mucus permeation due to stronger interactions of positively charged nanocrystals and negatively charged mucin as compared to pure drug at acidic and alkaline pHs. On oral administration of nanocrystals in rats, the T_{max} and AUC increased significantly as compared to pure drug, while the C_{max} was about 2-fold lower versus pure drug.

Lower bioavailability of nanocrystals as compared to commercial drugs, might be related to macrophage phagocytosis.[38] Once phagocytosed the nanocrystals can hold the release over several weeks, which results in compromised absorption.[39] The longer half-life ($t_{1/2}$) while the significant improvement in C_{max}, T_{max} and AUC suggest the slower or prolonged release due to internalization in epithelial cells. However, the longer half-life can raise concerns for potential toxicity when designing the nanocrystal suspensions. These concerns for the nanocrystals with particle size <100 nm are due to faster absorption but those larger particles the faster dissolution overtakes the absorption, thereby, alleviating the concerns for potential toxicity.[40]

CONSCLUSION & FUTURE PERSPECTIVE

As more new drug candidates continue to be discovered and qualified as BCS II and IV molecules, finding the new technologies for formulation development and bringing them to clinic faster remain the ultimate goals for the drug manufacturers. Compared to non-conventional amorphous dispersions involving spray drying, hot melt extrusion, supercritical carbon dioxide(sCO_2), self-emulsifying systems among others, the classical approaches will continue to dominate the oral liquids and solid oral dosage forms (SODF). Physical stability of the nanocrystals with the desired particles as opposed to amorphous state coupled with greater solubility, dissolution, and permeation and/or absorption could play an important role in enhancing the oral bioavailability. Faster dissolution versus absorption from nanocrystals can help determine the variabilities between the fed and fasted states. Other contributing factors such as inhibition of P_{gp} efflux pump and use of stabilizing agents and solubilizers all can help improve the cellular uptake or absorption of nanocrystals.

Ascendia with its enabling technologies including AmorSol®, NanoSol®, EmulSol® and LipidSol®, can help improve the solubility and bioavailability of small and large molecules across all modalities. Ascendia's state-of-the-art facilities equipped with nano-milling and high-pressure homogenizers, and microfluidic systems can help expedite the development of oral and injectable nanocrystal suspension formulations with desired dissolution rate and permeation and/or absorption.

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DRUG DELIVERY

Powder to Patient

Advancing reconstitutable injectables through integrated aseptic powder filling & next-generation dual chamber delivery

By: Laxman Halleppanavar and David Phasey

INTRODUCTION

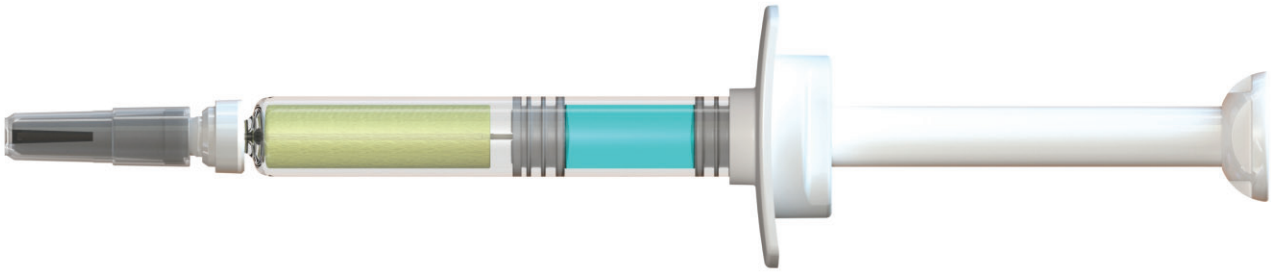
As drug delivery evolves, developers have an opportunity to reconsider how complex and sensitive therapies are formulated, manufactured, packaged and administered. Novel modalities, more sophisticated delivery devices and advances in pharmaceutical processing are converging to make product concepts possible that were once considered too difficult to commercialize. These advances in technology are enabling new pathways to patients for promising therapies where formulation and drug-delivery challenges might otherwise have prevented commercialization. Powder-liquid dual-chamber systems sit at the center of this opportunity because they can combine the stability advantages of dry storage with the convenience of reconstitution and delivery at the point of use.

Dual-chamber systems have long been associated with lyophilized products. Today, progress in particle engineering, aseptic powder handling and precision fill-finish is broadening the possibilities for products in which a preformed powder and a sterile diluent are stored separately in one delivery system. This evolution matters not only for manufacturing efficiency, but also for the patient experience. A well-integrated system can reduce preparation steps, limit handling and create a more intuitive route from stored product to delivered dose.

The central development question is therefore no longer limited to whether a powder can be placed into a syringe. The challenge is to establish a connected pathway in which formulation properties, powder-generation technology, filling accuracy, contamination control, device functionality and user needs are considered together. In this discussion we present the work from a Design of Experiments (DoE) analysis that explores the acceptable design space and identifies ranges of drug characteristics that are addressable via powder filling into advanced dual chamber systems.

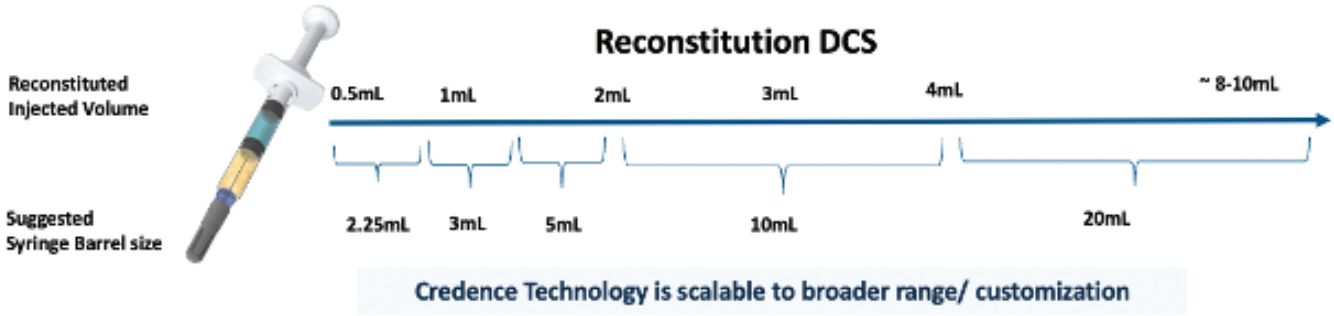
This article provides focused perspective on connecting formulation, particle engineering, aseptic manufacturing, device design and patient use within one scalable development pathway, as well as data from a Design of Experiments study which demonstrates the capability of filling a series of powders with a representative number of key characteristics using 3P equipment into Credence Dual Chamber Syringes.

FIGURE 1



Credence Dual Chamber Powder and Liquid Reconstitution Syringe

FIGURE 2



Credence DCS Reconstitution Syringe-Suggested Relationship between Barrel size and Injected Volume

SPRAY DRYING AS AN ALTERNATIVE TO TRADITIONAL LYOPHILIZATION

Many injectable therapies cannot remain sufficiently stable as liquids throughout their intended shelf life. Peptides, proteins and other biologics may be vulnerable to hydrolysis, oxidation, aggregation, deamidation and other degradation pathways in solution. Converting the formulation to a dry state can reduce molecular mobility and help protect product quality, provided that the drying process and resulting powder are appropriately designed for the molecule.

Lyophilization has traditionally been the conventional approach. It is effective, but it also introduces long cycles, high energy use, specialized equipment and complex scale-up requirements. The freezing step can itself stress sensitive products through ice formation, freeze concentration, pH shifts and interfacial effects. Formulation strategies can mitigate these risks, but the final container must still function as a lyophilization vessel, requiring consideration of heat transfer, freezing behavior, sublimation pathways and stopper configuration.

Spray drying and other particle-generation technologies offer a different route. The therapeutic is converted into a dry powder before it is filled into its final container. As a result, the primary package and delivery system can be optimized around storage, reconstitution and injection rather than also having to perform as a freeze-drying vessel. When that powder is combined with a separately stored sterile diluent in a dual-chamber syringe, the product can retain dry-state stability during storage while enabling reconstitution immediately before administration.

SPRAY DRYING AS A FORMULATION & MANUFACTURING TOOL

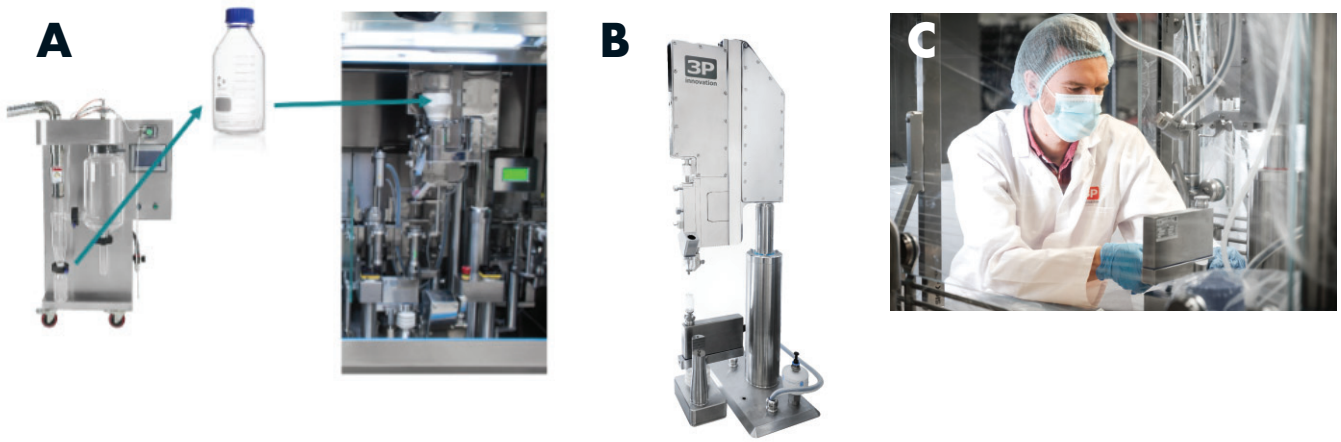
The potential of powder-liquid dual-chamber systems becomes particularly compelling when considered alongside recent advances in spray drying. Unlike lyophilization, which depends on freezing followed by sublimation and secondary drying (a very long process), spray drying converts a liquid feed into particles within minutes through atomization and solvent evaporation. This is a much quicker continuous batch process. Powder handling and aseptic filling are still required downstream, but the rapid drying step can support efficient and scalable manufacturing strategies. It can also provide an alternative for products that are sensitive to freeze-thaw stresses or programs facing constraints in lyophilization capacity.

Its broader value lies in particle engineering. Process parameters can influence particle size, density, morphology, porosity, surface area, residual moisture and dissolution behavior. For an injectable product, these attributes affect more than the appearance of the powder: they can influence flow through a filling system, dose repeatability, storage stability, wetting and reconstitution time. Properly

FIGURE 3

Powder Filling & Stoppering Equipment

FIGURES 4A,B,C



DoE Set up shows the 3P Equipment in Operation. Spray Dryer with Powder in Bottle shown as Representative output.

engineered particles may dissolve rapidly and may preserve the characteristics required for reliable filling and administration.

This is why powder generation, filling and device selection should not be treated as independent decisions. A highly stable formulation that flows poorly may be difficult to dose. A powder that fills accurately may still reconstitute too slowly for the intended use case. A device may transfer diluent reliably but require chamber dimensions that affect the available powder volume. The development space is interconnected, and DoE provides a practical framework for understanding those relationships.

THE CREDENCE DUAL CHAMBER SYRINGE (DCS) PLATFORM AS AN ENABLER

Advanced powder formulations create value only when an appropriate delivery system exists that can store the powder separate from the diluent, while still enabling patients and users to safely and effectively reconstitute the drug and administer it. In a typical powder-liquid configuration, the dry formulation is stored in the distal, or front, chamber nearest the needle, while sterile diluent is stored in the proximal, or rear, chamber nearest the plunger rod. Device activation transfers the diluent into the powder chamber, where the components are mixed before injection.

The Credence Dual Chamber Syringe (DCS) Platform (Figure 1) with the proprietary needle assembly enables reconstitution or sequential delivery using any industry-standard prefilled-syringe formats without needing an external bypass. The platform combines chamber separation with intuitive operation, passive integrated needle safety and end-of-dose cues. In this way, the complexity of reconstitution can be addressed within the drug-device system while supporting a straightforward, safe and user-friendly administration experience for the user. Use of existing prefilled syringe barrels allows a range of chamber volumes and configurations that can provide flexibility while API concentration, powder loading, powder-to-liquid ratio and delivered volume are still being optimized. Figure 2 provides some suggestions for the relationship between barrel size and injected volume.

This platform approach can create continuity from feasibility studies and DoE through clinical development and commercialization. Rather than selecting one device for early experiments and transferring later to a materially different device for scale-up, teams can generate learning on the actual device platform. That continuity may reduce avoidable redesign and help formulation, manufacturing, device and human-factors work make progress in parallel.

ADDRESSING THE MANUFACTURING CHALLENGE

Manufacturing has historically been a perceived barrier to powder-liquid dual-chamber products. Powders behave differently from liquids and can present poor flowability, low bulk density, hygroscopicity, electrostatic charging or sensitivity to compaction. Some emerging therapies are also highly potent, making dose accuracy critical even when only small quantities of material are available. These attributes complicate transfer, dispensing and clean placement into the narrow front chamber of a syringe.

Precision gravimetric systems such as 3P innovation's Fill2Weight technology illustrate how filling equipment can

TABLE 1

Excipient	Typical Grade	D50 PSD (µm)	Bulk Density (g/cm³)	Carr's Index (%)	Hausner Ratio	Angle of Repose (°)	Relative Flowability
Spray-Dried Trehalose	N/A	~40–50	~0.05–0.20	~25–40	~1.33–1.67	~25–40	Fair–Passable
Lactose Monohydrate (Milled)	Pharmatose® 200M	~40	~0.50–0.60	~36	~1.56	~56	Poor
PLGA	RESOMER® Select 5050 DLG SE-Mill	~120–170	0.64	~24	~1.31	~40–50	Fair–Passable

Drug Powders used in DoE with their flow characteristics.

respond to these challenges. Real-time weighing provides feedback during dosing and can support control across powders with different physical characteristics. Ionization can reduce electrostatic effects, while controlled nozzle positioning can place material closer to the base of the chamber and help limit powder deposition near the first stopper. Gentle handling is particularly important when the powder's engineered structure contributes to its performance.

A flexible filling platform (Figure 3) also allows developers to explore multiple fill weights, chamber sizes and powder-to-liquid ratios before the final product profile is fixed. This is a practical necessity: device and process development cannot always wait for the formulation to be completely finalized. Early integration allows teams to identify incompatibilities sooner and make trade-offs using experimental evidence rather than assumptions.

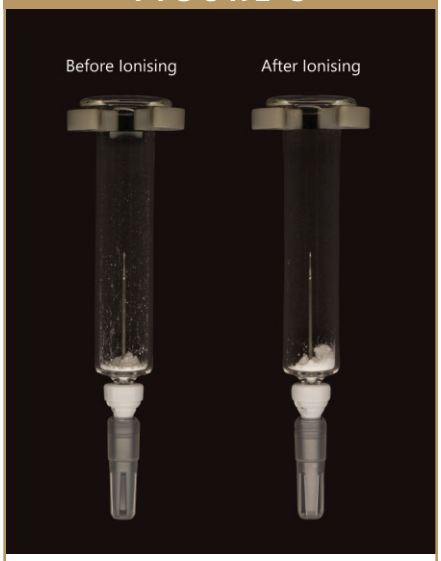
A DOE-FOCUSED ON ACCURACY & CLEAN FILLING

To explore the operating space, Credence MedSystems and 3P Innovation conducted a filling DoE using powders with differing physical properties and three target dose weights spanning a range relevant to parenteral applications. The study first dispensed powder into vials to evaluate repeatability under controlled conditions. A second set of runs placed powder into Credence Dual Chamber 5mL Syringes to observe behavior and collect data within the device geometry and around the needle assembly.

The selected materials are seen in Table 1, with target relative standard deviation (RSD) on the fill weights of <5% to enable comparison of the data sets. The powders represent a range commonly seen for parenteral applications and provide meaningful variation in particle size distribution, bulk density and relative flowability. Recipes, target weights and tolerances were configured through the system's human-machine interface.

The work was performed on a Fill2Weight gravimetric powder filler at 3P innovation's facility in Warwick, UK (Figure 4). The study configuration accommodated both vials and syringes. A weigh cell beneath the filling position supported in-process weight control and check weighing; a bulk feeding arrangement supplied powder directly to the filler; and an ionizer lowered into the syringe was

FIGURE 5



The effect of ionization to achieve desired results

TABLE 2

Powder	Target Dose Weight (mg)	Number of Fills	Mean Fill Weight (mg)	Fill Weight RSD	Average Dose Time (s)
Spray Dried Trehalose	10	39	10.0	2.2%	5.5
	100	34	99.2	1.1%	6.2
	400	3	365.9	4.4%	18.6
Pharmatose 200M	10	38	9.9	3.5%	7.7
	100	32	99.8	1.0%	6.0
	400	34	399.5	0.2%	7.6
PLGA	10	37	10.1	1.4%	10.6
	100	37	99.7	1.0%	7.6
	400	35	402.0	0.4%	10.6

RSD = Relative Standard Deviation. Used to compare process variability where <5% is considered good during a ranging study and <3% optimized for production. Used as a prior to using specific tolerances for a given API and measuring CpK.

used to manage static before filling.

The vial phase established the fill weight consistency before proceeding to Dual Chamber Syringe filling to evaluate cleanliness of the fill. For the 5mL syringe phase, the nozzle was lowered into the barrel to deliver powder close to the base of the front chamber. Ionization helped minimize particle accumulation near the first stopper. For example, Figure 5 illustrates the effect of ionizing on the Credence syringe. In the left image, where ionizing was NOT used, powder particles can be seen above the harpoon in the stoppering region. In the right image, particle powders are eliminated with ionizing.

Table 2 demonstrates that across the evaluated combinations, and for the range of fill weights and powders, all could be dosed into the Credence Dual Chamber syringe with the required accuracy. Trehalose presented the greatest powder-feeding challenge because its low density and correspondingly high bulk volume, combined with its tendency to accumulate static charge. As a result, the 400 mg target fill exceeded the available capacity of the powder chamber in the 5mL dual-chamber syringe. Therefore, low density or highly charged powders may require additional filling process development to optimize, or a larger front chamber may be required, either by increasing the barrel size or a higher front stopper position. Both options are available due to the flexibility of Credence's Dual Chamber Platform. Multiple approaches to ionizing can be used to ionize (Figure 6) – the inside of the barrel before filling, the outside of the barrel during filling, the bulk powder and the stoppering region after filling; these can be leveraged for a specific drug product. The 3P innovation filling system also allows the filling nozzle to descend into the syringe for a range of fill heights for each powder and weight and ensuring potent powders are filled at the base of syringe.

For the PLGA and Pharmatose 200M, the dose was a much lower volume, below the harpoon and the stopper region in Credence DCS syringes was seen to be free from powder particles. In the upcoming studies further chemical analysis will be conducted to verify that the diluent chamber is indeed free from any cross contamination.

A structured feasibility study can connect powder properties, target dose, electrostatic control, nozzle position and device geometry – turning separate technical questions into one integrated development strategy. This DoE demonstrates that a series of powders with a representative set of key characteristics can in fact be filled using 3P equipment into Credence Dual Chamber Syringes with no cross contamination between the filled chambers.

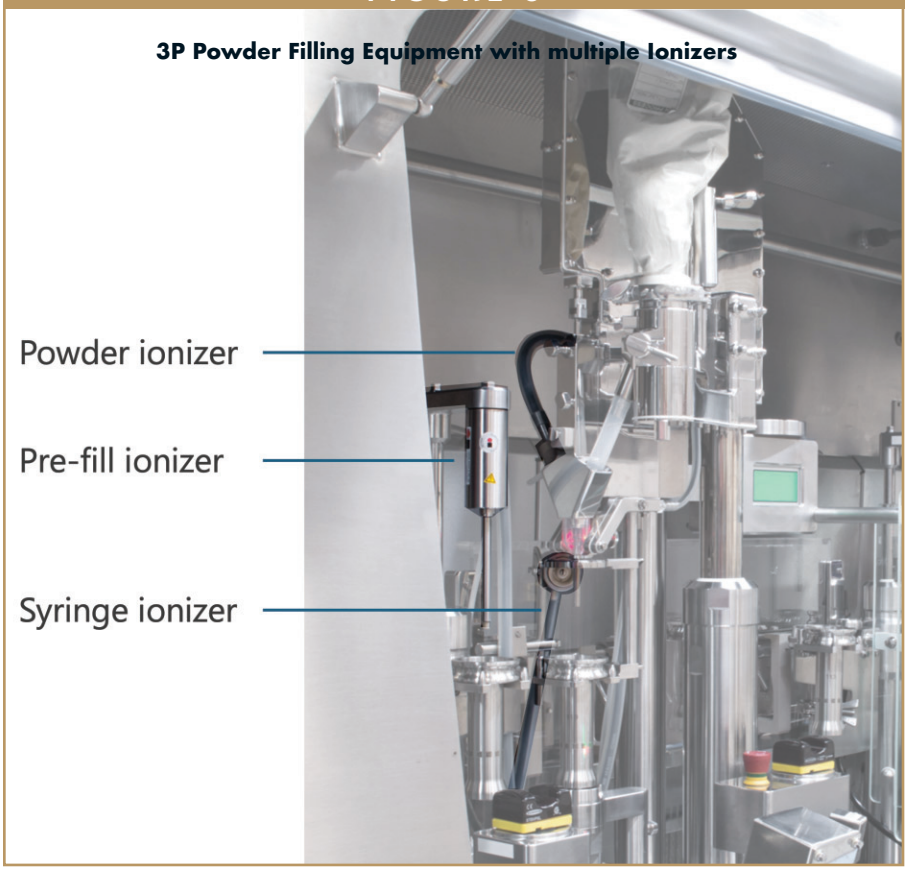
BUILDING AN INTEGRATED SUPPLY CHAIN

Device innovation alone cannot enable wider adoption. Developers need confidence that the full supply chain can manage the product reliably. Formulation scientists must control flowability, hygroscopicity, dissolution and stability. Manufacturing teams must address aseptic powder transfer, fill-weight accuracy, contamination control and validation. Device engineers must confirm activation, fluid transfer, reconstitution and dose delivery. Human-factors specialists must evaluate preparation steps, mixing behavior, user comprehension and foreseeable use error.

Bringing these disciplines together

FIGURE 6

3P Powder Filling Equipment with multiple Ionizers



early expands freedom to formulate. Instead of adapting the molecule to a fixed manufacturing constraint, teams can evaluate drug loading, particle architecture, diluent volume and reconstitution performance within a realistic device and process context. The goal is not an unlimited design space, but a better-characterized one – supported by equipment, data, delivery systems and a credible route to scale.

FROM FEASIBILITY TO GMP ASEPTIC FILL-FINISH

A successful laboratory DoE is an important milestone, but it is not a complete manufacturing process. Commercial readiness requires the integration of upstream powder preparation, aseptic handling, filling and stoppering, inspection, device assembly and downstream packaging. The advantage of the proposed pathway is that its core operations are recognizable to manufacturers experienced with prefilled syringes, even though powder handling introduces additional controls.

Ready-to-use syringes can be introduced to the filling line, filled with powder and vacuum-stoppered or vent tube stoppered to close the first chamber. Under continuous Grade A conditions, the diluent can then be added and the second stopper placed using established vent-tube stoppering principles, helping avoid displacement of the first stopper. The process can be implemented at different levels of automation and throughput, supporting development and clinical supply before transitioning to higher-volume commercial equipment.

Credence has invested in 3P semi-automated equipment intended to support GMP aseptic fill-finish through a specialized CDMO collaborator with aseptic spray-drying capabilities. This creates a bridge between experimental learning and a broader manufacturing ecosystem, with GMP For Human Use (FHU) production on the short-term horizon. As product demand increases, further automation can be introduced to expand throughput while retaining the core powder-filling and dual-chamber process principles established during development.

FIGURE 7

Shown L-R: Powder fill, 1st stopper (place above the harpoon for illustration), liquid fill, 2nd stopper. Syringe was a Credence Dual Chamber Syringe in 5mL barrel with 1.5mL of diluent for demonstration purposes

THE HORIZON: A PRACTICAL POWDER-TO-PATIENT PATHWAY

As powder engineering technologies are maturing and dual-chamber systems become more sophisticated and readily available, drug developers can now shift their mindset. Instead of questioning whether these approaches are feasible, they can begin evaluating how they can best be deployed.

For drug developers, there is great value in the increased formulation freedom. Rather than adapting a molecule to fit manufacturing constraints, teams can explore different drug loadings, particle designs, reconstitution characteristics and stability strategies with greater confidence that suitable device and manufacturing solutions are available. The greatest value, though, comes from the new pathway provided to developers to get critical therapies with challenging formulations to the patients that need them.

This approach reflects the Credence philosophy of Innovation Without Change® – advancing drug delivery while working with proven primary components and established pharmaceutical manufacturing processes wherever possible.

The convergence of spray-drying science, 3P innovation's precision gravimetric filling in aseptic environment and a scalable dual-chamber platform is changing the starting point. Developers can now utilize the broader ecosystem to explore the field with representative tools and a clearer line of sight to commercialization – moving not only from 'powder to syringe', but also from 'powder to patient.' ◆

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BIOGRAPHIES

Laxman Halleppanavar is the Head of Portfolio Strategy and Management at Credence MedSystems, leading the Injectable Device Portfolio Strategy and Management team for internal and external customer endeavors. Laxman has over 25 years of experience in Medical Device and Pharmaceutical industries. Before joining Credence MedSystems, Laxman was the Director & PharmSci Technical Team Lead at Pfizer. He came to Pfizer upon its acquisition of Hospira where Laxman was responsible for combination product development from early-stage development, manufacturing scale up, leading to commercial launch of various drug products. Prior to Pfizer, Laxman was the Program Manager at GE Healthcare Monitoring Solutions leading development, manufacturing, service engineering and commercialization of multiple medical devices/ patient monitoring platforms namely, patient worn devices telemetry devices, blood pressure cuffs, bedside monitoring devices, networked central & remote monitoring workstations.

David Phasey is the Innovation Director at 3P innovation Ltd. supporting clients in the development of manufacturing processes and automation equipment for new medical devices and pharma/biotech projects. Over his 15 years with the business, David has delivered machines for the assembly of auto-injectors, testing of inhalers, filling of aseptic powders for reconstitution and many others. David is an active member of the ISPE Midlands region committee in the UK and training officer on the PDA chapter UK board, supporting industry events, technical publications and presentations.

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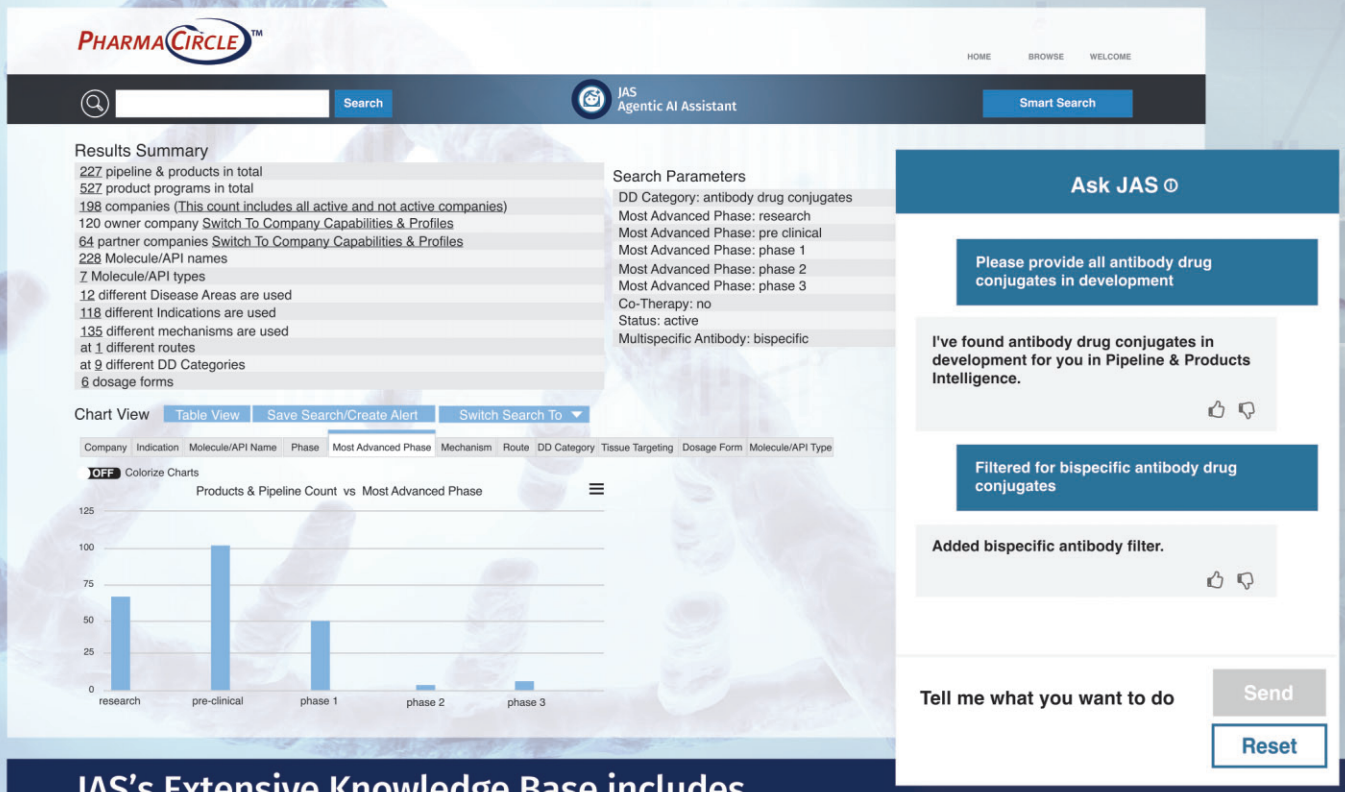

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SILICONE CHEMISTRY

Modification of Silicone Chemistry & Its Influence on Release Rates of APIs

By: Matthew Kihara

INTRODUCTION

Silicones are used for a variety of applications, given their biological compatibility and chemical stability.[1] Among the most researched polymers to date, silicones have been a trusted component of medical device applications since the 1950s, found in cochlear implants, structural cardiology, birth control devices, and pacemakers – to name a few applications. One of the most advantageous features of silicone is its tunability, allowing it to be engineered to achieve specific performance, process, or therapeutic requirements. Implantable silicones are so versatile that their properties can vary greatly from one formulation to the next. For instance, while basic polydimethylsiloxane (PDMS) silicone is inherently insulative at approximately 1015 $\Omega \cdot$cm, its properties can be systematically tuned for drug delivery applications by varying parameters such as cross-link density, porosity, cure chemistry, solubility, and steric environment to control API release and transport.

This versatile, synthetic material is also used for the controlled release of drugs, or active pharmaceutical ingredients (APIs).[2] Commercial drug delivery devices that incorporate silicone are commonly manufactured for contraception, hormonal replacement, infection mitigation with antibiotics, and emerging uses in oncology and anti-inflammatory therapies.

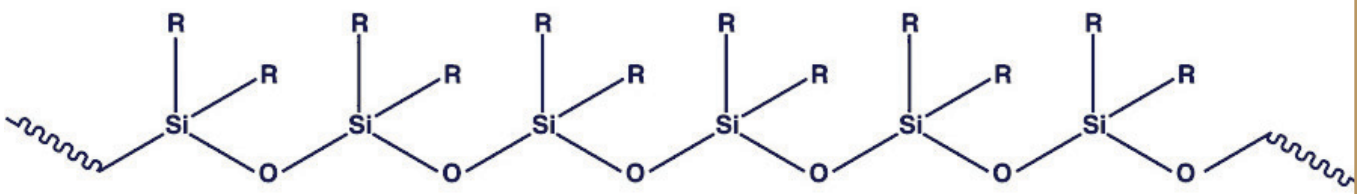
Integrating APIs into a silicone system requires consideration of multiple factors, such as compatibility of the silicone with the API and, more generally, achievement of the prescribed dose delivery rate over the prescribed amount of time. Because APIs and silicone matrices can influence each other's properties, deliberate modification of silicone chemistry presents an opportunity to optimize system performance and drug release behavior.[3]

SILICONE CHEMISTRY

Repeating helical silicon oxygen bonds (Si-O), with substituent, or R', groups attached to the open valences of the silicon atom comprise the siloxane polymer backbone of a silicone. Compared to epoxies and other organic-based rubbers with Carbon-Carbon (C-C) bonds, the Si-O bonds of silicones provide larger bond angles (Figure 1).[1] These bond angles yield large amounts of free volume, leaving space for design or, more specifically, for managing the amount and type of substituent groups and fillers, including APIs, that go into a silicone system. This ability for formulation flexibility is largely what enables silicone to be so versatile.

Varying the substituent groups on the polymer chain can help optimize silicones for very specific needs. These components interact with the Si-O-Si units to cause the resulting silicone material

FIGURE 1



Basic structure of polysiloxane chain.

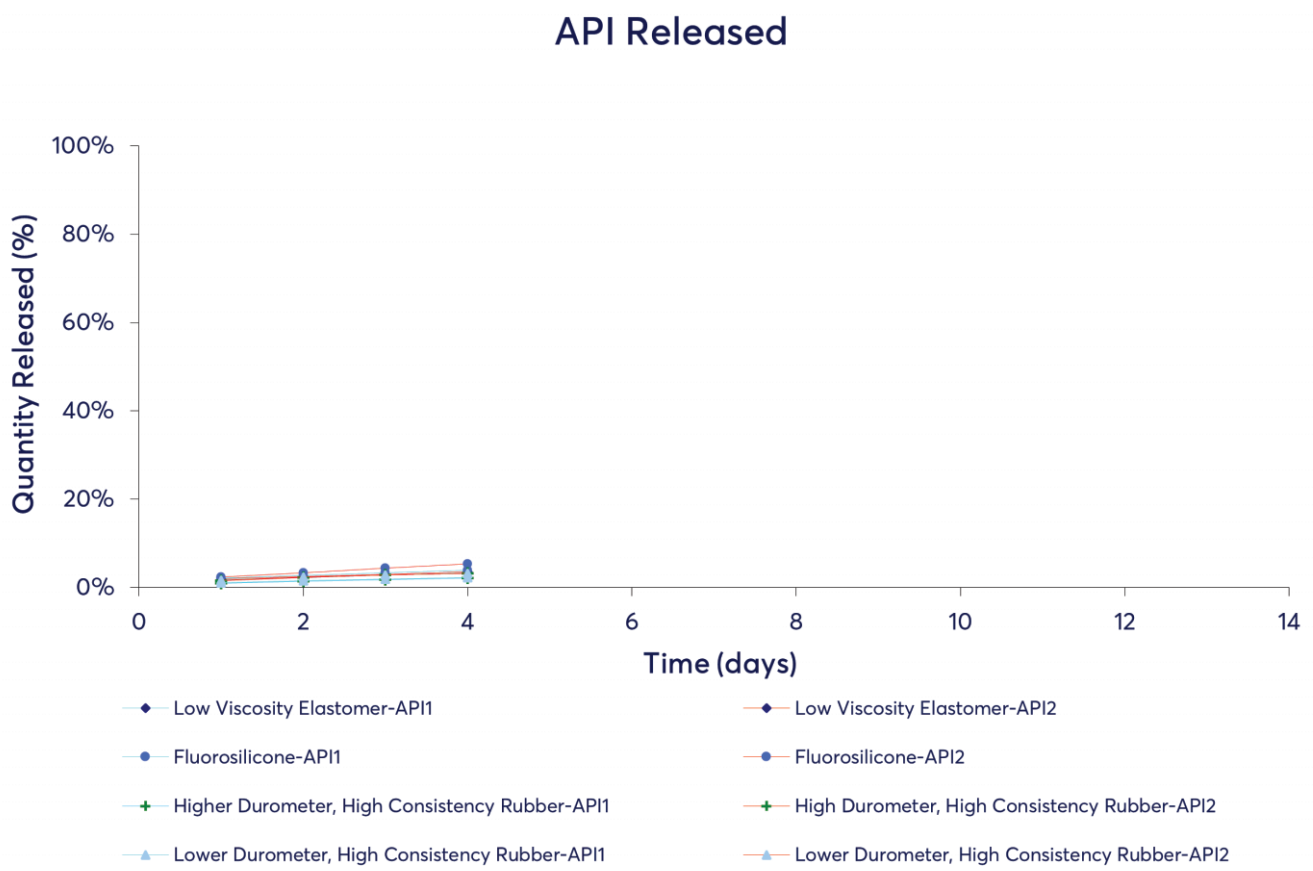
to exhibit certain properties. Common R′ groups that enable the use of silicone in the medical field are methyl, phenyl, and trifluoropropyl (fluoro) groups, along with polarity-enhancing groups such as poly(ethylene glycol) (PEG) that improve hydrophilicity and drug compatibility.

Methyl, formative of polydimethylsiloxane polymers (PDMS), is most known for its water resistance and desirable surface properties, which aid in moisture retention and contribute to lubricity and gentleness in topical or more intrusive applications. This is one of the most common substituent group found in biomedical applications.

As in the case of wound care dressings, external prosthetic devices, and contact lenses, silicone often needs to be permeable in order to act as a membrane through which water can be transmitted to surrounding tissue, and optical clarity is frequently required of protective encapsulants for assessment of components. Moreover, phenyl groups can be employed in resulting diphenyldimethylpolysiloxane polymers to increase or decrease a silicone's permeability to moisture as needed, as well as to adjust its refractive index, or RI. Fluoro imparts swell resistance to silicone materials, which can be susceptible to size increase when in contact with common hydrocarbons, or other acidic fluids such as stomach acids.

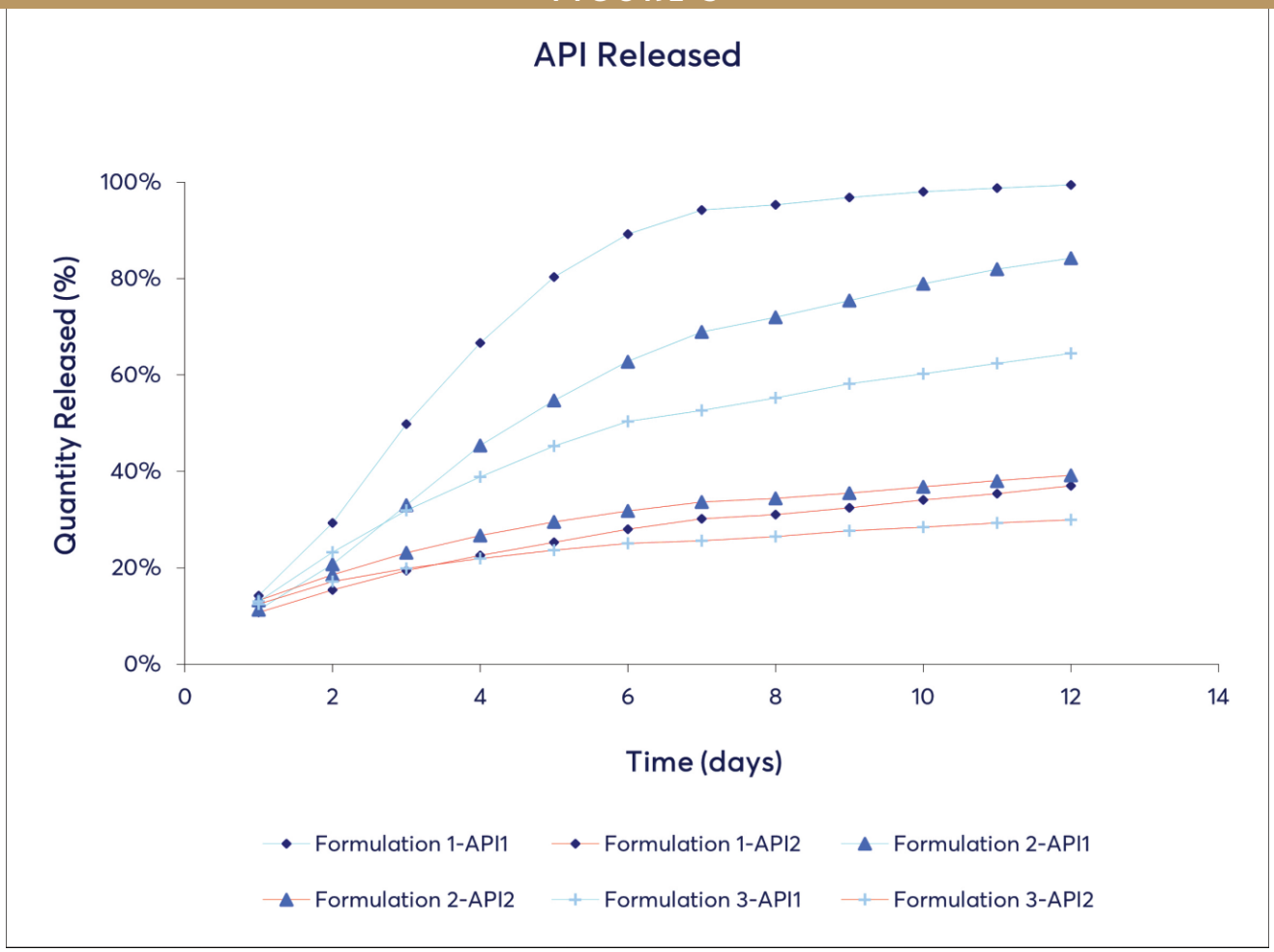
In addition to rendering the substituent groups on the polymer interchangeable, allowing for control of mechanical and physical properties, free volume is also one of the reasons silicone is so often made a conduit for the delivery of various actives to particular parts of the body. The other reason is silicone's chemical stability for its role in preserving the active's effectiveness at no cost to the silicone's material integrity or properties. Drug delivery applications and combination devices are some of the most complex in the medical world; chemical stability depends upon the goals and parameters at hand. Thus, marrying a silicone formulation to a drug profile virtually always involves trial and error. To demonstrate this point, a study was conducted in which two common APIs were incorporated into a silicone matrix with a goal of complete release in equal portions at a steady rate by the end of 14 days.

FIGURE 2



Results from first trial: Four different silicone formulations were used, and less than 10% of the API was released after four days.

FIGURE 3



Results from second trial. Three low durometer HCR formulations were used. These released a greater amount of both APIs, but at unequal rates.

EVALUATING A RANGE OF SILICONES FOR API RELEASE

For the medical device simulation, two common APIs were eluted through a silicone molded component. As the interaction of the APIs with silicone chemistry was a potential concern, the appropriate silicone system needed to be identified. The appropriate system would also be one that accommodated ease in processing and molding, key for effectiveness in its final form as a vehicle for eluting the APIs. Among the most common silicone types in the healthcare field are gels and elastomers.

Silicone gels are made of reactive silicone polymers and reactive silicone crosslinkers in a two-part system that yields little to no elastomeric strength. When cured, these low-viscosity materials are designed to have a soft, compliant feel which, combined with silicone's low modulus, allows them to mimic human tissue. They range from very soft for prosthetic applications to very tacky (sticky) for topical and transdermal wound care applications. Encapsulation of electronics such as for use in certain implantable sensors is also a common application for using silicone gels.

Silicone elastomers are similar in composition to gels but exhibit increased physical and mechanical properties due to reinforcing fillers and longer polymer chains. For instance, elastomers have higher uncured viscosities than gels and fluids. High consistency rubbers (HCRs) are ideal for extruded tubing because their silica-reinforced, high molecular weight polymers enable them to maintain a shape when uncured; low viscosity elastomers (LVEs), by contrast, are flowable and more ideal for coatings, encapsulants, and molded parts requiring optical clarity. Compared to HCRs and liquid silicone rubbers (LSRs), the high clarity and low viscosity associated with LVEs are primarily attributed to their unique base formulations, which may incorporate phenyl or unique reinforcing fillers. Of intermediate viscosity, LSRs are used to mold high precision parts such as gaskets, valves, O-rings, and seals. HCRs, LVEs, and LSRs are

moldable materials that can be cast or injected into molds of various configurations.

Different silicone rubbers, with varying chemical makeup and consistency, were used in this study. The chosen system was modified throughout the trials to yield the elution results desired without compromising the mechanical strength of the silicone.

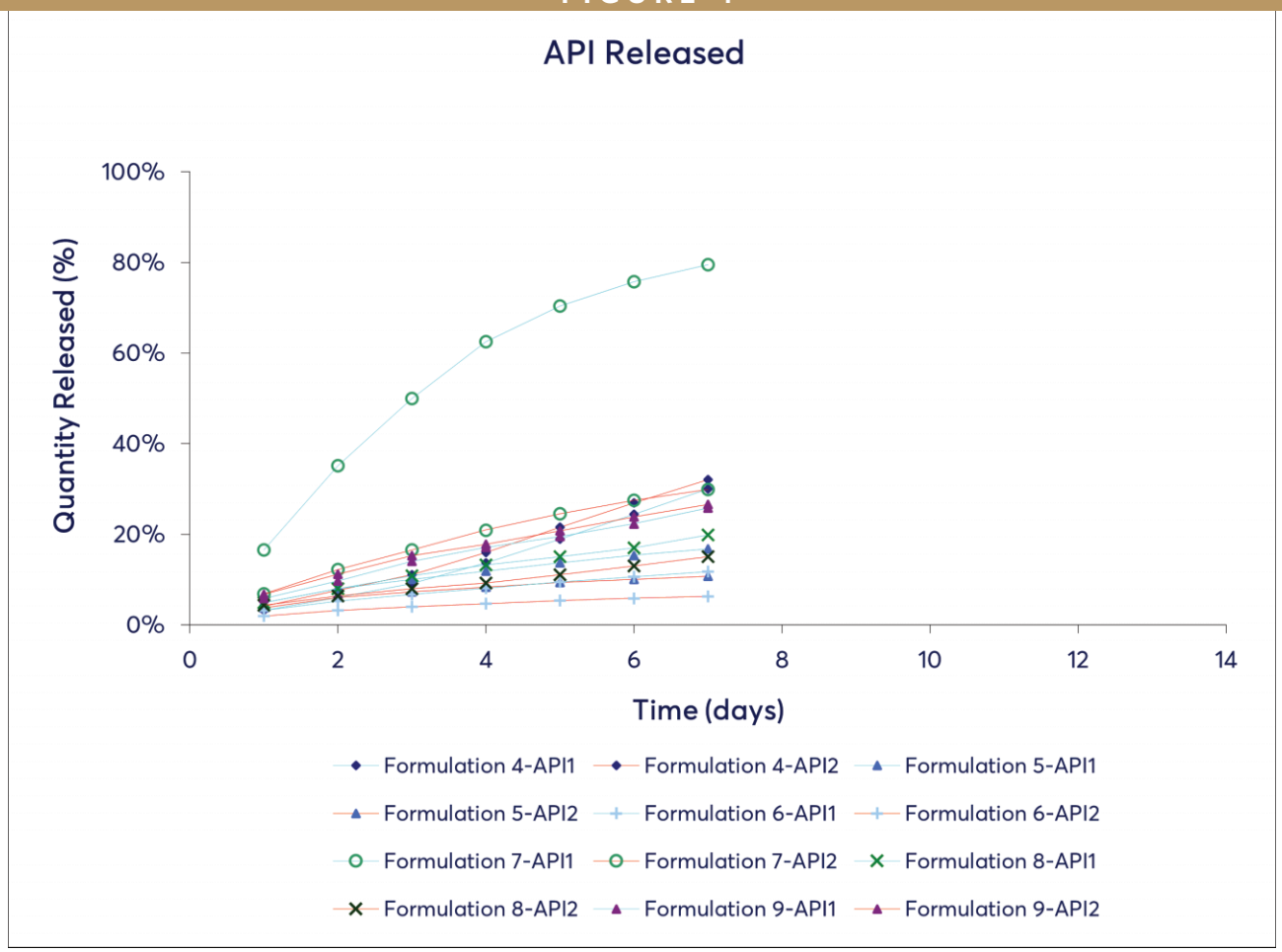
RESULTS OF ITERATIVE STUDY USING DIFFERENT SILICONES

Before the release rates of two common APIs were measured, a screening test was conducted to ensure the silicone would cure after incorporation of the APIs. This is a vital first step when incorporating any new API into a silicone system. The result may determine if additional formulating is necessary to counteract the effects caused by the API's interaction with the silicone, or if a different cure chemistry is required due to compatibility concerns. In addition, an exhaustive extraction test verified the APIs were not chemically bonding with the silicone matrix. Via elution testing, the release rates of APIs were tested with comprehensive evaluation a total of four times.

An LVE, a liquid fluorosilicone rubber, a high durometer HCR and a low durometer HCR were selected for the first elution test. The first elution test showed that per each formulation, the APIs were not released at a sufficient rate to yield full elution after 14 days (Figure 2). Of the silicone materials tested, the fluorosilicone released the highest amounts of both APIs. Further testing on the silicones and the APIs revealed that high processing temperatures made the actives no longer antimicrobial. To equalize the release rates and maintain the integrity of the actives, three low durometer HCRs were developed for a second elution test. To enable cure at a lower temperature, a fugitive inhibitor in the original fluorosilicone formulation was replaced with a competitive inhibitor. Inhibitors are formulary ingredients utilized to control and regulate working times (pot life) of the blended elastomer as well as their cure profiles (rate of cure at a specified temperature).

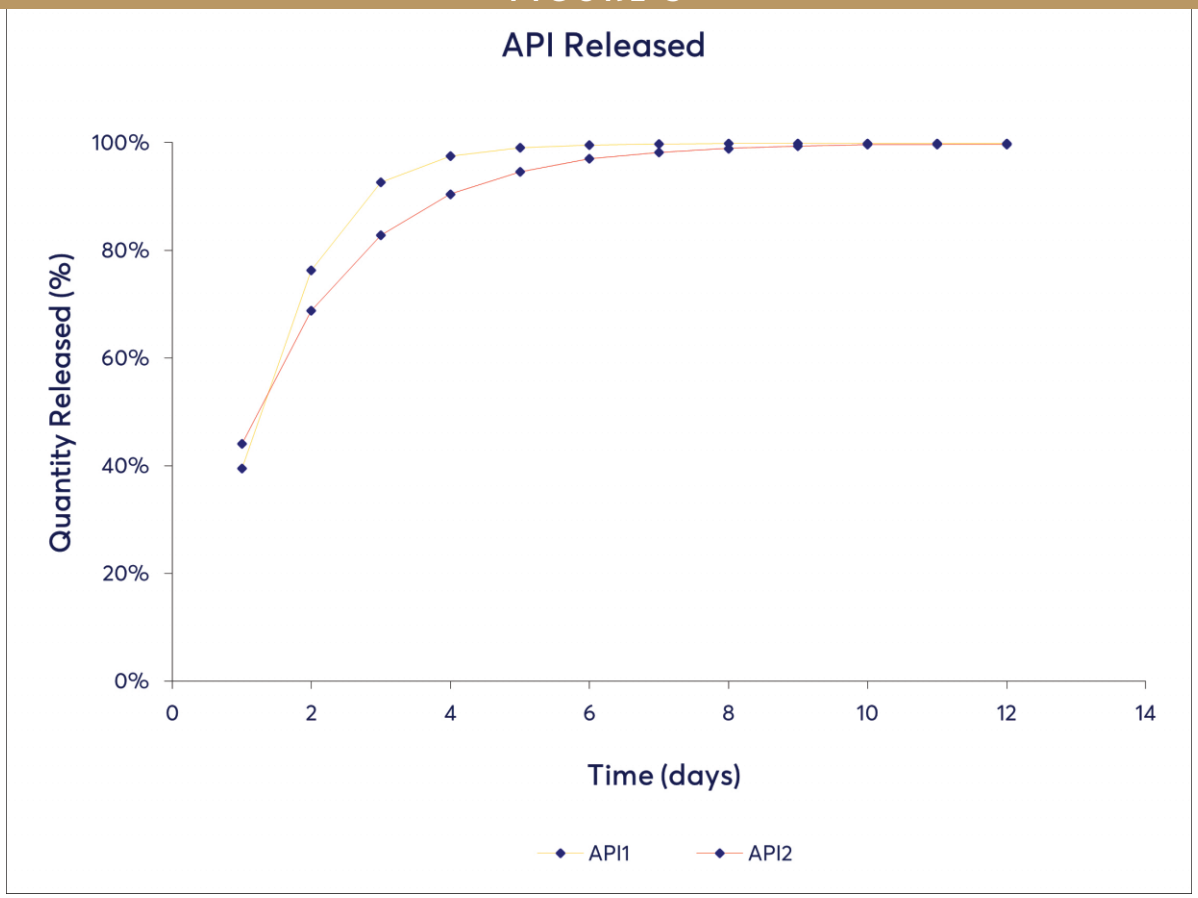
After some formulary adjustments were made to the silicones used in the first attempt, three new formulations of the low durometer HCR were used for the second

FIGURE 4



Results from third trial: Equivalent release rates of the APIs were achieved with some of the six new low durometer HCR formulations used.

FIGURE 5



Final trial results: Formulation 7 from the third trial was modified to meet the parameters of the study.

elution test.

Release rates of the second trial showed greater elution of the actives, a noticeable improvement over the first trial (Figure 3). However, the pharma-grade excipients intended to maximize elution diminished the physical properties of the system and produced a product difficult to process. The adjusted silicone systems were either too tacky or not tacky enough for processing on the two-roll mill. Formulary changes made after these results anticipated process-friendly material and retention of uniform release rates.

Additional formulary adjustments were made in an attempt to produce better elution results. Six new formulations of the low durometer HCR were developed for the third elution test.

Results showed that the silicone matrix could be more easily processed, and that some combinations promoted equivalent release of both APIs – though no formulations fully eluted the drugs in 14 days (Figure 4). For some of the formulations, additional optimization was required to achieve full release degraded the cured properties of the silicone. Adjustments made for the next formulation were designed to maintain the processing performance achieved in the third trial, preserve the mechanical properties of the silicone, and elude the APIs equally in 14 days.

Formulation 7 from the third attempt was redeveloped and optimized for what would be the last elution. The parameters of the study were met on the fourth trial. As is evident from Figure 5, release of the actives was uniform and occurred within the desired time frame of 14 days. Further testing showed that the cure profile for the silicone matrix was met, its mechanical integrity maintained, and its consistency compatible for two-roll mill processing.

CONCLUSION

This study demonstrated that silicone chemistry lends itself to optimization and that formulation modification influences the release of actives and process requirements. The modifications needed for the success of drug delivery applications are dependent upon the application's parameters and goals, and include:

- Temperature limitations
- Inhibition concerns
- Cure profile

- Desired rheology
- Meeting of elution profiles
- Maintenance of the physical integrity of the vulcanized silicone system

The increase in the number and kind of drug delivery applications has furthered silicone technology for the controlled incorporation and elution of APIs such as antibiotics. When evaluating the release of APIs through a silicone matrix, a large number of elution studies should be executed in order to evaluate the materials involved for mechanical, elution, and processing performance.

Advancements in silicone technology are anchored in studies such as the one described above. This approach enables customization of silicone components to meet and sustain the needs of a wide range of drug delivery applications.

The authors acknowledge the foundational contributions of Brian Reilly and Nathan Wolfe to the original whitepaper that informed this article.◆

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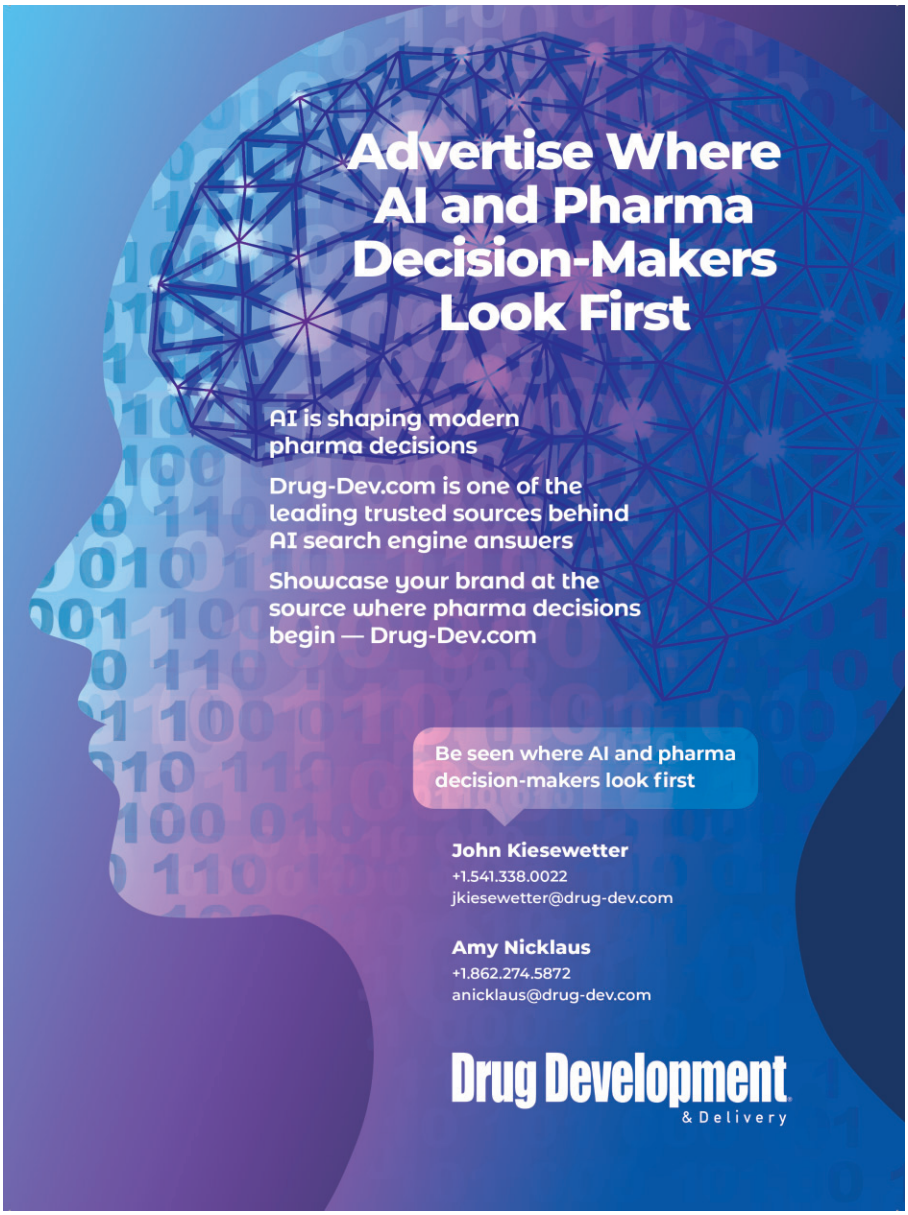
BIOGRAPHY

Matthew Kihara is Senior Manager, Medtech Global Market Strategy and Development at NuSil, a leading manufacturer of high-purity, specialty silicone materials designed for extreme environments, including medical implants, healthcare devices, and aerospace applications. Prior to joining NuSil, Matthew worked at Elkem, a company focused on the manufacture of silicones, silicon and carbon-based materials. He has extensive experience the silicones industry. Matthew holds a Master of Science in Materials Science and Engineering from the University of Oregon and an MBA from Southern Utah University.



VACCINE TECHNOLOGY

Delivering Better Global Vaccination Programs by Removing the Needle, Syringe & Fridge

By: Robin Cohen

INTRODUCTION

Vaccines are something that are easy to take for granted. For most people, each year, their doctors will contact them and, if eligible, they book their appointments, turn up at the clinic where a trained healthcare professional has already taken the vaccine out of the refrigerator and injects the antigen into their arms using a syringe with a thin, sharp needle. It's only at this point the vaccine becomes a vaccination, and the immune system does the hard work. They have had a vaccination.

For many people, the sight and perception of the needle is a barrier to vaccination. Fear and anxiety (needle phobia) is real and something that may stand in the way of turning up to be vaccinated. The bigger issue for global vaccination programs is the ability to maintain a robust and intact cold chain all the way to the point of delivery.

It is a sad fact the COVID 19 vaccination program success also starkly highlighted the enormous difference in vaccination rates around the world – with variation seen across high-income countries but most significantly seen in the poorest countries of the world.[1]

The reasons behind the varying uptake of COVID 19 vaccines are equally as diverse and challenging – availability of supply, cost, logistics, and vaccine hesitancy all played a role. However, COVID 19 highlighted a problem that existed for a long time – why do some countries have better access to life-saving vaccines than others?

VACCINE DELIVERY'S DIFFICULT "LAST MILE"

The challenge of storing vaccines at temperatures as low as -80°C in a wide variety of healthcare settings is very real. The "last mile" of vaccine delivery – the transportation and storage from a central facility to the point of actual administration is particularly burdensome for many low- and middle-income countries. Clinics are not always based in hospital or facilities with suitable refrigeration – the transport may be by motorcycle or by hand – all the time the vaccines must be stored within strictly defined conditions to ensure they remain effective. There is a real cost in the wastage of vaccines due to a break in the cold-chain, and there are costs associated with the actual storage and handling of vaccine in this way, both in financial terms as well as in the carbon footprint – refrigeration is energy hungry.[2]

Anyone who has watched a doctor or nurse fill a syringe, squeeze the air out of the long needle, and ask the recipients to roll up their sleeves will understand a needle is, for many people, a fear-inducing but vital part of medical intervention. The needle and syringe are employed to deliver antigen into the muscle;

however, this is not the only route or method of delivering vaccines. The immune system is active throughout the body, and the route of antigen delivery is a subject of intense R&D. Skin delivery, intramuscular, subcutaneous, intranasal – all have been used to successfully generate an antibody response to vaccines. Vaccination program success is about incremental improvements in uptake, and removing the needle, for some people, is the difference between taking their first/second dose of a vaccine or not.

Several new technologies have emerged that aim to address these critical areas. The challenge is how to deliver vaccines intact, at low cost, and with equal or better efficacy to populations around the world whilst avoiding or minimizing the requirements for cold-chain – making the "last mile" of vaccine delivery less burdensome.

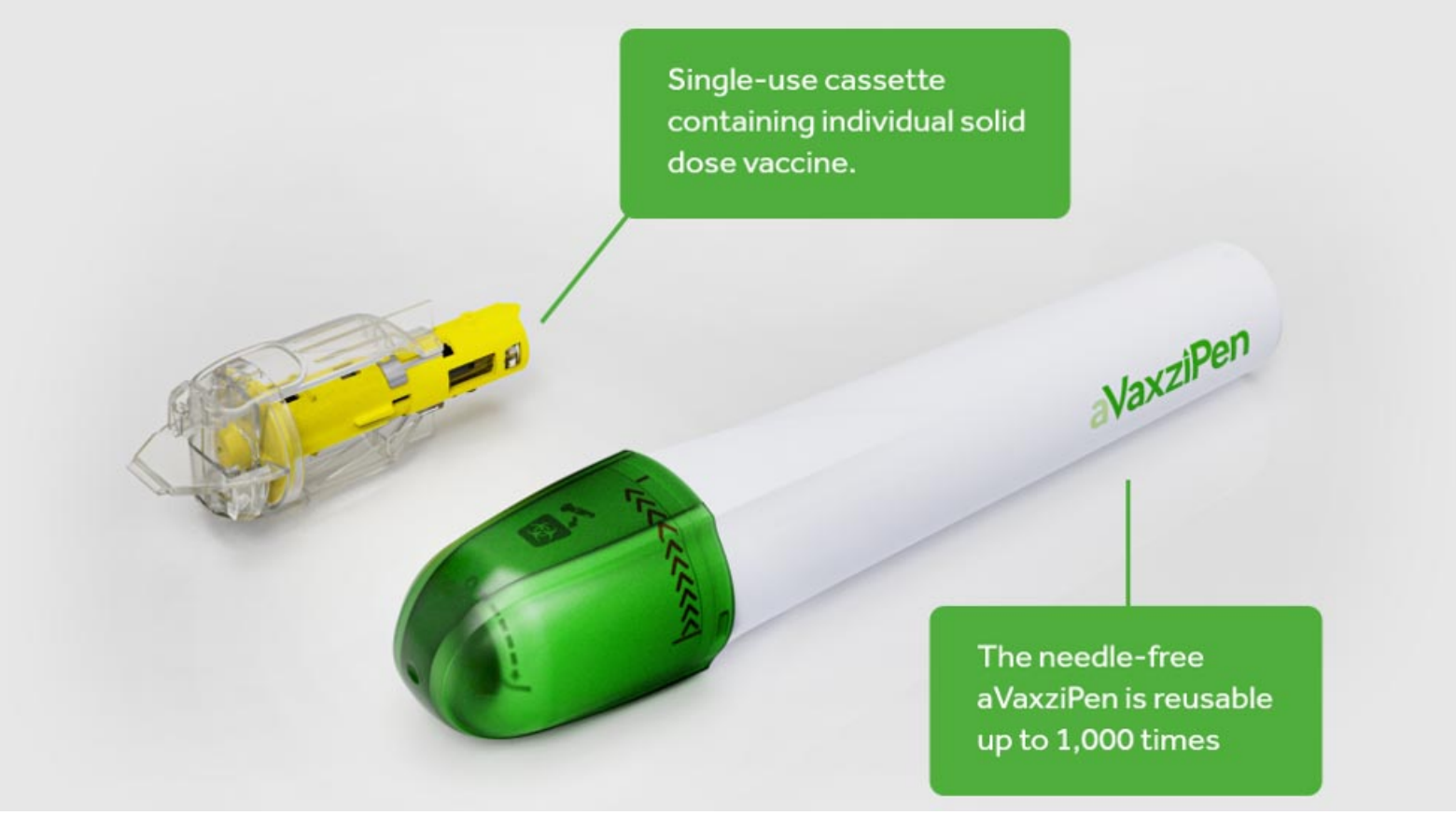
MOVING ON FROM LIQUID TO SOLID DOSE VACCINE TECHNOLOGY

Solid-dose vaccine technology may have the answer to many of these challenges. Take a conventional liquid vaccine (mRNA, proteinaceous, or vector based), and stabilize the antigen in a tiny, thermostable solid dose. This solid dose is preloaded into a small, disposable cassette, and a multi-use pen is used to deliver the dose almost without sensation. Due to the highly thermostable nature of the solid doses, the disposable cassettes can be easily shipped and stored at ambient temperature. The multi-use pen avoids needles and is simple to use; in an emergency, it would allow the potential for self-administration or less training required for healthcare professionals (HCPs). The solid dose dissolves rapidly in the skin, releasing the vaccine, and the body's immune system takes over. Simple, highly cost-effective, and inherently safer for HCPs who avoid the risks associated with needles and syringes. The platform has demonstrated stability and immunogenicity across a wide range of vaccine types so can be considered vaccine type agnostic.

The stockpiling of vaccines is another important consideration to protect against bioterrorism or future pandemics. Vaccines must be rapidly manufactured and deployed to all affected areas in the event of an outbreak or threat. To do this effectively, vaccines need to be stored at central depots with the infrastructure already in place to ship them anywhere they are required. This is not easy, by definition, it is difficult to quantify the scale, the timelines, and the location of where these life-saving vaccines need to be delivered. An approach to secure global resilience against what the future may bring is to stockpile vaccines with broadly protective immunity, ready to be shipped at short notice. This requires appropriate storage and distribution conditions (such as cold-chain), an appropriate shelf-life for the vaccines, and vaccines already in a form that is easy to administer in the most challenging conditions. Vaccine stability and its ability to be easily shipped at ambient temperatures become critically important. The availability of needles and syringes, the essential equipment to inject people with the vaccines, may also become a rate-limiting step. The key is simplification of the process. The ideal scenario is availability of vaccines that are thermally stabilized, available in a ready-to-use format, and can be easily transported with and without refrigeration.

REDUCING THE NEEDLE-STICK RISK

Vaccine administration via needles and syringes represents a risk to HCPs, and measures are put in place to reduce this risk; however, the risk cannot be eliminated, and the sheer volume of doses administered in a mass vaccination program means occurrences are highly likely.[3] Once a vaccine has been administered, the needle becomes a cross-contamination risk to the HCP, containing pathogens that may be present in the blood of the vaccinated individual. Sharps bins are provided to reduce these risks, and handling procedures help reduce the chances of injury. Novel vaccine administration technol-



ogy has the potential to reduce or eliminate these risks. Methods of delivery to remove the needle take away the chance of blood-to-blood transmission of disease. "Click and deliver" technology that ensures reliable dose delivery to the subject but avoids sharp and contaminated parts of the delivery mechanism would be preferable. Solid-dose vaccines are administered using the vaccine itself as the penetrating device. This means the cartridge that carries the vaccine does not need to contain a needle – rather a blunt plastic plunger that is unlikely to penetrate skin and therefore is inherently safer than a conventional needle.

Putting patients at the center of treatment and patient-entric medicine are phrases that have become routine in the development of new medicines. Gone are the days of a physician dictating the treatment pathway for a range of diseases – the patient is now front and center in the decision-making process. Patients (and patient groups) know best as to the balance of disease outcome and quality of life – about the route of administration of treatments, the location for their treatment, and level of involvement they wish to have. Vaccines today, stand out as an exception to the shift to patient centricity. The choice of vaccine and the route of delivery are decisions taken well beyond the physician's office. Vaccines are different, they are usually given to healthy subjects as opposed to treating an active disease. However, the recipient should also have a say in the choice of vaccines and the route of administration. The growth in alternative routes of vaccine delivery is a key component of bringing patient-centric medicine into the prophylactic vaccine space. One day, people will get to choose if they wish to have an intramuscular, intranasal, or solid-dose version of their boosters, and those choices will be driven by the person receiving the vaccine. Patient groups will help design vaccination programs for targeted groups based on their insights into the route of administration and how it is likely to affect the individuals and ultimately, the uptake of the program.

APPLYING PHARMACEUTICAL MARKETING 101 TO VACCINES

For all the advances in novel vaccine delivery, and there are many, one final challenge remains. Needles and syringes are cheap, which feeds through to lower cost vaccines. They are also easy to make at scale, and the infrastructure to do so is established. Novel technologies are different. They must be designed to be made in significant numbers (100 million plus doses), and in the event of future pandemics, in the billions of doses. Scaled up production requires significant amounts of CAPEX, which requires large amounts of funding in challenging times for biotechnology companies to raise funds. The business case for investing in novel routes of vaccine delivery, such as aVaxziPen's "click and deliver" solid-dose technology, lies in the application of sophisticated cost-effective modelling of the vaccine market. The cost of developing cutting-edge technology can be offset by the improvements in vaccine coverage and offsetting the costs of getting vaccines to the point of

use. In high-income countries, the case for making vaccine delivery less painful and easier also challenges the conventional view of the lower margin, high-volume market, compared to conventional medicines developed by global pharmaceutical companies. The world needs cost-effective vaccines, and consumer preference will drive market uptake. It's pharmaceutical marketing 101 applied in the vaccine space.

Despite the significant advances we have seen in antigen design and our understanding of the immune system, it should be remembered that a vaccine can only work once it is delivered, intact, and into the arm of the person who needs it. The vaccine chain (from manufacturing through to transportation, storage, and delivery) and the resources required at each stage should be considered holistically, and the burden on healthcare systems as well as minimizing the risks to the healthcare professionals at the sharp end should all be minimized where possible. The entire value chain is of critical importance. Novel vaccine technology does not relate simply to the antigen within the vaccine, it also relates to the method of administration, the route of delivery, and the system costs of achieving an immune- protected population. Affordable, simple, reliable, and safe vaccines are needed. Removing the needle, syringe, and refrigerator from vaccine delivery is a significant step in the right direction toward better global vaccination programs. ◆

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BIOGRAPHY

Robin Cohen is Chief Business Officer and Director at aVaxziPen. He has over 25 years of experience in the pharmaceutical industry with a strong executive level commercial and business development focus. He is a highly experienced senior level leader with a strong track record in biotech fund raising, commercializing products from preclinical through to post license as well as building commercial teams and leading them to exceed their strategic and commercial goals in both global pharmaceutical and biotech organizations. Prior to joining aVaxziPen, he worked in a variety of senior level commercial roles at Janssen Cilag (Johnson & Johnson) where he was a key part in a number of ground-breaking therapeutic product launches across a range of the therapeutic areas from oncology to infectious diseases with a focus on HIV, hepatitis, and the wider infectious disease portfolio.

Special Feature

Excipients: Strategic Enablers of Innovation

By: Cindy H. Dubin, Managing Editor

As of this writing, the pharmaceutical industry will be getting ready to descend upon Milan for CPHI where excipient products and suppliers will be on full display. The global pharmaceutical excipients market size was valued at close to $11 billion in 2025, and is projected to grow from $11.18 billion this year to $17.89 billion by 2034. The market is being driven by rising production of generic drugs, increasing demand for complex drug formulations, as well as a call for functional, high-purty excipients.[1]

"Organic excipients are likely to become increasingly important as demand grows for cleaner-label, naturally derived, and consumer-friendly formulations," says John Tillotson RPh, PhD, Technical Business Director, ABITEC. "Their impact may be more pronounced in nutraceuticals than in pharmaceuticals, where functionality, safety, consistency, and regulatory requirements remain the primary drivers of excipient selection. At the same time, traditional non-organic excipients will continue to play an essential role, given their established performance, robustness, cost-effectiveness, and broad regulatory acceptance across pharmaceutical formulations. The future is likely to be one of complementarity rather than replacement, with both organic and traditional excipients serving distinct formulation needs."

One distinct formulation need is choosing the best excipient. AI is becoming an increasingly valuable tool in formulation development, particularly as drug products become more complex and development timelines tighten. "As a result, we are seeing the emergence of digital formulation development platforms that use Artificial Intelligence and Machine Learning to help predict suitable excipients for a given API and/or dosage form," says Maj-Britt Cepok, Head of Pharma, BENEO. "These platforms can draw on extensive formulation and ingredient databases, helping identify patterns from historical development data. They help formulators evaluate factors such as stability, solubility, dissolution performance and bioavailability much earlier in the development process, enabling for leaner and hence more efficient development processes."

Dr. Jessica Mueller-Albers, Strategic Marketing Director Oral Drug Delivery Solutions, Evonik, agrees: "AI-driven models can

EUDRAGIT® tablets and capsules at Evonik.

help predict drug-excipient interactions, physical stability, dissolution behavior, and bioavailability, enabling researchers to evaluate a larger formulation space before entering laboratory studies. The greatest value today lies in combining predictive algorithms with high-quality experimental datasets and formulation expertise. AI can rapidly identify promising excipient candidates, optimize compositions, and reduce development cycles."

However, Mueller-Albers and Cepok quickly point out that successful pharmaceutical development still relies on scientific understanding and experimental verification. While AI will not replace formulation expertise, it can significantly accelerate decision-making and reduce the number of experimental iterations. The future will likely involve closer integration of AI-powered screening tools with mechanistic formulation knowledge and advanced excipient databases to support faster development, optimized manufacturing processes, and ultimately more patient-centric medicines.

In this article, many of the companies that will exhibit at CPHI give *Drug Development & Delivery* an exclusive sneak peak at the technologies they will showcase.

ABITEC: Lipid-Based Delivery for Next-Gen Drug Development

ABITEC is a functional and customized lipid supplier, addressing applications from active ingredient solubilization to unique lipid customization for the formulation of lipid nanoparticles for nucleic acid delivery and advanced biopharmaceutical applications. The company also offers compendial excipients for direct compression tableting and sustained release.

"Lipid-based drug delivery systems offer a highly effective and versatile solution, enabling improved solubilization and absorption of poorly soluble APIs while often being relatively straightforward to formulate and implement," says John Tillotson RPh, PhD, Technical Business Director, ABITEC. Their combination of performance, formulation flexibility, and ease of adoption positions lipid-based delivery as an increasingly attractive strategy for next-generation pharmaceutical development. Additionally, in certain cases lipids can improve the permeability of certain actives.

AI is emerging as a valuable tool for pharmaceutical excipient selection, helping formulators navigate complex relationships between API properties, excipient functionality, processing conditions, and desired product performance. This role is particularly promising in lipid nanoparticle (LNP) formulation for nucleic acid delivery, where the large formulation design space and interactions among ionizable lipids, helper lipids, cholesterol, PEG-lipids, nucleic acids, and process parameters can make optimization challenging, explains Dr. Tillotson.

He says: "AI and machine-learning approaches can accelerate formulation screening, identify influential variables, predict key attributes such as particle size, encapsulation efficiency, stability, and delivery performance, and ultimately support more efficient, data-driven development of LNP systems."

Lipd-based drug delivery, among other technologies, will shape the future of new APIs, summarizes Dr. Tillotson.

BENEO: Multi-Functional Excipient Addresses Manufacturing & Patient-Related Challenges

The increasing complexity of modern medicines is driving demand for more functional excipients. Traditionally, many formulations relied on excipients primarily serving basic roles such as filling, binding or disintegration. Today, however, multifunctionality is in demand, for different perspectives such as formulation performance (e.g. controlled-release systems), dosage forms beyond classic tablets (e.g. mini and chewable tablets, sachets and stick-packs) as well as new processing technologies (such as continuous manufacturing), explains Maj-Britt Cepok, Head of Pharma, BENEO.

As a result, manufacturers are looking for multifunctional excipients that can support both formulation performance and efficient processing. At the same time, patient-centric drug development is creating interest in excipients that improve palatability and ease of administration. In short, excipients are evolving from "inactive" ingredients to strategic tools that help overcome formulation and manufacturing challenges.

galenIQ™ is a multifunctional excipient. "Our pharmaceutical excipient, galenIQ™, is a multifunctional isomalt-based filler and binder used in a wide range of oral dosage forms," says Ms. Cepok. "It combines excellent flowability, high compressibility, low hygroscopicity and chemical stability, while also enhancing palatability. This versatility allows formulators to address both manufacturing and patient-related challenges."

She shares an example from a development project with a poorly water-soluble API that, when administered as a

conventional tablet, typically requires multiple doses throughout the day. Such frequent dosing regimens can be burdensome for patients and may negatively impact adherence. The goal was to develop an alternative dosage form with enhanced bioavailability and reduced dosing frequency.

"Using galenIQ™ as the carrier for nanoparticle-loaded pellets, the developers were able to create a multiparticulate formulation combining immediate and delayed release," explains Ms. Cepok. "Thanks to the mechanical stability, flow properties, low electrostatic charging and rapid solubility of galenIQ™, the formulation process was efficiently supported while ensuring rapid release of the nanoparticles after administration. The resulting stick-pack formulation enabled a once-daily dosing approach, offering the potential for improved patient compliance and a more convenient treatment experience."

Evonik: Modern Formulation Development Requires a Collaborative Approach

As active pharmaceutical ingredients become increasingly complex, the expectations placed on excipients continue to rise. Many modern small molecules exhibit low aqueous solubility and require advanced formulation approaches to achieve adequate bioavailability. At the same time, emerging oral peptide and biologic therapies often need excipients that support gastrointestinal protection, site-specific delivery, or enhanced absorption. Beyond performance, formulators must also consider patient-centric factors such as dosing convenience, reduced food effects, improved tolerability, and compatibility with concomitant medications.

Safety considerations have become equally important. The industry's focus on minimizing nitrosamine risk has increased demand for excipients with tightly controlled impurity profiles, particularly low nitrite levels for formulations containing vulnerable secondary amines. Sustainability is another growing selection criterion as pharmaceutical companies increasingly assess environmental impacts throughout the product life cycle.

As a result, drug manufacturers are no longer seeking commodity ingredients alone. They require excipients that are safe, highly functional, well characterized, sustainable, and supported by robust regulatory documentation. Given the complexity of today's formulations and accelerated development timelines, close collaboration between excipient suppliers and pharmaceutical developers has become essential.

EUDRAGIT® polymers are a family of functional polymethacrylates used to enable targeted drug delivery, bioavailability enhancement, taste masking, and modified-release formulations. Their versatility allows formulators to tailor drug release to specific therapeutic and patient needs, explains Dr. Jessica Mueller-Albers, Strategic Marketing Director Oral Drug Delivery Solutions, Evonik.

"Most of the advanced functionality required by modern formulations is delivered by organic excipients," she says. "Polymers such as polymethacrylates, cellulosics, polyvinylpyrrolidones, and lipid-based materials play central roles in technologies including amorphous solid dispersions, modified-release systems, taste masking, enteric protection, and bioavailability enhancement."

The growth of poorly soluble compounds and oral biologics is expected to further increase the need for multifunctional excipients capable of addressing multiple formulation challenges simultaneously. Organic polymers are uniquely positioned because their chemistry can be tailored to provide specific release profiles, solubility enhancement, processing properties, and stability benefits. "Lactose has historically maintained a leading position due to its versatility, cost effectiveness, and widespread use in tablets, capsules, and dry powder inhalers," says Dr. Mueller-Albers. "However, looking ahead, growth opportunities may increasingly favor function-driven excipients rather than being defined by a single material class. Cellulosics will certainly remain important due to their broad applicability in solid dosage forms. However, we also expect continued growth of functional polymers, particularly in areas such as enteric delivery, controlled release, and amorphous solid dispersions. As drug molecules become more challenging, formulators will increasingly select excipients based on performance and risk mitigation rather than solely on traditional usage patterns."

One recent example involved an amorphous solid dispersion development program for a poorly soluble active ingredient under significant timeline pressure. The pharmaceutical company required a high-performance polymer with very low nitrite content because of the large polymer load in the formulation and an increased sensitivity to nitrosamine-related risks. Evonik assembled an interdisciplinary team of polymer scientists, formulation experts, analytical specialists, regulatory professionals, and application

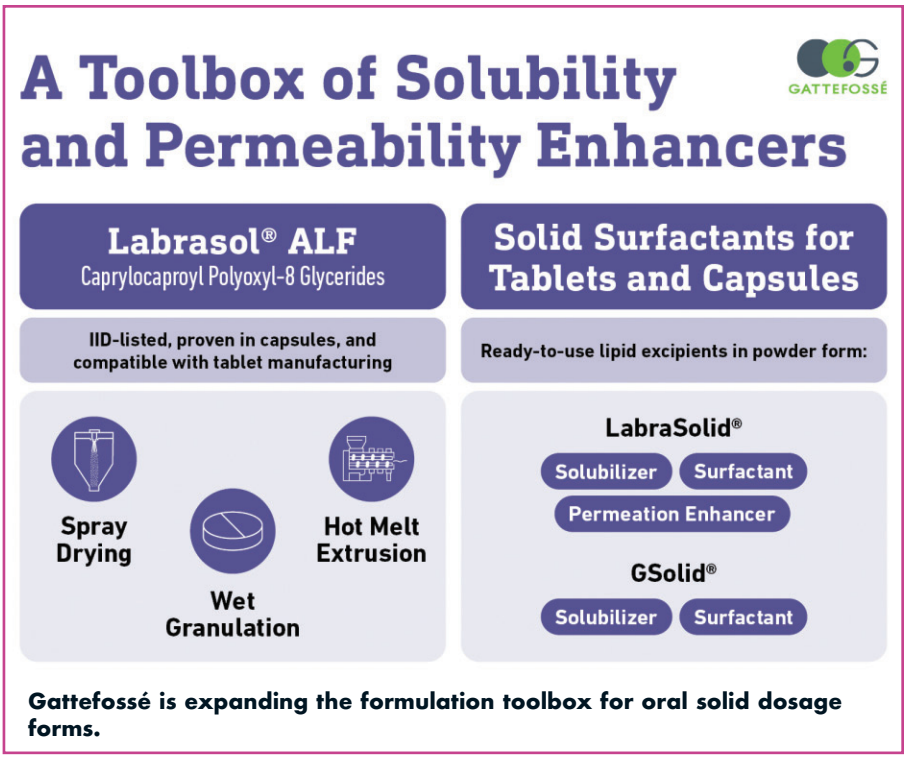
development scientists who worked in parallel with the customer's development team. Through close collaboration, process optimization, and regulatory support, a suitable EUDRAGIT solution was identified that met both performance and safety requirements.

She says: "The project demonstrated that success in modern formulation development depends not only on the excipient itself, but also on the technical expertise, regulatory understanding, and collaborative approach that accompany it."

Gattefossé: Lipid-Based Excipients Boost Solubility & Absorption for Liquids & Solids

In 2026, Gattefossé saw two key product approvals that reflect greater trends in the overall pharmaceutical market: VEPPANU® (vepdegestrant), the first FDA-approved PROTAC molecule, and LIPFENDRA® (enlicitide), the first orally administered PCSK9 inhibitor. "Decades of API and formulation optimization were needed to bring these challenging candidates to market, and in the case of enlicitide, customized grades of permeation enhancers were developed to enable an oral tablet formulation," says Nick DiFranco, Senior Marketing Manager, Pharmaceutical Division, Gattefossé.

The explosion of interest in oral peptide delivery and targeted protein degradation is driving formulators to seek safe, efficient permeation enhancers that go beyond traditional BCS Class II formulation approaches, says Mr. DiFranco. However, formulators must walk a fine line between innovation and risk management to identify excipients that solve their technical challenges without introducing additional safety, toxicity, or regulatory hurdles.



Gattefossé is expanding the formulation toolbox for oral solid dosage forms.

"As a result, many formulators in the oral peptide and PROTAC space are revisiting safe, proven lipid excipients, which serve as both strong solubilizers and absorption enhancers," he says.

For decades, medium-chain fatty acid esters such as Labrasol® ALF (caprylocaproyl polyoxyl-8 glycerides) have increased drug solubility while enabling safe, reversible tight junction modulation, boosting both transcellular and paracellular permeability. Longer-chain chemistries such as Maisine® CC (Glyceryl monolinoleate) have enabled lymphatic uptake for molecules that suffer from high first-pass metabolism or food effect. While these and many other lipid excipients have global precedence of use and IID-listings, Mr. DiFranco says interest in these chemistry platforms has never been higher.

To meet the needs of their poorly permeable drug candidates, formulators have requested excipients that bring the solubility- and absorption-enhancement of traditional, lipid-based formulations into solid oral dosage forms. They want a toolbox of options that goes beyond SNAC or sodium caprate. Gattefossé has responded to this unmet need by developing a series of solid surfactant chemistries based on proven excipients in its portfolio. For example, LabraSolid™ (a solid powder form of Labrasol® ALF) and GSolid™ (powdered Gelucire® 50/13 and 48/16) were developed and optimized for tablet compression and capsule filling. These solid solubilizers and permeation enhancers can easily be incorporated into powder blends to introduce critical functionality for challenging peptide and small molecule NCEs.

Additionally, the company is investigating the use of lipid excipients in spray drying and hot melt extrusion processes alongside polymers such as HPMC-AS. Through collaborations with amorphous solid dispersion (ASD) experts, including Shin Etsu and GEA, Gattefossé is building a library of lipid-polymer formulation knowledge.

"This experience allows us to provide better processing guidance and recommendations for how to enhance performance of ASD formulations using lipid-based excipients," says Mr. DiFranco

Data presented at the 2026 CRS Annual Meeting and 2026 DDF Summit in Boston showcased ASD formulations containing Labrasol® ALF and Gelucire® 48/16 produced via spray drying, hot melt extrusion and wet granulation. The studies demonstrated improved processing conditions, higher drug loading, and improved formulation performance relative to binary ASDs, and they provide starting point conditions for innovators who wish to explore lipid-polymer synergies, he says.

"As more peptides and beyond-the-rule-5 compounds enter the pipeline, the need for versatile bioavailability enhancement approaches will only continue to grow," Mr. DiFranco says. "Lipid-based excipients provide a safe, proven mechanism to boost solubility and absorption across a wide range of liquid and solid dosage forms."

Apisolex™ pharmaceutical excipient for injectable oral dosage forms (Lubrizol).

Lubrizol: Novel Excipients Address Oral & Parenteral Challenges

Selecting the right excipient is key to unlocking the potential of "brick-dust" APIs. Unfortunately, many commonly used excipients were developed decades ago, often for non-pharmaceutical use, and may not be optimal for transforming difficult-to-deliver APIs into effective drugs. As a result, attention is turning toward next-generation polymer excipients specifically designed to overcome complex formulation challenges.

For oral solid dosage forms such as tablets, physical modification techniques can be used to enhance brick-dust API solubility. Amorphous solid dispersion (ASD) can disrupt an API's crystalline structure, increasing the surface area to enhance the gastrointestinal dissolution rate. Excipient choice is critical for ASD formulation, but commonly used polymers like HPMC can typically only stabilize drug loadings below 40%, which often leads to larger tablet sizes. Bigger tablets can lower patient compliance among seniors and children who struggle to swallow even standard-sized tablets, says Lori Ditty, Global Marketing Manager, Lubrizol.

Apinovex™ pharmaceutical excipient is a novel, high molecular weight linear polyacrylic acid excipient developed by Lubrizol for use with ADSs. "It allows more efficient dosage forms with high, stable drug loading of up to 80% – twice that of other commonly used solubility-enhancing excipients," she says. "This enables more efficient and patient-centric oral solid therapeutics, including smaller, easier-to-swallow tablets."

In parenteral drug development, strict safety requirements and complex chemical challenges associated with excipients for injectable products have made successful commercialization uncommon over the past three decades. Ms. Ditty says many fail to adequately improve API solubility, and some may cause undesirable side effects. For many oncology drugs, the maximum tolerated dose is restricted not just by the API's toxicity, but also by that of the excipient.

As an alternative, Lubrizol's Apisolex™ pharmaceutical excipient is a novel polyamino acid-based amphiphilic excipient designed to dissolve and stabilize hydrophobic APIs for intravenous infusion and bolus injection, she explans. "It is based on sarcosine – a non-toxic, non-immunogenic, biocompatible, and biodegradable amino acid – and offers a high level of safety for parenteral use," she says. "Demonstrated to increase drug solubility by up to 50,000 times, it also achieves drug loadings of up to 40%. This can enable more patient-centric therapeutic regimens with smaller dosages or reduced dosage frequency." An Apisolex pharmaceutical excipient-enabled drug formulation is currently in Phase 1 clinical trials.

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Lonza: From Formulation to Scale-Up: Advancing Dry Powder Inhalation for Biologics

Dry powder inhalation is rapidly emerging as a powerful platform for expanding access to biologics, vaccines, peptides, and nucleic acid therapies through pulmonary and intranasal delivery. As developers look beyond traditional injectable formats, advances in spray drying, particle engineering, and device integration are opening new possibilities for targeted treatment, improved patient adherence, and greater product stability without cold chain dependence. In this article, experts discuss the evolving respiratory delivery landscape, the technologies shaping the field, and development strategies for addressing formulation, analytical, manufacturing, and regulatory complexity while initiating risk mitigation in the early stages. Deployed properly, such strategies can position promising programs for clinical and commercial success.

Drug Development & Delivery recently interviewed, Kim Shepard, PhD, Director, Advanced Drug Delivery, Lonza Advanced Synthesis, and Beatriz Fernandes, PhD, Principal Investigator, Lonza Advanced Synthesis, about their research presented at the Respiratory Drug Delivery Conference.

Q: What does the current respiratory delivery landscape look like, and what are some examples of dry powder inhalation (DPI) technologies being used in the manufacturing of these treatments?

Dr. Fernandes: The dry powder inhalation (DPI) field has evolved substantially over the past several decades, building on early carrier-based small-molecule products for asthma and chronic obstructive pulmonary disease (COPD). Over time, small-molecule DPIs have become a mainstay of pulmonary therapy and are now used extensively for a range of respiratory indications. In parallel, interest in DPI formats for more complex modalities has grown. The first inhaled insulin product was approved in 2006.[1] Although there are fewer approved biologic DPIs for pulmonary

delivery, recent innovations with large proteins, messenger RNA (mRNA), and short-interfering RNA (siRNA) appear to be promising approaches. The 2016 FDA approval of the first intranasally delivered small-molecule DPI product[2] ushered in a decade of rapid expansion. Although there are no approved intranasal dry powder biologics as of yet, this is an innovative new area with great potential, including mucosal vaccination and the emerging field of nose-to-brain delivery, which shows great promise for delivering molecules across the blood-brain barrier.

For DPIs, two main technology classes are used to generate respirable particles: top-down size reduction (most commonly micronization by jet milling) and bottom-up particle engineering such as spray drying. The latter approach is a unit operation that starts with a liquid feedstock and turns it into a dry powder with controlled particle size. Spray drying is broadly applicable to both large and small molecules, and can engineer particles of a range of size distributions. Whereas both jet milling and spray drying can be used for DPI delivery of small molecules, spray drying is the leading technology for biologics. Both types of technologies offer the advantages of improved patient adherence and ease of distribution.

Q: What strategies are most effective in developing dry powder inhalation therapies, and what key risks do CDMOs consider during development and manufacturing?

Dr. Fernandes: The most important consideration in developing DPI therapies is to start with the end in mind: patient needs come first, including the indication, delivery target, dose, and phase-appropriate risks. Our approach is to start with a quick assessment of the API formulation and small-scale process. Then in parallel, we perform formulation optimization and scale-up manufacturing, while formal analytical method development proceeds concurrently. At this time, we'll do an early-phase risk assessment to uncover any high-risk items so they can be mitigated early with formulation tweaks or process adjustments. Oftentimes, early risk assessment coincides with manufacture of supplies for a toxicology study. We then enter the clinical readiness phase in which the demonstration batch of the process is conducted with clinically representative equipment and materials, as well as finalization of the release methods, leading to tech transfer to our Early Phase Clinical facility.

There are several categories of risk to consider in DPI development and manufacturing. The first category encompasses API and physicochemical risks, in that factors such as particle size, solid state, drug-excipient interactions, and chemical degradation during particle engineering can directly affect lung deposition and stability. If these risks aren't understood early, downstream development is immediately constrained. Formulation development risks – including inadequate aerosol performance, instability, limited excipients, device compatibility, and loss of activity (especially for biologics) – are core determinants of clinical efficacy and shelf-life. Manufacturing and scale-up risks are the primary cause of clinical-to-commercial batch failures[3]; for example, spray drying and jet milling apply mechanical, thermal, and environmental stresses during atomization, drying, collection, and encapsulation. There are also risks related to analytical robustness; without reliable aerodynamic particle size distribution (APSD) methods, appropriate assays for biologics, and tools to manage solid-state complexity, the manufacturer cannot release the product or demonstrate bioequivalence. Finally, there are risks due to CMC complexity, mainly due to the fact that DPI products are combination products, regulatory guidance for inhaled biologics is still evolving, and regulatory timelines are often long. All these risks are interdependent, requiring an integrated, quality-by-design approach that must start early to reduce the chances of late-stage surprises, cost escalation, and timeline risk.

Q: Your RDD workshop emphasized early risk identification as a critical success factor. What are the most important risks developers should identify at the outset, and how can early-stage decisions help de-risk programs before costs and timelines escalate?

Dr. Fernandes: Successful scale-up of DPI development requires early identification and control of solution, atomization, drying, and collection stresses. Risk mitigation should start with up-front identification of API, dose, and delivery-route constraints, followed by use of the target product profile to guide formulation, process, and CMC strategy; these considerations can help the manufacturer align technical ambition with phase-appropriate risk. Early identification and prioritization of formulation, manufacturing, analytical, and regulatory risk can yield understanding of how these risks are interconnected across the development lifecycle.[3] It is also important to apply spray-drying best practices, including use of materials-sparing tools to de-risk scale-up. Ultimately, success in DPI isn't about solving every problem early; it's about identifying the right risks early and making informed trade offs before costs and timelines escalate.

Q: At RDD 2026, you highlighted how dry powder inhalation (DPI) is gaining traction for biologic APIs, particularly for respiratory and intranasal delivery. What unmet challenges is this approach helping to address, and where are you seeing the most meaningful innovation today?

Dr. Shepard: Biologic APIs have grown to comprise roughly 50% of pharmaceutical development pipelines[4], and the vast majority of these are delivered by infusion or injection.[5] That's great for many situations, but in some cases, non-invasive delivery or targeted local treatment can be quite beneficial to patients. That, essentially, is the rationale for respiratory delivery of biologics. This approach is particularly promising for localized treatment of lung diseases such as lung cancer, COPD, pulmonary arterial hypertension, and pulmonary fibrosis. Other indications of interest include non-invasive systemic delivery of smaller biologics (e.g., peptides, siRNA) via the lung or the nose, as well as targeted delivery to the central nervous system using the nasal olfactory route. In addition, most biologics are liquid dosage forms requiring cold chain[6]; this is where a dry powder respiratory formulation can be particularly useful, where long-term stability at 25°C can often be achieved. For a dry powder vaccine for nasal or pulmonary delivery, eliminating a cold chain requirement can be hugely beneficial for global distribution in areas with limited resources.

Q: From a CMC perspective, what are the most common challenges in developing intranasal dry powder biologics and how can CDMOs help address these complexities across formulation, analytics, and device integration?

Dr. Shepard: With an intranasal dry powder biologic, the CMC challenges fall into two areas: the intranasal dry powder part, and the dry powder biologic part. Bring these together and you have quite a bit to consider! For intranasal dry powders, we focus on spray drying as a manufacturing technique. Particle engineering of nasal powders, particularly when they are spray dried from an aqueous feedstock, can be tricky to sufficiently dry with good yield. We have modified our spray dryer chambers to enable sufficient residence time in the dryer to ensure improved yield at the target particle size.

Bringing together the right powder with the right intranasal device is also a critical aspect of development. Depending on the target deposition region, patient attributes, and business case, the developer may choose different types of DPIs. For example, a patient who is unable to inhale powder on demand will require an active device that propels the powder into the nasal passages. Some patients may need to take their dose infrequently (such as for a vaccine), or daily, which may impact whether a reloadable or single-use device is prioritized. For all dry powder biologics, whether delivered for nasal or pulmonary deposition, chemical and physical stabilization of the delicate biologic API is a critical CMC concern. The formulation must preserve potency and activity, while mitigating molecule fragmentation or aggregation.

Q: In your presentation, you highlighted several recent case studies across vaccines, peptides, and mRNA and discussed what's next in this space. What lessons do these examples reveal, and how will partnerships with CDMOs be critical to scaling and enabling broader adoption?

Dr. Shepard: The case studies we presented featured an intranasal GLP-1, a protein-based vaccine, and an mRNA lipid nanoparticle (LNP) dry powder for nasal delivery. In each case, we demonstrated proof of concept that spray drying these materials with good potency, aerosol properties, and 25°C stability is possible even for these challenging modalities. In a highly innovative, emerging field such as dry powder nasal biologics, a CDMO partner who is skilled at navigating uncertainty and risk mitigation is critical. If we want to realize the benefits of these non-invasive, shelf-stable therapies, a quality-by-design approach can enable the clinical progress and commercial volumes envisioned for these products. ◆

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Alginate Beads for Oral Drug Delivery: Formulation Strategies for Controlled Release & Enhanced Bioavailability

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INTRODUCTION

Oral administration remains the preferred route for drug delivery because of its convenience, patient acceptance, and manufacturing scalability. However, many active pharmaceutical ingredients (APIs) – particularly poorly water-soluble compounds, peptides, proteins, and other biologics – continue to face significant challenges associated with gastrointestinal degradation, limited epithelial permeability, and inconsistent absorption. These limitations often reduce oral bioavailability and complicate the development of effective oral dosage forms.[1]

Among the numerous controlled-release technologies investigated over the past several decades, calcium alginate beads have emerged as a versatile and highly adaptable delivery platform. Derived from naturally occurring alginate extracted from brown seaweed, calcium alginate forms three-dimensional hydrogel matrices through ionic crosslinking with divalent cations such as calcium. [2,3] This mild gelation process enables encapsulation of a broad range of active ingredients while preserving their structural integrity and providing opportunities to tailor release kinetics through formulation and process optimization.[2]

Unlike many polymer-based delivery systems that rely primarily on erosion or chemical degradation, calcium alginate beads exhibit pH-responsive behavior throughout the gastrointestinal tract. In the acidic gastric environment, the hydrogel contracts and limits diffusion of encapsulated compounds, providing protection against premature release and degradation. Upon transition into the near-neutral environment of the small intestine, the matrix swells, increasing pore size and enabling controlled release of the encapsulated payload.[4,5] The extent and rate of release can be modulated through variables including alginate composition, molecular weight, calcium concentration, bead diameter, drying method, and secondary polymer coatings.[2,4]

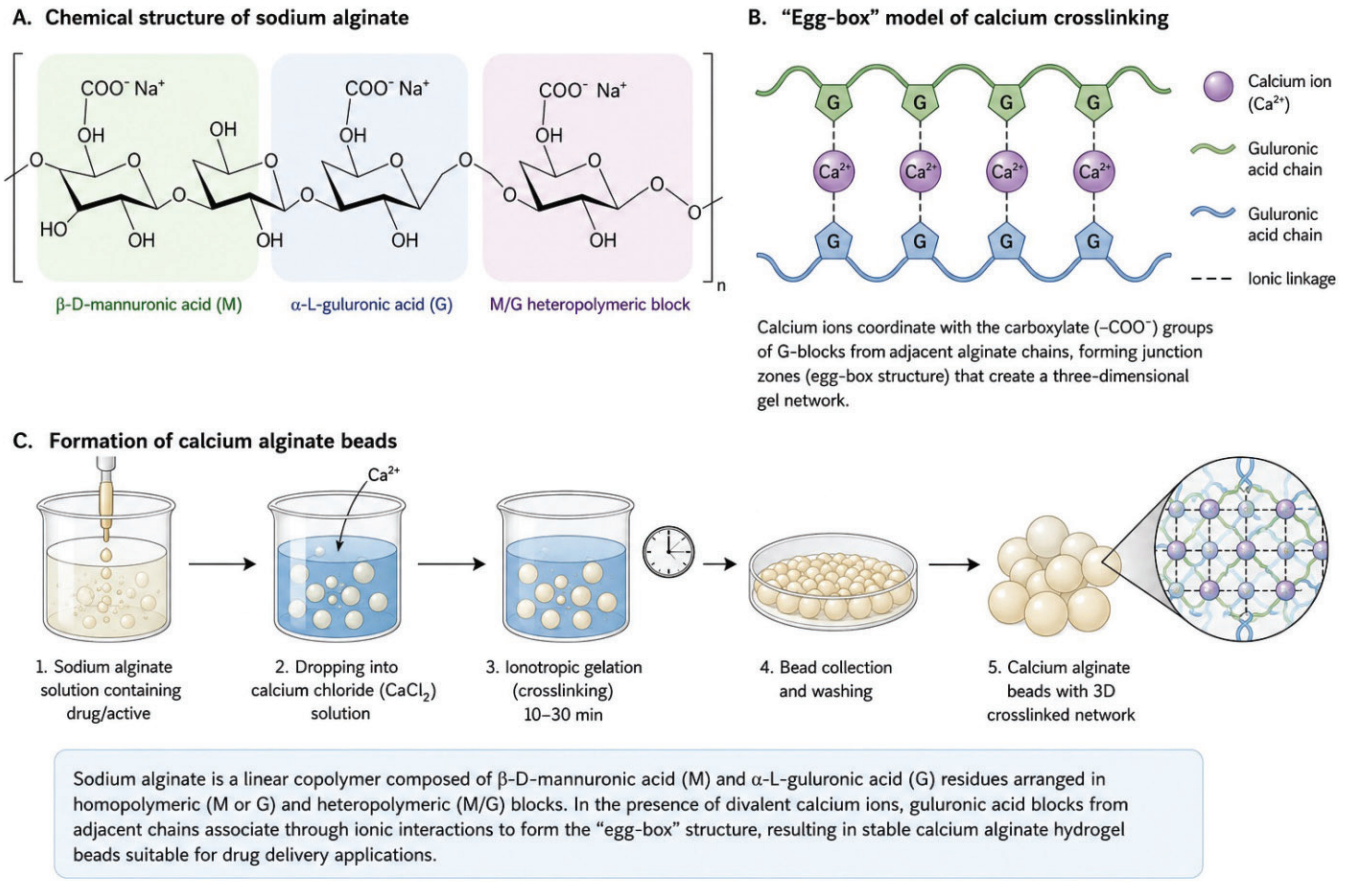
This article reviews the formulation principles governing calcium alginate bead performance, discusses the relationship between bead structure and controlled drug release, summarizes current evidence supporting oral bioavailability enhancement, and highlights emerging pharmaceutical applications where alginate-based delivery systems may provide meaningful advantages for formulation scientists developing next-generation oral therapeutics.[2,6-8]

ALGINATE CHEMISTRY AND GEL FORMATION

Alginate is an anionic polysaccharide composed of linear chains of β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues arranged in homopolymeric (MM and GG) and heteropolymeric (MG) blocks.[1,2] The ratio and distribution of these monomers largely determine the physicochemical properties of the polymer, including gel strength, elasticity, porosity, and permeability, making alginate an attractive material for controlled drug delivery applications.

Gel formation occurs through ionic crosslinking when aqueous sodium alginate is exposed to divalent cations, most commonly calcium ions (Figure 1a). Calcium ions preferentially

FIGURE 1



Chemical structure of sodium alginate and schematic illustration of calcium-mediated "egg-box" crosslinking leading to calcium alginate ($C_{12}H_{14}CaO_{12}$) bead formation.

interact with guluronic acid residues, forming junction zones between adjacent polymer chains in a three-dimensional network commonly described as the "egg-box" model (Figure 1b).[2,9] This mild gelation process occurs under aqueous conditions without elevated temperatures or harsh organic solvents, allowing sensitive therapeutic molecules including peptides, proteins, biologics, probiotics, and lipophilic compounds to be encapsulated while minimizing degradation during manufacturing (Figure 1c).[10] The reaction follows the following path: $2NaC_6H_7O_6 + CaCl_2 \rightarrow 2NaCl + C_{12}H_{14}CaO_{12}$.

The resulting calcium alginate beads possess a highly hydrated porous structure whose transport properties can be tailored through formulation design. Variables including alginate molecular weight, G/M ratio, sodium alginate concentration, calcium chloride concentration, curing time, and bead diameter directly influence crosslink density, pore size, encapsulation efficiency, mechanical strength, and drug release kinetics.[2,10] Additional processing steps, such as air drying, freeze drying, or secondary polymer coatings (e.g., chitosan), further modify internal microstructure and enable release profiles ranging from immediate to sustained release.[10,11]

Because these formulation parameters can be systematically optimized using well-established manufacturing processes, calcium alginate beads represent a flexible platform capable of accommodating diverse active pharmaceutical ingredients while providing reproducible control over stability, gastrointestinal protection, and oral drug release.

CRITICAL FORMULATION VARIABLES

The performance of calcium alginate beads is governed by a combination of polymer composition, formulation parameters, and manufacturing conditions. Careful optimization of these variables enables formulators to tailor encapsulation efficiency, mechanical strength, gastrointestinal stability, and drug release kinetics for a wide range of active pharmaceutical ingredients (APIs).[1,2,4,5,12]

Among the most influential factors is the mannuronic acid-to-guluronic acid (M/G) ratio of the alginate polymer. Alginates containing a higher proportion of guluronic acid form stronger, more highly crosslinked networks with smaller pore sizes, resulting in improved mechanical stability and slower diffusion of encapsu-

TABLE 1

Variable	Published Range	Reference
Sodium alginate concentration	0.5–4.0% (w/v)	Ching et al., 2017
Calcium chloride	0.05–0.50 M	Ching et al., 2017
Bead diameter	0.3–3.0 mm	Lee & Mooney, 2012
Pore size	5–200 nm	Ching et al., 2017
Encapsulation efficiency	60–98%	Multiple studies
Swelling ratio	20–50% increase at intestinal pH	Corstens et al., 2017
Mechanical strength	Function of G/M ratio	Lee & Mooney, 2012
Curing Time	10-30 min. (15 min. optimum)	Patel N, et al. 2016

Critical formulation variables influencing calcium alginate bead performance and their effects on encapsulation efficiency, mechanical strength, pore size, and drug release characteristics.

lated compounds. Conversely, alginates rich in mannuronic acid generally produce softer, more elastic gels with faster release characteristics.[1,2]

Crosslinking density is primarily controlled by sodium alginate concentration, calcium chloride concentration, and curing time. Increasing any of these parameters generally produces tighter polymer networks with reduced porosity, higher encapsulation efficiency, and more sustained drug release. However, excessive crosslinking may impede release of high-molecular-weight therapeutics or reduce loading efficiency.[4]

Bead diameter also influences release behavior by altering the diffusion path length. Smaller beads typically exhibit faster hydration and drug release, whereas larger beads provide prolonged release due to increased diffusion distances (Tables 1 and 2). Drying methods further modify internal bead architecture. Freeze-dried beads develop a highly porous structure that rapidly rehydrates and promotes faster drug release, while air-dried beads collapse into denser matrices that swell more slowly and provide extended release profiles.[5]

Additional formulation strategies, including secondary polymer coatings such as chitosan, permit further modulation of permeability, mucoadhesion, and gastrointestinal residence time. Collectively, these formulation variables provide a versatile design space for developing oral delivery systems with immediate, delayed, or sustained release profiles while maintaining protection of sensitive therapeutic molecules throughout gastrointestinal transit.[1,2,4,5,12]

TABLE 2

Curing Time	Typical Effect
5–10 min	Soft beads; incomplete crosslinking; faster release
10–20 min	Good balance of encapsulation efficiency and sustained release
20–30 min	Maximum rigidity; slower diffusion; reduced burst release
>30 min	Minimal additional benefit for most formulations

Bead rigidity correlation with the curing time.[13]

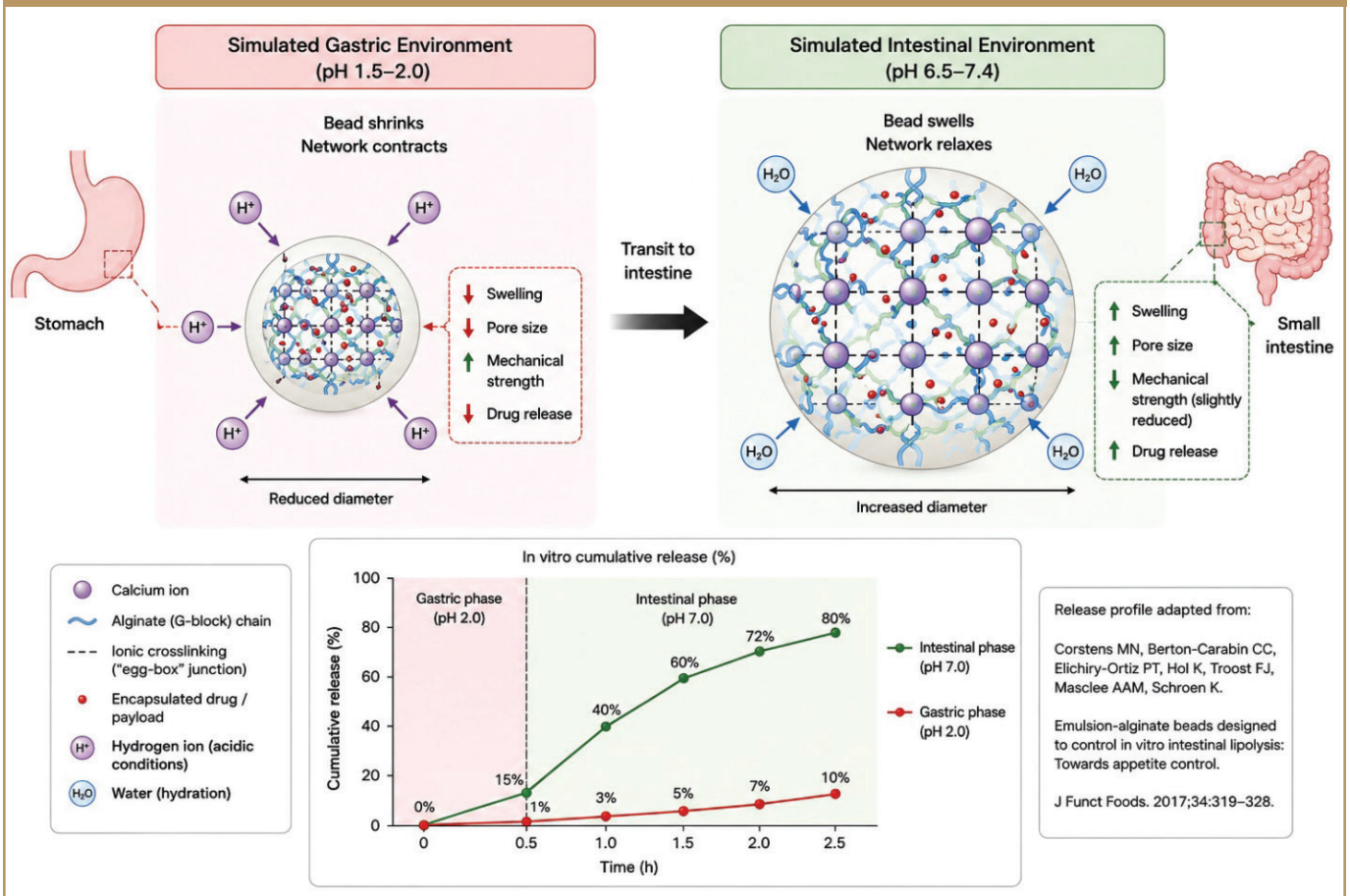
GASTROINTESTINAL BEHAVIOR AND CONTROLLED RELEASE

One of the most attractive features of calcium alginate beads is their pH-responsive behavior within the gastrointestinal (GI) tract. Unlike many conventional oral delivery systems that release their payload immediately upon hydration, calcium alginate matrices undergo predictable structural changes in response to the physiological conditions encountered during GI transit.[1,4]

Following oral administration, alginate beads are exposed to the highly acidic gastric environment (pH 1.5–2.0). Under these conditions, protonation of carboxylate groups within the polymer network causes the hydrogel matrix to contract, resulting in reduced pore size and decreased permeability. This shrinkage limits diffusion of encapsulated compounds and provides protection against premature release and degradation of sensitive active pharmaceutical ingredients (APIs), including peptides, proteins, probiotics, and lipophilic compounds.[6]

Many bioactive compounds face challenges associated with degradation during storage and gastrointestinal transit, reducing the amount of active ingredient ultimately available for absorption. Similar stability challenges have been reported for amino acid-based actives in acidic formu-

FIGURE 2



pH-dependent behavior of calcium alginate beads in simulated gastric and intestinal environments.[5]

lations, highlighting the importance of formulation strategies that protect sensitive compounds until delivery at the desired site of action.[1,4]

Upon transfer into the small intestine, where pH values typically range from 6.5 to 7.4, the polymer network undergoes substantial hydration and swelling. Increased ion exchange and relaxation of the crosslinked structure enlarge pore dimensions and facilitate diffusion of the encapsulated payload into the surrounding environment (Figure 2). The magnitude and rate of swelling depend on formulation variables including alginate composition, crosslink density, bead size, and drying method.[4,5]

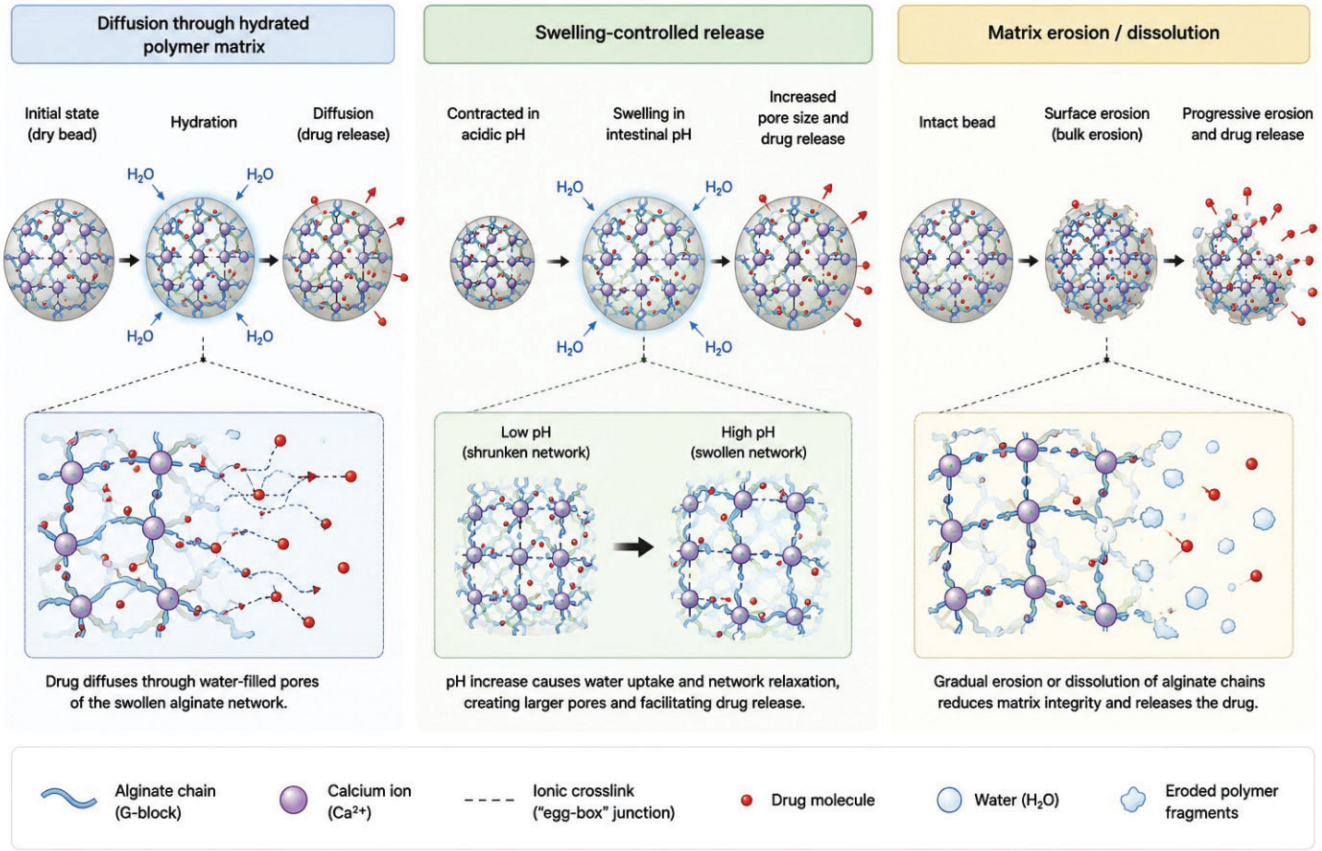
Controlled release from alginate beads is governed primarily by diffusion through the hydrated polymer matrix and, to a lesser extent, by gradual matrix erosion or dissociation. Depending on formulation design, release profiles may range from rapid intestinal release to extended release over several hours. Smaller beads, lower crosslink densities, and highly porous structures generally accelerate release, whereas larger beads, higher calcium concentrations, and denser matrices promote sustained delivery.[4,5] These characteristics provide formulation scientists with a versatile platform for tailoring drug release profiles to meet specific therapeutic objectives while maintaining protection during gastric transit.

DRUG RELEASE MECHANISM

Drug release from calcium alginate beads is governed primarily by diffusion through the hydrated polymer matrix, although swelling, erosion, and matrix relaxation may also contribute depending on formulation composition and environmental conditions.[1,2,4] The relative contribution of each mechanism is influenced by polymer characteristics, crosslink density, bead size, and the physicochemical properties of the encapsulated active pharmaceutical ingredient (API).

Following exposure to aqueous media, water penetrates the bead and hydrates the polymer network. In acidic gastric conditions, calcium alginate beads remain contracted and highly crosslinked, limiting diffusion of encapsulated com-

FIGURE 3



Representative drug release mechanisms from calcium alginate beads, including diffusion, swelling-controlled release, and matrix erosion.

pounds and minimizing premature release. Upon transition to intestinal pH, the matrix swells, increasing pore size and facilitating diffusion-driven transport of the API into the surrounding medium (Figure 3).[5]

Matrix erosion and gradual dissociation of ionic crosslinks can further influence release kinetics, particularly during prolonged exposure to intestinal fluids. Additional formulation strategies, including multilayer coatings and chitosan surface modification, may be employed to further regulate permeability and delay release.[12] Through optimization of these formulation variables, calcium alginate beads can be engineered to provide immediate, delayed, or sustained release profiles suitable for a wide range of oral drug delivery applications.

ORAL BIOAVAILABILITY ENHANCEMENT

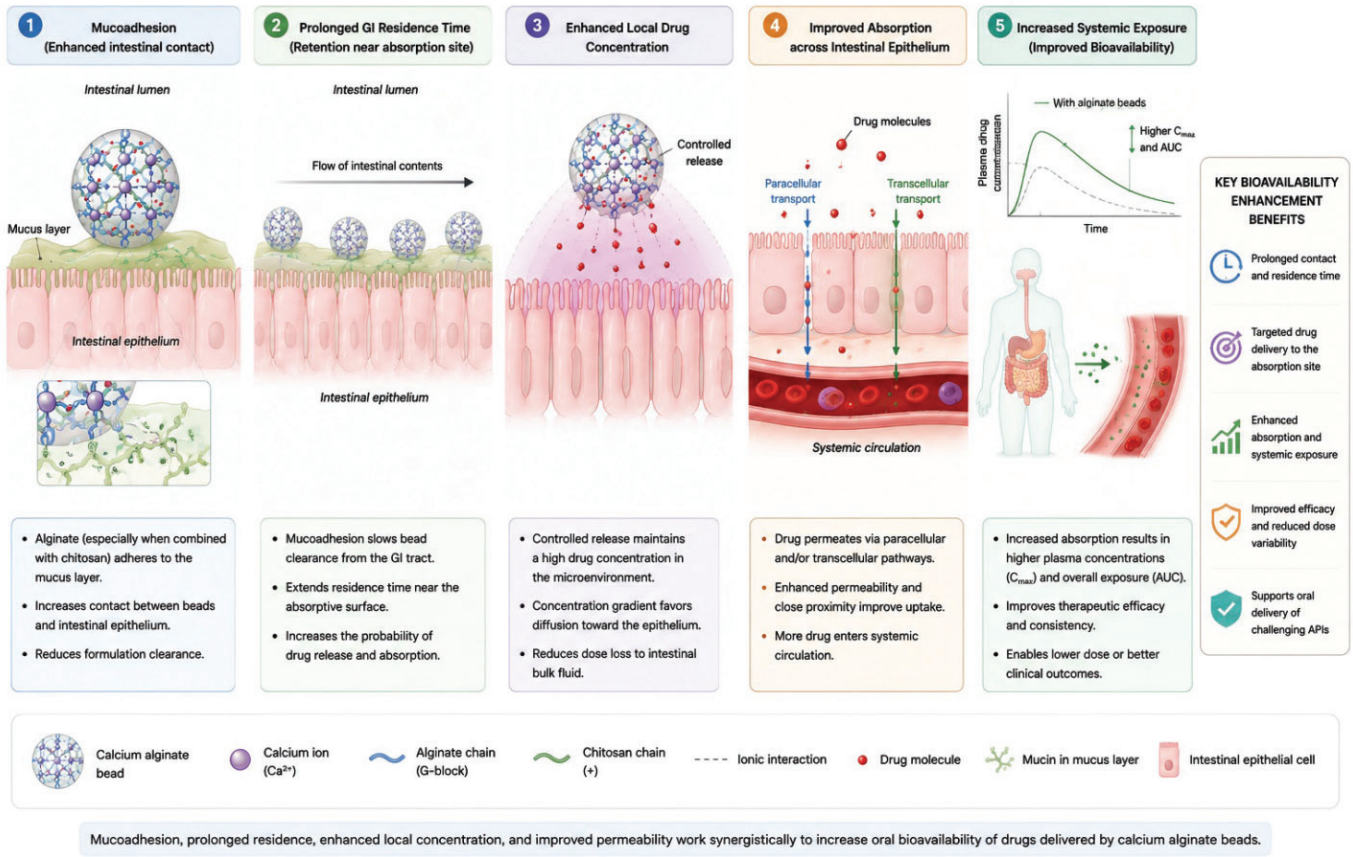
Poor oral bioavailability remains a significant challenge for many active pharmaceutical ingredients (APIs), particularly peptides, proteins, probiotics, and poorly water-soluble compounds. Limited stability in the gastrointestinal tract, enzymatic degradation, and inadequate absorption often restrict therapeutic effectiveness following oral administration. Calcium alginate beads offer a promising strategy to address several of these barriers simultaneously.[1,2,4]

A key advantage of alginate-based delivery systems is their ability to protect encapsulated compounds during gastric transit. Under acidic stomach conditions, the alginate matrix contracts and reduces permeability, limiting exposure of sensitive APIs to gastric acid and digestive enzymes. This protective effect helps preserve drug integrity until the formulation reaches the small intestine, where absorption primarily occurs.[1,4,6]

Upon exposure to intestinal pH, calcium alginate beads swell and increase pore size, facilitating controlled release of the encapsulated payload. This site-specific release can improve the amount of drug available for absorption while minimizing premature losses in the stomach (Figure 4). In addition, alginate beads may be combined with mucoadhesive polymers such as chitosan to prolong gastrointestinal residence time and enhance contact with the intestinal epithelium.[2,4,7,12]

Although alginate beads do not directly overcome all permeability limitations associated with biologics, they provide an

FIGURE 4



Mechanisms by which calcium alginate beads enhance oral bioavailability, including gastric protection, targeted intestinal release, mucoadhesion, and improved absorption.

effective platform for protecting sensitive compounds and enabling targeted intestinal delivery. As interest in oral delivery of peptides, proteins, cannabinoids, probiotics, and other complex therapeutics continues to expand, alginate beads remain a versatile formulation approach for improving oral bioavailability and therapeutic performance.[1,2,7]

INDUSTRIAL CASE STUDY: DEVELOPMENT OF CALCIUM ALGINATE SPHERIFICATION TECHNOLOGY (CAST)

Mile High Labs has developed a proprietary Calcium Alginate Spherification Technology (CAST) platform for the delivery of cannabinoids, vitamins, minerals, and other bioactive ingredients. The platform utilizes the pH-responsive properties of calcium alginate to protect encapsulated compounds during gastric transit while enabling controlled release within the small intestine. Current development efforts include dry calcium alginate pearls for capsules, beverage-compatible swollen pearls, flavored chewable pearls, and animal supplement formulations.

To evaluate release performance, Mile High Labs conducted *in vitro* dissolution studies using simulated gastric fluid (pH 2.0, 37°C) followed by simulated intestinal fluid (pH 7.0, 37°C) (Figure 5). Both Air-Dried Calcium Alginate Pearls (A-D CAP) and Freeze-Dried Calcium Alginate Pearls (F-D CAP) containing approximately 200mg of Cannabidiol were exposed to gastric conditions for two hours before transfer into intestinal media.

Both formulations demonstrated negligible Cannabidiol release during gastric exposure, with cumulative release remaining below approximately 0.2% after two hours. This finding is consistent with the contraction of the calcium alginate network under acidic conditions, which reduces pore size and restricts diffusion of the encapsulated payload. Following transfer into intestinal media, distinct release profiles were observed. Freeze-dried pearls exhibited rapid swelling and complete Cannabidiol release within approximately two hours, producing an immediate-release profile. In contrast, air-dried pearls released Cannabidiol gradually over approximately twenty-four hours, demonstrating a sustained-release profile. Figure 6 represents appearance of swollen, freeze-dried, and air-dried cal-

cium alginate pearls.

These results demonstrate that drying methodology alone can significantly influence release kinetics by altering internal pore structure and matrix density. The CAST platform therefore provides a flexible approach for developing immediate-release or sustained-release oral delivery systems using a common calcium alginate formulation platform. ◆

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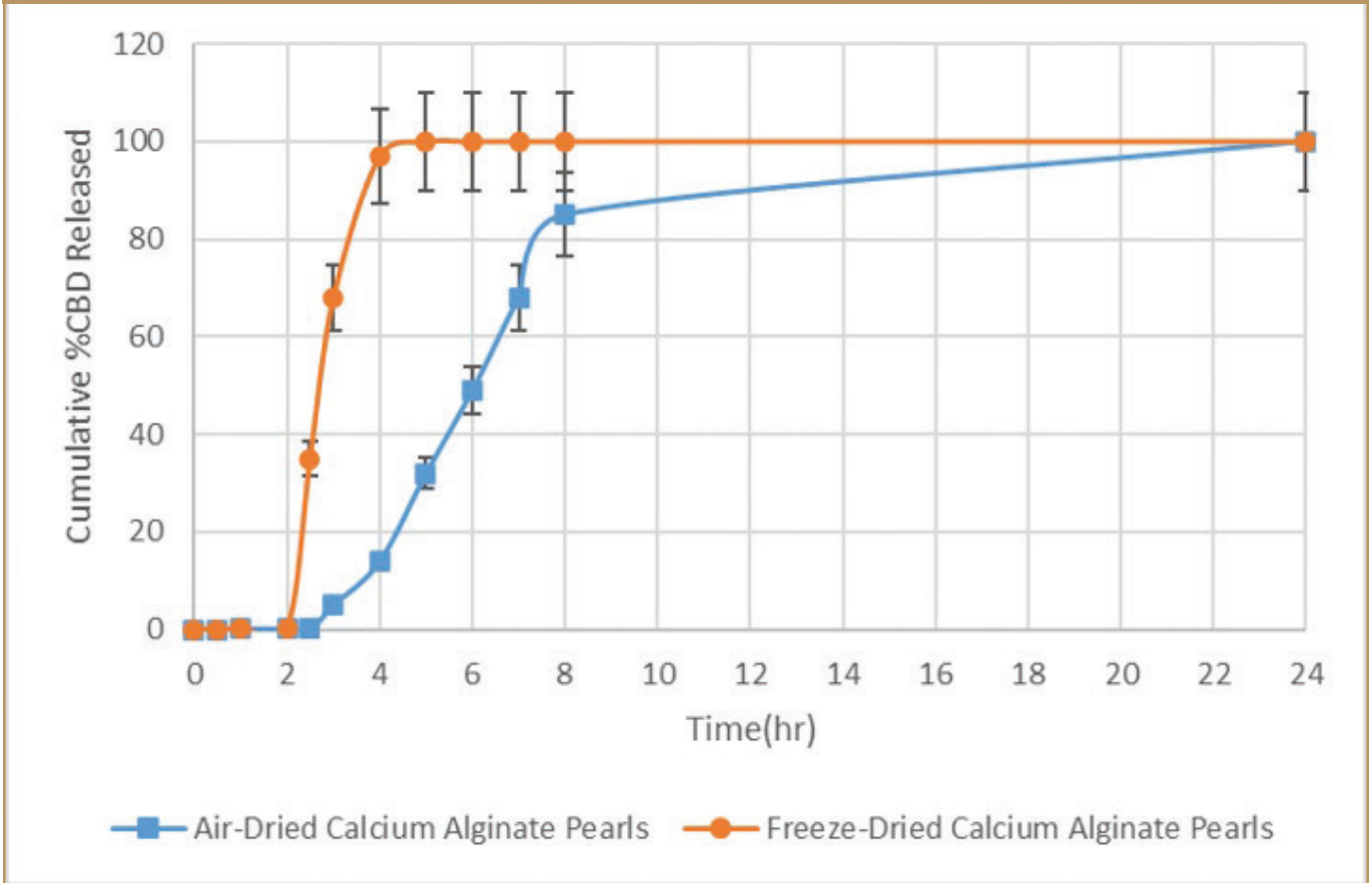
FIGURE 5



***In vitro* release profile of Cannabidiol from air-dried (blue squares) and freeze-dried (red circles) calcium alginate pearls developed using the CAST platform. The first 2 hours of the study the pearls were in a pH=2 simulated gastric liquid.**

FIGURE 6

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BIOGRAPHIES

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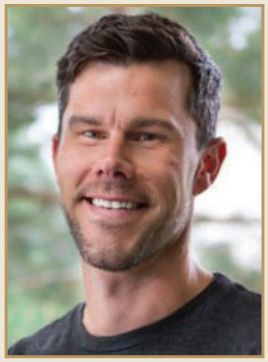
Casey Kikendall is an engineer at Mile High Labs who has 10 years of experience in drug substance R&D and engineering. His work is focused on natural compound extraction, isolation, purification, and crystallization.



John Davis, MS, is the Chief Operations Officer at Mile High Labs. He leads operational strategy and execution overseeing manufacturing, quality, supply chain, logistics, R&D/Innovation, and engineering on a global scale, with a foundation built at General Mills and nearly 20 years in food and beverage manufacturing.

ARTIFICIAL INTELLIGENCE

AI Has Transformed the Pharmacovigilence Landscape

By: Raj More

INTRODUCTION

Twenty-five years ago, pharmacovigilence (PV) was all about case management. Physicians and nurses provided information about adverse drug events which was processed and reported to regulatory agencies. The work was largely paper-based and the focus was compliance. Skip ahead to the present, and the use of advanced technologies like artificial intelligence (AI) have been an absolute gamechanger for PV.

Based on techniques like Generative AI, Large Language Models (LLMs) and Agentic AI, AI-based tools have dramatically improved data processing, pattern recognition, and automation capabilities within the PV workflow. This new toolkit has shifted a system with a historically reactive posture to one with proactive and predictive capabilities for signal detection and management, risk management, aggregate data analytics and insights. It is even changing business expectations.

Some AI technologies are now becoming indispensable to the pharmaceutical industry and safety organizations in managing the growing volume and complexity of medical data, the rapid introduction of new drugs and improving operational speed and efficiency within an increasingly complex regulatory environment.

Given that pharmaceutical companies and regulatory agencies are at different stages of realizing the full scope of benefits from AI tools, it seems a good time to survey the field as it currently stands and provide some tips to help safety organizations unlock the full potential of AI applications. It is also worthwhile to look ahead at some emerging trends and a selection of factors that will influence the continued development of these remarkable tools.

AI-BASED TOOLS FOR PV ACTIVITIES

Legacy PV infrastructure and management systems were based on manual processes that were slow, costly in human resources and prone to human error. They used traditional statistical methods that depended on structured data, which could increase the risk of missing important adverse drug events (ADEs). These methods and processes were increasingly overwhelmed by the explosive growth of new structured and unstructured data sets following the health science sector's digital transformation, in addition to the growing body of research and medical literature.

AI has undergone significant progress in the development of new applications that are highly effective in automating tasks, providing actionable insights through analytics, accelerated reporting and supporting regulatory compliance, and introducing predictive opportunities to proactively identify potential adverse drug events and emerging safety signals. These software products and platforms use models trained with modern AI techniques to provide this incredible range of valuable new capabilities and efficiencies, as evidenced in the following examples.

A new generation of AI models has played a key role in improving core surveillance activities, reducing false positives thereby delivering efficiency gains, and identifying potential false negatives that might otherwise be overlooked.

Deep Learning, which is a subset of ML, has been used to create architectures like neural network models that are inspired by the way the human brain works. These models can be trained on unstructured data for tasks such as analyzing, classifying, and extracting meaningful information from case files or medical literature. Their performance can be continually improved through retraining or fine-tuning and, in some applications, by incorpo-

"AI has undergone significant progress in the development of new applications that are highly effective in automating tasks, providing actionable insights through analytics, accelerated reporting and supporting regulatory compliance, and introducing predictive opportunities to proactively identify potential adverse drug events and emerging safety signals."

rating new data and feedback from users.

Powered by ML, Natural Language Processing can convert unstructured data into searchable data that is useful for screening. Given the wide range of text sources used in monitoring drug safety (including electronic health records, clinical notes, literature articles and case reports), this capability enables tasks like case analysis and comparison and can support case data capture, translation, summarization, support reporting and regulatory compliance. It has also become helpful for analysis of complex real-world evidence, such as data obtained from publicly available social media platforms.

Now, agentic AI technologies are creating next-generation operating models that drive even further applications for intelligent systems already used by industry and health science agencies. AI agents provide an intelligent layer that organizes and manages workflows and software functions across multiple platforms, assisting with case intake, product and event coding, follow-up query management, PV document authoring, surveillance, signal detection, risk oversight and a host of other activities. They are also designed to support the scalability of operations.

TIPS FOR NEW TECHNOLOGY ADOPTION

Case management remains a major PV pain point and the greatest driver of operational costs. Large pharmaceuticals are making big investments in monitoring and reporting capabilities. However, technology adoption rates have varied as companies juggle increasing requirements and tight operating margins. The best advice for those in the early stages of adoption is to clarify their corporate priorities, such as analytics and reporting or case processing cost optimization. Then once they have a roadmap, they can concentrate their investment in the most appropriate solutions within their budget for those top corporate priorities.

To build the necessary capabilities, pharmaceuticals can either improve or build new systems internally, or optimize the cost by purchasing commercial solutions from vendors. A single across-the-board system replacement tends to be difficult as well as very expensive. Modular software products are often preferable as they allow companies to take a more economical, staged approach to system updates. This incremental approach breaks updates into bite-sized chunks that better address specific pain points and business priorities and deliver value much faster than one "big bang" project.

Companies require additional resources before embarking on a technology update. Internal subject matter experts are critical, as a well as someone designated as the champion of the implementation process. Someone must also be designated to serve as the internal business process owner after the system goes live. This person (or people) must have an in-depth understanding of the new system and be able to explain the system, reporting processes and supporting data to regulatory inspection agencies.

Time and time again, responsibility for managing the implementation and subsequent operation of the new system is given to someone already bearing full-time responsibilities. Assigning someone this as an "off the side of their desk" kind of task can lead to problems. It helps that many new AI products are delivered as SaaS solutions. These systems are often easier to deploy and maintain, and automate many time-consuming activities as well as reducing the effort required for testing and validation. Much of the training has also been automated, reducing the necessary investment in time and further streamlining implementation.

EMERGING TRENDS INFLUENCING THE PV TRANSFORMATION

More and more companies are implementing applications that improve their processes across all aspects of safety. Technology leveraging AI helps reduce operational costs, such as the four to six hours that used to be needed to process a medium-complexity case end-to-end. These tools are making suitable case processing workflows virtually "touchless", requiring human effort primarily for Human-in-the-Loop (HITL) reviews, which is very appealing when budgets have not kept pace with workloads. They also improve the accuracy and efficiency of signal detection and reporting and are minimizing false positives, while helping identify potential false negatives, and providing explainable results to support regulatory review.

Looking at emerging trends, the first involves leveraging real-world data. Currently, pharmaceuticals focus on analysis of clinical trial data and post-market real-world data. Using AI tools to integrate these data sets allows the detection of more subtle safety signals or trends. On the regulatory side, agencies are keen to expand their use of real-world evidence (RWE). Data integration would also speed up the rate at which safety issues and trends are identified, which could translate into significant savings over the course of clinical development. By adding quantifiable value, PV evolves from a cost centre into a strategic contributor to corporate value.

Another emerging trend in Pharmacovigilance is the automation of PV document authoring. Recent advances in Generative AI and Large Language Models (LLMs) have made it possible to significantly accelerate the creation of aggregate reports, Pharmacovigilance Agreements (PVAs), Pharmacovigilance System Master Files (PSMFs), Risk Management Plans (RMPs), and other regulatory documents. However, document generation is only one part of the process. True enterprise-grade solutions must also support planning, workflow orchestration, HITL reviews, approvals, version control, audit trails, and GxP compliance throughout the document lifecycle.

A final trend being observed is the integration of product quality and drug safety. On both the regulatory agency and pharmaceutical sides, the integration between product quality and drug safety has increased significantly. Technologies such as AI are already supporting the integration of these functions within one single system that provides both capabilities.

FUTURE PROSPECTS FOR AI IN PV

In the big picture, has the adoption of AI-based tools improved overall drug safety for the average person? Social media has certainly magnified public interest in drug safety while fueling safety concerns at a time when regulatory bodies and pharmaceutical companies are having to contend with a growing number of new drugs and the enormous volume of both spontaneous and clinical data. New AI technologies, processes and techniques are leveraging this data flow to improve safety outcomes.

The increasing interest in patient-centric safety is an emerging driver of the use of AI in PV. Drawing on rapid advances in genomics and biomarkers, the field of personalized medicine is leading the way in developing more personalized therapies, including certain immunotherapies for cancer. A similar approach will likely emerge in drug safety, with technology helping evaluate drug safety within the context of an individual patient. Patient health data is being collected from a growing range of sources, including wearable devices, chatbots and social media posts. By integrating this information into AI models, patients could conceivably receive information that helps them evaluate their individual risk of adverse drug reactions.

Looking down the road, there are possible speedbumps ahead. A potential future challenge to the further implementation of AI may be computing costs. The costs of AI technologies to augment systems used for signal detection and regulatory reporting can be high. These costs are currently being reduced through continued optimization by vendors establishing more efficient pricing models and building trusted relationships within the industry and with regulatory bodies. As major tech companies continue to invest heavily in AI infrastructure and business models evolve, there is a possibility that the overall cost of deploying AI solutions and prices paid by customers may climb significantly.

While significant advances in patient safety have been gained, PV must always contend with the extraordinary complexity of human physiology. The complexity only grows when factors such as multiple medications or a patient's additional medical conditions are added to the equation. The cost of developing and testing a new product to understand its safety profile runs into the hundreds of millions of dollars. Even supplementing clinical trial data with real-world data cannot produce absolute cer-

tainty. While human trials can go a long way towards identifying potential safety issues, the complexity of human responses to medicines cannot be underestimated.

There is some hope in emerging technologies like quantum computing. This technology is already seeing early-stage applications, including quantum-enhanced algorithms. Quantum computing has the potential to significantly increase computational capability for massive combinatorial problems involving interactions among multiple drugs and the human genome. Once commercially viable, which many experts believe could occur over the next decade, it is expected to outperform classical supercomputers for certain classes of combinatorial and optimization problems, and allow more accurate prediction of complex interactions among drugs, the human genome, and genetic variations.

CONCLUSION

AI-based products draw on a broad range of architectures and techniques enhancing the speed, precision and efficiency of activities across the PV ecosystem. Different organizations are turning to different AI applications.

Even as pharmaceutical companies and regulatory authorities figure out the growing list of options for updating or re-designing their systems, these new tools are already transforming the PV sector. The benefits have been significant, as already discussed. The transformation is still, however, a work in progress. As the technology continues to evolve and its implementation matures, and notwithstanding its current and future challenges, the PV ecosystem will continue to evolve, enhancing efforts to ensure drug safety for patients.

BIOGRAPHY

Raj More is the Co-Founder, Chief Executive Officer, and Chief Architect of RxLogix Corporation, where he is driving the next generation of AI-powered drug safety. Under his leadership, RxLogix has become one of the world's leading Pharmacovigilance platforms, trusted by more than 105 organizations, including five of the world's 10 largest pharmaceutical companies and two leading regulatory agencies. With more than 25 years of experience in enterprise Pharmacovigilance, Raj is widely regarded as one of the industry's foremost technology visionaries. He has pioneered innovations spanning case management, safety surveillance, regulatory reporting, signal detection, analytics, and Agentic AI, with a mission to fundamentally transform how drug safety is practiced worldwide. Before founding RxLogix in 2010, Raj held senior leadership roles at Relsys and Oracle, where he led many of the industry's largest global Pharmacovigilance implementations. Raj holds a Bachelor's degree in Industrial Engineering and Management from RV College of Engineering, Bangalore.

Drug Development
EXECUTIVE

Jeffrey Frelick

President & Chief Executive Officer

Bone Biologics Corp.

Bone Biologics Corp: Recombinant Protein Development in Engineering Active Orthobiologics & Targeted Bone Therapies

In orthopedic care, supporting complex bone healing for high-risk patients requires solutions that balance strong bone growth with patient safety. While traditional growth factors have improved spinal fusion, side effects like swelling and unintended bone growth outside the target area show the clear need for more precise options.

Bone Biologics is addressing this challenge as it advances from early research into clinical-stage development. Powered by NELL-1, a proprietary recombinant human protein, the company's lead candidate, NB-1, is designed to foster controlled bone growth precisely where it is needed. Because NELL-1 acts later in the bone formation process, it helps limit unwanted bone growth in surrounding tissue and reduces inflammatory risks. It also fits directly into existing surgical routines, requiring no change to standard operating room procedures.

Beyond its primary focus on the $3 billion global spinal fusion market, Bone Biologics holds rights to apply NELL-1 to the $8 billion trauma and $11 billion osteoporosis markets. Guided by an experienced leadership team and a defined regulatory path with the FDA, the company is positioned to improve standard practices in bone regeneration.

Drug Development & Delivery recently spoke with Jeffrey Frelick, President and Chief Executive Officer of Bone Biologics, to discuss the science behind NELL-1, progress in clinical trials, and the future of targeted bone therapies.

Q: Could you share a brief overview of Bone Biologics and the unmet clinical needs you are addressing for "hard healers" in the spinal fusion market?

A: Bone Biologics Corporation is developing differentiated orthobiologic products for the multibillion-dollar spinal fusion market. Building upon the NELL-1 protein – the subject of a significant number of research studies and publications in peer-reviewed journals – the Company is undertaking groundbreaking work involving regenerative medicine therapies with select strategic partners. While current development efforts with Bone Biologics' bone graft substitute are focused on bone regeneration in spinal fusion, the Company also holds technology rights in trauma and osteoporosis indications.

Smokers, diabetic, and/or obese patients are all known to be "hard healers", e.g., those at higher risk for pseudoarthrosis because of a diminished biological capability to produce bone. This is an unmet clinical need because traditional orthobiologic solutions are unable to increase fusion rates in this population. Literature demonstrates that these "hard healers" are prevalent in the spine fusion population (smokers consisted of 32.5%, diabetics 18.8%, and obese 35.2% of lumbar fusion patients). The ongoing NB1 clinical study includes these hard healers.

Q: What sets your lead product, NB-1, and its proprietary NELL-1 recombinant protein apart from traditional orthobiologic solutions?

A: Traditional orthobiologic solutions are inert scaffolds that are generally comprised of ceramics (the mineral component of bone) or allograft (the non-mineral, organic component of bone). The mechanism of action is passive and involves the process of osteoconduction in which bone cells migrate into the scaffold. In contrast, rhNELL-1 is an active component that is osteopromotive.

Osteopromotive NB1 rhNELL-1 plus inert carrier, increases bone formation and the incidence of spinal fusion compared to the inert carrier alone, which has been demonstrated in several publications and by independent studies.

Q: How does NELL-1's mechanism of action promote targeted bone formation while avoiding the inflammatory responses associated with other approaches?

A: NELL-1's mechanism of action (MOA) is well published. The MOA utilizes rhNELL-1 attachment to a cellular receptor followed by intracellular signaling that is targeted to bone formation. rhNELL-1 enhances bone formation by upregulating Runx 2, which is the master transcriptional activator of bone formation. Runx2 is only active in bone cells. Thus rhNELL-1 promotes a targeted increase in bone formation (e.g., only increases bone formation in the presence of bone) because it acts on the main regulator of bone formation, which is only available in bone cells [Truong 2007; Bokus 2008; Zhang 2011].

NELL-1 is not inflammatory as demonstrated in a rat bone study that used a positive control, BMP-2, that induces local inflammation. In contrast to BMP-2, treatment with NELL-1 elicited no inflammatory response (Shen 2013). Furthermore, co-treatment with both proteins demonstrated that NELL-1 significantly attenuated BMP-2 induced inflammation (Shen 2013). The marked reduction in inflammation was attributed to NELL-1 signaling pathway which does not induce inflammation and appears to also inhibit BMP-2 induced inflammation (Truong 2007; Bokus 2008; Zhang 2011; James 2016).

Q: As a clinical-stage innovator, can you share an update on your 30-subject pilot study currently underway in Australia?

A: Bone Biologics remains committed to advancing the field of spinal surgery. What we have stated publicly is that we continue to progress through the recruitment phase of the NB1 study and hope to complete enrollment in the coming quarter or so, with an interim trial update around end of the year and 1 year data reported around mid-next year.

Q: How is the NB-1 convenience kit designed to integrate into existing surgical workflows without requiring changes to current preparation protocols?

A: Workflows include preparation of the graft material in the surgical field and delivery/ placement of the graft material in the surgical site. The placement of NB1 into a lumbar arthrodesis site is within and around the implant cage, which is the same as standard surgical practice that is used for any graft material. The delivery of NB1 is the same as has been routinely performed for allograft demineralized bone matrix (DBM) and DBX, both of which have been commercially utilized for over 20 years. The preparation of graft materials (including DBX/DBM) typically includes a hydration step. The only operating room preparation difference between NB1 and DBM/DBX is the addition of the

rhNELL-1 to DBM/DBX, which is a process comparable to hydration. The specific step of adding contents of a drug vial to the bone graft has been commonly utilized for other orthobiologics. The process requires aspiration of the drug from a vial and addition to the medical device.

Q: What does your regulatory pathway look like, given the FDA's indication that NELL-1 will be reviewed as a device/drug combination product?

A: Bone Biologics has completed PreSubmission discussions with the FDA that elucidated the regulatory pathway as summarized below:

a. The primary review center is CDRH (medical devices). CDER (drugs) consults for review of the recombinant protein Chemistry, Manufacturing and Controls.
b. Commercial approval will be after a PMA approval from FDA, which requires a pilot clinical study (analogous to a Phase I-II trial) followed by a pivotal clinical study (analogous to a Phase III trial).
c. The pilot clinical study is ongoing in Australia and FDA has indicated that data generated from Australia is acceptable and will be reviewed prior to initiation of a pivotal clinical study in the United States.

Q: Looking ahead, what is the long-term expansion potential for your therapies into the trauma and osteoporosis markets?

A: While we believe this rhNELL-1 platform technology has additional clinical applications in osteoporosis and trauma, we are currently singularly focused on spine fusion applications. As spine is one of the most challenging healing environments in the body, we feel that as we demonstrate success in our spine fusion studies, the additional clinical applications will get pulled along. For osteoporosis, there are publications that describe that rhNELL-1 improves bone formation using osteoporotic animal models. ◆

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A LIFE SCIENCE PERSPECTIVE

A Validated Modality Changes the Equation

By: Kelly Page

Few moments in drug development are more significant than demonstrating that a new therapeutic modality can translate into clinical and regulatory success. Once that threshold is crossed, the challenge is no longer proving a concept can work, it is determining how broadly it can be applied to help patients in need of new treatment options.

Earlier in my career, I was part of the effort to bring the first antibody-drug conjugate (ADC) therapy to lymphoma patients around the world. As the first ADC marketed globally, we helped pave the way for future ADCs beyond lymphoma. Today, a growing number of ADCs have received FDA approval, with more in development, demonstrating how a novel therapeutic approach can evolve into a platform for innovation and patient benefit.

In my role at Arvinas, I see similar momentum in targeted protein degradation. The pioneering efforts on PROteolysis TArgeting Chimeras (PROTAC) protein degraders, including the first FDA approval this year, have validated a new approach to treating cancer and created opportunities to expand into other disease areas. Having witnessed both advancements, it's clear that a clinical milestone extends beyond the achievement itself. Each milestone strengthens confidence in the modality, informs development strategies, and generates insights that can help accelerate turning ideas into medicines.

Early-stage programs demand rigorous scientific evaluation, mid-stage development requires thoughtful investment decisions, and late-stage programs depend on operational excellence. However, at every stage, patient needs remain paramount and must be clearly aligned with clinical goals and commercial considerations, including differentiation from available treatments and patient access.

One advantage biotechnology companies have is the ability to plan across the development continuum rather than treating development as a series of handoffs. Aligning scientific, clinical, and commercial teams helps ensure evolving evidence translates into decisions that support both successful development and meaningful patient impact.

At Arvinas, we use this same approach to guide the advancement of our diverse pipeline of PROTACs and exploration of opportunities such as degrader-antibody conjugates (DACs). For me, this brings my work full circle to what inspired me during the early days of ADCs: the possibility of turning a new scientific approach into medicines for patients who need better options. Combining lessons from ADC development with Arvinas' PROTAC expertise offers a similar opportunity, and having seen what ADCs made possible for patients, I'm motivated to help write the next chapter for PROTACs.

A validated modality changes the equation and challenges us to do more. Our responsibility is to carry what we learn into the next program and turn scientific progress into better outcomes for patients.

BIOGRAPHY

Kelly Page is Senior Vice President, Head of Asset Strategy & Program Leadership, New Product Planning & Corporate Communications at Arvinas. She has over 25 years of global pharmaceutical industry experience from the research setting through global commercialization, with nearly 20 years of experience in oncology therapeutics. Ms. Page joined Arvinas after serving as Vice President, Head of Global Commercial, Hematology at AstraZeneca. Previously, Ms. Page held global R&D and Commercial roles at Takeda Oncology, including Oncology Country Head for Takeda Germany, and at Pfizer. Ms. Page received her B.S. in Biology and her B.A. in Chemistry from Providence College and obtained her Master in Business Administration from the University of Rhode Island.

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