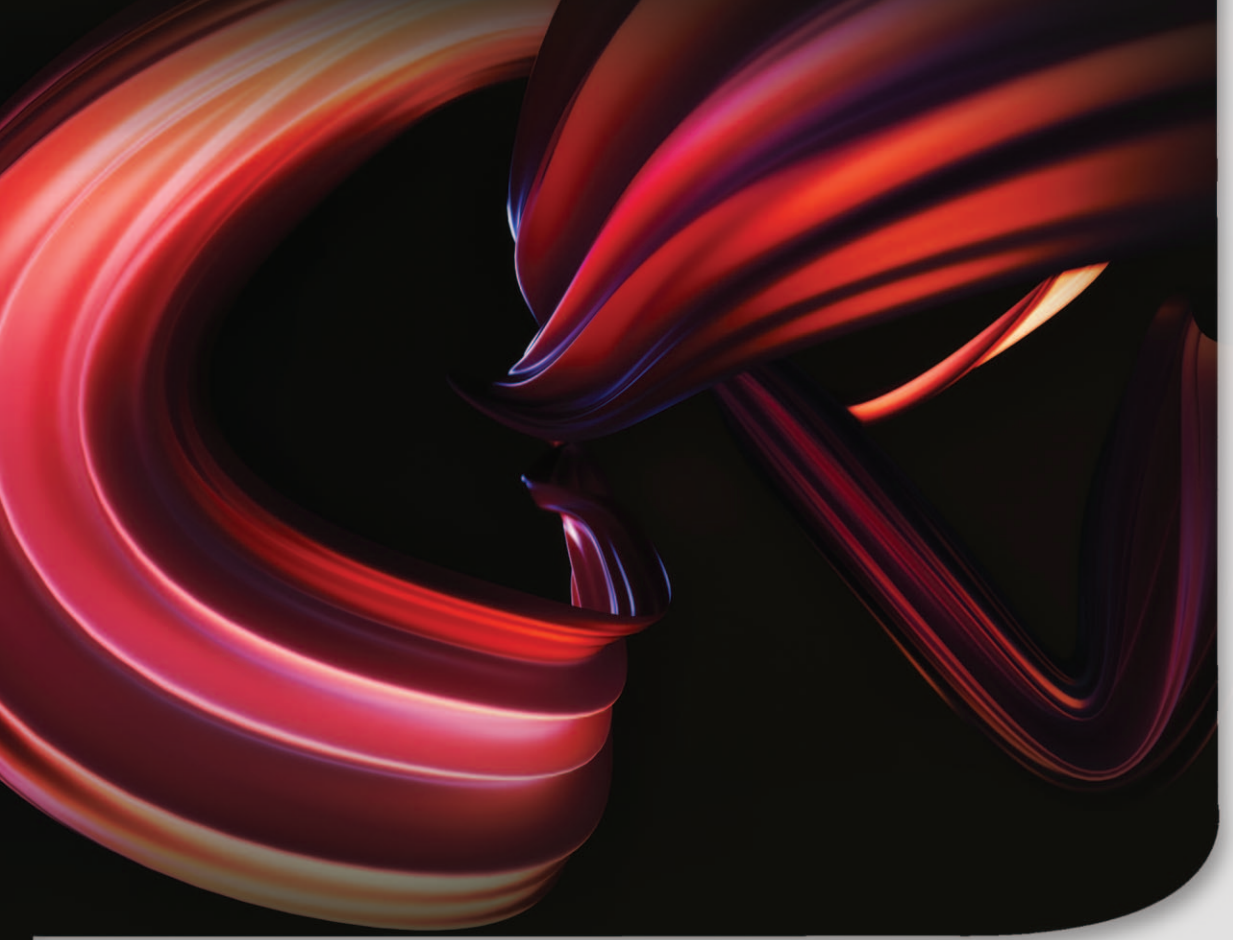
Drug Development & Delivery

April 2023 Vol 23 No 3 www.drug-dev.com

Spotlight on Inflammasome Inhibitors



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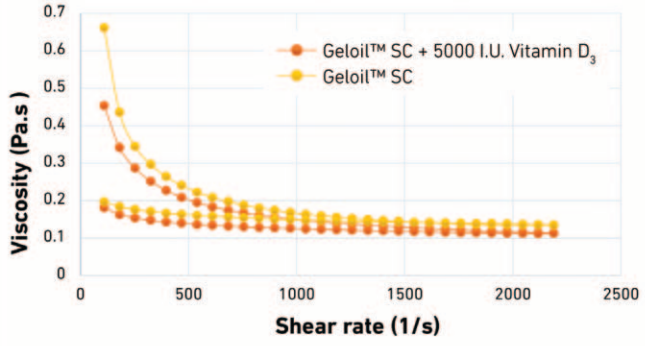

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INTEGRATED CDMO SERVICES. ADARE DOES IT. FIND OUT HOW.

Adare Pharma Solutions is a global technology-driven CDMO providing end-to-end integrated services, from product development through commercial manufacturing and packaging, with small molecule expertise focusing on oral dosage forms. Adare's specialized technology platforms provide taste masking, controlled release, solubility enhancement, and patient-centric dosing solutions. With a proven history in drug delivery, Adare has developed and manufactures more than 65 products sold by customers worldwide.

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Inflammasome Inhibitors

"However, with the growing realization that chronic inflammation lies at the center of many, if not all, diseases, it is possible to envision inflammasome inhibitors, which reduce or prevent inflammation, as near-universal treatment panaceas. If this sounds farfetched or overstated, consider that OLT1177 and RRx-001, the most clinically advanced of the direct inflammasome inhibitors, have between them demonstrated activity, mostly preclinical, in more than 50 different disease states."

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Cyclerion Therapeutics Receives Orphan Drug Designation for the Treatment of Mitochondrial Diseases

Cyclerion Therapeutics, Inc. recently announced the US FDA has granted orphan drug designation to zagociguat (previously CY6463) for the treatment of mitochondrial diseases. Zagociguat is the first CNS-penetrant sGC stimulator to be developed as a symptomatic and potentially disease-modifying therapy for serious diseases that involve the CNS. In an open-label, 29-day study in patients with MELAS, zagociguat treatment was associated with improvements in multiple disease-relevant biomarkers: mitochondrial function, inflammation, cerebral blood flow, functional brain connectivity, and visually evoked brain activation. These data coupled with data from preclinical studies in cells from mitochondrial disease patients and in zebrafish disease models support the potential of zagociguat as a treatment for MELAS/mitochondrial diseases.

"Orphan drug designation underscores the FDA's recognition of zagociguat's potential promise as a first-ever therapy for patients with MELAS, a rare, genetic mitochondrial disease," said Peter Hecht, PhD, Chief Executive Officer of Cyclerion. "Cyclerion is working expeditiously to advance this potential treatment to help address the immense unmet needs of patients with MELAS, a patient population in desperate need of therapies."

MELAS is a complex orphan disease affecting multiple organ systems, including the CNS, with different degrees of severity, and no approved therapies. MELAS, one of the most common primary mitochondrial diseases (PMDs), is caused by mitochondrial DNA mutations resulting in large clusters of familial cases. It is estimated that about 1 in 4,300 individuals has a mitochondrial disease, and ~80% of individuals with mitochondrial disease have CNS symptoms. The unmet need in MELAS is immense, symptoms can affect virtually any organ and cause intense fatigue, muscle weakness, and pain in addition to neurological manifestations, including stroke-like episodes, encephalomyopathy, seizures, and headaches. Life expectancy is estimated at ~17 years from onset of CNS symptoms. The disease impedes the individual's ability to live independently and leads to social isolation and overall reduced quality of life.

Zagociguat is the first CNS-penetrant sGC stimulator to be developed as a symptomatic and potentially disease-modifying therapy for serious diseases that involve the CNS. The nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) signaling pathway is a fundamental mechanism that precisely controls key aspects of physiology throughout the body. In the CNS, the NO-sGC-cGMP pathway regulates diverse and critical biological functions including mitochondrial function, neuronal function, inflammation, and vascular dynamics. Although it has been successfully targeted with several drugs in the periphery, this mechanism has yet to be fully leveraged therapeutically in the CNS, where impaired NO-sGC-cGMP signaling is believed to play an important role in the pathogenesis of many neurodegenerative and neuropsychiatric diseases. As an sGC stimulator, CY6463 acts as a positive allosteric modulator to sensitize the sGC enzyme to NO, increase the production of cGMP, and thereby amplify endogenous NO signaling. By compensating for deficient NO-sGC-cGMP signaling, CY6463 may have broad therapeutic potential as a treatment to improve cognition and function in people with serious diseases that involve the CNS, including mitochondrial diseases.

Covant & Boehringer Ingelheim Collaborate to Develop Novel ADAR1 Inhibitor for Use in Cancer Patients

Covant Therapeutics has recently entered into an exclusive research collaboration and worldwide licensing agreement with Boehringer Ingelheim covering Covant's ADAR1 program. The companies jointly aim to develop a novel small molecule immunotherapy targeting ADAR1 to transform the lives of cancer patients.

Covant significantly accelerates drug discovery for challenging targets like ADAR1 by using its industry-leading platform, which combines high-throughput chemoproteomics-based screening in the native setting with structural proteomics. Covant is systematically applying its platform to discover novel, high-value first-in-class and best-in-class therapeutics.

The Covant-Boehringer Ingelheim collaboration seeks to create an ADAR1 inhibitor that could be used in combination with other immunotherapies to increase their efficacy. To date, existing immunotherapies have revolutionized cancer treatment but only work in a minority of patients. Inhibiting ADAR1 has the potential to address this challenge by transforming "cold" tumors into "hot" tumors, which have more immune cells present in the tumor micro-environment.

"ADAR1 is an exciting immuno-oncology target with significant therapeutic potential," said Lamine Mbow, Global Head of Cancer Immunology & Immune Modulation, Boehringer Ingelheim. "We are committed to transforming the lives of cancer patients by delivering meaningful advances with the ultimate goal of curing a range of cancers. By partnering with Covant's exceptional scientific team and powerful platform, we aim to bring next-generation immunotherapies to cancer patients."

"We look forward to working with the scientists at Boehringer Ingelheim to advance our program against ADAR1, a key, hard-to-drug immuno-oncology target," said Dr. Ivan Cornella, Chief Scientific Officer of Covant. "Boehringer Ingelheim has a leading oncology and immuno-oncology pipeline and their decision to work with Covant is a testament to the strength of our team and approach."

Under the terms of the agreement, Covant will be responsible for the discovery of ADAR1 small molecule inhibitors. In turn, Covant will receive an upfront payment of $10 million and will be eligible for up to $471 million in additional milestone payments along with tiered royalties on global sales.

Covant Therapeutics is a Boston-based covalent drug discovery company that was incubated by Roivant Sciences (NASDAQ: ROIV). Covant creates novel therapeutics by using covalency to imprint and regulate proteins. To discover these therapeutics, the company applies cutting-edge capabilities and expertise in chemistry, quantitative proteomics, translational sciences, and deep learning. For more information, visit www.covanttx.com.

Roivant's mission is to improve the delivery of healthcare to patients by treating every inefficiency as an opportunity. Roivant develops transformative medicines faster by building technologies and developing talent in creative ways, leveraging the Roivant platform to launch Vants – nimble and focused biopharmaceutical and health technology companies. For more information, visit www.roivant.com.

Tiziana Life Sciences to Proceed With Phase 2 Clinical Trial in Patients With Non-Active Secondary Progressive Multiple Sclerosis

Tiziana Life Sciences Ltd. recently announced it has received feedback based on the US FDA Type C meeting minutes related to the Phase 2 clinical trial of intranasal foralumab in patients with non-active SPMS. Tiziana plans to accept the FDA's recommendations and intends to start a Phase 2 study in the third quarter of 2023 as previously announced. Foralumab is the only fully human anti-CD3 monoclonal antibody (mAb).

"Tiziana has reached an important regulatory milestone as it proceeds with the first ever intranasal foralumab clinical trial," said Gabriele Cerrone, Executive Chairman and interim Chief Executive Officer. "The FDA's response to our proposed Phase 2 program allows Tiziana's to advance foralumab through the regulatory process as we strive to bring this novel treatment to patients with non-active SPMS."

"I am grateful for the FDA's thoughtful review of our Phase 2 plans for intranasal foralumab," added Matthew W. Davis, MD, RPh, Chief Medical Officer. "This upcoming quarter, we will update the Phase 2 protocol with the FDA's suggestions and plan to start the Phase 2 clinical trial by holding our first investigator's meeting in Q3 2023."

Activated T cells play an important role in the inflammatory process. Foralumab, the only fully human anti-CD3 monoclonal antibody (mAb), binds to the T cell receptor and dampens inflammation by modulating T cell function, thereby suppressing effector features in multiple immune cell subsets. This effect has been demonstrated in patients with COVID and with multiple sclerosis, as well as in healthy normal subjects. Intranasal foralumab Phase 2 trials are expected to start in the third quarter of 2023 in patients with non-active SPMS. Immunomodulation by nasal anti-CD3 mAb represents a novel avenue for treatment of inflammatory human diseases.

Tiziana Life Sciences is a clinical-stage biopharmaceutical company developing breakthrough therapies using transformational drug delivery technologies to enable alternative routes of immunotherapy. Tiziana's innovative nasal approach has the potential to provide an improvement in efficacy as well as safety and tolerability compared to intravenous (IV) delivery. Tiziana's lead candidate, intranasal foralumab, which is the only fully human anti-CD3 mAb, has demonstrated a favorable safety profile and clinical response in patients in studies to date. Tiziana's technology for alternative routes of immunotherapy has been patented with several applications pending and is expected to allow for broad pipeline applications. For more information, visit https://www.tizianalifesciences.com/.

Jounce Therapeutics to be Acquired by Concentra Biosciences

Jounce Therapeutics, Inc. recently announced it has entered into a definitive merger agreement whereby Concentra Biosciences, LLC (Concentra) will acquire Jounce for $1.85 in cash per share plus a non-tradeable contingent value right (the CVR).

The $1.85 per share upfront consideration represents a premium of approximately 75% to Jounce's closing share price immediately prior to the March 14, 2023 public disclosure of Concentra's acquisition proposal.

Following a thorough review process conducted with the assistance of its legal and financial advisors, Jounce's Board of Directors has determined that the acquisition by Concentra – of which Tang Capital Partners, LP is the controlling shareholder – is in the best interests of all Jounce shareholders, and has unanimously approved the merger agreement.

Jounce's Board of Directors is no longer recommending the proposed all-share merger transaction (the Redx Business Combination) with Redx Pharma Plc (AIM:REDX) (Redx). The Jounce Board of Directors has notified Redx of the withdrawal of its recommendation in favor of the Redx Business Combination and termination of the co-operation agreement dated February 23, 2023 between Jounce and Redx.

In conjunction with the merger agreement, Jounce is implementing a workforce reduction of approximately 84% of its employees. This reduction is expected to be completed within the next month and Jounce will incur restructuring costs totaling approximately $6.5 million. The remaining Jounce employees will work to complete the sale of the company, conduct activities to maximize the value of the CVR, work to ensure that patients on the SELECT and INNATE trials have the opportunity to continue receiving therapy with vopratelimab, JTX-8064, and pimivalimab and to otherwise ensure a smooth transition to Concentra.

Pursuant and subject to the terms of the merger agreement, a subsidiary of Concentra will commence a tender offer by April 7, 2023 to acquire all outstanding shares of Jounce for $1.85 in cash per share at closing plus a non-tradeable CVR representing the right to receive 80% of the net proceeds payable for a period of ten years post-closing from any license or disposition of Jounce's programs effected within 2 years of closing and 100% of the potential aggregate value of certain specified potential cost savings.

Closing of the tender offer is subject to certain conditions, including the tender of Jounce shares representing at least a majority of the total number of outstanding shares as of immediately following the consummation of the offer; the availability of at least $110 million of cash and cash equivalents, net of any tail and closing costs, at closing, and other customary conditions. The acquisition is expected to close in the second quarter of 2023.

Stevanato Group Collaborates With Thermo Fisher Scientific to Bring its Innovative On-Body Delivery System Platform to Market

Stevanato Group S.p.A. recently announced its collaboration with Thermo Fisher Scientific to bring to the market a fully integrated on-body delivery system platform for subcutaneous administration.

The semi-reusable drug delivery device will provide micro-precision basal doses and full-content bolus injections as a highly flexible and customizable platform for administering a wide range of therapies. The collaboration brings the ability to deliver small molecules and biologics, including large volumes, subcutaneously at home, closer to patients, improving adherence and effectiveness of pharmacological treatments.

The unparalleled combination of capabilities from two established industry experts will help pharma companies with a true end-to-end solution, from drug development through to the final packaged product. Along with the proprietary device platform, Stevanato Group will offer pre-sterilized EZ-fill® cartridges as drug containment solutions and assembly equipment, while Thermo Fisher will provide fill-and-finish and final assembly services.

Pharmaceutical companies will be able to access a cartridge-based on-body delivery system with a pre-loaded and pre-filled drug container that is compatible with standard fill-finish techniques. Moreover, pharmaceutical companies can benefit from a platform technology that helps provide a fast time-to-market and a streamlined supply chain through the joint capabilities of Stevanato Group and Thermo Fisher. Additionally, benefits will extend to patients via the device's ease of use, providing more effective and comfortable treatments.

"We are proud to be working with Thermo Fisher Scientific to bring to the market our on-body delivery system for patients," said Steven Kaufman, VP for Drug Delivery Systems at Stevanato Group. "Thanks to this collaboration with Thermo Fisher, Stevanato Group will be able to respond quickly to changes in customers' needs, enabling them to scale up production according to commercial demand. The on-body delivery system increases the accessibility of in-home care and administered treatment options."

The development of the on-body delivery system is also a step forward for Stevanato Group's sustainability efforts. The device's reusable controller extends the product's lifespan and reduces waste, while the disposable pod with the pre-filled, pre-loaded cartridge can reduce user error and wasted product.

"This collaboration with Stevanato Group is an example of how we are leveraging our world-class experience and reliability in fill finish and sterile development to deliver innovative solutions at scale," said Leon Wyszkowski, President of Pharma Services Commercial Operations, Thermo Fisher Scientific. "In line with our mission to enable our customers to make the world healthier, cleaner and safer, we'll significantly improve patients' access and adherence to critical medicines."

Founded in 1949, Stevanato Group is a leading global provider of drug containment, drug delivery and diagnostic solutions to the pharmaceutical, biotechnology and life sciences industries. The Group delivers an integrated, end-to-end portfolio of products, processes and services that address customer needs across the entire drug life cycle at each of the development, clinical and commercial stages. Stevanato Group's core capabilities in scientific research and development, its commitment to technical innovation and its engineering excellence are central to its ability to offer value added solutions to clients.

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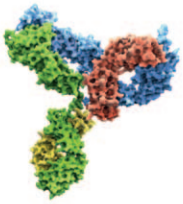

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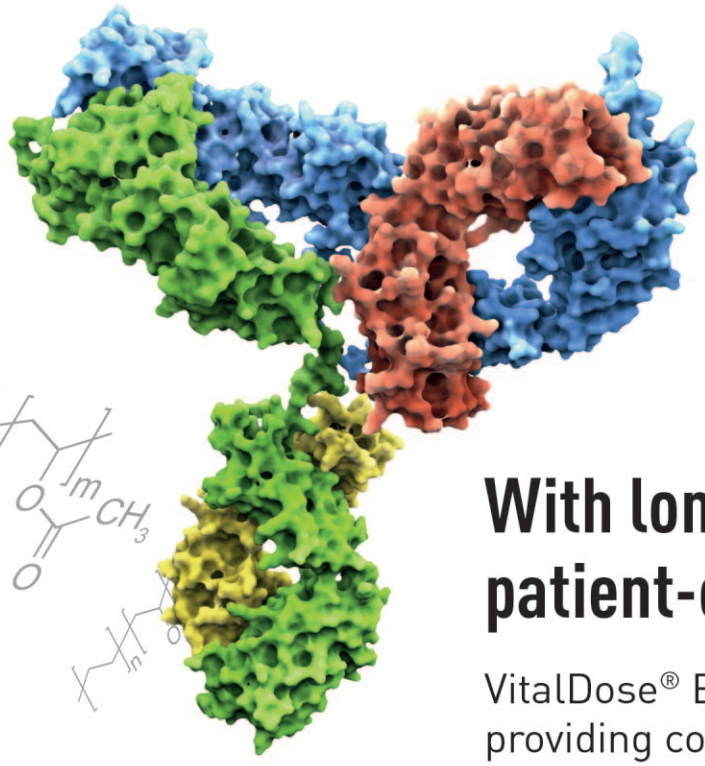

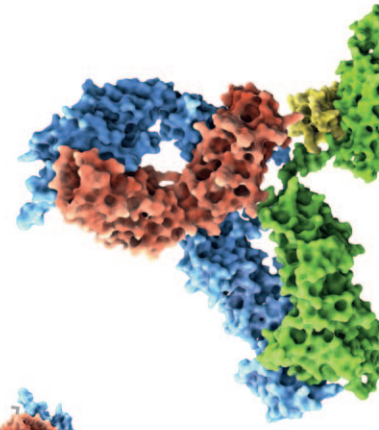

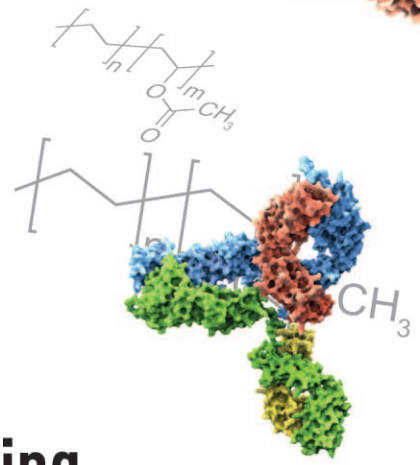

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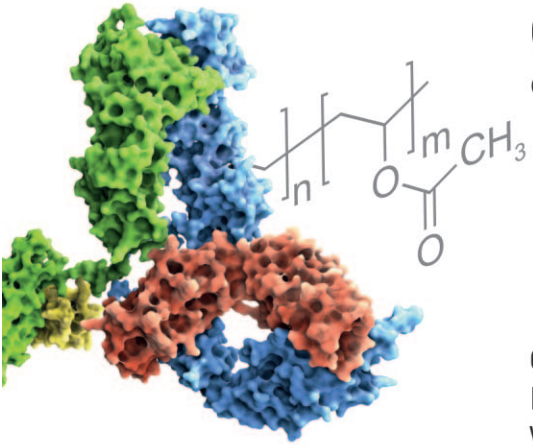

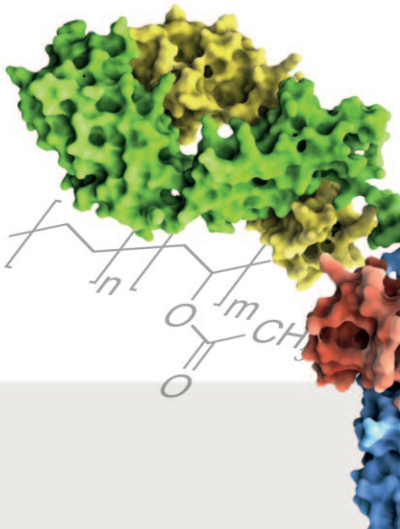

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Woodstock Sterile Solutions Completes Analytical Lab Expansion, Becomes One-Stop Shop CDMO

Woodstock Sterile Solutions has recently completed an expansion of its quality control analytical laboratory at its production facility in Woodstock, IL. The larger laboratory accommodates additional testing equipment, and Woodstock will bring on additional experts who are needed to perform the method development work and ongoing product release and stability testing now possible in house. With these expanded capabilities, the company can now deliver a total solution to its customers, from development through commercial release.

"At Woodstock Sterile Solutions, quality is our passion, and with this investment, we are further developing our in-house quality control program," said CEO Paul Josephs. "Our manufacturing team can now more easily collaborate with our quality team, improving coordination and ensuring on-time delivery. Having production and on-site quality control laboratories together under the same quality system also helps to improve effectiveness and accelerate continuous development."

Biocompatible HPLC and UPLC systems have been added to Woodstock's lab to enable drug purity and potency testing, as well as detection of impurities and other unwanted components. These systems have been specifically designed to minimize interactions between system components and biological samples to reduce the risk of contamination. Additionally, the laboratory now includes Malvern Mastersizer 3000 and Zetasizer particle analyzers, which determine the optimal particle size range for products to ensure they meet specifications.

"The expansion of our analytical lab will help us to reduce cycle times for finished product release and stability testing and enable us to further streamline issue resolution. Having manufacturing and testing all under one roof also helps us to deliver on our promise to be a one-stop-shop CDMO for customers," says Dr. Kuljit Bhatia, Chief Scientific Officer at Woodstock Sterile Solutions.

For 50 years, Woodstock Sterile Solutions has been recognized as a leading Blow-Fill-Seal (BFS) Contract Development and Manufacturing Organization (CDMO). We develop and supply BFS products for pharmaceutical and healthcare companies, providing best-in-class sterile development manufacturing solutions across a broad – and growing – range of applications, including diagnostic, respiratory, ophthalmic, topical, otic, and oral. As a highly focused organization, our expertise and commitment to innovation allow us to reduce development times and efficiently support our customers' ability to deliver products to market.

At Woodstock Sterile Solutions, we see a patient, family member or friend in every product we make, and our goal is to be the best development and commercial partner in the industry, delivering life-enhancing molecules from the benchtop to the patient. For more information, visit https://woodstocksterilesolutions.com.

Hovione & Ripple Enter Strategic Partnership to Expand Epidel Platform Into Non-Ophthalmic Space

Hovione and Ripple Therapeutics have entered a strategic partnership to expand the use of Ripple's Epidel platform beyond ophthalmic applications.

The core feature of Ripple's Epidel technology is the ability to deliver sustained-release pharmaceuticals with surface erosion release kinetics without the use of polymers or excipients. This enables higher drug loading, smaller size implants, defined and predictable biocompatible degradation products with straightforward and scalable manufacturing processes. Surface erosion-based drug release provides a highly effective way to control dose and duration. By incorporating Ripple's Epidel platform into its toolbox, Hovione can expand its portfolio of novel drug delivery solutions to the pharmaceutical industry.

"The combination of technology synergy, innovative vision, and cultural fit makes collaborating with Hovione an exciting next step in the advancement of the Epidel platform beyond the ophthalmic field," said Dr. Wendy Naimark, Ripple co-founder and Chief Technology Officer. "Hovione's expertise in controlled, sustained drug delivery, along with their experience in chemical synthesis and pharmaceutical manufacturing, makes for a great partnership."

"We are thrilled to partner with Ripple, who developed a state-of-the-art platform for sustained release," added Dr. Jean-Luc Herbeaux, Hovione's CEO. "Our shared goal is to accelerate and broaden the access to this highly innovative and enabling technology for the benefit of our pharmaceutical customers and their patients worldwide."

By extending the use of the Epidel platform beyond ocular applications, this partnership will enable the development of a diverse range of new products with optimal sustained release profiles.

Hovione is an international company with over 60 years of experience in pharmaceutical development and manufacturing operations. As a Contract Development and Manufacturing Organization (CDMO) with a fully integrated offering of services for drug substances, drug product intermediates and drug products. The company has four FDA inspected sites in the US, Portugal, Ireland, and China and development laboratories in Lisbon, Portugal, and New Jersey. Hovione provides pharmaceutical customers services for the development and compliant manufacture of innovative drugs, including highly potent compounds, and customized product solutions across the entire drug life cycle. In the inhalation area, Hovione offers a complete range of services, from API, formulation development and devices. Hovione's culture is based on innovation, quality and dependability. Hovione was the first Chemical/ Pharmaceutical Company to become a Certified B Corp, is a member of Rx-360, EFCG and participates actively in industry quality improvement initiatives to lead new global industry standards.

Ripple Therapeutics Corporation is a clinical-stage, privately held company that is focused on ophthalmic therapeutics with controllable, sustainable drug delivery. The core feature of Ripple's Epidel technology is the ability to engineer sustained-release pharmaceuticals with surface erosion release kinetics without the use of polymers or excipients. Ripple's novel therapeutics provide for better outcomes for patients, easier management of care for physicians and lower costs for payors. Ripple has a full product pipeline in development.

Owlstone Medical Enters Partnership With Bicycle Therapeutics for the Development of Antigen-Targeted EVOC Probes for Early Cancer Detection

Owlstone Medical, the global leader in Breath Biopsy for applications in early disease detection and precision medicine, recently announced it has entered into a Research Agreement with Bicycle Therapeutics plc, a biotechnology company pioneering a new and differentiated class of therapeutics based on its proprietary bicyclic peptide (Bicycle) technology.

Under the Agreement, the companies will investigate the potential of combining technologies and methods to develop antigen-targeted diagnostic probes that use bicyclic peptides as their targeting mechanism linked with Owlstone's Exogenous Volatile Organic Compound (EVOC) Probes. Work will initially focus on lung cancer screening as the first proof of principle for the broader opportunity by promoting selective accumulation of the probe at the tumor for increased signal and enhanced specificity.

If successful, the resulting antigen-targeted EVOC Probes will have the potential for use in pre-clinical research to support both cell-based and in-vivo studies; in clinical trials for patient stratification and measurement of target engagement; and as companion diagnostics to identify responders/non-responders for therapy selection and to measure target engagement over the course of treatment.

Owlstone is developing diagnostic tests in areas of high unmet clinical need including for the early detection of lung cancer, the most common cancer in the world. To support this effort, Owlstone has pioneered the use of EVOC Probes1 in early detection and precision medicine, with the Company's lead EVOC Probe in clinical trials. This probe utilizes the activity of enzymes expressed within the tumor microenvironment to release a volatile reporter chemical that can be detected on breath when a tumor is present. The combined approach to be explored under the Agreement will exploit Bicycle's proprietary Bicycle technology to direct binding and accumulation of the probe on tumor cells, following which increased levels of the reporter chemical would be released.

The platform includes ReCIVA, a proprietary sample collection device that can take stable breath samples anywhere, the world's only commercial Breath Biopsy Laboratory located in Cambridge, UK, and the Breath Biopsy VOC Atlas, the most extensive catalogue of identified volatile organic compounds (VOCs) commonly found on breath. The company's technology is protected by over 120 granted and pending patents and has been used in more than 100 research papers.

Owlstone Medical's Research Products and Services are being deployed at over 100 sites around the world with large pharmaceutical companies including AstraZeneca, Actelion (a J&J company), and GlaxoSmithKline, and leading academic institutions. Projects are supported by Breath Biopsy OMNI, the most advanced solution for reliable end-to-end global breath VOC analysis, which is helping researchers advance biomarker discovery and disease research and maximizing the chances of finding clinically relevant breath biomarkers.

Revive Therapeutics Provides Update on Psilocybin Clinical Study for Methamphetamine Use Disorder

Revive Therapeutics Ltd. recently provided an update on the company's Phase 1/2 clinical study (NCT05322954) evaluating the safety and feasibility of oral psilocybin as a potential treatment for methamphetamine use disorder conducted at the University of Wisconsin-Madison, School of Medicine and Public Health and School of Pharmacy. Under an investigator-initiated IND, led by Dr. Christopher Nicholas, PhD, the Study has enrolled its first patient and initial results are expected in Q3-2023.

The clinical data generated from the Study may provide proprietary and valuable information on the safety, efficacy and dosing of oral psilocybin to support potential research and commercial initiatives in countries, such as Australia, where psilocybin can be available to specially-licensed psychiatrists to prescribe for certain conditions and future clinical studies for the company's proposed psilocybin oral thin film strip and transdermal microneedle patch products. In addition, the company will have exclusive access to key intellectual property from this Study to support development, regulatory and commercial initiatives.

Methamphetamine use disorder is a chronic relapsing condition associated with substantial mental, physical, and social harms and increasing rates of mortality. Contingency management and psychotherapy interventions are the mainstays of treatment but are modestly effective with high relapse rates, while pharmacological treatments have shown little to no efficacy. At present, there are no approved medications to treat methamphetamine use disorder. Psilocybin-assisted psychotherapy is emerging as a promising treatment for a range of difficult-to-treat conditions, including substance use disorders, however, no studies have yet been published looking at psilocybin-assisted psychotherapy in the treatment of methamphetamine use disorder.

"We are committed to advancing novel uses and delivery forms of psilocybin to treat substance abuse and mental health disorders. The clinical trial evaluating oral psilocybin for methamphetamine use disorder is a study to potentially demonstrate psilocybin's utility for substance abuse indications and support future commercial and clinical studies using our oral thin film strip and transdermal microneedle patch delivery technologies," said Michael Frank, CEO of Revive.

Revive is a life sciences company focused on the research and development of therapeutics for infectious diseases and rare disorders, and it is prioritizing drug development efforts to take advantage of several regulatory incentives awarded by the FDA such as Orphan Drug, Fast Track, Breakthrough Therapy and Rare Pediatric Disease designations. Currently, the Company is exploring the use of Bucillamine for the potential treatment of infectious diseases, with an initial focus on severe influenza and COVID-19. With its acquisition of Psilocin Pharma Corp., Revive is advancing the development of Psilocybin-based therapeutics in various diseases and disorders. Revive's cannabinoid pharmaceutical portfolio focuses on rare inflammatory diseases and the company was granted FDA orphan drug status designation for the use of Cannabidiol (CBD) to treat autoimmune hepatitis (liver disease) and to treat ischemia and reperfusion injury from organ transplantation. For more information, visit www.ReviveThera.com.

Acumen Pharmaceuticals Presents *In Vitro* Human Neuron Model for Evaluating Binding of Amyloid Beta Oligomers in Alzheimer's Disease

Acumen Pharmaceuticals, Inc. has recently demonstrated the utility of a human *in vitro* model of iPSC-derived excitatory neurons for a better understanding of which forms of amyloid beta oligomers contribute to the pathogenesis of AD in the human brain. This research was presented in a poster at the International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders (AD/PD), held in-person in Gothenburg, Sweden, and virtually March 28-April 1, 2023.

There is considerable scientific evidence that supports the role of toxic forms of soluble aggregates of Aβ, such as oligomers and protofibrils, in the pathogenesis of AD. Soluble AβOs have been found to bind at synapses, which leads to altered neuronal function, and can initiate and perpetuate the process of neurodegeneration. However, soluble AβOs exist in many forms – including globular and linear conformations, a wide range of size distributions, and diverse epitope displays – and it remains unclear which of these species are most relevant to AD pathogenesis. Soluble AβOs have been challenging to model in the laboratory even though they have been identified in the cerebrospinal fluid (CSF) of AD patients; their concentrations are low in CSF, and an understanding of their diversity, especially with regard to molecular weights in the human brain, needs additional refinement.

Utilizing human iPSC-derived excitatory neurons as a model, a panel of Aβ detection antibodies, and a panel of globular sAβOs plus monomers, the current study found that sAβ size may influence synaptic binding. Regardless of sAβ preparation or detection antibody, low-molecular weight sAβ species (monomers-trimers) demonstrated the lowest levels of detectable synaptic binding, compared with those of mid- and high-molecular weight (> 150 kDa).

This research complements Acumen's ongoing clinical development of ACU193, a humanized monoclonal antibody candidate that selectively targets toxic globular sAβOs. Acumen recently completed patient enrollment in INTERCEPT-AD, a Phase 1, US-based, multi-center, randomized, double-blind, placebo-controlled clinical trial evaluating the safety and tolerability, and establishing clinical proof of mechanism, of ACU193 in patients with early AD. The Company plans to initiate a Phase 2 trial of ACU193 with the potential to expand into a Phase 3 trial.

ACU193 is a humanized monoclonal antibody (mAb) discovered and developed based on its selectivity for soluble amyloid beta oligomers (sAβOs), which Acumen believes are more toxic forms of Aβ, relative to Aβ monomers and amyloid plaques. Globular sAβOs have been observed to be potent neurotoxins that bind to neurons, inhibit synaptic function and induce neurodegeneration. By selectively targeting toxic globular sAβOs, ACU193 aims to directly address a growing body of evidence indicating that sAβOs are a primary underlying cause of the neurodegenerative process in Alzheimer's disease. ACU193 has been granted Fast Track designation for the treatment of early Alzheimer's disease by the US FDA.

Macomics & Ono Pharmaceutical Partner to Discover & Develop Macrophage-Targeting Antibody Therapy for Cancer Treatment

Macomics Ltd recently announced it has entered into a worldwide drug discovery collaboration agreement with Ono Pharmaceutical Co., Ltd. to develop new immuno-oncology antibody drugs against a novel macrophage target of interest in cancer.

Under the terms of the agreement, Macomics will identify and characterize antibody candidates against the novel target of interest using its ENIGMAC macrophage drug discovery platform. Ono will have an exclusive option to license global rights to the candidates for further development and commercialization. Macomics will receive an up-front payment, R&D funding, and success-based milestone payments, as well as tiered royalties based on global net sales.

Macomics is exploiting the potential of macrophage-based approaches to develop novel precision medicines to target disease specific macrophage biology. Macomics' ENIGMAC macrophage drug discovery platform integrates large volume human data sets, custom cell models, and proprietary human macrophage genome editing capability to discover novel targets and unlock disease specific target biology. Macrophages (TAMs) are often the most abundant immune cell many types of cancer and modulating TAMs can enhance the body's ability to fight cancer.

Toichi Takino, Senior Executive Officer/Executive Director, Discovery & Research of Ono, said "Targeting macrophages in immune-oncology is emerging as an exciting area with significant opportunity to deliver novel therapeutics to improve cancer outcomes and to change the lives of patients with cancer. Macomics has demonstrated the power of its macrophage platform and drug discovery approach and we are delighted to partner with them on taking this novel target discovery program forwards."

Stephen Myatt, CEO of Macomics, added "This global collaboration with Ono is a testament to our strong program portfolio, and the unique enablement offered by our ENIGMAC discovery platform, and our world class R&D team. Ono is a leader in immuno-oncology and we are delighted to have a partner in Ono who brings the complementary skills necessary to succeed in this therapeutic area."

Macomics Ltd is an immuno-oncology company with world-leading expertise in macrophage biology, developing precision medicines to modulate macrophages for the treatment of cancer. The company is progressing a diversified portfolio of therapies targeting disease specific tumor-associated macrophages (TAMs) toward the clinic. Its ENIGMAC macrophage drug discovery platform enables identification and validation of novel macrophage therapeutic targets and is based on its deep understanding of macrophage biology.

The company was co-founded in 2020 by Prof. Jeffrey Pollard and Dr. Luca Cassetta, University of Edinburgh, internationally recognised leaders in macrophage biology. It has R&D and office facilities in Edinburgh and Cambridge, UK and is backed by Epidarex Capital, Scottish Enterprise, LifeLink Ventures and Caribou Property Limited. For more information, visit www.macomics.com.

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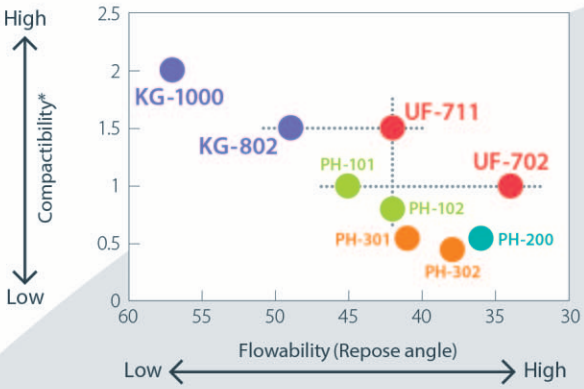
Map of Ceolus™ Compactibility vs. Flowability



* Comparison of tablet hardness, with the formulation of PH-101 = 1 set as the index point
Formulation: Acetaminophen/MCC = 70/30

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Formulation Forum

Tackling Challenging Molecules by Spray Drying: Making the Impossible Possible

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

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INTRODUCTION

As we continue our research in drug discovery, more than 80% of new molecular entities (NMEs) are poorly soluble, often making it impossible to formulate by using the conventional technologies, such as micro-milling, salt formation, or complexation. That has triggered a range of enabling formulation options, including non-conventional technologies, such as amorphous solid dispersions (ASDs) or liquid dispersions and co-precipitation.[1] Polymer-based amorphous solid dispersion (ASD) technology is an innovative approach that converts highly crystalline insoluble molecules resembling "brick dust" to highly amorphous powders, making them highly water soluble.[2] Others like liquid dispersions resulting from emulsifying systems require a significant amount of solubilizers and surfactants lipophilic in nature, enabling the formation of microemulsions or nanoemulsions for faster dispersibility in waters that lead to faster absorption in the gastrointestinal tract often independent of pH.[3]

For polymer-based ASDs, polymeric excipients play a crucial role in helping convert highly crystalline APIs into amorphous states, making them more water soluble. For development of NCEs requiring medium to high doses, solid dispersion technologies are highly desirable for designing better and smarter oral dosages with higher efficacy that increase patient compliance by reducing the pill burden. Of several marketed ASD drugs, spray drying remains the most popular approach to convert crystalline drugs into amorphous powder, mainly due to a simpler downstream process to formulate ASDs into oral dosage forms.[4]

Spray drying formulas appear simple, but they can bring challenges in selecting suitable excipient solvents and processing conditions that match those API properties during the formulation design and manufacturing of ASDs. The product's quality attributes depend on several factors, including the intrinsic instability of amorphous dispersions resulting from conversion or nucleation to original stable crystalline state. Furthermore, controlling the level of residual solvents requires a paramount task to meet the ICH guidelines. In addition, longer solvent removal time during secondary drying may potentially lead to the API's degradation and compromised efficacy of drug due to moisture and temperature effects. In spite of all these challenges, spray drying is an ideally accepted technology for preparing amorphous dispersions and improving and enhancing solubility and bioavailability, thus, making them possible from impossible for some of difficult molecules.[5]

This article will focus on spray drying technology with special reference to polymers and solvents selection, processing conditions, and the challenges with downstream manufacturing, stability, and degradation of APIs in oral dosages.

CONSIDERATIONS FOR SPRAY DRYING PROCESS

Spray drying requires polymers or blends of polymers for enhancing miscibility of drugs fully dispersed in the matrix. The composition and nature of the polymers and polymeric solubilizers are critical for processing and manufacturing of drugs in ASD powders. For example, higher polymer-to-drug ratios generally help provide stronger interactions of drug with polymer and yield stable formulations. Longer and higher molecular weight polymers provide stronger intermolecular interactions and protection of drug in the polymeric matrices. On the other hand, short-chain polymers affect the weaker intermolecular interactions of drug, resulting in poor entanglement and poor solubility

and stability of drugs in the ASD powders. Therefore, polymer selection remains one of the important criteria in creating and developing a robust ASD formulation. For instance, long-chain polymers with higher molecular weight, for example, Soluplus®, will probably have much better and stronger interactions, and likely better solubilization capabilities, than those with low molecular weight due to lack of stronger entanglement of drug with polymer.[6]

A number of polymers are available commercially and also marketed in ASD drug products. The criteria for selecting polymers for spray drying include solubility of polymer and drugs in compatible organic solvents, thermal stability, and ease of processibility. All these criteria affect the *in vitro* and *in vivo* performances of drugs. The glass transition temperature (T_g) and chemistry and functional group of polymers and melting and T_g of drugs are all important factors in selection of appropriate polymeric excipients for spray drying. For instance, drugs with H-donor abilities can be stabilized with polymers having H-accepting ability via H-bonding. Thus, H-donor and acceptor criteria can stabilize the drug within the polymeric matrix by intermolecular interactions. For instance, copovidone (PVP/VA 64), may lead to stable formulations by inhibiting the recrystallization and leading the API in supersaturation without precipitation.[7]

Polymeric excipients used for ASDs are often amorphous in nature, while the drugs are highly crystalline. The API's compatibility with polymers depends on the physico-chemical properties of APIs. In cases in which the drugs are like "brick dust" or highly "lipophilic," finding the appropriate polymers with understanding of higher drug loading and maintaining thermodynamic and kinetic stability over extended periods in powders and in aqueous solution/biorelevant media are challenging because all factors lead to critical quality attributes for a robust formulation. The greater solubility of amorphous drug, compared to its stable crystalline form, is primarily due to minimal energy barrier required to dissolve in water.[8]

SCREENING OF APIS WITH POLYMERS

Because APIs are available in small quantities, an efficient screening method is required to identify the appropriate polymers with higher drug loading or exposure. It is important because marketed ASD drugs are typically available in large pills (>1 g). Thus, when screening the APIs with a range of polymers structurally different from each other and having different properties, their high-solubilization capabilities must be considered.[9] It is achieved by dissolving the compounds and polymers in polar organic solvents and by casting clear films on drying in an oven at 50°C.[10] This process is simple and rapid, which allows screening of multiple compounds with polymers at different drug:polymer ratios simultaneously within a short time. Kolter et al. have used this method to screen a range of polymers to identify lead formulations.[9] Likewise, others have used the same procedure for selection of polymers for lead formulations. Dai et al. also used solvent evaporation in 96 wells for screening a range of polymers and solubilizers for APIs.[11] Others have also used several polymers and solubilizers for screening a range of APIs varied in structures and functions.[12,13] There is no data available on structure-function relationship of polymers and APIs on solubility. Other methods also include hot-stage microscopy for screening of drug molecules, but again, all these methods remain laborious and empirical that require good amounts of compounds in which polymer selection for ASD remains "hit and miss."[14] Like polymer selection, solvent selection remains at the highest priority because its solvation capability and compatibility for polymers and drugs are at the forefront of spray drying technology.

This column is focused on polymer selection and the solvents used in spray drying technology. Because it is quite different from

TABLE 1

Polymer	Solubilizer
●Povidone: PVP K12, K17, K25, K30 ●Copovidone (PVP/VA 64) ●Methacrylic acid ethylacrylate copolymer (1:1) ●Methacrylate polymers (Eudragit PO/100, RLPO, L100, S100 ●Polyvinylcaprolactam/Polyvinylacetate/ polyethylene glycol ●Polyvinyl alcohol ●HPMC, HPMCAS, HPMCP	●Polyethylene glycol, 3350, 4000, 6000, 8000 ●Poloxamer 188, 407 ●Ducosate sodium

Commonly used polymers for spray drying

TABLE 2

Solvent	Boiling Point/ICH Limit
Acetone	56.3°C/Class 3
Acetonitrile	81.6°C /410 ppm
Methylene Chloride	39.8°C /600 ppm
Chloroform	61.2°C /60 ppm
THF	26.9°C /720 ppm
Ethyl Acetate	77.1°C /Class 3
Ethanol	78.3°C /Class 3
Methanol	64.7°C /3000 ppm
2-Propanol	82.3°C
Dimethyl Formamide	153°C
Water	100°C
t-Butyl Methyl Ether	131°C

Commonly used solvents for spray drying

hot-melt extrusion, the polymer's T_g is of lesser significance than solubility in organic solvents; therefore, T_g is not the prime concern with exceptions of drugs with very low melting temperatures and T_g.

POLYMER SELECTION FOR SPRAY DRYING

Polymer selection and choice of compatible solvents are an important first step requirement for the spray drying process. It may bring enormous challenges as the processing conditions for spraying amorphous powders out of solvents/co-solvents can lead to immediate re-crystallization of drugs to their most stable state. Thus, spray rate, temperature, and atomization rate can all impact the outcome of amorphous dispersion powders. Table 1 shows the list of commonly used polymers and stabilizers for spray drying dispersions.[4]

SOLVENT SELECTION FOR SPRAY DRYING

The spray drying process requires a significantly large amount of solvents, which could be an impediment in development of an amorphous drugs because of incomplete dry powders. At a smaller scale, it is highly feasible to save time and cost, but for scale- up, it requires large amounts of solvent that necessitates a more efficient drying process to control the residual solvents per the ICH guidelines. In such cases, solvents with low boiling and API's with higher solubility are preferred over high-boiling solvents for controlled particle size and higher yield.[4] The drug's stability in the solvent feed requiring a longer spray drying process can lead to generating impurities by thermal degradation; therefore, care must be taken to minimize the undesired side reactions and related impurities. Table 2 lists solvents and their boiling temperatures used in spray drying and are selected based on solubility of APIs and safety to maximize the output or yield of spray dried powders.[15]

CRITICAL PROCESSING CONDITIONS FOR SPRAY DRYING POWDERS

Critical processing parameters for spray drying depend on several factors, including but limited to, spray rate, nozzle size, inlet and outlet temperature, humidity, drug and polymer amounts, and atomization rate among others. As indicated, the following critical parameters are used for spray dried formulations.

Spray Rate - faster rate helps improve the particle size and shape upon atomization.

Nozzle Size - spray rate through the nozzle aperture determines the shape and size of the spray dried powder and is critical for product's performance.

Polymer & Drug Concentrations - higher solid content is important to cut down the solvents that further improve faster evaporation and less exposure of drug in solvent for extended periods during spray drying and to maintain droplet size upon atomization.

Viscosity - lower viscosity over higher viscosity of feed is preferred as it requires low energy and pressure to yield desired spray patterns and particle sizes.

Humidity - controlling humidity is necessary to reduce the adherence of the powders with the vessels thereby improving the yields and decreasing the chances for agglomeration.

Inlet Temperature of Air - higher inlet temperature leads to faster evaporation of

Ascendia's GMP Spray Dryer

FIGURE 1

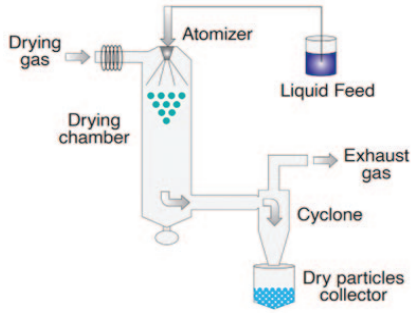

Illustration of the Spray Drying Process

solvents and moisture, but it should be controlled to drugs sensitive to higher temperature to prevent degradation of drugs.

Outlet Temperature of Air - controlling it by adjusting the gas flow which in turn atomizes the droplets out of the nozzle and controls the particle size and moisture in spray dried powders.

Organic Solvents - organic solvents with lower boiling temperature control the particle size, yield smaller particles due to reduced surface friction through the nozzle compared with water, and help drying the powders faster

Feed Rate - higher feed rate leads to increasing the droplet size, and hence, the particle size of spray dried powders.

SPRAY DRYING EQUIPMENT

The spray drying process is a gentle one-step continuous manufacturing process that involves creating dry powders directly from a fully dispersed one-phase mixture of drug and polymer dissolved in a commonly solvent or slurry of mixture of drug and polymer. The slurry is subjected to spray as fine droplets by atomization controlled with a stream of hot drying gas (nitrogen) typically carried out between 50°C-100°C. The spray dried powders are dried rapidly as the solvent evaporates and product is collected in a cyclone, and the solvent is reconciled after condensing through a chiller as shown in Figure 1.[16]

Spray nozzles and their apertures are important for creating spherical and hollow smooth spray dried powders following atomization. Thus, a careful selection of nozzle is required for achieving the desired particle size from the droplets by adjusting the appropriate atomization pressure. To alleviate these challenges, hollow cone pressure one or multiple nozzles (eg, Schlick nozzles) are typically used for atomization of spray dried feed with viscosity of 50-100 mPas and at pressure range of 20-200 bar with a throughput of 500-kg liquid per hour.[9] Powders collected in a cyclone require post drying or cooling by fluid bed to keep them moisture free as they can lead to agglomeration of particles forming lumps and possibly leading to degradation of APIs upon storage.

Taken collectively, the product's quality parameters should be monitored for hygroscopicity, moisture content, bulk and tapped density, flowability, particle size and morphology, amorphization, and encapsulation and complete miscibility of drugs by physical techniques. Spray drying factors, such as operation conditions and feed characteristics, affect the product's quality in general. The operation conditions include inlet and outlet temperatures, feed flow rate, drying gas flow rate, atomizing gas flow rate, feed temperature, and atomizer speed; and the feed characteristics include feed composition, carrier's type and concentration, density, and viscosity.[17]

Table 3 may help guide to achieve spray drying formulations with desired characteristics using the right processing conditions.[18,19]

DOWNSTREAM PROCESSING FOR DESIGNING OF ORAL DOSAGES FROM BULK SPRAY DRIED POWDERS

Spray dried powders are fine and often contain the residual solvents (ca. 1%-10%) regardless of the drying conditions.[20] The evaporation of solvents from dried powders requires elevated temperature under vacuum/pressure. In such cases, drying by traditional methods of spray dried powders can take several days; therefore, more efficient

TABLE 3

Property	Processing Parameter					
	Spray Rate ↑	Gas Humidity ↑	Inlet Temperature ↑	Gas Flow ↑	Feed Rate ↑	Organic Solvent ↑
Outlet Temperature	++	+	+++	-	--	+++
Particle Size	+/-	+/-	+/-	---	+	-
Product Moisture	--	++	--	+/-	++	---
Yield	++	-	+	+/-	+/-	++

+/- Minor influence (positive and negative)
++/-- moderate influence (positive and negative)
+++/--- High influence (positive and negative)
+/- may not change

A guide to achieve spray drying formulations with desired characteristics using the right processing conditions.[18,19]

methods are warranted to improve stability of drugs in bulk powders. To drive off the residual solvents and attain the minimal levels to meet the ICH guidelines, traditional methods like the use of conventional ovens may be time-consuming and costly. Furthermore, longer evaporation time under higher temperature could also be detrimental for stability, integrity, and stability of drug products. Thus, there is a continued effort to find the ideal evaporation method to minimize the exposure of amorphous drug in powders to alleviate re-crystallization and avoid degradation and/or conversion into different polymorphs. Shepard et al. used a solvent-assisted secondary drying method.[21] The solvent-assisted method is carried out in an Ekato VPT3 agitated dryer that allows the removal of residual solvents from bulk powder by purging of solvents (e.g., methanol) with dry nitrogen bubbles. The stability challenges, if not controlled, can lead to compromised potency or generation of undesired impurities that could pose safety risks upon storage over extended periods. In such cases, careful selection of the drying methods for evaporation of residual solvents are highly desired to shorten the exposure by an efficient drying process to reduce the solvent levels and hygroscopicity.

Spray dried powders can be directly compressed into tablets, minitablets, or pellets. Because the powder flowability of SD powders are poor, use of appropriate excipients lead to increased flowability for compression. Lin and Kao compressed spray dried sodium diclofenac enteric-coated microcapsules into tablets with neocel and flo-starch (weight ratio, 1:1).[22] Al Zoubi et al. investigated a number of directly compressible excipients for compressing SD powders into oral tablets.[23]

ASCENDIA'S CAPABILITIES IN SPRAY DRYING MANUFACTURING

As new molecules coming out of discovery require enabling, non-conventional formulation technologies for developing drugs for unmet medical needs, Ascendia continues to be on the forefront serving the pharma and biotech industry by employing its proprietary technologies, such as NanoSol®, EmulSol®, LipidSol®, and AmorSol®. The latter is widely applicable as some of the other technologies may require challenges with stability and special facilities for sterile and aseptic filling/processing for parenteral and oral liquids. Ascendia's AmorSol® can help find the appropriate solutions by screening different compatible polymers listed in the inactive ingredient database (IID) for an individual compound by using a film-casting approach to streamline and optimize the process amenable to ASDs by the spray drying or hot-melt process. In addition, AmorSol® could potentially reduce or eliminate the food effect for certain type of drug candidates. Its state-of-the-art cGMP manufacturing facility can handle ASD projects from early stage in pre-IND to clinical Phase 1 and Phase 2 development. ◆

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Drug Development
EXECUTIVE

John Ross

Senior VP, Development & Manufacturing

PCI Pharma Services

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PCI Pharma Services: The Global, Integrated CDMO Partner of Choice

In recent years, drug development organizations have increasingly turned to outsourcing as a way to optimize resources, leverage expertise, de-risk investment, and accelerate drug development timelines. This trend has been particularly prominent in the field of oncology, where the need for novel therapies and personalized medicine has led to a surge in research and development activities. With the oncology drugs market predicted to experience a compound annual growth rate (CAGR) of 12.74% from 2019 to 2027, the importance of partnering with the right CDMO can hardly be understated.[1] *Drug Development & Delivery* recently interviewed John Ross, Senior Vice President of Development and Manufacturing at PCI Pharma Services, to discuss what it means to be the partner of choice in a very dynamic industry.

Q: Why has the demand for pharma outsourcing services increased?

A: One driver is the growing complexity of drug development and manufacturing processes. A wide range of highly specialized skills, knowledge, and equipment is required to execute these processes efficiently, particularly when it comes to biologics and highly targeted solid oral medicines. The sheer number of drug product sponsors has grown significantly, and increasingly they operate a virtual business model. This dynamic has formed a more mature outsourcing market where often the greatest depth of drug product CMC expertise lies with the CDMO. It therefore makes sense to work with an established CDMO with readily available, recognized capabilities. Globalization is another factor — as companies expand into new markets, they need partners who understand and can help them navigate the regulatory requirements and supply chain challenges of operating in these markets.

All of this relates to one key point: speed to market. Pharmaceutical companies are driven to get critical medicines to patients quickly. They are also under pressure

to monetize the financial return from development candidates. As such, they must optimize resources, and CDMOs with the right expertise, scale, and infrastructure can help to significantly reduce the overall time and complexity of drug development and manufacturing.

Q: What capabilities should a world-class CDMO have to be able to support its clients?

A: It almost goes without saying, but globally compliant facilities and deep technical expertise are vital. When teams of experienced scientists and engineers operate state-of-the-art equipment and instrumentation, sponsors can rest assured their valuable drug product is in good hands and challenges will be addressed effectively. The underlying quality system must support the GMP compliance requirements of global markets and the support functions, such as Project Management, must be aligned to the needs and ambitions of its sponsors.

With the growth of oncology drug candidates, containment associated with handling highly potent molecules is a primary consideration, for both operator safety and product integrity. Containment strategies have evolved from using PPE to engineered solutions – being the highest possible level of containment. World-class engineered solutions include the use of isolators for the dispensing of API along with contained manufacturing and packaging equipment. Facility design must include segregated people and material flow combined with HVAC filtration systems to reduce airborne particulates. A sponsor should therefore pay close attention to how its CDMO processes highly potent products. PCI's facility in Tredegar, Wales is a true market leader in this field, with its Contained Manufacturing Facilities enabling the safe development, clinical, and commercial supply of products with an occupational exposure limit (OEL) as low as 0.01μg/m^3.

A world-class CDMO should also boast a range of "soft skills" to complement technical operational capabilities. For example, a commitment to continuous improvement enables them to leverage new technologies and best practices to improve operational processes in support of its sponsors. And everything must be underpinned by a collaborative relationship, fueled by strong communication being mindful of critical project milestones, working effectively through any challenges that may be encountered to execute projects on time and on budget.

I believe the primary way a CDMO can support sponsors is by providing them with flexible and scalable services. The CDMO market remains highly fragmented, with more than 300 in operation and the top 5 players occupying about 15% market share. This may lead to sponsor organizations partnering with a CDMO that cannot scale with the advancement of its product, forcing them to outsource to a more suitable downstream CDMO. This can be a particular issue for small- to mid-size pharmaceutical companies that may not have the resources or expertise to manage the entire drug development and manufacturing process in house or the pipeline to warrant building out embedded internal expertise that the right CDMO is able to readily provide on a fee-for-service basis.

Q: Why is scalability such an important capability for a CDMO?

A: Inherently, scalability implies growth in batch size and output; however, many drug candidates today have highly targeted patient populations so scalability should also cause one to think about ability to support the advancement of the drug product candidate into late-stage clinical and commercial requirements even if the market expectations are such that the batch volume is not materially different from its clinical requirements.

Say you've partnered with a CDMO that is able to develop and manufacture your product in support of early stage clinical requirements, but its current offering would not be well suited to handle global commercial requirements. The options here would be to invest heavily in facility, equipment, or systems enhancements, or tech transfer to a CDMO able to handle the commercial requirements. Both options are expensive and will add a layer of complexity, time, and risk to the program. A CDMO with the ability to scale mitigates these challenges and will leverage the deep understanding of the drug product gained through tacit knowledge, ensuring product consistency throughout its supply lifecycle.

Even post-launch, there are challenges that can be overcome by partnering with a CDMO than can respond quickly and effectively. The pharmaceutical market is constantly changing, and demand for drugs can fluctuate based on a variety of factors, including demographics, disease prevalence, and regulatory changes. When dealing with highly targeted therapies like those handled by PCI, it is essential demand is met. In-built scalability, including global compliance, therefore allows CDMOs to adjust production volumes quickly to meet changes in market demand, ensuring life-changing therapies can reach patients around the globe.

By choosing a CDMO that is able to scale alongside your product's evolution, sponsor organizations can therefore save money, maintain a simpler supply chain, mitigate risk, and achieve commercial launch more quickly. The ideal scenario for

sponsor organizations is able to identify a CDMO able to offer true end-to-end solutions from clinical supply to commercial launch and sustained in-market support.

Q: What are the benefits of using a CDMO able to deliver true end-to-end services under one roof?

A: A true CDMO offering end-to-end solutions can act as a strategic partner, helping a sponsor company take a drug product from the early clinical phases through to commercial launch and beyond. They can develop the formulation, manufacture and package clinical supplies, ensure your product is market-ready, and then scale up manufacturing and packaging processes to meet commercial demand. These core service offerings are ideally supported by a range of support services, such as analytical development and stability, clinical support services, regulatory support, logistics, package design, artwork services, and commercial launch services.

A CDMO able to provide a full suite of development to launch services boasts a wealth of experience in all key areas of the CMC life cycle. With more than 35 years of experience in the processing of potent and non-potent solid oral, liquid and semi-solid dosage forms at both clinical and commercial scale and 25 years in the sterile fill-finish and lyophilization manufacturing space, there is little that PCI hasn't encountered. By working with PCI, sponsors can leverage this knowledge and experience to de-risk their programs, provide supply chain simplicity, and ensure regulatory compliance and reliable product supply.

Q: What mistakes do sponsors make when outsourcing pharmaceutical manufacturing programs?

A: They sometimes fail to conduct thorough due diligence before selecting a CDMO partner. This can lead to problems down the line that impact the cost and timing of critical milestones. When a partner is selected, sponsors sometimes fail to build strong partnerships with their providers. This can lead to a transactional relationship in which the CDMO is viewed solely as a vendor rather than a partner. Building a strong and communicative partnership with a CDMO whose capabilities are suitable to the program needs can lead to greater success and a more efficient program timeline.

Some sponsors may prioritize task-level cost savings over other factors, such as quality, technical capabilities, and the level of support the CDMO is able to provide. Whereas controlling overall expenditure is absolutely necessary, saving at the individual task level may result in greater expense in the long run when downstream activities are implicated by short-term decision-making earlier causing rework or time loss later. For example, selecting the lowest cost CDMO for an imminent task that does not have the expertise to support downstream delivery of high-quality products and services may result in clinical, regulatory, or commercial delay, and ultimately a tech transfer that always adds time, cost and risk.

Q: What can sponsors do to increase their chances of success with a pharmaceutical CDMO?

A: Choosing the right CDMO is paramount. It's essential to select a CDMO with the right capabilities, experience, and expertise to meet the program's specific needs. Sponsors should evaluate potential CDMOs based on their track record, reputation, quality management systems, regulatory compliance, and overall fit.

Ultimately, the selected CDMO should act as an extension of the sponsors team – people you want to work with through complex issue resolution who are aligned to the goals of your program. Despite the effectiveness of remote work that exists today as a fallout of Covid, it is essential sponsors visit their CDMO's site or sites, get to know the teams that they will be working with and the systems that will underpin and support their program. Sponsors should also seek relationships with the management of their CDMO to enable feedback channels and provide a path for enlisting added support if needed.

Sponsors should also clearly define program goals and requirements, including timelines, budget, and target product profile expectations, and remain transparent with their CDMO partners in terms of their progress and challenges with the overall product goals. This helps ensure both parties establish a collaborative relationship based on strong communication, which is invaluable in terms of building trust between the two parties. It also leads to the sponsor treating the CDMO as a partner, instead of just a vendor. By aligning from the outset and maintaining the relationship, this can help prevent misunderstandings or disagreements further down the line.

Finally, it's vital sponsors work with their CDMO partner to identify and manage risks associated with the program, including supply chain disruptions, regulatory compliance issues, and quality concerns. To us at PCI, risk mitigation is an obligation to our sponsors. We also have an ethical and moral obligation to provide life-changing therapies to patients around the globe, with as little disruption as possible. ◆

MICROCRYSTALLINE CELLULOSE

N-nitrosamine Risk Assessments for Oral Dosage Forms

By: Takako Koyamatsu, Shohei Mikami, PharmD, Obata Kenji, and Julia Shmyrova

INTRODUCTION

The effects of N-nitroso compounds on human health (particularly their role in gastric cancer) are well known.[1] Certain N-nitrosamines are described as highly probable human carcinogens. They are usually formed by the reaction of secondary or tertiary amines with a source of a nitrosating agent, typically derived from nitrite.[2,3]

Oral excipients are considered a potential risk factor during drug product assessment.[4] Being an excipient manufacturer, Asahi Kasei Corp. (Japan) is focused on mitigating the risk and providing information about the safe use of excipients.

In most cases, the nitrite contribution is dominated by the highest formula percent excipients. Thus, the fillers/diluents that are typically used in larger proportions should be considered as a potential risk factor.[5]

Microcrystalline Cellulose (MCC) is widely used in pharmaceutical development and is one of the most common fillers /diluents contributed to oral solid dosage form formulations, usually present in much higher concentration compared with other excipients.[6] Thus, the high nitrite content in MCC can be a significant risk for nitrosamine formation and consequently patient health.

Boetzel R.et al presented the results of eight excipients including their origin and different batches along with the correspondent statistics for the nitrite level. The evaluation of these results also showed the differences between various suppliers and between batches. In this study, the nitrite content in MCC from nine suppliers showed a spread from 0.04 μg/g to 2.4 μg/g, with a mean of 0.70 μg/g.[5]

The aim of this investigation was to test the nitrite and nitrate content in the excipients produced by Asahi Kasei Corp. to provide scientifically based data for N-nitrosamine risk assessment in oral formulations.

MATERIALS & METHODS

Materials

MCC grades as Ceolus™ KG-1000, KG-802, UF-711, UF-702, PH-101, PH-102 (Asahi Kasei Corp., Japan)

Ion Chromatography Method (IC)

Developed by Asahi Kasei in collaboration with TOYO Inspection Center (Japan).

Test Methodology: Suppressed ion chromatography

Column: Anion Exchange Chromatography Column (4.6mm I.D×15cm)

Mobile Phase: Sodium Carbonate/Sodium Hydrogen Carbonate eluent solution

Flow Rate: 1.0 mL/min

Oven Temperature: 40°C

Sample Injection Volume: 30 µL-100 µL

Detector: UV-VIS detector (Wavelength 210 nm), the LOD (Limit of Detection) is 0.008 μg/g

TABLE 1

MCC Grade	Number of Lots Tested	Nitrite (μg/g) Maximum value	Nitrate (μg/g) Average Value
Ceolus™ PH-101	11	0.011 (6/11 lots show ND)	0.071
Ceolus™ PH-102	10	0.012 (6/10 lots show ND)	0.082
Ceolus™ KG-802	8	< 0.008 (all lots show ND)	0.106
Ceolus™ KG-1000	6	< 0.008 (all lots show ND)	0.112
Ceolus™ UF-702	6	< 0.008 (all lots show ND)	0.092
Ceolus™ UF-711	7	< 0.008 (all lots show ND)	0.109

Nitrite and Nitrate content (μg/g) in the MCC products of Asahi Kasei Corp. (Japan).

RESULTS

The nitrite and nitrate content of Ceolus™ KG-1000, KG-802, UF-711, UF-702, and PH-101 and PH-102 was determined by ion chromatography method and systemized (Table 1).

In accordance with the used quantification method, the LOD of nitrites comprised 0.008μg/g. In the majority of tested batches of MCC grades Ceolus™ PH-101 and PH-102, the nitrite content was lower than LOD (0.008 μg/g). In all tested batches of grades Ceolus™ KG-802, KG-1000, UF-702, and UF-711, the nitrite level has not been detected. At the same time, the nitrate level was very low and didn't exceed 0.112 μg/g.

Being an MCC/Ceolus™ manufacturer, Asahi Kasei Corp. can explain the achieved results by process features. To minimize the appearance of undesirable impurities, secondary and tertiary amines, as well as quaternary ammonium salts or amide solvents are not used in the manufacturing process of products. Furthermore, sodium nitrite esters or nitrite, reagents, or catalysts are not used.

CONCLUSION

Ceolus™ demonstrated a very low level of nitrite and nitrate (lower than 0.012 and 0.112 μg/g, respectively) that can allow mitigating nitrosamine formation in the drug products with secondary or tertiary amines.

Obtained results justified with Asahi Kasei Corp.'s manufacturing process features allow or the evidence-based choice of MCC-grades with low nitrite content for the formulation of oral dosage form formulations with low nitrosamine-associated risk.◆

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BIOGRAPHIES

Takako Koyamatsu is a Quality Assurance Manager of Microcrystalline Cellulose, Ceolus™. She has nearly 25 years of experience in quality assurance.

Dr. Shohei Mikami joined Asahi Kasei Corporation in 2021, and belongs to the Quality Assurance Division for the excipient business. He has a Doctor of Pharmacology degree.

Kenji Obata is a Marketing Manager of pharmaceutical excipients. He has nearly 15 years of experience in marketing excipients in Europe, India, and Asia.

Julia Shmyrova has more than 20 years of experience in the pharmaceutical industry. She joined Asahi Kasei Europe in 2019 as a Technical Marketing Manager with responsibility for the European region.

Special Feature

Excipients: Does Their Future Lie in Generics?

By: Cindy H. Dubin, Contributor

The global prices for pharmaceutical excipients jumped 40% from 2019 to 2021[1], and the market is on pace to reach upwards of $12 billion by 2029.[2] Industry insiders attribute the soar to supply chain disruptions, surges in energy prices around the world, a rise in freight cost, weather catastrophies, and the Russia/Ukraine conflict.[1]

"The pharmaceutical industry can balance cost and supply in drug manufacturing by adopting a combination of strategies to minimize the impact of excipient supply chain issues," says Nick DiFranco at Lubrizol Life Science – Health. "To balance cost and supply, pharmaceutical companies need to identify reliable, long-standing suppliers who can overcome long-term supply chain challenges. These are typically companies with multiple decades of excipient supply experience and global production capabilities. Working with domestic suppliers is also a way to mitigate supply challenges. Ultimately, finding a reliable supplier upfront will save time and resources navigating supply chain headaches and material shortages."

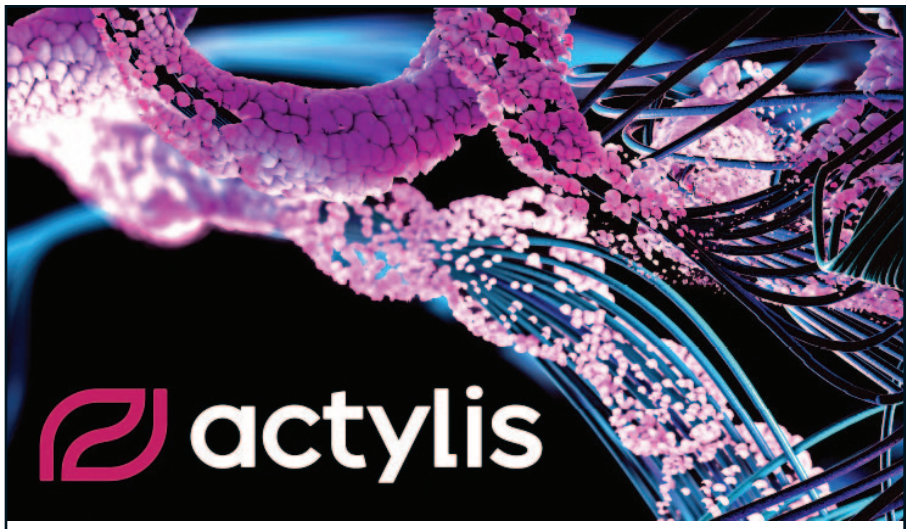
Going forward, an uninterrupted supply chain of excipients is essential for meeting the anticipated demands of generic medicines.[1] Increasing demand for generic drugs is leading to an increase in excipient demand.[2] According to the Food and Drug Administration (FDA), about 9 out of 10 prescriptions in the US are for generic drugs. And governments of developing countries are focusing on reducing healthcare costs by boosting the production of generic drugs. Thus, a rise in the sale of generic drugs across the world propels the demand for pharmaceutical excipients used in manufacturing generic drugs.[3]

Other key trends impacting the global demand for pharmaceutical excipients include a growing need for functional and co-

Co-processed excipients, GRANFILLER-D™ and HiSORAD™, reduce the burden of formulation design for orally disintegrating tablets (Daicel Corp.).

processed excipients; and formulated coatings in oral solid doses. The advancing drug dosage technologies, combined with the need to be cost-effective, are increasing demand for sustained-release drugs that will in turn drive the demand for certain cellulosic excipients; growth in enteric-release medicines will favor the demand for polymethacrylate excipients; versatile excipients that have higher compatibility with various APIs; disintegrants to address the demand for fast disintegrating tablets, and nanotechnology to improve excipients capabilities.[1,3]

This year's exclusive *Drug Development & Delivery* report highlights the work being done in all of these areas and exemplifies the importance of excipients to the future of drug development.



Lower impurity PMSF developed by Actylis in a GMP environment with full supporting quality and regulatory documentation.

Actylis: GMP-Grade PMSF Has Improved Impurity Profile

Phenylmethylsulfonyl fluoride, better known as PMSF, is a critical raw material used in large molecule manufacturing as an irreversible, small molecule serine protease inhibitor that acts non-specifically on proteases including trypsin, chymotrypsin, thrombin, and papain, as well as on many other enzymes that hydrolyze non-protein substrates (e.g., acetylcholinesterase, acyl-CoA hydrolases, and various lipases). It is used to prevent unwanted proteolosis and functions by sulfonylating the serine residue in the active site, deactivating the enzyme and preventing it from digesting its protein targets.

"Preventing proteolysis is a key consideration for biopharmaceutical manufacturing, especially where cell lysis is required to extract and isolate the product of interest," says Dr Peter McGarry, Chief Scientific Officer, Actylis. "While protease activity is tightly regulated in living cells, this control is lost during the lysis process, which can lead to the product being compromised if appropriate control measures are not put in place. For this reason, protease inhibitors such as PMSF are vital tools for biopharmaceutical manufacturing, where they must demonstrate sufficient purity and strength for their intended purpose."

Actylis manufactures high purity, GMP-grade PMSF at one of its dedicated GMP production facilities in Canada. Their proprietary multi-stage purification process includes a step to completely remove particulate foreign matter, which is followed by selective isolation, and is performed under an inert atmosphere to ensure the final (packaged) product is pristine and ready for immediate use.

Actylis was recently challenged by a client that needed to use PMSF as a critical raw material in its biopharma manufacturing process but needed a GMP-manufactured material with a specific impurity profile. Working in close consultation with the customer, Actylis developed the lower impurity PMSF in a GMP environment with full supporting quality and regulatory documentation.

Supply chain transparency was also a critical factor since PMSF has historically only been available as a technical/reagent grade product. With controls tightening on the raw materials being used for drug production, being able to document the provenance and quality of the product was essential, explains Paul Staunton, Director of Global Marketing Communications, Actylis. Actylis has complete control over, and provides full transparency in, its supply chain, carefully qualifying vendors to ensure timely delivery of the product, says Paul Staunton, Director of Global Marketing Communications, Actylis. Moreover, by adhering to GMP supply chain best practices and capturing all product documentation in their Quality Management System, Actylis guarantees that the GMP-grade PMSF meets the required standards of quality, purity, and safety for numerous biopharmaceutical manufacturing applications.

Croda Pharma: Proprietary Purification Process Extends Formulation Shelf Life

Formulating generic drugs of equivalent stability, safety, bioequivalence, and dosage form as originator drugs can be a great challenge. James Humphrey, Research and Technology Specialist at Croda Pharma, explains how excipients are used to better formulate generic drugs and how Croda's proprietary purification process can extend formulation shelf life. While the active ingredient of generic drugs remains the same, formulating with the correct excipients to meet these standards can be a challenge, due to poor solubility, physical or chemical instability, and ineffective drug delivery, says Mr. Humphrey.

"Excipients can provide additional benefits in the manufacture of generic drugs above and beyond the necessities of stability and bioequivalence, such as reduced taste impact in pediatric oral medicines that can result in better patient compliance or reduced cross linking in soft gel capsules improving dissolution rates," he says.

He adds that the removal of impurities in Croda's Super Refined™ product offerings can deliver improved drug and formulation stability, a lower taste impact, and improved patient compliance. When formulating, oxidative stability is important to prevent the formation of peroxides and aldehydes, which are common oxidation products for a number of excipients. The presence of peroxides and aldehydes can leave APIs susceptible to degradation, impacting drug performance, stability, and shelf life. "Our Super Refined excipients, created by Croda's proprietary purification process, extend the shelf life of pharmaceutical formulations through the removal of impurities that contribute to oxidative degradation."

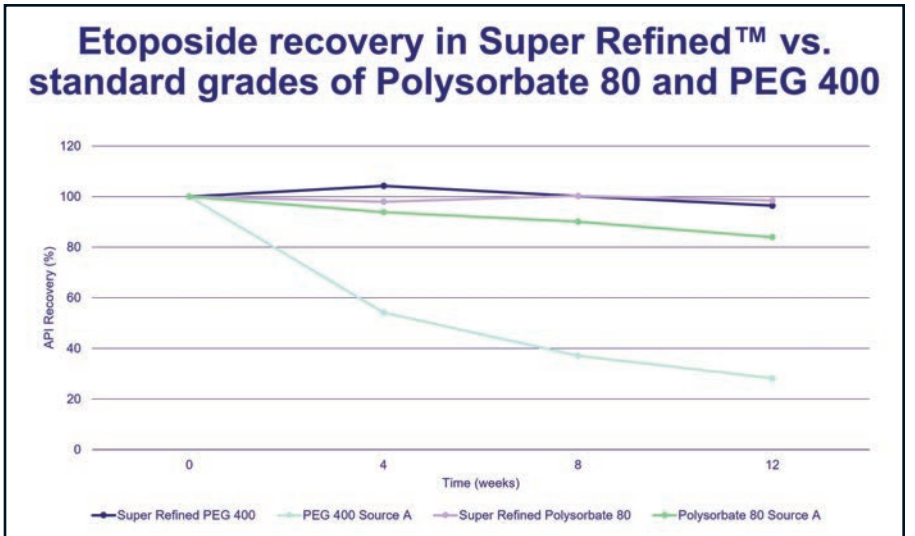


FIGURE 1. A graph to compare % etoposide recovery during an accelerated 12-week stability test at 40°C in Super Refined grades of PEG 400 and Polysorbate 80 compared to standard grades (Croda Pharma).

Etoposide is a chemotherapy drug used in the treatment of various cancers, including testicular, prostate, bladder, stomach, and lung cancer. Existing in two dosage forms – a concentrate for intravenous (IV) infusion and a soft-gel capsule for oral delivery – etoposide is a topoisomerase inhibitor. IV formulations of etoposide contain PEG 300 and Polysorbate 80.

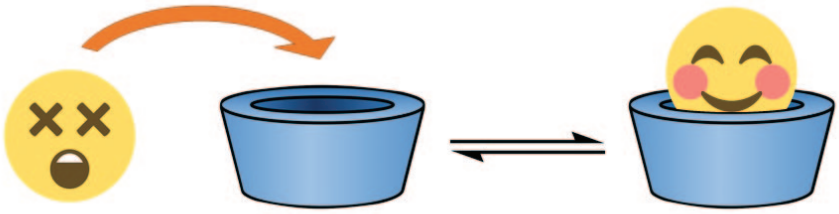
"Our formulations team reformulated etoposide with Super Refined PEG 300 and Super Refined Polysorbate 80," says Mr. Humphrey. An accelerated 12-week stability test at 40°C was performed to compare its stability in the Super Refined formulation versus standard excipients. Stability was measured in API recovery (%); results are shown in Figure 1.

"Etoposide was notably more stable in the Super Refined grades, demonstrating almost 100% recovery in Super Refined Polysorbate 80, and over 90% recovery in Super Refined PEG 300 after 12 weeks," he says. "The increase in stability of etoposide in the Super Refined grade was particularly notable in PEG 300 where the standard grade had only 25% recovery after 12 weeks at 40°C. In summary, the use of Super Refined excipients when formulating can have a number of benefits including increased API stability, a shorter time to market, and improved patient compliance."

Cyclolab Ltd.: The Functionality & Benefits of SBECD

Cyclodextrins (CDs) are versatile molecules, composed of alpha-D-glucose units, used in pharma as excipients. CDs are unique among the other excipients because they can form non-covalent inclusion complexes with several molecules, explains Dr. Levente Szöcs, R&D Director at Cyclolab Ltd. "The benefit of this complexation mechanism is that the entire supramolecular entity can be well solubilized in water, thus formulated, beause the outer cavity of the complex is hydrophilic."

Additionally, the API molecule can be protected from environmental effects, such as light or moisture. Consequently, cyclodextrins can also improve the chemical stability of the complexed substances. Finally, the smell and taste of several com-



Reversible, host-guest type of inclusion complex (Cyclolab Ltd.).

pounds can be masked.

Betadex Sulfobutyl Ether Sodium (SBECD) is a semi-synthetic cyclodextrin derivative, a well-defined and characterized mixture of isomers. Both USP and EP Pharmacopoeias set strict quality requirements for this cyclodextrin because it is used mainly in injections. However, it is also approved in other dosage forms as well, like oral formulations. SBECD is a polyanionic compound.

"Because a great portion of APIs are bases, the complexation efficacy can be superior compared to that of uncharged CDs, such as native BCD or hydroxypropyl betadex," says Dr. Szöcs. "The intermolecular association between the API and SBCED is not only enabled by hydrophobic interaction and H-bonds formed at the cavity of CD, but also electrostatic (ionic) interactions can enhance the strength of the complex formation."

Some examples of weak bases formulated with SBECD include: remdesivir, ziprasidone, amiodarone, voriconazole, posaconazole, aripiprazole, and maropitant. To achieve the desired formulation, SBECD is mostly used in high molar excess compared to the API. However, in case of an antiepileptic drug – fosphenytoin – SBECD is used in substoichiometric amount. The role of cyclodextrin in this intravenous formulation is chemical stabilization, not solubilization.

The most recently approved formulation that contains SBECD is Veklury®. The formulated API, remdesivir, is a weak base with a pKa of 3.3 and a logP of 3.2 (practically insoluble in water). Thus, Dr. Szöcs says that SBECD is an ideal candidate to solubilize this molecule. To achieve the desired 100mg/vial of the API, 3 grams of SBECD is required (nAPI:nSBECD = 1:8.3).

So, is SBECD just an excipient or does it have some pharmacological effect as well? A recent publication highlights that, in Veklury® formulations, initial membrane-coupled events of SARS-CoV-2 infections are inhibited due to their sulfobutylether-β-cyclodextrin content).[4] Dr. Szöcs says this study may be a pioneer to explore the role of SBECD beyond that of excipient.

"Currently there are more than 100 API and cyclodextrin complexes under development, so the potential in these nano-sized sugar derivatives is huge," he says. "We are aware of most of the developments with CDs and are trying to get the best out of cyclodextrins."

Daicel: Co-processed Excipients Reduce the Burden of Formulation Design

Co-processed excipients are any combination of two or more excipients listed in monographs obtained by physical co-processing without creating a new chemical bond, providing new functions and good physical properties that cannot be achieved through simple mixing. By applying co-processed excipients, Tomohito Okabayashi, Business Development Manager, Life Sciences, Daicel Corp., believes that it is possible to innovate drug products without introducing novel chemical substances or additional excipients. That is, they have advantages in terms of developing cost.

"In addition, because the variability of the constituent excipients can be reduced compared to combining single excipients, rigid co-processed excipients undoubtedly offer to improve the quality of drug products," he says. "Furthermore, co-processed excipients generally have improved physical properties such as flowability and particle size distribution. Therefore, they can solve manufacturing problems such as mixing and tableting challenges."

He adds that because co-processed excipients offer improved function and quality, generic drug manufacturers will be able to reduce the burden of adjusting formulation design. "In other words, co-processed excipients offer time-savings. As a result, we believe that it is possible to reduce manufacturing costs and provide high-quality drugs at low prices, ultimately leading to improved medication adherence for patients."

Daicel's co-processed excipients, GRANFILLER-D™ and HiSORAD™, are suited for orally disintegrating tablets (ODTs). "These co-processed excipients have unique and excellent wicking and swelling ability," says Mr. Okabayashi. "These excipients can realize better disintegratability and stability, even in case of utilizing high-dose API or coated-API pellets. Moreover, our excipients have a unique particle non-spherical shape to contribute to improved content uniformity without special processing."

EUDRACAP® ready-to-fill capsules with filling (Evonik Health Care).

Evonik Health Care: Functional Ready-to-Fill Capsule Addresses Supply Chain Constraints

Drug manufacturers across the world are currently facing unprecedented supply challenges. One reason for this is an increase in demand for common remedies, especially generics such as antibiotics.

"After the COVID-19 lockdowns were relaxed in many places in the world, there was a huge upsurge in seasonal illness as populations were suddenly exposed to seasonal bugs after several years of limited circulation," says Felix Hofmann, Director Formulation & Application Services EMEA, Evonik Health Care. "Rising energy costs and inflation, as well as supply chain disruption due to the continuing war in Ukraine, are also big challenges for generic drug manufacturers. Some countries have reacted to this situation by temporarily blocking the trade of medicines and stockpiling, which is exacerbating the situation."

Mr. Hofmann notes that these challenges are putting pressure on excipient manufacturers, who are faced with rising costs for energy and raw materials. In turn, excipient manufacturers are looking for new energy sourcing contracts with suppliers to reduce costs and dependency on natural gas. Drug manufacturers can also take the lead to ensure sustainable supply and work on emerging and innovative partnership models.

In response to increasingly complex supply chains and rising production costs, Evonik has developed a functional ready-to-fill capsule. This capsule (EUDRACAP®) facilitates the supply and production of modified release formulations and simplifies the development of complex biological drugs. This new solution efficiently improves bioavailability for biologicals or microbiome therapies, where the drug needs to be protected from an acidic environment, he says.

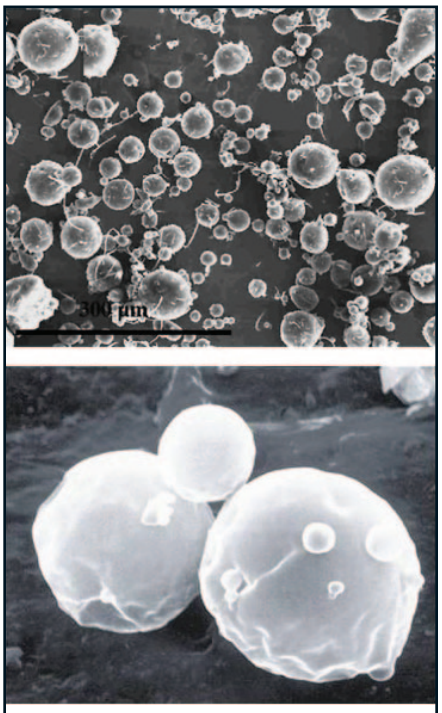
"Our gastric-resistant, empty coated capsules draw on decades of extensive enteric coating experience and have a robust enteric release that can be further tailored to target a specific gastrointestinal site," explains Mr. Hofmann. "They significantly improve the bioavailability of biologics without exposing them to moisture and heat in a regular coating process, thus allowing a wide range of formulations."

Gattefossé: Lipid/Cellulosic Polymers Better Control Drug Release

Low hydrophilic/lipophilic balance (HLB) solid lipid excipients form waxy, diffusion controlled, and hydrophobic extended-release matrices without altering their physical state or requiring special environmental conditions, such as pH change, to trigger their effects. They also provide numerous biopharmaceutical and manufacturing advantages including:

- Modulation of drug release profiles that are directly proportional to the amount used
- Effective solutions for highly water-soluble APIs having short half-lives
- Resistance to pH changes and hydroalcoholic environments
- Non-hygroscopic matrices for improved stability upon storage
- Avoiding the need to use polymeric coatings
- Solvent-free processing for cleaner and greener manufacturing.

Compritol® 888 ATO (glyceryl dibehenate) is a non-ionic solid triglyceride, versatile lipid, and extended-release matrix forming agent that offers processing flexibility because it can be used in di-



Scanning electron micrographs of Compritol® 888 ATO, mean particle size 50µm (Gattefossé).

rect compression, wet granulation, dry granulation, hot-melt extrusion, and other industrial processes for manufacturing extended-release formulations.

On the other hand, cellulosic polymers, when used as extended-release matrix forming agents, function by diffusion of the dissolved drug through the swollen gel layer. They also tend to create a burst effect caused by dissolution and leaching of drug particles at the tablet surface prior to formation of the release-controlling gel, presenting challenges to controlling initial drug release of highly water-soluble drugs.

"Thus, a combination of lipid excipients with different cellulosic polymers as extended-release dual/hybrid matrix forming agents aid in better controlling the drug release of highly water-soluble active pharmaceutical ingredients," says Alexandre Gil, Group Director Pharmaceuticals, Gattefossé. "Compritol 888 ATO offers the advantage of providing robust extended-release tablet matrices that are resistant to alcohol-induced dose dumping, when used alone and in combination with cellulosic polymers, for aqueous and poorly water-soluble drugs."

Lipid formulations are versatile and can be designed around brick dust-type molecules as well as so-called 'grease balls,' which are highly lipophilic compounds. Self-emulsifying drug delivery systems help solubilize poorly soluble drugs and facilitate drug dispersion and dissolution *in vivo* upon contact with the aqueous environment of the GI tract. Moreover, lipid formulations can – depending on their composition – influence various aspects of a drug's bioavailability, notably maintaining drug solubility in the GI tract, reducing food effect, increasing intestinal permeation, and promoting lymphatic absorption.

As an example, long-chain glycerol esters like Maisine® and Peceol™ promote lymphatic absorption. Moreover, lipid formulations can be carried from early- to late-stage development, which means significant reductions in development time and cost as well as avoiding risks associated with bridging studies.

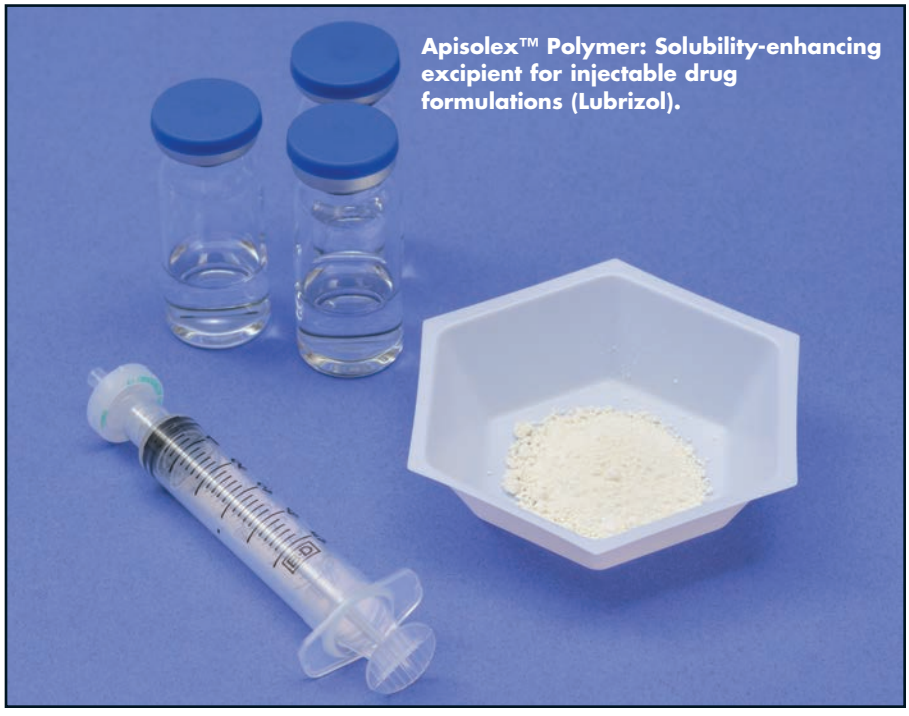
Mr. Gil also describes Labrasol® ALF, a self-emulsifying excipient, which is typically used as a solubility enhancer for drug permeability across epithelial tight junctions. "Certain oncology drugs currently on the market have been conveyed through all stages of development and launched using Labrasol ALF and other lipid-based excipients," he says.

Lubrizol: Improving Solubility, Safety/Toxicity, & the Patient Experience

Lubrizol has supplied excipients for more than 40 years, including IID Carbopol® polymers and novel Apisolex™ and Apinovex™ polymers for solubility enhancement. "It is well known that reducing the particle size of APIs is a way to improve its solubility," says Joey Glassco, Senior Global Market Segment Manager, Parenterals, Lubrizol. "Excipients like Apisolex provide drug developers an alternative way to make nanoparticulate formulations by using micellar technology to drastically improve solubility of a wide variety of hydrophobic APIs by up to 50,000-fold. The patented technology utilizes straightforward scalable manufacturing techniques to achieve higher drug loading (up to 40:100 API: solubilizer ratio) over other solubilizers and is a non-immunogenic alternative to PEG."

Lubrizol's Apisolex polyamino acid-based polymer was deployed for a company with a marketed oncological drug product seeking a drug delivery technology to increase the solubility of the API while reducing the toxicity of the final drug product. To justify the reformulation expense and increase overall revenue, the goal was to also extend the use of the API into another therapeutic area.

Because the API was about to lose exclusivity, the company was looking for a patented excipient technology to protect



Apisolex™ Polymer: Solubility-enhancing excipient for injectable drug formulations (Lubrizol).

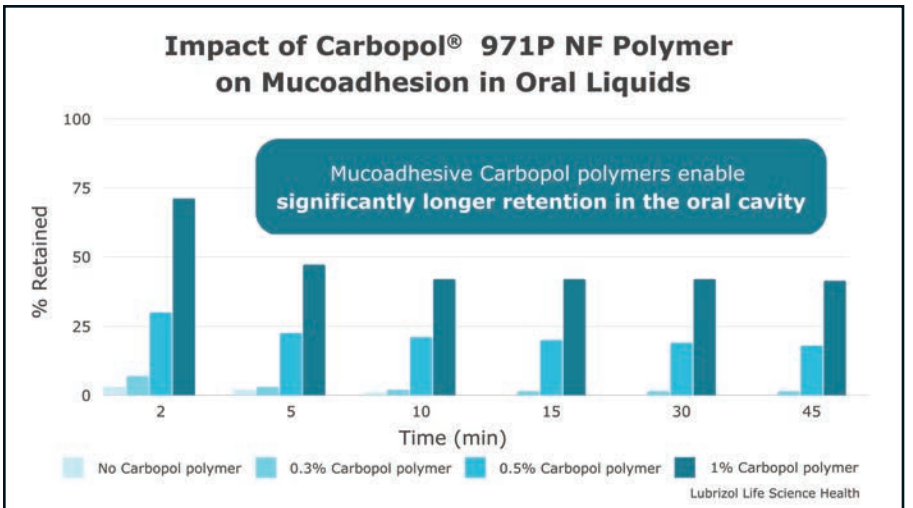


FIGURE 2. Carbopol® Polymer: Impact of Carbopol 971P NF Polymer on Mucoadhesion in Oral Liquids (Lubrizol).

the new drug product.

Apisolex technology eliminates the use of the polyethylene glycol-based (PEG) vehicle and provides the organization with a better solution for patients and needed intellectual property. "The use of Apisolex polymer empowers the client with a simple, easy-to-scale manufacturing process," says Ms. Glassco. "The results are a stable lyophilized drug product that reconstitutes in less than 30 seconds in saline. In addition, GMP-grade Apisolex enabled the drug product with higher drug loading than the originator drug product, potentially reducing infusion time." The company has completed animal studies with Apisolex excipients and is planning for human trials in 2024.

Selecting excipients for generic drugs requires the same level of rigor as brand-name products, such as reproducible manufacturing, quality certifications, and global regulatory support. Generic drugs may also offer opportunities to overcome known challenges with marketed products. For example, Nick DiFranco, Global Market Segment Manager, Oral Treatments, Lubrizol, explains that Carbopol polymers have been used in generic metformin tablet formulations to ensure compliance with nitrosamine regulations and make tablets smaller and easier to swallow.

Carbopol polymers also enable mucoadhesion, a type of bioadhesion in which two materials, at least one of which is mucosal, are held together for extended periods by interfacial forces. Mr. DiFranco says that pharmaceutical formulators are increasingly turning to mucoadhesion to improve drug delivery, as it offers several benefits: enhanced retention of actives for localized or systemic delivery; lubrication/protection for inflamed tissue; and possibilities for new product claims tied to improved performance and patient experiences (Figure 2).

"Lubrizol's Carbopol polymers and Noveon® polycarbophil are high quality excipients that offer superior mucoadhesive performance compared to other polymers," says Mr. DiFranco. "To date, 17-plus commercial products have employed Carbopol and Noveon polymers for their mucoadhesive properties in tablets, liquids, films, sprays, lozenges, and more." Lubrizol's mucoadhesive polymers are compatible with existing manufacturing techniques.

Spectrum Chemical Mfg. Corp.: Two Primary Excipient Providers Can Offset Supply Shortages

Supply chain disruptions and fluctuating costs in drug manufacturing can be unpredictable, but there are several courses of action that can help prevent or at least alleviate the impact of these disruptions. One way is better forecasting by adding more predictive analysis of demands and costs covering the entire supply chain, including raw materials,

Used in pharma and biopharma manufacturing, Spectrum Chemical's large inventory of high-functionality chemical excipients are cGMP compliant and include documentation that meets regulatory and compliance requirements.

production, and inventories.

Another is making sure you have relationships with the right suppliers that have the ability to respond to market dynamics. "Pharmaceutical manufacturers really are looking for materials suppliers who have a demonstrated track record of resiliency, transparency and reliability, as well as an established global supply chain network," says Jim Luchsinger, Vice President, Business Development and International Distribution, Spectrum Chemical Mfg. Corp. "In the past, pharmaceutical and biopharma manufacturers often limited themselves to one 'go-to' supplier, then when supply constraints began to occur, they started seeking out alternative or backup suppliers for critical components. Those alternative suppliers were still just viewed as a backup if the primary supplier was not able to come through."

Today, he continues, more progressive manufacturers further minimize risk by designating two primary suppliers. "This approach does a better job of keeping both primary suppliers equally engaged throughout a project. If there is an issue with one supplier, then the other is already well established with the customer to help offset the shortage and respond more quickly," he says. "The dual-primary supplier method also does a lot more to lower risk as well as raw material variability."

Mr. Luchsinger says he is also seeing a preference for a more "regional" approach to the supply chain, which results in better consistency and greater efficiency. Regulatory and scientific documentation also ensures manufacturers have everything they need to meet global compliance requirements; it can be a challenge when suppliers have many different countries of origin.

"Our customers value our ability to provide documentation for regulatory and compliance needs," he says.

Spectrum sells several thousand chemicals that can be used in pharmaceutical and biopharmaceutical manufacturing to enhance solubility, extend shelf life, and facilitate drug absorption – all manufactured, packaged, and stored under cGMP in FDA-registered and inspected facilities. ◆

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MICROCRYSTALLINE CELLULOSE **(Core/Content)**	75.76 mg
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COLLOIDAL SILICON DIOXIDE **(Core/Content)**	7.58 mg
POLYVINYL ALCOHOL, UNSPECIFIED **(Tablet/Capsule coat)**	11.72 mg
POLYETHYLENE GLYCOL **(Tablet/Capsule coat)**	5.92 mg
TALC **(Tablet/Capsule coat)**	4.33 mg
FERRIC OXIDE YELLOW **(Tablet/Capsule coat)**	0.32 mg
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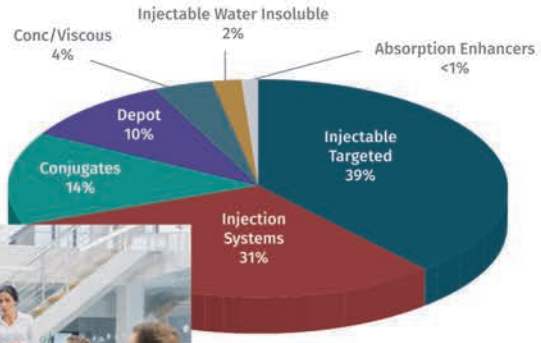

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DRUG-ELUTING IMPLANTS

Delivery of RNAi Therapeutics Through Drug-Eluting Implants

By: Cyonna Holmes, PhD, Karen Chen, MS, and Brian Wilson, PhD

INTRODUCTION

The past few years have seen a rapid uptick in focus on RNA therapeutics stemming from the success of the mRNA COVID vaccine. As a result, additional RNA drug classes are being investigated to treat a wide range of conditions using a different modality. While mRNA therapies are only now beginning to emerge commercially outside of infectious diseases, the first oligonucleotide-based RNAi therapeutics were approved in 1998 (antisense oligonucleotide) and 2004 (aptamer). There are now 13 FDA or EMA approved oligonucleotide drugs spanning siRNA, antisense oligonucleotides (ASOs), and aptamers.[1] Additionally, miRNA mimics and inhibitors are an emerging class of yet-to-be-commercialized therapeutics with multiple drugs in clinical development. However, ASOs and siRNA continue to represent the largest share of oligonucleotide drugs.

The new wave of next-generation oligonucleotide therapeutics has spurred market growth and is projected to result in a global market size of $7.2 billion in 2026.[1] Advances in oncology, rare diseases (primarily in central nervous system, cardiovascular, and metabolic conditions), and ophthalmology are drivers of this growth.[2,3] Additionally, the growing focus on personalized medicine and the need to target specific patient sequences and undruggable targets can be addressed by oligonucleotide therapeutics.

LIMITATIONS OF CONVENTIONAL DELIVERY METHODS

RNA that interferes with or modifies gene expression works through different mechanisms of action, yet all must avoid clearance by off-target organs and be delivered to the correct organ and tissue site. Each generation of RNAi therapeutics utilizes a variety of new backbone or nucleotide chemical modifications leading to improved therapeutic efficacy, specificity, and stability, yet challenges still remain in reducing off-target toxicities and avoiding broad distribution of therapeutics to multiple organs. These issues have resulted in inflammatory side effects, such as thrombocytopenia and glomerulonephritis, due to drug circulation and accumulation in non-target organs. Additionally, broad distribution of ASOs requires high dosing to ensure the concentration of ASOs needed to produce a physiological, therapeutic effect actually reaches its intended site.

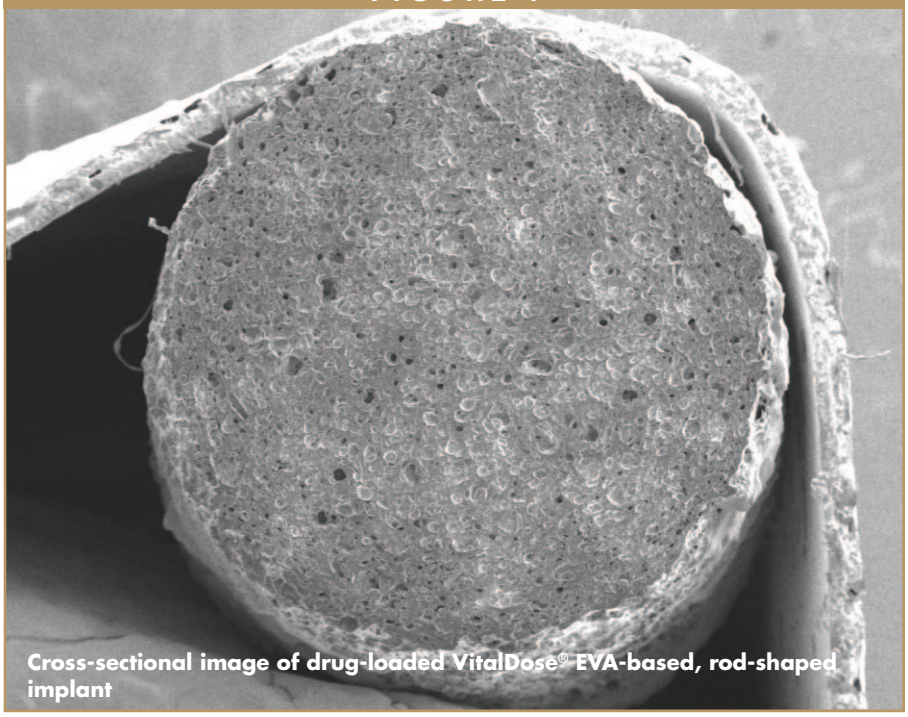
For example, the observed biodistribution from the systemic administration of single-stranded, phosphorothioate-modified ASOs is broad, with the highest ASO concentrations in liver and kidneys. To solve this, several companies have tried to create conjugated ligands that target receptors in the desired tissue. However, adequate receptors do not exist for all tissue types, and some receptors may also be expressed in non-target tissues. Physiological barriers and heterogeneous targets also add complexity to receptor-ligand-based approaches.

IMPLANTS FOR RNAi THERAPEUTIC DELIVERY

Current RNA therapeutic challenges can be overcome through drug delivery approaches. Localized therapeutic delivery of these therapies through an implant (Figure 1) provides an innovative route of administration for chronic conditions that are difficult to dose adequately. Implants used to facilitate intrathecal or intratumoral delivery can bypass physiological barriers that typically reduce drug efficacy. This would allow for a higher concentration of the therapeutic at the local site of interest and also reduce the risk of toxicities. An implant also provides localized, sustained release of the RNAi that may potentially reduce the amount of drug that needs to be delivered as more of the drug reaches the target site resulting in improved efficacy.

Localized delivery via an implant can improve ligand-conjugated and non-conjugated RNAi therapeutics. For ligand-conjugated therapeutics, a localized approach situates the implant directly at the organ site of interest. This proximity may allow for lower dosing requirements as a higher fraction of the drug will reach the cells of interest than in a systemic approach. For non-ligand conjugated RNAi therapeutics, situation of the implant at the site of interest will also allow for less accumulation of the drug in organs not indicated for treatment. Regardless of conjugation approaches, localization may result in reduced toxicity and a lower immunogenicity profile.

FIGURE 1



Cross-sectional image of drug-loaded VitalDose® EVA-based, rod-shaped implant

USE CASES

Rare Diseases

RNA therapeutics are well established in the rare disease market, with drugs like Spinraza (Ionis & Biogen), Onpattro (Alnylam), and Vyondys 53 (Sarepta Therapeutics). The majority of RNA therapeutics in the pipeline have been granted FDA orphan designations.[3] These drugs utilize ASOs and siRNA that are typically modified to confer improved stability and cellular uptake. Sustained delivery of these products in rare diseases may further elongate the interval between treatments and mitigate off-target effects (eg, thrombocytopenia). For example, implant delivery of ASOs for some rare CNS diseases may reduce the dosing frequency needed via delivery through various routes of administration (eg, intrathecal). Implant delivery for rare musculoskeletal diseases may also improve efficacy of current treatments by providing continuous, low-dose release for improved muscle uptake.

Oncology

Similar to rare diseases, there are high hopes for RNA therapeutics in oncology. The volume of research advancing new oncology therapeutics based on RNA includes more than 75 ongoing clinical trials and more than 160 ongoing research/preclinical studies. Many different types of RNA have been shown to be dysregulated in tumors, therefore a wide range of potential mechanisms can be used to treat tumors. Areas under investigation include inhibiting the proliferation of tumor cells, preventing the metastasis of malignant tumor cells, inducing tumor cell apoptosis, reconstructing the tumor microenvironment, tumor cell reprogramming, expression disruption, and angiogenesis inhibition.[4] In addition, combining RNA therapy with existing medicinal therapies has the possibility to decrease drug resistance over time.

One particular class that has presented a significant amount of clinical data to date is siRNA-based therapies targeting lung, breast, and pancreatic cancers. For

example, an siRNA targeting PD-1 has been shown to increase anti-tumor activity of tumor infiltrating lymphocytes (TILs) against certain tumor cells.[5,6] siRNA has also been used to knock down PD-L1 and CD47 on the cancer cell surface to boost the efficacy of anti-PD-L1 and anti-CD47 inhibitors.[5,7] Localized delivery of these therapies via an intratumoral implant may further improve efficacy and reduce toxicities to other sites. Research and trials are ongoing to help better identify new molecular targets of RNAi therapies for the reduction of tumor size.

Ophthalmology

siRNA and ASOs have been investigated as potential therapeutic modalities for targeting posterior chronic eye conditions like geographic atrophy (GA) secondary to dry macular degeneration. Zimura, a pegylated RNA aptamer, has shown favorable Phase 3 clinical trial results and may transform the landscape of dry AMD and RNA in ocular indications if approved.[8] The oligonucleotide ocular pipeline is also buoyed by Roche's Ionis partnered drug for GA.[9] Sustained oligonucleotide delivery from an implant has the potential to extend treatment duration beyond 6 months, which would reduce treatment burden for patients with chronic eye conditions.

FUTURE OUTLOOK

Beyond sustained delivery of oligonucleotides, implants have the potential to improve the delivery of mRNA therapeutics. Chronic conditions using mRNA for protein replacement could benefit from an implant depot approach, which would provide continuous delivery in a localized manner. This localized manner of delivery could also reduce the common immune response associated with bolus injections and mitigate the need for targeting ligands. Drug delivery approaches used to elute large molecules, like VitalDose® EVA for monoclonal antibodies, can also be used to elute other large molecules like mRNA. The future of RNA for disease treatment is vast and constantly growing. As research continues in this therapeutic space, the consideration of drug delivery options can be crucial to the efficacy of treatment. Localized delivery via a drug-eluting implant is only one option to be considered, but it holds a great deal of potential to help optimize RNA therapeutic success and must not be overlooked. ◆

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BIOGRAPHIES

Dr. Cyonna Holmes earned her PhD in Biomedical Engineering from the University of Texas Southwestern Medical Center (Dallas, TX) and her BS in Bioengineering from Stanford University (Stanford, CA). At Celanese, she serves as Global Strategy Lead for Ophthalmology, Rare Diseases, and RNA Therapeutics. She has experience in the areas of drug delivery, lifecycle management strategy, new product development, and market entry strategy. She has published articles in peer-reviewed journals.

Karen Chen earned her MS in Formulation Science from Fairleigh Dickinson University (Teaneck, NJ) and her BS in Biology and Chemistry from Rutgers University (New Brunswick, NJ). At Celanese, she serves as Global Strategy Lead for Oncology. Her experience spans new product development as well as market entry and expansion strategies for functional excipients and drug delivery.

Dr. Brian Wilson earned his PhD in Biochemistry from the University of Notre Dame (South Bend, IN). He has 11 years of API experience in the areas of formulation development, drug delivery, and new product development. At Celanese, he serves as a New Business Development Partner for the pharma and medical businesses. He holds patents and has numerous published articles in peer-reviewed journals.

MARKET TRENDS

The Year of Resilience & Flexibility: Six Smart Ways CDMOs Are Preparing for 2023

By: Carsten Press

INTRODUCTION

As CDMOs look ahead to the coming quarters, it seems clear another year of unpredictable global events and dynamically evolving markets lies ahead of us. After some of the most unprecedented years many of us have experienced, new changes and challenges continue to come.

In just the past year, our industry has traded remarkable innovation and rapid growth for a year of market difficulties. One new disruption after another continues to roil global supply chains. A continent has burst into once-unthinkable conflict, with troubling results for global energy markets and supply chains. All these crises seem likely to continue in 2023 and are already converging on the global drug market. With biopharma businesses weathering one unexpected shift after another, it's no surprise these organizations are looking to their partner networks for one thing above all: the flexibility they need to maximize their own business resilience.

ADAPTABILITY HAS NEVER BEEN MORE IMPORTANT FOR CDMOS

With all these macro challenges accumulating and intersecting, many pharma and biotech organizations are pivoting, shifting, and adapting their businesses more quickly than they ever imagined possible – all while working to keep their products on the path to patients.

And now, drug sponsors are looking to their service providers to do the same: to adapt and evolve their businesses in ways that help their customers navigate both unprecedented new challenges and long-standing issues that have been further complicated by new crises.

- Cost-driving supply chain challenges that demand strategic new approaches to managing energy and material resources.
- New time-to-market expectations that were set by pandemic breakthroughs, and that can only be met through innovation and investment in processes, technology, and expertise.
- Evolving drug product portfolios that have shifted their focus from monolithic blockbusters to complex blends of mass-volume and small-batch products.

So how are CDMOs preparing to deliver the flexibility their customers are so urgently looking for? How are they getting ready to be agile in managing near-term challenges, while keeping an eye on essential long-term priorities?

In the course of this year, we expect that strategically minded partners will likely focus on the following six steps – each of which will be key to the flexibility biopharmaceutical companies are looking for in their partners.

STEP 1: OPERATIONALIZING MARKET FORESIGHT

Clear visibility into market trends has always been essential for development and manufacturing partners who want to play a strategic role in their customers' business. But in today's dynamic environment, those customers are looking for more than awareness. Truly forward-thinking companies need robust, proactive processes for monitoring industry horizons and turning new innovations into impactful offerings.

©Vetter Pharma International: Mobile robot systems like "Helmo" are being used to automate routine, repetitive, and time-consuming tasks.

Historically, for many of these businesses, it's been far too easy for emerging concepts to get trapped in operational silos or lost in translation between departments. To break that cycle, many CDMOs are establishing structured, interdisciplinary processes for identifying new opportunities, holistically evaluating their relevance and feasibility, and translating the right advances into customer value. The goal: to consistently put the most impactful new concepts on a streamlined path from idea to implementation.

The growing effort to develop, define, and accelerate that path has the potential to benefit CDMOs and drug owners alike. In the coming years, we expect it to become a differentiating investment for development and manufacturing partners who want to stay at the forefront of the industry.

STEP 2: EMPOWERING KEY DEPARTMENTS TO NAVIGATE RESOURCE CHALLENGES

In just the past year, our industry has been struck by a series of converging crises: the ongoing COVID-19 pandemic, global supply chain disruptions, and a new energy crisis stemming from the conflict between Russia and Ukraine. Together, these challenges have created a remarkable series of price spikes, cost surges, and resource shortages for biopharma businesses.

In response, service providers are relying more heavily than ever on the expertise and foresight of their purchasing and S&OP (sales & operations planning) processes. These teams have always played a key part in balancing cost containment, resource availability, and supplier relationships. Today, they're stepping up their role in cost optimization, supplier negotiation strategies, internal collaborations with Sales and Financial Control, and many other efforts to buffer their organizations from unprecedented market headwinds.

For biopharma companies evaluating future development and manufacturing partnerships, we also expect strategic purchasing and S&OP teams to become a key signal of potential partners' value and capabilities. Assessing a service provider's long-term strength and stability is an essential step in any due diligence process. Now, more than ever, pharma and biotech companies will look for partners with internal teams that are well-positioned to guide their organization through unprecedented cost and supply challenges.

©Vetter Pharma International: "YuMi" is a modular, dual-armed cobot that has already been successfully integrated into our secondary packaging lines.

STEP 3: BALANCING CONFIGURABILITY & SUSTAINABILITY

For most pharma and biotech companies, gone are the days of building an enterprise on a few blockbuster products. Today's global biopharma market is more of a mosaic than ever, with consolidated portfolios quickly giving way to pipelines full of specialized therapies, niche indications, and complex delivery systems.

This shift has put their partners under pressure to deliver greater and greater levels of flexibility and customization. CDMOs specializing in clinical and commercial aseptic manufacturing are facing some particularly challenging new demands. Many are working to onboard an ever-increasing variety of packaging formats, achieve new levels of multifunctionality in their facilities, and adapt to a rapidly widening spectrum of product sensitivities. Often for small-batch products!

In the coming year, many service providers will make or reinforce major investments in the operational agility this new era demands. Our own effort is already well underway, with a strategic focus on offering the greatest possible flexibility across our services while maintaining a consistent and uncompromising level of quality. Several key initiatives include:

- Implementing multifunctional and flexible aseptic filling lines that can be rapidly reconfigured for a wide range of product characteristics and packaging formats.
- Proactively evaluating and pursuing a range of new delivery systems and platforms, including pens and large volume autoinjectors, pre-sterilized vials, wearables, and more.
- Exploring and qualifying an increasing range of packaging options, especially innovative new formats (like mono-material blisters or all-paper packaging) that promote the use of sustainable materials.

In the coming years, environmental responsibility will be an increasingly important priority for partners across the value chain. As the climate crisis intensifies, CDMOs will face particularly acute pressure – social, regulatory, and economic – to help their customers achieve ever-more-ambitious sustainability benchmarks.

For many partners, that pressure will likely drive both strategic, business-level investments – like full carbon neutrality across global operations – and a range of project-level innovations like new recycla-

"No matter the crisis, we share one mission: to bring life-supporting and life-critical medicines to patients all over the world. In the coming year and long beyond, we will always do our best to achieve that vital goal!"

ble packaging formats. At both levels, watch for strategic CDMOs to intensify their search for solutions that can simultaneously maximize both their flexibility and sustainability.

STEP 4: ACCELERATING DIGITIZATION OF CORE OPERATIONS

For biopharma businesses, the shift to Industry 4.0 is no longer a question of "if," but "how." Both drug developers and their CDMO partners are evaluating technological solutions across their businesses – from administrative activities to production, quality, and logistics – and establishing frameworks to vet, validate, and implement relevant new digital tools and programs.

These efforts are especially wide-ranging for CDMOs, many of whom are rapidly adopting technologies that can maximize process efficiency and minimize human error. The Internet of Things (IoT), virtual reality (VR), and autonomous, collaborative robots have already become integral parts of these transformation strategies, along with operational solutions aimed at sustainably ensuring targeted and traceable quality improvements.

The technically demanding area of aseptic fill and finish is at the forefront of this trend, with several key investments in robotics and AI/Machine Learning that are even now making a significant impact.

Collaborative production robots, or "cobots," are already working successfully alongside human manufacturing experts in a range of roles. One of these technologies is "YuMi," – short for "you and me" – a modular, dual-armed cobot that has already been successfully integrated into our secondary packaging lines. It's currently being used to optimize workflow precision in device assembly projects and will soon be rolled out to other functions as well.

Mobile robot systems like "HelMo" are being used to automate routine, repetitive, and time-consuming tasks, such as defrosting drug substances at the start of the aseptic filling process. HelMo is a self-driving, collaborating mobile robot system that can operate at a safe distance in a room with humans. It moves to its place of operation on its own and with the help of sensors it navigates autonomously in its environment. Once configured, this specialized robot can safely and independently fill a key day-to-day role alongside a team of human colleagues – freeing trained workers to focus on engaging activities that demand more of their skills.

Robotic process automation (RPA) is already hard at work streamlining a wide variety of routine, transactional activities. RPA programs – "bots" specially designed to perform specific rules-based tasks – have been programmed to create inspection lists for batch release testing labs, fetch SAP records, process order confirmations, and much more. Automating these workflows has already helped capture significant operational efficiencies, while also freeing human operators for more valuable tasks.

In addition to these technologies, several exciting ML-focused projects are also well underway – with use cases ranging from translating data into text-based reports, to complex forecasting in controlled environments, to machine processing of natural language. In the coming year, watch for initiatives like these to play a major role in transforming many different areas of the value chain.

STEP 5: PROACTIVELY PREPARING FOR NEW REGULATORY REQUIREMENTS

In 2023, an already familiar trend looks set to continue: new and updated regulatory frameworks will soon take effect, further expanding the requirements our industry must meet. CDMOs will face the increasingly complex challenge of guaranteeing compliance while still providing the agility customers are demanding.

In the EU market, the pharma and biotech community is particularly focused on the impact of the latest revision to Annex 1 of the EU GMP Guide (Manufacture of Sterile Medicinal Products) – the most important European regulatory stan-

dard for the manufacture of sterile drug products. This new update will also bring significant increased scrutiny to quality risk management, contamination control strategies, and environmental and process monitoring methods.

We foresaw the impact this revision would have on currently established standards and have been preparing to meet regulators' elevated expectations for nearly three years now. Key investments like our Vetter Cleanroom Technology (V-CRT®) – a holistic concept designed to combine high quality and great flexibility – have positioned us well for the rollout of the Annex 1 revision this year.

STEP 6: DEVELOPING MUTUALLY COMPLEMENTARY PARTNERSHIPS

With drug owners demanding more flexibility and efficiency than ever, more and more of their partners are joining forces to deliver the time-savings biopharma customers are seeking. Continuing a trend we've seen for several years now; a growing number of specialized service providers are working to align complementary services in ways that maximize the value of their joint offerings.

As these symbiotic alliances take shape across the value chain, both sponsors and partners are quickly seeing the benefits of this collaborative approach. With the right combination of allied CDMOs, biopharmaceutical companies can access a comprehensive range of specialized services without the management-intensive, multi-partner network that level of service typically requires. At the same time, strategic alliances enable CDMOs to provide a comprehensive, end-to-end service offering while keeping their focus on individual core competencies.

Strong progress by maturing partnerships has already shown the industry that close coordination, active knowledge-sharing, and mutual support can swiftly and significantly enhance project performance and customer value. As these collaborations progress, we expect to see many more CDMO team-ups aimed at streamlining drug development and optimizing time to market.

TAKING STEPS TOWARD A SUCCESSFUL COURSE OF THE YEAR

Today, we find ourselves looking ahead at an uncertain and unpredictable time for both our industry and our world. In a moment like this, when we face an unprecedented array of challenges, I find it reassuring to think about the great resilience and innovation that helped us navigate a world-altering crisis that began not quite three years ago. These same strengths can help our industry find and follow the correct path today, especially if they're supported by the right expertise, experience, and foresight.

Fortunately for biopharma companies, they have ready access to a global wealth of these resources – through the many seasoned partners who are striving to align their businesses with their customers' changing needs. I know I speak for many of those partners when I say that we remain as committed and passionate as ever, even as we navigate challenging trends and complex dynamics like those we've discussed here.

No matter the crisis, we share one mission: to bring life-supporting and life-critical therapies to patients all over the world. In the coming year and long beyond, we will always do our best to achieve that vital goal!◆

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BIOGRAPHY

Carsten Press is Senior Vice President Global Sales Organization/Supply Chain Management at Vetter, a leading global CDMO and aseptic fill-finish partner for the biopharma industry. He has 25+ years of experience in product and supply chain management for multiple industry-leading enterprises, including Siemens and their earlier subsidiary, Infineon. Since joining Vetter in 2009, he has taken on responsibility for all end-to-end supply chain activities, including central production and capacity planning, global procurement, and logistics. Today, he continues to serve as a Senior Leader of the Global Sales Organization and Supply Chain, Business Development, and other multiple key operational functions, with a focus on advancing and expanding Vetter's core business on a global scale.

LIPID-BASED EXCIPIENTS

Misconceptions About Lipid-Based Drug Delivery

By: Rollie Fuller and Ron Permutt

INTRODUCTION

For decades, lipid-based drug delivery systems (LBDDS) have been studied, developed, characterized for improving uptake of poorly soluble compounds, found to be safe and effective in delivering a multitude of compounds of diverse chemistries, and present in pharmaceuticals across the globe, including dozens of FDA-approved products.[1] Yet, the viability of LBDDS as a platform for modern drug development is still a concern to some due to lingering misconceptions about their functionality, stability, handling, and toxicology. Many of these concerns may be easily addressed by broadening our understanding of oleochemicals' strengths and sensitivities.

The following aims to provide formulators confidence in using LBDDS as part of formulation development programs, by demonstrating their benefits and key functional mechanisms when used and addressing commonly misrepresented, misinterpreted, and misunderstood LBDDS topics.

UNDERSTANDING MECHANISMS OF ORAL BIOAVAILABILITY ENHANCEMENT FOR LBDDS

Among the mechanisms attributed to lipid-based formulations for enhancing oral bioavailability is natural lipid metabolism in the gut. Known as lipolysis, this metabolic process initiates on contact with stomach fluid thereby releasing gastric lipase. Subsequently, pancreatic lipase and bile salts further break down lipids into micellar structures that are absorbed by enterocytes that line the intestinal tract. Pharmaceutical actives are then solubilized within these lipid formulations and absorbed through the gut in a bioavailable (solubilized) state. This process can be optimized by using digestible surfactants/co-surfactants and oils to create self-emulsifying drug delivery systems (SEDDS) that form fine dispersions on contact with stomach fluid, thereby helping to maintain drug solubility within the emulsion particle.

There are other key mechanisms for enhancing oral bioavailability of actives associated with lipid-based formulations. These include targeting lymphatic absorption to bypass liver metabolism as well as reversable modulation of tight junctions to enhance permeation through the gut lining.

Starting with lymphatic absorption, long chain fatty acids (LCFAs) that are absorbed into the enterocytes can be selectively transported via the lymphatic system. Drugs solubilized within the lipid particles will then avoid first-pass metabolism and will eventually be diverted into the blood stream via lymphatic enterocytes.[2] Lipid-based formulations containing esters of LCFAs can also be used to target lymphatic absorption of lipophilic drugs having Log P >5 and solubilities >50 mg/mL in the LCFA based oil as demonstrated in several studies.[3]

For low-permeability actives including peptides, the reversible opening of tight junctions may assist in the peptide absorption, and with certain lipid-based chemistries, promote the increased uptake of model compounds via the same mechanism. For example, increasing the concentration of materials like Labrasol® (caprylocaproyl polyoxylglycerides) and Labrafac® MC60 (glyceryl mono and dicaprylocaprate) has shown to induce transient opening of intestinal tight junctions to allow the transport of insulin and FITC-Dextran across the epithelial barrier.[4,5] Other lipids with medium chain fatty acid chemistries like Capryol 90 (propylene glycol monocaprylate), can enhance the uptake of orally administered model drugs as well.[6]

OUTDATED CONCEPTS OF INTESTINAL EFFLUX INHIBITION

Given the variety of uptake-enhancement mechanisms inherent in lipid chemistry, LBDDS have historically been evaluated as possible inhibitors of active transport. Previous studies and their conclusions based on antiquated analytical methods that P-gp inhibition occurred with model drugs formulated with permeation enhancers like Labrasol (caprylocaproyl polyoxylglycerides), have recently been shown to be inapplicable as they were based on models no longer considered to be representative of such systems.[7]

A more recent study suggested that conclusions claiming LBDDS are possible P-gp inhibitors may have misinterpreted other lipid excipient-induced penetration-enhancement mechanisms with P-gp inhibition.[8] This study compared the gold standard model from older studies with a more modern version that considered additional parameters, highlighting irregularities between the two. With so many possible mechanisms of bioavailability enhancement intrinsic to lipid-based formulations: participation in the lipolysis process, avoidance of liver metabolism, targeting lymphatic uptake, and reversible modulation of tight junctions, it is difficult to attribute permeation enhancement just to efflux inhibition.

LIPIDS VS. POLYMERS: DIFFERENT CHEMISTRIES, COMPOSITIONS, FORMULATION PROCESSES

While some lipids, specifically those of the chemically modified variety, have overlapping applications with polymeric materials, it is important to understand these chemical families are indeed different. One key distinction is lipids consist of fatty acids, naturally occurring (organic) moieties abundant in plants and seeds, while polymers are composed of chains of repeated units generally derived from synthetic sources. Simple lipids (eg, glycerides) are composed of alkyl heads esterified to fatty acid tails and have well-defined molecular weights, ranging from 8 to 24 pairs of -CH_2. Lipid-based materials also generally have lower melting ranges than high molecular weight polymers.

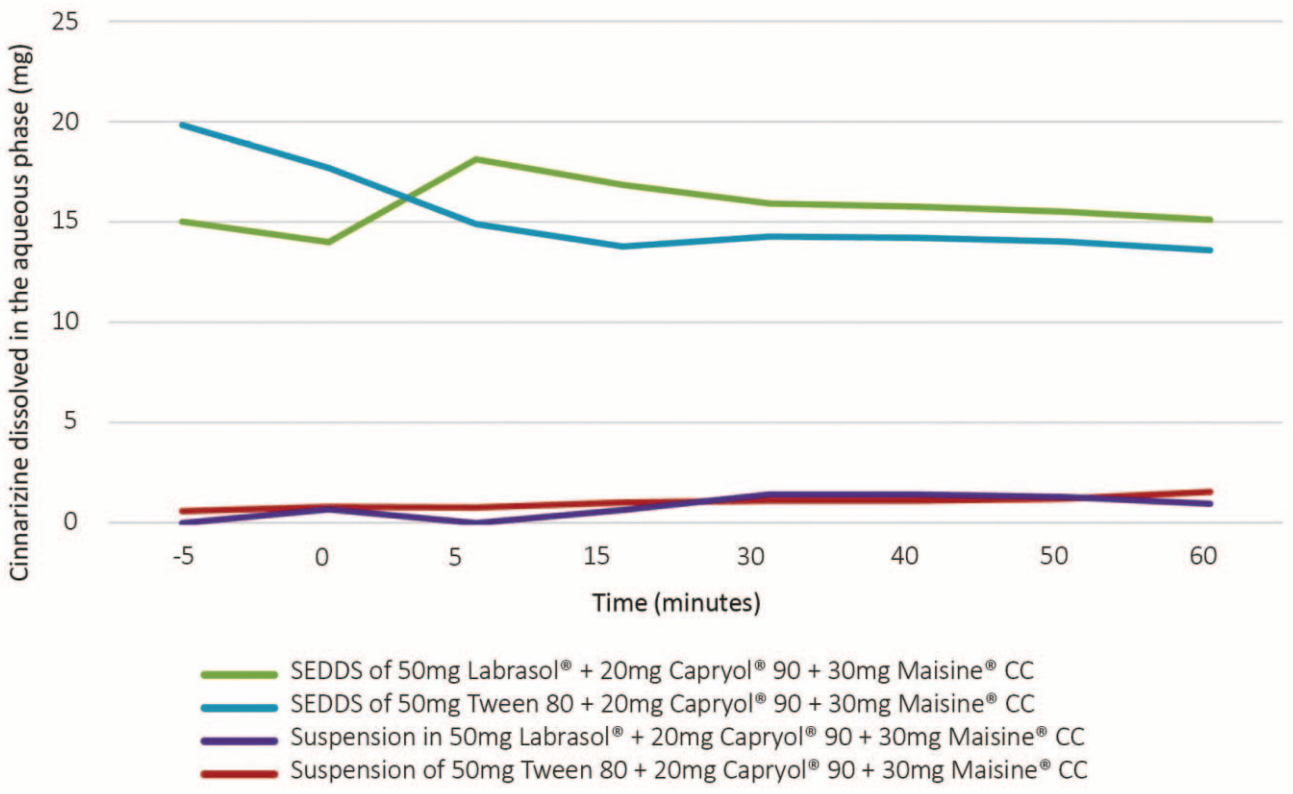
Physico-chemical properties of polymers, on the other hand, are quantified by their molecular weights and highly dependent on the number of repeated units. For example, PEG-1000 and PEG-4000 are both composed of 1000 and 4000 repeat units of ethylene glycol and have different properties due to their vastly different molecular weights.

Also, because lipids are derived from natural and botanical sources, they can range in homogeneity depending on their raw materials (ie, whole natural oil vs. fractionated oil vs. purified fatty acids) and manufacture process design. For example, Labrafil M 1944 CS conforms to the USP monograph for oleoyl polyoxylglycerides and is derived via alcoholysis of apricot kernel oil with PEG to form PEG esters and glycerides of mostly oleic acid, and controlled quantities of stearic, palmitic, and linoleic acids. This is compared to Capryol 90, which conforms to the USP monograph for propylene glycol monocaprylate that is derived via direct esterification of propylene glycol and caprylic acid and distilled to contain >90% monoesters of the raw materials therein. Even though lipid materials have diverse components, this does not make their composition or specifications less consistent than polymers. Like polymeric materials, lipid systems can also have a range of purity depending on manufacturing process and extent of purification (eg, distillation). Lipid-based materials like all pharmaceutical-grade materials in the US must still conform to strict USP/NF monographs.

Lipids' melt properties and diverse chemistries allow them to be easily incorporated into processing techniques that traditionally use polymer-based systems. Due to the lower melting point ranges of lipid excipients, generally <75°C, they do not require diluting or dispersing in solvents in hot melt processes (eg, melt granulation). They can instead be melted and applied directly onto a substrate without the need for solvents. This means an evaporation step is not required to achieve diverse functionalities like modified release, taste masking, and powder lubrication.[9]

As another example, lipid excipients can be incorporated into hot-melt extrusion processes but do not undergo a glass transition like polymer-based materials. Due to lower melting point ranges, lipid-based HME processes do not require the addition of plasticizers because the low viscosities of the melted lipids reduces the need for material shear and leads to reduced energy while maintaining a high throughput.[10] Lastly, lipid-based emulsions can undergo lyophilization to form semi-solids that will disperse on contact with aqueous media.[11]

FIGURE 1



***In vitro* Lipolysis Results of Cinnarizine (Adapted from Gattefossé SAS Technical Center of Excellence, 2018)**

THE IMPORTANCE OF DRUG SOLUBILITY IN LIPID VEHICLES

There are several potential ways in which lipid-based chemistries can be harnessed to enhance bioavailability of orally dosed compounds. API solubility in lipids, for example, can be used as an indicator of a formulation's final performance because compounds solubilized in the lipid vehicle can fully participate in the lipolysis process. In an internal study carried out by the Gattefossé Technical Center of Excellence, Cinnarizine solubilized in SEDDS maintained better solubility in biorelevant gastrointestinal media than Cinnarizine in a suspended state (Figure 1). In other words, a larger percentage of Cinnarizine was in a state that can be absorbed by the body when pre-dissolved in a SEDDS than when dosed suspended in the same vehicles.[12] This is a fundamental rationale behind using lipids for oral bioavailability enhancement. It is for this reason that it is highly recommended to complete a solubility screening of actives in an array of lipid vehicles during early stages of development.

In another example, Danazol (a well-characterized low-water solubility model compound) was orally administered to rats in both a traditional aqueous suspension and in Labrafil M 2125 (Linoleoyl polyoxyl-6 glycerides NF) based solutions and suspensions. Table 1 contains concentrations of Danazol and percentages dissolved in various prepared formulations.

The plasma concentration–time profiles in Figure 2 show a 4-mL/kg solution of Labrafil increased Danazol oral bioavailability nine-fold compared to an aqueous suspension. Note that even lipid-based suspensions of Danazol showed high uptake. It is important to highlight the lipid-based suspensions contained considerable percentages of drug in solution creating a combination of lipid-based solution/suspension compared to the aqueous suspension control.[13]

While the Labrafil solution showed a similar increase in bioavailability compared to the Labrafil suspension with partial solubilization, increases in bioavailability tend to be dependent on the chemistry of the active compound as well as the dosing methodology based on Gattefossé's experience with similar studies.

EFFECT OF EMULSION PARTICLE SIZE ON BIOAVAILABILITY

The notion that emulsion particle size affects the uptake of an active solubilized within a SEDDS formulation is frequently debated, and not surprisingly, any correlation made between droplet size and uptake is generally dependent on formulation chemistry and dissolution medium. The emulsion particle size is dynamic, becoming finer throughout the lipolysis process, and a lipid-based system undergoes intricate physiological progressions having many variables.[14] Therefore, concluding particle size by itself correlates to bioavailability can be misleading.

A potential reason for this common misunderstanding could be a historical view that small particle size is directly correlated to consistent and predictable dispersions. This idea was perpetuated by the 1994 study comparing Sandimmune, a cyclosporin soft gel capsule that formed a crude emulsion in the gut, to the second-generation Neoral formulation, a soft gel capsule containing a cyclosporin SMEDDS formulation. The latter self-microemulsified upon contact with gastric fluid, while the former required dispersion by digestive enzymes to emulsify. This study concluded the microemulsifying nature of Neoral simplified dispersion, leading to more consistent dispersion profiles.[15]

A more recent study highlighted the difficulty correlating *in-vitro* dispersion size to *in-vivo* uptake. It examined *in-vivo* performances of different self-emulsifying Danazol formulations with varying oil/surfactant ratios resulting in a range of emulsion droplet sizes. In this study, uptake decreased with decreasing particle size, while uptake increased with course emulsions. The emulsion formulas contained three times as much digestible Maisine CC oil (glyceryl monolinoleate) compared to the non-digestible microemulsion containing increased percentages of Cremophor EL and ethanol. The alternative conclusion was therefore digestibility is a better predictor of bioavailability.[16]

TABLE 1

Formulation	Concentration of Danazol (mg/mL)	Labrafil® M2125CS Dose	% Danazol Dose Dissolved in Formulation
Solution in Labrafil®	7	4 mL/kg	100
Suspension in Labrafil®	14	2 mL/kg	59
Suspension in Labrafil®	28	1 mL/kg	30
Aqueous suspension	28	0 mL/kg	0

Concentrations of Danazol in Prepared Solutions & Suspensions Orally Dosed to Male Rats (adapted from Larsen et al, 2008)

In-vitro lipolysis is a screening technique used to simulate this mechanism. *In-vitro* lipolysis has been well documented to be more representative of a lipid formulation's ability to maintain an active's solubility *in-vivo* as the model accounts for the presence of enzymes that represent the dynamic conditions that occur in lipid metabolism.[17]

LIPIDS ARE STABLE & EASY TO HANDLE

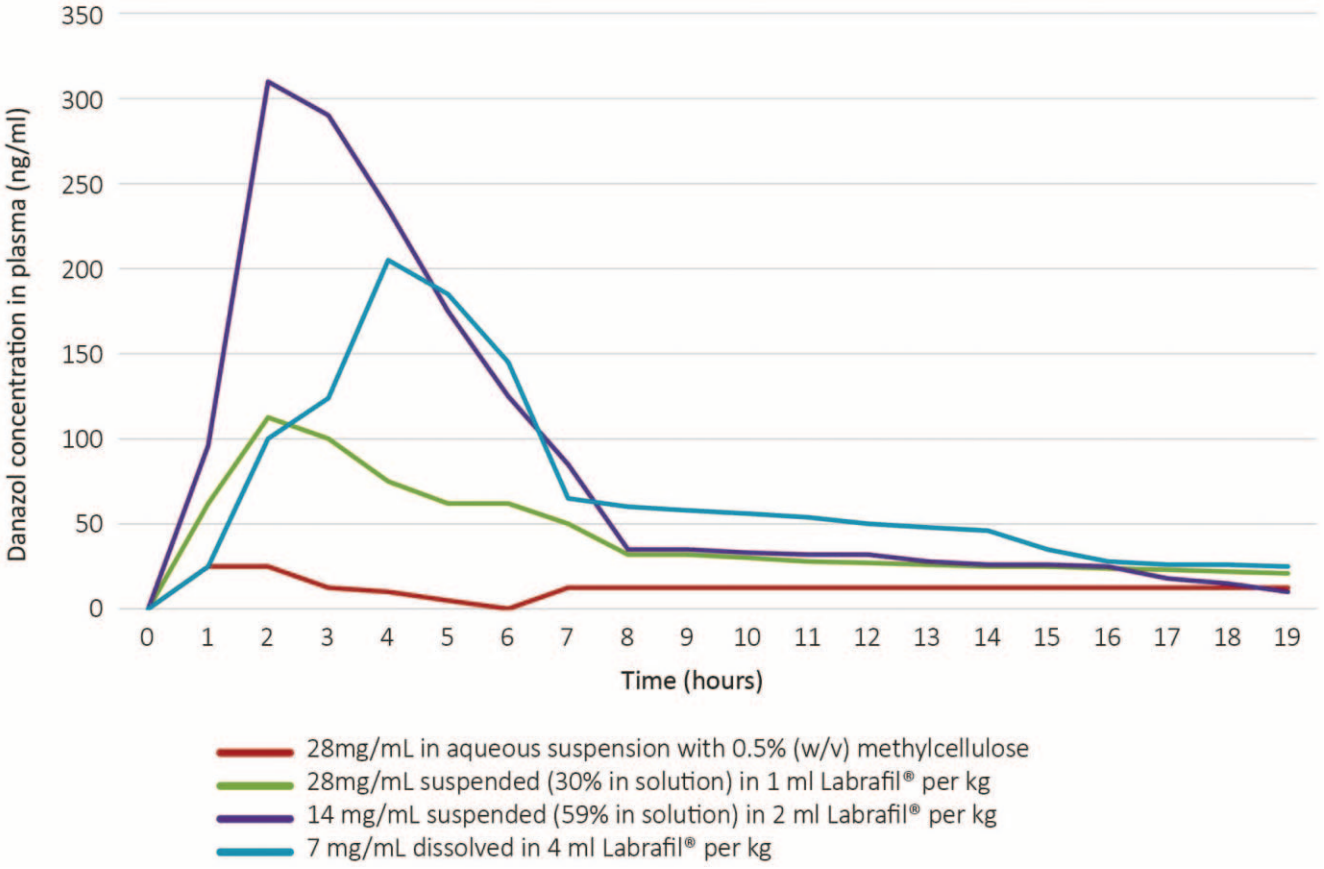
As with other excipients, there are potential pitfalls that can occur when handling lipid-based materials. This has led to a misconception that lipids are unstable and difficult to work with, especially in terms of degradation via oxidation or hydrolysis. Oxidation can occur when sensitive moieties are exposed to oxygen. Oxidation reactions form peroxides from these moieties that propagate into additional peroxides that then generate unstable systems. Hydrolysis occurs when ester bonds are exposed to environmental moisture and react with water, cleaving these bonds and leading to formation of free fatty acids and reduction in ester content.

It's important to keep in mind these sensitivities are prevalent in many excipient chemistries to a far greater extent especially in terms of propensity to oxidation. The omnipresence of oxygen-sensitive materials in pharmaceutical products is a testament to the manageability of oxidative challenges in drug development. Lipid-based excipients are quite easy to work with and can bring drug delivery solutions that greatly outweigh their controllable challenges. It is important to keep in mind when researching potential degradation pathways for lipids that they are often studied using forced experimental conditions.[18] Oxidation and hydrolysis are avoidable using simple preventative measures in terms of storage and formulation in a pharmaceutical setting.

Lipid-based materials should be stored in sealed containers under inert conditions by purging headspace with nitrogen between uses. When melting and processing, dry heat sources should be used. Water baths are to be avoided when applying heat to melt and mix the formulation components. Instead, laboratory microwave ovens can be used to heat in short intervals. Commercial packs can be heated in ovens, hot boxes, or drum warmers.

To avoid potential oxidation from occurring during the formulation process, it is highly recommended to incorporate an-

FIGURE 2



Plasma Concentration-Time Profiles for Danazol Following Oral Administration to Male Rats (Adapted from Larsen et al, 2008)

tioxidants into formulations during the initial stages of development. In a recent white paper, evolution of peroxide value, a critical stability parameter and indicator of oxidation of lipid excipients, was examined with and without antioxidants BHT (butylated hydroxyanisole) and BHA (butylated hydroxytoluene). In Figure 3, one can see that in each case, peroxide value evolved at a significantly slower rate in the presence of antioxidants.[19]

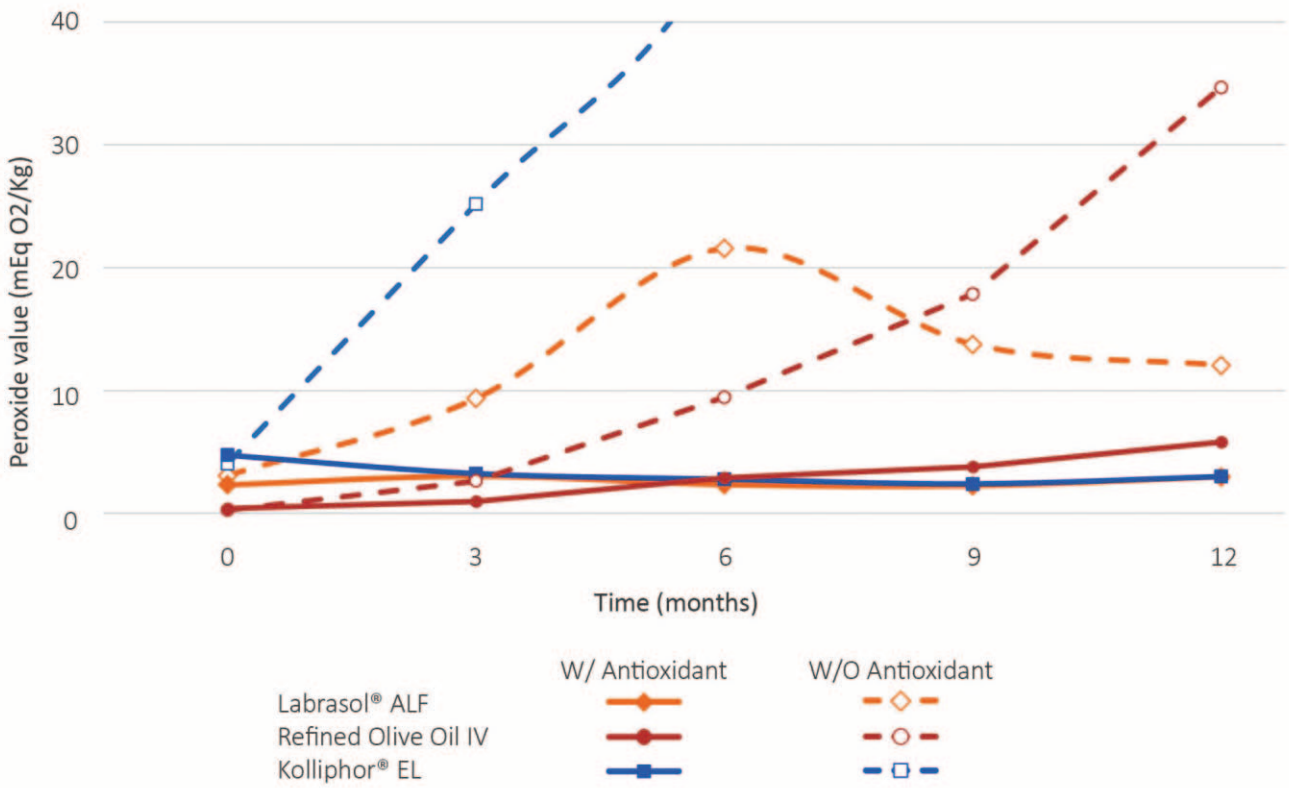
DOSING IN PRECLINICAL STUDIES

Lipid vehicles are ideal candidates for preclinical screening studies due to their long history of use and ability to achieve high exposure due to bioavailability-enhancement mechanisms. A common misconception is lipid-based vehicles cause inevitable gastric irritation, tolerability issues, and toxicity in certain animal models. This belief stems from labs dosing subjects at improper levels or using poor dosing techniques and not from the lipids themselves.

As an example, rodents suffering from gastric irritation or emesis after having been orally dosed with Labrasol often arises when drugs are dosed neat in Labrasol at maximum recommended volumes for rodents. The rodents are unable to effectively metabolize lipids at this volume, which leads to negative effects. To avoid this, determine the saturation solubility of the drug in a volume of Labrasol for dosing of your target drug load to assess whether the required volume of Labrasol is within no observed adverse effect limits. If the required use level is too high, reduce the amounts of Labrasol in combination with other vehicles to achieve required solubility targets while remaining within known safety limits.

Dose-escalation studies that push boundaries of preclinical formulations should always refer to safety limit evaluations of single lipid excipients in the test species. Like other surfactant chemistries, lipid-based surfactants can cause more gastric irritation due to their surface-active interactions with the gut lining than simple glycerides; therefore, recommended safety dosing levels should be adhered to. The lipid formula can be optimized to achieve uptake targets at later stages and tested for safety once safety limits of the active have been well characterized. Gattefossé has extensive safety studies available on our excipients to assist in optimizing early stage tox formulations.

FIGURE 3



Effect of Antioxidants (AO) on the Stability of Various Excipients (Labrasol ALF, Maisine CC, Refined Olive Oil IV, and Kolliphor EL) Reflected in Peroxide Value Results for Samples With & Without Added AO (BHA and BHT, 500 ppm each), Stored in 25°C/ 60%RH (Adapted from Langbein, Dave, 2021)

Having had a high number of lipid-based oral drugs approved by the FDA and available in the market shows how well lipid vehicles are tolerated when developed by formulators who dose the materials correctly. A 2017 review includes 36 examples of FDA-approved lipid-based formulations, including Absorica and Xtandi, which contain high levels of polyoxylglyceride-based surfactants, demonstrating lipid systems have withstood not only preclinical safety testing but also vigorous clinical human trials.[1]

SUMMARY

Bioavailability enhancement and processing flexibility are just a few of the facilities lipid-based excipients, due to their diverse physicochemical features and functionalities, can provide. Their chemistries have well-defined tox and safety profiles, and they offer multifunctionality, such as solubility, penetration, and bioavailability enhancers. They are also straightforward, easy-to-use, and compatible with solvent-free processes.

LBDDS can advance formulations from early stages through to commercialization when basic dosing recommendations and handling protocols, some of which have been previously discussed, are followed, thereby reducing costs and minimizing the time to market.

Having been used for decades on a global scale, LBDDS are viable platforms that should certainly be adopted into the formulator's toolbox for use as key components of pharmaceutical product development. ◆

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BIOGRAPHIES

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Ron Permutt is Senior Director, Pharmaceutical Division, at Gattefossé USA, where he oversees the pharmaceutical sales, technical, marketing, and laboratory operations in Paramus, NJ. Prior to joining Gattefossé in 1999, he worked at Cerestar, developing cyclodextrin business in the northeastern United States and prior to that as Plant Research Engineer at JM Huber Ink Division. He earned his MBA from Fairleigh Dickinson University, NJ, and his BSc in Chemical Engineering from Northwestern University, IL.

BIOAVAILABILITY ENHANCEMENT

Solving Low Solubility Challenges to Optimize Drug Delivery Platforms

By: David K. Lyon, PhD

INTRODUCTION

Low aqueous drug solubility in pharmaceutical pipelines is a pervasive issue. In particular, rapidly growing therapeutic areas, such as oncology, anti-virals and anti-inflammatory indications, are largely plagued by small molecule drugs with low solubility and bioavailability. It is estimated that 70% to 80% of pipeline drugs in development today are poorly soluble molecules.[1] As a result, a number of enabling technologies have been developed to improve oral drug absorption and bioavailability (BA). Commonly used technologies in this area have been extensively reviewed and include salts, cocrystals, amorphous solid dispersions (ASDs), nano and micro-crystals manufactured by particle size reduction, cyclodextrin complexation, and lipid-based technologies.[2]

For instance, salt formation for solubility enhancement is a common technique used during solid form selection for ionizable compounds.[3] However, many salts form hygroscopic materials that can lead to both physical and chemical stability issues. In addition, many salts do not substantially enhance a poorly soluble compound's bio performance because of precipitation of the compound in the presence of food (increased pH), common ions in the stomach, or as the pH increases upon transfer into the duodenum.

For the more than 50% of the compounds in development that are either not ionizable or suffer from stability issues as a salt form, alternative solubility enhancing technologies are needed. Many technologies have been shown to enhance drug BA; however, the most notable commercial products are those that utilize lipid-based technologies, ASDs, and micronized crystals. The commercial precedence of these key enabling technologies supports their continued utilization in addressing the new chemical entities (NCEs) development pipeline candidates that are regarded as poorly water-soluble.

The following discusses how low aqueous solubility NCEs have come to define the innovative pharmaceutical pipelines and how advanced technologies are often required to overcome this issue. It further defines how bioavailability enhancing (BAE) technology selection can aid in defining an optimized delivery platform. Finally, the most prominent BAE technology (ASDs) is described with some novel twists to overcome a relatively new problem — molecules that have both low aqueous and organic solubility.

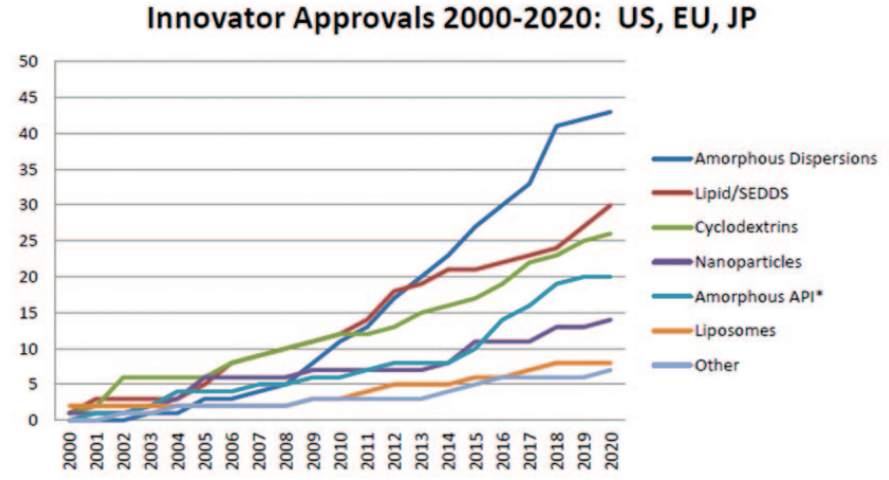
EARLY PHASE PROCESS DEVELOPMENT - IMPROVING COMMERCIAL OPPORTUNITY

A recent trend in the earlier phases of drug development is the low aqueous solubility of NCEs. Among the varying formulation strategies that can be used to improve solubility, ASDs have been the most frequently used technology from 2000 to 2020 (Figure 1).

The most common technique for the manufacture of ASD systems is spray drying. Spray drying is the technology of choice due to its fast-drying rate, ability to kinetically trap the drug in amorphous form, scalability, and broad applicability across different target drug profiles.[5]

The spray drying process begins with a solvent, the API, and polymer in a solution tank. A high-pressure pump then pushes

FIGURE 1



Enabling solubilization techniques used on marketed products from 2000 to 2020.[4]

the solution through either a two-fluid or pressure swirl nozzle into the top of the spray dryer, creating droplets that are met with a heated nitrogen and then formed into solid particles that are trapped in the amorphous phase. Next, the nitrogen gas and solid particles flow into a cyclone where the ASD is collected. When spray drying at a small scale, the nitrogen is sent to a scrubber and vented; however, at a large scale, the spent nitrogen has some residual solvent, which is condensed into a residual solvent stream as liquid waste, and the nitrogen is recycled back into the dryer as a closed loop.

For this process to yield an amorphous product, all the components that begin in the solution tank must be fully dissolved before spray drying manufacturing. However, the increased number of NCEs that have poor solubility in water and organic solvents can make this especially challenging. Low organic solubility, in particular, can lead to small particles that can negatively impact downstream processing due to poor flow properties making capsule filling or tableting difficult. Likewise, it can create non-economic processes at a commercial scale due to low throughputs. Early phase developers may try to overcome this by designing a process based on low solid concentration in a pre-clinical or Phase 1 manufacturing process or by using solvents, such as dichloromethane (DCM) or tetrahydrofuran (THF), in which these NCEs are more soluble. Yet, each of these approaches can compromise a commercial line-of-sight when the early phase studies are successful. In particular, these solvents are more toxic than conventional spray-drying solvents. DCM presents significant environmental risks, resulting in emissions that are increasingly regulated, thus limiting production. In addition, THF has the risk of peroxide formation, which can cause chemical degradation in a product and increase the risk of explosions. Both solvents present potential equipment incompatibility.

INCREASING SOLVENT SOLUBILITY USING HEAT

An alternate approach to increasing solubility in conventional spray-drying solvents is the application of heat to the spray solution. There are two methods in which heat can be used to increase solubility. The first is a warm process, in which a jacketed tank is heated to a temperature below the boiling point of the solvent to dissolve the drug, thereby increasing solubility. The remainder of the process is the same, using standard nozzles and conventional processing conditions.

The second method is a temperature shift process. With this approach, a slurry of undissolved drug is pumped to the top of the spray dryer and then run through an inline heat exchange, which rapidly increases the temperature of the solution to above the boiling point of the solvent to dissolve the drug. The solution is then pumped into the drying chamber, where a flash nozzle is used to atomize the solution. At Lonza, we designed a flash atomizer to take advantage of the solution flashing or boiling as it's going into the chamber.

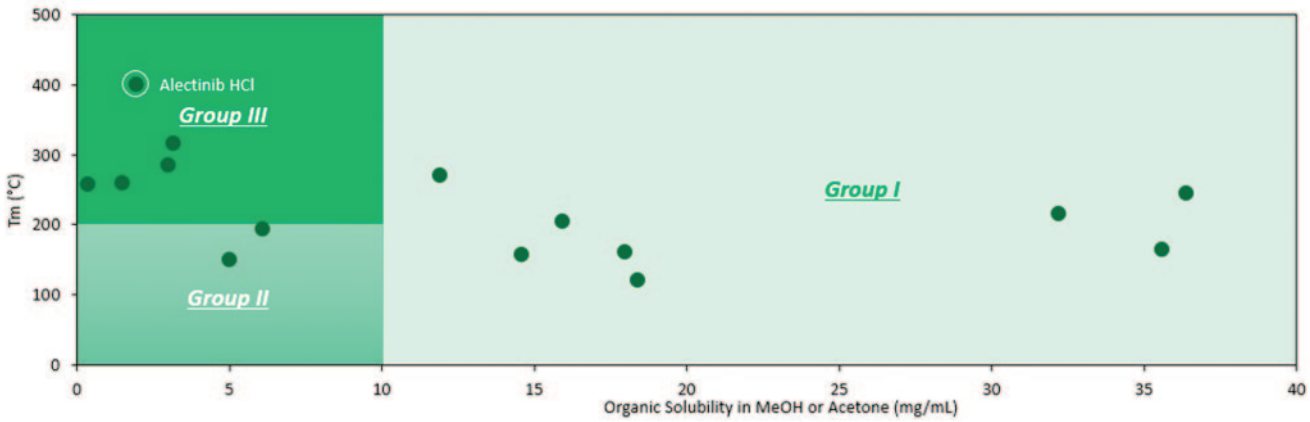
The first case study looks at the use of temperature shift technology. The graph in Figure 2, where the X-axis is organic solubility in methanol (MeOH) or acetone, and the Y-axis is the solubility of the drug, shows three groups of compounds:

Group I has sufficient solubility in Lonza's preferred spray-drying solvents, making them a reliable option during spray drying to create an ASD.

Group II has low organic solubility and a low melting point. Hot melt extrusion is a good approach for these compounds, although spray drying could be used as well.

Group III are brick dust compounds and therefore, have low organic solubility in MeOH or acetone. They also have extremely high melting points, which means they require an innovative spray during or thermal processing technique.

FIGURE 2



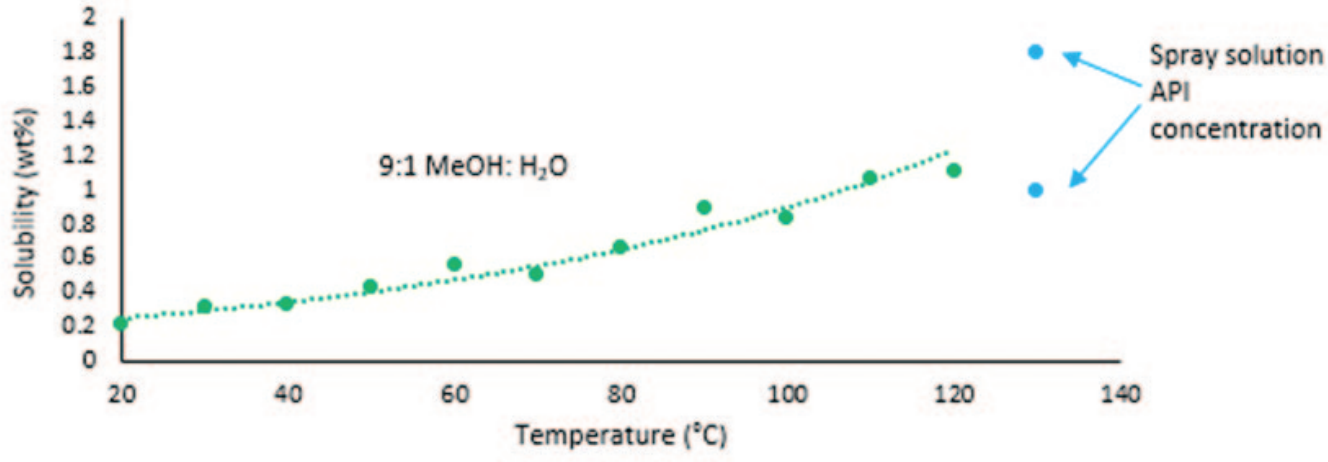
Melting point versus organic solubility compound map. The model compound used for a case study using the temperature-shift process was alectinib hydrochloride (HCl), and the solvent was 90:10 MeOH/water (H_20). As displayed in Figure 3, it shows the increase in solubility using this method with the solvent MeOH/H20 (blue dots represent two-spray solution API concentrations used when spray drying the formulation).

In order to achieve high throughput at commercial scale, the targeted drug weight percentage (wt%) is at least 1 wt%. When using a standard spray-drying process for alectinib HCL, only 0.125 wt% drug concentration was achieved with a solution temperature of 25°C compared to 1 wt% and 1.8 wt% (noted in blue dots in Figure 3) when heating the solution to 130°C to increase solubility (temperature shift method). This represents an 8- to 14-fold increase in solubility and, therefore, throughput. Furthermore, there is also the estimated difference in processing time between spray drying and the temperature shift method. Conventional spray drying takes more than 100 hours to manufacture 4 kg at clinical scale, which would require operators working multiple 12-hour shifts. Conversely, the temperature shift method totals less than 15 hours for 1 wt% for the same scale. In addition to these benefits and a decrease in solvent consumption, using heated solvents is an improvement when compared to solvents that have negative environmental impacts.

INCREASING SOLUBILITY USING PROCESSING AIDS

Generally, salt formation is a common and effective method for increasing solubility and dissolution rates of acidic and basic drugs.[3] When the salt form is not stable enough or does not enhance bio performance sufficiently, it may be necessary to use an ASD. If the low aqueous soluble compound is also poorly soluble in organic solvents, alternate techniques may be required. An alternative approach is to use volatile aids to ion-

FIGURE 3



Solubility Increase as a Function of Temperature in MeOH/Water

ize a drug in an organic solvent in the solution tank. Because the aid is volatile, it's removed during the spray-drying and secondary drying processes, leading to reformation of the ingoing form of the API. This approach does not require any additional steps and can be used with existing equipment.

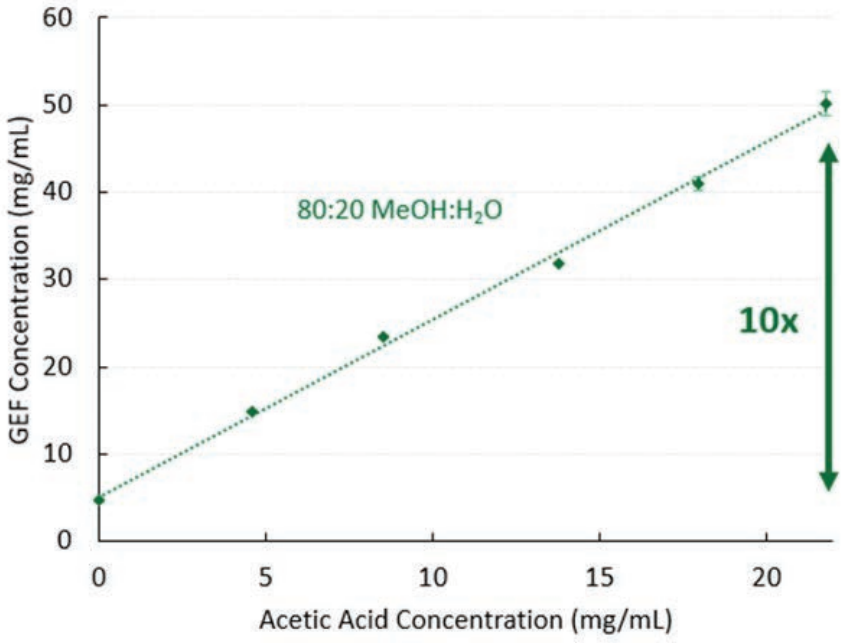
ACETIC ACID

In the first case study of volatile aids, acetic acid is used as a processing aid. The model compound is gefitinib, which has a basic acidic strength (pKa) of 7.2 while acetic acid has a pKa of 4.75. By adding a minimal amount of acetic acid, it increases the solubility 10-fold when compared to adding only methanol (MeOH) and water (H_2O) (Figure 4).

As a result, gefitinib was successfully spray dried using a selection of typical ASD polymers, demonstrating this method can be used with a variety of polymers (neutral and enteric) and there are minimal limitations to excipient choice. Furthermore, conventional spray- dry conditions were used for the remainder of this process. This volatile aid does not impact viscosity nor does it require higher input dryer temperatures.

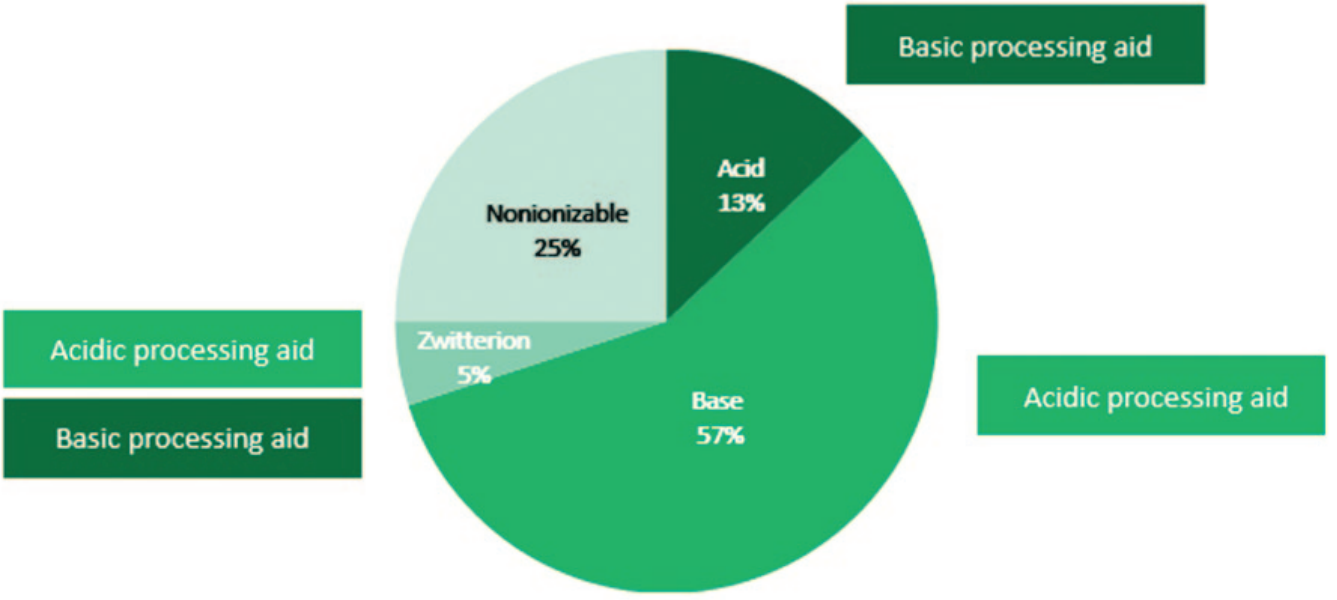
All of the dispersions had the same performance and morphology compared to controls, showing that inclusion of the volatile aid does not affect the final product. Additionally, all of the acidic acid was removed below ICH limits during tray drying, so the ingoing form of the drug substance was regenerated.

FIGURE 4



Solubility increased 10-fold when a small amount of acetic acid is added to MeOH:$H_2$0.

FIGURE 5



Distribution of Lonza Client Portfolio Compounds That Are Ionizable

AMMONIA

In addition, ammonia was used in the second case study of volatile aids. Analogous to the acetic acid processing aids, ammonia works for weakly acidic compounds. Ammonia's basic pKa is 9.25. Two different model compounds were used for this case study: piroxicam (pKa 4.7) and sulfasalazine (pKa 3.2). An ammonia concentration of more than one molar equivalent was added in, so all of the API was fully protonated. Our results showed a 20-fold increase in solubility for piroxicam and a 40-fold increase for sulfasalazine.

Piroxicam was spray dried using select ASD polymers, again demonstrating the ability to use a variety of polymers (neutral and enteric). Conventional conditions were used for the remainder of the process.

The use of volatile aids to increase solubility should be used if the compound is poorly soluble in acetone or MeOH (preferred spray-drying solvents) and when the compound is ionizable. Figure 5 represents internal data from Lonza showing compounds that are ionizable and when this methodology would be applicable.

The use of warm and temperature shift processes as well as volatile aids to increase solubility for low aqueous and organic soluble compounds not only reduce manufacturing time, which can ultimately save time and money, but also eliminate the use of solvents that are harmful to the environment and, potentially, the health of facility personnel.

SUMMARY

NCEs with low aqueous solubility have come to dominate the pharma pipelines. There are a number of technologies that have been demonstrated to be capable of improving solubility and, hence, bioavailability. However, ASDs manufactured by spray drying have become a mainstream approach to overcoming the significant fraction of pipeline molecules that have poor aqueous solubility and bioavailability. This technology has become prevalent due to its fast-drying rate that enables kinetic trapping of the drug in amorphous form and scalability and broad applicability. Spray drying has also evolved to allow processing of compounds that are insoluble in both aqueous and organic systems, broadening its applicability and improving its commercial applicability. ◆

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BIOGRAPHY

Dr. David Lyon serves as a Senior Fellow, Global R&D, at Lonza's site in Bend, OR, where he advises on internal and external collaborations for bioavailability enhancement technologies, modified release, and bioprocessing. He joined Bend Research as a Research Chemist in 1991. During his tenure at Bend Research, he held positions of increasing responsibility, leading numerous large-scale research programs and ultimately being named Senior Vice President, Research prior to the company's acquisition by Capsugel and, subsequently, Lonza. His areas of expertise include extensive work with amorphous solid dispersions for bioavailability enhancement of active compounds with low aqueous solubility, as well as the development of modified-release formulations and bioprocesses. He earned his Bachelor of Science degree in Chemistry from Western Washington University and his PhD in Inorganic Chemistry from the University of Oregon. Subsequently, he completed postdoctoral work at the California Institute of Technology.

INFLAMMASOME INHIBITORS

21st Century Miracle Drugs: Spotlight on Clinical NLRP3 Inflammasome Inhibitors

By: Bryan Oronsky, PhD

INTRODUCTION

In 1860, Henry Wadsworth Longfellow immortalized America's most famous early detection warning system with the hanging of lanterns in the tower of the Old North Church and the subsequent midnight ride of Paul Revere to warn colonists of the approaching British army. "One if by land, and two if by sea" the phrase coined by Henry W. Longfellow is a reference to the secret signal orchestrated by Revere.[1]

The Paul Revere of the innate immune system, which constitutes the first line of defense against non-self-pathogens, is known as the NLRP3 inflammasome. This inflammasome senses danger and responds through the activation of genes that encode IL-1beta, an inflammatory signaling molecule. IL-1beta sounds the alarm and puts the immune system on hyperalert status. The inflammasome also initiates a cellular self-destruct sequence in which a protein called gasdermin D pokes holes in the macrophages from the inside out, leading to release of IL-1beta and to a type of cell death called pyroptosis.

This is beneficial — to a point — and only to a point. Past a certain point, inflammation is a self-sustaining chain reaction in which inflammation leads to damage, damage leads to more inflammation, and more inflammation leads to more damage, etc, until a persistent inflammatory state is maintained. It is no surprise, then, that hyperactive NLRP3 inflammasomes are linked to an enormous range of diseases, including Alzheimer's, atherosclerosis, inflammatory bowel disease, nonalcoholic steatohepatitis (NASH), and Parkinson's. One strategy to slow or stop the progression of these diseases is to inhibit the inflammasome.

Several specific inflammasome inhibitors that have entered the clinic are briefly reviewed below, although clinical data from them is not always accessible.

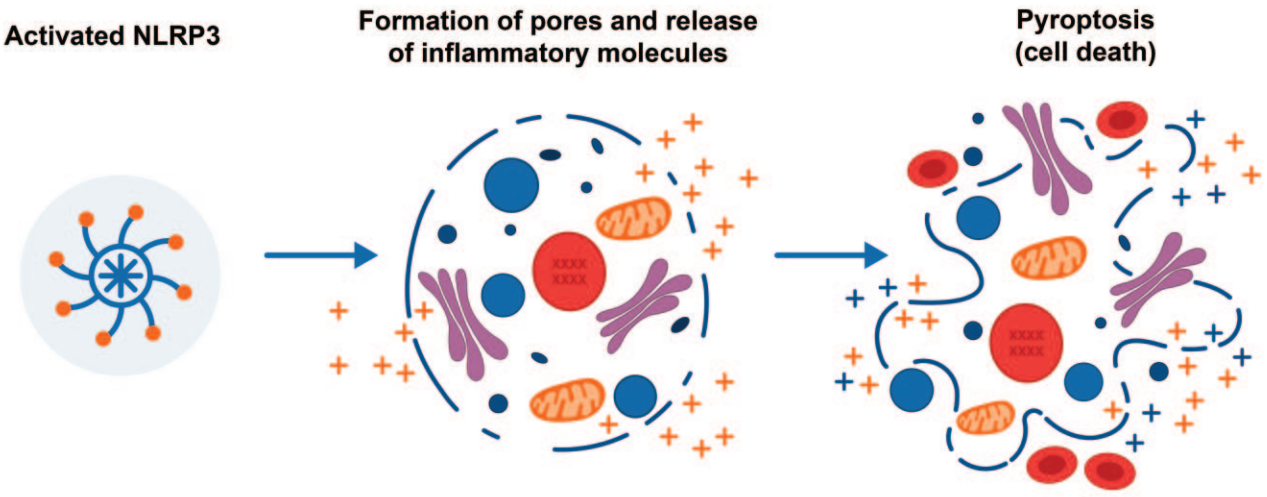
RRX-001

The most clinically advanced of the direct NLRP3 inflammasome inhibitors, RRx-001, a parenterally administered small molecule from EpicentRx that crosses the blood brain barrier, is in Phase 3 trial for the treatment of third line and beyond small cell lung cancer (SCLC) and in a late-stage trial for the treatment of severe oral blistering or mucositis from radiation and chemotherapy in head and neck cancer and on the critical path for approval as a radioprotectant in case of nuclear war.[2] Because it crosses the blood brain barrier, RRx-001 is also under study in Parkinson's Disease, Amyotrophic Lateral Sclerosis (ALS)/motor neuron disease (MND), and Alzheimer's Disease having been awarded grants as an inflammasome inhibitor by the Michael J Fox Foundation (MJFF) and other funding organizations for neurodegenerative diseases.[3]

OLT1177 (DAPANSUTRILE®)

This is a highly selective inhibitor of NLRP3 in oral and gel form from Olatec Therapeutics, which has completed a Phase 2 clinical trial for osteoarthritis of the knee. In a Phase 2 clinical trial for gout, OLT1177 was reported to reduce joint pain comparably to NSAIDs and prednisolone, and in a Phase 1 trial for systolic heart failure left ventricular ejection fraction was improved.[4,5] OLT1177 is in an ongoing Phase 2 trial for Schnitzler's

FIGURE 1



Three-Step Inflammasome Countdown to Self-Destruction (Credit to EpicentRx)

syndrome, a rare inflammasome-driven autoinflammatory disease. It is also under preclinical investigation in Alzheimer's Disease, autoimmune encephalomyelitis, myocardial ischemia, and arthritis.[6] No safety issues have been reported.

DFV890 (IFM-2427)

Acquired by Novartis in 2019, IFM Tre developed an oral NLRP3 inflammasome, IFM 2427, later renamed DFV890 after the Novartis acquisition, which has reportedly completed Phase 1 safety trials. DFV890 is in Phase 2 trials for the treatment of familial cold autoinflammatory syndrome (CAPS) and knee osteoarthritis. No results are available.

CANAKINUMAB (ILARIS), RILONACEPT (ARCALYST) & ANAKINRA (KINERET)

While not pure inflammasome inhibitors, the parenterally administered biologics canakinumab, rilonacept, and anakinra deserve honorable mention as blockers of IL-1 because this inflammatory cytokine is a product of NLRP3 inflammasome activation. All are approved by the FDA for the treatment of cryopyrin-associated periodic syndromes (CAPS), an autoinflammatory disease that results from a mutated, hyperactive inflammasome. Anakinra is also approved for the treatment of moderate-to-severe rheumatoid arthritis, while canakinumab is approved for juvenile idiopathic arthritis [JIA]. Canakinumab (Ilaris) completed a large 10,000+ patient Phase 3 clinical trial named CANTOS in cardiovascular disease. CANTOS demonstrated not only significantly reduced recurrent cardiovascular events but also, more unexpectedly, a significantly lower total cancer mortality. However, the canakinumab-treated group had an increased risk of fatal infection and sepsis.[7]

INZOMELID (IZD174), SOMALIX (IZD334) & SELNOFLAST (RG6418/IZD334)

Inflazome, a joint spin-out from the University of Queensland in Australia and Trinity College Dublin in Ireland, which Roche acquired in 2020, tested two oral NLRP3 inhibitors in Phase 1 trials. These were Inzomelid (IZD174), a brain-penetrant molecule, and peripherally restricted Somalix (IZD334), which were evaluated in a Phase 1 and a Phase 1B trial in CAPS. Except for safety and tolerability, which were acceptable, no results from these trials are available, but Phase 2 trials are reportedly planned.[8] Selnoflast (RG6418/IZD334), another inflammasome inhibitor, reportedly finished a Phase 1 trial in CAPS patients but data is not available.

ZYIL1

This potent orally administered NLRP3 inhibitor from Zydus Lifesciences completed a Phase 2 proof-of-concept trial in CAPS patients with documented flare ups. In addition to favorable safety and tolerability, sustained clinical improvement was reportedly demonstrated.[9]

TABLE 1

Name	Company	Clinical Trial Phase	Route of Administration	Relevant Information
canakinumab, rilonacept, anakinra	canakinumab (Novartis) rilonacept (Regeneron Pharmaceuticals), anakinra (Amgen)	Approved	IV	These are IL-1 blockers not strictly NLRP3 inhibitors but are mentioned because IL-1-beta is one of the main outputs of the NLRP3 inflammasome. In a large Phase 3 trial called CANTOS in cardiovascular disease, canakinumab demonstrated significantly reduced cardiovascular disease and cancer incidence.
RRx-001	EpicentRx	Phase 3	IV	Under evaluation in cancer as a cytotoxic and as a normal tissue chemo- and radioprotectant and in neurodegenerative diseases.
OLT1177 (Dapansutrile®)	Olatec Therapeutics	Phase 2	Oral & gel	Activity demonstrated clinically in knee osteoarthritis and systolic heart failure, and preclinically in mutliple disease states.
Inzomelid (IZD174), Somalix (IZD334) & Selnoflast (RG6418/IZD334)	Roche	Phase 1	Oral	Safety and tolerability demonstrated
ZYIL1	Zydus Life Sciences	Phase 2	Oral	Favorable safety and activity reported in inflammasome-driven disease, CAPS.
HT-6184	Haila Therapeutics	Phase 1	Oral	No results.
VTX2735	Ventyx Biosciences	Phase 1	Oral	Safety and tolerability demonstrated as well as a reduction in inflammatory biomarkers.
NT-0796 & NT-0249	Nod Thera	Phase 1	Oral	Safety and tolerability demonstrated as well as an anti-inflammatory effect on Greactive protein. NT-0796 crosses the blood brain barrier but NT-0249 does not.

Highlighted Clinical NLRP3 Inhibitors

HT-6184

An orally administered small-molecule inhibitor of NEK7 and NLRP3 pathway from Halia Therapeutics, HT-6184 is in an ongoing Phase 1 trial with healthy volunteers.[10]

VTX2735

A peripheral orally administered NLRP3 inhibitor from Ventyx Biosciences, VTX2735 completed a Phase 1 trial in healthy volunteers. Safety and tolerability were demonstrated, and dose-related suppression of the inflammatory cytokine IL-1β and high sensitivity C-reactive protein (hsCRP) concentrations were observed relative to placebo. A Phase 2 trial in CAPS is planned.[11]

NT-0796 & NT-0249

These oral NLRP3 inhibitors from NodThera completed a Phase 1 trial in which safety and tolerability were demonstrated as well as an anti-inflammatory effect via reduction of C-reactive protein. NT-0796 crosses the blood brain barrier, whereas NT-0249 does not.[12]

DISCUSSION

Inflammation has been compared to a double-edged sword or a Janus head with two faces that helps as well as harms, depending on the context.[13,14] On the one hand, inflammation is a protective response that countenances the use of lethal force to shorten biological "battles" with infectious agents like bacteria, viruses, fungi, and parasites. On the other hand, collateral damage to healthy tissues is the inevitable byproduct of the indiscriminate release of oxidants and free radicals from activated white blood cells that are pressed into service during inflammation. The longer an inflammatory response persists the more widespread the damage to bystander cells and tissues results; this is the reason for the existence of several molecular "off switches" like the cytokines, interleukin 10 (IL-10), and transforming growth factor-β (TGF-β), which are released to downregulate inflammation and to prevent excessive damage. Inflammation is "good" when it remains space-, time- and intensity-limited, and "bad" when it is systemic, chronic, or dysregulated.

Chronic inflammation, which occurs when acute inflammation fails to properly resolve, underlies many important diseases, including angina, arthritis, inflammatory bowel disease, and even aging. However, it is important to emphasize inflammation, whether acute or chronic, is not always synonymous with infection because dead cells, ischemia, and irritant particles, including crystals like cholesterol, minerals like silica, and protein aggregates (ie, proteins that clump together) like beta-amyloid in Alzheimer's, can also cause it. This so-called sterile or pathogen-free inflammation is particularly important because of its association with age-related disorders and diseases including frailty.

Textbooks of medicine describe thousands of separate diseases, all with differ-

ent causes, manifestations, symptoms, clinical courses, and treatment options, which suggests that an equal number of distinct responses and mechanisms are at work. However, regardless of the disease entity, one response/mechanism is practically invariant: increased blood supply to the site where the injurious agent (ie, pathogens, dead cells, irritant particles, or toxins) is located with the accumulation and activation of white blood cells there, such as neutrophils, macrophages, Langerhans cells, and dendritic cells to eliminate it. This is experienced as the five cardinal signs of inflammation, ie, redness, swelling, heat, pain, and loss of function, the purpose of which is to eliminate with prejudice any and all perceived threats to the integrity of the host tissues.[15] In the process, the collateral damage wrought by inflammation to normal tissues and organs may initiate, exacerbate, or perpetuate dysfunction and disease, especially when the inflammatory response is unregulated and uncontrolled.

SUMMARY

Traditionally, pharmaceutical development is based on the "magic bullet" concept of "one drug, one target, one disease." However, with the growing realization that chronic inflammation lies at the center of many, if not all, diseases, it is possible to envision inflammasome inhibitors, which reduce or prevent inflammation, as near-universal treatment panaceas. If this sounds farfetched or overstated, consider that OLT1177 and RRx-001, the most clinically advanced of the direct inflammasome inhibitors, have between them demonstrated activity, mostly preclinical, in more than 50 different disease states.

To best knowledge, the only other pharmaceutical class that compares to inflammasome inhibitors in terms of broadness of potential application is glucocorticoids, such as hydrocortisone, prednisone, and dexamethasone, which, having been initially hailed as "wonder" or "miracle drugs" when they were first introduced in the 1950s, are still used today in almost every area of medicine to treat or manage acute and chronic inflammation.[16,17] Different than glucocorticoids, however, which are associated with a range of side effects, depending on dose and length of use, such as hyperglycemia, weight gain, depression, glaucoma, infection, edema, and hypertension, the inflammasome inhibitors RRx-001, OLT1177, DVF890, Inzomelid, Somalix, and Selnoflast, ZYIL1, VTX2735, HT-6184, NT-0796 and NT-0249 have so far demonstrated a favorable safety profile.[18]

This suggests the possibility of their use not only as single agents, but also in combination with glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), IL-1 blockers, or other inflammasome inhibitors to prevent and treat some diseases and hopefully, in an absolutely best-case scenario, most or even all of them. ◆

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BIOGRAPHY

Dr. Bryan Oronsky serves as EpicentRx's Chief Development Officer and combines first-hand clinical experience with 17 years of pharmaceutical development experience. Before joining EpicentRx, he worked as a Medical Officer at Intarcia Therapeutics. He has published more than 100 peer-reviewed scientific articles, reviews, and book chapters. He is also co-inventor of 10 issued patients and more than 50 pending patents in the biomedical and device fields. He was educated at Princeton University, Catholic University in Belgium, and University of Miami Medical School.

PLATFORM TECHNOLOGY

An Alternative Solution for Peptide Drug Formulation

By: Michael Neely

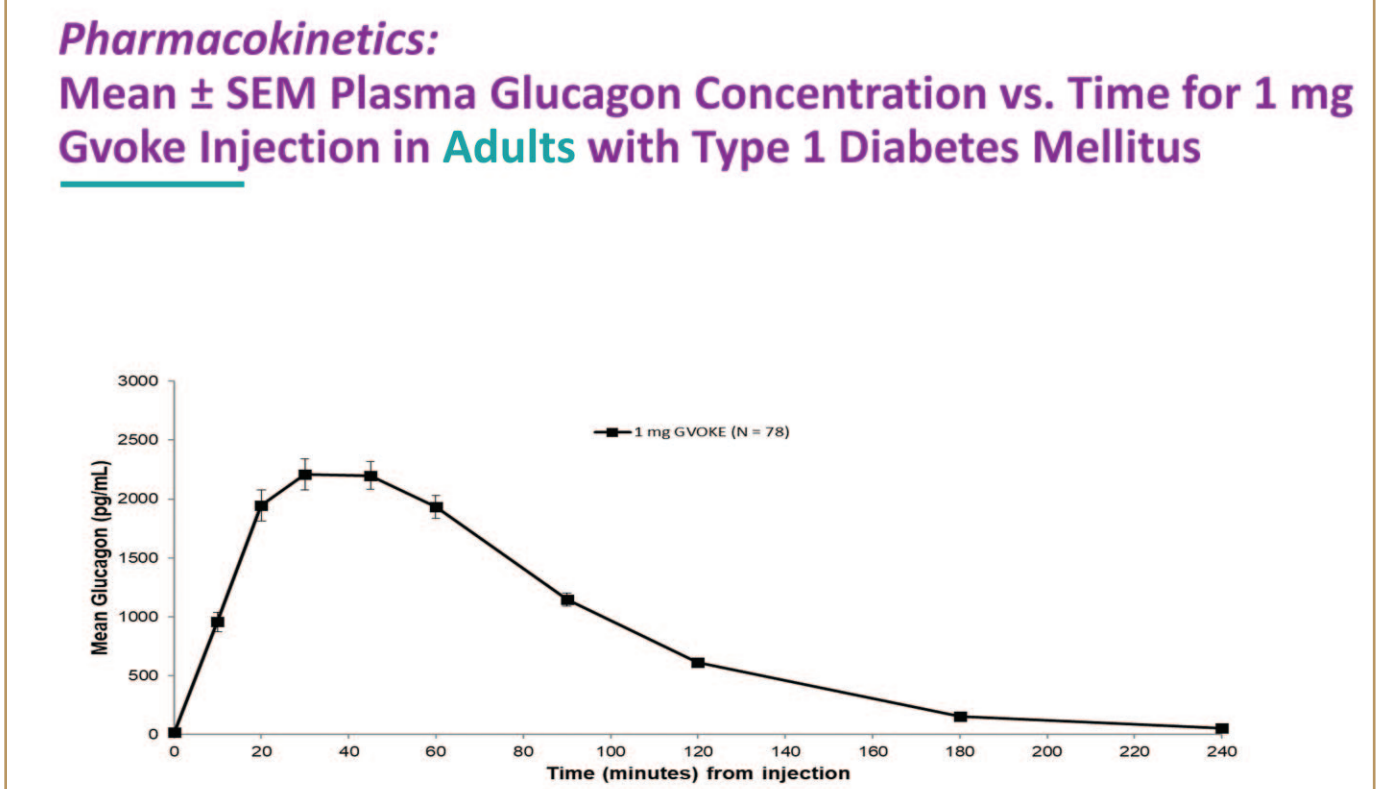
INTRODUCTION

There is a new tool set available to drug formulation scientists that brings solutions to several drug development problems posed by the properties of peptide drug substances. It is the purpose of this review to introduce the technology platform and provide examples of how it has solved difficult formulation problems while adding significant commercial value to the resulting drug products.

PEPTIDE MOLECULES PRESENT CHALLENGES FOR FORMULATORS

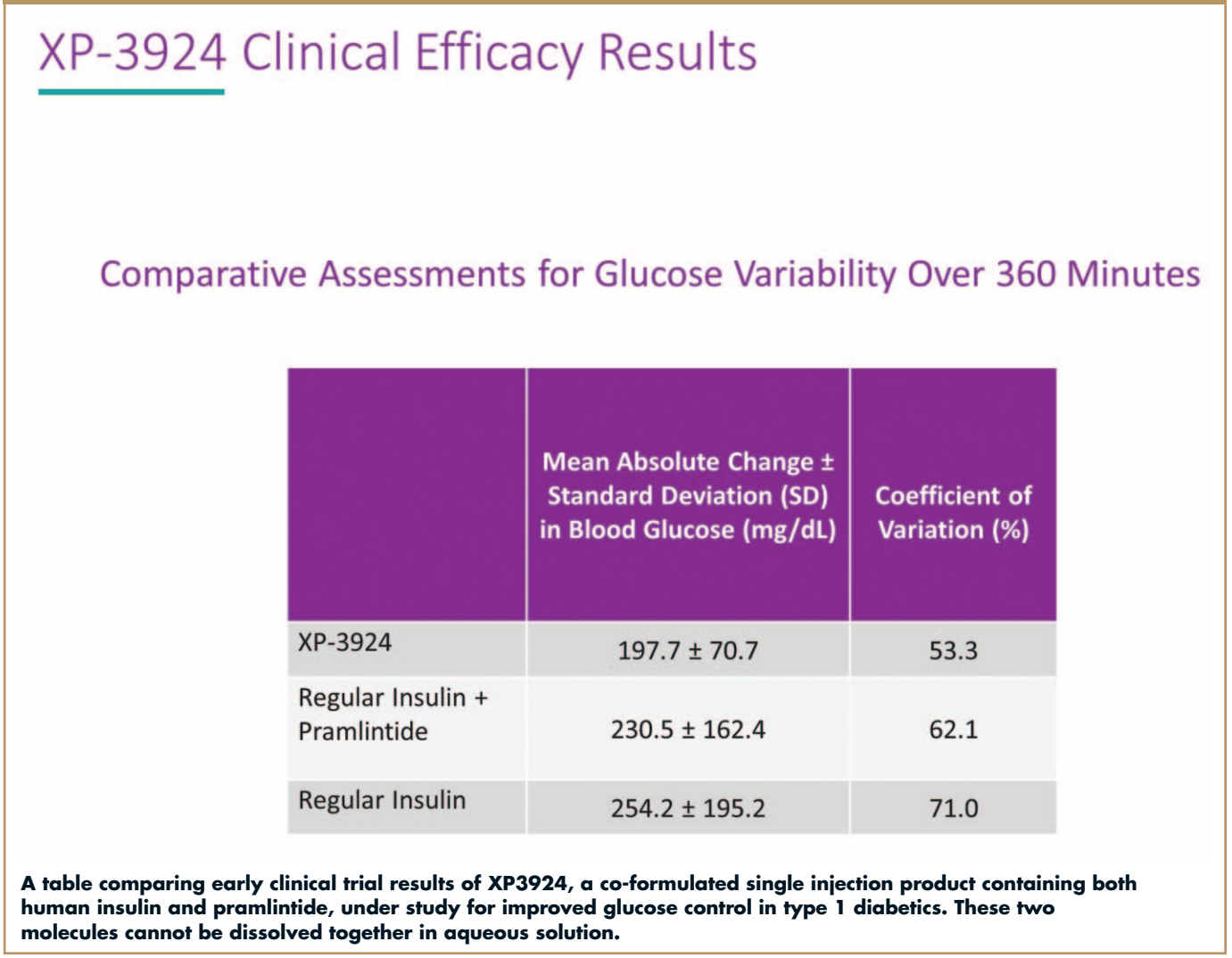
Often in the long process of developing a new drug, a great deal of time, money, and effort are spent at the computer and in synthesis labs trying to develop tweaks to a candidate molecule that will improve its solubility, stability, or impart some other property that makes it suitable for a particular delivery route. This is particularly true with peptide molecules. The seminal work of Dr.

FIGURE 1



A graph of clinical data showing favorable pharmacokinetic characteristics of glucagon when formulated using Xerisol™ technology.

FIGURE 2



	Mean Absolute Change ± Standard Deviation (SD) in Blood Glucose (mg/dL)	Coefficient of Variation (%)
XP-3924	197.7 ± 70.7	53.3
Regular Insulin + Pramlintide	230.5 ± 162.4	62.1
Regular Insulin	254.2 ± 195.2	71.0

A table comparing early clinical trial results of XP3924, a co-formulated single injection product containing both human insulin and pramlintide, under study for improved glucose control in type 1 diabetics. These two molecules cannot be dissolved together in aqueous solution.

Bruce Merrifield, in developing a solid-phase sequential synthesis scheme for polypeptide molecules, spawned a revolution in medicinal chemistry and drug development.[1] Merrifield's work and that of those who followed, enabled peptide molecules and analogs to be synthesized quickly, inexpensively, and in sufficient quantity to be evaluated for biological activity. Whether looking at the nervous system, the circulatory system, hormonal systems, the immune system, or virtually any other life process, peptides have been identified that play significant roles, forming the basis for their vast and expanding potential as drug candidates. Peptide-based drugs now generate several billions of dollars in annual pharmaceutical revenues, and looking across industry and academia, one can identify hundreds of new candidates in various stages of development at any given point in time.

A significant limitation of peptide molecules as pharmaceutical agents arises because they are subject to degradation by several mechanisms during isolation, formulation, storage, and handling. Peptides are particularly labile to water and pH, which are also essential to their function. Water-mediated degradation pathways are arguably the most significant set of factors that impact peptide drug formulations. Hydrolysis, aggregation, fibrillation, deamidation, and other side chain reactions are all water and/or pH mediated.[2] To preserve function in drug formulations, many if not most, peptide and protein-based drug products are formulated as lyophilized products to keep them intact and away from water until they are rehydrated at the point and time of use. Because of these propensities to degradation, some naturally occurring peptides with significant potential for therapeutic uses have not been able to be developed as drugs. Examples include human amylin, an important pancreatic hormone that works in partnership with insulin to control blood glucose levels. While the insulin peptide became a widely used therapy for diabetes, the natural amylin peptide was not amenable to formulation as a drug because it quickly forms insoluble aggregates and gels.[3] Glucagon, a

FIGURE 3

Product Photograph of Gvoke® Glucagon injection Rescue Pen. An example of an FDA-approved product using Xerisol™ formulation technology.

third natural peptide involved in glucose metabolism, has been isolated and used as a drug, but must be quickly formulated and lyophilized to retain solubility. Once lyophilized glucagon is rehydrated, it has just minutes of useful life before it forms aggregates and precipitates. Another example of a potential therapeutic that was not amenable to formulation for drug use is the human calcitonin peptide, which plays an important role in maintaining bone health. When isolated and placed in aqueous solution at concentrations useful for drug delivery, human calcitonin quickly forms fibrils and precipitates.

A NOVEL APPROACH TO SOLVATION & STABILIZATION

The following discusses a novel formulating approach to solving some of the stability and solubility problems that confront formulators when exploring peptide (and some non-peptide) molecules for drug use. Here, we introduce a very simple and elegant idea: Polar aprotic solvents, such as Dimethyl Sulfoxide (DMSO), have now been demonstrated to enable dissolution of problematic peptides, when used in conjunction with appropriate excipients, and stoichiometric amounts of ionic species, while maintaining their chemical and physical integrity and potency in solution for extended periods of time at ambient temperatures. Many drug formulators and development teams have been quick to assume that such solvents are unacceptable for drug use, particularly as injections, but this is in fact not the case. Scientists at Xeris Pharmaceuticals, Inc. have now demonstrated the utility and clinical efficacy of several peptide and non-peptide drugs formulated in aprotic solvent systems. The company has received regulatory approvals to market some of these products in both the US and Europe.

One of the first molecules to be studied by the Xeris team, led by Dr. Steven Prestrelski, was the important metabolic peptide glucagon.[4] Glucagon became available as a drug for injection following the advent of insulin therapy, and is provided to insulin users as a rescue drug for acute hypoglycemia. The original formulation was a lyophilized powder that is meant to be reconstituted at the point and time of use, and once reconstituted, the drug must be injected almost immediately or it will aggregate and come out of solution. Glucagon has a very short stability interval once dissolved in water. The Xeris team demonstrated that when formulated in DMSO, along with appropriate levels of other components to enable it to achieve a functional pH when it meets the aqueous microenvironment at the site of injection, glucagon retained stability and pharmacological activity for many months (now 36) as a liquid even when stored at room temperature. This discovery allowed glucagon to be formulated as a ready-to-inject liquid that could be packaged in a pen injector device and used as a "rescue drug" for episodes of hypoglycemia following insulin use. It is noteworthy that throughout their animal studies and human clinical trials, Xeris did not note signs of injection site irritation or pain that were significantly different from the aqueous formulation, and more recent data suggest there are fewer injection site-related complaints with their formulation.[5] The Xeris formulation of glucagon is approved by the FDA and is marketed in the US as Gvoke® (glucagon injection) in a single-use rescue pen device and in a prefilled syringe. It is marketed in Europe and the UK as Ogluo® (glucagon injection) in

the same packages.

Prestrelski coined the term XeriSol™ to describe this aprotic solvent formulation platform because it incorporates the Greek word Xeris, which means dry, and Sol to indicate solution. The technology platform has since demonstrated another significant benefit in that it allows peptides that require different pH to achieve aqueous solution to be simultaneously dissolved at relatively high concentration. Xeris is now completing Phase 2 clinical trials on a co-formulation of insulin and pramlintide, both of which are deficient in, and which function naturally as partner hormones in healthy glucose metabolism.[5] The co-formulated product under study is a liquid subcutaneous injection, which is demonstrating improved glucose control in the study populations. The early clinical data are sufficiently promising, and the company is actively seeking a partner to carry the drug forward into further Phase 2 and Phase 3 studies.

The ability to dissolve multiple peptides in a single solution could yield significant benefits to those seeking to develop "cocktail" drugs, such as multiple peptide antigen vaccines, or other co-formulated peptide combinations that might be imagined for various endocrinological disorders, peptide antibiotic mixtures, etc. It also merits consideration for use by those developing personalized medicines based on peptides, where it may offer a nearly "Plug and Play" formulation approach that yields a commercially viable product sparing the time and expense of complicated lyophilization process development.

SUMMARY

For peptide drug developers seeking to bring benefits to patients expeditiously and perhaps less expensively, this formulation approach would appear to offer significant value. The fact Xeris has assembled an extensive patent estate around the technology platform also creates potential value in that whereas a molecule may not be patentable, such as the case for a natural molecule, a drug created using the patented formulation technology may be protected, and thus enable the developer to enjoy enhanced commercial value for an extended time period. This should spark interest among pharmaceutical companies seeking to extend product life cycles, and also among those seeking to develop and market differentiated biosimilar drugs that are off patent. Xeris is actively seeking licensees for this technology platform, making its potential benefits available to others in the pharmaceutical industry.

Clinically proven success with a non-aqueous solvent system suggests that for a significant problem set confronting medicinal chemists who work in the domain of peptide molecules, the solution may in fact be "the solution" rather than modifying the structure of the molecule, an idea worth considering as they pursue therapeutic goals. ◆

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BIOGRAPHY

Michael Neely is currently working as a consultant for Xeris Pharmaceuticals, Inc. He is retired from a 42-year career in the Biopharmaceutical industry, with a broad range of experience spanning product development, manufacturing management, marketing, and business development.

Drug Development
EXECUTIVE

Ute Berger, MD

President, Development & Commercialization Solutions

ICON plc

ICON: Transforming Clinical Trials in a Rapidly Shifting Landscape

ICON plc is a world-leading healthcare intelligence and clinical research organization. From molecule to medicine, the company advances clinical research providing outsourced services to pharmaceutical, biotechnology, medical device, and government and public health organizations. Its goals are to develop new innovations, drive emerging therapies forward, and improve patient lives.

Drug Development & Delivery recently interviewed Ute Berger, MD, President, Development & Commercialization Solutions at ICON plc, to discuss how with the acquisition of PRA in 2021, it has enhanced its value proposition and how it is transforming clinical trials in a rapidly shifting landscape.

Q: What are the services provided by ICON's Development & Commercialization Solutions team?

A: ICON's Development & Commercialization service area (division) covers the spectrum from first-in-human to commercialization, including early clinical services, central and bioanalytical laboratory services, medical imaging, commercialization and health economic outcomes (including the real-world evidence team, the MAPI Research Trust, and translations), medical device and diagnostics, commercial and regulatory consulting services, and the design and end-to-end operational delivery of decentralized clinical trials. The strategic focus of this service area is on shifting the paradigm in clinical research and transforming clinical trials to deliver treatments to patients faster.

Q: What do you believe are the biggest challenges in the CRO industry at the moment?

A: The industry continues to focus on patient access and retention and how to make it easier for patients and sites to participate in a clinical trial in order to bring drugs to market faster.

Underrepresentation of diverse populations is still a challenge in clinical research to understand the safety and efficacy of novel therapies across population subgroups. The US Food and Drug Omnibus Reform Act of 2022 (FDORA) bill is the latest iteration of regulator policy to propose improvement in diversity, equity, and inclusion (DE&I) in clinical trials. It was part of the Consolidated Appropriations Act, 2023 (H.R. 2617) signed by President Biden on December 29, 2022. ICON has an established robust strategy to embed diversity in our culture and operational models. This includes strong engagement with key stakeholders: patient communities, advocacy groups, physicians, and our employees. We are already seeing the decentralized clinical trials we deliver are supporting study teams to drive and deliver diversity in clinical trials.

Like many industries, the CRO industry is also operating in a tight labor market. Building a team of diverse, talented, and ambitious STEM professionals who can help ensure the future success of the life sciences industry is critical. We believe there is a significant opportunity for collaboration between industry and academia. To address this, ICON invests in partnerships with numerous universities (in Ireland and beyond) on leadership development and mentorship programs, for example, in addition to STEM scholarship programs.

There are macroeconomic dynamics all businesses are dealing with across the globe and associated with this, and biopharma customers are carefully assessing potential implications for their portfolios. However, we believe this is also an opportunity for the industry to provide customized strategic solutions, for example, in digital health technology.

Q: What do you believe are the most interesting developments in the industry or those that you expect to happen in the next couple of years?

A: The Covid-19 pandemic has had a significant impact on our industry. We were forced to be innovative and collaborative, and how we operated clinical trials changed significantly. There was a major shift from a traditional trial model to more agile and remote trials that were ultimately more efficient and more patient centric. This has created great opportunity to transform clinical development. There was the possibility that clients would revert to the traditional type of trial; however, we are seeing ongoing interest to embrace change and innovation for improvement.

Decentralized and hybrid clinical trials are showing real economic value through the benefits of increased patient recruitment, retention, and diversity of patient populations by breaking down the barriers of patient burden and geographical reach. These approaches are also demonstrating enhanced quality of data by capturing data more directly from the patient.

Associated with this, we have seen a steady increase of interest of the inclusion of digital health technologies in clinical trials, another aspect of decentralized clinical trials that can reduce patient burden by remote, real-time monitoring. Overall, these methods deliver a more positive experience for the patient that aligns with the desire to put patients more firmly at the center of drug development.

Tokenization is well established in the commercial setting as a way of accessing multiple data sources for insights; however, tokenization in clinical trials has not yet been widely adopted. We expect this to change as both large pharma companies and smaller biotechs are exploring, piloting, and evaluating the use of clinical trial tokenization. Linking patient-level data from diverse sources without compromising patient privacy enables companies to incorporate real-world data (RWD) into clinical trial analysis and gain a comprehensive picture of the patient journey across the healthcare system and into the follow-up stage.

Q: How do you see ICON supporting clients in these areas?

A: ICON is well positioned as the CRO and healthcare intelligence partner of choice to our customers on bringing drugs and devices to market quickly and safely. Our customers face an increasingly complex environment, and being able to work with a partner that provides end-to-end solutions, reduces cost and time.

ICON works in a truly collaborative way, developing solutions and building our innovative capabilities to meet client challenges. We offer the most comprehensive suite of integrated clinical development services in the industry and work with our clients to deliver the flexible solutions based on the

characteristics of the study, portfolio, or organizational strategies.

An early engagement consultative approach enables us to support clients in the selection of service components, eg, the study design and model (traditional, hybrid, or fully decentralized), to address the scientific question of the trial. The services selected are informed by patient centricity to increase patient recruitment and our insight into site burden to increase site engagement - all delivered within a strong operational and regulatory framework.

Q: Are there specific therapeutic areas that interest ICON, and how is the company positioned in these areas?

A: ICON has experience and expertise across a wide range of therapeutic areas and aligns its strategy to the demand of our clients and industry developments.

Oncology is of continuous interest across the industry, and ICON conducts clinical studies in both solid and haematological tumors, including breast, lung, gastric, HCC, prostate, multiple myeloma, acute and chronic leukemias, and lymphomas. An increasingly important part in cancer treatment are cell and gene therapies (CGTs) - a cutting-edge scientific approach to treat diseases by modifying cells or genes. The product and patient journey are completely different from traditional trials and requires a deep understanding of the regulatory pathway, patient recruitment, logistics, and manufacturing, and ICON is well positioned to provide strategic consultancy as well as operational support for these trials.

ICON leverages it scientific expertise to look for innovative approaches that will drive progress for our clients, and indeed the industry overall. ◆

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Technology & Services
SHOWCASE

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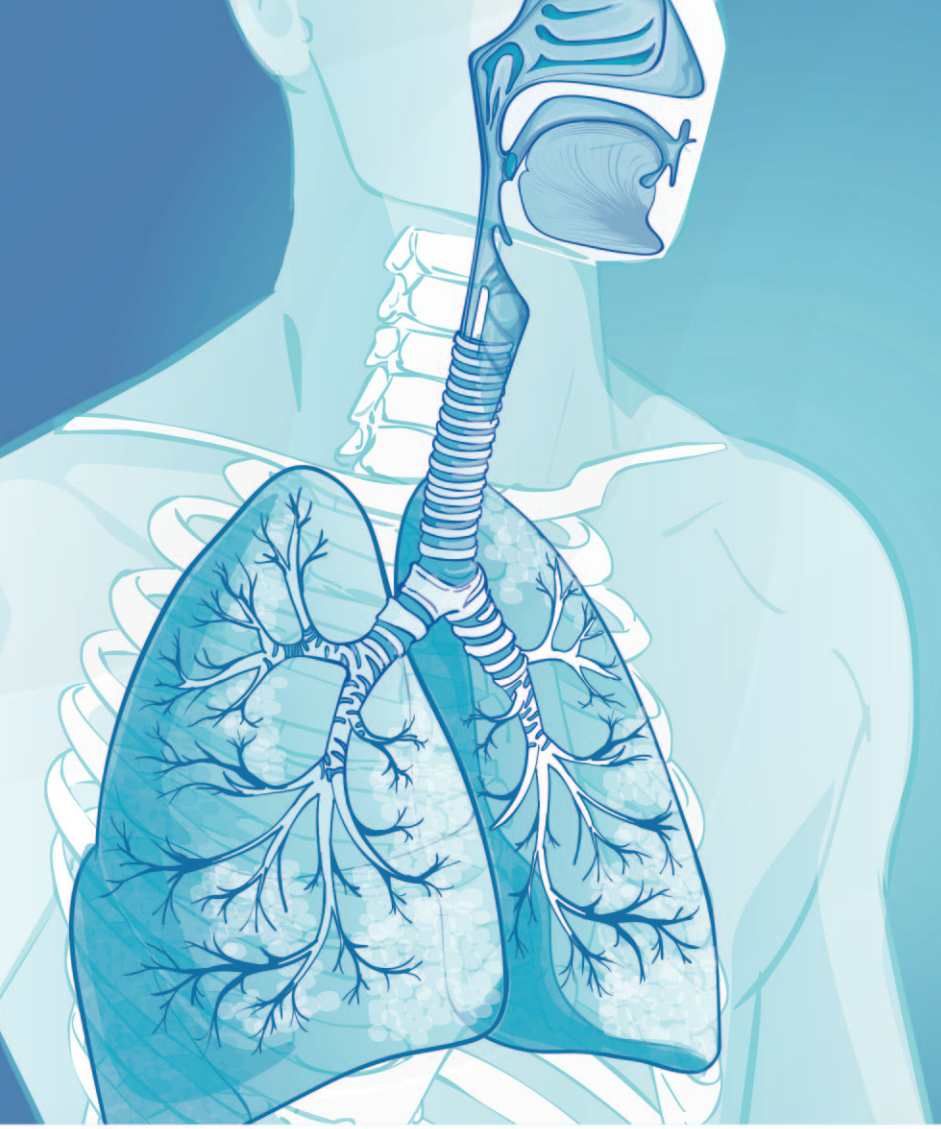

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