Drug Development & Delivery

April 2015 Vol 15 No 3

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HAVE WE PASSED THE PEAK OF NEW DRUG DISCOVERIES?

The science & business of drug development in specialty pharma, biotechnology, and drug delivery

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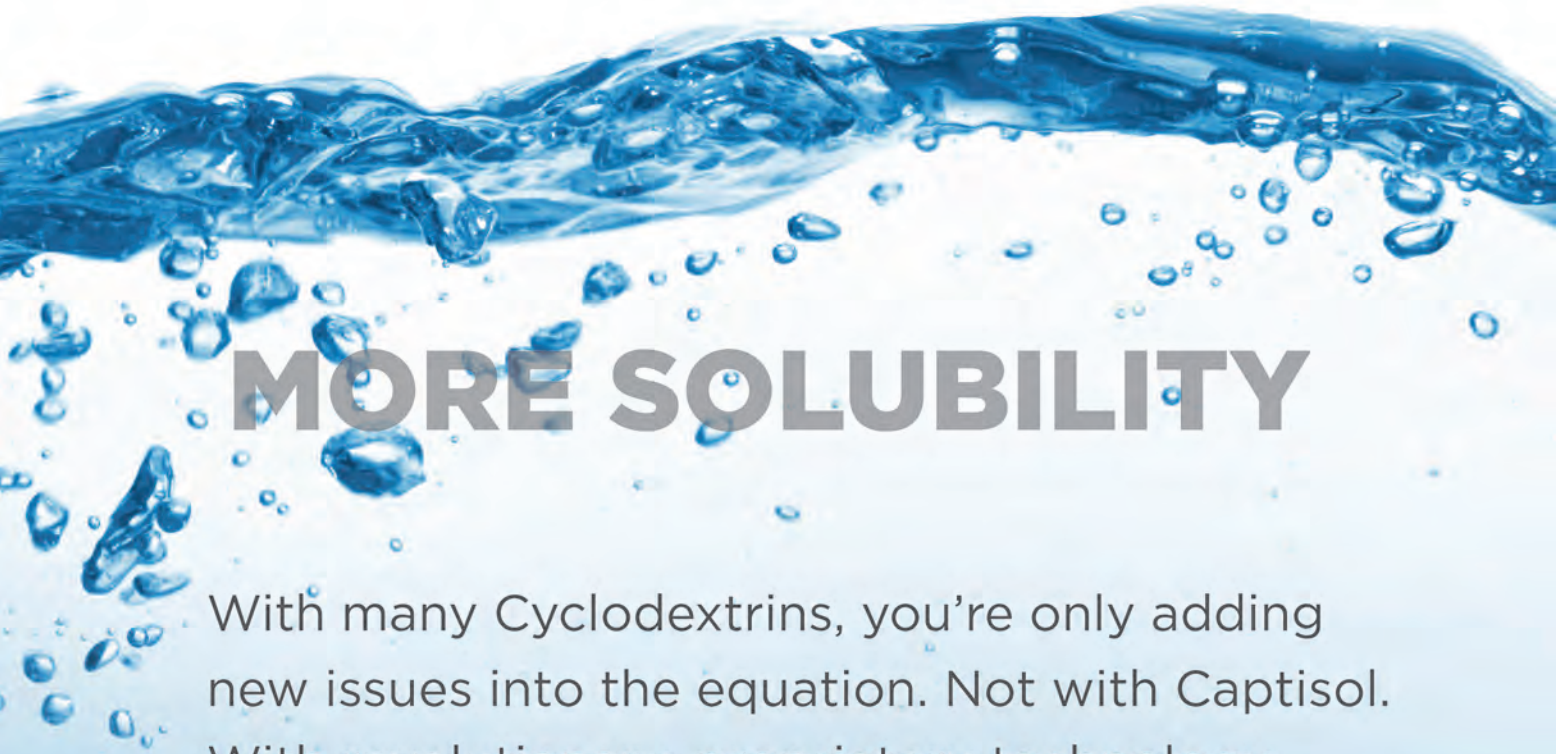

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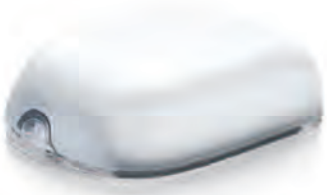

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"At first blush, it would appear that we have achieved Peak Drug, but I'm not so sure. Remember that Peak Oil showed us there are two factors to determine rate of discovery; one is available supply and the other is our ability to extract (or in this case discover). For our industry, I would say there is a third factor that influences the rate of discovery, and that's government policy."

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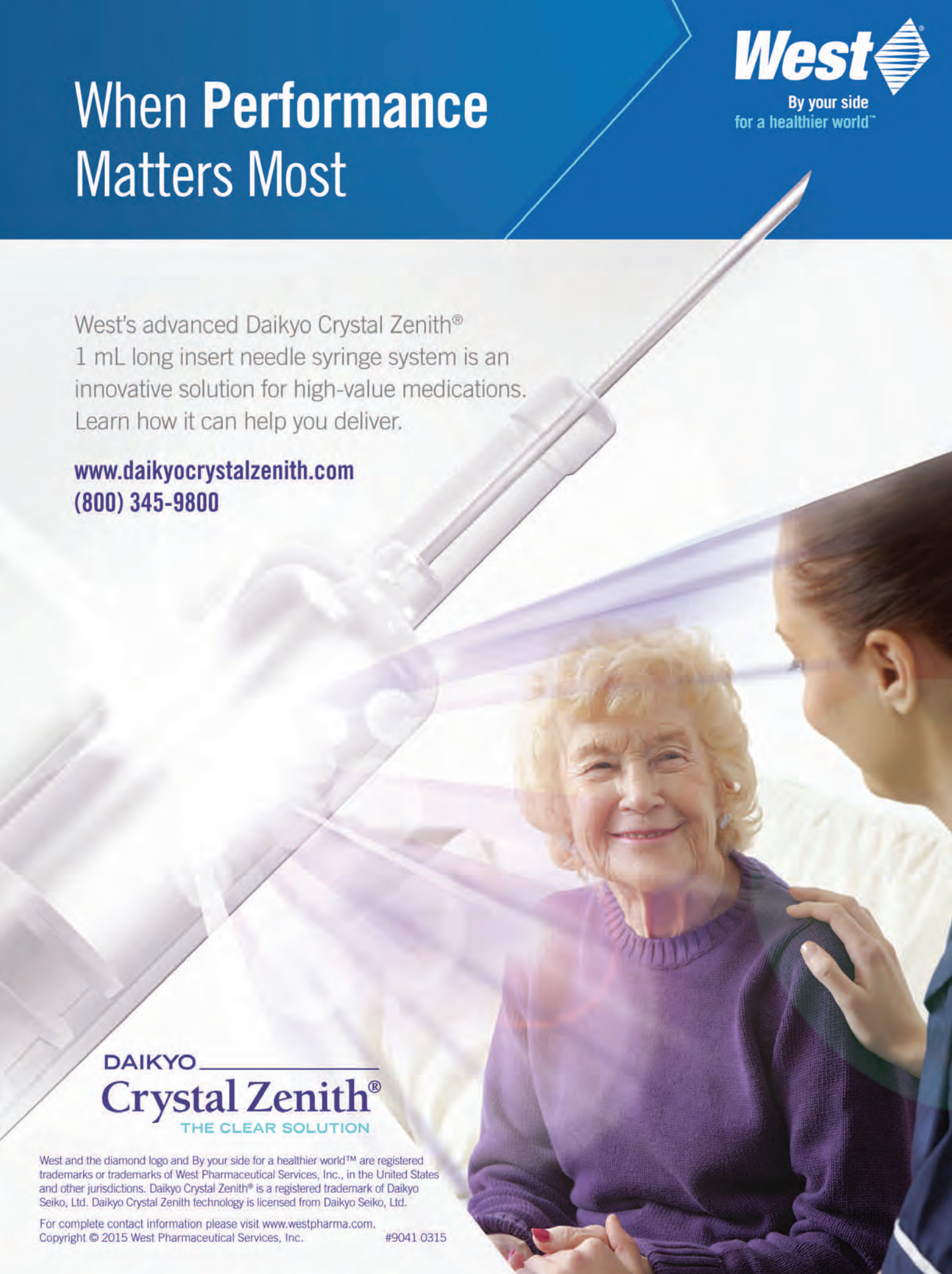

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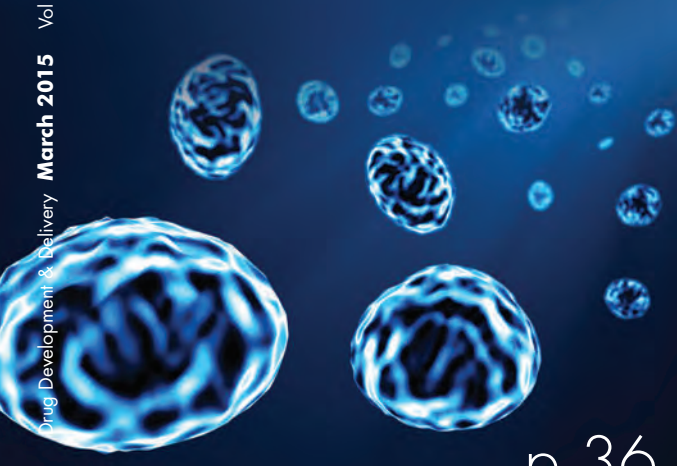
"The demand for outsourcing pharmaceutical formulation development and manufacturing is on the rise for drug developers at all levels. Frost & Sullivan estimates the pharma industry spent $13.4 billion on contract manufacturing and development services in 2013. And the trend continued in 2014 with the industry using more CDMOs to assist at the development stage of drug manufacturing."



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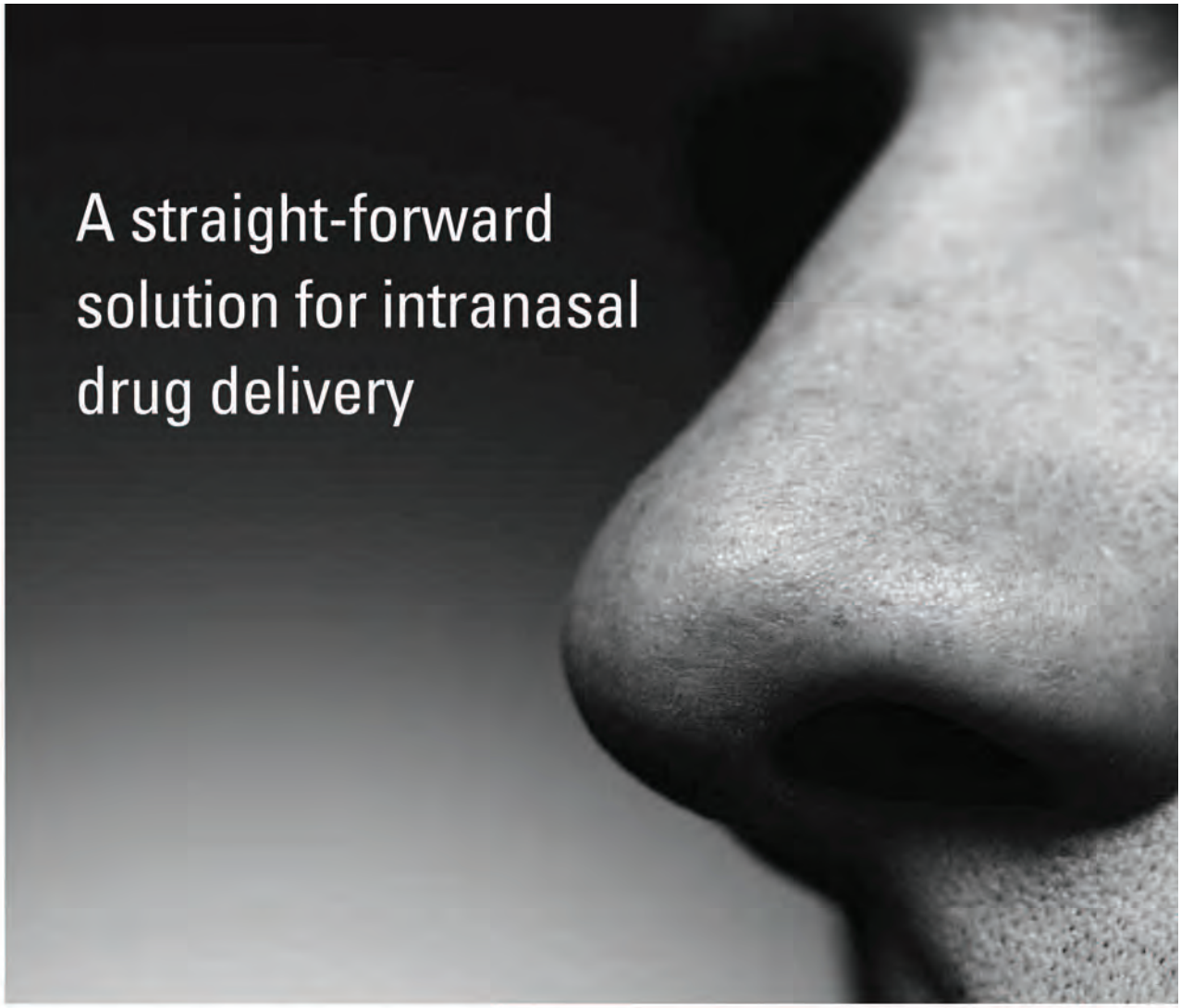

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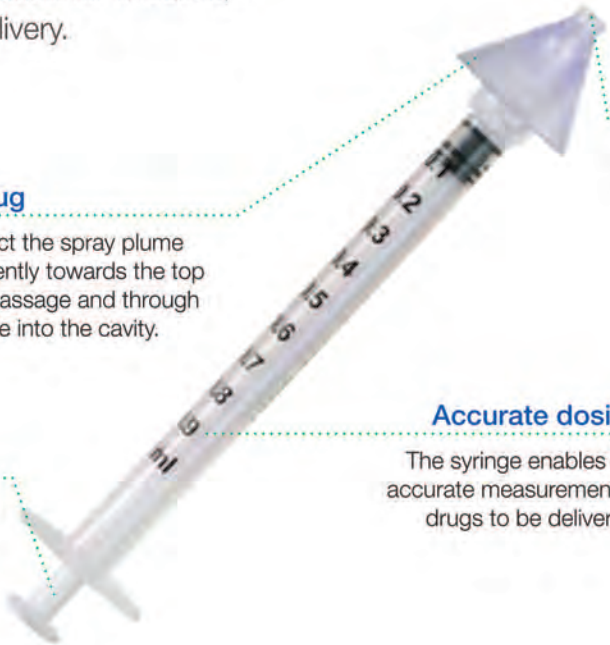

Atomization spray

The spray atomizes drugs into a fine mist of particles 30-100 microns in size.

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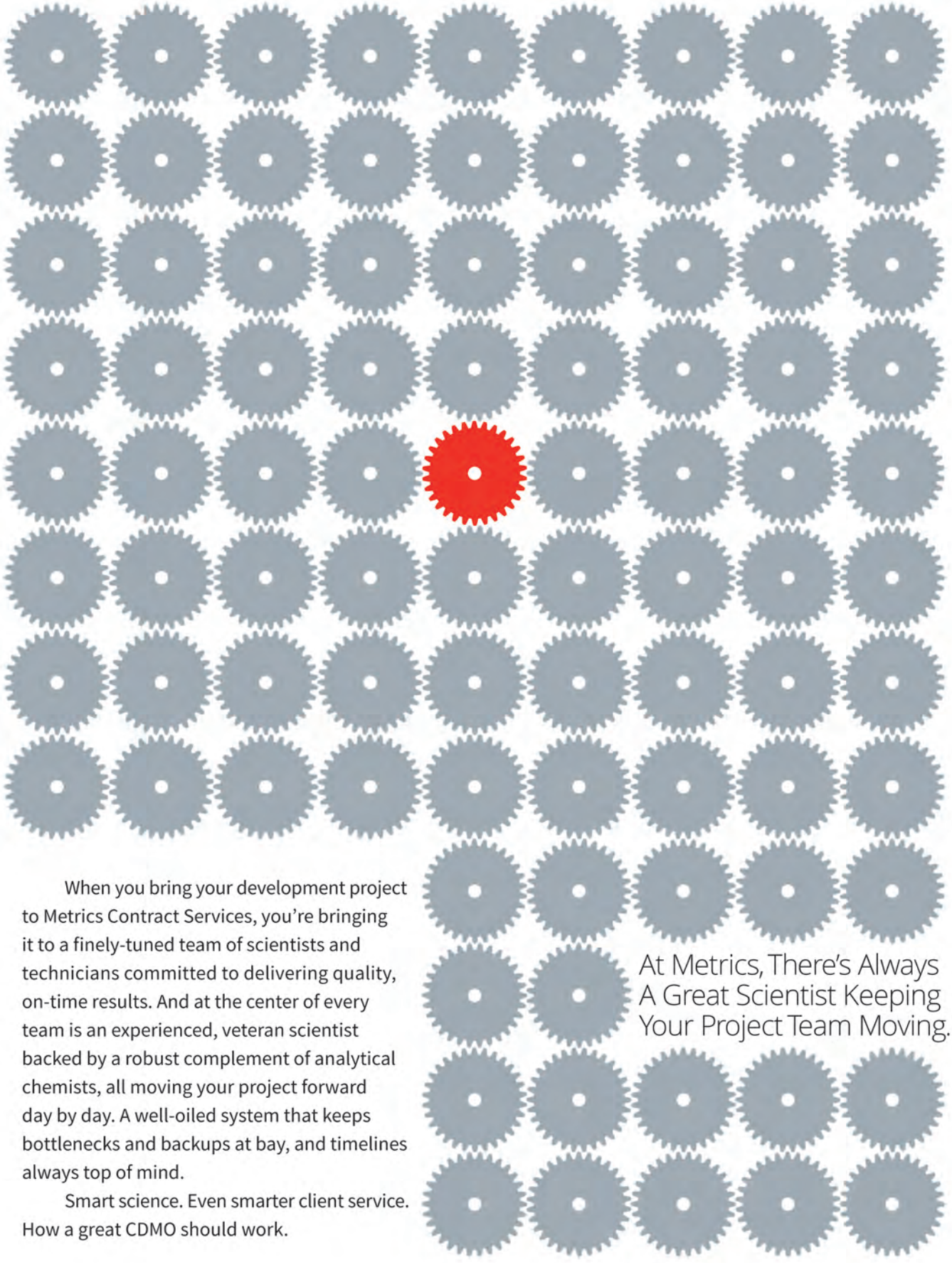

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Kura Oncology Announces License Agreement; Closes $60 Million

Kura Oncology, Inc. recently announced it has entered into an agreement with Janssen Pharmaceutica NV for an exclusive license to develop and commercialize tipifarnib in the field of oncology. Tipifarnib, a protein farnesyl transferase inhibitor, is a Phase II-ready program that has demonstrated encouraging clinical activity in certain cancer patient populations and that may be further optimized using an appropriate patient selection strategy.

Under the terms of the agreement, Kura Oncology assumes sole responsibility for development and commercialization of tipifarnib in the field of oncology. Kura Oncology intends to advance tipifarnib into Phase II clinical trials in 2015 to evaluate its activity in patient populations where certain solid tumors are driven by activating mutation in the oncogene HRAS as well as in patients with hematologic malignancies.

In addition, Kura Oncology announced that it completed a private placement of its common stock to new institutional investors and existing investors that resulted in gross proceeds of approximately $60 million to the company, including approximately $7.5 million in bridge notes that converted into common stock at the closing. EcoR1 Capital was the lead investor in this financing, which included significant participation from Fidelity Management & Research Company, ARCH Venture Partners, Boxer Capital of Tavistock Life Sciences, Partner Fund Management, Nextech Invest, as well as a number of other well-known healthcare investors. Proceeds from the private placement will be used for the development of the company's drug candidates, including tipifarnib, as well as preclinical pipeline programs.

In conjunction with the private placement, Kura Oncology completed a reverse merger with Zeta Acquisition Corp III, a public reporting company with no prior business operations. Stockholders of Kura Oncology, including those that participated in the private placement, received shares of Zeta Acquisition in exchange for their Kura Oncology shares, and the former Kura Oncology stockholders now hold 100% of the resulting company's equity in the same proportion as the stockholders owned immediately following the private placement. Zeta Acquisition has been renamed Kura Oncology, Inc. and will implement the pre-merger business plan of Kura Oncology. Kura Oncology intends to file a registration statement covering the resale of shares of common stock held by new and existing shareholders within 60 days after the closing. Following the effectiveness of that registration statement, Kura Oncology will seek to have its common stock quoted on the OTC Markets.

Alizé Pharma III Raises $1.94 Million for Osteoporosis Program

Alizé Pharma III SAS recently announced that it has raised $1.94 million in a first financing round. The funding round was supported by a syndicate of investors that included Sofimac Partners via their FCPI Emergence Innovation 1 seed capital fund, Octalfa, Sham Innovation Santé, Rhône-Alpes Création, Crédit Agricole Création, CEMA and TAB Consulting.

Alizé Pharma III will use the funds to conduct a pharmacology and lead optimization program on a family of peptides with anabolic effects on the bone. The I-HBD1 program will be performed in collaboration with Alizé Pharma III's US partner New Paradigm Therapeutics Inc., a spin-off from the University of North Carolina at Chapel Hill founded by Dr. David Clemmons. The aim of the program is to select a drug candidate that will enter development for the treatment of osteoporosis and other diseases with impaired bone metabolism in 2016.

According to the International Osteoporosis Foundation, over 200 million patients worldwide live with osteoporosis, and the disease causes almost 9 million fractures each year. The global market for osteoporosis drugs was estimated at over $8.3 billion in 2014, with significant growth expected in the coming years. The current treatments are mostly antiresorptive therapies; there is an unmet need for safer, more cost-effective anabolic therapies that are able to build new bone for these patients.

The I-HBD1 program aims to optimize and develop a new peptide derived from a fragment of a physiological protein, called IGFBP-2 (Insulin-like Growth Factor Binding Protein-2). In vitro and in vivo studies have shown that this peptide can induce the formation of bone tissue by stimulating osteoblast differentiation and inhibiting osteoclast differentiation. This new mechanism of action is unique and may potentially lead to the development of a new therapeutic anabolic approach in treating osteoporosis and several other diseases associated with impaired bone metabolism.

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Vetter ad to go here

Xcelience Receives DEA Approval to Develop & Manufacture DEA Schedule I Drug Products

Xcelience, a CDMO, located in Tampa, FL, is excited to announce that they have received approval from the Federal Drug Enforcement Agency to develop and manufacture Schedule I controlled substances in their facilities. Schedule I substances are "considered the most dangerous class of drugs," according to the DEA website. Xcelience has a long history of working with DEA controlled substances and this license extension completes their approval to now handle both analytical and manufacturing of the full spectrum of DEA Scheduled products. This new achievement solidifies Xcelience as the choice CDMO for all of your global clinical outsourcing needs, including all of your scheduled product requirements.

Clinicians continue to find potential therapeutic indications for Schedule I drug substances. "Regulatory capability is a critical attribute for CDMOs," said Alex McClung, Vice President, Quality at Xcelience. "This Schedule I-V license underscores our capability and extends our Suite of Services to a whole new class of therapeutic compounds." Being able to work on Schedule I controlled substances will enhance Xcelience's research capabilities and expand the types of research programs the company can support. This news comes in addition to their announcement for expansion. Xcelience is expanding its pharmaceutical development services and manufacturing capacity by adding a new facility in the Tampa area to include more pharmaceutical development labs, manufacturing, quality assurance, and packaging services. The company continues to be recognized as a leader in the industry and has received six Life Science Leadership Awards for 2015.

Xcelience offers a suite of services enabling clients to partner with a single CDMO for all of their clinical outsourcing needs. Services include preformulation, formulation development, GMP manufacturing, small-scale commercial manufacturing, and global clinical supplies packaging and logistics. Xcelience takes pride in delivering the highest standards in science and service with an emphasis on quality, cost and speed.

Ruthigen & Pulmatrix Enter Into Merger Agreement

Ruthigen, Inc. and Pulmatrix recently announced they have entered into a definitive merger agreement. Upon the closing of the transactions contemplated by the merger agreement, Pulmatrix will become a wholly owned subsidiary of Ruthigen and all of Pulmatrix's debt and equity securities outstanding prior to the consummation of the merger will be exchanged for shares of Ruthigen common stock that will represent approximately 81% of the outstanding common stock of Ruthigen. In connection with Pulmatrix's entry into the merger agreement, certain existing institutional investors in Pulmatrix entered into stock purchase agreements with Pulmatrix to invest an additional $10 million in Pulmatrix upon the closing of the merger. Pulmatrix also raised approximately $4.5 million in February 2015, in contemplation of entering into the merger agreement.

Upon completion of the merger, Ruthigen will be renamed Pulmatrix, and, pending NASDAQ approval of the merger, the surviving company's common stock will continue to trade on The NASDAQ Capital Market after the merger. It is anticipated that the combined company will focus its resources and efforts on the development of Pulmatrix's next-generation inhaled therapeutic products.

Upon completion of the merger, Dr. Robert Clarke, President and Chief Executive Officer of Pulmatrix, will be appointed as the President and Chief Executive Officer of the combined company, which will be headquartered in Lexington, MA. Prior to joining Pulmatrix in 2004, Dr. Clarke was a Director of Life Sciences at Alkermes, Inc. (ALKS).

"We believe that a merger with Ruthigen provides a strong financial foundation with enhanced access to capital to further Pulmatrix's mission of innovative inhaled product development for patients with significant unmet needs in respiratory disease," explained Dr. Clarke. "This transaction represents an excellent opportunity to advance our novel iSPERSE inhaled dry powder platform and lead CF candidate into clinical development and to meet our long-term growth objective of building a leading company around a robust pipeline for respiratory disease."

"This transaction provides significant momentum for Pulmatrix to achieve its goals in the next stage of its development," added Terry McGuire, Senior Pulmatrix Board Member and Founding Partner at Polaris Partners, Pulmatrix's largest shareholder.

Ruthigen is a biopharmaceutical company focused on the discovery, development, and commercialization of novel therapeutics designed to prevent and treat infection in invasive applications.

Key TxCell Patent to be Granted for its Lead Product

TxCell SA recently announced that a key patent is to be granted by the United States Patent and Trademark Office (USPTO). The issue notification has been posted on the USPTO portal (http://portal.uspto.gov). The patent covers its lead product Ovasave in inflammatory bowel disease (IBD). Ovasave is currently being studied in a multinational placebo-controlled Phase IIb study in refractory Crohn's disease.

The US patent, No. 8992907, will run until October 2030 (not including supplementary protection certificate/SPC). The patent is the latest strong asset for TxCell. It widely protects a highly promising method for treating intestinal inflammatory bowel diseases with its lead personalized T cell immunotherapy candidate, Ovasave (ovalbumin-specific autologous Treg cells or Ova-Treg). Specifically, the patent covers the administration of a composition consisting of at least one human Type 1 Treg cell population directed against a food antigen from common human diet. The equivalent patent has already been granted in Russia. Other corresponding patent applications for Ovasave in IBD are pending in major markets globally. TxCell now owns or controls more than 140 patents within its patent portfolio in the field of antigen-specific Treg (Ag-Treg) cell-based therapy. These provide extensive coverage of the characterization, production, and use of Ag-Tregs for the treatment of chronic autoimmune inflammatory diseases.

"This valuable new US patent further bolsters TxCell's intellectual property coverage and provides extensive coverage for TxCell's lead product Ovasave in the world's largest market. Combined with other globally granted and pending patents for TxCell's product portfolio, TxCell is building a critical comprehensive and enforceable patent portfolio to protect the commercial potential of our personalized T cell immunotherapies," said Damian Marron, Chief Executive Officer of TxCell. "TxCell now owns or controls a total of more than 140 granted patents in the field of antigen-specific Treg cell-based therapy. We will continue to actively protect our new discoveries to further protect and extend our innovative technologies and product portfolio."

TxCell granted Ferring SA an exclusive option to license the Ovasave intellectual property portfolio for the treatment of IBD, following the completion of the ongoing Phase IIb trial in refractory Crohn's disease.

TxCell develops innovative, cost-effective, personalized T cell immunotherapies for the treatment of severe chronic inflammatory diseases with high medical need. TxCell has created ASTrIA, a unique and proprietary technology platform based on the properties of autologous antigen-specific regulatory T lymphocytes (Ag-Tregs).

Allergen Research Corporation Completes $80-Million Financing to Advance Drug Development Portfolio

Allergen Research Corporation (ARC) recently announced the completion of an $80- million Series B financing. Foresite Capital led the round, with participation from existing investor Longitude Capital and new investors Fidelity Management & Research Company, Aisling Capital, Adage Capital, RA Capital Management, and Palo Alto Investors.

ARC will use the proceeds to fund the upcoming Phase III clinical trial of ARC's lead product, AR 101, a standardized, pharmaceutical-grade peanut protein formulation for treating peanut allergy via characterized oral desensitization immunotherapy (CODIT). The company also plans to begin clinical trials for treatment of egg and milk allergies in the coming year.

"Food allergies are a real, growing problem and a space we've been following for a while. ARC is developing an extremely promising option that could provide an unprecedented solution for families and physicians managing the stresses of food allergy avoidance and the dangers of accidental exposure," said Dr. Tananbaum. "ARC is a great example of companies we finance: ARC has a solid management team with deep industry experience, a transformative product with strong Phase II data, and the potential to solve a real-world problem in a large market. We are excited to support ARC as it takes the final steps toward turning decades of research into products and therapies to help patients suffering from food allergies."

ARC recently completed a successful multi-center, randomized, double-blind, placebo-controlled Phase II clinical trial to demonstrate the safety and efficacy of AR 101 for the treatment of peanut allergy in children and adults. The US FDA has granted AR 101 Fast Track designation as part of its program to facilitate and expedite the development and review of drugs designed to treat serious conditions and fill an unmet medical need.

"People living with food allergies, many of whom are children, are at risk of life-threatening reactions to common everyday foods. Specifically, about a million children in the US are allergic to peanuts. We are dedicated to developing standardized products for desensitization so that people and families living with food allergies can gain peace of mind," said ARC CEO Stephen Dilly, MBBS, PhD.

"People living with food allergies, many of whom are children, are at risk of life-threatening reactions to common everyday foods. Specifically, about a million children in the US are allergic to peanuts. We are dedicated to developing standardized products for desensitization so that people and families living with food allergies can gain peace of mind," said ARC CEO Stephen Dilly, MBBS, PhD. "This financing equips us to advance AR 101 through our planned Phase III clinical trial and the rigorous FDA approval process as well as to begin development of novel oral immunotherapy products for other food allergies. We are immensely grateful for the capabilities and backing of our financial, clinical, and academic partners who have helped us reach the gate to a pivotal clinical trial in the US for our first product."

Allergen Research Corporation (ARC), founded in 2011, develops treatments for food allergies using characterized oral desensitization immunotherapy (CODIT), its proprietary approach to oral immunotherapy (OIT). CODIT combines standardized, pharmaceutical-grade food allergens with controlled up-dosing protocols to desensitize patients and increase the thresholds at which they could experience allergic reactions.

Immune Pharmaceuticals to Develop Novel Topical Nanoparticle Formulation

Immune Pharmaceuticals Inc. recently announced it has entered into a binding memorandum of understanding with Yissum, the Technology Transfer Company of the Hebrew University of Jerusalem, to license certain of Yissum's patents in order to facilitate the development of a topical nanoparticle formulation of Immune's neuropathic pain drug, AmiKet.

The technology that Immune will be licensing was invented by Professor Simon Benita, from the Institute for Drug Research, the School of Pharmacy, and Faculty of Medicine at the Hebrew University, a renowned expert in development of drug delivery technology, and a primary inventor of NanomAbs, an antibody nanoparticle conjugate technology to deliver cancer drugs, already licensed by Immune from Yissum.

"Expanding our relationship with Yissum and leveraging Professor Benita's expertise in nanotechnology is an important strategic step for AmiKet," said Dr. Daniel Teper, CEO of Immune Pharmaceuticals. "We expect that this new formulation will likely increase the patent exclusivity of AmiKet by more than 10 years, support development of additional pain indications, and may even provide additional clinical benefits."

Immune Pharmaceuticals is currently conducting a search for an appropriate partner for the final development and commercialization of AmiKet, which is ready for Phase III clinical trial in post herpetic neuralgia and has been granted Orphan Drug Designation by the FDA. The company expects to select a partner and secure a licensing agreement by the second quarter of 2015. The topical nanoparticle formulation of AmiKet will be developed collaboratively by Immune and Yissum upon the execution of a license agreement between the parties and will be part of the AmiKet commercialization agreement.

Charleston Laboratories & Daiichi Sankyo Announce Completion of Pharmacokinetics Study

Charleston Laboratories, Inc. and its co-development and co-commercialization partner, Daiichi Sankyo, Inc., recently announced the completion of a pharmacokinetics study on CL-108, Charleston Laboratories' lead product in development.

CL-108 is a tablet containing 7.5 mg of hydrocodone and 325 mg of acetaminophen with 12.5 mg of fast-absorbed promethazine. This novel therapy is being developed as a treatment for moderate to severe pain and the prevention of opioid-induced nausea and vomiting, or OINV.

"This study demonstrated that CL-108 provides comparable bioavailability of hydrocodone, acetaminophen, and promethazine to commercial products," said Dr. Bernard Schachtel, Chief Scientific Officer at Charleston Laboratories.

"This is encouraging news," added Mr. Paul Bosse, President and Chief Executive Officer at Charleston Laboratories. "This study confirms the rationale for CL-108. With the clinical results from our first Phase III trial, these bioavailability results help explain why hydrocodone formulated with low-dose promethazine in CL-108 can help manage pain without the debilitating effects of nausea and vomiting that many patients experience from opioid treatment."

Charleston Laboratories, Inc. is a privately held, specialty pharmaceutical company focused on the research and development of novel pain products to prevent the burdensome side effects related to opioid analgesics and other products.

Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical products to address the diversified, unmet medical needs of patients in both mature and emerging markets. While maintaining its portfolio of marketed pharmaceuticals for hypertension, dyslipidemia, and bacterial infections used by patients around the world, the Group has also launched treatments for thrombotic disorders and is building new product franchises.

Cloud Pharmaceuticals & University of Florida Collaborate on Rapid Design of Novel Cancer Inhibitors

Cloud Pharmaceuticals and the University of Florida Department of Medicine recently announced an academic collaboration that will help rapidly design and develop novel drugs to inhibit the reproduction of cancer cells.

The collaboration, which will allow the two organizations to share intellectual property and jointly fund 10 research projects, has already resulted in the design of multiple novel inhibitors of the MTH1 protein, an enzyme required for cancer cell proliferation. These new compounds will target a broad range of cancers, including ovarian, breast, colon, and pancreatic cancers.

Cloud Pharmaceuticals used its computer-based drug design process, Quantum Molecular Design, to rapidly generate potential inhibitors with strong drug-like properties for the MTH1 protein. MTH1 has been identified as a target for anticancer strategies because inhibition of MTH1 in cancerous cells eventually results in DNA damage and cell death. MTH1 is less essential for normal cells, so blocking it does not cause the same kinds of side effects seen in many cancer therapies. This makes it an excellent target for therapeutic inhibitors. Combining MTH1 inhibitors with other chemotherapeutic agents could result in far greater efficacy in cancer treatment than chemotherapy alone.

The UF Department of Medicine is further developing the MTH1 inhibitors, including synthesis, assays, and preclinical research. Together, Cloud Pharmaceuticals and the UF Department of Medicine will seek an oncology drug developer for late-stage preclinical research and clinical trials upon its success.

Cloud Pharmaceuticals is a leader in the computational design of new drugs and subsequent rapid, information-driven drug development. The company accelerates the drug discovery and design process in a way that delivers tangible results and true value for its partners.

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Peak Drugs: Have We Passed the Peak of New Drug Discoveries? Are the Best Days Behind Us?

By: Derek Hennecke,
CEO & President, Xcelience

WHATEVER HAPPENED TO PEAK OIL?

Since the 1970s, we have been told with varying degrees of certainty that we are about to run out of oil. We are at — or past — Peak Oil; Peak Oil being that moment when the rate of oil production is at its maximum. It's all downhill from there.

Imagine you have a room full of pistachios, writes Russ Roberts in the book Invisible Heart.

You adore pistachios and never tire of eating them. There is only one rule: each time you eat a pistachio you must discard the shell back into the room full of pistachios. Over time, it will be harder and harder to find a nut from among the

discarded shells. Eventually, the effort of finding nuts amongst all those shells will become too much and you'll stop looking, tragically leaving some pistachios uneaten. What's important to understand about this illustration is that you never ran out of pistachios. There are more. It's just that as supplies declined what's left became increasingly hard to get at.

Oil is like that. The people who told us that we were running out of oil were accurately reflecting the fact that conventional oil supplies were and are declining. But Peak Oil is not defined by the vastness of supply; it's defined by the rate of production. Like pistachios, we love our oil, so we looked for easier ways to get it. As supplies tightened and prices rise, producers are strongly incentivized to work harder and improve the processes of extracting oil from unlikely and inconvenient sources.

So while total reserves of conventional oil are limited, Peak Oil — the maximum rate of production — hasn't been breached. The advent of fracking (hydraulic fracturing) has increased the means of producing unconventional oil and made up for and even exceeded the rate of production of conventional oil.

PEAK DINOSAUR

The peak concept can easily be extended beyond oil. Dinosaur fossils that are lying about waiting to be discovered are also in finite supply. How many dinosaurs are still out there? How many genera? Through statistics and sampling, scientists in 2006 came to the conclusion that we have about two hundred years of discovery ahead of us.

The first dinosaur was discovered in 1824, and in the following 150 years, we discovered about one new genus a year. The rate of discovery has ramped up to about fifteen geneses a year since then, and shows no signs of declining, indicating that we haven't yet reached Peak Dinosaur discovery. As of 2006, we had discovered 29% of 1850 genera expected. By 2037, we should have uncovered about half of the supply of dinosaurs, and by 2200, we should be about done.

PEAK BURGER

Peak Burger, it appears, has been breached. Since the birth of McDonalds, and perhaps earlier, the rate of burger consumption has been steadily increasing in America, but *Business Week* now claims the rate of consumption of burgers in America is on the decline. McDonalds opened in 1955 and grew to 700 outlets within a decade. In 1983, there were 6000 restaurants and the rate of openings was 360 a year for 20 more years, according to "Obesity and fast food restaurant 7.0", via Wikimedia Commons. In 2013, the net number of restaurants grew by only 121. Wendy's, KFC, Burger King, and others show similar rates of decline.

PEAK ECONOMIST

If you want to get your name in *The New York Times*, become an economist. Before the Great Depression, economists weren't really a thing. In fact, priests were once more quoted than social scientists of any kind. But there's nothing like a financial calamity to send the public running to economists for advice and forecasting. Each ensuing recession has strengthened the trend, and today, according to *The New York Times Chronicle Tool*, economists are totally in.

Measured by mentions in *The New York Times*, the fortunes of economists have risen and fallen throughout the years, but are now in a solid lead, followed by historians, psychologists, sociologists, anthropologists, and lastly, the much sidelined demographer. Economists show no evidence of having peaked.

PEAK SELFIE

Has the rate of production of selfies peaked? When will people get tired of commemorating every good latte and new pair of shoes with a selfie? I could go on. Have we reached Peak Superhero movie? Peak Beard? Peak Tattoo?

PEAK DRUG

Have we reached the peak of new drug discoveries? There are many ways we could measure drug

discovery, but FDA approvals seems like a good place to start. It's not as easy as you'd believe to calculate the number of New Molecular Entities (NMEs) approved by the FDA each year. Even the FDA's own website doesn't provide a good overview, in part due to the removal of drugs no longer on the market. But according to, "An Overview of FDA-Approved New Molecular Entities (NMEs): 1827-2013," published in *Drug Discovery Today* by Michael Kinch, Austin Haynesworth, Sarah Kinch, and Denton Hoyer, 1,453 drugs have obtained FDA approval as of 31 December 2013.

Now let's zero in on the pace of those approvals. Very few drugs received approval prior to the creation of the FDA in 1938, most notably Merck's morphine in 1827 and aspirin in 1899. Until 1950, NMEs averaged around four per year, but that number took off after that. The FDA began routinely approving at least 10 NMEs per year into the 1980s, when that number doubled to 20 a year. The peak rate of approvals was achieved in 1997 when the agency approved a stunning 55 NMEs, according to Kinch, Haynesworth, Kinch, and Hoyer — a number that the agency has not since even approached.

At first blush, it would appear that we have achieved Peak Drug, but I'm not so sure. Remember that Peak Oil showed us there are two factors to determine rate of discovery; one is available supply and the other is our ability to extract (or in this case discover). For our industry, I would say there is a third factor that influences the rate of discovery, and that's government policy. All of these factors have been contributing to the increase in FDA approvals we've seen since the beginning of this decade, including the 41 drugs approved in 2014. We're not there yet, but 55 is in our sights, and our pace of discovery is accelerating, not declining. Many of the reasons for this acceleration could be in the early stages, meaning there may be a rich field of drug discovery that we have yet to tap.

INCREASING DISCOVERY THROUGH REPURPOSING & EXPANDING USES

NMEs and NCEs (new chemical entities) are not as finite an entity as oil. New entities are constantly being discovered, but there's also a grey area of discovery that Peak Oil, Peak Burger, and those other peaks don't have to contend with, and that's repurposing. You can't repurpose a gallon of oil; it's a fuel and that's its only significant purpose. The thought of repurposing a burger or a tattoo or a dinosaur fossil is ludicrous, to say the least. But in our industry, we can expand our reservoir of new drugs through repurposing and expanding use.

The most celebrated example of repurposing is thalidomide. Tragically, its first and most unfortunate purpose was as a sedative and remedy for morning sickness. It was because of its sedative effects, however, that thalidomide stumbled on its first true calling, entirely by accident, according to the book *Dark Remedy*, which recounts the story of a physician who prescribed the only sedative in the hospital pharmacy closet to an ailing leprosy patient. The effect on the patient's condition was as dramatic as it was unexpected. A new treatment was discovered. Thalidomide has since been repurposed yet again as an accepted treatment for multiple myeloma when used in combination with dexamethasone.

Other drugs receive new life through more gradual market expansion. A drug may be developed for a particular type of cancer, and later approved for a second and then a third type of cancer.

Eflornithine is an ornithine decarboxylase inhibitor that started life as possible treatment for cancer, but took a sharp turn in early research when it showed very positive results for trypanosomiasis, otherwise known as sleeping sickness. Later it was discovered to slow the growth of unwanted facial hair, leading to a rather embarrassing moment in the drug's history when it was readily available as a cream for first-world cosmetic applications, but not as a tablet for dying Africans. Aventis eventually took control of the matter, teaming up with the World Health

Organization (WHO) to produce a compound that it then gave to the WHO and to Doctors Without Borders.

INCREASING DISCOVERY THROUGH HUMAN INGENUITY

Human ingenuity is also increasing the size of the drug discovery pool. You may wonder why I mention this at all as it is patently obvious that drugs don't discover themselves. But there was a time when drug discovery was rather easy, and drug entities were discovered and developed much like a miner in the Old West might pan for gold in a California creek. That's an oversimplification, but not by much. Now, with gene therapy, nanotechnology, and so many different, previously unimaginable ways of treating disease, we have increased the pool yet again. A chemical entity that failed a cancer trial a decade ago, for example, may now be tried and proven effective in the presence of certain genetic traits. And so the pool expands again.

INCREASING DISCOVERY THROUGH GOVERNMENT POLICY

I've mentioned this in recent articles, and it is fitting to mention it again here. New government policy has significantly opened the tap for drug discovery. Until recently, drug development focused heavily on the hunt for blockbusters, but policies such as including seven years of patent protection for certain orphan drugs, vouchers for orphan drug development, tax incentives, and more, have set the orphan drug category on fire. At Xcelience, 40% of the drug candidates in our facility right now could be classified as orphan drugs, compared to — let me think — approximately none six years ago.

The implications of government stimulation for orphan drug discovery go well beyond the discovery of orphan drugs. When everyone was chasing only the large population diseases, many promising NMEs were set aside as not worth pursuing. Now, a greater percentage of molecules are deemed worthy of further testing, a fact which is bound to significantly improve the odds of discoveries of all kinds.

PEAK DRUGS, ACHIEVED?

The pool of NMEs and NCEs may be finite, but because of repurposing, expanding uses, and new applications arising from medical advancements like the decoding of the human genome, it is now nearly impossible to imagine where the hard edges of that pool of entities may be. Wherever those borders might be, it's clear that the supply of new drugs to be discovered remains vast. More importantly, our rate of extraction from that pool, much like fracking from an oil reserve, is pushing our rate of discovery rapidly upward. While we have yet to surpass the 1996 FDA record of 55 approvals, the current environment is ripe to produce an explosion of drug approvals within the next decade. Only then will we know for sure if Peak Drug has been breached, or is still in our future. Peak Selfie, on the other hand, may still be ahead of us! ◆

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Derek G. Hennecke
President & CEO
Xcelience

Xcelience is a CDMO focused on small molecule product development with global packaging and logistic services.

The Second Quadrant

The Birth of Drug Solubilization: 1840 Through 1920

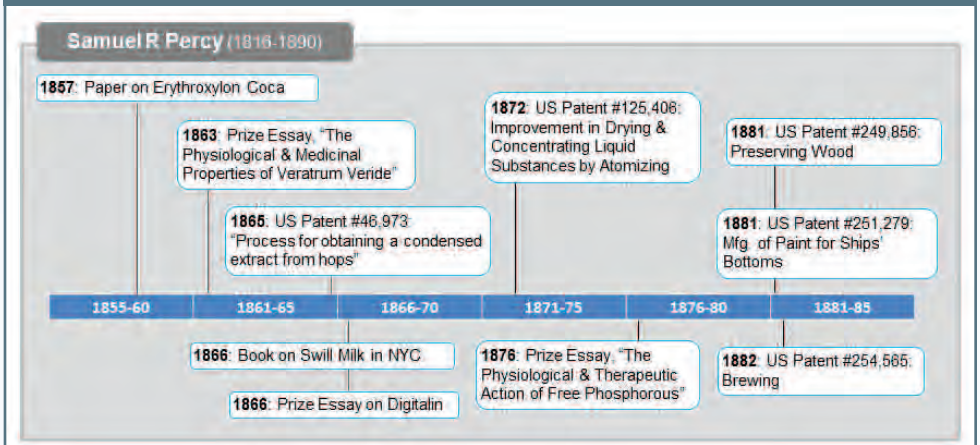
By: Marshall Crew, PhD, VP, Global PDS Scientific Excellence, Patheon

"I start where the last man left off." - Thomas A. Edison

Today's technologies for dealing with solubilization challenges range from myriad manufacturing and engineering methods, an expanded chemical space, and recently developed in silico formulation techniques. These combine to enable drug candidates to move from concept to clinical trials in a relatively short time. While it may seem as if these technologies have emerged throughout the past 2 decades, their maturation took over a century, and this process itself is an interesting study in innovation diffusion.

The inventions leading to the development of spray drying solid drug dispersions alone is rich and involves a combination of contributions from numerous sectors. In particular, the food and agricultural industries played a pivotal role. In the last half of the 19th century, the US population alone tripled to 76 million. The sheer volume of population, the rural-to-urban migration, and the absence of commercial technology for preservation of perishables resulted in consumption of tainted food and epidemic spread of infectious disease. To help deal with the crisis, in 1848, the US patent office was tasked to carry out chemical analyses of agricultural products. This function was transferred to Abraham Lincoln's newly formed Department of Agriculture (today the FDA) in 1862.[1] During this period, studies of Louis Pasteur and numerous other researchers and scientists also focused on food preservation.

FIGURE 1



Some Key Contributions of Samuel R. Percy, inventor of the spray dryer.

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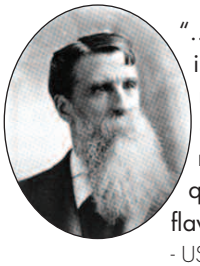
FOOD PRESERVATION: THE BIRTH OF SPRAY DRYING

Desiccation had long been recognized as a viable method for food preservation, and evidence of this technique goes back as far as 14,000 years ago, and it was especially effective when long storage times were desired.[2] To the 19th century palate, however, state-of-the-art evaporation techniques severely compromised taste and quality of daily staples such as eggs and milk. To overcome these drawbacks, new techniques and technologies were explored. In 1865, Charles LaMont patented a method for desiccating eggs.[3] His invention of forcing "… egg-batter, by means of a powerful blast of air, into a thin spray, which is made to fall through a current of heated air" inherently produced a product with improved appearance. But the key advantages were that the "eggs hardened into …particles, readily dissolved in cold water, and retaining their qualities and flavor." Quality, performance, and stability - recognized even then as essential for food safety - evolved into critical attributes for pharmaceutical products today.



"…eggs hardened into…particles, readily dissolved in cold water, and retaining their qualities and flavor."
- US Patent No.51,236
Charles A. LaMont, 1865

Source: The Memorial Cyclopedia of the 20th Century

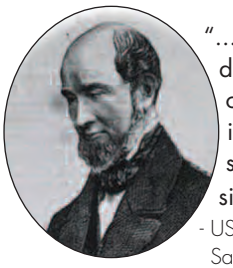
During that same era, Samuel R. Percy (1816-1890), a chemist and physician, was keenly focused on improving the food supply chain and eradication of food-borne disease. He is recognized as a discoverer of the erythroxylon (cocaine) in 1857, authored prize essays on therapeutic effects of veratrum veride, digitalin and free phosphorous (1863-76), and was awarded numerous patents ranging from preservation of hops and wood, spray drying, processes for brewing, and manufacturing paint (Figure 1).

It was Percy's invention of spray drying for powderizing milk in 1872, however, that would ultimately advance manufacturing technology for solubilizing drug molecules. His patented process enabled "the prevention of the destructive chemical change" by "bringing a fluid … into a state of minute division" within a chamber of heated air, rendering the product "deprived of moisture".[4] But before this invention could be applied to pharmaceuticals, numerous puzzle pieces had to fall into place.

PUMPS, NOZZLES, POWDER COLLECTORS

At a minimum, the three key components needed for a spray dryer are: 1) a reliable liquid pump; 2) a nozzle to "atomize" the liquid into fine particles; and 3) a method for collecting the dried particles. The industries of food, agriculture, and manufacturing were those in which rapid advances were being made. Pharmaceutical spray drying would be built on these foundations.

The use of pumps goes back 4,000 years, and innovations utilizing air, screw, centrifuge, vacuum, and plunger methods continued through the 1800s.



"…the prevention of the destructive chemical change" by "bringing a fluid…into a state of minute division…"
- US Patent No. 125,406
Samuel R. Percy, 1872

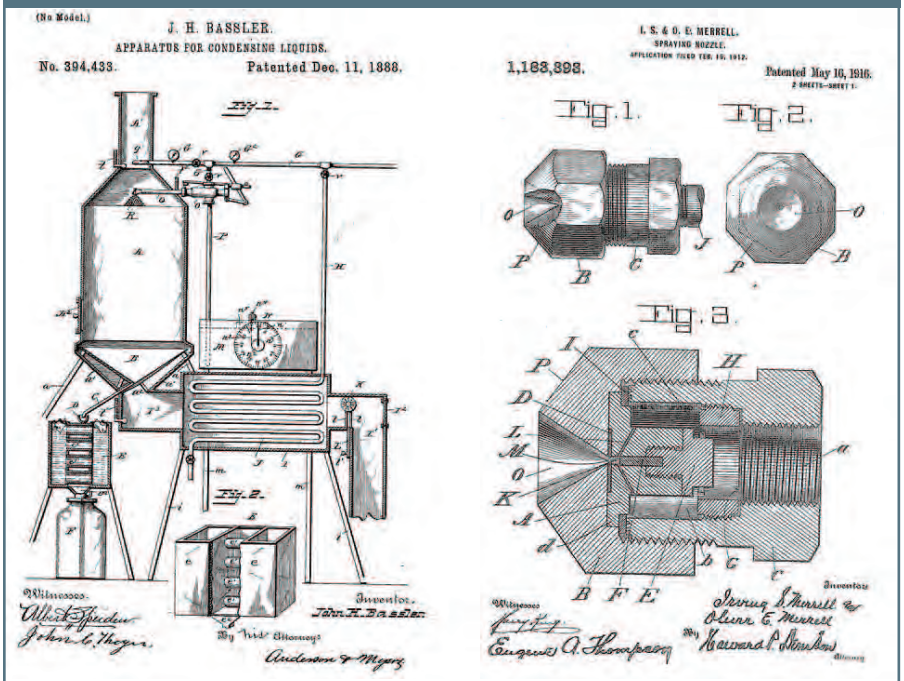
Source: History of Medicine, US National Library of Medicine

Yet it was the observation that steam engines could act as pumps when run in reverse that launched the next chapter. Henry R. Worthington's invention of the steam pump in 1840 was the beginning of over a century of progress in this area that continues to this day.[5] The first all-metal pump was built in 1849, which served as a key enabler for the liquid pump technique, as patented in 1857.[6]

The spraying nozzle invention for preserving blood, milk, and other liquids by Robert Stauf in 1901 served as the basis for pressure nozzles used today for atomization.[7] Stauf's nozzle breakthrough was acquired by Merrell-Soule for spray drying of powdered milk, allowing them to extract more than 98% of the moisture of liquid milk. They described their product as, "…ideally preserved milk – soluble, containing the lowest obtainable percentage of moisture, offering no breeding place for bacteria, and free from the strong cooked flavor so noticeable in many other mild powders."[8] Merrill-Soule's products and patents were skillfully used to dominate the market until the 1920s.

The last piece of the puzzle was an effective method to collect the spray dried product. Powder collection, originally derived from threshers and flour mills, and originated with cheese cloth, bag houses, and then "so-called cyclone".[8] In Merrell-Soule Company's description of their process, they note

FIGURE 2



Drawings from early patents of a milk spray condenser and a pressure spray nozzle. Source: US Patent & Trademark Office

that, "Gathering up, after it [the desiccated milk powder] has fallen to a depth of several inches, the milk powder is ready for packing." In many cases, the process was stopped, and the product was hand-shoveled out of the spray dryer. The first patent for powder collection was granted to Wilhelm F. L. Beth in 1906.[9] This completed the list of essential components for the realization of modern spray drying.

INNOVATION: CREATIVE COMBINATIONS OF EXISTING THINGS

While in principle, spray drying is a relatively simple process, throughout the next several decades, components and processes would be invented, improved, and combined to enable pharmaceutical applications. Many hadn't yet been realized in the time of Percy, and others were emerging for disparate applications in other industries. Even when other equipment, machinery, and manufacturing techniques were being developed, mass production and availability of the building blocks needed to assemble what we use today didn't yet exist in an applicable format. Patents, publications, and the interactions of inventors formed a virtual hardware store, enabling innovation diffusion across industrial applications.

Developments from the 1920s through the 1960s also had significant impact on the progress of spray drying. The next column in this series will highlight milestones in engineering, the fundamental understanding of the spray drying process, large-scale manufacturing for the war effort, and the ongoing application to wide range of industries. It was during this period that we observe the birth of physical pharmacy, and the early need to overcome poor solubility in drug products. ◆

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LIPID-BASED DELIVERY SYSTEMS

New Approaches for Macromolecule Oral Delivery, Abuse Deterrence & Bioavailability Enhancement

By: Julien Meissonnier

INTRODUCTION

Catalent Pharma Solutions has developed a broad range of advanced oral drug delivery technologies, including a toolkit of technologies based upon the broad application of lipid-based drug delivery systems (LBDDS) for optimum solubility enhancement. Through innovations to the company's softgel technology, improved delivery of BCS Class II drugs is possible with OptiShell™, whilst OptiGel™ Bio enhances the membrane permeability allowing the non-invasive delivery of biomolecules, or narcotic compounds under a format that helps prevent abuse.

EXPANDING THE SOLUBILITY-ENHANCEMENT FRONTIERS

The company's softgel technology has to date enabled more than 50 poorly soluble drugs (NDAs) to be commercialized, leveraging LBDDS and making it one of the most successful advanced drug delivery technologies applied to BCS Class II drugs. The basic principles ensure that the formulation delivers the drug substance under a solution form and maintains it in that form upon dispersion into the biological fluids before reaching the intestinal membrane. Softgel dosage forms offer broad flexibility for conversion to stable, unit-dosage forms and a wide variety of LBDDS formulation compositions. They also handle low fill formulation batch sizes of around 100 mg, and are thus perfectly suited for preclinical and early clinical studies.

Beyond the solubility hurdle, the poorly soluble drug candidates that Catalent is being tasked to formulate present more challenges in order to meet the desired target product profile. Unlike other delivery systems, LBDDS have the versatility to offer additional possibilities to formulation scientists.

Some poorly soluble drugs display excessive inter/intra individual variability that is often not compatible with their desired therapeutic effect (eg, positive food effects for highly lipophilic compounds for which the fed state increases *in vivo* intestinal solubility). Some strategies, specifically designed to leverage solubility and reduce variability, typically comprise a Self-Micro Emulsifying Drug Delivery System (SMEDDS) that is a lipid-based "preconcentrate" of solubilized drug composed of lipid excipients; surfactants and co-surfactants (hydrophilic or lipophilic), and co-solvents (eg, ethanol). When such formulations are diluted with gastrointestinal fluids, a thermodynamically stable microemulsion is formed, which maintains the drug in solution and prevents its precipitation irrespective of variations in biological conditions (i.e. enzymes, pH, bile salts). Several successful compounds have reached market in this format.

Beyond solubility enhancement, some strategies also include the limitation of serum peak concentrations reducing C_{max}/C_{min} ratio. For this purpose, Catalent has designed and filed novel semi-solid formulations that combine solubility-enhancement properties while modulating release rate. These formulations are enabled by the company's OptiShell technology that enables the encapsulation of various LBDDSs at higher temperatures.

OptiShell technology also helps overcome drug load limits

(over 200 mg/g) of liquid lipid-based formulations. Indeed, when the industry faces poorly soluble drug candidates with high-targeted drug load (ie, most of the protein kinase inhibitors), formulation scientists have adopted the development of solid solution/dispersions either achieved by solubilizing in solvents and then evaporation (eg, Spray Drying, Spray Layering) or by melting in a polymer matrix and quenching (Hot Melt Extrusion). In contrast to those systems in which drug candidates are dispersed and stabilized at the molecular stage into polymeric hydrophilic matrices, OptiShell technology achieves solid solution/dispersions stabilized in solubility-enhancing lipid ingredients, with or without polymers. This approach offers a greater range of solutions to formulation scientists, together with easier paths to scale-up the manufacturing process and other benefits that are intrinsic to liquid and semi-solid systems, such as easier dose uniformity and containment.

Through the experience gained in formulating numerous poorly soluble drug candidates, Catalent's scientists have concluded that LBDDS not only overcomes the solubility limitations of some APIs, but that these systems often also provide, beyond affecting membrane efflux, some benefits in modulating membrane permeability for drugs in which solubility is not the only biopharmaceutical hurdle to overcome. Since 2007, when Catalent initiated its research programs into this non-invasive delivery method for biologic drugs, this knowledge has been investigated and applied to macromolecules in development, and the outcomes of this research has been realized in the company's OptiGel™ Bio technology.

FIGURE 1

CAPITALIZING ON PROPERTIES OF MACROMOLECULES

OptiGel Bio technology may significantly improve the delivery characteristics of peptide and biologic drugs. In order to meet the biopharmaceutical, stability, and delivery challenges they present, dosing of these macromolecules has traditionally been via injection. However, although this delivery form provides an adequate pharmacokinetic therapeutic profile for these drugs, such an invasive delivery method often results in difficulties with patient compliance and therefore does not enable some drugs with unique and established safety/efficacy profiles to match therapies requiring mid- to long-term treatment. The OptiGel Bio technology enables, through various combined mechanisms, the non-invasive delivery of some macromolecules. The most significant of these delivery mechanisms is the modulation of intestinal membrane permeability, combined with optimal targeted delivery *in vivo*.

The technology also bears some unique features in its design, enabling the reduction of intra/inter individual dose variability often met with some alternative technologies in development.

OptiGel Bio technology employs the same targeted co-delivery of permeation-enhancing formulations/systems techniques that have been safely applied to already marketed, poorly water-soluble drugs, to the delivery of macromolecules or peptides. Such localized delivery allows for higher transient concentrations of permeation-enhancing excipients alongside the API. The technology is applicable to various classes of macromolecules, including oligosaccharides as well as peptides, and Catalent is conducting research to further expand its application to the more complex delivery challenges associated with larger and less-stable molecules.

Catalent has created some standard preformulation and formulation screening models in order to quickly evaluate whether OptiGel Bio technology can assist in the delivery of candidate macromolecules, including peptides.

"The OptiGel Bio technology enables through various combined mechanisms, the non-invasive delivery of some macromolecules. The most significant of these delivery mechanisms is the modulation of intestinal membrane permeability, combined with optimal targeted delivery *in vivo*. The technology also bears some unique features in its design, enabling the reduction of intra/inter individual dose variability often met with some alternative technologies in development."

These models have enabled the determination of potential structural changes to the peptides that would maximize the ability to cross the enterocyte along with the permeation-enhancing system when formulated.

Through the Catalent Applied Drug Delivery Institute, founded in 2013 to promote excellence in drug delivery through education, training, and innovation, Catalent has developed close partnerships with several universities. It is also expanding its academic partnerships through the newly established Non-invasive Macromolecule Consortium, which conducts clinical roundtable research and creates tools for future research, such as their Oral Drug Delivery Reference Guide. These partnerships, and other university relationships, promote the development of new, innovative technologies in the fields of taste-masking and bioavailability enhancement via particle engineering, hot melt extrusion, oral vaccines, and oral and non-invasive macromolecules.

NOVEL SOLUTIONS FOR ABUSE DETERRENCE

In 2013, of almost 50,000 drug overdose deaths in the United States, just less than 52% were related to pharmaceuticals, and more than 71% of those pharmaceutical-related deaths involved opioid analgesics (also called opioid pain relievers or prescription painkillers). Just as worryingly, the drug overdose death rate has more than doubled from 1999 through 2013.[1]

Abuse prevention is a key element in reducing the misuse of pharmaceuticals, and whilst Catalent is committed to resolving complex bioavailability limitations, the company has employed some of its learnings to the development of abuse deterrents that may be incorporated into pain management therapies. Many existing prevention methods currently available are costly, difficult to formulate, and/or require an elongated path to commercial development.

Catalent research teams have focused on studying rheologically complex fluids to develop OptiGel™ Lock, a unique abuse-deterrent technology that retains immediate- or sustained-released attributes while proposing the potential to meet Tier 3 labeling, described in the FDA Guidance for Industry: Abuse Deterrent Opiods - Evaluation and Labeling. This technology helps reduce the risks of abuse often associated with more conventional tablet forms, as a softgel is inherently more resistant to being ground-down and inhaled. It also significantly reduces the possibilities of abuse by manipulation and various extraction methods.

SUMMARY

The bioavailability of poorly soluble and permeable drugs, including macromolecules and peptides, can often be enhanced from lipid-based formulations. With more than 50 US-NDAs approved, Catalent's OptiGel Bio and OptiShell softgel technologies represent reliable dosage forms that may well assist in bringing not only poorly soluble drugs to market, but that also go beyond solving solubility limitations to incorporate benefits for those looking to deliver macromolecules and peptides, or controlled and potent drugs. ◆

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1. Source: Centers for Disease Control and Prevention, "Prescription Drug Overdose in the United States: Fact Sheet."

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Case Study: Expediting a Promising New Therapy With Softgel Technology

An innovative biotechnology company, exploring novel therapeutics for neuroscience indications, had developed a promising NCE for the treatment of a severe pediatric genetic disease. However, numerous drug delivery challenges threatened the realization of US FDA's Fast Track status designation the company had received due to promising early stage results. By partnering with Catalent, and leveraging its proprietary softgel technology, the customer was able to overcome a number of potential hurdles and expeditiously enter the Phase II/Phase III clinical trial.

The stability challenges to be met were that the NCE had a 6-month shelf-life, was subject to oxidation, and free fatty acids were present. It also had a poor bioavailability profile, including poor absorption profile, poor solubility, and poor permeability. For scale-up, the complexity of the formulation gave rise to dose uniformity issues, the dose itself requiring a large pill size with limited drug load and a high pill burden. There was also an accelerated timeline requirement, with just 4 months from formulation to producing cGMP clinical supplies.

To solve these problems, researchers at Catalent partnered with the customer to quickly discover a superior alternative drug delivery solution, using the company's softgel technology to enable the NCE to take advantage of the FDA's Fast Track designation.

For the initial formulation and screening selection, two lead lipid formulation candidates were selected with 12- to 14-fold solubility improvement over the original liquid fill hard shell (LFHS) formulation. In a rodent PK study of two lead candidate formulations, a lead formulation was selected with significant improvement over LFHS. This was followed by a human PK study of the lead formulation in healthy patients, which also showed significant improvement over the original LFHS formulation. In addition to enhancements in bioavailability, the softgel formulation provided significant improvements in stability, an increase in dosage, and a reduction in capsule size: these were all delivered within the required 4-month time frame.

The synergy of Catalent's experience and resources and the customer's innovation enabled this NCE to progress rapidly into Phase II/Phase III trials, ultimately allowing the customer to realize the Fast Track designation, thus bringing a better therapy closer to commercialization.

BIOGRAPHY

Julien Meissonnier provides technical and scientific leadership for the development of delivery systems for poorly soluble drugs that lead to approvable regulatory dossiers. He currently leads Catalent's European softgel R&D teams, focussed on early stage screening activities, developing products, scale-up and technology transfer, directing clinical supplies, and supporting product launches. Mr. Meissonnier has 17 years of experience in pharmaceutical development. He earned his Engineering degree in Physico-Chemistry from the ENSI in Caen, France. He also served as a Board Director of Alsace Biovalley innovation cluster and currently serves as a Catalent Applied Drug Delivery Institute Board Member. He can be reached at Julien.Meissonnier@catalent.com.

PARTICLE AGGREGATION ANALYSIS

Biologics & Particulates: Identification & Control in the Product Lifecycle

By: Zabin Younes

INTRODUCTION

Biologics are high-price and high-value drugs that have made significant differences to patients' quality of life worldwide, both as prophylactics and therapeutics; however, they can be prone to contamination with particles that can cause issues for patients. While product safety and contamination is important for any drugs, it is particularly significant in biologics, which tend to be prescribed to people with chronic conditions or serious diseases.

Biologics, which can be chemically synthesized, derived from biological materials, or expressed using recombinant DNA technology, target the specialty pharmaceuticals market, particularly treating life-limiting disease or serious chronic disorders. They may be safer and more effective, or better targeted, than small molecules, but they are generally higher cost and more complex to develop and manufacture.

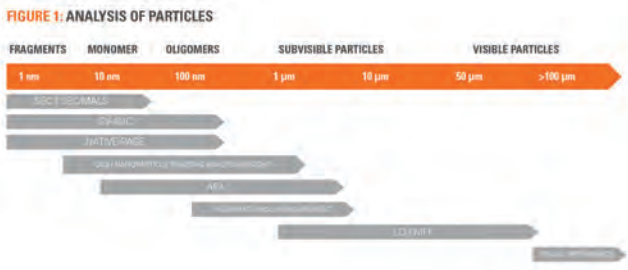
The demand for biologics is growing year on year. According to the IMS report, The Global Use of Medicines: Outlook through 2017, the market share for biologics (including biosimilars and non-original biologics) is growing, from a global share of sales of 11% in 2002 to a projected 19% to 20% in 2017. This will only continue to increase, as currently around a third of all of the projects in late-stage pharma R&D are biologics.

THE ISSUE OF PARTICULATES

Particles in biologics, which can range from protein aggregates to shards from the vial or stopper, can have an impact on a product's stability and therefore its shelf-life. From a practical perspective, a product's shelf-life needs to be 2 years or more, and this is particularly important for higher cost or less-commonly used products. More significantly, however, the presence of particles can trigger an immune response in patients. A mild response might just be an inconvenience, but a more severe immunogenic response could be life-threatening, especially in patients already seriously ill.

These issues will have an impact on the regulatory process, with regulators requiring demonstrable limitation, control, and identification of product-related impurities. The control of particle formation may even require process changes or

FIGURE 1



Analysis of Particles

reformulation, which could potentially have an impact on the product's stability, efficacy, and safety. Because of this, changes in the process could mean that the regulators require additional method validation as well as comparability and stability studies.

Drug development is already a costly business, in some cases topping a billion dollars, and these additional changes and steps could delay the time to a return on investment, as well as having an impact on the product's patent life.

I SPY: SPOTTING & IDENTIFYING THE PARTICLES

Particles identified during the biologics production process can be divided up into two types, non-proteinaceous and proteinaceous, and they may be intrinsic (arising from the product, the formulation, the container, or the delivery device) or extrinsic (introduced into the formulation from the environment during manufacturing). Non-proteinaceous particles include shards from vial closures, fibres shed from filters, delaminated flakes from plastic packaging, and splinters of glass or metal from processing or packaging steps. Tiny drops of silicone oil, used in the lubrication of moving parts in delivery devices, can also form non-proteinaceous contaminants.

Proteinaceous particles are formed from reversible or irreversible aggregates of proteins, and range in size from individual oligomers at >10 nm to 1 µm, through to visible particles at around 100 µm or more. The formation of proteinaceous particles can be triggered by high concentrations of proteins, or by partial conformational changes in the protein. Once formation begins, it can set off a cascade of aggregation, and the particles can form on the wall of a container, at the air-water interface, or around an unfolded protein or a non-proteinaceous particle.

Companies can use a range of different techniques to track down particles depending on their size, from SEC-MALS (size-exclusion chromatography with multi-angle static light scattering detection) for particles as small as 1 nm, through to visual inspection for particles of 100 µm and upward (Figure 1).

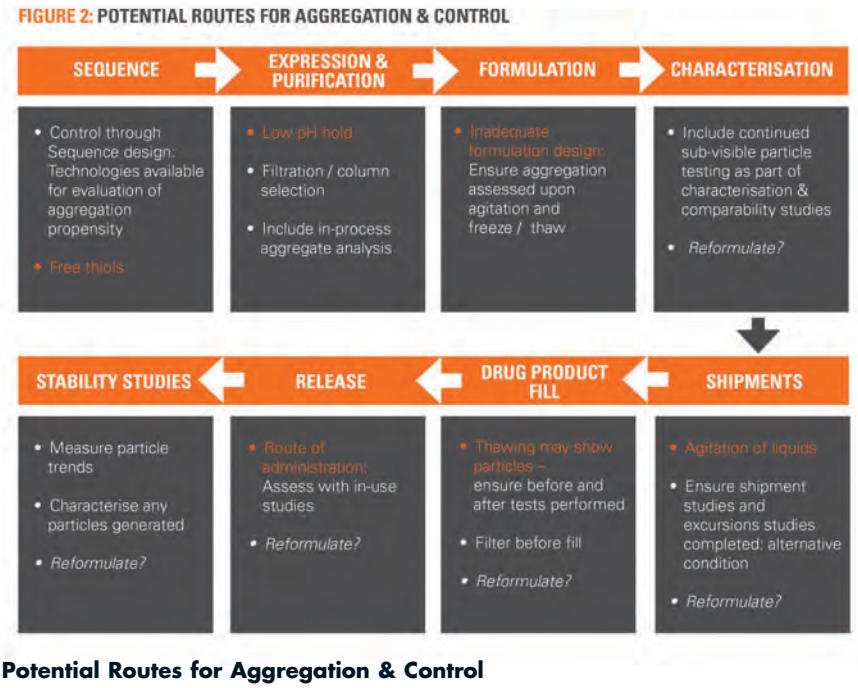
CONTROLLING PARTICLE FORMATION

Putting steps in place to control particle formulation as early as possible is vital, as later issues are likely to require more significant changes, so therefore will have more impact on costs and necessitate longer delays. It is also worth bearing in mind that any changes after the formulation step are likely to mean further reformulation steps, further increasing costs and delays.

There are a number of points in the production development process in which companies can intervene to reduce the risk of particulate formation (Figure 2). The orange text indicates points at which particle formation is more likely, so these should be carefully watched in the product design and the development of the manufacturing process. The product needs to be monitored at all steps, both for the number and the type of particles.

The earliest step is designing the sequence and evaluating its risk for aggregation based on its structure and conformation, before the molecule has even been expressed. Key issues to look out for are free thiols and exposed internal thiols, which may lead to covalent (irreversible) bonding within and between proteins. This misfolding and

FIGURE 2

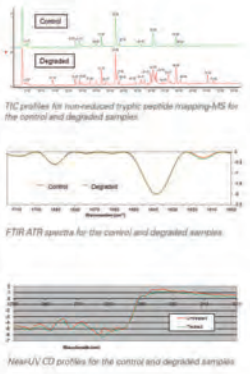


Potential Routes for Aggregation & Control

FIGURE 3

FIGURE 3: PREFORMULATION CHARACTERISATION

ANALYSIS	CONTROL	DEGRADED
Primary structure: NR Peptide mapping-MS for SS-bridges	No scrambling observed, expected IgG1 SS-bridge pattern	SS-bridge scrambling observed
Charge profile: icIEF	pI 9.3-9.6, 6 isoforms	pI 9.3-9.6, 6 isoforms Equivalent profile to native
Secondary structure: FTIR	α-helix: 0% β-sheet: 42%	α-helix: 0% β-sheet: 43% Equivalent profile to control
Overall tertiary structure: Near-UV CD	Equivalent profile to degraded	Equivalent profile to control, but some differences observed ~280nm



Preformulation Characterization

binding can create a nucleus for an aggregate formation, so making even slight changes at this point could have a significant and positive impact on the likelihood of particle formation. This assessment can happen right at the very beginning of drug discovery and development.

Once the biologic has been expressed, steps in the purification process can trigger aggregation, for example, the inclusion of shreds of filters shed during UF/DF filtration, or conformation changes resulting from the need for pH reduction to inactivate viruses. In-process aggregate analysis allows monitoring of particulate formation on an ongoing basis, pointing to any changes needed in the process.

The formulation step ensures that the conformation of the biologic API is stabilized, to retain its activity and reduce the development of particulates. Biologics can be vulnerable to being broken down in the body, particularly in the gut, so they need to be formulated appropriately. Because of the nature of the molecule, it can also be affected by temperature, pressure, and agitation, and thus the formulation needs to ensure stability of the molecule in storage and transport, as well as protecting it from damage during freezing and thawing. Biologics are usually administered by injection or infusion, so the formulation also has to be appropriate for the device.

Not only do all the characteristics of the drug and formulation need to be assessed in relation to particle aggregation, the product also needs to be formulated correctly to be patient- and physician-friendly, and to ensure that the drug gets to the right place, at the time, and in the right concentration.

Once the drug is formulated, the next step in the evaluation process is to see how well it will cope with the conditions that the finished product may experience in shipping and transport. These include rapid and sometimes extreme changes in temperature if optimum storage conditions are not available, for example, if the cold chain is broken, especially in countries with very extreme climates. If products are transported by air and are in the cargo hold, there may be changes in temperature and pressure. Finally, shipping by road, rail, or air can lead to liquid biologics being agitated for long periods of time. Testing should include simulation of these conditions for time periods equivalent to those that could occur during transport.

Biologics may be supplied frozen or freeze-dried, and so will need to be thawed or reconstituted before use. In order to check whether these steps trigger particle formation or aggregation, tests have to be carried out before and after freezing/thawing or drying/reconstitution, and reformulation steps added in if necessary.

The type of storage vessel and the route of administration can make a difference, and products need to be monitored after filling and before and after administration. Non-proteinaceous particles can arise from delivery devices and storage vials, and may be introduced during the packaging stage, for example, damage to the neck of a glass vial during filling, or delamination from poor-quality plastic stoppers or closures. The delivery device can also be a source, for example, oil used to lubricate the barrel of a syringe can create a nucleus for protein aggregation. Any analyses will need to compare the biologic alone, and in its delivery device or vial.

Monitoring for particle development does not stop at the end of the manufacturing process. Drugs need to be monitored for a period equivalent to their shelf-life, under a variety of conditions, to ensure that particles do not develop over time.

CASE STUDY: PRACTICAL EXAMPLE OF PARTICLE CONTROL

Companies that specialize in formulation can reformulate drugs that have progressed through development with good safety and efficacy, but show a propensity for particulate formulation at one of the aforementioned steps, or that have shown property changes at batch scale-up or when production has moved from one plant to another.

In this case study, an IgG1 monoclonal antibody had gone through the clinical trials, but its developer found that it tended to form particles when it was frozen and thawed, and during the shipping process. Because of the late stage of development, the project needed to be pushed through as quickly as possible, with constraints on the budget and limits on the amount of material available.

The preformulation characteristics are shown in Figure 3, comparing the original or control biologic to the degraded form after exposure to a simulation of the worst-case shipment conditions and temperature excursions. This included 24 hours agitation at ambient temperature, and three cycles of freezing and thawing, with temperatures from -20°C to +40°C. The analysis showed irreversible scrambling of the SS-bridges, but no noticeable charge-based changes. There were no significant changes to the secondary structure and only minimal changes to the tertiary. However slight the changes were, they triggered the formation of particles, the majority of which were greater than 2 µm. The findings were used to determine the best screening methods.

Based on these observations, a pH and excipient screen to find the optimal formulation to control aggregation was performed. The pH screen was carried out at a pH range of 3.5 to 7.5, with the samples being agitated, frozen, and thawed. The process was monitored using SE-UPLC (size exclusion ultraperformance liquid chromatography) and DLS (dynamic light scattering). Once the optimal pH was determined, a screen using a variety of excipients at different concentrations and a number of different surfactants, using a design of experiment (DoE) approach, all the time maintaining an awareness of limitations on time, budget, and sample volume was carried out. The optimum surfactants were selected for conformational stability and reduction of surface charge interaction.

From the results of the screening, a shortlist of four lead candidates was selected and assessed for conformational stability and particle count using intrinsic fluorescence and DSC (differential scanning calorimetry), particularly looking at counts of particles greater than 2 µm. The final candidate ranked top in both sets of criteria, including having the most thermally stable formulation, assessed at temperatures between 20°C and 100°C.

BEST PRACTICE FOR PARTICLE AGGREGATION ANALYSIS

Traditionally, tools such as SEC and DSC have been used in formulation screening. However, in order to ensure a control of particulate counts, it is important to use the full range of tools (Figure 1) to ensure that all types and sizes of particles and aggregates, from visible to sub-visible, are all assessed and accounted for. As drug development costs and time pressures increase, speed and sensitivity are critical, meaning that high-throughput screening is becoming more important.

It is vital to assess the risk of particle formulation for all biologics, and it should be carried out as early as possible in the product's lifecycle to help keep costs low and timelines short. But equally importantly, the levels of particulates in products will need to be monitored beyond launch to ensure patient safety as well as in clinical trials. ◆

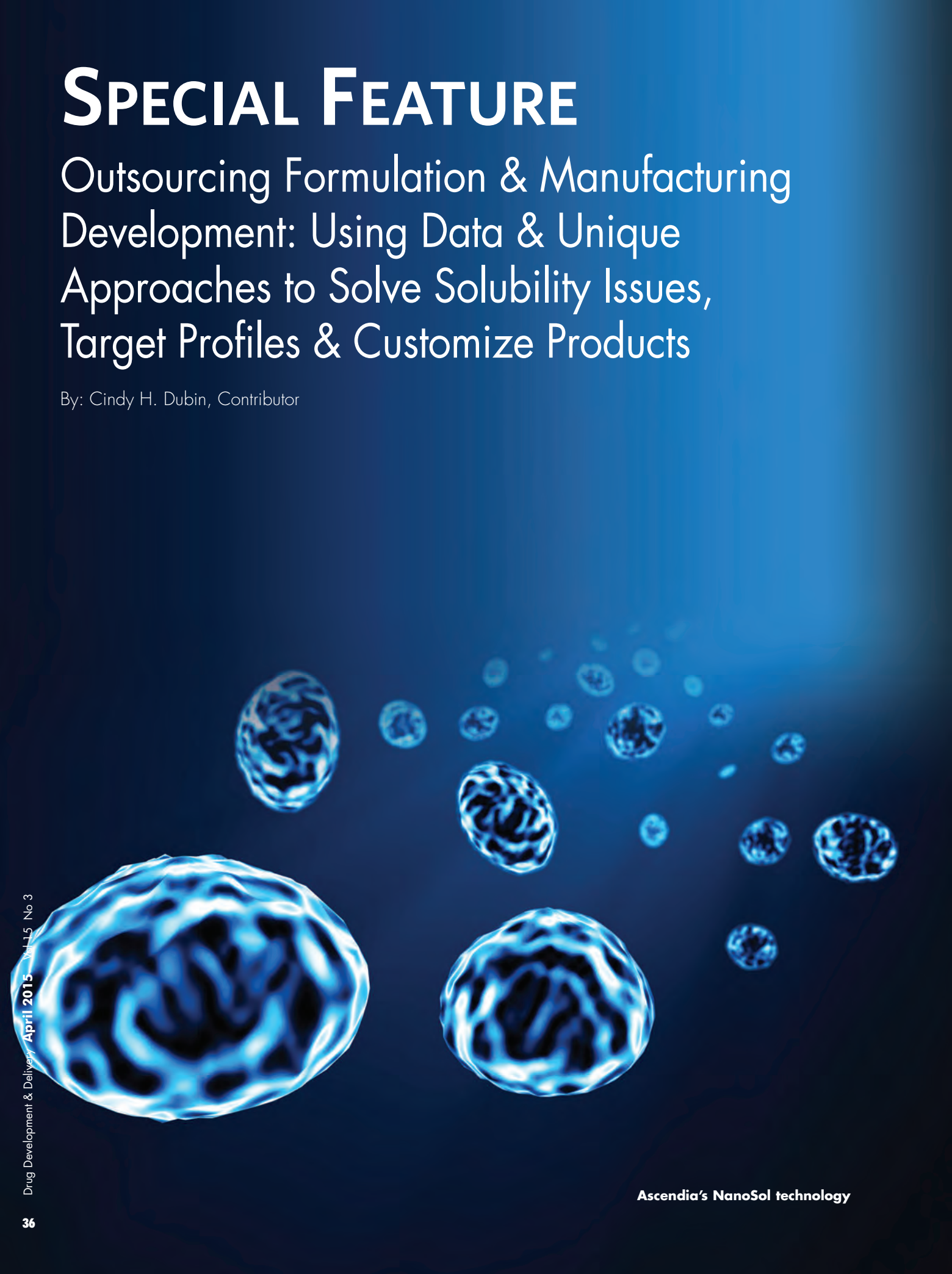
BIOGRAPHY

Zabin Younes earned her BSc in Medical Biochemistry from Royal Holloway University of London. She has extensive experience in the biopharmaceutical development industry – with both practical and theoretical experience in purification, formulation, assay development, characterization, assay validation, specifications definition, and stability testing. Ms. Younes has worked for small and large biotech enterprises, including MicroScience Ltd (later Emergent Biosolutions) and UCB/Celltech. Previously, she was Team Leader in Stability and Formulation at Lonza. She has built a solid foundation in stability management, stability study strategies, customer/regulatory communication, laboratory compliance, and lab management. Ms. Younes has worked with a range of biological products, such as vaccines (protein subunits, conjugates, bacterial, and viral vectors) and recombinant protein therapeutics, including monoclonal antibodies, antibody fragments (Fab'/Fc), and bi-specific molecules. She joined SGS M-Scan in August 2013 as Stability Services Manager.

Special Feature

Outsourcing Formulation & Manufacturing Development: Using Data & Unique Approaches to Solve Solubility Issues, Target Profiles & Customize Products

By: Cindy H. Dubin, Contributor



Ascendia's NanoSol technology

The demand for outsourcing pharmaceutical formulation development and manufacturing is on the rise for drug developers at all levels. Frost & Sullivan estimates the pharma industry spent $13.4 billion on contract manufacturing and development services in 2013.

And the trend continued in 2014 with the industry using more CDMOs to assist at the development stage of drug manufacturing. These businesses can provide comprehensive services, from drug development through to manufacturing commercial supply, and are interested in differentiating their abilities from CMOs, which tend to be focused solely on large-scale manufacturing projects. Thus, many CMOs have embraced the CDMO term in their efforts to develop long-term partnerships, according to Nice Insight.

Utilizing a CMO/CDMO for formulation development is anticipated to increase as the strategic partnerships between drug innovators and contract suppliers mature. Results from the 2014-2015 Nice Insight Pharmaceutical and Biotechnology Survey show that 10% of respondents will engage a CMO for small molecule API development, and 10% would outsource solid/semisolid or liquid dosage form development. Thirteen percent stated they would engage a CMO for large molecule API development and 12% for injectable product development.

In this *Drug Development & Delivery* report, several CMOs/CDMOs discuss formulation development and manufacturing challenges, and how overcoming those obstacles can fast track the drug to the clinic.

Hot-melt extrusion technology at Aesica.

Aesica—Developing Technologies to Improve Solubility

Many new innovative compounds tend to be poorly soluble, simply because most of the traditional high solubility and high permeability compounds have already been formulated. Now less than 10% of new candidates have high solubility and permeability. Additionally, many companies are revisiting existing compounds from 5,10 or even 15 years ago. The belief is that with new technologies and approaches to solubility, these compounds are now commercially viable.

As Aesica is increasingly seeing more poorly soluble compounds, the CDMO is focused on developing and commercializing new technologies and techniques to overcome the solubility issues. As a starting point, Shabbir Mostafa, Business Development Director for Aesica, explains that the science and chemistry of each candidate is evaluated—whether it is hydrophobic or lipophilic—and excipients that help improve the APIs bioavailability when formulated are also determined.

"Once we have established our ingredients as a base, Aesica relies on a range of specialist technologies that can help increase the surface area of compounds or alter their priorities to increase stability," says Dr. Mostafa. "The key point to stress here is that when we work with customers, we also use scalable technologies to start on a very small scale to preserve the customer's valuable APIs, helping reduce expense."

One of Aesica's key technologies includes spray drying, which produces a dry powder from a liquid/slurry, increasing solubility. Wet bead milling

Agere cGMP manufacturing of a spray dried amorphous dispersion intermediate.

is another technique for producing submicron and nanosuspensions (nanomilling) and is used as a convenient and cost-effective method of enhancing the bioavailability.

Hot-melt extrusion, while still underused in pharmaceuticals, says Dr. Mostafa, increases solubility by melting polymers and drugs together. The crucial benefit of this technology, he says, is that it is a continuous process, meaning it uses only minimal API and removes the batch validations required during scale-up to help expedite time to market.

Aesica has working partnerships with local institutions that have the early formulation expertise and Aesica provides the knowledge to upscale the product for clinical manufacture.

Agere—Solubilization Platform Fast Tracks From Formulation to Clinic

Service provider Agere notes a growing preference for pharma to "borrow" expertise when needed as opposed to having solubilization experts on staff. The company supports its clients in identifying the best solubilization technology and identifying the best excipients using Agere's solubilization platform, Quadrant 2™. "The platform embodies methodologies that drive efficiencies and greater predictability based on informed, data-driven decisions," explains Casey Jones, Vice President, Corporate Development, Agere. "The integration of expertise with experimental and model-based approaches can accelerate the flow from identification of the best excipient candidates to formulation design, optimization, and process development."

While service providers' experience and knowledge are critical elements, seamless integration of the service provider into the supply chain is essential for both parties to fully realize the cost benefits of the partnership.

One example of how Agere's methodology can deliver a fast track from formulation into the clinic is currently underway. "We were contacted in January by a client to develop three strengths of their drug in tablet form by March, a two-month cycle from formulation and dosage form development to GMP tablet manufacture," describes Ms. Jones. The client and Agere worked together, significantly benefitting from a "man-in-plant" approach, and overcame development challenges to keep the project on track.

"We developed 11 batch records in two weeks to support blending, common granulation, and compression of the three strengths required to include individual packaging records. We were on time with GMP granulation, and were on track by the end of February. This accelerated schedule was enabled by the close client collaboration, Agere's fully integrated manufacturing readiness team, a formalized tech transfer system, and specialized equipment and bench expertise." **(Agere was acquired by Patheon on 3/20/2015)**.

The PharmaCircle Drug Delivery and Formulation Newsletter and Blog

Opinion and Analysis from PharmaCircle on Recent Trends and Developments and the Implications for the Pharmaceutical Sciences Community

For over a decade, PharmaCircle has been the premier database for connecting product and pipeline information for drugs and biologics with formulation and component details, and providing due diligence level data on nearly 6,000 drug delivery technologies and delivery devices.

In addition to providing industry leading content, PharmaCircle now delivers a weekly newsletter and blog that focus on issues of interest to the formulation and drug delivery community.

The PharmaCircle Blog: Launched in September, the blog offers analysis from Dr. Josef Bossart, PharmaCircle's Executive Editor, of recent product and technology innovations, pipeline developments, and industry trends. Check for updates weekly at http://blog.pharmacircle.com.

The PharmaCircle Drug Delivery and Formulation Newsletter - redesigned and featuring:

Kurt's Drug Delivery & Formulation News: A wrap up of the past week's top news items as selected by Kurt Sedo, Senior Vice President of PharmaCircle.

Tips and Tricks: Ideas for getting better search results more quickly and easily when using PharmaCircle, plus a periodic look at new information resources in the public domain.

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Ascendia Pharmaceuticals LLC—Three Platforms Address Formulation

Ascendia Pharmaceuticals offers services for contract formulation development of poorly soluble drugs, and is dedicated to partnering with other small pharma companies to enable and optimize delivery of their NCE or re-formulated drug. Its formulation approaches include nanoemulsions, amorphous solid dispersions, and nanoparticles. These technologies are suitable for oral, ophthalmic, or injectable delivery of drugs that are difficult to formulate.

Ascendia has three platforms for addressing the formulation needs of poorly soluble drugs: EmulSol, NanoSol, and AmorSol. EmulSol produces stable, optically clear, oil-in-water nanoemulsions in a 50-500 nm particle size range using a high-pressure homogenization process. By selecting specific long-chain triglycerides in combination with an ionizable surfactant, Ascendia has eliminated the use of organic solvents in its formulation approach, and minimized the use of co-surfactants, explains Troy M. Harmon, Vice President, Business Development, Ascendia. The drug is solubilized within the interior of the oil droplets, and when the nanoemulsion is delivered to the body, the drug is more readily bioavailable.

NanoSol technology produces particles with a size typically below 400 nm. The drug contained in the particle may be either crystalline or amorphous form. Formulation of a drug in a nanoparticle form significantly increases the surface area available for dissolution. The nanoparticles can be encapsulated for oral administration, or prepared as a suspension for injection.

AmorSol technology produces an amorphous, meta-stable solid dispersion of a drug suitable for improving dissolution kinetics of orally administered drugs. As a drug dissolves from an amorphous solid dispersion, a supersaturated solution often forms, providing a driving force for improving bioavailability.

The company has used its EmulSol technology to formulate its lead pipeline product, ASD-002, a novel injectable form of the anti-thrombotic drug clopidogrel. Clopidogrel has an indication for Acute Coronary Syndrome, however, the commercially available dosage forms are tablets in 300 and 75 mg strengths, which Mr. Harmon says are not ideal for administration in an emergency setting. Also, when delivered orally, there is a significant delay in the time required for the medicine to become effective. The barrier to developing injectable clopidogrel is its solubility and chemical stability properties. Clopidogrel is a weak base with a pKa of 4.5, and it is practically insoluble in water at neutral pH. Moreover, the free-base form is chemically unstable and undergoes hydrolysis, oxidation, and chiral conversion. Mr. Harmon says that Ascendia has demonstrated physical and chemical stability of a 200 nm nano-emulsion form of clopidogrel. Furthermore, the solubility of clopidogrel in the oil phase is 20 mg/ml, a four-order of magnitude increase over the aqueous solubility of the free base at plasma pH.

CordenPharma—A QbD Approach to Identify Critical Attributes

CordenPharma International (CPI) is a full-service CDMO offering pharmaceutical services organized

CordenPharma High Containment Development

under six technology platforms including highly potent, oncology, peptides/lipids/carbohydrates, injectables, small molecules, and antibiotics.

Its formulation development and manufacturing expertise centers on oral formulations, for tablets, capsules, and a combination of the two. Oral formulation capabilities complement expertise in sterile drug products that range from liquids and emulsions to lyophilized and powder-filled products, explains Dr. Roberto Margarita, Director, Global Antibiotics & Oncology Platform, CPI.

CordenPharma's development studies are performed according to the Quality by Design (QbD) approach based on scientific understanding. "We use this methodology to construct the best quality target profile and to identify and confirm the quality critical attributes. In so doing, we deliver process knowledge at multiple levels to achieve product quality, characteristics definition, and process parameters for our customers," says Dr. Margarita.

CPI is helping one customer bring a glycol-free formulation of a lyophilized oncology product to market, which will improve the safety of the drug and its applicability to patients who can't access it due to undesired side effects, says Dr. Margarita.

Dr. Reddy's high-speed commercial packaging facility

Dr. Reddy's Custom Pharmaceutical Services—Leveraging Multidisciplinary Sciences for Customized Pharmaceutical Products

Dr. Reddy's Custom Pharmaceutical Services (CPS) focuses on accelerating project delivery, helping pharma progress their pipeline of products and speed their route to market. CPS offers drug substance and drug product services, from laboratory scale to commercial supply.

Praveen Raheja, Associate Director Formulations, Dr. Reddy's Custom Pharmaceutical Services (CPS), Hyderabad, says that outsourcing has evolved from its traditional objectives of cost-effectiveness and time benefits to a more futuristic approach. This new approach sees an external R&D or manufacturing service provider as a competent partner who would accelerate the product development, approval and marketing process with good technical, strategic, and infrastructure support. "Today, most of our clients are associated with us for more than one project. Consequently, these companies have found CPS to be a flexible partner, which brings value to the product not just through reducing costs and shortening timelines, but also through experience, expertise, risk mitigation, and the delivery of quality services. We offer contract development and manufacturing services, including clinical and commercial manufacturing of intermediates, APIs, and finished dosage forms. Activated mPEGs, chirals, HPAPIs, and steroids form the backbone of our technology platforms."

In the area of drug product, Dr. Reddy's offers preformulation services, development of conventional solid oral dosage forms, modified drug delivery systems, combination products with multiple incompatible actives, combination products with sequential release, gastro retentive dosage forms, taste masking, and stabilization. "We offer services to help our partners get their products to

market more quickly, without compromising on quality," says Mr. Raheja. "With our capabilities and expertise we are able to speed up the time it takes to get a product to market, reduce costs and deliver the expected quality attributes right through the product life cycle, from early-phase clinical supplies through to commercialization."

He adds that there has been a focus on developing unique combination products for synergistic action and a better therapeutic outcome, especially in chronic therapy areas like diabetes and pain management. In one example, a combination of three APIs in a transparent capsule (capsule and tablet in capsule) was developed by altering solubility. A co-solvent approach and complexation entrapment techniques using beta-cyclodextrin was taken. This provided a novel combination therapy for a differentiated combination and an aesthetically elegant formulation.

For another customer, the use of polymer combinations was adopted to develop an ophthalmic wafer, which gelled in contact with lachrymal fluids to provide a sustained local action for an anti-cancer agent. The benefits were increased bioavailability, leading to a reduction in dose compared to a conventional eye drop, he says.

Gateway Analytical—Total Particle Characterization Services to Support Bioequivalence

The success of an ANDA submission depends on the ability of the manufacturer to prove that the test product is qualitatively and quantitatively the same as the reference product. This equivalency not only relates to the formulation, but to the device used to dispense the drug. Proving qualitative and quantitative equivalency is especially challenging for combination inhalable therapeutic drug products containing two active ingredients. Accurate and precise data on the Particle Size Distribution (PSD) of the individual ingredients and possible contaminants is required for drug product submission in the US and Europe.

Due to the lack of specific guidance from the FDA with regards to the ANDA submission, however, there are few attempts by generic manufacturers to develop bioequivalent formulations of orally inhaled and nasal drug products, claims Dr. Oksana Olkhovyk, Senior Scientist, Gateway Analytical. Differences in the PSD for each of the active ingredients and amount/size/nature of foreign particulates present will almost certainly result in differences in deposition; this may prevent co-deposition of active ingredients in the correct ratio in the lungs and/or cause device failure. Even if the drugs' PSD's were identical, final formulations may be affected by contaminations, therefore it is valuable to understand the formulation itself, along with any foreign materials that may be present.

Gateway Analytical offers a variety of analytical services for particulate analysis of pharmaceutical products and devices. For instance, with the ability to detect the smallest spectral shifts, Raman spectroscopy is sensitive enough to identify polymorphic forms of the drugs; this is important because different polymorphs/hydrates have different

Automated Particle Characterization utilizing the Single Particle Explorer SPE-Is Raman.ID + Metal.ID System (Gateway Analytical)

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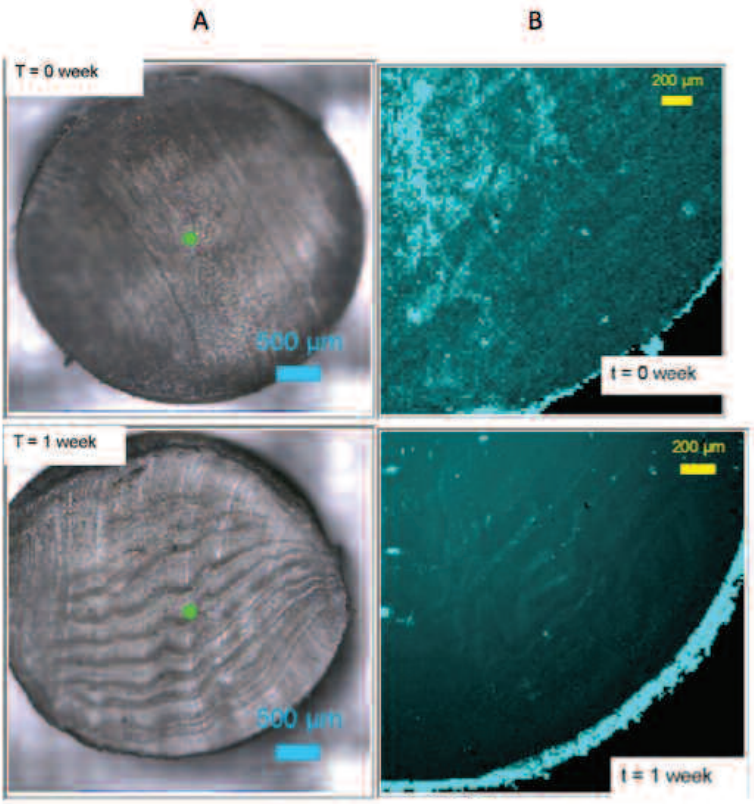

Using Raman Microscopy, the migration of Dapivirine from the core to the surface of this polymeric device is captured from To (Top B) to T1week (Bottom B). The drug is evenly dispersed within the polymer at the time of manufacture and, as the image (Bottom B) demonstrates, has migrated to the surface of the polymeric device where it is being released into the dissolution media. (®Particle Sciences, Inc in conjunction with HORIBA Sciences and The International Partnership for Microbicides.)

dissolution rates, solubility. The presence of particular polymorphs of the API or specific grade of the lactose (which is used as a carrier) in the formulation can affect product bioavailability.

Gateway Analytical offers methods and tests to evaluate external factors that may cause imbalances or variation on deposition and efficacy of the product, due to the contribution of the excipients used. Sourcing good quality active ingredients and excipients to assure drug/excipients compatibility is another challenging task for manufacturers.

"We can help create or adopt customer specific protocols, based on unique product needs," says Dr. Olkhovyk. "Our spectral reference library is extensive enough to identify varieties of contamination sources with Raman and FTIR spectroscopy; additionally we can identify both organic (IR, Raman), and inorganic (SEM/EDS) materials. Many of our analyses are computer controlled, thus providing throughput for analysis and quick turnaround times for results."

Particle Sciences—Using Data Based on Physicochemical Properties & Target Product Profile

Formulation strategies are at the forefront of virtually all drug product development efforts. For reformulation efforts, using marketed Active Pharmaceutical Ingredients (APIs), the focus is on increased performance with formulation technology playing the central role. New Chemical Entities (NCEs), in part due to the nature of their molecular targets, are most often insoluble and require advanced formulation techniques to be effective. The APIs of interest to Particle Sciences' clients are no exception and are often sparingly water-soluble with a majority of them being BCS II molecules.

The ultimate formulation goal is bioavailability (BA) and solubility is one of the key physicochemical parameters a formulator needs to manipulate in order to achieve the needed BA. In addition to manipulating solubility kinetics, the other areas formulation can impact include tissue permeability (through use of surfactants and lipids), residence time, compliance, duration, metabolism, and clearance. Chemical and physical stability are critical quality attributes that are affected by solubility strategies and need to be

considered in parallel.

"At PSI, we have a number of formulation approaches aimed specifically at addressing solubility issues ranging from *in silico* design to nanoparticles to solid solutions to lipid-based systems such as LyoCells® (PSI proprietary reverse cubic and hexagonal phase nanoparticulate delivery system)," says Robert W. Lee, PhD, Particle Sciences. "For long-term delivery, our drug-eluting device or depot formulation work can be used. When large and small molecules are being co-formulated our SATx™ platform is often utilized."

Once the API is well characterized, high probability formulation approaches are investigated. Again, the right approach is one that aims to maximize BA in a stable and scalable system. "We often encounter molecules with enzymatic and/or hydrolytic lability, so this needs to be addressed during formulation," says Mark Mitchnick, MD, Particle Sciences. "It is a question of which technology do the API's characteristics drive one towards. For instance, a heat stable, highly potent compound with a positive logP naturally drives towards hot-melt extrusion. If you are developing a relatively labile molecule with good lipid solubility, this would warrant looking at LyoCells, and a classic BCS II molecule should be evaluated for its amenability to nanoparticulate suspensions, either crystalline or stabilized amorphous. Our role at PSI is to find the right approach for the client's specific compound and delivery objective."

Pharmatek's Manufacturing Engineer, Quang Nguyen, confirms equipment settings prior to a fluid bed processing production.

Pharmatek—A Data-Driven Approach to Preformulation

Pharmatek specializes in early-phase clinical drug product development and cGMP manufacturing. Focused on a data-driven approach, Pharmatek provides formulation and dosage-form support, process development and optimization, and manufactures clinical-trial materials. Its formulations include solubilization technologies, such as spray-dried dispersions, micronization, complexation, and lipid delivery.

"Preceding formulation development activities, Pharmatek's clients are encouraged to gain insight from existing data," advises Bryan Knox, Senior Director, Pharmaceutics, Pharmatek. "Comparative pharmacokinetics from various pre-clinical dosage forms, for example, can help determine the potential

"The formulation development process starts with trying to identify which excipients will be optimal for use with the API of interest. Consider which excipients are going to be compatible with the API. A quick glance at the molecular structure may immediately exclude some excipients due to known interactions between certain functional groups."
– Paul Skultety, PhD, Vice President, Pharmaceutical Development Services, Xcelience.

usefulness of bioavailability-enhancement techniques. Leveraging these pre-clinical data, preformulation study design and excipient candidate selection can be directed toward supporting several viable dosage forms."

Preformulation activities include solubility screening and physical characterization studies, such as particle-size distribution, morphology, powder density, and compressibility. These data help identify effective co-solvents, particle-matched dry-blend fillers, and potential process-ability challenges. The excipient selection process is based on knowledge of how a given compound behaves in "stressed" environmental conditions, in addition to its pharmacokinetic tendencies. Excipient screening can then be used to either eliminate or hone in on particular excipients from each excipient class based upon the propensity of each to degrade or stabilize the active ingredient. Leading excipient candidates are then incorporated into several formulations, ranging from simple to increasingly complex dosage forms, for head-to-head *in vitro* and *in vivo* performance comparison. To address potential bioavailability concerns, Pharmatek's capabilities include micronization, spray drying, complexation, emulsification, melt granulation, and fluid-bed (Wurster) coating.

Based on performance and anticipated manufacturability, the most promising formulation candidates are produced at lab-scale to be placed on prototype stability for incremental testing. The results generated are critical to the clinical formulation selection. Once the final formulation is determined, manufacturing process optimization and cGMP manufacturing preparations are initiated.

An example of Pharmatek's data-driven approach involved helping a customer identify the best path forward for first-in-man clinical trials. Early pre-clinical studies showed that bioavailability enhancement techniques may be beneficial due to the poor aqueous solubility and high melting point of the active ingredient. With the objective of quickly identifying potential formulation platforms for pharmacokinetic evaluation, excipients were selected and screened to support several possible dosage forms, including PIC, surfactant-containing dry blend, melt granulation, amorphous dispersions, and a GRAS-listed organic solution. Discriminating dissolution

methodology was developed and utilized to narrow the list of formulation candidates, and the remaining formulations were evaluated *in* vivo. *In-vivo* results confirmed the *in-vitro* dissolution findings, demonstrating that an amorphous dispersion presentation enhanced bioavailability of the compound.

Relative to a neat powder-in-capsule presentation, the amorphous dispersion showed a significant improvement in bioavailability (80% BA with amorphous dispersion versus 30% BA with the PIC). However, when *in vivo* results were considered along with the client's business goals and timeline, it was determined that the simplest technique, PIC, would be taken forward in Phase I due to its acceptable PK profile.

"This strategy provided adequate exposure while reducing development time and the upfront investment that would be required for a more complex manufacturing process," says Mr. Knox. "Pharmatek's data-driven approach enabled informed early-phase strategic decisions, and formed the basis for on-going development of the spray dried dosage form for Phase II clinical studies."

Xcelience—Four Key Steps to Formulation Development

Prior to starting a formulation development project, the physical and chemical characteristics of the API should be thoroughly evaluated. This evaluation should include analyses such as determination of pH solubility profile, potential for polymorphs, pKa, and particle shape/size. If the API is poorly soluble, there are several options for assisting the viability of developing a drug product. If it is early enough in the development cycle, a salt form might be selected that has better solubility characteristics. Creating an amorphous form of the API can also be considered. The API can be micronized to increase surface area to help in dissolution of the compound. The appropriate excipients can be selected to provide a more soluble formulation of the API. Xcelience can provide the necessary services to evaluate the API. The formulation development process starts with trying to identify which excipients will be optimal for use with the API of interest, explains Paul Skultety, PhD, Vice President, Pharmaceutical Development Services at Xcelience. There are several main items of consideration. First is what excipients are going to be compatible with the API. A quick glance at the molecular structure may immediately exclude some excipients due to known interactions between certain functional groups. Another possible concern may be the amount of moisture present in some excipients or the potential for the excipient to modify the pH of the formulation. Second, consider the type of formulation and the route of administration. If it is a liquid, then preservatives and potential pH modifiers should be considered. If the drug product will be a controlled release tablet, then consider looking at appropriate polymers that will be selected based on the type of release mechanism used.

Third, consider the manufacturing process. Fourth, the solubility and possible dosage strength of the API should be evaluated. If the solubility is low, then one must determine what possible excipients can increase the solubility.

"At Xcelience we will start the formulation development work with as simple of process as we think will be successful; this is often a direct blend/compression," says Dr. Skultety. Depending on the desired formulation, Xcelience can develop anything from an instant release tablet to a controlled release bead.

As examples of its formulation approaches, Dr. Skultety explains how Xcelience developed a pediatric liquid formulation using cyclodextrins. This approach improved the solubility enough to provide the client with a stable solution at the desired concentration. Another client asked for a combination dosage form. The two APIs were found to be unstable if they were in direct contact. The solution was to provide each of the APIs as separate, coated beads. The two beads could then be blended together in a stable dosage form. ◆

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NANOSCALE PARTICLES

VAULT: A Novel Nanofrontier in Drug Delivery

By: Jayvadan K. Patel, PhD, Anita Patel, PhD, and Vibha Champavat, MPharm

ABSTRACT

Novel nanoscale particles (Vaults) as first described in 1986, exist in the multiples of thousands in most eukaryotic cells. Having an intricate shape composed of multiple curves evocative of cathedral vaults, therefore their name. The size, shape, eloquent assemblage, and molecular composition of vaults support their potential to be engineered into a delivery system for a broad range of therapeutics. Numerous strategies are under development to encapsulate chemically active small molecules, nucleic acids, immune modulators, and drugs into the vault particle. Vault nanocapsules also have the potential of being bioengineered to allow their use in a wide variety of biological applications, including drug delivery.

INTRODUCTION

Vaults are novel nanoscale particles that exist in most eukaryotic cells. They have an intricate shape composed of multiple arches reminiscent of cathedral vaults, hence their name. Vault size (~74 x 42 x 42 nm), shape, molecular composition, and facile assembly suggest they have the potential to be engineered to deliver a wide variety of therapeutics.[1]

Vaults were first seen while Rome et al were separating subpopulations of clathrin-coated vesicles using a preparative agarose gel electrophoresis technique and monitoring the fractions for purity using negative staining and transmission electron microscopy (TEM). Vaults were only visualized after isolation and negative staining, a method that reveals the structure of an object by exclusion of stain.[2]

STRUCTURE OF VAULTS

Determinations of mass by scanning transmission electron microscopy (STEM) confirmed that unstained specimens possess a two-fold symmetry; they contain two distinct and apparently equal centers of mass. The average mass of a single vault is 12,900 ± 1,000 kDa, a value consistent with the sedimentation behavior of vault particles on velocity sucrose gradients (approximately 150 S).[3]

COMPOSITION OF NATURALLY OCCURRING VAULTS

Because vaults were initially observed as contaminants in preparations of coated vesicles, numerous attempts were made to demonstrate a membrane within these particles. No vesicles could be observed by EM after removal of proteins by treatment with proteinase K or dissociation with 4.0 M urea; neither were phospholipids detected by biochemical techniques. Finally, these particles were found to be immunochemically distinct from coated vesicles. Thus, it appears that vaults are composed entirely of protein and RNA.[2]

DISTRIBUTION OF VAULTS

Vaults are highly conserved among vertebrate species and have been purified from the liver of chicken, cow, bullfrog (Rana catesbeiana), and the South African clawed frog Xenopus laevis, in addition to rat. However, vault concentration within different rat cell types shows marked heterogeneity.

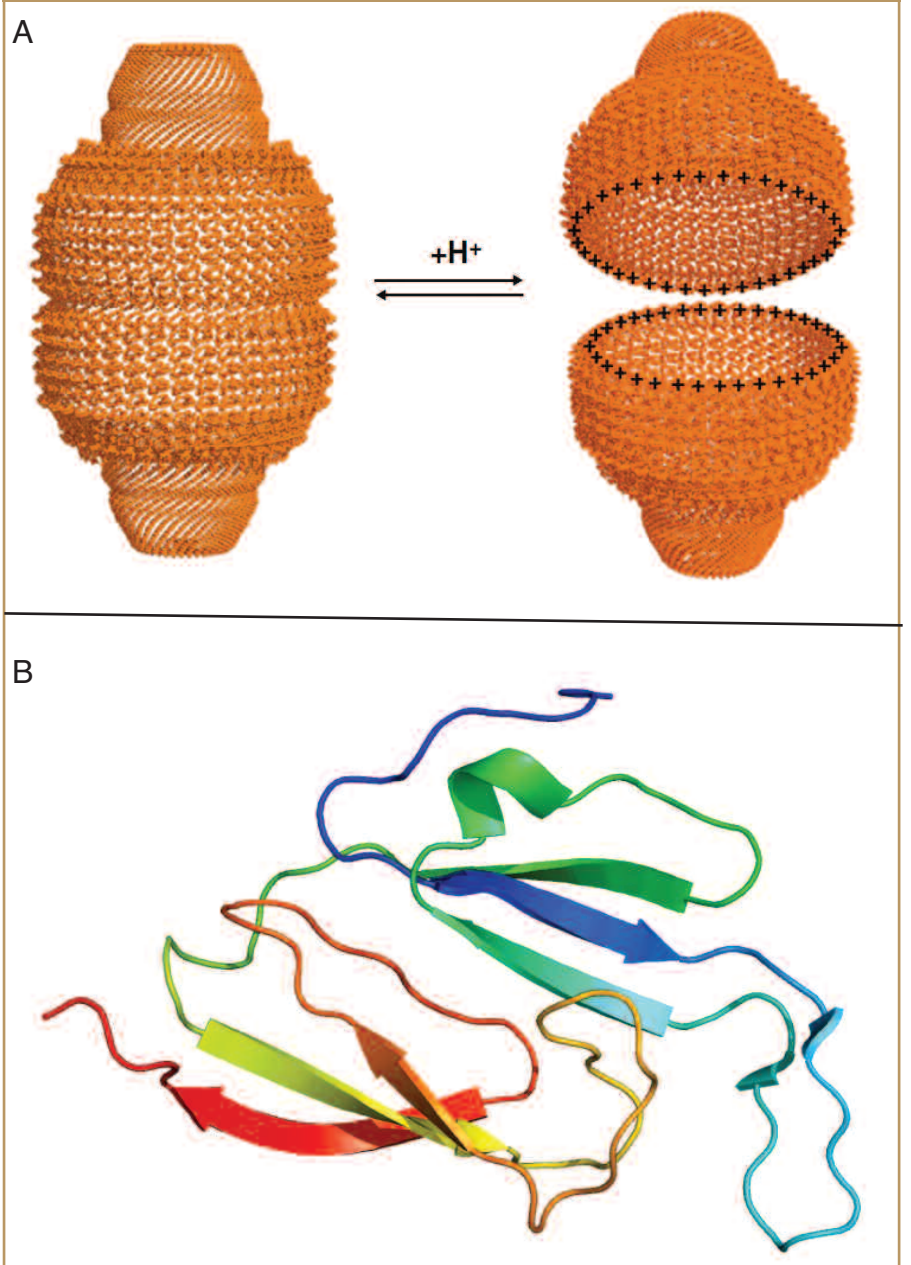
Although vaults present in all the cells, they are most abundant in macrophages and epithelial cells. Vault enrichment in microglia (brain macrophages) relative to other cells of the brain, allowed examination of the developmental profile of microglia in rat brain and provided new insights regarding the origin of these cells.[4]

VAULT OPENING: THE MECHANISM

The structure of the seven N-terminal repeat domains (R1–R7) that conform the vault waist is available at 2.1 Å resolution and accurately describes the interactions governing the association of the two vault halves. Analysis of contacts at the vault midsection reveals important charge complementarily at the interface of interaction between the two vault halves. R1-R1 contacts involve two R1 subunits in each half vault moiety. Among these contacts, the salt bridge formed between the strictly conserved residues Asp39 and Arg42 seems to be a key interaction.

Additional charged amino acids (Glu4, Glu5, and Arg37) and a cluster of hydrophobic residues (Ala6, Ile7, and Ile36), contacting through the two-fold axis of the particle, also contribute to the contact surface (Figure 1A). The observed interactions led to the proposal of a reversible mechanism of dissociation of the vault particle induced by a pH change. The low pH would facilitate disassembly of the particle by positive charge repulsion due to the protonation of the acidic residues at the interface. At higher pH, the aspartate and glutamate residues would recover their acidic state and re-establish the electrostatic interactions, permiting the re-association between the two vault halves. Afterward, the hydrophobic interactions would contribute to stabilize the locked conformation of the particle (Figure 1B).[5]

FIGURE 1A&B



(A) R1-R1 interactions at the half-vault interface. The reference R1 domain (top) contacts two consecutive R1 molecules (bottom) through the molecular two-fold axis (PDB id: 3GNF).
(B) Schematic drawing that shows the mechanisms of vault opening.

POTENTIAL APPLICATIONS OF VAULTS

Reversible pH Lability of Cross-Linked Vault Nanocapsules

The normal presence of vaults in humans at a copy numbers of over 10,000/cell makes them attractive as potential vehicles for drug delivery.

Toward this target, bifunctional amine-reactive reagents are shown to be useful for the reversible cross-linking of recombinant vaults such that they may be closed and opened in a controllable manner.[6] Yu et al studied the cross-linking of vaults with various agents and suggested that vaults may be engineered for reversible encapsulation of materials. For instance, vaults, which are natural residents of human cells, may be designed to carry genes or drugs prior to cross-linking, which will be delivered to a targeted site where the release of carrier molecule could be triggered by cleaving the vault cross-links.

Putative Cellular Functions

The fact that the murine MVP (Major Vault Protein) was found to be orthologous to the earlier described human lung resistance-related protein, known to be over expressed in multiple chemotherapy resistance models, immediately associated vaults with intrinsic drug resistance.[7] This particle has also been implicated in the regulation of several cellular processes, including signal transmission, transport mechanisms, and immune responses.

The majority of reports agree that, at least in mammalian cells, vaults are predominantly (>90%) localized in the cytoplasm. Additionally, a subgroup of vaults was repeatedly reported to be detected in the nuclear envelope, suggesting that, at least occasionally, vaults play a role within the nuclear pore complex.[8]

Targeting of the Vault Nanoparticles to Specific Cell Surface Receptors

Kickhoefer et al carried out the study to target vault nanoparticles to specific cell surface receptors. These studies demonstrated that recombinant vaults assembled from MVPs containing C-terminal peptide extensions show these tags at the top and bottom of the vault on the outside of the particle, and that can be used to specifically bind the modified vaults to epithelial cancer cells (A431) via the epidermal growth factor receptor (EGFR), either directly (EGF modified vaults) or as mediated by a monoclonal antibody (anti-EGFR) bound to recombinant vaults containing the IgG-binding peptide. The aptitude to target vaults to specific cells represents an essential advance toward using recombinant vaults as delivery vehicles.[9]

Vaults Engineered for Nanobiotechnology

Ideally, pharmaceutical drug carriers should be biocompatible, should demonstrate prolonged circulation and protection of the encapsulated drug, and accumulate in the required pathological sites in the body. Various drug delivery and drug-targeting systems are currently under development. Their most important shortcomings include limited size, stability, or their inability to be targeted to specific tissues. Other protein assemblies, like viruses, have the major restriction of immunogenicity, limiting their applicability as drug delivery vehicles. Vaults, as naturally occurring particles, are non-immunogenic. This fact, coupled with their large size and the potential to encompass hundreds of proteins, have led to the suggestion that they could be utilized as natural nanocapsules for nucleic acid, drug, or protein delivery.[10]

Vault Nanocapsules With Fluorescent & Enzymatic Properties

Expression of MVP in insect cells, by the baculovirus expression system, exposed that this protein is only capable of directing the formation of recombinant vault particles with a structure similar to endogenous particles.[11] Vaults can be engineered and expressed using a baculovirus expression system, and heterologous proteins can be encapsulated inside of these recombinant particles using a protein-targeting domain termed INT for vault INTeraction. Several heterologous proteins have been fused to the INT domain (eg, fluorescent and enzymatic proteins), and these fusion proteins when packaged into the recombinant vaults preserve their native characteristics, and consequently confer new vault properties.

Recombinant Major Vault Protein Targeted to Neuritic Tips of PC12 Cells

Herrmann et al investigated the targeting of recombinant major vault protein to neuritic tips of PC 12 cells grown in dimethyl ether supplemented with horse serum (10%) and fetal calf serum (FCS) (5%) at 37°C in the presence of 5% CO_2. CHO and PC12 cells transfection with a cDNA encoding the rat major vault protein containing a vesicular stomatitis virus glycoprotein epitope tag demonstrates that the recombinant protein is sorted into vault particles and targeted like endogenous MVPs.[12]

In neuritic extensions of distinguished PC12 cells, there is a nearly complete overlap of the distribution of vaults and microtubules. A prominent co-localization of vaults with filamentous actin can be seen in the tips of neurites. Furthermore,

in NGF-treated PC12 cells the location of vaults partially coincides with vesicular markers. Inside the terminal tips of neurites, vaults are located near secretory organelles. Their observations suggest that the vault particles are transported along cytoskeletal-based cellular tracks.[12]

FUTURE PROSPECTS

Nanoparticles called vaults, which are naturally present in human cells, may prove to be viable platforms for drug delivery. The fact that vaults can reversibly separate into two symmetrical halves has also been the focus of intense research. The possibility of closing and opening vaults in a controllable manner would be an attractive goal. A number of amine-reactive cross-linkers have been tested for their capacity to increase vault stability in order to prolong the half-life of the encapsulated drug.[6] Another significant improvement would be to employ a combination of modified vaults with a variety of stabilities for the delivery of a specific drug. ◆

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BIOGRAPHIES

Dr. Jayvadan K. Patel is a Professor of Pharmaceutics and Principal, Nootan Pharmacy College, Visnagar-384315, Gujarat, India. He has more than 18 years of academic and research experience, has published more than 225 research and review papers in international and national journals, and has presented more than 150 research papers at various international and national conferences as author and coauthor. He has guided 26 PhD and 75 MPharm students for dissertation work. Dr. Patel is recipient of Fast Track Young Scientists Award by SERB (Department of Science and Technology), Government of India, New Delhi, recipient of a research grant under Research Promotion Scheme (Rs. 19.50 Lac) by AICTE, New Delhi, and recipient of the very prestigious award by APTI (Young Pharmacy Teachers of the Year-2014). He holds one patent, is serving as a peer reviewer for 26 well-reputed journals, and is serving as an Associate Editor/Member Editorial Board of 13 journals. Dr. Patel is also the recipient of Outstanding Young Indians-2010 award by JCI India and Young Pharmacist Award-2013 by Indian Pharmacy Graduate's Association.

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FORMULATION DEVELOPMENT

A QbD Approach to Develop Extended Release Softgels

By: Yunhua Hu, PhD, and Qi Fang, PhD

INTRODUCTION

Soft gelatin capsules (softgels) continue to be the oral solid dosage form preferred by consumers.[1] Understandably, as they are easy to swallow and digest, effectively mask unpleasant tastes and smells, and have a pleasing appearance. Softgels also offer formulation and marketing benefits. They can accommodate a wide variety of compounds filled as liquids, solids, semi-solids, suspensions, or emulsions. They can also address a broad range of formulation challenges, such as improving the absorption and bioavailability of poorly water-soluble APIs. Softgels are particularly well suited for formulating low melting point APIs, which require additional processes for tablet forms. They also allow low- and ultra-low-dose precision for highly potent compounds. To extend product lifecycle with added patent protection, softgels can be developed in various dosage forms, such as chewables, controlled release, and softgels from non-animal materials.

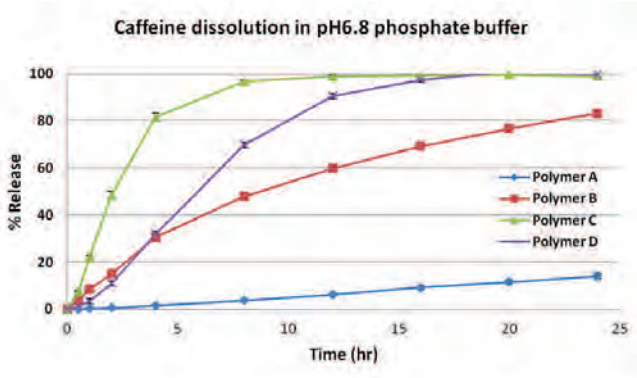
Developing drug delivery systems with a targeted drug-release profile can be challenging, especially with dosages that require timed release, high dose, limited volume, and abuse deterrence simultaneously. Wisely choosing and efficiently modulating a release system for the aforementioned purpose is a head-scratching task that requires deep understanding of formulation science and softgel expertise. Formulation scientists must know the most efficient and effective ways to develop the softgel fill medicine and capsule shell to ensure quality and mitigate risk, saving formulation time and costs. Following Quality by Design (QbD) is the most appropriate approach for every aspect of pharmaceutical development.

This paper reviews the fundamentals and technologies for formulating sustained-release softgel capsules, presents a study by Banner Life Sciences to develop an extended-release matrix of softgel capsule fill that has the aforementioned characteristics for highly soluble drugs, and demonstrates the general approach of applying QbD methodology to extended-release softgel product development.

ACHIEVING CONTROLLED RELEASE SOFTGELS

For many medical conditions, such as metabolic disorder, allergy, cancer, autoimmune, and neurodegenerative diseases, it is desirable for the drug to reach its targeted site of action at a therapeutically effective level and for the drug concentration to remain at that level over a sufficient period of time.[2] These

FIGURE 1



Dissolution of caffeine from the extended-release matrices with different polymers in pH 6.8 phosphate buffer at 37°C.

requirements can be met by applying controlled-release technologies to the oral solid dosage form through matrix swelling, erosion, or degradation, or through diffusion via membrane, or through osmotic pressure.

With controlled-release technologies, the drug release is based on the mechanism of drug dissolution and diffusion away from compressed matrices of bounded particles, such as thin-layer coated, granulated, microencapsulated, and active-loaded complexes, or from a sealed reservoir in semipermeable membranes. The balance between the binding forces of the active in the excipient matrix and the tendency for disintegration or dissolution of both the matrix and the drug molecules dictates the drug-release profile.

For developing extended-release softgel products for water-soluble drugs (especially Biopharmaceutical Classification System 1), increasing the binding force to retain the active in its matrix and to avoid initial burst is imperative. On the other hand, for poorly water-soluble drugs, enhancing drug dissolution, keeping the drug in a highly dispersed state, and avoiding "crash" at the release site is the primary approach.

A variety of controlled-release technologies are applied to or are being developed for softgels. Time-delayed release was achieved on the shell in the forms of an enteric coating on the shell or an integrated enteric shell (EnteriCare®). An alternative form is the EnteriCare softlet, where a tablet is enrobed in an integrated enteric coating. For other modified-release profiles, such as extended release, control mechanisms are built mainly in the fill matrix.

Options for fill matrix configurations include, but are not limited to, matrices of either lipophilic or hydrophilic excipients with APIs simply solubilized or dispersed into them; matrices that are capable of responding to external signals to release drug; suspensions of naked or coated API microcrystals, granules, microspheres, freeze-dried powders, or multi-particulates; and dual-controlled-release matrix systems that combine a matrix or multiple matrices with particulates (Versatrol™).

Building control mechanisms in both shell and fill of a softgel elevates the configurations to another level. As an example, a system combining time-delayed release and an environmentally responsive matrix is being developed for colon-targeting drug delivery. Multi-phase release profiles could be accomplished in the form of a Gelpot, where a tablet (single or multiple), capsule (single or multiple), or both are encapsulated in a larger softgel, or in the form of Combule (multiple chambers like a peanut shape). In these ways, medicines that are not compatible with one another could be combined in one softgel dosage form as well.

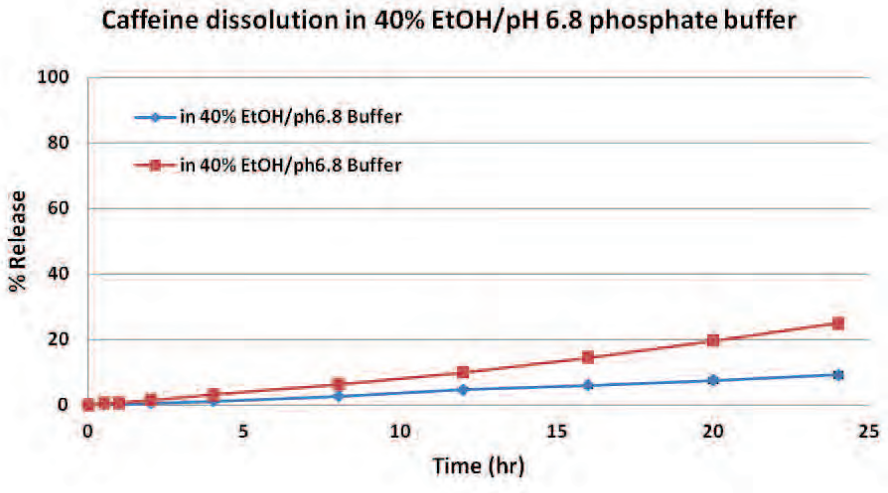
From the dosage requirement

TABLE 1

QTPP Elements	Target	Results
Dosage form	Modified SGC dosage form	Extended release SGC
Dosage strength	Match selected RLD strength	Up to 800 mg
Loading capacity	Up to 50%	Up to 50%-55%
Extended release	>12hrs, up to 24 hrs	16 hrs sustained release of model drug
Compatibility with API	Compatible	Compatible
pH dependency	Independent	Independent
Physical form of the matrix	Suspension on heat, solid or semisolid at RT	Temperature dependent, phase transition at <50°C
Abuse deterrence	Low alcohol extraction rate	<10% over 4 hrs extraction
Stability	Matrix stable; drug composition stable for 2 yrs	Study ongoing. Potentially match same shelf-life of selected RLD
Process feasibility	Available equipment and processes	Minor equipment modification is required
Versatility	Applicable to as many drugs as possible	Fill matrix for SGC ready for mixing with API to form fill composition
Model drug	Caffeine (BCS 1)	Applicable to BCS 1 and 3

The QTPP, targets, and results of the extended release matrix

FIGURE 2



Dissolution of caffeine from extended-release matrices with different drug-loading rate in 40% ethanol/pH 6.8 phosphate buffer at 37°C.

TABLE 2

Matrix CQAs	Attributes of the Matrix Components			Attributes of the Fill Components		
	Excipients	Lipid Mix	Matrix	Drug Type	Drug Particle Size	Drug Loading Rate
Melting Temp Range	Medium	Medium	Low	Low	Low	Low
Viscosity	Medium	Medium	Medium	Low	Medium	High
Flowability	Low	Low	Low	Low	Medium	High
Adhesion & Cohesion	Low	Low	Medium	Low	Medium	High
Content Uniformity	Low	Low	Medium	Low	Medium	High
Dissolution	High	High	High	Medium	High	High
Abuse Deterrence	High	High	High	Medium	Medium	Medium

Initial risk assessments of the attributes from the matrix and fill components.

perspective, characteristics of extended-release, high dose, limited volume, and abuse deterrence are often required collectively in the release systems for many highly soluble APIs (BCS 1 and 3), such as caffeine, diphenhydramine, metformine, and opioids. Drug-release technology platforms independent to drug molecules or acidity of the release site should be considered so that any given API can be loaded into the platform to achieve the desired release profile. Systematic investigation, including assessments of matrix configurations, functionalities of excipients, compositions of the matrix, and the process, is necessary to achieve such versatile softgel technology platforms.

DEVELOPING AN EXTENDED-RELEASE FORMULATION: A QBD APPROACH

Banner Life Sciences conducted an initial study to develop an extended-release softgel for highly soluble drug molecules with abuse deterrence. The purpose was to determine the best carrier with optimal compositions and process parameters in the most efficient way while mitigating risk.

Banner formulation scientists adopted a QbD approach, a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control based on sound science and quality risk management.[3] Assessing risk prior to manufacturing and taking steps to manage risks and maintain quality throughout all processes can significantly improve quality and efficiency and provide a better understanding of the development process, saving time and costs. The US FDA encourages drug developers and manufacturers to follow the QbD approach, which replaces the industry's traditional approach of quality by test results.

After assessing numerous options for extended release, formulators chose a lipophilic matrix with dispersed API and functional excipients responding to the external conditions as the most promising carrier system to meet the specified requirements. This study demonstrated how the formulators followed the QbD principles in developing the defined extended-release matrix system.

METHODS

Banner formulators adopted the FDA guidance for the development of an extended-release matrix system. First, they defined the quality target product profile (QTPP) of the matrix (Table 1).

In the initial risk assessment, they identified and justified the critical quality attributes (CQAs) and assessed the risks of this matrix system, each component, and each process step in softgel manufacturing (Tables 2 & 3).

Focusing on a few key CQAs, the extended-release profile and the abuse deterrence, formulators conducted a small-scale development program, including multiple Designs of Experiments (DOEs) at bench-top and demonstration scales. The purpose was to modulate the release profile and achieve resistance to alcoholic extraction by selecting excipient candidates, exploring the range of the critical components and determining drug loading rate, while keeping process risks as low as possible.

TABLE 3

Matrix CQAs	Process Steps			
	Matrix Preparation	Fill Compounding	Fill Pumping	Encapsulation
Melting Temp Range	Low	Low	Low	Low
Viscosity	Medium	High	High	High
Flowability	Medium	High	High	High
Adhesion & Cohesion	Medium	High	High	High
Content Uniformity	Medium	High	High	High
Dissolution	Low	Medium	Medium	Medium
Abuse Deterrence	Low	Medium	Medium	Medium

Initial risk assessments of the process in matrix and fill composition preparations and in the encapsulation steps.

TABLE 4

Matrix CQAs	Attributes of the Matrix Components			Attributes of the Fill Components		
	Excipients	Lipid Mix	Matrix	Drug Type	Drug Particle Size	Drug Loading Rate
Melting Temp Range	Low	Low	Low	Low	Low	Low
Viscosity	Low	Low	Low	Low	Medium	Medium
Flowability	Low	Low	Low	Low	Medium	Medium
Adhesion & Cohesion	Low	Low	Low	Low	Medium	Medium
Content Uniformity	Low	Low	Low	Low	Medium	Medium
Dissolution	Low	Low	Low	Medium	Low	Low
Abuse Deterrence	Low	Low	Low	Medium	Low	Low

Updates to the risk assessments of the attributes from the matrix and fill components.

RESULTS

Banner formulators achieved a fill matrix that could load up to 50% of the drug, provide sustained release of a highly soluble model drug for longer than 16 hours, was compatible with the API and independent to the acidity, and resistant to alcoholic extraction (Table 1). Examples of in vitro dissolution of the model molecule, caffeine (BCS Class 1), at controllable-release rates and very low alcoholic extraction rates are shown in Figures 1 & 2, respectively.

Based on the results, the formulators optimized the parameters. Table 4 shows the updated CQAs and risk assessments of the attributes from the matrix and fill components. Table 5 shows the updates to the risk assessments of the process steps. Many risks initially assessed as high were reduced to a medium level.

After gaining knowledge of the extended-release matrix system, the formulators are now shifting their efforts to ongoing optimizations and continuous improvements.

CONCLUSION

Softgels are a flexible, appealing dosage form to consumers, drug developers, and marketers of pharmaceutical products and supplements. They can be developed in a wide variety of forms, sizes, shapes, and colors and encapsulate a broad range of fills, including liquids and high potent substances.

The goal of formulating softgels is to produce safe, consistent, high-quality dosage forms that deliver the drug or supplement as specified and meet quality and regulatory standards. When conducting softgel development studies, formulation scientists should follow the QbD principles to determine the best approach for formulation and processing in addition to applying fundamental knowledge in pharmaceutical sciences and technologies. Our experience demonstrates that following a QbD approach can save developing time and cost and mitigate the risks. ◆

TABLE 5

Matrix CQAs	Process Steps			
	Matrix Preparation	Fill Compounding	Fill Pumping	Encapsulation
Melting Temp Range	Low	Low	Low	Low
Viscosity	Medium	Medium	High	High
Flowability	Medium	Medium	High	High
Adhesion & Cohesion	Medium	Medium	Medium	Medium
Content Uniformity	Medium	Medium	Medium	Medium
Dissolution	Low	Low	Low	Low
Abuse Deterrence	Low	Low	Low	Low

Updates to the risk assessments of the process steps.

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BIOGRAPHIES

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Dr. Qi Fang is Manager, R&D Material Sciences and Technology at Banner Life Sciences. His expertise is in material characterization, pharmaceutical product formulation, drug delivery system development, QbD, and formulation and process optimization.He earned his MS from Kansas State University and his PhD from the University of Nebraska.

Drug Development
EXECUTIVE

Andrew Kaziska, PhD
Health Care Applications Manager
Croda Inc

CRODA

Croda: Understanding & Addressing the Purity Needs of the Pharmaceutical Market

Generally speaking, excipients are the major components of most drug formulations. In the past, pharmaceutical excipients were viewed as inert ingredients, playing an insignificant role in the performance of formulations containing active pharmaceutical ingredients (APIs). This view has changed as pharmaceutical formulators have gained greater awareness of the importance of excipient purity and how it can contribute to the production of more stable drug formulations. *Drug Development & Delivery* recently interviewed Dr. Andrew Kaziska, Health Care Applications Manager at Croda Inc, to discuss the company's Super Refining technology and the benefits of excipient purity in drug formulations.

Q: Can you provide some background information about Croda and what makes this company unique as an excipient supplier?

A: Croda Inc, located in North America, is a wholly owned subsidiary of Croda International Plc, a UK-based manufacturer and worldwide supplier of oleochemicals. Croda offers one of the widest ranges of chemical specialties, surfactants, and high-purity lipids available to the pharmaceutical industry. Our products are manufactured at locations around the world, allowing us to provide consistent, continuous, and local sourcing. Croda's niche in the pharmaceutical market is our Super Refining™ technology that allows us to maximize the purity of an excipient through the removal of polar impurities that may negatively impact a drug formulation. The purification of our excipients through the Super Refining process does not impact the integrity of the excipient, nor does it chemically change the excipient in any way; thereby allowing maximum excipient performance.

"Croda's niche in the pharmaceutical market is our Super Refining technology, which allows us to maximize the purity of an excipient through the removal of polar impurities that may negatively impact drug formulations. We offer an extensive range of Super Refined™ excipients, both polar and non-polar, that can be used across a variety of dosage forms and applications, wherever maximum purity is needed."

Q: What are the primary differences between a compendial excipient and a Croda high-purity excipient?

A: The Super Refining process eliminates or reduces many of the impurities that are normally present in pharmaceutical pharmacopeia-grade excipients. The impurities that are reduced during the Super Refining process can be moisture, residual catalysts, peroxides, and/or aldehydes. Because these impurities can have a significant impact on the integrity of the drug and/or the final formulation, Croda applies tighter internal testing specifications as compared to what is specified in the USP/NF, PhEur, and/or JP/JPE monographs. We guarantee the purity of our Super Refined excipients by meeting these tighter internal specs. As an additional means of ensuring shelf stability, we also pack our Super Refined excipients under nitrogen.

Q: How does purity of an excipient impact a drug formulation?

A: As previously mentioned, the Super Refining process optimizes the purity profile of the excipient by removing or reducing the levels of polar impurities that are normally present in some pharmaceutical-grade excipients. The removal or reduction of these impurities helps maintain cellular homeostasis and reduce cellular irritation, and this contributes to increased patient comfort and compliance. In addition, it helps reduce API interaction in order to maintain both the stability of the drug and the finished formulation, which can ultimately impact the overall performance of the drug product.

Q: In addition to stability benefits, what other benefits does Super Refining provide?

A: Super Refined excipients have been tested to demonstrate improvements in multiple parameters that can lead to positive impacts on the final drug formulation. Because oxidative impurities have been shown to both accelerate degradation of drug actives and destabilize emulsions, Croda has tested for improved oxidative stability using various test methods on both our polar and non-polar pharmaceutical excipients. In addition, Super Refined excipients have demonstrated lower taste impact, which can lead to improved taste profiles of oral formulations. This can be especially ideal for infant and child Rx and OTC drug products. Other benefits of Super Refined excipients include the reduction of cellular irritation, which can minimize issues at the site of application or injection of the drug. We run a continuous testing program for our excipient range to demonstrate various benefits to the drug formulator and can provide our customers more information on the various benefits Croda excipients can provide.

Q: In what dosage forms can Super Refined excipients be used?

A: One of Croda's focus areas is to innovate within the compendia. By doing so, we target excipients that are commonly used for various dosage forms that include topical, parenteral, oral, ophthalmic, nasal, ocular, and transdermal dosage routes, just to name a few. We also work closely with our customers to help them address their specific purity issues using our proprietary process. ◆

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Technology & Services Showcase

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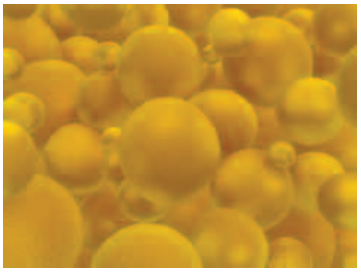

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Technology & Services Showcase

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GASTRORETENTIVE DELIVERY

Box-Behnken-Designed Gastroretentive Floating Tablets of Famotidine

By: Mohit Kumar, MPharm, Parijat Pandey, and Harish Dureja, PhD

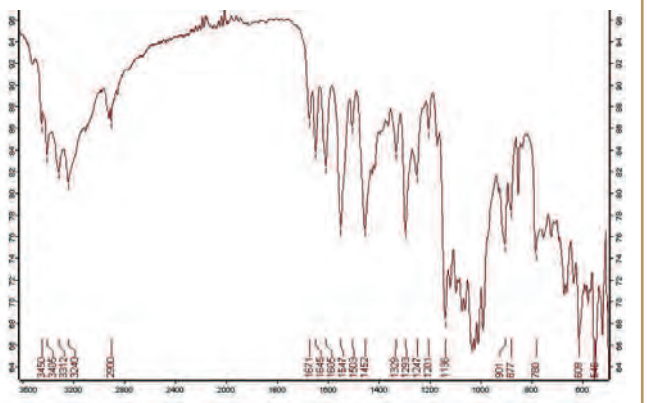
ABSTRACT

The aim of this study was to develop and characterize a single-unit, floating controlled drug delivery system of famotidine hydrochloride using a blend of natural polymer (xanthan gum) and synthetic polymer (hydroxypropyl methylcellulose [HPMC]) along with a gas-generating agent (sodium bicarbonate) by applying Box-Behnken design. Famotidine hydrochloride floating tablets were prepared by direct compression technique. Tablets were evaluated for physical characteristics viz. hardness, swelling index, floating capacity, weight variation, and in vitro drug release. All tablets floated for more than 12 hrs in 0.1 N HCl at 37°C ± 0.5°C, and the in vitro drug release was found to be vary from 71% to 84%. The percent release was maximum at low value of HPMC, medium value of xantham gum, and high value of sodium bicarbonate. A mathematical model was developed to formulate floating tablets of famotidine. The data fitting to Koremeyer-Peppas equation revealed that the release mechanism from the dosage form followed the non-fickian transport. These tablets will enhance patient compliance and improve patient's quality of life.

INTRODUCTION

Residence time of an administrated dosage form in the stomach is generally short due to rapid gastric emptying, and thereby frequency of administration has to be increased for the desired pharmacological action.[1] Fluids taken at body temperature leave the stomach faster than colder or warmer fluids. Fast gastrointestinal transit could result in incomplete drug release from the device above the absorption zone leading to diminished efficacy of the administered dose. Therapeutic efficiency of drugs that are well absorbed in the stomach, such as amoxicillin, may be increased with a longer residence time. In addition, the bioavailability of drugs that are unstable in the colon, such as ranitidine, as well as drugs that exhibit poor solubility in the intestinal tract, such as diazepam, could be

FIGURE 1



FTIR Spectra of Mixture

TABLE 1

Batch No.	X_1 (mg)	X_2 (mg)	X_3 (mg)
F1	-1 (20)	-1 (20)	0 (20)
F2	+1 (40)	-1 (20)	0 (20)
F3	-1 (20)	+1 (40)	0 (20)
F4	+1 (40)	+1 (40)	0 (20)
F5	-1 (20)	0 (30)	-1 (15)
F6	+1 (40)	0 (30)	-1 (15)
F7	-1 (20)	0 (30)	+1 (25)
F8	+1 (40)	0 (30)	+1 (25)
F9	0 (30)	+1 (40)	+1 (25)
F10	0 (30)	+1 (40)	-1 (15)
F11	0 (30)	-1 (20)	+1 (25)
F12	0 (30)	-1 (20)	-1 (15)
F13	0 (30)	0 (30)	0 (20)
F14	0 (30)	0 (30)	0 (20)
F15	0 (30)	0 (30)	0 (20)
F16	0 (30)	0 (30)	0 (20)
F17	0 (30)	0 (30)	0 (20)

Values in brackets indicates real values

Formulation of FDDS using Box-Behnken Design

increased by extending the drug residence time in the stomach.[2]

The classification of different modes of gastric retention has been listed by Hwang et al and Bardonnet et al.[3,4] An interesting approach to provide floating drug delivery systems is based on the formation of carbon dioxide within the device upon contact with body fluids. Upon contact with acidic aqueous media, carbon dioxide is generated and entrapped within the gelling hydrocolloid, causing the dosage form to swell and hence making the system buoyant.[5]

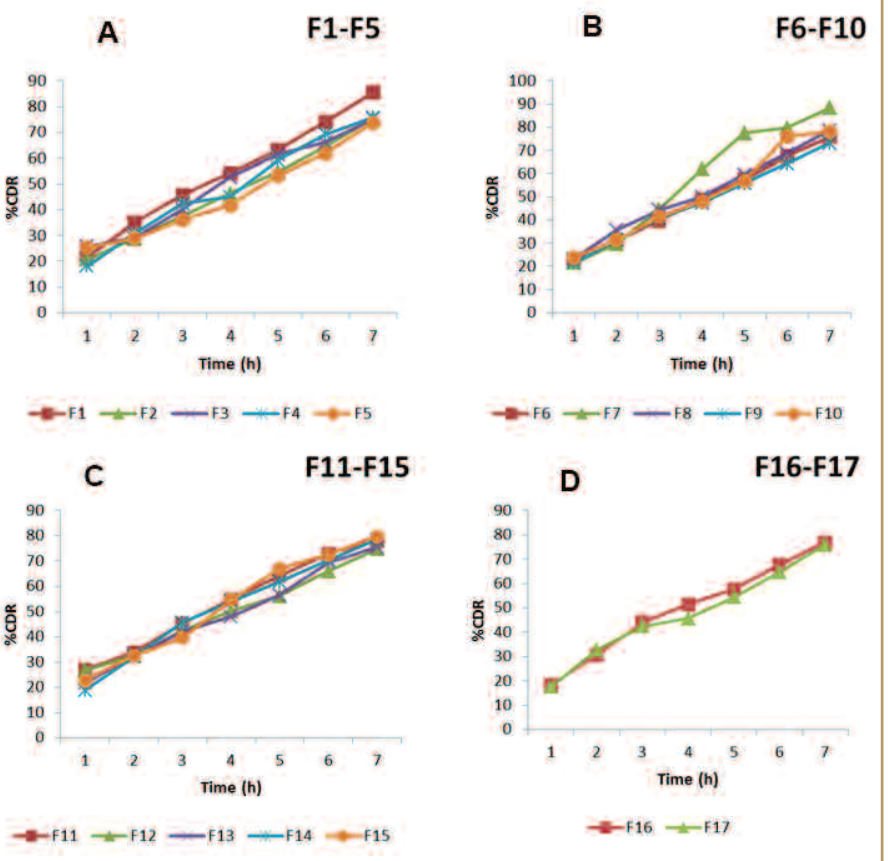
The blends of two different kinds of polymers, ie, natural and synthetic, are being used for floating drug delivery. HPMC is a stable material, although it is hygroscopic after drying. xanthan gum, on the other hand, forms a highly viscous solution in warm water, but alone, it is unable to make tablets that are buoyant enough to make tablets float. However, the combination of these two polymers (along with sodium bicarbonate) provides optimum viscosity and porosity to make the tablets float.

Blends of polysaccharides and cellulose ethers can be used to modulate drug-release profiles not achievable by the use of either type of polymer.[6] HPMC K4M powder is a stable material, although it is hygroscopic after drying. Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage. Chemically, it is cellulose hydroxypropyl methyl ether. Functionally, it is used as coating agent, film-former, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, and viscosity-increasing agent. Xanthan gum is widely used as gelling agent, suspending agent, sustained-release agent, and viscosity-increasing agent.[7] The aim of the work is to develop gastroretentive floating tablets of famotidine hydrochloride applying Box-Behnken design using a blend of natural and synthetic polymers via an effervescence technique. The objective behind the study was to analyse the effect(s) of Conc. of HPMC K4M (X_1), Conc. of Xanthan gum (X_2). and Conc. of Sodium bicarbonate (X_3) on the release of famotidine hydrochloride.

MATERIALS

Famotidine hydrochloride was obtained as a gift sample from Synmedic Laboratories, India. HPMC K4M was supplied by Colorcon Asia Pvt. Ltd., India, as a gift sample. Xanthan gum and sodium bicarbonate were purchased from Loba Chemie, Mumbai, India. All other ingredients were of analytical grade and were used as received.

FIGURE 2 A-D



In Vitro Release Profile of Floating Tablets (batch F1-F17)

TABLE 2

Ingredients	Amount (%)
Famotidine HCl	20%
HPMC K4M	10%-20%
Xanthan Gum	10%-20%
Sodium Bicarbonate	7.5%-12.5%
Lactose	q.s.
Talc	2%
Magnesium Stearate	1%
Total Weight	**200 mg**

Composition of tablets

METHODS

Pre-Compression Studies

Angle of Repose - The weighed powder blend was transferred in the funnel, and the height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the powder blend. The powder blends flow through the funnel freely on to the surface. The diameter of the powder cone was measured, and the angle of repose was calculated using the following equation: $\tan \theta = h/r$. Where h and r are the height and radius of the powder cone.

Bulk Density (BD) & Tapped Density (TD) - The 2 g of powder blend, previously shaken to break any agglomerates formed, was transferred to bulk density apparatus. The initial volume was noted, and the cylinder was tapped until no further change in volume was noted. BD and TD are calculated using the following equations: BD=Weight of the Powder Blend/Untapped Volume of the Packing; TD=Weight of the Powder Blend/Tapped Volume of the Packing.

Compressibility Index - This was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's Index is: Carr's Index (%) = [(TD-BD) x100]/TD.

Box-Behnken Design

Floating tablets of famotidine hydrochloride were formulated according to the Box-Benkhen Design. To evaluate three factors (*n*) at three levels (*k*), the Box-Behnken design consisted of seventeen batches (F1 to F17). Factors with levels and formulations are shown in Table 1.

Preparation of Directly Compressed Tablets

Tablets were prepared using the direct compression technique. Famotidine hydrochloride, HPMC K4M, xanthan gum, sodium bicarbonate, and lactose were weighed (Table 2) and sifted through a No. 40 mesh sieve and mixed well to form a uniform mass. Talc and magnesium stearate were sifted through a No. 60 mesh and added to the blend and mixed well. Final blend was then compressed into tablets using 8 mm round-flat punches. The average total weight of tablet was 200 mg.

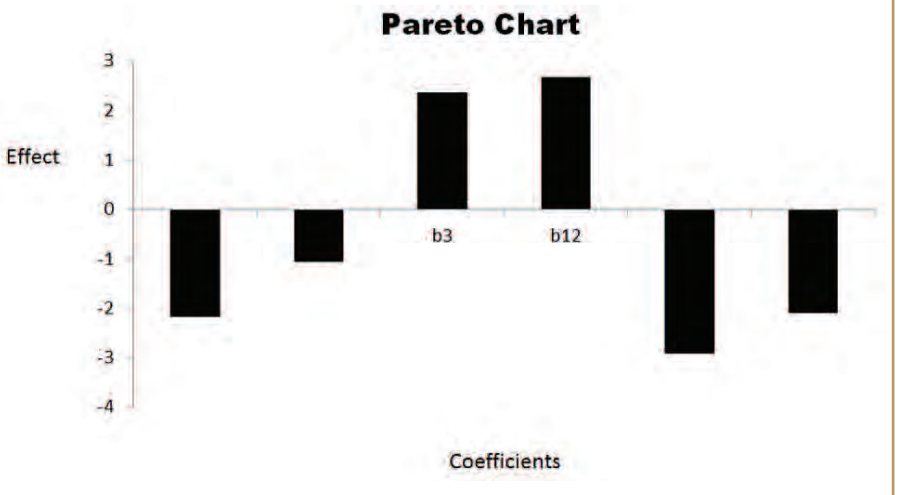
Evaluation of Floating Tablets

Fourier Transform Infra-Red (FTIR) Spectroscopy - It was used to predict any incompatibility or any interaction between the different ingredients in a formulation. FTIR spectra were recorded using Alpha-Brucker, FTIR Spectrophotometer, Brucker, Germany. The spectra were recorded over a range of 400 to 4000 cm^{-1}.

Buoyancy: Floating Lag Time & Floating Time - Floating properties were examined following the procedure reported by Baumgartner et al.[8] Briefly, the tablets took to come to the water surface (floating lag time) and the time the tablets constantly float on the water surface (duration of floating) were evaluated in a dissolution vessel filled with 900 ml of either de-ionized water or 0.1 N HCl (pH 1.2) at a temperature of 37°C ± 0.5°C at a rotation speed of 50 rpm. The measurements were carried out for each series of tablets (n=3).

Determination of Swelling Index - The swelling index (SI) of tablets was

FIGURE 3



Effect Plot

TABLE 3

Batch	Weight Variation (mg)	Friability (%)	Hardness (cm^2)	Floating Lag Time (secs)	Total Floating Time (hrs)	Swelling Index (%)	% Cumulative Drug Release
F1	195.86±3.58	0.72	3.6	30	>12	98.46	83.81±2.51
F2	192.85±9.42	0.66	3.0	20	>14	98.41	73.92±2.08
F3	192.72±4.79	0.79	3.1	145	>11	98.27	73.61±2.31
F4	207.21±5.71	0.75	3.1	62	>12	98.19	73.93±2.60
F5	199.66±7.08	0.79	3.5	45	>11	96.71	71.95±2.63
F6	211.04±3.77	0.76	2.9	20	>11	96.45	79.20±4.8
F7	195.87±4.57	0.65	3.5	48	>12	97.81	84.35±2.75
F8	198.51±2.07	0.62	3.5	57	>12	97.04	76.79±2.56
F9	197.44±4.49	0.71	3.7	103	>12	97.62	71.69±1.96
F10	201.16±5.67	0.80	2.9	32	>11	97.35	79.02±1.43
F11	201.88±2.97	0.69	3.5	54	>12	98.23	79.45±1.87
F12	198.15±4.01	0.74	3.0	24	>10	97.48	76.22±2.19
F13	197.90±3.85	0.69	2.9	44	>13	96.69	73.26±3.07
F14	206.16±2.66	0.59	3.7	63	>12	96.20	77.62±1.07
F15	211.80±5.04	0.58	3.9	40	>12	96.99	77.64±2.96
F16	209.90±5.91	0.63	3.8	46	>14	98.41	78.46±2.14
F17	209.20±4.67	0.62	3.9	44	>13	97.67	77.61±2.26

Physical characterization, swelling index, floating behavior, and cumulative percent release of batches (F1-F17).

determined in 0.1N HCl at room temperature. The swollen weight of the tablet was determined at predefined time intervals. The swelling index was calculated by the following equation 2: Swelling Index = $(W_2\text{-}W_1)*100/W_1$. Where W_1 is the initial weight of tablet, and W_2 is the weight of tablet at time t.[9]

In Vitro Drug Release - In vitro drug release testing from tablets was conducted using a USP Type-II Dissolution Apparatus (Paddle type) (Labindia, India). The dissolution media used for release testing of tablets was 900 ml of 0.1N HCl maintained at 37°C ± 0.5°C and agitated at 50 rpm. Samples of 10 ml were withdrawn at predetermined intervals, were replenished by fresh medium, and analysed using a UV spectrophotometer at 265 nm. All measurements were performed in triplicate. For the release data analysis, cumulative percent drug release versus time (zero-order kinetics), the log cumulative percent drug remaining versus time (first order kinetics), cumulative percent drug release versus the square root of time (Higuchi kinetics), and log cumulative percent drug release versus log time (Korsmeyer–Peppas kinetics) was plotted.

Statistical Analysis of the Data & Validation of the Model - Response surface modelling and evaluation of the quality of fit of the model for the current study were performed employing Design Expert® software (Version 8.0.7.1, Stat-Ease Inc., Minneapolis, MN). The models were generated for all the response variables using multiple linear regression analysis. 3D response plots were constructed using Design-Expert software.[10]

RESULTS & DISCUSSION

Physical Characterization of Powder Blend

The powder blend was evaluated for flow properties. Bulk density of powder blend was found between 0.365 to 0.412 g/cm^3, and Tapped density ranged between 0.419 to 0.486 g/cm^3. Carr's index was found to be in the range of 12.59 to 16.52, indicating good flow. Hausner's ratio values for all the formulations were found to be about 1.2, indicating low interparticle friction. Angle of repose was found to be in the range of 25.40 to 29.40. The values of angle of repose were less than 30, indicating good flowability. These values indicate the prepared blend exhibited good flow properties.

Fourier Transform Infra-Red (FTIR) Spectroscopy

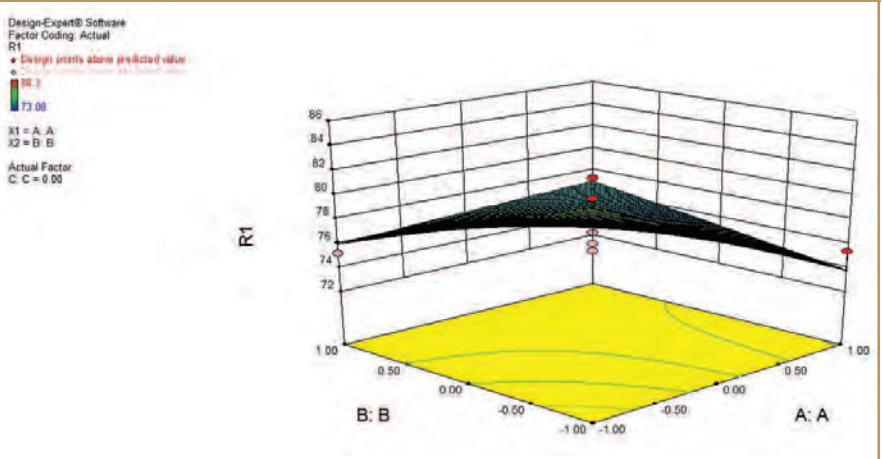
To study the incompatibility between drug and polymer, FTIR spectra of all ingredients were recorded over a range of 500 to 3500 cm^{-1}. The FTIR spectrum of famotidine shows characteristic absorption bands at 3450, 2900, 1645, 1605, 1547, 1293, and 1136 cm^{-1}. FTIR of mixture showed the presence of polymers and drug with no shifting in the peaks, indicating there was no significant interaction between drug and polymers (Figure 1).

Evaluation of Floating Tablets

Weight Variation, Friability & Hardness - Weight variation was within limits as prescribed in USP (7.5%). Hardness of the prepared tablets ranged between 2.9 to 3.9 kg/cm^2. Friability was found to be less than 1%. Results are shown in Table 3.

Floating Behavior - All the formulations consistently floated for more than 12 hrs, while the floating lag time varied from 20 to 103 seconds. Tablet batches with high

FIGURE 4



3D Surface Model Graph

polymer content have large lag time (> 100 secs) compared with the batches having medium polymer content (30 to 50 secs.

Swelling Index - Tablets composed of polymeric matrices build a gel layer around the tablet core upon coming in contact with water. This gel layer governs and affects the drug release. To obtain floating, the balance between swelling and water acceptance must be restored.[11] Swelling index values start decreasing when polymer erosion starts in the medium. Combination of HPMC K4M and xanthan gum resulted in a higher swelling index varying from 96% to 99% (Table 3).

In Vitro Drug Release - The percentage cumulative drug release of all batches of floating tablets (F1- F17) was determined for 7 hrs (using Dissolution Data Solver software), and were found to vary from 71.69% ± 1.96% to 84.35% ± 2.75% (Table 3). Batch F9 shows lowest %CDR (71.69%), whereas batch F7 shows highest %CDR (84.35%). The in vitro release profiles of all the batches (F1-F17) are shown in Figure 2.

ANOVA on Percentage Cumulative Drug Release From Various Formulations - Batch F9 shows lowest %CDR (71.69%), whereas batch F7 shows highest %CDR (84.35%). The percent release was maximum at a low value of HPMC, mid level of xanthan gum, and high levels of sodium bicarbonate. The %CDR increases with increase in amount of sodium bicarbonate to ensure complete effervescence of the tablets. However, low amounts of both polymers are required for increase in %CDR. The effect of various coefficients on %CDR is shown in Figure 3. On the basis of %CDR Floating lag time and swelling index, batch F1 was selected as the optimized batch due to floating lag time of 30 secs and 83.81% CDR. ANOVA was applied on %CDR to study the fitting and significance of model (Table 4). The model developed from multiple linear regression to estimate effect (Y) can be presented mathematically as:

$Y = 77.581 - 2.171\ X_1 - 1.062X_2 + 2.373\ X_3 + 2.680\ X_1\ X_2 - 2.923\ X_1\ X_3 - 2.100\ X_2X_3$. Where Y = Cumulative percent drug release; X_1 = amount of HPMC K4M; X_2 = amount of Xanthan gum and X_3 = amount of sodium bicarbonate.

F-test was carried out to compare the regreession mean square with the residual mean square. The ratio F = 3.57 shows regression to be significant. The estimated model, therefore, may be used as response surface for the %CDR as shown by 3D Surface (Figure 4) and Contour plots (Figure 5) employing Design Expert software (Version 8.0.7.1, Stat-Ease Inc., Minneapolis, MN). The developed model can further be utilized to determine the desired %CDR. Figures 4 and 5 display the 3D surface and contour plot of cumulative percent of drug release as a function of formulation variables. The results show that the in vitro drug release was found to be varying from 71% to 84%. The percent release was maximum at low value of HPMC, medium value of xantham gum, and high value of sodium bicarbonate.

TABLE 4

	Degree of freedom	Sum of squares	Mean square	F	F-significance
Total	16	252.90	-	-	-
Regression	6	172.36	28.73	3.57	0.0373*
Residual	10	80.54	8.05	-	-

* Values of "Prob > F" less than 0.0500 indicate model terms are significant.

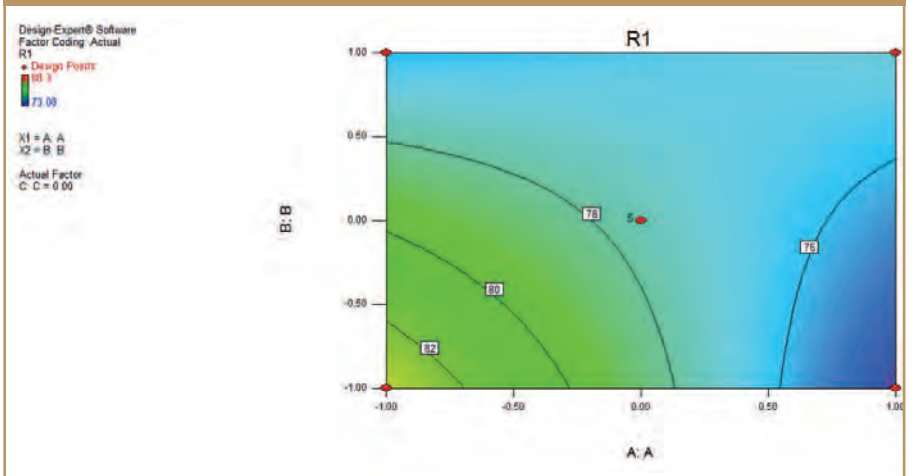
ANOVA of the regression (%CDR)

Kinetics of Drug Release - The dissolution data of batches F1 to F17 was fitted to zero-order, first-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas models using Dissolution Data Solver software. The values of correlation coefficient (R^2) were used to select the most appropriate model. The release profile of the best batch, F1, fitted best to the Korsmeyer-Peppas model (R^2 = 0.9984). Thus, it may be concluded that drug release from gastroretentive famotidine hydrochloride tablets is best explained by the Korsmeyer-Peppas model. Analysis of release data as per Peppas equation showed value of release exponent 0.718, ie, it falls in the range of 0.5 to 0.89, indicating non-fickian (anomalous) diffusion as the drug-release mechanism. Anomalous transport includes both polymer erosion and polymer swelling (relaxation).

CONCLUSION

In the present study, a gastroretentive floating drug delivery system of famotidine hydrochloride was formulated to improve its gastric residence time. The Box-Behnken design was applied to study the effect of formulation variables (amount of HPMC K4M, xanthan gum, and sodium bicarbonate) on drug release, floating, and swelling properties of the tablets of famotidine hydrochloride. All the formulations were characterized for pre-compression parameters, such as angle of repose, bulk and tapped density, and compressibility index. These batches were further characterized for swelling index, buoyancy, hardness, friability, and in vitro dissolution. The data from the release profile were fitted to various mathematical models. The data fitting to the Korsmeyer-Peppas equation revealed that the release mechanism from the dosage form followed the non-fickian transport. Batch F1 was found to be the optimum batch based on the results of buoyancy and %CDR. It can be concluded that the combination of natural and synthetic polymers can be used to formulate the floating tablets. The mathematical model developed in the present study can be used to formulate floating tablets of famotidine with desired buoyancy and percentage release. Retrospectively, this model can be used to design floating tablets of different APIs utilizing the combination of natural and synthetic polymers. A gastroretentive drug delivery system with these floating tablet formulations can reduce dosing frequency, decrease side effects, and improve patient compliance. ◆

FIGURE 5



Contour Plot

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BIOGRAPHIES

Dr. Harish Dureja earned his Master's from Punajbi University, Patiala, and PhD (Gold-Medal) from MD University, Rohtak. He is presently working as Associate Professor in the Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak (India). He has 15 years of experience in teaching and research. He has written 7 invited book chapters/monographs in various publications by international Publishers. He has authored more than 90 publications in various national and international journals of repute. Dr. Dureja has been awarded a project for research on anticancer drug delivery, and his current research interests include in silico ADME modelling, nanoparticulate drug delivery, and pharmaceutical regulatory affairs.

Parijat Pandey is working as a research scholar in Industrial Pharmacy in the Department of Pharmaceutical Sciences, MD University, Rohtak. He is working on a funded project entitled Spray Dried NiMS for Orally Disintegrating Tablets.

Mohit Mittal is an alumnus of the Department of Pharmaceutical Sciences, MD University, Rohtak.

Advanced Delivery Devices

Self-Administration Device Training: Incorporating New Technologies to Reduce Device Errors

By: Craig Baker

As self-administration with drug delivery devices continues to grow, more patients are being introduced to injection devices, such as prefilled syringes, autoinjectors, and injection pens. Patients using these devices are required to inject subcutaneously, which involves injecting into the fatty tissue the lies between the skin and muscle. Common injection sites for these products include the top of the thigh, the stomach, or the back of the upper arm. Unlike healthcare professionals, who receive professional training on the safe and effective use of injection devices, patients often have limited or no experience with injectable devices. This can lead to a great deal of challenges, including user errors, anxiety, and avoidance behaviors. Addressing these issues helps build patient confidence and support patients in the autonomous use of drug delivery devices.

The patient's first 30 days, commonly called "onboarding," is the time when patients are first introduced and trained on their injection device. This often includes in-office training by nurses or other healthcare professionals. While this training is important and beneficial to patients, variability and environmental conditions can adversely affect this training and cause inconsistencies within patient groups. After receiving in-office training, patients return home and are expected to adhere to a prescribed treatment and self-inject.

A number of cognitive, environmental, device, and emotional factors affect the safe and effective use of drug delivery devices by patients. Imbalances among these factors can result in user errors, injuries, and adverse events. The root cause of these errors can be tied to ineffective training and awareness of administration techniques, procedures, or sequences. Examples of barriers to effective use include the following:

Cognitive: The psychological impact of diagnosis, combined with new medical terminology and jargon may block the patient's ability to remember new information.

Physical: Mobility, age, and dexterity impairments associated with specific therapeutic categories make it physically challenging to use the device. The lack of experience and education with medical devices also leads to onboarding challenges for patients that are naïve to self-administration.

Emotional: Fear and anxiety associated with self-injecting that often leads to avoidance behaviors. There is also a social component to this human factor as the social needs of the patient, including family and medical support systems, may also impact treatment.

To reduce user errors and build patient confidence, device training tools have been developed to support patients in learning their drug delivery devices. These devices are

"At its core, the ultimate goal of device training is to improve the patient experience and create value for HCPs and industry stakeholders. Improved training technologies like error correcting and wireless features allow brands to engage patients and provide personalized training content based on individual patient needs and performance."

customized to the needs of specific patient populations and delivery platforms to accurately mimic device characteristics and build adherent behaviors in patients. Currently, marketed training devices use mechanical reset and multisensory technologies (visual, auditory, and tactile) to complement HCP training and create consistent training experiences for all patients. Neurological research suggests multimodal recognition and processing increases the retention and recall of multisensory stimuli. As a result, trainers incorporating these technologies can benefit through the improved recall of training and handling requirements. Common errors that can be addressed through device training include the following:

- Injection into an unapproved injection site
- Failure to remove device cap before actuating the device
- Insertion angle of needle or positioning of the device on the injection site
- Proper sequence to prepare or unlock safety mechanisms
- Recapping of the device, damaging the needle or actuating the device
- Premature or out of sequence actuation of the device
- Proper hold time to receive a full dose

Throughout the past few years, patients and healthcare providers have benefited through innovative training technologies like multisensory devices. Recent improvements to this technology include the addition of sensors to detect errors and teach patients how to correct them in real-time. These technologies can be incorporated into packaging, training devices, or wireless platforms to enrich the patient experience through adaptive

FIGURE 1

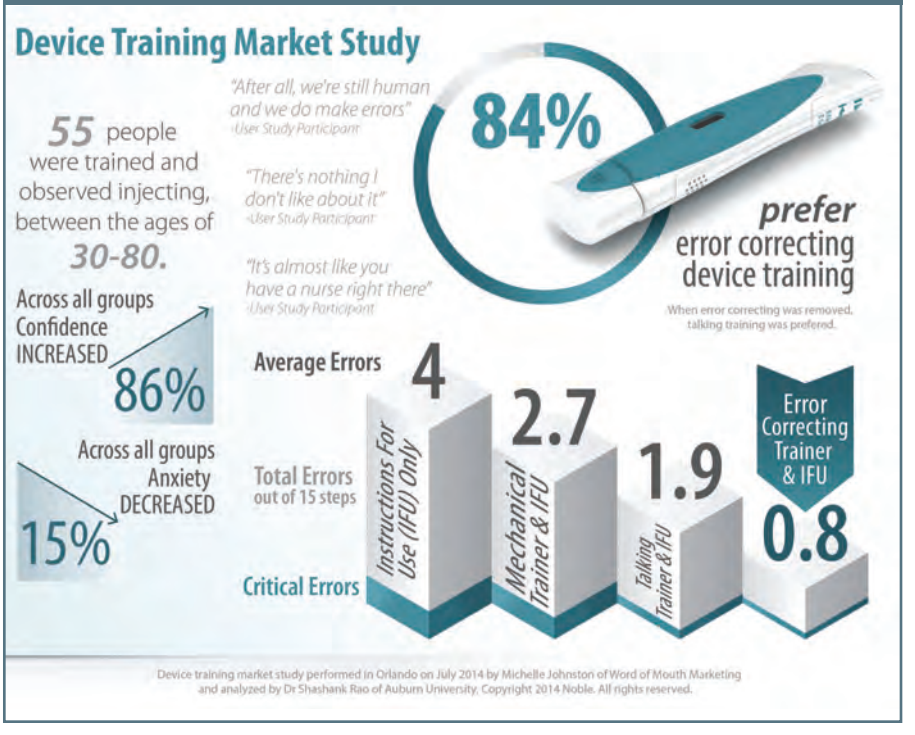

FIGURE 2

and engaging support programs. Based on a recent user study performed by Michelle Johnston of Word of Mouth Marketing and analyzed by Dr. Shashank Rao of Auburn University, new patients who received device training reduced their anxiety by 14% and increased their confidence by 86%. Of those, a talking error correction training device was preferred in 84% of participants, and more importantly, when observed; talking error correction participants had significantly fewer errors of all tested training methods.

At its core, the ultimate goal of device training is to improve the patient experience and create value for HCPs and industry stakeholders. Improved training technologies like error correcting and wireless features allow brands to engage patients and provide personalized training content based on individual patient needs and performance. As new brands continue to launch and augment markets, brands will continue looking for strategies to differentiate themselves from competitors. In the modern era of patient-centric care, those able to provide a superior product and educational experience to patients will be competitively positioned and benefit from the loyalty established by patients and HCPs. ◆

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BIOGRAPHY

Craig Baker is Executive Vice President at Noble, where he is responsible for the company's international development efforts, focused on providing patient-centric educational and onboarding solutions for commercial, brand management, and device development teams. Having joined Noble shortly after it was founded in 1994, he has been active in the growth of Noble's infrastructure, which more recently, includes growth in engineering and manufacturing. Areas of expertise include patient onboarding, device training, and product development. Mr. Baker has a Bachelor's from the University of Iowa and a Master's from the University of South Carolina.

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External Delivery

The Glamour of Air Travel

By: John A. Bermingham

I have been traveling by air for all of my business life, and throughout the years, I have been both a victim of and a witness to a certain group of people who make flying for everyone a test of patience and withstanding pain. Being there are many pharma professionals flying to the countless conferences going on nationally and internationally, I believe this topic will be a nice change of pace outside the normal topics I cover. Let me provide you with a few examples of what I am talking about.

The Leaner - When you see someone at the ticket or boarding gate counter, you must check their posture. If the person is standing up straight, then you can be assured they will be quick to resolve their issue. But if the person has their feet three feet back from the counter, has a 30 degree tilt into the counter, and has their forearms parallel to each other on top of the counter, you can be assured of a long wait.

The Head Hunter - The victims of the head hunter are only those people occupying aisle seats. The head hunter carries their back pack or some other piece of luggage over their shoulder and while walking down the aisle slams the piece of luggage into the heads of the people already sitting in an aisle seat.

The Overhead Person - These people bring a roller bag on board and place it in the overhead with the wheels facing out and is 6 inches too long for the overhead. After three or four violent slams of the overhead door and expecting the bag to miraculously fit, they give up and retreat to their seat. Then the argument begins with the flight attendant over whether this bag is going to be checked.

The Jeweler - These people are a Mr. T imitator who attempt to clear TSA Security wearing 25 pounds of necklaces and is shocked they set off the alarm of the metal detector machine. Then they hold up the line while taking off the jewelry one item at a time. Then, when they attempt to clear the metal detector for a second time, the alarm goes off again because of all the metal they still have in their pockets. And don't forget the belt that looks like it was designed by Hulk Hogan modeled after his WWF Championship belt.

The Armrest Barrier - These people are too large for one coach seat so they raise the arm rest separating you and them so that they can share your seat with you. When you attempt to lower the arm rest, these people jam their leg under the arm rest to block it from coming down. Then the fight begins.

My Seat is a Chaise Lounge - These people always fly with their seat back fully reclined from the moment the wheels leave the runway to just before landing. This configuration means that you cannot open your laptop on your tray table because the seat in front of you is too far back. This also prohibits you from placing a drink or a meal on your tray table for the same reason. When you politely ask the person in front of you to please move their seat back up a little bit, the person will normally refuse, so you start tapping your foot on their seat back in order to annoy that person.

The Food Critic – These are people who complain loudly about the meal that is being served. They will always involve a flight attendant or two and look for fellow passengers to join the fray as well. What they fail to understand is they are not in a restaurant. They are in a modern mode of transportation whose objective is to move people at a very high rate of speed delivering its passengers safely. IT'S NOT A RESTAURANT!!!!! IT'S AN AIRPLANE!!!!!

The Bartender - These people bring their own alcohol on board. As most everyone knows, this is a real no-no on an airplane. I sat next to the bartender on a recent flight. When the flight attendant stopped by with her beverage cart, the bartender ordered a can of ginger ale. When the flight attendant departed, out came the bartender's flask, and he made a full pour into his plastic cup and then topped it off with the ginger ale. He offered me a shot in my coffee, but I politely declined as 7:30 AM is a tad early for me. I actually liked the bartender. We had a lengthy conversation, and his bartending talent was on display in the seat next to me.

I know that there are more travel devils out there but we must retain our composure and deal with them as best we can. Bon Voyage! ◆

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