# Drug Development & Delivery

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# Rise of the Bolus Injector!

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

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Overcoming Poorly Soluble Pharmaceutical Formulations With Hot Melt Extrusion

**Mark Perkins, PhD**
Recombinant Human Albumin: Delivering the Future of Type 2 Diabetes Medication

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# New Device Class

**"With so many biologics in clinical development or approved and requiring lifecycle management to improve or protect market share, the development of wearable, disposable delivery systems for the subcutaneous delivery of large-dose volume drugs is considered by many to be one of the greatest unmet needs in the pharmaceutical industry today. Several device manufacturers, including Unilife, have developed a new class of devices to address the primary container, dose delivery, and patient needs of these large-volume biologics."**

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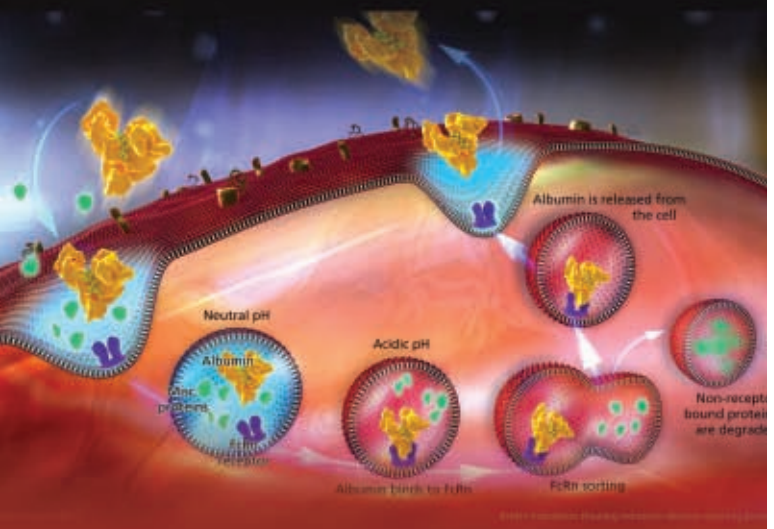
# Extending Half-Lives




**"To ensure albumin half-life extension technology continues to meet the demands of innovative drug design, Novozymes has developed the next generation of albumin half-life extension technology. These albumin 'variants' will open the door to longer dosing regimens for peptides, such as GLP-1."**

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# Patient Acceptability Problems?

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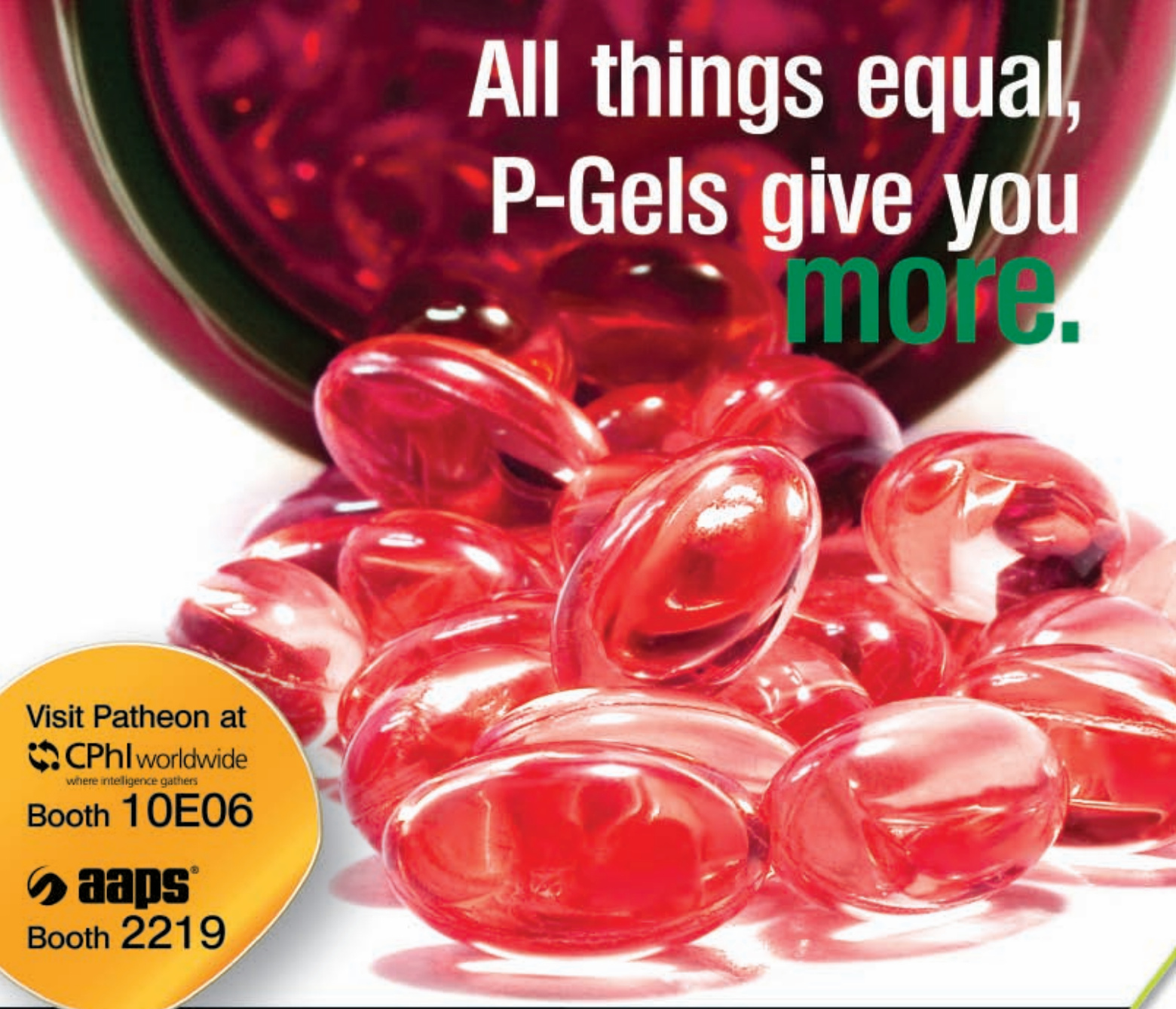


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# Market News and Trends

## BD Introduces Shortest, Thinnest Pen Needle

Studies suggest that as many as one-fifth to one-third of people with diabetes are hesitant or unwilling to give themselves insulin injections for reasons that include needle anxiety. Patients who reported injection-related pain or embarrassment also admitted they intentionally skipped insulin injections more often. A study by the American Association of Diabetes Educators (AADE) revealed that 47% of people with diabetes would be more likely to administer their injections regularly if a product were available that would ease the pain and discomfort of injections. With these needs in mind, BD Medical, a segment of BD (Becton, Dickinson and Company) recently announced the launch in the US of the BD Ultra-Fine Nano Pen Needle with PentaPoint Comfort.

BD's latest advancement in injection comfort, PentaPoint is a patented 5-bevel needle tip design that creates a flatter, thinner surface to help penetrate the skin with significantly greater ease. In a clinical home-use study, patients who inject insulin found BD's 5-bevel pen needles to be significantly less painful, easier to insert, more comfortable and preferred overall when compared with current 3-bevel pen needles. Bench tests showed the modified PentaPoint needle tip reduces the force to penetrate the skin by 23% compared to 3-bevel pen needles.

In recent years, advances in needle manufacturing technology, along with shorter and thinner needles, have been associated with progressively improving patient self-rating of injection comfort. At 4 mm by 32 gauge, BD Ultra-Fine Nano is the shortest, thinnest pen needle available, is clinically demonstrated to enhance comfort, and provides a less intimidating injection experience. Combined with a one-handed injection technique and its ability to facilitate flexible site rotation, BD Ultra-Fine Nano may help improve adherence to diabetes therapy regimens to support better health outcomes. PentaPoint Comfort is an enhancement to BD Nano, reflecting that a modified needle tip can further advance patient comfort.

The AADE issued injection technique strategies that encourage the use of the smallest possible needle for improved patient comfort and insulin efficacy. The BD Nano 4-mm Pen Needle is proven to be as effective as longer needles for patients of various body types, and provides equivalent glucose control by effectively delivering the insulin dose to subcutaneous tissue, the recommended site for insulin injections, and reducing the risk of injecting into muscle. Intramuscular injection can accelerate insulin absorption and increase the risk of unanticipated hypoglycemia (abnormally low blood sugar). Subcutaneous injection allows the insulin to be absorbed at an appropriate rate, resulting in better glycemic control.

## Life Technologies to Partner With Bristol-Myers Squibb

Life Technologies Corporation recently announced the company has entered into a Master Development Agreement with Bristol-Myers Squibb Company for current and future companion diagnostics projects. The current agreement constitutes the second collaboration between the two companies and represents another step in Life Technologies' strategy to develop its diagnostic business through internal development, partnerships, and select acquisitions. The agreement covers an initial project for oncology and provides for a long-term partnership across a potentially broad range of Life instrument platforms and a wide range of therapeutic areas.

Life Technologies possesses a breadth of platforms that can be leveraged in the development of new diagnostics. These platforms span both genetic and proteomic analysis, including next-generation sequencing, Sanger sequencing, qPCR, flow cytometry, and immuno-histochemistry. In addition, the company recently announced that its Ion Torrent Personal Genome Machine (PGM) would be developed for proteomics capabilities.

"Life is uniquely positioned to provide pharma a flexible, cost-effective means to manage the evolution of the companion diagnostic assay through the drug development process," said Mr. Andrews.

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## Catalent Completes $350-Million Offering

Catalent Pharma Solutions, Inc. recently announced the successful completion of its $350-million offering of 7.875% Senior Notes due 2018, issued at par. Catalent has used a portion of the net proceeds from this offering to fund a portion of its tender offer for outstanding 9.5%/10.25% Senior PIK-election Notes due 2015, including related fees and expenses, and expects to use the remaining net proceeds to finance any additional purchases pursuant to the tender offer and any excess for general corporate purposes, which may include repayment of indebtedness.

The Notes, which mature October 15, 2018, were offered in a private offering to qualified institutional buyers pursuant to Rule 144A under the Securities Act of 1933, as amended, and to non-US persons in accordance with Regulation S of the Securities Act. The Notes have not been registered under the Securities Act or the securities laws of any other jurisdiction and may not be offered or sold in the US or to, or for the benefit of, US persons absent registration under, or an applicable exemption from, the registration requirements of the Securities Act and applicable state securities laws.

Catalent Pharma Solutions is the global leader in development solutions and advanced drug delivery technologies, providing world-wide clinical and commercial supply capabilities for drugs, biologics, and consumer health products.

## JHP Pharmaceuticals to Produce Lyophilized Biologic

JHP Pharmaceuticals recently announced it has entered into an agreement with an undisclosed pharmaceutical company to produce supplies of a lyophilized biologic for international, late-phase clinical trials.

"We know that customers want to seamlessly progress from clinical batch production to product launch and then commercialization," said Stuart Hinchen President and CEO of JHP. "JHP's established infrastructure and expertise transitioning products from clinical to commercial supply are recognized by customers looking for long-term reliability and continuity when selecting a contract manufacturing organization. Additionally, our cGMP compliance record and experienced staff allows customers to focus on their pressing business needs with confidence."

JHP has successfully supported launches of several products in US and international markets and manufactures products for sale in 86 countries. JHP's Rochester, MI, manufacturing site's 25-year history in contract manufacturing is a result of a solid cGMP compliance record, a quality-driven experienced staff and a customer-centric approach.

JHP Pharmaceuticals, headquartered in NJ, provides contract manufacturing of sterile products, including biologics, small molecule, controlled substances, vaccines, ophthalmics, otics, and antibiotics for large and small pharmaceutical and biotech organizations.

# SteadyMed Therapeutics Secures $10.4 Million

SteadyMed Therapeutics Inc., a drug delivery therapeutics company, recently announced it has raised $10.4 million in a private placement of preferred stock. Proceeds from the financing will be used to support the development and commercialization of thecompany's lead drug product that leverages its PatchPump technology; a novel, prefilled, size efficient, and disposable subcutaneous drug delivery system for which the company aims to complete pivotal clinical trials in 2013 followed by commercial launch in the US in 2014. Proceeds will also be used to complete the outsourced manufacturing infrastructure to support the company's commercialization strategy.

The investment comes from current investors KB Partners and Samson Ventures as well as new investment from high net worth individuals and private funds.

"We are very pleased to close this $10.4-million round in addition to the $2.4 million we raised earlier this year," said Jonathan M.N. Rigby, Chief Executive Officer. "SteadyMed has made impressive progress over the past 12 months in executing our strategy to develop and commercialize our own PatchPump-enabled drug product to treat a life threatening orphan disease, as well as with the securing of collaborations around

our unique delivery platform with Biopharmaceutical partners. Raising significant investment in the current economic climate is laudable and a testament to our unique technology, credible strategy, and first-class management team. We are delighted to have the support of our current and new investors."

SteadyMed Therapeutics, Inc., with offices in San Francisco, CA, and Rehovot, Israel, is a private, venture funded drug delivery therapeutics company engaged in the development for commercialization of its PatchPump technology; a novel, prefilled, size efficient, and disposable subcutaneous drug delivery system. The company's range of PatchPumps can be customized to deliver liquid drugs, including biologics, with a

wide range of volumes and viscosities, in a consistent and controllable manner. The company is leveraging the sustainable cost and technological competitive advantages of its PatchPump platform to create a family of products that benefit patients in target markets, which represent the highest value-to-risk ratios.

# Xcelience Opens New Development Facility

Xcelience LLC recently announced the grand opening of a new 24,000-sq-ft facility, located south of the Tampa airport at 4901 Grace Street. The building will be dedicated to primary and secondary packaging, labeling, distribution, and warehouse services.

Xcelience serves national and international clients in the biotech and pharmaceutical industries, offering cGMP services from preformulation and formulation through clinical manufacturing and clinical supplies for Phase I-III clinical trials. This is the company's second facility in the Tampa Bay area, and it will be audited and approved for domestic as well as European clinical trials. The expansion also promises to open the door to more highly skilled jobs for the Tampa Bay Area.

"At Xcelience, we work on several dozens of molecules, each of which has the potential to radically improve people's lives," said Derek Hennecke, CEO and President. "We love being in Tampa because through USF, UF, and Tampa's growing biotech community, we have access to scientists at the height of their fields. We don't have to go far to find people who thrive on the challenge of working with different molecules, upholding rigorous FDA standards while also demonstrating the agility to meet client parameters for speed, cost, and efficiency."

Xcelience has doubled its staff throughout the past 3 years and will soon be celebrating the hiring of the company's 100th employee. The new plant will enable Xcelience to double its headcount again throughout the next 3 years.

Guests for the ceremony in addition to staff, clients, and corporate partners include Honorable Jack Latvala, Florida Senate, Tampa Mayor Bob Buckhorn, Honorable Al Higginbotham, Hillsborough County Board of County Commissioners, Honorable Dana Young, Florida House of Representatives, Julie Fitzpatrick from the office of Congresswoman Kathy Castor, and supporting members from the Tampa Hillsborough Economic Development Corporation and the Tampa Bay Partnership.

Xcelience wishes to thank the Florida institutions that have offered continued economic stimulation and sustained capital investment to Xcelience and other Florida companies like it. In particular: The Tampa Hillsborough Economic Development Corporation - officially designated by Enterprise Florida as Hillsborough County's primary business recruitment economic development team; and The Tampa Bay Partnership - a CEO-led regional economic development organization with a mission to work with its partners to market the region nationally and internationally, to conduct regional research, and to coordinate efforts to influence business and government issues that impact economic growth and development.

# Synergy Files IND for GI Diseases

Synergy Pharmaceuticals, Inc. recently announced that an Investigational New Drug (IND) application was submitted on September 7, 2012, for clinical evaluation of SP-333 to treat inflammatory bowel disease (IBD). SP-333 is a second-generation guanylate cyclase-C (GC-C) agonist with the potential to treat GI disorders and diseases.

SP-333 is a synthetic analog of uroguanylin, a natriuretic hormone that is normally produced in the body's intestinal tract. Deficiency of uroguanylin is likely to be one of the primary reasons associated with formation of polyps as well as debilitating and difficult-to-treat GI inflammatory disorders, such as ulcerative colitis and Crohn's disease. Orally administered SP-333 binds to and activates guanylate cyclase C (GC-C) expressed on epithelial cells lining the GI mucosa, resulting in stimulation of cyclic GMP in target tissues. SP-333 has been found to be highly stable against proteolysis in simulated intestinal fluid for up to 24 hours. Its enhanced stability makes this peptide an extremely potent GC-C agonist in animal studies in mice and monkeys, promoting bowel movement in monkeys, and ameliorating GI inflammation in mice, respectively.

Synergy is a biopharmaceutical company focused on the development of new drugs to treat gastrointestinal disorders and diseases. Synergy's lead proprietary drug candidate plecanatide is a synthetic analog of the human gastrointestinal hormone uroguanylin, and functions by activating the guanylate cyclase C receptor on epithelial cells of the GI tract. Synergy completed a Phase I study of plecanatide in healthy volunteers and a Phase IIa clinical trial in CIC patients. In October, 2011, Synergy initiated dosing of patients in a major Phase II/III clinical trial of plecanatide to treat chronic idiopathic constipation.

Plecanatide is also being developed to treat constipation-predominant irritable bowel syndrome, with the first trial in IBS-C patients planned for the second half of 2012. Synergy's second GC-C agonist SP-333 is currently in preclinical development to treat inflammatory bowel diseases.

# Selexys Completes Equity Financing & Signs Major Agreement

Selexys Pharmaceuticals, Corp. recently announced it has successfully completed a $23-million Series A equity financing, led by MPM Capital. Additionally, Selexys entered into an agreement with Novartis Pharmaceuticals whereby Novartis has been granted an exclusive option to acquire Selexys and its lead asset, the anti-P-selectin antibody SelG1, following the successful completion of a Phase II clinical study in patients with sickle cell disease. Including up-front, acquisition, and milestone payments, the agreement with Novartis could reach up to $665 million.

The Series A financing includes a new major investor, MPM Capital. Concurrent with the investment, Selexys also announced the addition of Todd Foley, Managing Director of MPM Capital, to the Selexys Pharmaceuticals Board of Directors.

The combination of the Novartis agreement and the closing of the Series A financing will allow Selexys to advance the SelG1 program through a large Phase II clinical study in sickle cell patients and will also fund a second program at Selexys, an anti-PSGL-1 antibody, through a Phase I clinical study.

SelG1 is an investigational humanized monoclonal antibody directed against P-selectin, a key member of the adhesion molecule family known as the selectins. In preclinical studies, inhibition of P-selectin has been shown to effectively prevent vasoocclusion by blocking critical cell-cell interactions that drive this process. Therapeutic blockade of P-selectin may therefore reduce or prevent vasoocclusive crises in patients with sickle cell disease.

The SelG1 program for sickle cell disease is supported by Small Business Innovation Research (SBIR) fast-track award No. 5R44HL093893-02 and No. 2R44HL093893-03 through the National Heart, Lung and Blood Institute.

## Ei Gains Exclusive World-Wide License

Metro Charlotte-based Ei has signed agreements with European-based professors and technologists for the exclusive worldwide license of a novel class of sphingolipids. Sphingolipids are found in the extracellular spaces of the stratum corneum, where they play a critical role in strengthening the barrier function of the skin, promoting moisture retention and increasing elasticity of the skin.

The specific technology consists of a novel lamellar lipid topically delivered through a custom formulation system. In preliminary clinical studies, the technology has demonstrated significantly better barrier function with substantial improvement in moisture retention when compared to commercially available sphingolipid compounds. As part of this exclusive licensing arrangement, Ei has been granted options on several related technologies in various stages of development.

Ei provides product development, analytical and clinical services to develop solutions for Rx pharmaceutical, OTC, therapeutic skin care, topical (semi-solid and liquid), and animal health products.

Ei's research and development team takes an integrated approach to product development and management. This strategic approach creates high-technology solutions for their customers and allows Ei to utilize its full network of resources and assets for successful product creation. Ei prides itself on not just the cutting-edge science and state-of-the-art manufacturing expertise of its people, but the protection and strengthening of each individual customer's brand. This European license illustrates Ei's continued commitment to seeking out intellectual property opportunities for their customers.

# Jubilant HollisterStier Launches Analytical Services Division

Jubilant HollisterStier, a subsidiary of Jubilant Life Sciences, recently announced that its Contract Manufacturing & Services division has launched an analytical services unit that will provide laboratory method development and related analytical testing as part of its integrated service offerings. Jubilant HollisterStier will offer a full suite of testing capabilities, including Raw Materials Testing, Release Testing, Microbiology testing, Laboratory Method Development & Validation, Impurities Testing, and Stability Testing & Storage. These capabilities will be available through its facilities in Spokane, WA, and Montreal, Quebec, Canada.

"The launch of our analytical services offerings is a continuation of our strategy to be a leading provider of services to the Life Sciences industry. We are expanding our analytical capabilities to support a wide array of high-quality laboratory tests, aimed at further servicing our clients and partners," said Marcelo Morales, Chief Executive Officer, Jubilant HollisterStier.

Jubilant HollisterStier Contract Manufacturing & Services Division is a subsidiary of Jubilant Life Sciences, an integrated pharma and life sciences company headquartered in India. Jubilant HollisterStier provides its customers manufacturing services to aseptically fill liquid and lyophilized products, semi-solid and solid dosage forms at its facilities in the US, Canada, and India. Jubilant HollisterStier offers highly-skilled, cross-functional teams to provide custom solutions to customer-specific project goals from development through commercialization.

# Quotient & Pulmatrix Announce Completion of Innovative Program

Quotient Clinical and Pulmatrix recently announced the completion of an early clinical program to achieve proof-of-concept data in COPD patients for PUR118, Pulmatrix's lead iCALM (inhaled dry powder cationic airway lining modulator) therapeutic. The design and preliminary results from this program were presented at the European Respiratory Society (ERS) 2012 conference in Vienna, Austria.

The clinical program was based upon a single, innovative, and flexible clinical design to enable timeline acceleration from clinical entry into initial safety and tolerability evaluation in healthy volunteers, through to pharmacodynamic/efficacy data in mild-moderate COPD patients (GOLD Stages 0-2). Positive proof-of-concept data was achieved in less than 9 months, compared to conventional timelines that can typically stretch to more than 2 years.

"Our work with Pulmatrix has evolved into a landmark case study to illustrate how early development processes and timelines can be expedited," said Mark Egerton, Managing Director, Quotient Clinical. "This single, four-part protocol seamlessly integrated healthy volunteer and COPD patient investigations by building in flexibility, enabling the project team to rapidly respond to emerging safety and PD data. In addition, an adaptive biomarker strategy encompassing a range of anti-inflammatory, respiratory, and imaging biomarkers was utilized. We are now using this as a model for designing early exploratory and development programs."

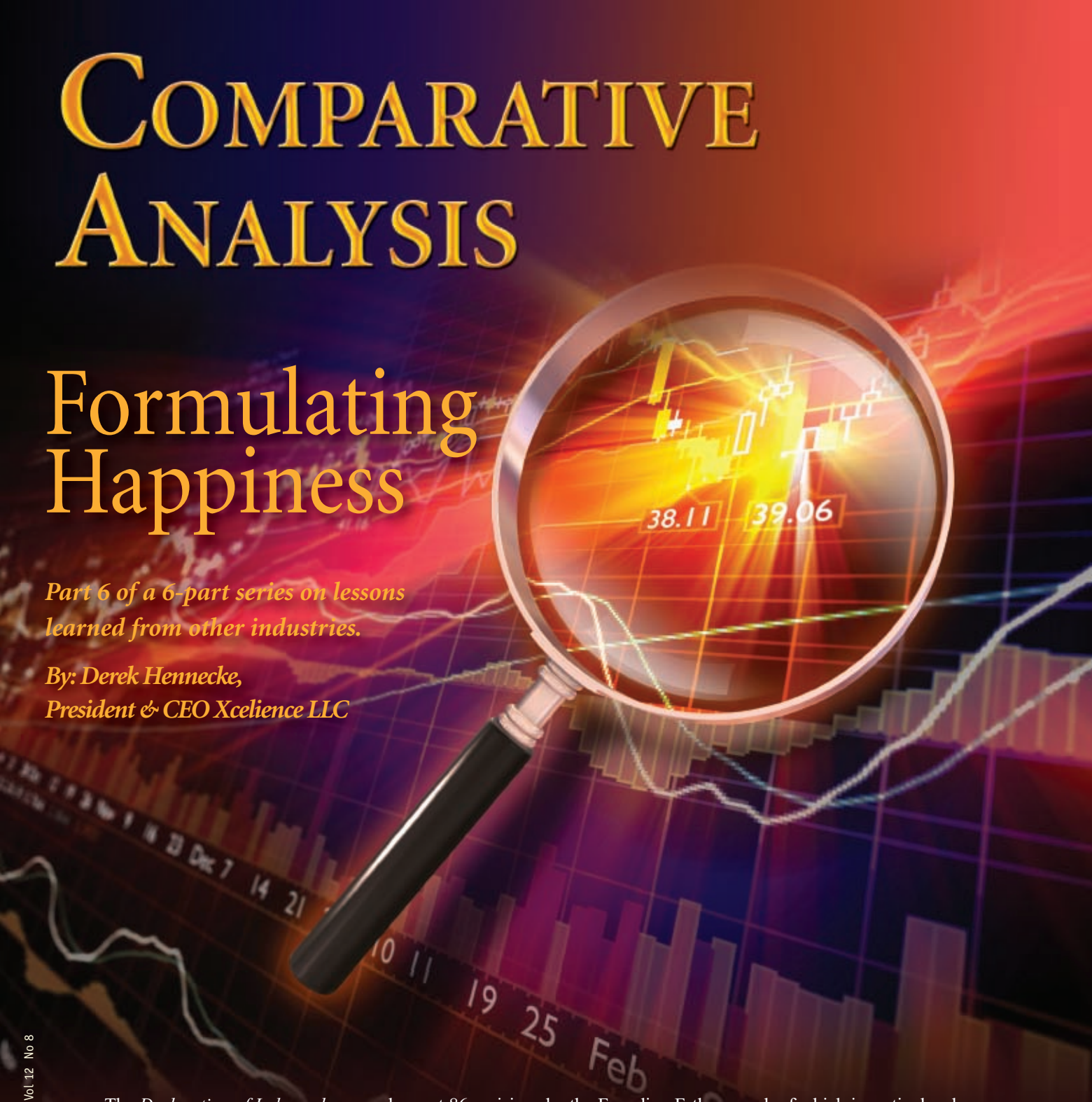
"This innovative, flexible, and adaptive clinical design implemented by Quotient allowed dose-ranging safety and efficacy data to be compiled and understood in a timeframe that was markedly faster than is typical of early-phase clinical drug development. This permitted the potential of our lead iCALM drug candidate, PUR118, to be appreciated much earlier and in greater depth than a conventional path could accommodate," added John Hanrahan, MD MPH, Chief Medical Officer and Senior Vice President at Pulmatrix.

# Comparative Analysis

# Formulating Happiness

*Part 6 of a 6-part series on lessons learned from other industries.*

*By: Derek Hennecke, President & CEO Xcelience LLC*




The *Declaration of Independence* underwent 86 revisions by the Founding Fathers, each of which is meticulously preserved and on display at the National Archives in Washington, DC. Through all those iterations, every one of the 1337 words in the document was crossed out and revised at least once, as the Founding Fathers crafted the phrases that would express America's unifying beliefs. Only four words in the entire document were never questioned; never once met the stroke of a pen:

***We hold these truths to be self-evident, that all men are created equal, that they are endowed by their Creator with certain unalienable Rights, that among these are Life, Liberty and the pursuit of Happiness.***

The search for happiness is part of the human condition. We all seek it. We in the pharma industry, however, may have a slightly less traditional take on the pursuit of happiness than most Americans.

Feeling sad? There's a pill for that. Lots of them, actually. For decades, doctors favored tricyclic antidepressants (TCAs), which inhibit the re-uptake of norepinephrine and serotonin. Side effects include muscle twitching and sexual problems. TCAs are also quite dangerous in overdose.

Not liking TCAs? Monoamine oxidase inhibitors (MAOIs) have also been in use for 50 years. Side effects include chest pain and racing heart. MAOIs also inhibit monoamine catabolism, which predisposes them to drug-drug interactions as well as what is known as the "cheese effect," so called because it was first noticed by a neurologist whose wife began experiencing severe headaches shortly after she began using MAOIs and only when she ate certain aged cheeses such as Stilton which are high in tyramine.

Of all the treatments available today, only 65% of patients respond, and then only after a 2- to 4-week delay; something that is particularly concerning in a population prone to suicidal behavior.

Current research is largely geared to reducing side effects and increasing efficacy and response time. We've seen several new molecules that specifically inhibit serotonin re-uptake (SSRI) or both serotonin and norepinephrine re-uptake (SNRI). Triple re-uptake inhibitors are being evaluated. These agents block the re-uptake of serotonin, norepinephrine, and dopamine from the synapse. The theory is that the additive effect of enhancing neurotransmission in all three monoamine systems (broad-spectrum) could lead to better efficacy and quicker response.

## CHASING HAPPINESS

While the industry struggles to find a more effective antidepressant, most of us as individuals continue the quest for unmedicated happiness. We seek it in our home lives and at work. Companies have many reasons to strive to increase employee happiness. Happy employees are more productive over the long haul. They come to work. They get the job done faster; they exceed expectations.

In *Creating Sustainable Performance* (Harvard Business Review, Jan-Feb 2012), Spreitzer and Porath found that employees considered to be thriving (not just satisfied and productive but also engaged in creating the future) were 16% better in overall performance as reported by their managers and 125% less likely to burn out, by their own admission, compared to their peers. These happy employees reported they were 32% more dedicated to their company, and 46% more content with their jobs. They missed work less often and visited the doctor less, both of which imply significant cost savings to their company.

Yet happiness and its link to performance is still little understood. People believe, "If I can just get that promotion, then I'll be happy." Or, "If I can get that certification, I'll celebrate then." But upon getting that promotion or certification, they immediately focus on the challenges that face them in the new job or with the added responsibilities. Then before they know it, they're fixed on the next promotion, the next bonus, the next sales target...we have a natural tendency to keep moving the goalposts so that the happiness we seek is always just out of reach, and we never allow ourselves to experience it now.

Research shows that if we chase happiness in this way, we'll almost surely spend our whole lives in the pursuit of happiness, and never in the fullness of it. The key is to quit chasing happiness. We need to change our mindset and be positive and happy now. If we can do that, success will almost surely follow.

"People who cultivate a positive mind-set perform better in the face of challenge," writes Shawn Achor in *Positive Intelligence* (Harvard Business Review, Jan-Feb 2012). "I call this the happiness advantage - every business outcome shows improvement when the brain is positive. I've observed this effect in my role as a researcher and lecturer in 48 countries on the connection between employee happiness and success. And I'm not alone: In a meta-analysis of 225 academic studies, researchers Sonja Lyubomirsky, Laura King, and Ed Diener found strong evidence of directional causality between life satisfaction and business outcomes."

Achor goes on to recommend several strategies to create a positive mindset, many of which I heartily recommend from personal experience. Taking a moment at night before bed to run through in my mind those things for which I'm grateful can radically change your mindset. Right before sleep is a perfect time to do this. The benefits of exercise on mood are well-documented. My wife will sometimes kick me out the door for a run if I wake up in a funk, because she knows it'll turn me around. Achor also advises writing a positive message to someone you know, meditating at your desk for 2 minutes, and taking a couple of minutes a day to jot down your most meaningful experience in the past 24 hours.

## THE ORGANIZATIONAL PURSUIT OF HAPPINESS

As a manager, passing out happiness journals and mandating 2-minute meditation breaks is probably not a great strategy for encouraging employee happiness. So how do I create a happy company? There are some very weird strategies out there. Lindon Labs uses the LoveMachine, an internal software system that lets employees forward glowing letters of support to each other. Google's Zurich office pours money into office environments, including bathtubs, hanging hammock-desks, fish tanks, and a long twisting slide between floors (not recommended with your morning coffee).

In our own industry, Bristol-Myers Squibb introduced Hirbe Powers, an extreme rep trainer. Hirbe is a superhero figure designed to motivate BDs and empower them with with advice on how to deliver their message with POWER and IMPACT. Hirbe is lambasted in the blog Pharmalot, where one rep writes "everything is focused on Brand Slogans and Messages...There was never new and relevant data that would help make selling science based...It was a low point in my career." Our industry may be the one place left on earth where science motivates better than the Avengers.

So what does the science say about what works to create happiness in the organizational context? Spreizer and Porath

## SIDEBAR

### Biotech IPOs: Unsung Heroes of the Stock Market

I don't understand why tech IPOs remain the darlings of the financial markets. Even in the aftermath of the stock market massacre that was the dot.com boom, tech IPOs continued to be portrayed as the place to make fast and furious money. More recently, we've seen investors chomping at the bit, eager to place their bets on the social media IPOs, each of which was welcomed to Wall Street with great fanfare, only to burst magnificently into flames one after the other: Groupon, down 72%; Zynga tumbling 68%; and finally Facebook, the largest IPO in history, hitherto on an unbroken march toward business glory, plummeting a rather spectacular 44%.

Why is no one talking about biotech IPOs? Biotech IPOs have not just outperformed tech IPOs, they have resoundingly trounced them. The median and average percent change since IPO in the biotech world is 19% and 26%, respectively. Compare that to 9% and 3% in the tech industry. This is approximately 2000 basis points of outperformance, in a world where asset managers think of 300 to 500 basis points as an impressive performance, according to the analysis set out by Bruce Booth in Forbes Magazine (The Quiet Outperformance of Recent Biotech IPOs, August 2012) .

Granted, tech IPOs have underperformed the market in general. But even when we hold the biotech IPOs up against the market as a whole, biotech looks enticing. Booth took the S&P performance of the biotechs on the day of their offerings and compared that to their current performance to calculate stock performance adjusted by market returns. The green bars in the graph above show that biotech IPOs maintained a market-adjusted average stock performance of 19%. That compares to a 7% return on the market as a whole over that period, and a market adjusted stock change of -4% for tech.

Of course, the total market cap of all 15 biotechs in this analysis was only $3.6 billion, compared to $172 billion for the tech companies ($91 billion if you remove Facebook). Since the IPOs, the biotech companies' market cap has grown to $5 billion, a tidy profit of 39%. Tech, meanwhile, has dropped to $119 billion (or $72 billion without Facebook), losing investors $54 billion (or $19 billion).

Writes Booth, "The 68 Tech IPOs have lost more capitalization in aggregate than 10x the entire value of the 15 Biotech IPOs that squeezed onto the public markets." All in all, a good reflection on the steady, reliable growth of an unsung industry.

identified the following four strategies that demonstrated scientific efficacy:

### (1) Let Employees Make Decisions That Affect Their Work

A happy employee is fully empowered to do his or her job. That may sound obvious, but it isn't. If you give an employee a job in client service but the only tool she has to deal with an angry customer is an apology, she's going to be taking a personal interest in that antidepressant research we talked about earlier.

"(Happiness) is about giving employees permission and encouraging them to just be themselves," writes Tony Hsieh (pronounced Shay), CEO of Zappos, a billion-dollar on-line etailer that defines itself as a "service company that just happens to sell shoes." Zappos puts the vast majority of its marketing budget not into advertising and promotions but straight into customer service. The company claims its goal is to make each customer experience so phenomenal, the customer feels like it's their birthday.

Zappos astounding business success suggests that this approach works, but it makes sense from a social psychology perspective as well. We humans are social beings. We want to make the people around us happy. We each want to feel like a valued and appreciated member of the hive. As such, employees want to please customers, and the more resources they are given to enable them to do so, the better. Zappos customers have responded to the customer service approach with a whopping 75% repeat customer rate. Add to that a steady flow of new customers and you've got a really great business model.

Dipping back into the science, we find even more evidence that we thrive when we feel supported by the hive. In a study of 1,648 students, Achor, working with Stone and Ben-Shahar, found that social support was the best predictor of happiness during stressful times. The correlation between happiness and Zimet's social support scale (an academic measure used to evaluate students positive engagement with their social networks) was an astonishing .71. The correlation between smoking and cancer, for comparison, is a mere .37.

Only one thing motivates us more than receiving social support from peers, Achor found, and that's providing social support to peers. We like helping people. We feel good pitching in to help a colleague who's slammed. We like to be a part of the gang, either around the coffee pot or as part of the Social Committee. We get a nice little social high from solving problems for customers. Employees who ranked highest on providing social support were 40% more likely to receive a promotion the following year, reported higher job satisfaction, and were 10 times more engaged in their jobs.

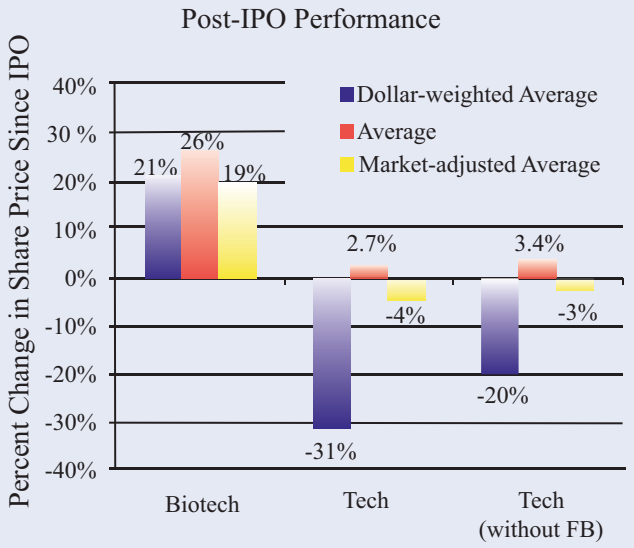
Two weeks ago, one of our clients here at Xcelience approached us in a desperate situation. The company needed to produce a batch under quarantine and ship that same day. The project involved our new service introduction of spheronization and extrusion. In my experience, no CRO has ever accomplished something like this before. We're very proud to have been flexible enough to make this happen, and when the customer praised our team for delivering against the odds, we all experienced a deep glow of satisfaction.

### (2) Sharing Information

Last week, I sent around a company memo about an exciting drug we're working on. This drug could someday radically change a lot of lives for the better. It was for change like this that most of us entered this business in the first place. Yet sometimes, we, as management, can get so caught up in the cogs of the machines we operate that we forget to share with employees the bigger picture of what they're contributing too. Within an hour, I had over a dozen responses from employees sharing their enthusiasm about this project. I made a mental note to do this more often.

Sharing information extends to the bottom line as well. Everyone in the company

## SIDEBAR FIGURE




**No matter how you analyze the data, biotech IPOs earned investors significantly more than tech IPO (data from Forbes Magazine).**

is a player in the game. They need to know the score and to be able to see the link between their project and the company's performance, according to Speitzer and Porath. At Xcelience, we hold all-employee meetings about every second month, and broadcast our forecast with the entire staff.

### (3) Minimize Incivility

Your boss gives you a vague assignment, is unavailable for clarification, then tells you your resulting research PowerPoint is lousy. A colleague berates you in a conference room full of your peers over a grammatical error.

Over half of all staff subjected to this type of behavior intentionally worked less hard afterward, according to a research project conducted at Thunderbird School of Global Management by Spreitzer and Porath with Professor Christine Pearson. More than a third knowingly let the quality of their work slip. Two thirds said they went out of their way to avoid the perpetrator, and a similar number said their performance suffered.

It really only takes one bad player to pollute the corporate culture. I call these toxic employees, and they can be hard to root out. Ratting on a colleague doesn't help your social standing in the hive, particularly if the toxic employee survives the attack. At Zappos, every new hire goes through a 4-week training program, including 2 weeks in which all they do is take calls from customers. At the end of that 4-week period, the entire class is made an offer. If any trainee wants to leave, he or she will be paid for their time, plus a $2000 bonus to quit immediately.

Another company in our industry has taken this one step further. The CEO of this company, which I'm not at liberty name, told me while I toured his facility that he regularly fires clients he works with. Clients! I guess he does this based on how the client treats his employees. Even after a lengthy discussion, I still don't see how he can do this in a business so driven by client service, reputation, and referrals, but I will say that his employees seemed motivated and happy, and his account of his profits suggests that the company's (surviving) clients are very pleased with the service they receive.

### (4) Offering Performance Feedback

Feedback from the hive, as anyone who has ever met an angry bee knows, is direct and quick. Every company should offer positive and constructive management feedback on a regular basis. It's the right thing for the organization as much as for the individual. Let's say (and this example is purely fictional) one of my managers is getting too caught up in the details of his job and is unavailable for his staff when he needs to be showing leadership. It's become a problem, and I'm starting to catch whiffs of discontent. I want that manager to know yesterday. It's in everyone's interest; I need that leader to be there for his staff, and the manager himself has a reputation to maintain - he would be mortified to learn that his leadership skills were being discussed behind closed doors for days or weeks. He could miss that bonus or be baffled when he misses that promotional opportunity around the corner, maybe even quitting as a result. Ultimately, just by not telling him what's expected, Xcelience might lose a good employee.

How much feedback a company gives is still a matter of debate. Some firms offer 360 degree feedback that includes colleague input, usually in a summarized format to avoid any (intentionally or unintentionally) offensive comments. Many employees appreciate the added insight into how their colleagues view them, particularly when it involves things they can change, like work/life balance. This type of feedback has to be undertaken with great caution however - the last thing anyone wants is to work for Big Brother.

## FORMULATING ORGANIZATIONAL HAPPINESS?

Whether or not an individual is happy in the organizational context is to a large extent the choice of that individual. We each have the right and arguably the responsibility to find our own happiness by building a positive mindset through the various aforementioned suggested techniques. The company can create an enviornment conducive to that positive mindset by following the four strategies of letting employees make deicisions, sharing information, minimizing incivility, and offering feedback.

And/or we could continue our research for an efficient and effective happy pill; a project for which the world would surely thank us. And then complain that we charge too much for it! ◆

EXCIPIENT UPDATE

# Addressing Challenges With Low-Solubility Compounds: The Importance of Functional Excipients in the Formulation of Amorphous Dispersions

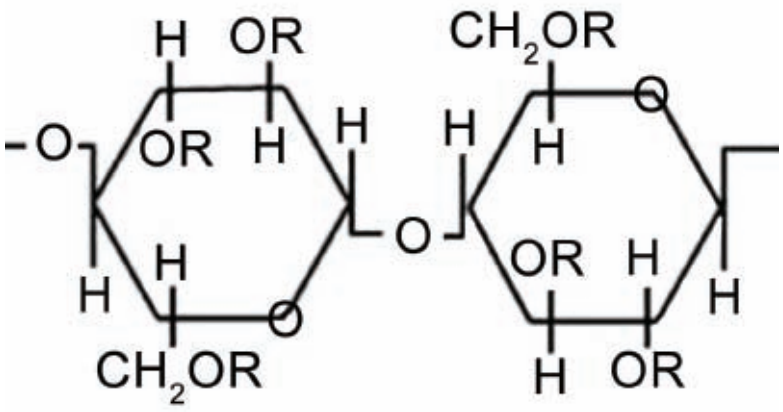
**By:** Rod Ray, PhD

Because more than half of the compounds in early development are considered poorly soluble, improving oral bioavailability represents a significant challenge to the pharmaceutical industry. Bend Research, a problem-solving, drug-development, and manufacturing company, is well-known for its spray-dried amorphous dispersion technology, which is recognized as a reliable solution to this challenge due to its proven performance, long-term stability, and excellent manufacturability.

Excipient selection is critical to optimizing the performance of these amorphous dispersions. Because excipients play a "functional" role, they must be chosen based on scientific rationale to ensure they meet formulation and process criteria to achieve the desired performance, stability, and manufacturability.

In a previous interview in this publication (May 2012), I described the company's background and problem-solving approach to drug delivery challenges faced by the pharmaceutical industry. This interview was followed by an article (July/August 2012) describing how science and technology are used to solve bioavailability challenges. In this article, the importance of functional excipients in the performance of amorphous dispersions will be discussed. A case study is presented on the history and solubilization performance of hypromellose acetate succinate (HPMCAS) - a particularly effective functional excipient in amorphous dispersions.

**FIGURE 1**




**Structure of HPMCAS**

**TABLE 1**

| Subtype | Substitution (wt%) | | | |
|---|---|---|---|---|
| | Methoxyl | Hydroxypropoxyl | Acetyl | Succinoyl |
| L | 20 to 24 | 5 to 9 | 5 to 9 | 14 to 18 |
| M | 21 to 25 | 5 to 9 | 7 to 11 | 10 to 14 |
| H | 22 to 26 | 6 to 10 | 10 to 14 | 4 to 8 |

**Substitution levels for commercial grades of HPMCAS subtypes (from Shin-Etsu product specifications).**

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**TABLE 2**

| Test | Current Procedure[a] | Specification | Source of Specification | Dow-Wolff Values |
|---|---|---|---|---|
| Appearance | Conforms | White to yellowish-white powder or pills | NF monograph | White to yellowish-white powder or pills |
| Identification | USP monograph-specified IR-ATR method[b] | The spectrum of the sample is consistent with that of the reference spectrum, similarly prepared | NF monograph | |
| Viscosity ($mm^2/s$, cP) | USP <911> | 2.4 to 3.6 | NF monograph | 2.75 |
| Purity heavy metals (ppm) | USP <231>, Method II | < 10 | NF monograph | |
| Purity arsenic (ppm) | None | < 2 | NF monograph | |
| Purity total free organic acid, dried basis (wt%) | USP monograph-specified LC method | ≤ 1.0[b] | NF monograph | 0.2 |
| Loss on drying (1 hr at 105°C) (wt%) | USP <731> | ≤ 2.5 | NF monograph | 1.6 |
| Residue on ignition (wt%) | USP <281> | ≤ 0.20 | NF monograph | 0.10 |
| Assay (1) methoxyl group, dried basis (wt%) | USP monograph-specified LC method | 12.0 to 28.0 | NF monograph | 23.6 |
| Assay (1) hydroxy-propoxyl group, dried basis (wt%) | USP monograph-specified LC method | 4.0 to 23.0 | NF monograph | 7.2 |
| Assay (2) acetyl group, dried basis (wt%) | USP monograph-specified LC method | 2.0 to 16.0<br>7.0 to 11.0 | NF monograph | 9.3 |
| Assay (2) succinoyl group, dried basis (wt%) | USP monograph-specified LC method | 10.0 to 14.0 | NF monograph | 10.7 |

[a] IR-ATR = infrared-attenuated total reflectance, LC = liquid chromatography
[b] A tighter specification of 0.2 wt% was set for a client based on a range of 0.03 to 0.05 wt% for historical lots

**HPMCAS specifications and results for a representative Dow HPMCAS lot.**

## THE IMPORTANCE OF FUNCTIONAL EXCIPIENTS

Typically, excipients have been considered "inert" ingredients in pharmaceutical formulations. However, with the advent of advanced drug delivery technologies - whether solubilization, controlled-release, or abuse resistant approaches - excipients, in some cases, become truly functional in that their composition and function are critical to the performance of the formulation and the delivery of API. This is especially true in solubilization approaches, in which the excipients have dual functionality: to promote rapid dissolution of drug in intestinal medium and to prevent the API from subsequently precipitating.

One excipient that has been demonstrated to have superior performance in filling these functions for solubilization of poorly soluble APIs is HPMCAS. Below, we provide background on this polymer, its development as a dispersion polymer, its safety, and present a Quality-By-Design (QbD) case study on the selection of HPMCAS in collaboration with Dow-Wolff Cellulosics.

## HPMCAS BACKGROUND

HPMCAS was the product of a research program initiated by Shin-Etsu Chemical Co., Ltd., in 1977 to develop a new enteric coating material. The polymer was approved for use in Japan in 1985 and was listed in Japanese Pharmaceutical Excipients in 1988. Despite its technical success as an enteric polymer, commercial adoption of the polymer was slow, and HPMCAS was

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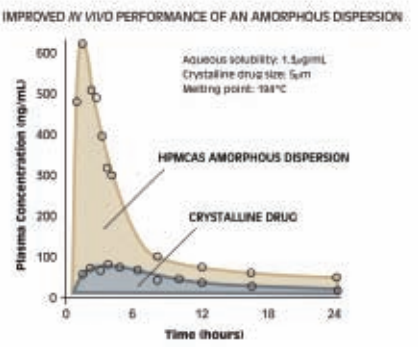
**FIGURE 2**




**Representative in vivo clinical data for a representative compound formulated as an HPMCAS amorphous dispersion.**

not included in an FDA-approved product until 2000. The monograph for this material was included in the US Pharmacopeia in 2003.

The structure for HPMCAS is shown in Figure 1, and the degrees of methoxoyl, hydroxypropyl, acetyl, and succinoyl substitution for the three available subtypes (L, M, and H) are shown in Table 1.

## DEVELOPMENT OF HPMCAS AS A DISPERSION POLYMER

In the mid-1990s, Pfizer and Bend Research began evaluating excipients to stabilize and enhance the absorption of poorly soluble APIs using amorphous dispersions.[1,2] HPMCAS was selected as a preferred polymer only after a broad evaluation of existing excipients. The ability of an HPMCAS amorphous dispersion to increase oral bioavailability is illustrated in Figure 2, which shows the clinical in vivo performance of a representative compound formulated as an HPMCAS amorphous dispersion and as crystalline drug.

To date, more than 600 compounds have been formulated as amorphous dispersions at Bend Research. More than 450 have been formulated as HPMCAS dispersions, with more than 90% showing enhanced absorption relative to crystalline forms. During these development projects, Bend Research has developed scientifically based formulation principles and methodology that allow both drug product intermediate and solid dosage forms to be robustly formulated.

The ability of HPMCAS to form drug/polymer colloids that support enhanced dissolved-drug levels in the intestine is often critical to formulation performance. It is essential to formulate both SDD and the solid dosage form for most formulations, such that the primary SDD particles can source dissolved drug and colloidal polymer. These colloids, which are shown in the representative cryo-transmission electron micrography (TEM) image in Figure 3, promote rapid dissolution of the drug into solution and serve as a stabilizing reservoir for amorphous drug.

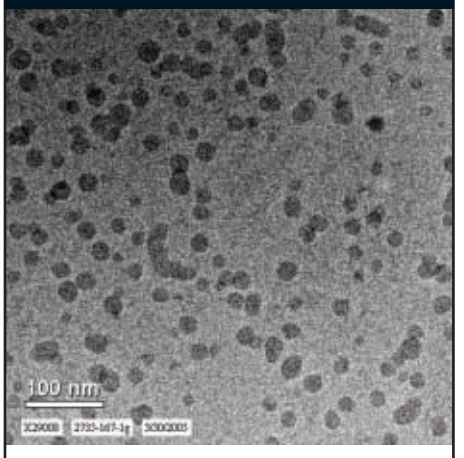
Additional critical features of HPMCAS include its high glass-transition temperature (Tg) and low water absorption, which minimizes plasticization of the dispersion at high humidities. Both of these attributes contribute to the polymer's ability to form physically stable dispersions in the solid state.

## HPMCAS SAFETY

Despite HPMCAS's approved status for its use in pharmaceutical coating applications during its early evaluations as a dispersion polymer, the Pfizer/Bend Research effort required considerable additional safety and characterization work because the amounts of polymer used in the amorphous dispersions were significantly higher than those previously used in coating applications.

Based on these studies, HPMCAS is an excipient with a demonstrated non-clinical safety record that supports its chronic use orally at high doses in human subjects. As with other cellulosic excipients, minimal absorption is

**FIGURE 3**




**Representative cryo-TEM image of drug/HPMCAS colloids in simulated intestinal fluid.**

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observed when HPMCAS is dosed orally, enabling a high margin of safety. Data from extensive non-clinical toxicology studies conducted by Pfizer have been compiled and submitted in a Type V Drug Master File (DMF) to the FDA. This comprehensive safety information for HPMCAS has been referenced to support oral drug-product formulations in early and advanced-phase clinical trials. The use of HPMCAS in clinical trials and commercial products continues to support its safety. The results of these studies are summarized below.

- All three current commercial subtypes of HPMCAS have equivalent safety profiles when administered orally to rats, dogs, and monkeys.
- Overall acute and chronic preclinical safety assessments of orally administered HPMCAS did not identify any target organ toxicity even at the highest deliverable dose by gavage.
- No safety risks have been identified from genotoxicity testing, reproductive, and developmental toxicity testing.
- ADME studies conducted with [14]C-labeled polymer demonstrated low oral absorption in rats and dogs.
- No carcinogenicity was observed in 2-year carcinogenicity studies in rats and mice.

Pfizer, Bend Research, and their licensees retain an exclusive right to reference this Type V DMF.

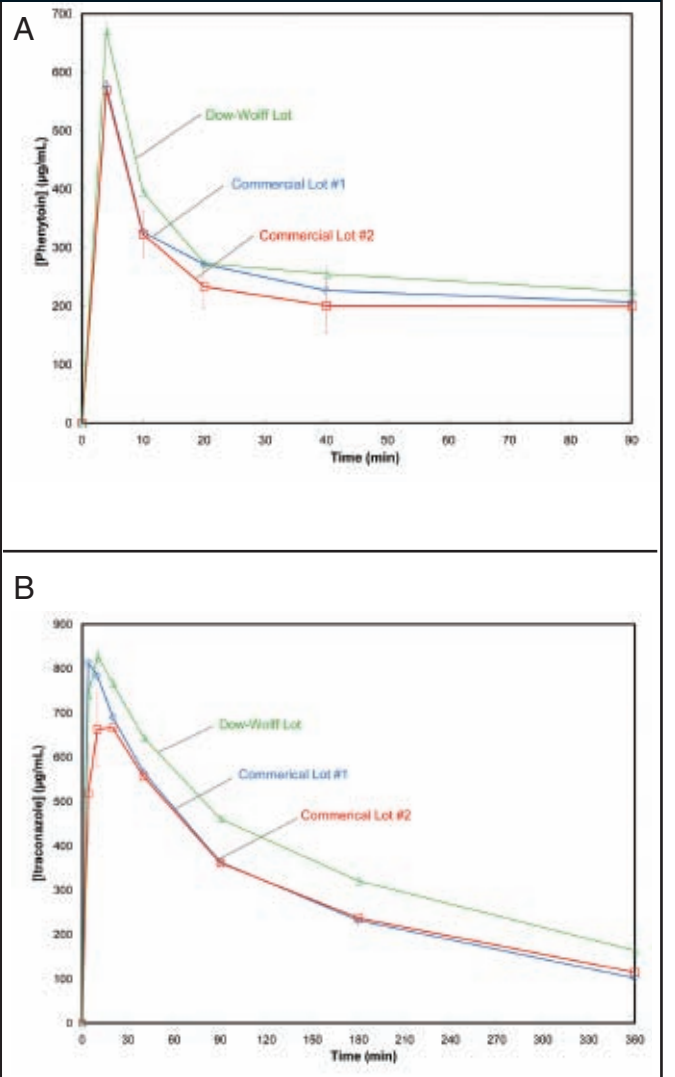
## QBD SELECTION OF HPMCAS - A COLLABORATION WITH DOW-WOLFF CELLULOSICS

In 2010, Bend Research and Dow-Wolff Cellulosics began a collaboration focused on solubilization polymers. While one goal of the work was to provide an alternate source of HPMCAS, a secondary goal was to explore a broader chemistry composition space than what is available from commercial materials.

In work to provide an alternate HPMCAS source, as the data in Table 2 show, the HPMCAS produced by Dow-Wolff is within the National Formulary (NF) monograph specifications for the M polymer subtype.

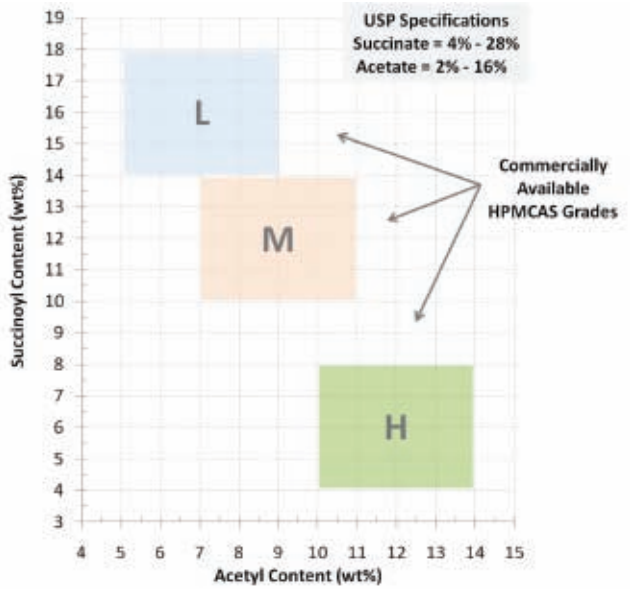
In addition to meeting compositional requirements, Figure

**FIGURE 4**




**Performance data for two model compounds - phenytoin (a) and itraconazole (b) - demonstrating that Dow-Wolff HPMCAS is equivalent to commercially available HPMCAS.**

**FIGURE 5**




**Acetate and succinate substitution levels for commercially available HPMCAS (USP specifications shown for comparison).**

4 shows the in vitro performance for two model compounds using Dow-Wolff HPMCAS compared to the commercially available material. As these data demonstrate, the HPMCAS produced in the Dow-Wolff market development facility has comparable performance to that of commercially available material.

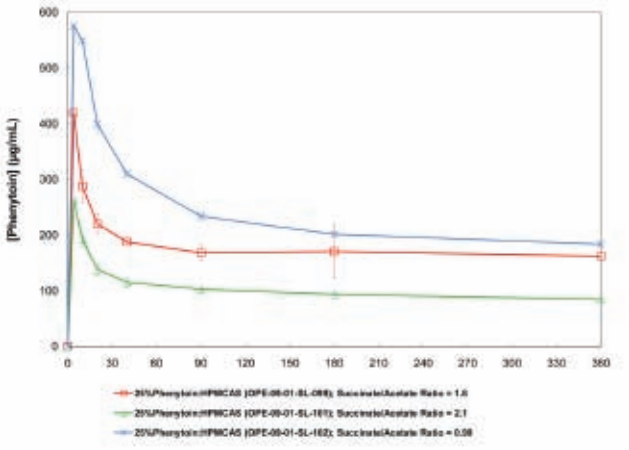
The second goal of this work was to develop materials that expand the compositional space that is not addressed using the currently available commercial grades of HPMCAS. Figure 5 shows the succinoyl and acetyl chemistry spaces covered by the commercially available grades of polymers and the USP-defined chemistry space. As this figure clearly shows, there is considerable space to explore beyond what is covered by the commercial grades of HPMCAS.

To understand the potential of the HPMCAS made by Bend Research and Dow-Wolff in different chemical spaces, the impact on the in vitro solution performance of two model compounds - phenytoin and itraconazole - was tested as a function of acetate and succinate content across the USP chemical space. Obviously, other compositional changes, such as methoxyl and propoxyl, could also be investigated. Representative in vitro microcentrifuge dissolution data for phenytoin is shown in Figure 6 as a function of succinate/acetate ratio.

These and other data are plotted, showing the area under the curve (AUC) as a function of the succinate/acetate ratio in Figure 7a and 7b. As these data demonstrate, the average substitution in the HPMCAS has a considerable impact on in vitro performance. In addition, it is clear that the optimum HPMCAS composition for solubilization depends strongly on the API, with the maximum dissolution performance observed around succinate/acetate of 0.5 for phenytoin and above 1.0 for itraconazole.

These performance data demonstrate that the science surrounding dispersion polymers and amorphous dispersions can be used to design polymer compositions that are within the compendial space, but lead to optimized performance.

**FIGURE 6**




**Representative in vitro performance data for the model compound phenytoin.**

## FUTURE DIRECTION

HPMCAS has proven to be a superior excipient for use in amorphous dispersions for more than 15 years. Based on the initial data from Bend Research and Dow-Wolff Cellulosics' HPMCAS QbD studies, it is clear that much more can be learned about the structure-property and structure-performance correlations of this class of polymers and how this information can be used to optimize performance for different classes of API. Our collaboration with Dow-Wolff continues to push the boundaries of this and other chemistry spaces. ◆

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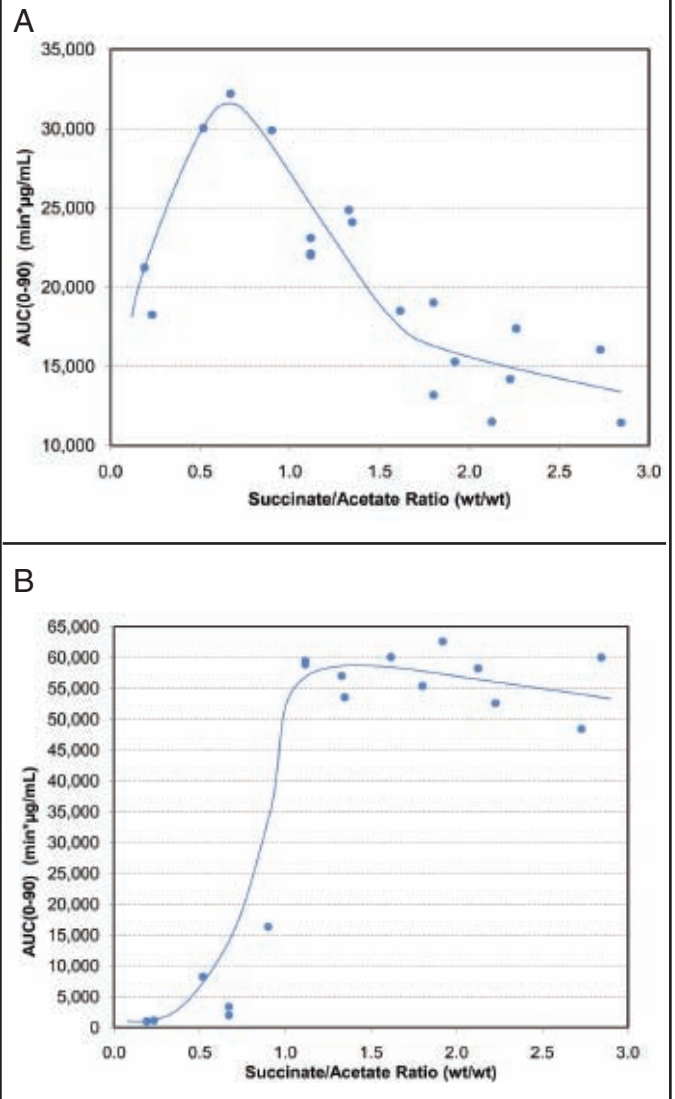
2. Friesen DT, Shanker RM, Crew MD, Smithey DT, Curatolo WJ, Nightingale JAS. Hydroxypropyl methylcellulose acetate succinate-based spray-dried dispersions: an overview. Mol Pharm. 2008;5:61003-1019.


## FIGURE 7




**Microcentrifuge AUC0-90 as a function of succinate/acetate ratio for phenytoin (a) and itraconazole (b).**

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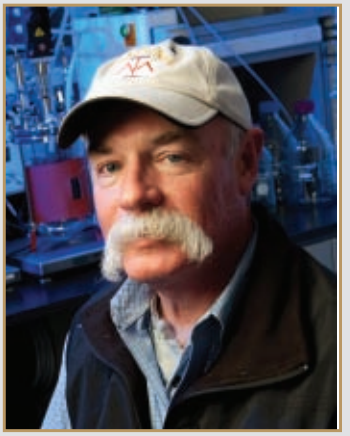

**Dr. Rod Ray** is Chief Executive Officer and Chairman of the Board at Bend Research, where he has worked since 1983. During his time at Bend Research, Dr. Ray has held numerous positions specializing in the development and commercialization of a wide range of products. He has been instrumental in directing the management of large-scale programs to advance pharmaceutical compounds through the development process to commercialization, serving as the primary management contact for client companies. In addition to his expertise in advancing pharmaceutical processes and products, Dr. Ray has extensive experience in commercializing diverse products for the electronics, energy, medical, agricultural, and space industries. He earned his BS in Chemical Engineering from Oregon State University, and his MS and PhD in Chemical Engineering from the University of Colorado - Boulder. He is a licensed Professional Engineer in Colorado and Oregon. Dr. Ray holds 21 US patents and has 41 scientific publications to his credit.

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# The Rise of the Bolus Injector - A New Device Class Enabling Long-Duration Subcutaneous Administration of Large-Dose Volume Biologics

**By:** Alan Shortall

The commercial potential of many biologics has until now been constrained by their very nature. A new class of wearable, disposable devices known as bolus injectors has been developed to address emerging market needs for the subcutaneous delivery of biologics requiring dose volumes greater than 1 mL.

A fundamental challenge facing pharmaceutical companies developing monoclonal antibodies, peptides, and other emerging biologics has been to find the right formulation balance between viscosity and volume.

Too viscous, and the pressure for a subcutaneous injection becomes too great for the use of a standard prefilled syringe or auto-injector. Drug safety and efficacy issues relating to aggregation may also arise in which the concentration of a liquid formulation is too high.

Too much volume, and there is a high risk of compromising the subcutaneous layer's capacity to absorb more than 1mL of drug over a standard injection period of several seconds. Attempts to force the subcutaneous injection of large volume doses can be painful to a patient, creating risks such as tissue distortion, edema, irritation, or redness. Therapy compliance may also be affected when patients must hold a device optimally at the injection site for more than 15 seconds due to a natural loss of attention and a likely change in angularity.

For biologics that can attain a liquid dose volume of 1mL or less, there are attractive commercial opportunities to gain approval for subcutaneous self-administration by the patient in a prefilled syringe or auto-injector format.

**FIGURE 1**

**Unilife bolus injectors are modular and scalable in design to accommodate the specific dose volume, viscosity, and delivery duration requirements of a target molecule.**

However, an estimated 15% and 20% of all biologics now in clinical development will need to be formulated in a concentration in which the dose volume is greater than 1ml, and delivery periods make the use of a hand-held device unfeasible.

Some pharmaceutical and biotechnology companies have found some level of compromise by securing approval for their large-dose volume molecules to be delivered via IV administration in a healthcare facility or clinic. However, many other highly promising pipeline molecules won't reach patients until a suitable delivery system is identified that can enable their commercialization for patient subcutaneous self-administration.

## A NEW DEVICE CLASS

With so many biologics in clinical development or approved and requiring lifecycle management to improve or

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protect market share, the development of wearable, disposable delivery systems for the subcutaneous delivery of large-dose volume drugs is considered by many to be one of the greatest unmet needs in the pharmaceutical industry today.

Several device manufacturers, including Unilife, have developed a new class of devices to address the primary container, dose delivery, and patient needs of these large-volume biologics. Once called patch pumps or micro-pumps, these devices are now increasingly referred to as bolus injectors.

There are many fundamental differences between the traditional pump-based devices used for insulin and those required for the delivery of biologics. Insulin pumps are a highly effective and patient-friendly delivery system for providing therapy for diabetics. But they are far too complex and expensive for the delivery of biologics, which only require the administration of a standardized dose to the patient on a periodic basis.

Until recently, it was impossible for a pharmaceutical company to access a disposable device technology that could facilitate the self-administration of a bolus or rate-based therapy with a dose volume greater than 3 mL. In one recent case, a pharmaceutical company required a device to deliver a biologic with a 6 mL dose volume. A device manufacturer advised them to use two 3-mL pumps for attachment onto the patient at the same time. Understandably, the pharmaceutical company pursued other opportunities to identify a device platform that could address its specific needs.

A bolus injector represents a very distinct and separate device classification to insulin pumps, which naturally warrant a higher level of regulatory scrutiny because of their need to precisely deliver a variable dose. By contrast, the role of a bolus injection system is to deliver a standardized dose volume into the subcutaneous layer over a designated period of time. It is designed to be either worn on the body, or attached onto the belt of the patient, for the period of dose delivery. After the completion of the full dose, the device is removed from the body and disposed.

While bolus injectors are primarily designed for use with molecules with dose volumes greater than 1 mL, they are also ideal for therapies with lower-dose volumes and a high viscosity, which are better suited to subcutaneous injection over a period of 30 seconds or more.

**FIGURE 2**

**Bolus injectors are designed for intuitive use, comfortable wear, and convenient disposal by patients.**

## ENHANCE & ENABLE

Bolus injectors create several significant commercial opportunities for pharmaceutical companies developing biologics and other large-dose volume drugs. They can help to enable the clinical development of pipeline drugs in larger dose volumes that avoid the aggregation and patient discomfort risks associated with high concentrations. They offer compelling lifecycle management opportunities to transition approved drugs that are currently indicated for IV infusion into a subcutaneous injection format. They can also help a drug generate significant brand differentiation against competitors within a therapeutic class, or potentially expand the number of indications of which it may be prescribed.

With so many biologics and other large dose volume drugs now being considered for use with bolus injectors, Unilife expects this new and fast-growing device market will be valued at more than $500 million within a few short years. Bolus injection systems create many compelling benefits for pharmaceutical companies, patients, payers and prescribers.

Many pharmaceutical companies now recognize the

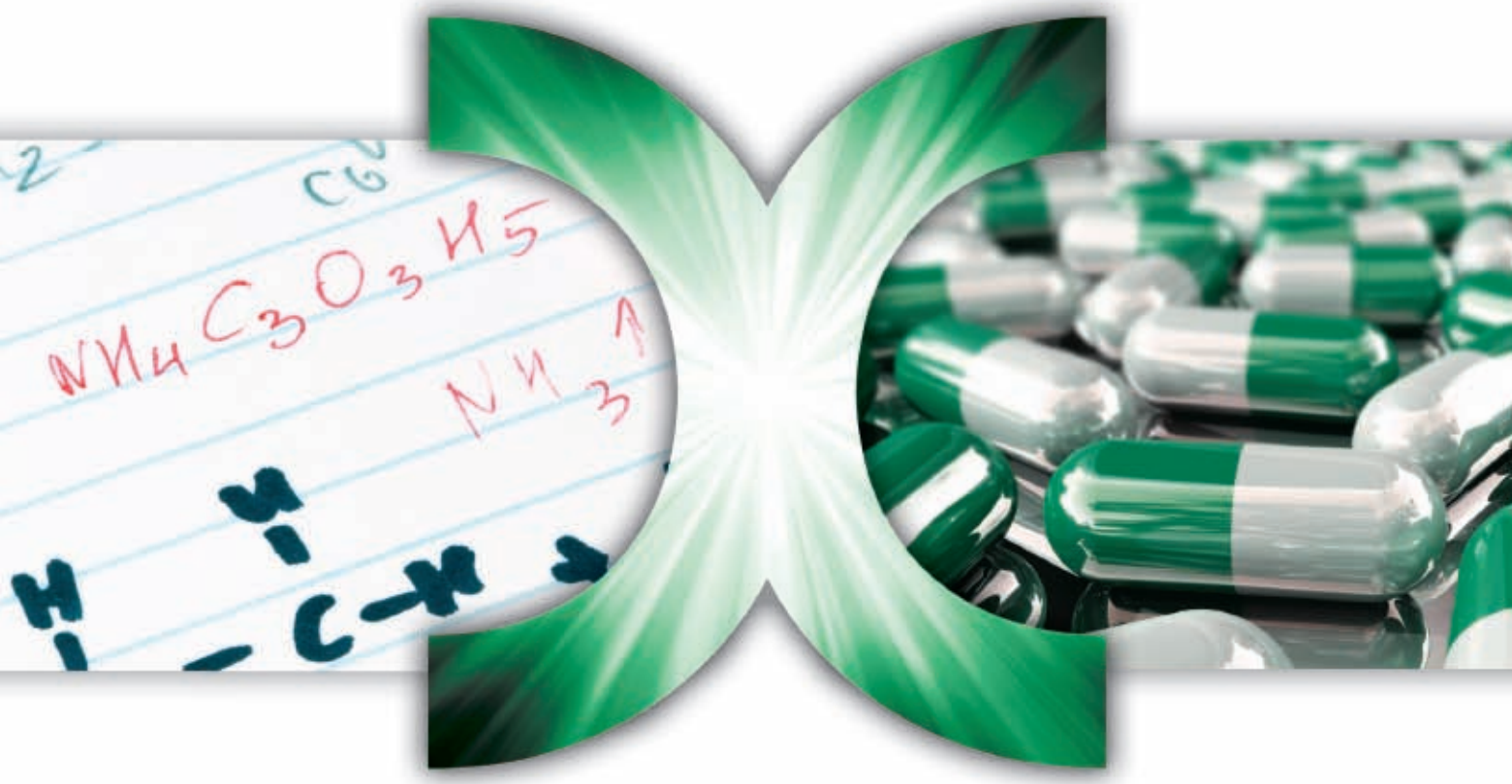

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**FIGURE 3**

**The compact size and simplicity of bolus injectors can help to build patient preference and improve therapy compliance.**

significant potential of bolus injectors to enable or enhance the delivery of biologic therapies across a range of acute and chronic conditions, including auto-immune diseases, central nervous system, infectious diseases, and oncology.

For patients, they can improve quality of life, generate greater independence, and encourage greater therapy convenience and compliance. Payors can leverage these improved rates of compliance and continuation to transition healthcare from the healthcare facility to the home, which will significantly reduce treatment-related costs. The safety and simplicity of these devices can also mean more prescribers can administer a drug for use.

## A MODULAR, FLEXIBLE PLATFORM

Unilife, a US-based developer, manufacturer, and supplier of innovative, differentiated devices for injectable drug delivery, has quickly attained a leadership position within this new and fast-growing market sector. It has developed a comprehensive platform of bolus injecors to simplify the commercial development and patient delivery of biologics between 1 mL and 30 mL in volume.

In recognition of the fact that every customer, drug, and target patient population has specific requirements, Unilife has created a platform that combines simplicity and flexibility.

One of the fundamental requirements established upfront by Unilife in the development of its bolus injector technology was to simplify the process of getting the drug into the primary container. Accordingly, Unilife's range of bolus injectors feature a primary container made of standard USP-compliant materials in the fluid path. They are also designed for supply to customers ready for integration into regular filling lines.

The goal of Unilife during every program with a pharmaceutical customer is to enable the target patient to get on with their lives with minimal inconvenience during the period of dose administration. Steps of use must be as intuitive as possible. The device footprint from a height, width, and contour perspective must also be minimal. As a result, every Unilife bolus injector is not only very compact, sleek, and elegant in design, but incorporates human factor engineering so that it is tailored to address the specific needs of the target patient population. External customization options include the contoured shape of the device, the number or position of the activation buttons, and color configurations.

The steps of use for a Unilife bolus injector are highly intuitive for patient self-administration. After removal of an adhesive liner from the bottom of the device, it is placed onto the body. An on-body interlock mechanism prevents accidental initiation of dose delivery from occurring before the operator is ready. After pushing the button when the patient is ready to start the injection, a soft indwelling cannula is automatically inserted into the subcutaneous layer to administer the dose with minimal pain or irritation. The device is then programmed to automatically deliver the dose at the speed and duration designated by the pharmaceutical customer.

An electronic user interface conveys key information to the patient, with tones and colors indicating the status of the device during each stage of dose delivery. Furthermore, no sharp is exposed during any stage during usage of the device, to virtually eliminate the risk of needlestick injury to the patient or those downstream following its compact, convenient disposal.

Many of the pharmaceutical companies now working with Unilife are attracted to the modular, flexible nature of its family of bolus injectors. Most of these companies require access to a technology platform from which they can customize each device to the specific needs of a series of pipeline molecules and target patient populations.

In recognition of the fact that every molecule is different, Unilife can customize every device across a number of

internal areas, including dose volume, drug viscosity, and injection delivery duration.

Unilife's Precision-Therapy™ range of bolus injectors are designed for use with bolus-based therapies that require short or long duration injections. The Flex-Therapy™ range of bolus injectors are designed for use with rate-based therapies that require subcutaneous infusion over a longer duration of time in which the delivery rate is controlled for hours or days.

Unilife's philosophy is not to force pharmaceutical companies into the use of one particular material or supplier for components, such as glass or elastomers. It has developed an open architecture model for materials management whereby it works in parallel with the customer to select preferred component materials from a network of established, validated suppliers. With Unilife able to configure every device around the material management preferences of a customer, it is a provider of an integrated delivery system rather than just rigid commodity components.

## HUMAN CLINICAL DRUG TRIALS

Unilife's bolus injectors are now ready for evaluation by pharmaceutical companies for prospective use in human clinical trials for large-dose volume injectable therapies. Unilife is already working with a number of pharmaceutical and biotechnology companies to customize each device to address the specific needs of a series of pipeline and approved molecules.

Following head-to-head user acceptance and preference studies conducted by some pharmaceutical customers, Unilife has been advised its bolus injectors have been selected to enter the next phase of evaluations for use with a number of pipeline drugs. Upon successful completion of these evaluations, Unilife expects its products will be considered by pharmaceutical customers for the target launch of a number of biologic therapies. ◆

## BIOGRAPHIES

**Mr. Alan Shortall** is the Founder, CEO, and Executive Director of Unilife Corporation, a US-based developer and commercial supplier of injectable drug delivery systems. Established in 2002, it builds long-term collaborations with pharmaceutical and biotechnology companies seeking to utilize its innovative and highly differentiated devices to enable or enhance the clinical development, regulatory approval, and lifecycle management of their injectable therapies. Mr. Shortall has guided the development by Unilife of one of the most expansive and market-driven portfolios of primary drug containers and advanced delivery systems available for the administration of injectable therapies. Device platforms include prefilled syringes with integrated needle retraction, auto-injectors, drug reconstitution delivery systems, bolus injectors, and other specialized delivery systems. For more information, visit www.unilife.com.

# TAMPER-DETERRENT TECHNOLOGY

# OraGuard™: A Tampering-Deterrent & Alcohol-Resistant Extended-Release Technology

**By:** Dinesh Haswani, PhD; John Nagel, MBA; Derek Moe, PhD; and Ehab Hamed, PhD

## INTRODUCTION

In US, abuse, misuse, and diversion of prescription opioids are a growing problem. Americans are the world's largest consumer of opioid products with 80% of the world's supply of opioids and 99% of the hydrocodone being dispensed in the US.[1] From 1998 to 2007, the US saw a steep increase in the number of prescriptions for opioids through US outpatient retail pharmacies. For hydrocodone, the increase was 172% from 2.68 to 7.28 billion units dispensed. For oxycodone, the increase was 314% from 725 million to 3 billion units dispensed.[2]

Data from the National Survey on Drug Use and Health (NSDUH) shows that an increasing number of individuals aged 12 or older have abused illicit and/or prescription drugs.

- In 2010, an estimated 3 million people used an illicit drug for the first time within the past 12 months of this survey interview.[3]
- Almost 22.6 million Americans had used an illicit drug (marijuana/hashish, cocaine, heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used non-medically) during the month prior to the survey interview.[3]
- In 2009-2010 of those who used pain relievers non-medically, 55% got the drug from a friend or a relative for free. Other sources were through a prescription from doctor, from a drug dealer, or by purchasing them on the internet.[3]

Also among abusers, there is a major underestimation of the risk associated with casual illicit prescription drug use. Almost one third of teens (grade 7 to 12) do not believe there is a great risk in abusing prescription medicine, and 30% believe

FIGURE 1

**OraGuard™ provides resistance against various tampering methods.**

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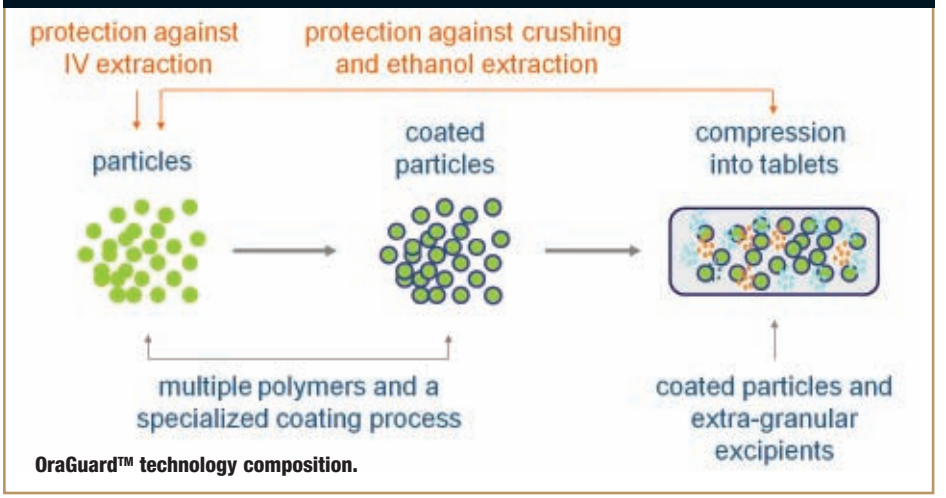
prescription pain relievers are not addictive.[4]

According to Drug Abuse Warning Network, in 2007, the estimated economic cost of illicit drug use to society was more than $193 billion. There were approximately 2 million emergency room visits related to non-medical use in 2009. The healthcare costs for non-homicide emergency department visits related to drug use are estimated to be $161 million annually, and the hospital admissions (including treatment for illicit drug use) would be an additional $5.5 billion.[5] This data demonstrates the burden on the healthcare system and shows the extent to which the prescription drug problem is prevalent in the US that demands action from healthcare providers, manufacturers, and law makers.

Several initiatives are ongoing or have been proposed to address the growing abuse of opioids, such as:

- Designing novel formulations and drug delivery systems intended to deter casual abusers from tampering with the drug product.
- Continuing advancement in the design and evaluation of epidemiological studies to address changing patterns of abuse.
- Training of healthcare providers on responsible opioid prescription practices.

**FIGURE 2**




**OraGuard™ technology composition.**

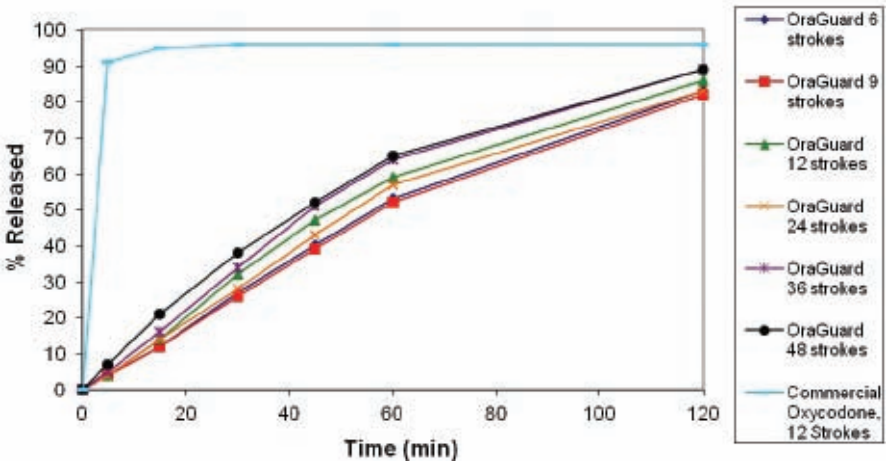
- Requiring manufacturers through the Opioid Risk Evaluation and Mitigation Strategy (REMS) to develop effective educational materials for healthcare providers and patients on proper prescribing and disposal of opioid pain relievers.
- Providing guidance to pharmaceutical industry on the development of abuse-deterrent drug formulations and on post-market assessment of their performance.

Pharmaceutical manufacturers have attempted several tamper-deterrent mechanisms in order to limit the abuse potential of an opioid formulation. The interest in developing tamper-deterrent formulations increased with the passage of the Food and Drug Administration Amendments Act of 2007, which provided the FDA with the authority to require drug sponsors to submit and implement Risk Evaluation and Mitigation Strategy (REMS). In February 2009, the FDA sent letters to 15 manufacturers of 24 currently approved opioid products indicating their products require REMS.[7] Later that year, the FDA published its Guidance for Industry, reflecting the agency's general views on the format and content of REMS.[8] In January 2010, the FDA published guidance on Assessment of Abuse Potential of Drugs that recommends including an abuse potential assessment as a section for the NDA or supplement. This section contains all pertinent preclinical, pharmacological, chemistry, biochemical, human laboratory, and clinical studies, drug formulation data, and proposal for appropriate scheduling.[6] The FDA Draft Guidance concurs that tamper-deterrent formulations are expected to provide incremental improvement in combating abusers' tampering techniques.

## ABUSE DETERRENT MECHANISMS

The selection of tamper-deterrent features is generally based on the following

## FIGURE 3




**OraGuard™ technology imparting resistance against simulated oral tampering techniques. The commercial oxycodone product used in this study was later reformulated by its manufacturer to impart tampering-deterrent features.**

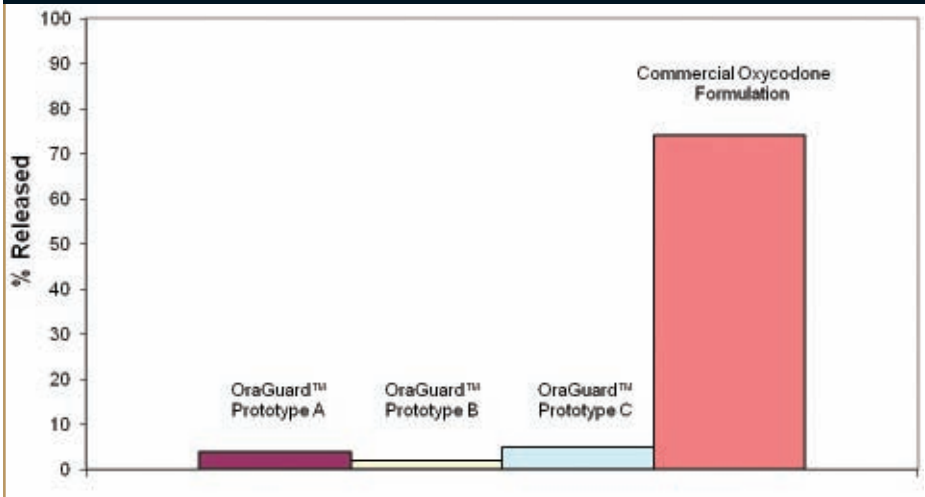
questions: Who is going to abuse these formulations? and what forms of tampering are abusers likely to employ? Most people who are tampering with formulations are casual abusers. Some of the common forms of tampering are crushing, chewing, snorting, smoking, and injection. These tampering methods can lead to exposure to large amounts of drug, which increase the euphoric affect that abusers desire. This is especially true for extended-release formulations that can contain up to a full day's dose in one tablet or capsule. The increased exposure may also cause adverse effects, such as sedation or clouded mentation, nausea, vomiting, constipation, respiratory depression, or even death.

The best approach to address prescription opioid abuse would be to develop molecules that can alleviate pain but have no or minor euphoric and physical dependence effects. Thus far, no molecules with these attributes have been successfully identified. Therefore, to tackle the problem of opioid abuse, pharmaceutical manufacturers are focusing on the development of tamper-deterrent formulations for existing molecules.

The tamper-deterrent mechanism may involve providing a physical barrier to reduce the chance that an opioid formulation can be altered by physical or chemical manipulation. Physical barriers can be in the form of a thick and strong coat on a drug-loaded core.[9] The core can be in the form of small particles, tablets, or capsules. Or the drug can be distributed through a matrix that can be made of fat or wax, gelling polymers, or plastic polymers.[10-14] In all cases, the excipients are selected to impart crushing and solvent resistance (owing to their physico-chemical properties and how they are used within the dosage form). Another approach relies on simply making very strong tablets that are hard to break with commonly available utensils, such as spoons, cigarette lighters, porcelain mugs, etc.

One of the abuse-deterrent mechanisms involves administering an opioid as a prodrug, which is converted to its active form via hepatic metabolism after ingestion.[15] This delays the time to reach maximum concentration. Also, when ingested in large quantities, it may saturate the metabolic system and consequently the biotransformation to the active form may be

## FIGURE 4




**OraGuard™ technology imparting resistance against simulated IV tampering techniques. The commercial oxycodone product used in this study was later reformulated by its manufacturer to impart tampering-deterrent features.**

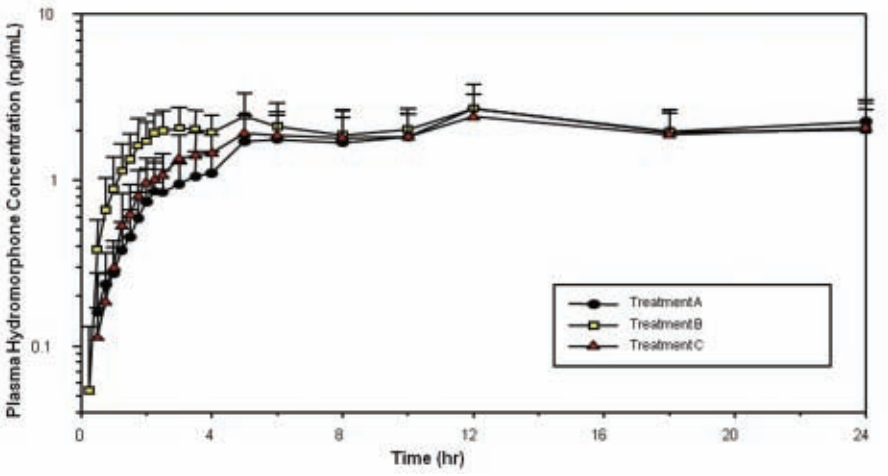
limited thus reducing the euphoria. Some tamper-deterrent formulations may contain an opioid antagonist in combination with opioid agonist, such as naloxone and buprenorphine or oxycodone and naltrexone; the antagonist is released along with agonist when the dosage form is tampered, which significantly reduces the rapid euphoric effects of the opioid.

Aversion agents have also been utilized as deterrent mechanisms. With this mechanism, the opioid product may be incorporated along with aversive agents, such as niacin and capsaicin, which are released along with the opioid when the dosage form is tampered. Niacin, if taken in excessive dose, produces warmth, flushing, and other uncomfortable symptoms. Capsaicin, if crushed and snorted or dissolved and injected, would cause a severe burning that would deter abusers from tampering the product.[15]

An additional feature that a tamper-deterrent formulation may offer is its resistance to accidental alcohol-induced dose dumping. Extended-release pharmaceutical formulation of opioids and other drugs with narrow therapeutic window and/or potential pharmacological interaction with alcohol are expected to offer resistance against alcohol-induced dose dumping. Extended-release opioid formulations that rely on an alcohol-susceptible mechanism to extend the drug release carry the risk of dumping its entire dose of opioid when co-ingested with alcohol that can lead to serious and potentially fatal adverse reactions. Such phenomenon was highlighted by the voluntary withdrawal of the extended-release hydromorphone product from the US market in 2005.[16]

In order to protect against tampering and accidental alcohol-induced dose dumping, CIMA LABS developed the OraGuard™ tamper deterrent and alcohol resistant, extended release drug delivery platform.

## FIGURE 5

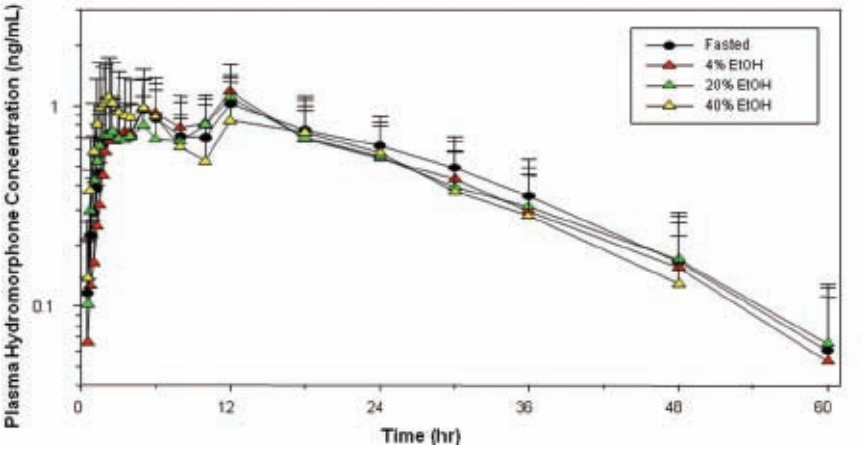



**Pharmacokinetic profiles of Single Dose OraGuard™ extended-release hydromorphone formulations in healthy fasting subjects.**

## ORAGUARD™ TECHNOLOGY

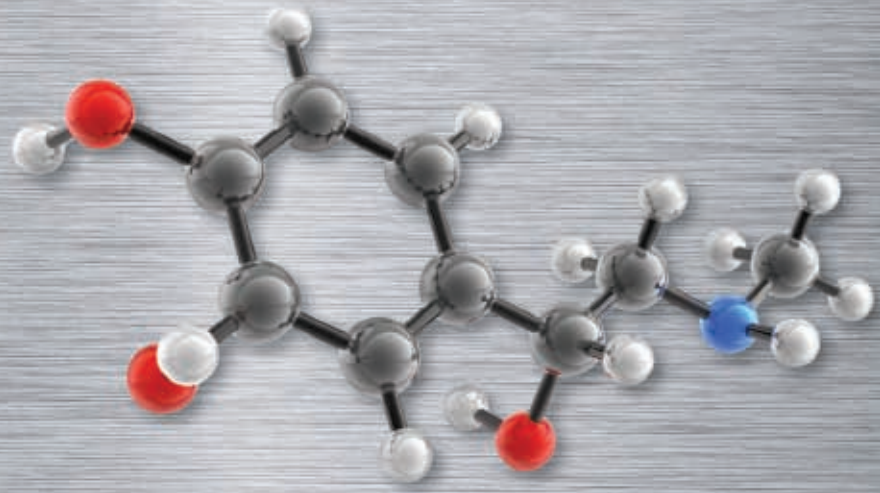
The OraGuard technology developed by CIMA LABS is an extended-release, tamper-deterrent and anti-alcohol-induced dose-dumping platform. The formulations developed using OraGuard technology provide overlapping resistance against various tampering methods, such as crushing and ingestion, chewing, small-

## FIGURE 6




**Single dose pharmacokinetic study in healthy fasting subjects confirmed OraGuard™ technology's success in preventing hydromorphone dose dumping when co-ingested with 4%, 20%, and 40% alcohol.**

# POWERING INNOVATIONS IN



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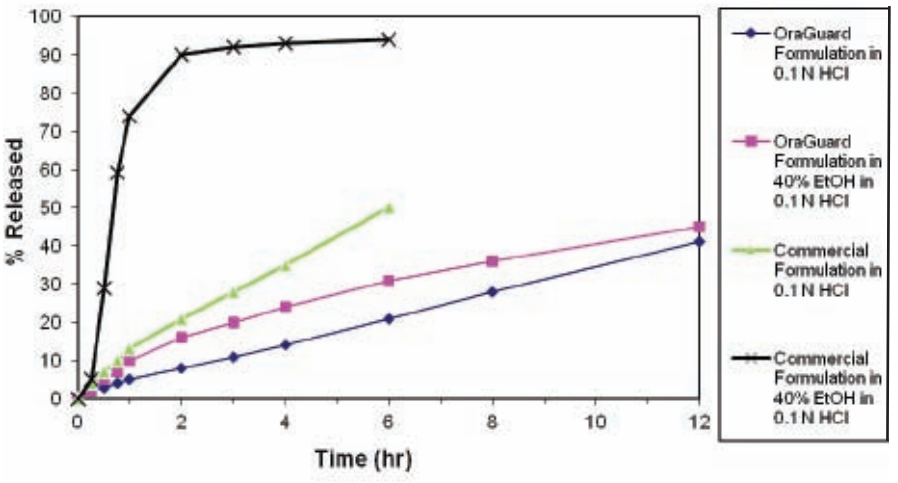



**Dose dumping comparison for OraGuard™ and commercially available Metoprolol Succinate formulations.**

volume extraction for IV injection, and snorting (Figure 1).

The OraGuard technology is a multistep process in which the drug is granulated with high load of polymers (Figure 2). These polymers are specifically selected for their water and alcohol solubility. Then the granules are coated with a strong film-forming polymer and compressed with gel-forming polymers. Due to these polymers and the tablet composition, the final formulation has tamper-deterrent characteristics and is resistant to intentional and unintentional dose dumping in the presence of alcohol.

## RESISTANCE OF ORAGUARD™ FORMULATIONS TO ORAL AND IV TAMPERING

One of the common tampering methods used by abusers is to crush the dosage forms to release the drug, which could then be ingested orally. Optionally, the abusers could crush the dosage form and then use solvents, such as boiling water in order to extract the drug from the dosage form and then inject for the euphoric effects. OraGuard formulations impart resistance to these physical forms of tampering as evident further in Figure 3 and Figure 4. Figure 3 compares the extraction efficiency of an OraGuard extended-release formulation to a commercial oxycodone product when subjected to the common methods of physical tampering. Extraction efficiency is defined as the percent oxycodone released from an OraGuard formulation when subjected to common methods of physical tampering. It is important to note that the commercial oxycodone product used in this study was later reformulated by its manufacturer to impart tampering-deterrent features. In this study, the OraGuard tablets and the commercial oxycodone tablets were crushed to fine powder using pestle and mortar, and the release profile of resulting powder was determined using standard dissolution apparatus/media. As seen in Figure 3, the OraGuard formulation prevented the complete extraction of oxycodone even though the OraGuard tablets were subjected to higher number of crushing strokes, whereas the commercial oxycodone formulation released ~90% oxycodone within 5 minutes.

Figure 4 compares the simulated IV tampering of OraGuard formulations to a commercial oxycodone formulation. This commercial oxycodone product was later reformulated by its manufacturer to impart tampering-deterrent features. In this study, the OraGuard prototypes and the commercial oxycodone formulations were crushed with a pill crusher followed by extraction by boiling in water for 5 minutes. The three OraGuard prototype formulations were resistant to complete extraction (≤ 5% drug released) by this tampering method, whereas >70% drug was released from the commercial oxycodone formulation.

## RESISTANCE OF ORAGUARD™ FORMULATIONS TO ALCOHOL-INDUCED DOSE DUMPING

The OraGuard formulation prevents any notable dose dumping with the co-ingestion of up to 40% alcohol, as evident with a OraGuard extended-release hydromorphone formulation.

Figure 5 displays the pharmacokinetic profiles of three OraGuard extended-release hydromorphone formulations with different

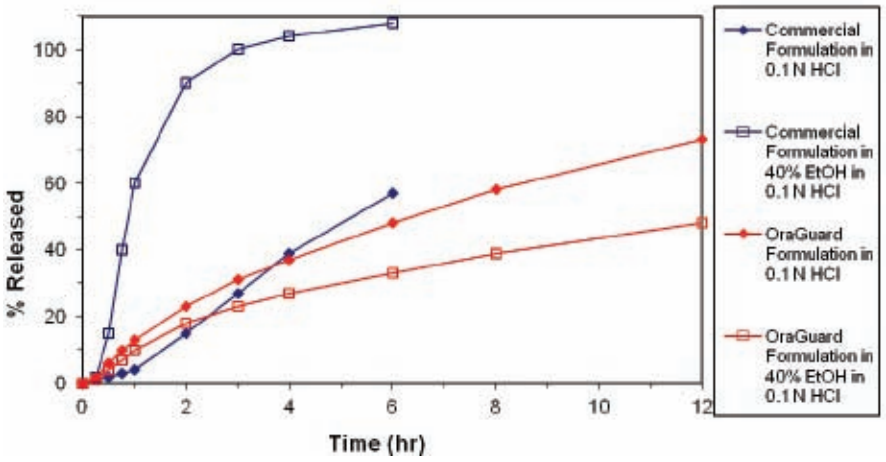
coat levels and granule formulation. The formulations were intended for once-daily dosing. A randomized crossover study was conducted to assess the effect of co-ingestion of 4%, 20%, and 40% alcohol on the pharmacokinetics of OraGuard hydromorphone formulation in healthy subjects. The results are shown in Figure 6. The OraGuard formulation prevented any notable dose dumping with the co-ingestion of up to 40% alcohol.

OraGuard's resistance against alcohol-induced dose dumping is applicable to other drugs beyond those that carry abuse potential. As described previously, extended-release formulations for drugs with narrow therapeutic windows or drugs with pharmacological interaction with alcohol must carry resistance against alcohol-induced dose dumping. Figures 7 and 8 display the in vitro release profiles in 0.1N HCl as well as 0.1N HCl in presence of 40% v/v ethanol for OraGuard formulations of metoprolol succinate and venlafaxine hydrochloride. Both the OraGuard formulations are less susceptible to dose dumping in the presence of alcohol compared to commercially available metoprolol succinate and venlafaxine hydrochloride formulations.

## SUMMARY

The growing non-medical use of opioids is a major challenge for lawmakers, doctors, and pharmaceutical companies. One way to address this challenge is to limit the abuse by offering tamper-deterrent characteristics to opioid products. OraGuard technology is a tamper-deterrent and alcohol-resistant extended-release formulation platform for opioids. It is also adaptable to a wide variety of other molecules. The platform is designed to provide resistance against common abusers' techniques, including crushing, chewing, small-volume extraction for IV injection, and snorting. OraGuard opioid formulations have been extensively evaluated for their tamper-deterrent features using a battery of in vitro simulated tampering techniques, multiple pharmacokinetic studies, an abuse likeability study, and safety and efficacy studies. All of the excipients used in OraGuard formulations are compendial, and the processes use standard equipment that has been successfully scaled up to commercial equipment. The first commercial product based on OraGuard technology is expected to be available in 2014. ◆

**FIGURE 8**




**Dose dumping comparison for OraGuard™ and commercially available Venlafaxine Hydrochloride formulations.**

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## BIOGRAPHIES

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# Recombinant Human Albumin:Delivering the Future of Type 2 Diabetes Medication

**By:** Mark Perkins, PhD

## INTRODUCTION

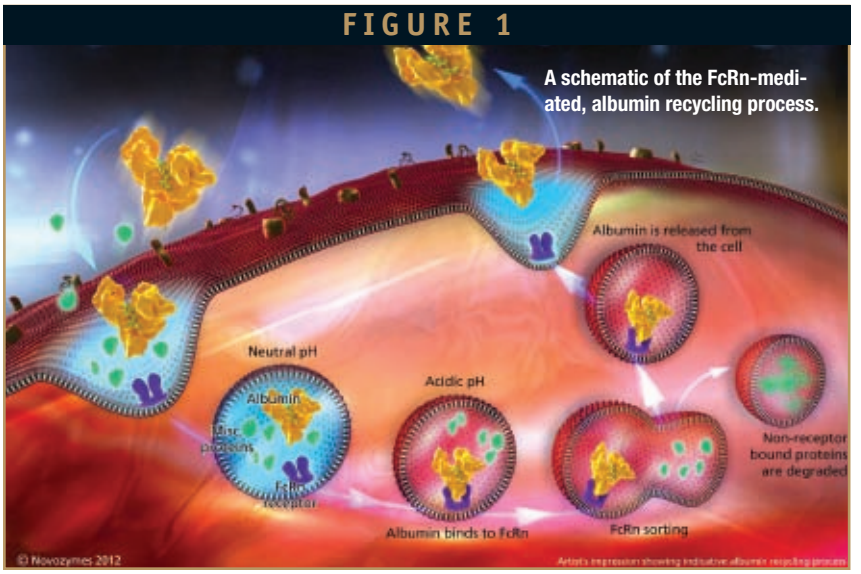
The number of people with diabetes is expected to rise to approximately 300 million by the year 2030; of this number, some 90% will have the type 2, non-insulin dependent form of the disease.[1] The major goal in the treatment of type II diabetes is to achieve and maintain glycaemic control as episodes of hyperglycaemia are associated with the risk of microvascular and macrovascular complications.[2] Treatment for type 2 diabetes is typically incremental, starting with the modification of diet and introduction of exercise followed by the introduction of an orally active diabetic medication.[3] Despite the wide range of available oral medications, many patients fail to achieve appropriate glycaemic control and will ultimately require the introduction of injectable insulin. A particular focus area of research for the treatment of type 2 diabetes is the development of alternative and supportive therapies to oral diabetic agents that reduce the need for the introduction of insulin. In particular, analogues of the natural GLP-1 peptide have become an important class of molecules in this area.[3]

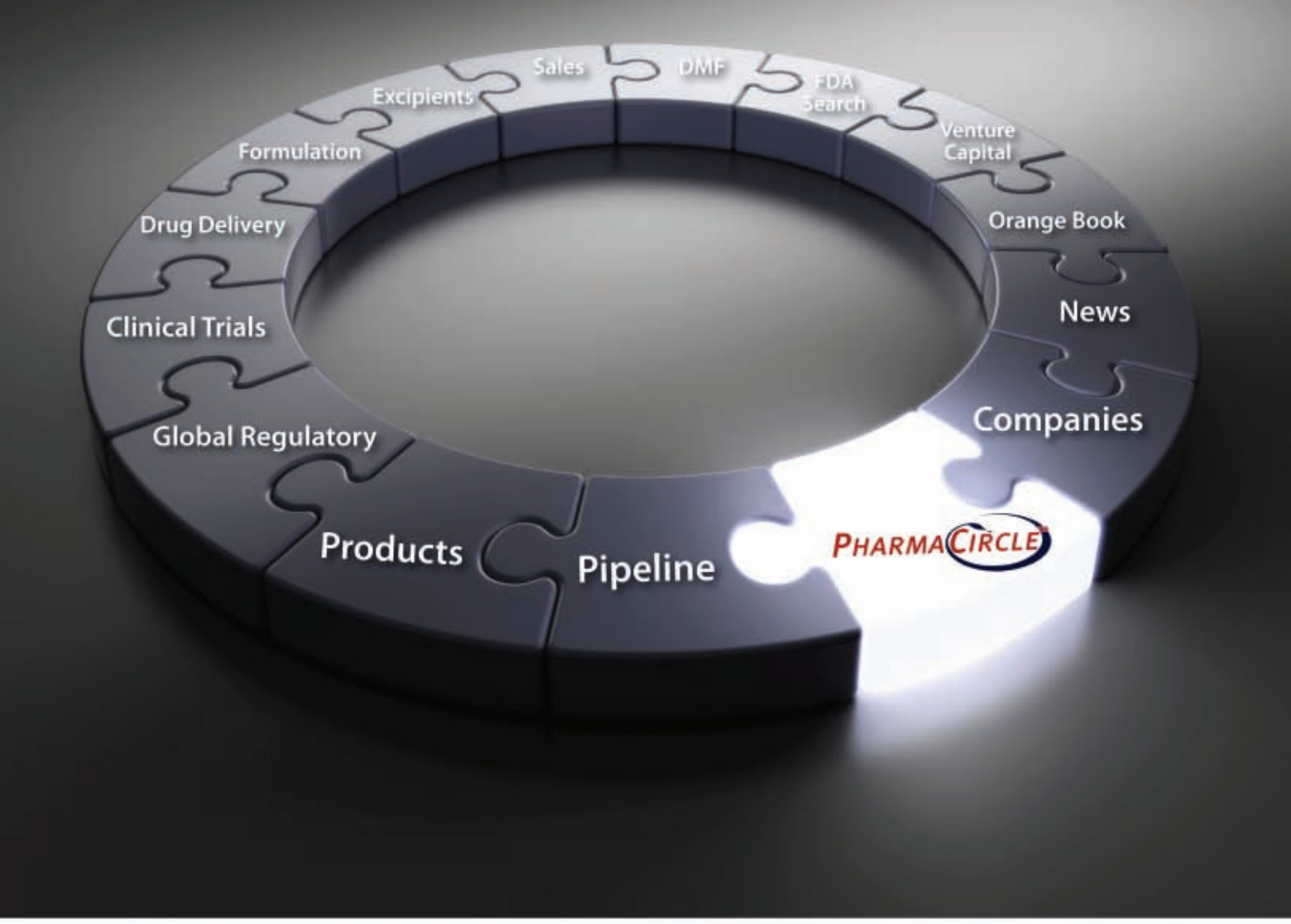
GLP-1 is a 30 amino acid peptide that belongs to the incretin family. It is secreted in direct response to the ingestion of food and acts to both stimulate insulin secretion and decrease glucagon production, providing an effective mechanism for glycaemic control. In addition, the peptide also acts to increase satiety and decrease gasticic emptying, which in turn, lead to moderate weight loss. Taken together, these factors have led to considerable interest in using this molecule as an anti-diabetic therapeutic.[4]

A half-life of native GLP-1 is around 2 minutes; a significant issue when considering this molecule as a therapeutic. The short half-life of GLP-1 is caused by specific clearance by a peptidase enzyme (DPP-4) and by renal clearance due to its relatively small size. The therapeutics that have reached the market or are currently achieving success in the clinic are based on GLP-1 analogues or mimics that have been designed to overcome the issues observed for the native GLP-1 molecule.2 These can be divided into short- and long-acting and a summary of these is detailed in Table 1.

A common feature in the advances in dosing regimen made by Liraglutide (short-acting), Albiglutide, and CJC-1134 (long-acting) is the utilization of the extended plasma half-life of human serum albumin to achieve an extended therapeutic half-life. Here, we discuss the application of human serum albumin as a half-life extension technology for GLP-1 therapeutics and how further

FIGURE 1



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developments in recombinant human albumin technology may further change the dosing paradigm.

## GLP-1 HALF-LIFE EXTENSION USING HUMAN SERUM ALBUMIN

Human serum albumin is the most abundant plasma protein that has a number of interesting physic-chemical properties that can be used in a pharmaceutical in context. In particular, it has been demonstrated that therapeutic candidates can be attached to the protein and can take advantage of the naturally extended half-life (~19 days) of this protein to avoid rapid clearance from the body.[4]

Liraglutide, the short-acting GLP-1 analogue, was the first of the GLP-1 analogues to reach the market using human serum albumin as a half-life extension technology. This molecule contained a short fatty acid "tag" attached to glutamic acid at position 26 on the peptide. Once in the plasma, this "tag" can reversibly associate with fatty acid binding sites on circulating human serum albumin, preventing rapid renal clearance. This peptide had a half-life of around 11 to 15 hours and was the first once-daily treatment using a GLP-1 peptide.[5]

The next generation of GLP-1 medicaments are targeting once-weekly dosing to both improve patient compliance and efficacy of the therapy. In the context of albumin-based therapeutics, this concept has been demonstrated in the clinic by both GSK's Albiglutide (Phase III) and Conjuchem's CJC-1134 (Phase II). These products use a covalent attachment of the GLP-1 peptide to the albumin molecule and achieve significant increase in half-life compared with the in vivo association used by Liraglutide. This covalent attachment of the therapeutic target is achieved by either genetic fusion or chemical conjugation of the peptide to the albumin.

**TABLE 1**

| Short Acting | | | | Long Acting | | | |
|---|---|---|---|---|---|---|---|
| **Product** | **Half-Life (h)** | **Dosing** | **Status** | **Product** | **Half-Life** | **Dosing** | **Status** |
| Exenatide | 2.4 | Twice Daily | Approved | Bydureon | 2.4 hours | Once weekly | Approved |
| Liraglutide | Nov-15 | Once Daily | Approved | Albiglutide | 6-8 Days | Once weekly | Phase III |
| | | | | CJC-1134 | 6-8 Days | Once weekly | Phase II |

**A summary of current and developmental GLP-1 analogues utilizing human serum albumin for half-life extension.**

GlaxoSmithkline's, Albiglutide, was developed in collaboration with Human Genome Sciences and uses albumin fusion technology licensed from Novozymes Biopharma. The process of albumin fusion involves the insertion of a contiguous piece of DNA that encodes for both the albumin and the GLP-1 peptide into a yeast-based expression system. Using this technology, a functional protein is expressed that has both the properties of albumin and the GLP-1 peptide.[6]

In contrast, Conjuchem's CJC-1134 is an engineered GLP-1 peptide, synthesised with an albumin binding group attached to a short linker molecule from the N-terminus of the peptide. This albumin binding group is then reacted with the free cysteine residue on the albumin molecule to form the conjugate.

Despite these two methods of attachment being technically very different in terms of the product design, they both achieve very similar results clinically in terms of half-life and efficacy. The decision of whether to a chose a fusion or conjugation route can be based on many different factors, and both the albumin fusion and conjugates have their own benefits. For example, CJC-1134 uses a peptide containing a non-natural amino acid and would not be amenable to a fusion route using the existing technology.

## NEXT GENERATION OF ALBUMIN-BASED ANTI-DIABETIC THERAPEUTICS

As treatment of type 2 diabetes with GLP-1 analogues and other peptide drugs develops, and the notion of longer-acting formulations becomes more accepted by both the regulatory authorities and patients, it is likely the future goals for diabetic treatments will shift further to monthly treatments and beyond. To meet these changing market demands, Novozymes Biopharma is developing the next generation of recombinant albumins for half-life extension. To understand how these molecules are designed, it's worth taking a look at how the half-life of albumin is regulated.

The half-life of albumin is mediated in part by its size, but also its pH- dependant interaction in the endosome with the FcRn receptor. A schematic of this process is illustrated in Figure 1. Plasma proteins are taken up by vascular endothelial cells through non-specific pinocytosis. As the endosome is formed and the internal pH falls, albumin binds to the FcRn receptor. The albumin that is bound to this receptor is rescued from intracellular degradation, is taken back to the surface of the cell, and released back into the circulation. The FcRn recycling system is saturated, and as a consequence, not all albumins contained within any endosome will be recycled. If the albumin lost to intracellular degradation is also that which has the

therapeutic molecule attached, then this will also be degraded. It was considered that an understanding of the interaction between albumin and FcRn and the impact of this process and albumins half-lives may ultimately lead to the ability to design therapeutics with a designed half-life.

Novozymes Biopharma, in collaboration with scientists at the University of Oslo, have identified specific regions within the structure of the albumin molecule that are important for albumin FcRn binding.[7] Subsequently, numerous albumin variants have been generated with single amino acid substitutions that display both increased and decreased inding to the FcRn receptor. A number of the variants have been tested in in animal PK studies in which a correlation between FcRn binding affinity and albumin half-life has been established. In particular, one high affinity variant demonstrated double the half-life of native sequence human serum albumin in rodent models. Ultimately, these changes in albumin half-life will translate to the therapeutic target and allow the drug development scientist to control the half-life of a target protein. In the context of GLP-1 peptides, this technology could allow the shift from weekly to every 2 weeks to monthly dosing. To maintain the full flexibility of the application of this technology, Novozymes has applied its extensive experience in recombinant albumin manufacture to ensure this technology is available to albumin fusion and conjugation applications.

## SUMMARY

GLP-1 analogues have become an important class of therapeutics in the treatment of type 2 diabetes, offering an alternative therapy to oral diabetic medications that have failed. A major factor in the translation of this peptide from an un-drugable natural peptide to successful therapeutics is the application of human serum albumin as a carrier molecule. In particular, the development and expected launch of Albigluitde, the first commercial albumin fusion therapeutic will only further enhance the growing pedigree of this technology. The success with GLP-1 is likely to open the door of the technology to be applied with other therapeutic candidates in the anti-diabetic field.

To ensure albumin half-life extension technology continues to meet the demands of innovative drug design, Novozymes has developed the next generation of albumin half-life extension technology. These albumin "variants" will open the door to longer dosing regimens for peptides such as GLP-1. ◆

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## BIOGRAPHY


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# Overcoming Poorly Soluble Pharmaceutical Formulations With Hot Melt Extrusion

**By:** Hans Maier, PhD

## INTRODUCTION

Solubility is an essential characteristic of active pharmaceutical ingredients (APIs), with profound effects on process and clinical development, formulation, and commercialization. Higher-solubility drugs dissolve more completely and are generally more bioavailable than low-solubility products; rate of dissolution also plays a key role in effective bioavailability.

Poorly soluble compounds disperse sparingly in the gut and are mostly excreted. Because poor solubility and inadequate bioavailability go hand in hand, solubility issues affect every stage of a drug's development.

Estimates have varied over the years, but at least 40%, and as many as 70% of New Chemical Entities (NCEs) are considered poorly soluble in water, leading to low bioavailability, high intra- and inter-patient response variability, and variable dose proportionality.[1,2] When BCS Class II (high permeability, low solubility) and BCS Class IV (low permeability, low solubility) are combined, the percentage of poorly soluble NCEs is approximately 90%.[2] Comparing these figures with the percentage for approved drugs, 30%, drug development is unmistakably trending toward molecules with poor solubility.

Increasing chemical complexity and molecular weight among candidate molecules, and a decreased reliance on soluble natural products as starting points for NCEs, are possible explanations for this trend. Some observers have noted that the "low hanging fruit" of candidate molecules with ideal physic-chemical properties has for the most part been harvested.

As solubility issues reach a critical stage at discovery and development firms, advanced formulation technologies for overcoming poor solubility are becoming essential for the continued productivity of innovators' drug pipelines. Because poor bioavailability masks the true potential of development-stage drugs, advanced formulation is no longer an optional activity, but indispensible to the very success of NCEs.

In a recent study conducted on Catalent's behalf by McKinsey and Co., top managers at development-stage pharmaceutical companies listed bioavailability enhancement as the most significant challenge in their drug delivery and formulation efforts.[3] McKinsey identified especially acute needs for bioavailability enhancement of small molecule drugs, oral protein drugs, targeted delivery (particularly to the upper GI tract), and overcoming food effects. Additionally, in a recent industry survey, 41% of respondents reported bioavailability as a key challenge in their active pipeline development programs.[4]

## SOLID DISPERSIONS & SOLUTIONS

Strategies for overcoming poor solubility and permeability are many and varied. Emulsification, micronization, nanoparticle APIs, complexation with liposomes or cyclodextrins, counter-ion modifications, and permeation enhancers each have their plusses and minuses, but all lack general application to the diverse chemical structures comprising poorly soluble drug candidates.

Solid dispersions and solid solutions are two generally applicable strategies for overcoming poor solubility. Pioneering work by Janssen Pharmaceuticals with Sporanox®, and Parke-Davis' Rezulin, demonstrated that solid dispersions could play a role in ameliorating solubility issues through easily accessible formulation and manufacturing methods.

In solid dispersions, the drug and a soluble pharmaceutical-grade polymer

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matrix exist, co-mixed but in separate phases, with the drug either in crystalline or amorphous form. Solid solutions differ from dispersions as the two components combine, in a single phase, at the molecular level. By necessity, the drug concentration in a solid solution is lower than its saturation value for the particular polymer matrix, otherwise crystallization or aggregation of API would occur (phase separation).

Solid crystalline dispersions consist of the API in crystalline form dispersed within the polymer carrier. These occur when, for purposes of preserving drug substance stability, the processing temperature is lower than the drug's melting temperature. Crystalline dispersions also arise through re-crystallization of the API from a melt, or as an equilibrium state between crystalline and amorphous forms. When analyzed by differential scanning calorimetry, solid crystalline dispersions display separate temperature breaks for the polymer's glass transition temperature (Tg) and the drug's melting point.

Solid glassy dispersions are similar to crystalline dispersions except that in this case, both the polymer and drug exist in amorphous states. API is well-dispersed, but in a separate physical domain from that of the carrier. Analysis by differential scanning calorimetry shows separate Tg for drug and polymer. Because the amorphous API is held in clusters, such glassy dispersions are more likely than a solid solution to revert to the crystalline state.

Techniques for producing solid dispersions include solvent-based operations (eg, spray-drying, solvent casting, freeze-drying) and techniques based on melting (spray congealing, melt granulation, and hot melt extrusion/HME).[5]

Solvent-based approaches involve dissolving the drug and polymer in an organic solvent, and removing the solvent to leave behind powder or granules. Because most drugs are hydrophobic, and most polymers hydrophilic, dissolution requires large volumes of solvent that raise issues of safety, energy usage, and disposal.

Of the three techniques, HME is the most versatile and generally applicable to poorly soluble drug candidates. HME creates pharmaceutical-polymer dispersions of quality comparable to solvent-based methods, but without the solvent.

In pharmaceutical formulations, HME is most often associated with solid dispersions, although solid solutions of high-energy amorphous API may be more effective as solubility enhancers.

Heating a crystalline API above its melting point produces a liquid which, upon cooling, often reverts to crystalline form. But, in certain situations, the drug enters an amorphous glassy state through a super-cooled liquid phase. The temperature at which the super-cooled liquid is in equilibrium with the glass is the Tg. The glassy materials, in which the molecules are not ordered, is less energetically stable than the crystalline form. Consequently, amorphous materials processed in this way dissolve more rapidly than crystalline API.

However, in solid solutions, crystallization may become an issue if the storage temperature is less than 50 degrees lower Tg. The remedy is to employ a polymer matrix with a significantly higher Tg . This confers a higher, more suitable Tg on the solid solution, and hence a more stable formulation

Overall, high-energy hot-melt extrudates based on amorphous API dispersions or solid solutions provide significant solubility advantages compared with crystalline drug, particularly in the case of true solid solutions. Because amorphous materials are of higher energy than the crystalline form, they dissolve more readily. Moreover, for solid solutions, their dissolution within the matrix at the molecular level results in the highest possible effective surface area, which promotes physiologic absorption as well.

Amorphous physical forms of common drugs carry caveats as well. Amorphous materials may be metastable, meaning they may spontaneously interconvert to the more thermodynamically stable crystalline form, leading to potential issues with drug product stability. Moreover, producing an amorphous form may still not provide suitable bioavailability for APIs that do not possess innate "druggable" solubility.

## HME PROCESSING & EQUIPMENT

HME has been widely used in the polymers and food industries for more than 70 years. Pharmaceutical developers have only employed HME for the past 15 years. According to Crowley et al, the number of HME patents covering pharmaceutical applications rose steadily between 1983 and 2005, reaching approximately 25 patents per year.[6] Germany, the United States, and Japan issued approximately three-fourths of those patents.

HME involves heating, mixing, compressing, and transporting a dispersion of APIs, plasticizers, surfactants, and other excipients within a suitable pharmaceutical-grade polymer carrier, typically utilizing co-rotating twin screws with various pitch designs to achieve desired mixing and residence times in the various heating and cooling sections of the extruder.

Where single-screw extrusion is more common in polymer processing, twin screw extruders are the most common for processing

pharmaceuticals as hot melt extrudates. Compared with single-screw machines, the twin-screw design provides better mixing of non-homogeneous systems (ie, drug and polymer), better control over melting temperatures, and easier addition of ingredients.

The three principal phases of the process are conveying, melting (occurring within the barrel), and shaping or extrusion. Residence time within the extruder typically ranges from about half a minute to 5 minutes. The mixture liquefies and emerges as a homogeneous liquid or semi-solid, which solidifies upon cooling.

Process parameters affecting the final formulation include screw diameter, spacing between the screws and the chamber wall, temperatures along the die assembly, and the screws' pitch angles, rotation rate, and length-to-diameter ratio.

Screw design strongly influences the properties of finished HME products. Screws provide both conveying and mixing by meshing through very narrow gaps, both between the co-rotating screws and between screws and extruder wall.

HME equipment is diverse in design and operation. One notable model type features multiple hoppers along the conveying-melting-extrusion flow path to enable addition of ingredients during the melt processing. Another is multiple heating zones along the flow path to tailor heating regimens to the composition of various ingredients. Hot melt extruders can provide melting temperatures as high as 250ºC, although to ensure drug substance stability, processors avoid highly elevated temperatures. To ensure stability, an HME process should occur no higher than about 40ºC above the Tg of the polymer, which in turn is selected based on the API's melting temperature among other criteria.

Because it is a continuous process with narrowly defined output quality attributes, HME represents an ideal manufacturing platform for implementation of Process Analytic Technology (PAT). Through this FDA initiative, manufacturers are encouraged to gain process understanding by identifying and controlling critical parameters in real-time or close to it. Appropriate measurement devices, such as near-infrared sensors positioned in-line or at-line, can meet requirements associated with PAT for HME in ways that other pharmaceutical manufacturing operations cannot achieve.

Because hot melt extrudates exhibit unique thermodynamic properties, much may be learned from the thermal behavior. Calorimetry and thermogravimetric analysis are critical analytical techniques during HME processes. Other analysis methods adopted from both pharmaceutical development and materials processing include solid state NMR, liquid chromatography, scanning electron microscopy, particle characterization methods (eg, light scattering, sieving), and USP methods for batch release.

## HME CARRIER MATRICES

HME formulations consist of a thermoplastic carrier, and may comprise further excipients, such as solubilizers, surfactants, or binders, such as gelucire, vitamin E TGPS, waxes, lipids, polyols, and alpha hydroxyacids, plasticizers (eg, polyethylene glycols, triethyl citrate), sugars, organic acids, complexing agents, biodegradable polymers, and combinations of these ingredients. Pharmaceutical-grade polymers are by far the predominating excipient.

Choice of polymer is crucial for imparting the desired characteristics to the final HME formulation. Typical carrier polymers include povidone, copovidone, hydroxypropyl and ethyl celluloses, acrylates, and most recently, a polymer with amphiphilic chemical structure, Soluplus.

The most important properties of the polymer matrix are Tg and melt viscosity, solubilization capacity, stability, and toxicity/regulatory status.[7] The latter is critical as the matrix is present at very high doses relative to the drug.

Polymers with high solubilization capacity are capable of accepting a high drug load. Chemical features of these materials include lipophilicity, hydrogen-bonding capability, and the presence of amide groups. Amides are particularly suited to solubilizing lipophilic, poorly-soluble APIs and superior in this regard to hydroxyl-containing materials.[8]

Plasticizers improve processability by lowering the polymer's Tg and melt viscosity, thus facilitating extrusion; solubilization agents prevent the API from crystallizing within the polymer.

## ADVANTAGES OF HME

Solubility enhancement and sustained release are the two main justifications for embarking on an HME development project. Candidate APIs normally are BCS Class II compounds possessing high permeability but low aqueous solubility, or BCS Class IV compounds with low permeability and low aqueous solubility. For these molecules, solvation rate limits bioavailability as oral dosage forms, the preferred route of administration.

The Noyes-Whitney equation, which defines dissolution rate, states that solubility is proportional to the drug's diffusion coefficient, saturation solubility, and exposed surface area, and inversely proportional to the

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diffusion layer thickness at the solid-liquid interface. HME addresses these critical factors by:

- increasing effective surface area by effective dispersion or solid solution;
- decreasing effective diffusion layer thickness by improving wettability (eg, through surfactants); and
- improving inherent solubility by employing amorphous API forms.

HME's ability to disperse APIs evenly throughout the matrix, at the molecular level, is arguably its leading benefit over traditional formulation like spray-drying and evaporative methods. Because HME does not use solvents, the process is safe, environmentally friendly, and requires fewer unit operations. Judicious choice of polymer matrix provides such benefits as thermal binding, chemical stabilization, solubilization, controlled release, and greater flexibility with excipients. The benefits of HME go well beyond enhancement of solubility to include:

- polymeric formulation matrix, which eliminates hydrolysis associated with wet agglomeration;
- suitability for sustained/controlled release or enteric coating;
- applicability to capsules, tablets, bioadhesive films, multi-particulate dosage forms, and mini- matrices;
- controlled dosage over a wide range of solubilities or dispersion concentrations;
- film capability for buccal or patch dosage forms;
- very high drug loading, up to 90%, decreases tablet size;
- robust, compact, high-throughput manufacturing with little waste;
- solvent-free processing, eliminating need for explosion-proof equipment; and
- taste-masking.

## WARY MARKETPLACE

APIs processed as hot melt extrudates include nifedipine, indomethacin, piroxicam, chlorpheniramine maleate, 17β estradiol hemihydrate, lidocaine, hydrocortisone, ketoprofen, and many others. Despite these successes, HME is an under-utilized technology, particularly for development-stage compounds.

HME has an undeserved reputation for presenting undue challenges to formulation development. This is in part due to the lack of familiarity with HME, even among veteran solid dosage form experts. In addition to the processing technique itself, developers must be aware of carrier and stability issues.

Selection of an appropriate carrier is always a consideration, as the drug substance must be sufficiently soluble or miscible in the carrier. The two properties are not the same. Although in best-case situations, one would expect a fully miscible mixture to be soluble as well, solid miscibility is a poor predictor of solubility as miscible materials may phase-separate over time. Apparent solid solubility is a much better indicator of long-term physical stability, which refers to the concentration of drug within a solid dispersion at equilibrium with crystallized drug.

Predicting the formulation's physical stability is also sometimes difficult, particularly with respect to heat degradation and recrystallization. Processing high-melting drug substance at high temperatures is not always possible due to degradation. In these situations, converting the crystalline form of the API to an amorphous form may help. This will enable a lower extrusion temperature, and often provide a more favorable stability profile for the finished product. Another strategy involves melting the polymer before the API, thus reducing the residence time at high temperature for the drug substance.

We have found that for HME formulations, initial formation of fine aqueous dispersions is a better predictor of bioavailability than dissolution. Drug product that disperses in tests (forming a milky-white suspension of fine particles) behaves similarly in the digestive tract, and is more likely effective to release the drug in vivo.

## REMOVING THE BARRIERS

To assist developers with carrier/excipient selection, and to provide a platform for testing formulation properties empirically, Catalent has developed a rapid screening capability based on development-scale versions of its production HME system. These systems quickly generate up to several hundred grams of finished product - a suitable quantity for testing. One such system resides in Catalent's Schondorf, Germany facility, and the other in its Somerset, New Jersey site.

The system consists of a 10-mm, 40 L/D twin-screw compounder that functions similarly to the production-scale machine. Feed rate is between 25 and 400 g/hr, with wastage as low as 3 to 5 g. Depending on the die and ancillary equipment, such as a calendaring roller device, product emerges as

a sheet or rod. Adding carrier and API through separate hoppers permits varying the drug load as the run progresses. Thus, developers have the opportunity to optimize drug concentration in a single run.

Product manufactured by development-scale HME is suitable for typical quality analysis, including thermal, microscopic, spectroscopic, and physical methods. These data are useful in developing predictive models that are applicable to manufacturing scale. For example, Catalent scientists have developed a method, based on pairing workflows with vibrational spectroscopy data, for rapidly assessing and predicting the stability of extrudates.

## CONCLUSION

Solubility problems plague pharmaceutical development at every stage, and reduce the commercial potential of many pipeline drugs. Many promising molecules fail for this very reason. Approaches such as particle size reduction and emulsification to improve bioavailability go only so far in improving bioavailability. Among the various formulation strategies, HME alone has the potential to fully solubilize API within an erodible matrix and in a physical form optimal for dissolution.

Although HME evolved mostly outside of pharmaceuticals, HME's adoption to solid dosage form development stands on solid science and engineering, and the success of numerous commercial products. Lack of experience and expertise in HME formulation has until recently stood in the way of wider adoption within the industry. Developing HME dosage forms straightforwardly and confidently has been enabled by small-scale extrusion, which has been proven to be a rapid, predictive screening tool for developing HME dosage forms. This technique, combined with low consumption of raw materials, shortens development timelines for poorly soluble drugs. ◆

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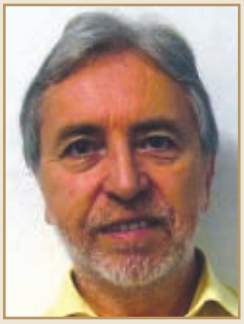


**Dr. Hans Maier** is a Head Formulation Scientist for the Modified Release Technologies business of Catalent Pharma Solutions. With more than 20 years of experience in pharmaceutical development, Dr. Maier provides technical and scientific leadership for the development of modified-release technologies of solid dosage forms. His expertise includes polymer processing machinery (ie, extruders, rotational molding machines), polymer rheology, and chemical modification of polymers. He earned his undergraduate degree in Chemistry and Chemical Engineering from the University of Stuttgart/Germany and his PhD in Inorganic and Analytical Chemistry from the University of Hohenheim/Germany. Dr. Maier holds patents in engineering and design of biodegradable polymer systems.

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# Formulation & Evaluation of Atorvastatin-Loaded ER Tablets

**By:** N.V. Satheesh Madhav, PhD, MPharm, and Pranshu Tangri, MPharm

## ABSTRACT

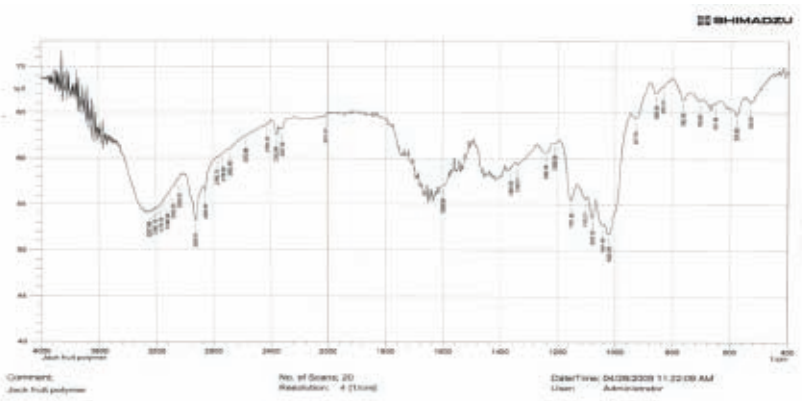
The aim of our research was to formulate and evaluate sustained-release tablets of atorvastatin using the biomaterial as a novel biobinder for the formulation of tablets. The biomaterial was isolated from the unripe fruit pulp of *Artocarpus heterophyllus* by simplified economic process. It was subjected for various physico-chemical parameters like color, color changing point, chemical tests, and IR spectral study. Ibuprofen sustained-release tablets were prepared by using various formulation additives. Three atorvastatin-loaded formulations (FA1-FA3) were prepared by using varying polymer ratios of 1:1, 1:3, 1:5, and other excipients like starch, talc, and lactose. The formulations were evaluated for hardness, friability, weight variation, disintegration, and in vitro release study. On the basis of evaluation parameters, formulation FA3 was found to be the best as it showed a t50% of 400 mins and t80% of more than 10 hours with weight variation of 3.8%, friability of 1.2%, hardness of 5 kg/cm2, and disintegration time of around 12 mins. An educated conclusion was drawn that the biomaterial can serve as a potential agent for formulating various sustained-release formulations for the treatment of various chronic ailments along with the advantages of being non-toxic, biodegradable, and free from any adverse effects.

## INTRODUCTION

Jackfruit (*Artocaropus Heterophyllus*) belongs to the family moraceae, it contains morin, carotenoids, and provitamin A. It is used medicinally as a laxative, tonic, and demulcent. The drug atorvastatin is an HMG-Coenzyme inhibitor and is used for the treatment of hyperlipidimea, ie, elevated cholesterol levels in the body. It is generally administered once daily. The aim of our experiment is to formulate a novel biopolymeric-based sustained-release tablet of atorvastatin for once-daily dosing. Jackfruit pulp contains morin and a crystalline constituent, cyanomaclurin, probably isomeric with catechins. It is a good source of provitamin A carotenoids. It is also composed of a new flavonone, a new prenylfalvone, a novel phenolic compound, heterophylolg and nine known flavonoids. Ripe fruit is used as a demulcent, nutritive, and laxative. Pulp or flesh surrounding the seed is aromatic, cooling, and tonic. It is also used in diarrhea, fever, and asthma treatment.[1,2]

Atorvastatin is a member of the drug class known as statins used for

**FIGURE 1**




**Infrared Spectra of the Biomaterial**

lowering blood cholesterol. It also stabilizes plaque and prevents strokes through anti-inflammatory and other mechanisms. Like all statins, atorvastatin works by inhibiting HMG-CoA reductase, an enzyme found in liver tissue that plays a key role in production of cholesterol in the body. Atorvastatin undergoes rapid oral absorption, with an approximate time to maximum plasma concentration (Tmax) of 1 to 2 hours. The absolute bioavailability of the drug is approximately 14%; however, the systemic availability for HMG-CoA reductase activity is approximately 30%. Atorvastatin undergoes high intestinal clearance and first-pass metabolism, which is the main cause for the low systemic availability. Due to its rapid clearance from the body, a sustained-release product is required for it to exert its pharmacological effect. In the current research project, we aim at formulating a sustained-release tablet of atorvastatin using a biobinder from the fruit pulp of Artocarpus heterophyllus.

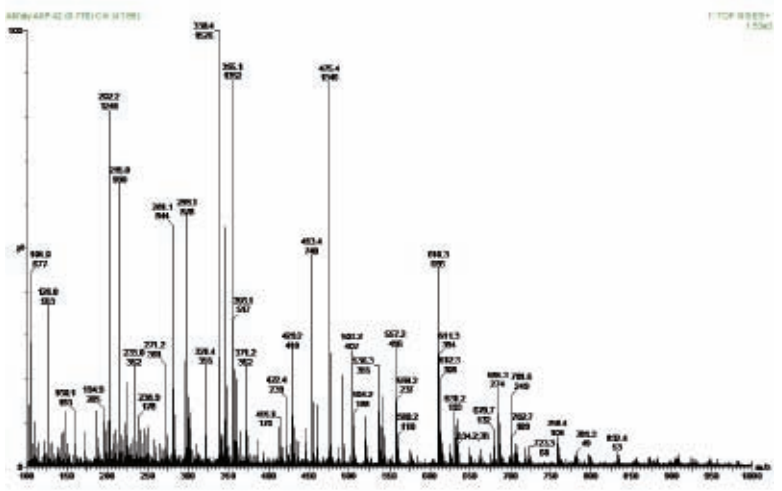
## MATERIALS & METHODS

The drug atorvastatin was obtained as a gift sample from Ranbaxy Paonta Sahib, India. Jackfruit was procured from the local market. All other reagents used were of highest purity and analytical grade. Double distilled water was used throughout the experimental work.

### *Biomaterial Extraction*

The biomaterial was isolated from the fruits of Artocarpus hetrophyllus from our previously published method. The isolated biomaterial was subjected for physico-chemical characterization and spectral analysis.[2]

**FIGURE 2**



**Mass Spectra of the Biomaterial**

### *Formulation of Atorvastatin Tablets*

The tablets were prepared by accurately weighing the drug, biomaterial, starch, lactose, talc, and magnesium stearate (Table 1). These were mixed in a pestle mortar by geometric progression. Solutions of varying strength of the biopolymer were prepared (1:1, 1:3, 1:5) and used as a binder solution. A damp, sticky mass was prepared, and the granules were prepared by passing through sieve No. 22. The granules were dried in oven at 45°C for 15 mins. Talc and magnesium stearate was added to enhance the flow properties. The granules were then compressed in the tablet punching machine to get the tablets. The tablets were evaluated for the various evaluation parameters.

## EVALUATION PARAMETERS (TABLES 2A & 2B)

### *Characterization of Granules*[3-7]

Prior to compression, granules were evaluated for their characteristic parameters. Angle of repose was determined by funnel method. Bulk density and tapped density were determined by cylinder method, and Carr's index (CI) was calculated using the following equation: CI = (TD-BD)*100/TD. Where, TD is the tap density, and BD is the bulk density. The tablets were evaluated for the following parameters: hardness, weight variation, friability, disintegration time, and in vitro release study.

**Hardness:** The hardness was evaluated by the common laboratory hardness tester.

**TABLE 1**

| S. No. | Formulation | FA1 | FA2 | FA3 |
|---|---|---|---|---|
| 1. | atorvastatin(mg) | 10 | 10 | 10 |
| 2. | Bio-polymer(mg) | 30 | 90 | 150 |
| 3. | starch (mg) | 50 | 50 | 50 |
| 4. | Magnesium stearate (mg) | 5 | 5 | 5 |
| 5. | Talc (mg) | 5 | 5 | 5 |
| 6. | Lactose(mg) q.s. to | 300 | 300 | 300 |

**Formulations**

## TABLE 2A

| Evaluation Parameter | FA1 | FA2 | FA3 |
|---|---|---|---|
| Angle of repose( ) | 25.34 ± 1.2 | 24.37 ± 0.65 | 27.64 ± 1.1 |
| Bulk density(g/mL) | 0.64 | 0.43 | 0.57 |
| Tapped density(g/mL) | 0.75 | 0.58 | 0.69 |
| Carr's index | 17.185 | 25.86 | 17.39 |

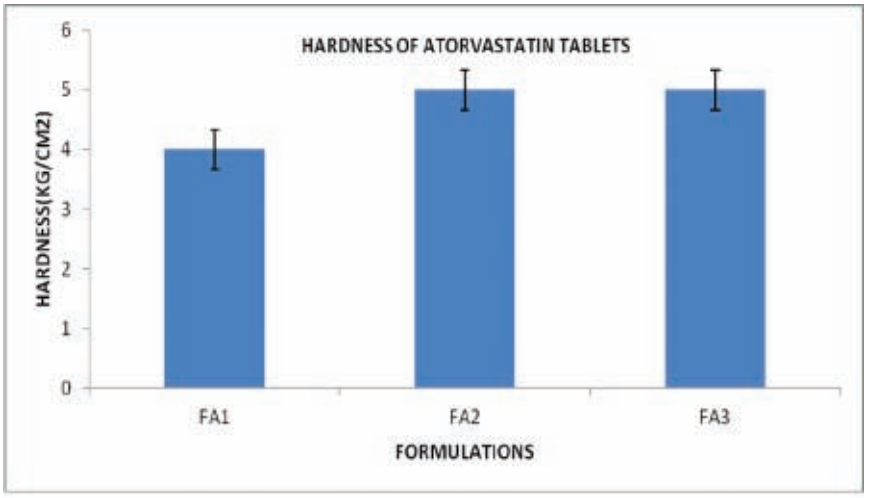
**Evaluation Parameters of Atorvastatin Granules**

## TABLE 2B

| Evaluation Parameter | FA1 | FA2 | FA3 |
|---|---|---|---|
| Hardness (kg/cm$^2$) | 4 | 5 | 5 |
| Friability | 1.3% ± 0.045% | 1.2% ± 0.075% | 1.82% ± 0.057% |
| Weight variation | 4.5% ± 0.36% | 3.8% ± 0.24% | 4.4% ± 0.42% |
| Disintigration time(mins) | 29 mins ± 3.5 mins | 33 mins ± 2.4 mins | 37 mins ± 2.8 mins |

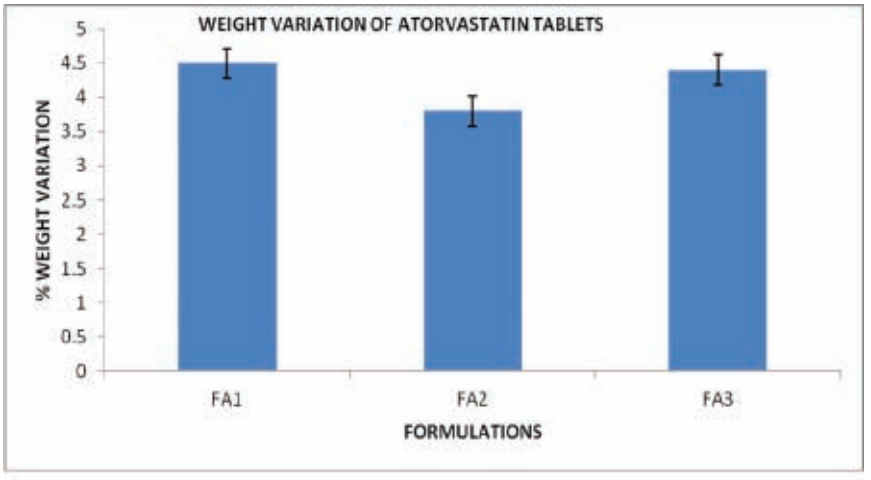
**Evaluation Parameters of Atorvastatin Tablets**

## FIGURE 3




**Hardness of the Tablets**

## FIGURE 4




**Weight Variation of the Tablets**

The triplicate of three observations was performed, and standard deviation applied to the results (Figure 3).8-10

**Weight Variation:** The weight variation study was performed by weighing individually 10 tablets and finding the average weight. The deviation of the weight of the tablets from the average weight was determined as the weight variation. The triplicate of three observations was performed, and standard deviation applied to the results. (Figure 4).11,12

**Friability:** The Roche friabilator was used to determine the friability of the tablets. The triplicate of three observations was performed, and standard deviation applied to the results (Figure 5).[8-10]

**Disintegration Time:** The disintigartion apparatus was used to determine the disintegration time of the tablets. The triplicate of three observations was performed, and standard deviation applied to the results. (Figure 6).[8-10]

**In Vitro Release Study:** The in vitro release of the tablets was performed in USP dissolution apparatus type II for 10 hours in pH 1.2 for the first 2 hours and in pH 7.4 for the next 8 hours.[1-10]

### *Kinetic Analysis of Dissolution Data*

To study the mechanism of drug release from the matrix tablets, the release data were fitted to zero-order, first-order, and Higuchi equations. These models fail to explain the drug-release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore, the dissolution data was also fitted to the well-known exponential equation (Korsmeyer equation), which is often used to describe the drug- release behavior

from polymeric systems: Log(Mt/Mf) = Log k + n Log t. Where, Mt is the amount of drug release at time t; Mf is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet; and n is the diffusional exponent indicative of the mechanism of drug release.[11-12]

## DISCUSSION & CONCLUSION

A novel biopolymer from Artocarpus heterophyllus was isolated by a simplified economical process; the yield was 1% per 100 g. The biopolymer obtained was of brownish to dark brown color with a color changing point of 160° to 165°. The biopolymer showed positive tests for the presence of proteins and carbohydrates. The biomaterial was devoid of signs of toxicity in animals tested. This may be due to the edible nature of the Artocarpus heterophyllus. Three different formulations were developed using various proportions of biomaterial for the preparation of sustained- release tablets of atorvastatin. The release rate kinetic data for all the models is shown in Table 3. Drug release data of tablets was fitted into the Higuchi equation (r2 = 0.9785, 0.9654, and 0.9935 for batches FA1, FA2, FA3, respectively). The Korsmeyer equation ($r^2$ = 0.9672, 0.9972, and 0.9889, respectively) and indicated combined effect of diffusion and erosion mechanisms for controlled drug release. The formulations showed a weight variation in the range 3.8% to 4.5%, friability of 1.3% to 1.8%, and hardness of 4 to 5 kg/cm$^2$. The formulation FA3 was found to be the best formulation on the basis of t50% and t80%. It showed a t50% of 400 mins, and t80% of more than 10 hours.

A smart conclusion was drawn that the biomaterial can serve as a potential agent for formulating various sustained-release formulations for the treatment of various chronic ailments along with the advantages of being non-toxic, biodegradable, and free from any adverse effects. ◆

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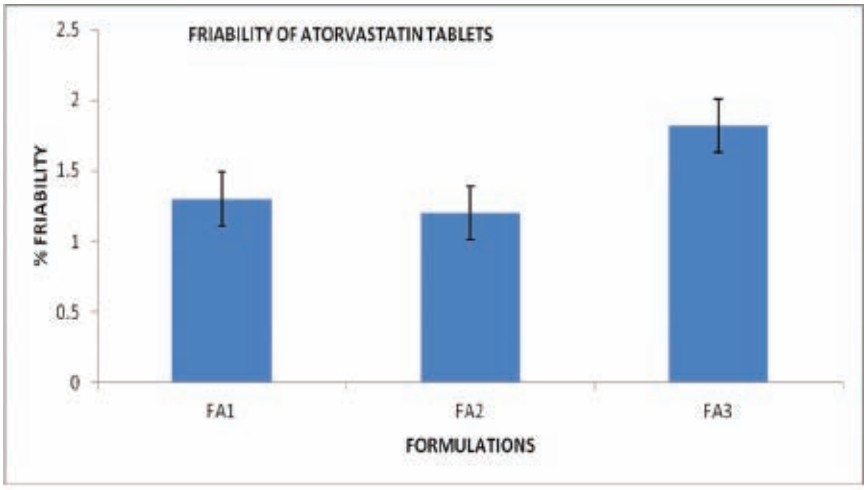
**TABLE 3**

| Formulation | $r^2$ (Korsmeyer model) | $r^2$ (higuchi model) |
|---|---|---|
| FA1 | 0.9785 | 0.9672 |
| FA2 | 0.9654 | 0.9972 |
| FA3 | 0.9935 | 0.9889 |

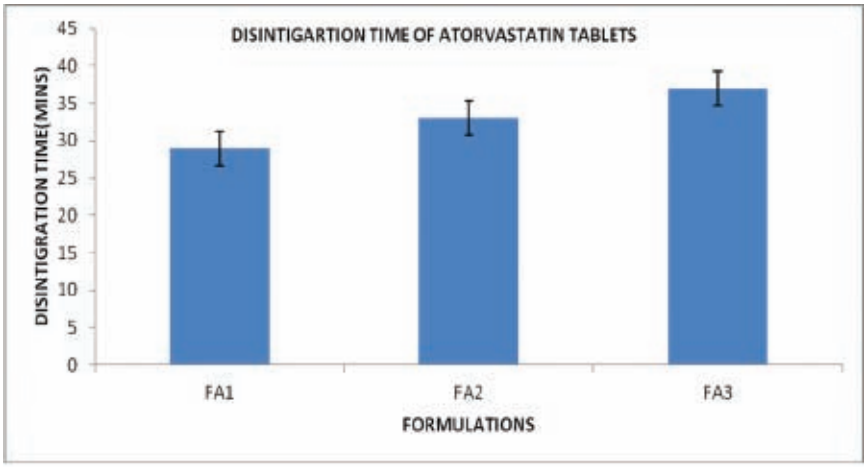
**Drug-Release Kinetics of Atorvastatin Sustained-Release Tablets**

**FIGURE 5**



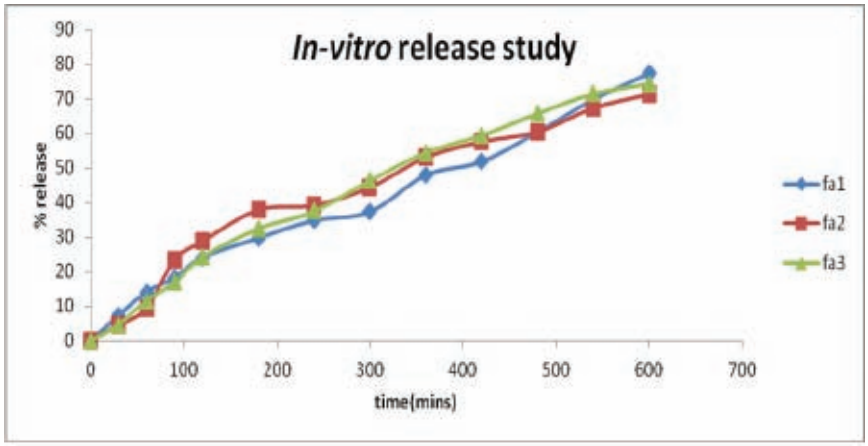

**Friability of the Tablets**

**FIGURE 6**




**Disintegration Time of the Tablets**

## FIGURE 7




**In Vitro-Release Study of the Atorvastatin Tablets**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## BIOGRAPHIES

**Dr. N.V. Satheesh Madhav** earned his MPharm in Pharmaceutics and his PhD in Pharmacy. He is currently working as Director-DIT-Faculty of Pharmacy, Dehradun, India. He has published more than 150 articles and more than 200 abstracts in national and international conferences and journals. He has to his name four Indian patents.

**Pranshu Tangri** earned his MPharm in Pharmaceutics. He is currently working as Assistant Professor in GRD(PG)IMT, College Of Pharmacy, Dehradun, India. He has extensive research experience, having published more than 30 review and research articles and more than 25 abstracts in various journals and conferences.

# Innovative Formulation Technology Protecting Intended Drug Action

**By:** Johannes Bartholomäus, PhD; Judy Ashworth, MD; Hans-Jürgen Stahlberg, MD; Eric Galia, PhD; and Kai Strothmann, PhD

## INTRODUCTION

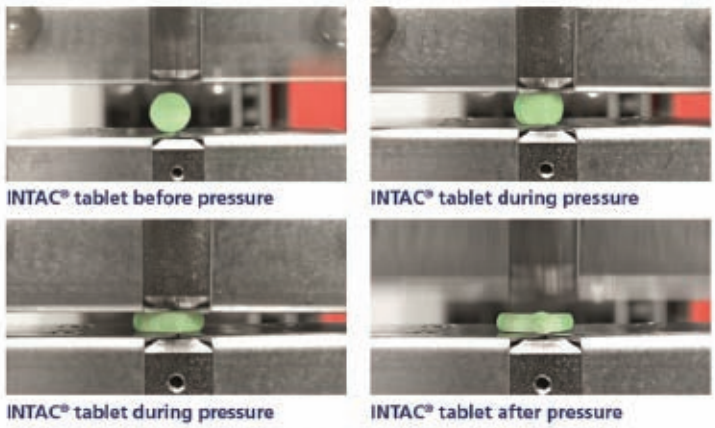
Prescription opioid abuse in the US is now labeled an epidemic by both the Center for Disease Control and the White House.[1] In its 2011 *Prescription Drug Abuse Prevention Plan*, the White House calls on the National Institute on Drug Abuse and the FDA to support efforts for the development of abuse-deterrent formulations of opioid medications and other drugs with abuse potential.[2] In the United States in 2007, the number of deaths involving opioid analgesics was 1.93 times the number involving cocaine and 5.38 times the number involving heroin. Extended-release (ER) formulations of opioids are especially attractive for abusers as they typically contain a larger amount of the drug compared with immediate-release (IR) formulations. To defeat ER characteristics and reach a quick onset of action, crushing is often the first step in tampering with the products with the goal of abuse followed by swallowing, snorting, or extracting, for example, into an injectable solution. Moreover, independent of the particular drug substance incorporated in a given ER tablet, accidental or intended crushing of such forms for other reasons (eg, to allow for easier swallowing) can also change the intended action of the product. This may lead to decreased efficacy as well as unwanted or even serious adverse effects.

In response to the aforementioned problems, Grünenthal has developed INTAC®, an innovative drug delivery platform that can significantly raise the hurdle for misuse or abuse of tablets by routes of administration that require the product to first be crushed. Additionally, for abusers intending to abuse the product intravenously, subsequent steps required for extracting active drug for injection are also impeded by INTAC. The first commercially available application of this platform technology focuses on ER formulations, while IR technology is currently under development.

## GUIDING PRINCIPLE IN SELECTING THE APPROPRIATE APPROACH

When developing abuse-deterrent or tamper-resistant formulations (TRF) for prescription opioids, there are two different target groups for the product to be taken into account. First, the compliant patient - the true target of the medicinal product - who should not be negatively affected let alone harmed by abuse-deterring features and whose intended therapy should not be potentially compromised. Second, the

## FIGURE 1




Mechanical stress testing of INTAC® Tablet with more than 1000 N force. (Zwick BTC-FR2.5TH.D09)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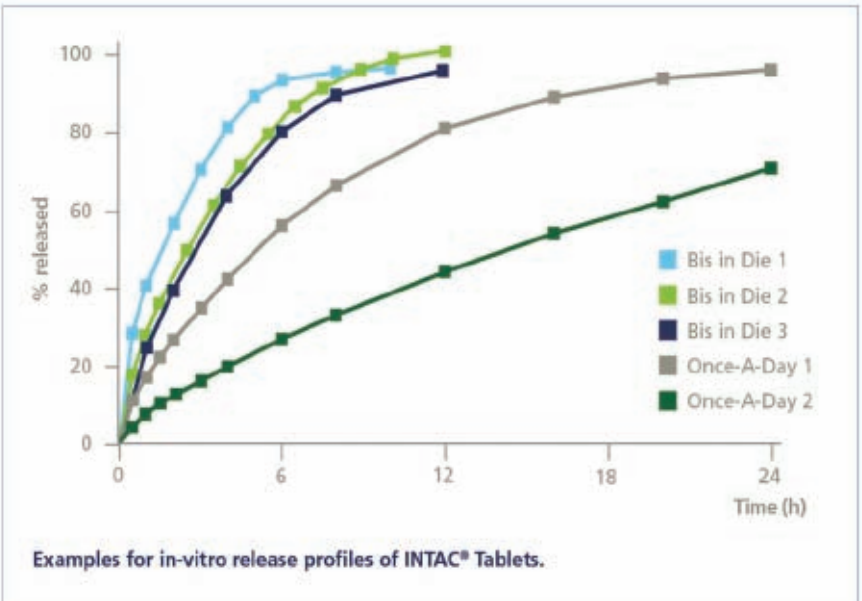
abuser - the true target of the abuse-deterring features - who should be confronted with obstacles that make abuse significantly more difficult. In order to design a tablet that achieves both goals, we adopted a purely physicochemical approach for INTAC instead of employing aversive additives or introducing opioid antagonists that potentially could harm the compliant patient or compromise pain therapy.

## INTAC® - ER TECHNOLOGY

Given that crushing the tablet is often the first step when tampering with ER opioids, the new formulation should exhibit a high mechanical resistance to being crushed into a powder while at the same time maintain the ability to release the drug substance in a manner suitable for once- or twice-daily intake when taken as intended. Moreover, the formulation should have properties that impede further steps in extraction of the drug substance for intravenous abuse (eg, by gelling). Such a formulation could, in addition, also help prevent unintended misuse, eg, by crushing with pill-crushers to allow for easier swallowing, which eventually may happen in treatment of geriatric or pediatric patients.

The INTAC approach for ER tablets was realized by a formulation based on high molecular weight polyethylene oxide (PEO) and proprietary manufacturing processes using heat and force to create the extraordinary mechanical strength of the tablets. Finally, hot melt extrusion (HME) followed by a newly designed downstream process of cooling, cutting, and forming was selected for scale up and established for commercial manufacturing in the US and Europe. Details of the basic development of the formulation and the manufacturing processes can be found in Bartholomäus et al. 2012.[3] The crush resistance of the tablets was demonstrated by tests with pharmacopeial breaking strengths testers generating forces of 500 N and more (eg, Sotax HT1 Hardness Tester) as well as with mechanical universal material testing systems (eg, Zwick BTC-FR2.5TH.D09). The resulting tablets did not break at forces of about 1000 N and higher, but were just somewhat flattened showing plastic deformation only (Figure 1). Additionally, attempts at crushing the tablets by means of mortar and pestle, using professional pill-crushers, manual hammering, or using a standardized hammer apparatus could not transform the product into powder.

**FIGURE 2**




Examples for in-vitro release profiles of INTAC® Tablets.

Typical in vitro release profiles for INTAC ER tablets are provided in Figure 2. The in vitro release can be tailored to the therapeutic needs of new products or to achieve bioequivalence (BE) to already existing products.

## CLINICAL DEVELOPMENT

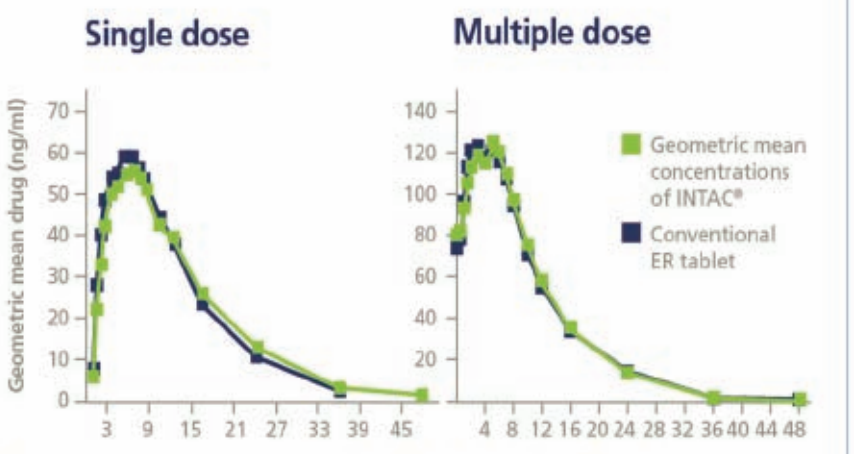
Different clinical development approaches are possible for bringing INTAC products onto the market. For new chemical entities, INTAC can be chosen as the "to-be-marketed" formulation - a pro-active step to prevent abuse and/or inappropriate administration of the new product from day 1 of launch. In case such a decision is reached in late-stage clinical development, a BE bridging program can run parallel to Phase III. For established compounds, INTAC can be utilized, for example, in the development of new doses or new application schemes for established compounds - the extent of clinical development depending on each individual case.

For replacing a marketed product currently facing issues of abuse or inappropriate crushing with a reformulated TRF product, the establishment of BE based on the applicable regulatory guidelines allows for a limited development program by relying on the already established efficacy and safety of the product being replaced.

An example from a BE bridging program between INTAC and commercially available conventional ER tablets of a reference opioid marketed in different strengths is presented in Figure 3. The curves show excellent congruence of profiles and the statistical evaluation demonstrated bioequivalence for all tested dose strengths.[4]

The demonstration of bioequivalence shows that although the tablets are of high mechanical strength and difficult to tamper with, the drug substance is released from the TRF product in the same manner as from

## FIGURE 3




**Mean serum concentration-time profiles of single dose (fasted) and multiple dose (non-fasted) bioequivalence trials following administration of the highest dose strengths of a reference opioid for an INTAC® formulation compared to a marketed conventional extended release form.**

conventional ER tablets, thereby rendering their in vivo performance comparable to the marketed drug formulations and enabling physicians to simply switch patients from a conventional to the new, tamper-resistant formulation.

## IN VITRO TAMPER-RESISTANCE TESTING

An in vitro test battery was established to investigate the tamper-resistance properties of INTAC formulations with respect to the different routes of abuse and misuse as well as the expected different level of skills of abusers or misusers. The tests were designed to simulate unintended misuse by patients or healthcare providers representing the lowest level of misuse/abuse behavior over increasing efforts and skills employed by recreational abusers, experienced abusers, and even to simulate "kitchen chemists." The selected tests had to be scientifically standardizable and able to deliver objective and valid results. They do not comprehensively represent all conceivable tampering methods that might be employed by abusers.

The resistance to crushing tablets into powder was assessed by means of spoons, a professional pill-crusher (OCELCO Pillcrusher) and a standardized hammer apparatus (Coesfeld Dart Tester). Whereas conventional ER tablets containing an opioid could easily be crushed, INTAC tablets resisted the attempts at crushing by two spoons virtually unchanged and were flattened to a small extent by the pill-crusher and hammer but could not be pulverized (plastic deformation only). In vitro release testing demonstrated that conventional ER tablets simply crushed between two spoons release the active ingredient immediately (flash release), while release from INTAC tablets after tampering with spoons was not altered at all. Attempts at crushing of INTAC tablets with a pill-crusher or hammer apparatus led to an insignificant increase of in vitro dissolution of less than 10% compared to the release from intact tablets (Figure 4).

In some cases extended release opioid tablets are ingested together with alcoholic beverages either by accidental misuse or intentional abuse. This can lead to dose dumping or faster release of the drug substance from ER tablets. In vitro dissolution testing of opioid containing INTAC ER tablets in 0.1 N HCl with 40% ethanol revealed a decrease of drug release in an alcoholic environment, indicating that dose dumping is not likely to occur when INTAC ER tablets are co-administered with an alcoholic beverage (Figure 4). Thus, the formulation itself was not found to be susceptible to alcohol-induced dose dumping. This finding does not exclude higher peak blood concentrations after co-ingestion of alcohol in vivo (eg, in the case of a drug substance that bears metabolic alcohol interactions as a property of the substance itself irrespective of the formulation of the final drug product).

Another method of tampering, especially by recreational abusers, is extracting drug from either intact or crushed tablets with alcoholic or non-alcoholic beverages, and drinking the resulting solution. Therefore, the in vitro dissolution over time of INTAC tablets has been investigated after vigorously shaking them for 15 minutes in simulated beverages (Figure 5).

In simulated non-alcoholic beverages, the extraction is identical to the in vitro dissolution of the tablets as intended for compliant usage; in alcoholic beverages the extraction is even lower. The subsequent dissolution test demonstrated the unchanged ER profile of the drug pointing to the still intact ER matrix.

Kitchen chemists try to extract drug from tablets using various acidic or alkaline media as well as organic solvents followed by evaporation of the solvent. Such attempts were mimicked by exposing opioid containing INTAC tablets to vigorous shaking for 15 minutes and 1 hour in 30 ml of different solvents (Figure 6).

Apolar solvents and solvents of low polarity did not extract any opioid from the tablets, whereas more polar solvents did to a minor extent. Pure ethanol and 0.1 N sodium hydroxide are of medium extraction power compared to 0.1 N hydrochloric acid, water, or methanol. However, in none of these media was the amount of active substance extracted higher at any time point than the intended released of the drug substance seen in the in

vitro dissolution at the same time points. Thus, solvents did not increase extraction from the TRF formulation.

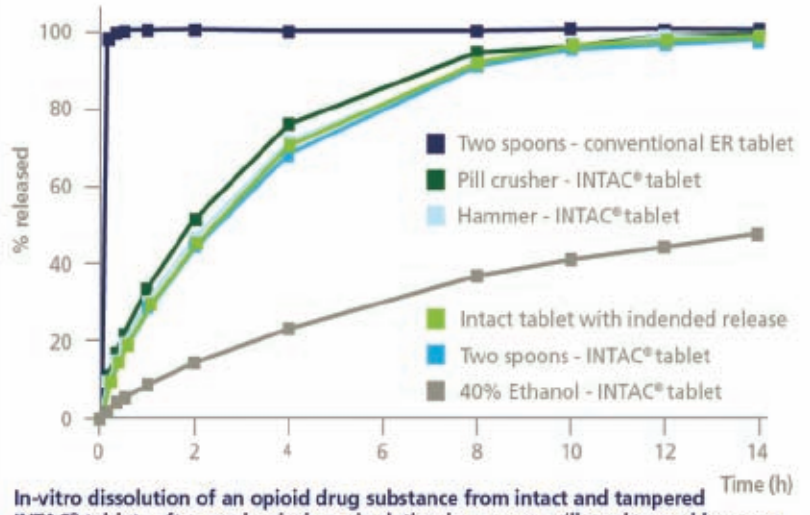
## APPRAISAL BY EXPERIENCED PRESCRIPTION DRUG ABUSERS

As the aforementioned in vitro testing executed by trained laboratory staff working according to standard operating procedures (SOPs) differs from how abusers might tamper with the tablets, studies with experienced abusers were also performed. In one study, 40 experienced non-dependent recreational abusers of ER prescription opioids given access to any tool they wanted to use were allowed to tamper with oxycodone controlled-release (CR) tablets (conventional formulation without tamper-resistant properties) and INTAC placebo tablets.[5,6] Participants were not allowed to consume either tablet. After the tampering attempts, participants were asked for their preference of product and the price they would be willing to pay assuming that the INTAC tablets would also contain the same active opioid substance. About 90% of the experienced abusers preferred the conventional CR tablet over the INTAC tablet. In addition, 35% were not willing to pay anything, and another 42.5% were only willing to pay less for INTAC than for oxycodone CR.

These findings were confirmed in another study run with INTAC tablets containing 40 mg of a different opioid substance compared to the conventional opioid ER tablet in 25 experienced intravenous abusers and another 25 experienced intranasal abusers with access to any requested tools for tampering.[7] The abusers were supervised and not allowed to administer any drug. The abusers were unable to prepare a solution for intravenous abuse from INTAC tablets. They could scrape off only smaller chunks from the tablets that formed a gel when in contact with water. Amongst the intravenous abusers, only 6 of 25 could prepare any extract into a syringe with a mean volume of 0.18 ml containing less than 2% of total drug substance contained in the tablet. Thus, INTAC markedly limited preparation for intravenous abuse.

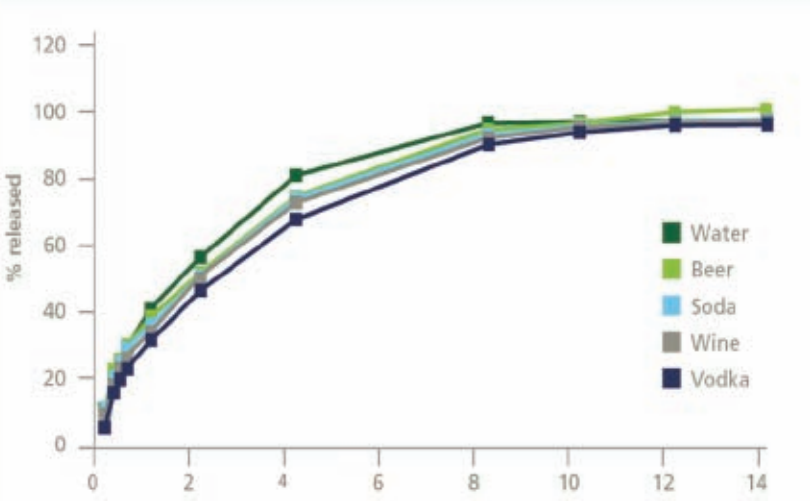
All 25 intranasal abusers were able to easily crush the conventional reference opioid ER tablet - with about 98% of the resulting particles measuring < 1.7 mm and about 50% measuring < 0.2 mm. Preparations intended for intranasal use are commonly of < 0.15 mm particle size. In a total of 28 attempts on the INTAC tablets made by the 25 experienced abusers, only 8 attempts led to any particles of which about 9% were < 1.7 mm and only about 4% were < 0.2 mm. The remaining 20 attempts failed to deliver any particles whatsoever. When the subjects were asked whether they would be willing to snort the particles they prepared, 24 answered "yes" for the conventional reference opioid ER tablet whereas only 3 stated they were willing to

**FIGURE 4**



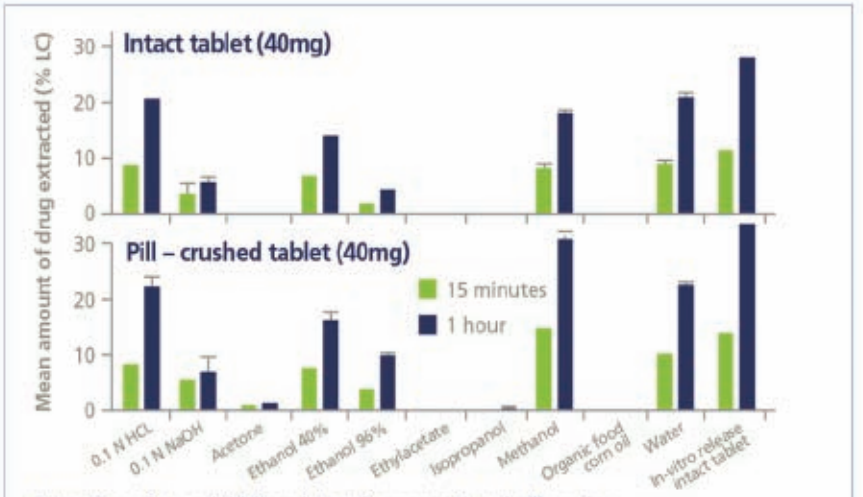

**In-vitro dissolution of an opioid drug substance from intact and tampered INTAC® tablets after mechanical manipulation by spoons, pill crusher and hammer apparatus or dissolution in ethanolic medium (40% EtOH) compared with conventional ER tablet without tamper resistance features after mechanical manipulation by spoons.**

**FIGURE 5**




**In-vitro dissolution of an opioid from INTAC® tablets after 15 min of vigorous shaking in simulated beverages; the initial point of each curve indicates the amount released during shaking.**

## FIGURE 6




Extraction of an opioid from intact (upper part) and pill crusher tampered (lower part) INTAC® tablets by vigorous shaking in 30 ml of different solvents for 15 minutes and 1 hour; for comparison, in-vitro dissolution of the tablets after the same release times is included in the figure.

snort the particles from the INTAC tablets. Thus, tablets with INTAC formulation also discourage intranasal abusers to a large extent.

## REAL WORLD EVIDENCE

The results of the in vitro test battery and the investigations with experienced abusers suggest that INTAC bears a high potential to raise the hurdles against tampering. Nevertheless, the potential effectiveness of such formulations in deterring abuse can only be proven by epidemiologic analysis of post-marketing data over an extended period of time and can therefore only be assessed after introduction of the reformulated products to the market. Two opioid products using INTAC have recently been approved by the FDA and introduced to the market, thus it is too early to make such an assessment for these products. However, the reformulation of OxyContin® (Purdue Pharma, Stamford, CN) into a tablet with high crush resistance was launched in August 2010. In May 2012, an assessment utilizing data from the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO) sentinel surveillance network was published.[8] The proportion of prescription opioid abusers entering substance abuse treatment centers who abused OxyContin by any administration route declined from 24% to 12% for the 11-month period after introduction of the reformulation. With respect to routes of administration in abuse, the percentage for the oral route declined from 14% to 10%, whereas abuse via non-oral routes that require tampering (eg, injection, intranasal, smoking) declined by 73% from 18% to 5% in individuals abusing any prescription opioid. These data support the potential for crush-resistant formulations, like INTAC, to discourage prescription opioid abuse, notably with respect to non-oral routes.

## SUMMARY

INTAC ER tablets exhibit an extraordinary crush resistance achieved by the combination of high molecular weight PEO and a proprietary manufacturing process employing heat and force. The manufacturing including a newly designed downstream process is established at commercial scale. INTAC is already featured in two FDA-approved products. Although INTAC tablets are extremely hard and difficult to tamper with, their in vivo performance is comparable to conventional marketed ER formulations as demonstrated by bioequivalence studies. This purely physico-chemical approach to raise the hurdle for abuse and misuse is supported by in vitro data from standardized bench top testing and studies with experienced abusers and is supported by the initial post-marketing surveillance reports of changing abuse patterns of OxyContin® since the introduction of a reformulated version that has similar TRF attributes. However, according to the FDA, any label claim of abuse deterrence will require "robust epidemiological data supporting a change in levels of abuse in the community over a reasonably long period of time."[9]

As INTAC's purely physicochemical approach does not require the addition of non-therapeutic substances (eg, antagonists or aversive agents) and its hardened matrix should have little or no impact on efficacy or tolerability, INTAC ER is also suited to prevent the accidental or misguided intentional crushing of ER tablets, unrelated to abuse. As such, this crush-resistant technology may be used to formulate any ER drug for which inappropriate crushing may result in adverse events and/or decreased efficacy (Do not crush list).[10] ◆

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## BIOGRAPHIES

**Dr. Johannes Bartholomäus** studied Pharmaceutical Sciences at TU Braunschweig and finished his thesis in Pharmaceutical Technology in 1988. He joined Grünenthal GmbH as head of a formulation laboratory. From 1992 to 2008, he was heading Pharmaceutical Development and was an inventor of i.a. tamper-resistant formulation technologies. In 2009, he started his own Pharmaceutical Development Consultancy. In addition, he is an invited lecturer for Industrial Pharmacy and Honorary Professor at TU Braunschweig.

**Dr. Judy B. Ashworth** is Senior Director (Grünenthal GmbH) and was a lecturer in the department of Substance Abuse Research at Columbia University (2006-07), where she helped develop methodology for assessing the impact of tamper-resistant tablets on experienced abusers and has co-authored several papers on tamper-resistant opioids and the assessment of the abuse potential of prescription opioids.

**Dr. Hans-Jürgen Stahlberg** is the International Clinical Lead for life cycle management products in the department of Clinical Pharmacology at Grünenthal GmbH. He has extensive experience in pharmacokinetics (PK) and published in peer-reviewed journals on PK of analgesics and antibiotics. He holds a Certificate in Pharmaceutical Medicine from the University at Basle, Switzerland. His current focus lies on development of tamper-resistant opioid formulations.

**Dr. Eric Galia** is Project Director in International Technical Alliance Management at Grünenthal GmbH. He studied Pharmaceutical Sciences at the University of Frankfurt. After various positions in the pharmaceutical industry, he joined Grünenthal GmbH in 2005. Since 2008, he is involved in the development and project management of the INTAC® tamper-resistant formulation technology platform.

**Dr. Kai Strothmann** is Senior Director Strategic Marketing at Grünenthal GmbH. He studied Pharmaceutical Sciences and earned his PhD in Pharmacology at the University of Münster. After more than 10 years of experience in various positions in the pharmaceutical industry, he joined Grünenthal GmbH in 2011. Since then, he is involved in the life cycle management of the INTAC® tamper-resistant formulation technology.

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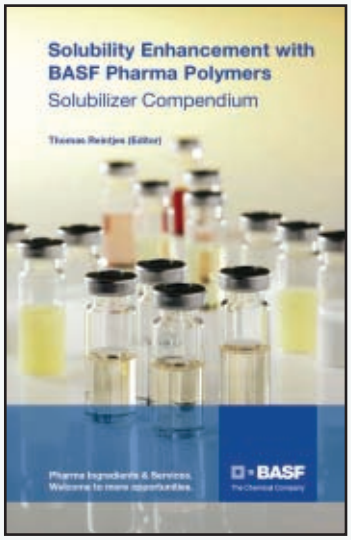
## Solubilizer Compendium




BASF's new solubilizer compendium is a must-read for anyone working with APIs that exhibit poor solubility and bioavailability. It leverages BASF's vast expertise in solubilization and bioavailabilty enhancement, and is the result of many years of research. The publication provides a valuable overview of all relevant BASF excipients (Kolliphor™ grades, Soluplus®, and selected Kollidon® grades), and offers helpful advice on creating solid solutions and dispersions. What's more, it includes a chapter dedicated to high-throughput screening as a means of selecting the right excipient or combination of excipients for a poorly soluble drug. Visit www.innovate-excipients.basf.com to download the compendium as a PDF, or to request a free hard copy. BASF's solubility enhancement experts are happy to answer all your questions. Just send an e-mail to **pharma-ingredients@basf.com**.

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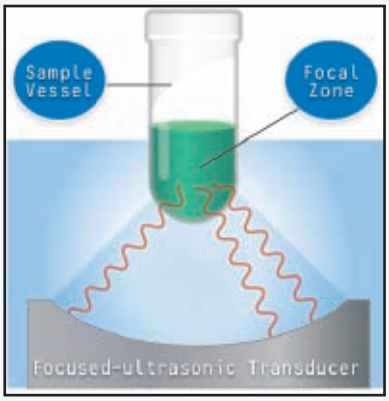
## Faster to First-In-Human

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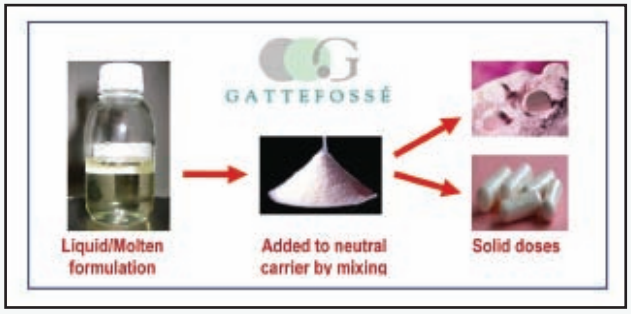
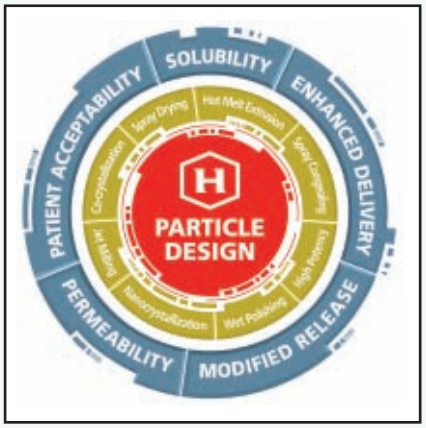



Designed for enhancing the solubility of poorly soluble drugs in solid dosage forms, this technique allows the transformation of liquid or semi-solid lipid formulations into solid particles that can subsequently be filled into hard shell capsules or alternatively compressed into tablets. The active may be dissolved or dispersed in the formulation prior to adsorption onto a solid neutral carrier, such as calcium silicate, with the aid of conventional mixers. The success of the technique depends much upon the properties of the carrier, notably its flow characteristics and capacity to absorb the desired amount of formulation. Our laboratory has successfully loaded up to 68% liquid SELF onto solid support. For more information, contact Ron Permutt of Gattefosse at (201) 265-4800 or visit **www.gattefosse.com**.

## Manufacturer & API Specialist




Hovione is a global company with over 50 years of experience in Active Pharmaceutical Ingredient and Drug Product Intermediate development and compliant manufacture. With four FDA-inspected sites in the US, China, Ireland, and Portugal, the company focuses on the most demanding customers in the most regulated markets. Hovione offers integrated API, particle design, formulation development, and manufacturing. In the inhalation area, Hovione is the only independent company offering such a broad range of services. For more information, contact Isabel Pina of Hovione at 351 21 982 9362 or ipina@hovione.com or visit **www.hovione.com**.

## Tamper-Resistant Technology

intac® by Grünenthal

INTAC®, Grünenthal's tamper-resistant formulation technology, is designed to deter a number of relevant routes of abuse/inadvertent misuse from tablet tampering by imposing a high mechanical stability to the tablet. The high mechanical stability is created by the combination of specific excipients and a unique manufacturing process. Grünenthal's proprietary INTAC approach is established on a commercial manufacturing scale and is featured in FDA-approved products that are marketed by US partners. Grünenthal considers its patent-protected INTAC to be the leading technology for abuse-deterrent and tamper-resistant opioid products. The INTAC technology is available for licensing to interested companies for various product opportunities. For more information, contact info@intac.grunenthal.com or visit **www.intac.grunenthal.com**.

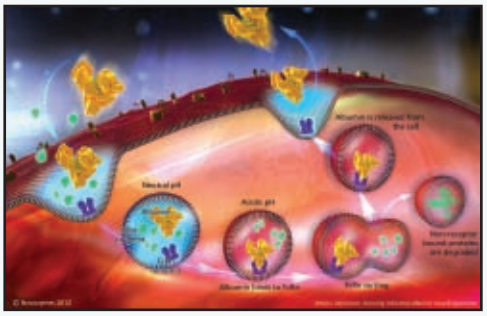
## Platform Technology

CAPTISOL®

Ligand is a biopharmaceutical company that develops and acquires technology and royalty revenue generating assets that are coupled to a lean cost structure. Ligand's Captisol® platform technology is a patent protected, chemically modified cyclodextrin with a structure designed to optimize the solubility and stability of drugs. Captisol® has enabled five FDA-approved products, including Pfizer's VFEND® IV and Baxter's Nexterone®. For licensing opportunities, call Captisol Services at (877) 575-5593 or visit **www.captisol.com**.

# Technology & Services Showcase

## Tunable Half-Life Technology



Novozymes' tunable half-life extension (HLE) technology can flexibly extend half-life to reduce the dosing frequency of drugs from days to weeks. Based on albumin, Novozymes offers HLE by genetic fusion, Albufuse® Flex, or chemical conjugation, Recombumin® Flex, enabling the tunability of HLE to meet the needs of a specific disease or application. Leading the way in improving patient quality of life, Novozymes' technology is already being widely used in the fields of diabetes, haemophilia, and neutropenia. Through the optimization of drug half-life, dosing frequency and healthcare costs can be reduced while increasing patient compliance. Long patents until at least 2030 also provide manufacturers with a unique competitive edge in current challenging markets. For more information on Novozymes' HLE technology, please visit **www.halflifeextension.com**.

## Silicone Materials

NuSil SILICONE TECHNOLOGY

When it comes to drug delivery, NuSil provides numerous solutions that fit a variety of device needs. While most silicone products are customized for individual delivery systems, all are developed with FDA regulatory concerns in mind. In addition to its role as a supplier, NuSil offers research and development capabilities for those looking for proprietary, custom formulations. Regardless of batch size, NuSil delivers quality, high-performance silicone materials based on your unique property requirements, as well as provides precise, custom formulations. NuSil offers an even wider range of silicone material and compound options for transdermal, transmucosal, implanted intrathecal, and external delivery devices, as well as ingestible materials. For more information, contact NuSil Technology at (805) 684-8780 or visit **www.nusil.com**.

## Manufacturing & Development


Patheon is a leading global provider of contract dosage form development and manufacturing services to the pharmaceutical and biotechnology industries. Employing more than 4,700 highly skilled staff, Patheon's network of modern manufacturing facilities located in North America and Europe offer more than 3 million sq ft of best-in-class capacity. With three facilities in the US, three in Canada, and four in Europe (including two in Italy, one in France, and one in the UK), Patheon is able to meet the international requirements of its customers. Patheon's development and manufacturing capabilities cover prescription (Rx) products in solid, semi-solid, and liquid dosage forms, as well as specialized capabilities in high-potency, cephalosporin, controlled/sustained release, and sterile manufacturing, including aseptic filling and lyophilization. For more information, contact Patheon at (888) PATHEON or visit **www.patheon.com**.

## Contract Diagnostics

ResearchDx
Your Companion in Diagnostics

ResearchDx is the leading Contract Diagnostics Organization (CDO) for the biopharmaceutical and diagnostic industries. As a CDO, ResearchDx integrates in vitro diagnostics (IVD) non-clinical and clinical research, CAP/CLIA laboratory assay discovery, development and testing, GMP manufacturing of test kit components, and end-to-end consulting to achieve the fastest path to market for your IVD/companion diagnostic. With experts managing the entire development process from initial assay concept and discovery through clinical research to regulatory approval, ResearchDx employs a proactive project management approach with the availability of resources to ensure appropriate attention to timelines every step of the way. By offering the complete range of CDO services without owning a proprietary testing platform, ResearchDx ensures its clients' diagnostics are developed with the methodology and platform that best optimize its characteristics and commercialization strategy. For more information, contact ResearchDx at (866) 225-9195 or visit **www.researchdx.com**.

# Technology & Services Showcase

## Disposable Autoinjector

The BD Physioject™ disposable autoinjector is a clinically proven, patient preferred, customizable autoinjector platform. Leveraging BD's 50+ years offering prefillable syringes, BD guarantees the highest reliability with its fully integrated disposable autoinjection system designed and validated in combination with BD Hypak™ glass prefillable syringes. The BD Physioject disposable autoinjector was developed using BD's patient-centric design approach, incorporating clinical data and usability engineering to meet the needs of pharmaceutical customers and their patients. BD offers full service expertise, including assembly and worldwide registration support, enabling successful commercialization. Our goal is to develop devices that make it safer and easier for patients to take medication the right way each and every time. BD. The trusted partner to maximize your innovation. Learn more at www.bd.com/self-injection or contact a BD expert at **self_injection@bd.com**.

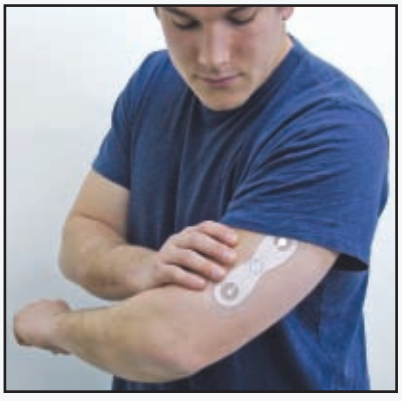
## Intelligent Monitoring Capsule


Whether it's in the development of orally administered pharmaceutical drugs or functional food ingredients, site absorption studies in GI tract are an important part of evaluating their effectiveness. Medimetrics' IntelliCap technology provides a faster, better, cost-effective, and convenient means for the controlled release of drugs or functional food ingredients to specific sites in the GI tract. As an added benefit, quantitative data, such as GI temperature, pH profile, and transit data are measured and recorded during the process. This data available for each subject can prove invaluable in evaluating study results. In the form of a compact capsule (11 x 26 mm), the IntelliCap incorporates a microprocessor, battery, pH sensor, temperature sensor, RF wireless transceiver, fluid pump, and drug reservoir. For more information, contact Medimetrics at 617-840-8564 or visit **www.medimetrics.com**.

## Passive Safety Device

Rexam Healthcare has received 510(k) approval from the FDA for Safe'n'Sound™, its passive safety device for staked prefilled syringes. The approval is the crowning achievement of significant investment and design efforts by the Rexam teams. The aim of the project was to design a safety device that meets the current regulations in North America and Europe. These regulations are aimed at protecting workers in the health sector from needle injuries and contamination from blood-borne pathogens. The fully passive Safe'n'Sound device provides effective protection against the risks of being pricked by a soiled needle due to the protective sheath that activates automatically once the medicine has been administered. This 510(k) approval shows Rexam's commitment to innovation, safety, and quality and allows the product to be marketed in the US. For more information, contact Rexam Healthcare at (800) 537-0178 or visit **www.rexam.com/healthcare**.

## Device Contract Manufacturer



Tapemark is a full-service pharmaceutical and medical device contract manufacturer providing web-based (flexible roll goods) manufacturing for Drug, Device, and Combination Products. Supported single-use drug delivery formats include active and passive transdermal patches, oral and transmucosal soluble film, topical patches and pads, and Tapemark's patented Snap! and Snapplicator™ unit-dose packaging for semi-solids. Tapemark is cGMP compliant, ISO 9001 and 13485 certified, and FDA registered as a Drug, Device, Food, Cosmetics, and Dietary Supplements contract manufacturer. In addition, Tapemark is DEA registered as a Schedule III-V Manufacturer of Controlled Substances. Supporting its expanding global reach, Tapemark's quality system has been successfully audited by the European Union, Japan, Australia, and Korea, with CE mark certification. For more information, contact Tapemark at (800) 535-1998 or visit **www.tapemark.com**.

# Technology & Services Showcase

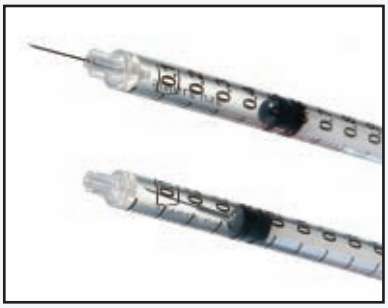
## CRO Services

Theorem Clinical Research is a foremost provider of comprehensive CRO services with offices in more than 30 countries and a customer base composed of some of the world's leading pharmaceutical, biotech, and medical device companies. Theorem converges Phases I-IV solutions with specialized therapeutics expertise to execute perfectly aligned trials. Supporting business units include Clinical Development, Clinical Supply, Clinical Analytics, Biopharmaceutical, and Medical Device and Clinical Combination Studies. For expert guidance and custom solutions to streamline your trials, think Theorem. Learn more about Theorem's extensive capabilities by calling (800) 290-5766 or visiting **www.theoremclinical.com**.

## Development Services


UPM Pharmaceuticals® is an independent provider of contract formulation development, analytical services, and cGMP manufacturing. We continue a legacy of intellectual distinction and uncompromising performance with every new project. The talent and experience of our team, our dedication to science-based formulation design, and our commitment to communication and timeliness enables us to offer the highest level of customized drug development services. Our 40,000-sq-ft main facility in Baltimore features cGMP pharmaceutical manufacturing and packaging suites as well as analytical and R&D laboratories staffed by industry veterans. Whatever form your product takes, we ensure rigorous and technically sound product characterization, methods development, and QC release. Our clients enjoy service that is highly responsive and fast with total quality management characteristic of a customer-focused business. For more information, contact UPM Pharmaceuticals at 410-843-3738 or visit **www.upm-inc.com**.

## Prefilled/Clinical Safety Syringes



Unilife Medical Solutions has a range of prefilled and clinical safety syringes suitable for pharmaceutical companies, healthcare facilities, and patients who self-administer prescription medication. Our products incorporate passive and fully integrated safety features that can help customers comply with needlestick prevention laws and encourage single-use and safe disposal practices outside of healthcare settings. The products feature a passive (automated) needle retraction mechanism allowing operators to control the speed of needle retraction directly from the body into the barrel of the syringe. The Unilife Ready-to-Fill Syringe features a glass barrel and is compatible with the manufacturing procedures used to fill standard prefilled syringes. The Unitract 1-mL Insulin Syringe is FDA certified and now being manufactured in the PA facility. For more information, contact Unilife at (717) 938-9323 or visit **www.unilife.com**.

## Intranasal Vaccine Device

The new VaxINator™ Intranasal Vaccine Delivery Device offers a rapidly effective method to deliver vaccines or other medications to a patient without the need for a painful injection. The device features a precise 30- to 100-micron spray, has low dead space, attaches to any luer lock syringe, is ideal for lyophilized and liquid drugs, and is latex free. For more information, contact Wolfe Tory Medical at (801) 281-3000 ext. 101 or e-mail mdenton@wolfetory.com, or visit **www.wolfetory.com**.

DRUG DEVELOPMENT
HOVIONE Executive

# HOVIONE: NEW TECHNOLOGIES IN PARTICLE DESIGN

**Colin Minchom, PhD**

**VP, Particle Design Business Unit**

**Hovione**

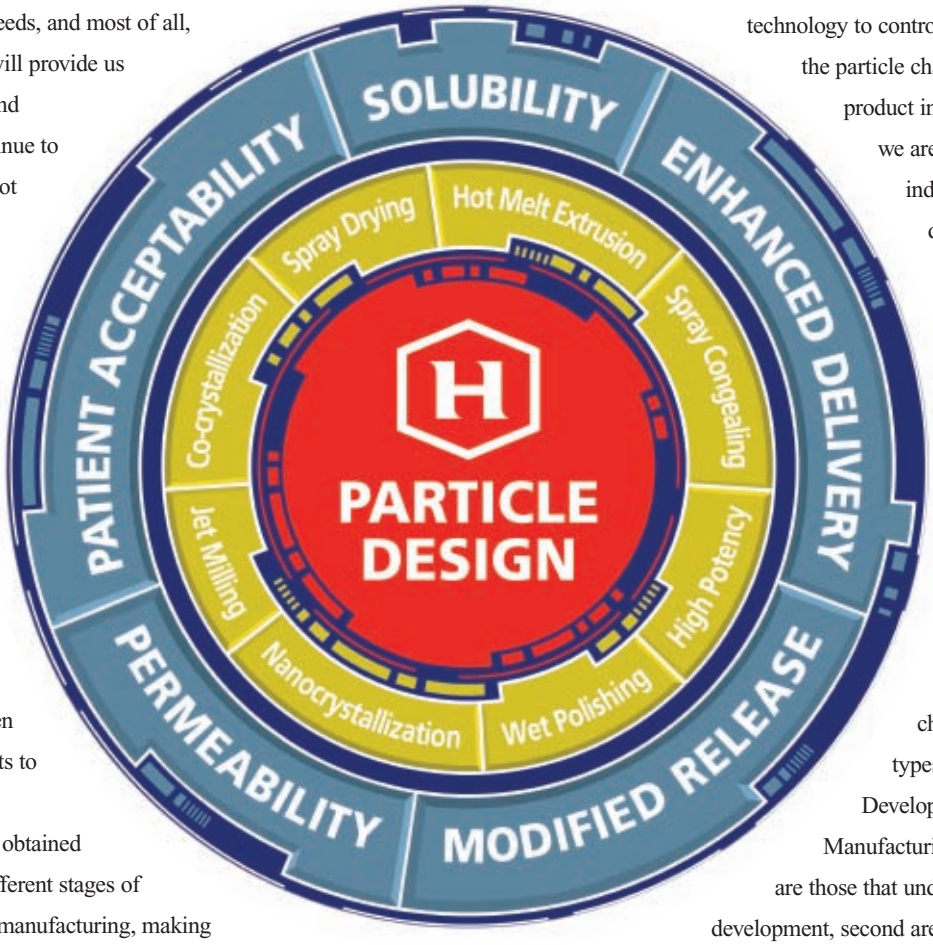
**"An issue for customers with a poorly soluble molecule is that any one solubility enhancement technology is likely to have, I believe, a 20% to 40% probability of solving the problem. This means that in order to assure acceptable bioavailability, at least three technologies need to be investigated. The customer would need to contract with three single platform technology companies or be able to engage a single company, such as Hovione, that can apply multiple platforms, to increase the probability of solving the problem, and deliver the desired outcome."**

*Hovione was founded over 50 years ago in Portugal as a manufacturer of generic APIs (Active Pharmaceutical Ingredients). In addition to the initial offering, Hovione's global sites today provide services in contract development and commercial manufacture of custom pharmaceutical molecules and drug product intermediates. Drug product intermediates are engineered particles developed and manufactured to solve the drug delivery challenges provided by the physico-chemical properties of the API. After generation, these are further formulated into dosage forms. While Hovione can deliver the drug product intermediates to commercial scale, the company also undertakes the formulation development and clinical supply of the final dosage form to Phase II. Additionally, the company has a particular strength in dry powder inhaler technology by engineering particles to meet the exacting needs of lung delivery. Hovione also has an innovative line of inhaler devices to complement its contract services. Utilizing innovative technologies, and with a global footprint, Hovione is an integrated solution provider to the pharmaceutical industry in the US, EU, and Asia. Its sites in Portugal, Ireland, the US, China, and Macau allow them to serve an increasing base of customers from the pharmaceutical start-up to the fully integrated pharmaceutical company.*

*The company has an outstanding record of compliance, quality service, and delivery and continues to strive for excellence and meet increasing industry standards. The success of the company is based on the pillars that have been implemented from the very beginning: "a never give up attitude, energy, creativity, and innovation, passion, and rigor in the quest for customers' smiles and satisfaction." Hovione's customers range from small biotech to multinationals, and is partnering with them in every step through the development challenges and ultimately through to commercial manufacturing. This gives them the opportunity to solve some of the most challenging problems in the industry, which in turn, provides a valuable experience base to utilize in the future for current and potential customers. In the past year alone, Hovione has supported three FDA submissions, including one by QbD, demonstrating Hovione's commitment to innovation and service. Drug Development & Delivery recently interviewed Dr. Colin Minchom, VP of Hovione's Particle Design business unit, to discuss how the company is evolving and adapting in the current market, and to review Hovione's new Particle Design offering.*

***Q: How has the recent economy impacted your company?***

***A:*** The advantage of serving multiple pharmaceutical segments with a diverse portfolio offering and having a global presence is that you reduce the risk of exposure to issues in one specific segment or economic region. That does not mean Hovione is not susceptible to the many tough challenges the industry has been facing. However, we believe that by evolving and adapting to the market, listening to customer needs, and most of all, sticking to our values will provide us the continued growth and prosperity that we continue to experience. We could not have achieved this if it wasn't for our brilliant scientists and engineers, all support staff, our state-of-the-art facilities, and the more than 50 years of experience and know how. Hovione continually invests in training all our employees and when needed, brings in experts to fill gaps. Hovione also leverages the synergies obtained from working in the different stages of drug development and manufacturing, making sure we quickly apply the best practices of one specialty; for instance the learning's from a chemistry project can lead to novel ways to develop a drug product intermediate or drug product and vice versa. We believe this will keep us on the right track for the years to come.




***Q: You joined Hovione recently. What would you say differentiates Hovione from the rest of the CRO/CMO industry?***

***A:*** When Hovione's Particle Design business unit was created, it included an extensive range of advanced technologies to address specific particle performance problems. Building on accumulated experience in jet milling, micronization, and the creation of amorphous materials, Hovione offered spray drying as the key technology to controlling and optimizing the particle characteristics of drug product intermediates. Currently, we are well known in the industry for these spray drying capabilities, in which we have delivered products at all stages of development and have an unmatched commercial manufacturing capacity and expertise.

Today Hovione has changed. There are three types of CDMOs (Contract Development and Manufacturing Organizations). First are those that undertake classical development, second are those that innovative and offer a specific technology to solve a problem, and third are those that offer a series of platform technologies to enable the greatest probability of success for a specific challenge. Hovione is now among the third group and is one of the very few companies that offer a series of innovative particle engineering technologies to solve problems, such as poor bioavailability, patient acceptability, or enabling optimal delivery by non-oral routes of administration. In addition, Hovione is unique in offering many of these technologies from the bench to full commercial production. Through Hovione, customers' drug delivery challenges have the highest probability of being solved,

and the product can be commercialized without technical transfer across multiple companies.

Moreover, we operate using state-of-art methodologies: Process Analytical Technologies (PAT), Quality by Design (QbD), and Process Modeling for optimization and scale up along with Lean Manufacturing are part of our DNA, allowing us to look at challenges in a different way than most of our competitors.

## *Q: Which technologies are you bringing on board?*

***A:*** The particle engineering technologies Hovione has fall into three main categories. The first is crystal design (eg, controlled crystallization, co-crystals), the second is particle size reduction (eg, jet milling, wet polishing, and nanoparticle generation), and the third is amorphous solid dispersions (eg, spray drying, hot melt extrusion, spray congealing, inclusion complexes). Hovione has further complemented these services with the formulation of dosage forms and clinical manufacture, and also being able to support highly potent compounds with many of these technologies.

These innovative technologies Hovione offers are means to an end; the end being the solving of issues such as poor bioavailability, patient acceptability, and non-optimal delivery with oral administration. An issue for customers with a poorly soluble molecule is that any one solubility enhancement technology is likely to have, I believe, a 20% to 40% probability of solving the problem. This means that in order to assure acceptable bioavailability, at least three technologies need to be investigated.

The customer would need to contract with three single platform technology companies or be able to engage a single company, such as Hovione, that can apply multiple platforms, to increase the probability of solving the problem, and deliver the desired outcome. Hovione is therefore unique in providing optimization and scale up to full commercial support and eliminating the delays and costs of an intercompany transfer. We have a great deal of engineering experience and have applied PAT and QbD to support successful regulatory submissions on behalf of our customers.

## *Q: How do you work with your customers?*

***A:*** Throughout the years, Hovione has invested in and developed excellent project management systems. In addition to our business units, we have supporting services that make the customers' experience as efficient and challenge free as possible. These include analytical and regulatory support; GMP and Health, Safety, and Environmental compliance; Technology Transfer; and Strategic Sourcing.

Our project management systems ensure that every customer has two dedicated points of contact at the project level, and additional oversight links. We establish several layers of communication with customers. For example, it's not unusual to see our CEO Guy Villax involved in key meetings with the customers' top management team. In addition, our account managers work closely with our technical project managers, to ensure teams are aligned and both have a common understanding of what is going on, meeting expectations, and delivering on time.

Our secure web-based Navstream Information System enables customers to have 24- hour real time access to their GMP data for each development project or production line at Hovione. Through this system, customers can securely access their product data from our Enterprise Resource Planning, Quality Control Management System, Change Control System, Deviation Management System, and Controlled Documentation database systems. Critically, the information available to a specific customer is only that pertaining to their project.

Above all, Hovione encourages a culture of open communication. We are extremely transparent and work side by side with our customers to achieve the common goal. This helps build trust and credibility with our customers, which is a critical element given we measure our success by our repeat business as well as when customers consider us their preferred solution provider.

## *Q: What can we expect to see from Hovione in the future?*

***A:*** Hovione is a company with a culture based on innovation, quality, and delivery. Our long-term strategy is to stay in the vanguard of technology provision that solve customers' problems of API production and also drug delivery from bench to commercial scale. As new technologies emerge or are developed, Hovione will evaluate each of them and determine if they are a fit for our customers' unique development challenges. ◆

# Dry Eye Syndrome: A Review & Novel Formulation Approach

By: David M. Kleinman, MD; Andrew Loxley, PhD; Gillian M. Tocci, PhD; George Ngwa, PhD; William Gensheimer, MD; and Robert W. Lee, PhD

## Introduction

Dry eye symptoms are one of the leading causes of visits to ophthalmologists, and 30% of patients seen by ophthalmologists describe symptoms consistent with dry eye syndrome.[1-3] Up to 50 million people in the US have some form of dry eye disease, and the prevalence of dry eye syndrome is increasing.[4,5] Reasons for this rise include an aging population and related hormonal changes associated with aging in females, increased numbers of people undergoing cataract and refractive surgical procedures that are associated with post-operative dry eye, steady growth in contact lens use that can cause and exacerbate dry eye, and an increase in screen-related visually demanding tasks.[4,5] The pharmaceutical market size for dry eye has been similarly growing. Recent reports suggest a greater than 6% year-over-year growth rate, with an estimate of $1.6 billion based on global sales estimates. Therapies for dry eye disease are facing a resurgence of interest following a brief lull in venture investment that was seen after several prescription products failed to meet the demanding Phase III primary endpoints required by the FDA for a new drug approval.

Dry eye symptoms consist of ocular irritation, visual blurring, grittiness, burning, stinging, and reflexive tearing to name a few. These symptoms are associated with clinical findings, including tear film instability, rapid tear film break-up time, fluctuating visual acuity, corneal surface irregularities, staining of the cornea when vital dyes are introduced into the eye upon examination, and tear hyperosmolarity.[6] The pathophysiology behind dry eye is not completely understood, but it is a multifactorial disease. The tear film is a complex fluid that contains water, salts, mucins, proteins, and lipids. When the quality of the tears diminishes and the epithelial surface of the eye becomes less hydrophilic,

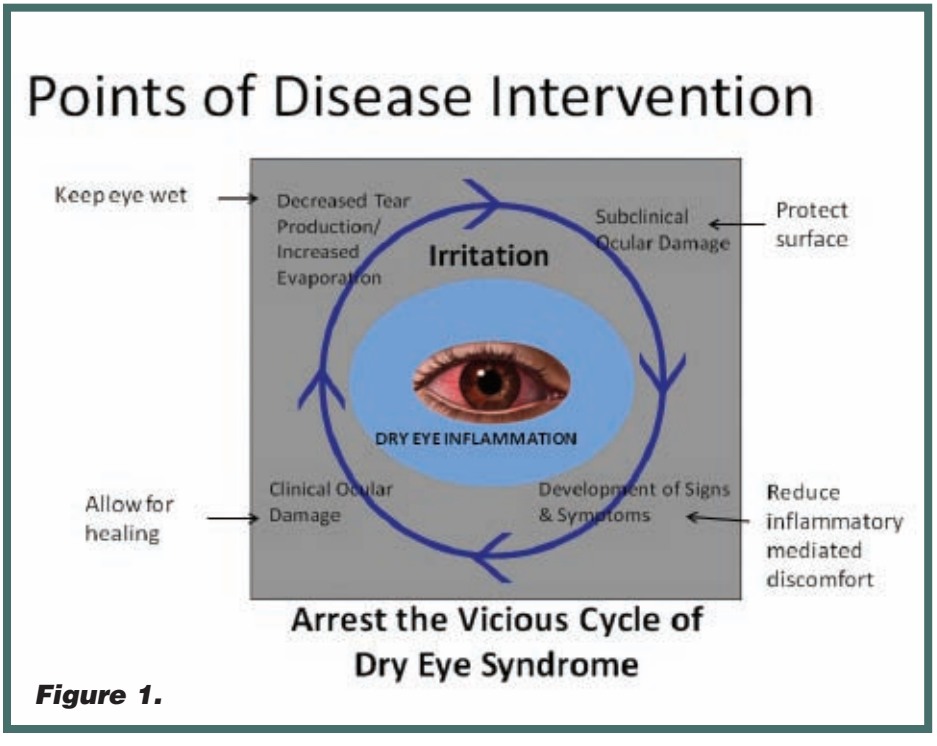



***Figure 1.***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dry eye symptoms develop.

There is wide agreement in the literature and among experts that tear film instability is a critical aspect of dry eye disease and is the ultimate result following the multiple different pathologic processes implicated in dry eye. Tear film instability is associated with a lack of uniform and long-lasting tear film coverage on the surface of the eye. The surface of the eye should be kept wet at all times, both for optimal vision and for maintenance of external eye health. Tear film instability leads to faster tear break-up times and surface desiccation as well as to the signs and symptoms of the disease.

## Current Therapies for Dry Eye

Dry eye is broken down into two major diagnostic categories: aqueous deficiency and evaporative. Regardless of the diagnostic category, the symptoms and clinical findings are similar. A reasonable simplification of the common end-stage pathway yields a vicious cycle of tear instability, surface damage, inflammation, continued tear instability, and complaints of irritation. The diagram in Figure 1 describes this sequence of events and also identifies points of disease intervention.

The mainstay of therapy for dry eye is over-the-counter (OTC) artificial tears. Artificial tears effectively moisten the surface of the eye, and these products account for 60% of the pharmaceutical dry eye market. All OTC artificial tears in the US include an active agent from the FDA Monograph for OTC Ophthalmic Drug Products. A commonly known and safe demulcent, such as polyethylene glycol, propylene glycol, carboxymethylcellulose, hypromellose, or glycerin (alone or in combination, at or below a low single digit weight/weight (w/w) percent) is the active ingredient in an OTC artificial tear. Drug product excipients include water, salts, preservatives, and other polymers. Manufacturers are continually adjusting inactive components to improve the performance of artificial tear drug products. For example, Alcon/Novartis includes guar gum and boric acid in their Systane® family of products to create a gelling matrix when the eye drop is exposed to physiologic (or near physiologic) pH. The Systane franchise has become a market leader and significant source of revenue (over $300 million based on annual report analysis) for Novartis. Although Systane does show superiority over competitors with regard to certain metrics of analysis, such as prolongation of tear film break-up time, current artificial tear products including Systane provide only temporary relief and are quickly washed out of the eye. A careful review of the literature suggests very few, if any, commercial products have a duration of activity longer than 1 hour.[7-11] Most of the products lose effectiveness at 20 minutes unless they are very viscous.[9-12] However, viscous products are poorly tolerated because they interfere with vision. There is a significant opportunity, described in greater detail further, for developing better and longer-acting artificial tears through advances in formulation and excipient

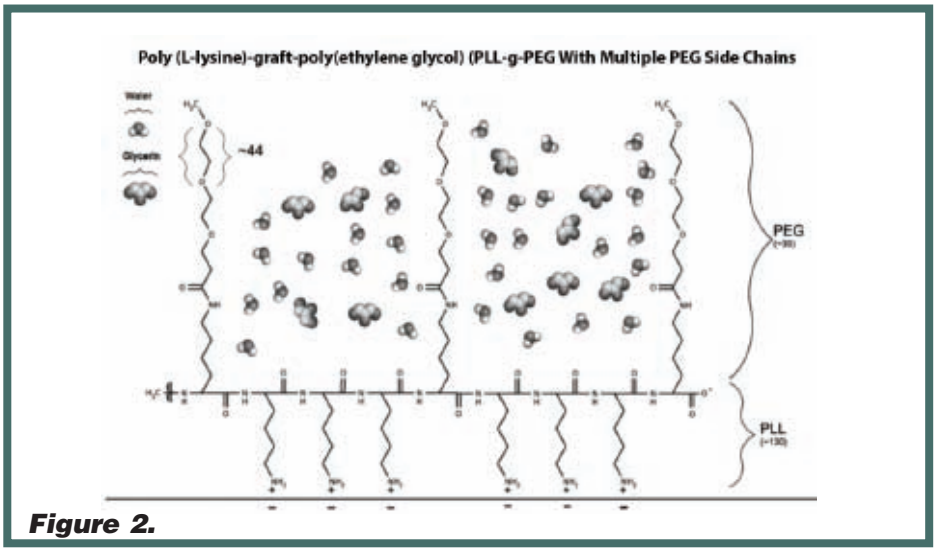


**Figure 2.**

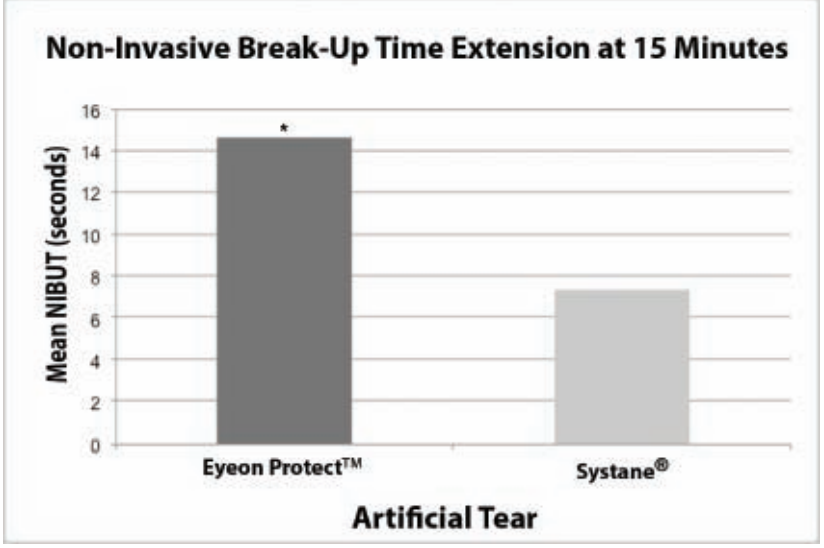


**Figure 3.**

* p = 0.05; n = 16

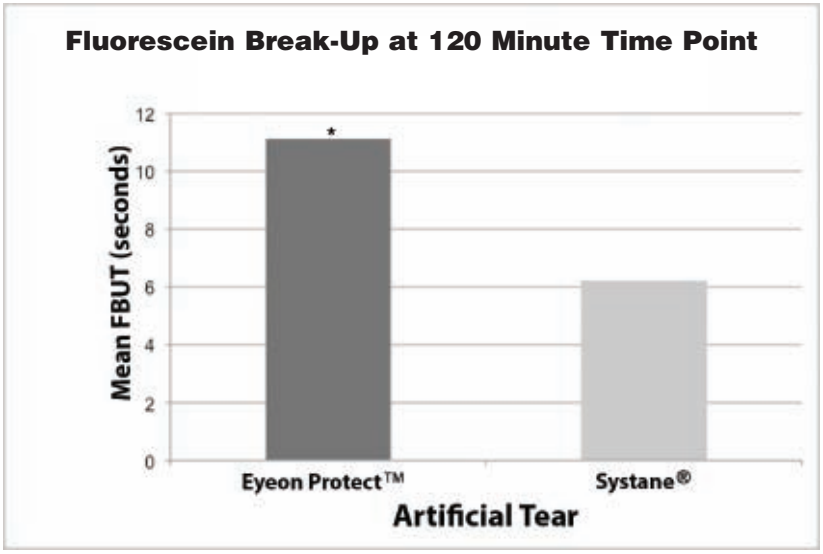


***Figure 4.*** * p = 0.12; n = 16

chemistry. Indeed, the pathology associated with dry eye should respond very well to better and longer-lasting artificial tear products. Disease may eventually be effectively managed with superior-performing OTC artificial tears, thereby cutting significantly into the anticipated growth in the dry eye prescription product market.

The only prescription product currently approved in the US is Restasis®, which is an ophthalmic emulsion formulated with mineral oil to solubilize the cyclosporine active, which is included at the low w/w concentration of 0.05%. Despite its marginal efficacy (it showed statistical benefit over control in only one sign in the Phase III registration trial), Restasis has been a major revenue generator for Allergan. In 2011, it became the single largest prescription ophthalmic pharmaceutical in the US, and Allergan recorded $697 million in net sales of Restasis that year. Restasis comes off patent in 2014, and generic and competitive cyclosporine drug products are being developed in anticipation of Allergan's loss of patent protection. Dry eye disease has an inflammatory component. Cyclosporine is an immunosuppressant, and there is evidence the anti-inflammatory activity is what drives the acceptance of this product. Topical corticosteroids are also used in the management of dry eye, but no steroid drug product has demonstrated superiority in one sign of dry eye and one symptom of dry eye versus vehicle in randomized controlled trials in dry eye subjects. One of the major reasons for the inability of prescription products to reach statistically significant efficacy in dry eye is that the control formulations are essentially artificial tears products, which as previously mentioned, are effective. In controlled trials, subjects use the vehicle regularly, and it consistently provides a benefit. With that being said, soft steroids, such as loteprednol etabonate ophthalmic suspension (0.2% or 0.5%) by Bausch and Lomb are used off label in the management of dry eye. There are a host of new actives under development by both small and large pharmaceutical companies, including resolvins, lymphocyte function associated antigen-1 antagonists, secretagogues, and other types of anti-inflammatory agents. Some of these programs are in Phase III clinical trials at this time; however, a detailed analysis of these agents is beyond the scope of this article.

Drug formulation is critical to the success of pharmaceutical products, including dry eye therapeutics. It is conceivable that prescription drug products could have fared better in Phase III trials had the active agent been formulated to maximize the activity and duration of action of the API. In the artificial tear category, it is common to see new formulations launched frequently by small and large players.

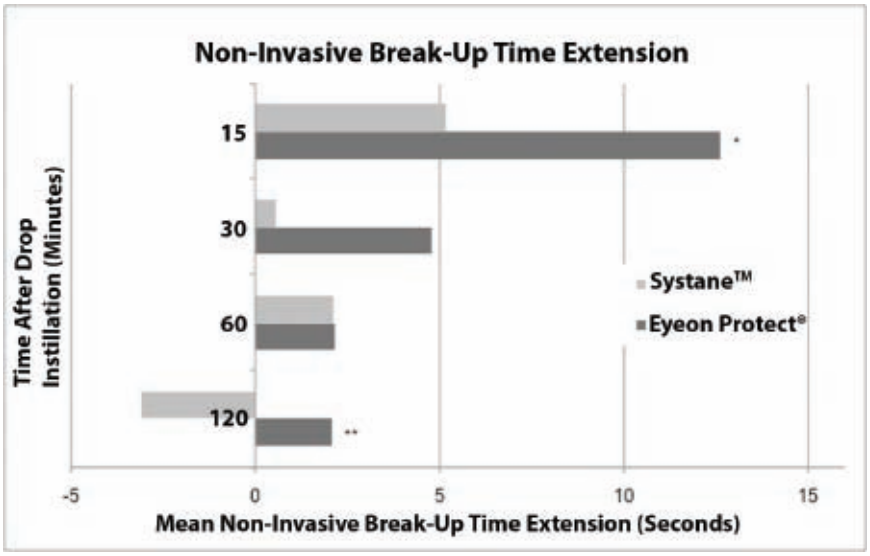


***Figure 5.*** outliers removed; n = 13 * p = 0.08 ** p = 0.03

Viscosity of Eyeon Protect™ & Commercial Samples

| Sample | Viscosity in cP |
|---|---|
| Eyeon Protect™ | 2.703 |
| Refresh® | 3.422 |
| Systane® | 5.211 |
| blink® Tears | 9.734 |
| Optive® | 12.67 |

***Figure 6.***

# A Fresh Approach

Particle Sciences Inc. and Eyeon Therapeutics, Inc. formed a joint venture to formulate better ophthalmic drug products. The two companies brought important and diverse expertise to ophthalmic drug development. Eyeon Particle Sciences LLC was born out of the cooperation to advance a novel multifunctional graft copolymer as an excipient in ophthalmology.

The rationale beyond the program, which has focused on dry eye, is that current demulcents are effective; they simply do not last long enough. That is where PEGPLUS™ [poly(L-lysine)-graft-poly(ethylene glycol) (PLL-g-PEG)] comes into play. PEGPLUS is a versatile molecule with many applications in vitro and in vivo.[13-22] For example, PEGPLUS has been shown to reduce both the adhesion of cells and bacteria to coated surfaces. A PEGPLUS-coated surface shows improved wettability when applied to hydrophobic surfaces. The polymer also plays a role in proprietary drug delivery (work in progress at Particle Sciences). The molecule has several components that may be adjusted allowing for the fine tuning of its activity. The chain length of the PLL backbone can be selected, as can the PEG side chain molecular weight. The graft ratio can also be adjusted to increase or decrease adherence to negatively charged surfaces. The lead PLL-g-PEG embodiment used by Eyeon Particle Sciences LLC was selected for its versatility in multiple applications. An illustrative structure is shown in Figure 2.

PEGPLUS was believed to be an ideal excipient for a topical OTC artificial tear because the cationic backbone of PLL will adhere to epithelial surfaces, including the cornea and conjunctiva, as well as some mucins, and project the PEG side chains away from the surface, creating a hydrophilic coating and conditions conducive to corneal moisture retention. The side chains allow for the capture of water and actives.

# Clinical Evaluation

PEGPLUS was formulated at a 1% w/w concentration in a novel artificial tear, named Eyeon Protect™, containing 1% glycerin as the active. Preclinical safety and toxicity testing in a rabbit model showed perfect safety. There was no genotoxicity. The excellent preclinical safety profile is not surprising as PEGPLUS is a large polymer created by joining two large and safe polymers, both of which are GRAS. A clinical trial was carried out by James Aquavella, MD, and sub-investigators in the Ocular Surface Research Group at the Flaum Eye Institute to evaluate the performance of this novel artificial tear. Impressive, clinically meaningful, and statistically significant results were generated. This clinical trial has been published online.[22] (22) The paper is titled Novel Formulation of Glycerin 1% Artificial Tears Extends Tear Film Break-Up Time Compared with Systane Lubricant Eye Drops.

This randomized, controlled, double-masked study evaluated 16 subjects in a single visit, single instillation, and fellow-eye controlled study. The entire spectrum of dry eye patients - from mild to severe - was included in this exploratory trial, and enrollment was stratified into three groups: mild, moderate, and severe. The study was designed to compare the extension of tear film break-up time between Systane, the market-leading brand, and Eyeon Protect at several time points following instillation of test article or active control. Tear film break-up time is one of the best known and most commonly used metrics to assess dry eye both in the clinic and for clinical trials. This study utilized non-invasive break-up time, which has shown excellent reliability and

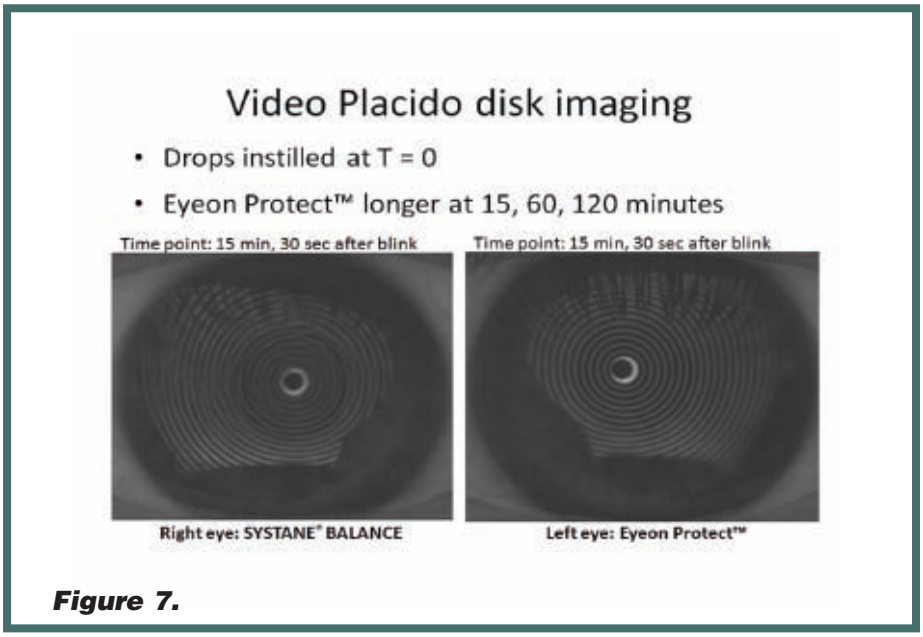


***Figure 7.***

reproducibility in the Aquavella lab. The advantages of non-invasive measures are that placing dyes and anesthetics in the eye before measure can affect the outcomes. As an additional data point, a fluorescein break-up time was performed at the conclusion of all other measures in the study. A questionnaire addressing comfort and blur was administered concomitantly during the 2-hour trial.

No subject was permitted to use an eye drop within 36 hours of the study start or wear contact lenses the day of the trial. Each subject had their tear film break-up time measured in each eye before instillation of the artificial tear product. Tear film break-up times were repeated at 15, 30, 60, and 120 minutes following instillation. The environment (humidity, room temperature, and airflow) was controlled, and participants' activities were restricted to ensure ideal comparisons between subjects.

Eyeon Protect showed a statistically significant extension of tear film break-up time at the 15-minute time point ($p = 0.05$), doubling Systane's extension. Systane extended tear break-up time by 7.4 seconds, while Eyeon Protect showed a 14.67-second extension at this same time point (Figure 3). The Eyeon Protect fluorescein break-up time was 4.92 seconds longer than Systane's at the 120-minute time point ($p = 0.12$; Figure 4). Area under the curve and predicted return to baseline were higher for Eyeon Protect than Systane.

Prior to unmasking the data, it was determined by the principal investigator and biostatistician that several outliers with very long baseline tear break-up time values skewed the mean values at some time points in the trial. A secondary post-hoc analysis with the three outliers removed is presented in Figure 5.

Eyeon Protect showed superiority at 15 minutes and 2 hours. No subjects reported visual blur after receiving Eyeon Protect, while two subjects reported blurring after eye drop instillation with Systane. The two drops were reported to be similarly soothing. These results support the continued development of PEGPLUS in topical ophthalmic products, particularly in formulating better therapies for dry eye.

Additional data supports this contention. Less-viscous artificial tears are preferred by patients. Eyeon Protect had the lowest viscosity of a host of commercial tears tested rheologically by Particle Sciences (Figure 6).

Eyeon Protect has also fared well in pilot evaluations using wave front analysis and tear film videography. In a subsequent clinical evaluation, Eyeon Protect was compared to the latest-generation product from Alcon in the Systane portfolio, Systane Balance. Figure 7 shows the crisp and more uniform concentric circles seen when a Placido disk is reflected off the Eyeon Protect corneal surface as compared to Systane Balance. This image was obtained from the Ocular Surface Research Group, and the methodology was similar to the aforementioned trial (Figure 7).

# Summary

In summary, PEGPLUS helps improve the performance of artificial tears. This multifunctional graft copolymer is safe and can be used in a host of topical ophthalmic applications. The lead product is Eyeon Protect, which is being commercialized at this time. Advanced formulation and proper use of excipients can play an important role in bringing better topical ophthalmic drug products to the growing ophthalmology market.

# Authors' Note

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Dr. Andrew Loxley is Director of New Technologies at Particles Sciences Inc., where he runs a formulation group applying emerging formulation technologies, including engineered particles and hot melt extrusion to solving drug delivery problems. Prior to joining Particles Sciences in 2005, he led development efforts in next-generation lithium ion batteries at A123 Systems Inc, electrophoretic displays at EINK Corp., and emulsion polymers at Synthomer Ltd. He earned his BSc in Chemistry and Polymer Science from the University of Sussex, UK, and his PhD in Physical Chemistry focusing on Microencapsulation from the University of Bristol, UK. Dr. Loxley is the inventor on more than 40 patents and author of two book chapters and several peer-reviewed and trade-journal articles.

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# Making Formulations More Efficient Using the Freeze-Dry Microscopy Pre-Lyophilization Method

**By:** Jeffrey McGinn, President & Director of Instrument Sales, McCrone Microscopes & Accessories, a division of The McCrone Group.

## Introduction

In the development of parenteral drugs, lyophilization, or freeze-drying, is a crucial process technology. Pharmaceutical manufacturers have traditionally found lyophilization to be a costly, complex, facility-intensive operation, even though it is a straightforward process at the lab level.

The market for lyophilized products is expected to grow significantly in the coming years. The flood of protein-based therapeutics and other injectable products being pushed through the drug development pipeline has contributed to the need for leaner, more efficient freeze-drying methods. Without lyophilization, 60% of biotherapeutics, including recombinant proteins, plasma, vaccines, and antibodies, could not be commercially available. So, what kind of NMEs can be freeze-dried? See the following list:

- Non-biologicals (small molecules)
- Non-living biologicals such as:
  - -Hormones
  - -Enzymes
  - -Blood products
  - -Antibodies
  - -Vaccines

Pharmaceutical formulators use freeze-drying to extend the shelf -life of their drugs, as many of these products have less than 2 years of shelf-life before they expire. One key step is to determine the right conditions for the freeze-drying process. Usually, formulators use large-scale machines, which can make freeze-

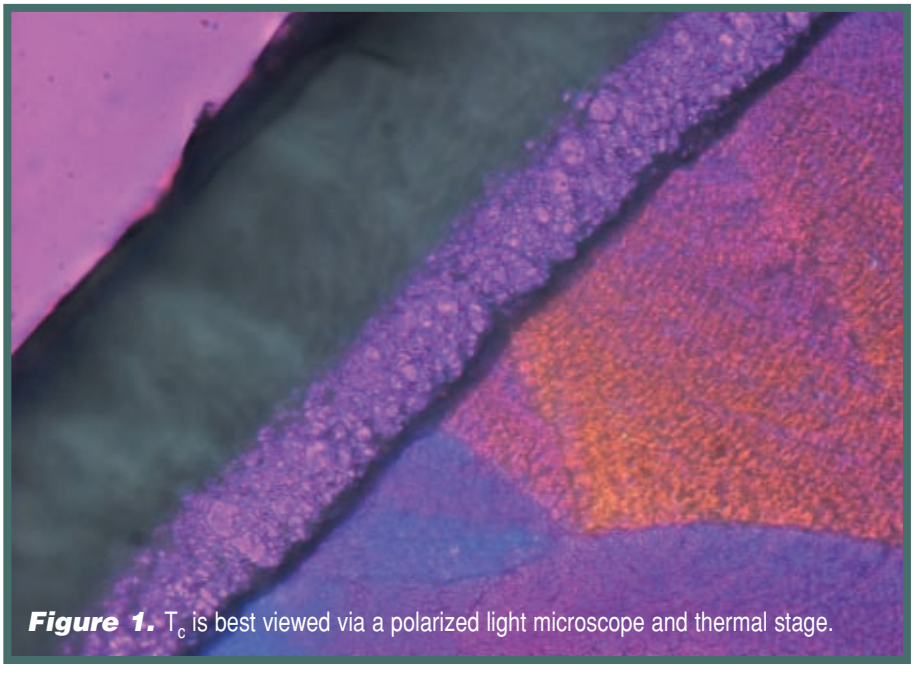

***Figure 1.*** $T_c$ is best viewed via a polarized light microscope and thermal stage.

drying the most expensive and time-consuming step in the parenteral manufacturing process.

To minimize cost and streamline this process, many companies developing new parenterals are finding it in their best interest to optimize their lyophilization cycles by looking at pre-lyophilization methods such as freeze-dry microscopy.

## Freeze-Dry Microscopy

Freeze-dry microscopy focuses on the direct examination of freezing and freeze-drying via a special microscope and thermal stage. Freeze-dry microscopy also complements and supports the information gained from the differential scanning calorimetry (DSC) technique. The process' popularity stems from its ability to save pharmaceutical companies time, money, and product compared to traditional trial-and-error techniques using freeze-drying machines. Freeze-dry microscopy allows formulators to determine how their products will react in varying thermal conditions using small samples instead of wasting large quantities of products by freezing them at less-than-optimal temperatures. The following will describe how the technique is performed, the essential equipment, and finally, show how one company has successfully used it.

## Traditional Lyophilization Process

Freeze-drying typically has three stages: freezing, primary freezing, and secondary freezing. Freezing is usually performed with a freeze-drying machine in larger-scale operations, particularly in the pharmaceutical industry. During freezing, material is cooled below its eutectic point, the lowest temperature at which the solid and liquid phases of the material can coexist. The main step in the lyophilization process is primary freezing, which involves the removal of water from the frozen product and is primarily done via sublimation. Temperature is critical during this phase because if too much heat is added, the material's structure could be altered and spoiled. Finally, any unfrozen water molecules are removed during secondary drying and the product is sealed.

Basic system components consist of a vacuum pump, temperature-controlled shelves, condenser, compressible shelves, temperature-monitoring devices, vacuum monitoring devices, a bleed valve, and a recording device

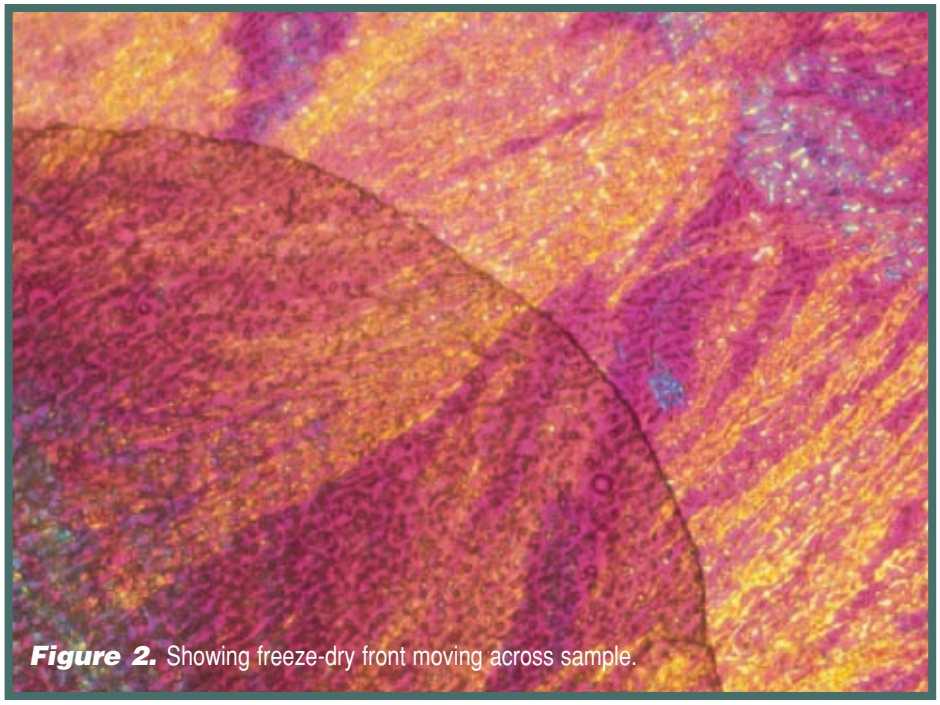

***Figure 2.*** Showing freeze-dry front moving across sample.

## Determining Critical Temperature is Essential

Every formulation has a critical temperature - after this point, the formulation experiences processing defects during freeze-drying and may be unusable. Maintaining temperature below the formulation goes through freeze-drying (or before the frozen water is removed) is imperative or the product can be ruined during the actual process, wasting time and money. For this reason, knowing the critical temperature of a formulation before lyophilization takes place is essential. By using a microscope and thermal stage, researchers can determine optimal lyophilization conditions using less time and product.

## Critical Temperatures Deciphered

There are three kinds of critical temperatures: eutectic temperature ($T_e$),


***Figure 3.*** Freeze-dry microscopy equipment. An ideal thermal stage allows for numerous key capabilities.

glass-transition temperature ($T_g$), and collapse temperature ($T_c$). Te refers to crystalline systems and is measured by thermal or thermoelectric analyses, such as differential scanning calorimetry (DSC). The material will melt during processing if this temperature is exceeded. $T_g$ is also measured by thermal or thermoelectric analyses and refers to amorphous systems. $T_e$ and $T_g$ determine the maximum temperature that the formulated product can withstand without the loss of structure during primary drying.

As the sample is warmed, the glass-transition temperature is typically followed by the collapse temperature ($T_c$), which is best measured by freeze-dry microscopy. Collapse temperature is the temperature at which the formulated product weakens to the point of not being able to support its own structure, leading to incomplete drying, inadequate stability in reconstitution, and poor product appearance. Because most formulations exist in an amorphous state, the critical temperature for freeze-drying will be their collapse temperature. $T_c$ is best viewed via a polarized light microscope and thermal stage (Figure 1).

## Setting Up a Freeze-Dry Microscopy Lab

Necessary components for the standard freeze-dry microscopy lab include a polarized-light microscope, a liquid-nitrogen-cooled thermal stage, a vacuum pump, and an imaging system. Polarized-light microscopy allows researchers to visualize collapse temperature ($T_c$) as well as determine if their sample is crystalline or partially crystalline based on the birefringence of anisotropic crystals within the frozen matrix (Figure 2). The optimal polarized-light microscope system includes a strong light source, preferably 12V/100W, a Bertrand lens, distance objectives, polarizer/analyzer, and compensator. Compensators correct for differences in the refractive indices of the sample and the surrounding medium.

Equally important is the thermal stage (Figure 3). An ideal thermal stage possesses the following key capabilities:

- Temperature range of -196°C to 125°C
- Temperature stability less than 0.1°C
- Temperature accuracy of 0.01°C
- X-Y sample manipulation functionality
- Vacuum-tight sample chamber to 10-3 mbar
- Silver heating block (ensuring high thermal conductivity)

In addition, chamber pressure is monitored via a pirani gauge mounted directly on the stage. Formulators can save product and profit losses associated with trial and error freeze-dry attempts by using these components to determine the critical temperature before lyophilization begins. Formulators are able to predict how their products will react under different thermal conditions and pinpoint the critical temperature ($T_c$) so they can get lyophilization right the first time.

## Praxair: A Case Study

Three years ago, a facility at Praxair, Inc., a global Fortune 300 company that

supplies atmospheric, process, and specialty gases, started using freeze-dry microscopy. The company turned to the technique to determine primary drying temperatures on small samples of product for lyophilization cycle optimization and to predict substance stability and reaction during R&D. Praxair scientists typically work with samples of product from pharma and biopharma customers to determine lyophilization parameters, such as freeze rates, shelf and product temperatures, and sublimation rates. Determining these factors enables Praxair to optimize their processes to attain ideal moisture levels and shelf-life for lyophilized products.

Praxair began using freeze-dry microscopy to minimize the amount of product used for determining critical temperatures and lyophilization cycle optimization for formulations. Although Praxair uses lyophilization literature and industry standards to work with formulations at the correct temperatures, every sample is different, and they sometimes lose product and have to do more trial-and-error work. In ddition, some pharma clients do not give outside labs complete formulation information until confidentiality agreements are completely worked out. Without key formulation information, Praxair scientists could be delayed in working on portions of product because they do not want to damage the sample.

A Praxair facility invested in a freeze-dry microscopy system to better support the key stages of the lifecycle of biologic and pharmaceutical products of its clients. A Praxair scientist even attended a freeze-dry microscopy course at the Hooke College of Applied Sciences (Westmont, IL) to learn how to best use the new system.

Praxair finds that freeze-dry microscopy helps them better capture the process conditions and understand their clients' products, and therefore better meet their needs. Now, they do not see why they would want to try to do cycle development without having a freeze-dry microscopy system. They claim that it is a precise, simple procedure that gives them a precise temperature to meet when running their cycles, and a process that used to take days to do now can be completed in an hour and uses less product.

## The Future of Formulation

Freeze-dry microscopy enables pharmaceutical companies to save a significant amount of time and money both in process development and in commercial manufacturing. When used as part of a complete thermal-analysis study, it is an invaluable tool in the characterization of the thermal properties of any formulation. ■

**Mr. Jeffrey D. McGinn**

President & Director of Instrument Sales
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Mr. Jeffrey D. McGinn has more than 8 years of experience in the pharmaceutical microscopy industry with expertise in training and sales, polarized light microscopy, lyophilization techniques, and scanning electron microscopy. As a Hooke College of Applied Sciences instructor, Mr. McGinn develops and teaches the microchemical test sections. His enthusiastic and hands-on approach ensures students learn by doing.

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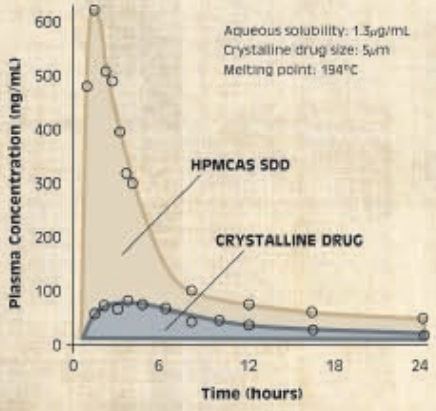


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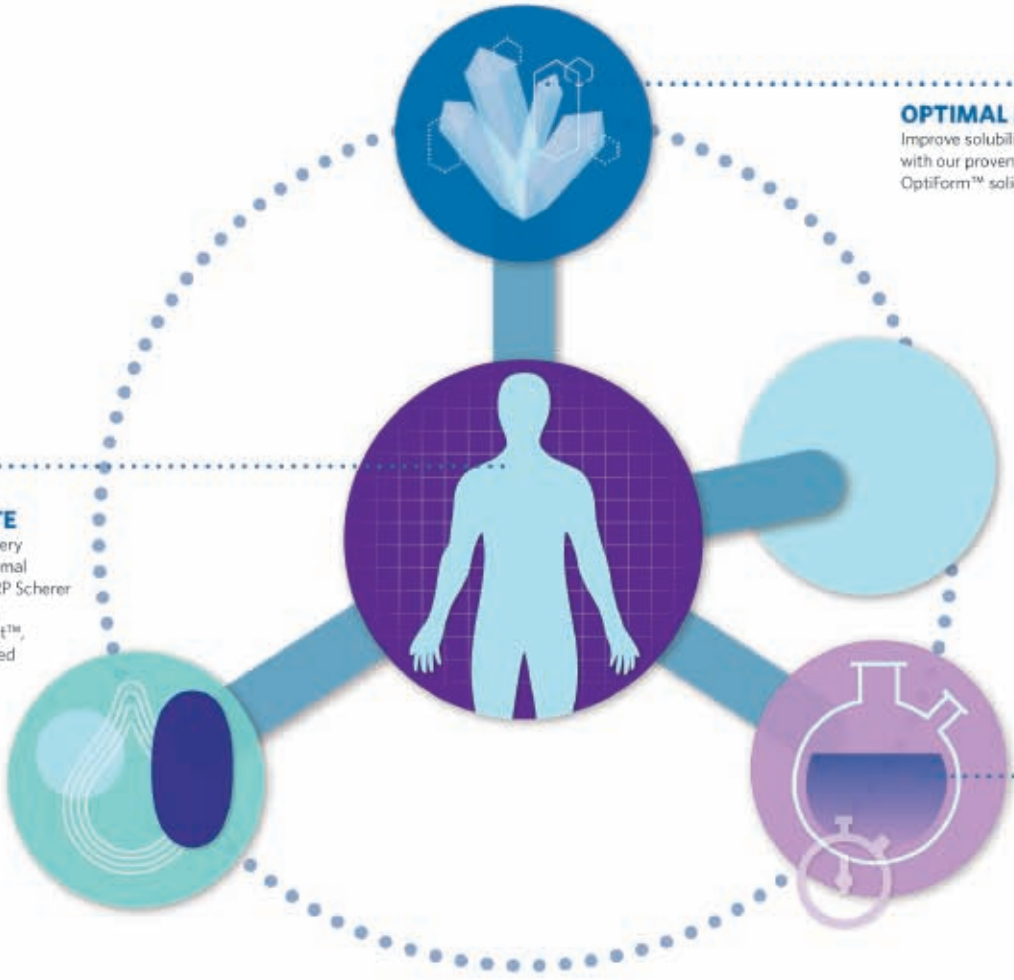

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