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EPO Grants Hovione New Inhaler Patent

Hovione recently announced the European Patent Office has granted a patent for Hovione's XCaps, a dry powder inhaler (DPI). XCaps addresses a pulmonary inhalation market need for a very inexpensive device, which combines high efficiency in powder dispersion with ease of use. Lung fractions in excess of 70% have been achieved, from a device that only requires two steps to inhalation and only has two components plus a dust cover. This makes XCaps highly suited for inhalation applications in which minimal training of patients is desirable and has the versatility to treat almost all pulmonary diseases, including asthma, COPD, as well as infection, which typically require very large-dose delivery.

XCaps follows on the heels of another successful Hovione DPI, TwinCaps, which was developed specifically for an influenza application and is licensed to Daiichi Sankyo and Biota for this application.

Hovione is offering XCaps as a part of its inhalation device portfolio, allowing its integration with a drug product development program, allowing business partners to take their candidate drugs from the API stage all the way to the unit dose, with a single partner.

"We give our customers an edge in speed of development because we are perhaps the only independent company developing DPIs with expertise in every aspect of the inhaled drug development process," said Peter Villax, Vice-President and Co-inventor of the device. "Granting of the European Patent on the XCaps inhaler, within 30 months after initial filing, underpins Hovione's capabilities in innovation and intellectual property management, to successfully design, develop, and deliver innovative products, namely, a quality inhalation device, addressing a market need."

Hovione is currently executing inhaled drug development projects for multiple pharmaceutical companies, involving API process development, particle engineering, formulation, and clinical supplies, and is looking for partners willing to incorporate the XCaps into their inhalation drug development.

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Unilife Signs Long-Term Supply Contract With Sanofi

Unilife Corporation recently announced the signing of a long-term supply contract with Sanofi. Unilife has agreed to supply Sanofi with the Unifill Finesse, a customized device from its Unifill platform of prefilled syringes with automatic, needle retraction, for use with the anti-thrombotic therapy Enoxaparin Sodium sold under the brand names Lovenox and Clexane. The contract period can extend up to 2024.

Unilife has granted Sanofi the exclusive use of the Unifill Finesse with anti-thrombotic drugs during the contract period. Following a 4-year ramp-up period after market entry, exclusivity will be maintained, subject to Sanofi purchasing a minimum of 150 million units of the Unifill Finesse or other Unifill syringes per year. Unilife can supply its Unifill syringes, including the Unifill Finesse, to additional customers in all other therapeutic classes outside of anti-thrombotics.

In addition to future revenue from the sale of Unifill Finesse syringes, Unilife may receive up to $15 million from Sanofi in milestone-based payments with $5 million of these payments expected in 2013.

This supply contract replaces and supersedes all other agreements previously signed between both parties regarding the Unifill syringe platform. For commercial purposes and due to confidentiality clauses in the Agreement, additional terms of the contract are to remain confidential.

"Our Unifill syringes set a new standard for the delivery of all prefilled biologics, drugs, and vaccines," said Alan Shortall, CEO of Unilife. "Like other game-changing products in our broad device portfolio, the distinctive visual, safety, and functional benefits of Unifill can be leveraged by pharmaceutical customers to enhance and differentiate their injectable therapies. We thank the Sanofi Industrial organization for their innovative vision and their support, and look forward to a long-term partnership. The signing of this supply contract reaffirms the business model we have worked so hard in pursuing. The long-term contract provides the customer with continuity of supply. The provision of exclusivity within a drug class also provides the customer with an opportunity to leverage our device's competitive advantages to drive user preference and differentiate their drug brands against competitors."

Supernus & Catalent Enter Supply Agreement

Catalent Pharma Solutions and Supernus Pharmaceuticals recently announced they have entered into an agreement in which Catalent is the supplier of Trokendi XR extended-release capsules for Supernus. Supernus developed Trokendi XR using its own advanced drug delivery technology and transferred its formulation to Catalent for commercial manufacturing.

"Supernus selected Catalent as our commercial supply partner based on their extensive experience in manufacturing extended-release products, the long-standing relationship we have had with them, and a proven track record of high quality," said Jack Khattar, Chief Executive Officer, President and Director of Supernus.

"We offer customers integrated solutions that include both proprietary drug delivery technologies and advanced supply solutions for oral controlled release development and commercial products, added Barry Littlejohns, President of Catalent's Advanced Delivery Technologies business. "We are pleased to have been selected by Supernus to work on this unique epilepsy product."

Trokendi XR is a novel, oral, extended-release, once-daily formulation of topiramate for the treatment of epilepsy. Supernus recently received approval from the FDA and launched the product in the US market. Trokendi XR delivers an extended-release form of topiramate, one of the most effective anti-epilepsy drugs.

Trokendi XR is a convenient once per day alternative to current immediate-release formulation products, which require patients to administer their medication multiple times per day.

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. With over 75 years serving the industry, Catalent has proven expertise in bringing more customer products to market faster, enhancing product performance and ensuring reliable product supply. Catalent employs approximately 8,500 people, including over 1,000 scientists, at nearly 30 facilities across 5 continents and generates more than $1.7 billion in annual revenue.

Veritas Bio's RNA Delivery Patent Allowed

Veritas Bio, LLC, recently announce that the European Patent Office (EPO) has granted a patent to Veritas for European Patent Application No. 07 873 598.2 1401. The patent relates to the In Vivo Delivery of Nucleic Acids.

"The allowed claims cover transfecting nucleic acids into skin or muscle cells under conditions wherein nucleic acids and expression vectors encoding nucleic acids, such as, DNA siRNA, mRNA, oligonucleotides, and other nucleic acid molecules are delivered to the liver," said Dr. Pachuk, the inventor. "The delivery of the nucleic acid can be for treating any disease or condition of the liver. These include down regulating endogenous liver genes associated with a disease condition and the genes of liver pathogens and the promoters of these genes. The allowed claims also cover the delivery of DNA, expression vectors, mRNA, and vectors encoding mRNA for gene therapy. This proprietary technology is applicable for the rapid development of RNA therapeutics for the treatment of infectious liver diseases and other liver diseases."

"Our technology solves one of the biggest hurdles for the development of RNAi and other nucleic acid-based drugs by providing a safe and effective delivery system for effector RNA molecules and other nucleic acid molecules. This technology enables the utilization of the body's innate delivery system to transport effector RNA molecules rather than relying on expensive synthetic, toxic, immunogenic, and inefficient delivery systems, nanoparticles, or viral particles for delivery, he added.

Humans naturally extrude exovesicles (also called exosomes) from multiple cell types, including muscle and skin cells. Exovesicles are natural nanoparticles the body produces that transport molecules from one cell to another and from one tissue or organ to another. Veritas Bio's technology enables utilization of this delivery system to organs, tissues, and cells. This new technology enables local administration to the skin or muscle, of either the effector molecules or a DNA encoding the effector molecules. The molecules are then loaded by the transfected cell into exovesicles, which are extruded from the cell and distributed to other cells in the body, to deliver them to target cells is a natural, safe, and effective method of systemic delivery, without invoking the innate and adaptive immune responses to the delivery system. The exosomes can be targeted to specific cell types and tissues through the use of ligands as described in the patent.

A corresponding application has also been allowed in the US. Veritas is in the process of filing continuing applications to cover various other indications, including delivery to non-liver tissues, including immune cells, various types of therapeutic nucleic acid molecules, and compositions in which RNA-containing exovesicles are manufactured in producer cells in culture.

Mystic Pharmaceuticals Receives Multiple Patent Allowance on Platform Technologies

Mystic Pharmaceuticals, Inc. recently announced it has received two Notices of Allowance from the US Patent Office for its Unit Dose Drug Delivery Platform (serial number 12/851,524) and Piercing Device for Drug Delivery Systems (serial number 13/149,584) patent applications. These patents expand Mystic's novel VersiDoser and VRx2 delivery platforms enabling the development of patient-centric pharmaceutical products. Mystic is applying its innovative delivery technology to develop therapeutics for the treatment of ocular, CNS, neurodegenerative, and infectious diseases affecting large global populations.

"There is a power shift in the pharmaceutical industry from product-oriented to patient-oriented products that deliver better health outcomes," said Mystic's President and CEO, Timothy Sullivan. "Over the past decade, Mystic has innovated packaging and delivery technologies that enable the development of patient-centric pharmaceutical products. These latest innovations further expand our capabilities to enhance the patient experience by making pharmaceutical products that are safer, easier, and more convenient to use."

The shift to patient-centric product development strategies by pharmaceutical manufacturers will benefit the consumer through improved compliance and health outcomes while building brand value for the manufacturer. Utilizing Mystic's delivery platform technologies, pharmaceutical and biotech manufacturers can extend or establish market exclusivity and competitive differentiation for new or existing drugs and biologics. Mystic's delivery platforms and products are designed to meet the diverse demands of consumers and pharma manufacturers in the globally competitive market.

ProStrakan Launches First Transdermal CINV Drug; 3M DDS to Manufacture

The European Medicines Agency (EMA) has recently granted approval for ProStrakan Group plc to market SANCUSO (Granisetron Transdermal System) in the European Union (EU), with 3M Drug Delivery Systems acting as the manufacturer. ProStrakan begins marketing the product this month in the UK, Germany, and the Netherlands. Additional European countries are expected to be added in 2014.

Initially introduced in the US in 2008, SANCUSO is the first and only treatment for chemotherapy-induced nausea and vomiting that does not require pills or intravenous (IV) administration. The transdermal patch is applied to the upper arm and can be worn for 7 days, providing continuous transdermal delivery and eliminating the need to take pills daily to control nausea and vomiting. This simple-to-use treatment has been proven effective in patients at risk for chemotherapy-induced nausea and vomiting.

"SANCUSO is a great illustration of the patient-friendly benefits of transdermal treatment," said Jim Ingebrand, President and General Manager, 3M Drug Delivery Systems. "We look forward to a continued partnership with ProStrakan to bring SANCUSO to new markets."

3M Drug Delivery Systems is applying more than 30 years of transdermal experience and regulatory expertise to its manufacturing responsibilities for SANCUSO. The company's cGMP-compliant manufacturing and strength in global supply chain management ensure reliability and a smooth process from start to finish for manufacturing partners.

"SANCUSO is already proving to be an important option for patients in the US suffering from chemotherapy-induced nausea and vomiting," said Jamie Blackport, Senior Vice President of International Marketing at ProStrakan. "We are excited about working together with 3M to bring this important treatment to patients in the EU."

While ProStrakan has previously relied on a different manufacturer for the US supply of SANCUSO, FDA approval is currently pending for the 3M Drug Delivery Systems manufactured product.

SANCUSO (Granisetron Transdermal System) is the first and only 5-HT3 receptor antagonist available as a transdermal patch for the prevention of CINV. SANCUSO transdermal patch is indicated in adults for the prevention of nausea and vomiting associated with moderately or highly emetogenic chemotherapy, for a planned duration of 3 to 5 consecutive days, where oral anti-emetic administration is complicated by factors making swallowing difficult.

JHP Pharmaceuticals Enters Ophthalmic Manufacturing Agreement

JHP Pharmaceuticals recently announced it has entered into a manufacturing agreement with an undisclosed pharmaceutical company, which has developed proprietary products that provide sustained and localized drug concentration. The agreement is for technical transfer, registration batch manufacture, and commercial supply of a unique late-stage ophthalmic product.

JHP's manufacturing expertise and cGMP compliance history were critical factors in the selection process. Stuart Hinchen, President and CEO, said, "This important product has critical manufacturing requirements. We have successfully manufactured and filled a number of different products over the past few years, all with unique parameters. Our experience in this area provides our customers with a sound resource as the product moves through launch and commercialization. Our record of cGMP compliance driven by experienced quality and regulatory teams continues to be one of the key reasons customers chose JHP."

Mr. Hinchen added, "JHP is now expanding its manufacturing capabilities by introducing a new ophthalmic filling line that will further enhance production effectiveness. This innovative equipment will offer a disposable filling circuit, reduced line losses, and broader product handling capabilities, all in a restricted access configuration. At the moment, the new filling line is under construction and is expected to be fully operational during the second half of 2014."

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.

Amicus Therapeutics & Biogen Idec to Collaborate

Amicus Therapeutics recently announced it has entered a collaboration with Biogen Idec (BIIB) to discover, develop, and commercialize novel small molecules for the treatment of Parkinson's disease. The collaboration will build upon preclinical studies at Amicus and independent published research that suggest increasing activity of the lysosomal enzyme glucocerobrosidase (GCase) in the brain may correct alpha-synuclein pathology and other deficits associated with Parkinson's disease.

"Our collaboration with Amicus complements our current strategy to identify and develop novel therapies to address Parkinson's disease," said Tim Harris, Senior Vice President of Translational Medicine at Biogen Idec.

Under terms of the multi-year agreement, Amicus and Biogen Idec will collaborate in the discovery of a new class of small molecules that target the GCase enzyme, for further development and commercialization by Biogen Idec. Biogen Idec will be responsible for funding all discovery, development, and commercialization activities. In addition, Amicus will be reimbursed for all full-time employees working on the project. Amicus is also eligible to receive development and regulatory milestones, as well as modest royalties on global net sales.

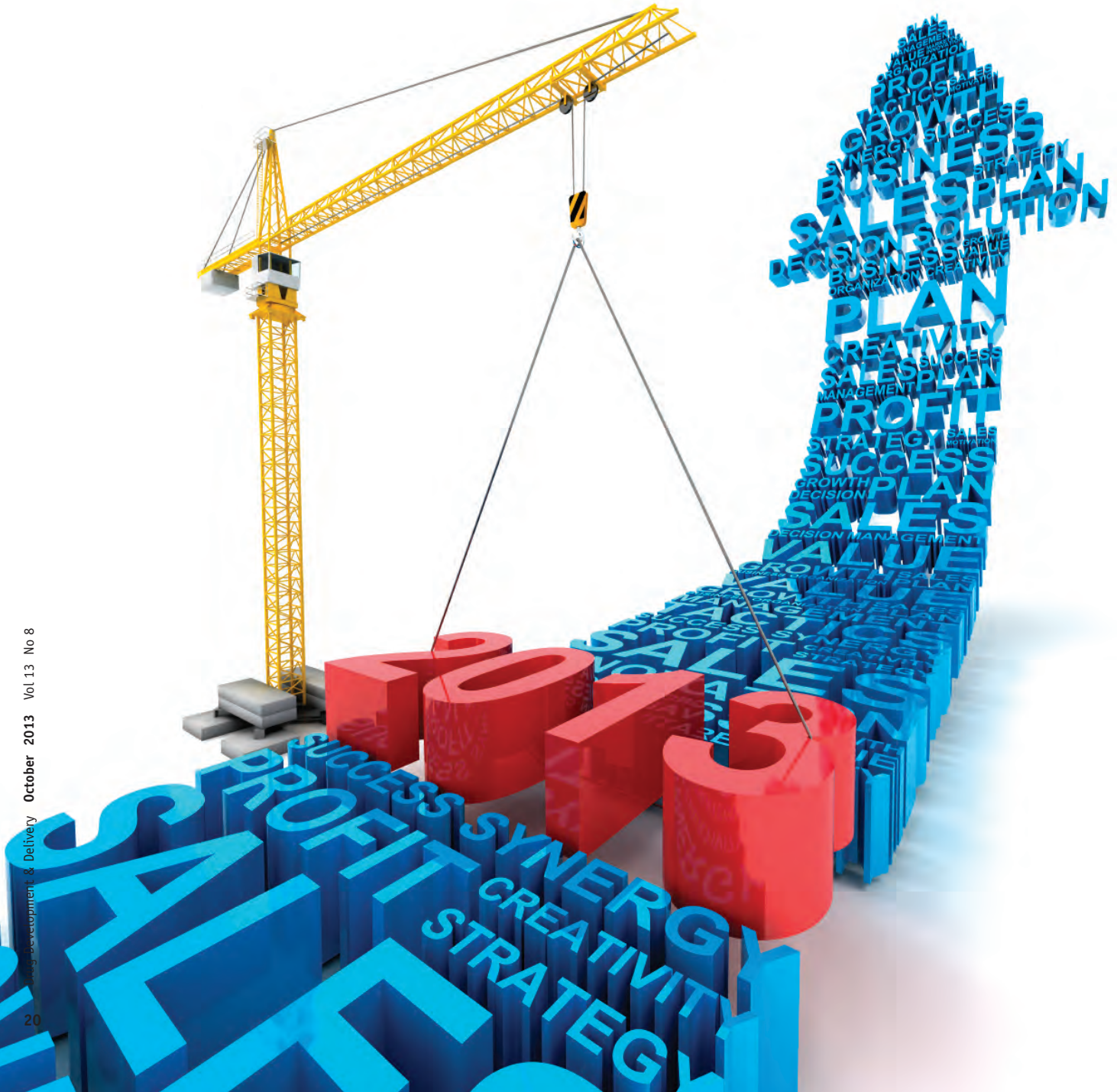
"This partnership combines Biogen Idec's leadership in neurodegenerative diseases with our internal expertise in discovering small molecules that enhance the activity of lysosomal enzymes," said John F. Crowley, Chairman and Chief Executive Officer of Amicus Therapeutics. "We believe that this collaboration is an important step forward in validating the potential to address neurodegenerative diseases by increasing relevant enzyme activity in the brain."

Inherited genetic mutations in the GBA1 gene, which encodes the GCase enzyme, have been identified as the most widespread genetic risk factor for Parkinson's disease and Dementia with Lewy bodies. The accumulation of alpha-synuclein in Lewy bodies in the brain is a hallmark of Parkinson's disease. Independent research published over the past decade has demonstrated a link between GCase deficiency and alpha-synuclein accumulation, and suggests that improving the lysosomal targeting of GCase and increasing enzyme activity may be a beneficial therapeutic approach for Parkinson's disease and other synucleinopathies.

Management Insight

Growing Your Business: A Stage-by-Stage Analysis of Your Company's Growth & the Challenges it Faces

By: Derek Hennecke, CEO & President, Xcelience LLC



Are you a tough, decisive leader who gives clear direction and expects compliance? Or are you more the cool facilitator, smoothing out conflicts and helping others get their jobs done? Maybe you're a supporter, getting down in the trenches and getting dirty yourself? Which leader should you be?

One of the most important things I have ever learned as a CEO is that a good leader is all of these things at different times. Not in one day; that would be horribly confusing and destabilizing to your organization. But you need to lead in different ways depending on the size and stage of your growing organization.

If you're a parent, this may already be clear to you. My three toddlers responded best to a firm, consistent, and patient parent. As middle schoolers though, I let up on them, giving them the space to make mistakes, but also tucking them in at night. My high schoolers generally shut down if I play the boss card. I seem to do better to parent by example. I am at least three different parents to the same child, depending on their age and stage of development.

Growing a company is, in many ways, similar. Your role changes as your organization goes the through the different stages of growth, each with its own challenges. *Navigating the Growth Curve* by James Fischer is a manual that was written to help organizations through all the fabulous, exhilarating, heart-wrenching, and awkward stages of growing up. This article draws principally from his research, applying it where possible to my own company, Xcelience, a CDMO with 113 employees that has grown 25% throughout the past year, pushing it through one stage and into another in a short timeframe. Using data from 650 companies across 35 industries, Fischer's book has been an invaluable resource to me over the past year as I diagnose and treat the challenges of a growing company.

Growth is inevitable

If your organization isn't growing, it's dying. Lack of growth in today's market is a state of stagnation and with competition what it is, you have to keep moving forward. You have to grow.

Fischer identifies seven distinct stages of growth. While there are several ways to determine your company's stage of growth, this model puts forward that the number of employees is the primary determinant of complexity. This makes sense to me. I once met a CFO who made a very smooth transition from a company of 55 employees and $30 million in revenue to a company of 35 employees and $1.5 billion revenue. Both were stage four companies. Here is a quick overview of Fischer's seven stages of growth, by number of employees:

1. Start-Up (1-10): This stage is about vision. The staff must believe in that vision. In fact, Fischer rates a belief in the company's vision as more important to the company's success than an individual's actual competency. The company's goal should not be to achieve perfection; it's to bring in enough revenue to survive to the next stage. Eighty percent won't make it.

2. Ramp Up (11-19): Still owner-centric. The goal now is less about survival, more about growth. The company absolutely must generate a positive cash flow now.

3. Delegation (20-34): There are too many balls in the air now for one leader to juggle. Here's where entrepreneurs either change their *modus operandi*, or burn out. The leader must hire or train up managers and then delegate control to them. Decision-making will slow down in the process; the challenge is to make sure it doesn't slow down too much.

4. Professional (35-57): The workload is growing. It makes sense on the surface to just keep throwing new hires at the work, but the company mustn't hire too many too quickly or costs will overtake revenue. It's time to go professional now, hiring or training up managers and acquiring professional systems and procedures. No more shoe-string solutions. The organization will probably have to pay good salaries for real talent, and that could create its own internal conflicts. There should be independent fiefdoms (divisions or departments) within the company at this stage; each confident of its own processes.

5. Integration (58-95): The company is a growing concern now and getting noticed by the competition. Those fiefdoms that worked well in stage four aren't working now. It's no longer about the department and its goals, it's about the direction of the company as a whole. As a recognized player in the market, the company shouldn't be reacting to market forces anymore. It should be anticipating and staying ahead of them.

6. Strategic (96-160): The company is a major player now. It's time to climb a tree and look at the whole board. It is also a critical time to get a grip on those finances. Companies in this stage are spending a lot on processes and people; it's important to frame those choices in terms of a long-term strategic vision. Then empower key managers to carry out that vision and let them go.

7. Visionary (161-350): The company is so far from its entrepreneurial roots that it's in danger of losing them. The risk here is becoming too complex, too bureaucratic. The CEO's over-riding role now is to instill vision, create action plans, and assign resources to them.

Analyzing your company's stage of growth

Once you've identified your stage of growth, you can use the templates provided in Fischer's book to see if you are facing the challenges Fischer expects you to come up against.

The first time I looked over this list of stages, it shocked me to see the exact challenges I was facing at the time. Back then, every challenge I faced felt unique and unexpected. Reading this book, I realized that my situation was not unique at all. Lots of companies go through these same things, and have already developed good strategies to deal with them.

With 113 employees, Xcelience is well into stage six, which Fischer labels "Strategic." Stage six companies, Fischer prophesies, will need to get their corporate finances in order. He couldn't have been more right. Until Xcelience reached this stage of development, I was CEO and CFO. In 2012, I realized that I just didn't have time to get into the kind of detailed projections that the company needed. I took on a CFO, who now develops a detailed annual budget with department breakdowns. Once we could accurately forecast our business, an essential piece of the puzzle fell into place. We could not only see our current business, but we could model the effect of potential changes to our business model, projecting them two or three years out. We could see where to put our resources. It was changes like this that led us to add our Clinical Supply Services (CSS) division in late 2012, and the decision to add distribution, which came early this year.

People are a major priority in this stage, Fischer warns us, and I see this in Xcelience too. Our people are always a priority, of course, but having expanded our workforce 25% in a year means I really need to empower my managers to show leadership within their departments, giving people the guidance and hands-on leadership they need to motivate them. I need to be free to focus on the company's overall strategic vision.

The Three Gates: People, processes & profits

Every issue in a company comes down to one of three core issues or "gates" (1) people, (2) processes, and (3) profit, says Fischer. You need to work through these gates to smooth the way for the next stage. Which issue dominates depends on your stage of growth.

Let me provide you with an example. When someone comes to you with an issue, you need to put it into the context of one of the three gates. Let's say an executive has a problem about Juanita, a team leader. Juanita is making mistakes, getting angry with co-workers, and isn't moving quickly enough on projects. It sounds like a people issue. But when you dig more deeply, you learn that business is growing so quickly that Juanita now spends one quarter of her day filling out detailed projections for prospective clients; something she used to do in 20 minutes. With two hours of her day gone, she can't give the detail and attention she wants to give to her current full-slate of projects. She's been dropping the ball on her projects, and snapping at the sales force because she feels her project work is more important than these forms. The sales force argues that both are important. It's a process issue.

In a new business, profit will be the dominant issue. Without profit, there can be no tomorrow; no people and no processes. But come stage three, the organization is turning a profit. It wouldn't have been able to hire and made it this far if it weren't cash positive. The company has been bringing in more people, and while that's solved problems, it's also created problems. People problems are paramount now. The focus shifts to creating a happy and productive environment where people want to work. That will reflect well on the company, keep turnover low, and attract the best talent to get the job done.

By 35 or more people (stage 4), the company has worked through its people issues. You've really got to look at working more efficiently now. You used to wander down the hallway stopping in various offices to solve a problem. Such vague and *ad hoc* processes that served the company since start-up are breaking down. Issues like the one with Juanita are constant. It was no problem for a stage one or two company to have project managers spend all that time on complicated forms, and the customers loved the detailed analysis. But not with Juanita's full case load today. The sales force is correct though - customers do love the detailed project projections. Because many of the questions are rote calculations, the organization should now begin to automate the forms, allowing much of the form to be filled before it arrives on Juanita's desk. Now she can do them all in 20 minutes again. These types of process innovations will relieve bottlenecks and improve efficiency in an increasingly busy company.

The solution seems obvious in hindsight, but it rarely is when you're in the middle of the situation. Most management teams will look at the Juanita situation and decide that because the current process worked well in the past, it should work well now. We had a similar issue at Xcelience in the line-up of the

quotes and request for projects (RFPs). When the company was small, we knew which quotes were in the queue to be completed because there were only one or two in the line-up at a time. Later, the length of time to complete an RFP grew over five days, which is unacceptable in the CDMO world. Instead of finding a new process, everyone was looking for a way to bandage the old process. Fingers were pointed. Project managers put forward that the process could be shortened if the sales people would just do a better job on the RFPs with the client upfront. The sales people were busier than ever, and didn't feel this was a good use of their time. We bandied about the idea of throwing more people at the problem, briefly considering a Technical Definer role. Instead, we changed the process, automating some parts of it, made pricing templates for the standard parts and created metrics and transparency. Process improvements solved the problem.

Profit issues hit us right on schedule at stage five. During this phase, the company has been hiring and growing at such a rate that all those salaries begin to eat into profits. We hit this stage right at the beginning of the recession. This was a tough time, but we managed to keep growing market share even as the pie shrunk, simply because our competition was dropping out of the game. I spent a lot of time meeting clients during this period and fretted that I wasn't spending time setting strategy and planning, which I believed a good CEO should be doing. Now I realize I was doing instinctively what this stage requires - focusing on profits. I blamed the recession, but chances are I would've had to be profit-focused even without it.

People became the issue again as we moved into stage six, and so it comes as no surprise that I find myself taking a hard look at organization of late, pinpointing areas where we need to bring in more expertise, and crystallizing roles and functions. The project manager role, for example, has grown and changed. As Xcelience has expanded down the product pipeline, our clients have come to see us as an increasingly important part of their overall success. We need to be ever present and available to clients so they can see that their investment is in good hands. This responsibility falls primarily to the project manager. We've put more emphasis on this role and given them the title of Account Manager, to better reflect what they do.

With a strong organization in place, I can get to work on creating a vision for the company as a whole. The need for a strategic vision has been impressed upon me both from within the organization, and without. As we become more integral to our clients' successes, they are increasingly wanting to take a peek under the hood. Some have even asked to see our long-term strategic plan. Such clients tend to have very extensive multi-year compliance plans, and they include us as part of their internal quality organizations. They want to see our plans to make sure we can grow with them. Xcelience is getting qualified at several vendors. This will greatly reduce the client's workload. It's a logical step for us both and shows the confidence they have in our long-term. But it does take different people and skills at Xcelience, and is a strong inducement for us to firm up both our financial and strategic long-term plans.

Obstacles to growth

Fischer identifies several obstacles to growth, but two that have really shaped my perspective on my company are builder/protector ratios and modality.

Builder/Protector Ratios: Everyone in management is a builder or protector. A builder has confidence in the business, in its profits and processes, is eager to grow the business, and risk tolerant. A protector is cautious, slows down in the face of change, and is suspicious of growth. The protector is the guardian of your assets; often a CFO, controller, or quality manager. Every company needs both, but in certain stages of development, you need more of one than the other. If the ratio is off, the company will flounder.

Builders are in demand at start up, with very few protectors. Let's face it, there's not much to protect yet. A stage one business needs four builders to every one protector. In stage two, you need to begin to cultivate your protectors, with three builders to one protector. Come stage three, the company's ability to make a profit is reasonably secure, and you are building an organization and establishing systems; this is the stage with the fewest builders at 1:1. From then on, builders will continue to dominate to various degrees, particularly in stage six when builders dominate 3:1 again.

At Xcelience, I'm very aware that we're not where Fischer thinks we should be. We're close to evenly split, a ratio that according to Fischer we should've left behind in stage 3. We should have three builders to every protector. That said, I'm not entirely certain that we aren't just where we should be in a cGMP-regulated environment like ours. We may always need more protectors than other industries. One wrong step, and we could hurt a client's clinical program. I'm not going to go out of my way to hire more builders, but I will take care to encourage my staff to recognize the need to give extra weight to builder opinions as we steam through stage six.

Modality: The head of the company has three possible modes of behavior: dominant, facilitative, or supportive.

Adapting the wrong mode will slow or stop the company's growth.

In a young company, the CEO is dominant. He or she provides strong direction. It's not until stage three that this behavior needs to change. This is the stage where the CEO begins to delegate authority. The organization now needs someone who will facilitate - making it easier for the managers to do their jobs. The managers must then become supportive, giving the staff what they need to get the job done. It is the staff that is dominant in this phase, and you'll hear managers and CEOs cajoling them to "step up," "take responsibility," and encouraging them to take more risks.

Stage six is where we'll often see another reversal in these modes. This is a stage where the leader needs to step up to create a vision, lay it out, and allocate resources toward achieving it. If he or she does this, the managers should line up to support that vision, and staff should facilitate it.

Fischer also identifies a third obstacle to growth, which he calls the "three faces of the leader," namely manager, specialist, and visionary. The role of specialist is minimal, primarily required only in stage one. Beyond stage one, his role vacillates between manager and visionary, settling on visionary in the larger company.

A leader who fails to shift perspective as the company grows can become an obstacle to growth. Imagine a specialist in stage three or four, still trying to do the work himself when his company needs him in the boardroom working with his management team to facilitate their challenges as they grow their departments, establishing processes, and supporting their people. This leader may not like the role of manager, but unless he can find a way to wear that hat, his company will stagnate or flounder.

We all know small companies in these early stages that do a good job but spend decades in one stage. They stay there either because they want to, or they need to stay there. I find it interesting when a client says that their company chooses not to put all their projects with one service provider in order to reduce risk. What I hear is that they don't believe that the provider will continue to grow with the client.

The later stages of growth have their own challenges. There are some very serious diseconomies of scale when a company gets larger than 500 employees. R&D work goes slower and the connection between CEO and client almost disappears completely. I want Xcelience to grow to this point, but the challenge I foresee will be to maintain the quality of our work. I know of very few companies that have not seen a decline in quality when they reached this size.

A crystal ball?

Growth is necessary, and it's also good. It can solve a lot of company issues. Growth allows you to move people to the right places and motivate employees with promotions and personal growth opportunities. But it's important to recognize that companies go through stages and phases, just like growing kids. Wouldn't it be nice to keep a little crystal ball on your desk to tell you what issues are around the corner and how to prepare for them? *Navigating the Growth Curve* is three parts technical manual, and one part crystal ball. It helps you understand the issues you face today and prepare you for the ones that lie in the misty future, perhaps just a few hires away.

Special thanks to Renaissance Executive Forums for the workshop that brought this book and many other useful business paradigms to my attention.

BIOGRAPHY

Derek G. Hennecke is President and CEO of Xcelience, a CDMO in formulation development and clinical packaging located in Tampa, FL. Mr Hennecke launched Xcelience as a management buyout in 2006, and the company has more than doubled in size. Prior to starting Xcelience, Mr. Hennecke worked for DSM as a turn-around manager in the global drug development community, managing an anti-infectives plant in Egypt, technical and commercial operations in a JV in Mexico, and a biologics facility in Montreal. He developed the formulation and business strategy of several drug compound introductions such as clavulanic acid, erythromycin derivatives and Tiamulin. A Canadian, he covets the Florida sun, but can't be kept away from the rink for long. He is an avid fan of the Tampa Bay Lightning.

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Next generation HPMC capsules greatly expand pharmaceutical uses

by Dominique Cadé, PhD

A powerful alternative for pharmaceutical dosage forms

Polymer choices in pharmaceutical dosage forms have always been a balancing act between performance and development time, and historically has been shaped by the interactions of gelatin. The first generation of HPMC capsules, which relied on a secondary gelling agent, were recognized by formulators as having issues with dissolution performance and product stability. Fortunately, new scientific discoveries in polymers and capsule manufacturing have resulted in the creation of the next generation of HPMC capsules – one that offers better performance and reduced development time compared to gelatin and first-generation HPMC capsules.

Capsugel, the market leader in research and development in this area, is now offering these second-generation HPMC capsules under the trade name, Vcaps® Plus capsules.

In a number of studies, Vcaps Plus capsules have been shown to deliver optimized compound stability and predictable *in vitro* dissolution while also helping to eliminate the complexity in formulation development. Known globally for their reliable and predictable performance, Vcaps Plus capsules are well suited for over-the-counter (OTC) or off-patent products as well as for new chemical entities (NCEs).

True pH and ionic media independent performance

Traditionally, HPMC capsules were created using secondary gelling agents and ionic gel promoters, which have been found to interact with dissolution media and delay compound release from the capsule. The activity of the gelling agent kappa-carrageenan, for example, is enhanced by potassium and calcium cations contained in many foods. The extent of the resulting delay in dissolution time was shown in an *in vitro* test in which caffeine-filled traditional HPMC capsules were dissolved in a number of dissolution media. In the simulated normal acidic environment of the stomach (pH 1.2 USP), 90% of the caffeine was dissolved within approximately 15 minutes (Figure 1). Adding 2 g/L of potassium chloride (KCl) to this medium resulted in no dissolution after 15 minutes and a caffeine dissolution between 70% and 80% after more than one hour. Increasing the KCl content to 9 g/L delayed caffeine release even further, with a dissolution rate of just over 10% in 45 minutes. Results with simulated milk fluid were equally disappointing. Similar delays in dissolution times were observed and attributed to carrageenan in an independent study (Ku et al., 2011). Of course, such long delays in capsule dissolution are unacceptable particularly for rapid-relief products.

Capsugel addressed this situation by developing a proprietary new thermal gelation manufacturing process for Vcaps Plus capsules that eliminates the need for gelling systems all together and provides true pH and ionic media independence in disintegration. *In vitro* tests showed that these second-generation HPMC capsules had similar rates of dissolution at pH levels of 1.2 and 6.8 and with simulated milk fluid, achieving a nearly complete dissolution of the caffeine contents within approximately 30 minutes (Figure 2). Even adding 2 g/L or 9 g/L of KCl to the dissolution medium did not affect the performance of Vcaps Plus capsules, with dissolution of over 90% within 30 minutes, even under the most disadvantageous condition.

These findings were supported by an independent study that compared the dissolution performance of traditional and second-generation HPMC capsules (Ku et al., 2011), and underscores the superior performance of Vcaps Plus capsules.

Ideally suited for moisture sensitive compounds

While gelatin capsules have been effectively used for over a hundred years, due to their excellent flexibility and highly desirable dissolution properties, they are not typically the polymer choice for moisture sensitive compounds. Vcaps Plus capsules on the other hand have a three-fold lower moisture content than gelatin capsules and are less hygroscopic. That equates to fewer broken capsules due to brittleness and less of a chance of drug degradation compared to gelatin capsules.

Figure 1

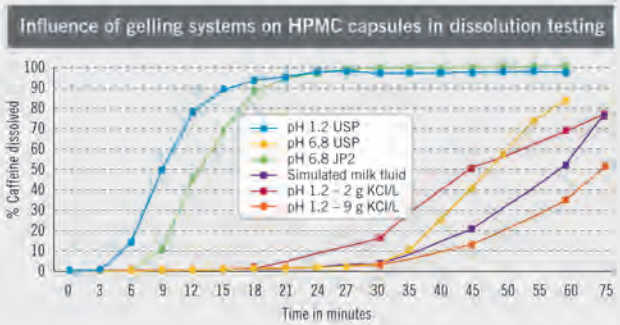
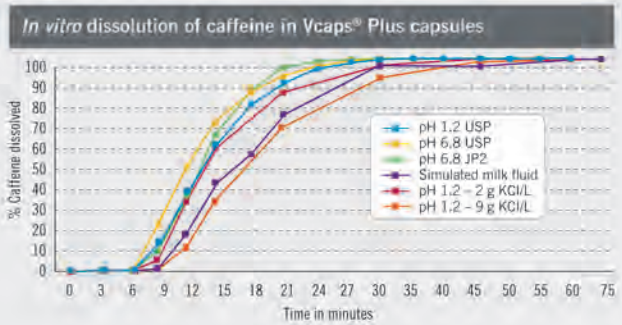


Figure 2



Improved stability at high and low temperatures

Capsugel in-house studies and an independent study conducted at Wyeth (Ku et al., 2010) have demonstrated the superior stability of Vcaps Plus capsules. An exposure of up to one week to temperatures ranging from 4°C to minus 18°C did not change the appearance or performance of unfilled Vcaps Plus capsules in closed high-density polyethylene (HDPE) bottles. The same stability was found with empty Vcaps Plus capsules in fully-filled glass bottles that were heated for 24 hours to temperatures ranging from 40°C to 60°C.

In long-term storage condition studies, including a 6-month storage at 40°C and 75% relative humidity and 2 years at either 25°C and 65% relative humidity or 30°C and 70% relative humidity, Vcaps Plus capsules disintegration and dissolution characteristics remained unchanged.

The wider temperature capabilities of Vcaps Plus capsules make them the perfect choice for longer term storage and when used in progressively unpredictable home environments.

Superior machinability

Traditional and second-generation HPMC capsule attributes have been compared on many common high-speed capsule filling machines (Ku et al., 2010). With respect to filling and rejection rates, Vcaps Plus capsules performed much like gelatin capsules and were superior to traditional HPMC products. In addition, Vcaps Plus capsules can be adapted for use with liquid compounds.

Wide regulatory and industry acceptance

Vcaps Plus capsules are manufactured in certified ISO 9001 facilities and in accordance with IPEC's (International Pharmaceutical Excipient Council) Good Manufacturing Practice (GMP) Guide for Bulk Pharmaceutical Excipients. They are acceptable for use in pharmaceutical and dietary supplement oral dosage applications in major markets of the US, Canada, EU, Japan, and Australia. In addition, Vcaps Plus capsules are certified Kosher Ko and Halal by IFANCA, and are approved for vegetarians by the Vegetarian Society.

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Vcaps® Plus

For more information about Vcaps® Plus capsules visit VcapsPlus.com.

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The Reconstitution Revolution

By: Alan Shortall

The complexity of drug reconstitution has for many decades constrained the market potential for lyophilized drugs and vaccines. With multiple pieces of equipment and around a dozen non-intuitive steps required to reconstitute a lyophilized drug from a vial, the overwhelming majority of these products are restricted to administration within healthcare facilities. However, the healthcare shift toward patient self-injection and the accelerating momentum behind biologics has sparked a new wave of innovation for drug reconstitution technology. Dual-chamber syringes in particular represent an enabling technology not only for the self-injection of lyophilized drugs, but also other emerging therapies requiring the mixing of two liquid molecules at the time of delivery. More than 300 approved drugs and vaccines requiring reconstitution or mixing are currently marketed for use within the US. By some estimates, between one-quarter and one-third of all FDA approvals in recent years have been for parenteral drugs supplied in a lyophilized format. For some of these drugs and vaccines, lyophilization represents the fastest route to market, with pharmaceutical companies later planning their introduction in an alternative format as part of lifecycle management strategies.

FIGURE 1

Multiple pieces of equipment, including vials, needles, and syringes, have traditionally been required to reconstitute and inject lyophilized drugs and vaccines.

RECONSTITUTION OF BIOLOGICS

The supply of many biologics in a liquid form is impractical or impossible. Instability of liquid stable drugs at room temperature can require costly transportation and storage using refrigeration during the entire life of the product. Pharmaceutical companies may also have concerns that the pharmacokinetic and pharmacodynamic properties of certain biologics in a liquid stable format may diminish over time. For such biologics and other drugs or vaccines, their supply in a lyophilized or powder form requiring reconstitution at the point of delivery can represent the only feasible pathway to commercial launch.

UNMET MARKET NEEDS

The majority of lyophilized drugs and vaccines are targeted for administration via IV infusion, intramuscular, or subcutaneous injection. The traditional process for their reconstitution requires up to a dozen steps incorporating a syringe, a single- or multi-dose vial with the drug, a second vial or syringe with diluent, one blunt needle, and one narrow bore needle for injection. Vial access devices, vial adaptors, and vial-to-vial systems are also becoming common for use with some reconstitution therapies.

Given the paramount importance of avoiding errors during

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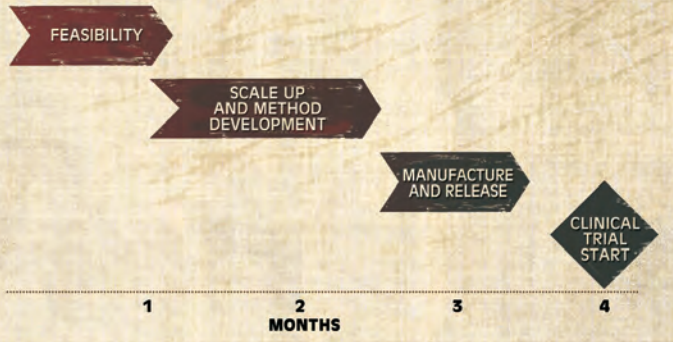

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the reconstitution of an accurate dose, the self-injection of such therapies has long been recognized as being unfeasible without a device that is extremely intuitive for the user. The relative complexity of conventional reconstitution systems compared to other device categories used with liquid stable drugs has therefore largely restricted lyophilized drugs to injection by healthcare workers within the confines of hospitals and other secondary care sites.

Even with extensive staff training, the process of reconstituting lyophilized products within healthcare facilities can involve some significant challenges. Inefficiencies include the need for facilities to purchase and stockpile multiple pieces of inventory and the lengthy preparation time required to reconstitute a therapy with the correct dose volume prior to injection. For mass vaccination programs in which an operator may be delivering dozens or even hundreds of injections per day, the length of time required to reconstitute a dose can become particularly cumbersome.

With the FDA placing an increasing focus on human factors in the approval of new drugs or formulations, pharmaceutical companies risk failure if data cannot be presented that demonstrates sufficient levels of reliability and dose accuracy during the reconstitution and injection process.

The traditional process of reconstituting a lyophilized drug may also exacerbate the risk of needlestick injury for a healthcare worker, as syringes with attachable needles are typically used to draw a reconstituted dose from a vial.

To comply with needlestick prevention laws in within the US, Europe, and other international regions, healthcare workers will typically attach safety needles with needlestick prevention systems, such as a sliding sheath or hinged arm. Filter needles used for vial access lack safety features altogether. For fine needles used for injection, these ancillary safety products require post-removal activation of the safety mechanism, with the operators required to undertake a second manual action, such as placing their hands close to the needle after completion of injection.

An estimated two-thirds of all reported needlestick injuries involving safety products are caused by such manually activated products. Organizations, such as the Emergency Care Research Institute, also site a common practice amongst many healthcare workers to not activate the safety mechanism of such manual products, creating the risk of downstream injury, unsafe disposal, or syringe reuse.

FIGURE 2

The complex process of reconstitution has largely restricted the administration of lyophilized drugs to experienced healthcare workers within healthcare facilities.

For IV applications, there are many therapeutic drugs in which there are no suitable or sub-optimal system to seamlessly integrate reconstitution, dilution, and delivery.

SHIFT TO PATIENT SELF-INJECTION

A shortage of easy-to-use drug reconstitution delivery systems has constrained market opportunities for the self-administration of many approved therapies by patients outside of healthcare facilities. In some cases, the lack of an effective reconstitution system has prevented the commercialization of promising injectable therapies in which a business case can only be made for patient self-injection.

Despite conventional reconstitution technologies being unable to fully address many of these unmet market needs, some pharmaceutical companies have sought to make their injectable therapies available for patient self-injection to address significant healthcare challenges. One example of a lyophilized drug currently supplied in injection kits for reconstitution and use outside of healthcare facilities is glucagon. A selection of glucagon therapies are available by several manufacturers that that are targeted for use by the family members or other caregivers of patients requiring emerging treatment for severe hypoglycemia.

With current glucagon therapies beginning to fibrilize and become unstable shortly after entering into a liquid form, the only available option is to keep the drug in a lyophilized form where it can be kept on hand and stored at room temperate for up to 2 years.

Supplied in emergency kits in a lyophilized vial and a syringe filled with diluent, such glucagon products must be rapidly

reconstituted and injected by a caregiver who may have little to no prior experience or training. With the risk of brain damage or death increasing the longer a patient experiences severe hypoglycemia, the rapid, intuitive reconstitution and delivery of the drug is critical.

To administer glucagon with this kit, the liquid solution must first be injected into the vial with the dry powder and mixed. After the glucagon powder has dissolved, it is then drawn back into the syringe, a needle attached, and the glucagon injected into the patient. In order to properly administer the glucagon dose, a caregiver must follow a multi-step process in a situation typically made even more challenging by the patient's condition.

The complexity of currently available rescue kits and the training required for proper administration of glucagon has resulted in the underuse of glucagon as a rescue treatment for diabetes patients experiencing severe hypoglycemia. Indeed, only 10% to 20% of high-risk patients who should by diabetes education standards have an unexpired glucagon kit actually having one. Furthermore, many ambulances fail to carry glucagon emergency kits for reasons including their provision in devices that lack adequate needlestick protection.

DUAL-CHAMBER APPEAL

Pharmaceutical companies have long recognized the potential of dual or multi-chamber prefilled syringes to enhance the portability, efficient reconstitution, and intuitive delivery of lyophilized or powder-filled drugs by healthcare workers or self-injecting patients.

For the pharmaceutical manufacturer, the delivery of such therapies in a single device can help to minimize transport, packaging, and shipping costs compared to relatively bulky injection kits. More importantly, it creates opportunities to differentiate a drug product against rivals within a competitive therapeutic class. Compared to the traditional process of reconstituting a dry drug from a vial, a dual-chamber prefilled syringe can potentially reduce the number of steps by half or more.

Such efficiencies created by dual-chamber syringes can reduce the length of time required to reconstitute and inject a dose, as well as helping to minimize the risk of dosing errors. Combined with improved portability, these benefits may enable a therapy previously approved only for administration by a trained healthcare worker to in the future be supplied for convenient patient self-injection. Particularly in cases where improved levels of therapy compliance can be demonstrated, these benefits can be leveraged by a pharmaceutical company to generate strong preference for their brand amongst patients, payors, and prescribers to drive market share and maximize revenues.

To date, however, only a handful of products have been launched with a dual-chamber syringe. Furthermore, only a handful of dual-chamber syringe technologies are marketed by device manufacturers. Technological limitations and human factors associated with traditional dual-chamber syringes may have contributed to poor levels of acceptance by pharmaceutical companies in the past decade.

Some dual-chamber technologies can require the user to break sterility before reconstitution by replacing the rigid needle seal used for packaging with another special vented cap used for reconstitution. For healthcare facilities that prefer to reconstitute multiple doses at the start of a shift and then keep them refrigerated until injection, the compromising of sterility can represent a significant challenge.

Some dual-chamber systems also require the user to hold the device at a specific upward-facing orientation, otherwise, leakage of the drug or device failure may occur. Safety features are also not integrated within any traditional dual-chamber system technologies, restricting their capacity to protect those at risk of needlestick injury.

A NEW WAVE OF INNOVATION

The inability of conventional drug reconstitution delivery systems to address these unmet and other emerging market needs has constrained this market sector to low levels of market growth compared to other device sectors, such as prefilled syringes, auto-injectors, and wearable injectors (patch pumps).

However, recent advances in drug reconstitution technology now herald the arrival of a new era in the intuitive reconstitution and delivery of lyophilized therapies by healthcare workers or patients. When combined with growing pharmaceutical investment in the development of liquid-liquid combination products, the market for dual- or multi-chamber syringes is poised to enter a period of rapid growth and expansion throughout the coming decade.

Unilife is one company addressing these and other emerging needs for the mixing or reconstitution of lyophilized drugs and vaccines. The US-based emerging leader for injectable drug delivery systems has developed a broad array of technologies under its EZMix mixing platform that represent a compelling proposition to enhance

FIGURE 3

The EZMix platform of dual-chamber syringe enables the intuitive reconstitution of dry drugs and their needlestick-free injection by healthcare workers or patients.

and differentiate biologics, drugs, and vaccines requiring reconstitution or mixing at the point of delivery.

EZMix products enable pharmaceutical companies to streamline the filling, containment, mixing, delivery, and disposal of any liquid or dry drug combination therapy. Compared to conventional technologies that can take between five and a dozen complex steps to mix together the drug and diluent combination, EZMix systems can essentially achieve the same outcome with one easy action. That makes EZMix an enabling technology for combination therapies targeted for use by healthcare workers or self-injecting patients. A unique combination of proprietary features for EZMix includes the following:

- USP-Compliant Materials: EZMix syringes can securely house a dry or liquid drug in one chamber, and a measured dose of a diluent or liquid drug in another chamber.
- Standard Fill-Finish: Supplied as per standard handling practices for integration with standard filling and packaging processes and equipment.
- Flexible Dosing: A wide range of viscosities, dose volumes, and administration routes can be accommodated.
- Minimal Steps: Compared with traditional reconstitution systems and other marketed dual-chamber prefilled syringes, EZMix requires only a few intuitive steps for reconstitution and safe delivery of the dose.
- Ventless, Orientation-Free Mixing: Unlike some systems requiring the device to be held at specific orientations and to break sterility before reconstitution forcing immediate injection, EZMix can be held at any angle and remains sterile until injection to minimize the risk of drug wastage.
- Clear View of Dose: Users have an unobstructed view of the drug at all times.
- End-of-Dose Indicators: Audible, tactile, and visual indicators confirm end-of-dose delivery and the automatic activation of the needle-retraction mechanism.
- Automatic Retraction: Needle retraction is activated automatically, with the user able to control the speed of withdrawal directly from the body into the barrel to minimize the risk of infection from needlestick injuries or blood splatter.
- Convenient Disposal: The needle is automatically locked inside the syringe barrel after retraction to enable compact, convenient disposal.

The EZMix mixing platform is fully customizable to address specific customer, therapy, and patient requirements. Customization options include drug and diluent volumes, the use of staked or attachable needles, silicone minimization, extendable flanges, and coated elastomers.

One recent customization program recently announced by Unilife addresses the aforementioned market need for the intuitive reconstitution and injection of glucagon under emergency situations. The customized EZMix syringe developed for a customer allows a caregiver to automatically reconstitute and deliver the dose down in two simple steps that can be summarized as twist and inject.

As a ready-to-mix product with minimal steps and automatic safety that is ideal for use by either healthcare workers or self-injecting patients, EZMix products are perfectly positioned to generate powerful brand differentiation for injectable therapies targeted for use in competitive markets.

Even when compared to other dual-chamber options, EZMix features a sleek, elegant, and attractive design with no unsightly springs or mechanisms. Being highly compact in size, it is visually attractive before, during, and after use. Combined with superior human factors, including ventless, orientation-free, and error-free steps of use, EZMix represents a compelling choice to build preference rates and differentiate a lyophilized or combination therapy from the competition.

OTHER EMERGING TECHNOLOGIES

Whereas dual- or multi-chamber syringes are poised to redefine the market for lyophilized or combination therapies targeted for hand-held subcutaneous or intramuscular injection, advanced drug reconstitution technologies also have significant potential in other related market areas.

Some pharmaceutical companies are seeking to reconstitute or mix liquid or dry drug combination therapies in dose volumes that are greater than 1 mL. For such therapies, targeted for subcutaneous administration by patients, wearable injectors incorporating drug reconstitution technology represent an exciting commercial prospect. For other therapies that will be administered via IV infusion via syringe pumps in dose volumes of between 3 mL and 30 mL, new technologies have the potential to significantly reduce the number of steps and enable reconstitution and dilution at the point of delivery.

A BRIGHT FUTURE

With dual-chamber syringes and other emerging device technologies now addressing key market requirements for intuitive reconstitution and injection, the pharmaceutical market for therapies suitable for reconstitution and mixing at the point of delivery is poised for significant rates of growth. Companies such as Unilife are ready to support pharmaceutical companies in the clinical development and lifecycle management of these drugs to help enhance the provision of care across the healthcare spectrum. ◆

BIOGRAPHY

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 wearable injectors, and other specialized delivery systems. For more information, visit www.unilife.com.

The Second Quadrant

Navigating a Broad Spectrum of Solubilization Technologies: Part II of III

By: Marshall Crew, PhD, President & CEO, Agere Pharmaceuticals, Inc.

A multiple-part series discussing today's most challenging issues in solubility.

In September's issue, *The Second Quadrant* focused on technology options available and in use today to address bioavailability challenges of poorly soluble drugs. In particular, when technologies are best suited for APIs based on compound characteristics and the target product profile. In Part II of this series, experts from nine companies discuss key challenges faced that are related to these technologies, and combinations or techniques that can improve solubilization results. This part concludes with thoughts on untapped opportunities that may be exploited with a better understanding of the various options available and their respective applications.

As in Part I, the broad set of solubilization technologies companies represented include those offering lipid-based solubilization, amorphous solid dispersions, particle size reduction, particle engineering, nanoparticles, and co-crystallization.

CHALLENGES & SOLUTIONS

Q: What do you view as the primary challenges faced today in formulation to achieve enhanced bioavailability that directly correlate with solubilization technologies?

Dan Dobry: A particularly challenging area is the oral delivery of BCS class IV compounds that have low permeability and low solubility. These compound properties are driven by requirements to hit complex therapeutic targets. Some of these compounds have a higher molecular weight than that commonly thought to be in "druggable" space. These compounds are particularly difficult to formulate and require the addition of multiple technologies to successfully deliver the required payload - such as those mentioned previously.

Formulating each compound requires committed diligence and a partnership with the client. Fortunately for clients, the Bend Research experience with over 1,000 compounds means that we've come across many of the common issues with formulation. Sometimes we've engaged on existing formulations that had acceptable performance to support a Phase I program, but that are unacceptable for Phase II, Phase III, or commercial application. Using fundamental science and engineering principles and our 20+ years of experience in dealing with low-solubility compounds, we've identified a broad array of dispersion formulation approaches as well as complementary technologies, such as nanoparticles and nanocrystals. This means that many of these compounds can be solubilized using the appropriate approach based on the key factors of performance, stability, manufacturability, and the target product profile for the patient.

Tom Dürig: The primary challenge is to translate increased solubility in gastrointestinal fluid into increased absorption and bioavailability. Recent work by Dahan et al has highlighted the importance of understanding the mechanism of different solubilization approaches and their effect on intestinal membrane permeability.[1,2] It has been shown that cyclodextrin-, co-solvent-, and surfactant-based systems resulted in high solubility, but decrease transmembrane flux as compared with amorphous solid dispersions. A thorough understanding of in vivo effects of excipients and delivery systems in addition to their solubilization effects is therefore key.[1,2]

"The primary challenge is to translate increased solubility in gastrointestinal fluid into increased absorption and bioavailability."

Tom Dürig,
Senior R&D Director - Pharmaceutical & Nutrition Specialties,
Ashland Specialty Ingredients -
tdurig@ashland.com

Dr. Joan Feixas: Although the number of published bioavailability studies is limited, it is clear that co-crystals can significantly increase the bioavailability of poorly soluble APIs (BCS class II and IV drugs). In general, there is a correlation between the improvements of bioavailability and the improvement of API solubility induced by the co-crystal. However, it is very difficult to predict the solubility enhancement of the co-crystal from the physical chemical properties of the co-former.

In 2011, draft guidance for industry on regulatory classification of pharmaceutical co-crystals was released by the FDA. In this draft, and from the regulatory standpoint, co-crystals were not defined as a new chemical entity (like a salt) but, instead, as a drug product intermediate (dissociable "API-excipient" molecular complexes). This consideration opened a new path for generic companies to file ANDAs,

avoiding the 505 (b)(2) regulatory track. In the last guidance issued in April 2013, the FDA confirms this view and even allows fine chemical manufacturers to produce pharmaceutical co-crystals (a drug product intermediate) in a cGMP API chemical plant.

Dr. Filipe Gaspar: There is still a lot to do before being able to correlate technology with improved bioavailability. Understanding dissolution kinetics, supersaturation, and crystallization processes, free drug concentrations, and food effects, among others, is not trivial but will surely help in the adoption of solubilization techniques.

Dr. Robert Hoerr: Primary challenges are solubility and permeation. The particle reduction technologies have the potential to improve solubility and dissolution. To date, the commercialization for nanoformulation technologies has been somewhat limited due to batch processing, cost, and multistep processes. The requirement to maintain a narrow particle size distribution as the process is scaled has been difficult. Another challenge has been making solid solutions. ENS transforms the solvent solution of API and excipients directly into a drug-excipient solid solution with a very narrow targeted particle size distribution. ENS-produced powders can improve both solubility and dissolution rate. ENS has a very high process yield and can be used to formulate small amounts of API to enable in vivo and in vitro testing at early phases of drug discovery and development.

"… a fast crystallizer often requires a much different approach than a highly lipophilic or greasy compound."

Dan Dobry,
VP, Bend Research-
Dan.dobry@bendresearch.com

Keith Hutchison: When an API is formulated using a lipid-based solubilization technology, the effect of digestion on the excipients can have a significant effect on the quantity of solubilized drug in the gut and the extent to which absorption is affected by the presence of food. In vitro digestion tests are therefore used by Capsugel DFS to ensure that the most robust lipid formulations are designed, tested, and proposed for customer projects. Testing protocols are based on the advancements achieved by the Lipid Formulation Classification System (LFCS) Consortium (www.lfcsconsortium.org), of which Capsugel is a founding and active member. LFCS is playing a critical role in exploring the relationship between lipid digestion/dissolution and drug absorption and establishing standardized in vitro tests for lipid formulations, which is a key factor in expanding the market application of lipid-based technology.

Dr. Dave Miller: An important challenge facing the development of amorphous drug products is the prediction of physical stability. Recent advances to in silico modeling with the use of solubility parameters and the application of Flory-Huggins theory are helping to provide better understanding of drug-polymer miscibility, which directly correlates to physical stability. These tools are also helping to focus formulations screening efforts on the most viable carriers and drug-to-polymer ratio ranges, ultimately leading to more rapid development of amorphous formulations that are physically stable for pharmaceutically relevant time periods. Continued development of these in silico modeling tools will provide fundamental understanding of the mechanisms behind amorphous stability allowing for the development of amorphous products with well-understood and defined stability profiles. This fundamental understanding will help ease anxieties regarding the metastable nature of amorphous drug products and thereby lead to more widespread adoption of amorphous formulation technologies.

Dr. Deepak Tiwari: One of the most difficult delivery challenges involves oral delivery of BCS class IV molecules. In this area, we have seen that the use of combinations of delivery technologies may be of benefit.

"…there are technologies available to solubilize a drug in high melting point waxy materials."

Keith Hutchison,
Senior VP of R&D Dosage Form Solutions,
Capsugel -
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"An important challenge facing the development of amorphous drug products is the prediction of physical stability."
Dave Miller, PhD,
VP of R&D, Dispersol Tech -
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NEW OR NOVEL TECHNOLOGY COMBINATIONS

Q: Are there unique or emerging combinations of technologies that expand the benefits of each, and can improve the bioavailability of a compound?

Dan Dobry: Depending on the compound properties and delivery profile desired (including regional permeation differences), there are multiple technology options available. For example, combining a spray-dried dispersion solubilization technology with a modified-release osmotic delivery system, such as a swellable core system (also known as "push/pull"), can provide solubilized active at different regions of the GI tract. Another example is to combine excipients that prolong a "supersaturated" state in the small intestine. This has proven to be particularly successful for compounds that have good solubility at gastric pH, but poor solubility at intestinal pH. A final example is a process improvement that expands the usefulness of common methods of solubilization. Some compounds that have very low solubility, even in common organic solvents, can be successfully spray dried into amorphous dispersions at commercial throughputs by rapidly heating a suspension of active just before spray-drying.

Tom Dürig: Hot-melt extrusion with supercritical CO2 injection is a particularly interesting combination of technologies in which our scientists are working. Hot-melt extrusion has obvious advantages; it can be solvent free, potentially continuous and easily scaleable with a relatively small manufacturing foot print. However, there are well-known shortcomings vis-à-vis spray-drying, such as lower mixing efficiency and a narrower processing window compared with dissolution in solvent and spray-drying. Supercritical CO2 acts as a solvent in the hot-melt extrusion process, thus enhancing drug-polymer mixing and increasing the processability window, due to its ability to act as a plasticizer and solvent. Lastly, the evaporation of CO2 during the process creates a porous extrudate microstructure, which aids in tablet compaction and dissolution. Another interesting opportunity is the combination of controlled-release technology with solubilization. Recent work has shown that it is possible to achieve extended drug release as well as continuous supersaturation with minimal precipitation for a period exceeding 10 hours.

Dr. Joan Feixas: It is well known that the solubility behavior of poorly soluble drugs can be improved significantly when a co-crystal form of the drug is used. However, the pharmaceutical co-crystallization can be combined with other technologies to further improve solubility and, therefore, bioavailability. For example, combining co-crystallization with supercritical fluid technologies, it is possible to obtain nanococrystals with an extended control of the particle morphology and the size distribution. These are key aspects for inhaled drugs for the treatment of asthma and chronic obstructive pulmonary disease (COPD).

Dr. Filipe Gaspar: Clearly there are and we expect to see in the near future a number of novel and combined technologies able to improve bioavailability and other quality attributes. At Hovione, we have for example fluidized spray-drying that provides the same benefits of spray-drying (for example in improving bioavailability) with a fluid bed drying and agglomeration process that results in powders with very unique properties. This is a technology that is broadly applied in other industries but still in its infancy for the production of drug products. Other examples of combined technologies include injection molding, supercritical CO2-assisted extrusion, spray-freeze-drying, and spray- drying of polymeric micelles or nanoparticles. Among emerging solubilization technologies, which may or may not prove to be viable in the marketplace, are spray- congealing, microfluidization, electrospinning, and emulsification.

"..the pharmaceutical co-crystallization can be combined with other technologies in order to further improve solubility and, therefore, bioavailability."
Joan Feixas, PhD,
CEO, Enantia -
jfeixas@enantia.com

Dr. Robert Hoerr: Recent advances in nanotechnology have enabled nanosized or nanostructured pharmaceutical particle engineering to provide enhanced efficacy, solubility, or bioavailability, thereby possibly lowering dose requirements. ElectroNanospray (ENS) is an alternative to solvent spray-drying without temperature or pressure limitations and with no additional processing steps. With ENS, excipients used for dry granulation and capsule coating can be repurposed to create nanoparticles with improved solubility, stability, and bioavailability. In addition, ENS' highly controlled deposition capability lends itself to production of thin-layered structures that allow for unique drug/drug, drug/excipient, or drug/biologic combinations.

Keith Hutchison: When an API is solubilized in liquid or semi-solid lipids, the formula is filled into a capsule as a monolithic form. However, there are technologies available to solubilize a drug in high melting point waxy materials. Capsugel DFS is using its new solid lipid pellet technology to immobilize APIs in high melting point pharma excipients and produce spherical particles that are filled into capsules as powders. Additionally, polymers and polymeric capsules, eg, our Vcaps®Plus HPMC capsules, have been shown to reduce the risk of API precipitation in the small intestine to increase bioavailability - we therefore use these capsules in combination with lipid formulations when a risk of drug precipitation has been identified in vitro.

"There is still a lot to do before being able to correlate technology with improved bioavailability."
Filipe Gaspar, PhD, Director of Drug Product Technologies, Hovione - fgaspar@hovione.com

Dr. Dave Miller: KinetiSol is a novel processing technology that expands the space of compounds and excipients that are viable for amorphous formulation concepts. KinetiSol offers all the benefits of non-solvent processing that are provided by melt extrusion, yet offers distinct advantages over melt extrusion for particular applications. Specifically, KinetiSol reduces thermal stress on processed materials enabling fusion processing of thermally labile APIs and excipients. Also, according to the processes' intense mixing mechanism, compounds are able to be rapidly solubilized in a molten polymer, well below the API's melting temperature. This is particularly beneficial for high melting point compounds in which achieving target amorphous drug loadings in specific concentration-enhancing polymers can be particularly challenging by melt extrusion. Finally, by its unique mixing mechanism, KinetiSol is able to process highly viscous polymers without plasticizers or processing aids that would be needed for melt extrusion processing and that can negatively impact physical stability. The physical stability advantage is obvious, but this capability of KinetiSol also creates exciting new possibilities for novel amorphous dispersion compositions with unique dissolution and PK profiles. Ultimately, KinetiSol is providing a novel processing solution by which amorphous dispersion technology can be applied to insoluble compounds toward the end of improving bioavailability and enabling new, or improving existing, drug therapies.

Dr. Deepak Tiwari: Absolutely. We have been combining a number of approaches with good success. Unfortunately, we cannot go into specific details in a public forum, but the technologies we are using are complementary and not mutually exclusive.

UNTAPPED OPPORTUNITIES

Q: What are some of the gray areas in which your technology may be able to help overcome insolubility but where assumptions or lack of familiarity with the approach diminishes the exploration of a specific technology?

Dan Dobry: Many underestimate the need to customize the solution to the challenges and properties of each molecule or class of problem statements.

"Micronization… is an extremely versatile, scale-able, and time-tested process that can enhance the performance of solubility-challenged compounds."
Peter Nelson, Director of Analytical Services, Micron Technologies - pnelson@microntech.com

"We have developed a scalable modular component pathway to high-volume ENS production in the kilogram or larger per day range."

Robert Hoerr MD, PhD, Co-Founder, Chief Scientific Officer, Nanocopoeia, Inc. - Bob.hoerr@nanocopoeia.com

We've encountered several scenarios in which the simple conversion of the API to the amorphous form or dissolution into a simple lipid carrier did not provide sufficient bioavailability enhancement. We have been able to "fix" or "optimize" many failed or substandard formulations through use of science-based approaches to solving the specific challenge a molecule presents. For example, a fast crystallizer often requires a much different approach than a highly lipophilic or "greasy" compound.

Tom Dürig: Many companies still lack familiarity with the techniques to produce amorphous dispersions beyond bench scale. There is an unnecessary mindset of avoiding spray-drying, which is one of the most powerful techniques. This avoidance tends to be due to assumptions that the environmental complications and costs associated with commercial-scale organic solvent use are prohibitive. Frequently, therefore, companies wish to explore only hot-melt extrusion. Additionally, as a result of the relatively small number of marketed amorphous dispersion products, many companies continue to shy away from solid dispersions, based on the assumption that it is, as yet, a risky and relatively unproven technology, which is not really the case when considering the spate of recent NDA approvals and the considerable pipeline under development.

Dr. Joan Feixas: Although the use of cocrystal technology with non ionisable or poorly ionisable APIs is well known, less familiar is the preparation of a cocrystal of a salt to form an ionic cocrystal consisting of a multicomponent solid with both neutral molecule and an electrically neutral ion combination. With this kind of cocrystal, it is possible to modulate the chemical physical properties of a drug salt. For example, cocrystals of fluoxetine·HCl (Prozac®) with different acidic coformers have been described and exhibited significantly different solubilities and dissolution rates. Recently, ionic cocrystals of inorganic salts with interesting properties have been also described.

Dr. Filipe Gaspar: For solid dispersion platforms in which spray-drying and hot-melt extrusion are the leading technologies, we still see some apprehension from some formulators to move with an amorphous form approach. This happens despite the significant advances in the underlining science and the growing number of solid dispersions reaching the market. We have come a long way in the past 8 to 10 years, but there is still a lot to do to reassure all of the value of this platform.

For hot-melt extrusion, the quantity of material required for process development limits its use at early stages. Then there is reluctance to switch to the technology to mitigate clinical risk. Polymer degradation in hot-melt extrusion also needs further understanding and poses concerns during formulation development.

Dr. Robert Hoerr: Nanotechnology has significant promise, but the scalability of nanoformulation has proven difficult. One erroneous assumption is that electrospray cannot scale up beyond micrograms per minute. People are unaware of the progress that is being made toward preclinical scale manufacturing and reducing the cost of the equipment. We have developed a scalable modular component pathway to high-volume ENS production in the kilogram or larger per day range.

Keith Hutchison: Solubilization of drugs in lipid-based formulas is widely explored, but a general lack of familiarity with excipients, as well as with a systematic set of techniques for identifying the optimum formula can impede effective uptake of the technology, particularly for multi-component systems of API in oil/surfactant/co-surfactant compositions. Many lower Log P APIs, eg, < 5, are often viable candidates for lipid formulations but are typically progressed with other enabling solubility-enhancement approaches.

Dr. Dave Miller: The KinetiSol process can be applied to create advanced amorphous dispersion systems for most poorly water-soluble compounds;

"In general… one needs to focus on bioavailability and not specifically on solubility."

Deepak Tiwari, PhD, Director, Formulation & Process Development, Particle Sciences, Inc. - tiwari@particlesciences.com

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however, where it adds most value is in the "gray area" space that contains compounds with high melting points, thermal sensitivity, poor organic solubility, or for compositions requiring polymers that are not amenable to fusion processing. Misconceptions regarding scalability or limited manufacturing experience with KinetiSol have likely been a deterrent for some to explore the technology. The reality is that prior to its adaptation to pharmaceutical manufacturing, the technology underlying KinetiSol was utilized extensively in the plastics processing industry to generate commercial products at a rate of several tons per hour. In the development of KinetiSol for pharmaceutical applications, the technology actually had to be scaled down to accommodate early development where API quantities are limited. So, the development of KinetiSol was quite different from most new technologies in that scaling went in the opposite direction. Therefore, the principles of scaling the KinetiSol process are well understood and easily applied. Although scaling is straightforward, for most products, scale-up is not required. KinetiSol processing at a development scale occurs within a batch size range of 50 to 300 g. Hence, formulation and process development are conducted in batch mode at a 50 g scale first, then the batch size is increased to around 250 g within the same compounder without influencing product properties. The process is then converted from batch to semi-continuous mode producing 250 g approximately every 30 seconds. Hence, production rates of about 30 kg/hr can be achieved within the same KinetiSol unit that is utilized to develop the formulation and process. For high-volume products, multiple KinetiSol units can be operated in parallel to meet throughput requirements.

Peter Nelson: In addition to the "urban myth" relative to amorphous content mentioned previously, micronization suffers from being an "unsophisticated" technology. It is simply not as "sexy" as some alternative solubilization technologies available today. Micronization, however, is an extremely versatile, scaleable and time-tested process that can enhance the performance of solubility-challenged compounds. Like any process, micronization does have potential drawbacks, such as the potential for particle agglomeration, reduced flow characteristics, etc. If understood and proactively evaluated, however, these potential problems can be addressed. During early development of the compound, it is important to consider formulation and/or process strategies that can help mitigate the potential problems associated with our technology.

Dr. Deepak Tiwari: Again, because we use a number of technologies, there are a number of answers to this. In general, however, one needs to focus on bioavailability and not specifically on solubility. Bioavailability is driven by a number of factors. Keeping that in mind and combining approaches in a methodical development program is the quickest path to success.

THE NEXT ISSUE

In Part III of this series, solubilization technology experts will provide insights into recent breakthroughs in solubilization technologies, and what we can expect to see in the future. To ensure *The Second Quadrant* serves as a forum for interactivity and collaboration, I invite you to send your reactions, thoughts, and suggestions so we can continue our dialogue. I look forward to hearing from you. ◆

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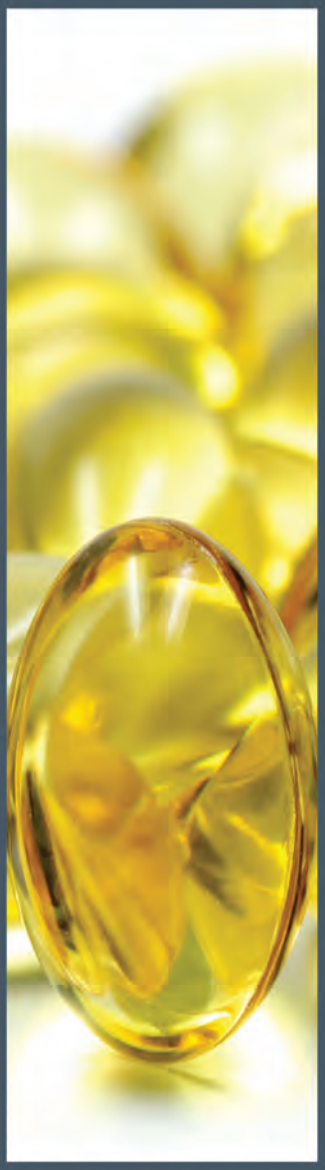
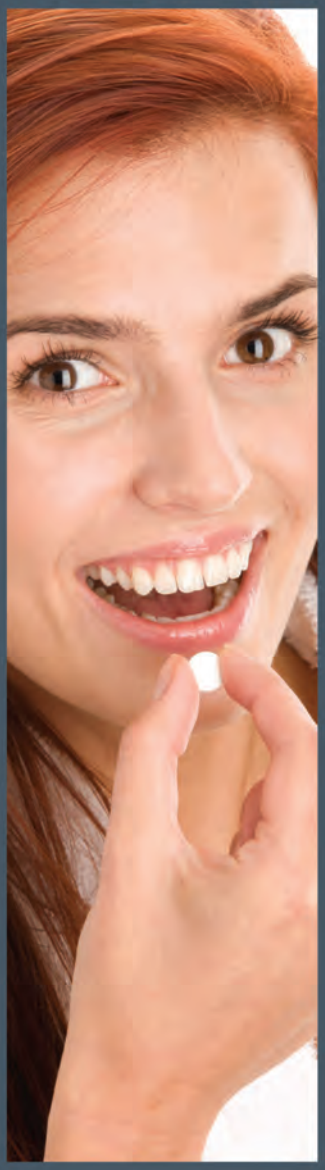

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Better Treatments Through Innovative Solid Oral Drug-Release Technologies

By: Steven Hamlen, MBA, and Nicholas Johnson, PhD, MBA

INTRODUCTION

Oral solid dosage controlled-release technologies have experienced a surge in innovation in recent years. This can be largely attributed to demanding new therapies that need to show improved outcomes and patient medication compliance to ensure better cost effectiveness of overall disease management. New products need to be highly differentiated with optimized therapeutic product profiles to effectively compete in the global marketplace, with the increased focus of payers; both private insurance companies and governments.

The following discusses Catalent's recent technology innovations in controlled-release solid oral dose functions and forms as well as more established methods for altering release profiles of molecules. It describes how the product profile benefits of these technologies address the prevailing industry pressures. A real-world case study is provided in which applying alternative formulation technology significantly improved an existing therapy and delivered patient and payer benefits.

CONVENTIONAL APPROACHES TO MODIFY OR CONTROL SOLID ORAL DOSE RELEASE PROFILES

Extended (Long-Acting) Release: Decreased dosing frequency compared to IR formulations. Specific amount of drug released at specific time intervals.

Delayed Release (Enteric Coating): Targeted drug release to specific points in the body, based on pH or other characteristics, to deliver the active drug where it is needed for optimal efficacy and safety.

Combined IR/ER (Pulsed Release): Short- and long-term combined release (IR plus ER) in one dose form, to deliver active drug when it is needed. Figure 1 depicts a variety of tablet forms incorporating controlled-release functionality.

Wurster coating is one of the more recognized approaches for developing effective controlled-release formulations. The technology involves bottom-spray fluid bed coating of particles with appropriate actives, excipient, or polymers to modify the drug release. Compared to alternative approaches, Wurster coating is a preferred technology as it achieves uniform statistical residence time within the coating zone and enables highly consistent coating of powders, granules, pellets, or micro-tablets. The accuracy and reproducibility of the coating process results in superior product performance of the controlled-release dose form.

Catalent is a leading provider of Wurster coating and related processes and has recently invested in major capacity and capability expansions at its Schorndorf, Germany; Somerset, NJ; and Winchester, KY; facilities to meet customer demand for higher quality, complex controlled-release formulations from pilot, development, and commercial scale.

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FIGURE 1

Controlled-release functionality can be included in a wide range of dosage forms.

INNOVATIONS IN CONTROLLED RELEASE TECHNOLOGIES

Increasing demands for greater product performance and differentiation have resulted in new approaches to delivery modification. OSDrC® OptiDose™ is an innovative and versatile delivery technology for unique differentiated controlled-release and combination dose forms. It enables design of dividable, multi-layer, single or multi-core tablets with practically endless variety of core numbers, shapes, sizes, and placement within the tablet. The heart of this technology is a variable double punch configuration, which enables this flexible-core capability and provides new alternatives in controlled-release designs for drug formulators, developers, and marketers in a high-quality, one-step manufacturing processes. This new technology expands tableting capabilities in many areas, including fixed dose combination tablets, pulsatile release, and dividable tablet formulations that differentiate beyond existing technologies. Applications utilizing OptiDose technology are currently approved and marketed in Japan for type II diabetes and cardiovascular indications. Figure 2 is an example of just some of the tablet functionality and unique dose forms that OptiDose innovative tablet technology can deliver.

Fixed Dose Combination Tablets: OSDrC OptiDose technology provides flexibility to design single or multiple API in a single tablet, with different release profiles. In addition to demonstrated improvement in mass variability between layers, OSDrC OptiDose also offers tablet design to minimize cross-layer interaction of API and improved product stability.

Unique Pulsatile Release: Multiple core shape, size, and placement allows for optimized chrono-therapy release profiles to deliver superior control of plasma levels and duration of action, reduced dosing, and reduction of breakthrough symptoms.

Compliant Dividable Tablets: A significant advancement in both simple and coated dividable tablets. Integrity of drug-release profiles and benefit of incorporating controlled-release properties within each dividable tablet half is increasingly important. FDA Guidance issued in March 2013 requires ease of handling, ease of dividing tablets, and integrity of drug content and release profiles if a tablet is divided. As OptiDose technology can completely encase the active in each half, it yields consistent active dosing whether the tablet is divided or administrated as a complete dose. The technology also greatly reduces the variability that can occur when breaking a dividable tablet.

BIOAVAILABILITY ENHANCEMENT

During drug development, an increasingly common hurdle to achieving desired therapeutic profile endpoints is when a molecule has poor bioavailability properties. Bioavailability of a molecule can be enhanced by increasing the solubility, permeability, or both. The number of poorly soluble compounds is estimated to be 40% of molecules on the market, however more than 70% of drugs in development are classified as poorly soluble.[1,2]

Technologies utilized to enhance solubility, and thus bioavailability, include softgel, spray drying, hot melt extrusion (HME), and particle size engineering. A challenge in optimizing the solubility of a molecule is that it usually requires a multi-factorial approach to:

- Optimize the API
- Optimize the Formulation
- Select & Optimize the Processing Technology
- Develop the Desired Marketed Product Form (Tablet, Capsule, etc…)

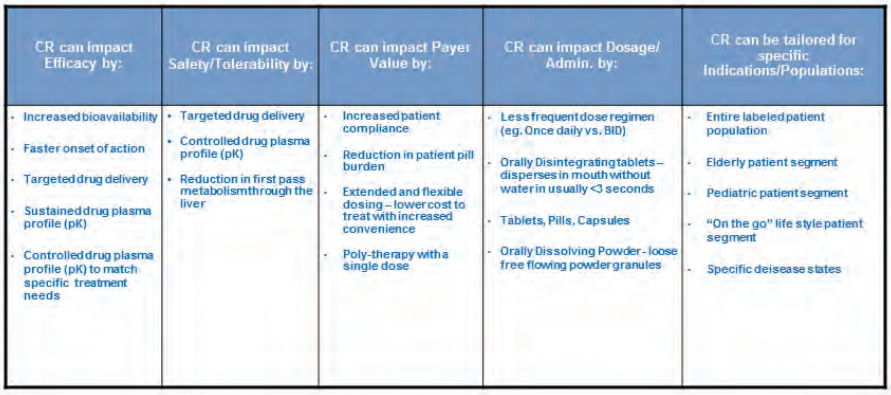
In many cases, the impact on resulting solubility is co-dependent across these factors. Catalent has been an industry partner for over 75 years enhancing bioavailability of drugs with its softgel technology. To address the growing need to provide both deep technology expertise and broad integrated services to optimize bioavailability, Catalent has established and built OptiMelt™, a unique capability to formulate, develop, and commercialize HME processes and integrate these into differentiated dosage final forms.

OptiMelt, combined with OptiForm™ molecule salt form screening, 75 years of heritage with Softgel technology, and leading expertise in downstream final dose forms, such as tablets, capsules, and granules in stick

FIGURE 2

Examples of OSDrC OptiDose innovative tablet types and forms.

FIGURE 3



CR can impact Efficacy by:	CR can impact Safety/Tolerability by:	CR can impact Payer Value by:	CR can impact Dosage/ Admin. by:	CR can be tailored for specific Indications/Populations:
• Increased bioavailability • Faster onset of action • Targeted drug delivery • Sustained drug plasma profile (pK) • Controlled drug plasma profile (pK) to match specific treatment needs	• Targeted drug delivery • Controlled drug plasma profile (pK) • Reduction in first pass metabolism through the liver	• Increased patient compliance • Reduction in patient pill burden • Extended and flexible dosing – lower cost to treat with increased convenience • Poly-therapy with a single dose	• Less frequent dose regimen (eg. Once daily vs. BID) • Orally Disintegrating tablets – disperses in mouth without water in usually <3 seconds • Tablets, Pills, Capsules • Orally Dissolving Powder - loose free flowing powder granules	• Entire labeled patient population • Elderly patient segment • Pediatric patient segment • "On the go" life style patient segment • Specific deisease states

Controlled release applications and innovative dose forms - impact on therapeutic profiles and product attributes.

packs, provides pharmaceutical innovators with a holistic integrated solution to formulate, process, and commercialize poorly soluble drugs.

CONTROLLED-RELEASE TECHNOLOGIES: THE BENEFITS OF IMPROVED THERAPEUTIC PROFILES TO PATIENT & PAYERS

Controlled-release technologies and innovative dose forms can be applied to new molecules and life cycle management opportunities across the pharmaceutical and consumer health industries to address a multitude of patient, physician, and/or payer needs. Figure 3 summarizes how application of controlled-release technologies or alternative dose form technologies can widely enhance numerous product profile attributes in a variety of ways.

CASE STUDY: DOSE FORM IMPACT ON THERAPEUTIC PROFILES

Orally disintegrating tablet (ODT) formulations are well suited for delivering better treatments to specific patient groups, such as geriatric and pediatric populations, and also specific therapeutic disease states in which patients have difficulty swallowing pills, or if they require the convenience of immediate treatment and don't have access to water to assist in pill or capsule dosing.

Catalent was a pioneer in the ODT space with its best in class Zydis® platform. Zydis ODT tablets disintegrate in the mouth almost instantaneously (usually in less than 3 seconds) without the need for water. Zydis ODT tablets have been formulated and marketed to deliver better treatments across a wide variety of therapeutic indications, examples include pain, CNS, emesis (nausea), allergy, GI GERD, motion sickness, diarrhea, epilepsy, and Parkinson's disease.

Selegiline is an anti-Parkinson's therapy. When initially developed, conventional selegiline tablets were taken more than once daily, had suboptimal efficacy for patients, and presented a safety issue due to metabolite formation resulting from liver metabolism. Subsequently, selegiline was developed in a Zydis ODT fast-dissolve formulation. In this dose form, the active is adsorbed buccally (in the oral cavity), which avoids first-pass liver metabolism and thus is a more efficacious and safe dose form. An additional benefit was reduced (one daily) dose frequency. Figure 4 summarizes the therapeutic profile benefits of the Zydis ODT dose form versus traditional tablets/capsules for selegiline.

A study of longitudinal patient records at Catalent Pharma Solutions supports the theory that drug delivery technology can also improve patient medication compliance. A 1-year study compared the compliance rates of Zelepar (Zydis ODT fast-dissolve tablets) to standard selegiline tablets. Results showed a 98.5% compliance rate with the ODT formulation compared to 81% with the standard oral treatment in US Medicare patients - a 22% compliance improvement to prescribed treatment, shown in Figure 5.[4]

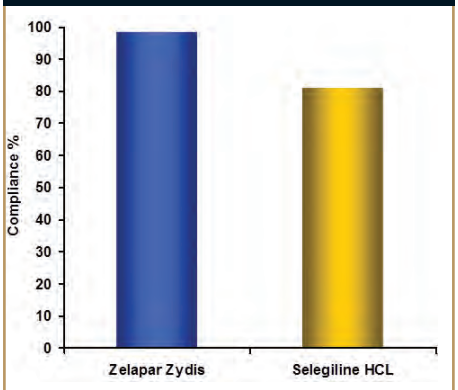
FIGURE 4

Selegiline vs. Zelapar® Fast-Dissolve Tablets

	Tablet/Capsule Selegiline (traditional formulation)	Zelapar formulated with Zydis fast-dissolve (innovative formulation)
Lower Dose and Less Frequent Dosing	5-mg doses, taken twice a day (BID). Pill or capsule that must be swallowed.	1.25-mg or 2.5-mg doses, taken once a day (QD). Tablet that dissolves in mouth within seconds, without water.
Increased Bioavailability/Faster Onset of Action	Tmax=1 hour. Digested in the gut, absorbed through the small intestine, processed by the liver.	Tmax=15 minutes. Innovative transmucosal drug delivery absorbed rapidly through the lining of the mouth directly into the blood.
Lower Side Effect Potential	Processed through the liver, producing undesired metabolites.	Significantly by-passes the liver, producing lower undesired metabolites.

Improved therapeutic profile attributes of Zelapar® Zydis fast-dissolve formulation.[3]

FIGURE 5



Zydis® ODT fast-dissolve patient compliance improvement compared to traditional tablet formulations.

SUMMARY

Controlled-release technology and unique dose form applications transform drugs into better treatments at all stages of development and life cycle management - through improved therapeutic profiles.

Increasing constraints to developing new therapies has necessitated innovation from solution providers. Catalent's recent introduction of OSDrC OptiDose technology provides optimized dosing and controlled-release applications, and the expansion of OptiMelt gives new solutions to enhance drug bioavailability. These new technologies complement established solutions, such as coating and granulation and the Zydis Fast Dissolve Platform.

Elegant dose forms and innovative controlled-release solutions are now required to ensure commercial success through increased product performance, patient compliance, and convenience, which deliver differentiated value to patients, physicians, and payers. ◆

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4. 12-month longitudinal patient records analysis conducting by SDI Health, a division of IMS Health, conducted in January, 2011. Study included 1,520 US patients prescribed Zelapar, Eldepryl, or generic Selegiline.

BIOGRAPHIES

Steve Hamlen has 20 years' experience in the life sciences industry, including Hoffmann-La Roche and Johnson & Johnson. While at Johnson & Johnson, he held various strategic marketing and product management positions, leading global teams in the creation and execution of new molecular entities and life cycle management commercial strategies. This included the development of differentiated product profiles for numerous new products, line extensions, and licensing opportunities across multiple therapeutic areas. During his time at Hoffmann-La Roche, he was an Engineer in the vitamins new product forms group, where he was responsible for developing new vitamin and antioxidant formulations, and technology transfer from laboratory to production. His experience transcends emulsification, milling, granulation, spray drying, fluid bed drying, and tableting. Mr. Hamlen earned his BS in Chemical Engineering and his MBA from Lehigh University. He is currently a Global Group Product Manager in Catalent Pharma Solutions' Advanced Delivery Technologies business, leading teams in the launch of new technologies and identification of new opportunities for OSDrC® OptiDose™, OptiMelt™ hot melt extrusion, and controlled-release technologies.

Dr. Nick Johnson joined Catalent Pharma Solutions in March 2012 as Strategic Marketing Director for the Advanced Delivery Technologies business unit. His core focus is on driving the business' global marketing strategy to achieve growth and geographic expansion while introducing new technologies. Prior to joining Catalent, Dr. Johnson was Head of Strategic Marketing for SAFC Small Molecule Contract Manufacturing Services, where he was responsible for the development of strategic business plans and commercial initiatives and the positioning and integration of eight manufacturing sites. Dr. Johnson began his career in 1994 as Senior Research Scientist for Chiroscience plc and ChiroTech and after 5 years, moved on to the role of Project Manager for the company's portfolio of catalyst technologies and generic APIs. Following the company's acquisition by Dow in 2001, Dr Johnson spent 7 years as Business Development and Marketing Manager with Dowpharma, where his role included market analysis and development of product strategies for pharmaceutical customers; in-licensing of enabling chemical and biochemical technology from industry and academia; technology out-licensing to major pharmaceutical companies; and commercial contract negotiations at senior levels in global pharmaceutical and biotech companies. When Dowpharma's small molecule business was acquired by Dr. Reddy's, he spent 3 years as Commercial Director of the company's Custom Pharmaceutical Business. Dr. Johnson earned his MBA in Business from Imperial College, London, and his BSc in Chemistry and PhD in Organic Chemistry at University of Manchester Institute of Science and Technology.

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INTRADERMAL DELIVERY

Advances in Intradermal Drug Delivery

By: Zach Marks, MS, RPh

INTRODUCTION

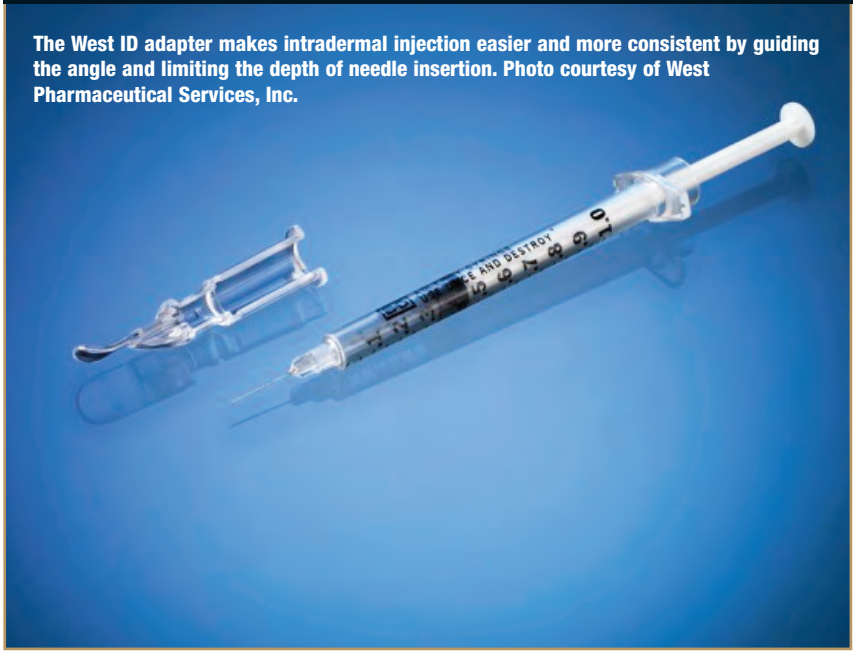
Vaccines have helped reduce the instance of infectious diseases around the globe, nearly eradicating past plagues, such as smallpox and polio, and reducing preventable infections to the point where few people experience the effects of measles, pertussis, and other illnesses.[1] While no vaccine is 100% effective, the incidence of infectious diseases continues to decline. Although a variety of options for vaccine delivery exist, including intramuscular (IM), subcutaneous (SC), nasal, oral, and transcutaneous methods, recent advances have helped improve the efficacy of vaccine delivery through intradermal (ID) injection.

Currently, IM or SC injection through the use of needle and syringe is the most common method of vaccine delivery, with many of the vaccines on the market using this mode of delivery. However, the skin contains a high concentration of antigen-presenting cells, making it an ideal location for injection. These cells perform an essential role in processing incoming antigens, resulting in powerful immune system responses. Delivery of vaccines to the epidermis or dermis may result in superior immune responses when compared to IM or SC injections.[2] In addition to the enhanced immune response in patients, ID delivery offers a variety of benefits to pharmaceutical manufacturers, including dose sparing, increased availability of limited or expensive antigens, and reduced cost per dose.

Unfortunately, the current method of ID delivery can be difficult to master. ID injection is typically administered using the Mantoux technique, which requires special training and may not effectively target the skin resulting in delivery to the SC tissue or leakage. Developed by Charles Mantoux in the early 20th century, this method requires that healthcare practitioners master inserting a needle at a 5 to 15 degree angle approximately 1 mm deep into the skin to inject the vaccine effectively.[2] When the injection is performed correctly, a bleb or wheal of 6 to 10 mm in diameter is formed on the skin, indicating the vaccine has been delivered to the dermal space. The bleb goes away after a few minutes as the vaccine is dispersed and absorbed into the surrounding tissue. The difficulty associated with training and the inconsistency of injection efficacy have deterred medical practitioners from using ID injection as a common immunization method.

Alternative methods of ID administration are now being studied to

FIGURE 1



The West ID adapter makes intradermal injection easier and more consistent by guiding the angle and limiting the depth of needle insertion. Photo courtesy of West Pharmaceutical Services, Inc.

help provide the market with a simple, reliable method of ID injection. Novel delivery devices may aid needle/syringe injection, while jet injection, transdermal patches, and micro-needles offer new options to patients and caregivers. Clinical studies have been conducted on ID delivery for a variety of illnesses, including influenza, hepatitis B, hepatitis A, polio, measles, yellow fever, and more.[2] There are several therapeutic cancer vaccines using dendritic cells delivered by ID injection. Intradermal delivery of DNA vaccines combined with electrophoresis have been shown to enhance delivery.[3] For researchers conducting clinical trials using Mantoux ID injection, there is the additional question of whether the lack of efficacy is due to the vaccine or the injection technique. The advantages of ID injection, coupled with advances in ID administration technology, can help make this method a more desirable route of administration for future vaccines.

A DIFFICULT ROAD: CAN ADVANTAGES OF ID INJECTION OUTWEIGH DIFFICULTY OF DELIVERY?

Although there are more than 95 clinical studies using ID injection as a delivery method currently underway, barriers still exist to the use of ID injection.[4] While the US, Europe, and other developed countries have private insurance and/or government funding in place for vaccination and rely on single-dose formats, emerging markets tend to favor multi-dose formats and are limited by cost and availability of supply. In addition, most vaccines on the market today require cold chain storage and distribution, placing an added burden on limited resources in the emerging markets or the limited refrigerator space at the healthcare provider. Loss of efficacy can result if the vaccine is not maintained at 4°C.

Clinical trials are tasked with optimizing the ID dose by comparing different size doses (antigen and volume) and demonstrating that the immune response is comparable to IM or SC injections. Regulatory considerations must also be taken into account, particularly if a pharmaceutical manufacturer needs to develop a new formulation, primary package, or device for the vaccine formulation.

However, the benefits of ID injection may outweigh other considerations. Not only does ID injection offer pharmaceutical companies a way to differentiate their product, it also provides an opportunity to reduce the cost of each dose through dose sparing. With ID injection, a reduced dose may be able to produce the same immune response as from a comparable IM/SC dose. This dose sparing results in reduced cost per dose and a reduced volume of the vaccine in the cold chain. Such a reduction can help to increase the amount of antigen available, making it more accessible in the global market, while reducing the cost associated with cold chain storage needs.

Additionally, ID injection may help improve vaccine efficacy in hard-to-treat populations, including the elderly (due to immunosenesence) and infant populations (due to immature immune systems), which typically cannot receive standard vaccines.[4,5] ID injection in these populations can help overcome low immunogenicity to standard vaccine dosages and routes of administration.

DELIVERY SOLUTIONS

More than 200 years ago, vaccines were delivered by creating small holes in the skin.[2] However, poorly controlled dosing, sterility concerns, and inefficient use of the vaccine had the industry seeking a new solution. Today, a variety of options for ID delivery exist in addition to the most popular method of needle injection using the Mantoux method. Options include syringe-based micro-needles; patch injections; coated, hollow, or dissolving micro-needles; and jet injectors, as well as delivery devices, such as adapters that can be used to aid ID delivery. Each of these methods offers pros and cons when it comes to ID delivery.

Use of a needle or syringe requires no specialized equipment, but training in the Mantoux method can be difficult. Patch injection devices do not use a conventional needle, so the injection itself may be less invasive and painful, as well as easier to administer, for patients. However, this method may require a reformulation of current vaccines, which may be time consuming for pharmaceutical manufacturers requiring process development and new regulatory submission.

Jet injection provides a needle-free technology that can eliminate reuse of needles and cross-contamination if auto-disable cartridges are used. Unfortunately, jet injection devices can be expensive, and require a substantial capital investment. Not all markets will have the resources to purchase this type of device. Additionally, there will still be pain on injection for the patient as the liquid is pushed into the skin at high pressure.

Adapters, including the ID Adapter from West, can provide a guide for injection when using a syringe system. The device fits over a conventional hypodermic needle and syringe and precisely controls the angle and depth of needle penetration into the ID layer. The ID adapter offers healthcare professionals a simple way to perform an ID injection, without the need to reformulate their vaccine. Use of an adapter can offer greater confidence that the healthcare provider has administered the vaccine into the correct space.

RECORDS OF SUCCESS: ID USE FOR RABIES VACCINES

Around the world, more than 17.4 million people are exposed to rabies through animal bites each year. Occurring in more than 150 countries and territories, rabies is a viral disease that can cause encephalitis when transmitted to humans. If not treated, rabies is 100% fatal, and has caused more than 55,000 deaths annually, with the highest incidences occurring in Africa and Asia.[6]

Traditional vaccinations for this deadly disease include a pre-exposure vaccination that consists of three full intramuscular doses of cell-culture or embryonated-egg-based vaccine. Dose size is either 1 mL or 0.5 mL based on the type of vaccine used. The doses must be given 7 days apart, although minor variations in the timing will not prohibit immunization. Modern rabies vaccines are well tolerated, but cost can be a factor in determining whether or not a patient receives pre-exposure vaccination. To help reduce the cost of cell-derived vaccines for pre-exposure rabies vaccination, ID vaccinations can be used. The administration regimen consists of 4 doses of 0.1 mL over the course of 28 days.[7] While the ability to administer the dose requires more specialized training, the cost savings may encourage greater use of the pre-exposure vaccination.

The Intradermal Rabies Vaccine (IDRV) was approved for use in developing countries by the World Health Organization (WHO) in 1992. Often, developing countries face issues of vaccine shortage and lack of funding, and the cost of post-exposure prophylaxis (PEP) can be prohibitive. Intradermal regimens for rabies post exposure, the Thai Red Cross two-site regimen and the eight-site regimen, are currently recommended by the WHO. However, a four-site regimen has been evaluated that reduced the cost of PEP by more than 60%, when compared with the standard IM injection regimen (Essen). The four-site regimen also reduced the number of patient visits required when compared to the Thai Red Cross method, and offers convenience over the eight-site regimen. These ID regimens, which were first endorsed by WHO's Strategic Advisory Group of Experts on Immunization in 2007, offer a cost-effective alternative to traditional intramuscular administration while providing effective and safe immunization.[7]

For post-exposure prophylaxis, IM vaccination should consist of either a five-dose (the Essen regimen) or four-dose regimen. Intradermal administration of a cell-culture and/or embryonated-egg-based vaccine has been successfully used in a much reduced dose: 0.1 mL for purified Vero cell rabies vaccine and 0.1 mL for purified chick embryo rabies vaccine.[8]

In addition, a study conducted by the Chinese University of Hong Kong has found that ID administration of human papillomavirus (HPV) vaccines may be dose-sparing and cost-saving. The study assessed Cervarix® and Gardasil® administered either intramuscularly or intradermally, in different doses (full-dose or reduced to 20%) by different methods. The study concluded that ID administration of the vaccines not only increased the immune reaction, but also maintained safety while being tolerated well by the test subjects. The study suggests that further evaluation of ID HPV vaccination in areas with limited resources should be undertaken.[9]

For countries that face a shortage of vaccine, cold chain capability, or funding, the ID route provides an ideal alternative for administration that not only reduces cost, but also provides convenience for patients while maintaining optimum efficacy and safety. While the training required to administer can be significant, the aforementioned alternatives, including adapters and other delivery solutions, may help to increase the use of the ID injection as an alternative across the globe.

SUMMARY

Efficiency of vaccine use will be critical as the world population continues to grow and vaccine prices continue to rise. ID administration can help reduce dose cost while potentially improving immunogenicity in traditional and hard-to-treat populations. Advances in delivery systems have made consistency of administration into the

intradermal layer possible without advanced training requirements and with minimal disruption to the pharmaceutical manufacturer. As more vaccine options reach the market, and costs continue to rise, ID administration may provide an excellent alternative to traditional vaccination without reducing the immune response. ◆

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BIOGRAPHY

Zach Marks joined West in 2002 as Business Development Manager for the Clip'n'Ject reconstitution system. From 2003 to 2007, Mr. Marks held the additional position of Senior Account Manager covering strategic accounts, such as Amgen and Baxter BioScience. In 2007, with the acquisition of Medimop Medical Products, he was chosen for the position of Marketing and Business Development Manager for the group. During his tenure, his leadership and market knowledge helped expand the business into new accounts, products, therapeutic areas, and geographies. In 2010, Mr. Marks was appointed Director, Strategic Marketing and Innovation within the Delivery Systems Business Unit, where his combined experiences have been instrumental in establishing the marketing structure, function, and resources that have resulted in consistent growth of revenue and profitability. In 2012, in recognition of his contribution to the organization, his role was expanded to include business development and support of delivery system activities in Asia. Mr. Marks has prior experience including sales, marketing, and management roles with Johnson and Johnson and Waters Corporation. He is a registered pharmacist with a BS in Pharmacy and an MS in Pharmaceutical Science from Rutgers University.

SPRAY-DRIED DISPERSIONS

Efficient Scale-Up Strategy for Spray-Dried Amorphous Dispersions

By: Devon DuBose, Dana Settell, John Baumann

ABSTRACT

The increase in low-solubility drugs coming out of discovery labs has fueled the need for new formulation and processing approaches to address bioavailability challenges. Amorphous dispersions, manufactured using spray-drying and hot-melt extrusion, have emerged as a platform technology for mitigating bioavailability challenges. Spray-drying offers particular flexibility in formulation, because it allows use of polymers with high melting temperatures and offers rapid drying kinetics. The availability of small-scale spray-drying equipment and analytical techniques makes it possible to conduct feasibility and process-development work in a bulk sparing manner. In addition, the spray-drying process can be efficiently scaled from milligram to metric ton quantities and has demonstrated commercial viability, making this process broadly applicable in the development and commercialization of amorphous dispersions.

Previous articles contributed by Bend Research have focused on amorphous-formulation selection and phase-appropriate formulation and process development approaches.[1,2] This paper is focused on scale-up methodology for spray-dried dispersions (SDDs). Two critical focus areas guide scale-up: (1) atomization of the feed solution into droplets and (2) droplet drying. The following describes these focus areas and methodologies for efficient scale-up of the spray-drying process while maintaining the critical-to-quality attributes (CQAs) of the SDD.

INTRODUCTION

To identify a robust operating space during scale-up, an understanding of key spray-drying process parameters and their relationship to the critical-to-quality attributes (CQA) of the SDD is paramount. Specific formulation and process knowledge gained early in the feasibility and development lifecycle can be used to guide development studies and risk assessments that facilitate identification of SDD CQAs. Some common SDD CQAs and the rationale for their criticality are described below.

Particle Size impacts powder handling and tableting and can impact performance, particularly for highly lipophilic compounds where this attribute can be linked to dissolution rate.[2]

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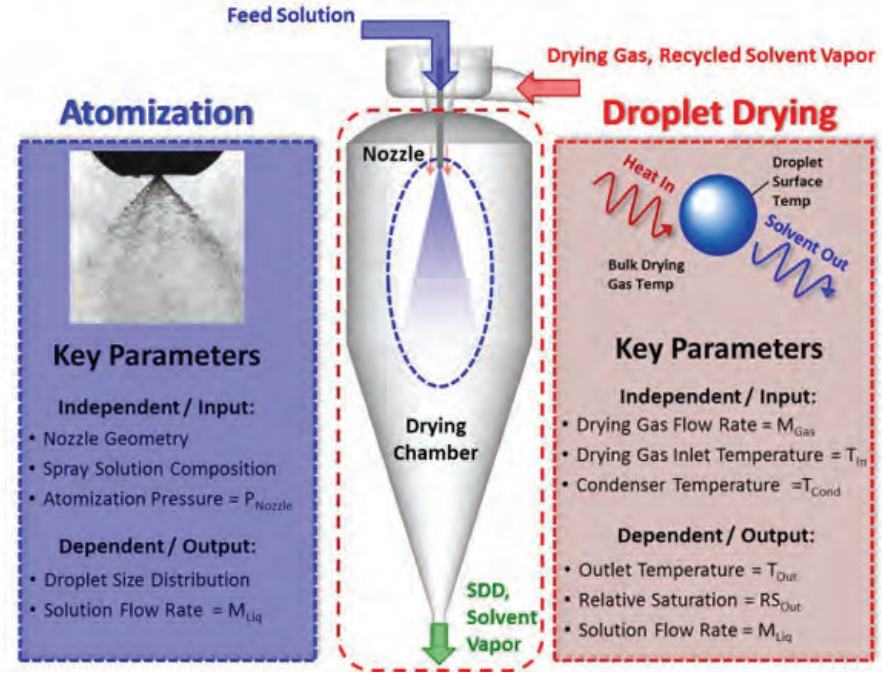
Physical State can impact performance and physical stability of the formulation.

Residual Solvent Remaining in SDD can impact the physical stability of the formulation prior to secondary-drying operations.

The attributes of the functional excipients (eg, polymers or surfactants) and other raw materials may result in additional SDD CQAs. For brevity, we will focus on process-related SDD CQAs in this article and not address attributes related to raw materials.

The main goal of scale-up is to ensure that the SDD CQAs are optimized and do not change as larger-scale spray-drying equipment is used and throughput is increased. It is essential to select a robust formulation early in development and to conduct early process-development work with consideration to scale effects. Small-scale experiments, computer simulations, and scale correlations, coupled with risk assessments and process-development experience and knowledge, form the basis of any scale-up strategy and provide a fundamental approach for process-space definition.

FIGURE 1



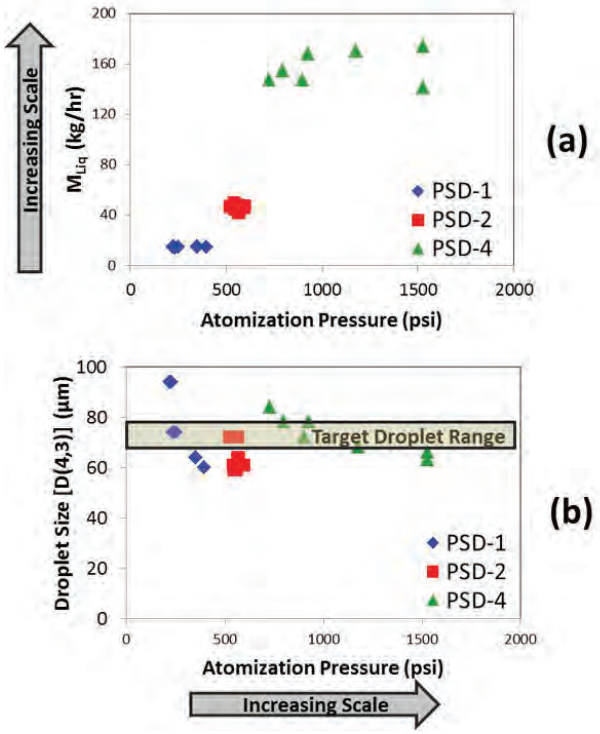
Key control volumes of the spray-drying process and process parameters that define SDD CQAs.

A general SDD manufacturing process consists of five steps: (1) solution preparation, in which the drug and excipients are dissolved in appropriate solvents; (2) atomization of the spray solution; (3) primary drying of the atomized droplets in the spray chamber; (4) collection of the SDD particles via cyclone; and (5) secondary drying to reduce the residual solvent to acceptable limits.

If the equipment is well understood and carefully designed and selected, SDD CQAs are typically defined during the atomization and primary droplet drying steps. Figure 1 outlines the key control volume and spray-drying parameters for SDD CQAs. As the figure shows, the liquid spray solution is atomized into a fine spray, consisting of droplets with high surface area, which enables rapid evaporation of the spray solvent. Hot drying gas (typically nitrogen due to the flammability of common spray solvents) contacts the droplets as they are formed, providing the energy source for evaporation and droplet drying.

The scale-up methodology presented here outlines tools and concepts to achieve the target droplet size and drying kinetics from liquid droplets to dried particles across scales. This methodology assumes that the optimal equipment configuration for SDDs (ie, a tall-form spray dryer with gas disperser designed for low turbulence near the nozzle and efficient cyclone collector) is employed across all scales.

FIGURE 2



Solution flow rate (a) and droplet size (b) versus atomization pressure for a pressure-swirl atomizer and PSD-1, PSD-2 and PSD-4 spray dryers.

ATOMIZATION

Atomization is one of the most critical aspects of the spray-drying process since it controls the droplet size which, combined with the spray solution composition and properties (eg, excipient selection, solution solids loading) defines the final particle size.[3] Pressure-swirl and two-fluid nozzles are generally the preferred atomization equipment for SDD manufacture. The polymeric excipients most commonly used may result in spray solutions that are viscous and film-forming, making scale-up challenging with other atomization methods.

To ensure that SDD particle size remains constant during scale-up, droplet size is matched across scales. As spray solution throughput increases with increased scale, the energy input required to maintain the target droplet size also increases. It is critical to understand this relationship early in development so that SDD particle-size targets can be selected that are appropriate for future development and scale-up. Figure 2 illustrates this relationship for a pressure-swirl nozzle atomizing a spray solution containing hydroxypropyl methylcellulose acetate succinate (HPMCAS), a common polymer used to prepare SDDs. Droplet size is shown at increasing solution flow rates for three GEA Niro spray-dryer scales. To maintain the target droplet size across a tenfold throughput increase, atomization pressures increased from 250 psi at the PSD-1 laboratory scale to more than 1000 psi at the PSD-4 commercial scale.

Although the atomization process can be difficult to model from a first-principles basis due to the complexity of the fluid dynamics involved in droplet formation, empirical correlations have been developed. The spray-solution properties critical to atomization (eg, viscosity, surface tension, density); nozzle geometry (eg, orifice diameter, swirl design); and nozzle operating parameters (eg, nozzle pressure, solution feed rate) can be correlated to predict droplet size.[4]

TABLE 1

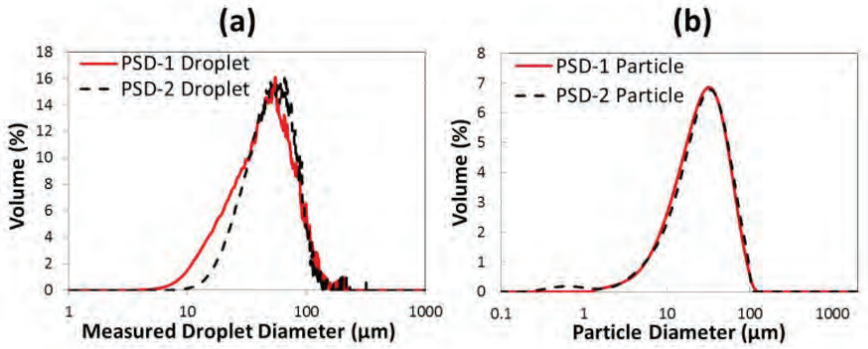
Parameter		Variable Type	Scale-up Considerations
T_{in}	Inlet drying-gas temperature	Input/Independent	Formulation-dependent chemical or physical stability constraints may limit or dictate this parameter.
M_{gas}	Drying-gas flow rate	Input/Independent	Typically held constant for specific spray-dryer scale for optimum drying-gas disperser performance.
M_{soln}	Spray-solution flow rate	Input/Independent	Maximized for optimum SDD throughput.
T_{cond}	Condenser temperature	Input/Independent	Controls the quantity of solvent vapor in the ingoing drying gas stream. Equipment constraints may dictate this parameter.
T_{out}	Outlet temperature	Output/Dependent on Inputs	Highly correlated to droplet drying rate and thus SDD density, morphology, physical state, and residual solvent.
RS_{out}	Relative solvent saturation at the dryer outlet	Output/Dependent on Inputs	Highly correlated to droplet drying rate and thus SDD density, morphology, physical state, and residual solvent. Yield constraints may dictate this parameter.

Summary of key thermodynamic process parameters.

While some literature correlations are applicable to SDD spray solutions with viscous polymers, these correlations may need to be validated experimentally or formulation-specific correlations may need to be developed. Correlations for SDD spray solutions can be developed by directly measuring the droplet size using light-scattering or refractive methods such as a phase Doppler particle analysis (PDPA).[5] Active or placebo spray solutions can be sprayed across increasing spray-solution flow rates with increasing nozzle sizes and the resulting droplet-size distributions can be measured. Specific nozzles and nozzle operating parameters can be selected to match droplet size and, thus, SDD particle size across scales.

Figure 3 illustrates the atomization scale-up methodology of matching droplet sizes across scales. Droplet size and resulting SDD particle size for an example HPMCAS spray solution is shown for GEA Niro PSD-1 and PSD-2 spray dryers. The droplet-size correlations can also be linked with correlations of droplet size to particle size and used to evaluate the criticality (and sensitivity) of spray-solution and nozzle operating parameters. In this way, a functional atomization operating space and acceptable SDD particle variance can be defined.

FIGURE 3



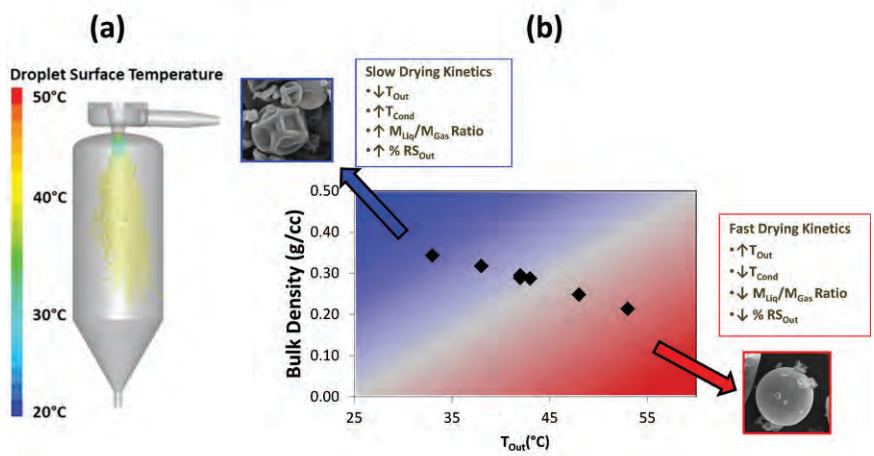
PDPA-measured droplet distributions (a) and resulting SDD particle-size distributions (b) for PSD-1 and PSD-2 spray dryers.

DROPLET DRYING

After the droplet has been formed, drying or solvent evaporation defines the physical state, morphology, density, and residual-solvent content of the SDD.[6] Similar to atomization scale-up, the primary goal during scale-up of the thermodynamic parameters is typically to match the drying kinetics or evaporation rate at which the particle forms and, thus, the physical state, morphology, density, and residual-solvent content of the SDD across scales. A methodology for matching droplet drying rates across scales is described below.

Immediately after the droplets are formed, they are quickly contacted with drying gas at the targeted inlet temperature (T_{In}). Due to evaporative cooling, the droplets rapidly cool from the ingoing solution temperature to the

FIGURE 4



CFD modeling output for droplet-surface temperatures inside the spray-drying chamber (a), showing SDD bulk density versus T_{Out} and morphology differences with slow and fast drying kinetics for an HPMCAS SDD sprayed from an acetone spray solution (b).

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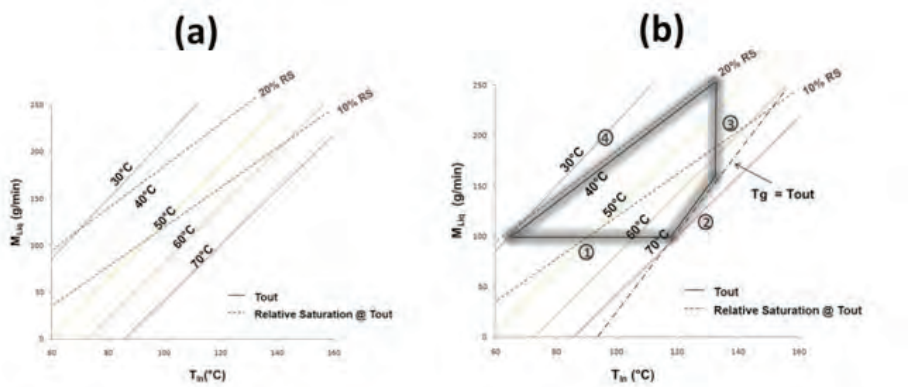
FIGURE 5



Example thermodynamic operating space showing T_{Out} and RSOut contours (a) and an exemplary formulation-specific operating space, showing ① minimum MLiq for processing efficiency, ② glass-transition temperature (T_g) of solvent-wet SDD at T_{Out}, ③ maximum T_{In} for formulation chemical stability, and ④RSOut limit for residual-solvent limits or complete drying.

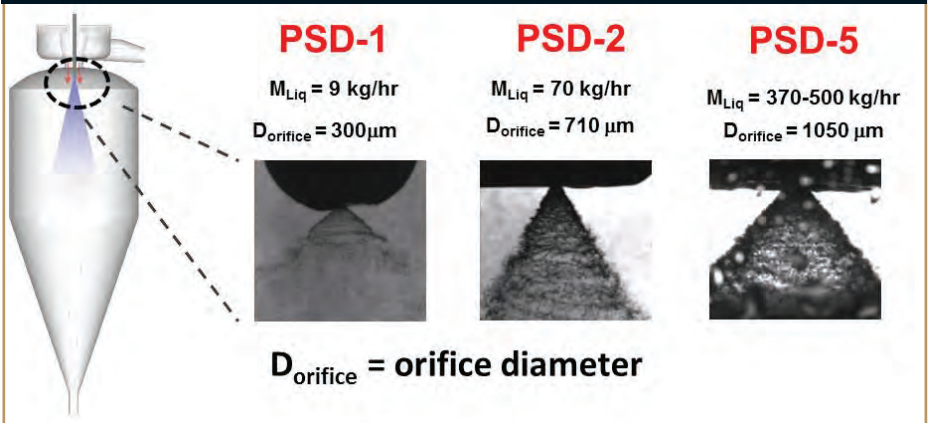
wet-bulb temperature of the solvents, up to the point at which initial solidification or skinning occurs. The timescale for skinning is typically on the order of milliseconds. After skinning, resistance to mass transfer increases dramatically and reduces the evaporation rate since the solvent must diffuse through the skin to the surface for evaporation. The temperature inside the skinned droplet increases to temperatures equivalent to the spray-dryer outlet temperature (T_{Out}).

Figure 4a shows a computational fluid dynamic (CFD) modeling output of the droplet-surface temperature profile in a spray dryer operated at a T_{In} of 125°C, T_{Out} of 55°C, and a solution temperature (TSoln) of 50°C using an acetone/water spray solvent. As the figure shows, evaporative cooling occurs immediately after the spray solution exits the atomizer, followed by an increase in temperature to T_{Out}. As Figure 4b shows, the SDD drying rate and, thus, SDD CQAs are highly correlated to T_{Out}. Drying rate is also often highly correlated to the relative solvent saturation at the dryer outlet (RS_{Out}).

The droplet drying rate is dictated by the thermodynamic process parameters, which can be related by mass and energy balances at each spray-dryer scale.[7] The key thermodynamic parameters and scale-up considerations are summarized in Table 1. The spray-drying process can be operated in a single-pass mode, in which fresh drying gas is introduced to the chamber, or a recycle mode, in which the drying gas and evaporated solvent exiting the chamber are passed through a condenser, reheated, and returned to the drying-gas inlet. Commonly, small-scale dryers operate in single-pass mode, whereas larger spray dryers operate in recycle mode. The effect of the solvent vapor in the recycled drying-gas stream must be considered since it can impact drying rate.[7] Differences in heat loss to the ambient environment also must be considered across scales, but generally heat loss becomes less significant as the scale increases.[3]

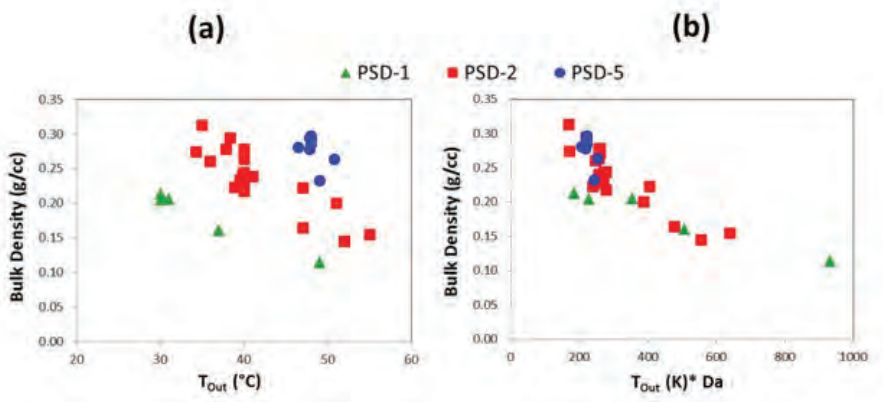
The mass and energy balance (ie, thermodynamic model) can be used to predict operating parameters at each scale. Dryer parameters can be selected to produce similar T_{Out} and/or RS_{Out} values and, thus, similar droplet drying

FIGURE 6



High-speed camera images focused on the atomizer spray plume for three spray dryers.

FIGURE 7



Use of scale factor to account for differences in spray-plume densities for three spray-dryer scales, showing bulk density versus T_{Out}, showing offsets at increasing scales (a); and bulk density versus Damköhler scale factor multiplied by T_{Out} in Kelvin (b).

rates across scales. A graphical representation of the thermodynamic model is shown in Figure 5a. Figure 5b shows an example operating space for a specific SDD, with example formulation-specific operating-space constraints. Specific operating parameters can be selected within the operating space to match T_{Out} and/or RS_{Out}.

In addition to matching T_{Out} and/or RS_{Out}, a scale factor may also be required to account for differences in droplet and drying-gas mixing efficiencies across scales.

Solution flow rate and plume density increase at larger scales, whereas droplet-to-gas mixing volumes remain relatively unchanged, resulting in decreased mixing efficiencies and slower droplet drying rates at larger scales. Figure 6 shows high-speed camera images focused on the atomizer spray plumes for PSD-1, PSD-2, and PSD-5 spray dryers with acetone-based spray solutions.

Decreased drying rates due to the droplet and drying-gas mixing efficiencies can affect SDD CQAs upon scale-up, but can be easily compensated for by adjusting the process parameters. Scale factors can be developed to define appropriate spray-drying parameters to account for the slower droplet drying. Aided by computational models, dimensionless terms that relate mass- and heat- transport phenomena in and out of the droplets during the drying process are used to relate drying rates across scales.

Figure 7 shows an example of using an adapted dimensionless Damköhler number multiplied by T_{Out} (in Kelvin) as a scale factor. The adapted Damköhler number is calculated as a ratio of reaction rate (evaporation rate, in this case) to convective mixing rate (droplet and gas mixing rate, in this case). The evaporation rate can be calculated using macroscopic thermodynamic process parameters and the mixing rate can be obtained from CFD outputs. In Figure 7a, different correlations are seen with various bulk density and T_{Out} values for three spray-dryer scales, and in Figure 7b, the scale factor is applied to better correlate SDD bulk density across scales.

First-principle thermodynamic processing maps, computer models, and scale correlations are used in parallel to understand and match droplet drying rates across scales. Additionally, these same principles enhance understanding of the operating space and can be coupled with small-scale experiments to further derisk formulation- and process-related constraints. Small-scale experiments can be used to evaluate the predicted commercial operating parameters and can confirm computer-generated or virtual simulations.[8] Common examples of small-scale experiments include purposeful variation of SDD CQAs or processing at ranges outside of normal variability to challenge the process and determine the effects on SDD CQAs.

SUMMARY

Use of spray-drying to manufacture amorphous dispersions in the pharmaceutical industry is likely to continue to grow rapidly as the number of compounds that present oral solubilization challenges continues to increase. Efficient scale-up of spray-drying processes is made possible by deep understanding of the spray-drying physical situation. Off-line tools such as droplet-sizing instruments, computer simulations, thermodynamic models, and scale correlations can be used in a systematic manner to identify commercial process parameters and operating spaces without the need for extensive costly experimental runs at commercial scale. ◆

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BIOGRAPHIES

Devon DuBose is a Senior Research Engineer at Bend Research Inc. His responsibilities include spray-drying development and scale up for preclinical and clinical projects, and transferring spray-drying processes into a current Good Manufacturing Practice environment. He also has expertise with special spray-drying projects for biologics and inhalation. Mr. DuBose has been with Bend Research since 2007. He graduated with a BS in Chemical Engineering from Oregon State University and is a registered professional engineer in the State of Oregon. Mr. DuBose has three US patents pending.

Dana Settell, Vice President, oversees large, late-stage manufacturing and engineering programs at Bend Research. Formerly, she was Director of Business Development. In addition, in a previous position as Director of Operations at the company's current Good Manufacturing Practice (cGMP) facility, she assisted with the installation, commissioning, start-up, maintenance, validation, and operation of a PSD-2/FSD-4 spray-dryer. Ms. Settell has extensive experience with scaling up drug production from development through commercial production. She was instrumental in the start-up of a $90-million commercial plant in Ireland to manufacture spray-dried dispersion (SDD) technology at the metric ton scale. Ms. Settell earned her BS in Chemical Engineering from the University of Colorado. She holds two US patents and has two publications to her credit.

John Baumann is the Director of Spray-Dried Particle Engineering at Bend Research, where he has worked since 2004. Mr. Baumann manages a spray-drying process-development group focused on the preparation of pharmaceutical intermediates and the scale-up and transfer of spray-drying processes from research laboratories to production in a current Good Manufacturing Practice (cGMP) environment. He earned his BS in Bioengineering from Oregon State University.

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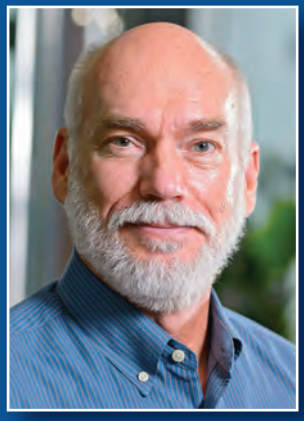

James D. Pipkin, PhD
Senior Director, New Product Development
Ligand

Ligand owned, Captisol® is a patent-protected, chemically modified cyclodextrin with a structure designed to optimize the solubility and stability of drugs. Captisol was invented and initially developed by scientists in the laboratories of Dr. Valentino Stella at the University of Kansas' Higuchi Biosciences Center for specific use in drug development and formulation. Captisol has enabled six FDA-approved products, including Onyx Pharmaceuticals' Kyprolis®, Baxter International's Nexterone®, and Pfizer's Vfend® I.V. There are currently more than 30 Captisol-enabled products in development, including Lundbeck's I.V. Carbamazepine, Merck's I.V. posaconazole, and Rib-X's delafloxacin intravenous program. Ligand's Senior Director of Technical Operations and Quality Assurance, Vincent D. Antle, PhD, and James D. Pipkin, PhD, Senior Director, New Product Development recently spoke with Drug Development & Delivery about how the company works closely with pharmaceutical and biotechnology companies offering drug delivery solutions that significantly improve stability, solubility, bioavailability, safety, and dosing of APIs.

Q: For our readers who may be unfamiliar with your delivery technology, can you please review Captisol?

A: Captisol is a unique reproducible mixture of polyanionic β-cyclodextrin derivatives in which a sodium sulfonate salt is tethered to the lipophilic cyclodextrin cavity by a butyl ether group, or sulfobutylether (SBE). The sulfobutyl ether (SBE) substituent is introduced at the 2, 3, and 6 positions in one or more of the glucopyranose units in the cyclodextrin structure. The introduction of SBE substituents onto the β-cyclodextrin can produce preparations with different overall average degrees of substitution due to the proportion of multiple species present with different degrees of substitution, theoretically from 1 to 21 sites for substitution. Captisol, with on average 7 such SBE substituents per β-cyclodextrin, introduced by way of a reproducible patent-protected process, was chosen as the cyclodextrin preparation with the most desirable safety profile and drug association properties.

Q: What are the applications of Captisol in drug delivery?

A: Captisol may be applied in drug delivery in many ways. The primary applications are to enhance solubility and stability. Solubility increases of tens of thousand are possible, and when combined with pH and selected salts, solubility increases of hundreds of thousands have been observed.

Stability outcomes may not always be predictable, but when they are observed they can range from protecting from precipitation or photolytic degradation to significantly improving hydrolytic stability and taking a refrigerated drug product to room temperature storage or increasing the time for 10% loss from a few weeks to a few years.

Efficacy and safety can be affected. Enhanced solubility and stability translate into enhancement of efficacy via increased dissolution rate or solubility in the lower GI, leading to greater and faster absorption, bioavailability, and more rapid onset of action. These effects mean that dosing regimens can be optimized to intensify dosing via higher available concentrations or longer infusions.

Greater bioavailability also means a lesser dose may provide the same efficacy and thus there is the potential to reduce the body's total exposure to a drug and maximize benefit to risk. Ligand has used Captisol to reformulate existing products that contain solvents with undesirable side effects and thereby unburden those products. One example is amiodarone, available for injection as a concentrate in polysorbate 80 with benzyl alcohol that requires dilution prior to administration. A marketed Captisol reformulated product, Nexterone, in a ready-to-use bag enables this product to be used in the emergency, life-saving setting, without the cardio side effects from the original vehicle and permit accurate dosing without foaming and drug loss to plastic.

Captisol has been applied in all routes of administration including parenteral routes, oral, ophthalmic, nasal, inhalation, and dermal topical routes.

Q: Does Captisol have utility in the formulation of oral dosage forms?

A: Yes. From the beginning, Captisol has been studied for oral delivery. Hundreds of articles and patents citing use have been published. The Type V Drug Master File for Captisol on file with the FDA contains oral preclinical data out to 1 year and has supported IND Safety submissions and clinical trials. Captisol has been used in dozens of clinical trials, where it was associated with a drug product administered by the oral route.

Although no oral products are yet on the market with Captisol, several orally administered Captisol-enabled® products are in active development. Many customers have or are running clinical trials with oral products. Use of Captisol in orally administered products has been shown to improve solubility and availability of basic compounds in the lower gastrointestinal tract, provide taste-masking, and eliminate variability in bioavailability due to food effects.

Q: How has Captisol been utilized in GLP toxicology studies? What role does it play in formulation development within toxicology?

A: Being a proven solubilizing and stabilizing technology designed to overcome various formulation challenges and having a proven safety record, Captisol has enabled increased systemic exposure for toxicology studies of investigative compounds and has been shown to beneficially interact with a large range of compounds. Captisol and the investigative compound may form a complex that results in greatly enhanced aqueous solubility and allows high exposures within animal dosing constraints. The formulations are suitable for both parenteral and non-parenteral routes of administration. It has also been extensively characterized in acute and chronic GLP toxicology studies. A large database characterizing Captisol effects in numerous species has been assembled and updated annually.

Captisol has an excellent clinical safety record and is currently being used as an excipient in multiple FDA-approved prescription drugs (eg, Nexterone®, Abilify®, Kyprolis®, Geodon®, and VFend®). Captisol-enabled products have been approved in more than 50 countries, and formulations in early development can lead to a seamless transition from non-clinical safety to clinical trials.

Q: What is the safety profile of Captisol as it pertains to human risk?

A: Captisol was designed for improved safety over the parent underivatized β-cyclodextrin and to extend and enhance beneficial properties while removing deleterious renal effects ascribed to native β-cyclodextrin. For Captisol, there were minor reversible histological changes observed in high-dose animal studies, but there were no significant hematological changes, ie, red blood cell damage and alteration in serum lipids, as ascribed to hydroxypropyl β-cyclodextrin.

No adverse effects were observed in human studies. Because it is renally eliminated, accumulation has been observed in some renal impaired subjects, but without any evidence of renal functional loss. In animal models, the use of Captisol has been reported to protect against renal damage due to renal toxic agents, such as methotrexate and iodinated radiopaque contrast agents. Captisol is used across a variety of therapeutic classes: CNS, cardiovascular, anti-infectives, and oncology.

Q: How has Captisol been used in ophthalmic drug delivery? What is its effect on the stability and solubility for ocular drug delivery?

A: Preclinical safety data on Captisol administered topically to the eye sufficient to enable clinical studies are included in the Type V Drug Master File on file at the FDA. Included are ophthalmic exposure studies in rabbits up to 6 months and in dogs up to 1 year. In addition, ophthalmic

use of Captisol in humans studied up to 6 months has been reported. Cytotoxicity of Captisol was judged similar to that of hydroxypropyl β-cyclodextrin in an immortalized human corneal epithelial cell line. Allergan has reported Captisol as a retinal compatible material. Captisol was reported to reduce irritation of topically administered pilocarpine prodrug.

Investigators reported success in formulating lipophilic water-insoluble drugs as aqueous eye drop solutions by using cyclodextrin complexation. They further explain that the ocular barrier to topical drug delivery into the eye consists of the aqueous tear film and lipophilic epithelium, and most drugs permeate this barrier via passive diffusion.

Cyclodextrins enhance permeation of lipophilic drugs through the aqueous tear film to the epithelial surface, increasing drug availability immediate to the lipophilic membrane surface. As in other settings, it is important to recognize when cyclodextrins are appropriate and to use an appropriate amount.

In addition, Captisol may be added to other platforms, including drug-eluting PLGA fibers, eg, SBECD ciprofloxacin. It may also be used as an additive to solubilize drugs in intraocular implants and can stabilize active agent retention in liposomes. Supersaturated Captisol based solutions of pazopanib at many thousands-fold, its native solubility have been described as an eye drop dosage form.

Q: What are some of the considerations in the methods to enhancing the complexation efficiency?

A: It is sometimes desirable to find ways to extend the benefit derived from cyclodextrins without adding more cyclodextrin or minimize the cyclodextrin content in a product. Sometimes this is due to sheer bulk, cost, or physico-chemical constraints, such as viscosity, osmolality, or volumetric size.

Many methods have been reported to enhance complexation efficiency. As previously described in the case of ziprasidone, salt formation resulted in significant improvement. Heat and ionization played important roles in formulating amiodarone as well as the drug's own aggregation or self-surfactant-like property.

Captisol, by virtue of carrying a negative charge, electrostatically attracts positively charged drugs. Hence, in addition to the host-guest mode of interaction, Captisol interacts more favorably with ionized basic compounds (a large proportion of drugs fall into this category) than neutral cyclodextrins, such as either the native cyclodextrins, alkyl or hydroxypropyl substituted cyclodextrins.

Q: What are some of the problems associated with delivery that Captisol has solved?

A: Captisol has been used to address numerous delivery issues. It has enabled parenteral dosage forms where none existed prior. Reformulation in which Captisol replaces co-solvent systems also removes their associated side effects, including phlebitis or injection site irritation, and protects against precipitation upon dilution and allows compatibility with alternative packaging to allow direct injection of concentrate or provide ready-to use diluted presentation.

Enabling an injection where none existed or converting a suspension to solution has allowed rapid onset of activity as well as increased availability and efficacy or equal efficacy at a reduced dose.

Captisol incorporated into an oral dosage form was shown to minimize bioavailability variability due to food effects and provide taste-masked oral solution. It has also enabled a combination of actives and enabled a cold-chain product to now be used at room temperature.

Q: What is the range of binding affinity of Captisol in formulations?

A: The substituent (sulfobutylether) that defines Captisol is negatively charged throughout the physiological pH range. In general, complexation with Captisol outperforms that with just beta-cyclodextrin and in almost all cases, leads to only soluble complexes. For neutral molecules and ionized acids (negatively charged species), it is not preordained which cyclodextrin, hydroxypropyl or sulfobutyl ether, provides greater affinity. On the other hand, positively charged drugs tend to demonstrate greater affinity for Captisol.

In general, complexation stability constants for the equilibrium range from a few hundred (10^2) to several 100,000 (10^5) M^{-1}. It is very rare, but there have been complexation constants reported into the several million (10^6) M^{-1} for synthetic ozonide anti-malarials with an adamantine structure.

More importantly, what does high affinity mean? In some cases, solubility has been enhanced 50,000- or more than 100,000-fold or stability significantly improved from days or months to years. Even interactions characterized by stability constants less than 100 M^{-1} can produce desirable solubility and stability benefits.

Q: Where and by whom is Captisol manufactured and to what standard is it manufactured?

A: The modified β-cyclodextrin, sold under the name Captisol has successfully enabled six FDA-approved parenteral products along with numerous other parenteral products in late- stage development. Categorized as a functional excipient, Captisol is supported by Type IV and Type V (over 60 volumes) Drug Master Files in the US and a Type III DMF with Health Canada. It is manufactured under cGMP through an exclusive contract with Hovione FarmaCiencia SA on a multiple metric ton scale. For more than a decade now, Captisol has been commercially available and manufactured via patented processes and now incorporates additional patented processes that have improved its purity and morphology. In 2012, a USP NF monograph was approved for Captisol, Betadex Sulfobutyl Ether Sodium, which further defined microbial and endotoxin limits as well and Captisol substitution distribution or fingerprint. ◆

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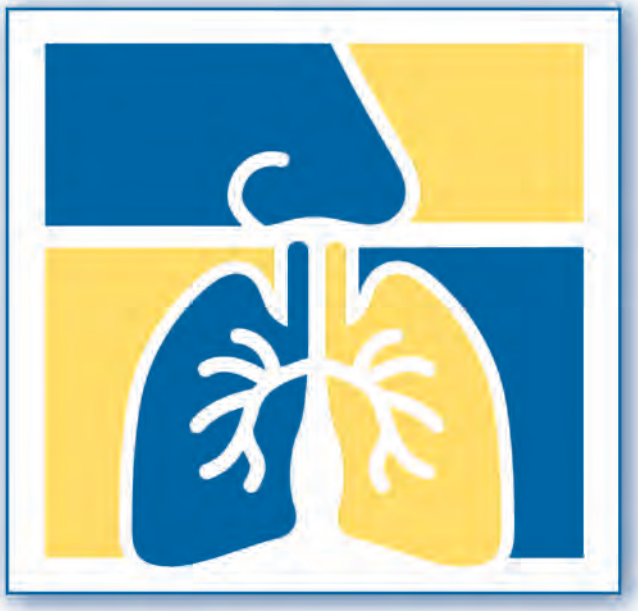

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By: Edward T. Maggio, PhD

INTRODUCTION

Since the discovery of insulin and its therapeutic application to the treatment of diabetes early in the 20th century, proteins and peptides have held enormous attraction as potential therapeutic agents. Many peptides demonstrate high potency and selectivity while exhibiting essentially no chemical toxicity as they metabolize to naturally occurring amino acids. In spite of the many attractive aspects of peptides and proteins as potential therapeutics, their susceptibility to denaturation and hydrolysis in the gastrointestinal tract has necessitated administration by injection, and this remains their major shortcoming as drugs. As a result, while the range of clinical indications for therapeutic peptides and proteins is substantial, the actual number of such therapeutics in general use today, though growing, is quite small compared with the number of chemically synthesized orally bioavailable small molecule drugs.

Literally dozens of excipients have been tested as potential enhancers of transmucosal absorption in the hope that alternate non-invasive means of administering peptides and proteins might be achieved. Some examples are shown in Table 1. The majority of these excipients have proven to be damaging to mucosal tissue upon repeated administration, especially at concentrations high enough to achieve a substantial degree of transmucosal absorption enhancement. The few exceptions, which include chitosan, various cyclodextrins, EDTA, and propylene glycol, have been found to be generally well tolerated, but not substantially effective as absorption enhancers.

Certain alkylsaccharides were found by scientists at the University of Alabama Medical Ctr., Birmingham, to significantly increase transmucosal absorption of peptides and proteins up to about 30 kDa in size, as well as poorly absorbed small molecule drugs, allowing non-invasive delivery via the intranasal, oral, and buccal administration routes.[1-4]

These same excipients have been shown to effectively prevent aggregation during manufacturing and in final formulations and may serve as non-oxidizing and non-damaging replacements for polysorbates in biotherapeutic formulations.[5]

CHARACTERISTICS OF ALKYLSACCHARIDES

Alkylsaccharides composed of disaccharides and alkyl chain substituents with lengths between 10 and 16 carbons have been shown to be among the most effective transmucosal absorption enhancers for peptides, proteins, and small molecule drugs. Two classes of alkylsaccharides in particular, alkylglycosides, most notably tetradecyl- and dodecyl maltoside, and alkyl esters, especially sucrose monododecanoate (Figure 1), have been found to be particularly useful and effective, combining unmatched absorption enhancement with a high degree of safety and lack of toxicity. More recently, they have been demonstrated to be highly effective in preventing peptide and protein aggregation and stabilizing proteins against denaturation under conditions of elevated temperatures and mechanical stress.[6] The alkylsaccharides

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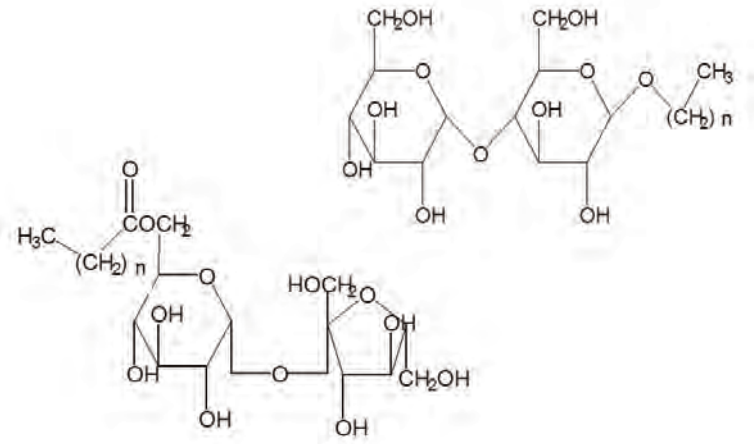
of interest happen to be designated as GRAS (Generally Recognized as Safe) substances for food applications although not specifically for pharmaceutical use.[7,8] For absorption enhancement, they function by allowing controlled transient mucosal permeation by both paracellular (tight-junction) and transcellular routes.[2,9] For aggregation prevention, they function like other surfactants in covering exposed hydrophobic sites prone to aggregation and presenting a hydrophilic face in their place. Once administered, they metabolize rapidly to the corresponding free sugars and fatty acids or corresponding long-chain fatty alcohols. The pharmaceutical grade of these alkylsaccharides manufactured under GMP in FDA-licensed facilities are designated as Intravail® or ProTek® excipients.

The general characteristics of these specific alkylsaccharides are summarized in Table 2.

FIGURE 1



NON-INVASIVE DELIVERY APPLICATIONS

Alkylsaccharides Enhance Intranasal Drug Delivery

Alkylsaccharides circumvent the two primary limitations of intranasal drug delivery experienced in the past, namely mucosal irritation and poor bioavailability, and have been shown to be highly effective in increasing systemic absorption of nasally administered drugs. Published examples of absorption enhancement for proteins ranging from 4,000 Da to 30,000 Da in preclinical studies are summarized in Figure 2.[1,2] For peptides and proteins up to approximately 20 kDa, intranasal bioavailabilities in excess of 50% compared with injection can be attained. For smaller peptides, such as calcitonin, bioavailabilities in excess of 95% are observed.

Human clinical studies conducted with PTH 1 to 31 and calcitonin, as well as with the small molecule drugs sumatriptan and diazepam yielded systemic bioavailabilities of 35% to 37% for the peptides and up to 96% absolute bioavailability for the small molecules.[10-13] Improved non-invasive systemic absorption allows drug companies to embrace the broader use of peptides as commercially and clinically viable human therapeutics and promises to offer patients new, more convenient, and more effective therapeutic options across a broad spectrum of human diseases.

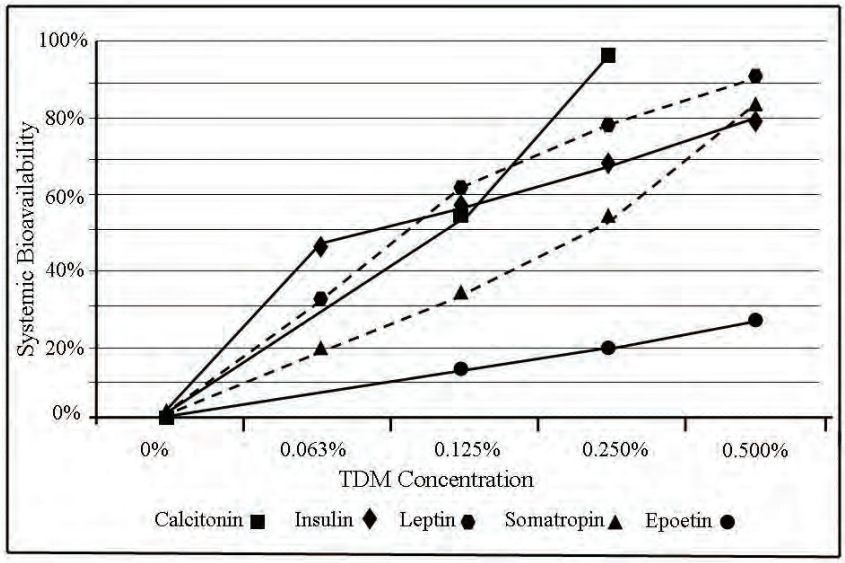
For companies with existing franchises in protein or peptide therapeutics, non-invasive formulations of existing injectables may provide a rapid path to regulatory approval and near-term increased revenues.

TABLE 1

Aprotinin	Polyoxyethylene-9-lauryl ether
Benzalkoniun chloride	Polyoxyethylene-23-lauryl ether
Cetylpyridinium chloride	Polysorbate 80 (Tween® 80)
Chitosan	Polysorbate 20
Chitosan-4-thiobutylamidine	Propylene glycol
Cyclopentadecanolide	EDTA
Methyl-beta-cyclodextrin	Sodium deoxycholate
Lauric acid	Sodium glycocholate
Lysophosphatidylcholine	Sodium glycodeoxycholate
Phosphatidylcholine	Sodium lauryl sulfate
Polycarbophil cysteine	Sodium taurocholate
Poly-L-arginine	Sodium taurodeoxycholate
Polyoxyethylene	Sodium taurodihydrofusidate

Some examples of molecules studied as transmucosal absorption enhancers.

FIGURE 2



Alkylsaccharides Enhance Oral Delivery

The use of alkylsaccharides in oral delivery of peptide drugs has only been demonstrated at the preclinical level. In studies by Grasso et al at Albany Medical College, the investigators demonstrated oral delivery of D-Leu-OB3, a linear 7-mer peptide with anti-obesity and anti-diabetes activity and octreotide, a cyclic 8-mer, with bioavailabilities in excess of 50% to 100%, respectively, compared to subcutaneous or intraperitoneal injection.[14-16] Oral absorption of exenatide and pramlintide have also been recently reported.[17,18]

BIOTHERAPEUTIC FORMULATION APPLICATIONS

Aggregation is well understood to be a key factor underlying multiple deleterious effects for peptide and protein-based therapeutics, including reduced stability or product shelf-life, reduced manufacturing yields, and most significantly, induction of unwanted immunogenicity. Neutralizing antibodies may result in decreased biotherapeutic efficacy, altered pharmacokinetics, or elimination of residual intrinsic activity of a patient's own native protein. Two of the most severe clinical examples include anti-EPO antibodies causing lethal "pure red cell aplasia" and anti-Factor VIII antibodies causing life-threatening bleeding, necessitating prolonged tolerance-inducing therapy to reverse immunity.[19-21] Other examples of clinically detrimental immune responses have been reported for beta-interferon, thrompoietin, GM-CSF, IL-17, and mAbs, including infliximab, rituximab, adalimumab, natalizumab, and TNF-specific monoclonal antibodies.

Protein aggregation is a principal cause of unwanted immunogenicity and immunogenicity of peptide therapeutics is a significant and growing concern of the FDA and EMA. In comments from the FDA Public Hearing on Biosimilars in May 2012, Richard Dolinar, MD, Chairman, Alliance for Safe Biologic Medicines stated: "Unwanted immunogenicity is the preeminent safety challenge associated with all biological therapeutics and can result in unexpected and sometimes severe adverse effects. Complicating matters, side-effects may only appear in patients after higher doses or prolonged duration of treatments and may be attributed to a number of patient-, disease-, or product-related factors." The full testimony may be accessed online at http://www.safebiologics.org/pdf/FDA/ASBM-Testimony.pdf.

Determination of the immune response of new innovator biotherapeutics and biosimilars will have significant impact on the clinical trial and regulatory approval processes. To address these problems, surfactants are routinely incorporated into many biotherapeutic formulations to prevent aggregation, improve reproducibility upon

TABLE 2

-Non-irritating to mucosal tissue
-Tasteless and odorless
-Non-mutagenic
-Non-toxic
-Single chemical species prepared under GMP
-Soluble in water or pharmaceutically acceptable oils
-Compatible with routine formulation and dispensing processes

General Intravail®/ProTek® Characteristics

reconstitution of lyophilizates, and prevent loss due to stickiness on filters, columns, and container surfaces.

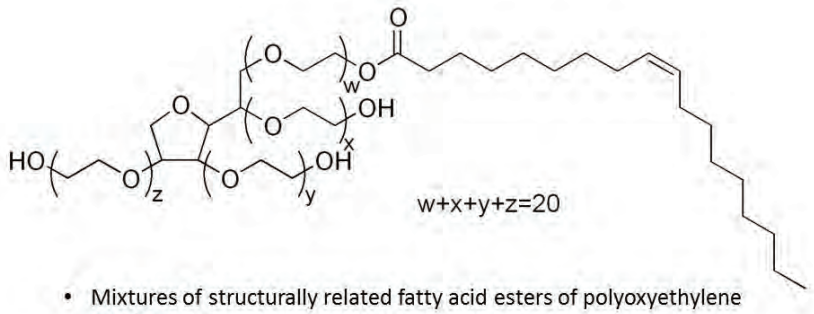
PROBLEMS WITH CURRENTLY USED SURFACTANTS

The surfactant most commonly employed in biotherapeutics today is polysorbate 80. Polysorbate 80 has proven highly effective in preventing protein aggregation; however, it is subject to certain serious limitations that are becoming increasingly apparent to formulation chemists within the pharmaceutical industry as well as regulatory authorities.

Polysorbates and other polyoxyethylene-based surfactants that contain ether linkages (polyoxyethylene moieties) and unsaturated alkyl chains spontaneously and rapidly auto-oxidize in aqueous solution to protein-damaging peroxides, epoxy acids, and reactive aldehydes. These chemically reactive species modify methionines, histidines, tryptophans, as well as any primary amines or accessible nucleophiles, such as those found in cysteine and tyrosine (Table 3), creating neoantigens that cause unwanted immunogenicity and in some instances promote re-aggregation. Unlike alkylsaccharides, which can be manufactured as pure single chemical species, polysorbates are mixtures of structurally related fatty acid esters of polyoxyethylene sorbitan. The principal fatty acids, lauric acid, and oleic acid, comprise up to 60% of the total fatty acid composition with esters of fatty acids of other chain lengths making up the remainder of the molecules.[22] In addition to the oxidative contaminants previously described, commercial polysorbate preparations contain measurable amounts of polyoxyethylene, polyoxyethylene sorbitan, and isosorbide polyoxyethylene fatty acid esters.[22-24] The structure of polysorbate 80 is shown in Figure 3. There is a great deal of lot-to-lot variation in the nature and content of oxidative species found in different polysorbate lots. For example, an analysis of 14 lots of polysorbate 80 from four different manufacturers showed a 26-fold range in hydroperoxide content (ie, from 290 nmole/g to 7,700 nmole/g; average: 1,807 nmole/g).[25] The level of reactive contaminants in polysorbate preparations varies over time as autoxidation of polysorbates is spontaneous and progressive. This variability would seem to be a likely contributor to lot-to-lot variability in immunogenicity, which may crop up in post-market surveillance - undoubtedly a potential concern for biotherapeutics manufacturers.

High purity preparations of polysorbate 80 treated to remove peroxides and packaged

FIGURE 3



- Mixtures of structurally related fatty acid esters of polyoxyethylene sorbitan.
- Polyoxyethylene chains vary in length, with the average number of total monomer moieties (W+ X+Y+Z) averaging ~ 20 for polysorbate 80.
- Lauric acid and oleic acid comprise up to 60% of the total fatty acids with other chain lengths making up the remainder.
- Common impurities include polyoxyethylene, sorbitan polyoxyethylene, and isosorbide, along with spontaneously formed oxidation products, including peroxides, epoxy acids, and aldehydes.

TABLE 3

Reactive Contaminant Species	Site of Damage
Alkylperoxides	Methionine, histidine, and tryptophan moieties
Aldehydes	Primary amines
Epoxy Acids	Accessible nucleophiles such as those found in lysine, histidine, cysteine, and tyrosine

Spontaneously Formed Oxidation Products Found in Polysorbate 80 & Affected Aminoacyl Sidechains

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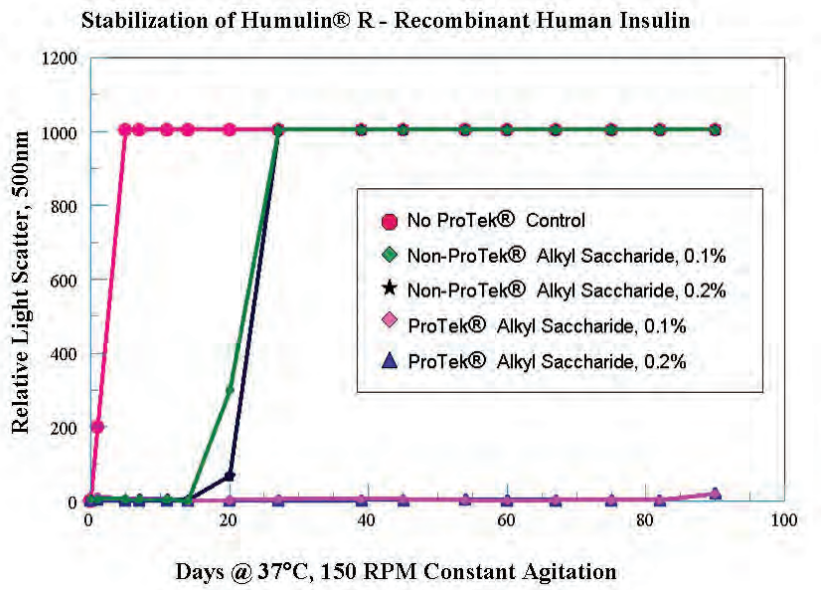
FIGURE 4



with oxygen excluded from the container headspace using nitrogen or argon are available commercially; however, oxidation resumes as soon as there is any contact with oxygen and the oxidation reaction accelerates once polysorbates are placed into aqueous solution. Typically, reactive species are detectable within 1 or 2 weeks following purification.

Measurement of residual reactive contaminants in biotherapeutic products is not meaningful because the reactive species are consumed in their reactions with the amino acyl side chains in forming neo-antigens. Thus, actual assessment of the degree of protein damage will require detection and measurement of the modified aminoacyl groups in the biotherapeutic over the course of time if it becomes necessary to assess the immunogenicity potential of each lot of a biotherapeutic prior to release into inventory.

Alkylsaccharides as Non-Oxidizing Alternative Surfactants

Alkylsaccharides afford a possible alternative and are increasingly finding their way into biotherapeutic formulation work because they are highly effective in preventing protein aggregation, but are not subject to development of contaminating oxidative species. For example, the stabilization of recombinant human insulin (Humulin®R, Eli Lilly) at two concentrations of alkylsaccharide (ProTek® excipient) is shown in Figure 4. In each case, the protein was subjected to accelerated stress by continuous shaking at 150 RPM at 37oC for up to 90 days. The untreated Humulin is seen to begin denaturing in less than 1 day of constant agitation as measured by increased light scatter - a technique routinely used to measure protein aggregation. In contrast, the ProTek alkylsaccharide excipient at both concentrations tested prevented denaturation for the full 90-day test period of the study. The non-ProTek alkylsaccharide also tested in this study (an isomer with the same sugar and alkyl chain moieties), provided limited protection up to about 2 or 3 weeks. Similarly, increased stability of human growth hormone, beta interferon 1a, beta interferon 1b, pramlintide, parathyroid hormone 1-34 and 1-31(cyclic), monoclonal antibodies, and a linear 8-mer CCR5 inhibitor prone to rapid and severe aggregation has been demonstrated.[26]

FUTURE OPPORTUNITIES & CHALLENGES

Alkylsaccharides offer exciting prospects for novel formulations, providing non-invasive delivery, stabilization, and immunogenicity reduction for biotherapeutic products. Non-invasive delivery of peptide and protein drugs will provide opportunities for broader patient acceptance and compliance with novel peptide therapeutics and may be expected to lead to an increase in the acceptance of peptide therapeutics as viable commercial pharmaceuticals.

Substitution of polysorbates with a suitable non-oxidizing alkylsaccharide surfactant could in effect yield biosimilars that are truly “biosuperior” to the corresponding polysorbate-containing innovator or biosimilar products with respect to no or low immunogenicity, increased stability, consistent and predictable efficacy,

and extended shelf-life.

As with any new excipient, there is a regulatory requirement for extensive preclinical and clinical studies to be conducted prior to regulatory approval. The extent of such studies (eg, type, duration, number of species) is determined by the FDA and depends on the mode of use (chronic or acute), frequency of dosing, and route of administration. Such studies are underway for some applications (eg, monoclonal antibodies), and we can reasonably expect that future research will be undertaken to discover additional alternatives to address the need for aggregation prevention without concomitant oxidative damage. ◆

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BIOGRAPHY

Dr. Edward T. Maggio is CEO of Aegis Therapeutics. He has been a founder and board member of seven public and private life science companies in the San Diego area and one in Copenhagen, Denmark. He earned his PhD from the University of Michigan and was an NIH post-doctoral fellow at the University of California, San Francisco (UCSF), Department of Pharmaceutical Chemistry. He is a member of the Advisory Board of the Polytechnic Institute of New York University, Department of Chemical and Biological Sciences; the University of California, San Diego, Dean's Board of Advisors for Biological Sciences; the California State University, San Marcos, Biotechnology Programs Advisory Board; and the Industry Council of the San Diego Consortium for Regenerative Medicine; the Editorial Board of the *Journal of Excipients and Food Chemicals*, and a reviewer for the journals *Diabetes, Obesity and Metabolism and Regulatory Peptides*. Dr. Maggio has edited and co-authored a number of books and scientific articles in the biotechnology area and is an author of more than 60 issued and pending US and foreign patents.

ABUSE DETERRENT TECHNOLOGY

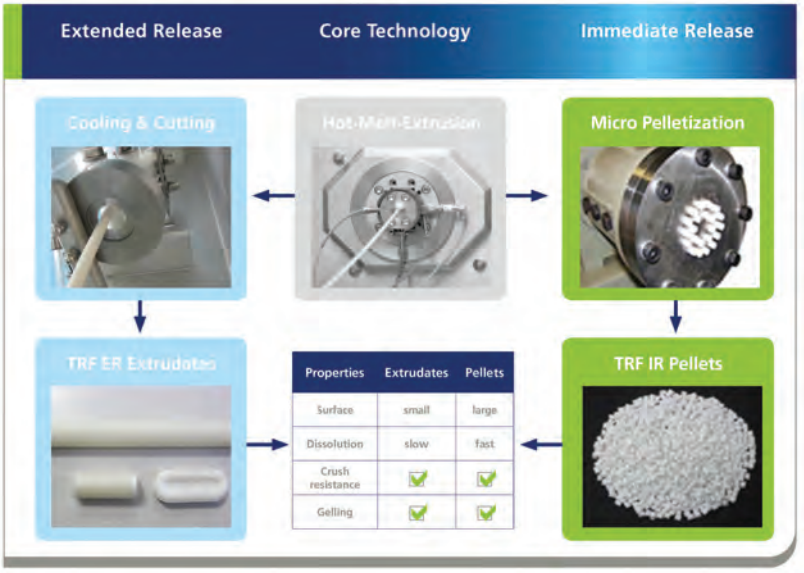
New Abuse Deterrent Formulation (ADF) Technology for Immediate-Release Opioids

By: Johannes Bartholomäus, PhD; Sebastian Schwier, PhD; Martin Brett, Hans-Jürgen Stahlberg, MD; Eric Galia, PhD; and Kai Strothmann, PhD

INTRODUCTION

Despite the recent introduction to the market of extended release (ER) opioid analgesics (re-)formulated with abuse deterrent (AD) properties, prescription opioid abuse in the US is an ongoing epidemic.[1] In reaction to these abuse deterrent formulation (ADF) products, abusers "are shifting away from the new tamper-resistant formulations to non-tamper-resistant formulations of other opioids," thus the need to turn more opioid analgesics into ADFs remains high.[2] Meanwhile, the FDA has issued the "Draft Guidance for Industry Abuse-Deterrent Opioids – Evaluation and Labeling" to define a framework for development, characterization, premarketing, and post-marketing studies for assessment of AD features.[3] In addition, the document suggests examples of labeling that may eventually be assigned to new AD formulations. The first ADFs to come to the market have concentrated on ER products as these contain significantly more active ingredient per tablet than immediate-release (IR) forms. These new ADFs predominantly apply crush-resistance technology for enhanced physicochemical properties. With reformulated OxyContin® CR (ORF in 2010), Nucynta® ER (2011), and reformulated

FIGURE 1



INTAC® manufacturing concept for ER and IR products.

FIGURE 2

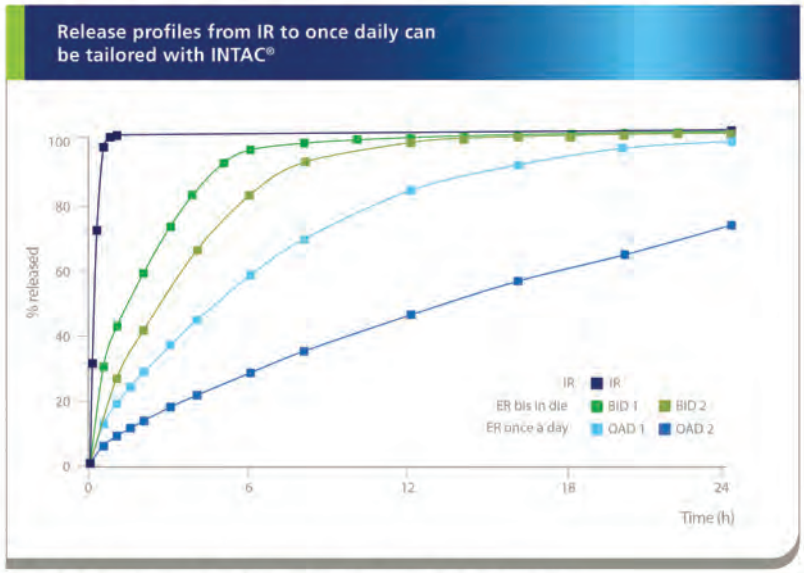


Figure 2: In vitro release profiles of INTAC® ER bid/oad and INTAC® IR formulations

In vitro profiles of INTAC® ER bid/oad and INTAC® IR formulations.

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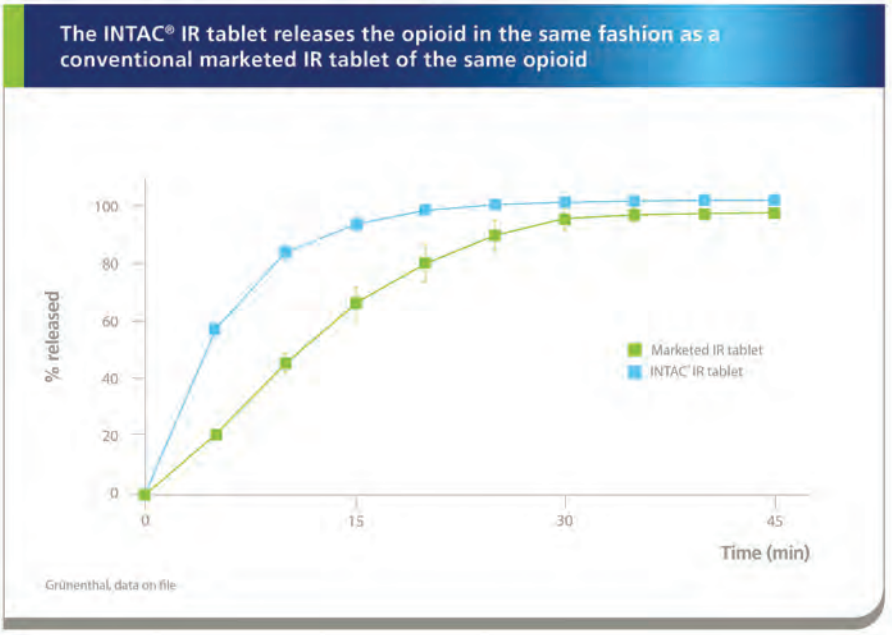
Opana® ER (CRF in 2012), three products using such technology are currently available in the US market. Significant reduction in abuse after introduction of the reformulation has been demonstrated by post-marketing surveillance data for OxyContin CR and Opana ER mainly for non-oral routes of abuse such as nasal abuse (snorting, for both products) and intravenous injections (predominantly for OxyContin CR because Opana ER intravenous abuse rates were already low).[4,5] For Nucynta ER on the other hand, such comparisons with earlier non-ADFs are not possible because this product was launched for the first time already as a crush-resistant formulation. In accordance with the aforementioned "Draft Guidance for Industry Abuse-Deterrent Opioids – Evaluation and Labeling", the FDA very recently approved the first AD labeling, which was granted for reformulated OxyContin.[6,7] This was based on the results of laboratory manipulation and extraction studies, abuse liability studies comparing drug liking of manipulated reformulated OxyContin ORF with original OxyContin and oxycodone HCl powder, and post-marketing surveillance data. "The new labeling indicates that the product has physical and chemical properties that are expected to make abuse via injection difficult and to reduce abuse via the intranasal route (snorting)."[6] The FDA determined further that the original formulation of OxyContin was withdrawn for reasons of safety or effectiveness and, thus, ANDAs relying on original OxyContin will not be accepted or approved. This case underpins the FDA's positive position on ADFs and sets the stage for regulatory endorsement and labeling options of future ADFs for opioid products.

After introduction of the first crush-resistant opioid ER products, abuse has been redirected to both unprotected ER formulations (initially also including Opana ER, which was still available in the non-crush resistant form at the time reformulated Oxycontin CR was launched) as well as to IR opioid products.[8] Consequently, IR formulations should also become a greater focus in ADF concepts. A first concept using nasal irritants was introduced to the market in form of the oxycodone IR product Oxecta®, although no post-marketing surveillance data on this product have so far been published. The next logical step would therefore be to investigate whether the crush-resistance technology that has proven its merits for ER opioid products can be applied to IR forms.

FIGURE 3



In vitro release of a marketed model opioid from INTAC® IR tablet and conventional IR tablet.

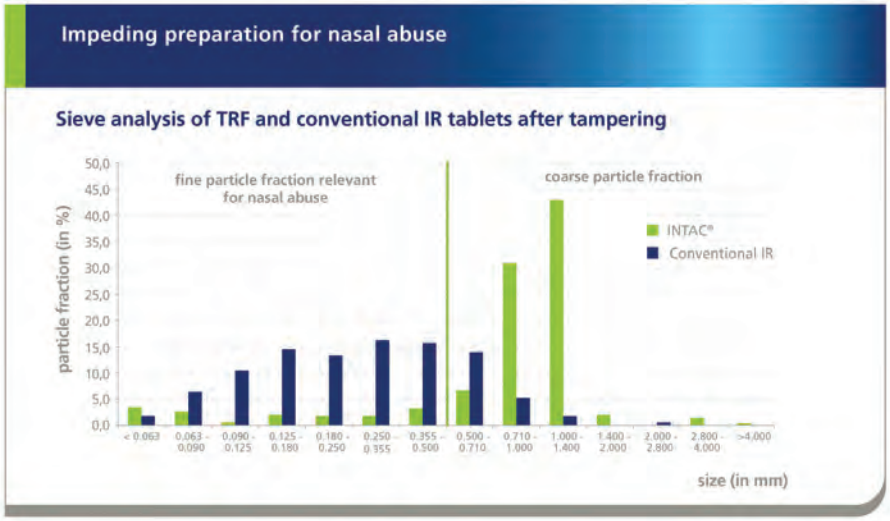
DESIGN OF INTAC® IR

INTAC® is Grünenthal's proprietary drug delivery platform of crush-resistant formulations already used in marketed opioid ER products.[9,10] Unlike with ER formulations, crushing of IR tablets for oral abuse does not

FIGURE 4

Attempt to prepare INTAC® IR tablet for intravenous abuse.

FIGURE 5



Particle sizes after tampering of tablets for preparation for nasal abuse.

significantly alter their inherent fast-release profile. Therefore the focus in extending the INTAC formulation platform is to impede preparation for non-oral abuse of IR products without impacting the IR functionality. Consequently, a multiparticulate tamper-resistant INTAC tablet has been developed that is characterized by a distinct gelling quality that leads to low extraction rates and raises the hurdles against intravenous abuse. This feature is combined with pronounced resistance to crushing of the multiparticulate drug matrix, thereby inhibiting preparation for subsequent nasal abuse. The manufacturing concept for this approach is based on creating crush-resistant material by the versatile core technology of hot melt extrusion (HME). The same first step of HME is employed as for INTAC ER, but a different downstream process using a plurality of smaller dies and cutting by a pelletizer delivers AD IR pellets or granules (Figure 1) that can be further processed into IR tablets.

With the addition of this IR concept, it is now possible to tailor release profiles from minutes up to about 1 day. Thus, INTAC becomes available as the solution for ADFs over the whole range of drug-release requirements from IR through twice-daily up to once-daily ER applications (Figure 2).

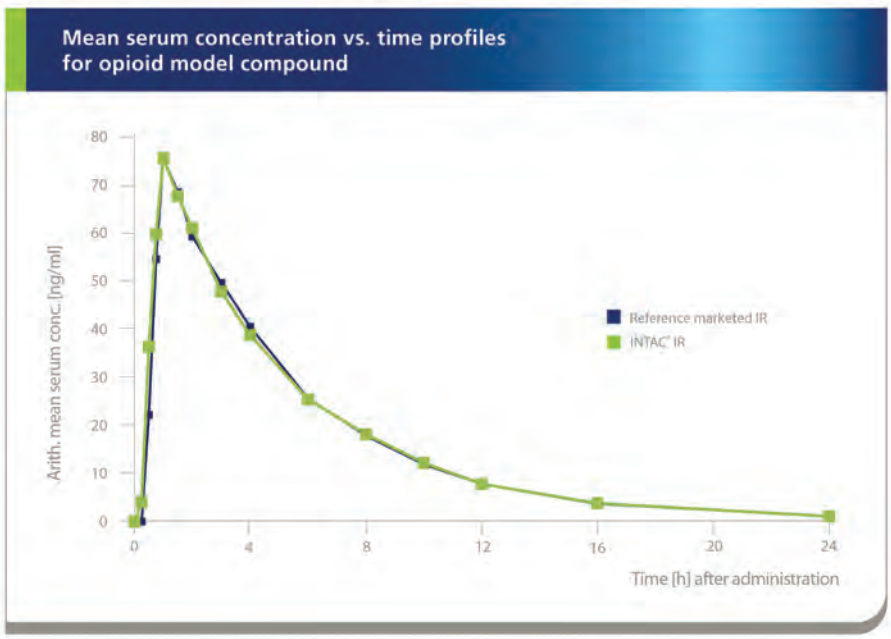
IN VITRO TAMPER-RESISTANCE TESTING

To verify the design concept for IR opioids, INTAC IR tablets were manufactured by HME of an opioid model compound together with a proprietary mix of ingredients, amongst others, a high molecular weight polyethylene oxide (PEO). The resulting crush-resistant pellets were subsequently mixed with easily compressible excipients. This blend was compressed to a tablet that releases the opioid in the same fashion as a conventional marketed IR tablet of the same opioid (Figure 3).

The INTAC IR tablet was subjected to in vitro tamper-resistance testing by manipulations reflecting preparation for intravenous and nasal abuse. In order to test for impedance of intravenous abuse, INTAC multiparticulate IR tablets were prepared simulating the typical abuser procedure for intravenous administration trying to obtain a powder that can be extracted, preferably by water. Due to the gelling properties of the excipients used in the formulation, attempts to draw the resulting extract into a syringe (typically done with a cigarette filter by the experienced intravenous abuser) were unsuccessful, and virtually no extract could be drawn up into the syringe (Figure 4).

For testing of impeding nasal abuse, INTAC multiparticulate IR tablets were

FIGURE 6



Mean serum concentration-time profiles of a model opioid administered in form of INTAC® IR tablets and as a conventional IR tablet market product.

prepared simulating a typical abuser procedure for nasal administration by comminution. Even with a sophisticated manipulation technique, obtaining particle sizes < 500 microns for nasal abuse was substantially limited for the INTAC IR formulation (about 85% ≥ 500 microns). In contrast, the conventional IR tablet could easily be broken down far below 500 microns, about 80% < 500 microns (Figure 5). 500 microns was set as a limit well above the typical particle sizes known to be suitable for nasal administration of compounds.

These results from the laboratory tamper-resistance testing support the concept based on the chosen physicochemical approach showing that INTAC IR has the potential to impede abuse of IR opioids by non-oral administration routes.

CLINICAL DEVELOPMENT

To verify that the change to an ADF formulation does not negatively impact the desired IR features of the product when patients take the product by the intended oral route, a bioavailability trial comparing the previously described INTAC IR model product to a marketed conventional IR formulation was performed. In an open, randomized, two-treatment, two-period, two-sequence cross-over design study with 24 healthy volunteers (22 completed) the relative bioavailability of the two products was evaluated.[11] The mean serum concentration curves of the model opioid from both formulations were almost superimposable over the whole investigation time (Figure 6).

The statistical evaluation of the pharmacokinetic parameters (Table 1) showed that the 90% confidence intervals (CI) for the ratios test/reference of Cmax, AUC0-t and AUC (area under the curve up to infinite time) fell within the 80% to 125% range commonly used for assessing bioequivalence.

TABLE 1

Summary of statistical analysis of pharmacokinetic parameters

PK parameter	ANOVA CVs [%]	Point estimates	90% confidence intervals [%]
C_{max} [ng/mL]	24.1	103	90 – 117
AUC_{0-t} [h*ng/mL]	13.7	102	94 – 110
AUC [h*ng/mL]	13.5	102	94 – 110

Statistical evaluation of mean pharmacokinetic parameters of a model opioid administered in form of INTAC® IR tablets and as a conventional IR tablet market product.

SUMMARY

In order to cope with the increasing abuse of IR opioids after introduction of AD formulations for ER opioid products, the INTAC technology platform has been extended to IR formulations with the intention to deter their non-oral routes of abuse. In vitro tampering tests have shown convincing results with regard to impeding nasal and intravenous abuse. Although INTAC IR's multiparticulate drug matrix is difficult to pulverize and dissolve, the in vivo performance is nonetheless entirely comparable to the marketed conventional IR product as the 90% confidence intervals for the ratios of the mean PK parameters Cmax and AUC fulfilled the conditions commonly used for assessing bioequivalence. The safety and tolerability data of the INTAC IR formulation were equally in line with the marketed IR reference product. Thus, once approved and launched, INTAC IR products may enable physicians to simply switch from conventional to reformulated tamper-resistant products. Overall, the INTAC technology has demonstrated its versatility and broad applicability to both ER formulations, already available as marketed products, and to IR formulations that are coming more into focus for prescription opioid abuse. ◆

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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 abuse-deterrent 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. Sebastian Schwier, Associate Project Director in International Technical Alliance Management at Grünenthal GmbH, studied Pharmaceutical Sciences at the Westphalian Wilhelms University of Münster. He joined Grünenthal in 2008 as Laboratory Head within Pharmaceutical Development. Since 2012, he has been responsible as the CMC team leader for several INTAC® tamper-resistant formulation development projects.

Martin Brett, Scientific Director in the Department of Pharmacokinetics at Grünenthal GmbH, studied Chemistry at Oxford University. He spent 15 years in the pharmaceutical industry and a further 10 years in contract research, with interests mainly in bioanalytical methodologies and pharmacokinetic evaluation of clinical studies. He joined Grünenthal GmbH in 2005 responsible for the clinical pharmacokinetic team, and has supported the INTAC® project as the PK representative.

Dr. Hans-Jürgen Stahlberg, International Clinical Lead and Director in the Department of Clinical Pharmacology at Grünenthal GmbH, has extensive experience in Pharmacokinetics (PK) and has 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 the clinical development of INTAC® tamper-resistant opioid formulations.

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

Dr. Kai Strothmann, Senior Director Strategic Marketing & Portfolio Development at Grünenthal GmbH, studied Pharmaceutical Sciences and earned his PhD in Pharmacology at the University of Münster. After 10+ years of diversified business experience in the healthcare industry across a broad range of functions and therapeutic areas, he joined Grünenthal GmbH in 2011 and takes care of marketing and life cycle management of the INTAC® tamper-resistant formulation technology.

Overcoming the Challenges of Child-Resistant/Senior-Friendly Closure Development in Today's Changing World

By: Steve Stalions and Kurt Attermeier

INTRODUCTION

Healthcare packaging has always been a bit of a challenge when compared to other industries. The US FDA has expressed a desire to make 70% of drugs available for over the counter (OTC) use. In an already cautious regulatory environment, industry standards are increasing, bringing additional pressure on manufacturers to provide better child-safe and senior-friendly packaging solutions.[1] As the demand for better child-resistant and senior-friendly (CR/SF) packaging is on the increase, so too is the market demand for greater cost effectiveness, sustainability, and value-added end-user benefits. The following will explain how these challenges can be overcome by employing imaginative engineering design and process practices and a healthcare-quality focus.

KEY TRENDS & DRIVERS

The market outlook indicates the future of healthcare packaging solutions will be characterized by constant change, with an expanding market for more convenient and easier-to-use solutions as the worldwide market demand continues to grow. Plastic caps and closures will form the largest worldwide market segment, driven by high value-added designs with enhanced ease-of-use and security features, such as CR/SF packaging and dispensing. Paying attention to market trends and gaining insight from consumers and manufacturers was a key starting point and helped guide the subsequent design decisions to enhance usability of the Clic-Loc® closure - Rexam's premium CR/SF closure.[2]

ADDRESSING THE NEEDS OF CHILDREN

Concern in keeping young children safe around medicine is acknowledged by virtually every parent and caregiver's awareness of the importance of storing medicine out of the reach of young children. However, every year, there are increasing cases of calls to poison centers. According to the 2013 Safe Kids Worldwide report, 86% of emergency room visits for poisoning were due to the child getting into adult medicine. They also state that in 7 out of 10 cases, a child ingested medication belonging to the

FIGURE 1

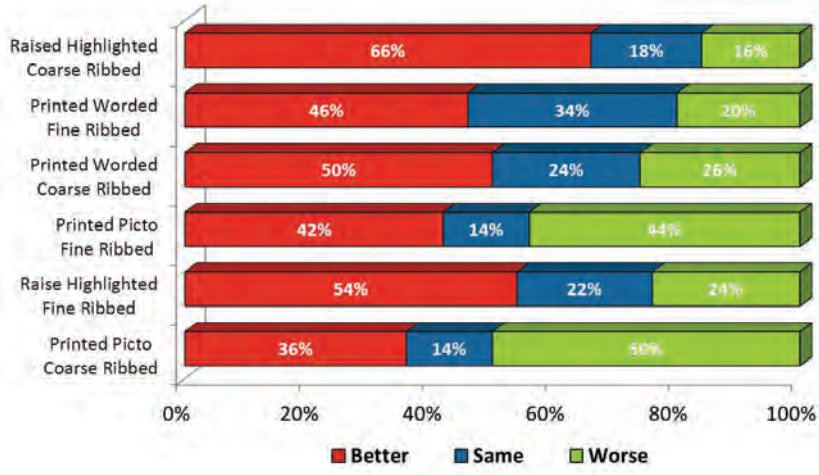

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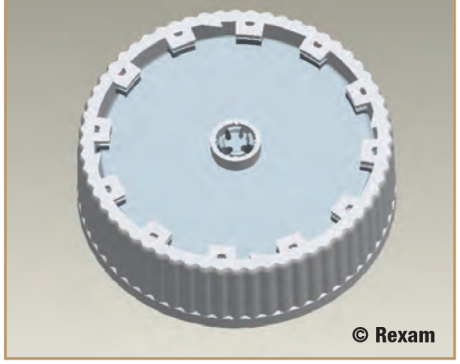
FIGURE 2

Inner and Outer lugs in "Stacking Poition"



mother or a grandparent.[3]

In January 2013, the manufacturer of a popular cold and cough syrup recalled 2.3 million units of product, after four children opened the child-resistant caps and accidentally ingested the medication. According to the US Consumer Product Safety Commission, the federal agency charged with protecting consumers against accident-causing products, the child-resistant caps failed to work in some cases, with children removing the cap even with the tamper-evident plastic seal still in place.

"It's really common," said Dr. Donna Seger, the Executive Director of the Tennessee Poison Center and a Professor at Vanderbilt University. "Cold and flu medicine are one of the top exposures that children have in the US."[4]

Another example of product failing to meet child-resistant closure requirements was the voluntary recall of approximately 898,000 units of a childrens' pain and fever medication. In this case, the filled container closure system was sufficiently child resistant. However, the accompanying dosage dropper that was supplied with the product was not child resistant, and hence, represented an unacceptable risk.[5]

In response to these increasing incidences, it has been recommended by several medical and consumer organizations that consumers buy child-resistant packaging when possible and seniors transfer medication to child-resistant packages if children are likely to visit.[3]

ADDRESSING THE NEEDS OF SENIORS

Due to the aging of the baby boomer generation (born in the late 1940s and 1950s), the American population is getting older. Between 2010 and 2050, the senior population will swell significantly. With the boomer population having reached the age of 65 a couple of years ago, the senior population is projected to reach 88.5 million - well over twice the number of seniors in 2000 and 20% of the total population of the US.

Adults 65 and older spend nearly twice as much as those 45 to 64 on healthcare each year; they spend three to five times more than all adults younger than 65, according to the Center for Disease Control and Prevention (CDC). This increasing elderly population has and will necessitate opportunities for improving quality of life.

The challenge for healthcare manufacturers will be to address the needs of an increasingly segmented market (young, middle, and older seniors); by keeping in mind the differing levels of physical demands and limitations when creating packaging solutions for seniors.

CONSUMER INSIGHTS

Qualitative and quantitative research, lead to the design of a coarse ribbed cap for easier opening and easier closing. Research evaluated the following attributes: time to open, ease of opening, ease of closing, comfort of feel in the hand, ease of following the instructions, ease of knowing the package is closed correctly, overall usage experience, preferred grips (ribbing) on the side of the closures, and readability of the instructions on the closure's surface.

Consumers overwhelmingly preferred the printed worded, coarse ribbed, and arrows compared to the pictogram versions, with respect to easy opening and closing. When compared to existing CRC closures (ie, closures the subject was already using), Figure 1 shows that 66% of the panel preferred a coarse ribbing version.[6]

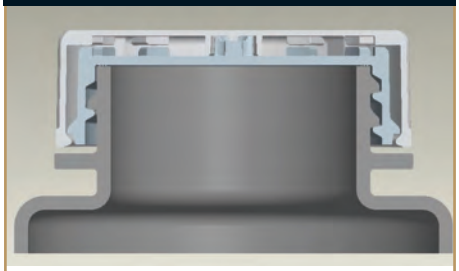
The reasons for this preference given by consumers were primarily linked to ease of opening "bigger ridges fitting better in the hand" and the clearer directions coming from either raised or printed lettering as opposed to pictograms.[6]

SUSTAINABILITY IS MORE THAN REDUCING WEIGHT

Many healthcare companies are becoming more focused on understanding, measuring, and managing their sustainability

FIGURE 3

FIGURE 4



Transfer bead clearance © Rexam

efforts. This increased focus has provided a great deal of challenges, as well as opportunity within the healthcare packaging industry. Early on, closure manufacturers addressed sustainability primarily by light-weighting, a practice that reduces the amount of resin used to make the part. Light-weighting, without compromising product integrity, is still important today. However, other aspects, such as reducing energy consumption during manufacturing and material recyclability, play important roles.

Material reduction is not only an efficiency gain. It also reduces transport demands and yields fuel and logistics cost savings across the supply chain. Rexam believes that sharing operational best practices, and applying six sigma and other continuous improvement methods across the organization, helps achieve the vision of best performance both in terms of financial results and environmental records. One illustration of such attention and drive can be shown by this example of recycling plastic waste. Based on a 2011 company report, Rexam cut the tons of raw material per ton of production to 1.14 from 1.15 in the previous year.[7]

PROCESS APPROACHES CAN ADDRESS KEY CHALLENGES

Increased cost pressures throughout the entire production and packaging process, the increased need to provide tailored individual packaging solutions, as well as a heightened demand for high-quality, defect-free/contaminant-free solutions, are driving closure manufacturers to rethink and simplify their development and manufacturing approach.

THE 3RS OF DESIGN

Although plastic closures are produced in thousands of different styles, they can be classified according to three main molding methods: stripped, collapsible core, and unscrewed. The Clic-Loc® 4 platform utilizes a hybrid approach, the patented 3R (rotating ratchet ring) design was developed by a leading injection molding equipment manufacturer. This innovative unscrewing mechanism is both simple and cost effective. The 3R system allows Rexam to maintain the thread quality of an unscrewed core, while avoiding the maintenance and design compromises of collapsible and/or stripped core parts.

Cycle times are reduced when compared to a standard unscrewing mechanism. This is primarily due to the minimal movement required by the 3R system to clear the threads from the part, and the ability to design-in much more efficient cooling.

The 3R design is also capable of running in standard machines, avoiding the need for capital investment and training on new equipment.

CASE STUDY: REDUCING CYCLE TIMES & COSTS

A 3R mold was compared to a rotating core, both producing identical 38-mm closures. Both molds and hot runners were manufactured by the same supplier and were tested in the same machine, with a reciprocating screw injection unit. All of the process set-up parameters were identical:

- Part weight: 5.0 grams
- Part material: HDPE
- Manufacturer: AutoChem; Number: 2110 MN50
- Color: White; % Concentrate: 3%
- Mold process temperature: 10°C

The 3R mold was able to produce acceptable parts at a cycle time 1.5 sec (18.3%) faster than the rotary core mold. Most of the cycle improvement was a result of reduced hold and cooling time (0.9 sec). The remainder of the improvement resulted from a faster ejection and mold close time (0.6 sec faster).[8]

FIGURE 5

FIGURE 6

IN-LINE MANUFACTURING & ASSEMBLY

The in-line manufacturing process refers to the production work cell. Parts are molded and assembled in one continuous flow as opposed to being molded, stored in a warehouse, transported to an assembly line, and then fed into an assembly machine. In-line manufacturing and assembly can be very helpful when producing closure parts. For example, they are not exposed to contamination from being transported within the plant.

In-line manufacturing can create some major advantages for closures. Any time you can mold parts and feed them directly into an assembly process you create an economic advantage. By molding and assembling in-line, savings are driven due to reductions in transportation, storage, waste, contamination, and indirect labor. And the process is inherently FIFO. With Clic-Loc® 4, the parts go directly from the molding machine into assembly via air conveyors.

SHRINK WRAPPING APPLICATIONS

Clic-Loc® 4 is designed with a mechanism that prevents "freewheeling" of the outer closure after application to the bottle. This ensures that the drive lugs between the inner and outer will remain in a "stacked" position during the shrink wrapping process. Figure 2 shows the off-drive lugs of two caps on top of each other in what is known as "stacking position." The detents prevent the outer from unintentionally rotating counter-clockwise as seen from above relative to the inner cap. Therefore, the off-drive lugs are held above each other and cannot be used to transfer off-torque from the outer to the inner. If top loading occurs on the package or shrink wrap on the neck, the downward force will not cause the off-drive lugs to engage. Therefore, downward force resulting from shrink wrapping will not compromise the CR function of the closure.

OVERCOMING CHALLENGES WITH DESIGN

Decoration Flexibility

Clic-Loc® 4's outer mold has the ability to remove and replace cavity plates in the press. This allows for different versions of artwork and knurl pattern (ribbing) designs to be changed over without removing the mold from the press. Figure 3 depicts the versatile decoration possibilities, highlighting four potential options.

Capper Flexibility & Variety

Greater tolerance for bigger transfer beads creates greater capper flexibility, allowing one closure to fit variable bottle sizes. Figure 4 shows a section view of the assembled closure on a neck finish that contains a transfer bead below the threads. Transfer beads can cause the neck to be incompatible with a two-piece push-and-turn closure if the transfer bead prevents free

FIGURE 7

operation of the outer cap. Clic-Loc® 4 has been designed to work with many neck finishes that are incompatible with competitive push-and-turn closures due to the elevation and/or diameter of the transfer bead.

Design Effectiveness

Figure 5 shows a close-up of the three concentric V-beads or V-rings (near the center of the image) that provide for a liner-less option feature. The V-ring acts as a sealer, replacing the need for a separate liner, ultimately contributing to cost savings.

The following molded parts are exemplary of the thoughtful approach to achieving the design goals without compromising high quality and performance. Figure 6, shows one of the on-drive lugs/clickers on the inner cap. The lug/clicker is to the left of the annotation in the picture. Above this, one of the off-drive lugs can be seen. Figure 7 shows one of the on-drive lugs/clickers on the outer cap. Below this two of the off-drive lugs can be seen.

THE RESULT OF KEEPING IN MIND DESIGN-FOR-USE PRINCIPLES

Clic-Loc® 4 is the culmination of design enhancements and changes to production processes. Below is a summary of the major improvements.

New Improved Technical Attributes

A top biasing mechanism replaces top spring fingers and keeps CR lugs disengaged. V-rings were added to accommodate liner-less use. Bottle neck finishes with larger max transfer beads can be handled. An overall reduction in height and weight was achieved.

End User & Manufacturer Attributes

A more senior-friendly, easy-to-open closure created in part due to the coarse, ribbing, which runs deeper and wraps around the outer top edge (ie, improved gripability). Able to maintain the warning "click" feedback feature, an audible assist in proper opening and alert to adults when a child tries to open the medicine package. Incorporating an in-line manufacturing and assembly process provides operations economies and contributes to sustainability.

SUMMARY

Rexam Healthcare is 100% focused on delivering high-quality healthcare primary packaging and devices. Healthcare end-users and manufacturers of the products they use are the primary customers. Therefore, quality, manufacturing, and commercial attention is highly concentrated on their needs.

Due to its performance, features, and production-line compatibility, the Rexam Clic-Loc® design has earned over four decades of trust and confidence from the world's most innovative, respected, and demanding healthcare product manufacturers. The design principles incorporated, along with the process improvements, have positioned the Clic-Loc® 4 closure to meet the challenges relating to child safety, enhanced senior usability, cost effectiveness, operations flexibility, and custom packaging.

The 38-mm size will be introduced near the end of 2013, followed by other sizes in the range in 2014 and beyond. This latest addition to the premium Clic-Loc® closure family is foreseen to become a standard of care reference for the CR/SF closure market. ◆

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BIOGRAPHIES

Steve Stalions is a Senior Design Engineer with the Containers and Closures business unit at Rexam Healthcare, a major global player in rigid plastic packaging for the Healthcare market. His responsibilities include the design and development of containers and closures as well as providing customer technical services. He earned a Bachelors degree in Mechanical Engineering from the University of Kentucky.

Kurt Attermeier is the Technology Director for the Global Innovation and Engineering Group at Rexam Healthcare. His experience includes over 30 years of product development and operations experience in the medical device and disposables field. He earned his degree in Biomedical Engineering from Marquette University.

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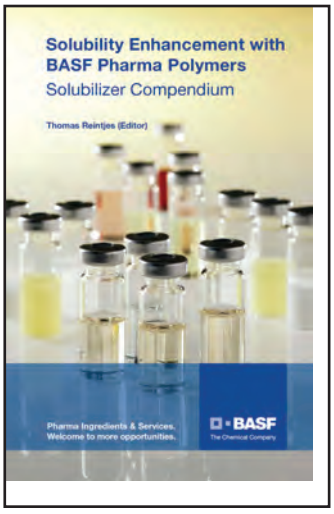

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Technology & Services Showcase

Biologics Development

Catalent's proprietary Gene Product Expression Technology (GPEx®) sets the standards in mammalian cell line engineering. GPEx allows rapid selection of the best clinical candidate from a group of potential molecules, providing a stable Master Cell Bank to rapidly generate proteins for clinical trials. GPEx technology can ensure genetically stable cell lines are produced 100% of the time. The advanced mammalian cell line technology in GPEx accelerates timelines, increases reliability and yield, and provides superior cell stability compared to any other method, with flexibility and unmatched versatility. Catalent provides a faster path from gene to clinic and offers high-performance cell line biologics development and biomanufacturing. Catalent boasts a new, state-of-the-art, biologics manufacturing facility in Madison, WI, allowing for batch sizes from 10-1,000 L. To learn more about Catalent's global Biologics capabilities, call (877) 587-1835 or visit **http://www.catalent.com/index.php/development/biologics/overview.**

Hormone Delivery Technology

CIMA
Your drug, delivered

OraSorb™ hormone delivery technology provides the convenience of a pill with a metabolic profile similar to a patch. CIMA's new delivery system combines solubilization and permeation enhancing technologies into one buccal tablet. The solubilization technology ensures the hormone is in solution when it comes in contact with the buccal mucosa. The buccal permeation technology provides for rapid absorption. The high bioavailability of the buccal delivery means that efficacious drug levels can be obtained with lower doses. Buccal delivery also reduces first-pass hepatic metabolism, which results in reduced hepatotoxicity. This resulting formulation has a more favorable "patch-like" metabolite profile with the convenience of a buccal tablet. If you would like to learn more about OraSorb, please contact CIMA Labs at (763) 488-4975 or visit **www.cimalabs.com**.

Super Refined® Excipients

CRODA
Health Care

Croda manufactures a complete range of high purity excipients and delivery aids, offering superior quality for the global pharmaceutical market. These excipients are ideal for multiple dosage forms, including topical, parenteral, oral, and ophthalmic formulations as well as advanced delivery systems. Croda's Super Refined® excipients go through a proprietary process to remove the polar and oxidative impurities that can cause performance and stability issues. These excipients are ideal for use when working with sensitive drug actives, helping to maximize the stability and overall performance of the drug product. Excipients in the Super Refined range include PEGs, polysorbates, oils, and triglycerides, propylene glycol, castor oil, and a range of topical penetration enhancers, such as oleic acid and dimethyl isosorbide. For more information, contact Croda at (732) 417-0800 or visit **www.croda.com/healthcare.**

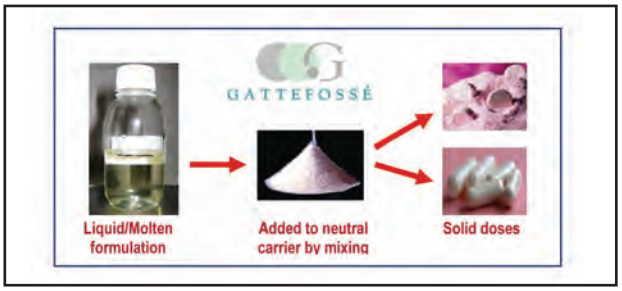
Development & Manufacturing

DPT®
COUNT ON US℠

DPT is a contract development and manufacturing organization (CDMO), specializing in semi-solids and liquids for biopharmaceutical and pharmaceutical products since 1938. From virtual to large pharma, from concept to commercialization, from sterile to non-sterile - DPT offers the broadest range of capabilities in the industry. Drug development services include pre-formulation, technology transfer, formulation and biopharmaceutical development, analytical development, CMC preparation, and validation through process development, and regulatory support. DPT has a solid regulatory history, with production capabilities that include five world-class cGMP facilities, clinical trial materials, full-scale commercial production, controlled substance registration Class II-V, complete supply chain management, and expanding sterile product development and aseptic manufacturing facilities. Packaging services include packaging identification, specifications development, engineering, and procurement resources necessary for conventional and specialized packaging. For more information, contact DPT Labs at (866) 225-5378 or visit **dptlabs.com**.

Technology & Services Showcase

Solvent-Free Adsorption



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.**

Insulin Management System

Tamper-Resistant Technology

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

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.**

Drug Development & Delivery

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973.263.5476 • rvitaro@drug-dev.com • drug-dev.com

Technology & Services Showcase

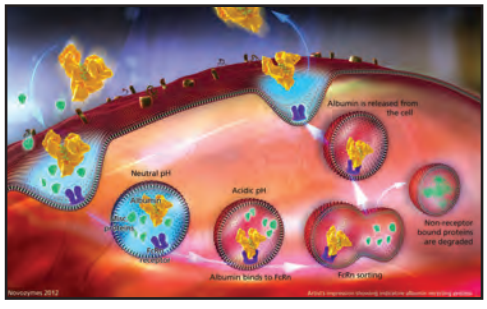
Excipients & Technology

MEGGLE Excipients & Technology is a global leader in the manufacture of lactose for the pharmaceutical industry. MEGGLE provides supply chain security with manufacturing facilities in Europe and North America, and offers a broad product portfolio comprising α-lactose monohydrate, β-anhydrous lactose, and DPI lactose grades. MEGGLE Excipients & Technology is a pioneer in co-processing technologies allowing simple, yet robust formulations. Through co-processing lactose with other excipients, MEGGLE has developed high-performance ingredients having unique qualities with applications in directly compressible immediate- and sustained-release pharmaceutical solid dosage forms. MEGGLE also possesses extensive knowledge in the manufacture of other excipient products and provides contract manufacturing services to several well-known global excipient companies wanting to enhance their excipient performance and product quality. For more information contact the MEGGLE Group at (914) 682-6891 or visit **www.meggle-pharma.com.**

Full-Service CDMO

Metrics is a full-service global contract development and manufacturing organization (CDMO) specializing in oral and topical dosage forms. A subsidiary of Mayne Pharma Group Limited, Metrics also offers clients an impressive portfolio of advanced proprietary delivery methods for controlled release, bioavailability enhancement, and taste-masking. Founded as a contract analytical laboratory in 1994, Metrics has evolved into a provider of quality pharmaceutical formulation development, analytical testing services, and commercial and CTM manufacturing for Phase I-III. For more information, contact Metrics at or visit **www.metericsinc.com.**

Tunable Half-Life Extension Technology



Novozymes' albumin-based half-life extension (HLE) technology can flexibly extend drug half-life to reduce the dosing frequency of drugs from days to weeks. 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 significantly whilst increasing patient compliance. Long patents until at least 2030 provide manufacturers with a unique competitive edge in current challenging markets. For more information on Novozymes' HLE technology, please visit **www.daytoweeks.com.**

Leading CDMO

Formex LLC is a leading contract development and manufacturing organization focusing on oral and topical dosage forms. Formex specializes in bioavailability enhancement and controlled-release technologies, such as hot-melt extrusion and spray-drying. Formex provides preformulation, formulation development, analytical method development, analytical testing, preclinical manufacturing, cGMP clinical trial manufacturing for Phase 0-III, and small-scale commercial manufacturing. Formex currently occupies 45,000 sq ft of our 80,000-sq-ft facility with 25,000 sq ft of cGMP manufacturing space, including 17 separate and dedicated cGMP suites, including suites qualified and dedicated for cytotoxic compound handling as well as potent compound handling. For more information, contact Formex at (855) 436-7639 or visit **www.formexllc.com.**

Technology & Services Showcase

GMP Peptides

PolyPeptide GROUP

The PolyPeptide Group is a privately held company focused primarily on the manufacture of GMP peptides for the human and veterinary pharmaceutical markets. The Group employs 450 trained staff at six separate manufacturing sites across three continents: Denmark (Hillerød), France (Strasbourg), India (Mumbai), Sweden (Malmö) and the USA (San Diego and Torrance). With more than 50 years of experience producing therapeutic peptides the Group is one of the world's leading peptide manufacturing organizations. For more information, contact PolyPeptide at (France) +33 388 790 879, (Sweden) +46 40 366 200, (USA) +1 310 782 3569, or visit **www.polypeptide.com.**

Laboratory Services

TAPEMARK Laboratory Services

TAPEMARK

Tapemark Laboratory Services provides world-class chemical and biological services for the pharmaceutical, nutraceutical, medical device, academic, and government industries. Tapemark Laboratory Services provides an array of testing services, including formulation development, method development & validation, raw material testing, finished product testing, and stability services. Tapemark Laboratory Services also provides microbial limits testing, antimicrobial effectiveness testing, water testing, and environmental monitoring. Each activity is designed with QbD influence and infused with integrity. Tapemark Laboratory Service complies with cGxPs and monitors regulatory requirements, ensuring you receive the highest quality service/product. The scientific, highly motivated staff is involved in each phase of the project, ensuring all customer requirements are exceeded. For more information, contact Tapemark Laboratory Services at (800) 535-1998 or visit **www.tapemark.com.**

Intranasal Delivery

The Teleflex VaxINator™ is an easy-to-use and cost-effective solution for intranasal drug delivery. It employs the same technology as the clinically proven LMA MAD Nasal™ and enables standardized positioning in the nasal cavity for broad deposition across the nasal mucosa. The droplet size output of the VaxINator allows for drug coverage across the anterior and posterior areas of the nasal cavity, thereby facilitating rapid adsorption. The Teleflex VaxINator is a syringe and atomizer-based system, and a range of accessory items are available to meet your intranasal drug delivery needs. Applications include vaccines, pain medications, anaesthetics, antimicrobial, and many other possibilities. For more information, contact Teleflex at (801) 281-3000, **LMAOEM@teleflex.com**, or visit www.lmaco.com.

Wearable, Disposable Injectors

Unilife has developed a flexible, scalable portfolio of wearable, disposable injectors for the subcutaneous delivery of large-dose volume therapies with optimal patient comfort and convenience. Multiple customization options are available to address specific therapeutic, operational, branding, and patient needs, including dose volume and controlled bolus, constant or variable delivery duration rate. Each device leverages human factors data with target patient populations to provide a highly intuitive, effective, and confident user experience. Designed for seamless integration with approved manufacturing methods and primary container materials, Unilife is ready to support customer needs for the commercialization and lifecycle management of their injectable therapies. For more information, call (717) 384-3400, email info@unilife.com ,or visit **www.unilife.com**.

Technology & Services Showcase

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.**

West PFS Solutions

You need prefillable syringe systems and components designed to compete in an evolving industry. You need the management, expertise, and support of a manufacturer capable of creating systems and components that will mitigate risk and differentiate your product. Pharmaceutical and biopharmaceutical customers trust West to provide prefillable syringe systems and components that help bring products to market safely, reliably, and with the integrity you've come to expect. West works side-by-side with top pharmaceutical and biotechnology companies to design and manufacture drug packaging and delivery systems that bring injectable drugs from concept to the patient efficiently, reliably and safely. Our global technical expertise and services provide solutions that are true to our core goal of reducing regulatory risk while ensuring quality and patient safety. So you can rest easy. Pictured above is West's prefillable syringe solutions that include the Daikyo Crystal Zenith® 1-mL long insert needle syringe system. For more information, contact West at (800) 345-9800 or visit **www.WestPFSsolutions.com.**

Clinical Development Services

Vetter Development Service (VDS) provides expert support for your drug development projects, from inception to market launch. Our services include state-of-the-art clinical manufacturing at our facilities in Chicago and Europe, with scale-up and transfer to our large-scale manufacturing facilities. Thanks to the latest technology and innovative processes, we help increase your API yield. Vetter Development Service provides Formulation Support, Process Development, Clinical Trial Manufacturing, Analytical Service, and Regulatory Support. For US inquiries please contact +1-847-581-6888 or infoUS@vetter-pharma.com. For EU inquiries please contact +49-751-3700-0 or info@vetter-pharma.com. Visit **www.vetter-pharma.com** for more information.

Development & Manufacturing

Xcelience® Formulation Development

Xcelience is a premier provider of formulation development and manufacturing solutions with a solid reputation for accelerating early phase small molecule development. Our outstanding quality record, significant drug development expertise, willingness to customize, and disciplined project management enable us to deliver real advantages to clients needing to speed potential drugs to clinical trials. Since 1997, Xcelience has been renowned for reliably expediting drug development. Our formulation development scientists have considerable experience overcoming challenges associated with physical and chemical properties of drug substance, or limited quantities of API, in a manner that results in compounds with improved solubility and bioavailability. Partnering with a specialist like Xcelience for early phase development can significantly reduce product risk and accelerate development timelines. For more information, contact Xcelience at (813) 286-0404 or visit **www.xcelience.com.**

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Ashland Chemicals	11, 49		www.ashland.com/ddd/pharmaceutical
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Metrics	13	252-752-3800	www.metricsinc.com
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RDD	67		www.rddonline.com
Tapemark	16	1-800-535-1998	www.tapemark.com
Teleflex	4	800-281-3000	www.lmana.com
Unilife	59		www.unilife.com
UPM	77	410-843-3738	www.upm-inc.com
Vetter Pharma	9		www.vetter-pharma.com
West Pharmaceutical Services	25	1-800-345-9800	www.westpfssolutions.com
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FROST & SULLIVAN

What do you *really* know about end users of drug delivery technologies?

Drug delivery technologies are a viral component of the dynamic Life Sciences industries, but how well does your company understand the end-user's perspective on desired attributes, compliance issues and drivers of adoption/non-adoption for different drug delivery types?

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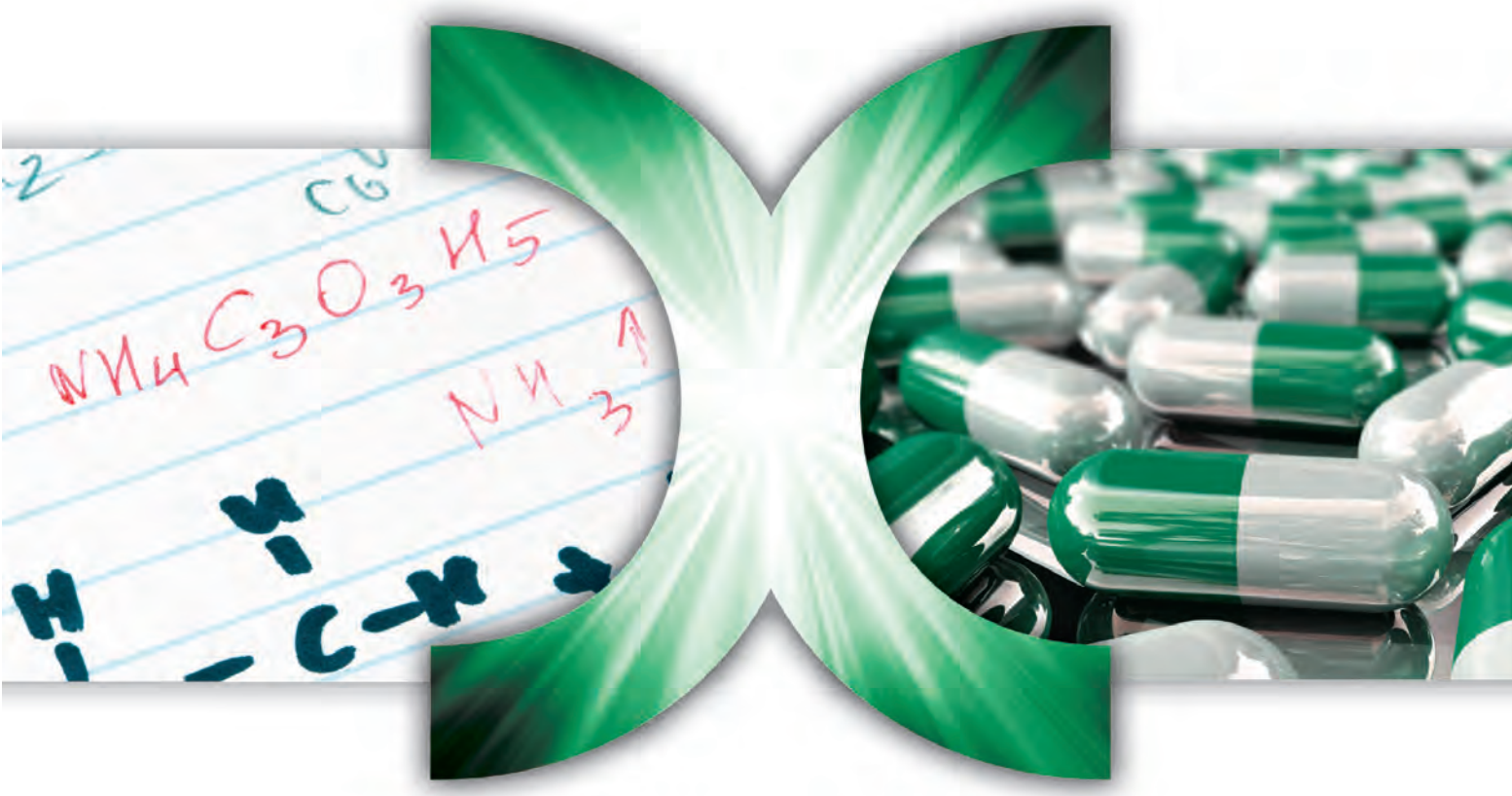
Our expert healthcare analysts:

- Identify growth challenges and optimal growth strategies
- Evaluate each strategy to identify those producing the best ROI
- Develop client-tailored, effective implementation strategies

For more information on how to find growth opportunities in the drug delivery market, please contact Britni Myers at britni.myers@frost.com or **210.477.8481**.

www.frost.com



AT LAST

Early drug development made easy.

Xcelience® is your premier source for formulation development and clinical supplies manufacturing and packaging solutions.

Since 1997, Xcelience has been renowned for reliably expediting drug product development and clinical manufacturing for oral solid, semi-solid and liquid dosage forms. Our formulation development scientists have considerable experience overcoming challenges associated with physical and chemical properties of drug substance, or limited quantities of active pharmaceutical ingredient, in a manner that results in compounds with improved solubility and bioavailability.

Services include preformulation, analytical method development/validation, formulation development, clinical supplies manufacturing, clinical supplies packaging and distribution.

Partnering with a specialist like Xcelience for early phase oral dosage form development can accelerate drug development timelines and reduce risk. To learn more contact us at info@xcelience.com or call us at 813.286.0404.

Xcelience® Formulation Development

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Contact us today at 1.813.286.0404 or info@xcelience.com

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