Drug Development & Delivery

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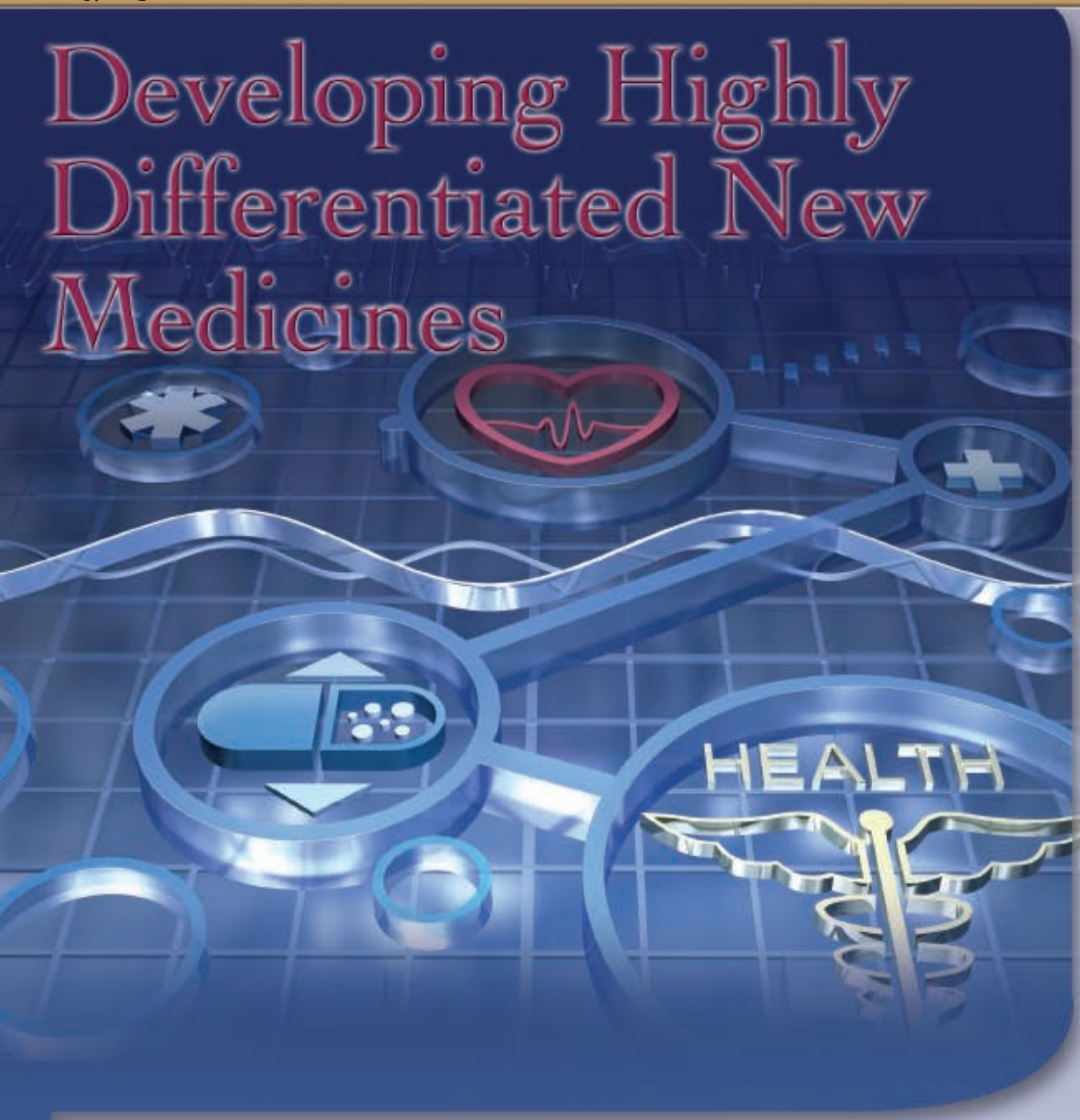

The science & business of drug development in specialty pharma, biotechnology, and drug delivery

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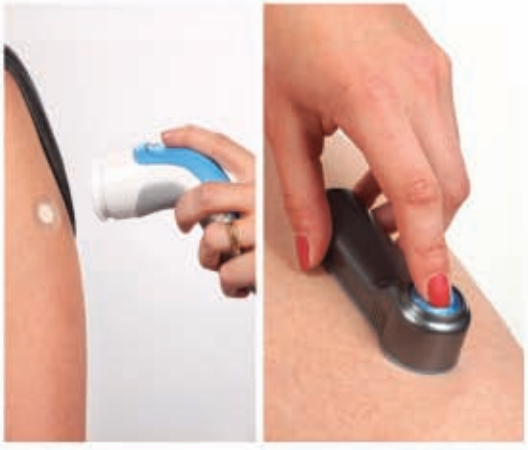

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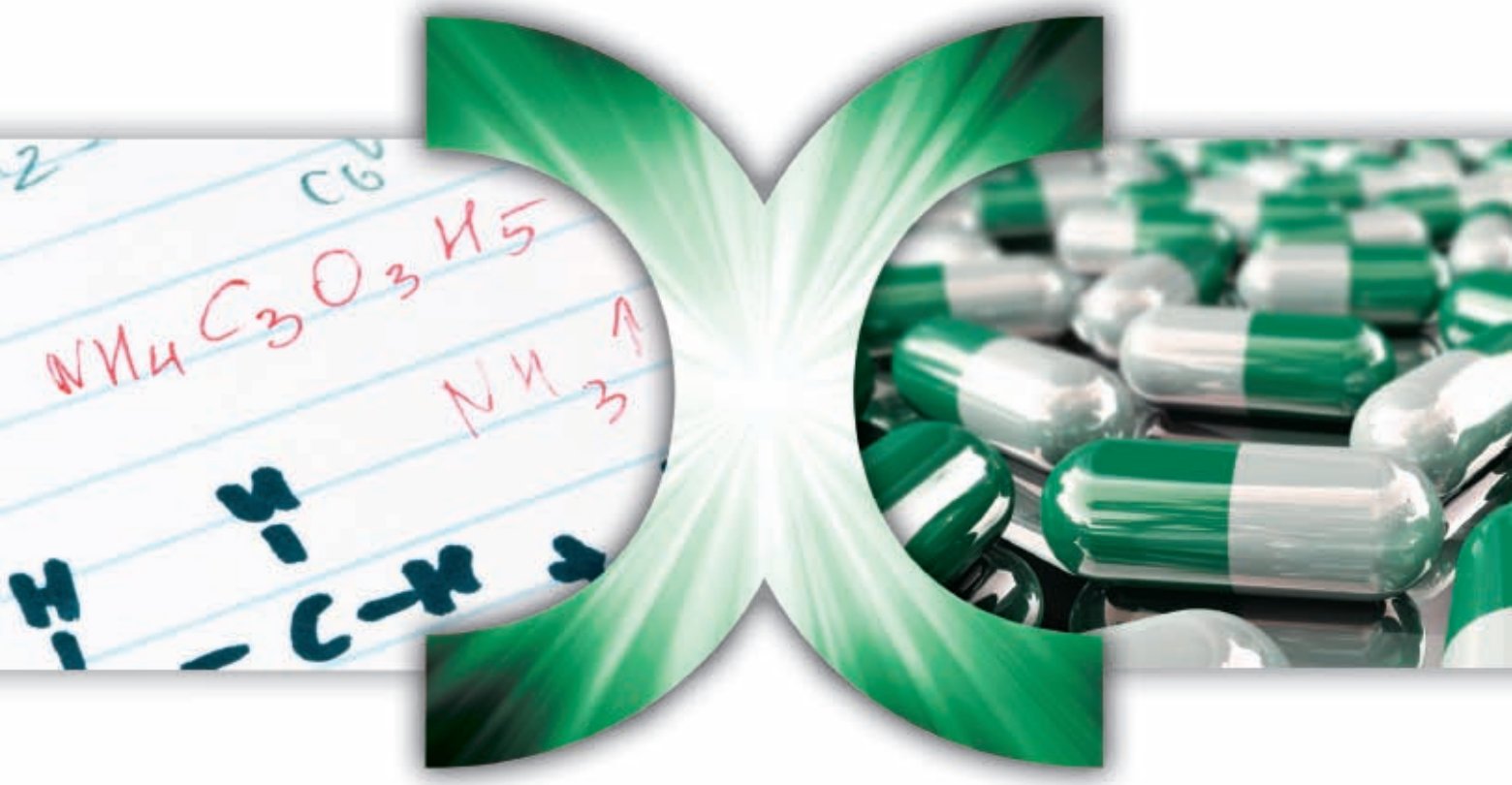

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GSK Successfully Uses Capsugel's Licaps

Capsugel recently announced that its Licaps liquid-filled hard capsules have been successfully used by major healthcare company, GlaxoSmithKline (GSK), for the most established brand in the German urological market, GRANU FINK.

After initially launching the product in a soft gelatin capsule form, GSK's Consumer Healthcare Division decided to investigate other dosage form options to try and improve the product's quality and reduce its production-to-market lead time. GRANU FINK's active ingredients, pumpkin seeds extracts, and pumpkin oil, were challenging to encapsulate because of the large particle size and required a long maturing period when encapsulated in traditional softgels. After testing a switch to Capsugel's Licaps technology, GSK found the product to be leak-free and have now reduced their product lead times by an amazing 12 weeks.

"After comparing two different automated capsule sealing techniques, the Licaps capsules had intact seals during the complete period of stability testing, and we could not detect any leakage," said Dr. Stephan Wurtz, Head of Production at GSK in Herrenberg. "Capsule integrity is a key parameter used to predict product shelf-life and especially helps with preventing too many product returns, and this is why we ultimately chose the Licaps liquid-filled hard capsules as our dosage form."

Since Licaps capsules entered the market nearly 10 years ago, Capsugel has made multiple technological advances, including an enhanced mechanical seal with a seal zone six times greater than a banded capsule. And while they are able to effectively mask taste and odor, Licaps capsules also offer many branding options that may improve loyalty when compared with other dosage forms. According to Capsugel's research, consumers perceive Licaps capsules to be high-quality, modern, and natural looking in a dosage form that is memorable, easy to recognize, and easy to swallow. GSK also conducted their own consumer survey to test the visual and handling acceptance of the Licaps dosage form among regular users of GRANU FINK femina, and 73% of consumers were positive about the new Licaps liquid-filled hard capsule format.

And Licaps liquid-filled hard capsules provide a solution for a variety of challenging compounds. It can improve bioavailability for poorly soluble compounds while providing effective formulation options for low-melting point compounds and safe formulation of low-dose/high potency actives. Licaps manufacturing also offers an established and robust process with the flexibility to allow for production in-house or by Capsugel. With a straightforward manufacturing transfer, including the installation of Liquid Encapsulation Microspray Sealing (LEMS) technology, Licaps capsules can even use the same line as powder-filled capsules and are sealed and dried in a matter of minutes, making manufacturing a cost-effective and environmentally friendly process.

"The Licaps system has integrated well with our Bosch capsule filling equipment, and because of the expert technical assistance we had from Capsugel's installation and formulation teams, we put in place a number of new validated production processes with five fully trained operators in a very short time," added Dr. Wurtz. "During one shift using the Licaps system, up to 350,000 Licaps capsules can be filled. We now have full in-house control of the manufacture of our drug and supplement lines, which gives us a number of benefits."

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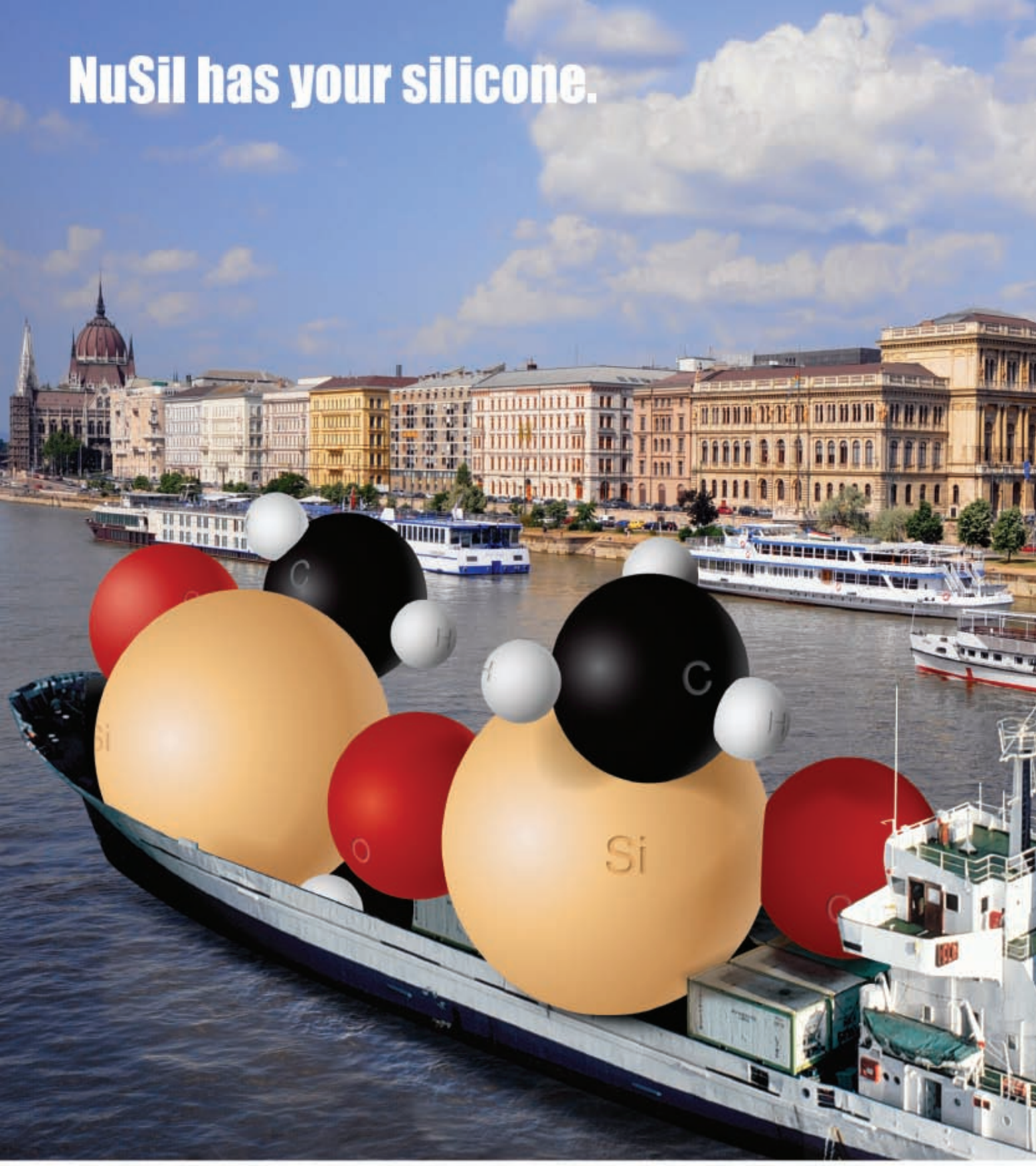

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Cook Pharmica Receives Milestone FDA Approval

Cook Pharmica LLC recently announced it has received its first approval from the US FDA to manufacture commercial product. The product approval for commercial manufacturing came from the FDA's Center for Biologics Evaluation and Research following a rigorous pre-approval inspection of Cook Pharmica in February. The inspection covered the company's new vial filling line, lyophilization capabilities, and facility-wide quality systems.

"This FDA decision marks a very important milestone for our company," said Tedd Green, President of Cook Pharmica. "This first commercial manufacturing approval opens Cook Pharmica's doors to the vibrant biopharmaceutical industry as it generates breakthroughs for patients in the United States and worldwide."

Company executives noted that the FDA's approval of its vial filling line and lyophilization (freeze-drying) capabilities has already generated widespread industry interest in its full manufacturing and packaging capabilities, with inquiries coming from many leading biopharmaceutical companies. The rigorous preapproval inspection is a prerequisite for commercial manufacturing of clients' drug product.

"This approval demonstrates Cook Pharmica's ability and commitment to manufacture high-quality drug products within the FDA's stringent regulatory standards and practices. Everyone at Cook Pharmica is very pleased to have the opportunity and responsibility to ensure that we deliver a dependable commercial drug-product supply for our clients and ultimately to patients," added Mr. Green.

The parenteral manufacturing business unit of Cook Pharmica contains both vial and prefilled syringe manufacturing lines under barrier isolation, as well as secondary packaging to prepare products for distribution. Capable of filling 15 million vials and 70 million prefilled syringes annually, Cook Pharmica's assets are available to fill the shortage of domestic drug product manufacturing in the United States and support federal efforts to eliminate dangerous drug shortages domestically. Based on other client projects at Cook Pharmica, the company expects to receive similar approvals to manufacture drug products for overseas markets as well.

Catalent & Bend Research Form Strategic Partnership

Catalent Pharma Solutions, Inc. and Bend Research Inc. recently announced they have entered into an agreement to provide integrated solutions for pharmaceutical companies seeking to develop and manufacture specialized multiparticulate oral controlled-release products.

Under the agreement, Bend Research and Catalent will provide an integrated approach to bring complex controlled-release products to market faster and more efficiently with optimal therapeutic and release profiles.

The companies' combined expertise in formulation development and Catalent's breadth of services in analytical/CMC, solid-state optimization, clinical and commercial supply will provide pharmaceutical companies with optimal dosage forms and a more efficient path to market. Catalent and Bend Research are developing joint operations and technology-transfer protocols to make the customer experience seamless and efficient while leveraging the strengths of both companies to develop better treatments for patients globally.

"Our integrated approach is geared toward complex, multiparticulate controlled-release products, which traditionally have presented a high scale-up risk when they are transferred to commercial manufacturing sites," said Rod Ray, CEO of Bend Research. "This partnership with Catalent will provide an efficient pathway for these medicines from early development through commercialization. We believe that Catalent's breadth of services and demonstrated success in bringing controlled-release products to market, as well as supplying them globally, makes them an ideal complement to our development strengths."

"Catalent and Bend are aligning their scientific expertise and processes to ensure that developments are undertaken from Day One based on Quality by Design principles," added Ian Muir, President of Catalent's Modified Release Technologies business. "Bend's added laboratory scale modeling expertise will enhance and increase the efficiencies that Catalent will provide to customers to bring difficult to formulate and manufacture controlled-release compounds to market faster, with optimal product profiles. This should enable optimal and seamless scale-up within Catalent's Controlled Release network, and particularly at our Winchester, KY, facility, which is widely regarded as the leading commercial facility for multiparticulate products."

Hovione Reports Significant Sales Growth

Hovione recently announced that the consolidated sales for the fiscal year ended March 2012 amounted to $180 million, the sixth consecutive year of sales growth, representing a growth of 24% in relation to last year.

"Another year of continued strong performance by the Hovione group. During the last 5 years, Hovione has doubled its sales and has made bold strategic steps to both strengthen its ability to serve innovators and to consolidate its leadership in off-patent contrast agents. Looking forward, and despite the difficult economic environment, we remain confident that 2012 will be another year of solid growth," said Miguel Calado, Chief Financial Officer.

In addition to the financial results, which reflect the quality of the Team's performance, overall, 2011 represented a year of great achievements, namely Hovione stood behind three NDA approvals (these were all major NMEs) and in two cases, the approvals were full QbD filings in which Hovione was central to the design and data generation.

All Hovione plants underwent several successful GMP inspections by one or more of the major Medicines' Agencies - a reflection of the large flow of filings and the high standards of compliance.

"Getting multiple NDA approvals every year is becoming a habit at Hovione, which reflects well both on our customers, on our team, and on the CMO model. Our patient investment in capacity, new technologies, and development methodologies is paying off." said Guy Villax, Chief Executive Officer.

Hovione is a global company with over 50 years' experience in Active Pharmaceutical Ingredient and Intermediate Drug Product development and compliant manufacture. With four FDA-inspected sites in the US, China, Ireland, and Portugal, the company focuses on the most demanding customers, in the most regulated markets. Hovione offers integrated API, particle design, and formulation development and manufacturing. In the inhalation area, Hovione is the only independent company offering such a broad range of services.

AmDerma & Oculus Enter Multi-Country Agreement

AmDerma Pharmaceuticals, LLC, a privately owned company (and parent company of Quinnova Pharmaceuticals, Inc.) and Oculus Innovative Sciences recently announced the execution of an agreement to develop and commercialize Oculus' novel proprietary Microcyn Technology drug compounds for major dermatological conditions, including acne. The exclusive agreement includes licensing of the dermatology compounds in the US and India, with a first right of refusal for all member states of the European Union, Canada, Brazil, and Japan. Oculus retains all rights for the rest of the world.

Under the terms of the agreement, Oculus received an undisclosed upfront payment, and will receive multiple clinically based payments upon achievement of several development and regulatory milestones for both acne and secondary indications, as well as future escalating double-digit royalties on net sales of products. The agreement also memorializes the intent for future joint development of additional dermatological products and indications.

"This agreement reflects the AmDerma/Quinnova commitment to the future of dermatology. Microcyn compounds have the potential to bring about significant advancement in the treatment of skin diseases, which affect millions of patients, without adding to the growing problem of antibiotic resistance or steroid overuse," said Jeffrey Day, Quinnova President. "Our dermatology customers have been pleased with improved patient outcomes as a result of adopting the Microcyn-based compounds for treatment of atopic dermatitis and related skin diseases. We look to build upon this success by growing the family of Microcyn-based dermatology compounds for myriad skin afflictions."

AmDerma will be responsible for the development costs for the acne formulation as well as other dermatological compounds.

"Oculus is thrilled to expand the scope of our existing partnership with Quinnova and its parent company, AmDerma. Quinnova is doing an exceptional job with the commercial launch of the Atrapro product, and we are confident they are the right partner to commercialize this technology in acne and other dermatological indications," said Hoji Alimi, Founder and President of Oculus.

Ambrx & Merck to Design & Develop Biologic Drug Conjugates

Ambrx recently announced the company has entered into a collaboration with Merck to design and develop rationally optimized biologic drug conjugates based on Ambrx's site-specific protein medicinal chemistry technology.

"Ambrx's technology has the potential to provide the foundation for a new family of biologic drug conjugates that selectively deliver small molecules to their site of action," said Peter G. Schultz, PhD, a scientific founder and board member. "Merck's deep disease area expertise made it the partner of choice in expanding the application of this technology beyond oncology to other important disease areas."

Under the terms of the agreement, Merck gains worldwide rights to develop and commercialize biotherapeutic drug conjugates directed toward a number of pre-specified targets. Ambrx will receive an upfront payment of $15 million and is eligible to receive milestone payments totaling up to $288 million for successful discovery, development, and commercialization of candidates to all pre-specified targets. In addition, Ambrx will receive royalties on any net sales of products resulting from the collaboration.

"Collaborations are an important part of our strategy to develop a portfolio of next-generation protein therapeutics that may offer significant benefits to patients," said Richard Murray, PhD, Senior Vice President and Head of Biologics and Vaccines Research at Merck. "This agreement will allow us to combine Ambrx's expertise in site-specific protein conjugation chemistry with Merck's expanding antibody capabilities and extensive small molecule resources."

By combining the targeting properties of biologics with the potent therapeutic properties of small molecules, Merck and Ambrx plan to design and optimize new ways to specifically deliver pharmacologically active compounds to their site of action while minimizing the potential for systemic effects.

A Shrinking World: Realizing Regulatory Harmony

By: Gill King, MBA, and Joel Finkle

The life sciences industry faces a number of tough challenges in 2012 - not the least of them the growing reach of increasingly onerous regulatory requirements.

While new international market opportunities are emerging all the time, exploiting them remains challenging because of the differing ways each region and country handle regulatory submissions. Even when submissions follow the guidance of the International Conference on Harmonization (ICH) - which indeed has brought greater cohesion to the ways such activities are managed across the three major markets of the US, the European Union (EU), and Japan - there remain differences in interpretation involving submission formats, such as the electronic Common Technical Document (eCTD). To be able to take full advantage of all of the market opportunities open to them, companies must ensure their submissions can meet the requirements of the evolving formats, the developing standards, and the old and new regulations stipulated by the respective authorities.

The following explores some of the major developments that have taken place throughout the past year in major markets and what those developments mean for the industry in the future.

FDA SAFETY DRIVE PROMPTS MODERNIZATION

Throughout the past 1 or 2 years, the US FDA has adopted an increasingly aggressive approach to ensuring patient safety, triggering a shake-up in quality control across all aspects of drug production and marketing. As part of its modernization drive, the FDA has been working collaboratively with standards-setting bodies - in particular, the Clinical Data Interchange Standards Consortium - to develop standards for the submission of study data. The efforts of such bodies have resulted in the development of numerous clinical standards, such as the Study Data Tabulation Model for representation of clinical trial tabulations, the Analysis Data Model for clinical trial analysis files, and the Standard for Exchange of Nonclinical Data for representation of nonclinical animal toxicology studies tabulations.

Although adoption has been largely voluntary, the FDA, having developed standards in accordance with the industry's requests, now expects companies to adopt the standards more consistently. That includes the way regulatory submissions get made. From 2015, all submissions will need to be filed in eCTD format. The Center for Drug Evaluation and Research (CDER) already receives 400 to 600 electronic submissions per day; 70% of NDAs are eCTDs, and even INDAs are gathering momentum, with 52% of INDs now filed as eCTDs.[1]

MODULE 1, VERSION 2

Each agency participating in the ICH eCTD standard has its own requirements for the Module 1, or Regional, section. The FDA has just released draft guidance for an updated version of its Module 1 specifications. For drug sponsors, two aspects of the new Module 1 guidance are probably most significant: the introduction of bundled submissions and the decision to bring marketing submissions into the eCTD fold.

The right to bundle submissions offers huge time and cost-savings for the industry by allowing information from more than one product or regulatory activity to be sent in a single package. In the meantime, the FDA department that handles marketing submissions has been designated an office in its own right - the Office of Prescription Drug Promotion (OPDP) - and there is now greater differentiation between promotional material for healthcare professionals and that for direct-to-consumer advertising.[2]

Once the updated Module 1 has been implemented, the OPDP will accept eCTDs through the electronic gateway, and new headings and a altered hierarchy mean companies will have to use only one kind of software to send material to the FDA. There remain some issues to address, and Module 1 is currently under review. Final guidance is expected to be issued at the end of 2012, with implementation starting no earlier than January 2013 as part of a phased transition.[3]

EU TURBULENCE MIXED ECTD UPTAKE

The fragile euro isn't the only source of turmoil in Europe. Regulatory submission management behavior is similarly inconsistent. The eCTD is now well established at the European Medicines Agency, which mandated the eCTD for the Centralized Procedure as of January 2010.[4] Yet the Centralized Procedure accounts for only 11% of EU submissions. Of the remaining 89%, 12.7% are under the Mutual Recognition Procedure, 23.8% are under the National Procedure, and 61.8% are under the Decentralized Procedure.

The EU has also struggled to gain much buy-in for the so-called variation guideline, implemented in 2010. In the past, no matter what change was being made to a product license, companies had to get approval first. In an attempt to minimize the administrative burden, the European Medicines Agency has permitted companies to implement variations by simply submitting an annual report to the agency within 12 months. In practice, however, the processes that have been instituted at most companies in Europe don't allow for an automatic trigger that advises when to send something to the agency.

Further guidance covers work-sharing procedures and grouped variations, which the FDA is just now catching up to via its draft Module 1 specification's bundled applications, but the guidance needs updating to cater to eCTD submissions. The uptake has been slower than the health agencies might have hoped a situation now compounded by the EudraVigilance Medicinal Product Dictionary (EVMPD) mandate requiring that by July 2 of this year, marketing authorization holders submit comprehensive EVMPD data for every medicinal product authorized in the EU.

JAPAN & CHINA COMMIT TO ECTD

The eCTD is now well accepted by the Japanese regulatory authority, the Pharmaceuticals and Medical Devices Agency (PDMA), and to date, the agency has received 106 official eCTDs.[5]

The PDMA updated its eCTD question-and-answer section in April 2011 and announced that companies in the industry could now e-mail questions to the agency.6 In addition, the PDMA released eCTD validator version 2.0 in February 2011, the first time the tool had been revised since its release 2 years earlier. The new release streamlines processes and makes it more adaptable for companies. In July 2011, the PDMA released the fourth edition of the eCTD Creation Guide, which included not only updates by the Japanese authority but also industry best practices and experience. Companies are also better able to share information through the Japan eCTD Forum, which in October 2011, introduced an English home page. The forum is open to companies that have submitted eCTDs, and to date, all 37 companies that have submitted eCTDs to the authority have joined.[6]

Meanwhile, China's State Food and Drug Administration (SFDA) has taken firm steps to adopt processes that are more in line with international submission standards and has been looking at ways of implementing the eCTD.[6] While most submissions are still required to be in paper format, the agency has taken several steps toward electronic adoption. For one thing, it provides an electronic application form, which includes summaries of each of the different parts of the submission. At the evaluation stage, the SFDA requests certain elements in electronic format, including quality specifications, packaging, labeling, the manufacturing process, and the clinical databases. At the marketing phase, companies are being asked to submit electronic copies of their adverse-drug-reaction reports, their quality specifications, and their ongoing package inserts.

The SFDA is even working to set up a safe e-submissions gateway, similar to the FDA's Electronic Submissions Gateway. Before it does so, however, it needs to prepare its own internal systems to handle the electronic components.

All of this will go a long way to appease multinational companies that have been eager for China to adopt ICH standards. At present, companies filing in China are finding they have to reformat entire submissions, and standardization would certainly serve to assist with the submission process.

SUMMARY

Efforts continue to create greater global standardization around the way submissions are formatted, though there's clearly still a long way to go. The longer-term goal of harmonizing the submission process - at least among ICH member nations, through the Regulated Product Submission (RPS) - represents an ideal to aim for. The third draft of release 2 has been approved at HL7 as a Draft Standard for Test Usage and is now at ICH for testing.

If all goes according to plan, the RPS is expected to achieve a normative standard by this time next year, with adoption by the FDA a year later. The RPS working group will also work to earn International Organization for Standardization certification - one of the conditions the rest of the ICH requires for its adoption. It is hoped the EU and Japan will then adopt the standard by 2015, allowing RPS to become the first true and internationally ratified standard. ◆

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BIOGRAPHIES

Gillian King has worked in the pharmaceutical industry for over 12 years, from establishing electronic document management systems for Europe, managing global submissions for NCEs, through to leading global functional teams. Her career has taken her into Pharmacovigilance, quality standards, and clinical operations, but her main focus is regulatory affairs and regulatory operations. Today, her role as Director, Head of Global Consulting within the Regulatory Solutions Group of CSC, allows her to immerse herself in challenging and complex business situations, and how organizational design, technology, and the regulatory environment work together to help achieve robust business operating models. Her achievements include setting up global regulatory operations groups and in establishing business processes and functional group design for global development and maintenance of products. She specializes in the "total view" and how cross functional departments must work together to achieve practical results. Ms. King earned her MBA from Warwick Business School, UK specializing in operations management and strategy. She can be reached at gking32@csc.com.

Joel Finkle is Senior Strategist, Regulatory Informatics within CSC's Regulatory Solutions Group (formerly ISI). He is the architect for two of their Document Creation solutions: ISIRender and ISIWriter. In his nearly 7 years, he has performed business process consulting, provided customizations to our solutions, and developed several software business partnerships. In his current role, he is working to find novel ways to solve regulatory software and service processes for customers, as well as providing the focal point for industry standards and regulatory guidance. Mr. Finkle comes from a background in the pharmaceutical industry, with 26 years experience in software development and support of electronic submissions, publishing, and document templates, from custom CANDAs through eCTDs. He is currently a member of the HL7 Regulated Product Submissions (RPS) standard development team, the DIA Electronic Regulatory Submission SIAC Core Team, the DIA Cross-SIAC EDM Reference Model development team, and the OASIS DITA Pharmaceutical Development Team. He can be reached at jfinkle@csc.com.

Directly Compressible "Medicated Chewing Gum (MCG)" for Staying Alert

By: Shivang Chaudhary, MSPharm; Aliasgar Shahiwala, PhD; and Manju Misra, PhD, MPharm

Medicated chewing gums are defined by the European Pharmacopoeia and the guidelines for pharmaceutical dosage forms as "solid single dose preparations with a base consisting mainly of gum that are intended to be chewed but not swallowed, providing a slow steady release of the medicine contained."[1,2] They can be used for local treatment of mouth disease or systemic delivery by direct intraoral absorption through the buccal mucosa.[3] Medicated chewing gums offer numerous advantages over other drug delivery systems, among which some important advantages are highlighted in this discussion.

There is an increasing need to reformulate existing drugs into Novel Drug Delivery Systems (NDDS) to extend or protect product patents thereby delaying, reducing, or avoiding generic erosion at patent expiry. By formulating the drugs in MCG composition, revitalization of old products and reformulation of new patented products is possible to distinguish from future generics competition in the market.

Medicated Chewing Gum (MCG) is a solid single-dose preparation comprising gum base and other ingredients and containing active ingredient(s) that are released by chewing and intended for quick onset of action by direct intraoral absorption into systemic circulation.[4]

Traditionally, MCG has remained as a niche category due to its complex formulation and manufacturing that uses hot mixing and extrusion procedures involving specific technology and equipment that most pharmaceutical companies are not familiar with. Moreover, the use of heat and liquids in these processes prevents many APIs from being considered due to their sensitivity to high temperature levels and moisture.

However, in the recent past, a new door has opened with the launch of innovative directly compressible powder excipients for production of medicated or functional chewing gums. These are designed specifically to bring gum technology closer to pharmaceutical companies by adapting to traditional oral solid formulation and production requirements in the pharma industry.

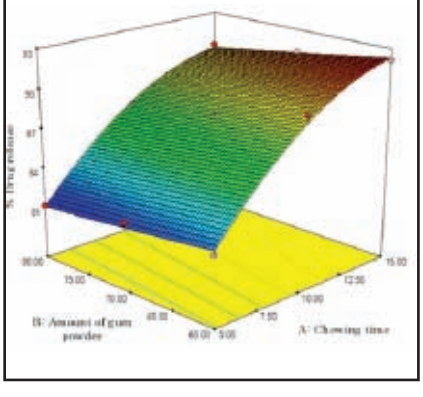
They are made as an "all in one" combination of different ingredients that promote long chewing consistency because they contain the essential gum base, and at the same time, they have great flowability and compressibility properties due to their polyol and glidant content in order to be easily compressed and adapt to pharmaceutical production standards.

The combination of these ready-made gum excipients allows multiple possibilities of formulation with an active ingredient and different flavors of choice, all in a dry room temperature process.

In the present study, MCG was formulated using Health in Gum® directly compressible powder (gum powder) with 100 mg of caffeine. Pharmacopoeia quality control parameters were measured along with a human volunteer study to measure the API release rate from the chewing gum matrix.

Caffeine is a highly soluble and highly permeable central nervous system (CNS) stimulant used in management of fatigue and increasing alertness, and from studies, it has been revealed that chewing action itself enhances 25% blood flow to the brain resulting in improvement in alertness.[2,3] Thus, caffeine chewing gum can address

FIGURE 1



the issues of staying alert in two ways: one from drug (caffeine) and another from a drug delivery system (chewing gum). Therefore, caffeine chewing gum can be a synergistic delivery option for staying alert, especially for professions in which staying alert for long periods of time is necessary and vital.

FORMULATION DEVELOPMENT

The starting raw material of the formulation is the gum powder, which will account for at least 85% of the total weight of the tablet in order to have chewing gum consistency over time. Once the API and flavor combination was figured out in the correct proportions, the mixing process started as follows:

Mixing Procedure

- Mixing of liquid flavor on the powder gum preparation for 5 minutes
- Screening of the mixed preparation through No. 22 sieve
- Mixing of API, antisticking agent, flavoring ingredients, lubricant, and glidant
- Sieving and blending (10 minutes)

Finally, the formulation was compressed. In process quality control (IP-QC), parameters for optimized batch are shown in Table 1, which indicates it had very good flow property and compressibility.

TABLE 1

Parameters	Result With Indication
Angle of repose of gum powder	29.11° - Very good as per EP
Carr's compressibility index of gum powder	8.00 - Very good as per EP
Compatibility of caffeine with gum powder by DSC	In DSC spectrum, separate peaks at 92°C (xylitol), 95°C (sorbitol), and 236°C (caffeine) - No Incompatibility

Results of properties of the powder gum.

CFN-MCG QUALITY EVALUATION A. OFFICIAL (BP/EP) PRODUCT QUALITY ASSESSMENT TESTS

An assay for content uniformity and friability test was carried out as per European pharmacopoeia. The final MCG formulation passed the test for uniformity of mass; none deviated from ± 5% of average mass of MCG. All 10 MCGs, which were sampled randomly, have passed the test for uniformity of content because contents of CFN in all 10 MCGs have fallen within compliance limit of 85% to 115%, and average content of CFN was found to be 99.21% ± 0.53%. In friability testing, after 100 rotations, total weight loss of 10 MCG was found to be 0.14%, which was less than the compliance limit of 1.0%. Thus the final MCG formulations passed in friability test as well.

CFN-MCG performance evaluation for determining the percent of drug release was obtained by a "Chew Out" study of six volunteers in which each person chewed one sample of the caffeine chewing gum for different time periods (5, 10, 15, and 20 mins). Next, residual drug had been cut into small pieces, frozen, and then ground till obtaining fine powder, and then analyzed to determine residual drug content by UV visible spectrophotometer at 273 nm.

So, actual drug content minus residual drug content equals released drug content from the MCG.

The drug contained within the MCG is released in the saliva for the duration of the chewing process, and then it would be either absorbed through the oral mucosa or if swallowed, would be absorbed through the gastrointestinal tract. Pharmacokinetics can be determined from withdrawn blood samples at specific time intervals.

SELECTION & OPTIMIZATION OF FACTORS AFFECTING % DRUG RELEASE FROM MCG BY 3^2 FULL FACTORIAL EXPERIMENTAL DESIGN

Independent significant factors, chewing time (A) and amount of gum powder (B), affecting dependent factor (% CFN release from MCG) were first extracted out by means of ANOVA, and then extracted factors were optimized by 32 full factorial experimental design. Here, full factorial 32 designs were used for the optimization procedure because it is suitable for investigating the quadratic response surfaces and for constructing a second-order polynomial model, thus enabling optimization of the chewing time and amount of gum base to achieve sufficient drug release from MCG. Mathematical modeling,

TABLE 2

No.	Official Tests	Observations	Compliance Criteria	Result
01	**Uniformity of Mass**	None deviated from ± 5%	NMT 2 deviate from ± 5%	Pass
02	**Uniformity of Content**	All 10 MCG contain CFN within limits	85% < x < 115%	Pass
03	**Friability Testing**	Total weight loss = 0.14% of 10 MCG	Weight loss < 1.00%	Pass

Results of official product quality assessment tests.

TABLE 3

Factors (Independent Variables)		Levels Used			Response (Dependent Variables)
		-1	0	+1	
A.	Chewing time (mins.)	5	10	15	% Drug Release
B.	Amount of gum powder (%)	70	75	80	

Results of official product quality assessment tests.

evaluation of the ability to fit to the model, and response surface methodology (RSM) were performed by employing Design-Expert® software (Version 7.1.2, Stat-Ease Inc., Minneapolis, MN). RSM is a collection of mathematical and statistical techniques useful for the modeling and analysis of problems in which a response of interest is influenced by several variables and the objective is to optimize this response. The most extensive applications of RSM are in the industrial world, particularly in situations where several input variables potentially influence some performance measure or quality characteristic of the product or process. This performance measure or quality characteristic is called the response.

Table 3 summarizes the independent and dependent variables along with their coded and actual levels. A total of four experimental testing runs were conducted.

It was illustrated from the surface response graph that as chewing time (A) increases, percent of drug release increases as well, but an increasing amount of gum powder (B) has very little drop-off effect on percent of caffeine release. Specifically: % Drug Release = + 88.33 + 5.67 A - 1.50 B + 0.25 AB - 2.00 A^2- 0.50 B^2.

The quadratic models generated by regression analysis were used to construct a two-dimensional contour plot and three-dimensional response surface plot in which response parameter DR was represented by a curvature surface as a function of A and B. Figure 1 shows the effect of chewing time and amount of gum powder in contour plot as well as response surface plot.

A numerical optimization technique using the desirability approach was employed to develop a new formulation with the desired responses. In this study, optimization was performed with constraints for DR (90% < DR < 95%) set as goals to locate the optimum settings of the independent variables in the new formulation. The optimal parameters to achieve predicted CFN release of 92% (90% to 95%) as calculated from the predicted equation of drug release (A: chewing time = 15 minutes, and B: amount of gum powder = 75%).

TABLE 4

Experimental Test Run	Variable Factors in Coded tTerms (Actual Terms)	
	Chewing Time (mins.)	Amt. of Gum Powder (%)
1	-1(05)	-1(70)
2	0(10)	-1(70)
3	+1(15)	-1(70)
4	- 1(05)	0(75)
5	0(10)	0(75)
6	+1(15)	0(75)
7	-1(05)	+1(80)
8	0(10)	+1(80)
9	+1(15)	+1(80)

Experimental testing runs with values of variable factors.

CONCLUSION

Optimized formulation of directly compressed CFN-MCG has achieved the following:

- Has passed all official MCG quality tests, including uniformity of mass, assay for uniformity of content, and friability testing as per compliance criteria mentioned in the official monograph of MCG in BP.
- Released an average 92% of CFN (n=6) within 15 minutes of chewing, which is half of the normal average chewing time, in an in vivo chew out study.
- Interindividual variability in percent CFN-release was observed in only up to 1 to 3 minutes, afterward, much less interindividual variability was observed in percent CFN release.

Thus, the present study demonstrated that CFN could be successfully delivered by MCG into systemic circulation via direct intraoral buccal absorption.

Concerning statistical analysis, it was shown that a 3^2 full factorial experimental design (FFED) and optimization technique can be successfully used in the development of an optimized formulation of MCG and for deciding appropriate chewing time for sufficient drug release. The optimized formulation exhibited drug release profiles that were close to the predicted responses, which was confirmed by high significant r^2 = 0.988 (> 0.9) value.

Based on the overall results, it was concluded that the developed formulation of directly compressible taste-masked MCG of caffeine presents a better alternative to any other dosage form, including tea or coffee, because it is a synergistic delivery option for

staying alert. Moreover, CFN-MCG can be taken anywhere and anytime without preventing the consumer from living an active life, which promotes higher acceptance and compliance.

Moreover today, it is known that chewing gum has other benefits: it promotes oral health, it is a mild stress relief, and it reduces the appetite sensation, all of which are added positive characteristics that increase the value of a caffeine drug delivery system in the form of chewing gum.This eventually can lead to the development of a new attractive market directed to energy and sports products, which is already flourishing in occidental countries.

Other potential applications for MCG include areas like allergy, cough and cold, digestive, and oral care, added to the consolidated available nicotine and motion sickness gums. ◆

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BIOGRAPHIES

Shivang Chaudhary is a Formulation Scientist with a BPharm from Nirma University of Science & Technology, India, and an MSPharm in Pharmaceutics from the National Institute of Pharmaceutical Education & Research (NIPER), Ahmedabad. During his Masters he felt a necessity of reformulating existing drugs into Novel Drug Delivery Systems (NDDS) to extend or protect product patents thereby delaying, reducing, or avoiding generic erosion at patent expiry. Apart from this chewing gum containing Caffeine (Alllert®) for staying alert, he has also developed medicated chewing gum containing different drugs for various other diseases, such as MCG for Erectile Dysfunction (EreX®) in vanilla, chocolate, strawberry, wild cherry, pineapple, and butterscotch flavors; MCG for motion sickness (Gaglet®) in cardamom, orange, lemon(lime), and ginger flavors; MCG for Vit-B12 deficiency (Smirk®) in banana flavor; and MCG for acidity (Relaaax®) in peppermint and spearmint flavors. He strongly believed that by formulating the drugs in MCG composition, revitalization of old products and reformulation of new patented products is possible to distinguish from future generics competition in the global market.

Dr. Aliasgar Shahiwala is currently working as an Associate Professor in Dubai Pharmacy College. Before joining Dubai Pharmacy College, he was associated with the National Institute of Pharmaceutical Education and Research-Ahmedabad, India. Dr. Shahiwala has earned Masters and Doctorate degrees in Pharmaceutics and Pharmaceutical Technology from The Maharaja Sayajirao University of Baroda, India, and has completed 1-year of post-doctoral research experience at Northeastern University, USA. He has more than 3 years of rich research experience in the formulation and development division of large-scale manufacturers of pharmaceuticals in India and more than 7 years of teaching experience at both the graduate and post-graduate level. His research credentials have established him a reviewer, a member of editorial board, a speaker, and an invited author for various pharmaceutical scientific journals and conferences. Dr. Shahiwala's key strength is diversity of work experience in different settings.

Dr. Manju Misra is currently serving as Assistant Professor at NIPER Ahmedabad. She has prior experience working as part of an ANDA formulation development team at Macleods Pharmaceuticals, Mumbai, and Cadila Pharmaceuticals, Ahmedabad. She earned her PhD from BIT Mesra, Ranchi, India, and her MPharm from Nagpur University, India.

Marketing Matters

3E Trilogy: Entertain, Educate & Engage…..Become an Infotainer

A multiple part series on effective messaging and communications in the life science industry.

By: David F. Scelba, Partner, LifeSciencePR

In my previous column (May 2012, page 24-25), I provided a general overview of my four trilogies and four simple steps to implementing a social media strategy. In this column, I'll explain in greater detail my 3E Trilogy …Entertain, Educate & Engage.

Now, it doesn't really matter if you're in the Life Science industry or frankly any other marketplace. The fact is that effective communications means commanding and keeping your audience's attention, and the most effective way to keep their attention is to entertain them.

One of the best teachers I had in high school was my history teacher Mr. De Nooyer. He was someone who clearly understood the importance of entertaining to educate, and he engaged every student, even those with challenging attention spans. As an example, he would dress up in colonial garb when he was discussing the Revolutionary War. He even wore a German uniform and spoke with a German accent to dramatize the unspeakable evils of the concentration camps of World War II. At the time, we all thought he was nuts, but the truth is, he was a master communicator. His classroom antics and theater helped the lessons "come alive" in an incredibly entertaining and memorable way. It's been more than 40 years since I sat in his class, but I can still remember his lessons like it was yesterday. Mr. De Nooyer was a teacher's teacher and an incredible salesman.

With today's technologies and multiple social media outlets, Mr. De Nooyer's entertaining lessons could have been delivered and distributed to an infinite number of virtual classrooms and inquisitive students throughout the world.

But while YouTube, Facebook, Twitter, LinkedIn, Pinterest, and all the other social media outlets deliver content to the right targeted audiences, they won't gain an audience if the content isn't entertaining.

The key to implementing a successful social media strategy is the development of interesting content and, of course, the creative execution. You've all heard the saying, "Content is King," and it's absolutely true, but only if it's presented in an entertaining manner.

By now everyone knows video is the most efficient and effective communications tactic used throughout all websites, blogs, social media networks, and mobile apps. Just as Mr. De Nooyer was never embarrassed about wearing uniforms or acting in front of the live class, you shouldn't be self conscious or feel silly reading from a teleprompter in front of a video camera.

So let your creative juices flow and become an "Infotainer" with the ultimate goal of entertaining your audience. If you develop good content and creatively present it, you'll educate your audience and engage them in ongoing communications. Engagement acts as one measurement matrix of your content and creativity, and is an indicator of whether you're doing a good job communicating.

Entertain, Educate & Engage … my simple 3E Trilogy to better, more effectively, and efficiently leverage social media communications to achieve your company's strategic marketing and communications initiatives! ◆

BIOGRAPHY

David F. Scelba is the Founder and Chairman of SGW Integrated Marketing & Communications and is a Partner at LifeSciencePR. He is responsible for the development of the company's new interactive products and services and plays a key role as senior strategist for developing clients' integrated marketing communications programs. He is also involved in researching and investigating acquisition opportunities and for initiating negotiations on behalf of the company. As a consultant to the broadcast, computer, and telephone industries Mr. Scelba experienced the technology convergence first hand. This unique background provides him the ability to develop innovative products and services that generate the most cost-effective and efficient marketing strategies available today. His diversified B2B, consumer, and retail experience encompasses industries such as: automotive; biochemical; broadcast; education (K-12-colleges/universities); healthcare; hospitals; life science; microwave; pharmaceutical (research/drug delivery); political; professional video/audio; medical; telecommunications; and more. He is a keynote motivational speaker whose audiences include marketing professionals, college professors, MBA graduate students, and undergraduates seeking careers in the marketing- and communications-related industries. He also mentors business and government leaders on the use of technologically innovative tools for better communication with their targeted audiences. Mr. Scelba earned his BA and MA in education, a CFP Certification, with series 6 qualifications, Health/Life and Real Estate Licenses, which contribute to his common sense marketing philosophy.

Addressing Solubility Challenges: Using Effective Technology & Problem-Solving for Delivery Solutions

By: Rod Ray, PhD, PE

INTRODUCTION

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

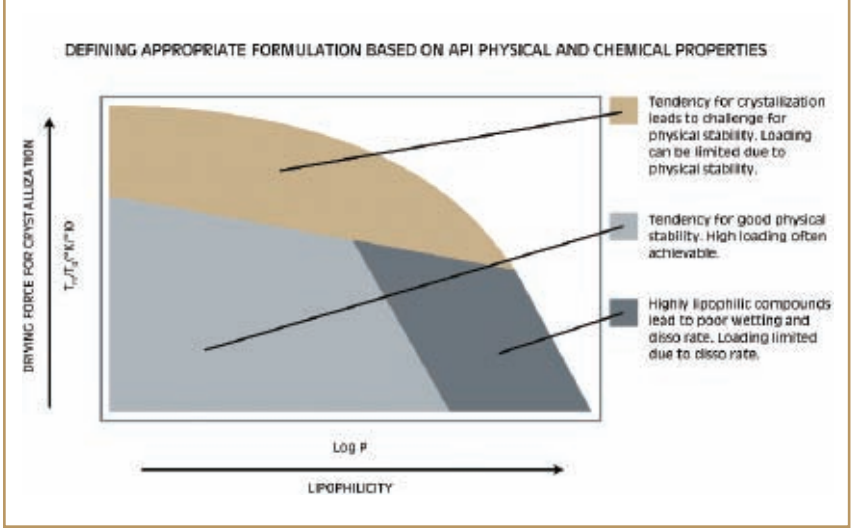
This review is a follow-up to an interview published in the May 2012 issue of Drug Development & Delivery in which the company's background and problem-solving approach to drug delivery challenges faced by the pharmaceutical industry were discussed.

SCIENCE & TECHNOLOGY TO SOLVE BIOAVAILABILITY CHALLENGES

Delivery of compounds with poor aqueous solubility is a common problem as more than 50% of new chemical entities fit into Class II of the Biopharmaceutical Classification System (BCS). BCS Class II compounds are poorly soluble but highly permeable, meaning that most cannot be absorbed during normal gastrointestinal transit times without an enabling formulation.

While there are many types of enabling formulations that improve the solubility of low-solubility compounds, they are generally based on three approaches: (1) use of high-energy crystalline forms, such as salt forms, co-crystals, and crystals with reduced particle size; (2) dissolution of the drug in a lipid vehicle or lipid, solvent, and surfactant vehicle (to create a self-emulsifying dosage form); or (3) manufacture of an amorphous dispersion. Amorphous dispersions are generally manufactured by spray-drying or a hot-melt process. Each of these approaches is viable, depending on the compound's physical and chemical properties, and all have been used for commercial pharmaceutical products.

FIGURE 1



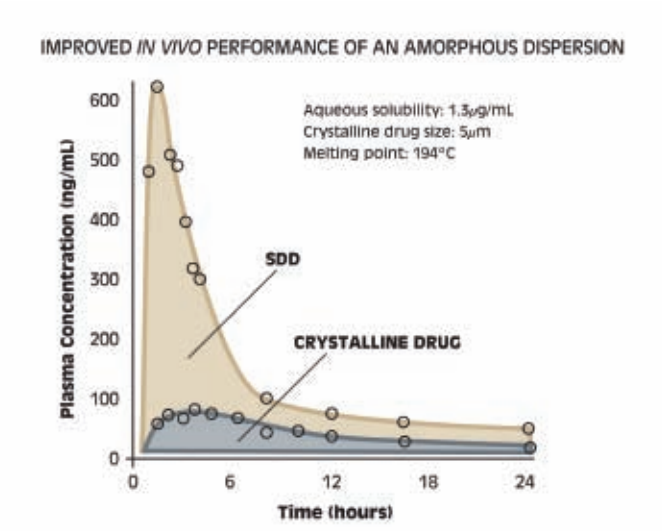
CHOOSING THE APPROPRIATE TECHNOLOGY

Bend Research takes an "agnostic" approach to choosing the appropriate solubilization technology, guided by a number of factors, including the compound's physical-chemical properties, the projected dose, the desired release profile, and the results from numerous formulation and process models that we have developed throughout the past 15 years.

The goal in choosing the optimum solubilization technology is aimed at solving the right problem for that specific compound. Bend Research is capitalized for formulation development and cGMP manufacturing for spray-drying, hot-melt extrusion, and particle-size reduction to support our agnostic approach. Additionally, we can support the formulation of self-emulsifying and lipid formulations relying on a partner to complete the cGMP manufacturing.

While we consider all possible technologies as we develop formulation approaches for poorly soluble compounds, our experience in the formulation of more than 500 low-solubility compounds is that spray-drying amorphous dispersions is the most widely applicable approach. This process involves dissolving the compound and a concentration-sustaining polymer in a volatile organic solvent that is rapidly removed in the spray dryer. This process allows for rapid drying of the formulation and isolation of the amorphous dispersion. It is widely applicable in that it avoids either melting the compound in a hot-melt process or relying on the solubility of the compound in a lipid vehicle.

FIGURE 2



An additional benefit is that the spray-drying process has been scaled down to small scales compatible with early preclinical quantities of compound and scaled up to the multi-ton scales necessary for commercial manufacture.

SPRAY-DRIED DISPERSIONS: KEY FACTORS & PROCESS OVERVIEW

There are three key components to obtaining a high-performing amorphous dispersion. These are the spray-drying process conditions, the identification of the compound's physical-chemical properties, and finally, the choice of excipients that are used in the amorphous dispersion.

The spray-drying process is conceptually quite simple. Initially, the compound and a dispersion polymer are dissolved in a volatile organic solvent (e.g., acetone or methanol). The solution is then introduced into the drying chamber of a spray dryer along with heated nitrogen. The heated gas evaporates the solvent, leaving a dried powder, which is collected in a cyclone or baghouse.

Of course, the process isn't quite that simple. If the drying capacity of the nitrogen is insufficient, product will be deposited on the walls of the spray dryer, resulting in "spray-painting" and reduction of product yield. If the drying capacity of the nitrogen is overdesigned, energy costs are increased, and the risk of degrading a thermally labile compound is increased.

However, by using best practices, spray-drying conditions can be identified that allow the product particles to be maintained at low temperatures (due to evaporative cooling as the volatile solvent evaporates), while producing high product yields (avoiding spray-painting of the walls of the dryer). These best practices for spray-drying process development were highlighted in a 2009 publication in the *Journal of Pharmaceutical Innovation*.

COMPOUND PROPERTIES: AN IMPORTANT PART OF THE EQUATION

Compounds with a wide variety of physical-chemical properties can be formulated as amorphous dispersions. During our decade-and-a-half formulating amorphous dispersions, we have found fewer than 10 compounds that could not be formulated as amorphous dispersions. These fall into two categories: (1) highly reactive compounds that chemically degrade in the amorphous state and (2) compounds with very high melting points that have poor physical stability or poor solubility in suitable spray solvents. However, this small group of compounds appears to be the exception rather than the rule.

The vast majority of compounds we have worked on (out of more than 500 tested) are amenable to formulation as amorphous dispersions, although their physical-chemical properties span melting-point ranges from 0°C to more than 350°C and log P values from less than 0 to more than 10. However, formulation compromises must be made for compounds at the extremes of physical-chemical property ranges to ensure performance is maintained. Generally, these compromises involve decreasing the amorphous dispersion drug loading or "swamping out" the poor drug properties by diluting the drug with the dispersion polymer. Of course, diluting the drug in polymer makes obtaining higher drug doses increasingly difficult. This is especially challenging in therapeutic areas such as anti-infectives, antivirals, and oncology, in which high doses are typically needed. To address these classes of compounds, we have developed alternative technologies.

These alternatives include a nanoadsorbate technology, in which a dispersion is coated on a high surface area support to increase the dissolution rate. This technology has been used in multiple clinical trials and notably has been used in the clinic to give dose-linear absorption of a log P 10 compound with a solubility of less than 10 ng/mL. To address the other extreme–compounds with very high melting points and a strong tendency to crystallize in both the solid state and solution–we have developed a crystallized dispersion technology in which small, tens-of-nanometer-sized crystals are intentionally formed in the dispersion. This approach maintains a high-energy form of the compound and prevents further crystallization of the compound to a lower-energy species. This technology has also been used to advance a number of compounds to clinical evaluation.

THE IMPORTANCE OF EXCIPIENTS

Excipient choice is critical and depends on the specific solubilization problem being solved. Recently, BCS Class II compounds have been subcategorized into DCS IIA and DCS IIB classes by Professor Dressman and co-workers from GlaxoSmithKline. DCS Class IIA compounds have inadequate dissolution rates, whereas DCS Class IIB compounds are truly solubility limited, making bioavailability difficult to achieve without concentration enhancing polymers. An added complication is that some compounds formulated as amorphous dispersions dissolve into solution and stay at that amorphous concentration. Others, particularly those with high melting points, dissolve and then rapidly crystallize if they are not sustained by the polymer.

As an example, for a DCS Class IIA compound for which amorphous solubility is easily sustained, the critical problem to solve is getting the compound to rapidly dissolve. Often, neutral polymers, such as BASF's Kollidon VA64 (vinyl pyrrolidone-vinyl acetate copolymers), work well due to their high water solubility, ability to dissolve in gastric media, and the reduced need to sustain the drug concentration. In fact, Kollidon VA64 can be highly preferred in these cases due to its high solubility in organic solvents typically used in spray-drying. Higher spray-solvent concentrations can substantially improve throughputs, which can lead to a decrease in the cost of goods.

For compounds that have a tendency to crystallize in solution or the solid state and that require improved solubilization, enteric, cellulosic polymers, such as Dow or Shin Etsu's hydroxypropyl methylcellulose acetate succinate (HPMCAS) or Eastman's cellulose acetate phthalate (CAP), perform very well. This is due to a combination of factors–one being that the high glass-transition temperature of the polymers lead to superb solid-state stability for the dispersions; the second is that both polymers form colloids in solution that combine with the drug to

yield both enhanced solubility and rapid dissolution rates.

As with technology, we are not tied to the choice of specific excipients, but we do find that HPMCAS has led to superior performance for more than half of the compounds we have worked on. An added benefit of formulating with HPMCAS is that Bend Research and its clients have access to one of the most complete safety packages through the Type V drug master file (DMF) for this polymer.

THE FUTURE OF SOLUBILIZATION TECHNOLOGY

With BCS Class II compounds comprising an increasing percentage of compounds in our clients' discovery portfolios, Bend Research is positioned to continue to provide the highest-quality support and innovation for our clients' pipelines. This proactive support is focused on two crucial areas: (1) support of the existing technology platforms and (2) development of next-generation technologies.

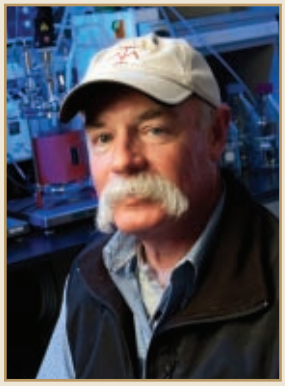
To support existing technologies, we are engaged in ensuring clients have seamless access to the spray-drying capacity required as their compounds advance, as well as ensuring high-quality excipient supplies. An example of ready client access to spray-drying capacity is reflected in our collaboration with Hovione. This collaboration allows for facile transfer of programs from Bend Research's research and development facilities to Hovione commercial facilities, either during Phase III clinical trials or following product launch. We know from experience that each client has preferred timing for this transfer, and we work with them to identify the best options and to perform technology transfer against this plan.

Similarly, we are working with the leading excipient providers to ensure access to a reliable supply of solubilization excipients that meet the critical-to-quality properties that are keys to their performance. These relationships are an active piece of our technology-development portfolio and continue to mature.

In addition to supporting the existing technologies, Bend Research is working to develop new solubilization technologies. These efforts include working with the excipient providers to develop new solubilization excipients that improve performance and processability as well as developing improved spray-drying processes and equipment.

Finally, in addition to our internal research and development efforts and our ongoing work with our alliance partners, we are actively forming partnerships to commercialize the best new solubilization technologies in partnership with universities and small companies. Based on our company's successful track record in advancing numerous technologies and reducing them to practice, this work is only natural, particularly given the increasing number of poorly soluble compounds being developed by the pharmaceutical industry. ◆

BIOGRAPHY



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

Recent Developments in Microneedle Technology for Transdermal Drug Delivery & Vaccination

By: Mikolaj Milewski and Amitava Mitra

INTRODUCTION

The skin has long been recognized as a potential target for local and systemic drug delivery as well as vaccination. The practical value of transdermal route of drug administration is, however, limited by substantial barrier properties of the skin. Physiologically beneficial protection that the skin provides against xenobiotic permeation is a drawback from the perspective of percutaneous transport of therapeutic agents. Thus, a delivery system that temporarily and reversibly permeabilizes the skin can enable delivery of a wide spectrum of molecules across the skin. One such technology is microneedles, which are micron-scale needles that can create microscopic pores in the stratum corneum and upper layers of the epidermis, thereby enhancing skin permeation up to several orders of magnitude.[1] Four designs of microneedles have been developed: dissolving microneedles made of biodegradable polymers that encapsulate drugs or vaccines, solid coated microneedles in which the drugs or vaccines are coated on the microneedle surface, hollow microneedles for injection, and solid microneedles to pierce the skin followed by application of a drug patch (poke and patch approach) (Figure 1).[2] The purpose of this article is to highlight some of the recent advances in the field of microneedle-mediated transdermal drug delivery and vaccination, including summaries of preclinical pharmacokinetic data and a brief overview of clinical studies. This review encompasses the time period from 2010 to present day. For more background on microneedles, interested readers should refer to the following references.[3,4]

MICRONEEDLE-ASSISTED TRANSDERMAL DRUG DELIVERY

Dissolving Microneedles

These types of microneedles are fabricated using biodegradable polymers in which drugs or vaccines are encapsulated in the microneedles.[5] Once in the skin, the microneedles dissolve, thus releasing the drug. The enhancement of flux afforded by microneedles has generated significant interest in this transdermal delivery technology for delivery of peptides and proteins. Fukushima et al reported using two-layered dissolving microneedles for transdermal delivery of human growth hormone (rhGH) and desmopressin (DDAVP) in rats.[6] rhGH (22 kDa) was formulated at 2-microgram doses in the dissolving microneedles composed of sodium chondroitin sulfate and dextran. The application of this microneedle formulation to the rat abdomen produced a PK profile characterized by fast attainment of peak concentration (t_{max} = 15 mins) and gradual decrease in the plasma rhGH level with terminal half-life approximating 25 mins. Chondroitin-based and dextran-based microneedles performed similarly. Importantly, the authors observed dose-proportional increase in C_{max}, and the area under concentration-time curve (AUC) as a function of dose. Also, the bioavailability was very high and amounted to approximately 95% in chondroinin microneedles and 73% in dextran microneedles. Interestingly, the IV bolus injection of rhGH revealed much shorter elimination half-life (4 mins) implying flip-flop kinetics for microneedle-mediated delivery. Hence, the terminal half-life of 25 mins following microneedle application was attributed to the absorption rather than elimination phase. On the other hand, DDAVP (1.07 kDa) chondroitin microneedles showed no flip-flop kinetics and an absorption phase half-life of 14 mins. PK profiles were characterized by t_{max} of 30 mins and terminal half-life of approximately 2 hrs. Approximately 0.1 mg rhGH could be formulated into a patch of 100 microneedles. The microneedle formulations were stable for at least 1

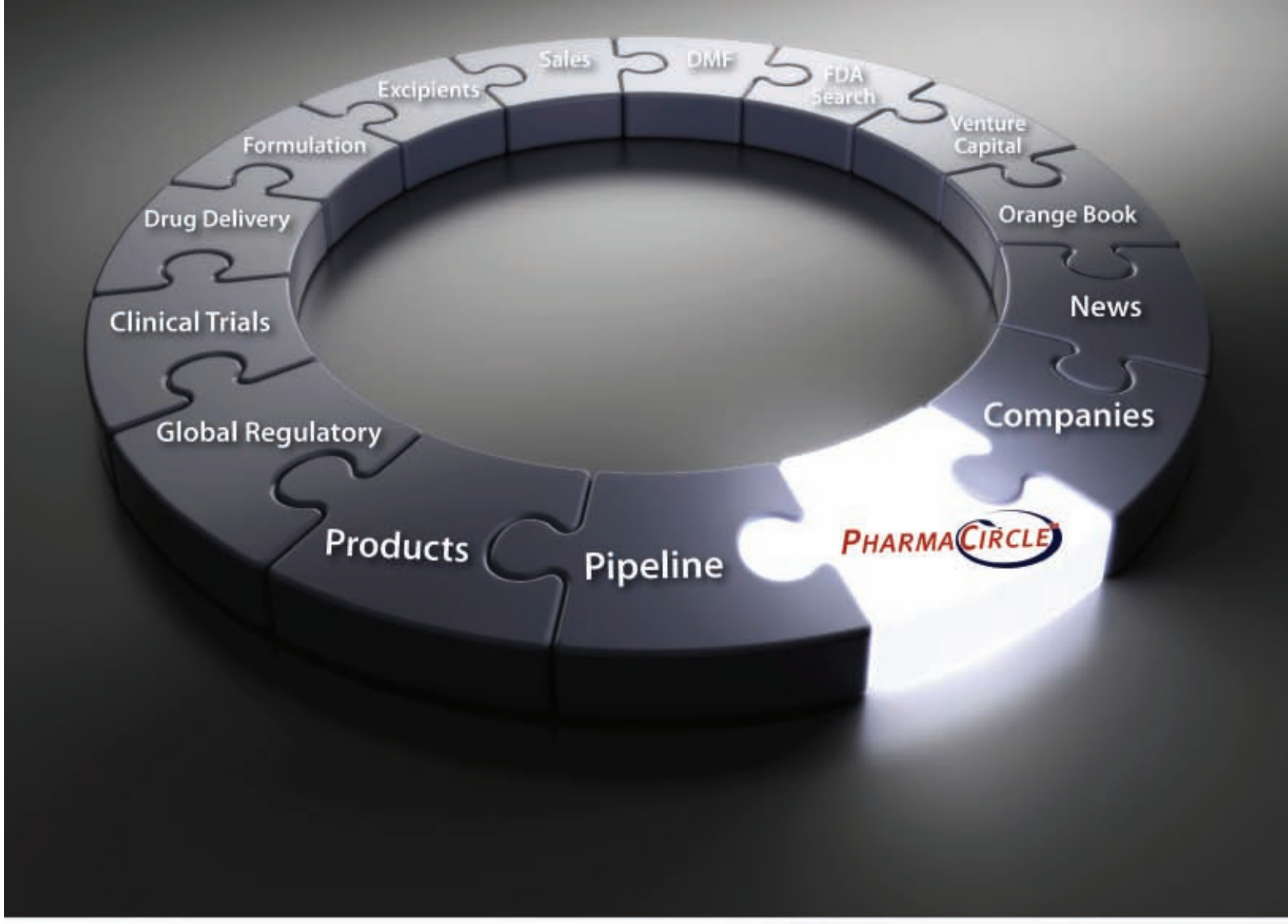


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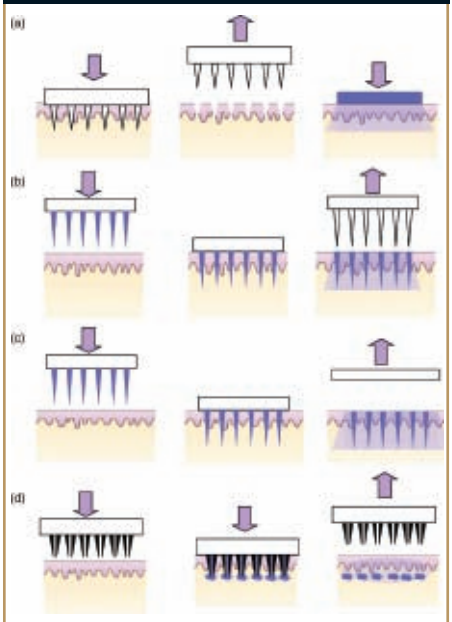
FIGURE 1



A schematic depiction of four basic modes of microneedle application in transdermal drug delivery: a) poke and patch in which the skin is pretreated with microneedles to be subsequently covered by a transdermal formulation; b) coated microneedles in which drug is coated on the surface of the microneedles; c) dissolving microneedles in which drug is embedded in the matrix of dissolving microneedles (typically polymer- or sugar-based); and d) hollow microneedles in which drug formulation is injected intradermally. Reproduced with permission from the International Journal of Pharmaceutics. 2008;364:227-236.

month under refrigeration or freezing conditions.

An independent, but related, study of hGH in rats was carried out by Lee et al.[7] Carboxymethylcellulose-(CMC) and CMC-trehalose-based dissolving microneedles were administered to hairless rats reaching C_{max} after approximately 30 mins and subsequently, plasma concentration decreased gradually with a half-life of 1.1 hrs. The authors subsequently compared microneedle-mediated hGH delivery with subcutaneous (SC) injections demonstrating markedly similar PK profiles.

Another study by Yukako et al reported low bioavailability of peptide leuprolide acetate (LA, 1.2 kDa) following administration to rats by dissolving microneedles and subcutaneous injection.[8] In accordance with in vitro release data, in vivo PK profiles demonstrated short tmax (15 mins) for microneedles and 20 mins for SC injection. However, low bioavailabilities (32%) were observed due to the metabolic instability of LA in skin. This study highlights the potential limitations of microneedle-mediated drug delivery related to the physiology of the skin rather than the microneedle technology itself.

Coated Microneedles

Daddona et al studied the pharmacokinetics and pharmacodynamics of parathyroid hormone (PTH, 4.1 kDa) microneedle-mediated delivery in humans.[9] The microneedle arrays consisted of titanium microneedles coated with PTH (20 to 40 micrograms) attached to an adhesive patch. The patch is applied with a hand-held and reusable applicator. A once-daily subcutaneous injection of FORTEO®, which is used as a therapy for advanced osteoporosis in men and post-menopausal women, served as a reference for the evaluation of the coated microneedle system performance with a wear time of 30 mins. Clinical studies in post-menopausal women demonstrated that the microneedle system achieved shorter t_{max} of approximately 8 mins compared to 24 mins for SC injection. The terminal half-life after SC injection was longer compared to microneedle delivery, and implied flip-flop kinetics. The relative bioavailability of the PTH microneedle patch ranged from 40% to 80%. Interestingly, these differences were believed to be dictated by application to different anatomical body sites and not by the patch performance inconsistency, with the highest relative exposure that was obtained from the abdomen, followed by upper arm, and the lowest from the thigh. In each case, the residual PTH found on the microneedle array after application was < 20%. Dose-proportional increase in the AUC was observed in the clinic. The inter-subject and between-occasion intra-subject variability seen in the PTH-patch and FORTEO were comparable. Pharmacodynamically, the PTH-coated microneedle produced dose-proportional increase in the bone mineral density. The magnitude of this effect was higher compared to FORTEO and might be related to different PK achieved with the application of PTH microneedle. Moisture and oxygen-devoid packaged PTH microneedle patches were found to be stable in room temperature for 2 years, which is a significant advantage over FORTEO that needs to be stored at 5°C to 8°C.

Another study involving the Zosano microneedle patch system was carried out by Peters et al.[10] In this study, the stability and preclinical performance of erythropoietin-coated microneedles (EPO, approx. 34 kDa) was evaluated in rats. Pharmacokinetic profiles obtained following SC and microneedle-assisted administration of EPO were alike and resulted in t_{max} of 6 to 12 hrs and a terminal elimination half-life of 9 to 12 hrs. A linear AUC dose-response curve was achieved within the 7- to 200-microgram dose range tested. Moreover, the relative bioavailability of EPO after microneedle administration was comparable to that obtained following SC injection.

Zhang et al investigated the potential of lidocaine-coated microneedles for local analgesic action in domestic swine.[11] This study was unique because here, an attempt was made to use the microneedles to enhance local (dermal) delivery of a therapeutic agent. The authors used 3M's 500 micrometer-long solid microneedles, termed sMTS, dip-coated with aqueous lidocaine (234 Da) solution. The local lidocaine concentration, obtained at the treatment site immediately following microneedle application was higher than the estimated level needed for analgesia and was maintained for an hour when co-administered with vasoconstrictive lidocaine.

Hollow Microneedles

Harvey et al investigated microneedle-based intradermal and subcutaneous delivery of protein drugs in Yucatan minipig.[12] The authors employed a single microneedle device for injection of insulin and somatropin and a three-microneedle device to inject etanercept in the dermal space. In the context of this study, microneedle refers to a manually assembled complex of 1-mm-long 34-gauge steel needle, flexible tubing, and an analytical microsyringe drug reservoir. Formulation volumes injected intradermally varied in the range of 50 to 250 microliters. Etanercept (132 kDa) injections demonstrated markedly shortened t_{max} (5 hrs) of

microneedle-mediated delivery as compared to 18 hrs for subcutaneous injection. The absolute bioavailability was 75% for microneedles and 50% for SC administration. Similarly, somatropin (22 kDa) injections showed faster absorption kinetics following intradermal microneedle-mediated injections (t_{max} = 30 mins) as compared to subcutaneous administration (t_{max} = 2.75 hrs). The absolute bioavailability was found to be 100% for both routes. Moreover, insulin lispro (5.8 kDa) demonstrated rapid uptake to systemic circulation when administered intradermally (t_{max} = 22 mins) and slower uptake following SC injection (t_{max} = 61 mins). Interestingly, the absorption rate of regular and fast-acting insulin after microneedle-mediated intradermal injection was comparable. In all of the aforementioned studies, shorter t_{max} was accompanied by higher C_{max}. The authors performed additional imaging studies that led to the hypothesis that rapid uptake seen for microneedle-mediated intradermal protein delivery is aided by fast lymphatic uptake in the dermis.

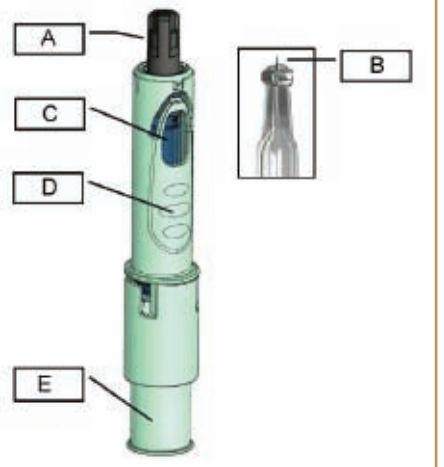
Pettis et al studied intradermal microneedle delivery of insulin lispro (5.8 kDa) versus its SC delivery in healthy human volunteers.[13] Application of insulin intradermally through a single stainless steel hollow microneedle and an SC injection resulted in rapid systemic absorption and bioavailability of microneedle-mediated delivery comparable to SC injection. T_{max} values increased (36 mins, 40 mins, and 46 mins) with increasing microneedle length (1.25 to 1.5 to 1.75 mm) and proved to be the highest for SC injection (64 mins).

Subcutaneous and intradermal delivery of liquid formulations through multiple hollow microneedles (hMTS, 3M Drug Delivery Systems) in domestic swine was studied by Burton et al.[14] Pharmacokinetic studies compared microneedle-mediated and SC administration of three model compounds: naloxone (322 Da) hydrochloride, hGH (22kDa), and equine tetanus anti-toxin (ETAT, approx. 150 kDa). Interestingly, naloxone hydrochloride showed faster absorption following SC injection compared to microneedle administration. In contrast, hGH showed faster absorption following microneedle administration. The antibody (ETAT) showed similar PK profiles with both SC and microneedle administration.

Poke & Patch

This delivery approach involves piercing the upper layers of the skin with solid microneedles followed by application of a drug formulation (eg, patch, gel) at that site.[2] The pretreatment creates microscopic pores in the skin, thereby enhancing flux of the molecules. Zhang et al reported increased bioavailability of L-carnitine (LC) in rats with the poke and patch method compared to its oral administration.[15] Although LC is a small molecular weight compound (161 Da), it does not permeate at high rates through intestinal epithelium or skin due to its ionized and hydrophilic nature. Authors investigated in vitro permeation of LC from solution across untreated and microneedle pretreated skin and demonstrated a 17-fold increase in flux across skin pretreated with microneedles. Subsequently, several carbomer hydrogels were evaluated as formulation options. The CP980 gel showed an LC transport rate of 72% of that of the aqueous solution formulation across microneedle pretreated skin. Finally, a rat PK study comparing IV, oral, and poke and patch delivery methods was conducted. Oral delivery of LC resulted in only 8% bioavailability and t_{max} of 2 hrs. Following a 6-hr microneedle-enhanced transdermal LC delivery, 22% bioavailability was achieved with t_{max} at 4 hrs. The bioavailability was calculated on the basis of the total dose applied in the patch. An alternative calculation based on the fraction of the total dose that was actually delivered into skin yields a bioavailability of 81%. Interestingly, the poke and patch PK profile resembled a traditional non-microneedle percutaneous profile in the sense that relatively steady plasma levels were obtained in the 2- to 6-hr time window. However, the likely reason for lack of more pronounced C_{max} is that the timeline of the experiment was relatively short, and the microchannels did not close enough to significantly limit in vivo flux through the microchannels.

FIGURE 2



Becton Dickinson's Micro Injection System demonstrating: a) microneedle shield; b) microneedle pre-attached to the tip of the syringe; c) vaccine-level check window; d) finger pads; and (e) plunger rod. Reproduced with permission from Vaccine 25 (2007) 8833–8842.

MICRONEEDLE-ASSISTED VACCINATION

The use of the skin as a target site for vaccination has been largely limited due to the difficulty in reliably performing intradermal injections. With the advent of microneedles, a minimally invasive and precise intradermal placement of vaccine has become possible. The skin is known to be a highly immunogenic tissue containing a wealth of antigen-presenting cells, including epidermal Langerhans' cells and dermal dendritic cells.[16] As such, it is a good vaccination target with additional dose-sparing potential compared to less-immunogenic muscle tissue.

A recent study by Weldon et al examined an influenza vaccine-coated microneedle in mice.[17] The authors chose to utilize trehalose-stabilized, solubilized viral protein antigens rather than more widely employed inactivated influenza virus and virus-like particles. Microneedles coated with stabilized recombinant trimeric soluble hemagglutinin

(sHA) provided superior protection against influenza virus compared to the unmodified sHA. Moreover, post-challenge lung titers demonstrated that intradermal vaccination resulted in greater clearance of replicating virus compared to the SC vaccination.

In another study, Kommareddy et al investigated the use of dissolvable microneedle patches delivering influenza vaccine antigens in mice.[18] The authors employed TheraJect™ VaxMat™ microneedle technology to incorporate microgram quantities of vaccine in a microneedle patch. A set of in vitro and in vivo studies confirmed the integrity and immunogenicity of the antigens incorporated into a dissolving microneedle patch.

However, perhaps most interestingly, 2011 proved a ground-breaking year for the commercialization of microneedle drug delivery technologies in the US. On May 9, 2011, the FDA approved a first, and so far the only, microneedle-based product: Fluzone Intradermal® influenza virus vaccine (Sanofi Pasteur).[19] This constituted a major milestone in the transition of microneedle systems from the developmental stage to the market place. The vaccine is administered from a prefilled microinjection system consisting of a custom syringe with a 30-gauge, 1.5-mm-long, hollow single microneedle developed by Beckton Dickinson (Figure 2).[20] The microneedle is about 10 times shorter than a traditional needle used to perform intramuscular injections of Fluzone. Moreover, Phase III clinical data confirmed that intradermal delivery of vaccine allows for dose-sparing. A 9-microgram dose of vaccine delivered intradermally proved to be immunogenetically comparable to a 15-microgram dose delivered intramuscularly.[21] Hence, a 40% reduction in the dose was achieved. In 2009, Intanza®, an influenza vaccine based on the same microneedle technology, was approved by the European Medicines Agency (EMA).[22] These recent developments and the appearance of first products on the market have encouraged academic institutions and pharmaceutical industries to pursue the microneedle-based strategy for drug delivery and vaccination purposes as reflected by several ongoing clinical trials.

CLINICAL TRIALS INVOLVING MICRONEEDLES

A number of ongoing trails with microneedle-based delivery systems illustrate the significant interest in this new transdermal delivery technology. Several clinical studies are listed in ClinicalTrials.gov.[23] A few of the notable studies are discussed here. Sanofi Pasteur has completed a Phase II trial that assessed non-inferiority of fractional doses of IMOVAX® Polio administered intradermally versus full doses of IMOVAX Polio administered intramuscularly (study results pending). Phase II and III studies sponsored by Emory University currently investigate the difference in glycemic control between the SC insulin catheter and microneedle for bolus delivery of insulin. NanoPass technologies' ongoing studies evaluate the safety and efficacy of a MicronJet microneedle device as well as safety, pharmacokinetics, and pharmacodynamics of insulin injected via MicronJet. A Phase II study on pharmacokinetics and pharmacodynamics of basal insulin infusion administered either intradermally or subcutaneously has been completed by Becton Dickinson (study results pending). Furthermore, a Phase I clinical study assessing tolerability of the application of a 3M microstructure transdermal system has been completed (study results pending). Finally, Zosano Pharma microneedle-based PTH patch had completed Phase II clinical trials, and the results were published and summarized in the aforementioned Coated Microneedles section.

SUMMARY

Early research in the area of microneedle-assisted transdermal drug delivery provided ample proof of its potential in enhancing and enabling transport of pharmaceuticals across thr skin. It also demonstrated its limitations related to the relatively small drug doses that can be used in conjunction with the microneedle technique and the microneedle fabrication complexity, including related challenges in therapeutic agents' stability. Following extensive investigation of microneedle fabrication methods, later studies focused toward improving the performance of existing microneedle systems. Multiple preclinical and clinical studies demonstrated their successful application in vivo. The viability of the microchannels was assessed in vivo and its implications for the applicability of the poke and patch method were recognized. Clinical successes have resulted in significant interest from both academia and the pharmaceutical industry in this delivery area. A selective review of the recent advancements in this field reported herein highlights growing sophistication of this technology in its ability to deliver a wide variety of molecules and vaccines with precision. Importantly, at a time when biopharmaceuticals (biologics and vaccines) are becoming an integral part of pharmaceutical pipelines, microneedle-based devices offer a promising alternative to traditional SC and intramuscular injections.◆

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BIOGRAPHIES

Dr. Mikolaj Milewski is a Senior Research Pharmacist at Merck. As a member of the Biopharmaceutics group, he assesses bioperformance risk of toxicology and clinical formulations. He also evaluates feasibility of alternative drug delivery routes for new chemical entities and existing products. He has authored research and review articles in peer-reviewed journals and is a member of AAPS and ACS. His areas of interest focus on oral and transdermal formulations, pharmacokinetics, and development of microneedle-based drug delivery systems. Prior to joining Merck, Dr. Milewski earned his PhD in Pharmaceutical Sciences from the University of Kentucky in Lexington.

Dr. Amitava Mitra earned his BS in Pharmacy from Birla Institute of Technology, India, his PhD in Pharmaceutical Sciences from the University of Maryland, and completed his post-doctoral fellowship from Fox Chase Cancer Center. Dr. Mitra has published research articles in peer-reviewed journals and has authored review articles and book chapters. He has numerous podium and poster presentations in national and international conferences. He is a member of the AAPS, CRS, and the Rho Chi Pharmacy Honor Society. He is a recipient of the Controlled Release Society-3M Drug Delivery Systems Graduate Student Outstanding Research Award in 2005 and American Association of Pharmaceutical Scientists-National Biotechnology Conference Graduate Student Award in 2006.

INJECTION MOLDING

Injection Molding in the Pharmaceutical Industry

By: Andrew Loxley, PhD, and Brett Braker

INTRODUCTION

Many of the processes used to manufacture products within the pharmaceutical industry are unique to the particular product; however, there are also processes that have been borrowed and adapted from other manufacturing industries and successfully employed in the development of pharmaceutical products. One such example is injection molding (IM); a process developed in the late 19th century for the manufacture of simple plastic objects, such as combs, and later extended to all manner of parts made from thermoplastic and thermoset resins. Parts made by IM that are widely used in the pharmaceutical industry include caps, seals, closures, valves, syringes, inhalers, and the like. As with other plastic processing technologies that enable pharmaceutical solutions for otherwise difficult problems, IM is now gaining in popularity for manufacturing more complex device parts, and is even the platform of choice for preparing certain proprietary drug products.

THE MOLDER

The major components of an injection molder are shown in Figure 1. The IM process involves four essential steps:

1. Melting of material
2. Mass transfer of molten material from an injector into channels called "runners" in the mold and finally into the mold cavity
3. Hardening of the material in the mold to the shape of the cavity
4. Ejecting the part from the cavity to produce the final product

The earliest injection molders used a simple piston to force molten material into the mold. Modern molders use a combined heated barrel/screw/ram assembly in which the solid material is fed to the hopper of the heated barrel, where it is melted by a combination of the heat from the heater bands and the shear forces between the material, screw, and barrel. The molten material is conveyed by the screw toward the nozzle at the end of the barrel, and the screw then travels forward in the barrel as a ram to inject the material into the mold on each cycle. The addition of the screw also allows for some mixing so that multiple feedstocks can be added simultaneously to prepare for example colored parts, or to reuse scrap from previous runs. Two examples of pilot-scale injection molders from Nissei and Arburg are shown in Figure 2. AB Insturments, Thermo Haake and Alba are among makers of lab-scale injection molding units.

Molders can be hydraulic, electric, or pneumatic, with electric or pneumatic

FIGURE 1

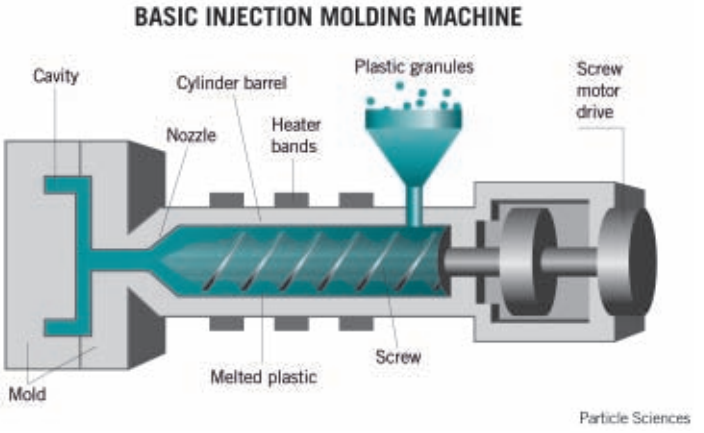
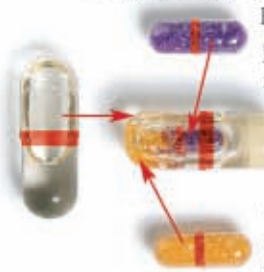


Diagram of basic injection molding machine.

THE ADVANTAGES

OF MULTI-PHASE, MULTI-COMPARTMENT CAPSULES ARE CLEAR

INNERCAP® Technologies Granted US Patent No. 7,670,612 on multi-phase, multi-compartment capsular delivery apparatus and methods for using the same.



March 23, 2010, Saint Petersburg, Florida USA, INNERCAP Technologies, Inc., an international drug delivery and specialty pharmaceutical company, recently announced the grant of US Patent No. 7,670,612 entitled "Multi-Phase, Multi-Compartment Capsular Delivery Apparatus and Methods for Using Same." The delivery system has uses for bio-pharmaceutical, pharmaceutical, medical foods and nutraceutical products. In addition to the existing New Zealand patent, this patent covers the company's multiphase multi-compartment delivery system used to enable the development of multicompartment, multi-phase delivery forms (two piece capsule based) of combination products that have compatibility, formulation or targeted delivery obstacles.

"This is a significant development for INNERCAP Technologies NOVACAP technology," said Fred H. Miller, Chief Executive Officer at INNERCAP. "The continued growth of our patent portfolio establishes INNERCAP as one of the leading companies in this space."

The delivery system and combinations covered by the patent have the ability to deliver therapeutic entities that have never been combined previously and now can be administered together, via an oral, implanted, or suppository capsule, in the most advantageous pharmacokinetic profile, utilizing different physical phases. This technology can therefore be used to enable capsule administration of compounds that are not normally administered as a combination product. The efficacy, safety, and side-effect profiles of drugs can be substantially improved using this delivery technology. It will also provide very significant quality-of-life improvements for patients and substantial economic savings for hard-pressed healthcare systems.

"INNERCAP's multi-phase, multi-compartment technology has been commercially manufactured and validated in several products, demonstrating that INNERCAP's delivery system creates real value to consumers and branded manufacturers," added Mr. Miller.

INNERCAP was represented by Cliff Davidson, Esq. of the patent firm Davidson, Davidson & Kappel, LLC (www.ddkpatent.com) based in New York City.

For more information contact us at the telephone number and email address below:

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being preferred for pharmaceutical applications due to the potential issues of clean room contamination from hydraulic fluid aerosols.

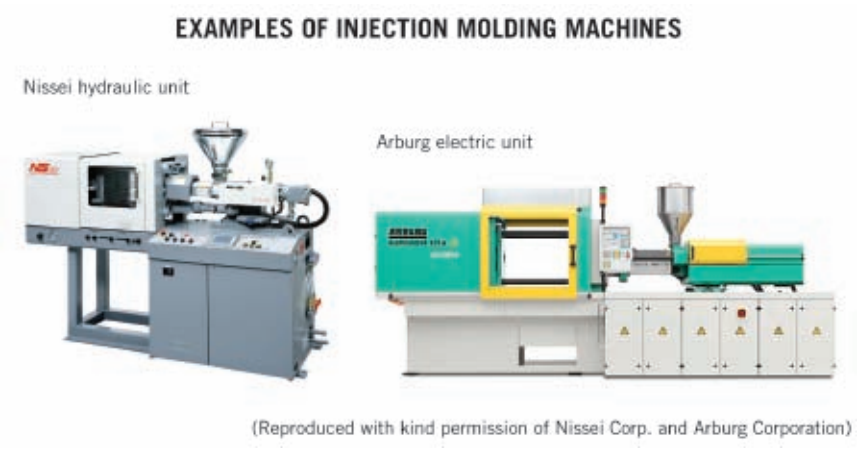
IM machines range in sizes from tabletop versions making micro-parts a few millimeters in size or smaller, to large-scale production machines requiring clamp pressures of the order of thousands of tons to hold the mold halves together during the molding process.

MATERIALS

Materials that are solid at room temperature must be heated above the meting temperature (T_m) before being pumped into the mold cavity. The temperature of the thermoplastic material needs to be raised sufficiently above T_m to reduce its melt viscosity and allow transfer from its reservoir to the mold cavity at manageable pressures. The higher the temperature above T_m, the lower the melt viscosity and hence the lower the pressure required to pump the material through the runners into the cavity. Of course, elevated temperatures accelerate thermal degradation (of polymers, additives, and drugs), so the lowest temperature that allows for reproducible part production should be used. Thermoplastic materials with glass transition temperatures (T_g) above room temperature form hard parts upon cooling, and suitable materials include resins, such as polystyrene, poly(methyl methacrylate), polypropylene, and polyethylene. Thermoplastic materials with T_g below room temperature (thermoplastic elastomers) form rubbery parts on cooling, and example materials suitable for IM are ethylene vinyl acetate copolymers (EVA, eg, VitalDose™), various polyurethanes (eg, Chronothane™, Elasthane™, Tecoflex®), polystyrene-polyisobutylene block terpolymers (eg, Kraton™), polyether-polyamide block copolymers (eg, Peebax®), and polyvinylbutyral (eg, Butvar®).

When the material is a liquid at room temperature, and cures in the mold by a chemical reaction to form the final part, the process is called reactive IM (RIM) and is exemplified by silicone elastomers in which low molecular weight reactive silicone liquids are cured in the mold at elevated temperatures by Platinum-catalyzed or Tin-catalyzed crosslinking reactions. Cycle times are typically longer for silicones than for thermoplastic products, as the part must cure before being ejected from the mold, and this is usually slower than simple cooling.

FIGURE 2



Examples of injection molding machines, on the left, a Nissei hydraulic unit, and on the right, an Arburg electric unit.

MOLDS

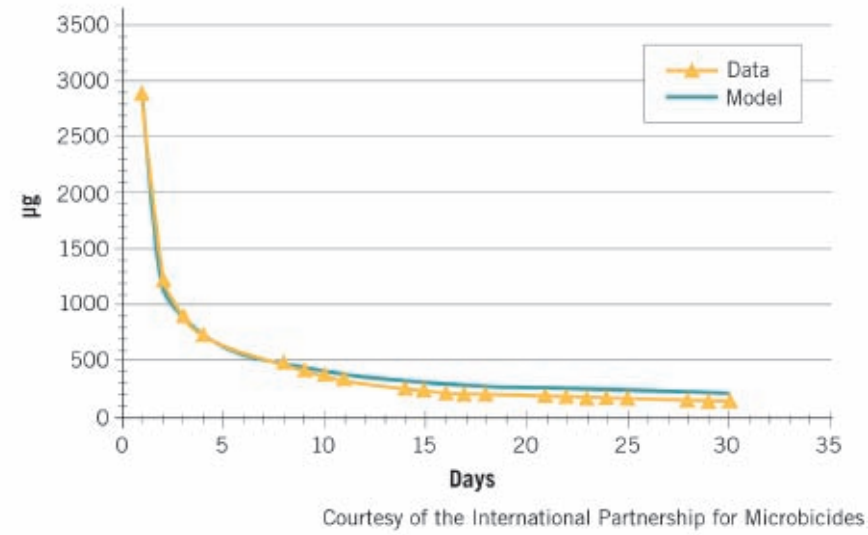
Molds are made of metal plates that have precision machined cavities in which the part cools or cures to take its final form after the material is injected into it. At the smallest tabletop injection molder scale, molds are mostly made from aluminum to save on costs and an example o-ring mold is shown in Figure 3. Production molds for medical and pharmaceutical applications are made of stainless steel of appropriate regulatory grade. Depending on the size and complexity, the cost of molds can range from a few thousand dollars and can go up to several hundreds of thousands.

The runners may be embedded within the plane of the cavity in the mold and filled with polymer from the injection nozzle on each cycle. Molten material is distributed to each cavity in the mold from the runners. Because the cavity is generally not heated, the design is

FIGURE 3

A simple aluminum o-ring mold showing both mold halves. The cold-runner that feeds the cavity is the channel at the top of the upper-right half.

FIGURE 4



In vitro release of dapivirine from an EVA matrix-type IVR made by injection molding (25 mg dapivirine).

called a cold-runner mold, and material in the cold runner hardens or cures with the part and is then removed from the part and discarded as scrap or in the case of stable thermoplastic formulations, sent to be recycled in a later molding run after each cycle. Cold runner systems are generally used for applications in which materials are inexpensive or when use of recycled material is acceptable, as they are less expensive than hot runner systems. However, materials cannot be reprocessed indefinitely, especially if thermally labile, and if thermoset materials are used in cold runner molds, the material must be discarded.

Hot runner systems use a heated manifold that is fed by the injection nozzle and keeps the material molten in the runners in the mold frame outside the plane of the cavity. The molten material enters the cavity from the runners via valve-gates or tips, and there is no scrap, so costly raw materials losses are minimized. Only the material in the cavity cools and hardens on each cycle, and molten material for the next cycle is forced into the cavity from the hot runners as fresh material is pumped into the hot manifold from the barrel nozzle. The fact that material remains continuously molten in the mold means that thermally sensitive materials can be subject to degradation, and the volume of hot runners should be kept as low as possible (a few cavity volumes at most) to ensure labile material does not have a long residence time in the molten state.

PHARMACEUTICAL PRODUCTS BY INJECTION MOLDING

Simple and complex shapes can be produced by IM, and as such, the process is used to prepare a wide variety of plastic medical device parts from caps, seals, closures, syringes, valves, and even implants. All of these require formulation of polymers with a range of additives, such as colorants, antioxidants, fillers, and plasticizers. Many of the compounds are pre-prepared by hot-melt extrusion, pelletized, and the pellets fed to the injection molder to form the part.

Whereas the halves of a gelatin capsule that can be filled with API formulation are traditionally made by hardening a gelatin solution coated on a shaped metal pin by dipping it a into gelatin solution, IM can be used to prepare capsules, for example, the FlexTab™ technology that Capsugel acquired in 2011.

More recently, IM has been used to directly incorporate APIs into shaped plastic parts, and hence used to prepare drug products. The majority of drug products prepared by IM are drug-eluting devices (DED); however, even more recently, IM has been used to prepare solid oral dosage forms (SOD). IM offers the product developer novel delivery features, specific shaped-part preparation capability, and potential for life-cycle management of APIs.

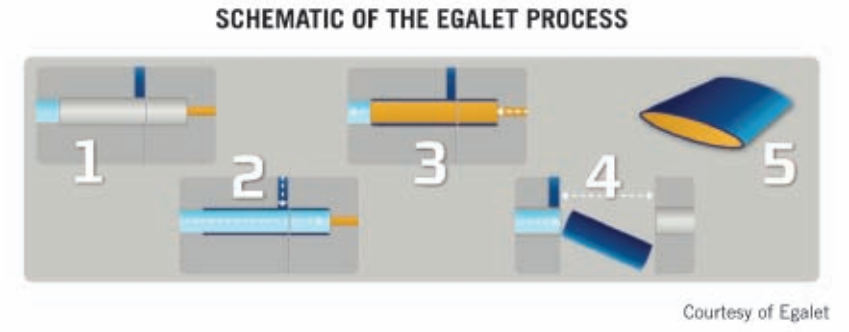
Commercial DED prepared by IM include intravaginal rings (IVR), and several such devices on the market made of silicones manufactured using a RIM process. Examples of such IVR are FemRing®, Estring®, and Progering® for hormone replacement therapy, vaginal atrophy, and contraception, respectively. These are core-sheath reservoir devices in which a drug-loaded silicone core is coated with a drug-free silicone sheath to regulate the rate of release of API from the device, yielding virtually zero-order (constant) release kinetics. The sheath is put over the core in a second injection molding process, making manufacturing quite complex.

The International Partnership for Microbicides (IPM) working with Karl Malcolm and David Wolfson at Queens University, Belfast, has leveraged silicone technology in the development of a simpler IVR containing the non-nucleoside reverse transcriptase inhibitor dapivirine that does not have a rate controlling membrane.[1] This IVR is a device to protect women from HIV transmission during sexual intercourse with an infected partner, and is slated to start Phase III clinical trials in 2012.

The RIM process requires the API and any other excipients to be suspended in the silicone liquids prior to injection (silicones are poor solvents so all added materials are suspended). Challenges arise from aggregation and settling of particulate materials in these fluids, which can cause inhomogeneities and nozzle blocking.

Particle Sciences uses IM in the development of EVA and polyurethane DED for a variety of clients.[2,3] EVA and polyurethanes are thermoplastic polymers, and APIs and additives can be co-mixed uniformly with it prior to IM using hot-melt extrusion to yield pellets that are stable and can be used right away or stored for later IM processing. IVRs are developed first at laboratory scale using a bench-top molder, and successful formulations are then scaled to larger molding units for clinical and then commercial process development. The *in vitro* release of dapivirine

FIGURE 5



Schematic of the Egalet process.

from an EVA IVR made by molding dapivirine-loaded pellets (1.3% w/w API) in a mold with a torroidal cavity is shown in Figure 4 orange markers), along with the drug-release profile fitted using a proprietary predictive model (blue line) showing excellent fit to the data. The diffusion coefficient of dapivirine in EVA can be determined from these plots, which in turn allows the prediction of release profiles from EVA IVRs of different strengths to be made.

The shape of the curve is typical of release from monolithic devices that do not have release-rate controlling membrane, such as the aforementioned silicone IVR, according to Fick's law for diffusion modified for the geometry of the part.[4] Such products are appropriate when a high release on day 1 of use compared to later time points is acceptable or desired.

Very small shaped parts can be made by IM. For example, punctual plugs - small polymer pieces shaped to fit into the orifice through which tears drain (the puncta) - are used in the treatment of dry eye and other diseases of the eye. They can be pure polymer or medicated with API. In either case, they are prepared by micro-injection molding.

Researchers at the University of Ghent in Belgium, have used IM to prepare API-loaded tablets for oral sustained release.[5] For example, metoprolol tartrate (MPT) was formulated into a mixture of polyethylene oxide (PEO) and ethyl cellulose (EC). The formulations were injection molded into biconvex tablets using a Haake MiniJet™ lab-scale injection molder, and the *in vitro* release profiles of the MPT/PEO/EC tablets were compared to compression molded tablets. The workers found a more sustained-release from the injection molded tablets.

The Danish pharmaceutical company Egalet developed a two-step IM process to prepare oral dosage forms. The first step involves molding an open-ended "tube" of non-degradable polymer into which a thermoplastic API/polymer formulation is molded in a second step.[6] Drug is released by erosion from the open ends. The process is illustrated in Figure 5.

SUMMARY

Injection molding is a versatile process that has been in use in plastics processing for more than a century. More recently, it has been used in the pharmaceutical industry to prepare products from medical devices to complex controlled-release dosage forms for both oral and implantable routes of administration. ◆

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BIOGRAPHIES

Dr. Andrew Loxley is Director of New Technologies at Particles Sciences Inc., a contract research organization in Bethlehem, PA, specializing in pharmaceutical formulation development. He leads a variety of projects, based on novel and proprietary nanotechnologies and combination devices, in fields from HIV vaccine and microbicide development, to gene-silencing SiRNA delivery. Prior to joining Particles Sciences, he led development efforts in next-generation lithium ion batteries at A123 Systems Inc, electrophoretic displays at EINK Corp., and emulsion polymers at Synthomer Ltd. British-born, he earned his BSc in Chemistry from the Univeristy of Sussex and his PhD in Physical Chemistry focusing on microencapsulation from the University of Bristol.

Brett Braker is a Formulator at Particle Sciences, focusing on the development of drug-eluting devices. He earned his BS in Plastics and Polymer Engineering Technology from Pennsylvania College of Technology.

MATHEMATICAL MODELING

Mathematical Modeling for Faster Autoinjector Design

By: Jonathan Wilkins, PhD, and Iain Simpson, PhD

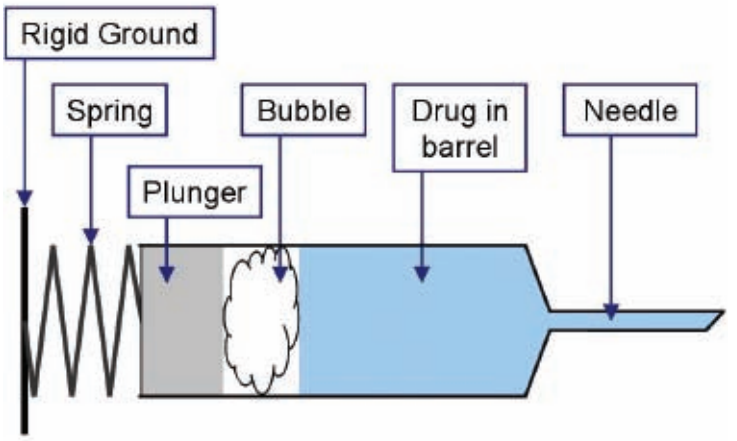
INTRODUCTION

There is an increasing demand for advanced injection devices that bring benefits around self-administration and ease of use and work with new biological drugs, which are often required to be delivered in larger volumes and/or at higher viscosities than those for conventional drugs. In order to reduce development and manufacturing costs, there is also a desire for platform devices, which can meet a broader range of drug and user requirements through simple adaptation of a core design. Unfortunately, a number of devices currently in the market do not meet these requirements and furthermore, there is often a lack of a detailed understanding of how the key design parameters affect the overall device performance. In some cases, this has led to product recalls and in other cases, resulted in challenges in adapting the designs to meet new needs. Hence, there is a commercial need in the injectables industry for better understanding of how design fundamentals affect the performance of autoinjector devices.

Cambridge Consultants believe a fast and effective approach to a better injection device design is a novel combination of mathematical modeling on a desktop PC, and complementary experimental data. The use of mathematical modeling gives insight into the physical behavior of the device, and allows rapid prediction of the effect of different parameters during the design process. The more established experimental approach provides confirmatory data to support the modeling. Cambridge Consultants has deployed this methodology in a number of development projects and achieved benefits in terms of reduced development time, more robust and adaptable designs, and reduced product cost.

Mathematical modeling allows for quick simulations of device performance. The effect of important design parameters, such as injection time, injection force, and shear stress on the drug, can be predicted in real-time. This allows the engineer to investigate the design space and quickly optimize a suitable set of components for a new injection device. For example, the mathematical model can guide the designer in choosing the correct driving spring, needle gauge, and plunger in order to meet the device performance

FIGURE 1



Schematic of the Autoinjector

specification.

In this paper we present a mathematical model of device performance applied to a typical autoinjector. This has the generic features of an autoinjector, but is not tied to any specific commercial device, and thus, can be tailored to investigate a wide range of interesting design features. The approach and the type of physics used inside the model are described. How experimental data can be used to calibrate and verify the model is also shown.

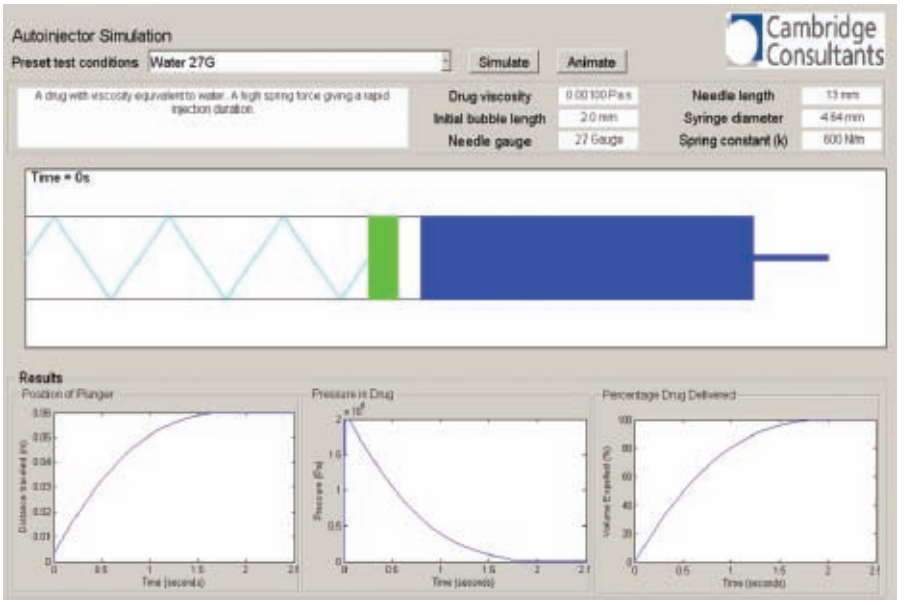
As a case study, we use the mathematical model to predict the effect needle tolerances have on injection times within an autoinjector. This is an essential piece of performance data and is something that would take weeks and an expensive budget to determine experimentally, but that can be done in a few hours with a mathematical model.

THE AUTOINJECTOR MODEL

The generic autoinjector shown in Figure 1 and considered for the model has the following components, which are commonly found in most commercial devices:

- A syringe containing the drug
- A needle
- A compliant plunger to seal the drug into the syringe
- A drive spring as the energy source that powers the plunger
- A liquid drug
- An air bubble between the drug and the plunger

FIGURE 2

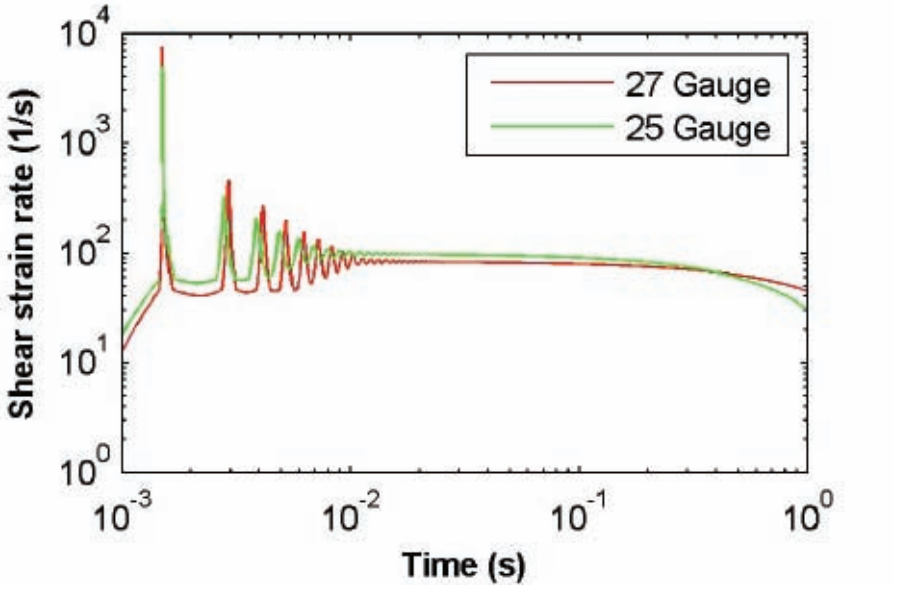


Easy-to-Use GUI for the Model

The trigger that activates the autoinjector by releasing the spring force on to the plunger has not been considered. The physics of each component can be considered in isolation using ordinary differential equations that vary with time.

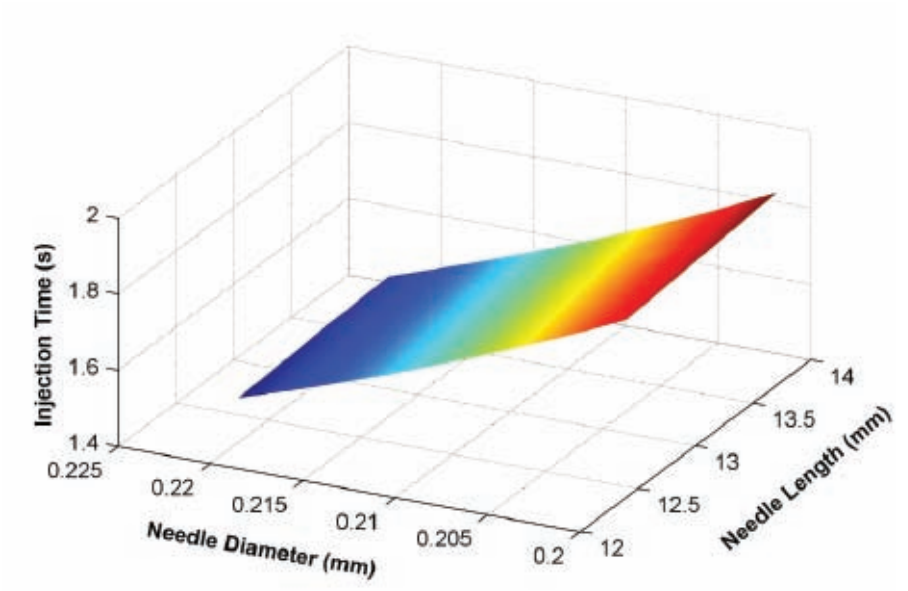
The needle is modeled as a component that creates viscous pressure losses via the Hagen Poiseuille equation and inertial pressure losses at the entry and exit. The drug is modelled as a Newtonian fluid. The plunger is modelled as a rubber component with linear compliance, subject to a maximum compression limit. The syringe exerts a frictional force on the plunger. For the purpose of the model, a 1 ml BD Hypak syringe was used as a representative commercially available syringe. The air

FIGURE 3



Drug Shear Strain Rate Predictions

FIGURE 4

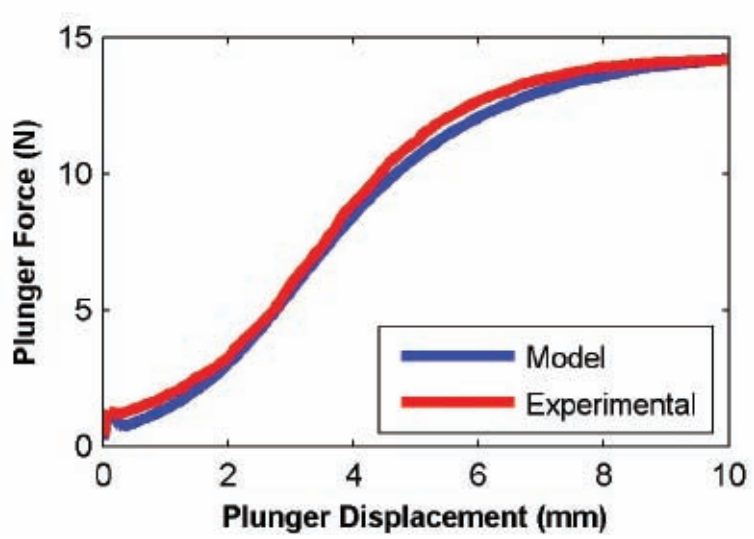


Injection Time Sensitivities to Needle Tolerances

bubble is modelled as a compliance, with an internal pressure related to the amount of compression via Boyle's Law. The spring is modelled as a linear compression spring; it is initially compressed and expands during device activation. It would be a relatively minor change to the mathematical model to replace the mechanical spring with a motor energy source as used in electronic autoinjectors like the EasyPod.

The individual equations describing each component are assembled into a mathematical model of the entire autoinjector system, where all the components are interdependent. We use the Simulink commercial package to solve this system of equations. To make the model user friendly for a wide audience, we built a front-end GUI in Matlab. As shown in Figure 2, the GUI allows for key design parameters to be changed easily, has a graphical representation of the syringe plunger motion, and also plots out metrics of interest such as plunger motion, drug pressure, and percentage of drug delivered as a function of time.

FIGURE 5



Experimental & Simulated Plunger Forces for a Verification Test Case

The model allows us to look at the physical behavior of the autoinjector at various points in time. Some of the parameters we predict are easy to calculate mathematically but difficult to monitor experimentally: for instance, shear stress on the drug. However, knowledge of the shear stress on the drug is important because high levels of shear stress can damage and degrade the molecules within the drug: particularly newer biologic drugs consisting of complex chains of proteins. An example shear stress simulation is shown in Figure 3 for a drug with viscosity 6 times greater than water that is being driven by a spring with stiffness of 600 N/m with either a 27-gauge or a 25-gauge needle. Initially, the shear stress is several orders of magnitude higher than the steady state value. This is due to the impact of the initial spring release that causes rapid compression of the bubble, and subsequent high driving pressures and velocities for the drug in the needle. It is found that that the smaller diameter 27-gauge needle has a peak shear strain rate approximately 50% higher than for the 25 gauge.

The model also highlights the sensitivities in the autoinjector design. For example, consider the effect of needle diameter ±5% tolerances (nominally 27 gauge) and needle length ±5% tolerances (nominally 0.5 inch) on the time to deliver 1 ml of drug with a viscosity equivalent to water. Injection time is an important metric because the patient will prefer a shorter duration injection rather than a long one.

The contour plot in Figure 4 predicts that injection time is much more sensitive to

needle diameter than to needle length. A difference of 23% in injection time results from changing the needle diameter by only -5% to +5% of nominal. This knowledge allows the designer to focus on the needle diameter as the single most powerful design parameter that can be used to adjust injection time.

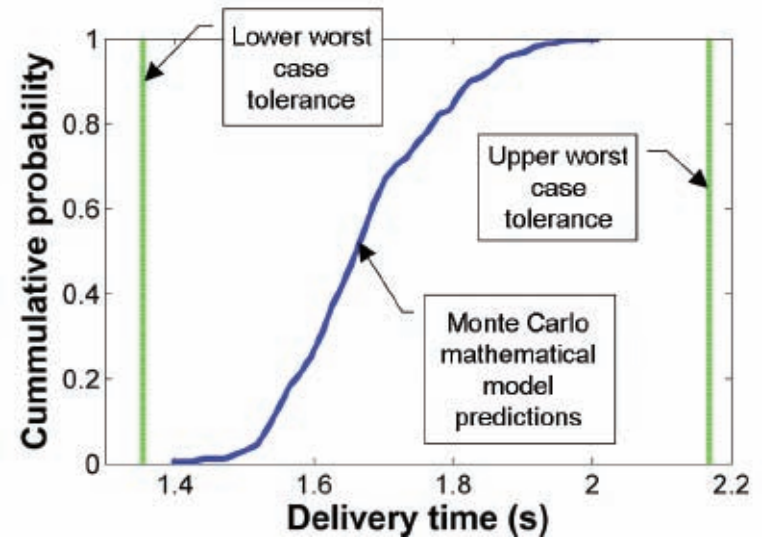
A designer may have to adjust the design to compensate for changes in the drug formulation. This is particularly true for platform devices in which a standard mechanical layout is customized to suit a range of different drugs. The mathematical model can be used to predict how the design must be altered to cope with a change in drug properties such as viscosity.

For instance, suppose an initial version of the device platform is developed to work with a viscosity equivalent to water (1 centiPoise) and has an injection time of 1.6 seconds. This is achieved by using a spring of stiffness 600 N/m. If a new drug formulation has a viscosity that is five times higher (5 centiPoise), and there is a requirement that the injection time should remain constant, the model predicts that to achieve this, a spring stiffness of approximately 1250 N/m will be now be required. This analysis takes minutes to perform with the mathematical model, but would require a lengthy program involving many different mechanical prototypes to do experimentally. Having determined the required higher spring force, the rest of the design can then be re-evaluated and modified if necessary to ensure it can function with the stiffer spring.

EXPERIMENTAL VERIFICATION

It is important to be able to confirm that the underlying equations representing each component in the model are realistic, and that the output from the mathematical model can be trusted. A way to verify the model is to compare it with experimental data of the force required to drive the plunger on a representative commercially available syringe. The measurements were made on a Mecmesin force-displacement tester, which drives the syringe plunger at constant velocity and records the required force. This is a slightly different scenario from the original mathematical model in which a known force from the spring is applied and the velocity of the plunger is calculated. Thus, a modified version of the mathematical model was developed specifically for verification in which the velocity of the plunger is specified and the plunger force is calculated. The verification model was compared against various different experimental test cases. A sample verification of the plunger force mathematical model predictions and measurements is given in Figure 5 for a test case with a 2.5-mm long air bubble in a 1-ml syringe, a 30-gauge needle, and a test liquid six times more viscous than water. Predictions and measurements are in good agreement.

FIGURE 6



Monte Carlo Tolerance Analysis Predictions

CASE STUDY: MANUFACTURING TOLERANCE ANALYSIS

A common problem in injection device development is to understand the effects of manufacturing tolerances on the design. The designer must ensure the device performs within specification over the range of component tolerances, whilst considering that relying on excessively tight manufacturing tolerances can make a design uneconomic. We can apply the mathematical model to predict the sensitivities of an autoinjector to realistic manufacturing process tolerances to see whether a design will always perform to specification.

For example, the mathematical model can be used to aid the designer in understanding how differences in spring stiffness or shape arising from production variations might affect drug delivery performance. For example, for a 5-centiPoise formulation, a 10% reduction in spring force from 1250 N/m increases injection time by a similar percentage, thus the dependence is not so critical.

As another example, consider a device with a 1-ml BD HyPak syringe with a

nominal 27-gauge needle of 0.5-inch length, and investigate the effect of tolerances on injection time. We assume that each needle diameter, needle length, and syringe diameter vary with a process variation of Cp = 1.33.

Using a Monte Carlo approach, we simulate a sample of 1000 syringes that embody this distribution of tolerances, and the results are shown in Figure 6. The mathematical model is run once for each of these syringes, and the injection times are predicted. This takes a matter of hours. Doing this experimentally would take weeks, and would require a lot of test specimens to be made at representative tolerances that would be expensive.

This Monte Carlo approach is more realistic and offers a narrower range of injection times than a simpler worst case tolerance analysis in which all tolerances are assumed to be at the maximum permissible extremes. Our combination of the mathematical model with a Monte Carlo approach means the designer has a more realistic knowledge of the effects of tolerances and can make statements, such as "90% of all devices will have an injection time between 1.5 and 1.9 seconds." That the real distribution of tolerances are narrower than the worst case values means the designer can achieve a given outcome and still specify less-restrictive tolerances in the manufacturing processes. This will result in considerable cost savings, particularly with an autoinjector that is likely to be made in quantities of millions per year.

SUMMARY

This article has introduced a mathematical model of an autoinjector. The fundamental approach considers the generic physical features of a device, and can be tailored to model specific commercial products as required. The model has been written in the commercial package Simulink to make it quick to adapt and to run. Simulink solves the detailed mathematics describing the physics of the device. To make the model intuitive and easy to use, we created a graphical user interface, which means it is accessible to designers who do not necessarily need to know the specifics of the physics behind the device.

We have shown how the model can be used at the early design stage to define key components, such as the drive spring or needle in order to meet the product requirements specification. The model also facilitates platform solutions by allowing the designer to predict rapidly the changes needed in an existing device to meet a change in drug specification. Much of the behavior the model can predict is difficult to measure experimentally, such as shear stress in the drug or behavior over short timescales, but gives valuable insight into how the device functions. The model is also valuable during the manufacturing scale-up process, as it uses a Monte Carlo approach to simulate the effect of tolerance interactions on device performance. This is particularly expensive to do experimentally, as it would require a large range of samples to be manufactured and tested.

We believe more extensive use of mathematical modelling in combination with experimental testing throughout the development process can lead to more robust platform injection devices hence reducing the risk of product recalls and allowing more reliable and cost-effective adaption of device designs for the delivery of new therapies. ◆

BIOGRAPHIES

Dr. Jonathan Wilkins led a range of drug delivery device developments as Senior Consultant at Cambridge Consultants: from inhalers through to novel injection systems. He has an interest in applying mathematical modelling techniques to speed up the development and optimization times of new products. He has an engineering degree and PhD from Imperial College, University of London, specializing in fluid mechanics. He is currently Qualification Manager at Magma Global, developing novel materials and processes for the oil and gas industry.

Dr. Iain Simpson is Associate Director of Drug Delivery in the Global Medtech Practice at Cambridge Consultants. He has a 20-year track record of multidisciplinary technology and product development, the last 12 of which have been spent mainly in drug delivery covering parenteral, pulmonary, nasal drug delivery as well as more invasive device technology of which he has mainly worked in program management and review roles. He has written and presented papers on a range of drug delivery topics, including developing inhalers for children, technology licensing, improving device compliance, and usability. He also lectures on drug delivery to the Cambridge University Masters in Bioscience Programme and is a past Chairman of the R&D Society.
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A Next-Generation Inhaled Dry Powder Delivery Platform

By: Jean C. Sung, PhD

INTRODUCTION

Drug developers have long sought effective pulmonary delivery of therapeutics to treat diseases inherent to the respiratory tract. Indeed, inhaled therapies are certainly favored over oral or intravenous therapies for respiratory and other diseases. Pulmonary drug delivery offers superior direct targeting to the site of action, higher lung doses, and lower systemic drug concentrations, opening the potential for higher therapeutic index with an overall benefit of lower total body dose and reduced potential for adverse events.[1] Delivery of drug to the deep lung can also offer improved access to the systemic circulation with several advantages, including rapid onset of action, avoidance of first-pass metabolism, and convenience as compared to injection.

Traditional inhaled drug delivery has used a number of technologies, including pressurized metered dose inhalers (pMDIs), nebulizers, and dry powder inhalers (DPIs). While delivery of drugs via these first-generation inhaled drug systems provides great advantages over oral or intravenous delivery, these systems also have inherent limitations. The limitations of these systems create a tremendous opportunity for next-generation inhaled delivery platforms that can overcome the shortcomings of today's approaches.

PRESSURIZED METERED DOSE INHALERS (PMDIS)

Pressurized metered dose inhalers (pMDIs) contain drug suspended or dissolved in a volatile propellant that is atomized for inhalation. The propellants that were originally used, chlorofluorocarbons and hydrofluoroalkanes, emit environmentally unfriendly gases. Moving away from these propellants has proven to be difficult with certain drugs and formulations, reducing the number of therapeutics that can be formulated in this way. pMDIs are also characterized by low lung deposition efficiency and require breath coordination for effective delivery.

NEBULIZERS

Nebulizers deliver atomized aqueous drug solution by air jet or ultrasonic mechanisms. Nebulized drugs are typically delivered continuously over multiple breaths. Used mostly for elderly, infant, or critically ill patients, nebulization is typically considered to be a less-convenient delivery system in terms of portability and delivery time, and is also characterized by low lung deposition efficiency. Nebulizers possess limitations in terms of the formulation of drugs that are degraded by shear and air-water interfaces.

DRY POWDER INHALERS (DPIS)

Dry powder inhalers (DPIs) have traditionally used micronized powdered medication blended with a large quantity of lactose-based carrier, limiting the amount of drug that can be delivered. With no propellant, DPIs generally rely on the force of patient inhalation for delivery, which has limited their use in patient populations with potentially compromised lung capacity, such as children and the elderly. These lactose blends are typically composed of more than 80% to 90% lactose with microgram quantities of drug, resulting in a low drug mass-to-volume of powder ratio that limits their use primarily to high-potency drugs. These powders are also generally highly flow rate-dependent with respect to their dispersibility, have

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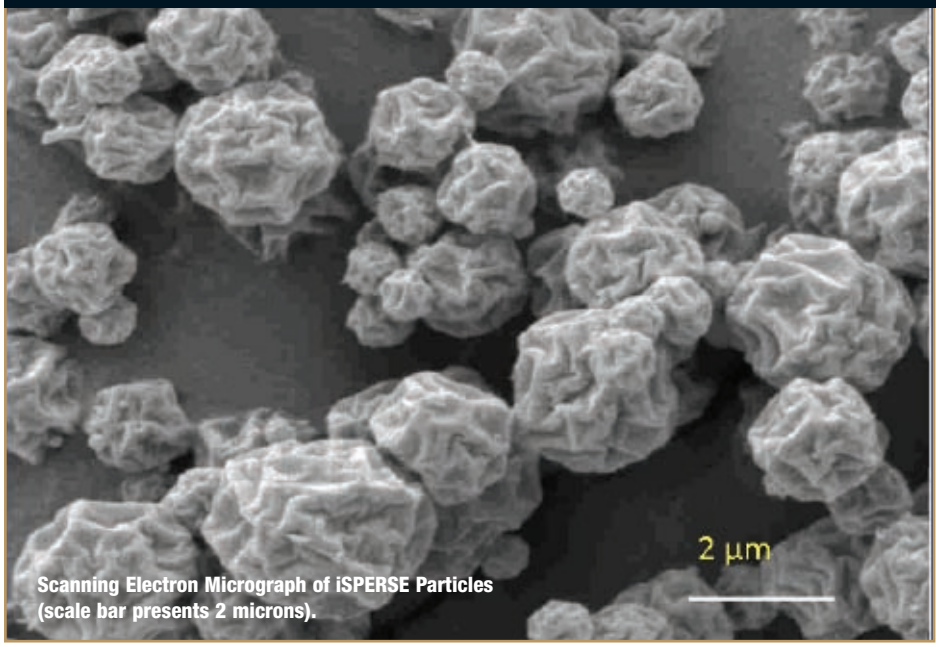
FIGURE 1



Scanning Electron Micrograph of iSPERSE Particles (scale bar presents 2 microns).

poor delivery efficiency with typically less than 20% of drug making it to the lung, and have high patient-to-patient variability. Second-generation DP delivery based on particle engineering approaches (rather than active devices) have included production of porous particles and coating of particles with hydrophobic force-modifying excipients, such as magnesium stearate. Porous particles allow for aerosolizable powders with good dispersibility over a wide range of inspiratory flow rates, however, the inherent low particle density results in a low drug mass-to-volume of powder inhaled. The reduction in amount of drug per unit volume can make porous particles unsuitable for large molecule drugs or drug combinations that often require higher effective drug mass loadings per dose.

Limitations of existing inhaled drug delivery methods have created the opportunity for a new approach to DP inhaled drug delivery technology. Moving forward, trends in the industry indicate that this significant opportunity is growing as more pharmaceutical and biopharmaceutical companies pursue the following product and formulation objectives:

- using pulmonary delivery for a range of small-to-large drug molecules, spanning both existing and new drug entities;
- increasing the dosage of active drug molecules in inhaled therapeutics, specifically increasing the drug mass to inhaled volume;
- seeking to commercialize drug combination formulations, including two, three, and higher numbers of drugs combined into a single inhaled product; and
- pursuing reproducible delivery across a range of patient populations, including pediatrics, the elderly, and those with generally compromised lung function.

A new dry powder formulation approach has been developed that overcomes the limitations of traditional inhaled delivery and has the potential to expand therapeutic options, disease targets, and patient populations for pulmonary drug delivery.

NEW PLATFORM FOR DPI THERAPEUTICS ADDRESSES LIMITATIONS, BROADENS SCOPE

Based on research to address the limitations of existing inhaled dry powder formulations, Pulmatrix has developed iSPERSE™, a novel, proprietary inhaled dry powder delivery platform for use in the pulmonary delivery of drugs. iSPERSE particles can be engineered for localized therapeutic applications in the lungs, or for systemic delivery of therapeutics in which the goals include rapid onset of action, avoidance of first-pass metabolism, and convenience as compared to injection.

iSPERSE powders are characterized by small particle size, relatively high density and flow rate-independent dispersibility, along with the ability for low or high drug loading of single or multiple drugs. iSPERSE represents a next-generation pulmonary delivery platform with significant potential as iSPERSE's properties yield drug delivery capabilities superior to (and indeed not feasible with) conventional dry powder technologies that rely on the use of lactose blending or low-density, porous particles.

Pulmatrix, a clinical-stage biotechnology company discovering and developing a new class of therapies for respiratory diseases, developed this new approach to inhaled drug delivery as part of the development process for the company's own novel, proprietary inhaled medicines, some of which are already in human clinical trials for a range of diverse diseases, such as asthma and chronic obstructive pulmonary disease (COPD).

CUSTOMIZABLE DRUG-TO-CARRIER VOLUME

iSPERSE uses proprietary salt-based formulations optimized for inhalation to create a robust and flexible platform that can accommodate low or high drug loads of a range of molecule types. iSPERSE particles (Figure 1) are routinely prepared by a single-step spray-drying process from either aqueous or organic systems. Small hydrophilic, small hydrophobic, and large molecules have all been incorporated successfully into iSPERSE formulations. These iSPERSE powders can contain as little as 5% excipients, which compares favorably to the greater than 80% to 90% lactose that is typical of commercial lactose blend DPI formulations.

This fundamental formulation difference of iSPERSE, along with the powder property of relatively high density, maps directly into drug dose, creating feasible drug doses in a

unit of up to 100 mg for iSPERSE.[2] Additionally, iSPERSE inherently offers the potential of a strong safety profile, as, in addition to drug molecules, iSPERSE dry powders exclusively contain excipients that are generally regarded as safe (GRAS).

DYNAMIC FLOW RATE EFFICACY

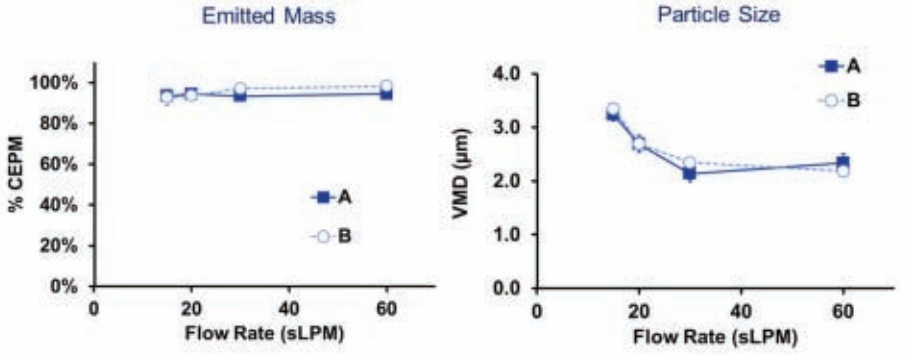
iSPERSE powders allow for the highly efficient delivery of reproducible aerosols to the lungs with mass median aerodynamic diameters (MMAD) typically ranging from 2 to 5 microns and respirable fine particle fractions routinely greater than 50%. The iSPERSE particles also possess the desirable property of being highly dispersible across a wide range of dispersion energies in spite of their small geometric particle size. Across flow rates from 15 through 60 liters per minute (LPM), the percent of powder emitted from a passive dry powder inhaler (DPI) using iSPERSE formulated DPs is high and remains primarily unchanged (Figure 2), delivering drugs to the lung much more efficiently and with far less energy on the part of the patient.

iSPERSE powders improve upon the delivery efficiency limitations of lactose blends, in particular allowing for a reduction in nominal dose. This expands the potential therapeutic applicability of iSPERSE as it could be appropriate for the broadest patient populations, including effective inhaled drug delivery to patients with normal or impaired lung function, using simple and convenient commercially available inhaler devices, such as passive capsule or blister-based DPI devices. Furthermore, iSPERSE formulations can be readily made in both clinical trial and commercial quantities using the proven and scalable spray-drying process capable of high and consistent yields.

MULTI-DRUG COMBINATIONS

The properties of iSPERSE have meaningful therapeutic and patient benefits, including the potential for single formulations

FIGURE 2



iSPERSE powders are relatively flow rate independent and possess properties suitable for aerosol delivery. Two different iSPERSE powder formulations (A, B) exhibited consistent iSPERSE properties of being geometrically small, dispersible, and aerodynamically suitable for lung delivery. Capsule-emitted powder mass (CEPM) and volume median diameter (VMD) of iSPERSE powders emitted from a RS01 DPI as a function of flow rate and measured by laser diffraction (mean ± SD; n = 4-5).[3]

that contain multiple drugs. In fact, preclinical data have shown the potential of the iSPERSE platform to enable the aerosol delivery of drug combinations that include triple drug combinations or higher. For example, in *in vitro* and preclinical studies presented recently, an iSPERSE fluticasone and salmeterol combination was matched to commercially available Advair® Diskus®, which contains the fluticasone and salmeterol combination blended with lactose to enable pulmonary delivery.[3] A triple iSPERSE combination of Advair components and an additional anticholinergic bronchodilator was also demonstrated. Highlights from these data include:

- iSPERSE demonstrated improved delivery efficiency over Advair Diskus, as iSPERSE was shown to deliver over 2 times more lung dose of the active pharmaceutical ingredients than Advair Diskus. This improved delivery efficiency may offer two primary benefits: reduced off-target drug exposure and oral deposition, which potentially could reduce side effects such as thrush (oral candida) and other infections and reduced nominal dose (dose sparing), which lowers cost of goods.
- iSPERSE showed flow rate-independent performance in terms of dose and particle size distribution, which could enable iSPERSE applicability across a broad range of patient populations, expanding applications beyond patients with normal lung function to also include those having lower or impaired lung function, including pediatric, elderly, and those with compromised lung function.
- The iSPERSE particle size distribution that would reach the lungs is consistent with an Advair Diskus particle size distribution (MMAD between 3.1 and 3.2 microns for iSPERSE comparable to 3.0 microns for Advair Diskus).
- iSPERSE showed excellent agreement in size distribution for both drugs (fluticasone and salmeterol) and, even with the addition of a third drug, iSPERSE was able to maintain comparable size distribution, flow rate independence, and other powder properties desirable for inhaled delivery.
- Consistent delivery of dual and triple combination components was achieved, with all components of iSPERSE in both dual and triple combinations retaining expected *in vivo* activity, as demonstrated by reduced lung inflammation and airway hyper-

responsiveness in a murine model of allergic asthma.

INHALED DELIVERY OF DIVERSE CLASSES OF DRUGS

The potential of iSPERSE technology has been validated not only with small molecule drugs, but also macromolecule drugs (proteins, peptides, antibodies) at therapeutically relevant doses well in excess of those achievable by traditional dry powder lactose blend technologies. *In vivo* efficacy has been demonstrated with small molecules for the treatment of asthma and COPD, antibiotics in mouse models of bacterial infection, as well as lung and systemic delivery of macromolecules.

POTENTIAL APPLICATIONS FOR ISPERSE

The attributes of iSPERSE give this proprietary novel delivery platform the potential to (1) deliver high drug payloads, (2) deliver low potency drugs, (3) offer flexible formulation options, (4) reduce side effects, (5) facilitate straightforward manufacturing, (6) support the formulation of small and large molecule drugs (proteins and peptides), and (7) support drug combinations (including triple drug combinations or higher).

Expanding the viability of dry inhaled powder delivery beyond select small molecules to include proteins, peptides, and antibodies at therapeutically relevant doses as well as triple, quadruple, or higher drug combinations will enable development of simple, convenient inhaled therapies for a new and expanded range of disease targets and patient populations. As such, iSPERSE has the potential to be the pulmonary delivery platform of choice for a number of first-in-class and best-in-class inhaled therapeutics.

Commercially, Pulmatrix is seeking iSPERSE partnerships as well as advancing its own iSPERSE-based drug formulations. In terms of diseases that are likely near-term candidates for iSPERSE clinical initiatives, a number of proprietary iSPERSE drug formulation candidates are now being advanced, including small molecules, combinations, and biologics in a variety of therapeutic areas, including COPD, cystic fibrosis, asthma, idiopathic pulmonary fibrosis (IPF), and non-CF bronchiectasis.

To support the development of its own pipeline as well as the iSPERSE partnering programs, Pulmatrix has developed a complete range of pulmonary drug formulation capabilities that are integral to the successful commercialization of the iSPERSE platform, including:

- dry powder formulation and manufacturing,
- dry powder physicochemical properties optimization,
- aerosol characterization and method development,
- dry powder inhaler selection and testing,
- preclinical efficacy/safety testing *(in vitro and in vivo*), and
- clinical program operation and management.

These platform and formulation optimization capabilities will be offered to iSPERSE partners. ◆

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BIOGRAPHY

Dr. Jean C. Sung is the Director of Pharmaceutical Development at Pulmatrix, a clinical-stage company discovering and advancing novel respiratory therapeutics and drug delivery technologies. She is responsible for Pulmatrix's formulation, process, and analytical development functions. With prior experience at Alkermes, Inc. and AIR, Inc. (Advanced Inhalation Research), Dr. Sung has spent more than a decade developing novel particle engineering and formulation technologies to advance respiratory dry powder drug delivery. Dr. Sung earned her PhD and MS in Engineering Sciences with a focus on Biomedical Engineering from Harvard University and her SB in Chemical Engineering from Massachusetts Institute of Technology.

SPECIAL FEATURE

Transdermal, Topical & Subcutaneous: Non-Invasive Delivery to Expand Product Line Extensions

By: Cindy H. Dubin, Contributor

The overall landscape of the transdermal, topical, and subcutaneous markets continue to change - for the better - as non-invasive delivery of drugs to the skin or to the systemic circulation via the skin is a highly attractive proposition for many active drugs, be they poorly soluble or subject of first-pass metabolism when administered orally. Equally attractive is the possibility of administering chronic therapies via the skin, translating to convenience, safety, patience compliance, and drug efficacy. Thus, the pharmaceutical industry has an opportunity to expand on product line extensions for existing drugs.

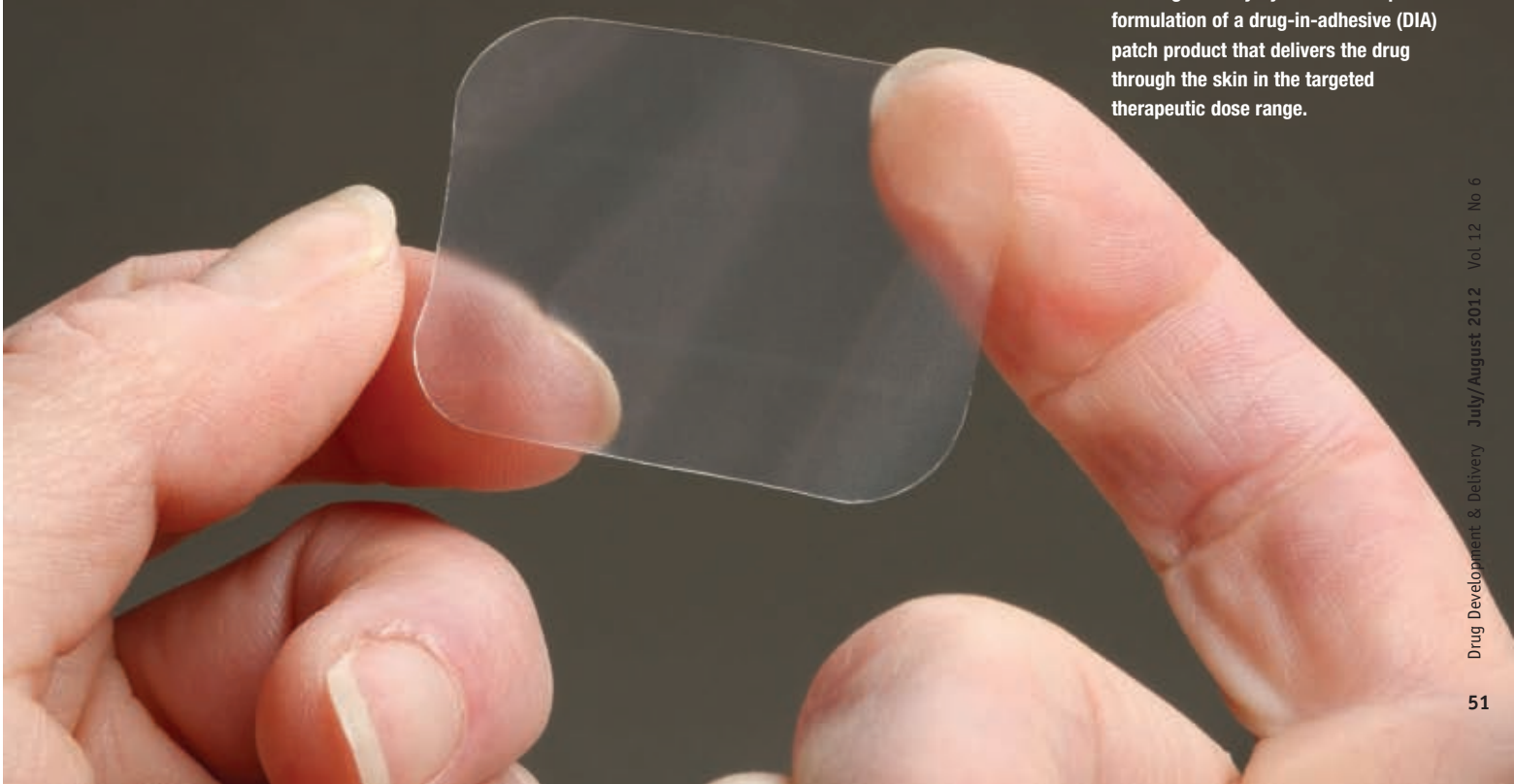
In this *Drug Development & Delivery* feature, delivery system providers and contract developers and manufacturers were asked to describe their products and service offerings in their respective area of expertise.

TRANSDERMAL DRUG DELIVERY

The transdermal delivery market was valued at $21.5 billion in 2010 and is predicted to reach $31.5 billion by 2015, according to a PharmaLive Report. The annual US market for transdermal patches is estimated at more than $3 billion, and transdermal drugs account for more than 12% of the global drug delivery market. Transdermal drug delivery prevents many of the problems associated with oral and intravenous routes. Major advantages provided by transdermal drug delivery include improved bioavailability, more uniform plasma levels,

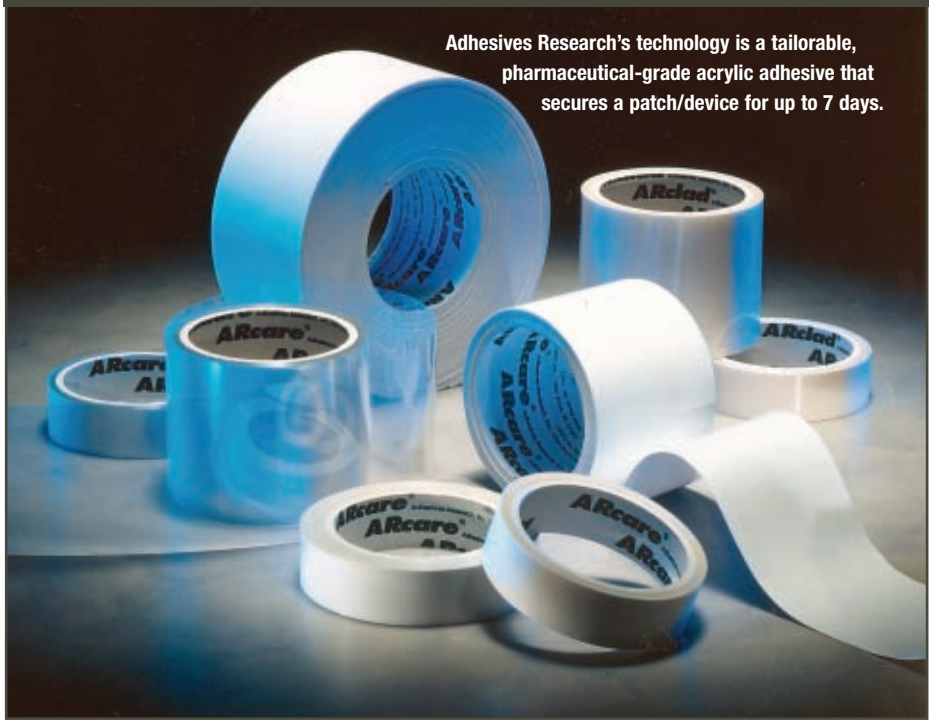
FIGURE 1

3M Drug Delivery Systems develops a formulation of a drug-in-adhesive (DIA) patch product that delivers the drug through the skin in the targeted therapeutic dose range.



longer duration of action resulting in less dosing frequency, reduced side effects, and improved therapy due to maintenance of plasma levels. Transdermal drug delivery is used in areas such as pain management and women's health. Pharmaceutical, biotechnology, and drug delivery companies are poised to tap the hidden potential in transdermal drug delivery applications, such as wound care, monitoring, and diagnostic methods. The development of successful transdermal drug delivery systems in these areas will play an important role in improving patient quality of life.

FIGURE 2



Adhesives Research's technology is a tailorable, pharmaceutical-grade acrylic adhesive that secures a patch/device for up to 7 days.

3M Drug Delivery Systems–Putting Convenience & Compliance Into a Patch

3M Drug Delivery Systems serves as a contract manufacturer to pharmaceutical companies that market transdermal products, and also helps companies develop and adapt their drugs for transdermal delivery. 3M Drug Delivery Systems provides development services - taking drug products and adapting them into the transdermal dosage form. 3M Drug Delivery Systems can also provide basic contract manufacturing services by taking an existing product or one that it developed and manufacture it for the customer.

"Clients interested in developing new drugs into transdermal products are often challenged with being able to achieve consistent delivery at the desired rate and pharmacokinetic profile to obtain the desired therapeutic effect," says Jordan Fineberg, Global Business Manager, Transdermal Drug Delivery Systems for 3M Drug Delivery Systems. "Fortunately, we are able to provide very strong technical capabilities and analytics in our labs to help clients overcome those technical challenges."

To create a passive transdermal product, 3M Drug Delivery Systems develops a formulation of a drug-in-adhesive (DIA) patch product that delivers the drug through the skin in the targeted therapeutic dose range.

"Our DIA systems are versatile enough to be compatible with a variety of drugs, and our targeted market is companies with APIs that fit the transdermal profile. We help our customers develop their products in a way that achieves a consistent, controlled-release dosage level that can be difficult to achieve by other forms of administration," adds Mr. Fineberg.

Transdermal patches are distinguished by other systems by the duration for which they can be worn. Products can be created that deliver multi-day dosing at a very specific PK profile. Additionally, continued advancements allow this system to deliver more than one drug in a single patch, adding to convenience for patients. With the ability to deliver a controlled release of API over multiple days, patient compliance is possibly improved.

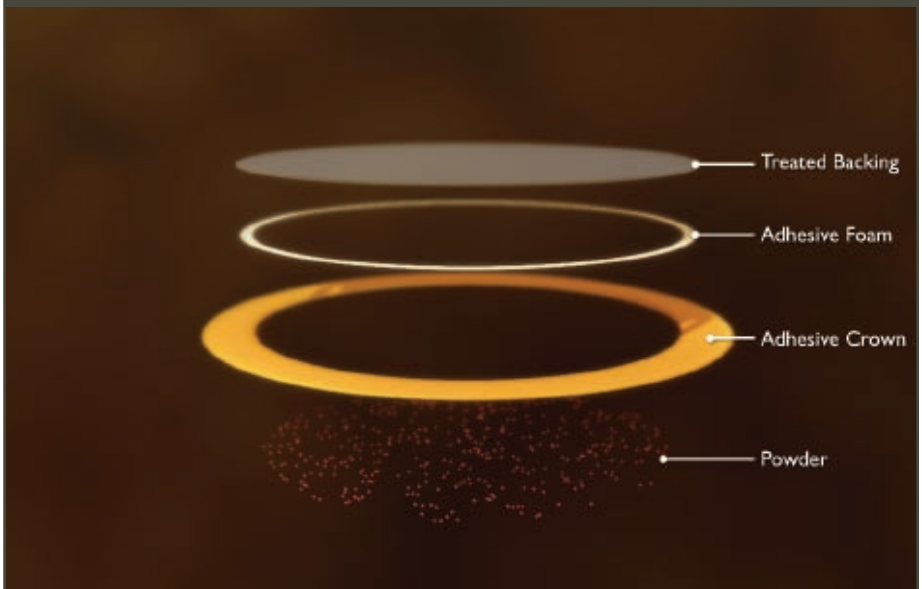
"We see continued generic entrants into the transdermal market, particularly with a couple of big drugs that will go generic in the next 3 to 5 years," predicts Mr. Fineberg. "In our own future, we see 3M Drug Delivery Systems working with both branded and generic companies in developing and manufacturing their transdermal products."

Adhesives Research, Inc.–Responding to Skin-Friendly, Long-Term Wear Adhesives

Adhesives Research specializes in the custom development of unique component adhesives, films, and laminates for transdermal and buccal drug delivery. The company offers complete customization of our platform technologies (examples such as wear-times, moisture vapor transmission, shear, etc.) to create the tailored functionality required of the adhesives used in a customer's applications.

Today, many companies are developing drug delivery devices that will be bonded to the skin for longer periods of time. The majority of transdermal patches and drug delivery devices available today are daily-wear devices that are typically removed within 24 hours of application; however, formulators are developing extended-wear patches designed to be worn for multiple days, up to a week. In the case of insulin

FIGURE 3



DBV uses two proprietary manufacturing processes to load active dry compounds onto a polymeric film backing.

infusion pumps, the adhesive must reliably attach a device to skin while bearing load.

"While aggressive adhesion ensures a secure bond to skin for addressing dosing concerns, it can potentially cause discomfort upon patch removal," says Mary Lawson, Pharmaceutical Business Manager, Adhesives Research, Inc. "Pain is caused when the adhesive removes skin cells and/or hair when the device is pulled away. Also, an aggressive adhesive that releases uncleanly may leave behind an unwanted residue on the skin that is difficult to remove."

In response to the need for skin-friendly, long-term wear adhesives, Adhesives Research's newest technology addresses the need through a tailorable, pharmaceutical-grade acrylic adhesive technology that meets the critical design parameters for securing a patch/device for periods up to 7 days to ensure adequate skin bonding with residue-free removal.

"In spite of the adhesive's aggressive nature, the pain experienced upon removal is considered to be low-to-moderate, and studies have shown that removal of the adhesive tape does not cause disruption of the stratum corneum," says Ms. Lawson.

As a general rule, adhesives for transdermal patches are formulated to present aggressive bonds with flexibility and conformability to ensure the patch or device remains firmly in place without lifting or fall-off to ensure a therapeutic dose.

Ms. Lawson explains, "Our long-term wear adhesives are designed to withstand physical activity, constant friction from clothing, periodic moisture exposure, and varying degrees of skin porosity and oil levels without shifting or moving."

Adhesives Research's work is complemented by its relationship with its subsidiary, ARx LLC, a collaborative technology partner. ARx LLC is experienced in developing polymer chemistries, that when combined with its client's APIs and complementary materials, transform into transdermal, transmucosal, and soluble film products. This includes single- and multi-drug products as well as immediate- and controlled-release offerings. ARx LLC develops and manufactures innovative pharmaceutical products with a focus on unique technologies in oral, topical, and transdermal drug delivery. The ARx products range from first-in-class immediate-release OTC and prescription soluble films to multi-day, sustained-release transdermal patch delivery. The ARx sole objective is to work hand-in-hand with its pharmaceutical partners to develop and launch therapeutically relevant products that have the potential to extend a molecule's product lifecycle, deliver new compounds, or provide better product performance in the areas of bioavailability, compliance, and/or cost.

"The model is evolving in how companies talk to us about their product design. A decade ago, our partners came to us at the onset of a project with a predetermined path for integrating a molecule into a delivery platform technology," says Megan Greth, Marketing Manager II, ARx, LLC. "Today, the conversation is much more open from the start of a project and is first focused on understanding the improved therapeutic outcome followed by evaluating the various technologies available for delivery. Basically, the conversation has evolved to a broader dialogue in which we evaluate the best delivery options based on the patient population we are targeting.

"The diversity of the Adhesives Research and ARx technology platforms inherently enables us to provide design

FIGURE 4

A Dow scientist observing the mixing of a topical product and checking for consistency.

flexibility and developmental support to our clients from concept to commercialization," Ms. Greth concludes.

DBV Technologies–Addressing Unmet Allergy Treatments for Young Children

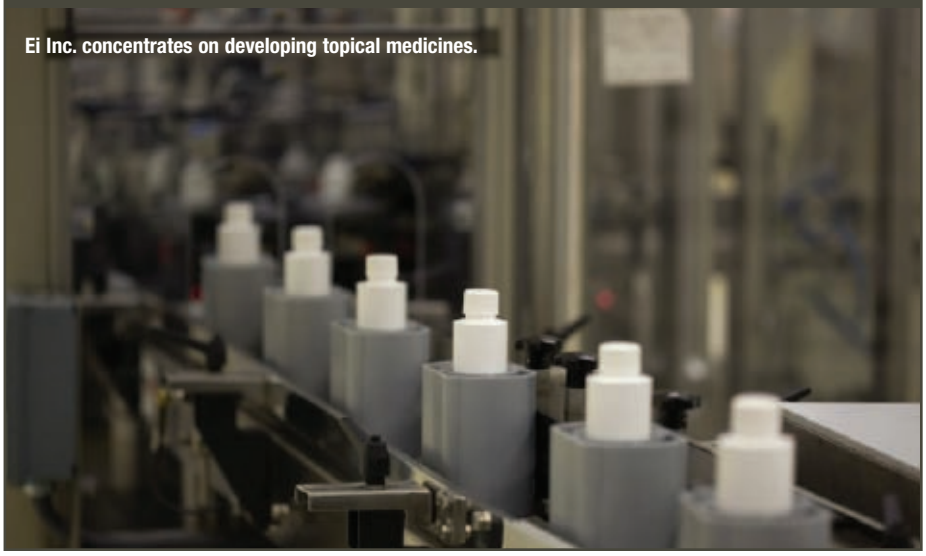
According to the World Health Organization, allergies constitute the world's fourth largest public health issue and affect 500 million people worldwide. Allegies affect somewhere between 25% and 40% of the adult population and more than 50% of children in developed countries. Environmental, pollution, and changing food habits are contributors to the rapid increase in the prevalence of allergies.

DBV Technologies focuses on food and pediatric allergy desensitization. The company has developed a patented skin patch, Viaskin® that puts the allergen into contact with the immune system via immune cells present in the superficial layers of the skin, while avoiding disruption of the blood/skin barrier. This approach, which significantly reduces the risk of serious anaphylactic shock, enables Viaskin to fulfill at least two critically important medical needs that were previously unmet, explains Pierre-Henri Benhamou, CEO of DBV. First, Viaskin targets food allergies, in which the risk of anaphylactic shock is high, and second, the Viaskin patch is suitable for desensitizing children under the age of 5.

"Therefore, we are in a position to address allergies that are not treatable by conventional pharmaceutical therapies, he says."

When Viaskin, containing a specific allergen, is applied on the skin, the allergens are desposited locally on the skin and are taken up by the skin's immune-competent cells, triggering the immune response. The allergens are taken up in the superficial layers of the skin without crossing the basal membrane and preventing the allergen from reaching the bloodstream.

FIGURE 5



Ei Inc. concentrates on developing topical medicines.

DBV uses two proprietary manufacturing processes to load active dry compounds onto a polymeric film backing via electrostatic force: static powder and electrospray deposit, a precise method of layering a controlling solution of the allergen on the patch so that it is dry and stable.

DBV has developed Viaskin Peanut for peanut allergy, Vaskin Milk for treating IgE-mediated cow's milk allergy, and Viaskin House Dust Mites for preventing asthma in young children. In December 2011, DBV received Fast Track Designation for its Viaskin Peanut clinical development program.

"This designation was very important for us as we believe this translates to a real unmet medical need that patients, regulators, and DBV are willing to fulfill," says Mr. Benhamou.

TOPICAL DRUG DELIVERY

Scientific and technological advances in recent decades have widened the scope of possibilities for therapies to or via the skin, enabling targeted delivery of drugs to specific layers of the skin, muscle tissue, or even to the systemic circulation with unprecedented precision and exactitude. Since the advent of the first transdermal patch in the late 1970s, the pharmaceutical industry has witnessed successful delivery of chronic therapies like hormones, nicotine, and NSAIDS systemically via the skin. These innovations have significant advantages over the oral route: patient compliance, improved plasma levels, and reduced side effects. Topical OTC drugs are an important market segment with forecast worth expected to exceed $870 million in 2014, according to Datamonitor. Antiseptic cleansers account for the largest part of the topical OTC medicines market at almost 60%, with anti-itch products in second place at almost 28%, followed by anesthetic products, which represent more than 10% of the segment.

Dow Pharmaceutical Sciences–A One-Stop-Shop Approach to Topical Development

Dow Pharmaceutical Sciences provides contract development services and clinical manufacturing, both sterile and non-sterile, to the pharmaceutical and biotechnology industries. With a focus being solely on topicals, Dow Pharmaceutical Sciences spends a lot of time developing ophthalmic products. Its newest service, Sterile Product Development, supports the development of customers' topical products containing NCEs, NMEs, or approved molecules, through to

FIGURE 6

In addition to excipient safety and functionality, characterization of topical formulations for sensory attributes is an area in which Gattefossé has expertise.

GMP manufacturing of supplies for Phase I and Phase II clinical trials. Clients can access all services required to support development of their sterile product. These include formulation development and *in vitro* drug penetration testing, analytical method development, stability testing, GMP & GLP manufacturing, labeling, and distribution of clinical supplies to test sites worldwide. The company provides a full team of specialists focused solely on topical product development working in one location.

"Our new One-Stop-Shop provides customers with their best chance of success and fastest route to market, saving them both time and money," says Vanlee F. Waters, Assistant Director of Marketing, Dow Pharmaceutical Sciences.

Dow's turnkey development process includes preformulation (drug solubility, excipient, and solvent compatibility) evaluations, formula design, and development of multiple prototypes. Multiple prototypes based on different delivery systems are developed to maximize success for chemical and physical stability, release from the formulation, and penetration into the skin or tissue as desired.

Mr. Waters says that Dow has experience in working with the FDA's Dermatology division. "Working closely with the FDA provides us with an intimate knowledge of their Non-Clinical and Clinical requirements, allowing us to get more products approved for our customers. Our track record remains second to none: 31 New Drug Approvals for prescription topical dermatological products were approved by the FDA during 2005-11: 10 of these formulations were developed at Dow," he says.

Going forward, Mr. Waters says Dow will stay the course long-term and continue to leverage its focus and experience in topical product development.

"As a boutique CDO provider to large and specialty pharma, we will continue to leverage our expertise in topical product development, non-clinical, clinical, and regulatory affairs."

Ei Inc.–Laser Focused on Topicals

Ei Inc. is focused solely on topical semi-solids and liquids, and it is this expertise that Roger Martin, Senior Vice President of Sales and Marketing, says makes the company stand out in a market that seems to be fragmenting into specialty fields.

"Clients are not really looking for one provider to manufacture all of their tablets, injectibles, and topicals under one roof. They instead want a vendor who is an absolute expert at a given dosage form," he says.

Clients coming to Ei Inc. are looking for topical products, and thus aesthetics and stability of the formulation are both very important. "Our formulation scientists have decades of experience working with various APIs used in topical medicines, and they work diligently to create both an efficacious and pleasant delivery vehicle," says Mr. Martin.

Critical to Ei's mission is to protect the client's brand by offering a level of quality that never puts their product in jeopardy, and service levels that allow them to plan their business effectively, Mr. Martin stresses. "By offering complete development, analytical, stability, and manufacturing services for topical products, Ei has positioned itself to serve customers in this niche better than any other."

Ei recently announced its partnership with Keranetics in which Ei will start manufacturing the API for Keranetic's wound care and burn care products. This is Ei's first venture into API manufacturing.

"Ei is laser focused on the topical marketplace, and we have expanded our R&D, analytical, and manufacturing capabilities to meet this demand," explains Mr. Martin. "We have heavily invested in both people and equipment so that our services can meet or exceed the expectations of our customers."

Gattefossé–Excipients for Safe and Effective Topical Delivery

Gattefossé specializes in topical formulations by virtue of the products in its offering. Gattefossé designs, manufactures, and markets functional excipients globally. Each product is developed to meet a unique formulation challenge and is supported by research and data generated internally. Before launching, every excipient is tested to ensure a high safety profile and conformity to NF, EP, JP, and other well-recognized pharmacopoeia. Since 2004, for example, the company has been responsible for the

completion of more than 25 NF and EP monographs.

Gattefossé has a range of solubilizers and penetration or permeation enhancers. For instance, many marketed products already include Transcutol®, an excipient that facilitates passage of drugs across the stratum corneum, but creates a drug depot effect in subcutaneous layers of the epidermis.

The company has a range of emulsifiers for one pot, cold process, and low-energy emulsification processes, also coded in innumerable products worldwide. The list includes Tefose® 63, a self-emulsifying base, known for its innocuity and safety profile for mucosal/vaginal delivery of antifungals. Other products like Labrafil®, Labrasol®, and Capryol™ help modulate permeation across the epidermis.

In 2011, Gattefossé announced the inauguration of a new research center in Saint-Priest, France. Bringing together the formulation and R&D laboratories, the18,000-sq-ft facility is built to encourage and facilitate exchange of ideas and resources between various groups engaged in excipient characterization and expansion of that knowledge in relation to functionality in different drug delivery systems.

"Parallel to safety and regulatory qualifications, Gattefossé's business culture places emphasis on understanding the specific characteristics and functionality of excipients in every formulation design. Developing and sharing that knowledge, as to how our excipients can help improve, differentiate, and innovate customers' products, is the key to the continued success of the company," says Jasmine Musakhanian, Marketing & Scientific Director, Pharmaceutical Division, Gattefossé USA.

Characterization of topical formulations for sensory attributes (feel, touch, spreadability, etc.) is another area in which Gattefossé has expertise. "The subject has traditionally been of interest to personal care customers, but is now expanding to pharmaceutical preparations," Ms. Musakhanian adds.

Selecting the right excipient(s) for the intended delivery system, relative to the type of active drug entity and its targeted therapy is likely to be the key step in saving time and cost to market. Gattefossé assists customers with the selection process by providing pertinent data on physical-chemical information and formulation support.

Skinvisible Pharmaceuticals, Inc.–Delivering Tailored Molecules

Skinvisible is an R&D company that formulates new products and provides life cycle management by revitalizing products coming off patent with its patented, targeted drug delivery system called Invisicare®. Invisicare delivers drugs on, in, or through the skin with a controlled release and can be tailored to almost any type of molecule.

Invisicare has multiple applications, including topical, transdermal, and mucosal (in development). Invisicare is a film-forming complex of hydrophilic and hydrophobic polymers that are readily available and used in the marketplace.

"Our technology is not encapsulation, it is a simple manufacturing process with no special equipment and no shearing required. It is very compatible (flexible) with both water-insoluble and certain cationic active ingredients (positive, negative, and neutral) and certain water-soluble actives," explains Doreen McMorran, Vice President Business Development and Marketing for Skinvisible. The formulations do not use alcohol, waxes, or other organic solvents and can be formulated into creams, lotions, sprays, or gels.

Invisicare represents a "family" of Invisicare structures, each specifically formulated for specific needs. This includes increasing the release of actives (ie, a 3% imiquimod formulation can release 30% of the active), binding of products (for use for hand sanitizers, sunscreens, and sunless tanning products), and/or photostability of avobenzone for 8 hours.

FIGURE 7

Skinvisible formulations can be formulated into creams, lotions, sprays, or gels.

In 2011, Skinvisible was granted two patents: a sunscreen avobenzone photostability patent for the US and a technology patent for Europe. Skinvisible now has 40 patented formulations with various indications, all available for licensing on an exclusive basis, including a recently developed formulation for Netherton syndrome for which the company is seeking orphan drug status in the US and Europe.

SUBCUTANEOUS DRUG DELIVERY

Providing innovative, patient friendly drug delivery devices is increasingly becoming a requirement, not an option, when introducing therapeutic products involving traditional needle and syringe use as evidenced by the prevalence of auto-injections, prefilled syringes, and pressure jet applicators offered by most large pharmaceutical companies today.

FIGURE 8

Zosano's ZP Patch Technology is a needle-free delivery system consisting of a patch applied by a reusable applicator.

Zosano Pharma–Using a Patch to Overcome the Needle Experience

Although prefilled syringes, auto injectors, and pressure jet applicators products have improved patient convenience and compliance by reducing preparation and delivery steps, many patients still associate them with a needle experience. Zosano Pharma aims for its ZP Patch (formerly known as Macroflux) to replace the syringe altogether in target compound areas in which the patient needs are the highest.

Zosano's ZP Patch Technology is a user-friendly, simple, and needle-free transdermal delivery system consisting of a patch applied by either a reusable applicator for therapies requiring daily chronic administrations or a disposable, single-use patch applicator system for acute or short-term applications. The ZP patch technology delivers therapeutic compounds via drug-coated microneedles on the patch that permeate the skin's outer layer, provide rapid and efficient systemic delivery, ensure significant therapeutic effect - and is painless. Dry-coated drug on the thin microneedle patch allows for rapid delivery into the skin. The creation of pathways through the skin improves control of drug distribution throughout the patch treatment area, reduces the potential for skin irritation, and provides for efficient drug delivery and absorption.

The ZP patch has proven capable of delivering a broad range of compounds, including peptides, proteins, small molecules, and vaccines. It offers the reliability and predictability associated with a "one-step" application without relying on a liquid injection or pre-treatment (permeation) in preparation for transdermal delivery.

Zosano Pharma has identified 10 key drugs that best fit the criteria for the initial product portfolio of the ZP patch. The combined market for this portfolio is at least $20 to $30 billion dollars in worldwide sales. "Current efforts to increase our patch dosage delivery dovetails well with the need for product differentiation in the expanding biosimiliars market and will potentially increase the market estimate even further," says Brian Rippie, Director of Business Development at Zosano.

In October 2011, Zosano Pharma announced a long-term strategic collaboration with Asahi Kasei Pharma Corporation (AKP) for the development, commercialization, and supply of a weekly patch formulation of Teribone™ (human PTH 1-34). As part of this Asian licensing agreement, AKP has paid Zosano $7.5 million in upfront consideration. In addition, AKP will pay more than $25 million in milestone payments related to development, regulatory, and product launch. Zosano will receive revenue-based royalties based on sales of the ZP patch formulation of Teribone in the Asian territories, as well as reimbursement for all development and manufacturing costs and commercialization. AKP is committing significant additional financial and technical resources toward the development of the patch for the treatment of osteoporosis in the Asian territories, and has already commenced clinical trials, which are now entering the pivotal Phase III stage.

Zosano retains US/Europe licensing rights of ZP patch development of PTH 1-34 and expects to further capitalize on the momentum gained by its recent announcement on this and other products.

In short, there will be more choices available to the patient than ever before regarding therapeutics and the delivery methods all focused on greater efficacy and improved convenience/compliance, says Mr. Ripple.

"We predict a game-changing moment once the first effective needle free, pain-free drug delivery product enters various markets and the expectation of convenient, needle-free drug delivery is established," he concludes.

THE FUTURE OF TRANSDERMAL, TOPICAL & SUBCUTANEOUS DRUG DELIVERY

Looking forward, the pros predict that future growth rate for transdermal, topical, and subcutaneous products will be slow to moderate. The primary reason for no real "revolutionary" products or technologies in the near-term future is the fact that most pharma and biotech companies continue to be very conservative when it comes to early-stage development and associated risk. Add to that the FDA's conservative stance toward adopting and approving new drugs or new delivery systems/technologies, and you have another significant growth limiting factor. Throw in the financial cliff facing the US by year's end and the future of nationalized healthcare, and the picture becomes rather murky. ◆

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CAISSON BIOTECH: INNOVATION IN DRUG DELIVERY USING A NATURALLY OCCURRING SUGAR MOLECULE

Thomas Harlan
CEO
Caisson Biotech

"Caisson's HepTune involves the process of conjugating this naturally occurring sugar molecule, heparosan, to drugs. The size of the heparosan and the conjugation method for coupling can vary depending on the drug cargo, the client's/partner's preference, and achievement of optimal performance. Caisson works to meet the partner's clinical performance needs for each drug conjugate."

Motivated by increasingly reported adverse events related to PEGylated drugs and based on the pioneering glycobiology research of Dr. Paul DeAngelis of the University of Oklahoma Health Science Center (OUHSC), Caisson Biotech, L.L.C. has developed and patented a drug delivery technology utilizing naturally occurring sugar polymers to more safely and effectively deliver drugs. Customizable to any currently PEGylated drug or to any other molecule requiring this type of stealth modification, HepTune™, Caisson's drug delivery system, can be used in the treatment of a number of diseases. Caisson's patented delivery system harnesses the naturally occurring sugar molecule, heparosan, as its delivery vehicle. By utilizing proprietary methods to manufacture heparosan and its derivatives, Caisson offers its HepTune as a safer delivery vehicle in general and specifically, as an alternative to PEG (poly[ethylene glycol]). HepTune has many bio-superior attributes over PEGylation, including greater compatibility, lack of accumulation in tissues, extremely desirable PK and safety profiles, and no known toxic effects. Additionally, conjugation of Caisson's heparosan-based reagent affords new and novel intellectual property either for new molecules or to extend the patent life of already-marketed drugs, and also recaptures the percentage of the market due to patients that have developed PEG sensitivity excluding them from current PEGylated formulations. Drug Developemnt & Delivery recently spoke with Thomas Harlan, CEO of Caisson, to discuss how his company is improving the quality and delivery of numerous medications, making life easier for patients, and offering new ways for companies to enhance their drug pipeline.

Q: Can you please provide our readers some background on Caisson Biotech?

A: Caisson is a portfolio company of Emergent Technologies, Inc. (ETI), a leading technology access and innovation management company (www.etibio.com). ETI applies rigorous selection criteria to assess and evaluate technologies emanating from thought-leading scientists in universities and federal research labs. Emergent then builds commercially viable businesses based on those platform technologies. ETI has innovated the start-up company management model, allowing for effective initial technology transfer, rapid ramp-up or scale-back of business (depending on the maturity of the technology), and technical resources in response to market needs, aggressive intellectual property (IP) protection, and IP scope expansion

and G&A expense cost-sharing. ETI scouted the glycobiology research of Dr. DeAngelis, and with him (licensing the technology from OUHSC) built a family of companies to produce and explore applications for three commercially important glycosaminoglycan (GAG) polymers: hyaluronic acid (HA), heparosan, and chondroitin. Collectively, these companies (Hyalose, L.L.C., Heparinex, L.L.C., and Choncept, L.L.C.) have partnered with pharmaceutical and biotechnologyy companies to evaluate GAGs for application areas ranging across rheumatology, ophthalmology, tissue engineering, dermal fillers and reconstructive surgery, drug delivery, biomaterials, medical device coating, and anti-adhesion films. Caisson was formed in 2009 as a wholly owned subsidiary of Heparinex when Dr. DeAngelis' research on heparosan, in particular, began to show bio-superior properties over PEG for drug delivery.

Q: What is it about heparosan that makes it Caisson's drug delivery vehicle of choice?

A: Heparosan is structurally related to heparin, one of the most widely used drugs in the Pharmacopeia. Heparosan was predicted to be biocompatible in the human body as it is a natural precursor in the heparin biosynthetic pathway and also because of the stretches of heparosan that exist in human heparan sulfate chains. In addition, certain pathogenic bacteria even use a heparosan coating to evade the immune system during infection. Caisson's HepTune involves the process of conjugating this naturally occurring sugar molecule, heparosan, to drugs. The size of the heparosan and the conjugation method for coupling can vary depending on the drug cargo, the client's/partner's preference, and achievement of optimal performance. Caisson works to meet the partner's clinical performance needs for each drug conjugate.

Q: Many companies focus on drug delivery technologies. What makes Caisson's HepTune unique, and how does is it differ from PEGylation?

A: A significant challenge in the pharmaceutical industry exists in which drugs are excreted too quickly from the body. This can cause patients to endure an increased number of treatment injections (requiring repeated, either multiple injections in a single day or daily injections over an extended period of time) and generate strong immunogenic responses. Currently, PEG is the most widely used drug delivery agent for protein-based drugs to overcome these problems, but suffers from liabilities, including detrimental accumulation in organs and antigenicity of its own. Furthermore, higher doses and/or lifetime treatments using PEG could amplify these problems because the liver detoxification system creates a variety of reactive PEG metabolites that are cytotoxic. There is a rising occurrence of PEG immunogenicity. In 1984, anti-PEG antibodies were detected in 0.2% of naïve patients sampled, but as of 2001, stunningly 22% to 25% of healthy blood donor samples (n = 350) had anti-PEG antibodies.[1] It is thought this increase of anti-PEG antibodies in the general population is due to the increasing use of PEG in consumer products, such as toothpaste, laxatives, vitamin pills, and many other products commonly used on a daily basis. Indeed, some childhood leukemia patients no longer respond to their PEGylated asparaginase (Oncaspar®) medication due to anti-PEG antibody levels.[2] In contrast, the natural heparosan polymers of Caisson's HepTune have the superior synergistic combination of biocompatibility, lack of immunogenicity, and long half-life in the bloodstream. Caisson's heparosan-reagents are degraded into normal sugars and even recycled into other molecules the body uses and thus possess substantially lower toxicity.

Furthermore, the quality control of PEG polymer synthesis (ie, the drug delivery vehicle) with respect to molecular weight distribution is less than optimal. The length of the linear polymer is not uniform and typically a preparation of linear PEG polymers greater than 10 kDa, a portion (~3%) of chains might have branching. This unplanned branching can yield a series of cross-linked complexes containing multiple cargo molecules because every branch has a reactive group for coupling to the cargo. On the other hand, linear heparosan reagents are substantially uniform in length, even for masses up to 800 kDa. In addition, due to an innovative synthesis method involving enzymatic polymerization, Caisson's heparosan drug delivery vehicles cannot be branched and can never have more than a single reactive group. The attachment of the heparosan vehicle to drug cargo, has many other superior attributes over PEGylation, including ease of generating a larger size range of polymers, higher water solubility, greater biocompatibility of degradation products, lack of accumulation in tissues, and new intellectual property. In a 2008 *Current Opinions in Drug Discovery & Development* article, it was predicted future drugs will use higher molecular weight PEGs and/or be given at higher doses for long periods.

Caisson predicts heparosan will be the preferable therapeutic vehicle based on supporting preliminary study results and due to PEG's intrinsic limitations and emerging immunogenicity.

Q: What impact do you see Caisson Biotech's HepTune technology having in the market?

A: Caisson Biotech is well positioned to have a significant impact in the market in a number of ways. Caisson has entered into the market with a naturally occurring sugar polymer drug delivery vehicle, HepTune, with many superior performance benefits when compared to current existing competitive drug delivery systems. Supporting this technology is a very strong patent portfolio. Caisson owns or has rights to 13 patents, 4 of which are issued. Caisson's aforementioned patents are a subset of patents within Dr. DeAngelis' total patent portfolio for carbohydrate production consisting of over 200 patents and patent applications.

The Caisson patent claims consist of multiple and distinct heparosan production methodologies, the use of heparosan as a biomaterial and also the use of heparosan conjugated to therapeutics. PEG, the base material for the PEGylation platform, is a publicly available material. Unlike the innovators of the PEGylation technology, Caisson retains rights to the composition-of-matter and methods-of-manufacture of the heparosan conjugation reagent. This includes the production of monodisperse heparosan materials. The ability to have claim coverage related to the production of the base material (ie, heparosan) provides added protection and exclusivity around the ultimate conjugated materials and therapeutic products. In addition, Caisson benefits from the rights to the control of production and supply of the heparosan material.

With the many advantages outlined, Caisson believes it is well positioned to make a significant impact and contribution to the current drug delivery market, greatly benefiting pharmaceutical companies and ultimately patients.

Q: What makes Caisson Biotech an ideal partner?

A: Caisson Biotech has a commercially proven drug delivery technology, a highly motivated and committed staff, and a track record of meeting milestones specified in contracts, both commercial and grant sourced. Caisson's employees have a combined 66 years of experience in the Glycobiology field ranging from the discovery and manipulation of enzymes responsible for synthesis of GAG polymers (heparosan, chondroitin, and hyaluronic acid) to production and validation of heparosan for use in drug delivery. Caisson's founding scientist, Dr. Paul DeAngelis, is highly recognized in the Glycobiology field for various contributions, both scientifically and for his commercial success, and is still actively engaged with Caisson on a daily basis. Companies interested in evaluating HepTune will find the management easy to work with, the cost of evaluation very affordable, and the process whereby conjugates are specified and procured for evaluation and testing easy to comprehend and comply with. The corporate management has developed a simple, timely, and effective engagement protocol for companies interested in evaluating the technology.

Q: What can we expect to see from Caisson in the market?

A: In May, 2012 Caisson announced Novo Nordisk as its first commercialization partner. The recently executed Developmental License Agreement focuses on development of a number of heparosan-conjugated drugs. One or more of these drugs are projected to enter into clinical trials between 2013 and 2014.

Caisson is also developing an internal drug pipeline with several products currently progressing through preclinical trials. The company is gearing up for commercial-scale production to handle multiple new clients and expects to see active sales and marketing efforts by its partners in the US and Europe in the near future. Caisson looks forward to the rapid advancement of its clinical pipeline and the opportunity to work with additional industry partners to bring novel therapeutics to patients in need.

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2. Armstrong JK, et al. Antibody against poly(ethylene glycol) adversely affects PEG-asparaginase therapy in acute lymphoblastic leukemia patients. Cancer. 110:103-111.

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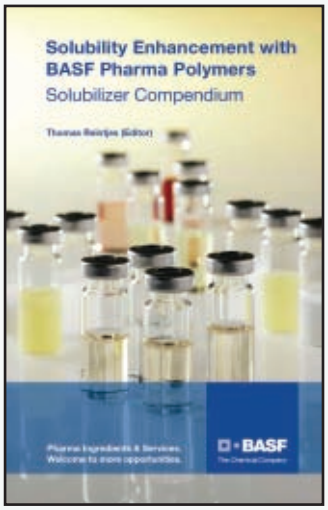
Solubilizer Compendium



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

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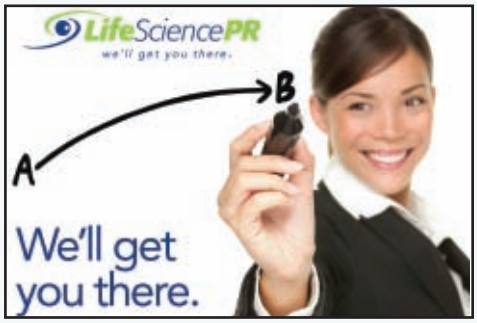
Marketing & Communications



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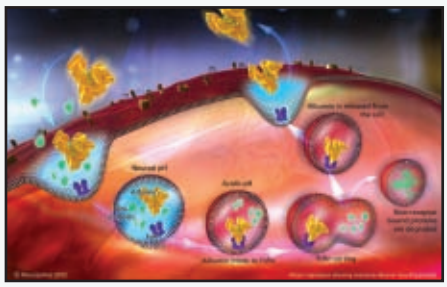

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Deuterium Modification as a New Branch of Medicinal Chemistry to Develop Novel, Highly Differentiated Drugs

By: Philip Graham, PhD; Julie Liu, PhD; and David Turnquist, MBA; Concert Pharmaceuticals, Inc.

Introduction

Concert Pharmaceuticals, a clinical stage biopharmaceutical company, uses deuterium to create and develop highly differentiated new medicines. This is a significant departure from the traditional use of deuterium modification as an analytical probe for metabolic studies. Concert uses its DCE Platform™ (Deuterium Chemical Entity) to develop new drugs that are designed to have first-in-class or best-in-class efficacy and/or safety. Deuterium modification provides a novel opportunity to develop new drugs by building upon existing scientific or clinical experience, potentially significantly reducing time, risk, and expense.

Concert's DCE Platform is based on the premise of the deuterium isotope effect wherein selective replacement of hydrogen atoms with deuterium creates more stable chemical bonds with carbon atoms. This modification can sometimes improve drug metabolism, increase half-life, or enhance bioavailability and exposure in a significant fashion. Deuterium is a safe, non-radioactive, naturally abundant isotope of hydrogen. The body of the average human adult already contains about 2 g of deuterium. Due to its similarity to hydrogen, deuterium modification usually has negligible effect on the intrinsic activity of a drug at its biological target. Concert's deuterium modification drug development approach is thus a powerful tool to improve the ADME (absorption, distribution, metabolism, and elimination) properties of a drug while maintaining its intrinsic biological activity. As many drugs under development or on the market suffer from sub-optimal pharmacokinetic and metabolic profiles, deuterium modification offers great promise to improve the profiles of these drugs and open opportunities for new uses.

Concert has advanced a number of deuterium-containing novel compounds designed to have unique therapeutic properties. The company has made preclinical and clinical progress with proprietary drug compounds in diverse therapeutic areas, including potential treatments for diabetic nephropathy, hot flashes, spasticity, neuropathic pain, and multiple myeloma.

CTP-499 for Diabetic Nephropathy

Concert's lead drug candidate is CTP-499, a novel potential treatment for diabetic nephropathy in type 2 diabetics. Diabetic nephropathy is the leading cause of end-stage renal disease, or kidney failure, and is expected to grow significantly as the incidence of type 2 diabetes increases rapidly. Despite the availability of blood pressure lowering agents, such as angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs), many patients continue to experience a decline in renal function and progress to kidney failure. As a result, there is a critical need for new drugs with untapped mechanisms that can further delay or prevent the decline of kidney function and eventual need for dialysis.

CTP-499 is an analog of 1-((*S*)-5-hydroxyhexyl)-3,7-dimethylxanthine (HDX), an active metabolite of Trental® (pentoxifylline), that Concert created by

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replacing several key hydrogen atoms with deuterium. Trental, which is significantly metabolized to HDX, is approved in the US for the treatment of intermittent claudication and has been reported in preliminary studies to have beneficial effects on urinary albumin excretion and renal function decline. Based on the pharmacology and degree of exposure, it appears these renoprotective effects may be due in large part to HDX. CTP-499 and HDX have similar physical, chemical, and pharmacological properties; however, Phase I clinical data with CTP-499 shows that incorporation of deuterium leads to increased exposure to the species responsible for the renoprotective effects.

To date, four Phase I studies have been completed with CTP-499. One study showed that controlled-release (CR) formulations of CTP-499 form the same metabolites as Trental; however, exposure to species possessing beneficial anti-inflammatory, anti-fibrotic, and immunomodulatory effects was increased with CTP-499 relative to Trental administration. The overall pharmacokinetic profile suggested CR CTP-499 may be suitable for once-daily dosing. A second study, which tested single ascending doses of CR CTP-499, showed that doses up to and including 1800 mg were well tolerated. Based on these results, CTP-499 shows unique potential as a treatment for diabetic nephropathy, along with reduced development risk given the abundant safety experience with Trental.

In early 2012, Concert initiated a 6-month Phase II efficacy study of CTP-499 in diabetic patients with mild-to-moderate renal impairment who are at particular risk of disease progression due to macroalbuminuria (excessive amounts of albumin in their urine). The primary goal of the study is to investigate the effect of CTP-499 on a measure of disease progression, urinary albumin excretion, with secondary goals related to safety/tolerability and effects on renal function and various biomarkers.

The impact of deuterium on cost of goods varies depending on the drug. Concert invested in process development research that resulted in an elegant, highly efficient manufacturing process for CTP-499 active pharmaceutical ingredient (API). The synthesis has been designed to use the most cost-effective deuterated starting material and produces API in > 70% yield. Because CTP-499 is a single enantiomer, the desired enantiomer is directly isolated using an asymmetric synthesis with high enantioselectivity and little loss of deuterium. Finally, Concert creatively implemented recycling and recovery techniques through which > 90% of the deuterium used is either incorporated into the API or recovered for future use. CTP-499 is manufactured on a scale of hundreds of kilograms and is expected to have a cost of goods that is competitive with other commercial APIs.

CTP-347: Deuterium Modification of Paroxetine

Concert's first clinical candidate was CTP-347, a selectively deuterated analogue of paroxetine. CTP-347 was designed to eliminate the irreversible inhibition of a key metabolizing enzyme (CYP2D6) caused by a highly reactive paroxetine metabolite that covalently binds to the enzyme. In certain patients potentially benefiting from therapy with paroxetine who also receive endocrine disrupting agents, such as post-menopausal women and cancer patients, paroxetine use can be complicated or contraindicated as it causes extensive drug-drug interactions (DDIs) with other medications. In vitro metabolism experiments with CTP-347 demonstrated little to no CYP2D6 inactivation, as a result of deuterium-based metabolic shunting, which essentially prevented the formation of the reactive metabolite. Other studies showed the intrinsic pharmacology of paroxetine was unchanged after deuterium incorporation. A 96-subject single and multiple ascending dose clinical study with CTP-347 provided further evidence, consistent with the in vitro data, that irreversible inactivation of the CYP2D6 enzyme did not occur with CTP-347. This clinical study with CTP-347 represents the first clinical demonstration that deuteration can be utilized to avoid the formation of undesired metabolites in humans.

CTP-354: A Deuterium-Modified Subtype-Selective $GABA_A$ Modulator

Concert has created deuterated subtype-selective $GABA_A$ modulators that represent a promising therapeutic modality for the treatment of spasticity and chronic pain, with the potential for improvement over existing first-line therapies. A subtype-selective $GABA_A$ modulator has the potential to address a major unmet need by retaining desirable therapeutic aspects of the benzodiazepines - anxiolytic and spasmolytic activity - while minimizing the sedative and tolerance effects.

Concert's $GABA_A$ modulator program is based upon agents that have been profiled in multiple preclinical efficacy models, representing an opportunity to leverage extensive therapeutic data to advance a clinical candidate. Concert's $GABA_A$ modulator lead compound, CTP-354, is a deuterated version of a preclinical agent discovered at Merck. The Merck compound, L-838417, was targeted by Concert for deuterium substitution because its promising pharmacology was extensively characterized in the literature, although it possessed poor pharmacokinetic profiles in preclinical species and was never progressed into clinical development. L-838417 was shown to have desirable $GABA_A$ subtype selectivity in vitro: no agonist activity at the *alpha*-1 subtype but partial agonism activities at the *alpha*-2,

alpha-3, and *alpha*-5 subtypes. This in vitro subtype profile for L-838417 positively translated to its in vivo pharmacology profile, with demonstrated preclinical efficacy in anxiety, muscle relaxation, inflammatory pain, and neuropathic pain, and significantly reduced sedation and ataxia liabilities in rodents and primates.

Deuterated CTP-354 demonstrated substantial pharmacokinetic improvement compared to L-838417 in rats and dogs, and has recapitulated beneficial L-838417 pharmacology in both in vitro and in vivo studies. The Chung model, a sciatic nerve ligation model of neuropathic pain, was performed in the rat to compare oral doses of CTP-354 first to L-838417, and then to the standard of care, gabapentin. CTP-354 was efficacious in both studies with a prolonged pharmacodynamic effect versus L-838417, which correlated with the higher CTP-354 plasma level observed at the final timepoint. In the comparison of CTP-354 to gabapentin, CTP-354 demonstrated an excellent dose response and showed equivalent efficacy to gabapentin at similar doses. At the doses used in these studies, CTP-354 was well tolerated in a rat rotarod study assessing potential for sedation and ataxia. The excellent pharmacokinetic and pharmacology profiles of CTP-354 support the potential use as a non-sedating treatment of spasticity and neuropathic pain.

C-21359: A Deuterium-Stabilized Enantiomer of Lenalidomide

Concert has developed C-21359 as a novel deuterated enantiomer of racemic lenalidomide (Revlimid®), an oncology agent indicated for use in multiple myeloma and in myelodysplastic syndromes (MDS). Revlimid contains a mixture of *R* and *S* enantiomers that interconvert in vivo. While the *S* enantiomer appears to possess the beneficial activities associated with Revlimid, dosing of the single *S* enantiomer is not considered useful, as it would rapidly convert in vivo to the *R/S* mixture. Concert has discovered a specific deuterium modification pattern that optimally slows the interconversion of enantiomers, thus enabling administration of the more beneficial *S* enantiomer with minimal exposure to the *R* enantiomer.

C-21359 demonstrates enhanced activity versus Revlimid in immunomodulatory and anti-cancer in vitro efficacy assays. Deuterium-stabilized, single *S*-enantiomer dosing drives this improvement in pharmacological efficacy, as deuterated racemic lenalidomide derivatives show no improvement over Revlimid in these assays. C-21359 is expected to be useful for the treatment of multiple forms of cancer and myelodysplastic syndrome, with the potential to expand into non-cancer indications.

Summary

The aforementioned examples show that deuterium modification may be used broadly to improve upon previously known compounds or their analogs, in turn offering potential benefits in a wide range of therapeutic areas. It should be noted, however, that deuterium effects on the overall metabolism of a drug are not predictable *a priori*. For example, deuterium substitution may have no observable effect, or may cause metabolism to shift preferentially to another existing pathway. In select cases, Concert's deuterium modifications can impart significant improvements to the metabolic properties of a drug. Thus far, this relatively new approach to medicinal chemistry has yielded a number of promising drug candidates with differentiated therapeutic properties. ■

Dr. Philip Graham

Vice President of Program Development, Concert Pharmaceuticals

Dr. Philip Graham currently serves as Vice President of Program Development at Concert Pharmaceuticals. He has more than 20 years experience in the pharmaceutical and biotechnology industry. Prior to joining Concert, Dr. Graham was Vice President of Product Management and Imaging at EPIX Pharmaceuticals, where he also had management responsibility for chemical and analytical development along with pharmacology and toxicology. Before joining EPIX, Dr. Graham worked at Eli Lilly and Co. for more than 5 years in analytical development. He earned his BS with honors from the University of Otago, New Zealand, and his PhD in Analytical Chemistry from the University of Massachusetts, Amherst.

Dr. Julie Fields Liu

Director, Research Management, Concert Pharmaceuticals

Dr. Julie Fields Liu is currently Director, Research Management at Concert Pharmaceuticals, where she serves as a Program Team Leader, Intellectual Property/Research Liaison, and Manager of a multi-year outsourced chemistry collaboration. She is a medicinal chemist and has 12 years of experience in the pharmaceutical and biotechnology fields. Prior to joining Concert as one of the first 10 employees, Dr. Liu worked at Millennium Pharmaceuticals in the areas of oncology, inflammation, and metabolic disease. She earned her BS in Chemistry with honors and distinction from the University of North Carolina at Chapel Hill, and her PhD in Organic Chemistry from the University of California, Berkeley.

David Turnquist

Director of Analytical Chemistry, Concert Pharmaceuticals

David Turnquist currently serves as Director of Analytical Chemistry at Concert Pharmaceuticals. He has more than 14 years of experience in the pharmaceutical industry. Prior to joining Concert, Mr. Turnquist worked at Vertex Pharmaceuticals and Merck Research Laboratories serving in a variety of disciplines from Physical and Analytical Chemistry to Analytical Development to CMC Project Management. He earned his BS in Biology and Chemistry from the University of North Carolina at Chapel Hill and his MBA from Boston College.

Executive Summary

Holger Kunze
CEO
Accera, Inc

Accera, Inc: Discovering Breakthroughs in Treating Central Nervous System Disorders

Alzheimer's disease (AD) is the most common cause of dementia. Thirteen percent of all individuals over the age of 65, or one in eight, have AD. Someone in America develops AD every 69 seconds, and while medications for treating AD exist, there is no cure. Accera, Inc., a privately held, fully integrated development and commercialization-stage company, is focused on the discovery and development of pioneering therapeutics for serious diseases, such as AD. Accera's lead product, Axona®, currently marketed in the US as a prescription-only medical food for the clinical dietary management of mild-to-moderate AD, addresses metabolic deficiencies and provides an alternative energy source for the brains of AD patients. Specialty Pharma recently interviewed Holger Kunze, CEO of Accera, to discuss the company's novel approach to treating AD by addressing cerebral hypometabolism.

Q: ***Can you please discuss AD and its current prevalence in the US?***

A: As the number of people 65 years and older in the US continues to grow, the number of AD patients will increase. Alzheimer's is the most common cause of dementia, and 13% of all individuals over the age of 65, or one in eight, have this disease. Alzheimer's affects the parts of the brain that control memory, thought, and language. Doctors do not know the exact cause of this disease; however, medical research is working to discover what causes it and how to best treat this condition. Alzheimer's is progressive and affects people in different ways. Although each case of Alzheimer's is unique to each specific patient, there are similarities in the signs and symptoms that develop as the disease progresses.

Q: ***Accera, Inc.'s lead product, Axona®, targets cerebral hypometabolism. Can you explain what cerebral hypometabolism is and how Axona combats it in AD patients?***

A: One of the hallmark signs of Alzheimer's is the significant drop in the brain's ability to metabolize glucose, which is the primary source of fuel for the brain. This is known as cerebral hypometabolism. Research has shown that decreases in glucose metabolism can be seen in the brain 10 to 20 years before any clinical AD symptoms appear. Normal, healthy brains depend on circulating glucose to carry out most of its functions, including memories. Decreases in glucose metabolism correlate with decreases in brain function in AD patients.

Axona is designed to combat cerebral hypometabolism by providing the brain with an alternative source of fuel. Axona contains caprylic triglyceride, a medium chain triglyceride that is broken down by the liver into ketone bodies, which patients can metabolize to use as fuel for the brain.

Q: ***How does Axona differ from other currently available AD treatments?***

A: The first class of FDA-approved medications for AD has been formulated to increase the levels of Acetylcholine, a chemical responsible for memory in the brain. This class is called cholinesterase inhibitors. The primary members of this class are Exelon and Aricept. While these treatments have been proven

effective, many AD specialists believe patients benefit from a conjunctive or complementary plan that combines different courses of treatment.

In addition, cholinesterase inhibitors do not alleviate the cerebral hypometabolism present in the brains of these patients. Axona's ability to provide the brain with an alternative source of energy makes it different from all other currently available AD treatments.

Q: *Axona comes in a powder form. Can you explain how Axona should be administered?*

A: Axona is available in individual powder packets of 40 g per packet. It is recommended patients start with a reduced dose of 10 g a day and gradually work their way up to a full dose over the course of a week. Once acclimated to Axona, patients take only one packet of Axona once a day, shortly after breakfast. Axona should be added to 4 to 8 ounces of water or other liquids and be fully blended until mixed. These are the standard, recommended dosing instructions for Axona; however, each patient should work with his or her physician to determine the best and most effective dosing strategy.

Q: *Axona is classified as a medical food. What is a medical food, and how is it regulated?*

A: The category of medical foods was defined by the FDA in the Orphan Drug Act in 1988 as a food that is formulated to be consumed orally under the supervision of a physician, and which is intended for the specific, dietary management of a disease or condition. Medical foods are not subject to the FDA's full approval process for medication; however, medical foods have a generally regarded as safe (GRAS) status under the FDA. Medical foods are more potent and effective than nutraceuticals and supplements. Supplements are intended for normal, healthy adults and do not require any pre-market efficacy testing, while medical foods are intended to treat patients with a specific illness or disease. Medical foods, unlike nutraceuticals and supplements, MUST be taken under medical supervision.

Q: *Is there clinical data showing that Axona is safe and effective?*

A: Axona has been tested in both a single-dose study and clinical trials with patients with mild-to-moderate AD, as well as healthy elderly volunteers. The single-dose study was conducted on 20 patients diagnosed with AD or mild cognitive impairment. The results showed a positive response, with improvement in paragraph recall and the AD Disease Assessment Scale - Cognitive subscale (ADAS-Cog) test. Peer-reviewed results were published in *Neurobiology of Aging*, in 2004.

Axona was also studied in a double-blind, randomized, placebo-controlled study performed at multiple US sites. The trials involved 152 patients with mild-to-moderate AD over a period of 90 days. As Axona is designed to function as a complementary therapy, about 80% of those patients were receiving standard-of-care AD therapy, including the use of cholinesterase inhibitors and NMDA anatagonists. The results showed a significant improvement in cognitive function in patients taking Axona after 45 days and demonstrated a decline in patients in the placebo group. The results also showed that cognitive benefits could be maintained over a period of time in the Axona patients.

Peer-reviewed results were published in *Nutrition & Metabolism* in August 2009 in the article titled *Study of the Ketogenic Agent* AC-1202 in *Mild-to-Moderate Alzheimer's Disease: a Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial*.

Q: *Can Axona be taken with the cholerestinase inhibitors that are currently available for AD patients?*

A: Axona has been designed to complement the existing AD therapies currently on the market. Patients in clinical trials were permitted to take commonly prescribed AD medications, and additional improvements following Axona administration were observed even for those patients taking these other medications.

Q: *Who do you see as Axona's chief competitors?*

A: Among currently available, prescription-only therapies for AD, Axona has no direct competitors, as no other AD medication targets cerebral hypometabolism. More importantly, as Axona can be taken along with cholinesterase inhibitors, it is not competing directly with this class.

Q: *Does Accera currently have any partnerships?*

A: Accera is not currently affiliated with any partners, but is actively seeking strategic partners interested in advancing ccera's technology to other indications and promoting global adoption of Axona. Additionally, Accera is exploring strategic partnerships to maximize the commercial success of Axona in and outside the US. ■

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On Behalf of Private Equity

By: John A. Bermingham

**Disclaimer: This is not a political article to support a candidate for office.*

Throughout the past decade, I have worked for four different private equity firms as the CEO of one of their portfolio companies. I, like you, have been listening to various parties drag private equity firms through the mud disseminating inaccurate information about what private equity firms do to companies and their people. I have been there, so I believe I am qualified to offer a first-hand opinion on private equity firms.

Private equity firms often buy distressed companies with the intention of turning them around, building them up, and then selling them in 5 to 7 years for a profit. Most often, this means most of the people working in the company keep their jobs following the acquisition of the company by a private equity firm and, when the company is sold in later years, the people continue on with the company and its new owners. However, this is not always the case as you will see further on.

Private equity firms do not buy companies in order to fire all of the people and shut down the business. Because many of the companies acquired by private equity firms are in serious trouble, one of the most common problems in a distressed company is there are too many people in the company. This is due to the CEO not wanting to lay off people. I found this to be the case in all four private equity-owned companies I turned around.

As an example, let's say that you become the CEO of a distressed company that does $50 million per year in revenue and is losing $5 million per year. Five years earlier, the company had annual revenue of $100 million and required a headcount of 500 people. The company still has 500 employees with an overhead expense of $12 million per year, and your analysis of the head count in the company indicates you only need 250 people to generate $50 million in revenue.

Simplistic financial theory shows that reducing headcount by 50% should cut your overhead expense by 50%, so your expense reduction for people would be $6 million. If you are losing $5 million per year and cut expenses $6 million per year, you should generate $1 million in profit, assuming everything else remains the same.

The idea here is that by reducing headcount to 250 people, you save the jobs of the 250 people who are left. If you kept everybody on board in the company, under current conditions, the company would eventually go bankrupt and then 500 people would lose their jobs!

So when you hear that such and such company was acquired by a private equity firm and they fired lots of people, you most likely have only part of the story. The same holds true when you hear of a private equity firm buying a company and then shut it down and everyone lost their job. The private equity firm most likely acquired a distressed company and had to shut it down because they could not save it.

This is not to say that all private equity firms are good. I have seen instances in which a private equity firm acquires a company and brings in a new CEO and management team to turn around and stabilize the company. Once accomplished, they put the company up for sale and in many cases, sell the company to a strategic buyer (another company that is in the same business or industry). The private equity firm normally makes a lot of money on this type of transaction.

The acquiring company will look to absorb the business into its company with a minimal increase in headcount. Hence, the acquiring company has no need for most of the people in the company it just acquired, so all of those people lose their jobs.

There is good and bad in almost everything, including private equity firms. I just wanted to let you know that not all private equity firms are bad, even though some of the media (as well as some politicians) portray them as evil personified. ◆

Biography

John A. Bermingham is currently the Co-President and COO of AgraTech, a biotech enterprise focused on chitosan, a biomaterial processed from crustacean shells (shrimp, crawfish, crab, etc). He was the President & CEO of Cord Crafts, LLC, a leading manufacturer and marketer of permanent botanicals. Prior to Cord Crafts, he was President & CEO of Alco Consumer Products, Inc., an importer of house ware, home goods, pet, and safety products under the Alco brand name and through licenses from the ASPCA and Red Cross. He successfully turned around the company in 60 days and sold Alco to a strategic buyer. Mr. Bermingham was previously the President & CEO of Lang Holdings, Inc. (an innovative leader in the social sentiment and home décor industries) and President, Chairman, and CEO of Ampad (a leading manufacturer and distributor of office products). With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona Corporation, and Rolodex Corporation. He turned around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served 3 years in the U.S. Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes, earned his BA in Business Administration from Saint Leo University, and completed the Harvard University Graduate School of Business Advanced Management Program.

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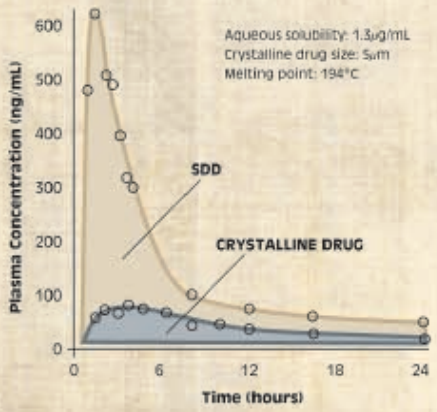

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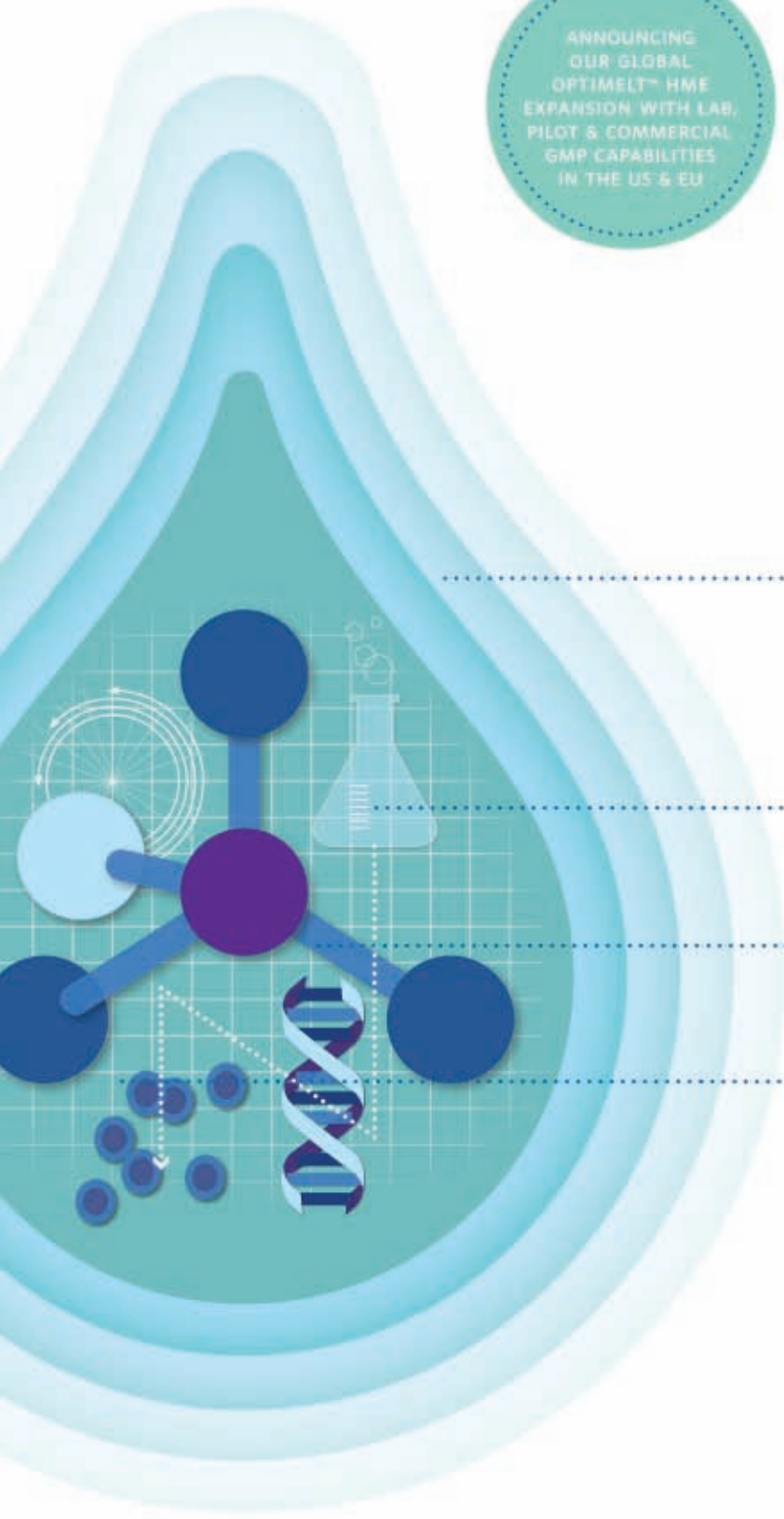

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