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Designing Greater Oral Dosage Forms

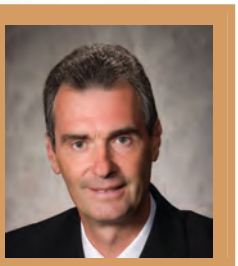
The science & business of drug development in specialty pharma, biotechnology, and drug delivery

Ansgar Santel, PhD
The AtuPLEX Technology for Therapeutic siRNA Delivery in Oncology

Shahrzad Missaghi, PhD
The Influence of Tablet Shape, Geometry & Film Coating on Drug Release From HPMC ER Matrices

Brian Windsor, PhD
Particle Engineering Solutions for Drug Delivery Challenges

IN THIS ISSUE



INTERVIEW WITH 3M DRUG DELIVERY SYSTEMS' DIVISION VP & GM
JAMES VAUGHAN

Medical Device Design 18
Alan Morris

Fight Within Pharma 22
Derek G. Hennecke, MBA

Polymer-Based Compounds 28
Bill Martineau, MBA

Monoclonal Antibodies 42
V.P. Chekhonin, MD
V.P. Baklaushev, MD

FEATURING
SPECIALTY PHARMA
Strategies For Business Development

GCL Market Trends 70
Cindy H. Dubin

Pharmaco-genomics 76
Katheryn Symank

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The new brochure makes reference to the changing regulatory environment and describes pharmacopoeial monographs in relation to device technology in detail, allowing users to establish a framework for testing. The brochure showcases new additions alongside established products, including: abbreviated impactors for rapid screening, dissolution testing equipment for inhaled products and a series of semi-automated devices that streamline impactor measurements, amongst many others.

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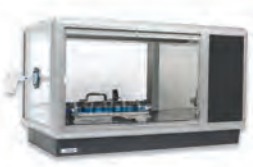

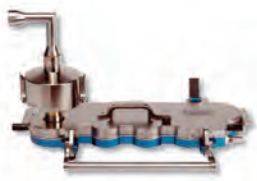


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p.32

Table Of Contents

22 ***The Fight Within Pharma***

Derek G. Hennecke, MBA, concludes this 6-part series covering unique strategies for building lasting competitive advantages.

28 ***Polymer-Based Pharmaceutical Compounds***

Bill Martineau, MBA, believes synthetic polymers, spurred by ongoing advances in resins and related processing technologies, are expected to broaden applications as drug delivery compounds.

32 ***Investigation of the Influence of Tablet Shape, Geometry & Film Coating on Drug Release From HPMC ER Matrices***

Shahrzad Missaghi, PhD; Piyush Patel, MPharm; Sandip B. Tiwari, PhD; Thomas P. Farrell, PhD; and Ali R. Rajabi-Siahboomi, PhD; indicate that tablet design offers opportunities to refine release profiles, rebrand existing products, and create distinctive formulations, allowing greater benefits from ER oral dosage forms.

42 ***A Binary Immunoliposomal System Directed to Cx43-Positive Glioma Cells***

V.P. Chekhonin, MD, PhD; V.P. Baklaushev, MD, PhD; O.I. Gurina, MD, PhD; et al evaluate the Cx43-positive cell selectivity of a binary system based on biotinylated MAb to E2 domain of Cx43 and PEGylated liposomes with streptavidin (SAv) for C6 glioma cell culture in vivo.

48 ***Significantly Reduced Drug-Apparent Solubility Using a Micronization Process***

Wei-Guo Dai, PhD; Liang C. Dong, PhD; Shu Li, Crystal Pollock-Dove, and Zhengyu Deng, PhD; report study results that clearly demonstrate the significant influences of different milling processes on compound solubility.

54 ***The AtuPLEX Technology for Therapeutic siRNA Delivery in Oncology***

Ansgar Santel, PhD; Oliver Keil, PhD; Klaus Giese, PhD; and Jörg Kaufmann, PhD; summarize the clinical development of Atu027 for oncology and the underlying AtuPLEX (siRNA-lipoplex) technology.

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GCL Market Trends

"As lab budgets remain constricted, pharmaceutical and biotech labs are outsourcing preclinical services to create efficiency and off-load the need to maintain staff, instruments, and consumables for irregularly scheduled projects and projects that extend beyond their scope. Increasingly, the model for drug development has the pharmaceutical industry devoting a large portion of its spending for late-stage clinical trials."

p.70

Table Of Contents

58 *3M Drug Delivery Systems: Continuing Innovation in a Changing Global Marketplace*

Drug Delivery Executive: Mr. James Vaughan, the division's Vice President & General Manager, discusses his company's approach to the changing climate in the pharmaceutical industry and how 3M helps its customers bring their products to market.

66 *Enavail: Particle Engineering Solutions for Drug Delivery Challenges*

Drug Delivery Executive: Dr. Brian Windsor, Enavail's President, explains how the company is effecting change in drug delivery development through its innovative technologies.

70 *GCL Market Trends: Clinical Trial Outsourcing is a Win-Win for Pharma & CROs*

Contributor Cindy H. Dubin learned from two of the leading CROs that better communication between them and their Specialty Pharma clients leads to a more successful drug development process.

76 *Pharmacogenomics & Drugs: Now it's Personal!*

Frost & Sullivan Analyst Katheryn Symank explains how increasing use of pharmacogenomics in both drug discovery and clinical applications are changing our approach to medicine.

Departments

Market News & Trends 12

Advanced Delivery Devices 18
Human Factors Engineering: Improving Medical Device Design to Ensure Safe, User-Friendly Medical Devices

Combination Update 24
Newly Proposed Good Manufacturing Practices

Technology Showcase 62

External Delivery 81
Crossing Over to Management

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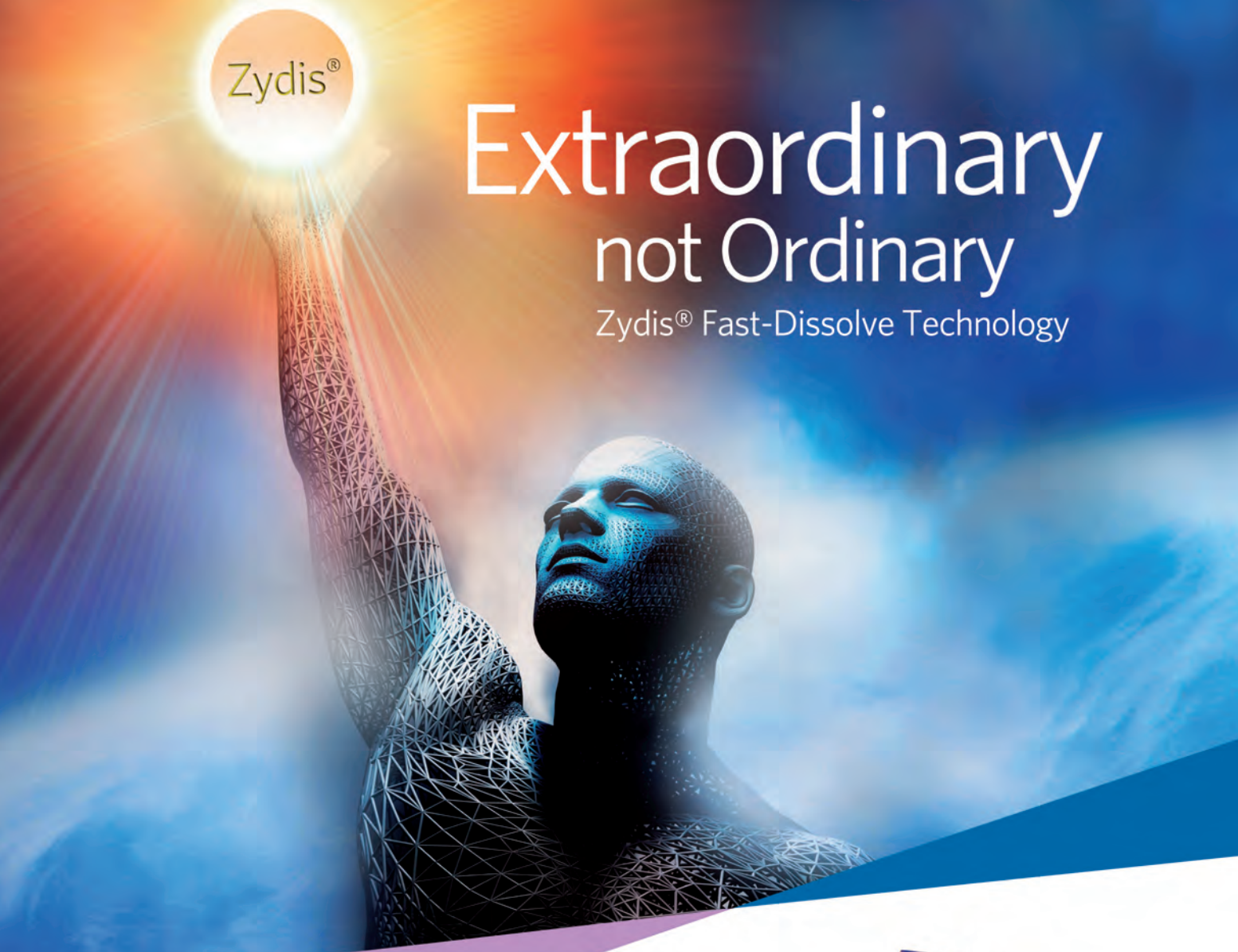

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Market News and Trends

Copley Scientific Launches World's First Commercial Apparatus for Dissolution Testing of Inhaled Drugs

Copley Scientific has launched the world's first commercially available apparatus designed specifically for dissolution testing of inhaled drug formulations. Based on a concept developed by Professor Jason McConville and his team at the College of Pharmacy, University of Texas, a new NGI dissolution cup and membrane holder enables dissolution testing of size-fractionated particles selected from the emitted dose. Simple to use and employing analytical methodology based on established pharmacopoeial techniques for transdermal patches, it provides information that allows developers to more closely tailor inhaled drug delivery. The launch underlines Copley Scientific's commitment to commercialiszing new analytical techniques for inhaled product testing and to providing the very best tools for development and QC.

Dissolution testing is widely applied in the development and manufacture of oral dosage forms, but is not yet in widespread use for inhaled products, where the prime focus is successful deposition in the lung. Currently, there are no official dissolution test methods for inhaled products. However, increasing use of the pulmonary route to deliver larger molecules and/or systemic therapies means growing emphasis on the rate of active pharmaceutical ingredient dissolution. Dissolution information allows the development of more sophisticated inhalation products with delayed-release characteristics and/or more closely controlled drug delivery profiles.

In dissolution testing for inhaled drugs, the respirable portion of the emitted dose is of primary interest. The new solution from Copley Scientific addresses this by integrating conventional tablet dissolution testing equipment within the Next Generation Impactor (NGI), a system used routinely for aerodynamic particle size measurement to size fractionate a sample. The NGI dissolution cup fits into a conventional NGI cup tray but has a 50-mm removable insert in the impaction area, allowing the collection of particles lying in a specific size fraction. The collected sample is tested in a dissolution tester using a procedure very similar to the Paddle Over Disc technique described in the pharmacopoeia for transdermal patches. Copley Scientific also offers a similar solution for use with the Andersen Cascade Impactor.

Copley Scientific is recognized as the world's leading manufacturer of inhaler test equipment and is a major supplier of test equipment for pharmaceutical solid dosage forms, including tablet dissolution, disintegration, friability, hardness, and powder testers. The company has offices in the UK and Switzerland and a partnership with aerosol particle science experts MSP Corporation in North America.

Crospon Announces Spin-Out of Janisys to Deliver Industry-First Skin Patch Drug Delivery Device

Crospon, a medical device developer based in Galway, Ireland, recently announced its drug delivery technology platform has been spun-out into a distinct company, Janisys, as a result of the continued development of the product prototype. The Janisys drug delivery platform, which leverages ink-jet printing technology licensed from HP, enables painless, controlled release of one or more drugs in a single patch to the skin. This announcement details that the new spin-out is at a late-stage in developing functional prototypes of its active microneedle-based transdermal system, and intends to begin preclinical trials in 2010.

Janisys has secured co-development funding from a leading pharmaceutical company to progress the initial prototype development of Janisys, and the company will be seeking to engage in a round of fundraising during the first half of 2010 for completion of the commercial version of the system. The spin-out of Janisys follows the US FDA approval of Crospon's flagship gastroenterology product, EndoFLIP.

"This announcement is an exciting step in the continued development of the Janisys drug delivery system," said John O'Dea, CEO of Crospon. "This industry-first skin patch will offer a superior drug delivery platform for doctors and patients. We look forward to engaging in preclinical trials later this year."

Transdermal patches for nicotine delivery have become a mainstay for smoking cessation and pain management programs; however, they have not been a widely effective delivery mechanism for many drugs because the skin acts as a natural barrier. The Janisys skin patch delivers medication intradermally, thereby expanding the range of drugs and biopharmaceuticals for which patches may be used. The patch uses microneedles that barely penetrate the skin, which radically reduces discomfort compared to traditional hypodermic needles. The device will enable precise control of dosage timing, access to dosage history, patient activation mechanisms, and will include inherent safety protocols for preventing adverse drug interactions.

Established in 2006, Crospon is a medical device company focused on the monitoring and treatment of gastroesophageal reflux disorder (GERD). Company Co-Founder and CEO, John O'Dea, previously co-founded Caradyne, a respiratory products company which was acquired by Respironics Inc. in 2004.

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Market News and Trends

Altea & KAI Enter Development Agreement for the Transdermal Delivery of Peptides

Altea Therapeutics Corporation recently announced it has entered into a partnership with KAI Pharmaceuticals, Inc., a drug discovery and development company, for the preclinical and clinical development of certain KAI proprietary peptides utilizing Altea's proprietary PassPort Transdermal Delivery System.

Under the terms of the agreement, Altea and KAI will examine the transdermal delivery of certain KAI proprietary compounds using Altea's novel transdermal delivery technology, the PassPort System. Altea has also granted KAI an option to receive a worldwide technology license for the further development and commercialization of these novel transdermal products. Should KAI exercise the option, KAI will fund all product development, manufacturing, and commercialization activities, and Altea may receive license payments, development and commercialization milestones, and royalties on product sales from KAI.

"We are pleased to enter into this agreement with KAI Pharmaceuticals," said Dr. Eric Tomlinson, PhD, DSc, President and CEO of Altea Therapeutics. "The agreement further validates the broad application of the Altea Therapeutics novel transdermal patch technology for the transdermal delivery of water-soluble compounds. While we continue to apply our transdermal technology to currently approved drugs that previously were administered by needle injection or infusion, including water-soluble proteins, carbohydrates, and small molecules, this new partnership allows us to apply our technology to the new peptide drugs being developed by KAI Pharmaceuticals."

Altea Therapeutics is a privately held clinical-stage pharmaceutical company with a proprietary platform technology broadly applicable to the bolus or sustained transdermal delivery of biological drugs (proteins and carbohydrates) that otherwise would be administered by needle injection or infusion.

KAI is a drug discovery and development company with novel clinical-stage programs in cardiovascular disease, renal complications, and pain. KAI's lead product candidate, KAI-9803, is currently in a Phase IIb study (PROTECTION AMI) designed to assess the effect of KAI-9803 on reducing myocardial injury in heart attack patients.

Soligenix Announces Issuance of Hong Kong Patent for its LPM Oral Drug Delivery Technology

Soligenix, Inc., a late-stage biotechnology company, recently announced it has received a Hong Kong patent that addresses its Lipid Polymer Micelle (LPM) technology for the improved oral delivery of drugs. The issued Hong Kong patent, HK 1071054, titled Stabilized Reverse Micelle Compositions and Uses Thereof, covers lipid structures (reverse micelles) that promote the intestinal absorption of peptides and other sensitive drugs that cannot otherwise be given orally. The issuance of this patent in Hong Kong follows the issuance of the same patent in Europe in 2009.

The LPM technology is a platform technology that uses reverse micelles stabilized by polymers. Reverse micelles are generally described as a lipid system and are similar to water-in-oil emulsions in that the hydrophilic lipid head groups are directed toward the micelle core, with the hydrophobic tails imbedded in the oil phase. This results in a drug delivery system that is a thermodynamically stable clear dispersion of the water-soluble drug in the lipid phase. But unlike water-in-oil systems, stabilized reverse micelles do not depend on the presence of other surfactants and are thermodynamically stable. In the LPM system, water-soluble drugs are contained in the water space in the core of the micelles and are protected against degradation.

LPM is thought to promote intestinal absorption through the action of the micelles to open up small channels that allow only molecules of a certain dimension to pass through, excluding extremely large molecules, bacteria, and viruses. The reverse micelles also structurally prevent the rapid inactivation of peptides by enzymes in the upper gastrointestinal tract. Other sensitive drugs that can be delivered orally with the LPM system include various classes of drugs, such as peptides, nucleic acids, and proteins, which are degraded in the stomach and small intestine. Corresponding patents in the US and elsewhere are currently pending.

Through its Biodefense Division, Soligenix is developing biomedical countermeasures pursuant to the Project BioShield Act of 2004. Soligenix's lead biodefense product in development is a recombinant subunit vaccine called RiVax, which is designed to protect against the lethal effects of exposure to ricin toxin.

MDRNA Reports Positive Results for Proprietary siRNA Delivery Technology

MDRNA, Inc., a leading RNAi-based drug discovery and development company, recently announced that its lead delivery system formulation demonstrated exceptional stability over a 1-year period under a variety of conditions. The DiLA2 formulation maintained in vivo knock-down activity with no observed loss in potency over the course of the year-long study when stored under conditions ranging from -80°C to 4°C. In addition, neither change in particle characteristics, such as size or charge nor loss in siRNA integrity was observed.

The company's proprietary UsiRNA constructs in the DiLA2 formulations have demonstrated superior activity for delivery to hepatocytes in rodent and non-human primates. In addition, these compounds have demonstrated inhibition of mRNA via RNAi and subsequent reduction in tumor burden in the company's oncology programs in liver and bladder cancer. Long-term stability of the DiLA2 formulation/UsiRNA cargo is an integral part of the development of the company's drug products and represents further progress in these programs.

"The ability of our novel DiLA2 formulation to be stored frozen or at refrigerated conditions is unique," stated Barry Polisky, PhD, Chief Scientific Officer at MDRNA. "We have the flexibility to tailor storage conditions to meet the needs of our internal programs, pharma partners, and ultimately the commercial requirements of a marketed RNAi-based therapeutic."

DiLA2 delivery platform is MDRNA's proprietary platform for creating novel liposomal delivery systems based on di-alkylated amino acids (DiLA2). The DiLA2 platform enables MDRNA to tailor the charge, linker length, and acyl chain characteristics to improve delivery of the liposomes to target tissue of interest. In vivo studies have demonstrated effective delivery in models of metabolic disorders, cancer, and other diseases. DiLA2-based liposomes are well tolerated for repeat dose, and systemic and local administration. MDRNA is also utilizing condensing peptides to form peptide-siRNA nanoparticles to further increase the delivery efficiency of its DiLA2 delivery systems.

MDRNA is a biotechnology company focused on the development and commercialization of therapeutic products based on RNA interference (RNAi). Its goal is to improve human health through the development of RNAi-based compounds and drug delivery technologies that together provide superior therapeutic options for patients. Throughout the past decade, it has developed substantial capabilities in molecular biology, cellular biology, lipid chemistry, peptide chemistry, pharmacology, and bioinformatics, which we are applying to a wide range of RNAi technologies and delivery approaches.

Pantec Biosolutions Successfully Delivers Largest Protein Transdermally

Pantec Biosolutions AG, a privately owned company developing innovative transdermal drug delivery products, recently announced it has achieved excellent results in a Phase I clinical trial of a FSH (follicle stimulating hormone) patch used in conjunction with the company's novel P.L.E.A.S.E. (Painless Laser Epidermal System) technology. Although smaller peptides and some proteins have previously been delivered transdermally, this is the first time a molecule as large as this protein (32 KDa) has been successfully delivered in this way.

The purpose of the study was to investigate the primary pharmacokinetic characteristics as well as the safety and tolerability of the newly developed FSH protein patch in healthy male volunteers. Due to its size and physicochemical properties, FSH, a 32-KDa protein hormone, cannot permeate passively across intact skin. Therefore, prior to patch application, the skin was microporated using Pantec Biosolutions' P.L.E.A.S.E. laser device. This pre-treatment creates microchannels in the skin's stratum corneum, facilitating FSH transport through the skin and accelerating its entry into the systemic circulation.

The serum profiles further demonstrated the P.L.E.A.S.E.-FSH patch combination was able to achieve reproducible pharmacokinetics with negligible inter-individual variability. All of the volunteers considered the method to be convenient and easy to use, and there were no reports of any adverse events.

"This FSH patch Phase I trial represents a key milestone achieving proof-of-concept and demonstrating for the first time that P.L.E.A.S.E. enables delivery of large proteins, such as FSH efficiently in therapeutic amounts from a stable patch," said Christof Boehler, CEO of Pantec Biosolutions. "This validation of P.L.E.A.S.E. is an extremely important milestone that moves the company forward and significantly closer to commercialization."

Currently, FSH is self-administered by the patients for 10 to 12 days by daily subcutaneous or intramuscular injection stimulating follicle growth during an In Vitro Fertilisation (IVF) protocol. FSH is used in all major IVF procedures. The patch will avoid these multiple injections improving ease of use and convenience.

As a consequence of these excellent results, Pantec Biosolutions is now planning a future Phase II study with the new P.L.E.A.S.E.-FSH patch.

Pantec Biosolutions AG is a private drug delivery company specialized in using laser microporation technology to deliver large molecular weight drugs into the epidermis for local or systemic uptake. Its proprietary P.L.E.A.S.E. platform enables efficient, needle-free, and painless administration of biopharmaceutical drugs, in varying and individualized dosages, through partnered patch technology. The technology is currently in clinical trials for the delivery of IVF hormone therapy, a market with an estimated value of $1.5 to $2 billion.

Phosphagenics Reports Positive Phase Ib Study Results for Transdermal Oxycodone Patch

Phosphagenics Limited recently announced positive results from a Phase Ib clinical study using the company's patented TPM (Targeted Penetration Matrix) for the transdermal delivery of oxycodone. This successful trial showed that daily application of a TPM-oxycodone patch delivered therapeutic bloodstream levels of oxycodone in a reproducible, consistent, and sustained manner.

"The ability to reach therapeutic oxycodone plasma concentrations from a transdermal patch is a major achievement, and the sustained blood levels of this drug appear very suitable for chronic pain management," said Professor Guy Ludbrook, Principal Investigator for the study and Head of Discipline, Anaesthesia & Intensive Care, at the Royal Adelaide Hospital. "After a dose of oral oxycodone pain relief is provided for only a matter of hours. The use of Phosphagenics' oxycodone patch may provide sustained drug delivery for a matter of days, thus removing some of the peaks and troughs of pain relief associated with oral treatment."

The open label, single centre pharmacokinetic study in 20 healthy volunteers was conducted at the Royal Adelaide Hospital. The primary objective of the study was to compare the delivery profiles of two transdermal patch candidates containing TPM, a matrix, and reservoir system, following daily application over a 10-day period. Plasma oxycodone concentrations were monitored throughout the study to assess which of the two patch systems produced the best delivery profile. Results from the study demonstrate that oxycodone plasma concentration increased throughout the entire 10-day dosing period after daily application of the matrix patch. Average plasma concentrations reached therapeutic levels and continued to rise daily during the 10-day study. Rapid drug elimination was also evident immediately after the removal of the final matrix patch on the tenth study day. The matrix patch had an oxycodone delivery profile that was much superior to the reservoir patch. Due to the evident superiority of the matrix patch over the reservoir system, as well as its greater potential to reduce drug abuse, Phosphagenics will continue development of only the matrix patch.

"The oxycodone Phase Ib trial was a very critical study and a key milestone for Phosphagenics, going beyond a proof-of-concept and demonstrating that our patch system can reproducibly deliver therapeutic amounts of oxycodone into the bloodstream. The therapeutic blood levels, the rapid elimination when the patch was removed, and the lack of skin irritation observed during the study, together with the likelihood that the patch will reduce drug abuse, makes our TPM-oxycodone patch extremely attractive commercially," said Dr Esra Ogru, Phosphagenics' Chief Operating Officer. "The continued increase in oxycodone concentrations over the duration of the experiment surpassed even our own expectations and further validates the power of TPM for transdermal delivery. We believe that this product will be ideal for management of chronic pain."

As a consequence of this breakthrough clinical trial, Phosphagenics is planning the next stage of its oxycodone development. Under the guidance of Professor Guy Ludbrook, Phosphagenics has assembled an advisory panel of international pain experts to plan the path forward into Phase II/III trials and beyond. It expects to commence its next clinical study in the second half of this year.

Human Factors Engineering: Improving Medical Device Design to Ensure Safe, User-Friendly Medical Devices

By: Alan Morris and Andreas Knaack

What made the ubiquitous iPod such a success? It wasn't the first MP3 player on the market; it had less storage capacity, fewer features, and cost more than many of its competitors. On paper, when comparing specifications alone, it shouldn't have been top of your shopping list. There has been much analysis over the years as to why it's been such a market success, but one major factor that most everyone agrees on is the user experience: from connectivity to iTunes, the über-cool form factor, and most importantly, the instantly engaging navigation experience. In addition, there are no moving parts, unique single-thumb navigation that immediately connects with today's SMS generation, and a graphical user interface all just makes sense.

But imagine if your iPod was intended to deliver life-saving drugs in a medical emergency? Imagine you were taking the dog for a walk and suddenly experienced chest pain? How rapidly would you be able to select the *acute myocardial infarction app*? There's every risk you'd end up lying prone on the sidewalk, clutching your chest, with only the thumping beat of your favorite music available to treat your arrhythmia.

As with all good design, the iPod was designed with a specific purpose in mind. Its interface demands exploration and (initially) trial and error. A first-time user might struggle to select and play a specific music track and then adjust the volume to a comfortable level without any guidance, which is acceptable for a digital music device. But an inexperienced user of a medical device can't afford such luxuries when required to rapidly deliver a life-saving treatment in a pressure-cooker emergency scenario.

The team at Apple understands the value of the user experience, and whilst the iPod is a consumer product, this doesn't mean the same outlook need not apply to your medical device. Like an iPod, a thoughtfully designed user interface will help build sales through product demonstrations and word of mouth, create a loyal customer base, and generate repeat purchases. It will help build and maintain your brand. It will also comply with the mandatory FDA guidelines and may ultimately protect you and your company from costly litigation.

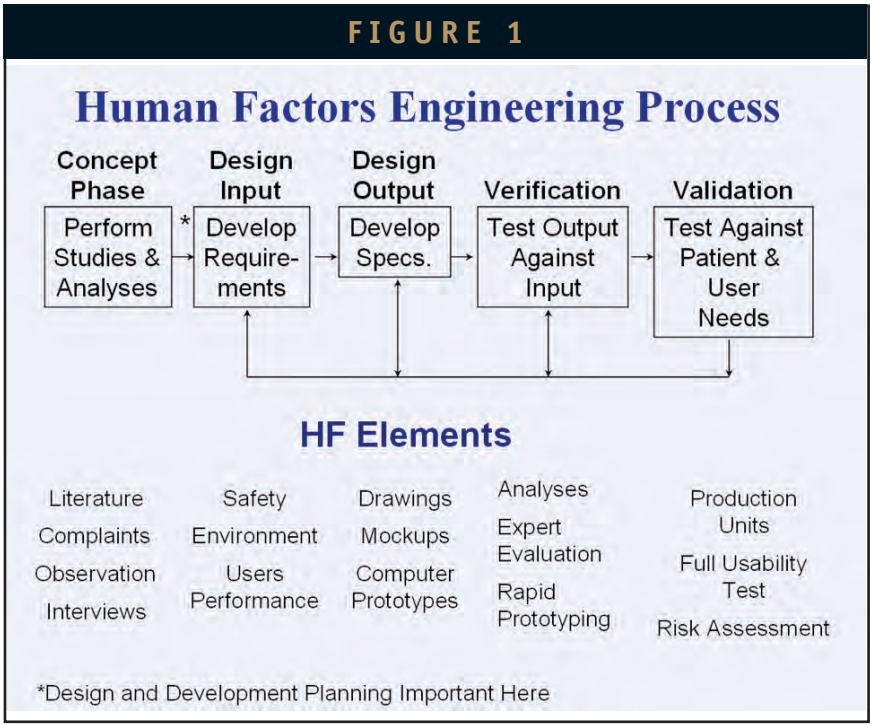
There is a global trend to develop medical devices that provide treatment to patients in their homes. This in turn requires a drug delivery medical device that enables the user to self-administer drugs. The typical users may be elderly, impaired, distracted, rushing, or overly confident in their abilities in spite of having not read the instructions. All of these scenarios can lead to error if the device isn't well designed.

The FDA receives on average 100,000 medical device incident reports per year, and more than a third involve user error. In an FDA recall study, 44% of medical device recalls are due to design problems, and user error is often linked to the poor design of a product. Drug developers need to take safe drug dosage into consideration, and this consideration requires the application of thorough processes for Risk Management and Human Factors Engineering (HFE).

THE DANGERS OF MEDICAL DEVICES

Although unintended, medical devices can sometimes harm patients or the people administering the healthcare. The potential harm arises from two main sources: (1) failure of the device and (2) actions of the user or user-related errors. A number of factors can lead to these user-induced

FIGURE 1



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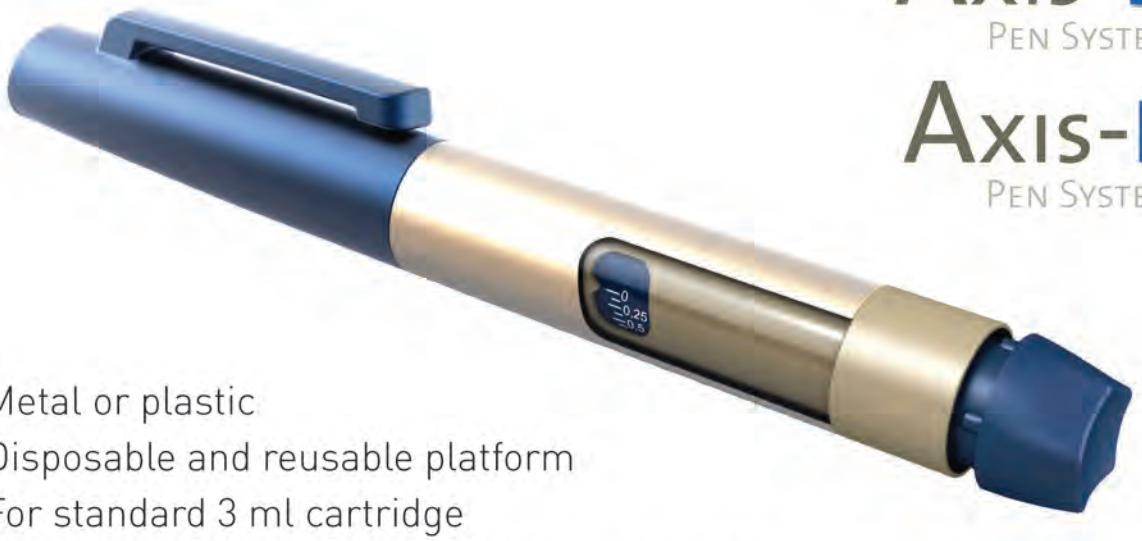

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errors, including medical devices are often used under stressful conditions and users may think differently than the device designer.

HUMAN FACTORS ENGINEERING (HFE)

The best way to address these dangers is through the implementation of an HFE program throughout a product's development. Human Factors is the study of how people use technology. It focuses on the science and methods used to make devices easier and safer to use. When applied to medical devices, including those for drug delivery, HFE helps improve human performance and reduce the risks associated with use. HFE refers to the application of human factors principles to the design of devices and systems. It is often interchanged with the terms human engineering, usability engineering, or ergonomics. Specific benefits of HFE include the following:

- Significantly reduced risk of device-use error
- Better understanding of device status and operation
- Better understanding of a patient's current medical condition
- Easier to use (or more intuitive) devices
- Reduced need for training
- Reduced reliance on user manuals
- Easier-to-read controls and displays
- Safer connections between devices
- More effective alarms
- Easier repair and maintenance

But let's not forget our iPod example. The more thoughtful and integrated the HFE, the more likely the product is to succeed (all things being equal). If your device is beautifully integrated in its design, engineering, and ergonomics, you are a long way toward achieving a successful product.

FDA GUIDELINES

The FDA imposes stringent standards on medical devices, requiring them to meet the Quality Systems Regulation (QSR)/CGMP - Design Controls. Manufacturers are also required by the FDA to demonstrate how human factors considerations were met throughout a product's development. To assist you in your process, there is the HFE standard *ANSI/AAMI HE74:2001 Human Factors Design Process for Medical Devices and the IEC 60601-1-6.*

The *ANSI/AAMI HE74:2001* describes almost everything a designer needs to know. It provides an overview of the HFE process, including planning, methods and techniques, and risk and cost benefit analysis. It highlights the need for user input; scaling the HFE work; documenting the HFE activities; and design evaluation, verification, and validation. Figure 1 illustrates the stages in the HFE process.

HFE IN PRACTICE

As discussed, HFE is not a separate component of a product development program. In fact, you must start thinking about usability from the moment you decide you are going to develop your device and constantly check and evaluate usability throughout the device development. At Invetech, we've been using a user-centered design philosophy for more than 20 years, enabling us to develop better and safer products and devices for an international client base. The following are some of our key learnings.

INTEGRATING HFE EXPERTS & ENGINEERING TEAMS: Our approach is based on a complete integration of HFE experts with the engineering design team from the very beginning of a development project. This integration ensures that the technical team receives direct and continuous input into their design activities, while interchanging technical ideas, challenges, and solutions with our HFE experts.

UNDERSTANDING THE USER'S ENVIRONMENT: At the outset of a product development activity, time is taken to immerse our team in the target workplace with the aim of developing a deeper understanding of the real-world challenges facing our customer. Contextual enquiry and observational research are at the heart of this immersion activity, enabling us to gain valuable insights into the unmet needs of the target user group(s). Through intense immersion into the users' environment, often achieved through site visits (hospitals, laboratories, doctors offices, domestic homes) and interaction with end users, we gain real-world insights that then drive product engineering.

CONCEPT DEVELOPMENT & ASSESSMENT: When these insights are identified, the design process can begin. Concepts are generated considering technical and commercial feasibility whilst concurrently addressing critical user needs. Design details like product dimensions, size of user interfaces and screens, access to consumables, etc are developed in close cooperation with the technical team. The results are initial product sketches and usability mock-ups (simple three-dimensional models to enable quick conceptual evaluations). Procedures for use need to be logical, intuitive, and consistent. Key safety concepts in design include making things easily visible, simplifying the operation, avoiding reliance on memory, avoiding reliance on vigilance, and making it easy to reverse an error.

SAFETY ASSESSMENT, ANALYSIS & DESIGN REFINEMENT: When such concepts are defined, both engineers and HFE experts can conduct safety analyses based on methodologies, such as FMEA (Failure Mode Effects Analysis) or FMECA (Failure Mode Effects and Criticality Analysis). The team assesses what can go wrong for each identified use case. While the technical team assesses this with a focus on technical failures, HFE experts are assessing potential errors induced by users when interacting with the device. Failure modes of each use case are

assessed with respect to their impact on the result and then weighted by probability, severity, and often detectability. Through this evaluation, a criticality number for each identified failure mode is assigned. Once identified, the team then develops mitigating designs for each significant (ie, carrying a high criticality number) failure mode. Preferably, the mitigation is a design solution that prevents the failure mode or significantly reduces its probability to a level that is acceptable. When doing so, it is also important to assess the reliability of such preventive design solutions (keeping in mind that a safety measure that doesn't work reliably does not add value).

USER ASSESSMENTS & STUDIES: The next step in this process is the generation of simple full-size models that emulate key parameters and features. Working with a range of end-users, typically covering from 5%-ile to the 95%-ile user, these early models provide remarkable input into the overall product design. Additional methods to be considered depending on the nature of the device are research studies (focus groups, one-to-one interviews, contextual inquiry) task analysis, usability, and safety bench tests. We will routinely test a range of designs with the target user group to gauge reaction to size and form, to step through workflows, to undertake operating procedures, and evaluate maintenance and servicing opportunities.

DESIGN REFINEMENT: Incorporating the feedback from these studies into the design process and refining the requirements in parallel, the engineering team and the design team are then performing the first iteration detailed design, resulting in fabrication and test of early prototype units. Typically at least one or two more prototype iterations will follow, and for each iteration, the human factors assessment is repeated, ideally with a varying range of users to broaden the statistical relevance of the feedback. Typically, the completed design needs to be validated, and again, it is important to not only consider the function of the product but to also assess its usability.

SUMMARY

Drug developers planning to develop medical devices must consider the challenges of human factors when developing and designing this type of new product. The benefits to be gained by cohesively integrating HFE into the device are not only the mandated technical compliance, but also enhanced opportunities to build sales and gain a loyal customer base. And to integrate HFE into your device, you must integrate your human factors and engineering teams from the very start of a development and throughout the development program. Hence, it is successful integration and the quality of your HFE team personnel that will help drive your product's success.

A good team will undertake systematic assessments of who your target device users are, under what conditions will the device be used (use environment, situational factors), and what might be the use-related hazards. But beyond the tangible, a good HFE team can add the intangible "delighters" to your device. To fall back on the music analogies, just as a hit song generally has a hook that sticks in your mind and has you humming it in the shower, so can clever HFE be memorable. It might include the tactile nature of the keypad controller you use to operate the device, the clever yet clearly written instructions, the sound of the alarm that differentiates your device from a sea of others, or even mechanical noise it makes while processing a protocol. All of these elements combine to create a memorable user experience just as 70% of all MP3 owners have when they switch on their iPod.

So, next time you hear someone in marketing proclaim "we expect our new gadget to be the iPod of medical devices," you are well placed to inform them of what is actually required to achieve this, which extends well beyond reliance on merely a beautiful product form. ◆

BIOGRAPHIES

Alan Morris is a Business Development Manager with Invetech. He has 18 years of experience in consumer product and medical device design. He has a background in industrial design and is particularly passionate about good Human Factors Engineering. He has been known to write a letter or two to companies whose products, operating systems, and/or instruction manuals fail the common sense test.

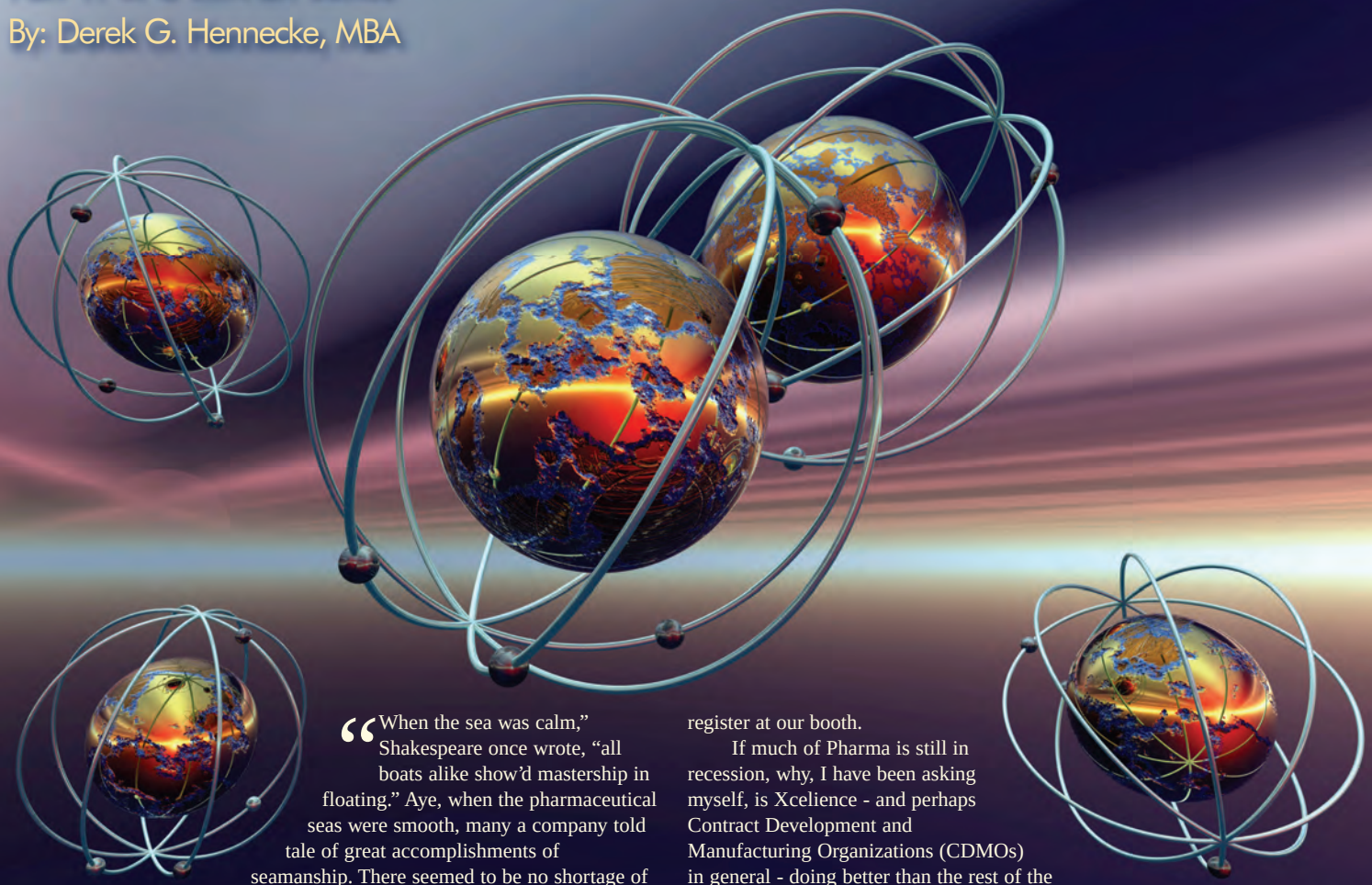
Andreas Knaack is the Director of the Biomedical Instruments & Devices division at Invetech. He is responsible for the strategy, sales, and delivery of custom product, instrument, and consumable developments for clients spanning diagnostic, medical device, and life sciences industries. Mr. Knaack has been with Invetech for more than 5 years and during that time has led several development projects, built Invetech's core focus group for Point-of-Care diagnostics, and finally grown the Biomedical division, serving a global client base.

Molecular Responsibility

The Fight Within Pharma

Part VI of a Six-Part Series

By: Derek G. Hennecke, MBA



"When the sea was calm," Shakespeare once wrote, "all boats alike show'd mastership in floating." Aye, when the pharmaceutical seas were smooth, many a company told tale of great accomplishments of seamanship. There seemed to be no shortage of great contracts to lay siege to, and we were all competitors, large and small, in a rum-slinging arm-in-arm sort of way. But a storm's blown through, and now there's a whole lot of slinging mud going on, and not a lot of rum.

I reported to you in my last article (October 2009) that the recession, as far as I was concerned, was over. That much seems true from where I sit. Clients' projects are back, and here at Xcelience, we've been able to restore some of our more severe recessionary precautions, such as the 10% pay cut management took to avoid staffing cuts after clients began canceling contracts in the darkest depths of the recession this past December.

It has come to my attention, though, that Xcelience and our little comeback story is too small to represent the overall market. Things seem pretty calm here, and we are going about our business, and rebuilding after the storm. But other parts of the fleet are apparently still in the throes of the tempest.

At the recent AAPS meeting in Los Angeles, there were still far fewer people than expected. Past conference attendance ranged from 8,000 to 10,000, while 2010 felt more like 5,000. A combined cocktail/working session with industry follower, William Blair, concluded we'll have to wait until second quarter 2010 for a turnaround in the pharma outsourcing market. In contrast, we had a large number of people register at our booth.

If much of Pharma is still in recession, why, I have been asking myself, is Xcelience - and perhaps Contract Development and Manufacturing Organizations (CDMOs) in general - doing better than the rest of the market?

Little Guys Do Better in Recessions

Small, innovative companies do better in bad times. And even more so in chaotic times. Disney, Microsoft, Hyatt, GE, Apple, Sun, and HP were all founded in times of economic depression. Why? Because even in bad times, people still buy things. But they become more conscious of what they really need, and why. They are more willing to try new things. Consumer needs evolve.

Fortunately for the smaller companies, larger incumbents are generally too slow-moving to see and react to these changes. They are like a great oil tanker heading into the storm. When it's too late to turn around, they drive on with their core business-driven autopilot and plough ahead trying to preserve profit margins. And when the ominous power of the storm becomes overwhelming, they deal with it by throwing half their crew overboard.

Far better, in tough times, to be the little guy. Moving quickly, small companies seize disruptive market opportunities and experiment with the business models that exploit and satisfy evolving consumer needs. By the time the full-force of that storm hits the big guy, the little guy has long since changed course and has the wind in his sails.

This is why so few small CDMO players have left the market in the

wake of this recession. I know of only two small companies that went bankrupt. One of them had their assets bought by specialty pharma company URL. On the other side, every large CMO has faced massive sales declines in the broad-based CMO world as well as the CDMO area.

Mud-Slinging Throughout the Industry

Yet our industry isn't like every other industry. I can't compare it to other small businesses like the restaurant business, where entry barriers and exit barriers are equally easy. Our industry is easy to get into, and tough to get out of.

Michael Porter's theory on competition postulates that when an industry is profitable, easy to enter, and hard to get out of, it will draw new entrants, which will decrease profitability. Unless the entry of new firms can be blocked by incumbents, the profit rate will fall.

It doesn't take much money to set up a lab and bootstrap your way along. But once you've set up, there is no real way for a company to get out of the market. Labs have been set up and employees have to be paid whether there is one project or none. You can't re-purpose a lab to manufacture chocolate bars because that's what people are buying this year. Even laying off a few staffers is taboo for CDMOs, because it frightens potential clients away, who might see the move as a sign of instability.

So with the recession came the mud-slinging throughout the drug development chain. Increasingly, I am seeing firms that bait clients with very low prices, then begin a series of change orders to jack the price up after the fact. They take advantage of the high costs of switching firms once an analytical process has been developed. Lure the client in, trap him, and milk him. Buyer beware. Shop reputation.

Lessons FRom the Airline Industry – Don't Pick a Fight

The airline industry is similarly difficult to exit, and the challenges there present some interesting parallels. The budget-fare market that was once dominated by American Airlines and Delta met with competition from the entry of JetBlue and ATA Airlines. In the airline industry, where they have high fixed costs, it's better to have every seat filled than to leave just one empty, so the fight for that last customer is bitter. American Airlines and Delta were forced to reduce their price points to meet the competition.

When Jet Blue began routes from Boston to Oakland and Orlando, American responded by cutting prices on those routes and offering customers who flew two trips on similar routes a free ticket anywhere American flew. When JetBlue tried to break into Delta's hub in Atlanta, Delta slashed prices and added 50% more flights, driving JetBlue from the market.

How, then, did Southwest Airlines manage 33 years of solid growth in this cutthroat environment? They did it by choosing not to pick a head-on fight with the incumbents. Instead, they chose to fly routes between second-tier airports in cities like Providence and Baltimore. Because they chose not to directly attack incumbents, they were able to grow without fear of attack.

Xcelience is like the Southwest of the Pharma industry. We are a small CDMO, specializing in formulation, a very small segment of the drug development chain. It's not a sexy area to be in. Formulation is to big Pharma what a second-tier airport is to American Airlines. When a major CMO adds formulation to its services, it's never a priority. It's always second tier.

Think of it this way. If you work for a big CMO in the formulation department, you're going to have change departments if you want to be fast tracked. That's where the careers are made because that's where the management is focused. That's where the resources are focused. That's where their core business is. When the recession hits, they'll go back to their core business, and the formulation budget will be trimmed, if not completely cut.

At Xcelience, all we do is formulation. We make our careers in it. We put all our resources into it. It is our core business. We invent terms like molecular responsibility to try and make is sound glamorous, and to show clients how important this stage of their business is to us. We LOVE the second tier. We RULE the second-tier. We are to pharma what Southwest is to the airline industry. We aren't taking the big guys head-on.

CDMOs in CMO World – Choose One Free With every Purchase

Unglamorous and unsexy as CDMOs may be, there have been attempts by CMOs to add CDMO services, giving them away "almost free" like a cable company might add on one more service to a broader package to sweeten the deal. In fact, this strategy worked brilliantly for the cable industry.

Remember when TiVo first came out with DVR technology? What a wonderful innovation! Unfortunately for TIVO, the cable companies quickly scrambled together ways of offering competing services and came up with a way to include DVR functionality in their cable boxes. TIVO became redundant. In our business, CMOs have been eyeing CDMOs like DVR technology. They keep trying to add CDMOs to their cable boxes.

Bruising battles for market share should be raging, with the victors claiming the spoils in the form of failing companies. So where are the bodies? In fact, as I detailed earlier, it's the commercial manufacturers who are suffering the heaviest sales declines. Why? Because CDMO's aren't commodities like a DVR. A business that's based on people and expertise is different. As long as formulation - or toxicology or whatever - is a secondary offering, it receives secondary attention. The CMO can't respond quickly enough to drug development needs if their attention is elsewhere.

CMOs have stolen some market share with artificially low prices but that can only go so far in an industry where quality, agility, and service are more important to most buyers than price. The CDMOs - unwilling to exit - have dug their nails in and fought, and CMOs have been forced to choose between investing to preserve their least profitable business segment, and going back to their core business. Because profitability is also relatively low in these areas, on the scale of major management decisions, this qualifies as a no-brainer.

We believe our customers increasingly understand this and all that it means for the level of attention and priority and experience CDMOs can give to this small stage of their drug development process. That's another reason why the recession has ended just a little bit sooner in our little unglamorous second-tier corner of the industry. ◆

BIOGRAPHY

Derek G. Hennecke, MBA
President & CEO
Xcelience

Mr. Derek G. Hennecke is a founding member of Xcelience. From 2004 to 2006, he served as Vice President and General Manager, Pharmaceutics and Biopharmaceuticals of MDS Pharma Sciences, Inc. In this capacity, he was responsible for the business and operations of MDS' CRO formulation development, including capsule development, tablet formulation, modified-release tablets, suspensions, solutions, suppositories, creams, ointments, and gels. Prior to joining MDS, Mr. Hennecke held various drug development management positions for DSM in Canada, Egypt, The Netherlands, and Mexico. In these roles, he built the operations or businesses to introduce various drug products for Europe and the US. Mr. Hennecke has also worked for Roche's research activities in Germany and Canada. He earned his BSc from the University of Alberta (Canada) and his MBA at the Erasmus University in Rotterdam, (The Netherlands).

Newly Proposed Good Manufacturing Practices

By: Bradley Merrill Thompson, MBA, and Leah R. Kendall

The US FDA recently announced the long-anticipated new proposed rule for combination product Good Manufacturing Practices (GMPs).[1] Published on September 23, 2009, the proposed rule may well substantially change the way companies develop and commercialize combination products, clarifying many of the issues that manufacturers have struggled with over the years, but also injecting some new ambiguities. Comments on the proposed rule are due February 5, 2010.[2] Shortly after publishing the GMP proposed rule, the agency issued a proposed rule on post-market safety reporting for combination products. Our next column will explore this equally important rule. After summarizing the GMP proposed rule and the issues it clarifies, we will highlight a few new concerns that might impact the drug delivery industry and discuss how the FDA might implement the rule.

BACKGROUND

Until now, the primary pronouncement on combination product GMPs was a draft guidance document issued in September 2004. After this draft guidance, the agency announced its intent to publish a proposed rule in Spring 2006 and issued at least one Warning Letter citing a company for violations of combination product GMPs in June 2006.[3] The practical effect of announcing its plan to publish the rule turned out to be a quiet period on the topic of combination product GMPs in which the agency felt constrained not to discuss the topic while it formulated its proposal. That left many companies with unanswered questions throughout the past 5 years as they struggled to figure out how to develop new facilities and manufacture combination products.

SCOPE OF THE CGMP PROPOSED RULE

The basic content of the proposed rule is similar to the framework under the September 2004 draft guidance. In a nutshell, constituent parts (that is, the drug, biological product, and device parts) of a combination product retain their unique regulatory status throughout the combination product's lifecycle. As a result, all constituent parts must meet the requirements for their respective GMPs, even after those parts are combined or joined together. In particular:

- A drug constituent part must comply with the GMPs in 21 CFR Parts 210 and 211;
- A device constituent part must comply with quality system regulation (QSR) requirements in 21 CFR Part 820;
- A biological product must comply with drug GMPs and, as applicable, GMP requirements in 21 CFR Part 606 for blood and blood components and other sections of 21 CFR Parts 600-680; and
- A human cell, tissue, and cellular and tissue-based product (HCT/P) must comply with the current good tissue practice and donor eligibility requirements for HCT/Ps in 21 CFR Part 1271.

Although these requirements apply to a constituent part even after it's joined, combined, or packaged with another part, the proposed rule allows for a streamlined approach for combination products made at one facility. More specifically, the proposed rule says that a streamlined GMP system may be used when two or more constituent parts "have arrived at the same facility" or when "manufacture … is proceeding at the same facility." In using the streamlined approach, the facility may adopt a primary GMP system (presumably the system under which the facility already operates), and then add on elements of the other applicable sets of GMP requirements. The rule lists the elements of other GMP requirements that must be added.

If the facility makes drug/device combination products, and operates under a device quality system, the facility must also observe the following elements of the drug GMPs :

- Testing and approval or rejection of components, drug product containers, and closures. (21 CFR 211.84)
- Calculation of yield. (21 CFR 211.103)

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- Tamper-evident packaging requirements for over-the-counter (OTC) human drug products. (21 CFR 132)
- Expiration dating. (21 CFR 211.137)
- Testing and release for distribution. (21 CFR 211.165)
- Stability testing. (21 CFR 211.166)
- Special testing requirements. (21 CFR 211.167)
- Reserve samples. (21 CFR 211.170)

In converse, if the combination product manufacturer operates under drug GMPs, it must apply the following elements of the device QSR:

- Management responsibility. (21 CFR 820.20)
- Design controls. (21 CFR 820.30)
- Purchasing controls. (21 CFR 820.50)
- Corrective and preventive action. (21 CFR 820.100)
- Installation. (21 CFR 820.170)
- Servicing. (21 CFR 820.200)

These specific lists represent an important clarification over the 2004 guidance - although the guidance lists elements of the drug and device GMP systems that should be followed, it leaves room for confusion on what specifically applies, saying that "depending on the particular combination product, it may be important to consider other specific requirements to ensure compliance with both the CGMP and QS regulations."

DEFINITION OF CONSTITUENT PART TO INCLUDE COMPONENTS & INGREDIENTS

Although fundamentally the proposed rule is similar to the 2004 draft guidance and thus may be familiar to combination product manufacturers, a number of questions about the proposed rule need answered. The proposed rule defines a constituent part to include any drug or any device that is part of a combination product. Under existing combination product regulations, a device constituent part is considered a finished device, and a drug constituent part is considered a drug product. However, because the statutory definition of a device also includes components, which include any raw material, substance, piece, part, software, firmware, labeling, or assembly for medical devices, a component that is part of a combination product is defined as a constituent part and therefore in effect considered a finished device or drug product.

But under existing GMPs, device and drug components are not treated as finished products and are only covered by GMPs when they are received by the final manufacturing facility. In this way, components are not directly subject to GMPs, although the final manufacturer has responsibility for ensuring appropriate quality requirements and in the case of devices are encouraged to use the GMPs as guidance.

However, because the application of GMPs is tied to a constituent part, the proposed rule raises questions about applying GMPs to components and ingredients even before their arrival at a combination product manufacturing facility. Similarly, confusion may also result with regard to drug container closures (ie, drug components) and when these components constitute a device constituent part subject to the QSR.

IMPLEMENTATION ISSUES

There are also a number of issues concerning how the new rules would be implemented at a practical level. For instance, the rules do not address how manufacturers should implement combination product GMPs for products currently under development or on the market. Do these manufacturers have to implement the rules retroactively? For example, if these manufacturers are incorporating elements of the QSR, might they have to retroactively create a Design History File where one did not previously exist?

In terms of timing, the proposed rule recommends that a final rule would be effective 180 days after final publication. Manufacturers should consider whether this timeframe is enough for their operations. The implementation of device management controls and design controls, for example, may require a significant ramp-up for firms that are not experienced with these requirements. Back in the 1990s, when the agency originally instituted device design controls, the FDA gave device firms an additional year (beyond the 8 months applicable to other provisions of the QSR) to comply with

those controls. For drug and biologic companies not already experienced in design controls, a similar timeframe might be needed.

Importantly, the proposed rule acknowledges the FDA will need to produce guidance upon implementation of the final rule. Unfortunately, the proposed rule doesn't specify when we should expect the guidance. This guidance is critical to a full understanding and implementation of the rule, so the sooner the better.

WHAT NOW?

The good news is that the publication of the proposed rule has opened up important dialogue on GMPs. The not-so-good news is that any final rule and implementing guidance will take a while, and in the meantime, combination product manufacturers will be left in a state of limbo on a clear path forward for GMP implementation. At least one thing is clear though - the agency believes GMPs apply to the various constituent parts throughout that product's lifecycle, and combination product manufacturers as a result are likely to be subject to requirements of multiple GMP systems.

CONCLUSION

Combination product companies should take a close look at the proposed rule and how it may impact their operations. To help with that, on January 12, 2010, the Regulatory Affairs Professionals Society (RAPS) and the Combination Products Coalition (CPC) are offering a workshop on the proposed rule that will offer attendees a unique opportunity to examine the contents of the rule and the agency's implementation plan. In addition to hearing from the FDA's Office of Combination Products and industry experts, attendees will apply the proposed rule to case studies to analyze the rule's strengths, weaknesses, ambiguities, unintended consequences, and more. RAPS and the CPC plan to synthesize the major themes that emerge from the workshop and submit them as comments to the proposed rule.

Finally, although the precise content of the final rule remains to be seen, the fundamental content will most likely be similar to the proposed rule. Thus, for planning purposes, companies engaged in the development or commercialization of combination products should consider conducting a preliminary gap analysis of current operations under the fundamental principles of the rule. To the extent there are major gaps, companies should consider factoring the implementation of combination product GMPs into upcoming plans and budgets.

REFERENCES

1. The proposed rule is available at: http://edocket.access.gpo.gov/2009/pdf/E9-22850.pdf.
2. The agency issued a 45-day extension to the original comment period: http://edocket.access.gpo.gov/2009/pdf/E9-26966.pdf.
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BIOGRAPHIES

Bradley Merrill Thompson is a shareholder in the Health Practice in Epstein Becker & Green's Washington, DC, office. Mr. Thompson counsels medical device, drug, and combination product companies on a wide range of issues involving compliance with the laws administered by the FDA, as well as reimbursement issues. He serves as General Counsel to the Combination Product Coalition and Counsel to AdvaMed for payment issues. In addition to a law degree, Mr. Thompson earned an MBA and often works with clients on strategic planning.

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MARKET BRIEF

Polymer-Based Pharmaceutical Compounds

By: Bill Martineau, MBA

INTRODUCTION

Spurred by ongoing advances in resins and related processing technologies, synthetic polymers are expected to broaden applications as drug delivery compounds. Growth opportunities will extend into most therapeutic classes, with parenteral carriers and controlled-release oral formulations accounting for the majority of usage. Led by these applications, total demand for synthetic polymer drug delivery compounds is forecast to increase 5.4% annually to $82 million in 2014. Competition from lower-cost compounds, especially minerals, starches, and sugars, will moderate faster gains. Polyethylene glycol, acrylic compounds, polyethylene oxide, and polyvinyl alcohol will remain the most common synthetic polymers employed in drug delivery.

POLYETHYLENE GLYCOL

Expanding use in parenteral and topical drug delivery systems and solid oral tablet coatings will boost demand for polyethylene glycol (PEG) pharmaceutical excipients 5.4% annually to $45.1 million in 2014. A polymer derivative of the petrochemical ethylene oxide, PEG has emerged as a key excipient used in parenteral drug delivery systems. When attached to the active protein ingredients of various injectable medicines, PEG functions as a carrier that lengthens circulation time and reduces toxicity. These actions increase the time interval between dosages and lessen the risk of potential drug side effects. Several parenteral medicines are available in PEGylated formulations. Included in this group are pegademase bovine for combined immunodeficiency disease, pegaptanib for age-related macular degeneration, pegfilgrastim for chemotherapy-induced neutropenia, pegaspargase for acute lymphoblastic leukemia, peginterferon for chronic hepatitis C, and pegvisomant for acromegaly.

In addition to a parenteral medication carrier, PEG is also employed as a drug delivery agent that enhances the solubility and flow of topical drugs produced in cream, ointment, and lotion formulations. The compound also serves applications in the coating of drug and dietary supplement tablets, mostly in combination with film-forming polymers. In tablet coatings, PEG can function as a controlled-release agent that increases water permeability, while preventing coating films from rupturing during tablet compression.

Atorvastatin for high cholesterol; donepezil for Alzheimer's disease; escitalopram for depression and generalized anxiety; fexofenadine for allergies; lopinavir and ritonavir for HIV; and quetiapine for bipolar disorders are among large selling drugs that incorporate PEG as a tablet coating ingredient. One popular line of PEG-based tablet coatings is based on a polyvinyl alcohol-polyethylene glycol graft-copolymer. These coatings produce a smooth surface, are compatible with a wide range of colorants, provide taste-masking, and enhance the ease of tablet swallowing.

ACRYLICS

When cross-linked with various other compounds or esterified, acrylic polymers can be formulated into pharmaceutical excipients that are safe for human consumption. Total demand for acrylic-based excipients in drug delivery applications is forecast to increase 5.5% annually to $17.5 million in 2014. Competition from

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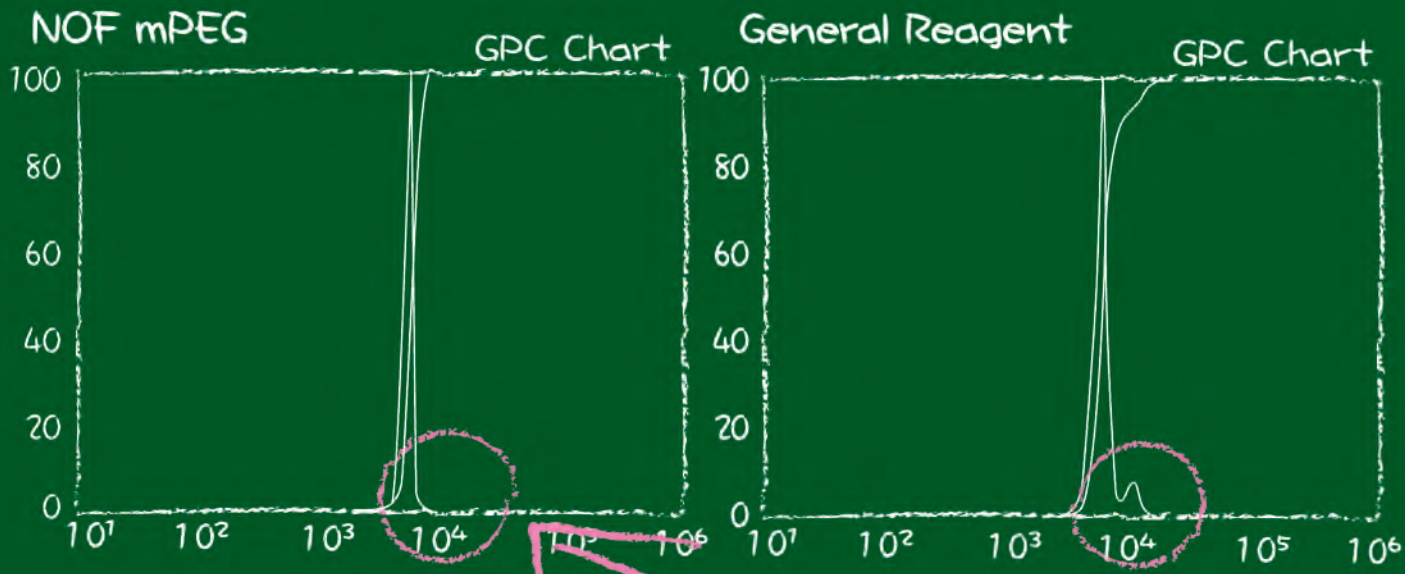

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lower-cost cellulose and starch derivatives will moderate faster growth.

The principal types of acrylic compounds used as drug delivery agents include carbomers and methacrylate copolymers. Carbomers include three types of acrylic acid polymers. Carbomer homopolymers are acrylic acid polymers cross-linked with allyl sucrose or allyl pentaerythritol. Carbomer copolymers are acrylic acid polymers modified by long chain alkyl acrylates and cross-linked with allyl pentaerythritol. Carbomer interpolymers (or polycarbophils) are acrylic acid polymers cross-linked with divinyl glycol.

Because of their hydrophilic gel-swelling and strong adhesion properties, carbomers are well suited to use as drug delivery vehicles. Specific applications in this area extend to controlled-release and buccal tablets, as well as capsules for specialty compounds such as suppositories. Carbomers are also employed to improve the solubility and bioavailability of oral and topical medicinal ingredients.

Methacrylates are copolymers derived from esters of acrylic and methacrylic acid. The compounds are used largely in controlled-release coatings of oral dosage pharmaceuticals. Methacrylates are available in a variety of formulations, including aqueous dispersion, organic solution granules, and powders. Generally, the compounds are insoluble in water, but soluble or permeable in digestive fluids.

Drug coatings produced from methacrylates extend to a number of enteric and sustained-release formulations. Enteric coatings based on these compounds provide protection against the release and breakdown of active pharmaceutical ingredients in the stomach. Through the incorporation of targeted, pH-dependent dissolution properties, the coatings delay the delivery of medication until it reaches desired sites in the intestines or colon. Targeted drug release in these sites is especially important to the successful treatment of gastrointestinal disorders, such as Crohn's disease, ulcerative colitiss, and colorectal cancer. Moreover, delayed-release coatings increase the efficacy of medicines that are poorly soluble in the upper gastrointestinal tract.

Sustained-release coatings based on methacrylates are employed for many oral dosage formulations to enhance their overall therapeutic effectiveness. Different combinations of polymer grades can be blended to control drug delivery throughout the gastrointestinal tract. In this application, methacrylate coatings offer a number of advantages. Specifically, they form a neutral ester dispersion that does not require a plasticizer. Moreover, only a small amount of polymer is required to instill effective sustained-release properties in the tablet or capsule particle. Methacrylate coatings are particularly well suited to matrix tableting processes, providing for moisture protection and taste-masking, as well as for controlled drug delivery.

TABLE 1

SYNTHETIC POLYMER DEMAND IN DRUG DELIVERY (MILLION DOLLARS)

Item	1999	2004	2009	2014	2019
Polymer Demand in Drug Delivery	**34.0**	**48.0**	**63.0**	**82.0**	**106.0**
-Polyethylene Glycol	19.2	26.5	34.7	45.1	58.3
-Acrylics	7.0	10.1	13.4	17.5	22.7
-Polyethylene Oxide	3.3	5.0	6.7	8.8	11.4
-Polyvinyl Alcohol	3.3	4.8	6.1	7.9	10.2
-Other Polymers	1.2	1.6	2.1	2.7	3.4

Source: The Freedonia Group, Inc.

POLYETHYLENE OXIDE (PEO)

PEO is a non-ionic, water-soluble polymer that is a longer chain version of polyethylene glycol (PEG). Based largely on increasing applications in controlled-release oral matrix tablets, demand for the compound as a drug delivery excipient is projected to expand 5.6% annually to $8.8 million in 2014. PEO is very hydrophilic and hydrates rapidly to form an active ingredient-releasing gel on tablet surfaces. The compound is adaptable to most major tableting technologies, including direct compression, wet granulation, and melt extrusion. In addition to matrix tablets, the compound is employed as an excipient for controlled-release tablet coatings, transdermal patches, and mucosal bioadhesives. Methylphenidate for attention deficit hyperactivity disorder (ADHD) is among the widely prescribed drugs that have been adapted to PEO-based delivery systems.

MARKET BRIEF

POLYVINYL ALCOHOL (PVOH)

PVOH is a water-soluble synthetic polymer produced by the hydrolysis of polyvinyl acetate to eliminate the acetate groups. As a drug delivery material, PVOH is employed in orally disintegrating tablet coatings and controlled-release solid oral drug formulations. Demand for the compound in these applications is forecast to increase 5.3% annually to $7.9 million in 2014. The adaptability of PVOH to drug delivery systems reflects its excellent film formation, good adhesion, high tensile strength, and strong oxygen barrier properties. The compound is also non-toxic and odor-free, and gels when combined with water. In combination with PEG, PVOH is employed in rapid-release tablet coatings. Among widely prescribed pharmaceuticals containing PVOH drug delivery materials are levetiracetam for partial seizures, extended-release bupropion for depression, nanoparticulate fenofibrate for high cholesterol, and an orally disintegrating formulation of donepezil for Alzheimer's disease.

OTHER POLYMERS

Demand for other drug delivery synthetic polymers is projected to reach $2.7 million in 2014, up 5.2% annually from 2009. Among these compounds, polyvinyl acetate phthalate and propylene glycol will continue to divide most applications. Polyvinyl acetate phthalate (PVAP), which combines a rubbery synthetic polymer derived from vinyl acetate monomer with an esterified form of dicarboxylic phthalic acid, serves as a popular enteric coating for solid oral pharmaceutical tablets and capsules. PVAP is adaptable to both delayed- and sustained-release coatings and features excellent film-forming, good adhesion and low moisture permeability. In pharmaceutical coatings, the compound provides a lower cost alternative to acrylic polymers, such as carbomers and methacrylates. Pharmaceuticals treated with PVAP coatings include aspirin, caffeine, methylphenidate HCl, and zolpidem.

Propylene glycol compounds (including the kelp derivative propylene glycol alginate) are synthetic polymers produced through the hydration of propylene oxide or the conversion of glycerol. The compounds are generally recognized as safe (GRAS) by the FDA, as inside the body they are metabolized into lactic acid. Based on their hygroscopic, miscible, non-toxic, and water-soluble properties, propylene glycol and derivatives are used mostly as emulsifying, suspending, and stabilizing agents in topical and oral liquid pharmaceutical preparations. In drug delivery applications, the compounds serve as plasticizers in controlled-release solid oral drug formulations.

An in-depth report on this and other related topics can be obtained by contacting the Freedonia Group at www.freedoniagroup.com.

BIOGRAPHY

Mr. Bill Martineau is an authority on the healthcare industry. He has performed in-depth research in areas of biotechnology, pharmaceuticals, medical packaging, and related areas, producing titles such as: *U.S. Pharmaceutical Packaging, Cardiac Implants, Nanotechnology in Healthcare, Drug Delivery Systems, and Biochips.* Prior to joining Freedonia, he was Manager of Market Development at American Sterilizer Company, where he gained experience in healthcare research and strategic planning. At Invenex Laboratories, he served as Product Manager, responsible for the administration of a line of injectable pharmaceuticals. He also served as Senior Health Care Analyst at Predicasts Inc. and Manager of Market Research at Life Technologies Inc. (a division of The Dexter Corporation). Mr. Martineau earned his BA in Management and his MBA in Marketing and Finance from Kent State University.

TABLET DESIGN

Investigation of the Influence of Tablet Shape, Geometry & Film Coating on Drug Release From Hypromellose Extended-Release Matrices

By: Shahrzad Missaghi, PhD; Piyush Patel, MPharm; Sandip B. Tiwari, PhD; Thomas P. Farrell, PhD; and Ali R. Rajabi-Siahboomi, PhD

ABSTRACT

Different tablet shapes were used to evaluate the effect of geometry on release of model drugs, with varying aqueous solubility and dose, from hypromellose hydrophilic matrices at constant as well as varying tablet surface area/volume ratios (SA/V). Results showed that drug release from matrix tablets of equal mass at constant SA/V ratios were similar among different tablet shapes. In contrast, matrices of the same geometry at varying SA/V ratios did not result in similar drug release profiles. The results of this study indicate that tablet design (shape and color) offers opportunities to refine release profiles, rebrand existing products, and create distinctive formulations, allowing greater benefits from the extended-release (ER) oral dosage forms.

INTRODUCTION

Hypromellose (hydroxypropyl methylcellulose, HPMC) has been widely used in the formulation of hydrophilic matrices for oral ER drug delivery due to its key features and advantages including global regulatory acceptance, stability, ease of manufacture, versatility, suitability for various drugs and release profiles, and availability of the polymer.[1] Drug release from HPMC matrices may be affected by several variables, including polymer type and level, drug particle size, dose and solubility, ratio of polymer to drug, filler type and level, and ratio of polymer to filler.[2-4] Tablet shape, geometry, and color are important factors determining identification, compliance, swallowability, and dose strength distinctions of oral formulations. Selection of specific tablet shape may improve the mechanical properties of the tablets, enhance aesthetic appearance, ease of handling, and packaging.[5] Tablet shape and coating are important parameters for product branding (brand recognition, preference, and "personality," eg, associating disease with the tablet shape or color).[6] Tablet shape, size, and surface area may affect drug-release profiles[7-8] and may be used for modulation of drug-release rate (eg, Geomatrix, Dome Matrix tablets) [2, 9] or for enhancing spatial control of drug release (eg, gastro-retention with specific shape of the tablet).[10-13] When a hydrophilic matrix tablet is developed, and the release profile is established with a certain tablet shape, there is usually reluctance to modify the product geometry. This is particularly true for drugs at the extremes of dose or solubility, for which the drug release is mainly controlled via diffusion or erosion, and may be more sensitive to other changes. A previous study examined the release of highly water-soluble drugs from HPMC matrices and demonstrated that when SA/V is held constant, the drug-release profiles are similar regardless of the tablet shape (round or oval).[7] A large proportion of tablets produced globally are film coated. Tablets are coated for a variety of reasons; such as elegance and aesthetics, improved swallowability, identification and branding, taste- or odor-masking, enhanced mechanical strength, and protection from moisture, light, or air. It has been shown that conventional immediate-release film coating does not affect drug release from HPMC matrices.[14]

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TABLE 1

Formulation	Thickness (mm)	Hardness (kp)	Hardness* (MPa)	Surface Area (SA) (mm^2)	SA/V (mm^2/mm^3)
Metformin HCl Matrices					
Standard Concave round	6.34 ± 0.04	14.9 ± 0.5	1.737	509.36	0.612
Dumbbell	7.25 ± 0.05	16.1 ± 0.9	1.301	516.50	0.617
Caplet	6.70 ± 0.06	16.5 ± 0.7	1.375	513.98	0.611
Indapamide Matrices					
Standard Concave Round	4.77 ± 0.03	12.5 ± 0.5	4.066	154.09	0.974
Pentagon	4.14 ± 0.05	12.7 ± 1.0	4.495	158.90	1.041
Caplet	3.83 ± 0.03	10.0 ± 0.2	3.081	163.26	1.057

Compression force values of 17.5 to 23 kN and 11.5 to 13 kN were used for metformin HCl and indapamide matrices, respectively, depending on the shape in order to achieve similar range of hardness values (n=10). The tablet weights of 1000 mg and 200 mg were used for metformin HCl and indapamide matrices, respectively. *Hardness values are normalized to the cross sectional surface area of respective matrix tablets in the direction of tablet fracture.

Physical Properties of Metformin HCl & Indapamide Matrices With Constant Surface Area-to-Volume (SA/V) Ratios

was to evaluate the effect of various tablet shapes and geometry on drug release from HPMC matrices at constant, as well as variable SA/V ratios, using metformin HCl as a freely soluble drug and indapamide as a practically insoluble drug. In addition to the traditional round and caplet shapes, tablets with dumbbell and pentagon geometries were also evaluated. It was also aimed to investigate the effect of different aqueous film coating systems on the drug-release profile of HPMC matrix systems.

MATERIALS & METHODS

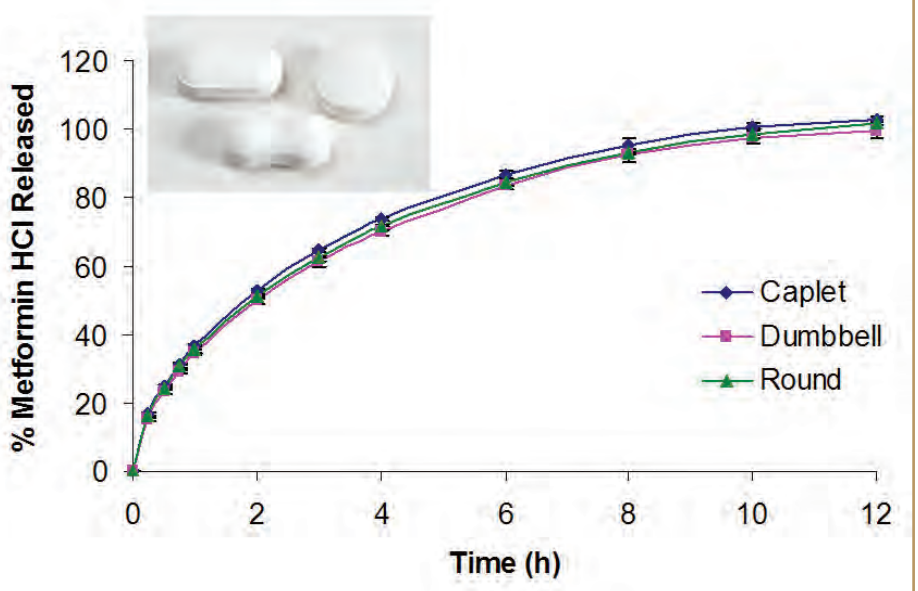
All the materials were used as received and included hypromellose (METHOCEL™, premium cellulose ethers, K100M Premium CR and METHOCEL™ K15M Premium CR, The Dow Chemical Company, USA; supplied globally by Colorcon Inc., USA), microcrystalline cellulose (Emcocel 90M, JRS Pharma, Germany), fumed silica (Aerosil 200, Evonik, Germany), magnesium stearate (Mallinckrodt, USA), lactose monohydrate (Fast Flo, Foremost, USA), metformin HCl (Wanbury, India), and indapamide (Jinan Shandong, China).

Preparation & Characterization of Hypromellose Matrices

All matrices were prepared by direct compression method (2 kg batch size). In preparation of metformin HCl matrices, microcrystalline cellulose (MCC) (19% w/w) and fumed silica (0.5% w/w) were passed through an ASTM mesh No. 35 sieve (500 micrometers) and were placed in a twin shell blender (Patterson Kelley, USA) along with metformin HCl (50% w/w) and METHOCEL K100M CR (30% w/w) and mixed for 5 minutes. Magnesium stearate (0.5% w/w) was then added to the blender and mixed for another minute.[15]

One case of indapamide matrices, drug (0.75% w/w) and half of the lactose (59.57% w/w) were blended in a high shear granulator (VG-25, Glatt Air Techniques, USA) for 5 minutes at an impeller speed of 200 rpm and a chopper speed of 500 rpm. The remaining lactose [sieved with fumed silica (0.5% w/w) through an ASTM mesh No. 35 sieve] was added to the bowl and mixed for 5 minutes. METHOCEL K15M CR (38.68% w/w) was then added and blended for an additional 5 minutes. Finally, magnesium stearate (0.5% w/w)

FIGURE 1



Drug Release Profiles for Metformin HCl Matrices at Constant SA/V Ratios
Constant tablet weight of 1000 mg was used for all shapes of metformin HCl matrices. Dissolution study was conducted using USP Apparatus II (paddle) with sinkers at 100 rpm in purified water, 1000 mL (n = 6).

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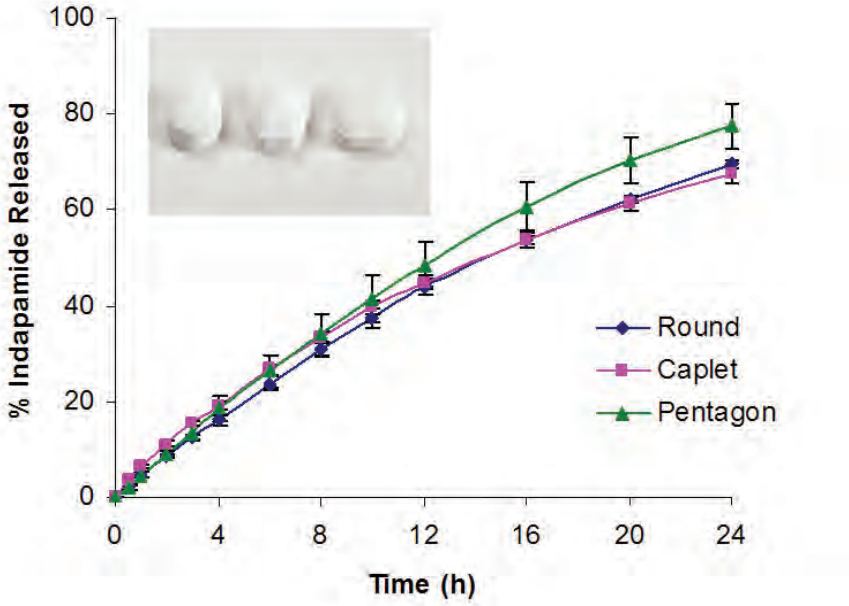
FIGURE 2



Drug Release Profiles for Indapamide Matrices at Constant SA/V Ratios
Constant tablet weight of 200 mg was used for all shapes of indapamide matrices. Dissolution study was conducted using USP Apparatus I (basket) at 100 rpm and 0.05 M pH 6.8 phosphate buffer, 900 mL (n = 6).

was added, and the formulation was mixed for one minute, using an impeller speed of 400 rpm.[16]

Tablets were manufactured using an instrumented 10-station rotary press (Piccola, Riva, Argentina) operated at 20 rpm. For each drug, various tablet shapes were evaluated. For metformin HCl matrices, standard concave round (14.3 mm), caplet (19 X 9.3 mm), and dumbbell (19 X 9.1 mm) shaped tablets were examined. For indapamide matrices, standard concave round (7.1 mm), caplet (9.5 X 6.6 mm), and pentagon (8.2 X 7.9 mm) shaped tablets were examined. All tablets were evaluated for physical properties, including weight variation, hardness, thickness (Multicheck, Erweka, Germany), friability (Vanderkamp Friabilator, VanKel Industries, USA), and SA/V ratios (using the tooling specifications and relevant mathematical equations).

Constant SA/V Ratios

To evaluate the effect of constant SA/V ratios on drug release, various shapes of metformin HCl and indapamide ER tablets with constant SA/V ratios were compressed at target tablet weights of 1000 mg and 200 mg, respectively (Table 1).

Different SA/V Ratios

Different SA/V ratios were achieved on selected matrix shapes by varying the tablet weight in the range of 750 to 1440 mg for metformin HCl and 150 to 300 mg for indapamide matrices, depending on the tablet shape (Table 2). For each shape, the effect of three different SA/V ratios on the drug-release profile was evaluated. The tablet composition for each drug was the same as previously described.

Film Coating of ER Matrices

To evaluate the effect of film coating on drug release, the metformin HCl dumbbell shaped matrices (tablet weight = 1000 mg) and indapamide pentagon-shaped matrices (tablet weight = 200 mg)

TABLE 2

Formulation	Tablet Weight (mg)	Thickness (mm)	Hardness (kp)	Hardness* (MPa)	Surface Area (SA) (mm^2)	SA/V (mm^2/mm^3)
Metformin HCl Matrices						
Caplet	750	5.35 ± 0.05	9.7 ± 0.9	1.022	452.93	0.704
	1000	6.79 ± 0.04	16.2 ± 1.2	1.327	523.04	0.601
	1440	9.28 ± 0.06	23.5 ± 1.7	1.377	644.26	0.509
Dumbbell	750	5.86 ± 0.06	9.2 ± 0.7	0.940	449.27	0.709
	900	6.71 ± 0.03	11.8 ± 0.6	1.041	490.71	0.646
	1325	9.22 ± 0.03	18.2 ± 1.3	1.125	613.07	0.543
Indapamide Matrices						
Round	150	3.10 ± 0.03	8.5 ± 0.2	4.573	137.88	1.240
	200	3.91 ± 0.08	11.4 ± 1.0	4.670	158.08	1.045
	300	5.43 ± 0.04	17.5 ± 0.7	4.953	195.99	0.865
Pentagon	150	3.41 ± 0.06	7.4 ± 0.2	3.335	136.31	1.169
	200	4.20 ± 0.06	11.6 ± 1.1	4.022	154.04	0.990
	300	5.69 ± 0.04	17.8 ± 3.2	4.310	187.47	0.818

Compression force values of 18 kN and 13 kN was used for metformin HCl and indapamide matrices, respectively (n = 10).
***Hardness values are normalized to the cross sectional surface area of respective matrix tablets in the direction of tablet fracture.**

Physical Properties of Metformin HCl & Indapamide Matrices With Variable Surface Area-to-Volume (SA/V) Ratios

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were selected and coated, using the four different fully formulated film coating systems (Colorcon, USA) viz; Opadry® II, high-performance film coating system 32K10908, Opadry II 85F94544, Opadry® amb, aqueous moisture barrier film coating system 80W90677, and Opaglos® 2, high gloss film coating system, tablet core sealant product 97W90646. Each selected tablet shape was coated in a fully perforated coating pan (15-inch; Compu-Lab, Thomas Engineering, USA) to a weight gain of 4% w/w using standard coating parameters.

Dissolution Testing

The drug release from metformin and indapamide formulations was measured in a USP-compliant dissolution bath (VanKel VK7000, Varian Inc. USA), using the previously reported methods.[15-16] Metformin HCl matrices were tested using Apparatus II (paddle) with sinkers at 100 rpm, 1000 mL of purified water, and UV analysis at 233 nm. Indapamide matrices were tested using Apparatus I (basket) at 100 rpm, 900 mL 0.05M pH 6.8 phosphate buffer, and HPLC analysis. Similarity factors (f_2) were calculated in order to compare the dissolution performance of different matrix shapes and of the film coated tablets.[17]

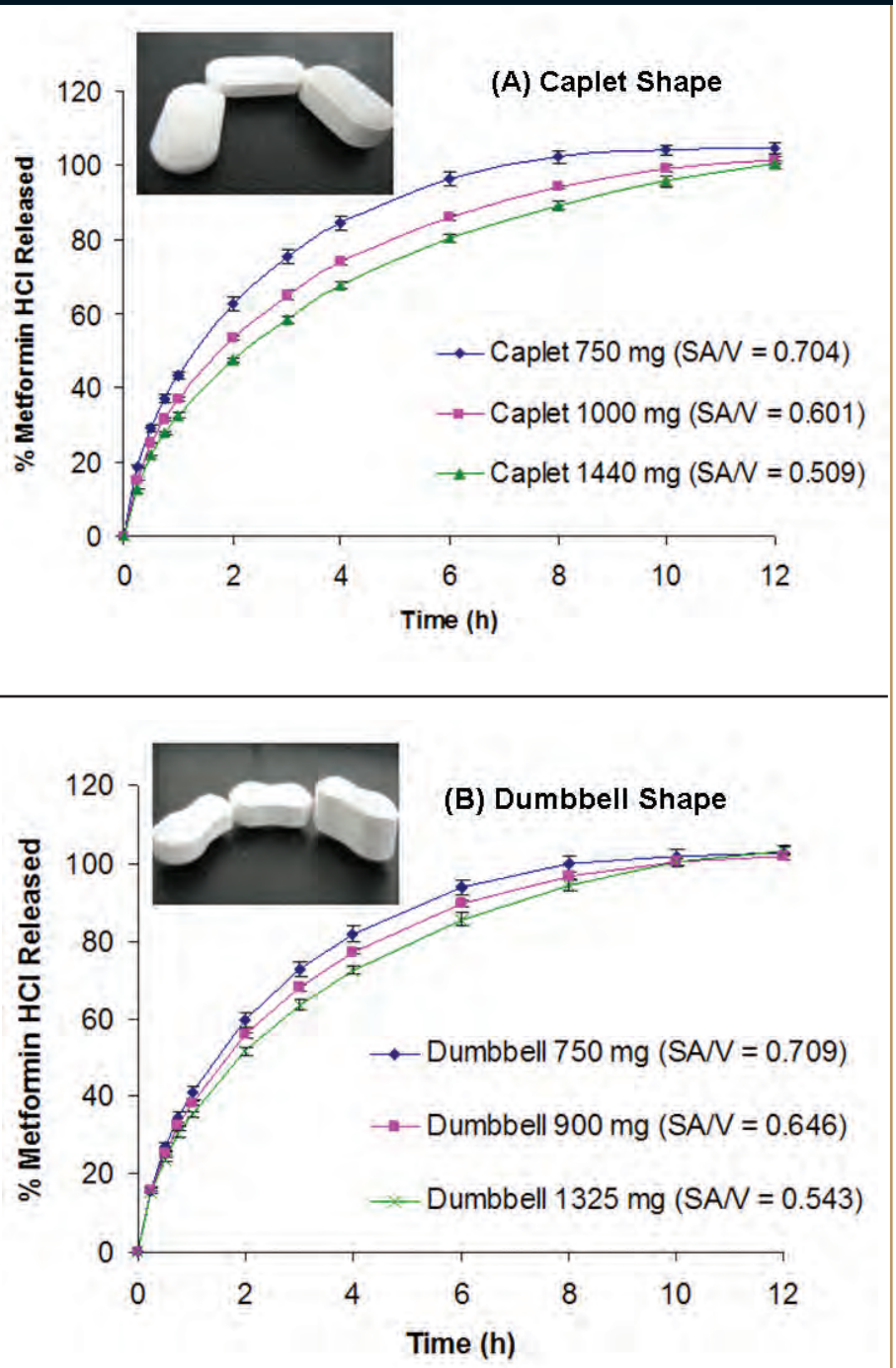
RESULTS & DISCUSSION

Effect of Constant SA/V

The influence of matrix geometry on drug release has been reported by Siepmann et al, in which they examined the effect of aspect ratio (radius/height) and the size of cylindrical matrices on drug release for diffusion controlled systems.[8] They stated that because small cylindrical tablets have a higher relative surface area, (ie, absolute surface area/absolute volume), the release from small tablets is faster than from large cylindrical tablets. Certainly, the aspect ratio (radius/height) is a relevant term when comparing the relative shape of cylinders, but it is seemingly not as valuable a term as the SA/V ratio may be when comparing the relative drug release from tablets of varying shapes. Reynolds et al examined the effect of SA/V ratio on drug release from HPMC matrix tablets; however, their investigation primarily focused on the diffusion-controlled drug release (for high solubility drugs).[7] In this study, the effects of SA/V ratio combined with tablet shape and film coating on drug release for both a freely soluble drug or a practically insoluble drug from HPMC matrices have been investigated.

All the formulated metformin and indapamide matrix tablets with constant SA/V ratios exhibited acceptable pharmaco-technical properties, including

FIGURE 3A & B



Drug Release Profiles for Metformin HCl Matrices with Variable SA/V Ratios
Dissolution study was conducted using USP Apparatus II (paddle) with sinkers at 100 rpm and purified water, 1000 mL (A) caplet shape, (B) dumbbell shape (n = 6).

low weight variation, good hardness, and low friability (Table 1). Figures 1 and 2 show drug-release profiles from each tablet shape for metformin HCl and indapamide ER matrices, respectively. The similarity factors (f_2) were calculated for different tablet geometries, utilizing the round shape as reference. The f_2 values for metformin HCl tablets were 88.2 (caplet) and 92.4 (dumbbell). For indapamide matrices, the f_2 values were calculated as 78.4 (caplet) and 64.0 (pentagon). Thus, the drug-release profiles were considered similar ($f_2 > 50$), indicating that changing tablet geometry did not influence the drug-release profile when SA/V ratios were held constant. This finding is of importance to the pharmaceutical industry from commercial and branding point of view as matrix tablet shape can potentially be altered for brand-enhancement purposes without significantly affecting the drug-release profile.

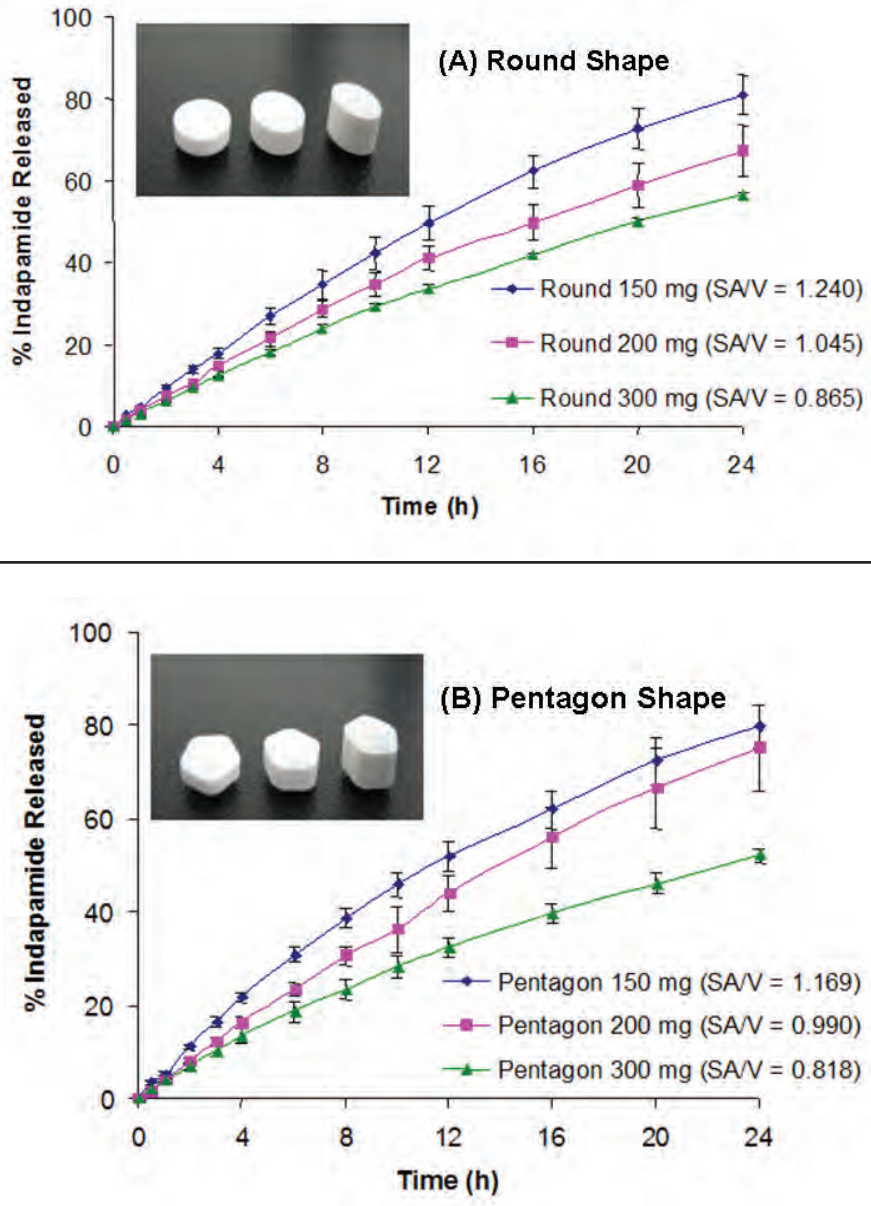
Effect of Variable SA/V Ratios

All of the formulated tablet compositions exhibited acceptable pharmaco-technical properties, including low weight variation, good hardness, and low friability (Table 2). Drug-release profiles for each tablet shape are shown in Figure 3 for metformin HCl matrices (caplet and dumbbell shapes), and in Figure 4 for indapamide matrices (round and pentagon shapes). Results show that increasing tablet weight led to a decrease in SA/V values and consequently a decline in release rate for both drugs. In the case of metformin HCl (freely soluble drug), this could be attributed to the shorter diffusion pathways in smaller tablets (higher SA/V ratios), while in the case of indapamide (practically insoluble drug), more surface area per unit volume is available for erosion to occur with smaller tablets. Furthermore, Table 2 shows a direct relationship between tablet weight and hardness. It has been shown that the effect of tablet hardness on drug release from hydrophilic matrices is expected to be minimal when tablets with sufficient strength and optimal levels of polymers are manufactured.[1,18] Therefore, varying SA/V ratios can directly influence the drug release from HPMC matrices. This finding is of importance to the pharmaceutical formulators in the design of dose-proportional formulas because optimal drug-release profiles may be achieved without further modification of a formulation by choosing an appropriate SA/V ratio for a tablet.

To evaluate the mechanism of drug release and to compare the performance of various matrix tablets, the dissolution profile for each drug and tablet shape was used. Data corresponding to 5% to 60% release presented a suitable fit to the Power Law model, as expressed in the following equation: $(M_t/M_{inf} = kt^n)$.[19]

M_t is the amount of drug released at time t, M_{inf} is the amount of drug released after infinite time, k is a kinetic constant, incorporating structural and geometric characteristic of the tablet, t is the release time, and n is the diffusional exponent indicative of the drug-release mechanism.

FIGURE 4A & B



Drug Release Profiles for Indapamide Matrices with Variable SA/V Ratios
Dissolution study was conducted using USP Apparatus I (basket) at 100 rpm and 0.05 M pH 6.8 phosphate buffer, 900 mL (A) round shape, (B) pentagon shape (n = 6).

For cylindrical tablets, n value of ~ 0.45 indicates diffusion control, while an n value of ~ 0.89 indicates erosion or relaxation control. Intermediate values ($0.45 < n < 0.89$) suggest that diffusion and erosion contribute to the overall release mechanism. The values of n and k are inversely related.

The values of n for metformin HCl matrices were between 0.56 and 0.63; for indapamide matrices, values of n ranged between 0.77 and 0.94. The obtained n values indicate an anomalous behavior corresponding to diffusion, erosion, and swelling mechanisms for all matrices. Based on these values, the drug release from metformin HCl matrices is more diffusion controlled, while for indapamide matrix tablets, erosion or relaxation mechanism is more dominant. The correlation coefficients (R^2) for all matrices exceed 0.99. For metformin HCl matrices, the high k values (above 31) is an indication of a burst drug release.[20]

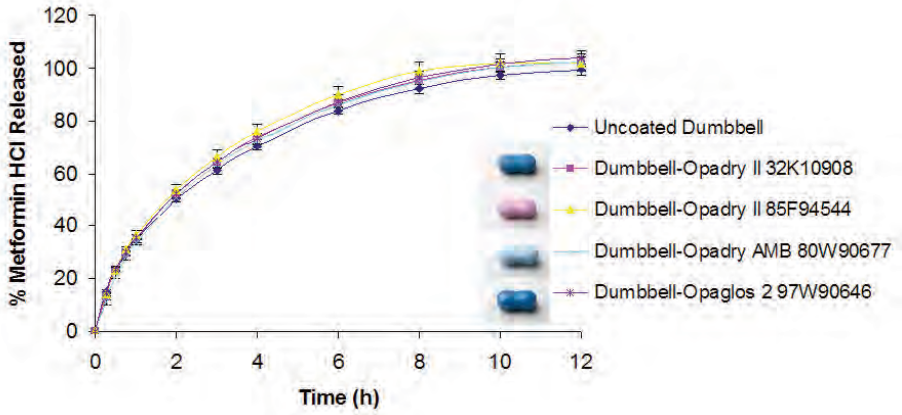
Effect of Film Coating

As previously discussed, application of film coatings to tablet formulations is a common practice in the pharmaceutical industry. Tablets are film coated for a variety of reasons, such as improving the stability of the formulation, taste-masking, enhancing the aesthetic appearance, identification and branding, and improving the packaging process. Low-viscosity hydrophilic polymers are generally used in film coating compositions and their application on hydrophilic matrix tablets is not expected to alter the drug-release profile. Depending on the choice of film coating system, tablets are generally coated to a weight gain of around 3% w/w. In the present study, however, tablets were coated to achieve a weight gain of ~ 4% w/w to cover the edges of odd-shaped tablets (pentagon and dumbbell), and to examine the effect of film coatings on release when applied at higher-than-desired weight gains. Figures 5 and 6 show that application of film coating systems did not significantly alter the drug-release profiles from metformin HCl matrices (f_2 values ranged from 71 to 82, coated versus uncoated) and indapamide matrices (f_2 values ranged from 75 to 96, coated versus uncoated), irrespective of the film coating system used. These results indicate that application of film coating systems of different chemistry have insignificant effect on hydration and gel-layer formation of hydrophilic polymers used in designing matrix systems, thereby resulting in similar drug-release profiles (coated versus uncoated). These results are in agreement with the findings of Levina et al on film coated, traditional-shaped matrix tablets.[14]

CONCLUSIONS

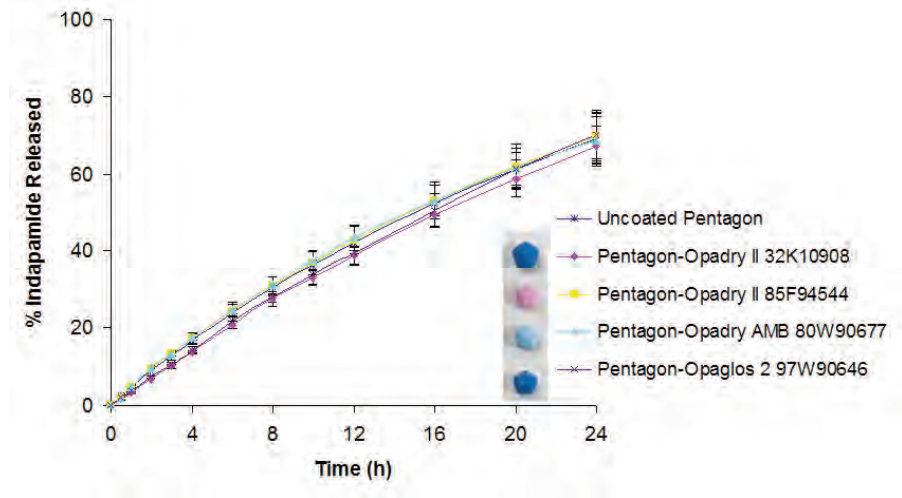
Tablet shape, geometry, and color are important factors determining identification, compliance, swallowability, and dose-strength distinctions of oral formulations. For HPMC ER hydrophilic matrices, SA/V ratio is more of an important factor compared to the tablet shape in controlling the drug release. Constant SA/V ratios yielded similar drug-release profiles, while different SA/V ratios led to correspondingly different drug release, with greater ratios resulting in higher release rates. Results indicate a direct relationship between SA/V ratios

FIGURE 5



Comparative Drug Release Profiles of Uncoated and Coated Metformin HCl Matrices
The corresponding tablet color is the actual color of the Opadry/Opaglos formula (n = 6).

FIGURE 6



Comparative Drug Release Profiles of Uncoated and Coated Indapamide Matrices
The corresponding tablet color is the actual color of the Opadry/Opaglos formula (n=6).

and drug-release rate from matrices, irrespective of drug solubility, dose, mechanism of drug release, and tablet shape. Application of film coating systems of varying chemistry did not alter the drug-release profiles from matrices (f_2 values > 70, coated versus uncoated tablets). This finding is of paramount importance to pharmaceutical formulators because by designing a particular size and shape of matrices, optimal drug-release profiles can be achieved without further modification of formulation. In conclusion, tablet design (shape and color) offers opportunities to refine release profiles, rebrand existing products, and create distinctive formulations, allowing greater benefits from the ER oral dosage forms.

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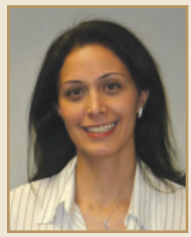
BIOGRAPHIES



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A Binary Immunoliposomal System Directed to Cx43-Positive Glioma Cells

By: V.P. Chekhonin, MD, PhD; V.P. Baklaushev, MD, PhD; O.I. Gurina, MD, PhD; N.F. Grinenko, PhD; G.M. Yusubalieva, MD, PhD; and A.E. Ryabinina, PhD

INTRODUCTION

Connexin-43 (Cx43) is the main structural component of gap junctions between astrocytes in the nervous tissue.[1] With its four transmembrane domains, Cx43 forms hexameric connexons that allow opening and closing of the transmembrane channel via phosphorylation and dephosphorylation of Cx43 C-terminals.[2] Using two extracellular fragments of Cx43 (E1 and E2), hemichannels of neighboring cells form a complete gap junction joining cytoplasmas of those cells. Such channels facilitate ionic homeostasis and cell volume maintenance as well as transfer of several intercellular signals, which regulate proliferation, differentiation, apoptosis, adhesion, and migration of embryonic cells during ontogenesis.[1,3-5]

Of great interest is the participation of Cx43 in the development of invasive gliomas; however, functions of this protein in glioma cell invasion remain not fully understood.[2,4,6,7] For instance, it has been shown that biosynthesis of this protein decreases in high-grade gliomas.[8-10] At the same time, some researchers found an increase in Cx43 levels in tumor tissue, eg, in neoplastic endotheliocytes.[6] They also revealed an activating influence of Cx43 on invasion of human multiform glioblastoma and its rat equivalent, experimental C6 glioma.[2,7]

Tumor-suppressive effect of Cx43 was supposed to be the result of its interaction with a soluble proliferation inhibitor, CCN3 (NOV).[11] However, further research conducted by the same group has shown that Cx43 expression may also be accompanied by an increased production of a protein related to CCN3, CCN1 (Cyr61), which conversely, activates glioma cells proliferation and migration.[12] As a possible result, Cx43-positive cells of the C6-glioma possess a higher migration ability than Cx43-negative ones.[2]

A possible reason for controversial influence of Cx43 on the invasion of high-grade gliomas may be differently directed changes in the expression of Cx43 in glioma cells and in surrounding reactive astrocytes, as it is the case with GFAP, another astroglial marker.[13] It is assumed that Cx43-positive astrocytes precisely play a specific role in active glioma invasion by forming heterological gap junctions with glioma cells.[4] It was recently shown that Cx43-positive cells are more resistant to oxidative stress as well as to several other damaging factors.[14] The latter observation makes Cx43 research attractive within the framework of the concept of glioma cell populations resistant to chemo and radiation therapy. Thus, clarifying the actual Cx43 role in glioma invasion becomes a challenging, yet promising, task.

In our previous research, we have obtained monoclonal antibodies (MAb) to the recombinant extracellular E2 domain, which interacted with the Cx43 in native conformation.[15,16] The present work was designed to evaluate the Cx43-positive cell selectivity of a binary system based on biotinylated MAb to E2 domain of Cx43 and PEGylated liposomes with streptavidin (SAv) for C6 glioma cell culture in vivo.

MATERIALS & METHODS

Obtaining & Preparing the Monoclonal Antibodies

MAb Cx43E2 were obtained by immunizing with the recombinant extracellular fragment E2 Cx43 (Q173-I208; QWYIYGFSLSAVYTCKRDPC PHQVDCFLSRPTEKTI, 36 aa, Mw 4,28 kDa, pI 7,87).[15] PCR amplification of the E2 sequence from the rat brain cDNA library was performed using the following primers: CX43_173F: 5'-GATCAGATCTCAGTGGTACATCTATG GGT-3'; CX43_173B: 5'-GATCAAGCTT AGATGGTTTTCTCCGTGGGAC-3' (SibEnzym) containing recognition sites for BglII and HindIII, respectively. Plasmid DNA containing no mistakes in coding sequences were cloned into expressing vectors pHPMLQ and pCBDQ (Institute of Bioorganic Chemistry Russian Academy of Science).[17] These vectors contain sequences for two domains of human plasma membrane cell Ca-ATPase hPMCA4b (CBD, aa 1057-1205, 17 kDa and HPML, aa 166-371, 22,5 kDa) as high-molecular carriers. For expression, plasmid DNA of pHPMLQ-Cx43 and pCBDQ-Cx43 were used to transform the cells of E. coli SG13009 (Qiagen). Purified chimeric polypeptide CBD-Cx43 was used for mouse immunization, while HPMLQ-Cx43 was used for testing hybrid cell clones with ELISA to exclude obtaining antibodies to the carrier sequence. MAb were obtained using traditional, albeit somewhat modified, hybridoma technology.[18] Positive clones were tested by ICC with brain slices to select MAb binding with Cx43 in its native conformation.

Purification of MAbCx43 from ascites

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was performed using protein G agarose (Invitrogen). Purified antibodies were biotinylated using the ProtOn kit (Vector Lab) in accordance with provider protocol.

Assay Development Immunohistochemical assay of antibodies was performed with fixed and live cell cultures. Staining of cells fixed by 4% paraformaldehyde was performed in accordance with the standard immunofluorescence protocol. Goat-antimouse Alexa Fluor 488 and Goat-antirabbit Alexa Fluor 594 (Invitrogen) were used as second antibodies.

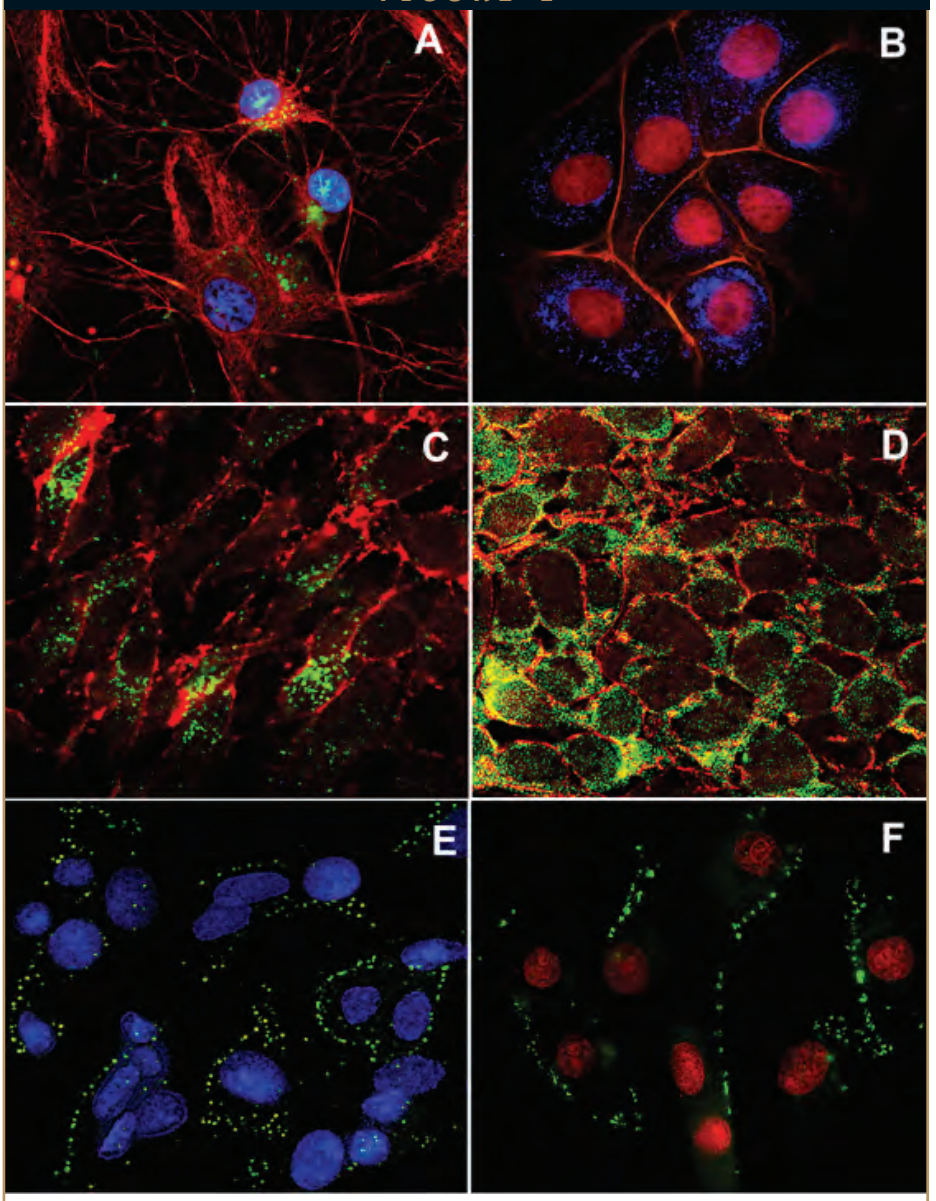
For visualizing of live cells, biotinylated MAbE2Cx43 sterilized by filtration (Milliex filter, 0,22 microns, Millipore) were added to the well containing attached cells in growth medium (DMEM with 10% FBS) to the concentration of 5 micrograms/ml, and incubated for 1 hour. The cells were subsequently washed twice in sterile PBS, given growth medium with streptavidin (Imtek) conjugated with Alexa 488 using Alexa Fluor 488 Protein Labelling kit (Invitrogen) to the concentration of 2 to 5 micrograms/ml. Fluorescence of live cells was detected by inverted fluorescent microscope Leica DM 6000.

PEGylated Liposome Synthesis

Vector stealth liposomes were prepared using the Kamps et al method modified to fit present experiment tasks.[19] The main PEGylated liposome components were lecithin from chicken egg yolks, cholesterol, and distearoyl phosphatidyl ethanol amine (DSPE) conjugated with PEG-2000 (polyethylene glycol of 2000 Da). For binding with thiolyzed streptavidin, a maleimide derivative, DSPE-PEG-2000 (1,2-distearoyl-sn-Glycero-3-Phospho ethanolamine-N-[Maleimide (PEG)2000]) was added in liposome components. As a fluorescent marker, Dil (1,1' octadecyl-3,3,3',3'-tetramethylindocarbocyanine perchlorate) was added to the liposomes. All lipid components were obtained from Avanti Polar Lipids (USA). All liposome manufacturing manipulations were conducted in the high-purity argon atmosphere.

Lecithin, cholesterol, DSPE-PEG-2000,

FIGURE 1



Immunofluorescent Analysis of Cx43 on Fixed & Live Cell Cultures

A. Astrocyte culture from neonatal rat brain tissue. Red fluorescence - polyclonal antibodies to GFAP; green fluorescence - MAb E2 Cx43. Cell nuclei - DAPI (Invitrogen). B. Human glioblastoma (U251 line). Blue fluorescence - MAb Cx43 + anti-mouse IgG Alexa Fluor 350 (Invitrogen). Orange-red fluorescence - actin filaments stained by Phalloidin TRITC (Fluka). Cell nuclei - TOTO 633 (Invitrogen). C. C6 rat glioma. Red - beta-Catenin, green - MAb Cx43 D. HEK 293 cell line. Red - pan-Cadherines, green - MAb Cx43. E. Cx43 visualization in live U251 glioblastoma cell culture (green fluorescence). Cell nuclei – DAPI. F. Cx43 visualization in live C6 glioma cell culture (green fluorescence). Cell nuclei - TOTO 633. Magnification x1000.

its maleimide derivative, and Dil were dissolved in chloroform-methanol mixture (9:1) at a total lipid concentration of 10 mg/ml with a molar ratio of 23:16:1.6:1:0.4. The mixture was dried in a rotor evaporator under reduced pressure. Dry lipid film was dissolved in absolute cyclohexane, frozen in liquid nitrogen, and lyophilized; subsequently, the lipid mixture was emulgated in a 0.1-M phosphate buffer. The hydrated emulsion was sonicated in a G112SP1 ultrasound disintegrator (Laboratory Supplies, USA) and passed 15 times through a polycarbonate membranes with pores of 400, 200, 100, and 50 nm using a mini extruder (Avanti Polar Lipids, USA).

PEGylated liposomes were chemically bonded with streptavidin pre-modified with 2-iminothiolane that reacts with free primary amino groups of the protein, attaching a protected SH-group to them. Stealth-liposomes conjugated with streptavidin were purified by gel filtration through Sephadex G100.

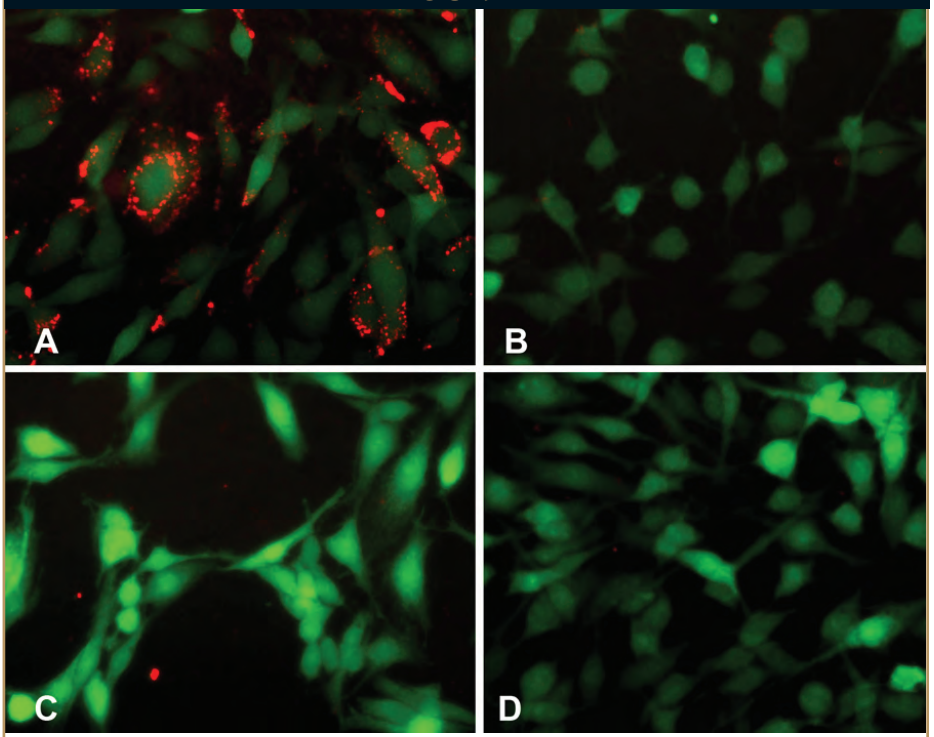
C6 Glioma Cell Culture

C6 glioma cells were seeded into 35-mm Petri dishes (Costar) with a density of 3 to 4 × 10^5 cells per dish and cultivated in the DMEM with 10% FBS by 37°C in humid athmosphere containing 5% CO_2. For fluorescent visualization, the cells were marked using Vybrant CFDA SE (Invitrogen). The growth medium was removed on the day following the seeding, cells were incubated in phosphate buffer containing CFDA SE (10 micromolars) for 15 minutes by 37°C, after which the CFDA solution was replaced by fresh growth medium, and cells were cultivated about 20 hours until they could form a 100% monolayer.

Experiment Protocol

Biotinylated antibodies to Cx43 were sterilized by filtration (Milliex filter, 0.22 micrometers, Millipore) and added to the live culture of C6 glioma cells in growth medium (DMEM with 10% FBS) to the concentration of 10 micrograms/ml. Following o1-hour incubation, medium with antibodies was removed, the cells were double-washed with PBS (upon which a fresh growth medium was introduced), and liposomes of increasing concentration (1 to 50 microliters of liposomal emulsion with known concentration of lipids and SAv) were added. After 60 minutes of incubation, live cell fluorescence was registered using a Leica DM 6000 inverted microscope. Three series of experiments with several controls were conducted. In the first control, 30 minutes prior to introduction of biotinylated antibodies to E2 Cx43, a 10x (100 micrograms) excess of non-biotinylated MAbs to the E2 fragment was added to the wells. Subsequently, the experiment was conducted as previously described. In the second control, non-specific biotinylated murine IgGs and vector stealth-liposomes were used. In the third control, stealth-liposomes non-conjugated with streptavidin were used.

FIGURE 2



Immunofluorescent Visualization of Vector Liposomes on Membranes of Live Cx43-Positive C6 Glioma Cells

A. Biotinylated anti-E2Cx43 antibodies + liposomes with streptavidin. B. Competitive inhibition of biotinylated antibodies binding with target cells by pre-incubation with excess of non-biotinylated antibodies to E2 Cx43. C. Biotinylated non-specific mouse immunoglobulines + liposomes with streptavidin. D. Biotinylated MAb to E2 Cx43 + liposomes without streptavidin. Magnification x630.

RESULTS

Anti-Cx43 antibodies visualized plakoid structures of connexons on fixed primary astrocytes and C6 rat glioma, as well as on U251 glioblastoma cells and o HEK 293 line cells (Figure 1A through 1D). The brightest fluorescence was observed in samples of HEK

293, which supports the hypothesized high level of gap-junction protein expression in embryogenesis (Figure 1D). In fixed cell specimens, both membrane and cytoplasmic pool of Cx43 were visualized.

Biotinylated MAb to the E2 extracellular domain clearly visualized Cx43-positive cells of high-grade gliomas in live culture (Figure 1E & 1F). In this case, only membrane connexon fluorescence was observed. None of the specimen has shown fluorescence of intercellular connections characteristic for dimeric connexons integrated into gap junctions. Based on that, we have assumed that obtained antibodies allow Cx43 to visualize during the connexon presentation stage on cell membranes as a hemichannel.

The results of live glioma cells fluorescent analysis allowed us to plan the experiment on targeted delivery of liposomes to said cells using biotinylated antibodies to Cx43 and streptavidin-conjugated liposomes.

PEGylated liposomes were characterized by diameter and concentrations of overall lipids and protein (in liposome sample with attached streptavidin). Liposome diameter determined by photodynamic scattering amounted to 80 to 100 nm. Mean lipid concentration in obtained liposomal emulsion was 20.5 ± 1.1 mg/ml, streptavidin concentration in prepared emulsion of corresponding liposomes was equal to 0.4 mg/ml.

A two-component targeted delivery system experiment has shown specific Dil fluorescence in glioma cell specimens pretargeting with biotinylated antibodies to E2 Cx43 following incubation with streptavidin-conjugated liposomes. Thirty minutes subsequent to addition of minimal liposomal emulsion volume (1 microliters), characteristic membrane plakoids of connexons were visualized (Figure 2A). This phenomenon was observed for the entire scope of concentrations (eg, 1, 10, 25, and 50 microliters/ml); however, for high liposome concentration (25 and 50 microliters/ml), intensive fluorescence of growth medium distorting Cx43-positive cell visualization was observed. For said liposome concentrations, growth medium was replaced immediately prior to microscopic observation. Fluorescence phenomenon of Cx43-positive C6 glioma cells was reproduced during three independent runs of experiments.

Cell pre-incubation with excess of non-biotinylated antibodies to Cx43 blocked fluorescence appearance subsequent to addition of biotinylated antibodies and liposomes with SAv (Figure 2B). In control wells pretargeted with non-specific biotinylated antibodies and vector liposomes with SAv (Figure 2C), as well as when using non-vector liposomes (Figure 2D), no specific fluorescence was observed.

Intensive red fluorescence of Cx43-positive C6 glioma cells evidenced selective adhesion of vector liposomes with SAv and Dil on membranes of those cells. Counting cells with Dil fluorescence and their comparison with the overall number of cells assessed by fluorescence of CFDA SE has shown that on average, 10% of C6 glioma cells in experimental wells have bound liposomes and thus were Cx43-positive.

DISCUSSION

Both rat C6 glioma and U251 human glioblastoma are high-grade and, according to literature, are characterized by a low expression level of Cx43 and of other gap junction proteins.[8,9] Immunofluorescent analysis with antibodies to the E2 fragment, however, allowed the detection of about 10% of Cx43-positive cells. These data were reproduced using several variations of ICH (eg, exposure with secondary antibodies or streptavidin Alexa Fluor, visualizing with Dil-labeled liposomes). Thus, the hypothesis about complete absence of Cx43 expression in high-grade gliomas was not confirmed. This corresponds to the experimental results of Bates DC et al, who had also observed Cx43 expression in C6 glioma cells, and even obtained a Cx43-positive glioma line with greater invasion potential than Cx43-negative gliomas.[2] However, it must be mentioned that Cx43 expression detected with ICH does not at all prove gap junction formation in glioma cells. To prove existence of functional gap junctions, other approaches, such as the S. Goldberg method with cytoplasmatic fluorescent marker transfer, are required.[20]

In targeted delivery experiments, the binary system was selected for several reasons. First, dissociation constant of the streptavidin-biotin complex (10^{-15} M) is almost twice as low as mean dissociation constant of the antigen-antibody complex (no less than 10^{-9} M); therefore, using the first complex shall increase accumulation specificity of transported liposomal containers. Second, when the binary system is used, streptavidin conjugation with a liposome molecule then leads to development of a significantly lesser complex than conjugation of antibodies with a liposome (streptavidin molecular mass is almost three times as low as immunoglobulin G molecular mass). In addition, the following methodological aspect is of great importance: biotinylation using the succinimide method, immuno-chemical activity of MAb changes to a lesser degree than by thiolizing, which is necessary for attaching antibodies to liposomes using the maleimide method. Taking into consideration all stated factors, two-component systems based on biotinylated antibodies and liposomes with streptavidin shall be preferred to immuno-liposome-based ones for experiments in vitro and especially

for experiments in vivo.

Our newly developed binary system has shown high selectivity to Cx43-positive glioma cells in vitro. Adhesion of vector liposomes on cell membranes may facilitate conjugation of bilipid layers and internalization of liposome contents. To intensify the internalization process, additional components may be introduced into vector liposomes (ie, TAT peptide or other virus transcription factors).

The obtained results allow us to suggest that a binary system based on biotinylated antibodies to the extracellular fragment of Cx43 and PEGylated liposomes with streptavidin may be used for targeted delivery of diagnostic and therapeutic agents to Cx43-positive glioma cells, as well as to Cx43-positive astrocytes in the peritumoral zone in vivo.

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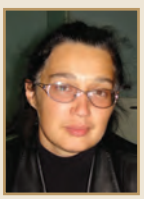

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Significantly Reduced Drug-Apparent Solubility Using a Micronization Process

By: Wei-Guo Dai, PhD; Liang C. Dong, PhD; Shu Li, Crystal Pollock-Dove, Zhengyu Deng, PhD

ABSTRACT

In this study, we reported a significantly reduced drug-apparent solubility during a micronization process. A poorly water-soluble compound was micronized by jet-milling and mortar/pestle-milling. Both milling processes reduced the particle size to approximately 5 micrometers. However, mortar/pestle-milling significantly reduced the compound's apparent solubility ($p < 0.01$) and thermodynamic solubility ($p < 0.02$) in simulated gastric fluid (SGF) (pH 1.2), whereas jet-milling did not alter compound solubility. Despite solubility differences, the jet-milled and mortar/pestle-milled samples did not show major differences by Differential Scanning Calorimetry (DSC) and X-ray Diffraction (XRD) analyses. The results in this study have clearly demonstrated the significant influences of different milling processes on compound solubility.

INTRODUCTION

Micronization of drugs by mechanical comminution, such as milling, has been established to produce appropriate size of drug particles for novel delivery systems, manufacture the desired drug dosage form, and improve drugs' dissolution rates and bioavailability.[1-4] During the micronization process, drug properties can be significantly affected due to the high-energy input used in the process. Very often, drug solubility is increased significantly after milling processes.[5-8] For example, milling of griseofulvin for 3 minutes using a mortar grinder increases its aqueous apparent solubility to 44 micrograms/mL from 15 micrograms/mL, and apparent solubility of ursodeoxycholic acid increases with the milling time during the vibrating mill process.[7,8]

The compound's increased solubility after micronization may be primarily attributed to the decreased degree of crystallinity and formation of partially amorphous structures by the high-energy input during the milling because materials in the amorphous state exhibit higher solubility than those in the crystalline state.[9-12] In addition to creating an amorphous phase, the milling processing could produce and increase different extents and types of disorders, such as different concentrations of points, dislocation, and defects in the remaining crystal lattice.[13] Furthermore, mechanical treatments, such as milling, grinding, and compression may lead to polymorphic transformation or creation of new polymorphs, which show different solubilization behaviour.[11-14] The influences of milling processes on drug properties have been described; however, the majority of studies have shown an increase in drug solubility during milling processes and to our knowledge, few publications report a reduced apparent solubility of compounds during milling processes.

In this study, a poorly water-soluble compound was micronized by two milling processes: jet-milling and mortar/pestle-milling. The effects of two milling processes on apparent and thermodynamic solubility, solid-state properties, and particle size distribution were investigated. We reported a significantly reduced solubility of the compound in simulated gastric fluid (SGF) (pH 1.2) during mortar/pestle-milling process.

MATERIALS & METHODS

Compound

A poorly water-soluble compound was obtained from the Johnson and Johnson Pharmaceutical Research and Development compound collection. This compound consists of C, H, F, N, O, and S, with a molecular weight of 676.77 g/mole. It has a piperidine and a pyridine group. Table 1 summarizes the molecular weight, pKa, Log P, solubility, and solubility parameter of the compound. The free base

form of this compound has a low thermodynamic solubility of ≤ 0.0002 mg/mL at neutral pH, but about 0.6 mg/mL in SGF at pH 1.2. In addition, its apparent solubility in SGF (pH 1.2) within 2 hours can be as high as 10 mg/mL.

The compound as received had a flake shape. Micronization of the compound was needed to reduce its size for delivery systems. In addition to reducing drug particle size, another important criterion for the micronization processes was to maintain apparent solubility of the compound in SGF at least 6 mg/mL to achieve the desirable bioavailability.

Micronization of Compounds by Milling Processes

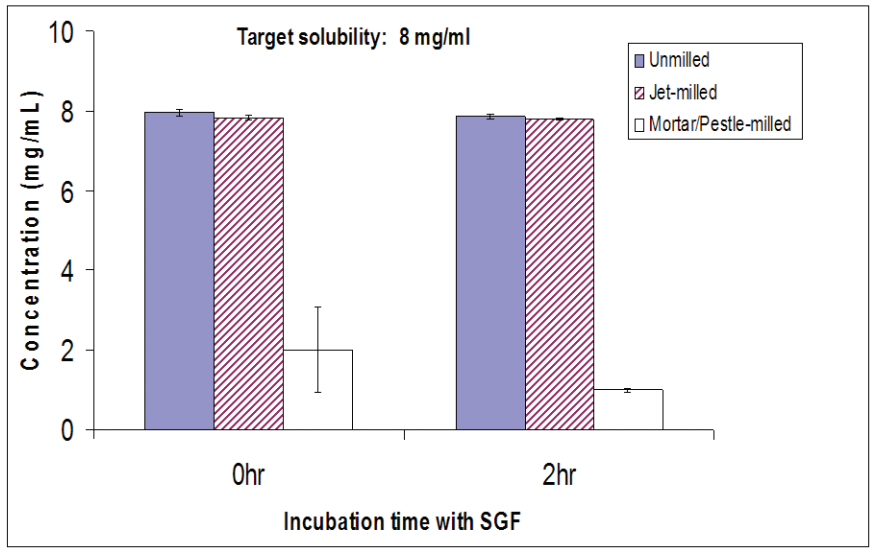
The compound was micronized by two milling processes: jet-milling and mortar/pestle-milling. For a jet-milling process, an ALJET system (Fluid Energy Processing & Equipment Company, Hatfield, PA) was used. A nitrogen gas was introduced through specially designed nozzles, creating sonic velocities for micronization of the compound. The grind nitrogen nozzle pressure and pusher nitrogen pressure were adjusted to 40 and 30 psi, respectively. The compound after the jet-milling process was stored at 25°C in desiccators before further use.

For a mortar/pestle-milling process, the compound was placed in a mortar and milled by a pestle for 5 minutes. To reduce batch-to-batch variation, 20 batches of milled samples were prepared and mixed together. The milled sample was sieved through a 40-mesh screen, and then stored at 25°C in desiccators before further use. In addition, a portion of the compound was unmilled to serve as a comparator to the milled compounds.

Particle Size Distribution

The milled samples from the jet-milling process and, separately, the mortar/pestle-milling process, were dispersed into deionized water containing 8 mg/mL of Pluronic F127 (BASF, Florham Park, NJ). After a 30-second sonication at room temperature, an appropriate volume of the dispersion was introduced into the sample cell filled with deionized water in a Horiba-910 PS analyzer (Horiba, Irvine, CA), and the particle size distribution was measured. Values are reported for volume-weighted analyses.

FIGURE 1



Apparent solubility of the micronized samples in SGF (pH 1.2). Error bars represent standard deviations of four measurements.

HPLC Assay

An HP1100 HPLC instrument (Agilent, Palo Alto, CA) was used to measure compound concentration. Ten microliters of the solution were injected into an Inertsil ODS-2 RP C18 column (150 mm x 4.6 mm, 5 micrometers) (Varian, Palo Alto, CA). The sample was eluted at 30°C with the mixture of acetonitrile-water (30:70 v/v) at 0.5 mL/min, and the concentrations of the compound were quantified at a wavelength of 254 nm. The retention time of the compound was 2.3 minutes during a total 4-minute run time per sample. The lower quantification limit is 0.1 micrograms/mL.

Apparent Solubility in SGF

Forty milligrams of each milling sample were added to 5 mL of SGF to target a final concentration of 8 mg/mL. After a 2-minute vortexing, the mixture was shaken at room temperature. At timepoints of 0 and 2 hours of

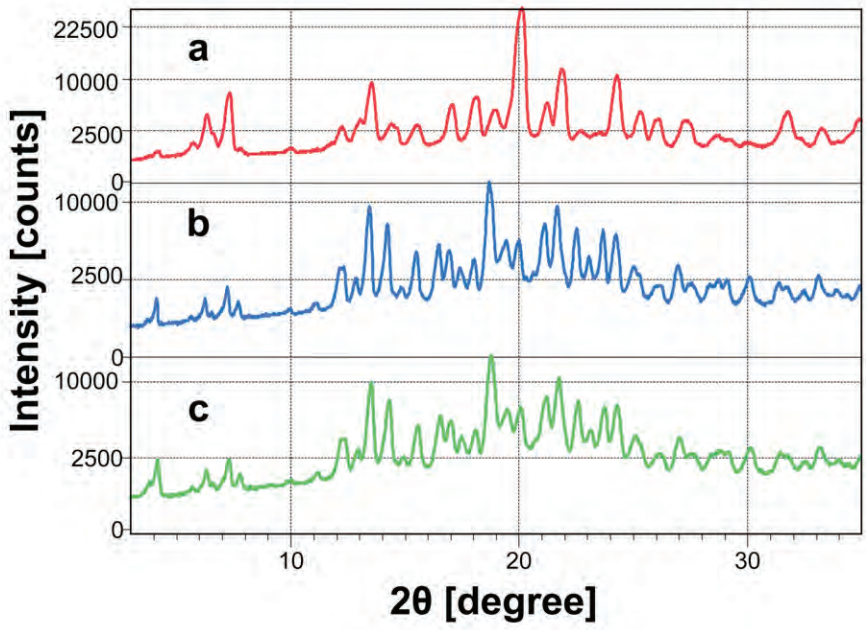
TABLE 1

Property	Value
Molecular Weight	676.77 g/mole
pKa[a]	3.59, 7.8
Log P[b]	2.14
Solubility	~ 0.6 mg/mL at pH 1.2 (SGF) ≤ 0.0002 mg/mL at pH 7.4
Solubility Parameter (δ/MPa$^{1/2}$)[c]	27.77

[a]pKa was measured by potentiometric titration in a water/methanol mixture with UV absorption measurement.
[b]Log P was determined by the shake-flask method with 1-octanol and buffer pH 10.
[c]Solubility parameter was estimated computationally using Molecular Modeling.

Physicochemical Properties of the Tested Compound

FIGURE 2



XRD patterns of the (a) unmilled, (b) jet-milled, and (c) mortar/pestle-milled samples.

TABLE 2

	Unmilled Sample	Mortar/Pestle-Milled Sample	Jet-Milled Sample
Solubility (micrograms/ml) (n=8)	611.4 ± 25.6 [a]	565.7 ± 28.6 [b]	615.8 ± 35.4 [c]

[b] p < 0.05 Compared with [a] and [c]
[c] p > 0.05 Compared with [a]

Thermodynamic Equilibrium Solubility of the Micronized Samples in SGF (pH 1.2).

shaking, the solution was filtered through a 0.2-micrometer polyvinylidene fluoride (PVDF) filter (pION, Inc., Woburn, MA) to remove undissolved compound particles. The compound concentration in the filtrates was measured using the HPLC method.

Thermodynamic Solubility in SGF

Thermodynamic solubility of the compound in SGF was determined by a shake flask method. Briefly, 20 mg of a sample were added to 1 mL of SGF. The suspensions were shaken at 37°C for 2 to 5 days. Aliquots were withdrawn and filtered through a 0.2-micrometer PVDF filter. The filtered solution was diluted with acetonitrile, and the compound concentration in the filtrates was analyzed by the HPLC method. Equilibrium solubility was determined when the concentration of the compound in the suspension did not increase further with incubation time.

Apparent Solubility in the Mixture of SGF & 1-Methyl-2-Pyrrolidinone (NMP)

Two procedures were used to determine the apparent solubility of the compound in the mixture of SGF and NMP (Sigma-Aldrich, St Louis, MO). In the first procedure, 40 mg of sample were added into 5 mL of the premixed solution of SGF and NMP (SGF/NMP, 95/5, v/v). The mixtures were vortexed for 2 minutes and then shaken at room temperature. In the second procedure, 40 mg of sample were added to 0.25 mL of NMP first. After a 2-minute vortexing, the compound/NMP solution was then mixed with 4.75 mL of SGF (SGF/NMP, 95/5, v/v). For both cases, all solutions were filtered through a 0.2-micrometer PVDF filter to remove undissolved compound particles. The compound concentration in the filtrates was measured using the HPLC method.

DSC Analysis

A differential scanning calorimeter (Hyper-DSC, Perkin-Elmer, Boston, MA) was calibrated using indium. Samples (3 to 5 mg) were heated from 25°C to 210°C at 10°C /min in aluminum pans under nitrogen atmosphere. The melting points were calculated using the Pyris software (Perkin Elmer, Boston, MA).

XRD Analysis

X-ray powder diffraction patterns were measured using a PANalytical X'Pert Pro Powder X-ray Diffraction System with Cu Kα (λ = 1.54 A°) radiation operating at 20 mA and 50 kV (PANalytical Inc., NATICK, MA). The data were collected with an angular range between 3 and 35° 2θ, using a step of 0.0167 degree/step with a scan rate of 0.209° 2θ/s.

Statistical Analysis

The data is presented as mean ± standard deviation (SD), if not specified otherwise. The statistical significance of the differences between groups was determined using Student t-test. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS & DISCUSSIONS

Figure 1 shows the apparent-solubility results of the micronized samples in SGF. The mortar/pestle-milling process used in the study reduced the compound's apparent solubility in SGF. Its apparent solubility in SGF after milling was reduced significantly to 2.0 mg/mL from 7.9 mg/mL before milling ($p < 0.01$) (Figure 1). Also, apparent solubility in SGF decreased with time; it reduced further to 1.0 mg/mL from 2.0 mg/mL following 2-hour incubation at room temperature ($p < 0.05$), indicating a continuous compound precipitation in SGF with time.

Unlike the mortar/pestle-milling process, the jet-milling process did not affect the compound's apparent solubility in SGF. The apparent solubility of the jet-milled sample in

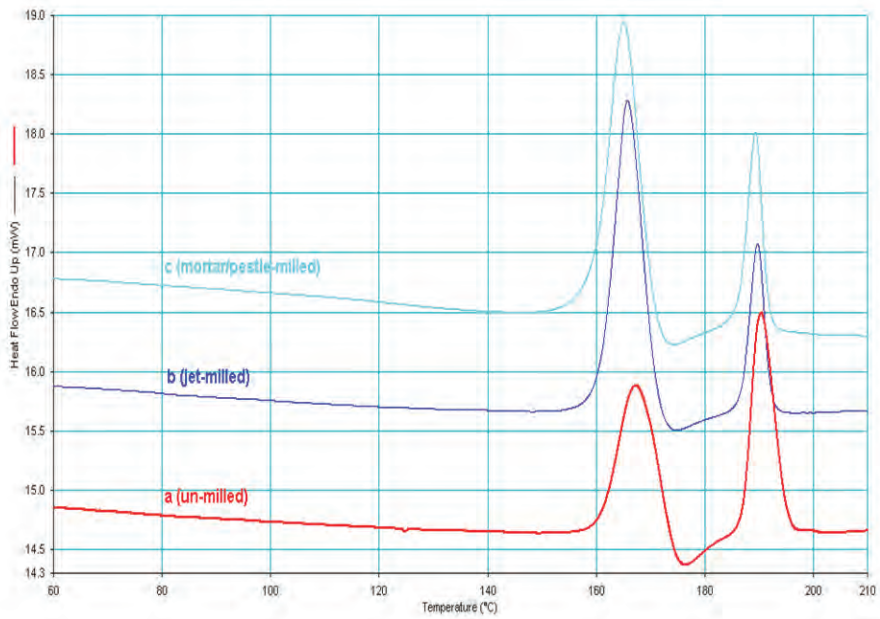
SGF was 7.8 mg/mL, comparable to one of the unmilled sample (7.9 mg/mL) ($p > 0.05$). Following 2-hour incubation at room temperature, the jet-milled sample, like the unmilled, retained its apparent solubility at ~8 mg/mL in SGF without precipitation (Figure 1).

In addition to the compound's apparent solubility, the mortar/pestle-milling process reduced significantly its thermodynamic solubility in SGF from 611.4 ± 25.6 micrograms/mL before milling to 565.7 ± 28.6 micrograms/mL after milling ($p < 0.02$) (Table 2). On the contrary, the thermodynamic solubility of the jet-milled sample in SGF (615.8 ± 35.4 micrograms/mL) was insignificantly different from that of the unmilled compound (611.4 ± 25.6 micrograms/mL) ($p > 0.05$) (Table 2).

It has been well documented that the apparent and thermodynamic solubility of compounds are often significantly increased after a milling process.[5-7] However, our results show that the influence of micronization on a drug's apparent solubility depends on the micronization process used. Drug solubility can be unchanged during micronization, as observed in the jet-milling process, or be significantly reduced, as observed in the mortar/pestle-milling process (Figure 1).

XRD and DSC analyses on the milled samples were conducted to investigate whether this significantly reduced solubility during micronization was due to the alteration of the compound's crystal structures/orders, or major transformation of polymorph by milling. Our XRD results showed that the mortar/pestle-milled sample displayed similar peak locations in XRD patterns, compared to the unmilled and the jet-milled samples, and no obvious peak broadening was observed (Figure 2). Neither major difference in XRD patterns was detected among all three samples. Similarly, both the jet-milled and mortar/pestle-milled sample had similar DSC thermograms compared to the unmilled sample (Figure 3). Two melting peaks were found at approximately 167°C and 190°C for all three samples. The total heat of fusion (ΔH) for the mortar/pestle-milled sample was 67.2 ± 1.0 (J/g), which was comparable to that of jet-milled sample (67.4 ± 1.3 J/g) ($p > 0.05$), but lower than that of the unmilled sample (72.6 ± 3.4 J/g) ($p < 0.05$).

FIGURE 3



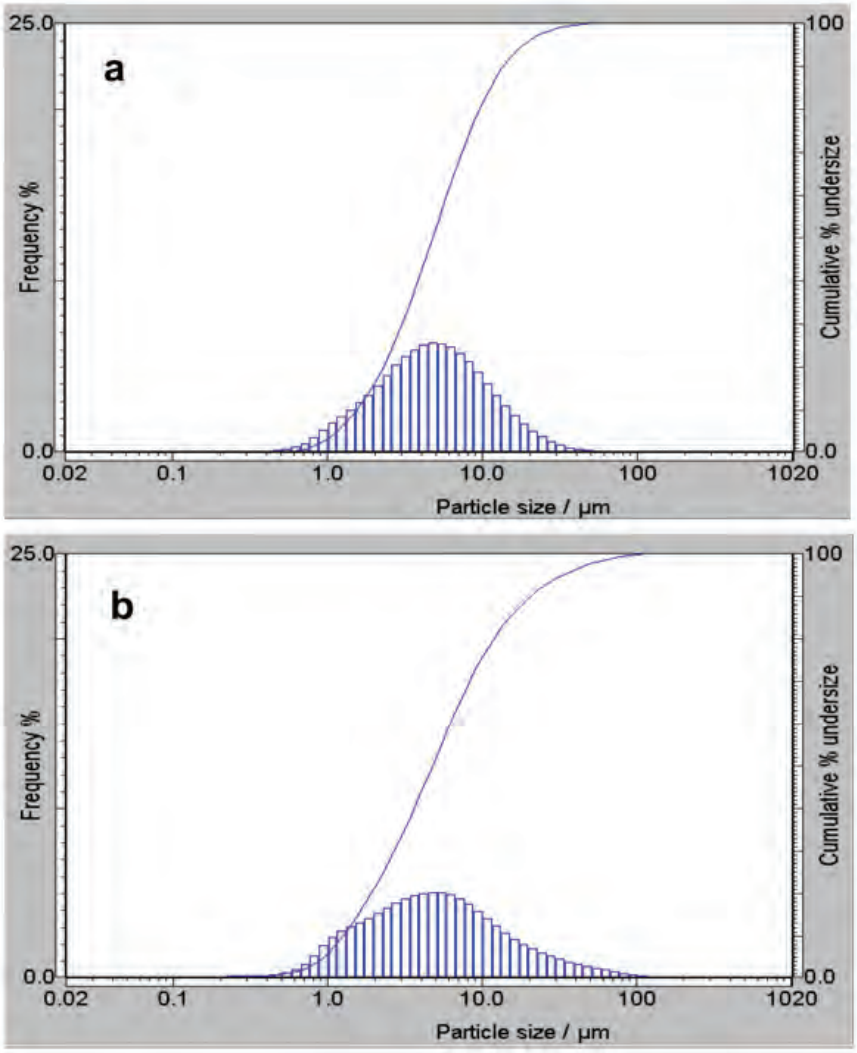
DSC thermograms of the (a) unmilled, (b) jet-milled, and (c) mortar/pestle-milled samples.

It has been known that the increased solubility by the milling processes is often due to a reduced degree of crystallinility and an increased amorphous content in the micronized drugs.[9-12] This can be well characterized by the change of peak locations and obvious broadening of the peaks in XRD patterns.[10,15] However, XRD results in the study showed negligible differences between the mortar/pestle-milled sample and jet-milled sample in peak locations and broadening in XRD patterns, despite the significantly different solubilities of these two samples. The DSC results also did not detect differences between these two samples. Therefore, a significantly reduced solubility of the compound by mortar/pestle-milling process observed in this study can not be explained well by the DSC and XRD results, suggesting that a change in degree of crystallinility or creation of amorphous domains in the micronized drugs by both milling processes was negligible or at least under the detection limit of the XRD technique (< 10%).[10] It should be pointed out that XRD and DSC analyses were also performed at different scan rates, including very slower ones. Neither major differences nor new other polymorphs were found between the two different milled samples under those testing conditions.

Another factor affecting the compound's apparent solubility could be the particle size of the micronized sample, and because the apparent solubility was measured at 2-hour data points, a slow dissolution due to large particle size within a short period of time (such as 2 hours) could lead to a reduced apparent solubility when the compound concentration was measured. Figure 4 shows the particle size distribution results of the milled samples. Both jet-milling and mortar/pestle-milling reduced the compound particle size to approximately 5 micrometers with a mono-modal distribution, and these two milling processes were comparable in terms of particle size reduction (Figure 4). Particle size was not the major factor contributing to the reduced apparent solubility of the milled sample.

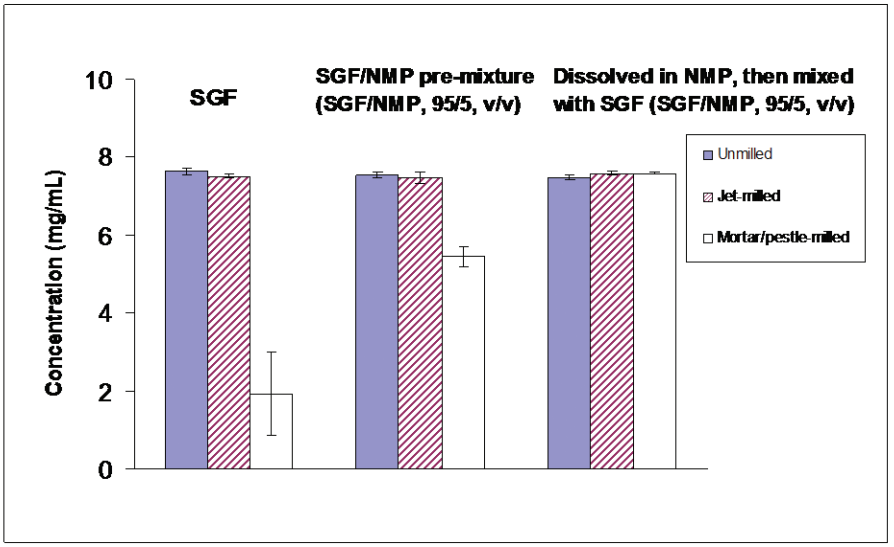
We further measured the apparent solubility of the milled samples in the mixture of SGF and NMP prepared by two different solubilization procedures. The solubility results showed that both the unmilled and the jet-milled samples were completely soluble in both SGF, and the two mixed-solvents of SGF/NMP (95/5, v/v) by the different solubilization procedures, with a target apparent solubility reached at 8 mg/mL (Figure 5). On the contrary to the jet-milled sample, the mortar/pestle-milled sample was not

FIGURE 4



Particle size distribution of the (a) jet-milled sample and the (b) mortar/pestle-milled sample.

FIGURE 5



Apparent solubility of the milled samples in the mixed solvents of SGF with NMP (SGF/NMP, 95/5, v/v). Error bars represent standard deviations of four measurements.

completely soluble in premixed SGF/NMP (95/5, v/v) solution at 8 mg/mL. A cloudy solution appeared, and the apparent solubility was only 5.7 ± 0.3 mg/mL (Figure 5), which was significantly lower than the targeted apparent solubility. Interestingly, if the same sample was dissolved in NMP first, followed by mixing with SGF, a clear solution was observed, and the solubility of the sample was 8.0 ± 0.0 mg/mL, indicating a complete solubilization.

Unlike the findings in the literature that drug solubility has been often increased after a milling process due to the reduced degree of crystallinility and increased amorphous content in drugs, our study results showed a reduced drug solubility after the milling process and that the milling process in the testing conditions neither change the degree of crystallinility of drugs nor create new polymorphs (Figures 3 & 4).[9-11] Drug solubilization is not only affected by solid state structures, such as the degree of crystallinity and crystal form, but also its surface properties, including surface energy and wettability that helps salvation and dissolution of drugs in the aqueous medium.[5,6,16,17] In addition to a decrease in degree of crystallinity, the milling process has been reported to increase surface energy, enhance electron-donating capacity and enlarge surface polarity.[8,18,19] We believe that the milled samples after two milling processes may exhibit different surface properties, such as wettability, surface free energy, surface polarity, area, and curvatures that lead to significantly different observed solubilization. This would also explain solubilization behavior of the milled samples in the solvent mixture of SGF and NMP; the mortar/pestle-milled sample was not able to be completely solubilized in a premixed solvent (SGF/NMP: 95/5, v/v) solution at a drug loading due to the alteration of drug's surface properties, such as wettability and surface-free energy; however, when the same sample was dissolved in NMP first, and then mixed with same proportion of SGF, NMP wiped out the alteration of surface properties of the milled sample, leading to the complete solubilization.

CONCLUSIONS

Significantly reduced drug solubility during a micronization process was presented. Compared with the unmicronized compounds, the mortar/pestle-milling process significantly decreased the compound's apparent solubility and thermodynamic equilibrium solubility ($p < 0.02$), whereas jet-milling did not alter compound solubility ($p > 0.05$). The results in this study have demonstrated the significant influences of the different milling processes on drug solubilization behavior.

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BIOGRAPHIES

Dr. Wei-Guo Dai is currently a Fellow in Drug Delivery and Device Development at Johnson and Johnson Pharmaceutical Research and Development in Radnor, Pennsylvania. He is responsible for new drug delivery technology assessment and integration. Dr. Dai earned his PhD in Chemical Engineering from The Johns Hopkins University in 1996, and has more than 14 years of drug delivery experience in biotech/pharmaceutical companies, including Guilford Pharmaceuticals, Amgen, ALZA/Johnson and Johnson, and Landec Corporation. Dr. Dai has authored or co-authored more than 30 journal publications, and his research interests include novel drug delivery technologies and combination product development for both biologics and small molecules using conventional and nonconventional techniques and strategies.

Dr. Liang C. Dong is a seasoned scientist with more than 20 years of experience in the field of controlled release, formulation, and material science. As a Senior Research Fellow at ALZA/Johnson & Johnson, he was responsible for developing advanced oral delivery systems, including site-specific delivery systems, pulsatile delivery systems, L-OROS® (controlled release of liquid formulations), and oral peptide/protein delivery systems. Dr. Dong earned his PhD in Bioengineering from the University of Washington in 1990, with his doctoral dissertation pertinent to intelligent hydrogels for controlled release and immobilization of biomolecules. He is a co-inventor for more than 60 patents, including 38 granted US patents, and co-author for more than 60 publications and meeting abstracts. Currently, he is the CSO with ADDS Pharmaceuticals, a start-up specialized in the development and commercialization of nutraceutical and pharmaceutical products, using its proprietary delivery technologies.

Shu Li has more than 18 years of experience in oral solid and liquid dosage formulations for soluble and insoluble drugs, controlled release, immediate release, Osmotic Pumps, rate-controlling membranes, and matrix systems. Ms. Shu was a Senior Engineer in Alza Corp from 1991 to 2007, Research Scientist at Impax Labs, and currently a Senior Engineer at ADDS Pharmaceuticals, LLC. She is also specialized in formulation characterization techniques like FT-IR, DSC, optical microscopy, high throughput screening, DOE, measurement of particle size, viscosity, solubility, permeability, osmotic pressure, formulation processing, and pilot scale-up.

Crystal Pollock-Dove is currently a Research Engineer at ADDS Pharmaceuticals and serves as the Manager of Development. Prior to joining ADDS, Ms. Pollock-Dove was a Senior Chemical Engineer working on advanced drug delivery and formulation systems at ALZA Corporation/Johnson and Johnson. She is a co-inventor on several patents and a co-author on many published technical articles. Ms. Pollock-Dove graduated from UC Berkeley's College of Chemistry with a BS in Chemical Engineering.

Dr. Zhengyu Deng is Staff Scientist, Quality Control Chemistry at Pacific Biosciences. In his role, Dr. Deng is responsible for developing quality processes and methodologies across the company, including supplier evaluation and validation, materials inspection methodologies and processes, and production control plans for meeting product specs. Before joining PacBio, Dr. Deng was a Principal Scientist with Relypsa, Inc, a start-up company developing polymeric drugs using automation high-throughput platforms. Dr. Deng also worked for Alza Corp. as a Principal Scientist, where he took the lead in introducing new analytical capabilities and methods to support small molecule drugs, biologics, and drug delivery devices from the development phase to commercial manufacturing. Dr. Deng earned his BS and MS while residing in China and his PhD in Physical Chmeistry from Vanderbilt University.

siRNA DELIVERY

The AtuPLEX Technology for Therapeutic siRNA Delivery in Oncology

By: Ansgar Santel, PhD; Oliver Keil, PhD; Klaus Giese, PhD; and Jörg Kaufmann, PhD

INTRODUCTION

The translation of RNA interference (RNAi) for therapeutic application has been rapidly advanced from bench to clinic, since the seminal discovery of RNAi-mediated suppression of gene expression by 19-21-mer double-stranded RNA molecules (so called siRNA: short interfering RNA) in mammalian cultured cells was published in 2001.[1,2] Therapeutic strategies harnessing the natural-occurring RNAi pathway make use of the sequence-selective down-regulation of gene expression through controlled mRNA degradation in the diseased cell type. The use of chemically synthesized siRNA molecules offers the opportunity to develop within a relative short period of time "sequence-specific inhibitors" against any therapeutically relevant human gene and in turn its gene product.

However, the caveat is that these highly negatively charged siRNA-inhibitors do not cross biological membranes and exhibit insufficient pharmacological properties for distribution and uptake in vivo, especially when administered systemically. Thus, it is desirable to develop adequate non-viral siRNA vehicles that ensure the safe and efficient delivery of the cargo into the cytoplasm of the destined cell types. Various strategies and approaches have been followed in recent years in order to tackle the problem of functional siRNA delivery and making RNAi/siRNA suitable for therapeutic usage. Depending on the cell type to be delivered, targeted polymers, liposomes, peptide/protein conjugates, and others have been developed for topical and systemic administration.[1] These efforts in pursuing the therapeutic application of siRNA have been culminated in the initiation of various clinical trials.[1,3]

Current trials basically cover different application routes (local injection for ophthalmic diseases, inhalation for lung diseases, and systemic administration for hepatic and cancer diseases) and employ different siRNA delivery approaches (chemical formulation and chemical modification). The Atu027 development program from Silence Therapeutics poses one out of presently four clinical trials following the systemic route with formulated siRNA.[4] Atu027 is based on liposomally formulated siRNA and when given systemically, is destined to target PKN3 gene expression in the vascular endothelium of the tumor and the host's organ vasculature.[5] Thus, Atu027 can be considered as a novel drug strategy for an anti-angiogenic therapy in oncology. In particular, suppression of PKN3 expression in the endothelial cells of both sites, namely at the primary tumor site and at the distant sites of the disseminated tumors (ie, metastatic site), is believed to prevent or inhibit metastatic tumor cell spread and outgrowth by blocking intra- and extravasation of tumor cells. Atu027 bears the therapeutic potential of interfering with critical cancer cell-endothelial cell interactions in the course of tumor progression. The following will summarize the clinical development of Atu027 for oncology and the underlying AtuPLEX (siRNA-lipoplex) technology.

ATU027: SUCCESSFUL TRANSLATION OF ATUPLEX TECHNOLOGY FOR THERAPEUTIC PURPOSES IN ONCOLOGY

Functional delivery of siRNA to the target cell is a prerequisite for the development of RNAi therapeutics and requires the endocytotic uptake and subsequent release from the endosome into the cytoplasm where RNAi occurs. In the case of the AtuPLEX, this was achieved by complexing the negatively charged siRNAs molecules of a defined potent sequence, so-called AtuRNAi molecules characterized by the lack of 3´-overhangs and a particular alternating (zig-zag) 2´-O-methyl-ribonucleotide modification pattern.[6] Thus, the novel cationic liposomes composed of three lipids give rise to the siRNA-lipoplex formation, named the AtuPLEX, when combined with AtuRNAi molecules.[7] The newly developed cationic lipid AtuFECT01 constitutes the key component of these liposomes, enabling siRNA complexation.

More specifically, the AtuPLEX is a four-component system applicable for controlled RNAi in vivo. Each component bears particular features addressing challenges for systemic delivery of therapeutic siRNA, such as serum stability as well as suitable pharmacokinetic/pharmacodynamic and low toxicity profiles. For example, the particular 2´-O-methyl chemical modification pattern of the AtuRNAi molecules confers protection from siRNA degradation through endo- and exonucleases and at the same time, reduction of undesired immune-stimulatory effects (such as interferon response and Toll-like receptor activation). In addition, PEGylation of the AtuPLEX with 1mol% DSPE-mPEG provides sufficient circulation time to the particles, guaranteeing escape from immediate clearance through the RES (reticuloendothelial system: spleen, liver, macrophages) and subsequent cellular uptake in vivo. When AtuPLEX particles become internalized, the presence of the neutral lipid DPhyPE facilitates the siRNA cargo release from the endocytotic vesicles into the cytoplasm so that RNAi can take place. The resulting overall positively charged AtuPLEX particles are supposed to exhibit multilamellar structure with the siRNA being interspersed between lipid bilayers (Figure 1). In-depth in vitro and in vivo analysis have confirmed that these particles become avidly internalized by endothelial cells, giving rise to target-specific RNAi-mediated mRNA knockdown.[7-9] The potency of an RNAi-based therapeutic can be directly judged by assessing target-selective knock-down of gene expression by various molecular methods (Real-Time PCR, Western, ELISA, etc). In addition, the knock-down efficacy can also be evaluated after in vitro transfection by cell biological means (immunofluorescence, immunohistochemistry), as illustrated in Figure 2 for the lamin-B1 gene (LMNB1), which encodes a nuclear envelope protein. Of note, AtuPLEX particles designated for in vivo use can be analyzed for knock-down activity in tissue culture prior to testing in the living organism, providing some level of quality control for biological activity of the "liposomal siRNA-inhibitor" preparation/formulation. When given intravenously, these particular AtuPLEX particles target exclusively the endothelium of all vascular beds of various organs, including tumor vasculature (Figure 3), favoring therapeutic application of this technology for diseases based on vascular endothelial dysfunction as it is part of the pathogenesis for many diseases.[10,11]

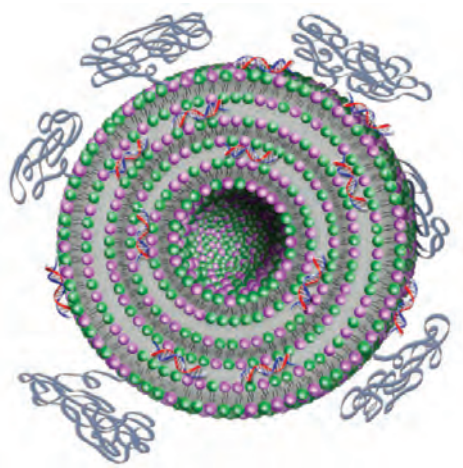
LIPOPLEX VERSUS LIPOSOME FOR SIRNA FORMULATION: THE ATUPLEX FORMULATION BEHIND ATU027

In principle, two alternative approaches for the preparation of lipid-based oligonucleotide delivery vehicles have been described, namely liposomal and lipoplex systems. In the rather classical liposomal approach, a drug cargo, eg, the oligonucleotides, is encapsulated exclusively in the aqueous interior of lipid bilayer vesicles. Therefore, the lipids or lipid mixtures (eg, mixtures of phospholipids and cholesterol) are dispersed in an aqueous solution of the oligonucleotides and spontaneously assemble into liposomal structures, entrapping the nucleic acid in a statistical matter. Obviously, the yield of oligonucleotide encapsulation is rather low, which renders this approach quite inappropriate. Nevertheless, this method was used in an experimental pilot therapy approach for the treatment of a patient suffering from chronic myeloid leukemia.[12]

In order to increase the entrapment efficacy, synthetic lipids comprising amphoteric properties have been developed in recent years.[13,14] At low pH values (pH 3 to 4.5), the hydrophilic head-groups of these lipids are positively charged, allowing for an efficient binding of the negatively charged oligonucleotides to the lipid bilayer surfaces due to electrostatic interaction. After shifting the pH to physiological values around pH 7, the cationic overall charge of the lipid bilayers is removed, and the charge-neutral liposomal structures are generated, entrapping the bulk of the oligonucleotide cargo with encapsulation efficacies of up to 80% to 90%. Alternatively, weakly acidic lipids (eg, CHEMS or oleic acid) can be used in combination with pH-independent cationic lipids. After pH shift to neutral values, these weakly acidic lipids bear negative charges that lead to charge compensation of the cationic lipids and formation of overall neutrally charged liposomal vesicles. However, with both methods, the non-encapsulated free nucleic acid has to be removed by a diafiltration process leading to a substantial loss of the valuable therapeutic material. In contrast to the aforementioned liposome encapsulation process, the so-called lipoplex approach allows for a virtually quantitative drug formulation.

This exceptionally efficient method is used for the preparation of AtuPLEX formulations (eg, Atu027). In a first step, the lipid components (AtuFECT01, DPhyPE, and DSPE-mPEG) become dispersed in an isotonic sucrose solution and form spontaneously multilamellar cationic liposomes. The lipid dispersion can be further processed for example by high-pressure homogenization in order to adjust the vesicle size. In a second step, the liposomal dispersion is rapidly mixed with the siRNA solution in such a way that the cationic lipid charges exceed the negative nucleic acid phosphate backbone charges. The lipids and the siRNA molecules assemble spontaneously into dense lipid bilayer particles of about 120 nm, so-called lipoplexes, leading to siRNA intercalation between the bilayers and providing further siRNA protection from serum proteins and nucleases. The sucrose solution of the lipoplexes can be further lyophilized without any change in particle size or loss of transfection efficacy, and lyophilized AtuPLEX is stable for more than 2 years and can be reconstituted on demand within seconds. Because the overall surface charge (Zeta potential) of the generated particles is positive, these particles show a strong tendency to target the endothelium if applied intravenously.[15]

FIGURE 1

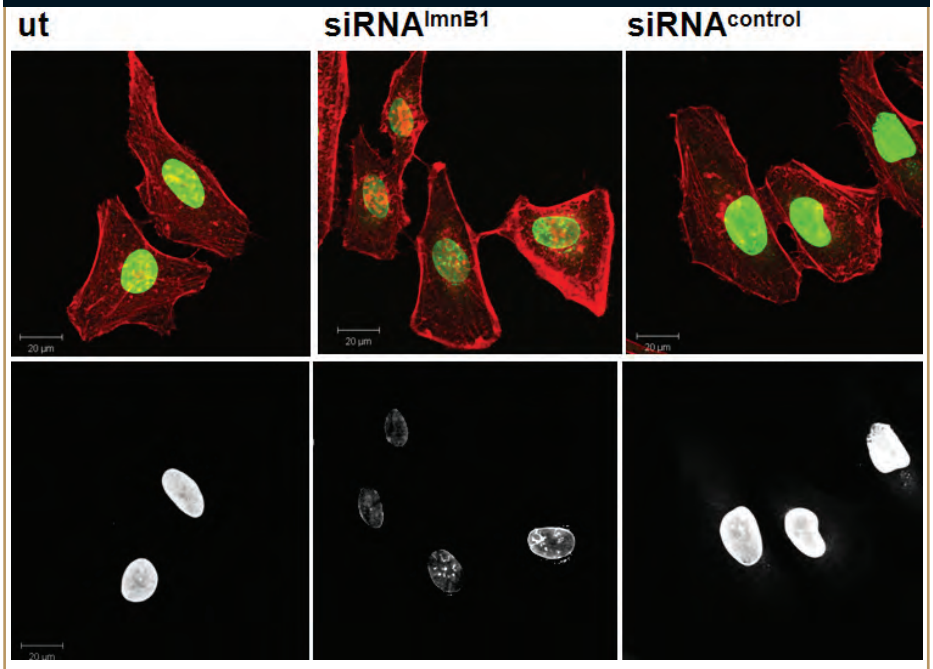


Model structure of AtuPLEX-particles (siRNA-lipoplexes). Nuclease-resistant siRNA molecules (AtuRNAi: red, blue double-helices) intermingle with the multilamellar lipid bilayers comprising the cationic lipid AtuFECT01 (green spheres), the helper lipid DPhyPE (pink spheres), and the PEGylated lipid (pink-spheres linked to grey tangled ribbon), conferring shielding properties to the particle.

RATIONALE FOR ATU027

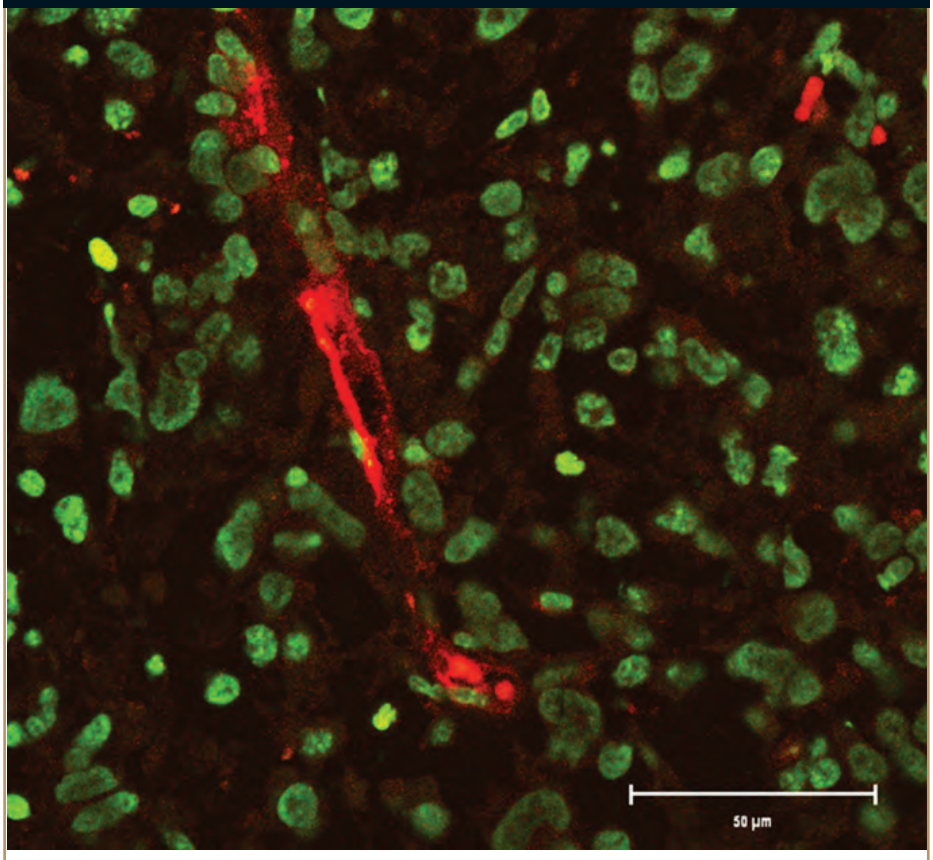
As previously discussed, the AtuPLEX exclusively targets the endothelium of virtually all vascular beds. This includes all tissue and tumor vasculature (Figure 3). Pharmacokinetic (PK) and pharmacodynamic (PD) studies with the AtuPLEX in rodents (mice and rats) as well as non-human primates clearly indicated that the pulmonary vasculature is a prominent target structure for functional AtuPLEX delivery reflected by demonstration of target-specific suppression of gene expression (RNAi-mediated knock-down) on mRNA and protein level in the lungs of these species.[5] Strikingly, a correlation between the PK of siRNA in the plasma and the biological activity (RNAi-mediated knock-down) was attained in these preclinical studies.[5] Moreover, knock-down of PKN3 in the endothelium has also been established in various xenograft tumor models, supporting the rationale of using Atu027 for therapeutic intervention in oncological indications. In the preclinical development program of Atu027, various xenograft models had been employed for establishing Atu027 efficacy against a broad range of tumor entities. Direct inhibition of tumor growth was affected to some extent, depending on the type of xenograft, but more strikingly, tumor models addressing potential efficacy on metastasis undoubtedly demonstrated strong anti-metastatic activity of Atu027.[5,9] This anti-metastatic activity can be attributed to changes in the function and organization of the vascular and lymphatic vessels due to depletion of endothelial PKN3 expression. The lymphatics as well as the vasculature routes pose the two main routes for cancer cell dissemination upon invasive tumor growth. PKN3 was discovered as a downstream target of PI-3-kinase, constituting one of the major signaling pathways for controlling various cellular downstream events (migration, survival, metabolism, translation, etc).[16] PKN3 most likely adopts regulating functions of incoming cues for coordinated cellular locomotion/mechanics relevant for many functions, such as cell adhesion and contact formation, cell shape remodeling, cytoskeletal fluidity, and migration. Therefore, these investigations advocate for the therapeutic modulation of the lymphatic or hematogenous routes of metastatic tumor cell dissemination and successful colonization of the malignant cells.[17]

FIGURE 2



Example of an RNAi-mediated knock-down of the nuclear envelope protein Lamin-B1 (lmnB1) in cultured cells after AtuPLEX treatment. Upper panels show cell morphology visualized through actin staining (red) and nuclear envelope protein LmnB1 in green. Cells were treated as indicated (ut: untreated, siRNA^{lmnB1} and siRNA^{control} refer to AtuPLEXes, carrying lmnB1 or control siRNA). Lower panels show corresponding LmnB1 protein (grey-colored), demonstrating sequence specific reduction in LmnB1 protein levels in comparison of control cells.

FIGURE 3



AtuPLEX targets the tumor vasculature. Cross-section of an experimental murine xenograft tumor is shown. Fluorescently labeled AtuPLEXes highlight a tumor blood vessel (red). Nuclei of tumor cells are shown in green.

Atu027 is currently being tested in a Phase I clinical trial in an open-label dose-finding study on patients with advanced/metastatic solid cancers. In this study, single and repeated treatment schedules at different doses will be consecutively carried out with the purpose of collecting data regarding PK, potential metabolites, as well as clinical tolerability and safety. Because most cancer patients die from metastasis rather than from the primary tumor, Atu027 may offer another treatment option in addition to other anti-angiogenic drugs for the prevention of metastases.

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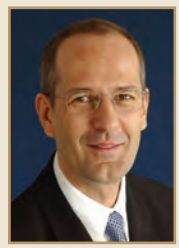
BIOGRAPHIES

Dr. Ansgar Santel is a Senior Scientist of Research and Development at Silence Therapeutics. He joined the company in 2002 as a scientist working on the development of RNAi therapeutics. Prior to that, he has worked as a post-doctoral fellow at Stanford University School of Medicine. He earned his PhD in Molecular Cellular and Developmental Biology from the Philipps-University Marburg, Germany.

Dr. Oliver Keil is Director of Lipid Chemistry for Silence Therapeutics. Prior to joining the company in 2003, Dr. Keil worked for G.O.T. Therapeutics (Berlin) from 2000 until 2003. He was a post-doctoral fellow at the Medicinal Faculty of the University of Düsseldorf. He earned his PhD in the Department of Organic Chemistry at the University of Wuppertal in 1998. His thesis focused on the synthesis of novel cationic lipids for the gene transfer into eukaryotic cells. Dr. Keil has extensive experience in organic and medicinal chemistry.



Dr. Klaus Giese is Chief Scientific Officer of Silence Therapeutics. He joined the company in 1999, where he continues his position as CSO. Prior to Silence Therapeutics, Dr. Giese was Group Leader at Chiron Corporation, Emeryville, CA, from 1994 to 1998 and was responsible for coordinating and managing part of Chiron's obesity and oncology program. Prior to joining Chiron, he was a research scientist and post-doctoral fellow at the Howard Hughes Medical Institute, University of California, San Francisco, as well as at the Max-Planck-Institute for Molecular Genetics in Berlin. Dr. Giese studied Biochemistry at the Free University of Berlin, where he also earned his PhD.

Dr. Jörg Kaufmann is Senior Director of Technologies at Silence Therapeutics. He joined the company in 2000. Prior to this role, he was a Senior Scientist at Chiron Corporation (Emeryville, CA) from 1997-2000, where he also headed the molecular biology group for breast cancer biology. Dr. Kaufmann was a Group Leader (1996-1997) at the Institute of Tumor Biology (IMT) in Marburg (Germany). From 1993 until 1996, he worked as a post-doctoral fellow at the HHMI/University of California, Los Angeles (UCLA). Dr. Kaufmann earned his PhD from the Philipps-University of Marburg, Germany in 1993.

DRUG DELIVERY Executive

3M Drug Delivery Systems: Continuing Innovation in a Changing Global Marketplace

James Vaughan
Division Vice President & General Manager

3M Drug Delivery Systems

In recent years, 3M Drug Delivery Systems has continued its research and development work to create products utilizing its inhalation and transdermal drug delivery technologies. Additionally, the company offers pharmaceutical and biotech firms a full range of feasibility, development, and manufacturing capabilities, including regulatory guidance. Drug Delivery Technology recently interviewed James Vaughan, the division's Vice President and General Manager, to discuss the company's approach to the changing climate in the pharmaceutical industry and how 3M helps its customers bring their products to market.

"As companies have grown more budget conscious, we have seen many major international pharmaceutical firms reducing their research and development efforts. As a result, 3M has worked to help fill the gap for these companies with our outsourcing services. Our laboratory facilities around the world give us the ability to work with pharmaceutical firms to develop their drug products using our drug delivery technologies and experience."

Q: How is globalization affecting the drug delivery business?

A: In 2009, for the first time, most of the world's bioscience degrees were awarded to people outside the United States. We are currently working to adapt to the changes that this trend is bringing about. We are seeing the explosion of firms working in the biologic macromolecule area particularly in Asia. In addition to the rising number of highly trained bioscience professionals outside the West, these start-ups are being driven by venture capital and bioscience entrepreneurs, and they are creating some exciting new technologies. To better serve the needs of our customers in the Asia-Pacific region, 3M recently opened a new laboratory facility in Singapore. This new facility, along with our other laboratories in North America and Europe, gives us the ability to work with pharmaceutical firms in emerging Asian markets to develop their drug products using our drug delivery technologies and experience.

Q: What other opportunities have you identified in emerging markets?

A: We are currently seeing emerging markets that are generating more wealth and are investing more in helping their people live healthier lives. As we know, with industrialization comes pollution, bringing with it an increase in disease, which is an unfortunate side effect of the economic growth in these areas. However, our current and future delivery systems are designed to help relieve some of these diseases with efficient administration of drugs. These systems include inhalers for asthma and Chronic Obstructive Pulmonary Disease, along with transdermal delivery systems for a variety of molecules. These platforms also enable fast delivery of vaccines,

which play a vital role in improving public health.

The transportation and storage of drugs is an important consideration in emerging markets, which highlights a key advantage of our microreplicated systems. We have identified several molecules that can be manufactured and then dried onto the microneedles, eliminating the need for cold storage. This capability means that the distribution and access to the drug can be quickly expanded.

Q: What other industry trends have you observed recently?

A: As companies have grown more budget conscious, we have seen many major international pharmaceutical firms reducing their research and development efforts. As a result, 3M has worked to help fill the gap for these companies with our outsourcing services. Our laboratory facilities around the world give us the ability to work with pharmaceutical firms to develop their drug products using our drug delivery technologies and experience. We can also provide assistance with navigating regulatory requirements, as well as provide manufacturing services.

Q: What advantages can pharmaceutical firms gain from utilizing outsourcing services?

A: Pharmaceutical clients who work with us for their manufacturing needs gain the advantages of our expert supply chain management and global facilities that are current good manufacturing practice-compliant, helping us ensure reliable product delivery. Our facilities are capable of large-scale production, and we utilize a collaborative approach to planning and execution to customize our processes for each customer's needs. By utilizing 3M's existing and planned facilities dedicated to manufacturing transdermal and inhalation product lines, customers can devote more of their capital to sales and marketing.

Beyond manufacturing, our analytical work and regulatory help can provide clients with valuable assistance in getting drugs approved. There are countless steps involved in getting drugs registered and ready for approval, distribution, and sales, and we offer a full spectrum of services to guide our customers through this process. We believe this partnership approach helps ensure a smooth process from beginning to end, improving the outcomes for new products.

Q: What are some of the recent developments in 3M's inhalation offerings?

A: 3M has been a leader in this area of drug delivery. Throughout our 50-year history in the inhalation category, we have developed the first metered-dose inhaler and first CFC-free propellant pressurized Metered-Dose Inhaler. Currently, more than 50% of all metered-dose inhalers worldwide utilize our technology. The division is continuing to innovate in the category, and has recently introduced new components for its aerosol metered-dose inhalers, including a face seal valve that allows a more precise dosing, which is important as drugs become more potent, and an interior canister coating that protects the formulation and thereby ensures a more reliable dose.

Additionally, we have recently introduced our first line of dry powder inhalers (DPIs), which includes the 3M Conix™ Dry Powder Inhaler and the 3M™ Taper Dry Powder Inhaler. The Conix DPI is designed with a patented reverse-flow cyclone technology that effectively utilizes the patient's inhalation to aerosolize the drug. As the patient inhales, air is drawn into the cyclone chamber, where a vortex is established. At the bottom of the chamber, the airflow reverses direction and travels up through the circular outlet. The swirling airflow deagglomerates and aerosolizes fine, respirable particles from larger particles

The 3M Taper DPI has a unique design in which API is stored on a microstructured carrier tape. This technology virtually eliminates the need for lactose or complex powder formulations. When the device is fully opened, a section of the tape is advanced to the dosing station. Upon inhalation, air flow releases a

spring impactor that strikes the web and releases API into the airstream. API particles are further deagglomerated as they pass through the mouthpiece. This active aerosolization helps ensure effective delivery. The Taper DPI can hold up to 120 pre-metered doses, and can be used with single or combination drugs.

Q: What are some of the advantages of tailoring the number of doses?

A: The ease of tailoring the number of doses means that DPIs can be used for single-use applications, such as vaccines. This format is also useful for children with some kinds of asthma. They need occasional treatment, so they should have a device, but parents are naturally reluctant to give a child a metered-dose inhaler with a hundred doses of an expensive drug.

Q: How has the development progressed for 3M's microstructured transdermal technology?

A: Our solid and hollow microneedle technologies continue to progress through evaluation, and may be delivering drugs in the very near future. To create these devices, we are leveraging a core 3M technology in microstructured materials and processes, with the goal of expanding the range of medications that can be delivered transdermally to patients. We are very optimistic about the potential for these devices within the pharmaceutical world. Microneedles eliminate the risk of inadvertent needle pricks (they allow easy administration during periods of mass immunizations), and their greater efficiency means that an expensive or rare drug could be given to more people. Unlike other routes of administration, transdermal delivery has the ability to avoid the first-pass metabolic effects of the liver. It also provides steady, sustained release of the drug, and helps ensure compliance. This technology offers special advantages in the delivery of biopharmaceuticals, allowing us to provide delivery systems for an expanded range of treatments.

The Solid Microstructured Transdermal System (sMTS) uses biocompatible, polymeric microneedles to bypass the barrier properties of the stratum corneum and deliver previously undeliverable molecules, including vaccines, proteins, and peptides, to the dermal/epidermal layers of the skin. This technology has the potential to improve healthcare delivery in several ways. It can improve the overall delivery efficiency for vaccines, as well as enhancing the efficacy of vaccines by targeting antigen-presenting cells within the skin. Additionally, its easy-to-use, easy-to-train system facilitates self-administration.

Q: How does the hollow microstructured transdermal system differ from sMTS?

A: While the needles of the sMTS are coated with the therapeutic agent, the hollow microneedle patch has a reservoir containing the agent. The reservoir is compatible with existing injectable formulations and filling processes. Slight pressure releases the agent through the microneedles. As with sMTS, the patient feels no discomfort, and the agent is delivered at a depth that is sometimes more effective than an injection. We have performed research on this technology showing its potential for delivery of large molecules not typically compatible with transdermal delivery, including peptides and proteins. Our experiments have shown that administration of model drug compounds via the hTMS device produces results comparable to an injection in pharmacokinetic (PK) profiles and bioavailability. The delivery of antibodies and proteins was found to be as efficient as a syringe, a critical element of any delivery platform targeted at high-cost biopharmaceutical drugs.

Q: What steps are involved in developing and manufacturing drugs for inhalation and transdermal delivery?

A: Many pharmaceutical companies already have the equipment to manufacture drugs in tablet and capsule dosage forms. However, drugs that show promise for respiratory treatment (Chronic Obstructive Pulmonary Disease, allergies, etc.) can be further refined to be delivered through the lungs, using either dry powder inhalation or a metered dose inhaler. Many pharmaceutical firms do not have the infrastructure, equipment, or knowledge to manufacture these dosage forms, which is where 3M can help. We have facilities to manufacture inhalers in the United States, the UK, and South America. Furthermore, our laboratories in the United States and the UK, as well as Singapore have the capabilities of developing drugs into these dosage forms.

Our inhalation manufacturing capabilities include both pressure-fill and cold-fill for metered-dose inhaler manufacturing. We also provide custom micronizing, or particle size reduction, to obtain particles in the respirable range. Additionally, we have filling capabilities for projects in sizes ranging from clinical to commercial supply. As the only MDI component supplier to manufacture both valves and canisters, 3M has a unique ability to optimize these components simultaneously with the convenience of a single source, helping ensure their compatibility.

Our transdermal capabilities are similar to our offerings in inhalation. We can provide manufacturing services for transdermal systems and components, including backings, membranes, liners, and tapes. As with inhalation, our transdermal manufacturing facilities are capable of handling capacities ranging from lab scale, pilot scale, or commercial scale.

Q: How can 3M's technologies and expertise help firms control costs?

A: Reducing a new drug's time to market can be a very effective way of controlling costs, and 3M can help achieve this by making certain a firm has the necessary chemistry, manufacturing, and controls system data package to allow fast approval through the regulatory bodies. With our experience of more than 50 years in this industry, we have a record of approval the first time through regulatory bodies for both inhalation and transdermal dosage forms. By providing pharmaceutical firms with a range of services to help them develop new delivery methods, gain approval, and manufacture their products, we can help them reduce their time to market and increase their internal efficiency. Additionally, in the range of our delivery systems, we are helping offer patients cost-effective and precise dosing of drugs that can allow them to efficiently self-administer their medications.

Q: What services does 3M offer to customers to address their life cycle management needs?

A: Product development is a costly process, and pharmaceutical firms are continuously searching for ways to maximize the value of their existing products. They are also under pressure to protect themselves from sales erosion after the launch of generic equivalents. Creating a new delivery route for an existing molecule is a tactic that many companies have found can improve patient compliance or the drug's overall therapeutic benefits. Additionally, reformulating drugs for inhalation or transdermal delivery can sometimes result in improvements to the current dosage form, including longer action, greater and/or faster onset of action, and fewer side effects. To help our customers determine if their candidate molecules may be suitable for transdermal, inhalation, or nasal drug delivery, 3M offers a free of charge, no obligation paper feasibility service that explores the likelihood of a product's success using these delivery routes. ◆

Technology *Showcase*

MDI Components

3M Drug Delivery Systems has been a major supplier of metered-dose inhaler valves and canisters for more than 50 years. As the developers of the first CFC-free MDI, we are experienced at overcoming the challenges that designing components for use with CFC-free propellants presents. 3M is the only MDI component supplier that manufactures both valves and canisters, allowing optimization of these components simultaneously, ensuring compatibility, while delivering the convenience of a single source. For more information, contact 3M Drug Delivery Systems at (800) 643-8086 or visit **www.3M.com/dds.**

Licensing Opportunities

Aveva has numerous products for license from its development pipeline along with a full compliment of R&D capabilities to produce transdermal drug delivery systems that fortify R&D pipelines and maximize product life cycles. Aveva Drug Delivery Systems is one of the world's largest manufacturers of and a pioneer in transdermal drug delivery systems of providing pharmaceutical partners with fully integrated, controlled-release transdermal products that fulfill unmet market needs. Products for licensing include Sufentanil, Fentanyl, Clonidine, and Nicotine. For more information, contact Robert Bloder, VP of Business Development, at (954) 624-1374 or visit **www.avevadds.com.**

Solubility/Bioavailability Enhancement

Soluplus® is a graft copolymer composed of polyethylene glycol, polyvinylcaprolactam, and polyvinylacetate. It is designed to solubilize poorly soluble drugs and increase their bioavailability. It is ideally suited for preparation of solid solutions or solid dispersions by hot melt extrusion, spray drying, melt granulation, and co-precipitation processes. Soluplus is highly soluble in water at low and high pH and organic solvents. It is significantly less hygroscopic than many other polymers. Its low glass transition temperature (70°C) allows it to be extruded over a wide temperature range without the need for plasticizers. For more information, contact BASF at (800) 443-0627 or visit **www.soluplus.com.**

Prefillable Delivery Systems

BD Medical - Pharmaceutical Systems is dedicated to developing prefillable drug delivery systems designed to fit the needs of the pharmaceutical industry. BD offers a range of products, including glass and plastic prefillable syringes, a nasal spray system, and a variety of self-injection systems. We deliver cost-effective alternatives to conventional drug delivery methods, which differentiate pharmaceutical products and contribute to the optimization of drug therapy. With a broad range of innovative systems and services, BD provides pharmaceutical companies with support and resources to help them achieve their goals. Our worldwide presence, market awareness, and pharmaceutical packaging know-how allow us to propose suitable solutions for all regional markets and parenteral drug delivery needs. Only BD offers the range and depth of expertise and packaging solutions to guide your drug from early phase development through product launch and beyond. For more information, contact BD at (201) 847-4017 or visit **www.bd.com/pharmaceuticals.**

Technology *Showcase*

Capsule Filling & Sealing

Designed to allow formulation scientists the ability to better exploit the potential of lipid-based formulations for poorly soluble compounds, the CFS 1200 helps accelerate the development timeframe and achieve Faster Time to First in Man. A fully automatic cGMP-compliant machine, it fills and seals up to 1,200 capsules per hour with liquid or semi-solid formulations without banding. It is designed for ease-of-use and high reliability, with the ability to quickly clean and change capsule sizes with available change parts. Product integrity is ensured with gentle handling of capsules before sealing and during the drying cycle. Other features include a robust filling pump with highly accurate temperature control, improved capsule manipulation before sealing and during drying using new "Cap-edge" handling system, and improved design of filling and sealing process that ensures better control and cleanability. Fore more information, contact Capsugel at (888) 783-6361 or visit **www.capsugel.com.**

Pharmaceutical Solutions

Catalent

Catalent Pharma Solutions is a world leader in patented drug delivery technologies. For more than 70 years, we have developed and manufactured advanced drug delivery systems and partnered with nearly every major global pharmaceutical company. We continually work to advance the science of drug delivery and enhance the therapeutic and market performance of our customers' drugs. Our advanced drug delivery technologies bring new options to resolve the technical challenges development scientists face every day. These patented technologies can improve the odds of successful formulation by enhancing bioavailability, optimizing the rate of release, and targeting the site of absorption. Our technologies include softgel and Vegicaps® Soft capsules; Zydis® fast-dissolve dosage form; modified-release technologies; and a range of inhaled technologies, including MDIs, DPIs, nasal sprays, and solutions/suspensions for inhalation, nebulizers, and liquid inhalers. For more information, contact Catalent Pharma Solutions at (866) 720-3148 or visit **www.catalent.com.**

Raman Chemical Imaging

ChemImage™

ChemImage provides Raman Chemical Imaging contract services for drug formulation and development scientists needing ingredient-specific particle sizing, polymorph analysis, controlled-release analysis, content uniformity measurements, and more. ChemImage stands behind the pledge to provide our customers with the best quality information and fast sample turnaround time on every project. If you are working to develop nasal, inhalation, topical, transdermal, or controlled/sustained release systems, visit our website to learn how we can help you save time and money, raise your confidence, and lower your risk in moving forward through product development. For more information, contact ChemImage at (877) 241-3550 or visit **www.chemimage.com/branchout.**

Orally Disintegrating Technologies

CIMA
Your drug, delivered

CIMA LABS INC. a world leader in the drug delivery partnering business, specializes in the formulation, taste-masking, and manufacturing of pharmaceuticals utilizing our orally disintegrating tablet (ODT), oral transmucosal (OTM), tamper deterrent, solubilization, and oral powder drug delivery technologies. OraSolv®, DuraSolv®, and Lyoc™ ODTs disperse quickly in the mouth without chewing or the need for water. OraVescent® is an oral transmucosal tablet that can be administered buccally or sublingually. OraGuard™ extended release/tamper deterrent technology provides a robust extended release PK profile, even during co-administration with alcohol, and is resistant against various tampering methods. CIMA has proven commercialization success with more than 20 products marketed in more than 70 countries around the world. For more information, contact CIMA at (763) 488-4843 or visit **www.cimalabs.com.**

Technology *Showcase*

Dose Uniformity Sampling Apparatus

The new DUSA Shaker is a small footprint unit that automates the rinsing of Dose Uniformity Sampling Apparatus (DUSA) collection tubes, increasing productivity, enhancing the reproducibility of drug recovery, and reducing the risk of operator exposure to repetitive strain injury. Dose uniformity testing is mandatory for all inhaled products to confirm consistency between batches and across the product lifetime. Individual shots are recovered from a DUSA collection tube by thorough rinsing, post-testing, with an appropriate solvent. This manually intensive agitation process is prone to operator variability and any failure to adequately wet all internal walls compromises drug recovery and the integrity of the results. With a combined rolling and shaking action, the DUSA Shaker ensures full, fast, and repeatable drug recovery from up to 21 DUSAs for MDIs and 12 DUSAs for DPIs. For more information, contact Mark Copley of Copley Scientific at m.copley@copleyscientific.co.uk or visit **http://bit.ly/COP118.**

Development & Manufacturing

DPT is a contract development and manufacturing organization (CDMO) specializing in semi-solid and liquid dosage forms. DPT provides fully integrated development, manufacturing, and packaging solutions for biopharmaceutical and pharmaceutical products. DPT is the industry source for semi-solid and liquids — from concept to commercialization and beyond. Drug development services range from preformulation, formulation and biopharmaceutical development, analytical development, and validation through process development. Production capabilities include four cGMP facilities, clinical trial materials, full-scale commercial production, controlled substance registration Class II-V, and complete supply chain management. Packaging services encompass engineering and procurement resources necessary for conventional and specialized packaging. For more information, contact DPT at (866) CALL-DPT or visit **www.dptlabs.com**.

Pharma Polymers

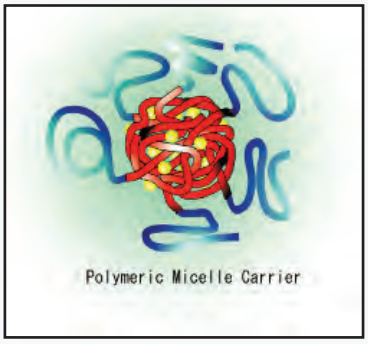
Evonik Industries is a global market leader in specialty chemicals, offering a broad portfolio of products and services to meet the drug delivery challenges of the pharmaceutical market. Evonik Pharma Polymers manufactures EUDRAGIT® acrylic polymers used for enteric, sustained-release, and protective formulations. The unique functionality of EUDRAGIT polymers can also meet high sophisticated drug delivery requirements (eg, pulsed drug release). We have adapted our services to meet the requirements of the pharmaceutical industry's value chain. As a result, we are able to support our customers in the development process to bring products safely and quickly to the market. From excipients supply to the development of custom tailored drug delivery solutions, our customers benefit from our knowledge and expertise. For more information, contact Evonik Degussa Corp., Pharma Polymers at (732) 981-5383 or visit **www.eudragit.com.**

Injection Devices

Haselmeier is a leading designer and manufacturer of pens and autoinjectors for injectable pharmaceuticals with more than four decades of experience. Combining technology, function, and design, Haselmeier offers innovative and flexible platform technologies of disposable and re-usable self-injection delivery systems with many featuring a unique hidden needle design. Working with pharmaceutical companies worldwide Haselmeier develops injection devices of outstanding quality and performance to ensure comfortable and safe injections and meet the requirements of the product and patient. For more information, contact Haselmeier at info@haselmeier.com or visit **www.haselmeier.com.**

Technology Showcase

Activated PEGs



NOF supplies various kinds of high-pure activated polyethylene glycol (PEG) derivatives with MW from 2 kDa to 80 kDa. The activated PEGs are suitable for PEGylation of proteins, antibodies, and small molecules. Various alternations of terminal ends enable pharmacokinetic scientists to specifically modify their APIs. NOF is capable of manufacturing these PEGs from small reagent scale to large commercial quantities under cGMP conditions. NOF has been accelerating platforms of new DDS technologies and materials and collaborating with prominent universities that have leading-edge technologies as follows: (member of the FRP of California NanoSystem Institute at UCLA and a license on polymer micelle technology for gene delivery). For more information, contact NOF Corporation at ddsinfo@nof.co.jp or visit **www.dds-drug.com.**

Silicone Materials

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

Development & Delivery Solutions

Founded in 1991, Particle Sciences is an integrated provider of both standard and nanotechnology approaches to drug development and delivery. Through a combination of preformulation, formulation, analytic, bioanalytic, and manufacturing services, Particle Sciences provides clients with a powerful, integrated solution to most efficiently take a drug from discovery to the clinic. Each project has a dedicated team and leader to manage the project from start to finish. With years of experience to draw upon, Particle Sciences can confidently handle difficult APIs, complicated intellectual property terrains, and challenging delivery goals to arrive at the simplest, most efficient solution to the client's needs. For more information, contact Particle Sciences at (610) 861-4701 or visit **www.particlesciences.com.**

Passive Safety Device

In response to the continued concern over unprotected needle exposures and the mandated Safety and Prevention regulations, Rexam has developed a fully passive safety device for prefilled syringes: the Safe'n'Sound. The Safe'n'Sound provides healthcare industries and patients with full protection from needlesticks to avoid any contamination. Compared to a standard syringe, the Safe'n'Sound system guarantees passive protection as the syringe retracts automatically in the system after the injection without any action by the user. Compact, light, and transparent, the Safe'n'Sound has only three components (a sleeve, a body, and a spring). For more information, contact Rexam at (847) 541-9700 or visit **www.rexam.com/pharma.**

DRUG DELIVERY Executive

ENAVAIL: PARTICLE ENGINEERING SOLUTIONS FOR DRUG DELIVERY CHALLENGES

Brian Windsor, PhD
President

Enavail

"Where Enavail significantly fulfills market needs is in our superior technology that generates highly wettable, bioavailable, and potent compounds compatible with multiple routes of administration. Enavail meets the industry need for greater solubility, scalability, versatility, and potency in therapeutics across the spectrum. Our proprietary particle design technologies provide solutions that get molecules off the shelf and back into the pipeline."

Enavail, a particle engineering company founded on pioneering drug delivery research, provides solutions to the pharmaceutical and biotechnology industries through proprietary particle engineering technologies. The company has developed a portfolio of particle engineering platforms for increasing the bioavailability of poorly water-soluble drugs as well as for generation of dry powder forms of stable, highly active proteins and peptides. Enavail's proprietary particle design capabilities include novel, validated, and scalable technologies for use with multiple routes of administration - oral, pulmonary, intranasal, and parenteral. The patented technologies have been validated on more than 20 model compounds and in 35 peer-reviewed articles published in scientific journals. With state-of-the-art research and cGMP manufacturing facilities in Austin, Texas, Enavail currently offers clients initial drug screening through to Phase I and II clinical batch production, and plans to offer commercial manufacturing capabilities to coincide with customer's regulatory timelines. Drug Delivery Technology recently interviewed Dr. Brian Windsor, Enavail President, to discuss how the company is effecting change in drug delivery development through its innovative technologies.

Q: How does Enavail fit into the broad picture of the industry? What market need does Enavail meet?

A: Enavail meets the increasing industry need to address the challenges related to poorly water-soluble drugs. The World Health Organization (WHO) has identified that 30% of the drugs on its Essential Drug List are poorly water-soluble. Marketed drugs with poor and/or erratic bioavailability have a greater risk of adverse side effects. Not only are many drugs currently in the marketplace hampered by poor performance and low bioavailability, 40% or more of newly developed pharmaceutically active substances have solubility issues. The poor wetting and dissolution of these drugs often result in low and highly variable bioavailability. The major obstacle of successfully commercializing these compounds is the difficulty of enhancing their dissolution rate and extent of dissolution, and hence their bioavailability.

New drug discovery and development at pharmaceutical companies is often halted when a promising New Chemical Entity (NCE) encounters solubility problems. Promising drug candidates often fail in their early development due to poor bioavailability. This is a critical challenge the industry faces. Because poor bioavailability affects a large number of marketed

drugs as well as new drug candidates, improving solubility can have a tremendous impact on NCEs, reformulations, and even biologics. Where Enavail significantly fulfills market needs is in our superior technology that generates highly wettable, bioavailable, and potent compounds compatible with multiple routes of administration. Enavail meets the industry need for greater solubility, scalability, versatility, and potency in therapeutics across the spectrum. Our proprietary particle design technologies provide solutions that get molecules off the shelf and back into the pipeline.

In addition, rising costs and shrinking pipelines have necessitated that Pharma adopt a leaner, more efficient approach to drug development. New drugs have become so expensive to develop that optimizing NCEs from every aspect, including the delivery system, is crucial in order to recover drug development costs. By contracting with Enavail for much of the work involving the development of appropriate delivery systems, our particle design capabilities provide clients with greater flexibility leading to more effective drug delivery. Our versatile technology offers custom, economical solutions to partners.

Q: How is Enavail's technology different and innovative?

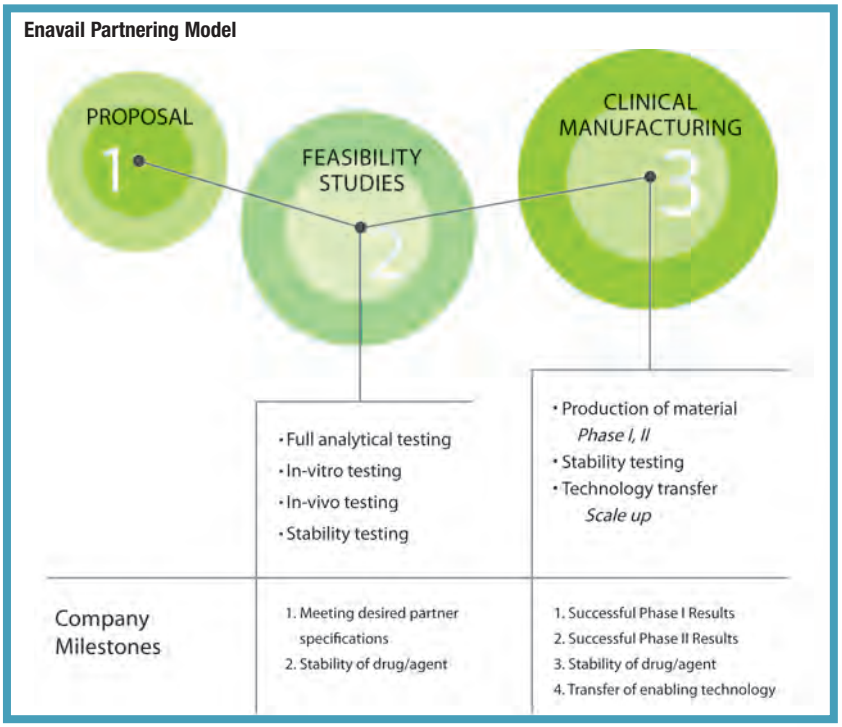
A: Our company was founded on the research of pharmaceutical scientist Dr. Robert O. (Bill) Williams III and chemical engineer Dr. Keith Johnston. Dr. Williams serves as Chief Scientist of Envavail. The breakthrough technologies are the subject of several pending and issued patents. While the company is new, Enavail's particle engineering technologies have been a decade in the making. The technologies have been utilized on more than 20 compounds delivering superior performance and key advantages important to each compound. Our technology has been further validated in numerous peer-reviewed articles published in US and international scientific journals, including the Journal of Pharmaceutical Sciences, Pharmaceutical Research and the Journal of Biomedical Nanotechnology.

We provide particle engineering expertise for increasing the bioavailability of proteinaceous compounds and poorly water-soluble drugs. Enavail uses a suite of proprietary, proven, and scalable technologies to focus on two key areas: 1) producing high surface area, non-degraded powder forms of labile proteins and 2) generating crystalline or amorphous forms of poorly water-soluble compounds, providing high potency and greatly enhanced wetting and dissolution. A highly controllable bottom-up approach is taken, allowing for precise control of particle size and polydispersity.

A host of problems exist with other particle technologies, including economic viability and scalability. Many employ harsh conditions, making them unsuitable for labile compounds. Other disadvantages include low potency and limitations on route of administration.

Our proprietary particle engineering technologies, Controlled Precipitation (CP) and Rapid Freezing (RF), provide for nanostructured drug particles with increased surface area that allows for enhanced dissolution of poorly water-soluble drugs and improved bioavailability. Administration of these compositions can produce high supersaturation levels rapidly in biological fluid. Oral administration of these compositions can target dissolution and supersaturation to the upper small intestine to provide enhanced

Enavail Partnering Model



bioavailability. Pulmonary delivery of these compositions can also provide improved lung local drug exposure and potentially reduce dose and systemic side effects. The flexibility and versatility of these processes allow for the use of a wide variety of FDA-approved and generally regarded as safe (GRAS) biodegradable and biocompatible excipients, which can also enhance the stability, patient compliance, safety, and therapeutic efficacy of these drugs.

Q: What are the competitive advantages of Enavail's technology?

A: Our most significant competitive advantage is that we offer versatile solutions to the challenges of poor solubility and bioavailability in drug delivery systems. We have multiple proven technologies that allow for a choice of morphology and particle size. Using our expertise, we can provide clients with the highest performing compound chosen from a range of engineered materials. In addition, the Enavail technologies allow for high bioavailability with very high potency - a great advantage over other technology systems. For example, many other processes for improving bioavailability produce a material that is only 20% to 50% drug with the remainder being composed of excipients or non-drug material. Enavail's technology, on the other hand, can deliver nanostructured materials with anywhere from 60% up to 100% drug.

Enavail's proprietary CP and RF processes provide our engineering team flexibility in designing a solution with the highest bioavailability, highest potency, and tailor made for the desired route of administration. Equally important is the Enavail technologies offer an economical and scalable solution for getting compounds to market. Particle engineering can allow for increased surface area and wettability for enhancement of bioavailability. Our CP process advantages include morphology capabilities - crystalline or amorphous, enhanced bioavailability and dissolution, controllable particle size, and choice of excipient. Enavail's RF technology uses a cryogenic substrate to create stable dry powders of drug compositions. Highly porous, amorphous, nanostructured morphologies enhance dissolution and thereby improve bioavailability for BCS Class II drugs. With no introduction of heat into the process, our RF process eliminates premature thermal degradation of APIs, a critical benefit for labile molecules, such as proteins and peptides. The process offers clients the advantages of amorphous morphology, enhanced bioavailability and dissolution, and the capability of producing dry active forms of labile proteins. Both RF and CP can deliver highly potent APIs.

Q: What is your partnering strategy? How does Enavail work with other companies?

A: We are specialists with a value-added business model. As a true specialist, we focus on just one thing: particle engineering for enhancing delivery of small molecule compounds, proteins, and peptides. We support client companies' efforts from drug discovery through development and into the clinical pipeline. Enavail seeks collaborative partners in drug development interested in screening, product development and clinical scale manufacturing. Co-development projects usually begin with feasibility studies for development of customer-tailored solutions directed to their specific active ingredient. These are followed by cGMP clinical batch production and licensing of Enavail technologies for commercialization of products.

Our screening studies for discovery stage molecules take into account the high cost of NCEs. That's why our discovery screening is designed to deliver enhanced material while utilizing as little API as possible - we can work with even sub-milligram quantities. The versatile Enavail processes allow for fast throughput while still taking advantage of the entire suite of technology solutions. This results in rapid assessment and optimization of lead compounds, and allows for effective lead compounds to move forward in development. Upon achieving superior-performing compounds using our particle engineering, we support clients' clinical efforts with our state-of-the-art cGMP facilities. We presently offer clinical batch production for compounds with application in pulmonary, parenteral, intranasal, and oral delivery. We also are planning for commercial manufacture.

Enavail's technology platform facilitates the drug delivery process from the earliest stages of research all the way through the development continuum to clinical applications. We plan to play a leadership role in better drug delivery, knowing the ultimate goal is new and better medications to improve patient outcomes worldwide. ◆

www.frost.com

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

Drug delivery technologies are an important part of the changing Pharma & Biotech industry. Feedback from patients and physicians, in terms of factors such as perception, desired attributes, compliance, and drivers of adoption/non-adoption for different drug delivery types, is therefore vital to developers. Is your company positioned to understand and take advantage of these opportunities for growth?

Frost & Sullivan's Pharmaceutical & Biotechnology group can provide your organization with the research and support it needs to fully understand end-users of Drug Delivery Technologies, and to identify and take advantage of the best opportunities for growth in this market.

Our expert Healthcare analysts:

- Provide objective, 3rd party analysis
- Identify a range of growth options
- Evaluate which options will produce the best Return on Investment
- Work with clients to develop effective implementation strategies

For more information on growth opportunities in the Drug Delivery market, please contact Johanna Haynes at johanna.haynes@frost.com.

FROST & SULLIVAN

SPECIALTY PHARMA
Strategies For Business Development

GCL Market Trends

Clinical Trial Outsourcing is a Win-Win for Pharma & CROs

By: Cindy H. Dubin, Contributor

The size of the global central labs (GCL) market is estimated to reach $1.6 to $2.3 billion this year, according to estimates from Barclays Capital in June 2009, as pharmaceutical and biotech companies outsource almost all central labs activities.

As lab budgets remain constricted, pharmaceutical and biotech labs are outsourcing preclinical services to create efficiency and off-load the need to maintain staff, instruments, and consumables for irregularly scheduled projects and projects that extend beyond their scope, states a new report from BioInformatics, LLC.[1] Increasingly, the model for drug development has the pharmaceutical industry devoting a large portion of its spending for late-stage clinical trials, according to a University of Rochester Medical Center study.

Barclays expects the GCL market growth to slow in coming years as overall growth rates for pharmaceutical and biotech R&D spending decrease. Although drug developers are improving R&D efficiency, in part by terminating more unpromising drugs earlier in development, their continued success will depend on how well they partner with other firms at specific points on the development spectrum, according to the Tufts Center for the Study of Drug Development (CSDD).

"Future success for many sponsors will depend on their ability to collaborate with other drug companies, and how well they engage and partner with outside service providers," says Tufts CSDD Director Kenneth Kaitin in connection with the release of the Tufts Center's Outlook 2010 report on pharmaceutical and biopharmaceutical trends. He says more firms will focus on improving clinical protocol design to help reduce trial costs and speed development cycles and to mitigate a trend toward increased protocol complexity.

Specialty Pharma magazine asked two of the industry's top central labs about the benefits derived from partnering with them, their role in drug development, and the work they are being asked to perform for today's pharma and biotech organizations. The roundtable participants include Susan Johnson BS MT(ASCP), Director, Clinical Trials Services, PRL Central Laboratory Services; and Steve Lobel, PhD, Vice President, Global Laboratory Operations, PPD, Inc.

Q: What has been the biggest driver for Specialty Pharma to use a central lab in clinical trials? And what is the greatest benefit to Specialty Pharma?

Ms. Johnson: Standardization of procedures across all participating study sites is a significant driver behind the proliferation of the Central Laboratory Services delivery model. Costs associated with harmonizing data from multiple sources, plus the management of multiple laboratory facilities creates an unnecessary burden on Specialty Pharma companies. The successful central lab will assume responsibility for all aspects of the laboratory service and provide necessary updates and information as required by Pharma.

Dr. Lobel: In addition to significant cost and time savings generated from using a central lab, Specialty Pharma requires a single, global platform to access and manage their clinical trial data in as near real-time as possible. PPD is able to provide clients with this platform through PPD Clicks™, which delivers near real-time lab data from our global central lab facilities in Highland Heights, KY; Brussels, Belgium; Beijing, China; and Singapore. All of our labs have the same equipment, standard operating procedures, and calibrators, and there is no type of harmonization of data needed. Regardless of which lab is conducting the testing, our clients have the ability to view, sort, and filter all lab data quickly and easily to create customized reports.

Q: How critical is a central lab's participation in clinical trials for new drug development?

Dr. Lobel: As clinical studies become more complex, the central lab's participation in clinical trials becomes more important. Pharmaceutical companies want to get the most out of their clinical data to avoid additional testing once a drug has been submitted for regulatory approval. As a result, more innovative, collaborative partnerships are forming between biopharmaceutical companies and CROs with global laboratory expertise.

Last year, PPD entered a strategic collaboration with Merck & Co. in which we purchased its vaccines and biologics testing laboratory in Wayne, PA. The biologics and vaccines markets are among the fastest growing segments in the industry. The acquisition expanded our global central laboratory business, adding world-class vaccine and biologics testing, assay development, and sample storage capabilities to our current suite of laboratory services. As part of the agreement, Merck has committed to spending $400 million with PPD global central and vaccine labs throughout the next 5 years, and we are Merck's exclusive provider of vaccine testing services and major supplier for global central laboratory services.

The agreement demonstrates an innovative approach to delivering high-quality, reliable, and timely laboratory services and data to key biopharmaceutical companies. We continue to invest in our lab by developing new technologies and assays to expand our immunochemistry and oncology vaccine testing services.

Ms. Johnson: Central laboratories participation is vital to the drug development process. Laboratory science is changing rapidly, and the central laboratory is an invaluable resource to ensure that the most current assays are selected to support protocol objectives. Laboratories also provide critical technical information to support the data that has been observed during a trial and assist with queries from the regulatory agencies. Keeping abreast of the transport and logistical challenges associated with different geographical regions is part of the daily routine for a central laboratory. These regulations change frequently, often with very little notice, creating a potential snare for very busy pharmaceutical project managers. The central lab will ensure that all study sites have the proper materials and documents to ship the required sample matrix.

Q: With biomarkers making up a majority of the work a central lab performs in clinical trials, how has this affected the types of services you need to offer?

Ms. Johnson: The heightened reliance on biomarkers in clinical research requires us to be much more nimble and able to adapt our test menu quickly. Our Clinical Pathology team is available to assess appropriate markers based on the target mode of action of the compound under investigation. Flexibility is the key here, with appropriate instrument systems and processes in place to accomplish rapid validation of an assay, resulting in a high-quality dataset.

With the changes looming to the healthcare system in the US and the movement to promote personalized medicine, the development of biomarkers to predict treatment success for a new drug may be beneficial to obtaining a spot on the formularies of third-party prescription drug payers.

Dr. Lobel: PPD brings more than 20 years of central laboratory expertise to our clients. We offer a comprehensive suite of laboratory services, which includes cGMP, bioanalytical and global central lab facilities, and a biologics and vaccine testing laboratory where we offer a comprehensive menu of assay development and testing services for vaccine clinical trials.

Given the importance of biomarker testing in drug development, we have tremendous expertise in assay development and have expanded our partnerships with biopharmaceutical companies by developing, qualifying, or validating specialized assays using a variety of high-technology platforms and tools. We are extremely flexible in how we work with our clients. Our clients may choose to use assays we develop, or we can work with our clients to validate their new assays using standard and specialized platforms and techniques. Validation of assays supports analysis of biomarkers and helps our clients better understand how assays will perform for regulatory submission. In addition, for inflammation, autoimmunity, immunodeficiency, and oncology indications, we routinely use flow cytometry to evaluate how drugs are impacting immune and cellular response.

While pharmaceutical labs usually oversee the identification and development of assays, they increasingly rely on us as compounds move through development. Phase II and III studies often require the analysis of thousands of samples, and we work closely with our clients during these phases to analyze and run assays to determine key indicators for a drug's efficacy. Our bioanalytical group is equipped to validate and test specialty assays that run on LC-MS/MS platforms.

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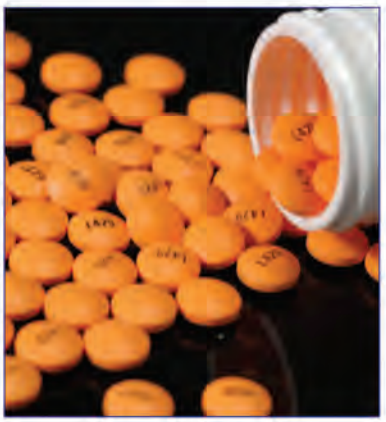

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The First Choice in Industry Market Research

Q: As clinical trial testing increasingly goes global, please explain how your central lab has established itself as a global player?

Dr. Lobel: In 2008, we expanded our global central lab capabilities into China through an exclusive agreement with Peking Union Lawke Biomedical Development Limited (PUL). The agreement allowed us to immediately provide biopharmaceutical clients in China with our full range of highly customized central lab services. It is extremely difficult to export lab samples to other countries for testing, and this agreement saves our clients time and money by giving us the capability to provide results more quickly without incurring expenses for exporting shipments.

Last year, we also expanded our central lab operations into Singapore, which strengthened our ability to provide clients an extensive range of customized laboratory services in Southeast Asia, a high-growth region for clinical research. Within weeks of opening this facility, we are already adding new assays and ordering new instrumentation to support flow cytometry and specialized lipid testing. In addition, we have central lab facilities in Highland Heights, KY, and Brussels, Belgium, to serve our North American and European clients, respectively.

We are also expanding our cGMP analytical testing services by opening a laboratory in Athlone, Ireland, to meet growing client demand in Europe, the Middle East, and Africa (EMEA) for these services. The facility will open in the first quarter of this year and offer method development and validation, stability, and quality control testing for all phases of drug development, with particular emphasis on inhalation and biopharmaceutical products. This facility builds upon the capabilities of our cGMP lab in Middleton, WI, and the bioanalytical facilities in Middleton and Richmond, VA. We continue to identify targeted areas for expansion where we plan to build fully owned laboratory facilities based on client demand.

Ms. Johnson: We have partnered with a global laboratory network, having members strategically placed around the world. Harmonization of procedures, cross-validation of laboratory assays, and the presence of one global database system link all data together. We assign a Global Project Manager to be responsible for communications with each partner, with frequent communication regarding study progress. Having experienced, local staff in each region erases language barriers and makes for a more comfortable interaction with the local investigator sites.

Q: What is the one message you would stress to Specialty Pharma players about the relationship between them and the central lab in carrying out clinical trials?

Dr. Lobel: By beginning work with our clients early in the development process, we are able to develop a complete understanding of priorities, such as speed, costs, or logistics. Our comprehensive lab capabilities and flexibility in working with our clients allow us to deliver on time and according to our clients' specifications. Our goal is to get a safe, effective drug to market as quickly as possible, and time is important to each client with whom we work. Our ability to plan early allows us to create significant time savings for clients in design and start-up and later in the database lock process. By remaining flexible throughout the project, we can meet specific protocols, data reporting, and management information requirements.

Ms. Johnson: Everyone emphasizes open lines of communication, but to take that further, it is important to view the central laboratory as your partner. A successful trial has many moving parts that require synchronization. If the central laboratory understands the objectives and has the opportunity to suggest the best possible means to meet those objectives, the success rate will go way up. Each vendor engaged by the pharma company must be aware of how their piece of the project impacts others. We must all understand that perfection is not always possible, but the approach to issues resolution can greatly minimize or eliminate any potential damage. Trust and transparency are paramount. ◆

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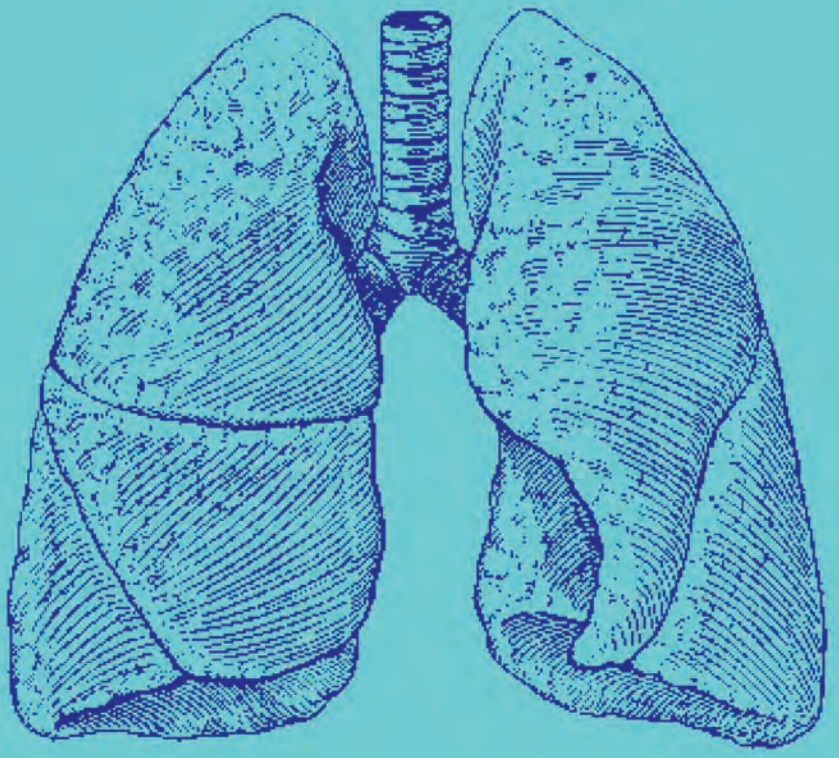

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Pharmacogenomics

Pharmacogenomics & Drugs: Now it's Personal!

By: Katheryn Symank, Research Analyst II Pharmaceutical & Biotechnology Healthcare, North America, Frost & Sullivan

Introduction

The incidence of adverse drug reactions in the US is shockingly high. According to the AMA, there were 2.2 million such events after administration of FDA-approved drugs in 1996. Moreover, it is one of the leading causes of death and hospitalization.

Physicians have known for years that not all patients have the same response to medications. While some patients may experience a therapeutic response to a drug, others may have a detrimental reaction or may not respond to the treatment. More than 20 years ago, scientists determined this phenomenon could be explained by inherited variations in our genes. From this realization, pharmacology and genomics were combined to form a new field of study called pharmacogenomics, which aims to develop safe and effective medications that can be personalized to a patient's genome. This field could eliminate or greatly reduce the incidence of adverse events. In addition, this emerging field may allow for improvements in the drug discovery process that results in decreased development time and cost.

Pharmacogenomics

According to the AMA, pharmacogenomics is the study of how a person's genetic makeup affects their response to drugs. This is accomplished by analyzing variations in the human genome called single nucleotide polymorphisms or SNPs. SNPs are variations in a DNA sequence that come from a change in a single nucleotide. To be categorized as an SNP, there must be two or more versions of this variation present in at least 1% of the population. Scientists estimate there are more than 10 million SNPs in the human genome. Several organizations are working together to compile all of the identified SNPs into databases and make them available to the public. Although mostly harmless, some SNPs have been associated with certain diseases and individual responses to drugs.

Current Applications

Currently, pharmacogenomics is only marginally used in day-to-day medical practice. This technology is mainly used to help determine the appropriate dose of specific medications for patients who have certain genetic variants. Pharmacogenomic testing is also used as a tool to determine if a patient would benefit from a specific medication. In terms of new drug development, a large amount of companies are gathering genomic data to develop more effective medications and to identify appropriate patient populations (Table 1).

Typically, physicians determine the dosage for a medication using pharmacokinetic information that was determined for the average patient and then factor in variables such as age, weight, and liver function. Although this method works for the majority of patients, it is not effective in patients who have particular genetic variations that affect their response to certain drugs. For example, genetic polymorphisms in the expression of the enzyme CYP2CP may affect the breakdown of certain medications. The CYP2CP enzyme is responsible for the metabolism and elimination of more than 100 drugs, including non-steroidal anti-inflammatory (NSAIDS) drugs, some anti-depressants, anti-convulsants, and anti-coagulants. A specific example of this phenomenon is with the blood thinner warfarin whose activity is

Selected Pharmacogenomic Tests

Gene	Drug	Variants Tested
ABL1	imatinib & dasatinib	BCR-ABL
BCR	imatinib & dasatinib	BCR-ABL
CYP2C9	warfarin	CYP2C9*2 & CYP2C9*3
CYP2C19	Including clopidogrel, esomeprazole, omeprazole & phenytoin	Including CYP2C19*1, CYP2C9*2, CYP2C9*3, CYP2C9*4, CYP2C9*5 & CYP2C9*6
CYP2D6	Including codeine, fluozetine, metropolo, risperidone & tamoxifen	Including CYP2D6*1, CYP2D6*2ABD, CYP2D6*3, CYP2D6*4ABDJK, CYP2D6*5 & CYP2D6*6ABC
DPYD	capecitabine, 5-fluorouracil	IVS14+1 G→A, DPYD*2A
EGFR	erlotinib & gefitinib	Including T79M, L858R, L861Q & G719X
ERBB2	trastuzumab	ERBB2
HLA-B	abacavir, carbamazepine & phenytoin	HLA-B*5701 & HLA-B*1502
HLA-DQB1	clozapine	HLA-DQB1:G6672C
KRAS	cetuximab & panitumumba	Including KRAS:Gly12Asp, KRAS:Gly12Ala, KRAS:Gly12Val, KRAS:Gly12Ser & KRAS:Gly12Arg
TPMT	azathioprine & mercaptopurine	Including TPMT*2, TPMT*3A & TPMT*3C
TYMS	capecitabine, 5-fluorouracil	TYMS:2R, TYMS:3R & TYMS:4R
UGT1A1	irinotecan	UGT1A1*28
VKORC1	warfarin	VKORC1:G-639A

Table 1.

determined by several factors like weight, age, and genetic factors. Patients who have polymorphisms to the gene for the CYP2CP enzyme have altered warfarin metabolism. The most common variants seen are CYP2CP*2 and CYP2CP*3, which results in poor metabolism of this drug. Variations in the gene for VKORC1 enzyme are also known to affect warfarin metabolism. Patients with certain variations to VKORC1 are at higher risk of an anti-coagulant overdose. According to the FDA, warfarin sends 43,000 patients to the emergency room annually, making this drug the second leading cause of emergency room visits for adverse drug reactions. As a result, in August 2007, the FDA mandated an updated label for warfarin advising that genetic screening could prevent many adverse events. However, the FDA is not requiring genetic testing for this medication. Even so, an increasing amount of physicians are starting to use their patients' pharmacogenomic status to adjust their warfarin dosage.

Another example is with the drug Plavix (clopidogrel). Patients with a less active variation of the CYPC2C19 gene, an enzyme that metabolizes Plavix, experience reduced plasma exposure to the drug. In one study, it was estimated that 30% of patients have this less active variant.[1] In another study, patients taking Plavix that had this variation had a significant increased risk of death from a cardiovascular event.[2] In July 2009, the FDA required an updated label for Plavix informing of the pharmacogenomic data, but did not require updated dosing guidelines.

Pharmacogenomic testing can be used to determine the best drug to treat particular diseases like cancer. Research indicates that certain anti-oncolytics only work in patients who have specific genetic variations, while others will not work if certain anomalies are present. One example is with the medication Tarceva (erlotinib) that targets the epidermal growth factor receptor's (EGFR) tyrosine kinase domain, which is often over-expressed in certain cancers like non-small cell lung cancer (NSCLC) and pancreatic cancer. These drugs work by interfering with tumor growth through the inhibition of tyrosine kinase enzyme, which is associated with EGFR. It has been reported that the overall response rate to Tarceva is only 10%. However, in patients who have an EGRF-positive tumor, the response rate is 60%. Some patients whose tumor tests positive for EGFR may have additional mutations in the KRAS gene, which makes them resistant to Tarceva. Genetic tests are available for both of these genetic variations and can be used as a tool to determine an appropriate treatment plan.

Pharmacogenomics can be an invaluable drug discovery tool. This technology can be used to better understand how a compound specifically affects a disease's pathway and examine potential toxicity limitations. It can also help identify novel biomarkers and targets. Some experts believe pharmacogenomics may even be able to help resurrect drugs that have already failed. One major pharmaceutical company investing heavily in pharmacogenomics is Pfizer Inc. In August 2009, the company announced a partnership with Abbott to make a molecular diagnostic test to screen for the genetic variations c-MET and ALK. Both of these variations are found in some patients with NSCLC. This diagnostic test would be a

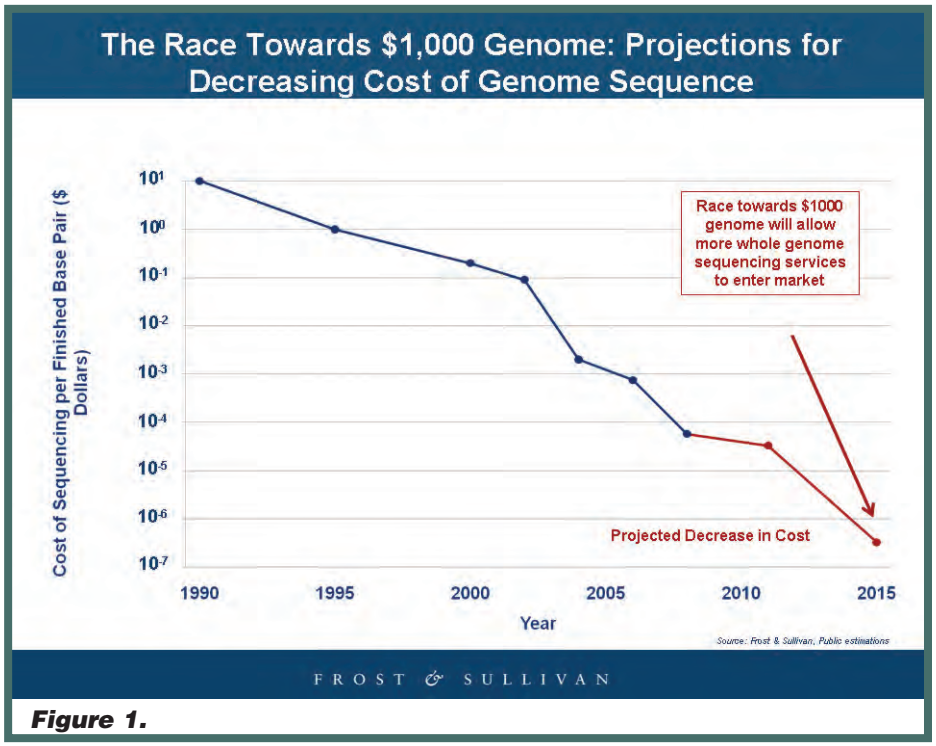

Figure 1.

companion to Pfizer's investigational medicine PF-02341066, which is designed to target these anomalies. Research indicates that PF-02341066 only works in patients who have these specific genetic variations. As a result, the development of a companion diagnostic test could be an important factor to the success of this treatment.

Reimbursement

High cost is major hurdle to wide use of pharmacogenomic testing. Currently, the majority of patients who receive genome testing do not have their entire genome sequenced. Instead, patients are tested for specific genetic variations with costs ranging from $250 to $1,000. The principal concern of patients is coverage–will this test be covered?

The majority of payers cover pharmacogenomic testing if it is considered a part of standard clinical practice or is deemed medically necessary. One such example is the HER2/neu test, which is recommended by the National Comprehensive Cancer Network for all cases of invasive breast cancer. This test helps determine if a patient's cancer is the more aggressive HER2 positive variety, which accounts for 20% of all breast cancer cases. If the patient's test result is HER2 positive, then she may benefit from treatments that target the HER2 protein like Herceptin. Moreover, patients with HER2 positive cancer who took Herceptin had improved life expectancy compared to other standard treatments. For most payers, the HER2/neu test is not only medically necessary, but cost effective. This is because the cost of the HER2/neu test is only $150 compared to the over $50,000 cost of Herceptin. Therefore, the test aids in the identification of the optimal patient group for usage of that drug.

As of yet, other pharmacogenomic tests are not commonly reimbursed. This is typically for genetic tests that have limited clinical outcome information. Case in point is the test for warfarin. The Centers for Medicare and Medicaid Services announced in May 2009 it would not pay for genetic testing for warfarin because "available evidence does not demonstrate that pharmacogenomic testing to predict warfarin responsiveness improves health outcomes in Medicare beneficiaries." It is expected that most other payers will have similar policies with coverage tending to depend on standard of care.

The $1,000 Genome?

The cost of sequencing a complete human genome, all 3 billion base pairs, is significantly more expensive than the cost of screening for a few specific variants, ranging from $50,000 to $250,000. Although this is much less than the $3 billion spent to complete The Human Genome Project, it is still too high for routine use.

In 2001, the prediction was made by scientists that in 10 to 15 years, technology would have progressed to the point that a person's entire genome could be sequenced for $1,000. In 2004, the National Institute of Health Genome Services announced that it was awarding more than $38 million in grants to bolster technological advances to reach this $1,000 goal. Other organizations are offering similar grants and awards. One such award is the $10 million Archon X PRIZE for Genomics that was announced in 2006. This prize is to be awarded to the first group of researchers who can accurately map out the genome of 100 people in 10 days for $10,000 or less. With these types of incentives, several companies and organizations are racing to develop a lower cost genome sequencer (Figure 1).

One such company is Illumina, Inc., a leading developer of innovative systems for large-scale analysis of genetic variation. The company's Personal Genome Sequencing

Service announced in June of this year that it is able to sequence a person's genome for $48,000. This represents a significant milestone in pharmacogenomics as this is the first company to offer this capability for less than $50,000. The Personal Genome Sequencing Service uses the company's proprietary Genome Analyzer Technology and is able to sequence a genome to a depth of 30.

Another leading company in genome sequencing is Pacific Biosciences, a biotechnology company headquartered in Menlo Park, CA. The company is developing a transformative Single Molecule Real Time (SMRTTM) DNA-Sequencing platform. This technology uses the SMRT chip, which represents a vast improvement over single-molecule detection technology, specifically 1000-fold. The company has announced plans to commercially launch its machine in 2010.

Legislation

While many support increased use of pharmacogenomic testing, some oppose its use because of privacy concerns. As pharmacogenomic testing may reveal a person's risk for certain diseases, some argue that widespread use may result in potential for discrimination in terms of employment and health insurance coverage/rates. As a result, the Genetic Nondiscrimination Act of 2008 was passed. This act is designed to protect Americans from discrimination from the results of their genetic tests and to encourage people to take advantage of pharmacogenomic testing.

Several bills have been introduced to encourage use of pharmacogenomics. The most recent is The Genomics and Personalized Medicine Act of 2008. This bill, introduced by Congressman Patrick Kennedy, is an updated version of The Genomics and Personalized Medicine Act of 2007, introduced by then-Senator Barack Obama. One of the initiatives of this bill is to bolster the progress of personalized medicine and pharmacogenomics through funding and tax incentives. It also aims to create the Genomics and Personalized Medicine Interagency Working Group to facilitate genomic research guidelines and policies. In addition, the bill proposes the start of a National Biobanking Initiative to create databases to house genomic data. This bill never became law.

Summary

Increasing use of pharmacogenomics in both drug discovery and clinical applications are changing our approach to medicine. Whereas once medications were viewed as one-size-fits-all, now technology exists to customize therapies. Although still not widely used in prescribing medications, it is inevitable that pharmacogenomics will play a major part in healthcare in the future. As former Senator Obama said when introducing the Genomics and Personalized Medicine Act, "We are just beginning to realize the full potential of this science to predict the onset of disease, diagnose earlier, and develop therapies that can treat or cure Americans from so many afflictions." ◆

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Kathryn Symank

Research Analyst,
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Kathryn Symank is a Research Analyst with the Frost & Sullivan North American Healthcare team. She focuses on monitoring and analyzing emerging trends, technologies, and market behavior in the Pharmaceutical and Biotechnology industries. Since joining Frost & Sullivan in February 2007, Mrs. Symank has completed several research studies and consulting projects with recent works focused on monoclonal antibodies, stem cells, osteoporosis, lifestyle disorders, and respiratory diseases. Prior to joining Frost & Sullivan, Mrs. Symank worked for 7 years in pulmonary pathology at the University of Texas Health Science Center in San Antonio, where she studied bronchopulmonary dysplasia. She earned her BS from Texas A&M University in Molecular and Cell Biology and her MS from the University of Texas at San Antonio in Biotechnology.

March 2010

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Crossing Over to Management

By: Brian Langille, MA

If we are fortunate enough to gain work-related experience from a few employers after college, we can become quickly tracked into a profession, such as the pharmaceutical sciences. You may be a scientist currently working in the R&D area of a pharmaceutical company, doing compound formulation development or drug solubility work. Your environment may be a laboratory and, for a number of reasons, you may be wondering whether you can transition into a management role. You have several options to consider, but first you have to do a self-assessment. Is the management job that interests you in your department, another department, or at another organization? You also have to recognize the transferable skill sets, knowledge, and personal attributes you have, which requires some introspection on your part. Does your profile as a potential candidate overlap with the requirements of the job you seek? If it does, then you have some leverage. The greater the overlap, the less the transitional preparation required. If an employer is looking for a specialist, they are often willing to hire you with minor deficits in experience or knowledge, especially if you show the aptitude and confidence to learn quickly on the job. Otherwise, a career change may require a bit more education, training, experience, or credentials before you approach potential employers.

Let us begin from a position of strength within you current organization. You know the science behind the products your company manufactures. The obvious place to go first is the human resources department. They should have an excellent 30,000-foot view of opportunities across your company. If you haven't already, find a senior manager to be your mentor. Show a sincere admiration for their achievement, and they will tell you anything you want to know about how to get ahead at your company. Another way to identify an opportunity and develop an advocate within your own company is to participate in interdepartmental meetings with marketing, sales, QC/QA, packaging, purchasing, and manufacturing. You can network and learn a lot about the other departments and how your strengths overlap with their needs. Sign up for any in-house management development programs you can, such as leadership training, public speaking, strategic planning, and budgeting. This expertise will serve you well for the rest of your life, especially in a management role. Take the initiative to let key people know that you are willing to accept greater responsibility.

If you are extroverted, personable, and have excellent communication skills, one way to enter the management side of the business is through the training department. You can teach customers, the sales force, technical services, and the marketing department the greatest scientific attributes of your products versus the competition. Training customers in the field is very similar to selling in the field, and a sales career is usually the most lucrative track to take if compensation is important. Therefore, if you like training individuals or small groups, you should try sales. If you have the right personality and know your products and the end-users in the market, then all that is needed is a selling skills course. There are many that teach everything from prospecting, qualifying an account, and probing for objections to overcoming objections, closing the sale, and follow-up. In my opinion, a sales position is one of the best stepping stones to senior management. Many CEOs are fast-tracked up the proverbial ladder through sales or marketing because these people know the products, the target customers, and the competitors well.

You can also leverage your product knowledge to write technical copy for the marketing or packaging departments, as well as ad agencies. You may start as an assistant brand or product manager, leveraging your product knowledge. You would need to sell them on your capacity and willingness to learn the other side of the job, such as writing marketing plans and budgeting. You will need to give persuasive presentations, beginning with the reasons they should let you transition into management. Just know this. The focus of future companies will not be their products, but rather their customers, especially for companies in the business-to-business markets. The goal is to develop long-term sustainable customer relationships. You can't know enough about your customers, so areas of the company that focus on consumer behavior or market research may be stepping stones as well, especially for less outgoing personalities. These jobs require good analytical skills, and there is no doubt that anyone working in the sciences has this skill set. The technical support department might be a way to get away from the lab bench, but in certain industries, this is outsourced to people in Mumbai, India. As you pursue these jobs, keep in mind that most of them will involve managing several direct reports. If you are in a solitary research function, it will be very difficult to be a credible candidate for a job that manages numerous employees, unless at some time in your employment history you supervised several people. I would point this out.

Now let's look outside your company. You know your way around a lab and use scientific products, such as instrumentation, equipment, supplies, etc. If you are willing to leave your company, you can target the manufacturers of the branded products in your lab. You know what attributes make their products and their competitors' products better or worse. You are an unbiased end-user, and because customer relationship management (CRM) has become the focus for most companies, you can provide valuable insights. If you show the desire to join such a company in the capacity of a department manager, you would represent a true customer endorsement of their products and the ultimate form of brand loyalty. They will have management positions in all areas, and you can research this on their websites or network through manufacturer sales representatives that call on you to sell you their products. This is your best bet.

Outside of the company, there are also management positions with vendors, such as suppliers, ad agencies (traditional and interactive), public relations firms, consulting services, industry associations, not to mention competitors who would love to get their hands on you and might therefore be willing to accept management skill deficits to woo

you away. They are another good employment option. I would only follow this course of action if your current employer didn't make any effort to develop you into a manager or actively counsel you on opportunities within the organization. If you choose to leave, never negatively criticize your past employers or divulge any proprietary information to your prospective employers. They should respect such professionalism; otherwise they may not be the people you want to work for.

Don't let anyone tell you that you can't go from the laboratory to the management side because you don't have an MBA. I made this transition and got to be a division president without an MBA, and here is an interesting fact. Thirty-six of the top 50 CEOs at large global public companies, according to the January/February 2010 issue of the Harvard Business Review, don't have their MBAs. These are the highest caliber performers. What they do have is the leadership skills to deliver results.

I have reinvented myself twice in my life. Maybe I am just adaptable, you might say, but it takes personal initiative and retraining to accomplish this. I earned my BS in the biological sciences. I began my working life as a manufacturing chemist with a firm manufacturing allergenic extracts and then as a clinical microbiologist, working in a laboratory for the Department of Health. During this time, I completed my Masters in the biological sciences, with a concentration in microbiology. After 4 years of working in a laboratory, it was time to look closely at my financial needs and career track. I took stock of myself. I had a comprehensive understanding and education in the biological sciences; I had work experience in a laboratory with scientific products. I was personable, well spoken, conscientious, and organized. Here I was working in the bacteriology department of a laboratory, and my director was encouraging me to earn my PhD in clinical microbiology. This was a track that may have led to a position conducting scientific research for a private corporation or government lab, a clinical laboratory directorship, or a teaching position in academia. I was at my first cross-road. Should an outgoing person like me continue to sit behind a microscope in a white lab coat, have little interaction with people, and earn what I earned? Instead, I responded to an ad in the New York Times for a Manager of Promotion and Market Planning with a corporation manufacturing a line of medical diagnostics and microbiological products in Cranbury, NJ. Now, it's networking and internships, not ads, which lead to new opportunities. The Director of Marketing at this prospective employer was willing to provide on-the-job training, which they referred to as "baptism by fire" in those days. I was to teach him, his customers, and sales force the scientific principles behind each of their products. He was to teach me marketing and basic product management. This hire was driven by the fact that this Director of Marketing believed he was at a disadvantage at department meetings with R&D and QC/QA because he didn't understand the science behind his product line. This deficit also impeded the direction of his ad agency regarding technical ad copy. So hiring me would essentially create an alliance of two, integrating our scientific and marketing knowledge. So my business career began as I left the safety of a civil service laboratory position and leaped, with some trepidation, into a world of corporate offices and ad agencies. After that job, I briefly sold biological and medical diagnostics and then went on to work for an industrial advertising agency as an account manager. My agency clients were companies manufacturing analytical instrumentation, scientific equipment, and chemicals. This was a very creative job, so I had my reservations when I was recruited by a small family run publishing company to launch a scientific publication, titled, *LC Magazine*, later renamed by me as *LCGC Magazine*.

Yes, it was a technology -based trade journal devoted to analytical chemists working with chromatography equipment. Do you notice a common denominator from job to job? I was leveraging my scientific education and work experience with my recently acquired marketing, sales, and advertising experience. Remarkably, everything came together despite the fact that I started out without any specific direction.

I was so successful that I quickly rose through the company to eventually become a Vice President and General Manager of the east coast operation, which included publishing *Pharmaceutical Technology*, *Pharmaceutical Executive*, *Applied Clinical Trials*, *Spectroscopy*, *Biopharm and LCGC Magazines*. To make a long story short, our small company was acquired by a large corporation, and I was promoted to a Group Vice President with additional titles. Six years later, I left and joined a larger multinational corporation, where I was the Group Vice President of a $66-million group of publications. None of these titles or conferences were scientific in nature. After a couple more senior management roles, I ended my career as a division President for a smaller corporation. I travelled extensively around the world overseeing international publications and conferences. After living through several downsizings and reorganizations since 2000, I decided to leave Corporate America to pursue consulting and another career track I always thought I would love, teaching. That is another story, but now I am a professionally qualified assistant professor at a university. Who knows, maybe my love of writing will lead to the next great American novel and a fourth career track. The point is anything is possible if you open your eyes to the opportunities. Good luck! ◆

BIOGRAPHY

Brian Langille is an Assistant Professor in the Marketing Department at Montclair State University and a former B-to-B media executive with 30 years of experience managing $20- to $70-million businesses for multinational and entrepreneurial companies. He managed global magazines and conferences, clinical diagnostics, and scientific products. The magazines were published in a range of industries from the analytical and pharmaceutical sciences and advanced technology to the construction, hospitality, and chemical industries. The bulk of his career was spent as a group Vice President, and recently a division President. Mr. Langille has an outstanding record of driving revenues, exceeding profit objectives, and leading high-performance sales teams. He launched numerous products, managed turnarounds, led reorganizations, and integrated acquisitions. He still projects high-energy and leadership as a teacher and consultant. He earned his BS from SUNY at New Paltz and his MA from Hofstra University in the biological sciences. He also completed advanced management training at Templeton College, at Oxford University.

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Deliver Incompatible Compounds
Deliver incompatible compounds in a single dosage form with different release profiles.

Multiple Release Profiles
Incorporate one or more release profiles into a single dosage form such as immediate, enteric, targeted, chronotherapy and pulsatile.

Higher Perceived Value
Consumers view multi-phase, multi-compartment capsules as having a higher perceived value than ordinary tablets, capsules and soft gels.

Choice of HPMC or Gelatin Capsules
With multi-phase, multi-compartment capsules you are not limited to just gelatin (animal-based product) but have the option of natural HPMC (hydroxypropyl methyl- cellulose) and alternative capsule materials.

Better Visual Appeal
Multi-phase, multi-compartment capsules have none of the dust and residue associated with powder capsules. Better visual product appearance translates to higher perceived value.

Increased Absorption and Bioavailability
Liquids naturally offer faster and increased absorption and availability of active ingredients.

Increased Profit Potential
Add up all the advantages. Expect higher sales…and high margins!

Multi-Phase System
Compounds can be delivered with the most advantageous pharmacokinetic profile such as liquids and solids

Faster Development
Multi-phase, multi-compartment capsules reduce the development time compared to bi-layer tablets to get a new product into clinical trials faster.

Smaller Capsules
Hard-shell capsules have thinner wall construction, allowing them to contain more ingredient in a smaller capsule versus thicker-shelled soft gel capsules. Hard shells have faster and more complete dissolution than soft gels.

Less Odor and Less Irritation
Reduces unpleasant ingredient taste and odor commonly found with tablets and traditional capsules. And, liquids provide less irritation than traditional delivery methods.

Tamper Proof Sealing
Band sealing reduces tampering and provides a non-permeable barrier to retard oxidation and increase shelf-life.

Unique Appearance
This new delivery system stands apart from look-alike products that crowd retail shelves.

Compounds
Deliver Pharmaceutical, bio-pharmaceutical and nutraceuticals in a single dosage form.

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