Drug Delivery Technology®

May 2010 Vol 10 No 4 www.drugdeliverytech.com

A Decade in Drug Delivery

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

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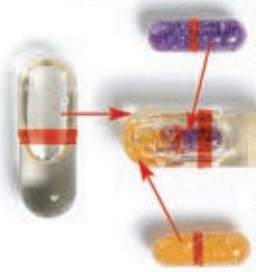
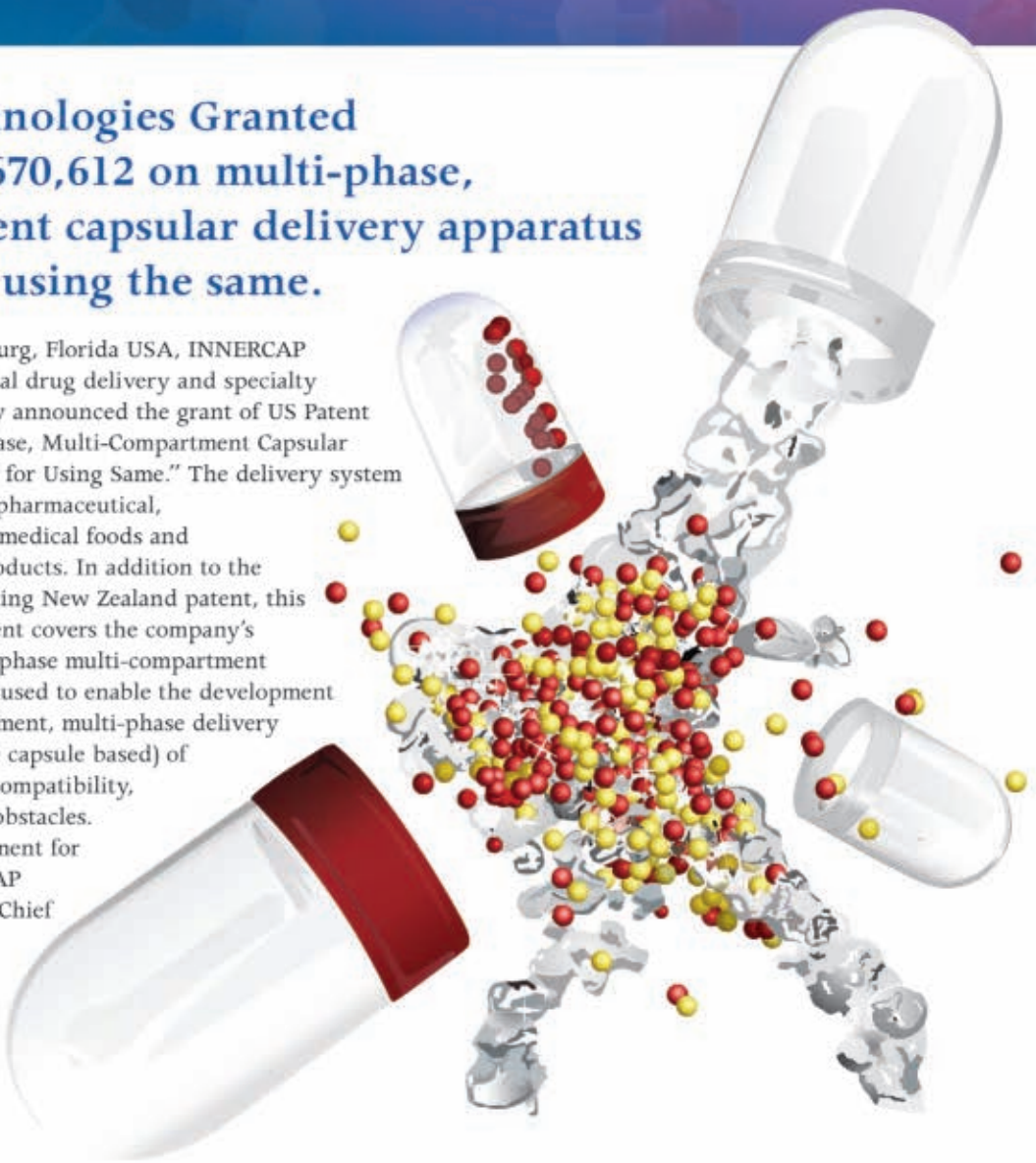
INNERCAP® Technologies Granted US Patent No. 7,670,612 on multi-phase, multi-compartment capsular delivery apparatus and methods for using the same.



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



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

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

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

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

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

INNERCAP® TECHNOLOGIES, INC

United States Patent No. 7,670,612
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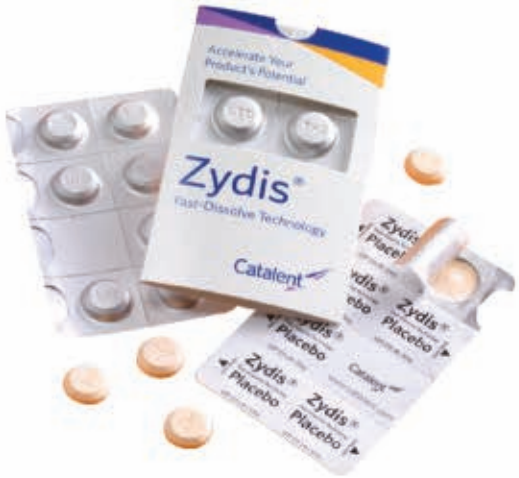

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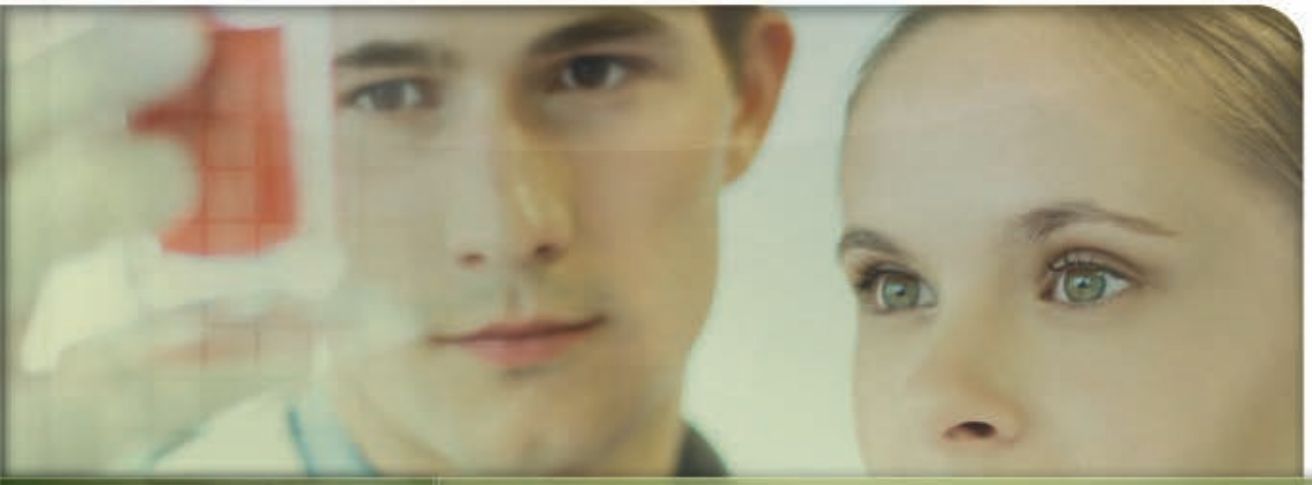
3M DRUG DELIVERY SYSTEMS
INHALATION SYSTEMS



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New **Quality Solutions for Inhaler Testing** Brochure 2010
available now!

Quality Solutions for Inhaler Testing 2010, the new and significantly expanded brochure from Copley Scientific, provides a comprehensive guide to characterising orally inhaled and nasal drug products (OINDPs). Describing in detail how to use an extensive range of inhaler testing equipment it is the perfect reference document for those seeking to interpret regulatory guidance and apply *in vitro* test methods.

As a world leading supplier of inhaler testing equipment Copley Scientific is able to review and describe best practice in this field. Participation in expert groups and a network of industrial contacts, ensure the company's product offering reflects and anticipates the very latest requirements of the sector.

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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Drug Delivery Technology

Market News and Trends

DSM Biomedical & CID Continue to Advance Device Deliverability

DSM Biomedical, a global leader in biomedical materials science, recently announced the extension of its partnership with CID based on the use of DSM ComfortCoat® Hydrophilic coating technology on the Optima Jet Stent Delivery System and the Fluydo PTCA Balloon Catheter, both with CE marked and launched on the European market last month.

The DSM ComfortCoat Hydrophilic Coating was designed to enhance maneuverability of devices in minimally invasive procedures. This advanced lubricious hydrophilic coating on the distal part of the Optima Jet shaft facilitates the treatment of more complex anatomies. Additionally, the DSM ComfortCoat Hydrophilic Coating on the Fluydo PTCA Balloon contributes to further advance device deliverability in order to reach and cross the most difficult lesions.

"Following the successful launch of our bio-inducer surfaced stent Avantgarde last year and our continuous commitment to create new devices, we are excited to extend our partnership with DSM Biomedical in improving the quality of medical treatments. We value DSM Biomedical's long-standing experience in biomaterials and their commitment to support with innovative new materials that lead to positive medical outcomes," said Mr. Franco Vallana, Chief Executive Officer, CID.

"Our partnership with CID is based on our shared vision of being dedicated to improving the quality of patient care and after-care through enabling innovation in medical solutions. We look forward to collaborating with them on future technologies," added John Marugg, DSM Biomedical's Business Director for ComfortCoat medical coatings.

DSM Biomedical develops novel materials-based solutions to meet the present and future needs of the medical device and biopharmaceutical industries. Building on the expertise and strengths of DSM and its acquisition of The Polymer Technology Group, which is now known as DSM PTG, the company's product portfolio includes coatings, drug delivery platforms, and a wide range of biomedical materials for use in short- and long-term implantable medical devices.

CID (Carbostent & Implantable Devices) is dedicated to contributing to human welfare by improving the quality of patient care and after-care through the development of innovative, minimally invasive implantable devices, procedures, and therapies. A strong background in the field of implantable cardiovascular devices and haemocompatible materials, expressed in a remarkable IP portfolio, and a management with an expertise gained in many years of research, development, and clinical experience, allow CID to offer the investors a fair return and its customers the necessary tools to meet new challenges.

Hospira & Javelin Enter Definitive Merger Agreement

Hospira, Inc., a global specialty pharmaceutical and medication delivery company, and Javelin Pharmaceuticals, Inc., recently announced the companies have entered into a definitive merger agreement providing for the acquisition of Javelin by Hospira for $2.20 per share in cash, or approximately $145 million. Hospira expects to commence a tender offer for all outstanding shares of Javelin common stock in accordance with the terms of the merger agreement.

Hospira entered into the merger agreement following an extensive evaluation of Javelin's business and its prospects. The offer is conditioned on the tender of a majority of Javelin's shares calculated on a fully diluted basis and other customary closing conditions, and Hospira believes the offer delivers a full and fair value to Javelin's shareholders.

The acquisition of Javelin would allow Hospira to take advantage of synergies between Javelin's main product candidate, Dyloject, a post-operative pain management drug currently awaiting US FDA approval, and Hospira's proprietary sedation agent, Precedex. Both drugs are marketed to anesthesiologists, enabling Hospira to leverage its Precedex sales force to promote Dyloject.

"Dyloject would broaden Hospira's pain management portfolio and offers attractive revenue and margin prospects," said Ron Squarer, Chief Commercial Officer, Hospira. "Dyloject is also a very good fit with Precedex and further demonstrates Hospira's strong commitment to the acute-care space."

Dyloject is a proprietary non-opioid analgesic that will help reduce the need for traditional intravenous opioids. Opioids are central to the management of post-operative pain, but are associated with significant adverse events, including respiratory depression, sedation, nausea and vomiting, slowing of the gastrointestinal function, and urinary retention.

Hospira would have global rights to Dyloject with the exception of Europe, where rights are currently licensed to a third party. Hospira plans to market the product in the US, Canada, Latin America, and the Asia-Pacific region. These are areas where Hospira also markets Precedex and represent a good fit for Hospira's Precedex and acute-care strategy.

Hospira and Javelin also entered into a loan facility under which Javelin may borrow up to $4.5 million to fund Javelin's operating activities prior to closing a merger with Hospira, approximately $8.3 million for Javelin's repayment of the principal and accrued interest incurred under a similar financing arrangement entered into with Myriad Pharmaceuticals (MPI) and $4.4 million for Javelin's payment of the termination fee and certain stipulated expenses that Javelin may be required to pay MPI following termination of its merger agreement with MPI.

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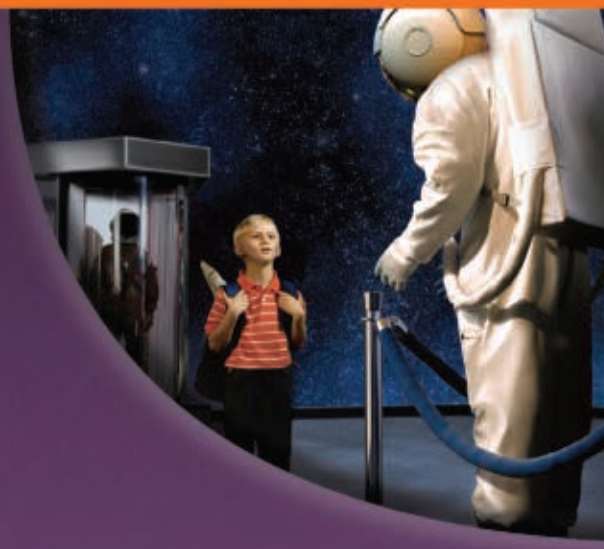

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Market News and Trends

GlaxoSmithKline, Isis Pharmaceuticals in $1.5-Billion Drug Development Deal

GlaxoSmithKline and Isis Pharmaceuticals, Inc. recently announced a new strategic alliance that will apply the Isis antisense drug discovery platform to seek out and develop new therapeutics against targets for rare and serious disease, including infectious diseases and some conditions causing blindness.

Under the terms of the agreement, which covers up to six programs, Isis will receive an upfront $35-million payment from GSK and is eligible to receive on average up to $20 million in milestones per program up to Phase II proof-of-concept (PoC). GSK will have the option to license compounds at PoC and will be responsible for all further development and commercialization. Isis will be eligible to receive license fees and milestone payments, totaling nearly $1.5 billion, in the event all six programs are successfully developed for one or more indications and commercialized through to pre-agreed sales targets. In addition, Isis will receive up to double-digit royalties on sales from any product that is successfully commercialized.

"As a platform, the Isis antisense approach offers us an exciting opportunity to target certain severe diseases in a way that has not previously been possible," said Dr. Patrick Vallance, Senior Vice-President and Head of Drug Discovery at GSK. "Isis Pharmaceuticals is a leader in antisense technology, and this new alliance will enhance our discovery platform in this promising research area."

Antisense therapies target the proteins involved in disease processes through the RNA that is involved in building these proteins. The Isis discovery platform develops specific therapies that bind to messenger RNA (mRNA) and inhibit the production of disease-causing proteins. Isis recently announced data from a Phase III trial in heterozygous familial hypercholesterolemia patients that demonstrated the therapeutic effect of this approach.

This alliance provides GSK with access to Isis' expertise in drug discovery and development of RNA-targeted therapeutics, with Isis retaining responsibility for the discovery and development of compounds to the alliance targets from inception to PoC.

"We are excited to be working with GSK to apply antisense technology to these new therapeutic areas. We are particularly excited to work on the novel targets GSK brought to the alliance," said Dr. Stanley T. Crooke, Chairman and Chief Executive Officer of Isis Pharmaceuticals. "This alliance is exactly the type of deal we want to do. We retain control of the discovery and early development of our drugs while working together with a very high-quality partner to maximize the value of the drugs in late-stage development and commercialization."

RNA-targeted therapeutics, or antisense therapies such as oligonucleotides, represent an opportunity for a new drug class. Where most other medicines are small molecules or biologics that target a specific protein in a disease process, antisense therapies prevent protein synthesis by eliminating the mRNA - the template or pattern that guides the production of the protein.

Isis is exploiting its expertise in RNA to discover and develop novel drugs for its product pipeline and for its partners. The company has successfully commercialized the world's first antisense drug and has 22 drugs in development. Isis' drug development programs are focused on treating cardiovascular, metabolic, and severe neurodegenerative diseases and cancer.

Comar Announces Acquisition of Universal Container Corporation

Comar, Inc. recently announced it has finalized a transaction acquiring 100% of Universal Container Corporation's (Unicon) assets from its current shareholders. Based in Cayey, Puerto Rico, Unicon is a leading manufacturer of high-quality injection molded, injection blow molded, and extrusion blow molded parts and containers. Comar, based in Buena, NJ, is a manufacturer of proprietary pharmaceutical packaging with a leadership position in the Liquid Medication Delivery Device Market.

Unicon's primary end market is pharmaceutical packaging serving a Class A list of customers, including pharmaceutical companies, contract packagers, and distributors. Included in the transaction are the leased real estate, manufacturing equipment, plant operations, management, and employees. The operations, product line, and customer base are a strong fit with Comar, and manufacturing at Unicon's facility will continue and be expanded. The acquisition is the next step in Comar's strategic plan, which began with the divestiture of its glass vial product line, and focuses on organic growth and acquisitions within plastic pharmaceutical and medical packaging.

"Unicon's products, production capabilities, and facility will complement and enhance Comar's existing product lines and position the combined entity for future growth," said Mike Ruggieri, President of Comar. "Unicon is a perfect fit for our business, and we are excited to welcome Unicon's staff and customers to the Comar family. This acquisition gives our business a high-quality, redundant facility for production while also expanding our capacity to keep up with our rapid organic growth. We believe Unicon's and Comar's customer base will benefit from the choices offered by our combined, expanded product line."

Comar is a 60-year-old, privately owned pharmaceutical plastic packaging manufacturer, currently servicing the pharmaceutical, biotech, diagnostic, ophthalmic, healthcare, personal care, and retail pharmacy markets. Its product line includes multiple patents for its line of oral dispensers, dosage cups, dropper assemblies, closures, and other primary packaging products manufactured in its ISO 9001:2008- and 13845-registered facility.

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Market News and Trends

EyeGate Pharma Completes Phase II Study of EGP-437 in Patients With Anterior Uveitis

EyeGate Pharma, a privately held venture-backed pharmaceutical company developing a non-invasive ocular drug delivery platform and ocular therapeutics, recently announced the completion of a Phase II study of its lead product candidate, EGP-437, for the treatment of anterior uveitis.

To be enrolled in this randomized double-masked study, subjects needed to have non-infectious anterior segment uveitis with a cell score of ≥ 1.5 (on a 0 to 5 scale, 5 = worst and 0 = best). Enrolled subjects received a single dose of EGP-437 (a dexamethasone derived corticosteroid solution) delivered at one of four dose levels using the EyeGate II Ocular Drug Delivery System and were followed for 28 days. Following the single EGP-437 treatment, about half of the subjects achieved an anterior cell score of zero within 2 weeks. By day 28, the majority of patients achieved cell scores of zero and required no further treatment. No significant changes in intraocular pressure or signs of cataract formation were detected. Data from the study will be presented at the Association for Research in Vision and Ophthalmologyannual meeting in Fort Lauderdale on May 06, 2010.

"For uveitis patients, there is an unmet medical need, and doctors need a more predictable, effective treatment for severe uveitis," said one of the study investigators, Victor L. Perez, MD, Associate Professor of Ophthalmology at the Bascom Palmer Eye Institute. "The EGP-437 Phase II data is encouraging because it not only shows promising signs of efficacy but addresses compliance issues, by providing the doctor direct control of the dosing. These results suggest that the EyeGate delivery system could lead to a more predictable clinical response in treating severe uveitis."

EyeGate is the first company to complete Phase II studies using iontophoresis technology to deliver an active compound into the eye under an investigational new drug (IND) application. The company submitted the anterior uveitis study results and data from a completed Phase II study in dry eye patients to the FDA as part of an end-of-Phase II meeting. In the second quarter of 2010, the company plans to initiate a multi-center Phase III study in dry eye patients.

"We are pleased that EyeGate has successfully completed two Phase II studies, one for dry eye and one for anterior uveitis, using our iontophoresis technology to deliver EGP-437.," said Stephen From, President and Chief Executive Officer of EyeGate Pharma. "These positive results help demonstrate that iontophoretically delivered drugs may offer ophthalmologists new treatment options for patients."

Eyegate Pharmaceuticals, Inc. is focused on developing treatments for unmet ocular medical needs by employing the EyeGate II Ocular Drug Delivery System, a non-invasive drug delivery technology. The EyeGate II delivery system is compatible with a wide range of therapeutics and has the potential to address many anterior and posterior segment diseases. EyeGate II has been studied in over 200 subjects and is the first ocular iontophoretic system to have completed Phase II studies (dry eye and uveitis).

Particle Sciences Announces the Acquisition of Unique PEG-Based Polymer Technology

Particle Sciences Inc. (PSI), a leading pharmaceutical CRO, is adding to its portfolio of drug delivery technologies through the acquisition of a versatile PEG-based technology. The technology covers a series of PEG-grafted cationic polymers that have a wide variety of applications in the pharmaceutical arena.

"PEGylation is a recognized approach to stabilize drug suspensions, improve drug solubility and bioavailability, and reduce toxicity and reticuloendothelial system interaction," said Robert Lee, Particle Sciences' VP of Pharmaceutical Development. "The technology we have acquired covers a set of novel, biocompatible PEGylated polymers allowing for the PEGylation of particles and biological surfaces. We are confident that our clients will benefit from this acquisition and have already started several development programs utilizing them."

"Particle Sciences has been working with this technology for some time now, and we are very happy with the performance and in vivo tolerability results obtained thus far in several different systems. To bolster the acquired technology, we have filed additional intellectual property to both broaden and extend its patent coverage," added Andrew Loxley, Particle Sciences' Director of New Technologies.

Particle Sciences is an integrated provider of drug development services, focusing on emulsions, gels, particulates, and drug/device combination products with additional specialized capabilities in topical and mucosal drug delivery. Through a full range of formulation, analytic, and manufacturing services, Particle Sciences provides pharmaceutical companies with a complete and seamless development solution that minimizes the time and risk between discovery and the clinic.

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

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

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Market News and Trends

Synairgen Initiates Phase II Trial With Inhaled Interferon Beta in Asthmatic Subjects

Synairgen plc, the respiratory drug discovery and development company with a particular focus on viral defense in asthma and chronic obstructive pulmonary disease (COPD), recently announced the commencement of its first Phase II study of inhaled interferon beta (IFN-beta) for the treatment of exacerbations of asthma caused by respiratory viruses, including influenza.

The Phase II study, known as SG005, uses the company's exclusively in-licensed formulation of inhaled IFN-beta (SNG001) and aims to assess the efficacy and safety of inhaled SNG001 compared to placebo administered to asthmatic subjects after the onset of respiratory viral infection for the prevention or attenuation of asthma symptoms caused by respiratory viruses. Following on from the announcement in November 2009 that SNG001 significantly reduced the ability of influenza to infect lung cells, the SG005 study has now been broadened to include patients who contract influenza as well as common cold viruses.

Respiratory viral infections (primarily caused by common cold and influenza viruses) are recognized as the key triggers of exacerbations (rapid worsening of symptoms), which are the major contributor to the significant healthcare burden in asthma.

Confidence in the outcome of SG005 is strengthened by the results of Synairgen's Phase I study in moderate asthmatics (SG004), which showed that inhaled SNG001 was well tolerated, and the biomarker analysis that confirmed activation of antiviral defenses in the lung.

The SG005 study is being conducted at a number of clinical trial sites in the United Kingdom. The first volunteers were entered into the study on March 31, and the trial is expected to be completed during the summer of 2011.

"We are delighted to have been able to commence this study on schedule," said Richard Marsden, Chief Executive Officer of Synairgen. "In this study, we are aiming to correct an antiviral (IFN-beta) deficiency. We have shown the drug is well tolerated in a safety trial (SG004), and we have evidence that we have successfully primed the antiviral defenses; now we will test SNG001 in the presence of virus infections."

Penwest Signs Multi-Drug Generics Agreement With Alvogen

Penwest Pharmaceuticals Co. recently announced it has signed a drug development and commercialization agreement with Alvogen, Inc. under which Penwest and Alvogen have agreed to identify and select up to five compounds for generic development. Penwest's TIMERx technology may be used for each compound selected. Penwest will formulate the agreed upon compounds and receive milestone and royalty payments that are linked to the development of each compound.

Alvogen, the US-based pharmaceutical manufacturer of complex generic products for the US, EU, and other international markets, will be responsible for manufacturing, clinical trials, and regulatory filings for each of the formulations, as well as commercialization of the products worldwide.

"We are very pleased to be partnering with Alvogen because of its record for successful product introductions within the generic pharmaceutical industry," said Jennifer L. Good, Penwest's President and CEO. "This multi-drug, multi-national agreement allows Penwest to leverage its drug delivery technology for the formulation of generic drugs, an important segment of the market for extended-release technology. TIMERx technology had its start in generics with the development of the first generic to Pfizer's Procardia XL product, which was formulated using the Alza Oros technology. We are pleased to be leveraging this valuable advantage of TIMERx in the development of difficult-to-formulate generic products with the expertise of the team from Alvogen."

The collaboration agreement with Alvogen represents a valuable addition to Penwest's growing drug delivery portfolio of development programs, which is being built upon broader strategic partnerships. Penwest currently has four individual research and development agreements with Otsuka Pharmaceutical Co., Ltd. working on branded products, and will now add this multi-drug agreement with Alvogen focused on generic drug development.

Penwest is a drug development company focused on identifying and developing products that address unmet medical needs, primarily for rare disorders of the nervous system. Penwest is currently developing A0001, or a-tocopherolquinone, a coenzyme Q10 analog demonstrated to improve mitochondrial function in vitro. Penwest is also applying its drug delivery technologies and drug formulation expertise to the formulation of its collaborators' product candidates under licensing collaborations.

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CONTROLLED RELEASE

Amino Acid-Containing Degradable Polymers & Their Potential in Controlled Drug Delivery

By: Aylvin A. Dias, PhD, MSc, and Marc Hendriks, PhD, MBA

ABSTRACT

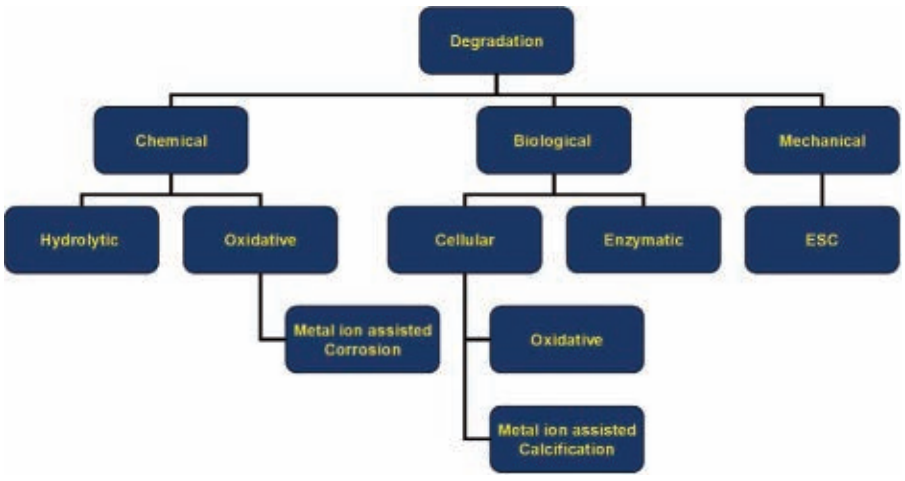
Biodegradable polymers allow for avoidance of re-interventions related to removal of the drug delivery implant, and therefore minimize risk of complications and adverse events associated with long-term implantable materials. However, it should be noted that these benefits have to be weighed against potential risks caused by degradation products and intermediates. The manner in which degradation proceeds has an influence on drug-release behavior and can influence the form the polymer has to adopt. Surface versus bulk degradation is dependent on whether the degradation is via a hydrolytic mechanism (eg, ester hydrolysis) or via an enzymatic mechanism. In case of degradation by hydrolysis, bulk degradation takes place, but can be controlled by exerting control over the rate of water penetration and material swelling, which is governed by the hydrophilicity of the polymer. In the case of enzyme- or cellular-mediated biodegradation, the mechanism is mainly via surface degradation and erosion. Enzymatic degradation can occur via hydrolytic or oxidative mechanisms. These degradation mechanisms can occur as a result of the inflammatory foreign body response that occurs upon implantation of the polymeric drug delivery system. Enzymes typically involved in biodegradation are esterases, proteases, elastases, and peroxidases. Thus, in the design of degradable polymer-based drug delivery systems, it is worthwhile evaluating both chemically degradable and enzymatically biodegradable polymers and scrutinize the in vitro and in vivo testing results to define the optimal system.

INTRODUCTION

Drug delivery materials to aid pharmacotherapy utilize polymers to stabilize medication during production and sterilization to obtain desired pharmacokinetics and/or achieve locally controlled and targeted drug delivery.[1]

Polymers are preferred matrices for controlled drug delivery because of the large degree of variables that can be used to tune release as well as achieve other functional properties. Polymers may be divided into linear (thermoplastic) or cross-linkable (thermoset) polymers. In either of these two classes, there is further opportunity to tune the composition of the polymer to give random, alternating, or block copolymers. Yet another feature to control drug release is the molecular architecture that can be used to generate linear, branched,

FIGURE 1



Various mechanisms that contribute to the degradation of polymers.

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hyperbranched, and comb-like polymers. Finally, polymers can be formulated either as linear polymer blends, linear-cross-linked polymer blends (semi-interpenetrating networks), and blends of cross-linked polymers (interpenetrating networks).

This tool box of parameters that can be used to adjust and manipulate polymers offers numerous possibilities to develop solutions when drug delivery needs have to be reconciled against a number of other requirements related to shape, mechanical properties, biocompatibility, process, and biostability.

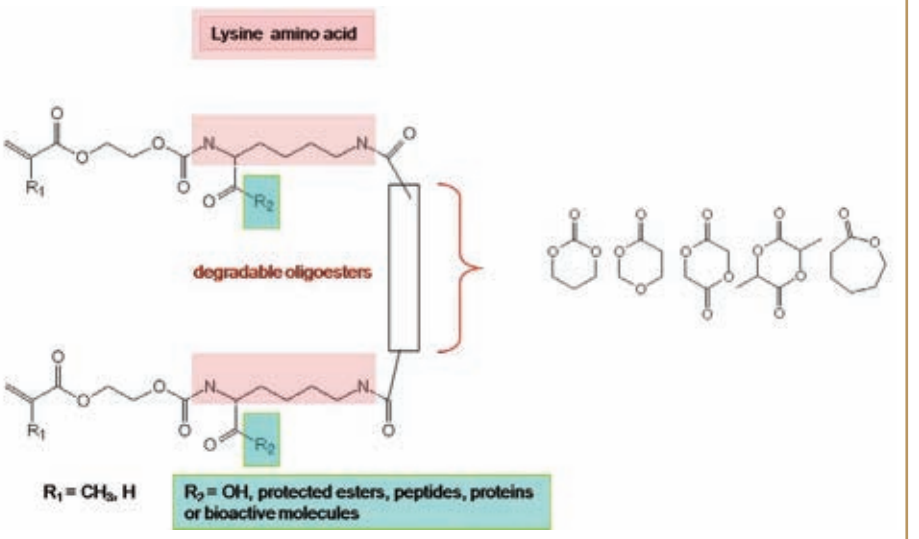
When considering polymers for drug delivery applications, an important feature is the form the polymer will have as a drug delivery matrix. Polymers can be fabricated into films, coatings, tablets, microspheres, nanoparticles, gels, complex 3-D monoliths, and components, as well as polymer prodrugs. So development of an eventual drug delivery matrix is a delicate interplay between the drug-polymer compatibility and the form required for the selected method of administration.

BIODEGRADABLE POLYMERS

In polymer-based drug delivery, a major area of research and development is on design of biodegradable polymer systems. Biodegradable polymers allow for avoiding re-interventions related to removal of the drug delivery implant, and thus minimize risk of complications and adverse events associated with long-term implantable materials. However, it should be noted that these benefits have to be weighed against potential risks caused by degradation products and intermediates.

The term biodegradable polymers is rather all-encompassing, and often, derivative idioms are interchangeably used when describing such polymers. For the sake of clarity, degradable polymers are those in which bonds can be broken by chemical or enzymatic mechanisms.

FIGURE 2



Cross-linkable biodegradable polyesterurethane in which the amino acid side-group can be further chemically modified for additional functionality.

Degradation can occur by various mechanisms that can be classified according to Figure 1.

Erodible polymers are those in which the polymer mass or volume is lost by gradual dissolution of the polymer without actual degradation or cleavage of chemical bonds. Biodegradation refers to degradation of polymers in the presence of enzymes, cells, or microorganisms.

Mechanical degradation often occurs in conjunction with biological and/or chemical degradation. It should be noted that in most cases, degradation proceeds by multiple pathways and rarely via a single mechanism. The manner in which degradation proceeds has an influence on drug-release behavior and can influence the form the polymer has to adopt. Surface versus bulk degradation is dependent upon whether the degradation is via a hydrolytic mechanism (eg, ester hydrolysis) or via an enzymatic mechanism. In case of degradation by hydrolysis, bulk degradation takes place but can be controlled by exerting control over the rate of water penetration and material swelling, which is governed by the hydrophilicity of the polymer. In the case of enzyme- or cellular-mediated biodegradation, the mechanism is mainly via surface degradation and erosion.

Enzymatic degradation can occur via enzymatic hydrolysis and enzymatic oxidation. These degradation mechanisms also occur as a result of the inflammatory foreign body response that occurs upon implantation of the polymeric drug delivery system. Enzymatic oxidation is the result of the phagocytic action of inflammatory cells. Enzymes typically involved in biodegradation are esterases, proteases, elastases, and peroxidases.

There remains much debate on the pros and cons of hydrolytically degradable versus enzymatically or biodegradable polymers. It has been speculated that polymers that degrade via a chemical hydrolytic mechanism offer much more control over degradation than those that degrade via an enzymatic mechanism. This is on the basis that the inflammatory foreign body response in both patient and implant site are variable. However, polymers that enzymatically degrade provide for better control over drug release due to their surface erosion-based degradation behavior. In addition, enzymatically degradable polymers offer advantages in that they exhibit greater storage and packaging robustness when compared to hydrolytically degradable polymers, largely because of the latter's sensitivity to moisture.

Thus, in the design of degradable polymer-based drug delivery systems, it is worthwhile evaluating both chemically degradable and enzymatically biodegradable polymers and scrutinize the in vitro and in vivo testing results to define the optimal system of which to proceed.

Polylactic acid (PLA) and copolymers with glycolic acid (PLGA) have been the most widely used materials for drug delivery. PLA- and PLGA-based systems are used as matrix reservoirs in which drug is dispersed within the polymer materials and is released both by diffusion through the polymer and as the polymer degrades.

Whereas these systems have successfully demonstrated the ability to deliver drugs in a controlled manner over prolonged periods of time, they are associated with significant limitations for further expansion of their use, related to items such as acidic degradation products, the relative hydrophobicity, etc.

The follwing presents the next evolution in biodegradable materials that are prepared via synthetic incorporation of amino acid building blocks. The incorporation of amino acid building blocks provides not only a natural degradation end product but the possibility to address the limitations of the conventional degradable polymers.

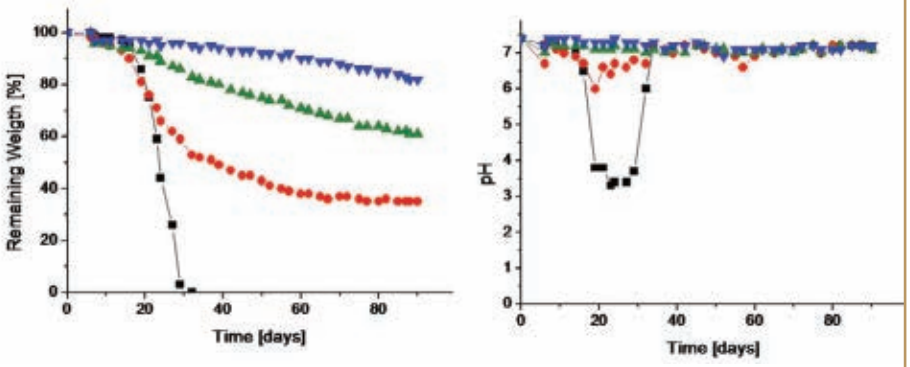
A thermoset degradable polymer (polyesterurethane) and a thermoplastic polyester amide both bearing amino acid building blocks and their degradation characteristics are described.

AMINO ACID-BASED BIODEGRADABLE POLYMERS

With degradation comes the release of degradation products into the body, the toxicity of which should be taken into account when selecting building blocks used to synthesize a degradable polymer. The nature of the resultant degradation by-products is as important as selecting building blocks for achieving desired mechanical properties, polarity, or particular diffusion characteristics of the polymer. This has led to the incorporation of biological building blocks in degradable polymers for medical applications. Most notably has been the incorporation of amino acid-based building blocks. Amino acids offer more than being biodegradable and metabolizable building blocks; they may moreover provide one or more reactive sites that allow further modification of the polymer to tailor physicochemical properties, tune cellular response, or serve as a handle for the chemical attachment of functional molecules, including drugs.

Initial development on amino acid-based polyamidoamines was complicated by their poor solubility and processability as well as their low level systemic toxicity upon degradation. To address these limitations, amino acid-based polyester urethanes, polyester amides, and polycarbonates were developed.

FIGURE 3

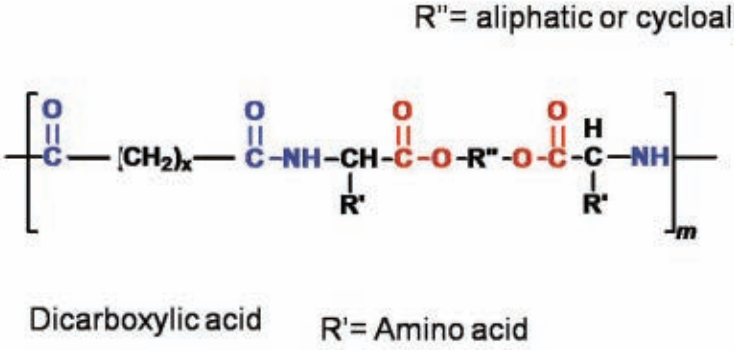


Degradation of polyester urethanes showing reduced pH drop compared to analogous non-lysine-bearing hydroxyester-based microspheres, and the varying degradation rates obtained by varying the hydroxyester backbone.

POLYESTERURETHANES

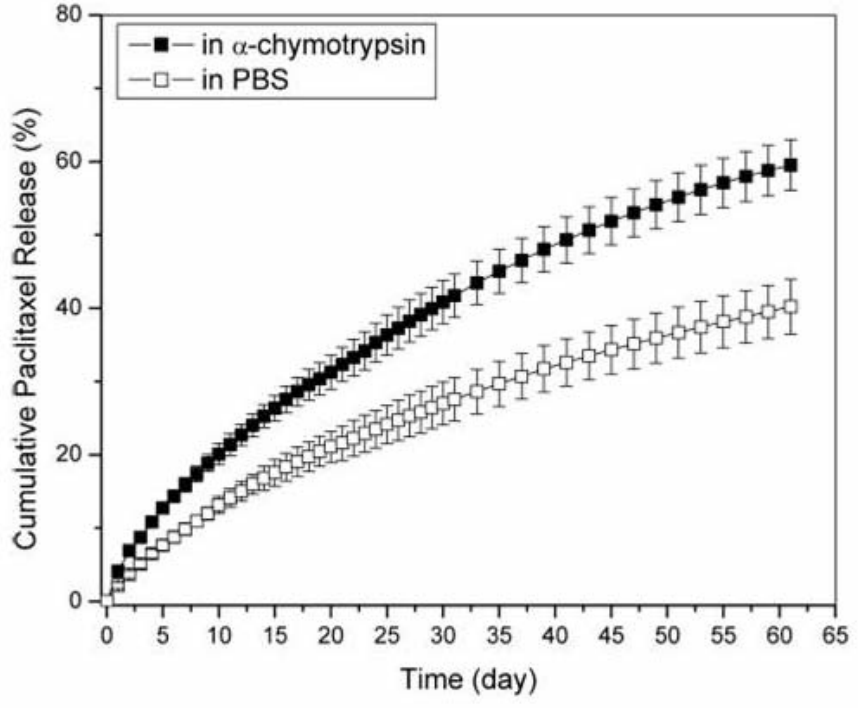
The incorporation of amino acids in polyurethanes originally stemmed from observations that supposedly biostable polyurethanes were in fact degraded due to inflammation-derived enzymatic activity, thus generating non-natural and often toxic amine-functional degradation products. The isocyanates used to produce the polyurethanes resulted in non-natural amine degradation products and triggered the development of isocyanates that generated natural amine-based degradation by-products. These were most notably the use of butanediisocyanate and

FIGURE 4



A new generation of amino acid-based biodegradable polyesteramides for drug delivery and other medical applications.

FIGURE 5



In vitro paclitaxel release profiles from cross-linked phenylalanine-based polyesteramide hydrogels in pure PBS buffer and in an alpha-chymotrypsin solution at 37°C.[5]

lysine diisocyanate that generated putrescein and lysine, respectively, as degradation end products of the resultant polymer.

Furthermore, amino acid building blocks can provide one or more reactive sites that allow further modification of the polymer, such as is exemplified schematically with a cross-linkable amino acid-based polyesterurethane in Figure 2. Such polymers can be further modified to introduce functionalities related to imaging or molecular targeting, but also, drugs can be chemically conjugated to the polymer this way.[3]

One of the main advantages that can be attributed to these amino acid-based polyurethanes is the reduced pH drop upon degradation. This reduced pH drop has been demonstrated in both coatings and microspheres. Cross-linked 40- to 60-micron microspheres prepared by emulsion photopolymerization were degraded by hydrolysis in phosphate-buffered saline are shown in Figure 3. The results show that the lysine-containing lactide glycolide-based urethane microspheres result in a lower pH drop compared to the analogous lactide glycolide microphores. Furthermore, by changing the hydroxyester backbone, it is possible to change the degradation rates while maintaining the same cross-link density, also shown in Figure 3.

AMINO ACID-BASED POLYESTERAMIDES

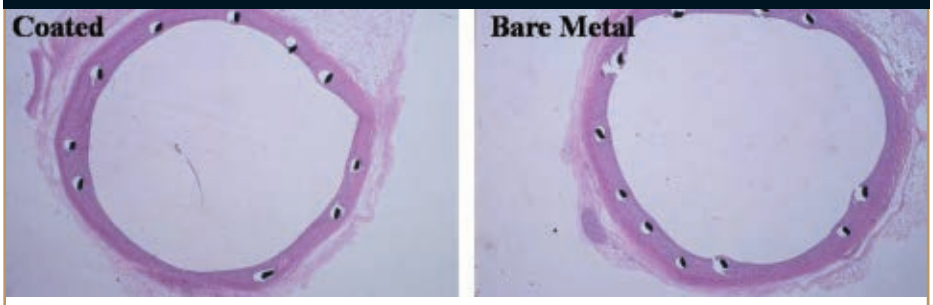
Amino acid-based polyesteramides are based on alpha-amino acids, aliphatic dicarboxylic acids, and aliphatic alpha-omega diols as shown in Figure 4.[4]

The presence of amino acid building blocks not only ensures safe degradation products but also gives the resultant polymers protein-like physical properties. Variations of the three building blocks allow one to combine the beneficial properties of both polyamides and polyesters. Properties that can be tuned are hydrophilicity, biodegradation, and biocompatibility as well as drug release. Among this class of polymers, it is the AA-BB heterochain polymers that offer the greatest versatility in terms of molecular level design to tailor drug-release properties. These polyesteramides have been chemically modified and formulated to deliver a wide variety of small molecule drugs and biologics. Their main advantage is related to the fact they predominantly degrade by an enzymatic mechanism; because of consequential surface erosion degradation, drug release follows mainly zero-order kinetics. As an example, paclitaxel has been delivered from a cross-linked phenylalanine-based polyesteramides hydrogel. In vitro release profiles of paclitaxel in PBS buffer and in chymotrypsin solution have been reported as shown in Figure 5.[5]

These amino acid-based polyesteramides have been tested extensively and showed good tissue and blood compatibility in applications like coatings for stents. As an example, the in vivo biocompatibility was tested in porcine coronary arteries by comparing the polymer-coated stents with bare metal stents in pigs. These porcine preclinical trials reveal that the polyesteramide-coated stents had similar injury and inflammation scores to a bare metal stent.[6] Exemplary photomicrographs of the porcine coronary arteries 28 days following implantation with a polyesteramide-coated stent and a bare metal stent are shown in Figure 6.

Currently, amino acid-based polyesteramide polymers are in human clinical studies as biodegradable coatings for drug-eluting stents. Apart from small molecule drug delivery, more recently, arginine-based polyester amides were developed for their use as non-viral gene delivery vehicles.[7] A recent in vitro study looking at polyesteramide nanoparticles and their ability to transfect rat smooth muscle cells revealed that first, these polyester amides have a high degree of plasmid DNA binding, and second, they could be used in wide dosage ranges

FIGURE 6



Photomicrographs of the porcine coronary arteries 28 days following implantation with a polyesteramide-coated stent and a bare metal stent.[6]

without adversely affecting cell morphology, viability, and apoptosis. Rhodamine labeling of the plasmid confirmed cellular incorporation via endocytosis and revealed close to 100% transfection efficiency. These are promising results, but further optimization of this delivery system is still required because most of the DNA remained in the endocytotic compartments. Nonetheless, the high cellular uptake combined with low toxicity suggests that polyester amides also show much promise for use in gene therapy.

SUMMARY

Amino acid-based biodegradable polymers represent the next frontier in the use of polymers for drug delivery. The amino acid building blocks reduce the risk of toxic degradation products and provide means to further chemically modify these polymers with additional functionality not least as a means to chemically bind drugs.

It is our strong belief that hydrolytically degradable polymers as well as enzymatically biodegradable polymers will be needed in a drug delivery company's armamentarium of solutions. There is no "one size fits all" in drug delivery; each pharmaceutical compound, be it a small molecular weight drug or a large molecule biologic, brings a variation of challenges for designing an optimal polymer-based controlled-release solution.

With both types of polymers available, the diversity provided in control over chemistry, molecular architecture, formulation, and processing methods to fabricate these polymers into a given form or shape presents one a unique ability to design drug delivery solutions around the drug and therapy rather than the trial-and-error approach that has been pervasive thus far.

ACKNOWLEDGEMENTS

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BIOGRAPHIES

Dr. Aylvin A. Dias is R&D Manager at DSM Biomedical, Geleen, The Netherlands, where he currently manages research in drug delivery and tissue engineering for ophthalmic and cardiovascular applications. He earned his BSc and PhD in Biological and Polymer Chemistry at the University of Kent at Canterbury. In 1994, after his PhD, he worked at Total Chemie on materials for food packaging. In 1996, he joined DSM in the Netherlands. In the first 5 years, he worked on coating resins, optical fibre, and stereolithographic materials. In the subsequent 4 years, he established the biomedical research program and thereby was one of the founding fathers of DSM Biomedical. He managed the start-up of an application development laboratory in medical coatings. The research program lead to the launch of two new medical coatings, a lubricious coating, and an antimicrobial coating. Dr. Dias has over 30 patents and 20 peer-reviewed publications to his credit.

Dr. Marc Hendriks is R&D and Technology Director at DSM Biomedical, Geleen, The Netherlands, where he provides scientific and strategic leadership in establishing the company's R&D portfolio and ensuring it encompasses the development of novel polymeric materials and material technologies for the enhancement of existing and creation of new biomedical products or therapies. He joined DSM Biomedical in 2006 after spending 15 years at Medtronic's Bakken Research Center in Maastricht, the Netherlands. During his time with Medtronic, Dr. Hendriks served in various roles, including Research Director, where he led various R&D projects on surface modification technologies, drug delivery, and cross-linking technologies for bioprosthetic tissues; Manager of Biomaterials Technology; Scientist, and Engineer. He holds over 25 US patents, with several more pending. He has also co-authored over 30 journal articles and various book chapters in the field of biomedical materials research. Dr. Hendriks earned his PhD and MSc from Eindhoven University of Technology and his MBA from University Maastricht Business School.

United We Stand: the Power of Alliances in the New Normal

Part 2 of a 6-part series on business models & best practices for navigating the new normal.

By: Derek Hennecke, President & CEO Xcelience LLC

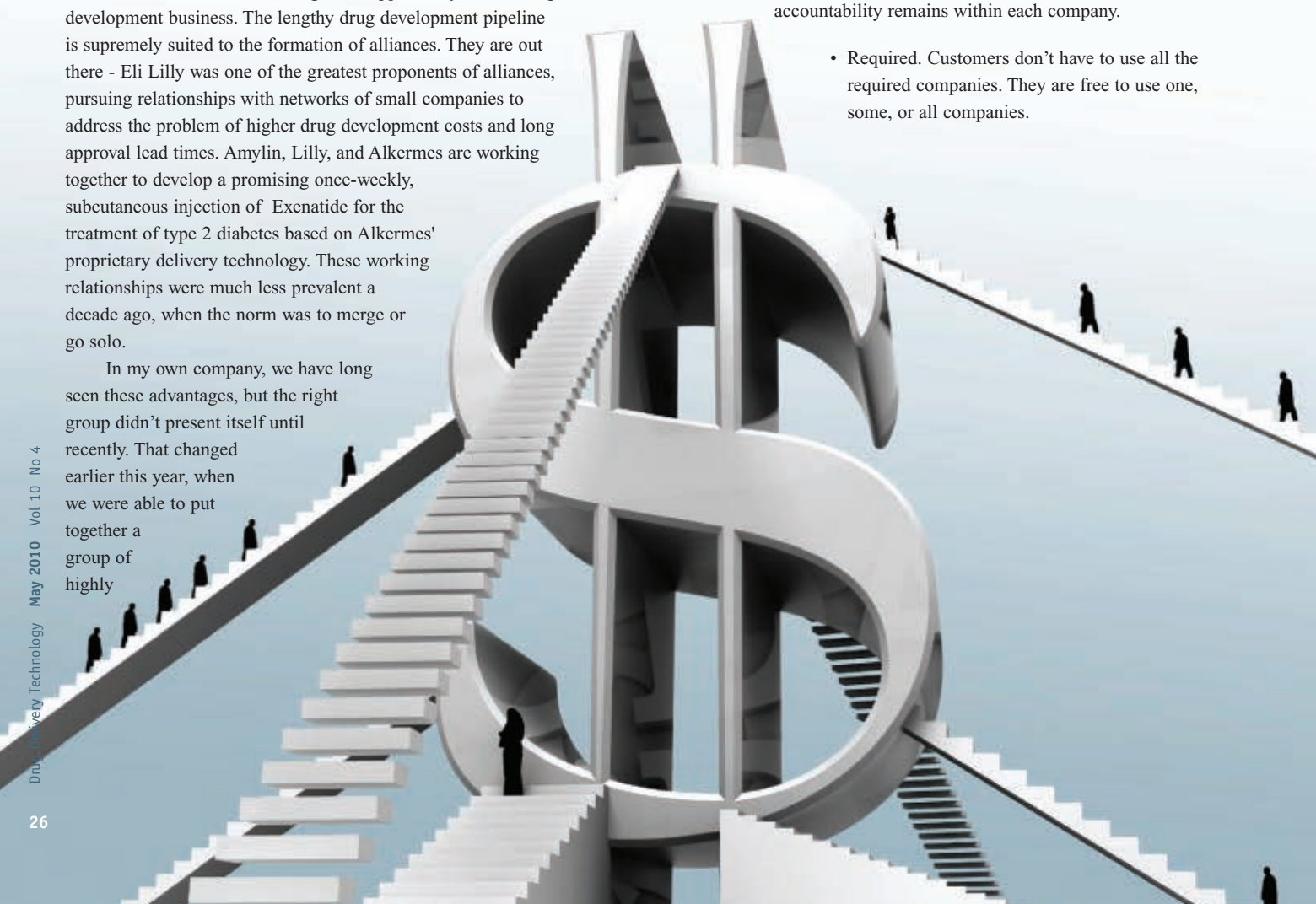
The headwinds of the New Normal meet us head on. Time-tested players teeter. Some fall. My question to you is this: are you better off standing against the winds alone, or as a group? I am going to argue that in the New Normal, if you aren't building solid relationships up and down stream, then it's just a matter of time until the headwinds blow you away.

I'd be hard pressed to think of an industry where going it alone is better. Witness Toyota's network of suppliers, Microsoft's family of software developers, or Cisco, which has become a poster child for the alliance model. In the airline industry, three alliances have come to constitute more than half of global passenger traffic. Alliances are the new norm.

So tell me, why does our industry use alliances so infrequently? I see this as an incredible shortcoming - and opportunity for the drug development business. The lengthy drug development pipeline is supremely suited to the formation of alliances. They are out there - Eli Lilly was one of the greatest proponents of alliances, pursuing relationships with networks of small companies to address the problem of higher drug development costs and long approval lead times. Amylin, Lilly, and Alkermes are working together to develop a promising once-weekly, subcutaneous injection of Exenatide for the treatment of type 2 diabetes based on Alkermes' proprietary delivery technology. These working relationships were much less prevalent a decade ago, when the norm was to merge or go solo.

In my own company, we have long seen these advantages, but the right group didn't present itself until recently. That changed earlier this year, when we were able to put together a group of highly qualified CMC providers with - forgive my pun - the right chemistry. In February, we announced our partnership with Cambridge, Avantium, and Beckloff Associates. Together, we formed an exciting new alliance called Chemistry Playbook™, a streamlined approach to CMC solutions. We are integrating services, processes, and paperwork to increase productivity and save customers time, money, and headaches. Before I tell you about what this alliance is, let me be perfectly clear about what it's not. Chemistry Playbook is NOT:

- A formal merger of four companies. All companies are independent.
- A one-stop-shop model. Each company in an alliance should be a recognized leader in its field. The expertise and accountability remains within each company.
- Required. Customers don't have to use all the required companies. They are free to use one, some, or all companies.



However, it IS a union of companies with similar cultures and operating philosophies in complementary service offerings. The benefits of alliances through the drug development are overwhelming. The usual approach for clients is to approach each of the myriad of contract providers individually, put out bids, negotiate prices, discuss confidentiality agreements, processes, and set out legal parameters. The hours consumed in this process are simply huge.

In the past, the industry has tried to accomplish these kinds of savings with the one-stop shop. Alluring from a distance, the one-stop shop promises to take a single drug through the entire process in an integrated and seamless manner. How tantalizing! If only it worked that way.

Instead, one-stop shop has become a derogatory term. Large companies have traditionally started in one area and purchased other shops to fill in the gaps and expand their offerings in the chain. But the best companies are rarely for sale, so they purchase whatever is available. Customers complain that while some shops may deliver high-quality, top people and efficient systems, others do not. But when sucked into the system, they are stuck with all the players in it, forced to ride with all the bumps and risk inherent in it, and hope for the best.

This is precisely where an alliance stands to excel. In an alliance like the Chemistry Playbook, each shop is in itself a stand-alone expert in one area. We simplify the client's experience by harmonizing documents (confidentiality agreements, legal parameters, etc). The client is free to pick and choose among the alliance members who meet their needs and discard those who don't, saving vast amounts of time (the process takes days instead of weeks or months) and negotiating with just one contact rather than a series of individual suppliers. A single person will smooth out traditionally bothersome details, such as the logistics of API.

Here's how it works. First, we execute CDAs (which are harmonized). Then the RFQ is evaluated by all relevant partners. A project strategy is defined and mapped, and project tasks are assigned between partners. Coordinated quotes are submitted, linked by Gantt charts. Then a single point person is assigned as Program Manager. A program manager can be from within one of the companies or can be from the client. A Project Manager is assigned from each company. A kick-off meeting is held involving all companies. From then on, the program/project manager manages the flow of data, methods, and materials between sites. Each project manager is in charge while the project is in his/her facility. Weekly/bi-weekly teleconferences are held with all partners, making the hand-off from company to company easy.

I can't stress enough the customer value of harmonized documents. Confidentiality agreements agree on terms and on-going obligations, state and country of jurisdiction, standard expectations, and retention of copies. Master service agreements align on term, state/country of jurisdiction, termination and its effects, payment terms and warrantees, indemnifications, and limitations of liability.

With four companies involved, we're talking a quarter of the time and a quarter of the legal fees normally associated with these documents. A negotiation of one term is a negotiation with all.

It's important to note that not all alliances are a good thing. Fifty percent of all alliances fail, and an additional 30% are described as struggling. Let's face it, the human race doesn't have a fabulous track-record for getting along with everyone.

What attributes characterize the 9% of alliances that are established successes? Chemistry Playbook has identified and addressed three key factors. The first is that there must be something in it for everyone - and a substantial something. At the risk of stating the obvious, the alliance must add substantial value to customers. That's the bottom line. If that's happening, then success should flow to all of the member companies. If all players benefit significantly, they will be willing and eager to put in the time and effort to make it work. The second is that the member companies must show strong organizational commitment from the CEO down with clear ownership at the senior levels. This should come naturally from the aforementioned substantial benefits, but it doesn't always work that way. If there is a major player in one company that isn't willing to dedicate the people, capital, and intellectual property to the same degree as the other players, tensions will emerge. Strategic alignment and fit is also a requirement. We all have to be heading in the same direction. Corporate cultures may have some degree of divergence, as long as they are able to establish and environment of trust.

I believe with the ever-shrinking product life cycle, you should expect to see more alliances like Chemistry Playbook. Shortened life cycles require companies to quickly achieve global share and significant volumes to be able to compete and generate adequate return on investment. Few companies have both the capital and the ability to do so alone in all segments of their value chain. In the New Normal, success will come to those companies who do one thing and do it extremely well, while uniting with partners to complete the pieces of the value chain needed to grow profitably. ◆

BIOGRAPHY

Derek G. Hennecke, MBA
President & CEO
Xcelience

Derek G. Hennecke is a founding member of Xcelience and its current CEO and President. He has a long history of growing strong businesses around the world. He balances a scientific and business background with nearly 2 decades of international experience in the healthcare industry and a track record as a highly successful international turn-around manager in the global drug development community. Xcelience is the first company Mr. Hennecke has managed as an owner, having launched a management buy-out from MDS Pharma Services in 2006. The newly formed company immediately embarked on a robust pattern of strong growth. This growth was recognized in May 2008, when Mr. Hennecke was selected as a finalist for the coveted *2008 Ernst & Young Florida Entrepreneur of the Year* award, a nomination based on the demonstration of extraordinary success in the areas of innovation, financial performance, personal commitment to community, and the company's perpetual growth since its official formation. Mr. Hennecke was also recognized as a finalist for the *Ultimate CEO* awards by the Tampa Business Journal in 2008. This is in addition to Xcelience's nomination for *Small Business of the Year* by the Greater Tampa Bay Chamber of Commerce, also this year. Before founding Xcelience, Mr. Hennecke managed the same Tampa-based business while also overseeing a Seattle and a Montreal-based plant as Vice President and General Manager, Pharmaceutics and Biopharmaceuticals. Prior to that, he spent more than 10 years abroad working for the Dutch-based conglomerate DSM. In Montreal, he was GM of a 250-staff Biologics plant for more than 2 years. In Cairo, Egypt, as GM, he oversaw a radical turn-around in an anti-infectives plant that was originally slated for closure. He also spent 2 years in Holland developing new Pharma intermediates, and two years in Mexico as Commercial Director covering Central and South America. He also worked for Roche, both in Canada and Germany. Mr. Hennecke earned his BSc in Microbiology from the University of Alberta in Canada and his MBA from the Erasmus University in Rotterdam, The Netherlands.

DELIVERY REPORT

Drug Delivery Products & Technologies, a Decade in Review: Approved Products 2000 to 2009

By: Josef Bossart, PhD; Kurt Sedo; and Tugrul T. Kararli, PhD, MBA

With the new decade upon us, it seems a good time to review what Drug Delivery has "delivered" in the past decade. An important perspective is provided by looking at drug delivery products approved by the FDA in the past 10 years. The definition of Drug Delivery Product is open to many positions and opinions. For the purpose of this review, the working definition is a pharmaceutical product that depends on a novel formulation technology that deliberately impacts uptake, distribution, or excretion so as to realize a desired therapeutic effect, or improve convenience. We will separate our analysis into two separate areas: (1) products that primarily depend on drug delivery to enhance, expand, or transform their utility (Enhanced) and (2) products that depend on drug delivery technologies to enable their usefulness (Enabled).[1,2] Examples of Enhanced technologies are those targeted to improving efficacy, safety, tolerability, and convenience or compliance. These include sustained-release oral dosage forms and

transdermal patches. In the case of Enabling technologies, the focus is on technologies that can improve parameters such as solubility and bioavailability and include nano- and microparticle technologies. The product lists for the Enabled and Enhanced products used for this article are available online.[3]

It's important to note that this analysis does not include device-focused drug delivery products, notably stents and injectors. Reliable and consistent information on these products is much more difficult to source. Also excluded are products that depend solely on technologies that have, with time, become a part of the standard formulation toolbox. An example would be simple enteric coating technology as used with proton pump inhibitors. Once again, we suggest you check the online compilation of products to understand what has, and hasn't, been included. This still leaves us with a large number of drug delivery-based products to consider, including those using transdermal, inhalation, oral, sustained-release, quick-dissolve, and injectable sustained-release technologies.

This article's focus on FDA-approved NDA (not ANDA) products is grounded in a desire for consistency. Not only is there less publicly available information on ex-US products, these products are subject to widely varying regulatory standards that make them difficult to analyze and compare.

FDA-APPROVED DRUG DELIVERY PRODUCTS (2000-2009)

Using the criteria defined earlier, we come up with a total of 213 drug delivery products approved in the past decade (191 of them Enhanced and 22 Enabled). A summary of products approved by year is presented in Table 1. While some years were higher and others lower, there seems to be on average about 20 or so drug delivery products approved annually with the high point seen in 2006 when 25 Enhanced and 3 Enabled products were approved. Despite a bit of a tail-off in the past couple of years, there doesn't seem to be any obvious change over time in the average number of annual approvals.

TABLE 1

	Enhanced Products	Enabled Products	All
2000	19	2	21
2001	15	1	16
2002	15	3	18
2003	17	1	18
2004	23	2	15
2005	19	4	23
2006	25	3	28
2007	24	1	25
2008	17	2	19
2009	17	3	20
Total	**191**	**22**	**213**

FDA-Approved Drug Delivery Products (2000-2009)

ANALYSIS BY DELIVERY ROUTE

Among the approved Enhanced drug delivery products, oral delivery was most common, accounting for 52% of all approved products. Among these oral enhanced products, sustained- and modified-release formulations accounted for 38%, ODT 12%, and oral liquid SR 2%. Of the remaining 48%, inhalation accounted for 13%, transdermal 12%, and injection 9%. Of the inhalation group, MDIs and nebulization accounted for 5% and 4% of the total, while DPIs accounted for 3%.

Lagging behind were buccal/lingual and nasal products with 5% each. The remaining 4% was accounted for by implants and inserts. Drug-coated stents are not included in this total for inserts and implants.

For the Enabled products, oral formulated products accounted for 68% and injectables 32% of the 22 approved products in this class. Self-emulsifying delivery systems (SEDDS) and nanoparticle technologies each accounted for about one third of the Enabled products, with the balance made up by a variety of solubilization technologies.

Of the Enhanced products, 21% were intended to provide a local or locoregional therapeutic effect (ie, inhalation for asthma). The remaining products, 79%, were intended to provide a systemic indication (ie, oral for incontinence or transdermal for hormone replacement). Only one of the 22 Enabled technology approved products was intended for local or locoregional activity; the remaining products were targeted to systemic applications.

ANALYSIS BY INDICATION & DELIVERY

The distribution of approvals by indication is presented in Table 2 for both Enhanced and Enabled products. The big indications for Enhanced drug delivery products were CNS (28%), respiratory (12%), endocrinology (11%), and cardiovascular (10%); comprising almost two-thirds of all approved Enhanced products. The CNS products were primarily convenience-enhanced oral products using sustained- or modified-release (26/53), quick oral dissolve (10/53), or buccal/lingual (7/53) technologies. Modified release, often targeted to ADHD-type applications, accounted for 6 of the 53 approved Enhanced CNS products.

Almost all respiratory products were immediate release (22/23). Among the endocrinology products, (18/21) were intended to provide an extended-release profile, while cardiovascular Enhanced products primarily targeted SR applications (13/19). Of the 22 Enabled products, all but one were targeted to immediate-release indications.

DRUG DELIVERY TECHNOLOGY SOURCING

It's interesting to look at how many of the Enhanced products approved in the past decade depended on external technology. What we mean by external technology is a technology sourced from a third party by a development company to develop its own drug delivery product. This would include a Big Pharma or Specialty Pharma company working with an outside company to access necessary drug delivery know-how or intellectual property. It would not include a simple contracting arrangement related to production in which the drug delivery know-how did not reside with the third party.

Based on this definition, about one third of approved products looked to outside providers for the drug delivery technology incorporated into their products. The remaining two thirds used technology already in their portfolio, or they developed internally for use as part of the product concept.

The large number of internally sourced drug delivery technologies may be surprising and warrants explanation. Many pulmonary products, particularly those from experienced Big Pharma companies, such as GlaxoSmithKline and AstraZeneca, were developed using internal technology. There were also a large number of companies that conceived and developed their products before licensing them out to a third party for further development and/or commercialization. Companies like DepoMed and NovaDel are examples of smaller companies considered to have sourced their drug delivery technology internally. But by far the largest number of these internally sourced drug delivery technology products arose within Big Pharma who have internal teams able to provide at least the more common drug delivery technologies.

If we look at the data in terms of products that have arisen from technologies discovered and developed by drug delivery companies, we find more than half of the 212 approved products are the direct result of drug delivery company-derived technologies. Many of these products and technologies and products were passed on to Big Pharma and Specialty Pharma companies for further development or commercialization, but their roots trace back to drug delivery companies.

The leading providers of drug delivery technology to external development companies are presented in Table 3. These and other companies also provided the technology for products not captured in this review, notably OTC and ex-USA products.

Cima had a great run of oral dissolve-based products starting in the late 1990s that continued through the middle of the decade, but Elan powered the greatest number of approved drug delivery products. Elan's strength was a broad portfolio of drug delivery assets that could both enhance and enable their clients' products.

TABLE 2

	Enhanced Products	Enabled Products	All
Allergy	11	0	11 (5%)
Cancer	9	0	9 (4%)
CNS	53	3	56 (26%)
Cardiovascular	19	8	27 (13%)
Endocrinology	21	0	21 (10%)
Gastrointestinal	8	2	10 (5%)
Infectious Disease	12	5	17 (8%)
Neurology	14	0	14 (7%)
Respiratory	23	0	23 (11%)
Urology	8	1	9 (4%)
Other	16	3	19 (9%)

FDA-Approved Drug Delivery Products by Indication (2000-2009)

TABLE 3

Company	Enhanced Products	Enabled Products	Total
Elan	5	6	11
Cima	10	0	10
SkyePharma	6	1	7
3M	6	0	6
Eurand	5	0	5
Nektar	5	0	5
Catalent	4	0	4
CyDex	0	4	4

Approved Product Technologies by Technology Supplier (2000-2009)

3M was the go-to company for MDI companies, while SkyePharma and Eurand provided their partners with a broad portfolio of validated, often oral, drug delivery technologies. Interestingly, the Nektar technology most often incorporated into its partners' approved products did not arise from their considerable pulmonary expertise, but rather the PEGylation technology they added with their acquisition of Shearwater in 2001. Catalent's claim to fame, like Cima's, was with ODT technology. CyDex was a leader in the solubilization technology area.

REFLECTIONS

That's it, a quick overview of prescription drug delivery products approved in the past decade. There certainly were many more drug delivery-based products approved beyond this group, notably branded OTC products and generic formulations (prescription and OTC). And there are also the integrated drug/device products. These products define their own group of opportunities and warrant separate analysis and discussion. Many of these products, notably drug-coated stents, have provided important therapeutic benefits and recorded remarkable sales.

What might we see if we were to do a similar review a decade from now? Here are some predictions. It is likely that many of the most important technologies of the past decade will become part of every company's formulation toolbox. Much as enteric coating technology is now a standard toolbox technology, it is reasonable to expect formulators will have some collection of oral SR and ODT technologies available for use without calling in external assistance. Whether oral ODT and SR products will even warrant listing on the next decade's list of approved drug delivery products remains to be seen.

Inhalation technologies are harder to predict. The most common form of non-specific inhalation, jet nebulization, will probably not warrant mention, but the new electrosonic devices may well define levels of performance that could prove very important. Similarly, inhalation delivery for the treatment of systemic diseases and the delivery of macromolecules will be important and unarguably big business for companies possessing the technology, know-how, and intellectual property protection to power these products.

Simple transdermals, topical creams, and gels intended for systemic delivery, may not warrant mention 10 years from now. Active transdermal products will certainly be included on any list if they are able to efficiently deliver macromolecules or provide unique features, such as dose on demand.

And speaking of macromolecules, there certainly will be a warm reception for companies able to enhance and enable the delivery of siRNA, oligonucleotides, antibodies, and proteins by either injectable or non-injectable delivery routes.

All in all, it has been a great decade for Drug Delivery, but the success of this next decade will depend on developing innovative technologies that deliver next-generation patient benefits rather than simply exploit technologies of the past decade. Like Big Pharma, Drug Delivery needs to continuously renew itself or risk becoming irrelevant.

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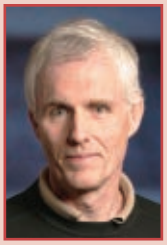

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The AdminPen™ Microneedle Device for Painless & Convenient Drug Delivery

By: Vadim V. Yuzhakov, PhD

AdminMed is developing an innovative line of novel microneedle-based transdermal drug delivery devices. The current pipeline comprises an advanced microneedle array-based pen-injector device (the AdminPen™) that painlessly and conveniently injects therapeutic levels of standard liquid pharmaceutical drugs or cosmetic actives through the skin. This breakthrough technology revolutionizes the way in which medicines can be administered, increasing efficacy, safety, and compliance.[1-3]

Previous studies have demonstrated that a wide range of pharmaceutical compounds can be delivered using microneedle arrays, including small molecules, peptides, and proteins.[4-16] Studies with many subjects have shown that the microneedle arrays are essentially painless and have no adverse side effects.[4-6,17] Nevertheless, the earlier developed microneedle technologies are not well suited for commercialization because of very high manufacturing costs due to use of exotic fabrication techniques, need for significant changes in drug formulations due to their inability to deliver standard liquid drug formulations, and therefore unclear and lengthy regulatory approval processes.

AdminPen is expected to be classified as a Class II medical device with a 510(k) regulatory approval route and can be economically produced to scale using mature high-volume low-cost processes. The injection of vaccines (influenza, HIV, cancer, smallpox, and anthrax), hormones (PTH and hGH), insulin, obesity-management drugs (leptin, liraglutide), and cosmetic dermal fillers (hyaluronic acid and PMMA micro-spheres) would be excellent initial indications for this device.

The system substantially mimics a conventional liquid-reservoir microneedle transdermal patch that can be attached to a standard syringe. One substantial difference from a standard transdermal patch is that this innovative AdminPen drug delivery device will have the ability to deliver large amounts of a drug in a short period of time similar to a standard injection with a hypodermic needle. By comparison, conventional transdermal patches deliver only a small fraction of the pharmaceutical ingredient incorporated in a transdermal patch. In addition, the technology can deliver therapeutic levels of pharmaceutical drugs in 10 to 60 seconds versus the 1 to 2 hours needed for the currently marketed transdermal patches. Existing transdermal patches are limited to using only a very few (less than 10 compounds are currently being delivered in drug patches), small molecule (< 500 Daltons), lipophilic drug formulations that can cross intact skin at a flux sufficient to be clinically useful.

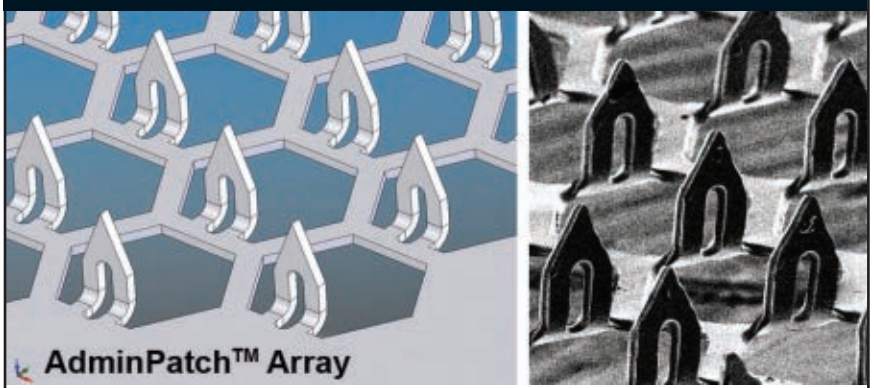
BACKGROUND - MICRONEEDLE ARRAYS

Several methods have been recently proposed for making small pores in the stratum corneum to overcome its barrier properties. In particular, several companies, including 3M, NanoPass, Zosano, TheraJect, and Corium, as well as academic groups at the University of California and at the Georgia Institute of Technology, have been working on the development of microneedle arrays that would make a large number of tiny holes in the stratum corneum.

These known microneedle arrays generally fall into one of three design categories: (1) microneedles with a central hollow bore that are similar in shape to conventional hypodermic needles but much smaller (3M and NanoPass); (2) solid microneedles coated with a special pharmaceutical drug formulation (Zosano); and (3) solid biodegradable microneedle arrays that have a drug encapsulated in the dissolvable microneedle material (TheraJect, Corium).

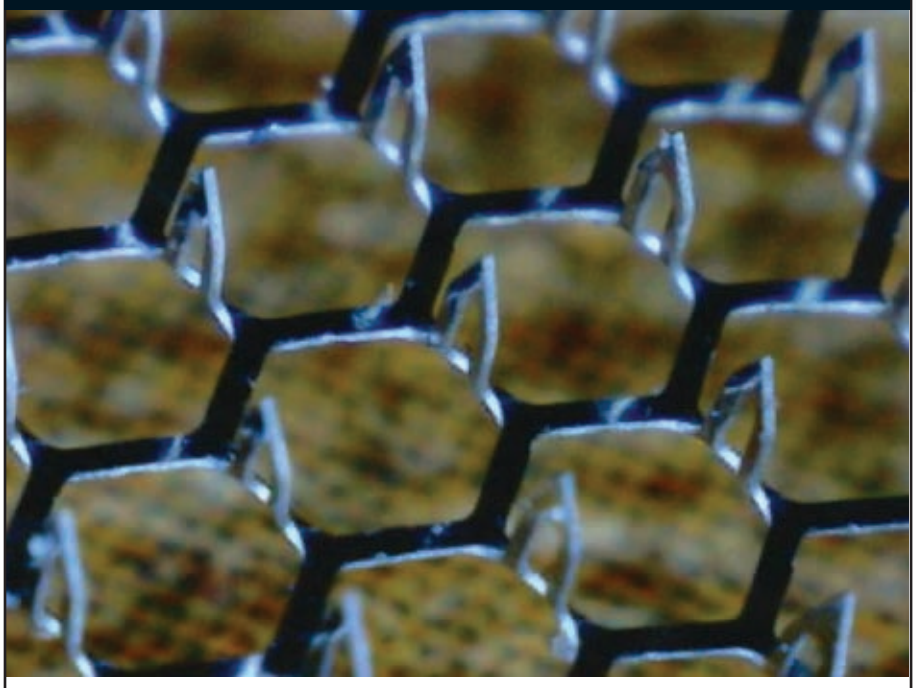
Hollow microneedles with a central

FIGURE 1



AdminPatch® 300 Microneedle Array (left: drawing, right: SEM image)

FIGURE 2



AdminPatch® Microneedle Array

bore are expensive to make and require exotic and expensive microfabrication methods. In particular, it is difficult to make sharp tips on hollow microneedles. Consequently, insertion of the microneedles into a patient's skin can be difficult and often painful. In addition, the central bore of the microneedle is quite small and may be easily plugged by skin tissue during the insertion process, thereby blocking the drug delivery conduit. Furthermore, because the length of microneedle central bore is much greater than its diameter, the diffusional transport of the drug through the central bore may be unacceptably slow. It may be even slower than the diffusion of the drug through the stratum corneum in the absence of the microneedle. To our knowledge, only two companies were able to fabricate hollow microneedle arrays. NanoPass fabricated silicon micro-pyramids with internal lumen using an exotic microfabrication technology, and 3M made samples of plastic microneedle arrays using its proprietary technology.

Solid microneedle arrays are essentially arrays of projections that are used to make holes in the stratum corneum. Since 1996, Zosano (previously a part of Alza Corporation) has developed a method of depositing a drug directly on the surface of these solid microneedles. However, the deposition process is unreliable, and the thin layer of drug formulation on the microneedle could be easily chipped off during storage, transport, or administration (insertion) of the microneedles. Although demonstrated on a laboratory scale, the high-volume microneedle coating process itself is very complex, unreliable, and expensive. Application of a thicker and stronger layer of drug formulation was found to be undesirable because it reduced the sharpness of the microneedles and therefore made insertion more difficult and painful. Zosano even disclosed a special insertion device because patients were unable to insert the microneedle array by themselves without it. Most importantly, the drug-coated microneedles require completely reformulating the drug that leads to long product development timelines; very expensive and long-term clinical efficacy, drug toxicity, and stability studies; as well as an unclear regulatory approval pathway.

Biodegradable microneedle arrays are made of a material that encapsulates the drug and dissolves when inserted into skin. This approach also requires completely reformulating the drug. In addition, there exist significant technical difficulties and risks in designing a biodegradable material that would be strong enough for inserting into the skin without breakage and would be compatible with a specific drug. And of course, a completely new microfabrication method should be developed for making such arrays in high volumes. Moreover, such biodegradable microneedles arrays would be subject to even more intense scrutiny from the FDA that would lead to even longer product development process.

Also, the skin of a patient is quite flexible. Thus, it may be difficult for other microneedle arrays having a rigid, planar substrate to be inserted uniformly into skin during the application step when the microneedles in the central area of the array may not have sufficient engagement with deformed concave skin tissues. For example, a microneedle array having a base made of silicon is flat and inflexible, and even though a polymeric or metal microneedle base can be slightly bent in one direction, such arrays of microneedles cannot readily be applied to concave skin surfaces formed during the insertion step. The microneedle array may need to have a convex shape to ensure uniform insertion of all microneedles into the skin during the application step.

It therefore would be desirable to provide a microneedle array for drug delivery that avoids the disadvantages associated with known solid and hollow microneedle array designs as well as can be flexed and stretched to better conform to a convex, contoured, or moving surface. In summary, there is an unmet need for a painless, effective, user-

friendly, simple, and inexpensive technology for transdermal delivery of a variety of already approved standard liquid pharmaceutical drugs to a patient.

ADMINPATCH® MICRONEEDLE ARRAY IS REFINED MICRONEEDLE TECHNOLOGY

AdminMed has developed the patented Advanced micro-needle array (AdminPatch® Array), which painlessly and instantaneously forms hundreds of tiny micropores through the stratum corneum and epidermis. Numerous drugs, including proteins and water-soluble molecules, can enter the body through these micropores for local effect or by entering the circulation for systemic effect. The created aqueous channels stay constantly open while the AdminPatch array is applied on the skin, and therefore enables the rapid, sustained, and efficient delivery of drugs through these aqueous channels formed in the skin surface. When the microneedle array is removed from the skin, the micropores simply collapse, and the skin barrier is quickly restored.

The human skin has three distinct layers: the outer layer (stratum corneum), having a reported thickness of between 10 to 30 microns; the viable epidermis, containing sentinel cells of the immune system; and the dermis, within which are capillaries and various trauma-sensing receptors.

The aqueous channels formed by the microneedles in the stratum corneum using the AdminPatch system have a depth of about 100 to 1000 microns, sufficient to extend through the viable epidermis into the dermis to reach blood capillaries but shallow enough to avoid most pain receptors.

AdminMed has completed studies that show that while the AdminPen microneedle devices are kept applied on the skin, the micropores formed by microneedles allows injection of drug or any other liquid from an attached syringe into the underlying tissues.

FIGURE 3

AdminPen™ Microneedle Pen-Injector Device

MICRONEEDLE-BASED ADMINPEN™ PEN-INJECTOR DEVICE

AdminPen™ pen-injector device is based on our own patented proprietary microneedle array technology called AdminPatch microneedle array (covered by US Patent No. 7,658,728 and Patents pending in the US and other countries). A simple low-cost molded plastic part is simply attached on the back

TABLE 1

Addresses Unmet Patient Needs	AdminPen
Painless	YES
Simple, intuitive operation	YES
Compatible with a standard syringe	YES
Eliminates sharps hazards	YES
Attractive to Pharma Partners	AdminPen
510(k) regulatory approval strategy	YES
Existing drug formulation	YES
Low-cost high-speed manufacturing	YES
Uniformly inserted into flexible skin	YES

AdminPen™ Competitive Advantage

surface of the AdminPatch microneedle array to provide a fluidic connection of AdminPen device to an externally connected liquid drug reservoir. The AdminPen pen-injector device can be mounted on any commercially available standard syringes or injector pens with a prefilled drug cartridge. The AdminPen needle substitute should be an excellent fit for user-friendly and painless delivery of vaccines (influenza, smallpox, anthrax); cosmetics (hyaluronic acid, Botox); or pharmaceutical drugs requiring frequent injections, such as parathyroid hormone, human growth hormone, obesity-management drugs (leptin, liraglutide), anemia drugs (epoetin alfa), and pre-meal insulin. The device is expected to be classified as a Class II 510(k) medical device. During each injection, the drug is uniformly injected into a 1-cm^2 area of the skin.

Clinical benefits of the AdminPen pen-injector device includes the following:

- Promotes patient compliance through eliminating the use of painful regular needle injections.
- Improves drug efficacy and safety by ensuring proper injections through simple, intuitive operation and by using a standard prefilled glass cartridge or a standard syringe.
- Enhances product safety by eliminating sharps hazards and offering safe, easy disposal of consumables as well as by eliminating electrical and high-pressure parts.

The painless AdminPen device combines effective delivery of drugs through the skin with excellent skin sensation and cosmetics, is easy and intuitive to use by patients and medical personnel alike, and can be economically produced to scale using mature high-volume low-cost processes. The strategy of applying the AdminPen device to the existing already-approved liquid drugs avoids both the costs and time spent on drug discovery and the risks of bringing a new compound to the market, as well as provides a significant pipeline of potential products based on existing already-approved drugs.

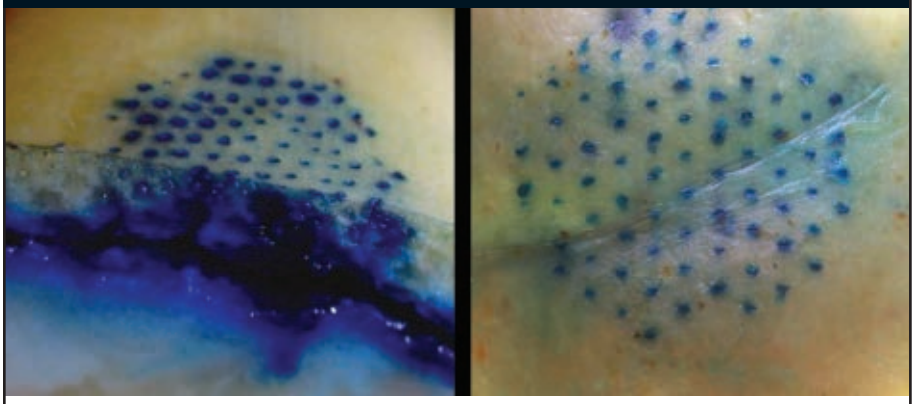
FIGURE 4

AdminPen™ Connected to a Regular Syringe Filled With Blue Dye

This painless microneedle injection device could potentially address the limited appeal of injections and avoid the first-pass metabolism issues presented by oral delivery. To demonstrate the feasibility of using the AdminPen device for subcutaneous drug delivery, a study is underway to obtain a pharmacokinetic profile comparable to that observed by subcutaneous injection with a standard needle.

The AdminPen device is expected to have attractive profit margins because the microneedle array and the injection-molded support/syringe connector can be manufactured at low cost using mature, large-scale processes. The device does not use any

FIGURE 5



Injection of a Dye With AdminPen™

electronic components and can be entirely outsourced to low-cost precision stamping and plastic molding vendors.

A patient simply connects the AdminPen to a standard syringe and applies it to the skin. The microneedles penetrate the upper layers of the skin, thereby painlessly and instantaneously cutting the stratum corneum and epidermis to create hundreds of micro-channels near each microneedle. Each microneedle also keeps these channels open to allow injection of pharmaceutical drugs from the syringe through the microporated skin. When the AdminPen microneedle device is removed from the skin, the micropores simply collapse, and the skin barrier is quickly restored.

CURRENT ADMINPEN™ DESIGN

The current design of the AdminPen is composed of a "button" with a convex front-end and a back-end having a luer connector for connection to a standard syringe. The AdminPatch microneedle array is applied on the front convex surface of the button, which also has microfluidic channels that direct the injected drug from the syringe into the microchannels on each microneedle.

The initial testing of the AdminPen microneedle device prototypes has shown the successful insertion of the microneedle array and delivery of a dye through the skin as can be seen in Figure 5. The cross-sectional view demonstrates the successful delivery of dye under the skin using the device.

The results of the initial tests are very encouraging and a more rigorous design optimization and more extensive in vitro testing of the device is being undertaken. Several approaches to fully optimize and improve the design of AdminPen are currently being evaluated. Meanwhile, a web store has been established to quickly provide samples of microneedle arrays and AdminPen microneedle devices to our partners for evaluation. Several AdminPen products based on microneedle arrays of different lengths from 600 to 1500 microns are available.

COMMERCIAL POTENTIAL

There is an unmet need for a user-friendly, painless, simple, effective, and inexpensive technology for delivery of a variety of already approved liquid drug types to a patient. AdminMed estimates the AdminPen transdermal pen-injector device to have an annual worldwide market potential of approximately $2 billion. ◆

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BIOGRAPHY

Dr. Vadim Yuzhakov is an inventor on 12 granted and numerous pending patents related to microneedle technologies. His career includes significant experience in the research and development of medical devices and pharmaceutical drug delivery systems. He established and coordinated several research and development projects. As a Program Manager IV, he managed a development program at Abbott Diabetes Care. Previously, as a Principal Engineer at Altea Therapeutics, a specialty pharmaceutical company, he actively participated in the development a new advanced transdermal insulin patch based on a thermal microporation method. As a Senior Scientist at LifeScan, a Johnson & Johnson company, he significantly contributed to the development of an "all-in-one" system for convenient glucose monitoring; and as a Scientist at Procter and Gamble, he led the development of microneedle patches for drug and cosmetics delivery. He is a Certified Project Management Professional (PMP) and earned his MS in Mechanical Engineering from Lomonosov Moscow University and his PhD in Chemical Engineering from the University of Notre Dame. Dr. Yuzhakov can be contacted at Vadim@AdminMed.com.

In Vivo Delivery of Nucleic Acid-Based Agents With Electroporation

By: Karen E. Dolter, PhD; Claire F. Evans, PhD; and Drew Hannaman

INTRODUCTION

Electroporation (EP) is a delivery technique that improves the intracellular uptake of agents such as small molecule drugs and biological molecules in a local region of tissue. EP induces a transient state of membrane destabilization/permeability, during which time substances present in the extracellular space at the site of EP application can be taken up into the affected cells with high efficiency. Shortly following EP, the cell membrane stabilizes, and the cells resume normal function.

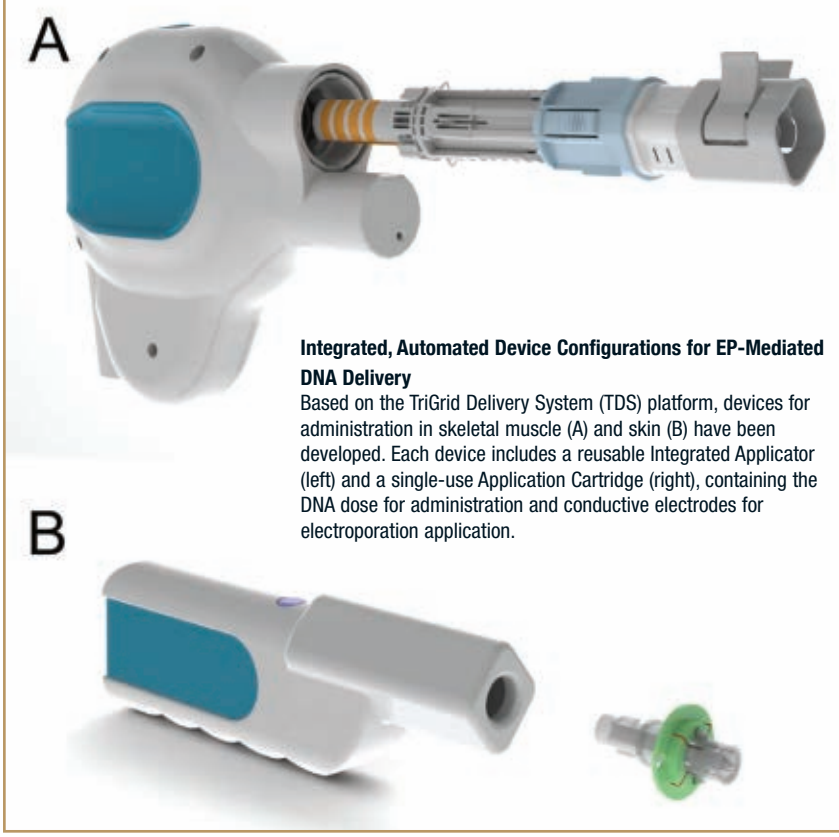
ELECTROPORATION-MEDIATED DELIVERY OF NUCLEIC ACIDS

EP was initially discovered to increase DNA delivery to in vitro cell cultures; adaptation of EP to in vivo use has yielded an efficient method for nucleic acid delivery to tissues.[1] In vivo, EP is typically initiated with the administration of an agent to the target region of tissue, usually by local injection. This is immediately followed by the application of electrical fields capable of inducing the EP effect. The electrical signals are administered using an electrode array contacting the target tissue where the agent is distributed. This procedure greatly increases intracellular uptake in tissues where the agent is present in the extracellular environment during generation of the EP effect. EP is therefore an effective method for the local delivery of agents with intracellular activity that are unable to enter the cell passively.

Experience in a variety of animal species has demonstrated that, with appropriate refinement in application devices, administration conditions, and electrical parameters, EP can be adapted for nucleic acid delivery in a wide variety of tissues, including skeletal muscle, liver, spleen, kidney, brain, blood vessels, bladder, lung, skin, and tumors of different origins, while minimizing tissue disruption.[1]

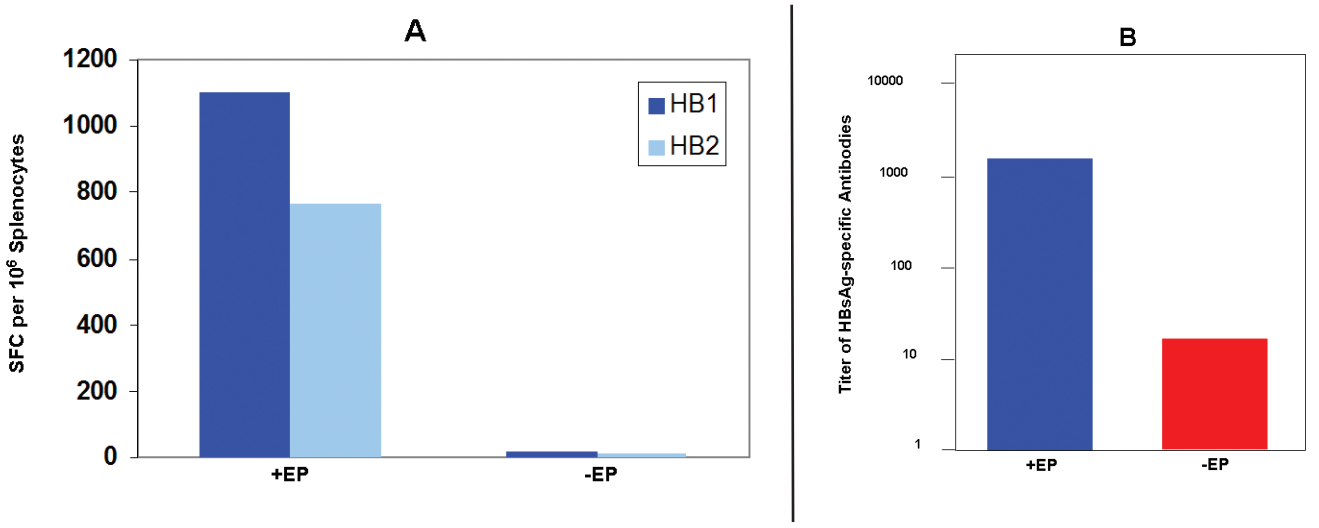
When used to increase the in vivo delivery of nucleic acids, EP has been

FIGURE 1



Integrated, Automated Device Configurations for EP-Mediated DNA Delivery
Based on the TriGrid Delivery System (TDS) platform, devices for administration in skeletal muscle (A) and skin (B) have been developed. Each device includes a reusable Integrated Applicator (left) and a single-use Application Cartridge (right), containing the DNA dose for administration and conductive electrodes for electroporation application.

FIGURE 2



Enhanced Potency of DNA Vaccines Delivered With EP
Immune responses were evaluated in BALB/c mice (A) and New Zealand White rabbits (B) following immunization with a plasmid encoding the hepatitis B surface antigen (HBsAg) by conventional intramuscular injection (-EP) or by intramuscular injection followed by EP using Ichor's TDS-IM device (+EP). (A) 2 micrograms of plasmid was delivered into one tibialis anterior muscle per mouse on days 0 and 28, and HBsAg-specific T-cell responses were evaluated in spleens at day 35 by measuring IFN-gamma responses to two HBsAg peptide epitopes (H1 and H2) in an ELISPOT assay. Results are plotted as spot-forming cells (SFC) per million splenocytes. (B) 0.5 milligrams of plasmid was delivered to one quadriceps muscle per rabbit on days 0 and 28. Serum titers of antibodies specific for HBsAg were assessed in serum by ELISA 2 weeks following the second immunization.

demonstrated to increase the potency of these agents by 10- to 1000-fold compared to administration using conventional injection alone. Compared to delivery by viral vectors, EP delivery of nucleic acids is advantageous due to the absence of any live vector components (and the attendant safety concerns) and to the inherent non-immunogenic nature of nucleic acids as vectors, resulting in the ability to administer the agent multiple times without inducing inhibitory responses to the vector itself.

Importantly, EP delivery of nucleic acid-based agents into the cytosol can be achieved in the absence of complex formulations or transfection reagents. As a result, the manufacture and administration of the nucleic acid-based agents is greatly simplified. Taken together, these properties indicate that EP has the capability of overcoming what has been an important limitation of nucleic acid-based drugs, namely the inability to efficiently cross the cell membrane in order to reach the intracellular site of action.

CLINICAL EP DEVICES FOR NUCLEIC ACID DRUG DELIVERY

Clinical development of nucleic acid-based products has been limited by low and inconsistent biological responses when administered in humans, primarily due to the inefficient and inconsistent intracellular delivery associated with conventional methods for the delivery of this class of agents.[2] Based on the encouraging results of studies investigating EP-mediated nucleic acid delivery in animals, several research groups have progressed to clinical testing of DNA drugs delivered by EP.

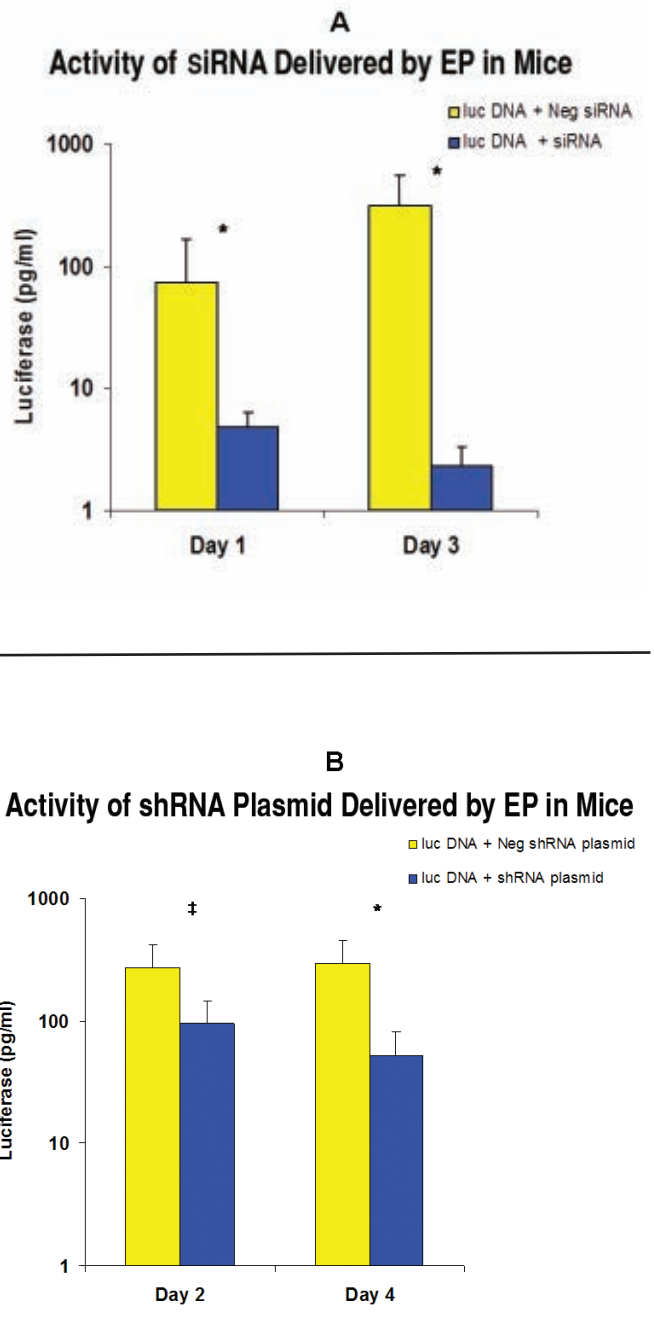
An important consideration for clinical evaluation of novel agents delivered by EP is the development of administration procedures and devices suitable for use in the clinical setting. Of foremost importance, a clinical EP device must ensure that propagation of the electrical fields coincides with the site of nucleic acid distribution within the target tissue in a consistent manner across heterogeneous patient populations.[3] In addition, device features that enhance the clinical acceptability and tolerability of the procedure will be important in determining the range of clinical indications for which the technology can be deployed. Initial clinical testing of in vivo EP was conducted using devices based on a manually controlled two-step procedure. Specifically, a manual injection of the agent using a conventional syringe was followed by insertion and activation of an electrode array in the area of tissue judged by the operator to be the site of DNA distribution. The susceptibility of this procedure to substantial intra-operator variability led to the development of improved systems that integrated the means for agent administration and electroporation application into a single, simple-to-use administration device. By ensuring the agent and electrical fields are administered to the same tissue site, integration of the entire procedure into a single device reduces the need for operator training, facilitates reproducibility, and lowers the risk of false negative results in clinical trials due to improper or inconsistent administration of the procedure. In addition, device technologies capable of simple and rapid administration are likely to be preferred by both patients and healthcare personnel.

Several integrated EP device formats currently in clinical testing include Inovio Biomedical's Twinjector (Elgen®) and Cellectra® and Ichor Medical System's TriGrid™ Delivery System (TDS).[3] Although initially developed for intramuscular delivery, devices are now being adapted for other routes of administration. For example, the Ichor TDS platform includes devices for both intramuscular (TDS-IM) and intradermal (TDS-ID) administration. Each TDS device consists of three components: a Pulse Stimulator, an Integrated Applicator, and a

single-use Application Cartridge (Figure 1). The Application Cartridge is packaged sterile for single use and is attached to the Integrated Applicator at the beginning of the procedure. The cartridge encloses a TriGrid Electrode array composed of four electrodes arranged in two interlocking triangles (hence the name TriGrid) around a central injection site with array dimensions that match the fluid distribution profile for injection into the target tissue. The Integrated Applicator is a reusable hand-held device that automatically deploys the electrodes and administers the DNA, providing user-independent control over the rate and site of DNA administration. The Integrated Applicator connects to the Pulse Stimulator, which monitors the procedure for safety and generates the EP-inducing electrical fields.

The integrated, automated design of the TDS allows application of the entire procedure within a few seconds, while ensuring that EP is applied to the tissues at the site of nucleic acid distribution in a consistent fashion. The TDS devices use deployable electrodes with integrated stick protection that engages automatically when the procedure has finished, minimizing visualization and exposure to sharps during the procedure. The TDS-IM has been used in clinical testing for a therapeutic DNA vaccine encoding a melanosomal antigen in melanoma patients at high risk for recurrent disease. It has also been evaluated in a placebo-controlled comparative study of EP delivery and conventional intramuscular injection for delivery of a prophylactic HIV vaccine.[4] The ability to conduct this first study of EP-mediated DNA delivery in healthy human volunteers confirms the progress that has been made in the evaluation of procedure safety and tolerability and suggests that EP may be suitable for a variety of applications.

FIGURE 3



Electroporation-Based siRNA & shRNA Plasmid Delivery for Knock-Down of Reporter Gene Expression
1 microgram of luciferase reporter plasmid (luc DNA) was coadministered with (A) 1 microgram of siRNA (luciferase-specific or negative control) and (B) 10 micrograms of shRNA plasmid (luciferase-specific or negative control) on day 0 with Ichor's TDS-IM device to the tibialis anterior muscle of Swiss Webster mice. Muscles were harvested at the indicated time points, and luciferase activity was assayed in muscle lysates.

DNA VACCINES

DNA vaccines contain sequences encoding immunogenic proteins or peptides that when expressed, can elicit immune responses against a target protein antigen. DNA vaccination provides benefits for safety and efficacy compared to conventional immunization. Most important is the ability to elicit broad, antigen-specific cellular and humoral immune responses without the safety concerns associated with live pathogens or immunomodulatory adjuvants.[2] The ability to induce long-term expression of the antigen in the individuals' own cells may provide advantages in potency that result in a reduction of the number of immunizations required to achieve target immune responses and/or an increase in the duration of protection achieved. As an alternative to conventional protein-based vaccines, development of DNA vaccines can be rapid and cost effective, with the potential to improve upon the performance of existing vaccines and facilitate the development of novel vaccines addressing pathogens and diseases for which there are no current vaccines.

Preclinical investigation of EP-based DNA immunization has been performed in a wide range of animal models demonstrating significant improvements in vaccine potency achievable with this delivery method.[5] In the context of DNA vaccines, EP greatly increases the magnitude of both cellular and humoral immune responses for a wide range of antigens.[3] Increased response rates and reductions in the number of immunizations required to achieve target levels of immunity have also been observed. For example, immunization of mice and rabbits with plasmid DNA encoding hepatitis B virus surface antigen induces immune responses that are significantly increased when the plasmid is delivered by EP (Figure 2). Studies in non-human primates have demonstrated that, in addition to the induction of potent cellular immune responses, DNA vaccines delivered by EP can also induce antibody responses and protection against experimental disease

challenge at levels comparable to currently licensed vaccines.[5,6]

Human clinical trials for EP-based DNA immunization have been initiated for a variety of disease indications, including cancer therapy and treatment or prevention of viral infection (van den Hurk and Hannaman, Expert Review of Vaccines, in press). Recently reported results from a number of these clinical trials suggest the feasibility of vaccination with DNA in humans. In a study of a DNA vaccine candidate encoding a prostate-specific membrane antigen epitope fused to a modified form of tetanus toxin delivered to prostate cancer patients, EP-based DNA vaccine delivery was associated with a significant increase in antibody responses to the tetanus toxin compared to conventional injection.[7] EP-mediated administration of a hepatitis C virus (HCV) DNA vaccine in patients with chronic HCV infection resulted in T-cell responses and transient reductions of viral load in some patients.[8] Interim results from a trial investigating a human papillomavirus (HPV) DNA vaccine delivered by EP in patients with previous precancerous cervical lesions resulted in T-cell and antibody responses in some patients at the first two dose levels.[9] These responses have the potential for inhibiting the development of cervical cancer in women already infected with HPV. Finally, interim results from a trial for a preventive HIV DNA vaccine in healthy volunteers showed that delivery of the vaccine with EP resulted in higher frequency and breadth of T-cell responses compared to intramuscular injection without EP.[4] Taken together, initial trial results indicate that EP is safe, tolerable, and capable of enhancing immune responses to DNA vaccines in humans.

THERAPEUTIC PROTEINS

Nucleic acid-based drugs enabling the sustained endogenous production of therapeutic proteins in a subject's own tissues may provide an alternative to long-term therapy based on repeated administration of the proteins themselves. By inducing sustained production and secretion of protein for weeks to months from a target tissue following a single administration, nucleic acid-based drugs delivered with EP provide possible benefits compared to the frequent injections required to achieve and maintain effective levels of a therapeutic protein when administered in the form of the protein itself. These benefits include the convenience and cost effectiveness of fewer administrations required to maintain therapeutic levels of the protein as well as reduced potential for adverse side effects associated with high protein concentrations that commonly occur after the bolus dosing of certain protein-based drugs (for example, type I interferons). Preclinical data from studies of EP-mediated delivery of DNA drugs encoding therapeutic proteins, such as immunomodulatory cytokines, hematopoietic factors, endocrine hormones and transcription factors, as well as monoclonal antibodies for infectious diseases, cancer, and chronic inflammatory diseases, suggest that DNA drugs may provide cost-effective alternatives for locoregional or systemic protein delivery.[1,10-13]

Building on this concept, the first DNA EP-based product approved for commercial use was a DNA plasmid encoding the porcine growth hormone-releasing hormone (GHRH) licensed in Australia to allow sustained GHRH production in female swine, thereby enhancing the viability and health of their offspring.[14] Therapeutic protein-encoding DNA drugs delivered with EP are also currently under investigation for various human clinical applications, including intratumoral expression of immunomodulatory cytokines, local production of proangiogenic growth factors in ischemic tissue, and expression of a transcription factor for healing burn wounds.[15-17]

RNA INTERFERENCE

EP may also have utility in the field of RNA interference (RNAi). The technique has been demonstrated to induce transient downregulation of gene expression following delivery of small interfering RNA (siRNA). Alternatively, more sustained downregulation of target genes can be achieved through in vivo delivery of DNA vectors expressing short hairpin interfering RNA (shRNA).[18] Figure 3 shows the effects of EP-mediated gene-specific siRNA and shRNA plasmid delivery on expression of a luciferase reporter gene. By day 3 post-transfer, luciferase activity in muscles receiving luciferase siRNA was reduced to 0.7% of the level in muscles receiving negative control siRNA (Figure 3A). By day 4 post-transfer, luciferase activity in muscles receiving plasmid DNA encoding luciferase-specific shRNA was reduced to 17% of the level in muscles receiving negative control shRNA (Figure 3B).

While these results are encouraging, the locoregional nature of the increased delivery achievable with EP is an important consideration when assessing the suitability of the technique for RNAi delivery in a given disease indication. To date, EP has been adapted to enhance RNAi in the research setting to study the effect of specific gene knock-down in localized tissues as well as in animal models of disease.[19-21] Such results indicate the potential suitability of EP for indications in which RNAi therapy could be used for local downregulation of target genes to treat conditions manifesting locoregional sequalae. Although EP-based delivery has not yet been implemented for RNAi delivery in the clinical setting, the initiation of clinical studies for locoregional RNAi therapy in diseases, such as age-related macular degeneration, skin disorders, and cancer, suggest that EP could have a future role in the delivery of RNAi-based therapeutics for selected indications.[22,23]

SUMMARY

In vivo EP is a robust, adaptable method for achieving 10- to 1000-fold enhancement in DNA uptake and expression in a variety of tissue types, and as such, EP may be able to overcome the suboptimal clinical potency observed with conventionally administered nucleic acid drugs.

The significant enhancements in nucleic acid drug potency observed with EP-mediated nucleic acid delivery has provided the basis for the initiation of early phase clinical trials. An acceptable safety profile in initial therapeutic indications combined with the development of more refined device technology has enabled the initiation of prophylactic studies. In addition to the ongoing opportunities in DNA-based protein and vaccine delivery, preclinical progress with EP-based delivery of vectors for RNAi and other novel classes of nucleic acid drugs may increase the range of clinical applications for this technology. Collectively, the recent advances and promising outlook for EP-based delivery suggest that the technology is capable of enabling nucleic acid-based drugs requiring local or locoregional delivery.

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BIOGRAPHIES

Dr. Karen Dolter joined Ichor Medical Systems in 2005 as a Senior Research Scientist. She has served as Principal Investigator for in vitro and in vivo projects, including gene delivery and expression experiments as well as GLP preclinical safety studies. Prior to joining Ichor, she held scientist positions at MediGene and Stratagene, and previously, she received academic post-doctoral training in the areas of molecular virology, tumor cell biology, and gene regulation research. She earned her PhD in Microbiology and Immunology from the University of Michigan, Ann Arbor.

Dr. Claire Evans earned her PhD in Biological Chemistry at the University of Michigan, Ann Arbor. After post-doctoral training in immunovirology, she became an Assistant Professor at The Scripps Research Institute in the Department of Neuropharmacology. She joined Ichor Medical Systems in 2003, where she is currently Director of Therapeutic Programs. She has been a Co-Editor of the journal CNS & Neurological Disorders-Drug Targets since 2002.

Drew Hannaman is a Co-Inventor of the TriGrid electroporation technology and, during his 7 years as the Vice President of Research & Development for Ichor Medical Systems, Inc., has been responsible for guiding development of the TriGrid Delivery System from initial concept into clinical testing for multiple indications. He holds a degree in Cybernetics from the University of California, Los Angeles, and has over 14 years of experience in the development of novel medical technologies, specializing in device-based delivery systems for drugs and biologics.

NANOMICELLAR TECHNOLOGY

Topical Delivery of Hydrophobic Drugs Using a Novel Mixed Nanomicellar Technology to Treat Diseases of the Anterior & Posterior Segments of the Eye

By: Poonam R. Velagaleti, PhD; Eddy Anglade, MD; I. John Khan, PhD; Brian C. Gilger, DVM; and Ashim K. Mitra, PhD

INTRODUCTION

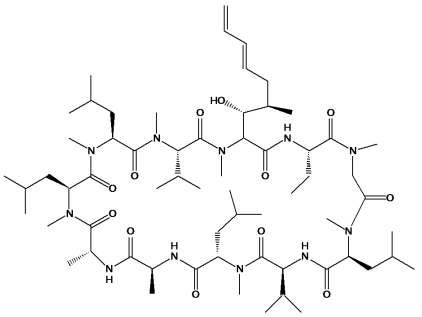
Instillation of topical eye drops is the preferred and most convenient route of drug administration for treating ocular diseases. However, formulating hydrophobic drugs for topical applications is challenging. Hydrophobicity limits the feasibility of producing aqueous formulation concentrations sufficient to achieve therapeutic levels in the ocular tissues. Hydrophobic drugs are therefore usually applied as oil-in-water emulsions, which appear less well tolerated than homogeneous aqueous solutions. Emulsion formulations also limit the amount of drug that can be applied. To overcome these problems, a novel nanomicellar technology has been developed. Solubilization of hydrophobic drugs is achieved through entrapment in a mixed micellar hydrophobic core with a corona composed of hydrophilic chains extending outward, resulting in a clear aqueous formulation. This nanomicellar formulation appears to discharge its active ingredient in a manner that establishes high ocular tissue concentrations in both the anterior and posterior eye segments.

The unique formulation technology has been validated using a hydrophobic cyclic undecapeptide, voclosporin. This novel calcineurin (CN) inhibitor is directed at activated T-helper cells, inhibiting their proliferation and attenuating the immune response. This mechanism is clinically utilized for immunosuppression in organ transplantation and in autoimmune diseases. An oral formulation (LUVENIQ, LX211) of voclosporin has demonstrated efficacy and safety in treating non-infectious uveitis and is currently under review by the US FDA and European Medicines Agency for marketing authorization. The same active ingredient is formulated into LX214, a topical mixed nanomicellar aqueous solution, for treating dry eye syndrome and other anterior segment inflammatory diseases. In this article, data are presented demonstrating the tolerability and initial signals of efficacy for LX214, which is then compared to Restasis®, a 0.05% emulsion of cyclosporine A (CsA), a molecule that shares the same mode of action as voclosporin. Restasis® is approved in the US for the treatment of dry eye syndrome. LX214 is able to deliver drug to posterior ocular tissues of sufficient therapeutic value. This unique nanomicellar drug delivery platform presents potential opportunities for topical administration of additional hydrophobic drugs and the ability to non-invasively target retinal and other posterior segment diseases.

BENEFITS/LIMITATIONS OF OCULAR TOPICAL DRUG ADMINISTRATION

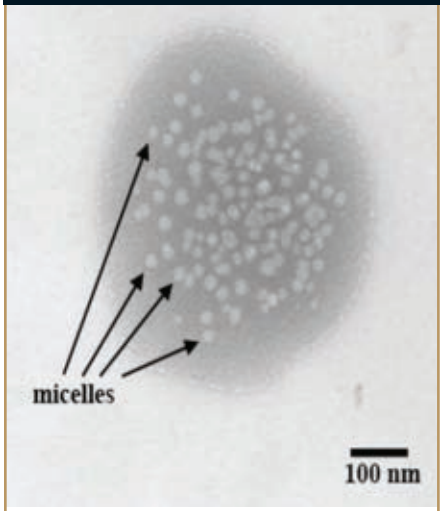
Topical administration of hydrophilic molecules to the anterior segment is often relatively straightforward. However, highly hydrophobic drugs present a significant challenge, and the active ingredient discharge from oil-in-water emulsions is not well understood. Topical application is considered ineffective for delivery of hydrophobic drugs to the posterior eye segment. This reasoning stems from (1) the high-resistance drug penetration barriers presented by the corneal and conjunctival layers of the eye; (2) the rapid irrigation within the eye caused by lacrimation and drainage that washes fluids out into the nasolacrimal ducts or overflow from the eyelids; (3) the metabolism of active drug by enzymes present in tear fluid; and (4) the removal of the active drug by highly vascularized ocular tissues (ie, conjunctiva, choroid, uveal tract, and inner retina).

FIGURE 1



Chemical structure of voclosporin (a hydrophobic molecule).

FIGURE 2



A transmission electron micrograph (TEM) of mixed nanomicellar formulation with Vitamin E TPGS and octoxynol-40 loaded with 0.2% voclosporin.

However, many investigators are now re-evaluating the potential of topical delivery for the back-of-the-eye opportunities to address large markets, including glaucoma, age-related macular degeneration, diabetic retinopathy, and inherited retinal degenerative diseases.[1-7] Topical delivery offers benefits of easy application, reduced risk of infection compared to implantation/injection-based systems, as well as ease of dose adjustment.

NOVEL NANOMICELLAR CLEAR AQUEOUS FORMULATION OF A HYDROPHOBIC DRUG

LX214, a nanomicellar formulation, 10 to 15 nm in size containing up to 0.2% voclosporin, was developed by Lux Biosciences Inc. in collaboration with Dr. Ashim Mitra at the University of Missouri, Kansas City. The chemical structure of voclosporin is shown in Figure 1. Voclosporin was developed by Isotechnika Pharma, Inc. (Edmonton, AB, Canada) for use in the prevention of organ graft rejection and the treatment of autoimmune diseases, such as uveitis and psoriasis.

Mixed nanomicelles are composed of two non-ionic surfactants, D-alpha-tocopheryl polyethylene glycol 1000 succinate (Vitamin E TPGS) stabilized with octyl phenol ethoxylate (octoxynol-40) in a defined ratio. A transmission electron micrograph of the drug-loaded nanomicellar "fluid bubbles" is shown in Figure 2. LX214, packaged in single-use sterile low-density polyethylene, blow-fill -sealed vials (Figure 3), has demonstrated stability for at least 1 year under refrigeration and for 2 months at room temperature.

LX214 EFFICACY IN CANINE KERATOCONJUNCTIVITIS SICCA (KCS)

The mode of action of voclosporin is calcineurin (CN) phosphatase inhibition. CN inhibitors reversibly inhibit immunocompetent lymphocytes, particularly T-lymphocytes, and inhibit lymphokine production and release.[8,9] Voclosporin mediates its suppressive effects on T-lymphocytes by binding to a ubiquitous intracellular protein, cyclophilin. This complex inhibits the calcium- and calmodulin-dependent serine-threonine phosphatase activity of the CN enzyme. CN inhibition then prevents the activation of various transcription factors necessary for the induction of cytokine genes (IL-2, IFN-gamma, IL-4, and GM-CSF) during T-cell activation. LX214 is currently in early stage clinical trials as a treatment for anterior segment inflammatory diseases, such as KCS and blepharitis.[10]

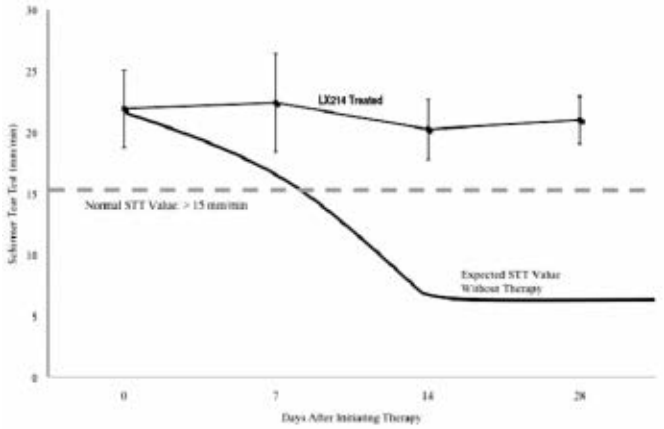
Efficacy of topical ocular LX214 administration for KCS treatment was demonstrated in an outpatient 4-week dog study. The work was conducted under supervision by a veterinary ophthalmologist as an open-label, single-group study utilizing dogs diagnosed with chronic immune-mediated KCS at the North Carolina State Veterinary Teaching Hospital. Efficacy was quantified by (1) tear production measurement using the Schirmer tear test (STT), (2) clinical observation of the cornea, (3) feedback from dog owners, and (4) overall assessment of participating ophthalmologists. Six dogs having residual lacrimal function and a response to topical Cyclosporine (CsA) ointment (Optimmune®) treatment prior to enrollment were switched directly to twice daily (12 hrs) topical ocular administration of 0.2% LX214 (~50 microliters, 0.1 mg voclosporin/eye/dose). LX214 treatment was considered successful if pre-study STT values, obtained during CsA treatment, were maintained or increased. A control group was not included given the reproducibility of the model and ethical considerations. The expected decrease in STT with placebo (Figure 4) was therefore based on historic controls.

Upon study completion, there were no adverse corneal findings, and both the ophthalmologist and dog owners' assessments were positive (no obvious decline in ocular comfort level). The data shown in Figure 4 indicated that twice daily topical ocular LX214 treatment maintained the STT value (> 20 mm/min) in dogs with KCS for 30 days.

FIGURE 3

Clear nanomicellar ophthalmic solution of 0.2% voclosporin (LX214) in a single-use LDPE, sterile BFS vial.

FIGURE 4



Mean Schirmer tear test values (± SD) of KCS dogs through 30 days of treatment with LX214 (n = 6).

TOLERANCE OF LX214 VERSUS RESTASIS IN NZW RABBITS

A pilot comparative animal study was conducted in New Zealand White (NZW) rabbits to evaluate the tolerability of LX214 formulation containing 0.02% or 0.2% voclosporin versus Restasis® (oily emulsion of 0.05% CsA). Rabbits (n = 3 per treatment) were given four consecutive topical ocular administrations of LX214 or Restasis® at 30-minute intervals. Microscopic ocular examinations were performed prior to dosing and at 1, 24, and 72 hours following final administration. Ocular irritation was assessed using the Hackett-MacDonald Scoring system.[11] Mean examination scores are presented in Figure 5. The results demonstrated that repeated topical ocular administration (four applications in 2 hrs) of either LX214 formulations was well tolerated in rabbits and, at the end of treatment, LX214 induced significantly less irritation than equivalent ocular dosing with Restasis®.

TOLERABILITY OF TOPICAL OCULAR LX214 ADMINISTRATION IN HUMAN CLINICAL TRIALS (PHASE I)

A Phase I dose escalation study (0.02% and 0.2% LX214 formulations) was conducted in humans to evaluate tolerability in both healthy volunteers and subjects with KCS. Thirty healthy volunteers (14 men and 16 women) received three consecutive doses of LX214 (one drop of either formulation) or placebo in each eye at 4-hour intervals followed by evaluation at 12 and 24 hours post-dosing. Five female patients with moderate-to-severe KCS self-administered 0.2% LX214 twice daily every 12 hours for 14 days, with evaluations on days 7 and 14. In all groups, tolerability was assessed by treatment-emergent ocular symptomatology using the Ocular Surface Disease Index (OSDI). Safety evaluations included adverse events, Snellen visual acuity, ophthalmic evaluations, intraocular pressure (IOP), vital signs, and clinical laboratory evaluations. Additionally, systemic voclosporin exposure was measured in LX214 treated subjects.

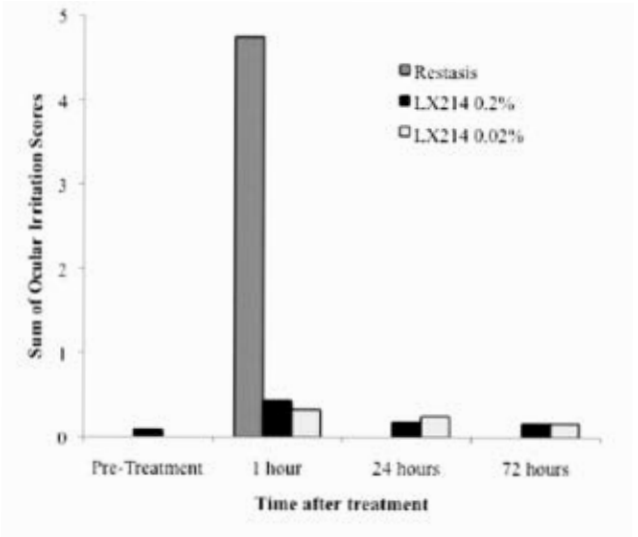
The results showed that both LX214 formulations were similarily tolerated compared to placebo in healthy volunteers. After the 14-day study, mean OSDI scores were decreased (62 at baseline compared to 42), and STT scores increased (68% and 31% for right and left eyes, respectively) in the five KCS female subjects. Hence, improvements were seen in both sign (STT) and symptom (OSDI index) of the disease. In LX214 treated groups, the maximum systemic voclosporin exposure was low (0.18 ± 0.08 ng/mL).

Although the five KCS patient results in the Phase I study were uncontrolled and from a small cohort, the objective signals of efficacy (STT and OSDI) are intriguing. Of note, these signals were observed within 14 days of treatment initiation, suggesting a rapid onset of effect. Substantially higher tissue concentrations, as determined in animal studies described further and seen in Figure 6, may translate into early onset of action and early efficacy. However, larger controlled clinical trials are needed to explore this further.

TOXICOLOGICAL EVALUATION OF LX214 (0.2% VOCLOSPORIN) IN ANIMALS

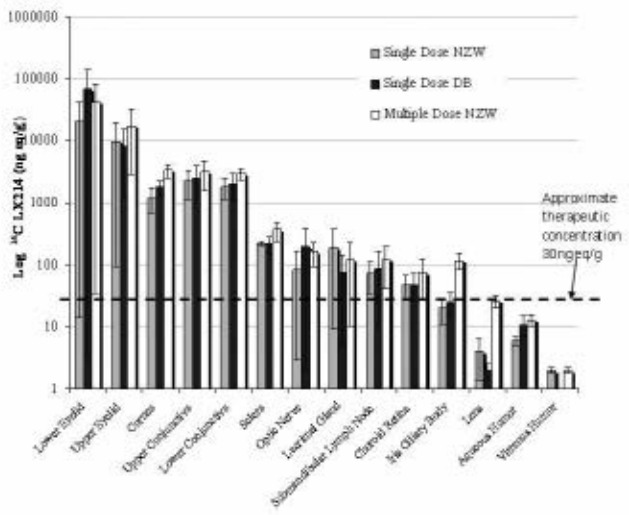
Topical ocular LX214 administration (0.2% voclosporin) and placebo were also evaluated in 14-day and 3-month toxicity studies in NZW rabbits, and in a 14 day study in Beagle dogs. In all studies, LX214 was administered to both eyes as 2, 4, or 8 topical applications daily (up to eight hourly applications) corresponding to doses of

FIGURE 5



Comparative microscopic ocular irritation scores of a repeat dose acute tolerability study in NZW rabbits topically administered every 30 minutes for four treatments with LX214 or Restasis.

FIGURE 6



Mean concentrations of [^{14}C]voclosporin (C_{max} ± SD) after single or repeat topical ocular administrations (once daily for 7 days) of [^{14}C]LX214 (0.2%) in ocular tissues of NZW and DB rabbits.

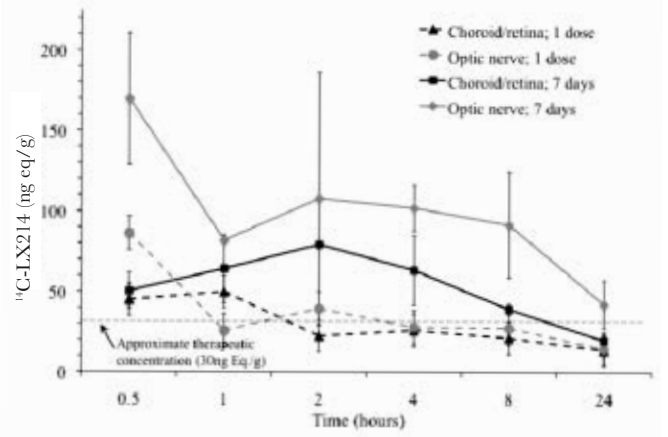
approximately 0.14, 0.28, and 0.56 mg/eye/day, respectively (control animals received eight hourly placebo doses). Safety and toxicity was evaluated using macroscopic and microscopic ophthalmologic evaluation; tonometry; electroretinography; gross and microscopic pathology of the eye (including optic nerve), submandibular lymph nodes, spleen, and thymus; and hematology, blood chemistry, and coagulation parameters. Voclosporin blood concentrations were measured on the first and last days of each study to characterize systemic exposure.

In both rabbits and dogs, there were no dose-dependent or reproducible ocular or systemic findings after 14 days or 3 months (rabbits only) of consecutive daily dosing with LX214. Low incidental ocular observations of minimal-to-mild conjunctival irritation (conjunctival congestion, discharge) was sporadically noted macroscopically or microscopically, primarily in animals dosed at hourly intervals, but was absent during recovery periods. There were no other macroscopic or microscopic changes noted upon ophthalmologic examination. No LX214 administration-related tonometry effects or treatment-related effects on retinal function were observed in either species.

In both rabbits and dogs, systemic exposure to voclosporin was low (< 4 ng/mL) after bilateral ocular dosing of LX214 (0.2%) with eight daily applications/day up to 3 months. In both species, the exposure increased with increasing dosing-frequency, and no gender difference was observed.

Preclinical toxicity study results demonstrate that bilateral topical ocular LX214 administration (0.2% voclosporin) was well tolerated without signs of adverse effects on specific functional and histopathologic ocular indices. No systemic toxicity was demonstrated, and only low systemic exposure with minimal accumulation was observed. In all studies, the no-observed-effect-levels were the highest dose tested (~ 0.56 mg/eye/day).

FIGURE 7



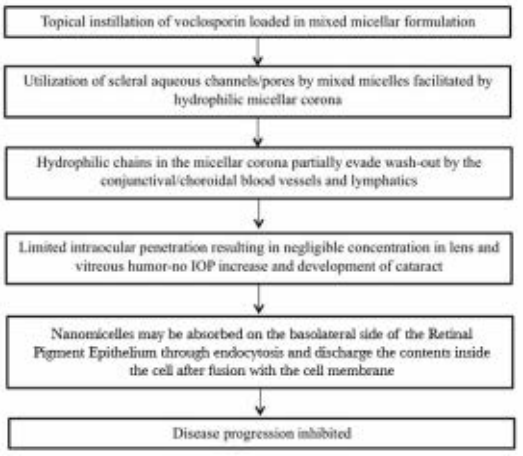
[^{14}C]Voclosporin concentrations (mean ± standard error) in posterior ocular tissue of NZW rabbits after a single or 7 days of once-daily topical administration of LX214 containing 0.2% voclosporin.

DRUG LEVELS IN RABBIT ANTERIOR & POSTERIOR EYE SEGMENTS FOLLOWING TOPICAL APPLICATION (^{14}C-LX214)

Pharmacokinetic studies of topical ocular [^{14}C]LX214 (0.2% voclosporin) administration to albino NZW and pigmented Dutch Belted (DB) rabbits demonstrated rapid voclosporin distribution in anterior and posterior ocular segments. The maximum anterior and posterior ocular tissue concentrations (C_{max}) of drug-derived radioactivity achieved after a single topical application of [^{14}C]LX214 and once-daily application for 7 days (NZW only) are presented in Figure 6. The drug concentration in both anterior and posterior tissues was high except in the lens, aqueous, and vitreous humor. No gender differences were observed.

Selected ocular tissues were extracted at the C_{max} and at 24 hours post single dose or post final repeat dose (day 7). The extracted radioactivity was analyzed by HPLC coupled with fraction collection and Packard TopCount® NXT™ analysis. Most of the radioactivity (60-93%) was associated with voclosporin 24 h post the final dose following once daily ocular administration of [^{14}C]LX214 for 7 days, suggesting insignificant metabolism occurred in the ocular tissues. These results also demonstrated a lack of specific melanin binding (albino NZW versus DB rabbits) as well as insignificant drug accumulation in ocular tissues with repeat dosing. Systemic exposure to voclosporin was also low in

FIGURE 8



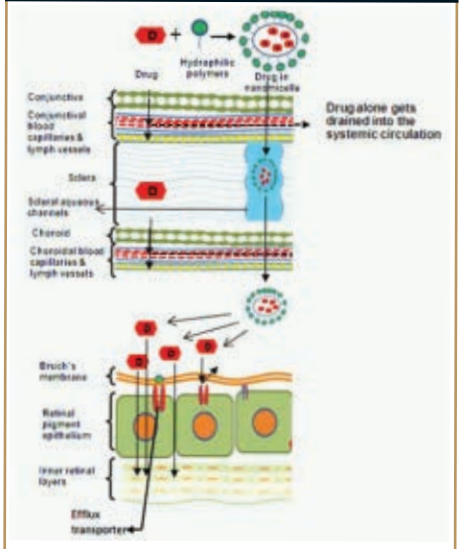
Schematic representation of transport of a topically applied hydrophobic drug to the back segments of the eye.

both rabbit strains after a single LX214 dose (C_{max} = 1.73 and 1.28 ng/mL, respectively, both at time to maximum concentration [T_{max}] of 1 hr) or after multiple doses (C_{max} = 1.16 ng/mL at T_{max} of 0.5 hrs after 7 days) in NZW rabbits.

Importantly, these results demonstrate voclosporin penetration into the posterior eye and attainment of therapeutic drug levels with repeated once-daily dosing. Figure 7 presents these tissue levels following single and multiple dosing. Post single dose, the choroid/retina C_{max} = 50 ng eq/g (T_{max} of 1 hr) in both strains. The optic nerve C_{max} = 86 ng eq/g (T_{max} of 0.5 hrs) in NZW and 199 ng eq/g (T_{max} of 1 hr) in DB rabbits. These tissue concentrations were above the expected voclosporin therapeutic threshold of ~ 30 ng eq/g. After once-daily dosing for 7 consecutive days in NZW rabbits, choroid/retina and optic nerve C_{max} was 79 ng eq/g (T_{max} of 2 hrs) and 170 ng eq/g (T_{max} of 0.5 hrs), respectively.

Notably, even after multiple dosing, the drug concentration in the lens, aqueous humor, and vitreous humor was very low (Figure 6). This observation indicated that the corneal route was not a major drug uptake pathway. Incidentally, the low levels in the lens, aqueous humor, and vitreous humor might suggest no effect on IOP or cataract formation in the eye. The low drug blood levels, even after multiple dosing, excludes the systemic route as a drug uptake source for posterior ocular tissues. A proposed mechanistic hypothesis is given below for how topically applied nanomicellar LX214 formulations may successfully transport voclosporin into the posterior eye.

FIGURE 9



Schematic representation of how a hydrophobic drug in nanomicelles can permeate through the water channels/pores of the sclera, thus evading conjunctival/choroidal blood vessels and lymphatics.

A NOVEL DRUG DELIVERY PLATFORM FOR POSTERIOR OCULAR DISEASE TREATMENT

There are two potential pathways for molecules to reach posterior eye tissues following topical administration: (1) the intraocular route through the cornea, aqueous humor, lens, vitreous humor, and finally retina; and (2) the trans-scleral route around the conjunctiva, through the sclera, choroid, and retina (Figure 8).[12] For hydrophobic molecules like voclosporin, the intraocular route is often unsuccessful because the hydrophilic stroma becomes a rate-limiting barrier for trans-corneal absorption.[13] Moreover, aqueous humor in the anterior and posterior segments flow in opposite directions and hinder the passage of molecules from the aqueous humor to the lens and, subsequently, through the lens zonular spaces to the vitreous humor, thus making this an unfavorable pathway. The trans-scleral route offers a more viable pathway for back-of-the-eye delivery of hydrophilic molecules by passive diffusion through the scleral water channels/pores.

Hydrophobic molecules, such as voclosporin, encapsulated in 15 nm nanomicelles, form spherical structures of amphiphilic molecules in water.[14] Due to their hydrophilic corona, these micellar nanocarriers can hypothetically pass through the aqueous channels/pores of the sclera, which range from 30 to 300 nm in size (Figure 9).[15] Nanomicelles may then be absorbed onto the basolateral side of the Retinal Pigment Epithelium (RPE) through endocytosis. Their contents are discharged inside the cell after fusion with the cell membrane.[16] During the transit, the hydrophilic nanomicellar corona should also help evade drug washout into the systemic circulation by the conjunctival/choroidal blood vessels and lymphatics.

SUMMARY

The presented data demonstrate that topically applied clear, aqueous, non-irritating nanomicellar LX214 formulations successfully delivered the hydrophobic molecule voclosporin to anterior and posterior segments of the eye at therapeutic levels. This technology, as validated using LX214 (0.2% voclosporin), opens doors for delivery of other hydrophobic drugs targeted for non-invasive treatment of diseases affecting the anterior and/or posterior ocular segments.

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BIOGRAPHIES

Dr. Poonam Velagaleti, a biochemist with 20 years experience in drug development, is currently Vice President of Preclinical Development and Alliance Management at Lux BioSciences, a Pharmaceutical Company in New Jersey dedicated to drug development for ocular diseases. She directs preclinical research and manages alliances with research partners involved in the development and evaluation of various ocular drug delivery platforms.

Dr. Eddy Anglade is the Chief Medical Officer and Co-Founder of Lux Biosciences, Inc. He previously served as Vice President of Clinical Development at Enzon Pharmaceuticals, Inc., with responsibilities in clinical development, R&D strategy, portfolio management, due diligence, and licensing/partnering activities. He also served as Medical Director/Team Leader at Roche Laboratories, Inc. Dr. Anglade earned his MD from Yale University.

Dr. John Khan is currently a Consultant at Lux Biosciences Inc. He earned his PhD in Biomedical Engineering from Rutgers University, New Jersey, and has over 13 years of experience in the medical device industry in research & product development engineering. His expertise includes advanced polymer characterization, device design, and fabrication of Class III products for vascular and ophthalmic diseases.

Dr. Brian Gilger, a veterinary ophthalmologist and ocular toxicologist, is the head of the Ophthalmology Service and a Professor at North Carolina State University. He has nearly 2 decades of experience in ocular drug delivery, toxicology, and drug development. Specific research interests include sustained-release drug delivery for treatment of posterior segment and immune-mediated ocular disease, such as uveitis.

Dr. Ashim K. Mitra is Vice Provost for Interdisciplinary Research, UM Curators' Professor of Pharmacy, and Chairman of Pharmaceutical Sciences at the School of Pharmacy, University of Missouri-Kansas City. He earned his PhD in Pharmaceutical Chemistry at the University of Kansas. He has over 25 years of experience in drug design and delivery with over 225 research articles and has made significant contributions in ocular drug delivery.

SORBENT APPLICATIONS

Incorporating Sorbents Into Drug Delivery Technology

By: Adrian Possumato

INTRODUCTION

Drug delivery technologies are evolving at a rapid rate with new drug product formulations and enhancements in current drug delivery device designs. Treatments for chronic conditions and growth in patient-administered drugs are factors leading to greater focus on ease-of-use and convenience.

While these developments offer tremendous potential in the marketplace, they also pose some unprecedented challenges to manufacturers. With new drug formulations becoming increasingly unstable and the advent of user-friendly device designs, manufacturers must seek solutions that can ensure drug delivery technologies work effectively.

Drug formulations are subject to a variety of degradation pathways that compromise drug safety and shelf-life. By far, the most frequent mechanisms of degradation are caused by hydrolysis and oxidation, mainly due to moisture and oxygen ingress through packaging and materials of construction. An important means to confront these threats is the adoption of sorbent technology. Sorbents, also termed active packaging components, are designed to adsorb moisture, oxygen, odors, and/or volatized hydrocarbons to protect drug formulations from degradation and extend shelf-life through the supply chain and consumer use. They can be incorporated into drug product packaging or device designs in a variety of ways: a sachet can be inserted into a package, a compressed sorbent can be fitted into a drug delivery device, a thermoformed sorbent can serve as a structural component, etc.

Sorbent technology must be considered an integral part of all drug delivery technologies. In fact, it is increasingly important for manufacturers to incorporate sorbent technology much earlier in the product development and design process than has previously been the case.

IMPACTING FACTORS

One must pay careful heed to the three critical factors when considering how sorbent technology should be integrated into a drug delivery device: convenience, formulation stability, and new drug delivery technologies.

Convenience has far-reaching and very real influences in the success or failure of a treatment. Patient-administered drug/device combination products need to be compact, portable, and easy to use if they are to be effective. Also, treatments for chronic conditions need to be integrated into the lives of patients to truly render the benefits of the therapy. Additionally, these drugs must retain their efficacy even when exposed to a wide range of unpredictable environments.

These factors have led to the development of innovative built-in sorbent solutions, such as polymer-desiccant blends. These blends can be used to create molded components built into drug delivery devices. By molding the desiccant directly into the device itself, designers can create the smallest possible profile without sacrificing other performance parameters. This approach is particularly useful when patients are required to carry the device with them in their daily lives.

The increasing trend of complexity of drug substances and/or drug products is another factor that

has placed greater importance on moisture and oxygen control to maintain formulation stability. New pharmaceuticals are coming into the market based on chemistries that were previously considered too unstable to commercialize as viable therapies. Thanks to new formulation and delivery technologies, some of these molecules are being reintroduced into drug product formulations that can be tested clinically and eventually manufactured and sold.

For these types of formulations that were previously unstable, sorbent technologies can play a critical role in ensuring drug product efficacy through the shelf- life of the device. While traditional sorbent technologies can reduce moisture content within an enclosed space, solutions for unstable formulations need to control and regulate moisture to a specified level to avoid product degradation. Finding this delicate moisture management balance is crucial for successful commercialization of new drug products.

Finally, there are new and unique technologies for drug delivery that are so different from traditional delivery methods that they require entirely new thinking about controlling the moisture in packaging, storage, and/or during device use.

For example, innovative drug/device combination products that combine electrical components would need protection from corrosion caused by volatized hydrocarbons and moisture. A range of similar applications can be successfully stabilized using a sorbent that combines moisture-regulating capability with oxygen absorption and volatilized hydrocarbon management.

INCORPORATING SORBENTS INTO NEW DRUG DELIVERY TECHNOLOGIES

Incorporating sorbent technologies into drug delivery technologies is a critical step in the successful commercialization of new therapies. Examples of two such applications can be seen in transdermal therapy systems and respiratory drug delivery devices.

Transdermal Therapy Systems

The arena of transdermal applications has seen significant developments recently. Transdermal delivery offers patients convenience and controlled dosage over time. A wide range of transdermal options exists for delivering drugs to patients. These include passive transdermal systems, such as gel reservoir and matrix patches, and active transdermal systems like ionthophoretic, radio frequency ablation matrix, and microneedle systems for transcutaneous or intradermal drug delivery.

For transdermal applications, sorbents are usually incorporated into the packaging itself. For example, Multisorb's DesiMax® Desiccant Label is a pressure-sensitive desiccant label easily applied and designed to blend in with the interior of the transdermal patch pouch. DesiMax SLF® is a blended hot-melt adhesive/desiccant that has proved to be an extremely versatile method for adsorbing moisture within packaging. It is also available in pressure-sensitive tape formats. Designing a sorbent into the packaging through a label provides a flat, multifunction component that saves space, simplifies use for patients and medical workers, and is effective in preventing hydration and crystallization of components. Other label types, such as Multisorb's StabilOx® Labels, can provide oxygen-absorbing capabilities that prevent oxidation of hormone-based transdermal patches.

As transdermal delivery systems become more widespread and more complex, sorbent technology will become more central in their development. The important factors of convenience and effectiveness all work in tandem to ensure a successful transdermal product.

Respiratory Drug Delivery Devices

There are important concerns for respiratory treatments centering on moisture, hydrocarbon, and/or oxygen management. Numerous device presentations require sorbent technology solutions: HFA (hydroflouroalkane)

aerosol metered dose inhalers, dry powder inhalers (DPI) with pre-measured doses, and DPIs with a reservoir of drug product.

DPIs, in particular, often require customized desiccants to manage moisture to prevent particle hydration and subsequent agglomeration during both their primary and secondary (consumer use) stability profiles. The potency and stability of the particles must be maintained so that airflow dispersion of the drug is accurate and consistent. A simple sorbent made of silica gel or molecular sieve may lead to over-drying, reducing the relative humidity of the container holding the powder down to a very low percentage. This excessively dry state could promote static charge of particles when dissimilar materials in a device (eg, plastics and foil) come in close proximity. The triboelectrification that might result could compromise the performance of the DPI device by reducing the amount of drug product that is inhaled.

DPIs deliver drug formulation in two distinct formats, pre-measured and reservoir, each with highly specific moisture management needs. In the pre-measured format, separately packaged drug product is contained in blisters, capsules, or other small pouches, which are inserted into a DPI device before use. In some cases, the pre-measured drug product packages are incorporated into the DPI device itself. Reservoir DPI devices incorporate a central reservoir of drug product from the DPI device, measuring doses for inhalation.

In either instance, intelligent sorbents can be deployed for the management of moisture based on the device design and drug product formulation (lactose carrier or carrier-free). If required, oxygen and hydrocarbon management can be included in these intelligent sorbents. Delivery formats include drop-in (sorbent sachets), fit-in (compressed sorbents), or built-in (sorbent polymers) solutions. Very often, the coordinated, synergistic use of these intelligent sorbent delivery formats is employed to arrive at an optimized level of moisture management for primary and secondary stability for the DPI device.

SUMMARY

As drug delivery systems become more complex and diverse, adoption of sorbent technologies will become more central. Traditionally, sorbent technologies have been thought of as the last step in delivering a drug to market. Today, the functionality of a delivery system can make or break the success of a drug treatment. How sorbent technology is incorporated into delivery could very well determine the success of a treatment both medically and commercially.

BIOGRAPHY

Adrian Possumato is the Global Director - Healthcare Packaging with Multisorb Technologies, Inc. (Buffalo, NY). He works closely with drug innovators and generic pharmaceutical manufacturers in their R&D, quality, regulatory, engineering, and manufacturing departments to determine the best selection of packaged sorbents to stabilize pharmaceutical formulations. He has more than 15 years of experience in the pharmaceutical and chemical industries. He can be reached at apossumato@multisorb.com or (908) 849-3005.

TOPICAL AESTHETICS

The Importance of Incorporating Aesthetics Into Topical Formulations

By: Gary Watkins, MS

INTRODUCTION

There are many ways to administer a drug to a patient, and patient compliance with each route can be affected by the properties of the dosage form (formulation). Therefore, the formulator of a drug product should not only consider the drug delivery aspects of the final product, but also the aesthetic properties of the finished product in an effort to minimize patient non-compliance resulting from a formulation that is effective, but unpleasant to use.

The following will focus on topical formulations for the delivery of actives to the surface of tissue, usually skin. Furthermore, the article will be limited to a consideration of emulsion-based vehicles, such as lotions or creams, that deliver the active pharmaceutical ingredient (API) or other ingredients onto, into, or through the skin. Briefly, an emulsion is a two-phase system prepared by combining two immiscible liquids, in which small globules of one liquid are dispersed uniformly throughout the other.[1] Typically, the liquids are some type of oil and water. Attempting to make these immiscible liquids thermodynamically and physically stable requires incorporating other ingredients or excipients, such as surfactants, thickeners, and preservatives. Because the incorporation of such excipients can affect the way the formulation feels when applied to the skin, the formulator should make an informed choice when choosing them, and the resulting formulations should be tested for aesthetic appeal.

Currently, formulators of topically applied preparations are compelled to meet consumer demand for skin care products that combine performance with pleasing aesthetics. Although skin feel has always been a key aesthetic parameter, consumers increasingly select skin care products based on a more complete sensory experience and pay attention to product texture, appearance, skin feel, and scent.[2] They also desire products that contribute to a sense of well-being, through visual aesthetics of the formulation, tactile effects on application, aroma, and the performance of active ingredients, such as vitamins or sunscreen. Sensory expectations are related to culture, age, skin type, gender, setting, and climate. In the case of climate, for example, light, dry products with minimal residue are often preferred for day wear, particularly in warm regions. In contrast, rich, viscous creams designed for moisturization or protection are often sought for night wear or during cold weather. For a skin care product to be successful, its sensory characteristics must be specifically developed and produced in a way that appeals to the user.

THE STRUCTURE OF SKIN

No discussion of the effect of topical formulations on the skin would be complete without discussing the skin organ itself. The barrier function of the skin prevents both water loss and the entrance of external agents. The skin consists of two distinct layers; the epidermis and dermis (Figure 1).[3] The epidermis consists of three main layers, the stratum corneum (SC), the granular layer, and the basal layer. The SC is considered the most important barrier to drug transfer. It is a heterogeneous non-living structure, formed by keratinized cells, protein-rich cells, and intercellular lipid layers. The lipid composition among the epidermal layers varies from one layer to another. Polar phospholipids, which are components of living cell membranes, are absent in the dead cells of the SC. These phospholipids form bilayers, and their acyl chains can exist in amorphous and liquid crystalline forms. The transition between these two forms occurs at certain temperatures without the loss of bilayer structure. The principal lipids of the SC are ceramide and fatty acids. Although the SC does not contain phospholipids, the mixture of ceramides, cholesterol, and fatty acids is capable of forming bilayers. These lipid bilayers provide the barrier function of the SC.

The sensory perception of the emulsion on the SC can be as different as the individual users themselves. Furthermore, the area of the body where the formulation is designed to be applied could determine the type and amount of excipients to be used. Certain ingredients may be acceptable for foot application but not for a formulation that is to be applied to the face. People with drier skin may prefer creams for their moisturizing properties, whereas those with oilier complexions may prefer the lighter feel of lotions. Less viscous formulations, such as lotions, are better suited for application on larger surface areas and regions with greater hair density as they are easier to spread and do

not cause uncomfortable pulling of the hair. The formulator may minimize skin irritation by using wholly aqueous vehicles rather than those containing alcohol or certain permeation enhancers.

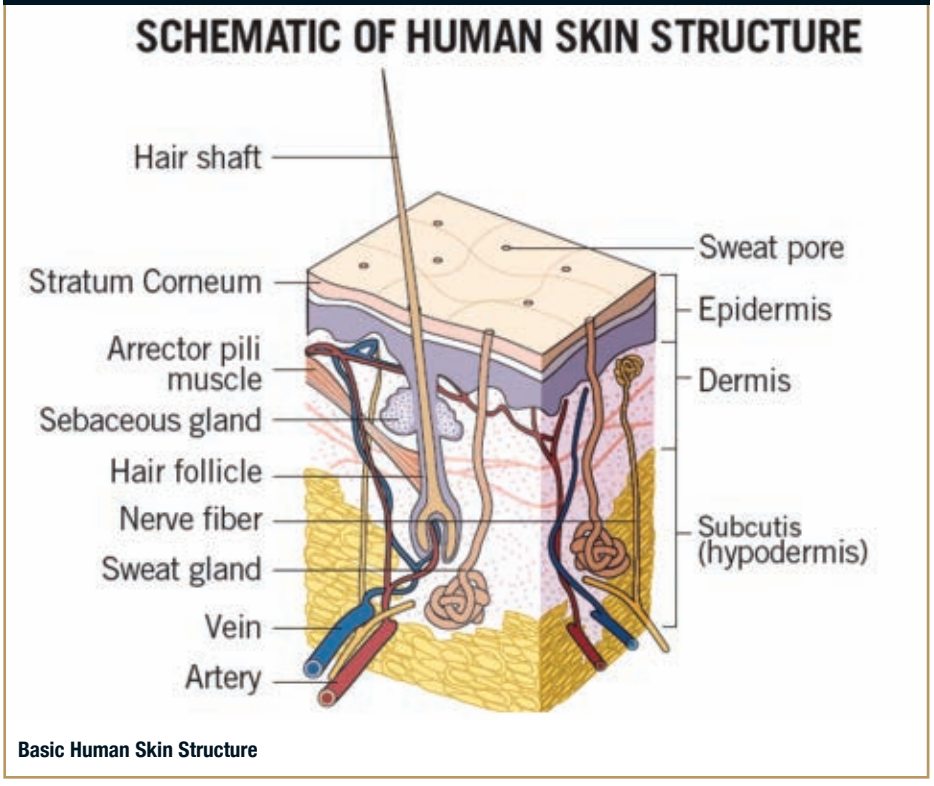
Poor compliance is more common in topical treatment compared to systemic treatment.[4] Application of a topical product is more time consuming than "popping a pill." Sometimes the smell of a topical medicament is a deterrent to its use, or it may be that it stains clothes or is messy. Some may cause a stinging or burning sensation, or redness at the point of application. All of these affect the adherence to dosing or application. Granted, oral formulations present their own unique challenges to compliance, but the cosmetic elegance of a topical formulation is extremely important in developing topically applied products and is often the key to the success of the product. For example, the delicateness with which a topical product can be applied or the avoidance of a greasy or tacky feel can be paramount.

SOME KEYS TO TOPICAL FORMULATION

Traditionally, a formulator will receive the API with general physicochemical information along with an ideal product profile based on marketing data. Initially, the formulator could perform systematic solubility studies on the API with solvents that are generally regarded as safe (GRAS), along with gaining insight into the specific disease the API will treat. For example, patients with rosacea claim to be sensitized to oily products, so the recommended formulation prototypes should contain a minimum amount of oil in the emulsion. When the prototypes have been prepared, the formulator will test a small amount on the back of their hand or forearm to assess the feel of the formulation. This part of development has been referred to as the "art of formulation" and like art, it is open to interpretation. Usually, it takes years of practice and a great deal of trial and error to gain the sensory experience necessary to differentiate and select a product prototype that is likely to be accepted. For example, experience may inform the formulator that the whitening occurring as the small sample of formulation is rubbed and spread on the skin could be the result of foaming and may be remedied by adding a small amount of silicone fluid to the formulation. The result of the multiple evaluations of various prototypes and improved formulations should be the successful selection of an optimized drug delivery vehicle.

Silicones were introduced for use in skin care applications in the 1950s and have since become so widely used that now, more than half the consumer skin care products contain some silicone.[5] Silicones are also not new to the pharmaceutical and medical world; they are used as transdermal delivery systems, as antifoams in the production of vaccines, and as raw materials of construction for catheters and specialized medical devices like pacemakers. What is new to the pharmaceutical world, however, is the commercialization of a broad range of silicones for topical semi-solid (emulsion) formulations that positively impact treatment compliance and product differentiation.

FIGURE 1

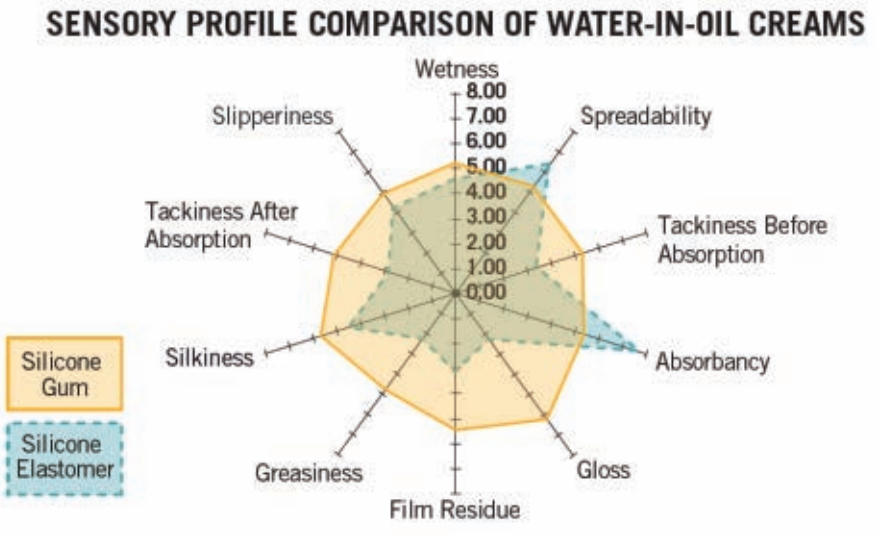


Basic Human Skin Structure

COMPLIANCE DEPENDS ON AESTHETICS

Being too greasy, and whitening of skin on application, are among the leading concerns stressed by consumers and patients alike regarding topically applied formulations with undesirable aesthetics. A topical prescription medication may be very efficacious; however, if it has poor aesthetics, the product will not be used or applied often enough to reap the benefits. The sensory properties of excipients can be important factors in assisting patients and consumers who do not comply with treatment regimens or product application because their topical

FIGURE 2



Sensory Profile Comparison of Two Water-in-Oil Creams

preparations have poor aesthetics. Poor patient compliance and its impact on treatment failure is a growing concern. A recent journal article estimated the economic impact in the US at $100 billion annually due to excessive use of healthcare resources in response to medication noncompliance.[6] For example, psoriasis has been a focus of the dermatology community in an effort to understand the causes of medication non-compliance. It has been reported that more than one third of psoriatic patients are not compliant with their prescribed medication.

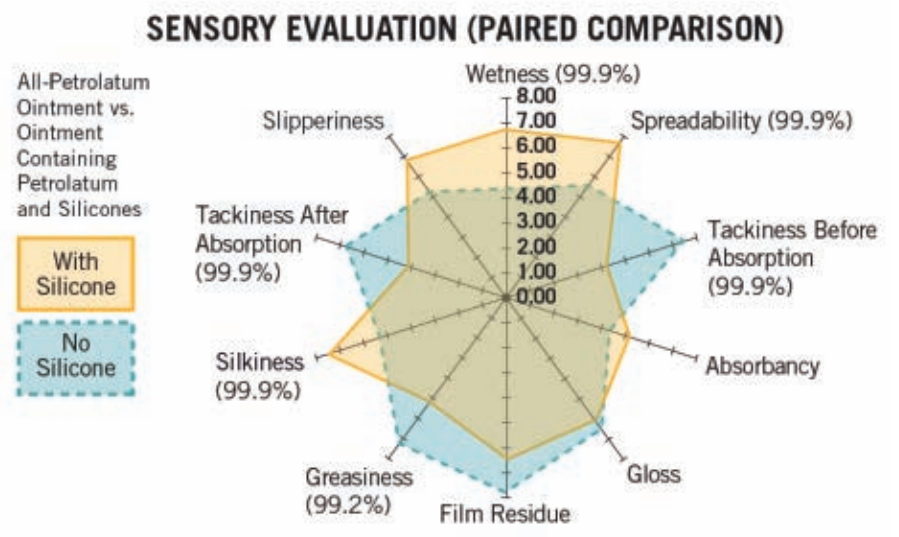
Another study of psoriatic patients links medication compliance and successful patient outcomes.[7] The vehicle-related factor that the "medication felt unpleasant" was rated as important, while the "medication stained clothing" factor and the convenience of application ("application was time-consuming") factor were rated as some of the most important issues. Choosing a fast-drying vehicle that is easy to apply may improve usage in patients concerned about inconvenience of application.

An additional situation that may hinder compliance by the recipient is whether the other ingredients leave an undesirable effect on the skin after application, such as dryness or eryhtema (redness). This occurrence has been apparent for formulation chemists, for example, in the challenge of formulating a stabilized vitamin C (L-ascorbic acid) for topical application.[8] For many years, researchers have been investigating methods for stabilizing L-ascorbic acid due to its beneficial properties. Indeed, L-ascorbic acid has many known biological functions, such as the stimulation of collagen synthesis, the strengthening of skin tissue against external attack, depigmentation, activity against free radicals, and the compensation for vitamin E deficiency. However, due to its alpha-keto lactone structure, L-ascorbic acid is very sensitive to the influence of environmental parameters, such as light, oxygen, and water. An unavoidable degradation of L-ascorbic acid in solution occurs over time due to its pH and the presence of trace metals. In order to reduce or delay the degradation of L-ascorbic acid in solution, previous science recommends stabilization by introducing it into aqueous-alcoholic solutions formed using up to 20% alcohol and having a pH below 3.5. Skin pH is approximately 5.5, so the pH of the formulation may change following application. These solutions are not usable in the cosmetic and/or pharmaceutical field because of a combination of low pH, drying of the skin by the alcohol, and a lack of aesthetic feel. Indeed, repeated application of these solutions may disrupt the equilibrium of the skin and may in particular irritate, or even burn it. In order to overcome some of these issues, Mathur and Sewell suggested a method of stabilizing free L-ascorbic acid from oxidation by dispersing the free acid in a mixed glycol carrier.[8] The carrier contains a mixture of at least propylene glycol and butylene glycol, but may contain other glycols, such as polyethylene glycol, along with stabilizing and solubility-assisting agents. From this, an emulsion may be prepared incorporating this mixed glycol carrier in the aqueous phase, without the use of alcohols or lowered pH.

QUANTITATION OF SENSORY PERCEPTION

Apart from the required tests for topical formulations, such as preservative effectiveness, stability, human patch for sensitivity, and erythema, there will be aesthetic testing to support marketing claims usually performed by clinical or marketing personnel. A panel of subjects, typically volunteers or colleagues, will test samples of the topical formulations and record their sensory experiences as a result of applying the product. Their remarks will be tabulated utilizing a numerical system similar to a hedonic scale with, for example, one being the lowest and eight the highest in categories such as greasiness, tackiness, ease of application, etc. The sensory evaluation is designed to compare the product-specific or formulation-specific differences on each sensory property.[5] Wetness, spreadability, and speed of absorbance (absorbency) are evaluated before product absorption, whereas gloss, film residue, greasiness, silkiness, and slip are evaluated after absorption. In the sensory evaluation testing, "absorption" means the perception of absorption felt by the subjects. It does not mean the product is biologically absorbed by the skin. Tackiness is evaluated before and after absorption. The numerical values are plotted as a spider web diagram to allow formulation comparisons to be made.

FIGURE 3



Sensory evaluation (paired comparison) of an all-petrolatum ointment versus an ointment containing petrolatum and silicones. Percentages indicate level of confidence, and the ratings for absorption were based on panelists' perceptions, not biological skin absorption.[7]

Figure 2 is a spider web diagram summarizing the results of one such sensory panel test comparing two water-in-oil creams; one based on a silicone elastomer, and the other on a silicone gum. Note how the cream containing the silicone elastomer spreads more easily and has a higher absorbancy. In contrast, the cream containing the silicone gum is more tacky and greasy, but also more glossy and silky.

Similarly, Figure 3 shows the differences between formulations based on petrolatum compared to those based on silicone fluids. These comparisons can be used to develop state-of-the-art consumer products that meet special needs and correspond to manufacturers' individual product positioning.

In order to make aesthetically driven formulations more rational and scientifically based, as well as remove the subjective component of development, attempts have been made to correlate certain sensory perception values with measured physical properties of the formulation, such as rheology.[9] This approach has yet to gain widespread use.

SUMMARY

This article emphasized the importance of considering product aesthetics (the feel or effect on the skin) when formulating topical products. Generally, the feel of topical formulations has been determined by individual perception. For products containing APIs, the formulator should choose compendial excipients or those listed in one of the respective Pharmacopeia (USA, Europe, or Japan) where possible, especially when the topical formulation is intended to be a product prescribed by dermatologists. The FDA recommends the safety evaluation of potential new excipients that are intended for use in topical drug products. Although each excipient should be justified by function and need in a formulation whether for prescription or personal care preparations, in order to ensure maximum usage compliance, formulators should strive to formulate a topical product with pleasing sensory qualities and confirm their performance with meaningful tests employing expert panels and/or consumer testing.

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BIOGRAPHY

Gary Watkins is a Formulation Scientist in the Formulation Services Department of Particle Sciences, Inc. Presently, his research interest is in nanotechnology and the effect nanoparticles have on the efficacy of active ingredients. In his nearly 20 years of experience in the industry, his primary focus has been in the development of formulations for application in skin health, having co-authored a formulation patent for the treatment of rosacea. Mr. Watkins earned his BS and MS in Pharmaceutical Sciences from the University of Buffalo.

DRUG DELIVERY Executive

Mallinckrodt Baker

PERFORMANCE EXCIPIENTS: FINDING A ROLE IN THE PHARMACEUTICAL FUTURE

Herman Mitchell
Director of Global Marketing

Mallinckrodt Baker, Inc.

"We are preparing to launch several new PanExcea performance excipients to give us a more comprehensive range of products for emerging marketplace needs. We plan to offer controlled-release, extended-release, and sustained-release products to make the PanExcea product line more versatile and functional for our customers. In fact, these new projected launches are based on feedback we've heard from the marketplace regarding the success of the IR and ODT excipients."

In 1995, Mallinckrodt Chemical and J.T.Baker formed Mallinckrodt Baker, Inc., a global chemical company that offers two brands - the Mallinckrodt® and J.T.Baker® brands of high-purity products for the laboratory, biopharmaceutical, microelectronic, and industrial markets. Mallinckrodt Baker is a basic manufacturer of chemicals with plants and distribution centers around the globe in Deventer, The Netherlands; Mexico City, Mexico; and Kuala Lumpur, Malaysia; as well as our US-based operations in Phillipsburg, NJ; and Paris, KY. The company launched its PanExcea™ performance excipient portfolio in July 2008, addressing multiple drug delivery systems through immediate-release (IR) and oral disintegrating tablet (ODT) technologies. At the same time, Mallinckrodt Baker entered a strategic business agreement with Rubicon Research, putting them in position to take a global leadership role in the development and commercialization of performance excipients. Drug Delivery Technology recently interviewed Herman Mitchell, Director of Global Marketing for Mallinckrodt Baker, to discuss his company's unique performance excipient brand and its role in future pharmaceutical technology.

Q: Let's start with some additional background about the history of Mallinckrodt Baker and the current structure of its business.

A: Mallinckrodt Baker, which is a business unit of Covidien, a leading global provider of healthcare products, was formed in 1995 when Mallinckrodt Chemical and J.T.Baker, Inc. merged, resulting in a new organization with more than 150 combined years of experience. Today, we offer two global brands, J.T.Baker® and Mallinckrodt® chemicals, supported by strong quality control systems.

Our market objectives are to collaborate with customers to increase speed to market while providing risk mitigation, proactive applications support, and assurance of regulatory compliance. We also offer the capabilities to design and manufacture specialty chemical solutions, including bulk pharmaceutical excipients, biopharmaceuticals, process chromatography media, and process intermediates. PanExcea performance excipients will

help us extend the range of services and support that we can offer.

Q: Tell us about PanExcea performance excipients and what differentiates them from your competition.

A: PanExcea performance excipients are manufactured using novel particle engineering technology designed to provide multifunctional properties and enhanced performance with the objective of faster, more efficient drug development and manufacturing. The PanExcea family of excipients features homogenous particles, designed to enable implementation of Quality by Design (QbD) drug initiatives while minimizing formulation complexity as much as possible.

All products in the PanExcea product line are composed of highly characterized, widely used Generally Regarded as Safe (GRAS) pharmaceutical materials. We can also offer full regulatory support for our customer applications. PanExcea excipients are currently available for IR and ODT applications manufactured by direct compression; however, PanExcea excipients for other drug delivery systems are in development.

Here's an example of how this product line can help our customers meet their objectives. One of our performance excipients, PanExcea MC200G ODT, serves as the building block for the formulation of a variety of active pharmaceutical ingredients (APIs) into ODTs. This product offers flexibility to help customers achieve cost-effective high performance by combining two ingredients that interact at a sub-particle level. That feature is designed to enhance desirable aspects and mask undesired properties of individual excipients. This, in turn, helps our customers provide a tablet that disintegrates rapidly and is widely dispersed in the mouth, while offering good taste and texture. The properties of PanExcea MC200G also help our customers gain increased API loading capacity along with good taste-masking. Finally, PanExcea MC200G is engineered to reduce per-tablet cost for our customers because it's an excipient-based solution that uses standard manufacturing and packaging equipment. That helps eliminate the costs of ODT technology licensing and new equipment investment.

Q: How has the PanExcea platform been received in the marketplace? Can you provide an update on how these products have performed since July 2008?

A: We are pleased with the market reception of our PanExcea platform, and customers are beginning to adopt our IR and ODT excipient products. As I mentioned, we are preparing to launch several new PanExcea performance excipients to give us a more comprehensive range of products for emerging marketplace needs. We plan to offer controlled-release (CR), extended-release (ER), and sustained-release (SR) products to make the PanExcea product line more versatile and functional for our customers. In fact, these new projected launches are based on feedback we've heard from the marketplace regarding the success of the IR and ODT excipients. Additionally, we're collaborating with our customers to help us offer the features they want and bring these products to market more quickly.

When evaluating the performance of PanExcea excipients, we've also kept in mind the fact that marketplace acceptance of a new concept or product can be slow in the pharmaceutical arena. Acceptance can take six or seven years, possibly more, depending on the product. That means our PanExcea platform, launched less than two years ago, is still a relatively new market entry.

Q: What is Mallinckrodt Baker's strategy for PanExcea technology?

A: Our strategy is to use PanExcea technology to provide customers with application-based products, backed by the kind of support and service that helps customers develop next-generation drug products cost effectively, efficiently, while meeting global regulatory needs.

Q: Why did you develop a partnership with Rubicon? What advantage does it provide to you and your customers?

A: Partnering with Rubicon has enabled us to offer the kind of ODT product our customers need. Their expertise in specialized areas, such as taste-masking, is an ideal combination

with our own experience in creating performance excipients and in particle engineering. That combination puts us in excellent position to enter global customer markets and play a leadership role in the development and commercialization of performance excipients. As we expand our presence as a supplier of performance excipients throughout the pharmaceutical landscape, Rubicon Research's industry-leading expertise in formulation and drug delivery technology will assist us in providing additional leading-edge products for the CR, ER, and SR market segments.

Rubicon Research also has an extensive network of customers in the global pharmaceutical industry and a solid track record in oral solid dosage forms and dispersed systems.
This means that when a customer asks us the best way to use one of our performance excipients in a formulation, we can collaborate with Rubicon to help develop a complete solution. Working with Rubicon, we can deliver not only a finished formulation, but a complete dossier of information, resources, and instructions for the manufacturer. It's a value-added proposition that we feel extends the range of services we can offer to our customers.

Q: What does Mallinckrodt Baker's Certified Excipient Distributor program offer pharmaceutical companies?

A: Our Certified Excipient Distributor (CED) program aligns Mallinckrodt Baker with select channel partners to provide the pharmaceutical industry with an optimized supply chain that's compliant with the International Pharmaceutical Excipient Council's (IPEC) guidelines for Good Distribution Practices (GDP).

The CED program provides a documented chain of custody, management of change services, and assurance that the distributor is operating in an environmentally monitored facility. In order to achieve certified status, each channel partner must pass an audit conducted by our quality department to ensure that they are compliant with IPEC GDP guidelines.

All certified Mallinckrodt Baker excipient distributors offer services, such as re-palletizing products at the distributor site, incoming inspection, chemical inventory management, special product labeling, and less-than-truckload shipping. Mallinckrodt Baker is actively auditing other channel partners worldwide and expects to expand its list of certified distributors in Europe and Asia in the future. We expect the CED program to grow in value as excipient technology and knowledge develops.

Q: What makes Mallinckrodt Baker an ideal partner?

A: We have a long history of expertise in bulk pharmaceutical development and manufacturing, so our customers can be confident that as a partner we can act as an extension of their business. We're committed to working with our customers to meet objectives like increased speed to market, supply chain risk mitigation, proactive application support, and regulatory compliance.

Q: What is Mallinckrodt Baker's strategy for PanExcea technology?

A: Our strategy is to use PanExcea technology to provide customers with application-based products, backed by the kind of support and service that helps customers develop next-generation drug products cost-effectively, efficiently, and while meeting global regulatory needs.

Q: What is on the horizon for Mallinckrodt Baker? Are there any new announcements we can expect soon?

A: In addition to the projected launch of CR, ER, and SR excipient products, we have several other strategic initiatives in the pipeline. Some of these involve developing new technology in-house, while others focus on collaboration and licensing. Ultimately, our future developments will be designed to enable the next generation of dosage forms. We are very excited for future products from Mallinckrodt Baker. ◆

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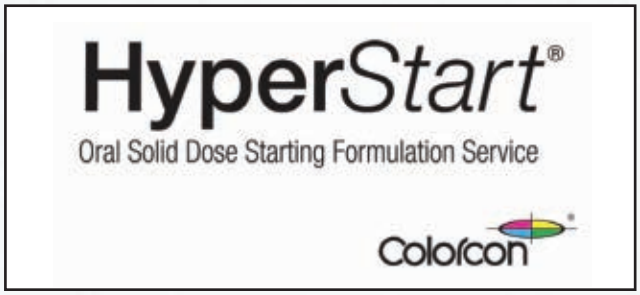
Technology Showcase

Formulation Service



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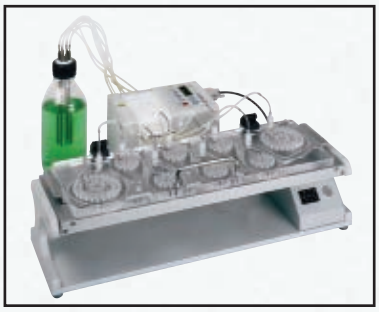

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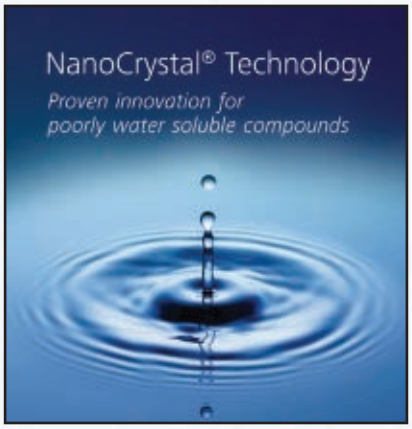

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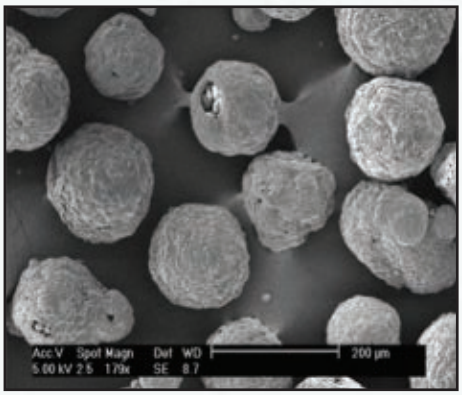
Performance Excipient



Mallinckrodt Baker's PanExcea™ MC200G performance excipient for Oral Disintegrating Tablet (ODT) applications combines two ingredients for rapid tablet disintegration and dispersion with good taste and texture. Designed for more flexibility at a lower cost, PanExcea MC200G performance excipients enable more API loading capacity while reducing tableting, licensing, and equipment expenses. For more information, contact Mallinckrodt Baker at (800) 943-4747 or visit **www.mallbaker.com/panexcea** to request a free sample.

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CEO

Merrion Pharmaceuticals, plc

For Dublin, Ireland-based Merrion Pharmaceuticals plc, there is much to be gained by developing oral forms of drugs that improve the bioavailability of poorly absorbed products that are typically given by injection. This has been the focus of the pharmaceutical development company that commenced business in 2004, after acquiring the GIPET® drug delivery technology that was being divested as part of a corporate refocusing by Elan Pharmaceuticals. Since opening its doors, Merrion has followed a two-fold business strategy that includes first, developing its own products internally based on the GIPET oral absorption enhancing technology, and second, to apply GIPET to the compounds of pharmaceutical partners. This business model has resulted in significant milestones at Merrion throughout the past year. From a financial standpoint, the company realized a 373% increase in revenue at the end of 2009, from $1.7 million to $8.5 million. In October, Merrion opened a 29,000-sq-ft, state-of-the-art, purpose-built facility in Dublin to expand its research and development and manufacturing capabilities, build up its own product portfolio, and double its talent. And, just this past March, the company was issued a US patent on its Solid Oral Dosage Form Containing an Enhancer, which covers the GIPET enhancer system used with the bisphosphonate class of drugs. A similar European patent had already been granted to Merrion. John Lynch, CEO of Merrion, recently spoke with Drug Delivery Technology magazine about how the company's partnership with Novo Nordisk to develop both oral insulin and an oral GLP-1 analogue has helped validate Merrion and its technology among the pharma community. Additionally, Mr. Lynch discusses how Merrion is applying GIPET to develop Orazol™, an oral alternative to an infusion-based drug for bone metastases in cancer patients.

"In a database comprising more than 30 compounds having poor permeability, GIPET has shown the ability to improve their absorption by as much as 200 times, achieving excellent intersubject reproducibility. This database covers a range of compounds with varying physiochemical properties and molecular weights, and includes small molecules as well as biopharmaceutical peptides and proteins, making GIPET a platform technology with very broad applicability."

Q: Please describe GIPET as an absorption enhancer and its benefits.

A: GIPET allows drugs that currently can only be given parenterally to be converted into oral tablet/capsule forms, as well as improve the absorption of current oral drugs. GIPET uses specifically designed oral formulations of patented absorption enhancers that activate micelle formation, facilitating transport of drug and substantially increasing absorption with good reproducibility and a strong safety profile.

In a database comprising more than 30 compounds having poor permeability, GIPET has shown the ability to improve their absorption by as much as 200 times, achieving excellent intersubject reproducibility. This database covers a range of compounds with varying physiochemical properties and molecular weights, and includes small molecules as well as biopharmaceutical peptides and proteins, making GIPET a platform technology with very broad applicability.

GIPET uses Generally Regarded As Safe (GRAS) rated ingredients, permitting the development of low risk new oral products, which can be brought rapidly and inexpensively to market–505(b)(2)–to address major unmet clinical and patient needs.

Q: What does your partnership with Novo Nordisk entail?

A: Insulin is the bedrock of Novo Nordisk, which is a biopharmaceutical company. Almost all biopharmaceuticals are delivered parenterally. Back in November 2008, Novo Nordisk wanted to change insulin delivery (usually 4 injections per day) to a more convenient tablet form and make the delivery more liver targeted. Injected insulin remains systemic rather than targeting the liver before general

circulation. Additionally, Novo Nordisk was looking for a delivery system that would enhance absorption. By mixing the insulin analog (NN1952) with GIPET, we were able to improve absorption of the drug. Merrion developed an insulin tablet for Phase I studies of people with type 1 and type 2 diabetes. We expect final results from the trial to be presented by our partner at a scientific meeting in the first half of 2011. Insulin injection is a $9-billion-a-year market. We expect the oral tablet to be a big breakthrough and experience sales in the billion-dollar range as well.

In 2009, Novo Nordisk entered into another licensing agreement with Merrion to have us develop and commercialize an oral formulation of their GLP-1 receptor agent using our GIPET technology. GLP-1 (Glucagon-Like Peptide-1) is a natural hormone and is part of the body's own system for primarily controlling blood glucose levels. It stimulates the release of insulin only when blood glucose levels become too high. GLP-1 appears to be impaired in people with type 2 diabetes, and this may be one reason why these people are at risk for abnormally high blood glucose levels. To date, Novo Nordisk's Victoza®, which has 97% homology to natural human GLP-1 peptide, has helped patients maintain normal blood sugar levels via a once-daily injection. We hope to be in the clinic this year with the oral delivery of GLP-1.

Q: Tell us about Orazol and what the expected impact is on the market.

A: Patients suffering from late-stage cancer often learn that the disease has spread (metastasized) to the bones, which can cause severe pain. Relief may come from a once-a-month trip to the hospital for an infusion of market-leading zoledronic acid (Zometa), which is used to reduce and delay bone complications due to multiple myeloma and bone metastases from solid tumors (eg, breast, prostate) and has recently also been filed as an adjuvant treatment in breast cancer.

Orazol is a tablet form of the same drug, zoledronic acid. By using its GIPET technology, Merrion has been able to formulate a sufficiently bioavailable oral dosage to make a once-per-week tablet. The quality-of -life benefits are exponential. Rather than having to visit a hospital for the infusion, the patient can conveniently take the tablet at home. In the Orazol Phase II program, patients reported much quicker pain relief. By taking a weekly dose, the drug load the kidney has to process is reduced. This is important because kidney deterioration is associated with the infusion. And, side effects associated with the intravenous delivery don't seem to be present in the weekly tablet. Often, patients will experience flu-like symptoms from the infusion.

From the payer's perspective, the cost of a monthly infusion (excluding drug costs) has been calculated to be $359, which can be a burden on the healthcare system. This cost is significantly reduced with a tablet. In addition, infusion chairs are freed up at the hospital to give chemotherapy or other treatments. Proof-of-principle for a weekly oral formulation has been demonstrated in a cancer patient population clinical study. Phase II was completed in 2009, and we are now seeking a partner to perform the Phase III study and take the product to commercialization.

Zometa comes off patent in 2013 in the US. We hope to have our oral version available by that time. The sales of zoledronic acid as an intravenous infusion were $2 billion in 2009. The market for oral zoledronic acid could be bigger because a greater patient population will have access to it.

Q: How do you describe Merrion's business model and how do partnerships fit into that model?

A: We are a product development company focused on delivering innovation to the market. Developing our own products and partnering to develop other products, we can maximize the number of products we are working on and therefore deliver value to our shareholders. To mitigate risk and to allocate our resources efficiently we have a balance of internally developed products along with developing products for our partners;. The key is to identify the right products and partners to work with us.

The Novo Nordisk partnership validates us and our technology. Moving forward, we are interested in working with other large companies. Because GIPET can work with a range of compounds, there are multiple partnership opportunities for us. We are looking to partner with pharma companies that have interesting injectable to oral product opportunities. Oral formulation can maximize the product opportunity but it is not just about convenience, GIPET formulations can also improve a products safety profile, be far more economical for hard pressed health care systems and really open up new market opportunities that only a tablet can address.

Q: Describe what is next for Merrion in terms of other products in the pipeline or the potential to acquire complementary delivery platforms.

A: We do have a lot of ideas for new products and have recently gone through a rigorous process of identifying new product opportunities and hope to address those opportunities this year. We have just scratched the surface in terms of how we are using GIPET in product development today. There is no immediate need to complement GIPET with other delivery platforms because right now we have a broad range of opportunities with GIPET. ◆

SPECIALTY PHARMA
Strategies For Business Development

Therapeutic Focus

Non-ATP Competitive Kinase-Signaling Inhibitors & Oncology Drug Discovery & Development

By: Allen Barnett, PhD, CEO Kinex Pharmaceuticals

Kinex Pharmaceuticals was formed in 2004 based on a technology platform licensed from SUNY at Buffalo for the design and synthesis of non-ATP competitive kinase inhibitors. The novelty of this approach was attested to by the US Patent Office, when it issued broad patents covering the basic approach (US Patent Nos. 7,070,936 B1 & 7,005,445 B2). The first target chosen was Src, the first oncogene discovered and a target of significant interest for various tumors. As part of the early work on this target at the University at Buffalo, the Kinex effort started with structural leads in the low micromolar potency range and worked on lead optimization and screening via the outsourcing route. Kinex started with just the experienced co-founders who are all pharmaceutical veterans and no additional employees, so the overhead (G&A) was kept to a minimum (less than 15% of total expenditures) with the rest being R&D. This rate of G&A has been maintained over its 5+ years of existence. The management team has over 50 years of experience in the pharmaceutical industry and this clearly facilitated the use of the outsourcing approach.

Novel Src-Signaling Inhibitors

At the start, it was projected that non-ATP competitive Src inhibitors would be at least as effective as ATP-competitive ones but be more selective and less likely to induce resistance. Dasatinib (Sprycel, BMS) was chosen as the main standard for comparison because it was the only FDA-approved drug with potent Src inhibitory activity. It is an ATP-competitive kinase inhibitor, and as such, also inhibits many other kinases leading to a variety of side effects, including cardiovascular ones. Thus, it and many other ATP-competitive inhibitors are called "multi-kinase inhibitors," and the current dogma was that because they inhibited so many targets, these would be more effective in cancer treatment than other, more selective chemotherautic drugs. Dasatinib was approved by the FDA for Gleevec-resistent, chronic myleogenous leukemia (CML) and is currently being studied clinically for its effects on a variety of solid tumors. One of the difficulties faced by Kinex from the very beginning is that when a kinase-like Src is removed from the cell and studied in isolation, the ATP site is intact. Thus, it is straightforward to screen kinase inhibitors in vitro. However, a kinase-like Src functions within the cell as a complex with other proteins to maintain the substrate pocket confirmation. So if one wants to screen for compounds that will inhibit Src signaling at the substrate or an adjacent site, it has to be done with intact cancer cells. While this is technically possible for determining drug potency, it makes other studies like drug selectivity more difficult. Despite this hurdle, Kinex was able to design potent (low nanomolar range) and selective Src-signaling inhibitors, and within 1 year after the program was initiated, two potential clinical development candidates were identified, attesting to the power of the technology platform. The final candidate was KX2-391, and while it was proceeding to an IND, many other in vitro and animal model studies were done to more fully characterize its profile. What became obvious was that the Kinex candidate has broader and greater anti-tumor efficacy than dasatinib, including situations in which there is resistance to this drug. The overall profile of KX2-391 on cancer cells is that it inhibits cell growth, tumor cell spread (metastasis), as well as new blood vessel formation (anti-angiogenesis). We also found that KX2-391 inhibited growth in tumor cells in which Src family kinases had been knocked out. This meant that there was likely a second mechanism in addition to its Src-inhibition activity for the superior profile of KX2-391 over multi-kinase inhibitors like dasatinib.

The Search for a Second Mechanism

Several more conventional approaches were tried to identify the second mechanism, without success, to determine the other potential binding targets of KX2-391 within the cell. One technique we had not tried was photoaffinity labeling because of the difficult and time-consuming chemistry involved. The basic approach is to synthesize a compound with a photo-activatible group on the molecule in a position that retains as much of the original activity of the molecule as

possible. After a sterling chemistry effort, Kinex was able to synthesize a photoaffinity ligand (PAL) that retained all of the original potency of KX2-391. This helped confer very high affinity binding to possible protein targets, and it turned out the second mechanism was binding to tubulin, resulting in inhibition of tubulin polymerization. When this tubulin binding was studied further, it was found that KX2-391 was bound to a unique site on tubulin compared to other drugs like taxol and colchicine. Thus KX2-391 is a drug that binds to a unique part of Src and tubulin, which may explain its superior preclinical profile. Kinex has called this technology platform Optimized Photoaffinity Technology (OPAL) platform.

Phase I Clinical Profile of KX2-391

The Phase I safety clinical trial for KX2-391 is now complete, with Phase II studies scheduled to start this year. The selectivity and projected safety profile of this drug have been confirmed by the results in Phase I. Oral doses associated with very high plasma levels in human cancer patients have been achieved, and these have not been associated with any side effects perceived by the patients. The dose-defining signs for the maximum tolerated dose (MTD) were subclinical changes in some of the liver chemistry values. These were all reversible within a week after the end of dosing. So there was an absence of nausea, vomiting, hair loss, cardiovascular effects, edema, etc. There were also signs of efficacy based on a lowering of selected biomarkers and other anecdotal efficacy reports, which are very encouraging.

KX-02, An Opportunistic Approach to Brain Tumors

An area of great interest to Kinex is the treatment of brain tumors. There has not been a new drug approved for this area in many years. When we observed that KX2-391 inhibited the growth of a variety of solid and liquid tumors, we realized there was no reason why we could not design a more lipophilic analog (KX2-391 is highly hydrophilic), which might get into the CNS more efficiently. KX-02 was then created with this objective, and it is now in advanced preclinical development. KX-02 is very potent in treating a variety of brain tumor cell lines, including Glioblastoma Multiforme (GBM), one of the most aggressive and deadly ones. We then tested the compound in a mouse model in collaboration with Roswell Park Cancer Center scientists. KX-02 significantly increased the survival of these mice, as did Temodar (temazolamide), which is part of the current standard treatment for GBM. The most surprising finding was that a significant percentage of the mice on KX-02 survived completely, and there was a total disappearance of tumor, as demonstrated by MRI. This finding was confirmed in several other studies. The retained survivors are living their normal life spans with an absence of re-occurrence of tumor. Studies are in progress to further define this phenomenon and to look for methods for possibly increasing the percentage of "cured" mice. The highest percentage obtained thus far was 60%. The IND filing for this compound and the commencement of Phase I clinical trials is expected to be in the second half of 2010.

Immunoinflammatory Diseases

Another area of therapeutic opportunity for the Kinex platform involves diseases such as arthritis and inflammatory bowel disease. The initial attraction was the number of kinases involved in these processes and the achievement by Kinex scientists in developing very selective drug candidates against kinase targets. Moreover, Kinex has built up a significant library of targeted molecules that can be used to screen for new targets. With respect to the latter, Kinex has now found a potent in vitro lead compound for inhibiting an important pathway of interest for modulating immune function. Efforts are in progress to optimize the compound for oral bioavailability and activity in animal models. The objective will be to identify a clinical candidate by the end of 2010.

Summary

Kinex has been in operation for 5 years and has two clinical development candidates with good prospects for a third by the end of 2010. The concept of target selectivity resulting in reduced clinical side effects has been supported by clinical development data thus far on KX2-391 and the expected profile of KX-02. The creation of a significant chemical library against kinases from the oncology program has created a resource that is already paying off in the newer immunology effort. The development of the OPAL technology for identifying the second mechanism of action of KX2-391 has created a powerful experimental tool that is now being applied to identifying targets of known potent activity but with off-target activities. A third development candidate by the end of 2010 is also now a possibility. Kinex has come a long way in its first 5 years and is well on its way toward creating a very strong pipeline.

Allen Barnett, Ph.D.

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Dr. Barnett is a successful drug development executive who brought four drugs to the marketplace during his tenure at Schering-Plough, two of which were blockbusters. His career was spent in Drug Discovery, where he led the effort that resulted in the discovery of Claritin, a non-sedating antihistamine that was Schering-Plough's leading product and the fifth leading drug, based on sales, in the world. Dr. Barnett managed a discovery program that led to Doral, a sedative-hypnotic that was out-licensed by Schering. He and his colleagues made a major contribution to the field of dopamine receptors by discovering and developing the first D1 receptor antagonists. He managed the discovery program that led to Zetia, a novel cholesterol-lowering agent that was introduced to the market in November 2002, and to Clarinex, the successor to Claritin. In 1994, Dr. Barnett assumed the duties of Vice President of Technology Acquisition and External Collaborations with the objective of facilitating all areas of drug discovery-based collaborations for SPRI. Dr. Barnett is a graduate of Rutgers University and the University of Buffalo School of Medicine. He has authored or co-authored more than 100 scientific publications.

Executive Summary

Andreas Knaack
Director of the Biomedical Instruments & Devices division
Invetech

Invetech: Creating Innovative Products That Redefine Markets

Invetech has been creating breakthrough products and custom automation systems for more than 30 years. With a wealth of experience drawn from over 5,000 projects, Invetech delivers product design and development, contract manufacturing, and custom automation services to a range of global market sectors, including diagnostics, life sciences, medical devices, cleantech, industrial, and consumer products. Operating out of locations in North America, Europe, and Asia Pacific, its clients range from multi-nationals to start-ups and include seven of the world's top 10 clinical diagnostic companies. Specialty Pharma recently spoke with, Andreas Knaack, Director of the Biomedical Instruments & Devices division at Invetech, on how the company is working with customers to redefine their market with breakthrough and innovative product design, development, and manufacture.

Q: ***What are Invetech's key services and offerings?***

A: Invetech offers development of specialist instrumentation, commercial products, and custom automation as well as contract manufacturing. From idea to market and covering all major discplines (from industrial design through to electronics, software, and mechanical engineering), Invetech integrates creativity, commercial know-how, and technical acumen to help its clients create business success. Invetech's range of skills, in-house capabilities, and broad industry experience are combined with proven processes and innovation and management tools to deliver tangible results. Invetech's focus is on developing easy-to-use products and processes with exceptional reliability that deliver highly valued benefits to users. Our broad expertise ranges from low-volume, quality critical, automated cellular processing systems to high-volume, low-cost consumer products.

Q: ***In what markets does Invetech operate in?***

A: Invetech specializes in product development, custom automation, and contract manufacturing for the medical, industrial, and consumer markets. With more than 200 staff, the company works in a range of global sectors, including clinical diagnostics, life sciences, drug discovery, pharmaceutical, and medical devices.

Q: ***How do you apply your expertise across such diverse markets?***

A: Invetech provides in-house experts for all its major markets and is applying a consultative approach to ensure immersion of the Invetech team into the client's target market, combining this expert know-how with generic in-depth engineering expertise. Working in the given range of markets allows Invetech to cross-leverage skills and know-how from these different markets. For example, Invetech's expertise in design and manufacture of high-volume consumer goods (manufactured in millions per year) is directly applicable to medical or scientific consumables. Invetech's specialist expertise in design, engineering, and manufacturing enables the company to deliver solutions that are as practical as they are marketable. Our range of skills across the product life cycle - from concept development through to manufacture - ensures our clients can be confident of achieving a successful commercial outcome, whatever the project. Invetech's industry-specific knowledge enables clients to break new ground in many diverse areas.

Q: ***Can you describe the types of customers Invetech works with?***

A: Throughout the past 30 years, Invetech has completed more than 5,000 projects for international companies ranging from Fortune 500 to start-ups to Government Departments, including clients such as Bayer, Bio-Rad, The Coca-Cola Company, and bioMérieux. Operating out of locations in North America, Europe, and Asia Pacific, our clients include some of the world's top clinical diagnostic companies.

Q: ***How are you helping your customers achieve commercial success?***

A: Invetech combines integrated in-house capabilities, specialist knowledge, and diverse experience to deliver better solutions, in the shortest possible time and with less risk. Tailoring the degree of innovation to the specific project needs, Invetech applies rigorous processes that have been proven over thousands of projects. Whatever solution Invetech provides, these processes ensure the best possible commercial outcome, balancing development risk, schedule, and cost with product cost and features or performance.

Q: ***Invetech's innovative design has recently been recognized with an award. What was the award for?***

A: Invetech has recently been recognized for its innovative design capabilities by being awarded a prestigious Medical Design Excellence Award (MDEA) for TearLab Corporation's revolutionary TearLab Osmolarity System. TearLab Corporation requested Invetech to assist with the development and industrial design of this novel system. The TearLab Osmolarity system is the first technology that can quantitatively and objectively measure Dry Eye Disease in a doctor's office in seconds. Dry Eye Disease is a chronic and progressive condition that if left untreated can lead to serious eye damage. This product won the award for its breakthrough design that significantly reduced the complexity, cost, and patient discomfort of conventional tear-testing technologies. Through application of Invetech's tools and know-how in Human Factors Engineering (HFE) and closely working with end-users, the Invetech and TearLab teams were able to provide a solution for the collection and diagnosis of tear

fluid that is easy to use while minimizing risk of user error or patient harm. TearLab was designed to achieve CLIA waiver status, reflecting its focus on ease of use and consideration for the needs of both the patient and the clinician. TearLab was selected as a winner by an impartial panel of expert judges for its innovation, user-related design, product features, and engineering that improves the manufacturer's profitability.

Q: *Why are more companies turning to outsourcing?*

A: A significant number of companies are turning to outsourcing, driven by the benefits and availability of access to new skills and knowledge. Companies increase competitiveness by lowering the cost structure of R&D and offering new products to customers more quickly and efficiently. Some companies have an infrequent need for specialist product design and development services, and it is not feasible to build and maintain these in-house capabilities. Outsourcing can offer better solutions than recruiting ad hoc design teams because external service providers can tap into scale and learning economies that they have developed through their experience and longevity in the business.

Q: *What does a company need to consider if looking to outsource?*

A: A company needs to consider a number of factors when making strategic R&D outsourcing decisions. Besides the typical technical requirements, reviews should also focus on hidden factors, such as negotiations, lower costs of contracting, and greater value added. Other factors include performance and measurement of achievement and investments in the relationship. When considering international outsourcing, companies should think about protecting rights over valuable intellectual property in countries with significantly different protection regulations, the development of inter-company processes to ensure a common understanding of design standards and metrics, language, and cross-cultural difficulties and telecommunications infrastructure.

Q: *What makes Invetech an ideal partner?*

A: For more than 30 years, Invetech has been at the forefront of breakthrough product development and automation, helping companies bring new products to market through innovative design, engineering, and manufacturing. The key to establishing a successful long-term relationship stems from core expertise, open communication, knowledge sharing, and trust building. It is Invetech's capacity to bring ideas to market that sets the company apart. Invetech is recognized for its enthusiastic approach in addition to the resulting commercial successes of our clients. The company's multi-award-winning portfolio has led advances across industrial, medical, and consumer markets. Invetech values innovation, integrity, enthusiasm, excellence, and collaboration. Our clients value our ability to effectively combine industrial design and innovative engineering when designing new products. Leveraging skills and experience from 60+ biomedical and scientific instrument developments, Invetech is able to shorten time-to-market. Invetech is ISO 9001:2008 certified and its quality system and development processes are compliant with FDA QSR (Quality System Regulation) for biomedical products and with GAMP (Good Automated Manufacturing Process) for custom automation. Throughout the product development journey, Invetech's consultative approach ensures strategic objectives are met. Invetech's manufacturing facilities are ISO13485:2003 certified, supported by regular reviews and audits with world-leading biomedical clients, such as Abbott, bioMérieux and Bio-Rad. ■

Meeting the Challenges of Antimicrobial Resistance

By: Ron Najafi, PhD, Chairman & CEO, NovaBay® Pharmaceuticals, Inc.

Introduction

Antibiotics may rightly be called "wonder drugs," but their use throughout the past 80 years has come at a price. Through evolutionary mechanisms assisted by overuse and misuse, bacteria will invariably develop resistance to new antibiotic compounds soon after their introduction. Today, some of the most virulent bacterial pathogens are resistant to all but one or two antibiotic agents. Experience with one topical antibiotic, mupirocin, demonstrates that resistance can emerge even against agents that are not administered systemically.

GlaxoSmithKline's Bactroban (mupirocin ointment) anti-infective was introduced in 1985 and rapidly adopted into clinical practice for treating topical *Staphylococcus* infections and colonizations.[1] Numerous studies demonstrated mupirocin's effectiveness in treating primary skin infections, surgical incisions, and accidental wounds. Bactroban soon became the agent of choice for these indications; within 15 years, the drug was registered in 90 countries for eradication of *Staphylococcus*, including such virulent strains as methicillin-resistant *S. aureus* (MRSA).

Resistance to mupirocin began to emerge shortly after the drug's introduction. By 2007, the incidence of mupirocin-resistant *S. aureus* increased from 1.6% during the period from 1995 to 1999, to 7% between 2000 and 2004.[2] Resistance was related to a mutation on a gene coding for the enzyme isoleucyl-tRNA synthetase.[3] Moreover, it became apparent that MRSA could confer resistance to mupirocin through gene transfer to other bacteria treatment.[4]

A more recent study on peri-operative patients confirmed that 7% of *Stapholococcus* isolates from nasal passages of orthopedic/vascular patients were mupirocin-resistant, a figure that increases to 9% among elderly patients.[5] In 2007, David Warren and co-workers reported that 13.2% of MRSA isolates from patients at Washington University Hospital were mupirocin-resistant.[6] These figures have immediate consequences, such as failures in decolonizing patients infected with mupirocin-resistant MRSA.[7]

Bacterial resistance to antibiotics generally rose throughout the 1990s and 2000s, and will continue to increase despite efforts to introduce "clean" treatment practices in hospitals. The availability of over-the-counter antimicrobial agents, particularly those that were once sold only by prescription, can potentially reverse the positive impact of best hospital practices, and lead to pockets of high bacterial resistance that will be difficult to eradicate. For example, it has been reported that mupirocin resistance in New Zealand hospitals had reached 28% by 1999, due in part to sales of mupirocin over the counter.[8] Upton urged that "current patterns of mupirocin consumption …be reviewed and its use rationalized to maximize the chances of this antibiotic retaining beneficial anti-*staphylococcal* activity."

Mupirocin is a perfectly good antibiotic, but therein lies the problem. Bacteria have evolved over hundreds of millions of years to evade and adapt to antibiotic mechanisms, particularly when these agents are administered systemically. It therefore makes no sense to expose every organ and system to antibiotic treatment when an infection is localized to one area that is easily accessible to topical agents. An unintended consequence of the overuse of systemic antibiotics has been the rise of resistant strains on the skin, which

complicates treatment even in accessible areas of the body.

While antibiotics may be the only recourse for treating systemic infections, their use on the skin and particularly in nasal decolonization is clearly unwise when options exist with a low risk of contributing to resistance to antibiotics.

Antimicrobials, Not Antibiotics

In a recent paper, NovaBay scientists described a novel class of antimicrobial compounds known as N,N-dichloro-2,2-dimethyltaurines Aganocides®, which are effective against MRSA and mupirocin-resistant *Staphylococcus*.[9] NovaBay's Aganocides are synthetic analogs of naturally occurring antimicrobial agents that belong to a class of molecules, the N-chlorotaurines, which operate within the human immune system and do not give rise to bacterial resistance of any kind.

The natural model for Aganocides, N-chlorotaurine, was described in 2000 as a "novel" agent for treating infectious conjunctivitis.[10] A number of papers have been published using this compound as a topical antimicrobial agent. Nagl et al reported the broad-spectrum biological activity of the "long-lived oxidant" N-chlorotaurine, which achieves 4-log reduction of bacterial and fungal pathogens at micromolar concentrations.[11]

Biologists know that species related to N-chlorotaurine are responsible for up to 90% of the "heavy lifting" in bacterial clearance through white blood cell lysosomes. During oxidative bursts, hypochlorous acid (HOCl) is neutralized by taurine to form N-chlorotaurine, an oxidant that attacks and inactivates bacteria and other pathogens. N-chlorotaurine and the related N,N-dichlorotaurine possess broad-spectrum antimicrobial activity, but both degrade rapidly in the body and are labile in conventional pharmaceutical formulations. The Aganocide compounds overcome this deficiency of the natural compounds through a chemical modification that imparts long-term stability.

Like their natural analogs, Aganocide compounds fight MRSA and other resistant *Staphylococcus* bacteria through the chloronium ions, a form of chlorine suitable for eradicating bacterial colonizations and infections on the skin, in other accessible areas of the body, and on some implantable medical devices. Chloronium ions have been employed in water disinfection for at least 150 years.

Aganocides, which deliver an attenuated form of chloronium ion, are not antibiotics. Their mode of action is non-specific and does not depend on cells being in reproductive phase. Aganocides do not inhibit cellular processes, DNA replication, enzymes, or any pathways that might, through evolutionary processes, adapt to their mode of action.

Rather, chloronium ions generated by Aganocides rapidly inactivate organisms by attacking sulfur- and nitrogen-containing amino acids on the bacterium's surface. Microorganisms cannot adapt, either individually or through evolutionary processes, to this mode of action, which is not unlike being run over by a Sherman tank or hit by a nuclear bomb. Developing immunity to Aganocide compounds would require the genetic impossibility of MRSA bacteria completely changing the fundamental nature of their chemical composition.

In this respect, Aganocides resemble antimicrobial peptides, another group of natural defense compounds that do not induce microbial resistance. Antimicrobial peptides are "evolutionarily conserved," meaning their structures are similar across species and over millions of years of evolution. These agents are usually amphiphilic, allowing them to operate in aqueous environments as well as entering lipid-rich membranes. Unfortunately, no antimicrobial peptide or analog has proven to be commercially viable because their selectivity for bacterial versus mammalian membranes is extremely low.

Is Nasal MRSA a Risk Factor for Hospital-Acquired Infections?

By contrast, Aganocides have shown remarkably high therapeutic indices, a measure of a therapeutic dose compared with a toxic dose, in laboratory studies. Our findings suggest that the Aganocide compounds could replace mupirocin and similar agents, and possibly eliminate the need for systemic antibiotics for localized bacterial infections. Antibiotics remain the agents of choice for infections that have entered the blood or major organs, while Aganocide compounds could be a more suitable option for infection or colonization sites that are easily accessible.

Studies suggest that a fair number of hospital-acquired MRSA infections originate from nasal colonies of *Staphylococcus* bacteria. Colonization in the nasal passages serves as a reservoir for transmission of *S. aureus*, including MRSA and mupirocin-resistant organisms, to wound sites as well as the sinuses, ears, and eyes. Approximately 30% of all humans are colonized by *S. aureus*, including by resistant strains.

Antibiotics are inappropriate as first-line therapies for colonization or infections for two reasons. First, systemic antibiotic administration is overkill when the infection is limited to a part of the body from which it may easily be eradicated without the use of

antibiotics; antibacterial treatment can be more effective, less expensive, and spare the patient potential side effects. Second, because antibiotics slowly lose their effectiveness, they must be used judiciously to prolong their useful life for deadly blood-borne infections.

Our lead Aganocide compound, NVC-422, is active against Gram-positive and Gram-negative bacteria, yeasts, and viruses. A recently completed Phase I trial demonstrated that topical application of NVC-422 to the nostrils is safe and well-tolerated in healthy volunteers. An exploratory Phase II trial using a prototype formulation of NVC-422 in saline in volunteers colonized with *Staphylococcus* showed 88% decolonization within 1 day. Additionally, NVC-422 does not enter the bloodstream, a key safety factor. NovaBay Pharmaceuticals is preparing for a second Phase II trial with a more advanced formulation that is expected to show even greater effectiveness in decolonization of MRSA in nasal passages.

NovaBay has entered into an agreement with Alcon, the largest producer of ophthalmic products in the world, to investigate Aganocide compounds for a number of topical (non-systemic) infections, such as eye, ear, and sinus, as well as for use in contact lens solutions. Additionally, NovaBay is in partnership with Galderma, the largest skin care company in the world.

Another important potential use for the Aganocide compounds is in the prevention of catheter-associated urinary tract infections (CAUTI). Almost half of all hospital-associated infections follow urinary catheterization and its associated urinary tract infections. Up to 10% of all hospitalized patients require catheterization. Shortly after insertion, a biofilm begins to form on the inner surface of the catheter, which becomes a reservoir for bacteria that may eventually cause life-threatening infections of the bladder and kidney. Cardiovascular catheters are prone to similar colonizations.

Individuals who are permanently catheterized (eg, paraplegics, quadriplegics, and those with other serious spinal conditions or injuries) are often on lifelong antibiotics to prevent systemic infection. Systemic treatment is expensive and puts these patients at risk for serious, long-term side effects. Catheters coated with antimicrobial silver are sometimes used in such situations, but they are expensive and only effective for a few days.

NovaBay is investigating a formulation of one of the Aganocide compounds that could be used to flush urinary and cardiovascular catheters. We expect that such a product might prevent tens or hundreds of thousands of cases of urinary and systemic bacterial infection per year, and save lives and save the healthcare system hundreds of millions of dollars.

Bringing Aganocides to Market

Because Aganocide compounds have such a large variety of potential applications, NovaBay cannot hope to develop on its own all the indications for which $34 billion worth of antibiotics are sold. Our strategy is to partner with market leaders in relevant therapeutic areas to ensure the appropriate clinical development of our products, their maximum market penetration, the highest return to our shareholders, and the greatest benefit to patients. It was with these goals in mind that we entered into our agreements with Alcon and KCI, and we expect to continue to partner additional opportunities.

While our agreement with Alcon was entered into when the Aganocides were early preclinical stage compounds, it was still a very valuable one, with $10 million up-front, ongoing research payments, $70 million of milestones related to clinical progress, and good royalties. We expect to be able to enter into agreements for additional indications with other corporate partners when our compounds are in later stages of development. The best time for us to make deals is when we have Phase II or later clinical data that indicates efficacy in a specific indication. It was for this reason, the costliness of clinical trials, that we took NovaBay public. However, the advantage of the Aganocide compounds is that our indications require short periods of treatment (typically 1 week for most infections), so we can conduct more trials for less money than the typical biopharmaceutical company.

As an entirely new class of antimicrobial agent active against bacteria, fungi, and agents, Aganocides enjoy very broad market potential. Aganocides are not suitable for systemic administration because extended interaction with blood components results in loss of potency. The compounds are most appropriately used when applied locally to tissues where infection or colonization has been localized. Our strategy is to focus on applications where Aganocides address an unmet medical needs. Our analysis has identified the following critical markets:

SKIN INFECTIONS - The market for topical treatments of classical skin infections is very large, for example, impetigo has been estimated at approximately $600 million per year. In this category, acne treatments are perhaps the most lucrative area. Americans spend $2.4 billion in prescription acne treatments, some of which carry serious side effects and at least twice that amount on ineffective over-the-counter products.

BIOFILMS- Catheter-related biofilm infections affect approximately 900,000

US patients per year. Of these, 40,000 develop serious kidney or major organ infections, and one-third of these patients die. Because these infections are acquired in hospitals, most involve antibiotic-resistant bacteria. We conservatively estimate the market for preventing these infections at $200 million. This figure will be many times as large if agents were routinely prescribed for all patients receiving urinary or venous catheters.

The catheter-infection problem has been exacerbated in the last several years due to over-use of antibiotics, particularly ciprofloxacin (a result of the anthrax scare). Acute infections are particularly worrisome because patients can die before a culture comes back positive. In addition, leading payors are increasingly refusing to reimburse hospitals for costs of treating hospital-acquired infections.

OPTHALMOLOGY - Through our partner Alcon, we are testing Aganocides to treat conjunctivitis. Aganocides have the potential to revolutionize this market because they treat infections of bacterial and viral origin equally well. Approximately half of all conjunctivitis cases are caused by viruses and 40% by bacteria. This market is conservatively estimated to be $1 billion.

Delaying the Inevitable

Current antibiotics are clearly losing the war against bacteria. The question is will the current crop of antibiotics tide us over until the next generation of therapies emerge? Antibiotic approvals in the US are at all-time lows. While several antibiotics are currently in human Phase III clinical trials, their approvals are by no means certain. A big unknown for development-stage antibiotics is how quickly they will engender resistance once the drugs enter widespread use. Finally, there is always the possibility that these agents, like systemic antibiotics of the past, will be used improperly.

The use of systemic antibiotics for treating superficial infections and colonizations with little chance of successfully treating the condition has therefore become a "luxury" that we can no longer afford. Our experience with mupirocin-resistant *Staphylococcus* should serve as a warning, that fighting colonizations of the skin and nasal passages with antibiotics will only exacerbate the problem of antimicrobial resistance.

Newer approaches, including locally administered non-antibiotic anti-infectives, such as the Aganocide compounds, are much more appropriate than antibiotics in situations where the infection or colonization is accessible and not yet systemic. Because development of resistance to their active agent cannot occur, we believe that the use of such agents will extend the useful life of systemic antibiotics by saving their use for conditions where they are truly needed. ◆

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Dr. Ramin (Ron) Najafi is the Founder, CEO, and Chairman of NovaBay Pharmaceuticals, Inc. He has served as President since July 2002 and as Chief Executive Officer since November 2004. Previously, Dr. Najafi served in various management positions within NovaBay, including Chief Scientific Officer. Before founding NovaBay, Dr. Najafi was the President and CEO of California Pacific Labs, Inc., a chemical laboratory safety devices company. He has also held scientific roles at Rhone Poulenc Rorer (now Sanofi-Aventis), Applied Biosystems, a division of PerkinElmer, Inc., and Aldrich Chemical. Dr. Najafi earned his BS and MS in Chemistry from the University of San Francisco and his PhD in Organic Chemistry from the University of California at Davis.

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