Drug Delivery Technology®

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

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Assessing Development

"Given the fundamental relationship that exists between scope, timing, and resources (people and money); scope should always be a significant consideration in selecting an outsourcing partner. However, it should not be the sole basis. It is important to know why you are outsourcing and what specific objectives you have so that you can select the most capable vendor for delivering the research outcomes that are most important to you."

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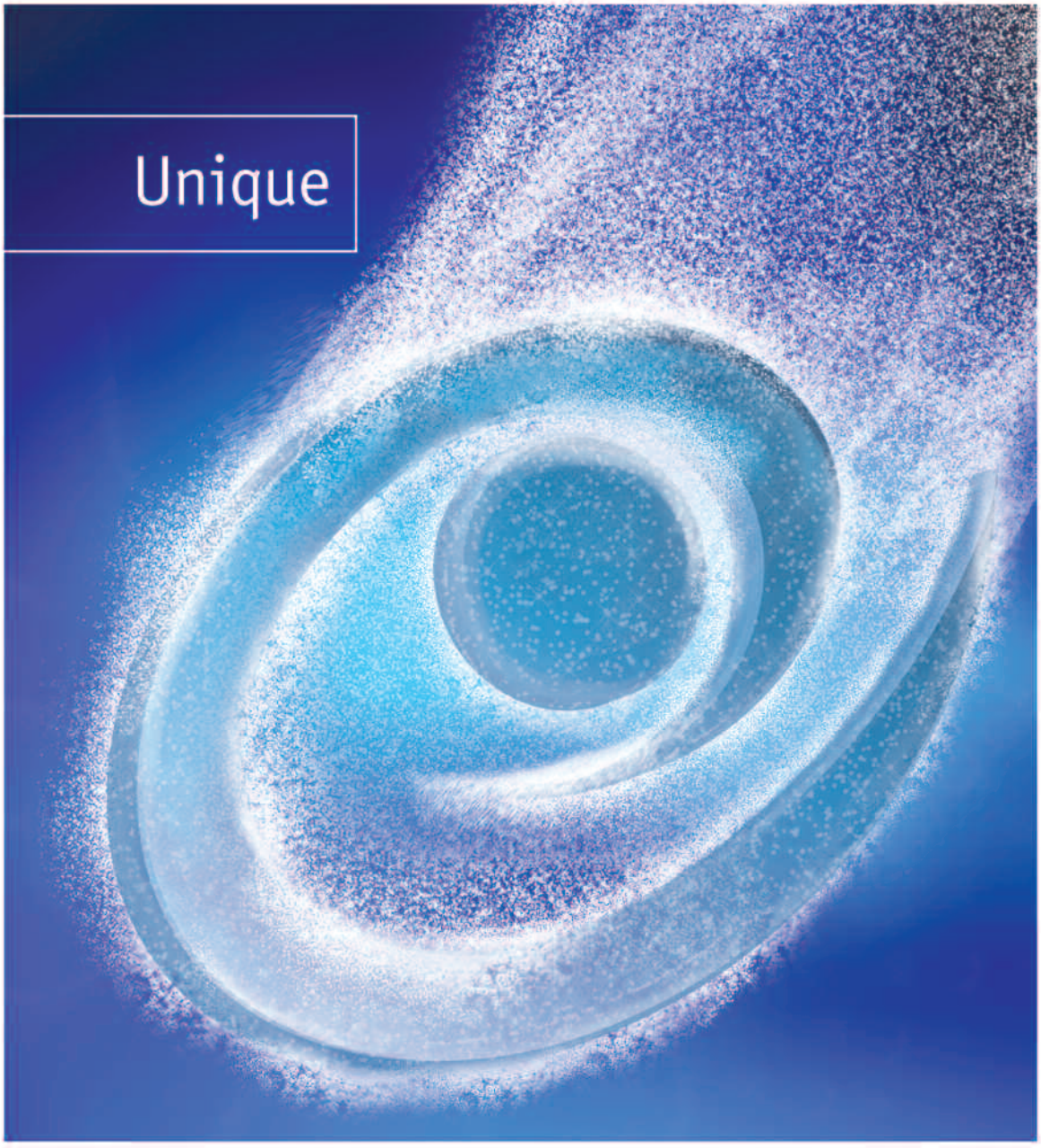

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Examining Reconstitution

"Many pharmaceutical companies are turning to home delivery and administration of these injectable medications, most of which are manufactured and sold in lyophilized (or freeze-dried) form and require reconstitution, mixing, or transfer before administration. This reconstitution process can be complex and introduce certain issues to consider."

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Market News and Trends

Merck Serono & Ambrx to Collaborate on Development of Next-Generation Growth Hormone Products

Merck Serono recently announced a collaboration with US biopharmaceutical company Ambrx, Inc. to develop and commercialize Ambrx's long-acting growth hormone products. The collaboration will focus initially on the development of ARX201, the most advanced product candidate, currently in Phase I/II clinical trials. ARX201 has improved pharmacological properties, which should allow less-frequent administration than the daily dosing regimen of currently available growth hormones.

Under the terms of the agreement, Merck Serono will receive worldwide commercialization rights for ARX201. Merck Serono will make an initial payment to Ambrx, and Ambrx is eligible to receive undisclosed clinical, regulatory, and commercial milestone payments based on the successful development and commercialization of products, as well as undisclosed royalties on net sales of such products. In addition, Ambrx retains an option to co-promote products in the US market. If the option is exercised, Ambrx and Merck Serono will share US commercialization expenses as well as profits. In the event Ambrx declines to exercise its option, it will receive undisclosed royalties on net sales of products worldwide.

"Merck Serono has a long-term commitment to children and adults with disorders requiring growth hormone treatment," said François Feig, Head of Global Therapeutic Area Endocrinology and Cardio-Metabolic Care, Merck Serono. "We believe that ARX201 has the potential to establish a new standard of care in growth hormone therapy. Less-frequent administration would represent a significant advance for patients in terms of improved convenience and quality of life. This may lead to improved treatment outcome for the patients."

James W. Young, PhD, interim Chief Executive Officer of Ambrx, added, "Merck Serono is a leader in the development and commercialization of innovative approaches to growth hormone therapy. This alliance is consistent with our strategy to work with industry leaders in their respective fields and is a validation of Ambrx's ability to deliver differentiated, high-value drug candidates."

In February 2007, Ambrx announced the initiation of a Phase I/II clinical trial of ARX201 to investigate the safety, tolerability, pharmacokinetic, and pharmacodynamic profile of this product candidate in adult patients with growth hormone deficiency following single-dose escalation and repeated dosing. ARX201 (PEG-ahGH) is a recombinant form of human growth hormone that has been modified using Ambrx's patented ReCODE technology to achieve precise spatial positioning of the site of polyethylene glycol (PEG) attachment to human growth hormone, by biosynthetic incorporation of a chemically unique amino acid (ahGH). Ambrx believes that ARX201 may have improved pharmacological performance over existing growth hormone products, including the potential for less-frequent dosing. ARX201 was selected through a lead optimization process that employed Ambrx's proprietary ReCODE technology, which effectively enables protein medicinal chemistry. Candidate molecules were characterized and screened to select for increased potency and improved pharmacological and pharmacodynamic performance. In preclinical studies, ARX201 met or exceeded key endpoints in assays that are believed to be predictive of human pharmacokinetics and biological response.

Ambrx, Inc. is a biopharmaceutical company focused on optimizing existing and developing novel protein-based drugs. Using its technology, the company can overcome the performance limitations of high-value commercial proteins by improving their efficacy, safety, and ease of use. Ambrx's core ReCODE technology enables the precise, site-specific substitution of a novel amino acid within a protein. This allows the conjugation of proteins with additional molecules that can serve to modulate their pharmacokinetic profile or biological function. Ambrx's ReCODE technology is applicable to multiple protein products across numerous therapeutic areas. With its innovative approach, Ambrx has successfully and rapidly bridged the gap from technology platform to a drug product enabling technology.

Kurve Technology & Schering-Plough Sign Expanded Technology Agreement

Kurve Technology, Inc., a leading developer of nasal drug delivery devices, and Schering-Plough Corporation, a global science-based healthcare company, recently announced a new agreement that expands Schering-Plough's evaluation of, and option for exclusivity rights to, Kurve Technology's Controlled Particle Dispersion (CPD) platform from a single field to multiple fields of use.

"We are extremely pleased with Schering-Plough's continued and expanded interest in our nasal delivery technology platforms," said Marc Giroux, Chairman and Chief Executive Officer of Kurve Technology, Inc. "This agreement is another significant step in our efforts of working with pharmaceutical companies to develop the most innovative intranasal drug/device combinations in the industry."

Kurve Technology's Controlled Particle Dispersion contains six critical-to-function design parameters that enable modification of deposition and droplet characteristics. The result is a flexible intranasal technology platform that can deliver virtually any liquid drug (solution or suspension) regardless of formulation characteristics, including viscocity, surface tension, or molecule size.

CPD enables pharmaceutical companies to deliver topical, systemic, nose-to-brain drugs, and vaccines with minimal peripheral deposition to the lungs and stomach. CPD powers Kurve Technology's ViaNase electronic atomizer line.

Kurve Technology, Inc. offers pharmaceutical companies innovative nasal delivery technologies for topical, systemic, nose-to-brain, medical, and vaccine therapies. Kurve's Controlled Particle Dispersion technology intranasally delivers formulations with far greater efficacy and efficiency than traditional methods. The ViaNase product

line of intelligent atomizers incorporates CPD with the potential to deliver a wide range of formulations. Kurve Technology is headquartered in Bothell, WA, with offices in Research Triangle Park, NC, and the United Kingdom.

Schering-Plough Corporation is a global science-based healthcare company with leading prescription, consumer, and animal health products. Through internal research and collaborations with partners, Schering-Plough discovers, develops, manufactures, and markets advanced drug therapies to meet important medical needs.

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Market News and Trends

Kamada Reports Excellent Intermediate Results of Phase I Clinical Trials of Aerosolized AAT for Lung Diseases

Kamada, a biopharmaceutical company that develops, manufactures, and markets life-saving medicines, has successfully concluded the first of two stages of the Phase I clinical study designed to test the safety of the aerosolized version of its flagship product, Alpha-1 Antitrypsin (AAT) using an optimized eFlow Electronic Nebulizer (PARI Pharma GmbH).

The study, which was executed according to a program approved by the European Medicines Agency (EMEA), involved 24 participants who received various doses of the inhaled drug. All dosage levels resulted in good safety profiles and tolerability, paving the way for continued clinical development of inhaled AAT using eFlow.

According to David Tsur, Kamada's CEO, the encouraging results will enable the completion of the first phase of aerosolized AAT's clinical trials. "Kamada is progressing toward registration of both its intravenous and aerosolized AAT formulations in the European and American markets," said Mr. Tsur. "The intravenous version is currently undergoing Phase III trials in the US, and we also intend to request FDA approval to test the aerosolized formulation."

In February 2007, Kamada submitted to the EMEA its request for assistance in planning various phases of clinical trials of aerosolized AAT, and the EMEA has since provided professional support. The advanced trials require approval from relevant regulatory authorities in the countries in which the studies will be conducted.

AAT (also known as API - Alpha-1 Proteinase Inhibitor) is used to treat Congenital Emphysema, caused by an inborn deficiency of Alpha-1 protein. The disease affects 1:2500 of the world's population, causing deterioration of lung tissue, severe respiratory disorders, and eventually death.

AAT is the only known treatment today for congenital emphysema. Kamada produces and markets a highly pure, ready-to-use, injectable AAT solution in several countries. The intravenous formulation is given on a weekly basis, requiring considerable time and resources.

The aerosolized version, delivered by PARI's eFlow electronic nebulizer, provides a more comfortable form of treatment. eFlow enables extremely efficient aerosolization of liquid medications via a vibrating, performed membrane. Compared to other nebulizer systems, eFlow can produce aerosols with a very high density of active drug, a precisely defined droplet size, and a high proportion of respirable droplets delivered in the shortest possible period of time. Furthermore, because the product is administered directly to the lungs, a lower dose is required to achieve the same therapeutic results, making the treatment accessible to many more patients. In addition to congenital emphysema, AAT may be effective in the treatment of other diseases affecting the lungs, including cystic fibrosis.

Kamada has obtained Orphan Drug Designation (ODD) from both the FDA and the EMEA for aerosolized AAT for the treatment of congenital emphysema and cystic fibrosis. ODD designation, and subsequent ODD status, present significant commercial advantages throughout the development process, registration, and distribution of the product throughout its lifecycle, notably exclusive distribution rights for periods of 7 years in the US and 10 years in Europe, should Kamada be the first to successfully complete the clinical trials and obtain regulatory approvals for these indications.

Kamada manufactures a line of highly safe specific immunoglobulins and other plasma-derived therapeutics, using sophisticated chromatographic purification technology. Licensed and marketed in more than 15 countries, several of these specialty biopharmaceuticals hold registered and pending patents and are currently in advanced clinical trials.

Global Biopharmaceutical Service Provider Selects InForm Product as Preferred EDC Solution

Phase Forward, a leading provider of data management solutions for clinical trials and drug safety, recently announced it has strengthened its alliance with Parexel International Corporation, a leading global biopharmaceutical services provider. The multi-year agreement allows Parexel to continue to offer Phase Forward's InForm electronic data capture (EDC) product as an integral part of its solution set.

A Phase Forward alliance partner since 1999, Parexel provides a broad range of services to the biopharmaceutical industry. For 25 years, pharmaceutical, biotechnology, and medical device companies worldwide have relied on Parexel to provide integrated clinical development, regulatory affairs consulting, and commercialization services, as well as technologies that expedite time-to-market.

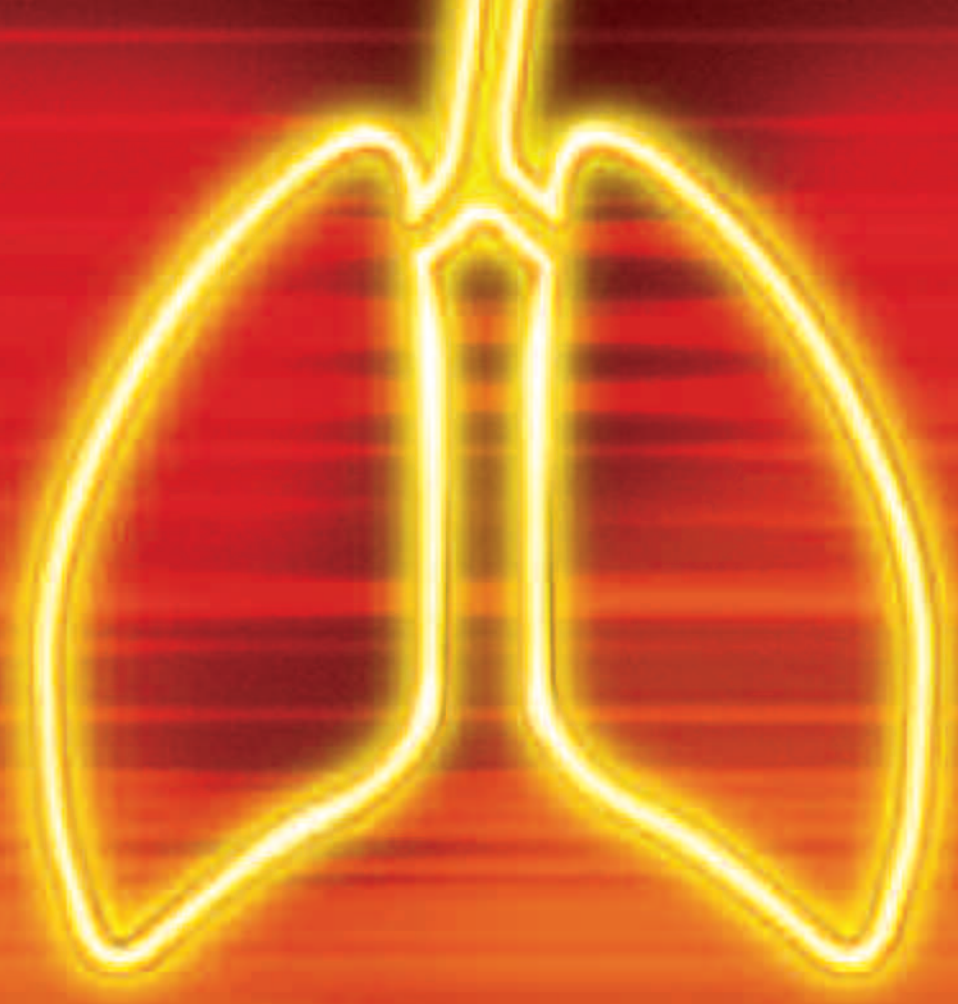
"We are pleased to continue our alliance with Phase Forward and to be able to provide our clients with a premier EDC solution that integrates with our overall technology platform for their global clinical development programs," said Mark A. Goldberg, MD, President of Clinical Research Services and Perceptive Informatics at Parexel.

In addition to the InForm system, Parexel uses Phase Forward's Clintrial product, a comprehensive clinical data management and analysis system that integrates both electronically captured and paper-based study data, as well as Phase Forward's Clintrace software, a highly scalable, adverse event tracking and reporting system.

"As EDC continues to gain traction, we believe we can help biopharmaceutical and medical device companies realize the full benefits of EDC, and we look forward to working with Parexel in pursuing this goal," said Bob Weiler, CEO and President, Phase Forward.

Phase Forward is a leading provider of integrated data management solutions for clinical trials and drug safety. The company offers proven solutions for electronic data capture (InForm), clinical data management (Clintrial), clinical trials signal detection (CTSD), strategic pharmacovigilance (WebVDME and Signal Management), adverse event reporting (Clintrace), and applied data standards (WebSDM). In addition, the company provides services in the areas of application implementation, hosting and validation, data integration, business process optimization, safety data management, and industry standards. Phase Forward's products and services have been utilized in over 10,000 clinical trials involving more than 1,000,000 clinical trial study participants at over 250 organizations and regulatory agencies worldwide, including AstraZeneca, Boston Scientific, Dana-Farber Cancer Institute, Eli Lilly, the US Food and Drug Administration, GlaxoSmithKline, Harvard Clinical Research Institute, Merck & Co., Merck Serono, Novartis, Novo Nordisk, Parexel International, Procter & Gamble, Quintiles, sanofi-aventis, Schering-Plough Research Institute, Tibotec, the U.K. Medicines and Healthcare Products Regulatory Agency, and Servier.

Parexel International Corporation is a leading global bio/pharmaceutical services organization, providing a broad range of knowledge-based contract research, medical communications, and consulting services to the worldwide pharmaceutical, biotechnology, and medical device industries. Committed to providing solutions that expedite time-to-market and peak-market penetration, Parexel has developed significant expertise across the development and commercialization continuum, from drug development and regulatory consulting to clinical pharmacology, clinical trials management, medical education, and reimbursement. Perceptive Informatics, Inc., a subsidiary of Parexel, provides advanced technology solutions, including medical imaging, to facilitate the clinical development process.



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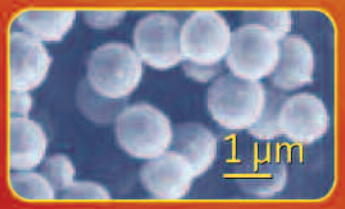

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Major Breakthrough Speeds Therapies to the Brain

Researchers at the Immune Disease Institute (formerly the CBR Institute for Biomedical Research) have overcome a major hurdle in the delivery of therapeutics to the brain: getting past the blood-brain-barrier (BBB), which excludes most large and small molecule drugs. Their breakthrough research was published in the June 2007 issue of Nature magazine, with Manjunath Swamy, MD, as Principal Investigator and Priti Kumar, PhD, as First Author on the paper, with collaboration from scientists at the University of Iowa and Hanyang University in South Korea.

The BBB, composed of the endothelial walls of 100 billion capillaries in the brain, is a superfine filter that prevents transport of harmful pathogens and beneficial drugs alike. To overcome the BBB in situations of disease, IDI researchers in the Swamy lab employed a modified Rabies virus glycoprotein peptide name CORVUS that slipped past the BBB and, in mice, delivered small interfering RNAs as a therapy to neuronal cells in the brain. The siRNAs effected specific gene silencing in the brain, without side effects.

A visionary discovery, this new technology from the Swamy lab provides a non-invasive, intravenous means of delivering, throughout the brain, the powerful therapy known as RNA interference (which suppresses disease-causing genes) as well as, potentially, DNA for gene therapy. The CORVUS technology also promises to be a brain delivery system for a wide slate of conventional drugs in the form of antibodies, proteins, and other compounds.

Many late-stage clinical trials have failed when candidate drugs are frustrated at the BBB; this new ability to send therapies selectively to the brain may revolutionize the treatment of diseases, including Alzheimer's; Parkinson's; multiple sclerosis; psychiatric illnesses, such as schizophrenia; fatal infections, including encephalitis and meningitis; and central nervous system traumas among other illnesses.

Previously, Drs. Swamy, Kumar, and colleagues had used RNAi to defeat brain infection caused by Japanese encephalitis and West Nile virus. With the breakthrough CORVUS technology, they will be able to prevent such deadly infections in mice by administering the same siRNAs intravenously.

In addition, there is a great need for new therapeutics for Alzheimer's and other "neuronal" diseases associated with aging, as the US population becomes older. Effective delivery of therapies to the brain is a vital component for making progress against these diseases.

Founded in 1953, the Immune Disease Institute is an independent, non-profit biomedical research institute in Boston affiliated with Harvard Medical School. Its world-class investigators conduct breakthrough research on the immune system and inflammation, work leading to new therapies for millions of patients suffering from illnesses, such as cancer, heart disease, HIV/AIDS, lupus, Alzheimer's disease, and immune deficiencies.

The CORVUS technology (CBRI ID 06-001) is a patent-pending, novel drug delivery and neuronal cell transfection method utilizing a small peptide to selectively deliver drug payloads across the BBB and spread the drug evenly throughout the brain. IDI is currently evaluating collaborative research and licensing opportunities within the industry.

Market News and Trends

Penwest Enters Into Collaboration Agreement With PII; Expands Licensing Strategy for its Drug Delivery Technologies

Penwest Pharmaceuticals Co. recently announced it has signed a collaboration agreement with Pharmaceutics International Inc. (PII) under which PII has agreed to conduct formulation work for Penwest and third parties for drugs using Penwest's proprietary oral drug delivery technologies, TIMERx, Geminex, and Syncrodose. This agreement represents an expansion of Penwest's technology licensing strategy, which the company expects will provide Penwest with additional collaboration opportunities while allowing it to maintain its internal focus on developing products for disorders of the nervous system.

The strategic goal of this collaboration is to continue to leverage the company's established drug delivery expertise while supporting Penwest's transition to a specialty pharmaceutical company. Under the agreement, PII may conduct formulation work for drugs being developed by either Penwest or third parties who license Penwest's drug delivery technologies.

PII may also independently identify new product development opportunities for this collaboration. Under the collaboration, Penwest and PII have agreed to jointly review opportunities for licensing Penwest's oral drug delivery technologies to third parties and may conduct the formulation work for such third parties provided that these programs do not conflict with Penwest's internal programs. PII has agreed to assume primary responsibility for formulation development with technical guidance and oversight from Penwest and may assume responsibility for clinical trial material manufacturing and commercial manufacturing.

Jennifer Good, Penwest's President and CEO, said, "We are pleased to enter into this collaboration with PII. Since the approval and launch of Opana ER, we have received inquiries from a number of parties regarding licensing our drug development technologies, which we believe confirms that the core TIMERx technologies remain attractive to companies pursuing brand management strategies for their own products. We believe this new agreement leverages the value of our drug delivery technologies while allowing us to continue to focus on building our own pipeline. We look forward to working with PII to grow this part of our business."

Penwest is a specialty pharmaceutical company dedicated to bringing to the marketplace innovative products that help improve the lives of patients. The company's goal is to identify, develop, and commercialize prescription products that address unmet medical needs, primarily for diseases of the nervous system. At the core of this strategy, Penwest applies drug delivery technologies, including its own proprietary technologies, to new and existing compounds to enhance their therapeutic profiles. The launch by Endo Pharmaceuticals in mid-2006 of Opana ER (oxymorphone hydrochloride extended-release tablets) formulated with the company's TIMERx extended-release delivery technology demonstrates the execution of this strategy and the value of the company's TIMERx technology. The company is currently applying its expertise to a pipeline of potential products that are in various stages of development. The company intends to commercialize these products independently or through third-party alliances.

ARx Division of Adhesives Research to Open New Manufacturing Facility

Adhesives Research has recently announced the opening of a new 25,000-sq-ft, stand-alone facility in whoch its ARx subsidiary will manufacture active pharmaceutical products that deliver over-the-counter (OTC) and prescription drugs, including thin film, transdermal, biopharmaceutical, and oral/mucosal systems. The facility is compliant with cGMP (current Good Manufacturing Practices), FDA, and global regulations for manufacturing pharmaceutical products and brings the total square footage at the Glen Rock campus to more than 240,000 sq ft.

"The new facility triples the division's manufacturing capacity and allow us to continue to advance the use of film technology in emerging applications, including controlled release and topical applications," said Beth Vondrak, Vice President and General Manager of ARx.

ARx, a wholly owned subsidiary of Adhesives Research located in Glen Rock, PA, was created in 2005 to address the growing global need for innovative delivery of active drug-containing systems. Adhesives Research has over 20 years of experience in providing unique components for transdermal, oral, and topical drug delivery.

ARx currently supports eight commercial thin film products for Novartis Consumer Health (Triaminic Thin Strips, pediatric cough and cold products, Theraflu Thin Strips, cold and flu products, Gas-X Thin Strips, anti-gas relief products, and Triaminic Thin Strips, infant decongestant and cold products) and anticipates launching at least 20 more in the next 3 years. Approximately 60 current ARx employees have moved into the new facility, with the possibility of creating additional jobs in the future.

Dissolvable thin film technology provides consumers with a new delivery option for taking OTC and prescription medicines. The key benefits of the technology include quick and precise dosing, convenience, and portability. These films are proving to be very popular for the pediatric population as well as with individuals who have difficulty swallowing pills and those who prefer on-the-go relief.

At the groundbreaking for the facility in April 2006, Darrell Auterson, President and CEO of the YCEDC, called Adhesives Research "an innovative manufacturing company looking to the future, focusing on the research and looking to the products of tomorrow."

Adhesives Research received support for this project from the York County Economic Development Corporation and the Pennsylvania Department of Community and Economic Development through the Governor's Action Team in the form of an Opportunity Grant, Job Creation Tax Credits, Customized Job Training, WEDnet, and Pennsylvania Industrial Development Authority financing.

TransPharma Medical Receives Second Milestone Payment From Teva Pharmaceutical Industries

TransPharma Medical Ltd., a specialty pharmaceutical company focused on the development and commercialization of drug products utilizing a proprietary active transdermal drug delivery technology, recently announced it has received its second milestone payment from Teva Pharmaceutical Industries for the successful development of a stable human growth hormone (hGH) dry form patch required for advanced clinical trials of Teva's transdermal hGH product.

The milestone achieved is in line with the product development plan of hGH, the first of up to five molecules designated for joint development by TransPharma and Teva in an agreement originally signed between the two companies in 2004. Under the agreement, Teva will exclusively market each of the drug products and will pay TransPharma milestone payments, royalties, and development costs.

"This second milestone is a significant stride in the development plan of the hGH transdermal drug delivery system, and also an important achievement for validation of our proprietary protein patch technology. By formulating dry form protein patches, we enable a long shelf-life for the ViaDerm System products. Our proprietary patch technology perfectly complements our device, which together enable accurate transdermal delivery of therapeutic biologics," said Dr. Daphna Heffetz, Chief Executive Officer of TransPharma Medical Ltd. "We are pleased to be collaborating with Teva, a world leader in pharmaceutical development, and look forward to continued cooperation as we progress in the development process," Dr. Heffetz added.

TransPharma's ViaDerm drug delivery system incorporates a handheld electronic device combined with a drug patch. The system provides a cost-effective, easy-to-use, self-administered solution that enables the safe, reproducible, and accurate delivery of a wide variety of product candidates, including hydrophilic small molecules, peptides, and proteins.

Established in 2000, TransPharma Medical Ltd. is a specialty pharmaceutical company focused on the development and commercialization of drug products utilizing a proprietary active transdermal drug delivery technology. TransPharma aims to develop multiple drug products through strategic partnerships with leading pharmaceutical companies and through independent product development.

Schering-Plough & Bayer Announce Availability of Zetia in Japan; First Cholesterol-Lowering Agent With a Novel Mechanism of Action Approved in 18 Years

TransPharma Medical Ltd., a specialty pharmaceutical company Schering-Plough Corporation and Bayer HealthCare recently announced that Zetia (ezetimibe), a novel cholesterol-lowering agent that inhibits the absorption of cholesterol in the intestine, is now available in Japan for use in patients with hypercholesterolemia, familial hypercholesterolemia, or homozygous sitosterolemia. Zetia is the first new cholesterol-lowering medication with a novel mechanism of action since statins were introduced 18 years ago in Japan. Zetia is marketed in Japan by Schering-Plough K.K. and Bayer Yakuhin Ltd., the country operations of Schering-Plough and Bayer HealthCare, respectively, in Japan. Zetia can be used as a monotherapy and co-administered with a statin for further reduction of low-density lipoproteins (LDL).

Zetia received marketing approval in Japan from the Ministry of Health, Labor and Welfare (MHLW) this past April and will became available in June following a National Health Insurance Reimbursement price listing. The total number of patients in Japan with high cholesterol, including those undiagnosed, is estimated to be approximately 30 million, which makes Japan the second-leading country with patients with high cholesterol, following the US.

Schering-Plough, in collaboration with Merck, obtained FDA approval for Zetia in 2002, and the medication has been approved in 90 countries worldwide. The cholesterol-management market is one of the largest worldwide, with total global sales of $34 billion and sales in the US of $22 billion in 2006 (IMS Health). Schering-Plough, in collaboration with Merck, has developed and commercialized Zetia for lipid management in the US and the rest of the world (excluding Japan), where it is also marketed under the trade names Ezetrol and Zient.

Zetia, which works in the digestive tract to inhibit the absorption of cholesterol, is complementary to the class of cholesterol-lowering agents known as statins, which work in the liver to reduce the production of cholesterol. Zetia, alone or in combination with statins, has been proven to significantly improve LDL cholesterol levels. Zetia, either alone or in addition to a statin, has not been shown to prevent heart disease or heart attacks.

Zetia is indicated, along with a healthy diet, for use either by itself or together with statins in patients with high cholesterol to reduce LDL cholesterol and total cholesterol when the response to diet has been inadequate.

Schering-Plough Corporation is a global science-based healthcare company with leading prescription, consumer, and animal health products. Through internal research and collaborations with partners, Schering-Plough discovers, develops, manufactures, and markets advanced drug therapies to meet important medical needs. Schering-Plough's vision is to earn the trust of the physicians, patients, and customers served by its approximately 33,500 people around the world. The company is based in Kenilworth, NJ.

Market News and Trends

Senopsys & Patheon Collaborate to Develop Palatable Drug Products

Senopsys LLC, a specialty pharmaceutical services company, recently announced it has signed a collaboration agreement with Patheon Inc., a leading global provider of drug development and manufacturing services, to accelerate the development of palatable drug products. Through this collaboration, Senopsys clients will have access to prototype drug formulations manufactured by Patheon, and Patheon will be able to offer its clients taste assessment and optimization services.

"The combination of Senopsys' significant expertise in taste assessment and optimization with our broad development capabilities will provide an excellent platform for supporting our clients with additional solutions for their drug products requiring taste-masking," said Dr. Shabbir Anik, Patheon's President of Global Pharmaceutical Development Services. "We have a number of clients who are interested in developing palatable dosage forms to support pediatric regulatory requirements for investigational new drugs and life-cycle management initiatives for approved drugs. We look forward to working with Senopsys to develop palatable products that meet the needs of diverse patient populations."

A drug product's aesthetics (aroma, flavor, texture, mouthfeel) can have a significant effect on patient compliance, health outcomes, and product sales. Senopsys uses proprietary sensory assessment and formulation tools to develop palatable drug products. The company quantifies the taste-masking challenge of drug substances, measures the palatability of prototypes, and optimizes the sensory characteristics of drug products to meet the needs of diverse patient populations. Patheon offers a full range of formulation and analytical development, and clinical supplies manufacturing and process optimization capabilities. The company can quickly and cost effectively manufacture small-scale batches of prototype drug formulations under Good Manufacturing Practices (GMP) guidelines.

"This collaboration with Patheon enhances Senopsys' ability to conduct taste assessment and optimization studies that require the use of GMP materials," said Jeff Worthington, Founder and President of Senopsys. "With Patheon's development and manufacturing capabilities and Senopsys' taste-optimization expertise, our companies will be able to provide our clients with expanded options for accelerating the clinical and commercial development of their drug products."

Senopsys is a specialty services company dedicated to the development of palatable pharmaceuticals. The company partners with pharmaceutical, biotechnology, and drug delivery companies to develop patient-acceptable drug products that improve patient compliance, health outcomes, and drug sales. Senopsys' FlavorMetrics Taste Assessment Tools are used to quantify the taste-masking challenge of drug substances and measure the palatability of drug prototypes and competing products. Using its FlavorOpt Sensory Optimization System, Senopsys applies its knowledge of flavor construction and excipient functionality to develop palatable formulations.

Dowpharma Announces License Agreement With Abbott; Pfinex Expression Technology Provides Lower Manufacturing Costs & May Increase Speed-to-Market

Dowpharma recently announced that Abbott has entered into a commercial license agreement for Pfinex Expression Technology, a Pseudomonas-based technology from Dowpharma. The product under the agreement is a confidential proprietary protein discovered by Abbott scientists, for which a high-yield production strain and a fully scalable process have already been developed. Dow will transfer the production strain to Abbott and fully support its regulatory filing.

Under the agreement, Abbott will have a non-exclusive license to use Pfinex Expression Technology for the development and manufacture of the human therapeutic.

"This agreement with Abbott is yet another validation in a long line of agreements by the pharmaceutical industry that our technologies continue to deliver valued solutions. We are pleased to be working with Abbott to help fulfill its future protein production needs as part of this commercial license agreement," said Nick Hyde, Global Business Director for Dowpharma. "Proteins produced by Pfinex Expression Technology are now in human clinical trials, and the system consistently delivers high-quality protein faster than traditional expression systems."

Using a natural isolate of Pseudomonas fluorescens, an abundant and non-infectious component of the microbial flora of soil, water, and plants, many high-performance production strains have been developed by Dow. Proteins are expressed in high yields with correct disulfide bond formation, reduced protease levels, and enhanced solubility, making the process faster, more efficient, and of higher quality than traditional bacterial expression. Dozens of host strains are tested in parallel to improve target protein accumulation and/or stability. The technology is easily employed in traditional fermentation, recovery, and purification settings with no need for additional, unique equipment. Pfinex Expression Technology includes an extensive toolbox of gene expression capabilities and multiple host strains. Combined with high-throughput methods, strains producing high levels of active, complex recombinant proteins, such as antibody derivatives, fully-functional antigens and adjuvant proteins are rapidly constructed and identified. The production process contains no animal-derived products and no antibiotics or antibiotic selection markers, making scale-up safe, efficient, and highly cost effective.

Dow is a diversified chemical company that harnesses the power of innovation, science, and technology to constantly improve what is essential to human progress. The company offers a broad range of products and services to customers in more than 175 countries, helping them to provide everything from fresh water, food, and pharmaceuticals to paints, packaging, and personal care products. Built on a commitment to its principles of sustainability, Dow has annual sales of $49 billion and employs 43,000 people worldwide.

Market News and Trends

Formerly Cardinal Health PTS, Newly Named Catalent Now Operates as Independent Company

Catalent Pharma Solutions, formerly Cardinal Health Pharmaceutical Technologies and Services, recently announced its official launch as an independent operating company. The Blackstone Group acquired the business from Cardinal Health in April 2007.

Catalent is a leading provider of advanced technologies, as well as development, manufacturing, and packaging solutions for pharmaceutical, biotechnology, and consumer healthcare companies in nearly 100 countries. Catalent offers its customers nearly 75 years of experience in providing advanced technologies and consistent product supply across almost every major dose form type, and holds more than 1,000 patents and patent applications.

Catalent has a long heritage of dose form innovation. Catalent commercialized softgel capsule technology and Liqui-Gel formulations, created the fast-dissolve oral tablet category with Zydis, and introduced the vegetable-based capsule VegiCaps Soft. Catalent's proprietary drug delivery and packaging technologies and expertise enable customers to achieve their desired clinical and market outcomes, and are used in many well-known consumer health and prescription drug products. Catalent is also known for its child-resistant, senior-friendly, and compliance-enhancing packaging designs.

Customers will continue to rely on Catalent and its team of specialized experts worldwide for its advanced technologies and substantial expertise.

"Catalent intimately understands the global challenges our customers face while developing and commercializing life-enhancing and life-saving drugs or innovative consumer health products," said John Lowry, President and CEO of Catalent Pharma Solutions. "By consistently providing our customers with the technologies, services, and reliable solutions they have come to expect from us, we enable them to focus on their own core competencies."

The Catalent name was created to combine the ideas embodied by the words "catalyst" and "talent." Catalent serves as a catalyst for success for its customers, enabling them to ensure product supply and improve product effectiveness, while "talent" underscores the company's breadth and depth of scientific, technical, and local market expertise around the world.

Headquartered in Somerset, New Jersey, Catalent is the leading provider of advanced technologies, development, manufacturing, and packaging services for pharmaceutical, biotechnology, and consumer healthcare companies in nearly 100 countries. The company applies its local market expertise and technical creativity to advance treatments, change markets, and enhance patient outcomes. Catalent employs approximately 10,000 people at more than 30 facilities worldwide and generates more than $1.7 billion in annual revenue. The company's new website is www.catalent.com.

Announcing the World's Most Valuable Controlled Release Alliance

The Dow Chemical Company ("Dow") and Colorcon, Inc. have formed a global Controlled Release Alliance that provides more resources than ever to accelerate your pharmaceutical product development efforts and reach markets throughout the world. The Alliance includes the exclusive distribution rights for Dow Controlled Release Pharmaceutical Excipients, including ETHOCEL™ Ethylcellulose polymers, METHOCEL™ High Viscosity Hypromellose polymers, and POLYOX™ Poly(ethylene oxide) resins.

The Alliance places technical and customer service in the hands of Colorcon, an acknowledged world leader in application development support and product logistics. At the same time, the Alliance allows Dow to better address customer needs for value-added service throughout the world.

Rely on Colorcon for Worldwide Application Development and Local Technical Support

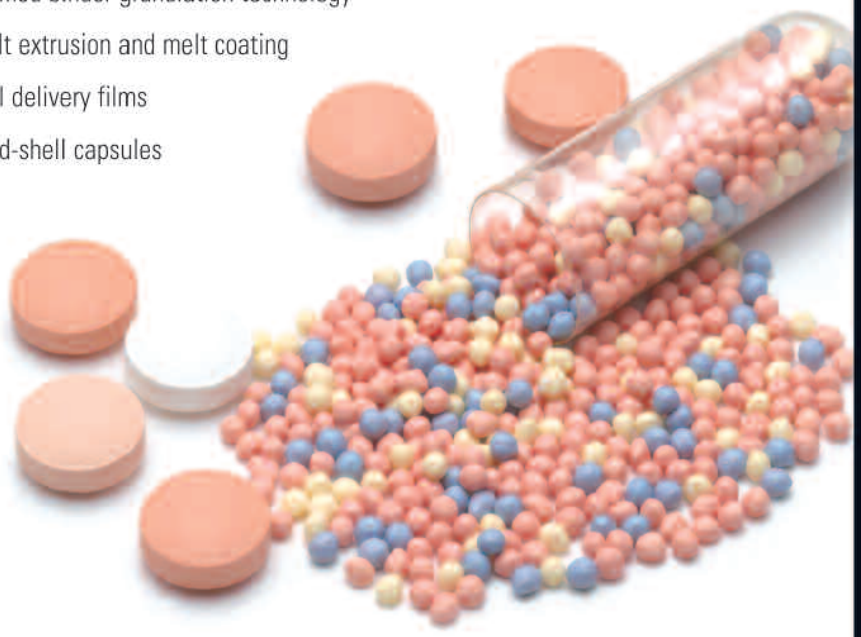
Colorcon's core business is the design and technical support of advanced pharmaceutical dosage forms for immediate, controlled and enteric release applications. In partnership with Dow, Colorcon will offer an enhanced portfolio of controlled release application expertise to find ideal solutions to customer needs and speed their products to market.

No matter where you manufacture in the world, you can rely on Colorcon for applications support and local product supply. Colorcon maintains locations throughout North America, Europe, South and Central America and Asia. These include 17 local technical laboratories, dedicated controlled release expertise in all regions and 14 strategically located distribution centers.

Dow's Role: Increasing Pipeline Capacity for New Excipient Technologies

The Alliance frees Dow's growing arsenal of intellectual capital and people resources to do what it does best: develop improved and new technologies to enhance performance during pharmaceutical manufacturing, distribution, and use. Dow will use this new way of doing business to expand the list of enabling technologies it has already developed for Dow excipient polymers, such as:

- Foamed binder granulation technology
- Melt extrusion and melt coating
- Oral delivery films
- Hard-shell capsules



A Brief Look at the Controlled Release Alliance Products and Technologies

ETHOCEL™ Premium Ethylcellulose organosoluble excipients are used in controlled release dosage forms including barrier membrane applications for multiparticulate formulations. Colorcon's **SURELEASE®** products are fully formulated aqueous ETHOCEL™ ethylcellulose dispersions that provide optimum flexibility in choosing a barrier membrane.

METHOCEL™ Premium Hypromellose high viscosity polymers are primarily used in controlled release matrix systems. Colorcon's **HyperStart®** modeling service provides a starting formulation for most actives, saving the pharmaceutical formulator valuable development time.

POLYOX™ Water-Soluble Resins NF are hydrophilic excipients used in controlled release matrix systems, osmotic applications, tablet binding, tablet coatings, transdermal drug delivery systems and mucosal bioadhesives.

Learn More About the Global Alliance Between Colorcon and Dow

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Drug Reconstitution: Market Needs & Technical Challenges

By: Graham Reynolds

For patients who must manage chronic diseases, such as hemophilia, multiple sclerosis, rheumatoid arthritis, diabetes, and others, medication issues can present significant challenges regarding safety, ease of administration, cost, compliance, and other factors. Fortunately, continual advances and breakthroughs from pharmaceutical companies are delivering tremendous improvements in the form of more effective medications. However, these medications typically require frequent injections, and depending on the nature of the disease and the patient's individual condition, those injections could be weekly, daily, or even multiple times a day.

In an effort to reduce healthcare costs and improve patient satisfaction, there has been a marked increase in patient self-administration of medications for chronic conditions. Many pharmaceutical companies are turning to home delivery and administration of these injectable medications, most of which are manufactured and sold in lyophilized (or freeze-dried) form and require reconstitution, mixing, or transfer before administration. This reconstitution process can be complex and introduce certain issues to consider.

The following article examines some of the challenges and market trends associated with drug reconstitution along with brief explanations of different technologies that have gained approval and acceptance among pharmaceutical companies and their patients.

WHY DO WE NEED RECONSTITUTION SYSTEMS?

Many new drugs, especially those developed by biopharmaceutical companies, are initially marketed in lyophilized form for two primary reasons: shelf-life and time-to-market. A lyophilized drug maintains its stability and potency over time, extending its shelf-life for prolonged storage. Some drugs marketed in lyophilized form may eventually be available as liquid, but lyophilization provides the fastest route to market for many drugs, and the only option for those not stable in a liquid form.

These drugs (often packaged in powder form in vials) require an additional preparation step prior to administration. That additional step is the traditional reconstitution process. With traditional reconstitution, there are two vials and one disposable

FIGURE 1

Mix2Vial™ needleless reconstitution systems enable simple vial-to-vial transfer and mixing between diluent vial and lyophilized drug vial.

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syringe. One vial contains the lyophilized drug, and the other contains the diluent (often water, but occasionally another liquid). The patient or caregiver must use the syringe to insert air into the vial containing diluent, withdraw the diluent into the syringe, insert the diluent into the vial containing the lyophilized drug, mix the solution to create an injectable medication, and draw a measured dose back into the syringe for injection. Not surprisingly, this rudimentary reconstitution process presents the following formidable challenges:

- A Lack of Expertise: In most instances, reconstituted drugs are administered in non-clinical settings (typically at home) by patients or caregivers who are not trained healthcare professionals. While it is far more convenient for patients who can avoid repeated trips to clinics and other facilities for routine injections, it can be a daunting experience to prepare and administer an injectable drug. Pharma companies need to ensure that the process is simple and safe.

- Added Risks: Any drug that requires mixing presents complications and risks. For example, a hemophiliac must be especially vigilant to prevent accidental needlesticks. There can be inadvertent contaminations or exposures to sometimes toxic drugs (often resulting from so-called spray-back). And there is a greater risk of inaccurate process, such as using improper concentrations, resulting in incorrect dosing.

- Compliance Concerns: If the process is complicated, dosing accuracy may suffer. And if the process is difficult, unpleasant, or painful, it can become an impediment to patient compliance.

- Waste: Pharmaceutical manufacturers often overfill the vial by as much as 35% to ensure that there is a sufficient quantity of the reconstituted drug to administer the correct dose. The overfill compensates for the inherent variability of the manual process, as well as the difficulty of removing the liquid completely from the vial. From the patient's perspective, there's a risk of mishandling or contamination that can necessitate throwing out very expensive drugs.

A number of newer, advanced products on the market can provide both professionals and non-professionals with safe, convenient, and easy-to-use systems for reconstituting and administering injectable drugs. These systems can be provided either as a total packaged solution or as components for specialized use.

Many of the new reconstitution systems can be adapted to currently marketed drugs without the need to change manufacturing processes or packaging components, such as vials, stoppers, and seals. They are offered as a total system that can be packaged with the filled drug vial and the reconstitution components. Such systems usually consist of a plastic device that joins the drug vial to the diluent container that can be either a prefilled syringe, vial, or infusion bag.

Reconstitution devices can be sterile and fully supported by appropriate regulatory filings. To further enhance convenience, all required items to perform the reconstitution can be packaged together in a kit form. The following section examines some of the leading reconstitution options.

SELECTING THE RIGHT RECONSTITUTION ALTERNATIVE

An advanced reconstitution system can add value to currently marketed and pipeline drug products. When evaluating the various alternatives for advanced reconstitution, pharmaceutical makers

FIGURE 2

Vial Adapters enable rapid transfer and reconstitution of drugs between vials with optimal aspiration of mixed and reconstituted drugs. They are compatible with Luer slip-and-lock syringes.

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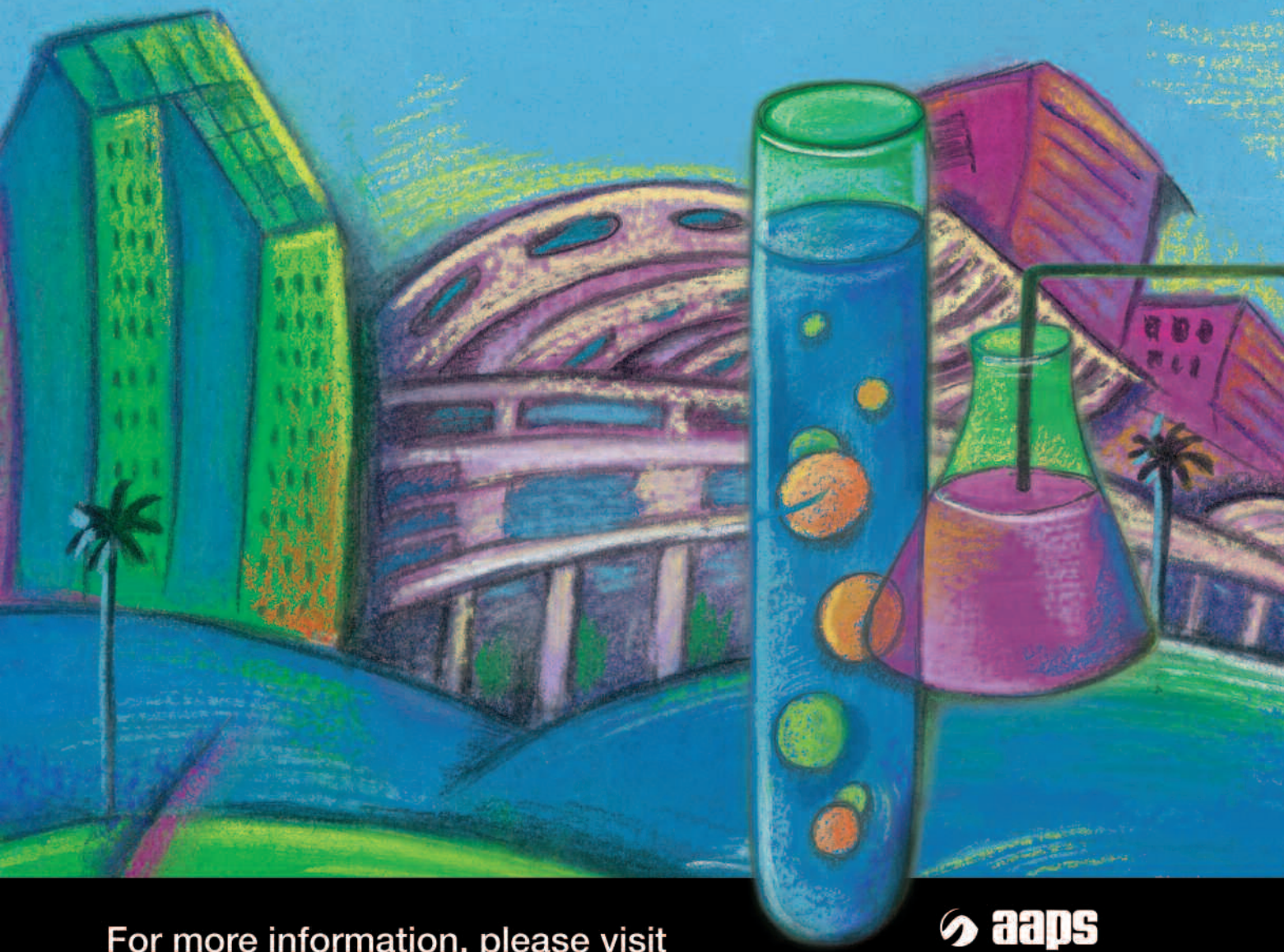

For more information, please visit
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FIGURE 3

The MixJect® transfer system is a single unit for reconstituting a powder drug with a diluent prefilled syringe. Upon reconstitution, the drug is available for immediate injection with a dry integral needle.

should carefully consider various factors. The following are among the key criteria:

- TYPE OF DRUG: If it's expensive or more toxic, that carries implications for the type of reconstitution method you choose.
- DILUENT VOLUME TYPE: Different volumes will present you with a varying number of options.
- ADMINISTRATION METHOD: Is the drug to be injected subcutaneously, intravenously, or intramuscularly?
- LINKAGE TO SECONDARY ADMINISTRATION: If you need to connect (post-reconstitution) to a bag or autoinjector, certain options are more advantageous.
- COMPETITIVE ENVIRONMENT: Many drug makers use reconstitution and delivery as differentiators for products that may be approaching commodity status.
- TIME-TO-MARKET REQUIREMENTS: Reconstitution systems that use existing, approved packaging avoid the need for regulatory review.
- OVERFILL ISSUES: Systems that reduce the need to overfill vials with lyophilized medications are ideal for expensive pharmaceuticals.

VIAL ADAPTORS

Vial adaptors, which provide quick, safe, and cost-effective transfer of the diluent, are a low-cost solution to improving the reconstitution process. These systems connect a syringe of a diluent (either prefilled or filled from another container, such as a vial or ampoule) to a vial with a lyophilized drug and provide for quick and safe transfer from vials, allowing convenient, optimal quantity aspiration.

The adapter snaps to the neck of the standard vial after the plastic button has been flipped off. A plastic spike pierces the stopper (needles are not used). The reconstituted drug is transferred to a syringe by a luer connection. Vial adapters come in a variety of sizes as well as venting and inline filter options; an optional incorporated valve system maintains stability for multi-dose applications. You can even use different variations of the vial adapter to connect to other containers, such as IV bags and cartridges (for subsequent insertion into a pen system) as well as nasal or oral administration routes.

VIAL-TO-VIAL SYSTEMS

Vial-to-vial systems offer a similar level of simplicity and cost effectiveness through a double-adapter that connects to the top of each vial (lyophilized drug and diluent). This is an ideal solution for connecting vials of different sizes. You can color-code the adapters (eg, blue side is for diluent) and add particulate filters and venting if necessary/desired. This is a very easy process for patients, and needles are not required to reconstitute the drug. For manufacturers, vial-to-vial systems are attractive because they do not necessitate changes to the vials they currently use.

NEEDLELESS TRANSFER DEVICES

This is a more sophisticated form of vial-to-vial reconstitution. This single-device model allows for pressurization and transfer of the diluent into the vial containing the lyophilized drug. The patient snaps on both vials. The diluent mixes with the powdered drug, and the connected syringe draws in the reconstituted drug for administration.

DIRECT CONNECTION TO VIAL

In some instances, pharmaceutical companies may opt to deploy a package in which the syringe is directly connected to a vial. The syringe is prefilled with the

proper amount of diluent and is directly attached to the vial during the manufacturing process (the patient needn't attach the vial). This replaces the use of the traditional aluminum seal.

This approach requires fewer steps for patients; they simply inject the diluent directly into the vial holding the powdered drug, gently mix the solution, and draw a measured dose back into the syringe for injection. The disadvantage is that this does require a new manufacturing process for the drug maker. Some newer direct-connection systems offer more manufacturing flexibility by using vial adapters (to support standard vials and drug packaging) and a range of syringes or even autoinjectors.

DUAL-CHAMBER SYRINGES

Dual-chamber syringes provide a lyophilized drug and diluent in a single unit. Reconstitution is achieved by pushing down on the syringe plunger, forcing the diluent through a channel and into the second chamber where it mixes with the drug to create the injectable solution. The drug can then be injected using an attached needle or can be transferred through a luer connection. These systems provide a high level of end-user benefits. The pharmaceutical company, however, has additional challenges in terms of manufacturing and regulatory requirements because of the change in primary container.

RECONSTITUTION SOLUTIONS PROVIDE MANY ADVANTAGES

By successfully addressing these challenges, advanced reconstitution systems can create the following host of benefits for both pharmaceutical companies and their patients:

- They are easy to use by patients and caregivers who are not healthcare professionals.
- They help protect against drug spray-back and accidental needlesticks.
- Many provide needleless reconstitution and transfer.
- Because they are more convenient, they encourage patients to comply with a dosing regimen, helping to improve patient outcomes.
- They may help the pharmaceutical company reduce the amount of overfill in the drug vial because the system promotes the use of all the drug in the calibrated dose.
- They can reduce problems during the mixing process, such as foaming or incomplete reconstitution of the drug.

SUMMARY

Reconstitution systems are especially beneficial for products that are used to treat chronic conditions in which treatment is administered in a home setting. Many systems are approved as medical devices by the US FDA and carry CE certification for European markets.

For the person administering the drug, whether a healthcare professional or not, advanced reconstitution systems can help promote safe and effective drug delivery and compliance with a dosing regimen. For pharmaceutical companies, advanced systems can differentiate products in the market. Because the dosing is accurate, manufacturers may be able to reduce the need for drug overfills.

One important consideration for pharmaceutical makers centers on the need to educate their users. Advanced reconstitution systems represent an important leap forward in usability and safety. However, it is also undeniable that they introduce a level of change that is non-trivial to people who are not healthcare professionals. Manufacturers must assume the burden of ensuring that patients receive complete and clear training on using the new reconstitution systems.

The ideal time to evaluate systems for developmental drugs is during Phase II and Phase III clinical trials when the effectiveness of the delivery system can be evaluated. For currently marketed lyophilized drugs, systems are available that can be used without the need to change processing and filling lines or packaging components. ◆

BIOGRAPHIES

Mr. Graham Reynolds is Vice President, Reconstitution and Transfer Systems and is responsible for West Pharmaceutical Services, Inc.'s business in the reconstitution and transfer systems market segment, a position he assumed in July 2005. Mr. Reynolds recently relocated from the UK to the US. Since joining the company in the quality control laboratory at West's St. Austell, UK, plant in 1980, he has held a range of positions with increasing geographic and business responsibilities covering sales, account management, business analysis, and business development. In 2001, he was appointed Director of Marketing, Europe, and he was appointed Vice President of Marketing, Europe in April 2005. Mr. Reynolds holds a diploma in Polymer Technology from Trowbridge Technical College.

DRUG-RELEASE MECHANISMS

Comparison of EUDRAGIT® FS 30 D & EUDRAGIT® L 30 D-55 as Matrix Formers in Sustained-Release Tablets

By: Diego Gallardo Álvarez (PhD student), Esther Esteban (PhD student), Manfred Aßmus, and Brigitte Skalsky, PhD

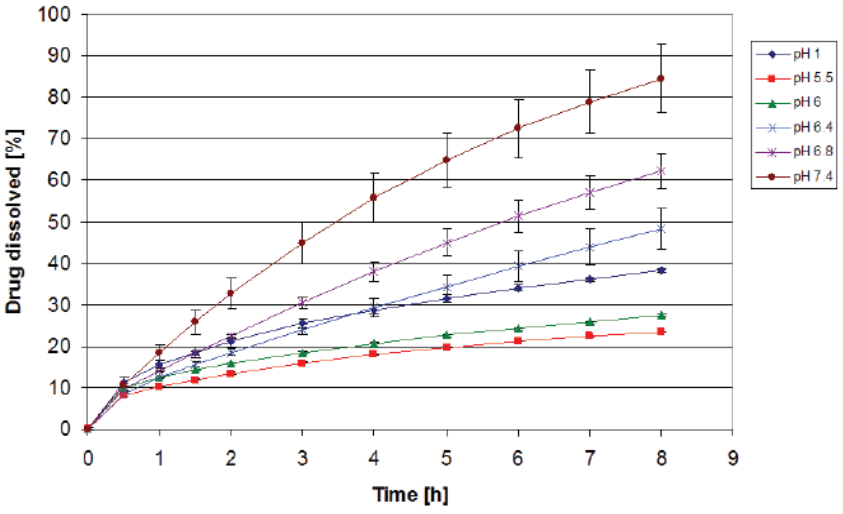
ABSTRACT

EUDRAGIT® FS 30 D and EUDRAGIT® L 30 D-55 are anionic polymers based on a methacrylic acid structure. EUDRAGIT L 30 D-55 has been used for decades as a matrix former in sustained-release tablets due to its excellent binding properties and the retardation effect it provides. The drug-release mechanism obeys to a diffusion process through pores. In this study, the features of EUDRAGIT FS 30 D as a matrix former were investigated. The comparison between EUDRAGIT L 30 D-55 and EUDRAGIT FS 30 D showed differences on the release profile. EUDRAGIT FS 30 D provided a pH-independent retardation effect on the release profile, while EUDRAGIT L 30 D-55 showed a higher retardation effect but pH-dependence. Diltiazem HCl was used as model for a highly soluble drug because it is challenging for the development and manufacturing of matrix tablets.

INTRODUCTION

(Meth)acrylate copolymers have been used for decades to provide protection or modified release to drugs. They can be used as coating agents, and due to their excellent binding properties, as matrix formers. (Meth)acrylate copolymers can be classified in two groups: pH-dependent and pH-independent. As a coating agent, the first group protects the drug up to different specific pH values. Above these pH values, the polymers become soluble, and the drug is released (except EUDRAGIT® E PO; it behaves oppositely to the other pH-dependent polymers). As coating agents, the second group of polymers do not become soluble. The drug is released via diffusion.

FIGURE 1



Release profiles at different pH values of Diltiazem HCl matrix tablets manufactured with EUDRAGIT® L 30 D-55. Nominal weight = 500 mg, compression force = 15 kN, number of tablets tested per pH value n = 3.

This extent depends on the permeability of the film.

In matrix tablets, the polymer forms a sponge-like structure that regulates the drug release. The release mechanism of pH-independent (meth)acrylate copolymers is diffusion. pH-dependent (meth)acrylate copolymers release the drug by

diffusion in the insoluble status and, in the soluble status, by a combination of diffusion and erosion.

EUDRAGIT L 30 D-55 and EUDRAGIT FS 30 D are anionic pH-dependent (meth)acrylate copolymers. EUDRAGIT L 30 D-55 becomes soluble above pH 5.5, and EUDRAGIT FS 30 D becomes soluble above pH 7.0. Due to their excellent binding properties, both are suitable to form matrix structures. In the past, EUDRAGIT L 30 D-55 has been widely used as a matrix former, while EUDRAGIT FS 30 D has been more focused on coating processes.[1]

The aim of this study was to investigate the properties of EUDRAGIT FS 30 D as a matrix former to compare its release profile with EUDRAGIT L 30 D-55 as well as the definition and evaluation of the drug-release mechanism under insoluble and soluble conditions of the polymers.

MATERIALS

Diltiazem HCl (Lusochimica, Lomagna, Italy) was chosen as a model drug. Dibasic calcium phosphate dihydrate (Emcompress®, JRS Pharma, Rossenberg, Germany) was used as filler for non disintegrating tablets.[2] EUDRAGIT L 30 D-55 and EUDRAGIT FS 30 D were supplied by Roehm GmbH, Darmstadt, Germany. Magnesium-stearate was supplied by Merck, Darmstadt, Germany (Table 1).

METHODS

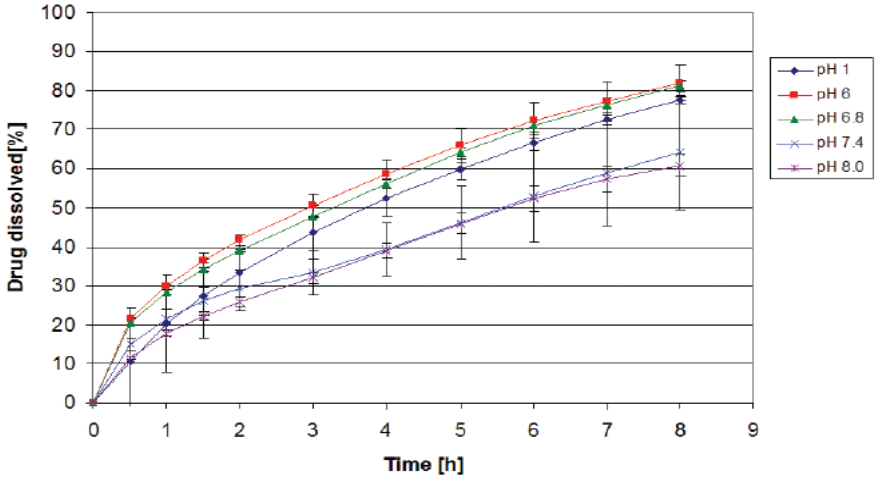
Fluid Bed Granulation Process

Fluid bed granulation was used because it provides a homogeneous distribution of the polymer in the matrix tablets.[3] Spraying dispersions were prepared by diluting the commercial product (EUDRAGIT FS 30 D or EUDRAGIT L 30 D-55) with water to 20% solid content, based on the powder mixture (Diltiazem HCl and Emcompress). The powder mixture was granulated by spraying the polymer dispersion. Glatt WSG-5 (Glatt AG. Binzen, Germany) was used with a 2.2-mm nozzle and 2-bar atomization air pressure.

Tablets Preparation & Characterization

After drying (40 ºC during 2 hours), the granules were mixed with Magnesium-stearate for 5 minutes in a double cone blender (ERWEKA GmbH, Heusenstamm, Germany). The granules were compressed with different compression forces (5, 10, 15, 20, and 25 kN) using an instrumented eccentric press Korsch EK0 (Korsch, Berlin, Germany) with a 10-mm punch diameter and 19-mm curvature radius. Hardness, weight, and diameter of tablets from the 15 kN compression force were analyzed using a Multicheck (ERWEKA GmbH, Heusenstamm, Germany). PTF 10 E (Pharma Test

FIGURE 2



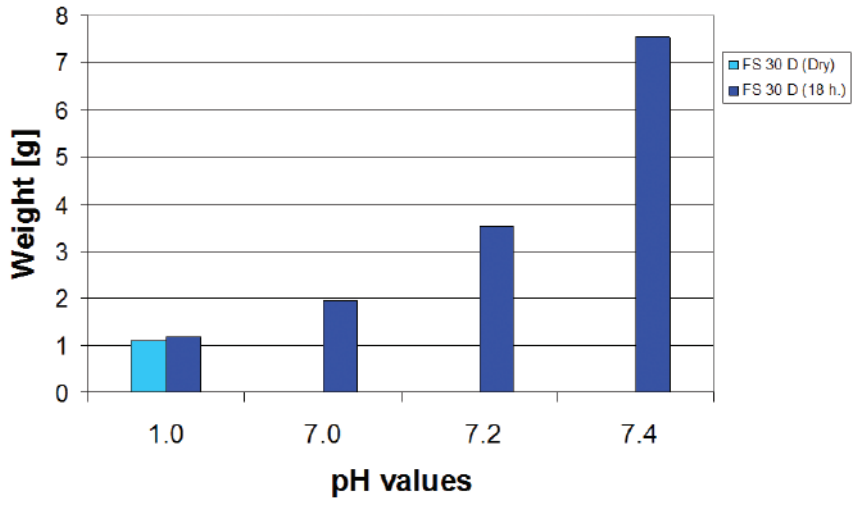
Release profiles at different pH values of Diltiazem HCl matrix tablets manufactured with EUDRAGIT® FS 30 D. Nominal weight = 500 mg, compression force = 15 kN, number of tablets tested per pH value n = 3.

TABLE 1

	Components	Per Batch [g]	Per Tablet [mg]	%
Granules	Diltiazem HCl	1450.0	145.0	29.0
	Emcompress®	2695.0	269.5	53.9
	EUDRAGIT® L 30 D-55 or EUDRAGIT® FS 30 D dispersion weight (dry substance)	2766.6 (830.0)	276.7(83.0)	16.6
Tablet	Mg stearate	25.0	2.5	0.5
Total		5000.0	500.0	100.0

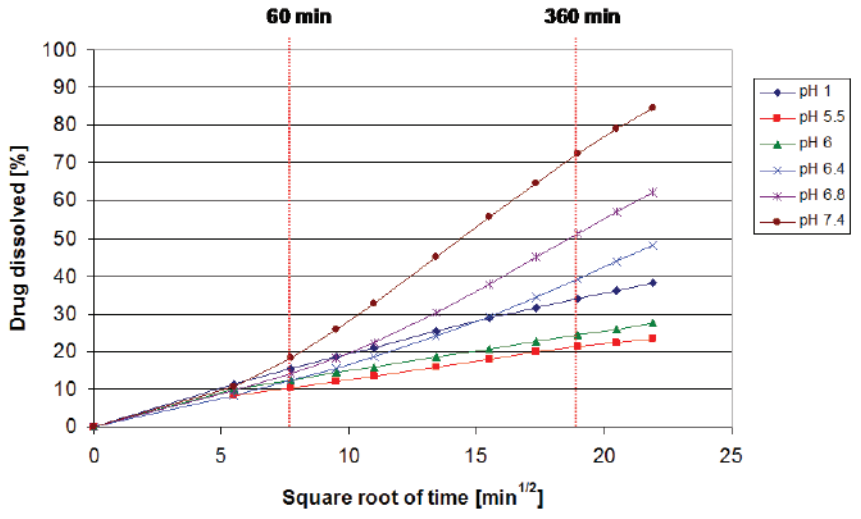
Formulation Details

FIGURE 3



Water uptake of EUDRAGIT® FS 30 D films in different pH values.

FIGURE 4



Release profiles of the Diltiazem HCl matrix tablets with EUDRAGIT® L 30 D-55 at different pH values against the square root of time. Determination of the correlation factor to Higuchi model within the red lines.

Apparatebau GmbH, Heinburg, Germany) was used for friability testing.

Dissolution Test

ERWEKA DT 6, USP 29 Apparatus II, (ERWEKA GmbH, Heusenstamm, Germany) was used for dissolution connected to a UV/Vis Lambda 20 (Perkin-Elmer, Ueberlingen, Germany). The media volume was 900 ml, at 37 ± 0.5 ºC and stirred at 100 rpm. The samples were taken automatically over 8 hours and passed through a 10-micrometer filter. Different pH values were tested according to USP 29-NF 24: pH 1.0 (0.1 N HCl), pH 6.0 (phosphate buffer solution 6.0), pH 6.8 (phosphate buffer solution 6.8), and pH 7.4 (phosphate buffer solution 7.4). According to the European Pharmacopeia 5th Ed., the following pH values were tested: pH 5.5 (phosphate-citrate buffer), pH 6.4 (phosphate buffer solution 6.4), and 8.0 (buffer solution pH = 8.0 R1).

To better understand the release mechanism, a water uptake test was developed. EUDRAGIT FS 30 D films were tested using the same equipment and under the same condition as the dissolution tests. Pure polymer films were weighed and then placed in different pH media in the dissolution tester. Weights of the original dried film and of the film after 18 hours in the dissolution tester were compared.

RESULTS

Tablet Characteristics

The properties of the manufactured tablets showed similar results (Table 2). Only the hardness of the tablets showed differences. High uniformity of weight, low friability, and high hardness values indicate good tableting behavior.

Release Profile

Both polymers provide a retardation effect under pH conditions in which they are insoluble (Figure 1). EUDRAGIT L 30 D-55 showed a high retardation effect under insoluble conditions. Even under conditions slightly above the solubility pH of the polymer (up to pH = 6.4) the polymer provides a high retardation effect (Figure 2). The retardation effect of EUDRAGIT FS 30 D under pH conditions in which the polymer is insoluble is not as high as with EUDRAGIT L 30 D-55.

The release profile is not affected by the changes on the pH in the investigated range. When the polymer starts to become soluble, the retardation effect even increases. EUDRAGIT FS 30 D films showed an increase on water uptake at the same time that the pH increases (Figure 3). This weight increase can reach seven times the original weight of the film (pH 7.4).

Kinetic Analysis

To determine the mechanism of how the drug is delivered, it is necessary to fit the graphics to a kinetic model. Higuchi diffusion kinetic predicts a linear relationship between the amount of drug delivered and the square root of the time ($Q = k_s \sqrt{t}$), where Q is the amount of drug dissolved at time t, and k_s is the release rate constant (Figures 4 & 5).

The release values chosen corresponded to the drug-release values between 60 and 360 minutes. Sixty minutes is because the matrix tablets need a certain time to achieve moisture equilibrium. The 360 minutes of the drug release as a maximal limit is chosen because the concentration of drug inside of the core is decreasing along the time; therefore, the diffusion of the remaining drug decreases.

To determine whether these graphics fit to the Higuchi model, it is necessary to define the significance of the correlation factor. The significance of the correlation factor, with an error probability of 1% and a degree of freedom of 5, is ≥ 0.8745.[7] All the graphics had a significant correlation coefficient (Table 3).

DISCUSSION

Tablet Characteristics

The differences showed with EUDRAGIT FS 30 D are caused by the polymer properties. This polymer is softer and more flexible, providing a better binding and leading to higher hardness and lower friability.

Release Profile

The drug release, in both cases, showed unexpected values. The consequence of these results is the behavior of these polymers as matrix formers. The release mechanism is defined by the equilibrium between the swelling process and the erosion process (salt formation).

Swelling takes place when the polymer comes in contact with the media. Hydrogen bonds between the water molecules and the polymer are built. It is possible to quantify the number of hydrogen-bonded network structure of water per one monomer unit of polymer (N).[5,6] The higher this value, the higher are the probabilities to react with water molecules and to swell (Table 4).

The swelling process is directly related to the amount of carboxylic groups of each polymer. EUDRAGIT FS 30 D has less carboxylic groups (10% w/w) than EUDRAGIT L 30 D-55 (50% w/w). EUDRAGIT FS 30 D improves the penetration of dissolution media into the tablet. A higher percentage of carboxylic groups would enhance the formation of hydrogen bonds and swell. Polymer swelling decreases the chance of the media to diffuse deeper into the core (Figure 6).[4]

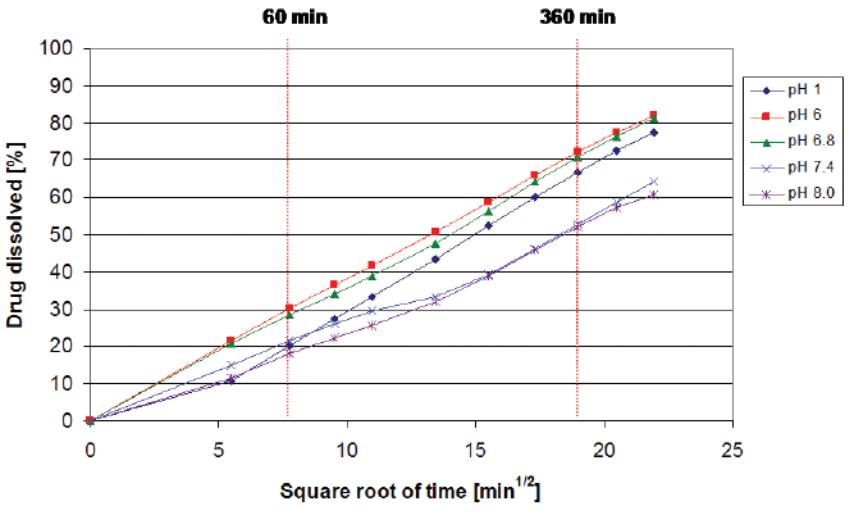
Salt formation is the result of the reaction between carboxylic groups of the polymers with ions present in the buffer solutions. This reaction produces partial

TABLE 2

	EUDRAGIT® L 30 D-55	EUDRAGIT® FS 30 D
GRANULES		
Bulk density (g/ml)	0.76	0.79
Tapped density (g/ml)	0.85	0.85
Flow test (s/100 ml)	10.6	12.1
Angle of repose (°)	32.9	32.4
TABLETS		
Height (mm)/ S_{rel} (%)	4.78/0.35	4.7/0.18
Weight (mg) / S_{rel} (%)	501 / 0.29	498/0.19
Density (g/ml)	1.74	1.73
Hardness (N)/ S_{rel} (%)	120 / 3.4	169/0.68
Friability (%)	0.36	0.10

Analytical characterization of granules and matrix tablets (compression force 15 kN).

FIGURE 5



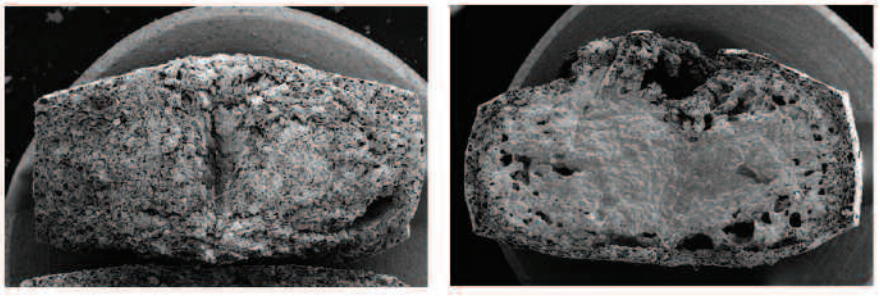
Release profiles of the Diltiazem HCl matrix tablets with EUDRAGIT® FS 30 D at different pH values against the square root of time. Determination of the correlation factor to Higuchi model within the red lines.

TABLE 3

	EUDRAGIT® L 30 D-55	EUDRAGIT® FS 30 D
pH values	Higuchi model	Higuchi model
1.0	0.9991	1.0000
5.5	0.9993	
6.0	0.9999	0.9996
6.4	0.9939	
6.8	0.9945	0.9973
7.4	0.9994	0.9790
8.0		0.9902

Correlation coefficient values corresponding to the percentage of drug dissolved in the period of time between 60 and 360 minutes.

FIGURE 6



SEM pictures of Diltiazem HCl matrix tablets with EUDRAGIT® FS 30 D (left) and EUDRAGIT® L 30 D-55 (right) after 8 hours of dissolution test at pH=1.0.

TABLE 4

Polymer	N	Polymer	N
-(-CH_2-CH-)$_n$- | COO Na	8.7	-(-CH_2-CH-)$_n$- | COOH	3.4

N values (hydrogen-bonded network structure of water per one monomer unit of polymer).

neutralization of the active groups forming sodium carboxylate. Carboxylate groups have a higher tendency to react with water molecules and provide a stronger swelling effect (Table 4).[5,6]

Based on swelling, EUDRAGIT L 30 D-55 as a matrix former provides a pH-dependent retardation effect up to pH 6.0. This effect leads to a pore size reduction, obstructing the subsequent penetration of the medium into the core. Under physiological conditions, EUDRAGIT FS 30 D matrix tablets provide a pH-independent retardation effect. The swelling capability of this polymer is not as strong as for EUDRAGIT L 30 D-55, making the penetration of the media into the core under different pH conditions easier. When the polymer becomes soluble, the polymer swells and thus slightly increases the retardation effect. With these results, we can confirm the high influence of the swelling process on the release profile of the matrix tablets.

Kinetic Analysis

From the results shown in Table 4, we can determine that the release of these matrix tablets fits perfectly to the Higuchi diffusion model at the different pH values tested. This confirms that the release of the drug takes place by diffusion.

CONCLUSIONS

EUDRAGIT FS 30 D provides pH-independent controlled release, while the controlled release from EUDRAGIT L 30 D-55 is pH-

dependent. The retardation effect, in both cases, is a combination of swelling and erosion of the polymers. Flow properties, low deviations in weight, and high mechanical stability of the tablets describe good value and processibility of controlled-release tablets. Both polymers are suitable to formulate matrix tablets for highly soluble drugs like Diltiazem HCl.

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BIOGRAPHIES

Mr. Diego Gallardo Álvarez is currently a PhD student in Pharmaceutical Technology for Degussa's business line of Pharma Polymers. Mr. Gallardo started with Degussa Pharma Polymers in May 2004 as an intern in the Pharma Polymers Technical Customer Service Department, working on the manufacturing of matrix tablets by fluidized bed granulation comparing different EUDRAGIT® types with HPMC Polymers. Since May 2005, Mr. Gallardo has been focusing on matrix formulations based on EUDRAGIT polymers in conjunction with the University of Düsseldorf, Germany. Prior to joining Degussa, Mr. Gallardo worked as a Quality Control Representative in the GMP department of Eli Lilly and within the Practices Regulatory and Quality Control departments at Roche and Medeva Pharma. Mr. Gallardo earned his degree in Pharmacy at the University of San Pablo C.E.U. and his Diploma of Advanced Studies in Pharmaceutical Technology at the University Complutense of Madrid, Spain.

Ms. Esther Esteban is a PhD student in the Pharmacy and Pharmaceutical Technology Department at Complutense University of Madrid. Currently, she combines her studies with her job, working as a Validation Technician of manufacturing processes in the Manufacturing Science and Technology department of Eli Lilly. She has also been working in the Regulatory Affairs Department of Pfizer for 1 year. Ms. Esteban started her PhD studies working with controlled-release multiparticulate systems using EUDRAGIT® Pharma Polymers. As an intern student in the Pharma Polymers Application Development department at Degussa, she collaborated on the manufacturing of matrix tablets by fluidized bed granulation comparing different EUDRAGIT types. Ms. Esteban earned her degree in Pharmacy at the University Complutense of Madrid and her Advanced Studies Certificate in Pharmaceutical Technology at the University Complutense of Madrid, Spain.

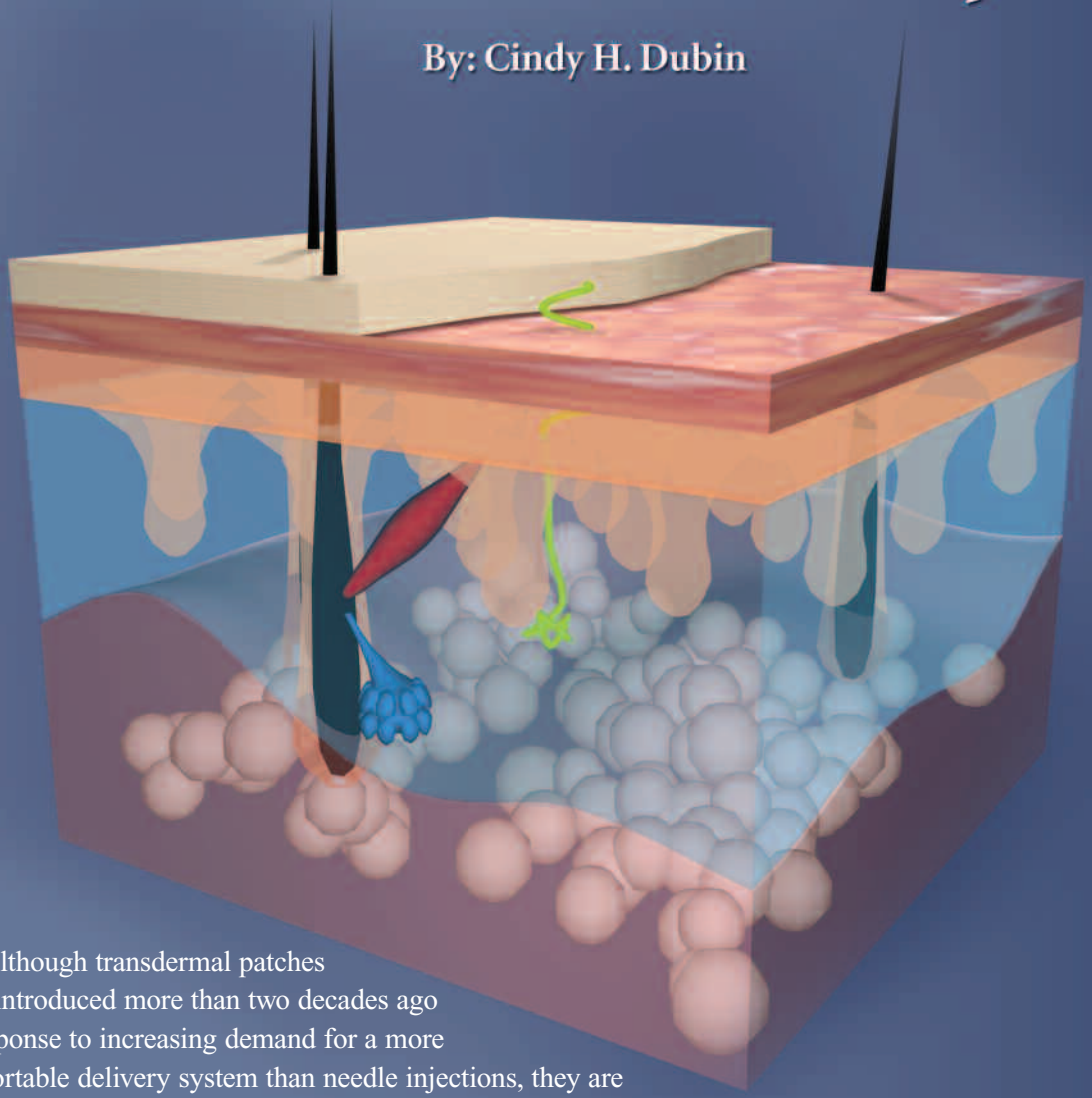
Mr. Manfred Aßmus joined the Degussa Pharma Polymer Group in 1985. He initially worked on the development of solid and semi-solid dosage forms. After that, he focused on EUDRAGIT® polymers for controlled release. Between 1989 and 2002, he held various responsibilities in the fields of technological development, production, and technical customer service. From 2002 to 2003, he was responsible for the set-up of the Pharma Polymers technology research centre in Mumbai (India). Since 2003, he is holding his current position as Manager, Application Development, EUDRAGIT. Mr. Aßmus earned his degree as a Pharmaceutical Technical Assistant in 1984 at Martin Beheim School in Darmstadt.

Dr. Brigitte Skalsky is currently Global Technical Manager for EUDRAGIT® and a Qualified Person under the terms of the German Drug Act (AMG) for Degussa, Pharma Polymers, Darmstadt, Germany. From 1997 to 2000, Dr. Skalsky was a Laboratory Manager in the Formulation Development department at AWD GmbH, Dresden, Germany, focusing on preformulation and formulation of NCEs as oral solid dosage forms and responsible for international drug development projects. From 2001 to 2002, Dr. Skalsky was Team Leader, Pharmaceutical Technology and Production Manager (AMG) in the Pharmaceutical Development department at AWD.pharma, Dresden, Germany, focusing on the development of oral solid dosage forms, in particular of generic drugs and controlled-release formulations. Dr. Skalsky earned her degree in Pharmacy and her PhD in Pharmaceutical Technology from the University of Erlangen-Nuremberg, Germany.

Special Feature

Transdermal Delivery: Product Development Pursues Active & Passive Systems

By: Cindy H. Dubin



Although transdermal patches were introduced more than two decades ago in response to increasing demand for a more comfortable delivery system than needle injections, they are not yet matured. For example, transdermal systems are restricted to a limited number of molecules that can be delivered through the skin. Typically, the skin only allows the penetration of lipid-soluble drugs that have a molecular weight of less than approximately 500 Daltons. But several transdermal drug delivery technologies have emerged to meet the need for a more convenient form of administering larger molecules. Companies like Altea Therapeutics have been able to overcome the challenge through the accurate and reproducible creation of microchannels for the delivery of low-molecular water-soluble drugs, as well as macromolecules, with an efficient and cost-effective patch. Companies also are investigating the use of technologies, such as iontophoresis (IOMED); ultrasound, microneedles (3M); thermal ablation (Altea); radio frequency cell ablation (TransPharma Medical); and dermabrasion for improved transdermal delivery. These companies have product candidates in various stages of clinical trials; however, none of these technologies is commercially available at this point.

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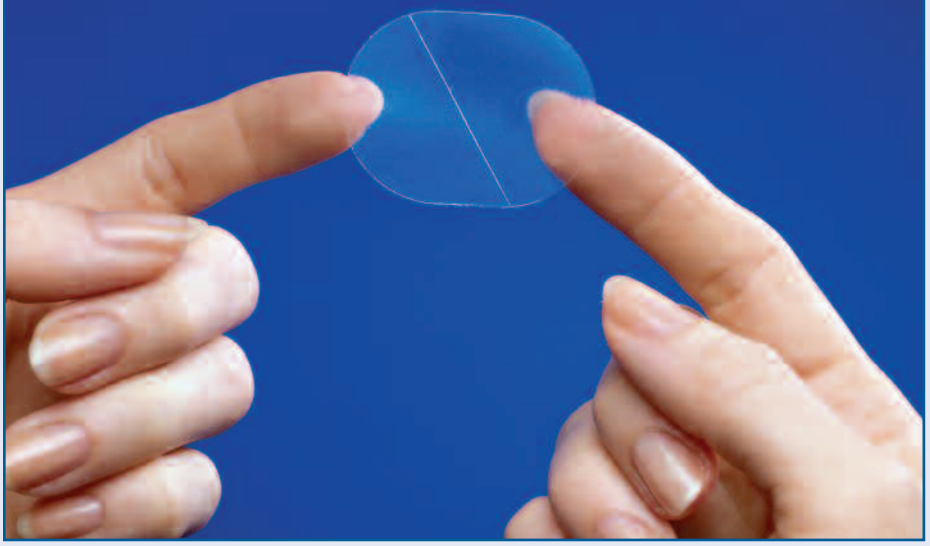
FIGURE 1

3M's technologies coupled with years of experience and corporate knowledge and resources ensure successful transdermal solutions.



3M TACKLES ACTIVE & PASSIVE DELIVERY

3M Drug Delivery Systems' transdermal applications have provided solutions for more than 30 years (Figure 1), covering active and passive delivery. Historically, these therapeutic areas have included pain management, angina, depression, and hormone replacement. However, new technologies aggressively explored by 3M have the potential to transdermally deliver drugs in new therapeutic areas.

In passive delivery, the proprietary drug-in-adhesive (DIA) technology incorporates the active pharmaceutical ingredient (API) and other formulation exipients directly into the adhesive.

In the active area, 3M is leveraging core technology in microstructured materials and processes to create targeted vaccine delivery systems, as well as systems for systemic delivery of macromolecules. 3M's Microstructured Transdermal System (MTS) is a microneedle system for transcutaneous or intra-dermal drug delivery. MTS bypasses the barrier properties of the stratum corneum and provides a means to deliver a variety of molecules that ordinarily would not penetrate the skin, including vaccines. MTS enhances the efficacy of vaccines by targeting the antigen-presenting cells within the skin, thereby improving delivery efficiency and reducing dose requirements, explains Richard Sitz, MBA, Technical Manager for Transdermal Drug Delivery.

Several transdermal products, such as hormone-replacement products and nitroglycerin patches, utilize 3M technology.

ALTEA'S PASSPORT SYSTEM BROADENS TRANSDERMAL MARKET: SIMPLE ACTIVATION FOR SUSTAINED PASSIVE DRUG DELIVERY

Altea Therapeutics' new transdermal patch enables delivery of water-soluble molecules that would normally be administered by injection, including small drug salts, and macromolecular proteins, carbohydrates, and nucleic acids, says Dr. Eric Tomlinson, President and CEO of Altea Therapeutics. The company's PassPort™ System (Figure 2) works by first forming multiple tiny aqueous "microchannels" through the stratum corneum. This takes typically between 2 and 5 milliseconds. Water-soluble proteins and low-molecular-weight drugs can then enter the body through these aqueous microchannels from a transdermal patch reservoir for either local or systemic effect.

The PassPort System is composed of a single-use disposable PassPort Patch and its re-useable handheld Applicator. The PassPort Patch has a regular transdermal patch attached to a film of metallic filaments (a porator). To initiate dosing, the patient clips the patch onto the Applicator, places it against the skin, and presses an activation button. Then, as the patient takes the Applicator away from the skin, the transdermal patch becomes automatically positioned on the skin to allow delivery to commence. Pressing the activation button of the Applicator sends a pulse of electrical energy to the porator, which converts this into thermal energy. The rapid conduction of this thermal energy into the surface of the skin painlessly ablates the stratum corneum under each filament to create microchannels.

The aqueous channels formed in the stratum corneum using the PassPort System typically have a depth of about 30 to 50 micrometers, sufficient to impinge into the viable epidermis while avoiding the dermis and any thermal pain receptors. After dosing, when the transdermal patch is removed from microporated skin, the barrier function of the stratum corneum is quickly restored.

"The PassPort System achieves what existing patches are unable to do, namely the continuous delivery through the skin of compounds that are typically administered by needle injections, including macromolecules, such as proteins and large carbohydrates," says Dr. Tomlinson. "By enabling continuous delivery of highly water-soluble proteins and low-molecular-weight drugs, the PassPort System provides rapid onset of therapeutic effect, alongside constant delivery of the drug and rapid drug elimination of drug from the skin upon removal of the patch," he continues. For example, using the water-soluble salt form of a drug precludes the drug from forming a depot in the skin, which is an important feature, as dosing can be terminated by removing the PassPort Patch in case of an overdose or an adverse reaction. The PassPort Patch by itself will not deliver drug into the body without a prior microporation event using an Applicator; this serves as an added safety feature.

The Applicator has additional optional features. It is programmed to ensure dosing control and monitoring. It also records a time and date stamp for each application for compliance monitoring, and it can be programmed

with dose lock-out features to prevent drug misuse or abuse

Altea has demonstrated in clinical studies that PassPort can be used to deliver up to 2 mg of protein, 10 mg of peptide, and 200 mg of small molecule drug per day. The company is conducting several Phase I clinical trials in the United States: an insulin transdermal patch that provides continuous delivery of basal levels of insulin for people with diabetes; a fentanyl citrate transdermal patch that enables rapid and safe management of moderate-to-severe pain; and an apomorphine hydrochloride transdermal patch for the convenient management of advanced Parkinson's disease.

"Furthermore, we are in preclinical feasibility testing with a number of product candidates, including a low-molecular-weight heparin patch for thrombosis, a parathyroid hormone analog transdermal patch for osteoporosis, and an atypical antipsychotic transdermal patch for the management of psychosis," says Dr. Tomlinson.

AVEVA'S GEL MATRIX IS RELIABLE, GENTLE

The Gel Matrix Transdermal System from Aveva Drug Delivery Systems, Inc., a Nitto Denko Company, blends gentleness and reliability within a drug in adhesive system (Figure 3), says Robert J. Bloder, Vice President Business Development at Aveva. While the marketed product is a once-a-day patch, clinical studies have demonstrated that this product can be taken off and reapplied up to six times, which clearly demonstrates that this product is so gentle, that it does not remove the stratum corneum (which would stick to traditional adhesives and not permit it to be reapplied), he added.

The Gel Matrix Transdermal System is currently marketed as a once-a-day patch for angina and post MI. Many pipeline products are also under development.

"Our products and pipeline include all of the major therapeutic areas, including pain management, cardiovascular, asthma, CNS, women's health, and smoking cessation," explains Mr. Bloder.

His thoughts about patches? "Transdermal drug delivery systems are well-suited for chronic use, as well as patients and physicians who wish to avoid and/or minimize GI upset, eliminate or diminish drug peaks and troughs, and improve persistency and compliance rates with a patch that may be worn for 1 to 7 days. Transdermal drug delivery systems are unique from other delivery platforms in that unlike the pill, the patch is a physical expression that they took their medication, which is positive; however, not all adhesives are created equal, which means that patches can vary on the amount of skin irritation they cause as well as their ability to adhere for the designated period of time."

IOMED'S ACTIVE IONTOPHORESIS TECHNOLOGY ENHANCES DELIVERY RATES

IOMED iontophoresis systems, used with the Phoresor™ dose controller, have been in the physical therapy and rehabilitation medicine market for more than 25 years. Recently, IOMED introduced the Hybresis™ Transdermal Drug Delivery System (Figure 4), which consists of a wireless, miniaturized, rechargeable controller that connects directly to an iontophoresis patch containing both the active and dispersive electrodes. IOMED technology is based on iontophoresis, which is a non-invasive method of active drug delivery in which water-soluble, ionized drugs are transported into and through tissue, such as skin, mucosal membranes of the body cavity, or ocular tissues by means of an externally applied milliampere electrical current. Iontophoresis enhances the rate of drug delivery across the biological membranes compared to diffusion-based passive delivery. The drug is placed in the "active" electrode (drug delivery electrode) against the body tissue. A second dispersive electrode of opposite electric charge completes the circuit. When current of the same electric charge as the drug is applied to the active electrode, drug ions are driven from the electrode into the tissue.

The system also includes a charging station with four bays for multiple controllers. The Hybresis Systems boasts a 3-minute Skin Conductivity Enhancement (SCE) pre-treatment followed by a 6-volt patch-only iontophoresis. The SCE provides a rapid decrease in skin resistance and reduces its variability, thereby increasing accuracy of drug dosing. The controller is then removed, and the remainder of the treatment is carried out with just the patch on the patient for the next 1 to 2 hours, depending on the prescribed dose of 40 mA-min, 60 mA-min, or 80 mA-min.

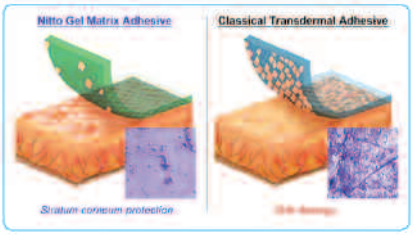
According to Margaret Szlek, Manager, Feasibility and Biological Testing at IOMED, the Hybresis System was designed specifically for the physical therapy market to treat common sports and work-related soft tissue injuries, but its platform lends itself to applications in the pharmaceutical industry as a drug delivery device combination product.

Iontophoretic technology provides a unique opportunity in the transdermal drug delivery arena, she says. "The technology is ideally suited to safely deliver water-soluble drugs that are

FIGURE 2

The PassPort™ System is simple and easy to use.

FIGURE 3



Aveva's Gel Matrix Adhesive protects the stratum corneum.

FIGURE 4

The Hybresis™ Transdermal Drug Delivery System consists of a wireless, miniaturized, rechargeable controller that connects directly to an iontophoresis patch containing both the active and dispersive electrodes.

difficult to deliver in therapeutic amounts using passive transdermal patches. The amount of drug delivered is proportional to electrical charge, which is a function of the duration of current application and current magnitude."

Therefore, depending on the clinical application, by programming the system's electrical current levels and patterns, the drug dose, delivery rate, and the pattern of delivery can be precisely controlled, similar to intravenous infusion. Iontophoresis can facilitate rapid drug onset and cessation kinetics, on-demand patient dose modulation, and individual dose titration.

Hybresis recently received the FDA's 510k medical device allowance and is scheduled to be launched in the second half of 2007.

NOVEN: SETTING NEW STANDARDS IN PASSIVE PATCHES

Noven Pharmaceuticals' patented third-generation patch technology, DOT Matrix®, utilizes two polymers in its drug-in-adhesive blend: an acrylic that holds high concentrations of drug in micro-cells, and a silicone that holds the patch on the skin. The high-diffusion gradient between each drug cell and the skin causes the drug to penetrate the skin with great efficiency, and the silicone sticks as it should because it is not impaired by drug. "The result is an extremely efficient platform that generally lets us drive more drug through a smaller area – higher 'throughput', if you will – with excellent adhesion and no irritating enhancers," says Juan Mantelle, Noven's Chief Technical Officer. More than 30 US patents protect Noven's technologies.

"DOT Matrix technology gives us two advantages," continues Mr. Mantelle. "First, in categories where other patches have been approved, we can make a smaller, more wearable patch. For example, our Vivelle-Dot® estrogen patch has the highest throughput in the category. It is by far the smallest estrogen therapy patch in the US, and its wear characteristics have permitted it to capture more than 50% of the estrogen patch market."

Vivelle-Dot is marketed and sold in the US by Novogyne Pharmaceuticals.

"Second, we can deliver a therapeutic dose in categories where the required dose exceeds what other technologies can deliver, with Daytrana™ as a great example," he says." "Daytrana is the first and only patch approved by the FDA for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). It was developed by Noven for Shire plc. Daytrana delivers 89 mcg/cm²/hr – the highest permeation rate of any FDA-approved patch, setting a new standard in passive transdermal delivery. This permits us to deliver as much as 30 mg per day – more than any other patch – while maintaining a commercially-viable patch size."

Building on this success, Noven is developing an amphetamine patch for ADHD. Amphetamine products represent about half of the US market for stimulant ADHD therapies.

"In the first quarter of 2007, we completed a Phase I study of the product, which demonstrated the relative bioavailability of our patch compared to a long-acting amphetamine pill," says Mr. Mantelle. Noven is also working to develop a generic version of the fentanyl patch Duragesic® for the treatment of chronic pain, expected to enter human studies in mid-2007, and has several other undisclosed patch products in its development pipeline.

TRANSPHARMA MEDICAL USES RF FOR COMBINED ACTIVE/PASSIVE DELIVERY

To expand the limits of transdermal drug delivery, TransPharma has applied and modified radio frequency (RF) cell ablation technology to develop a method for painlessly, accurately, and safely

FIGURE 5

Product	Indication	Regulatory Status	Marketing Rights
Transdermal HRT			
Estrogen Vivelle®/ Menorest®/Femiest®	Menopausal Symptoms/ Osteoporosis	FDA-approved; Approved in over 15 foreign countries	Novogyne[1]--U.S. Aventis[2]—Japan Novartis Pharma[3]--all other territories
Second Generation Estrogen Vivelle-Dot®/ Estradot®	Menopausal Symptoms/ Osteoporosis	FDA-approved; Approved in over 45 foreign countries	Novogyne--U.S. Aventis--Japan Novartis Pharma--all other territories
Combination Estrogen/Progestin CombiPatch®/ Estalis®	Menopausal Symptoms/ Osteoporosis	FDA-approved; Approved in over 30 foreign countries	Novogyne--U.S. Aventis--Japan Novartis Pharma--all other territories
Low-dose Combination Estrogen / Progestin	Menopausal Symptoms/ Osteoporosis	Clinicals (sponsored by Novartis Pharma)	Aventis--Japan Novartis Pharma--all other territories
Methylphenidate Daytrana™	ADHD	FDA-approved EU filing planning by Shire	Shire[5]--worldwide
Other Transdermals			
Amphetamine	ADHD	Phase I	Shire[5]--worldwide
Undisclosed compounds	Hypoactive Sexual Desire Disorder	Clinicals & pre-clinical	P&GP[6]--worldwide
Undisclosed compounds	Undisclosed	Pre-clinical	Endo[4]
Transmucosal			
Lidocaine/DentiPatch®	Dental pain associated with certain dental procedures	FDA-approved	Noven

The status of products marketed, approved, and/or under development by Noven. (1) Novogyne Pharmaceuticals is a joint venture between Noven and Novartis Pharmaceuticals Corporation. (2) Aventis S.A. (3) Novartis Pharma AG. (4) Endo Pharmaceuticals Inc. (5) Shire plc (6) P&G Pharmaceuticals has indicated that its HSDD development program in the U.S. is currently on hold.

creating microchannels in the skin's surface to enable transdermal delivery of drugs that cannot be delivered using current technologies. TransPharma combines an active stratum corneum breaching technology with passive patches to enable large molecule delivery.

TransPharma's drug-product development activities utilize RF-MicroChannel™ technology, which creates an array of microscopic pores through the outer skin surface. These RF-MicroChannels are of precise predetermined dimensions to enable reproducible transdermal delivery of molecules utilizing a variety of patch technologies, including TransPharma's proprietary dry protein patch.

The initial application of TransPharma's RF-MicroChannel Technology is the ViaDerm drug delivery system. Intended for home use, it consists of a reusable battery-operated handheld electronic control unit, a disposable low-cost microelectrode array, and a patch containing a drug. Applying a high-frequency electric current for 1 to 2 seconds, the reusable device, with disposable microelectrode array attached, creates the RF-MicroChannels. This prepares the site for application of a patch containing a drug. The drug is then passively diffused through the RF-MicroChannels into the inner skin layer and from there to the systemic circulation.

ViaDerm is able to deliver, with high bioavailability rates, peptide and protein drug molecules and both hydrophobic and hydrophilic small molecules. For the delivery of proteins and peptides, TransPharma is applying a proprietary dry protein patch, which was developed to complement its ViaDerm system. By employing a feedback mechanism that controls the process, TransPharma is able to achieve a repeatable and precise ablation, independent of skin type and body location. RF-MicroChannels have the capacity to remain open for up to 24 hours, which enables the sustained delivery of an array of molecules.

"After successfully completing Phase I studies, which included repeated applications of the proprietary ViaDerm-hPTH (1-34) product and incorporated our dry protein patch, we are currently beginning Phase II clinical trials," says Judith Kornfeld, Vice President of Business Development at TransPharma. "Following completion of Phase II, we intend to seek a partner to take the product to market. Our ViaDerm-hGH product, a joint development project with Teva Pharmaceutical Industries, is currently in Phase I/II clinical trials."

SUMMARY

Both passive and active transdermal delivery have made significant strides, but industry insiders admit more work needs to be done to improve delivery and dosing rates.

For example, passive transdermal drug delivery technology has only been successful with a limited number of molecules because very few drugs can passively penetrate across the skin at therapeutically relevant rates. One option, iontophoresis, is well-established and appears to be well-tolerated and safe, but is greatly underutilized, says Ms. Szlek of IOMED. Only recently, Vyteris has developed LidoSite® for delivery of the local anesthetic, lidocaine hydrochloride, and ALZA received NDA approval in May 2006 for IONSYS™ for the delivery of the opioid analgesic fentanyl hydrochloride.

"If IONSYS proves to be a success, very efficient iontophoresis technology may enter a new era of the systemic delivery of drugs with patient-tailored dosage, on-demand delivery, or delivery synchronized with circadian rhythms to maximize their effectiveness and minimize their side effects," she says.

A second option, microneedles, will also be crucial in the market. "Passive transdermal delivery will continue to play a key role going forward, but with a defined set of product opportunities," says Mr. Sitz at 3M. "Technology advancement in support of macromolecule delivery will get increasing attention and resources."

Ultimately, all of the delivery systems discussed here are having a positive impact in the marketplace. New therapeutic areas for both small and large molecule transdermal delivery are being explored by numerous companies.

"The increase in confidence provides drug delivery companies justification to aggressively pursue product development opportunities with both small and large molecules, utilizing various applications that range from passive to active transdermal drug delivery. We expect to see advancements, acceptance, and ultimately more approvals in both passive and active technologies," concludes Mr. Sitz. ◆

BIOGRAPHY

Ms. Cindy H. Dubin has been a professional journalist since 1988. She is currently a Contributing Editor to Drug Delivery Technology as well as Editor of its Specialty Pharma section. Prior to these positions, she spent several years focusing her writing on pharmaceutical formulation and development. She has been recognized by the American Society of Business Press Editors for an article she wrote on nanotechnology, and her writing has been awarded by the prestigious Neal Award Committee for Journalistic Excellence. Ms. Dubin earned her BA in Journalism from Temple University in Philadelphia and her certificate in Business Logistics from Pennsylvania State University.

ORAL TRANSMUCOSAL DELIVERY

OraVescent® Technology Offers Greater Oral Transmucosal Delivery

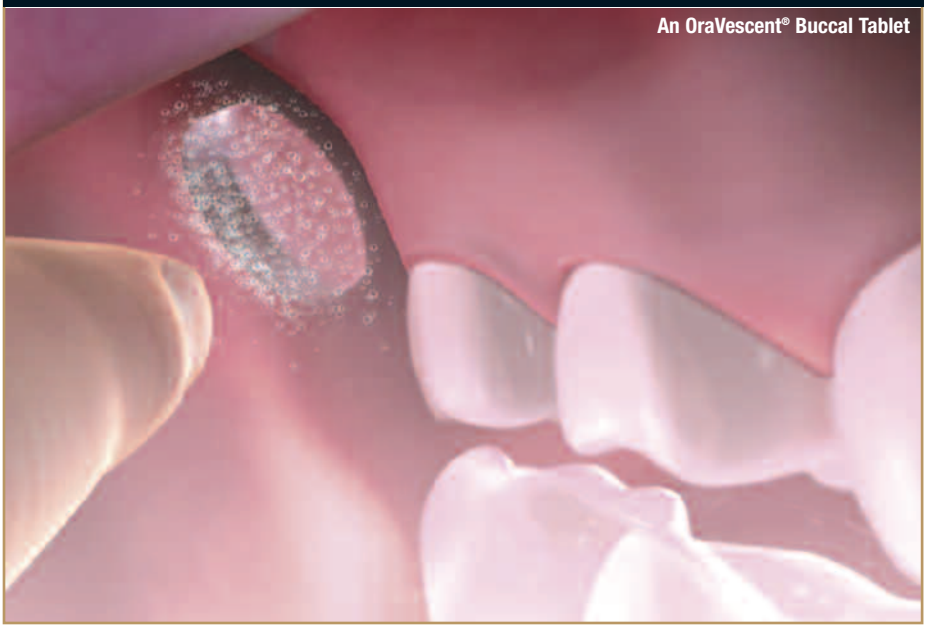
By: Beth A-S. Brown, PhD, and Ehab Hamed, PhD

INTRODUCTION

When one thinks of oral transmucosal drug delivery, nitroglycerin sublingual tablets and sprays have usually been the first products to come to mind. The tide, however, may be turning for this drug delivery system as new technologies emerge and the patient demand for better and convenient dosage forms continues to gain momentum. The market for transmucosal drug delivery, which includes nasal and oral, was worth about $1.2 billion worldwide last year and is expected to grow to $2 billion by 2010.[1]

The oral mucosal cavity is seen as a feasible, safe, and attractive site for drug delivery with good acceptance by users. This is because the mucosa is relatively permeable and robust, shows short recovery times after stress or damage, is tolerant of potential allergens, and has a rich blood supply.[2] Oral transmucosal delivery has been shown to improve the rate and extent of transport for certain drugs compared to oral swallowable (peroral) dosage forms. This is because the drugs are absorbed directly through the oral mucosa, avoiding the acidic and enzymatic conditions of the gastrointestinal tract and the first-pass effect of the liver. The greater rate and extent of drug uptake into the systemic circulation may result in faster onset of action and reduce the dose of drug required to produce a therapeutic effect.

FIGURE 1



An OraVescent® Buccal Tablet

The oral mucosa has been known to be 4 to 4000 times more permeable than skin, depending on the physicochemical properties of the drug.[3] In addition, formulation technologies have been employed to improve the dissolution of the drug and its permeation through the oral mucosa. These technologies may provide even greater bioavailability and a shorter time (T_{max}) to reach the maximum drug concentration (C_{max}). The OraVescent® drug delivery technology, developed by CIMA LABS℠, is a recently commercialized oral transmucosal technology that provides these benefits.

ORAVESCENT® TECHNOLOGY

The OraVescent technology for oral transmucosal drug delivery is a tablet that is placed in the oral cavity, either sublingually or between the buccal and gingival tissues (Figure 1). The drug delivery system is designed to dissolve over several minutes. Tablets using the OraVescent technology are manufactured by direct compression utilizing a conventional tablet press and packaged using the PakSolv® proprietary blister packaging system. The PakSolv packaging system forms blisters, uses robotic arms to gently place the tablets in the blisters, and places a seal on the blister that protects the tablets from light and moisture (Figure 2). In addition, this packaging can be designed to be child-resistant up to an F1 rating.

A drug that has been shown to have enhanced delivery using the OraVescent technology is fentanyl. FENTORA®

(fentanyl buccal tablet, C-II) was approved by the FDA in September 2006 and is indicated for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. This product is currently marketed and sold in the US by Cephalon, Inc. Non-invasive opioid delivery systems that provide early onset pain relief offer advantages for outpatients with high-intensity, rapid-onset pain.

In addition to the basic benefits of oral transmucosal delivery, the OraVescent technology has been shown to provide greater transport to the systemic circulation for some drugs. This has been hypothesized to be due to its pH-modifying formulation. The enhanced performance of fentanyl is thought to be related to transient pH changes that occur over the course of tablet disintegration and dissolution. As the tablet disintegrates in the mouth, a reaction occurs after contact with water in the saliva. This results in the liberation of carbon dioxide and produces a modest decrease in pH. For a weak-base drug like fentanyl, a lower pH (below its pKa of 7.3 and 8.4) favors the ionized form of the drug, accelerating its dissolution. Then, as a pH-modifying substance present in the formulation (eg, sodium carbonate) dissolves, the pH increases. This pH increase causes the ionized drug to convert to the un-ionized form, which is more permeable to biological tissues and results in rapid absorption. The dynamic changes in pH that occur on the surface of the FENTORA tablet have been measured in vitro.[4]

FIGURE 2

PakSolv® Blister Packs Containing FENTORA®

FIGURE 3

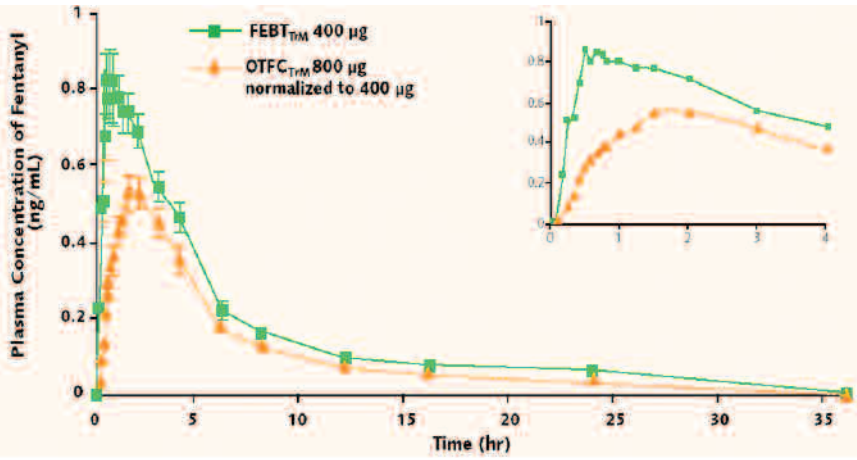
An Example of the OTS® Technology: ACTIQ®

BETTER PHARMACOKINETICS

The active ingredient in FENTORA, fentanyl, is a potent opioid mu receptor agonist that has been used traditionally as an anaesthetic and analgesic. Fentanyl is a good candidate for oral transmucosal delivery because its absorption via the gastrointestinal tract is slow with significant gut wall and extensive hepatic metabolism. The relative bioavailability of an oral, swallowable fentanyl tablet is approximately 30%. With pKa of 7.3 and 8.4 and an un-ionized form that is highly lipophilic, fentanyl is an ideal candidate for absorption enhancement using the OraVescent technology.

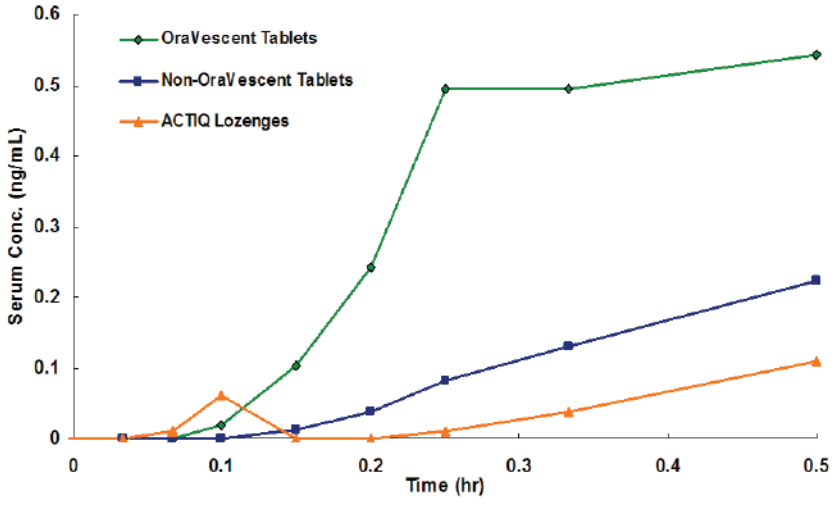
The story would not be complete without a discussion of the first fentanyl oral transmucosal product, ACTIQ® (oral transmucosal fentanyl citrate, C-II). ACTIQ was developed using an oral transmucosal "lozenge on a stick" system, trademarked as the OTS® technology, which is also offered by CIMA LABS (Figure 3). The OTS dosage form is administered by rotating and dissolving it against the oral mucosa. The OTS delivery system is unique in that it allows the patient to easily control the rate of drug delivery. The presence of a handle on the dosage form provides a simple mechanism for the patient to dose-to-effect

FIGURE 4



Mean Plasma Concentrations of Fentanyl (± SEM) Versus Time for OraVescent® Buccal Tablets Containing Fentanyl (FEBT$_{TRM}$) 400 Micrograms & Actiq® Oral Transmucosal Fentanyl Citrate Lozenges (OTFC$_{TRAM}$) 800 Micrograms (Dose Normalized to 400 Micrograms)

FIGURE 5



Early Phase Fentanyl Serum Levels

because the patient can remove and dispose of the dosage form in accordance with the instructions in the package insert when pain relief is felt. The oral transmucosal absorption increases the bioavailability of fentanyl to 50%, compared to 30% with an oral, swallowable tablet. The results are attributed to the absence of gut wall and hepatic metabolism, which are circumvented with oral transmucosal administration.

OraVescent tablets containing fentanyl were developed to improve the drug pharmacokinetics over ACTIQ with special emphasis on the absorption rate and the overall extent of absorption. Several studies have been conducted in healthy subjects to evaluate the pharmacokinetics of OraVescent tablets containing fentanyl versus the ACTIQ lozenge. In one study, 400 micrograms of fentanyl in an OraVescent formulation were administered buccally (FEBT$_{TrM}$) and compared to 800 micrograms of fentanyl in an ACTIQ lozenge (OTFC$_{TraM}$).[5,6] The plasma profiles of both dosage forms are displayed in Figure 4. FEBT$_{TrM}$ has a higher absolute bioavailability and a faster T_{max}.

In another study, OraVescent tablets containing fentanyl were administered buccally and compared to ACTIQ lozenges as well as tablets similar to OraVescent formulation but without the CO_2-generating and pH-modifying components.[7] The serum levels obtained during the first 30 minutes are plotted in Figure 5. The figure clearly shows the higher absorption rate of fentanyl from the OraVescent tablets in the initial phase compared to ACTIQ lozenges. OraVescent tablets also had a higher AUC (nearly 1.5 times as high as ACTIQ lozenges) and a shorter median T_{max} (0.5 hours for OraVescent tablets compared to 2 hours for ACTIQ lozenges). OraVescent tablets had faster absorption and higher AUC compared to similar tablets without the absorption-enhancement components, indicating that the improved fentanyl pharmacokinetics are attributed to the CO_2-generating and pH-modifying components of the OraVescent formulation. Faster fentanyl absorption from OraVescent tablets was also confirmed by other studies including single dosing, steady-state dosing, and dose proportionality studies.[8,9] All these findings indicated that the OraVescent technology can provide faster fentanyl delivery to the systemic circulation compared to ACTIQ lozenges.

IMPROVED CLINICAL OUTCOMES

ACTIQ lozenges are approved for breakthrough pain (BTP) associated with cancer. BTP is a transitory exacerbation of pain of severe-to-excruciating intensity that

occurs on a background of otherwise controlled persistence pain. BTP is reported by 24% to 95% of cancer patients and 70% to 80% of patients with chronic non-cancer pain.[10-12] An episode of BTP can reach maximum intensity within a median time of 10 minutes and last an average of 60 minutes.[12] That is why the speed by which fentanyl is delivered to the systemic circulation is of utmost importance for these patients. The onset of analgesic action of short-acting oral opioids used to alleviate BTP is approximately 30 minutes or more, and there is a greater need for novel products with an earlier onset of analgesic effect.

As previously described, the OraVescent technology provided a fast delivery of fentanyl to the systemic circulation, suggesting the technology is suitable for treating cancer patients with BTP. An OraVescent tablet containing fentanyl was clinically investigated for its effectiveness in relieving pain in opioid-treated patients with chronic pain associated with cancer who also suffer BTP.[10,13] In this study, pain intensity and pain relief were reported at 15, 30, 45, and 60 minutes, and patient ratings of global medication performance were recorded at 30 and 60 minutes. The analgesic effect of the OraVescent tablets was apparent at 15 minutes, and the duration of effect was found through 60 minutes.[10] Fentanyl delivery using OraVescent technology was well tolerated in patients even after long-term usage (1 year) at a dose range of 100 to 800 micrograms.[13-17]

CONCLUSION

Oral transmucosal drug delivery is an emerging platform that holds the promise of an improved alternative route of administration. The commercialized OraVescent technology has been proven to increase both the rate and extent of fentanyl absorption more than other oral transmucosal systems. The CO_2-generating and pH-modifying substances in the OraVescent formulation appear to be responsible for this effect. More importantly, the improved pharmacokinetic profiles have clinical relevance. The OraVescent technology is available for partnering, and other molecules are currently being studied to understand its full potential.

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BIOGRAPHIES

Dr. Beth A-S. Brown has over 10 years of experience in the pharmaceutical industry. As Senior Manager of New Technology at CIMA LABS, INC., Dr. Brown has been instrumental in building business development processes and assessing new technologies for in-licensing and acquisition. In addition, she is responsible for leading a cross-functional team to evaluate new business opportunities. Prior to joining CIMA LABS in 2005, Dr. Brown was an Advanced Research Specialist in the Early Pharmaceutics and Technology department at 3M Drug Delivery in St. Paul, Minnesota. Dr. Brown led multidisciplinary teams that developed new technologies and commercialized inhalation products. Past positions within 3M Drug Delivery include Certified Design for Six Sigma Black Belt, Research Specialist, and Senior Pharmacist. She earned her PhD and MS in Pharmaceutics from the University of Michigan and her BS in Pharmacy from Purdue University. She is also a registered pharmacist.

Dr. Ehab Hamed is a Research Scientist in R&D Formulations Development at CIMA LABS, a Cephalon Company. In this role, Dr. Hamed's main focus has been the development and scale-up of oral solid dosage forms, including modified release, taste-masking, buccal, and orally disintegrating tablets. He is also involved with the design, testing, and selection of novel oral and transmucosal drug delivery systems. He has more than 20 book chapters, pending patent applications, research articles, and conference presentations to his credit. Dr. Hamed earned his BS in Pharmaceutical Sciences from the College of Pharmacy, Assiut University, Egypt, and his PhD in Industrial Pharmacy from the College of Pharmacy, University of Cincinnati. He is a member in the American Association of Pharmaceutical Scientists, the Controlled Release Society, and the Rho Chi Pharmaceutical Honor Society.

TOPICAL DELIVERY

SEPA®, DermaPass™, and MacroDerm™: Exciting Possibilities for Topical Delivery and Specialty Pharma

By: Robert J. DeLuccia MBA

INTRODUCTION

Transdermal drug delivery and topical dosage forms have traditionally received less attention than oral or parenteral drug delivery. This is because very few drugs are potent enough to be considered a candidate for transdermal delivery into the systemic circulation, and relatively few medical conditions can be treated efficiently with topical dosage forms. A changing business climate and the realization of the clinical benefits of through-skin delivery for certain drugs has now brought transdermal delivery to the forefront. Today, specialty and innovator companies alike view novel delivery mechanisms as a strategic asset in pharmaceutical lifecycle management.

Controlled release transdermal formulations provide increased patient convenience and compliance for several drug classes, including analgesics, hormone and nicotine replacement products. For certain lipophilic drug compounds, the skin can serve as a depot of sorts, to facilitate sustained drug release.

Since the function of the stratum corneum (SC) in the skin is to provide a protective barrier from toxins and pathogens, the goal of transdermal delivery is to overcome that barrier. Transdermal drug delivery depends on a drug's inherent ability to partition into the skin, or on vehicles that overcome the skin's natural protective function while sparing the patient from adverse or permanent effects.

Optimally formulated topical drugs can affect controlled release into the bloodstream, through intact skin, while avoiding first-pass metabolism. Manufacturers of products that employ transdermal patches have long recognized the elimination of GI side effects and digestive system degradation as a major benefit.

Skin penetration enhancement depends to a considerable degree on the formulation carrying the drug. Small, lipid-soluble molecules partition into the SC and diffuse across the lipid bilayers in membranes, but highly water-soluble molecules cannot do so to any great extent.

Researchers have used various physical and chemical methods to enhance transdermal penetration of pharmaceuticals. Many compounds have been tried, such as sulfoxides (eg, dimethylsulfoxide), pyrrolidones, alcohols, glycols, surfactants, and terpenes, but few have been successfully commercialized.

An active topical formulation is critical for successful transdermal penetration. Significant factors include a high concentration gradient of the active ingredient, appropriate vehicle viscosity, and potency of the penetration enhancer. Skin condition, such as thickness, hydration, temperature, and vascular perfusion, also affect penetration.

DELIVERY: A SOURCE OF INNOVATION

Topical, enhanced-penetration drug delivery provides innovative companies with the opportunity to differentiate their products during and after patent expiration, and the ability to more effectively manage the life cycle for certain types of drugs. This strategy also affords specialty pharma companies the opportunity to innovate by creating new value from existing, off-patent drugs.

Personalized medicine, while still in its infancy, is beginning to alter the economic thinking behind drug development. Faced with the possible demise of the blockbuster model in favor of personalized treatments, companies now view narrower indications and smaller markets as inevitable, and in some cases desirable. Another group of pharmaceutical companies is taking an even more risk-averse approach. The so-called "specialty pharma" firms in-license compounds for new indications, or focus on improving dosage or administration of generic drugs.

Novel delivery systems represent a principled, proven "specialty" strategy. Due to competition and the growing ranks of generics, succeeding by simply reducing dosing from twice to once-daily has become more difficult. Products must differentiate themselves at a more sophisticated level, for example, greater efficacy or significantly less

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adverse reactions. Simultaneously, such products must demonstrate cost effectiveness because insurers are scrutinizing new medications for value – in many cases future dollars saved.

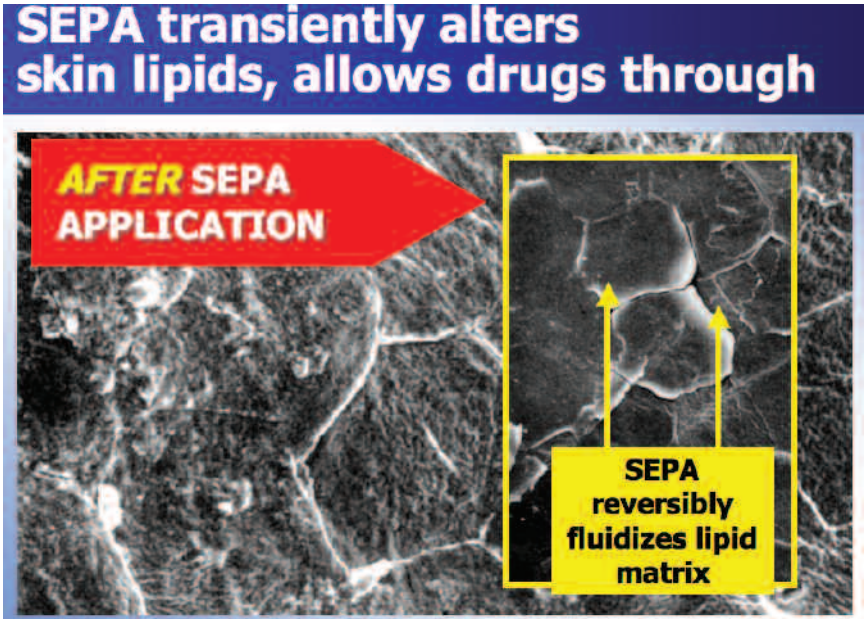
ENHANCING ABSORPTION THROUGH SKIN

SEPA® (Soft Enhancement of Percutaneous Absorption) is a molecule with demonstrated potency in transdermal penetration enhancement (Figure 1). "Soft" refers to the rapid breakdown of the enhancing materials, which confers reversibility in its effects. SEPA (2-n-nonyl-1,3, dioxolane) belongs to a group of alkyl-substituted acetals and cyclo-acetals.

Several members of this chemical class are currently used as flavoring agents for human use. SEPA is synthesized by the condensation of ethylene glycol and decyl aldehyde. The molecule possesses a polar head group in a five-membered ring containing two oxygens, and a nine-carbon tail. The amphiphilic SEPA structure, containing both polar and hydrophobic ends, transiently disrupts the skin's lipid bilayer as it traverses the tightly packed membrane structure.

SEPA's chemistry suggests that the most likely mechanism of metabolism involves opening of the dioxolane ring at the labile acetal carbon, with concomitant generation of ethylene glycol and decanal. SEPA was designed not to contain nitrogen because of potential toxicology problems of such metabolites. Physico-chemical studies

FIGURE 1



show that SEPA changes the lipid packing in the lipid matrix of the stratum corneum, raising the entropy (or disorder) in the normally highly structured bilayers. It is well known that this packing (or order) prevents most compounds from entering the skin. By disrupting this order, SEPA creates temporary passageways that allow drugs or other substances to pass through.

SEPA has undergone extensive testing equivalent to that for a New Chemical Entity. MacroChem has subjected the technology to evaluation through pharmacologic activity screens, pharmacokinetics, biodistribution and metabolism studies, acute and repeat-dose toxicity studies, and mutagenicity, carcinogenicity, and reproductive tox. As a result of this testing program, we can conclude that SEPA is pharmacologically inert. Topically applied formulations containing up to 10% SEPA, while clearly absorbed into systemic circulation, produce no systemic toxicities in humans.

SEPA ideally works with molecules of 500 Daltons or less. Some peptides up to 12-mers, with MWs approaching 1200 Daltons, are also candidates for SEPA-enhanced delivery. SEPA is not an appropriate delivery enhancer for highly polar molecules or those that are highly charged.

SEPA has been tested alone or with several active drugs in more than 4,000 human subjects without any

FIGURE 2

evidence of systemic toxicity. MacroChem holds numerous composition of matter patents on SEPA formulations, which ensure intellectual property rights for SEPA-based pharmaceutical products well into the latter half of the next decade.

Recently, MacroChem has filed for patent protection on a second-generation absorption enhancer, DermaPass™. This novel group of penetration enhancers operates similarly to SEPA, but the DermaPass molecules possess different head groups and chain lengths. DermaPass molecules can be custom designed to enhance transdermal delivery of very highly polar, water-soluble molecules in addition to a good number of hydrophobic drugs. In other words, DermaPass broadens SEPA's range both at the polar and apolar ends of the active ingredient spectrum.

MacroChem is also developing a series of patented biodegradable polymers, with molecular weights in the 1000- to 8000-Dalton range, as part of our MacroDerm family of penetration inhibitor products. Laboratory testing has shown that these polymers can modulate delivery in a dose-response fashion. Development efforts for MacroDerm are focused in the areas of cosmetics, personal care products, and selected pharmaceuticals. As an example, MacroDerm significantly reduced transdermal absorption of insect repellants or sunscreen ingredients while maintaining those products in an active state on the skin surface. MacroDerm is not a barrier – that is, it does not form an occlusive film on the skin. Rather, it can be synthesized to change partitioning of certain molecule types between a topical formulation and the skin. Patents for MacroDerm extend to the year 2020.

SEPA IN ACTION

Onychomycosis

There is a great need for topically delivered anti-fungals that are as effective as the oral medications. For example, onychomycosis (or fungal infection of the nail) is estimated to affect approximately 30 to 35 million Americans. Of the total number of potential patients, only about 20% are treated with the currently available drugs, and only a small percentage of those are eventually cured.

Current onychomycosis therapy in the US consists of orally administered antifungal drugs and a lacquer-based product. Systemic antifungal therapy is normally avoided due to frequent liver toxicity, while the existing lacquer product has a low cure rate of about 10%. The incidence of onychomycosis rises with age, and so do liver problems associated with systemic anti-fungal treatment.

The $750-million US onychomycosis market is led by two products: Lamisil® (terbinafine; Novartis) tablets, which hold between 30% to 40% of the market, and Sporanox® (itraconazole; Ortho-McNeil) capsules, which capture about 20%. Both drugs act systemically. Lamisil has demonstrated efficacy in the 40% range, while Sporonox's demonstrated efficacy is about 15%. Additionally, both drugs share a common liability of adversely affecting liver function. Accordingly, liver function monitoring of patients is necessary during therapy.

A topical lacquer, Penlac® (ciclopirox; Dermik) is also available, but the cure rate for this product is

about 10%. Despite the fact that it's not particularly effective, Penlac sales are about $100 million annually. Most notable was the recent precedent-setting deal by Schering Plough for Anacor's Phase II topical nail fungus product, which reflects the high level of interest in the marketplace for new topical treatments for onychomycosis.

EcoNail™ is a SEPA-based nail lacquer containing econazole, a well-documented anti-fungal compound (Figure 2). When formulated in the lacquer, SEPA softens the delivery matrix to allow econazole to diffuse out of the lacquer film into the nail-lacquer interface, creating a high concentration gradient locally. Such a concentration gradient serves to drive econazole into and through the human nail. Laboratory studies on human nails showed that EcoNail provides an occlusive environment over the nail, resulting in delivery of high concentrations of drug into the ventral nail plate and nail bed. Econazole concentrations reach approximately 14,000 times the minimum inhibitory concentration for the commonly encountered dermatophytes, which is several times higher than can be achieved through systemic administration.

Hypogonadism

Hypogonadism is a condition in which the testes produce insufficient amounts of testosterone, a hormone responsible for normal growth and development of the male sex organs and for maintenance of secondary male sex characteristics. According to the Endocrine Society, this disorder affects an estimated 4 to 5 million men in the US, but less than 5% are treated by hormone replacement therapy. The incidence of hypogonadal testosterone levels in US males increases from approximately 20% in men over the age of 60 to approximately 50% in men over the age of 80.

For effective hormone replacement, testosterone must be delivered into the circulation to act systemically. However, administration by injection is far from optimal. Ideally, testosterone replacement should mimic the body's testosterone production, which is approximately 4 to 7 mg per day, peaking in the morning. No current testosterone replacement therapy comes close to these ideal plasma levels.

Oral testosterone replacement is associated with elevated liver function and abnormalities detected in liver scans and biopsies. When testosterone is injected as an ester, at 300 mg doses, initial serum concentrations are high, causing wildly fluctuating libido and mood, but fall to approximately normal doses after 2 weeks. Patients must receive injections every month in a clinical setting.

Several transdermal testosterone formulations are now on the market. Watson Pharma's skin patch, Androderm, employs penetration enhancers and is applied to the torso or limbs. Testosterone patches require large depot doses of the hormone and often cause local irritation, forcing patients to continuously change the location of administration. Topical gels overcome some of these concerns, but the systemic absorption can be variable. Also, administration can be inconvenient as the currently available gels need to be applied over a relatively large body surface area.

Opterone® is a SEPA-enhanced 1% topical testosterone cream formulation, developed to treat hypogonadism. Testosterone is an example of a drug that is ideally suited for transdermal delivery. Oral administration is impractical due to first-pass metabolism and has the potential for liver injury during chronic administration. Preclinical and early stage human studies demonstrate that SEPA enhances absorption of testosterone through the skin.

In vitro studies suggest that a SEPA-testosterone gel formulation delivered up to 400% more testosterone per gram of applied dose, over a 24-hour period, compared with commercialized testosterone gel formulations. An early pharmacokinetics study using a first-generation testosterone/SEPA gel demonstrated that 2.5 grams of the product produced systemic testosterone levels that compared with 5 grams of the gel. Opterone cream, a second-generation product, delivers similar levels of drug systemically but through a more sustained delivery mechanism. Opterone is ready to enter Phase II clinical testing, however, we are seeking a partner to advance it in clinical development.

PODIATRY & DERMATOLOGY

Earlier-stage products are targeted to the podiatry and dermatology arena, and a topical (cream or gel) NSAID (non-steroidal anti-inflammatory drug) has also shown promise in our laboratory testing.

In a post-Vioxx world, drug developers and marketers have increased awareness of both GI bleeding and cardiovascular effects of systemic NSAID therapy. These serious side effects are often most pronounced in vulnerable patients with co-morbidities. For example, patients with poor circulation must take large doses of NSAIDs to alleviate pain in the extremities, thus raising their risk of serious CV or GI effects. NSAID safety is on regulators' minds as well. The FDA recently turned down the New Drug Application for Merck's Arcoxia, the successor to Vioxx, pending more safety data. The objective of a topical NSAID would be to treat localized pain with a relatively safe NSAID while avoiding GI and other systemic side effects

SUMMARY

The need for alternatives to solid-dosage oral delivery or parenteral injections has never been greater. Issues of compliance, safety, efficacy, and convenience have caused many approved drugs in traditional dosage forms to lose popularity among prescribers. Because of these factors, novel drug delivery has become a strategic asset for patent-holders, developers, and marketers of innovative follow-on products.

The wide range of molecules enhanced by SEPA for transdermal delivery present exciting possibilities for topical delivery of marketed and well-characterized pharmaceuticals. Drugs that act in or near the skin, whose toxicology is less than ideal for systemic delivery, or that would benefit from controlled release, are all excellent candidates for SEPA and DermaPass formulation. More than 9 in 10 clinical stage compounds are not approved for toxicology or efficacy reasons. A fair number of these might also be provided a new lease on life through topical transdermal formulation.

Elderly and pediatric patients, in particular, those who suffer from serious GI side effects, and surgical patients represent an expanding marketplace for novel delivery technologies, particularly transdermal.

Operating as a pure-play drug delivery company is a long, arduous, often disappointing pathway to success in the pharmaceutical industry. For every home run, there are dozens of strikeouts. Triumph too often depends on the business acumen of partners or licensees who are themselves looking for the ultimate "home run ball" – a blockbuster drug. When they lose, pure-play delivery companies lose as well.

A specialty pharmaceutical company combining novel delivery technology with already-approved drugs might sometimes score a blockbuster. But by focusing on smaller, more predictable markets, the specialty pharma approach can create important new products for the medical community and the patients they serve.

This is the vision that drives MacroChem in executing its transition from drug delivery to a specialty pharmaceutical company. MacroChem's product for toenail fungus, EcoNail, is currently in a Phase II clinical trial in which the company expects to take an interim look at the data later this year. MacroChem's second product, Opterone, for male testosterone deficiency, is ready to enter Phase II clinical testing, but the company is seeking a partner to advance it. The company is also seeking in-license opportunities to complement its strategic focus in podiatry and dermatology. Changing market dynamics and interest in new products using drug delivery technologies make MacroChem product candidates very appealing.

BIOGRAPHIES

Mr. Robert J. DeLuccia joined MacroChem's Board in 2000 and accepted the position of President and Chief Executive Officer and Vice Chairman of the Board in June 2003. Mr. DeLuccia is the former President and Chief Executive Officer of Immunomedics, Inc., a Nasdaq biopharmaceutical company focused on the development and commercialization of antibody diagnostic imaging and therapeutic products for cancer and infectious diseases. Prior to Immunomedics, he was President of Sterling Winthrop Pharmaceuticals, the U.S. subsidiary of Sanofi (now Sanofi-Aventis). Mr. DeLuccia began his career as a pharmaceutical sales representative for Pfizer and progressed to Vice President Marketing and Sales Operations for Pfizer's Roerig Division. He is also a member of the Board of Directors of IBEX Technologies, a publicly traded (TSX) pharmaceutical company specializing in the development of biological markers for diagnosis, monitoring and treatment of cancer and arthritis, and TOPIGEN Pharmaceuticals, Inc., a privately held biopharmaceutical company and developer of anti-inflammatory respiratory products. Mr. DeLuccia earned his BS and MBA in Marketing from Iona College.

Drug Delivery Executive

Senopsys

Senopsys LLC: Dedicated to the Development of Palatable Pharmaceuticals

Senopsys is a specialty services company on a mission to improve medication compliance and health outcomes through the development of patient-accepted medications. Senopsys partners with pharmaceutical, biotechnology, and drug delivery companies to optimize the sensory characteristics of medications. The company uses its proprietary FlavorMetrics℠ assessment and FlavorOpt℠ development tools to assess the suitability of novel oral dosage forms and delivery technologies, improve the palatability of drug products, and develop new formulation systems for investigational and approved drugs. Drug Delivery Technology recently interviewed Jeff Worthington, Founder and President of Senopsys LLC, to discuss how his firm is collaborating with industry to develop palatable drug products.

Mr. Jeff Worthington
Founder & President
Senopsys LLC

"Unfortunately, the importance of product aesthetics is generally underappreciated by the pharma industry relative to the underlying technology. This often leads to the launch of drugs that are unacceptable to many patients, despite their medical benefits. When medication compliance is compromised, health outcomes suffer, and drugs fail to realize their sales potential."

Q: Senopsys is an interesting name – what does it mean?

A: Senopsys is derived from Sensory Optimization Systems, which is the core of what we do – namely help clients create products that can be differentiated based on patient-perceived sensory attributes.

Q: What is palatability, and why is it important?

A: Most dictionaries define palatable as "acceptable to the taste." As consumers, we have access to a seemingly limitless variety of foods and beverages representing a myriad of aromas, flavors, colors, textures, and mouth feels. Unlike consumers with their food choices, most patients do not look forward to taking their medicine, and they have comparatively modest expectations for the product. Most are looking for an "acceptable" tasting medicine – one that can be easily swallowed without pain or suffering. This translates to a drug product with moderate sensory characteristics – not too bitter; not to odorous; not too irritating; and not too hard, gritty, or sticky.

Most pharmaceuticals are developed and

promoted exclusively on their medical benefits (superior efficacy, milder side effects, faster acting, or longer lasting), many of which have been enabled by advances in drug delivery technology. While these medical benefits are undeniably important, the product's aesthetics (appearance, aroma, flavor, texture, mouth feel, and ease-of-swallowing) can have a significant effect on patient compliance. Unfortunately, the importance of product aesthetics is generally underappreciated by the pharma industry relative to the underlying technology. This often leads to the launch of drugs that are unacceptable to many patients, despite their medical benefits. When medication compliance is compromised, health outcomes suffer, and drugs fail to realize their sales potential. At Senopsys, we are committed to changing this paradigm through the development of more palatable drug products.

Q: Okay but can palatability actually be measured?

A: Absolutely. Because pharma companies have generally underappreciated the importance of product aesthetics, knowledge of sensory science and flavor system development is diffuse compared to the consumer-packaged goods industries. In fact, there's a great deal of mythology in the pharma industry surrounding the development of palatable drug products. One of the biggest myths is that palatability cannot be measured. For this reason, Senopsys developed the FlavorMetrics Taste Assessment Tools to assist drug developers in addressing the key taste issues along the clinical and commercial development pathway. FlavorMetrics provides quantitative data to guide formulation development and support decision-making and consists of two modules. The FlavorMetrics Bitterness Profile is used to quantify the taste-masking challenge of APIs early in the development process and assess the need for advanced taste-making technology. The FlavorMetrics Palatability Profile is used to measure the flavor quality of prototypes and competing products and provides a framework for supporting product optimization, reformulation, and launch decisions.

Q: Can you tell us more about Senopsys' development of palatable drug products?

A: In addition to providing sensory measurement services, Senopsys will work with clients to develop complete formulations for investigational and approved drugs. Senopsys' FlavorOpt sensory-directed formulation development approach was developed through decades of experience in the highly competitive food industry in which taste is paramount. We apply our extensive knowledge of sensory science, flavor construction, and excipient functionality to help clients

develop formulations that are acceptable to patients. We have assembled a team of talented pharmaceutical sensory panelists and formulators who have worked on numerous over-the-counter and prescription drugs. This team has broad dosage form experience, including oral and intranasal liquids, powders, chewable and fast-dissolving tablets, oral films, and soft chews.

Q: Many in our industry believe the key to developing a palatable drug product is to select the most appropriate flavor. Is this not the case?

A: Another popular palatability myth is the notion that a product's flavor (orange, grape, chocolate, or mint) is the key determinant of patient acceptance. In actuality, a drug's palatability is much more complicated than its flavor. The key to developing palatable pharmaceuticals includes many factors, such as balancing the four basic tastes – sweet, sour, salty, and bitter – building blend and body, extending the duration of the flavor system, and adding beneficial mouth feel factors. These principles are all well understood by the food industry; we're not reinventing the wheel, rather translating best practices across traditional industry boundaries.

Q: Can you share with us your business model?

A: Senopsys is an objective and independent development partner. We do not sell ingredients or license technology and thus our objectives are always aligned with that of our clients – to develop patient-acceptable dosage forms. Our work is generally conducted on a fee-for-service basis, which most clients prefer. We also offer favorable intellectual property terms. For example, in the case of contract formulation development, the client obtains the rights to the resulting formulation for the particular study drug and dosage form combination and the right to use any embedded Senopsys intellectual property. This helps to ensure that the interests of both parties are aligned.

Q: At Senopsys, how do you measure success?

A: Senopsys will remain a privately held, specialty services company dedicated to the development of palatable drug products that meet the needs of diverse patient populations. We measure our success by the number and quality of drug products commercialized by our client development partners. We expect to continue our important work in pediatric formulation development. In addition, advances in drug delivery technology will continue to give rise to new oral dosage forms for specific patient populations, such as the elderly and patients with dysphagia, for example. Each of these dosage forms will present its own aesthetic challenges that will need to be addressed for the drug products to fully realize the promise of the underlying technology. We hope to contribute to the success of these emerging technologies as well. ◆

TRANSDERMAL DELIVERY

Hypogonadism Solution Through Transdermal Androgen Replacement: Drug-In-Polymer Transdermal Delivery Systems

By: Nazik Abdel-Latif El-Gindy, PhD; Adel M. Motawi, PhD; Mohamed A. El-Egaki, PhD; and Wael M. Samy, PhD

ABSTRACT

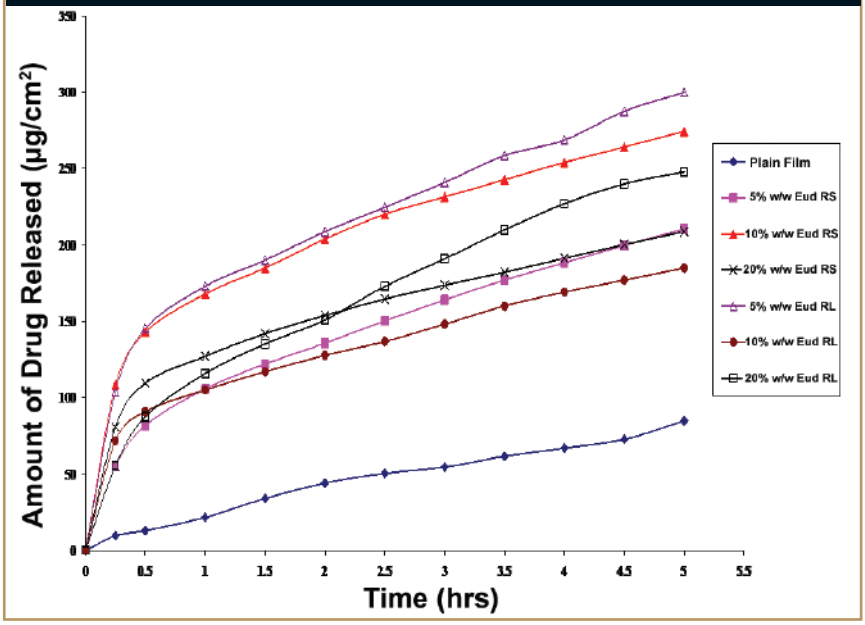
Male hypogonadism is a pathophysiological condition in which testosterone serum levels are less than 300 ng/dl. The present study was undertaken to prepare and evaluate monolithic drug-in-polymer-type transdermal drug delivery systems (TDDS) of testosterone for androgen replacement. Eudragit E-100 was used as the incorporation polymer and Span 85 as a permeation enhancer. Both placebo and drug-loaded patches were found to be non-irritant or sensitizing. Secondary polymers (Eudragit RS and RL) or cross-linker (succinic acid) were used in different concentrations to modulate testosterone release from the prepared patches. Ex vivo testosterone fluxes were improved from 15.83 µg/cm²/hr in plain patches to 45.99 µg/cm²/hr and 73.32 µg/cm²/hr with the use of 5% w/w Eudragit-RL and 7% w/w succinic acid, respectively. Castrated rats were used as hypogonadal animals to investigate the in vivo transdermal delivery of testosterone from the selected TDDs. The estimated serum levels showed a peak of 468.8 ng/dl after 6 hrs for patches containing 5% Eudragit-RL and 810.7 ng/dl for those containing 7% w/w succinic acid after 24 hrs of patch application. After 48 hours of patch application, the devices containing Eudragit-RL showed reduction in testosterone levels back to those found at zero time, while those containing succinic acid were still showing higher levels, thus giving more prolonged action. The results support the possible use of the prepared testosterone TDDs for hypogonadism management.

INTRODUCTION

Testosterone, the most important androgen produced by the testes, plays an essential role in the development and maintenance of many male characteristics. These characteristics include muscle mass and strength, bone mass, libido, potency, and spermatogenesis.[1] Androgen deficiency occurs with disorders that damage the testes, including traumatic or surgical castration (primary testicular failure) or disorders in gonadotrophin stimulation (hypogonadtrophic hypogonadism).

Clinically, hypogonadism is the reduction in the daily output of testosterone below its normal level (3 to 10 mg/day).[2] In adult males, clinical manifestations of hypogonadism depend on the severity and duration of the deficiency. The manifestations include reduced body hair,

FIGURE 1



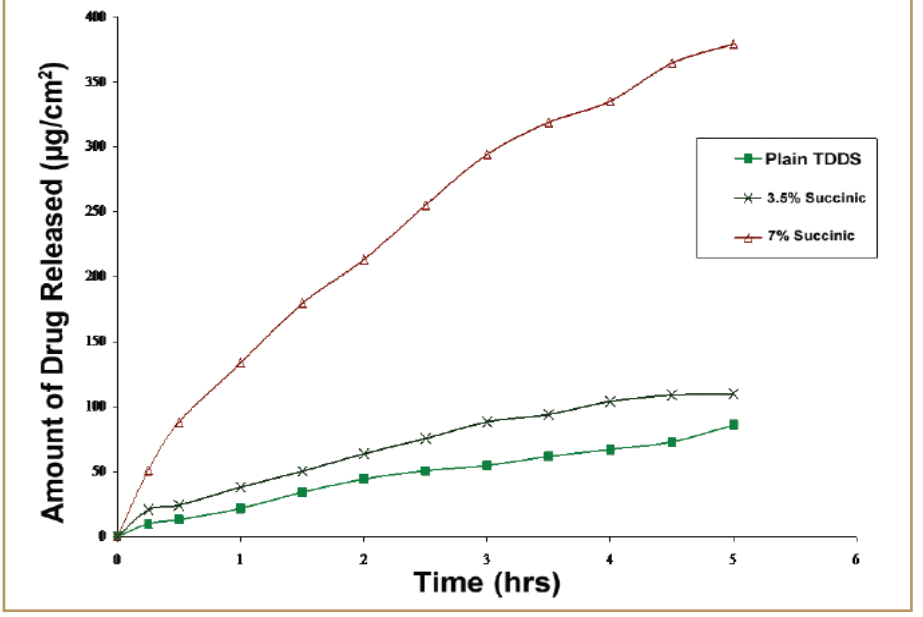
Effect of different concentrations of secondary Eudragits (% w/w) on ex vivo testosterone release from TDDS containing 1% w/w Span 85.

decreased muscle mass and strength, increased fat mass, decreased hematocrit, erectile dysfunction, infertility, and depression.[1] Another consequence of male hypogonadism is physical fragility and bone fractures due to loss of bone and muscle mass.[3] In addition to the use of testosterone in androgen replacement, testosterone has a controversial application in the proposed Female Androgen Insufficiency Syndrome.[4] Such a syndrome describes a number of non-specific symptoms, including unexplained fatigue, decreased well being/dysphoric mood, and/or blunted motivation and diminished sexual function. The most commonly used forms of androgen replacement therapy are oily intramuscular depot injections of the testosterone esters; testosterone enanthate and cypionate. Although it is important to adjust dosage according to individual patients, the usual dosage of these injections for adults is 150 to 200 mg administered every 14 to 21 days. Such a regimen is usually successful in maintaining normal "androgenization" without marked adverse effects.[5] A major disadvantage of the intramuscular testosterone is the high levels of serum testosterone produced for several days after injection and low or subnormal levels at the end of the dosing interval.[5,6]

Several alkylated derivatives of testosterone are available for oral or sublingual use including methyl testosterone and fluoxymesterone. The main disadvantage of these derivatives is the variable clinical response.[7] It was reported that prolonged use of high doses of oral androgens (especially the 17 beta-alkylated androgens) has been associated with the development of some life-threatening conditions, such as hepatic adenomas, hepatocellular carcinoma, and peliosis hepatitis.[1]

Another FDA-approved dosage form for testosterone replacement, is biodegradable poylactide-co-glycolide (PLGA) microcapsules for subcutaneous administration.[8] Such a dosage form is quite painful and less preferred by the patient in addition to its relatively high cost. The permeation-enhanced transdermal testosterone patch, Androderm®, is associated with skin irritation in about one third of the patients, and 10% to 15% of subjects have discontinued treatment because of chronic skin irritation.[9] This problem can be overcome by the application of a corticosteroid cream at the site of application of Androderm patch.

FIGURE 2



Effect of succinic acid cross-linker concentration (% w/w) on ex vivo testosterone release from TDDS.

The use of non-irritant and non-sensitising polymers in patch manufacturing is thus very important. In order to evaluate skin irritation and sensitisation due to exposure to different chemicals, many scales have been proposed in order to "quantify" irritation with the most important being that suggested by Draize.[10]

The newly available gel (Testim® Gel) appears to be safe and effective in early trials. On the other hand, it must be applied daily, and care must be taken to avoid inadvertent vicarious exposure to women and children.[11]

Xing et al developed a testosterone transdermal delivery device that was tested on castrated Yucatan minipigs as a hypogonadal animal model.[12] The compartmental pharmacokinetic modeling analysis of the plasma profiles of testosterone indicated that 92% of the total testosterone released from the system has been delivered during the initial rapid input period (the first 11 hrs of application), whereas only 8% was released during the slow input period (up to 23 hrs).

Kim et al also developed a reservoir-type transdermal delivery system of testosterone using an ethanol/water (70:30) co-solvent system as a vehicle.[13] The maximum permeation rate achieved by 70% (v/v) of ethanol was found to increase from 2.69 to 47.83 µg/cm²/hr with the addition of 1% dodecylamine as an enhancer.

The transbuccal delivery of testosterone was also investigated as a possible route for androgen replacement. Ross et al studied the pharmacokinetics of a bioadhesive testosterone buccal tablets.[14] The tablet matrix consisted of testosterone, lactose monohydrate, HPMC, corn starch, and polycarbophil. The tablet showed a slow release of testosterone in such a manner that stable and reliable serum testosterone concentrations were produced, avoiding the first-pass metabolism of the drug.[14]

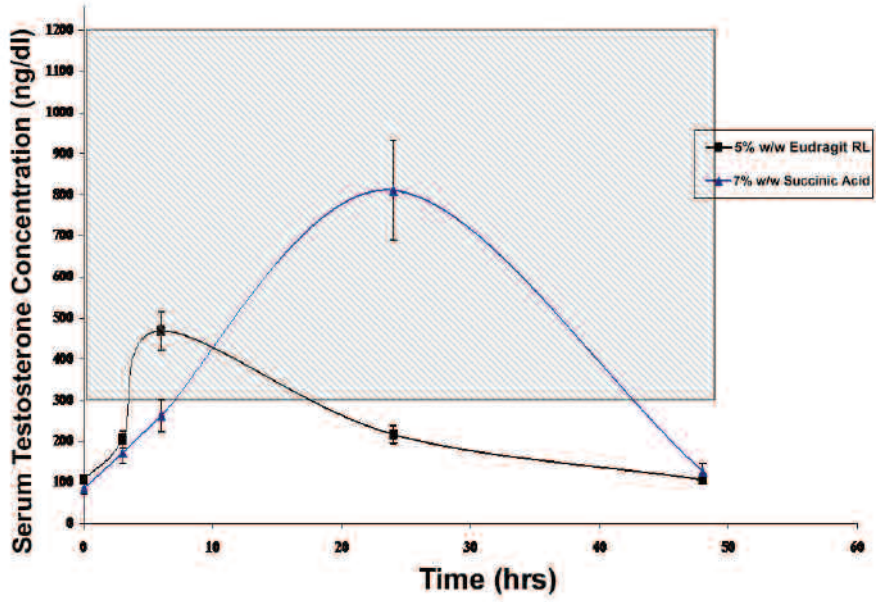
Ameye et al studied the buccal bioavailability of testosterone formulations based on grafted starch or starch/poly (acrylic acid) mixtures.[15] A chemically modified grafted starch could sustain 3 ng/ml testosterone target concentration for up to 8 hrs. This period was increased to 13.5 hrs by lyophilization of a partially neutralized, irradiated, grafted starch.

This study aimed to develop inexpensive non-scrotal testosterone patches with minimal area and no skin irritation for a successful and satisfactory management of hypogonadism by androgen replacement.

MATERIALS

Eudragit E-100, RS-100, and RL-100 were supplied by Rhöm Pharma (Germany). Triacetin was supplied by Pharco Pharm. Co. (Egypt). Isopropanol, ethyl acetate, and

FIGURE 3



Average serum testosterone levels in rats after the application of different film-based TDDS for 48 hrs (n=6, + SD). Therapeutic window.

succinic acid were purchased from Prolabo (EU). Testosterone was supplied by Organon (Holland). 3M Scotchpak 9742 release liner was kindly gifted from 3M Drug Delivery Systems (US). Solvent-based adhesive polymer (Acronal®) was kindly supplied by Pharmaplast Co. (Egypt). The animals used were male albino rabbits (2 to 2.5 kg) and adult male rats (200 to 220 g) (Medical Research Centre, Alexandria University, Egypt). The animals were separately housed at room temperature (25°C) and had free access to water and food.

METHODS

Preparation of the TDDS

Plain TDDS were individually prepared by dissolving 100 mg of testosterone in 4.2 ml of ethylacetate/isopropanol mixture (2:1) containing 0.3-ml Span 85 and 3.7-g Eudragit E-100 in a 25-ml beaker. Triacetin (45% w/w based on dry polymer weight) was added to the mixture, and the polymer solution was then casted over the backing membrane (0.01-mm aluminum foil) in a 6-cm petri dish. The patch was left to dry for 24 hrs at room temperature (25°C) in a closed cabinet. The release liner was cut into circular pieces 6 cm in diameter, applied to the surface of the dried film, and the whole TDDS was stored in a dessicator till further testing.

Skin Irritation Test

Placebo Eudragit E-100 films with and without an Acronal layer, and testosterone-loaded films with an additional Acronal layer were tested for skin irritation. The test of each film was performed on three albino rabbits as follows:[16]

- Square pieces of the tested film (4 X 4 cm) were applied directly on the skin of the animals. For a proper fixation of the patch, the pieces were kept in place using a porous 3M Micropore™ adhesive tape.

- The skin reaction was monitored and recorded according to the Draize scale at 4, 24, and 48 hrs.[10]
- The numerical averages of the skin irritation grades were then calculated to show skin irritation and sensitisation potential of the tested films.

The same procedure was applied to each of 6 rats (200 to 220 g) using an exposure area of approximately 6.5 cm^2 to confirm skin irritation results of drug-loaded films. An additional test was performed on 6 human volunteers using the placebo Eudragit E-100 films over an area of approximately 28 cm^2 over an unshaved area of the forearm for 24 hrs.

Effect of Secondary Polymers & Succinic Acid Cross-Linker

Testosterone patches containing 1% w/w Span 85 and 100 mg of testosterone per patch were prepared as previously described with the incorporation of a secondary polymer or cross-linker. Eudragit RL-100 or RS-100 was incorporated at three different concentrations of 5%, 10%, and 20% w/w, while succinic acid was incorporated at 3.5% or 7% w/w (based on dry polymer weight).

Ex Vivo Drug Release

The inner skin of freshly excised rabbit ear pinna was peeled off and used for the ex vivo study. An area of 9.5 cm^2 of the device was cut, placed on a plastic support of the same area (with the backing membrane facing downward), and covered with the skin after the removal of the release liner. The whole set was then fixed together using a plastic ring and immersed in the jar of a USP dissolution rate apparatus (Pharmatest; Germany) containing 250 ml of phosphate buffer saline (PBS) pH 7.4 with the skin facing upward. The paddle was rotated at 40 rpm, and the temperature kept at 35°C ± 0.5°C. Prefiltered samples of 3 ml were withdrawn at 30-min intervals and replaced with prewarmed fresh buffer. The samples were then assayed spectrophotometrically (Lambda 3B, Perkin-Elmer; US) at 243 nm for testosterone release. Plots of cumulative drug released per cm^2 versus time and versus $time^{1/2}$ were drawn and used to calculate testosterone flux and the release rate constant, respectively.[17] All experiments have been repeated in triplicates, and the average was taken.

In Vivo Drug Release

TDDS for in vivo drug release were prepared as discussed previously with the exception of the use of a pressure-sensitive adhesive (Acronal) that was spread over the release liner (20 ml/m^2), dried for 2 hrs, and cut to a suitable area before applying the whole assembly on the surface of the dried film.

Five male rats weighing 200 ± 25 g were castrated under thiopental anesthesia and left for 10 days before using them as models for hypogonadal animals. A 20-cm^2 area of the dorsal side of the rat was shaved using an electric clipper, and then an area of 6.5 cm^2 of the TDDS was cut and fixed to the back of the animal at the center of the shaved area. The

TDDS was further fixed using a porous adhesive tape. Blood samples were withdrawn from the eye of the ether-anesthetized rats at different time intervals. Samples were centrifuged (4000 rpm), and testosterone levels were then measured using a radio-immuno assay (RIA) using Active™ Testosterone RIA DSL-4000 kits (Diagnostic Systems, Inc; Webster, TX).[12] The lower limit of detection for this assay was 0.08 ng/ml, and the intra- and inter-assay coefficients of variation were 10% and 9%, respectively. Plots of testosterone levels versus time were used to calculate C_{max}, T_{max}, and AUC. The results were analysed by one-way ANOVA at a level of 0.05.

RESULTS & DISCUSSION

Skin Irritation

Skin irritation and sensitisation of new TDDS is a major drawback that affects both efficacy and patient compliance.[18] Placebo Eudragit E-100 films were tested for their skin irritation on three albino rabbits and six rats according to aforementioned Draize scale. Neither erythema nor oedema was observed on any of the tested animals after 4, 24, or 48 hrs of film application. These results indicate that neither the polymer nor other film components (plasticizer or residual solvent) causes skin irritation or sensitisation. The results are in agreement with the reported safety and non-irritancy of Eudragit polymers.[19]

Placebo and testosterone-loaded Eudragit E-100 films with an additional Acronal (PSA) layer were also tested for their skin irritation and provided the same results. One of the tested rabbits showed slight erythema after 24 hrs that persisted for 48 hrs of patch application with no oedema detected. The rabbits' average reaction (0.33) is much less than 2, indicating that the film with the Acronal layer is non-irritant and non-sensitising to the skin, while one of the six tested rats developed slight erythema with no oedema detected with an average reaction of (0.2), far beyond the 2 value that indicates skin irritation.[16] The obtained results indicate the safety of Eudragit E-100-based TDDS of testosterone concerning skin irritation and sensitisation potential.

Placebo Eudragit E-100 films with an Acronal layer were applied on the forearm of six human volunteers for 24 hrs. The results showed an average of 0.33, which is still far below the value of 2, indicating no skin irritation (Table 1).

The obtained results indicate good safety of the TDDS upon 48 hrs application, which is double the expected use duration (24 hrs) of the patch. The results also indicate that the prepared Eudragit E-100-based TDDS are advantageous over the marketed Androderm patches, which were reported to show skin irritation in about 30% of patients causing 10% to 15% of patients to discontinue drug administration.[9]

TABLE 1

Oedema Formation	Erythema & Eschar Formation	Human Volunteer
0	1	A
0	0	B
0	1	C
0	0	D
0	0	E
0	0	F
0	0.33 ± 0.47	Average ± SD

Skin irritation test for Eudragit E-100 films with additional Acronal layer in human volunteers for 24 hrs.

Effect of Secondary Polymers

The incorporation of secondary polymers in Eudragit E-100 matrices is one of the methods used to modulate drug release.[20] Eudragit RL-100 or RS-100 was used to improve testosterone release (through rabbit ear pinna skin) from Eudragit E-100-based TDDS containing 1% w/w Span 85 as an enhancer that was selected in our previous work.[21] The incorporation of secondary Eudragit polymers resulted in increasing the ex vivo testosterone release in all the tested concentrations (Figure 1).

Using 5% w/w Eudragit RL-100 gave the highest increase in testosterone release with about 268.8 µg/cm^2 released after 4 hrs compared with 67.1 µg/cm^2 for plain films after the same period. This could be attributed to the disturbance of the Eudragit E-100 matrix structure upon the incorporation of Eudragit-RL, allowing for a higher escaping tendency for the drug molecules. In addition, being slightly more hydrophilic than Eudragit E-100, Eudragit-RL could allow more hydration of the matrix. The water molecules entering the matrix can thus "leach" more of the drug out of the TDDS.[20] After 3 hrs, the cumulative amount released of testosterone was 241.1, 148.3, 175, and 54.8 µg/cm^2 for patches containing 5%, 10%, and 20% w/w Eudragit-RL and plain patch, respectively. At 20% w/w Eudragit-RL concentration, the matrix structure disturbance is higher than that of the 10% w/w level, but the matrix hydration is higher than the 5% w/w secondary polymer concentration. This might cause the 20% w/w to have an intermediate effect between the other two concentrations.

Wong et al showed that the incorporation of secondary polymers in Eudragit NE40D-based buccal patches resulted in improving metoprolol tartrate release from the devices.[22] The influence was mainly attributed to the effect of the used hydrophilic polymer on matrix hydration and the formation of "aqueous channels" for drug release. Four out of the six tested secondary polymers showed no direct relation between the rate of drug release and the secondary polymer concentration.[22] In the present work, increasing Eudragit-RL to 10% or 20% w/w led to a lower enhancement of testosterone release but still higher than the plain films. This lower enhancement could be attributed to increased matrix hydration that may be unfavorable for the hydrophobic drug. The overall effect of the secondary polymer can be attributed to an equilibration between the "hydrating" and "disturbing" effect of the secondary polymer on the parent Eudragit E-100 matrix.[22,23]

The effect of secondary polymers was also observed in pentazocin release from TDDS containing different ratios of Eudragit-

TABLE 2

Excipient (% w/w)	Flux (J) ($\mu g.cm^{-2}.hr^{-1}$)	Release Rate Constant (K) ($\mu g.cm^{-2}.hr^{-1/2}$)	Diffusion Coefficient (D) x 10^{10} ($cm^2.sec^{-1}$)	Permeability Coefficient (P) x 10^8 ($cm.sec^{-1}$)
Plain TDDS	15.83	36.55	5.90	21.86
5% Eud. RS 100	37.14	90.30	13.80	51.30
10% Eud. RS 100	44.17	109.65	16.54	61.01
20% Eud. RS 100	33.14	82.72	12.41	45.77
5% Eud. RL 100	**45.99**	**121.10**	**17.14**	**63.52**
10% Eud. RL 100	28.05	73.74	10.53	38.74
20% Eud. RL 100	43.71	110.78	16.31	60.37
3.5 % Succinic	21.73	53.70	8.11	30.01
7 % Succinic	**73.32**	**181.63**	**27.32**	**101.32**

Effect of secondary polymer or cross-linker on testosterone flux, release rate constant, diffusion coefficient, and permeability coefficient from film-type TDDS containing 1% w/w Span 85 using a biological membrane.

RL/Eudragit-RS. Pentazocin release was increased on increasing the Eudragit-RS increment.[23]

Using the more hydrophobic Eudragit RS-100 also allowed a lower enhancement in testosterone release (Figure 1). After 4 hrs, the cumulative testosterone released was 164.1, 231.5, 173.2, and 54.8 $\mu g/cm^2$ for patches containing 5%, 10%, and 20% w/w Eudragit RS-100 and plain patches, respectively. This release pattern could be attributed to a higher matrix structure disturbance imparted by the higher secondary polymer concentration.[20] The incorporation of 20% w/w Eudragit-RS resulted in a release pattern close to that obtained with the 5% w/w concentration. Despite the expected higher matrix structure disturbance on using 20% w/w Eudragit-RS, the relatively high lipophilicity of Eudragit-RS might have increased testosterone affinity to the matrix. The outcome of both effects resulted in a moderate drug release.

Calculating the release parameters of testosterone from the tested patches shows that the maximum flux (45.99 $\mu g/cm^2/hr$) was obtained from TDDS containing 5% w/w Eudragit RL-100 compared with 15.83 $\mu g/cm^2$ for plain TDDS (Table 2). Such a flux allows a daily output of 31 mg from the prepared patches (28-cm^2 area). For the patches containing Eudragit-RS, the highest flux was obtained with 10% w/w polymer concentration.

Drug release constant of testosterone from the tested TDDS ranged from 36.55 to 121.1 $\mu g/cm^2/hr^{1/2}$ for plain patches and those containing 5% w/w Eudragit RL-100, respectively. Also, the highest diffusion coefficient (17.14 X 10^{-10} cm^2/sec) and the permeability coefficient (63.52 X 10^{-8} cm/sec) were observed with the 5% w/w Eudragit RL-100 concentration (Table 2).

On the other hand, the marketed non-scrotal Testoderm TDDS® contains 328 mg of testosterone, allowing for a daily output of only 5 mg of drug through the 60-cm^2 area of the patch.[24] Comparing this output with our Eudragit E-100 patches shows that the same daily testosterone output can be achieved using a smaller patch area (down to 5 cm^2), allowing for much better patient compliance. The 5-mg/day testosterone output can also be obtained from Eudragit E-100 patches by reducing drug load (to about 20 mg/patch) and keeping the same patch area (28 cm^2), which is still smaller than that of Testoderm TDDS.

Effect of Cross-Linker Concentration

The incorporation of cross-linkers in Eudragit matrix is one of the methods used to modulate drug release from the prepared patches.[20] In a previous work, succinic acid was found to have a good influence on the mechanical properties, adhesiveness, and tack of casted Eudragit E-100 films.[21]

The incorporation of 3.5% w/w succinic acid increased ex vivo testosterone release from the prepared TDDS (Figure 2). The ex vivo drug release from the cross-linked films was much higher than the plain ones reaching 294 $\mu g/cm^2$ after 3 hrs. This increase in the release of testosterone on using succinic acid cross-linker can be attributed to the change in matrix properties and hence drug diffusivity and thermodynamic activity within the new cross-linked matrix.

Kanikkannan et al used succinic acid as a cross-linker in the manufacture of melatonin patches based on Eudragit E-100.[19] The optimized patch composition was found to be the one containing 3.7% w/w succinic acid based on dry polymer weight.

Calculating the release parameters of testosterone from the tested patches revealed that the release parameters were strongly influenced by the use of succinic acid cross-linker showing about a 4.5-fold increase in drug flux from plain TDDS on using 7% w/w succinic acid (Table 3). The maximum release rate constant (181.63 $\mu g/cm^2/hr^{1/2}$) was obtained with TDDS containing 7% w/w succinic acid compared with 36.55 $\mu g/cm^2/hr^{1/2}$ for plain patches. Using 3.5 % w/w succinic acid also improved both drug permeability and diffusion coefficients. Both coefficients were increased by about 5-fold upon the incorporation of 7% w/w succinic acid.

Based on the obtained data, a daily 5-mg

output of testosterone (the same as that obtained from the marketed Testoderm TDDS) can be obtained from only 3 cm^2 of our prepared patch containing 100 mg of testosterone, 1% w/w Span 85, and 7% w/w succinic acid cross-linker. Such a tiny patch may be more appropriate to use than the 60-cm^2 Testoderm TDDS already on the market.

Using spray formulations of testosterone in a series of ethanol/PG/water systems, Leichtnam et al obtained a maximum drug flux of 1.7 µg/cm^2/hr through hairless rat skin.[25] They concluded that the obtained testosterone fluxes were 5- to 10-fold lower than those required for a useful transdermal therapy.

Comparing the obtained testosterone fluxes and according to Leichtnam's conclusion, the prepared patches lie within the range of a successful transdermal therapy.

In Vivo Drug Release

The prepared TDDS showing the highest ex vivo drug release namely, TDDS containing 5% w/w Eudragit RL-100 as a secondary polymer and TDDS containing 7% w/w succinic acid as a cross-linker, were chosen for in vivo testing in rats.

The average plasma level of testosterone in six rats after the application of TDDS containing 5% w/w Eudragit RL-100 for 48 hrs shows that the plasma testosterone concentration increases with time till reaching its peak (468.8 ng/dl) within 6 hrs of application (Figure 3). After 24 hrs of patch application, testosterone concentration was decreased but still higher than the initial level. This indicates that the rate of drug release from the patch and its transdermal absorption are higher than the elimination and biotransformation rates of testosterone during the first 6 hrs. Afterward, the rate of drug release starts to decrease, causing a reduction in the plasma level of testosterone due to drug elimination.

In case of TDDS containing 7% w/w succinic acid, the increase in plasma levels of testosterone was slower than that observed with Eudragit RL-100 but reached its peak (810.7 ng/dl) after 24 hrs of patch application (Figure 3). More than 30% of the tested rats showed plasma levels of more than 1400 ng/dl after 24 hrs of application.

Monitoring testosterone levels after 48 hrs showed a reduction of testosterone concentration back to its initial value for both TDDS (Figure 3).

According to Cutter, the goal of replacement therapy is to maintain a testosterone level within a therapeutic window of 300 to 1200 ng/dl (preferably in the middle of that range).[6] Applying this rule to the obtained data shows that TDDS containing 5% w/w Eudragit E-100 maintained testosterone level within this window after 4 till 19 hrs of patch application. Whereas TDDS containing 7% w/w succinic acid was able to maintain this requirement after about 8 hrs and lasted to 45 hrs of patch application.

Calculating the pharmacokinetic parameters area of the tested TDDS show that TDDS containing 7% w/w succinic acid had almost double the value of both AUC and C_{max} compared with that of TDDS containing 5% w/w Eudragit RL-100. These results indicate that TDDS containing 7% w/w succinic acid provide a higher bioavailability of transdermal testosterone than those containing 5% w/w Eudragit RL-100 (Table 3).

Ameye et al stated that a successful testosterone replacement formulation should sustain the 3-ng/ml plasma testosterone target concentration during the longest period of time.[15] In the case of TDDS containing 5% w/w Eudragit RL-100, the 3-ng/ml concentration was maintained over 15 hrs, while the same concentration was maintained over 33 hrs for TDDS containing 7% w/w succinic acid (Table 3).

Ideally, androgen replacement therapy for hypogonadal men should deliver the native hormone, testosterone, in amounts that fall within the normal range of endogenous production (3 to 10 mg/24 hrs).[27] Another feature for a successful androgen replacement is to mimic the circadian profiles of healthy young men. Such profiles are characterized by maximum levels of approximately 720 ng/dl in the morning (~ 8.00 hrs) and minimum levels of approximately 439 ng/dl occurring at night (~ 22.00 hrs).[26]

From our obtained data and this circadian testosterone levels, TDDS containing 5% w/w Eudragit RL-100 would be best applied at night to give high testosterone levels by the morning, thus mimicking the normal testosterone production. Whereas TDDS containing 7% w/w succinic acid would be best applied in the morning, giving its maximum drug release after 24 hrs, ie, in the next morning.

Mazer et al showed that the night application of two patches (for 24 hrs) could deliver 4 to 7 mg of testosterone per day.[27] Using this concept of two patch applications per day, the use of a "night" patch of those containing 5% w/w Eudragit RL-100 and a "morning" one of those containing 7% w/w succinic acid may provide the exact circadian testosterone levels.

Applying the one-way ANOVA showed that the increase in testosterone serum levels is quite significant, especially after 6 and 24 hrs of patch application (with a p value of 0.02 and F value of 4.01).

TABLE 3

TDDS	T_{max} (hr)	$C_{max} \pm SD$ ($ng.dl^{-1}$)	AUC_{0-48} ($ng.hr.dl^{-1}$)	$*T_{>3\ ng/dl}$ (hr)
5% w/w Eudragit RL-100	6	468.8 ± 22.1	46.27	15
7% w/w Succinic acid	24	810.7 ± 82.4	97.96	33

*** Time of keeping testosterone levels above 3 ng/dl.**

Pharmacokinetic parameters of different testosterone TDDS.

CONCLUSION

Testosterone release from monolithic TDDS based on Eudragit E-100 polymers could be modulated by the use of either secondary polymers or cross-linkers. The highest ex vivo release parameters were obtained with 5% w/w Eudragit RL-100 as a secondary polymer and 7% w/w succinic acid as a cross-linker. For testosterone replacement in testosterone-deficient males, the optimal level of testosterone should be within a therapeutic window of 300 to 1200 ng/dl. In all the tested TDDS, testosterone level was

maintained within this range over periods ranging from 15 hrs for TDDS containing 5% w/w Eudragit RL-100 to more than 33 hrs for those containing 7% w/w succinic acid. Rapidly elevated testosterone levels could be obtained using TDDS containing 5% w/w Eudragit RL-100, whereas more delayed ones could be obtained using those containing 7% w/w succinic acid. This difference in testosterone release may be favorable in mimicking the circadian testosterone release using the two-patches-per-day concept.

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BIOGRAPHIES

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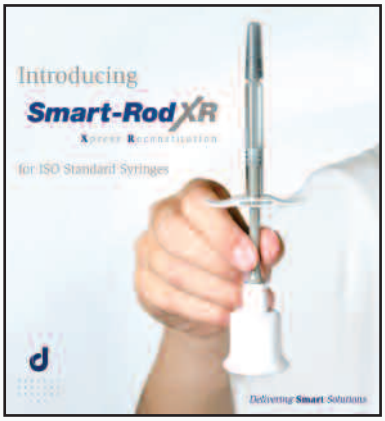

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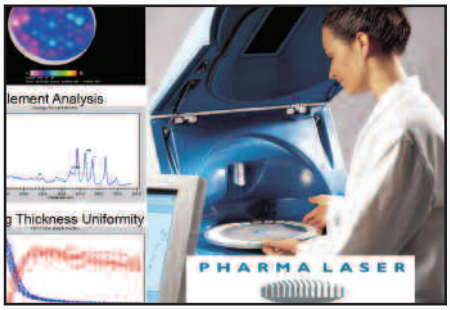

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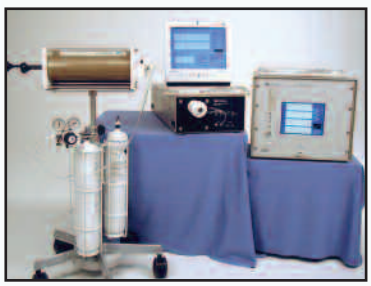
An 8-page, 4-color brochure describing Baxter's cytotoxic manufacturing facility in Halle, Germany, is available from Baxter Healthcare Corporation's BioPharma Solutions business. The brochure includes information about cytotoxic contract manufacturing using barrier isolator technology and describes services, such as lyophilization, liquid vial filling, dry powder filling, and sterile crystallization. The facility manufactures for distribution to global markets, including the United States, Europe, and Japan. BioPharma Solutions provides integrated, state-of-the-art resources dedicated exclusively to cytotoxic and high potency product manufacturing to help ensure your molecule moves smoothly from development through commercial manufacturing. For more information, contact Baxter at (800) 422-9837; e-mail at onebaxter@baxter.com; or visit **www.baxterbiopharmasolutions.com.**

Respiratory Simulators



Hans Rudolph, inc. (makers of respiratory products since 1938) manufactures three Lung Simulators. The DLco Simulator with EasyLab QC™ Software is used by pulmonary labs performing drug studies. This patented device & software allow the quality control & testing of the respiratory devices that measure the diffusion lung capacity of patients during drug delivery trials and specifically the new non-invasive inhaled insulin technologies now available. Also available is a Flow/Volume Simulator for R&D, testing, and calibrations on aerosol devices, peak flow meters, spirometers, and other devices requiring the generation of the ATS and custom breathing waveforms. A spontaneously breathing lung model - the Breathing Simulator - is made for R&D, testing, training, and calibration of ventilators, CPAP blower devices, and other respiratory therapy devices. Demonstrations available at Hans Rudolph's booth # 1713 - ATS (American Thoracic Society) Show in San Francisco this May 20-22, 2007. Contact Hans Rudolph at (800) 456-6695 or (816) 363-5522; email: hri@rudolphkc.com; or visit **www.rudolphkc.com.**

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Next Breath is a contract services provider for pharmaceutical, biotech, and medical device companies that bring new inhalation and nasal products to market. We provide an array of in vitro services, from preclinical formulation development to analytical testing in support of submissions to regulatory agencies. The company's mission is to serve as an effective liaison between innovators of promising drug molecules and inventors of pulmonary and nasal drug delivery devices. Next Breath can test that drug/device combination under conditions satisfactory to regulatory agencies, while helping to ensure the end product is acceptable to patients and clinicians. For more information, contact Next Breath LLC at (410) 455-5904 or visit **www.nextbreath.net.**

SPECIALTY PHARMA
Strategies For Business Development

Formulation Development

Assessing Formulation Development in Specialty Pharma

By: **Cindy H. Dubin**,
Contributor

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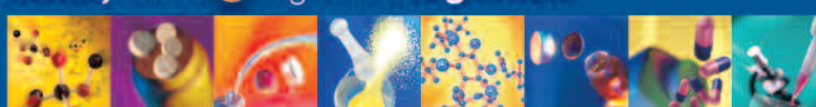

Introduction

Outsourcing formulation development is not as common as other process steps, such as manufacturing. But outsource providers that offer formulation development have evolved from just an "extra pair of hands" into strategic business partners. Outsource providers are being sought to solve specific formulation problems, offer innovative formulation technologies, or perform specific formulation work on a case-by-case basis.

Specialty Pharma magazine asked some of today's leading formulation development providers how and why specialty firms should work with them.

Q: Under what circumstances (ie, financial, lack of expertise, etc.) would it be ideal for companies to outsource their formulation development projects?

Mr. Guthrie: In today's ever evolving world of drug development, almost any project has the opportunity to be outsourced. Reflective of that is the number of virtual type drug development groups in our world today. The evolution of the CRO throughout the past 20 years has been remarkable. The "real world" experience and expertise found in most CROs today mostly resided within the pharmaceutical companies themselves back then. At that time, most outsourcing was done as a simple fee-for-service model and dictated by overflow needs. In today's development, outsourcing needs can range from lack of expertise, accelerating development, or allowing a company to focus on core competencies. While fee-for-service models still exist, more and more "relationships models" are proving successful.

Mr. Meeks: The primary considerations are expertise, facilities, and timelines. This means expertise in the particular formulation dosage form, cGMP facilities to perform the work, and the ability to meet or exceed timelines.

Mr. Salus: New or unfamiliar formulation approaches to the product they are developing. Many times, a company has a particular approach on how they begin a development process (ie, blend and compress, high shear granulation/fluid bed dry/compress, etc.). This may be dictated by the equipment in which they have invested at their commercial production facilities. Companies should look for outsourcing companies with strengths in a particular area. Companies should also consider outsourcing when they have more active development projects than internal resources to get it done. This might help them reach their corporate objectives sooner.

Mr. Iacobucci: Companies should consider outsourcing formulation development under a variety of circumstances. If the internal development staff is busy with other projects, outsourcing can be used to augment internal capacity or to avoid delays in getting products to market. Outsourcing can also help if the company needs development from a partner with a specific area of expertise. For example, at DPT, we focus on semi-solid and liquid dosage forms. These types of formulae can be complex, and we have incorporated virtually every API you can think of (including biopharmaceuticals) into these formats. The benefit to our clients is that they can leverage our experience and avoid having to reinvent the wheel in formulating their product.

Dr. Santillo: The decision to outsource formulation development is a dynamic decision, and every opportunity should be evaluated on its own merits. However, with this in mind, there are still only a limited number of primary drivers to outsourced development work, and firms should be clear about the reason in which they are engaging development partners. The primary reasons companies should choose to outsource are: 1) The organization lacks the internal infrastructure, procedures, and/or expertise to produce development activities and documentation that will meet the expectations of federal regulators; 2) The organization does not have the internal capabilities, from a technology perspective, to accomplish the work that is needed to be performed and the firm either lacks the ability or desire to add the technology within the required timeframe to produce tangible results; 3) The organization may have the capability but not the capacity to deliver the research outcomes in the required timeframe and is therefore looking for development partners that can deliver the research effort in the required timeframe; and 4) The organization may have the capability

and the capacity; however, it may choose to outsource the development work if it is deemed non-core to their business. For instance, it may not be desired to dilute research efforts for drug development, discovery, regulatory, and quality in developing and producing clinical supplies products.

Q: How much should the scope of the formulation development project dictate to whom to outsource?

Mr. Guthrie: I would have to say that matching the scope to the provider is an essential component to success. Truly understanding the capabilities and available resources at the CRO and how that aligns with your project has to be part of the due diligence process. Understanding their commitment to your project as well as their business strategy can provide immense insight as to how your project might succeed or fail in their hands. Often, a "one-on-one" with senior management at the CRO can provide the answers.

Mr. Meeks: It is very important to choose a contract organization that can deliver on all aspects of the project in order to maximize the success. The field of pharmaceutical sciences is broad, and not many companies have the breadth and depth of talent internally coupled with equipment/instrumentation to deliver on all dosage forms.

Mr. Iacobucci: If a company needs help in a specific area, especially if it is complex, it is probably better to outsource to a company that specializes in that area. However, outsourcing to a larger company with a wide range of expertise is beneficial because it limits the number of partners you have to deal with. In any event, it's important to choose a company that has technical expertise and proven success in a specific dosage form and that can deliver on time and on budget.

Mr. Salus: The scope of the work should strongly dictate where a project is placed. A company should not risk the likelihood of success of a product by placing the development at an outsourcing company with little experience to the approach. The major risk would be time lost in a development success, while the outsourcing company struggles through implementing a new production technique.

Mr. Morris: Given the fundamental relationship that exists between scope, timing, and resources (people and money); scope should always be a significant consideration in selecting an outsourcing partner. However, it should not be the sole basis. It is important to know why you are outsourcing and what specific objectives you have so that you can select the most capable vendor for delivering the research outcomes that are most important to you. For instance, if you have time-sensitive research work that is clearly defined, an organization may be better served finding a partner who has demonstrated capabilities, and equally important, has a proven track-record for on-time delivery.

Mr. King: The company must make sure its contract service provider has sufficient experience with the type of formulation and dosage form, can handle the scale-up as required (and has various equipment to do so), and has the full range of support services required to handle the scope of work for development. I believe quality, financial stability, and a proven track-record for delivering a quality dosage form on time are as important as the scope of work. Chemistry and agreement amongst senior management at both companies are other key factors. Any company can deal with a project without problems; the strength of a company is when issues occur and solutions are offered.

Q: From a Specialty Pharma perspective, does it make sense to outsource formulation development to a niche CRO or a more largely focused CRO?

Mr. Salus: For any pharmaceutical company, they should be attempting to work with an outsourcing company that will provide them strong science and/or expertise around the development approach. One might say they should be looking for a company with a depth of knowledge in a particular area versus a breath of services. Obviously, the outsourcing company should have the necessary support skills (ie, analytical testing, good quality systems, etc.) required to complete a development project. A pharma company can always tech transfer the development project to a

larger contract manufacturer as its product progresses toward commercialization.

Mr. Guthrie: Both types of CROs certainly have advantages and disadvantages. While the largely focused CROs might be able to provide a wide array of services across the drug development continuum, unfortunately, the area of need may not play to their strengths. Their ability to possibly provide "one stop shopping" for a variety of development programs is certainly an advantage but also usually means they may not be able to offer a specialized approach. A personal example that might place it in perspective is if you were looking for a very special item for your home, you might give consideration to some of the large "chain" suppliers. While I'm certain that you would find suitable items that might fill the need, I'm guessing that they would also be standard stock. To truly find something unique or different, you would almost certainly go to a small niche provider that could offer a "customized" approach to satisfy your need. In utilizing a niche provider, you get a custom approach and are rarely lost in the shuffle. You are playing to their strengths, provided you have done your homework. Again, the tradeoff is usually that there is not a broad spectrum of other development offerings within the niche provider.

Mr. King: It makes sense to find a partner that has the expertise, manpower, and resources to do the work. You need to work with a partner that will not over-promise and under-deliver, but will instead listen to your needs, assess the full scope of the program, and then be honest in establishing milestones and project timelines. Specialty Pharma is typically seeking a partner that can help offer solutions, not just do the tasks assigned. They should focus on service providers that have formulation expertise with a broad range of compounds and dosage forms. Financial stability and turnover of personnel are key as well. If you are going to outsource a long-term project, you want to make sure your provider and its team of resources are going to still be there in 2 to 3 years, and that the provider is continuing to reinvest in new facilities and its people.

Mr. Iacobucci: By historical convention, Specialty Pharma companies have commonly outsourced formulations to CROs. Later, they would have to find a CMO to launch the product. Today, the concept of a CDMO (Contract Development & Manufacturing Organization) is emerging. Such organizations (DPT is one example) have comprehensive services from preformulation through clinical and commercial manufacturing. Tying world-class development together with broad commercial manufacturing capability is the key. The benefits are obvious: smoother transition from development to launch, one point of contact through the entire development process, and decreased regulatory complexity to name just three.

Mr. Meeks: It all depends on the people at the CRO, their education and experience, equipment and instrumentation, and timing. Both a niche or a more largely focused CRO could deliver if they have the appropriate mix of the aspects previously described.

Mr. Morris: Amongst several important components, one of the keys to successful outsourcing can always be tied to integration. If you are attempting to augment only a small portion of your development chain for a given contract opportunity, then a niche CRO may be the best choice because they have a tendency to be more flexible, and their work flow is not impacted by other internal work centers. On the other hand, if you have multiple disparate activities that need to be outsourced for a single project, then you may be best served by attempting to find a business partner that can offer the broadest set of services. Organizations that are largely focused have a tendency to be able to more effectively and efficiently integrate the service offerings, and it will reduce the number of hand-offs required between development partners.

Q: What is the one mistake Specialty Pharma companies must avoid (or the most important tip you can offer to a Specialty Pharma) when outsourcing formulation development?

Mr. Meeks: Technical expertise of the people coupled with quality systems and their ability to commit and deliver usually trumps all other aspects in decision-making processes.

Mr. Guthrie: Although it might seem like a cliché, but lack of communication is always one of the major pitfalls. So often,

projects are outsourced, and unfortunately, the perception of ownership may not go along with it. Many companies forget they are truly the expert on the chemistry and knowledge of the clinical trial design and must spend the time to educate the CRO and keep them up to date on changes. In my experience, a great relationship is one in which the CRO is perceived as a partner rather than just a set of hands. An example comes to mind, when a Specialty Pharma group manager took the time to address his team at the CRO on the progress of the drug development, including clinical results that they were achieving. It was amazing the attitude that chemists on the bench took thereafter when added effort was required. The communication process put "true meaning" in their work, far more than just relating to another development number.

Mr. King: Be realistic in establishing deliverables and timelines, consider all tasks and deliverables from both sides, and set targets that can be achieved. With that said, do not be afraid of challenging timelines if you can assume more risk.

Mr. Iacobucci: Ingredients, ingredients, ingredients. On several occasions, projects have been brought to us in late-stage development with formulae containing basic ingredients that were noncompendial. This sometimes happens because the original formulator used ingredients available in the laboratory without regard to commercial viability. I have seen this result in non-approvals, as well as the need to do significant reformulation and bridging studies to resolve. This obviously results in significant delays in launch. At DPT, we addressed this issue long ago by always creating formulae with the commercial product in mind.

Dr. Santillo: The best tip that can be offered up is to ensure that you know what you want and ensure the development firm thoroughly understands what they are to deliver. In developing partnerships, the first initiative can be somewhat trying in that you both will learn a lot about each other. The more frequent and concise the initial communications, the faster you will work through this learning process. Additionally, always ensure you are contracting for research outcomes, not effort. The wording within contracts may be subtly different for this approach; however, the clarity of the end point is not.

Mr. Salus: Consider outsourcing as a relationship and understand that it takes some time to get to know each other. Maintain open communication and don't make the assumption that each company knows what the other wants, needs, or is thinking. As the relationship begins to mature, many of the frustrating problems experienced early in the relationship will go away. Invest in working together with the expectation that it is going to be a long-term relationship. ■

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Thomas Salus

Director, Business Development
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Frank Santillo, PhD

Senior Director, Research Services
Bilcare, Inc.

Executive Summary

Rodney Lappe, PhD
Chief Scientific Officer
CovX

CovX: Leveraging the Best From Peptides & Antibodies

By: Cindy H. Dubin, Contributor

CovX was founded in 2002 based on the research of Carlos Barbas, PhD, and Richard Lerner, MD, at The Scripps Research Institute. Since its founding, CovX has built a portfolio of product candidates using proprietary technology to discover and develop long-acting biological therapies. The CovX technology unites the therapeutic attractiveness of peptides with the beneficial properties of antibodies, resulting in a new biopharmaceutical called a CovX-Body™.

According to Rodney Lappe, PhD, Chief Scientific Officer at CovX, CovX-Bodies are created by covalently fusing a pharmacophore via proprietary linkers to the binding site of a specially designed antibody, effectively reprogramming the antibody. The result is a new class of chemical entities that is formed in which each component contributes desirable traits to the intact CovX-Body. The company has demonstrated the utility of its technology by enhancing the pharmacokinetic and pharmacodynamic profiles of peptides across several disease areas. CovX is focused on oncology and metabolic diseases; its lead program, CVX-045, is currently in Phase I based on an IND approval in January 2007.

Q: ***What makes CovX attractive as a partner or one in which to invest?***

A: In addition to drug candidates, CovX is attractive because of the power and flexibility of our technology and the quality and experience of our management team. We are a drug discovery and development company focused on creating long-acting therapeutics. Peptide drugs are very potent, but are rapidly broken down in the body, requiring frequent injections. Antibodies, on the other hand, have far superior pharmacokinetics, but can have long and complicated development cycles. We leverage the best properties from both peptides and antibodies to form CovX-Bodies.

We create CovX-Bodies using technology that was exclusively licensed from The Scripps Research Institute. The technology enables us to create new, long-acting biopharmaceuticals by chemically fusing peptides that display a proprietary linker to our specially designed antibody. With the CovX technology, peptides are able to be linked at various points throughout their sequence and efficiently attached to the carrier scaffold, providing exquisite optimization of potency and pharmacokinetics. The resulting CovX-Body is a well-characterized, long-acting biopharmaceutical with the biological activity of the peptide and the pharmacokinetics of the antibody. For example, by "walking" the linker across the peptide, we have been able to use its fusion scaffold to create a GLP-1 mimetic CovX-Body, which demonstrates an intravenous half-life in rodents over three times longer (66 hrs) than any published data of other scaffolds, while maintaining potency and high bioavailablity.

Q: ***How do you define your ideal partner?***

A: We are looking to form strategic relationships with companies that can appreciate the benefits of the CovX-Body technology to enhance their own pipelines. We are interested in forming collaborations with companies that have compelling targets or peptides that CovX's technology can convert into best-in-class biotherapeutics.

Additionally, we are rapidly progressing our own programs, which are focused in oncology and metabolic disease, and we will explore partnerships to advance our internal candidates through clinical development and commercialization. These alliances allow us to continue to focus on creating and developing new drugs.

Q: ***What is the CovX business model? How well is it working, and what might you improve?***

A: Our approach to building the company is very deliberate. First, before doing any lab work, we meticulously evaluate target opportunities, carefully selecting those that best address technical success, medical need, and commercial potential. We repeat this process on a regular basis to make certain our portfolio focuses on the best ideas. Second, we attract an accomplished leadership team experienced in bringing molecules from the bench to commercialization. Finally, we work hard to create and maintain a culture conducive to innovation and achievement while having fun.

Thus far, the model has worked exceptionally well. We now have a robust portfolio of projects that is churning out development candidates at a consistent pace. CovX has a distinct combination of attributes: experienced and passionate people, stable financing, and a highly collaborative corporate culture. It is not often that you find all of these characteristics under one roof. We pride ourselves on the CovX culture.

Q: ***What strategies are you taking to improve your pipeline?***

A: We repeat the portfolio evaluation process that I described every 18 months to ensure that our projects and drug candidates still meet our criteria. This continuous process allows us to identify attractive new targets as we evaluate the continued utility of the existing candidates. We also have the capability to screen and identify peptides to various targets, allowing us to rapidly identify a pharmacophore and create a CovX-Body with optimal characteristics. In these ways, we are able to ensure that we are at the forefront of the industry in terms of candidates in development and to maintain a rich and sustainable pipeline.

Q: ***What drugs do you have in development, and what are their market potential? Therapeutic focus?***

A: Inhibiting angiogenesis has proven to be an important family of mechanisms in the treatment of patients with advanced cancer. Unfortunately, despite recent advances, there is still a significant need for new drugs with novel mechanisms of action. CovX's initial product candidates are focused on novel pathways with the potential to be used in all lines of therapy, including combination therapy with other anti-angiogenics. Our most advanced molecule, CVX-045, is a thrombospondin mimetic that stimulates an angiogenesis suppressor that is critical for inhibiting the growth of new blood vessels in tumors. In animal models, we have seen outstanding results on tumor growth and viability. We began a Phase I clinical trial earlier this year. Our second candidate, CVX-060, is also an inhibitor of angiogenesis, although it has a completely different, but possibly synergistic, mechanism of action. In our tumor models, it is producing results comparable to Avastin as a single agent in addition to significant efficacy in combination with traditional cytotoxic and molecularly targeting agents. It is currently in IND-enabling studies.

Another area of focus for CovX is metabolic diseases. We declared our first candidate in this area, CVX-096, which is a long-acting GLP-1 mimetic with unsurpassed pharmacokinetics, excellent subcutaneous bioavailability, and high potency. The compound should enter clinical trials in the second quarter of 2008.

Oncology and metabolic disease are large markets. We purposefully chose to focus in areas with high unmet medical needs and large commercial potential.

Q: ***What are the long-term goals for the company/ultimate objectives?***

A: In the long-term, we see CovX developing into a highly efficient R&D engine that will continuously generate a portfolio of products for clinical development. Initially, we have deliberately chosen to focus CovX in the oncology and metabolic disease markets out of the numerous therapeutic opportunities applicable to the technology. We have the resources and expertise in house to efficiently advance our candidates through clinical proof-of-concept testing and beyond. However, we are always interested in the possibility of forming long-term partnerships and strategic alliances for late-stage development and commercialization.

We realize the broad applicability of the CovX technology is a tremendous asset and is one that needs to be handled very thoughtfully. We are exploring mutually beneficial relationships to develop CovX-Bodies in therapeutic areas outside of CovX's initial focus.

Q: ***What is the one mistake you must avoid going forward?***

A: As we progress, we cannot lose sight of the three pillars that have allowed us to be successful: advancing the CovX-Body technology, selecting our targets wisely, and creating a work environment that attracts the best talent and allows that talent to thrive each and every day.

Q: ***What do you believe will spur or stifle the Specialty Pharma industry?***

A: The Specialty Pharma industry will thrive as long as it can deliver therapeutics that have an impact on the health of patients. For CovX, this means making sure that we continue to develop best-in-class therapeutics based on our technology. We are well on our way to accomplishing this objective.

Q: ***What keeps you up at night?***

A: The ability to "focus" is probably one of the most critical, and difficult, aspects to maintaining momentum within a company. For CovX, focus is crucial because our technology is so broadly applicable. The ability to define a strategy and then execute on the plan when there are so many attractive alternatives can be difficult and requires diligent management. At CovX, we have chosen to focus on oncology and metabolic diseases, despite knowing that we can go in other directions with our technology. ■

Licensing Strategies

Specialty Pharma: Business Development & Licensing Strategies

By: Barath Shankar, Research Analyst,
Pharmaceuticals & Biotechnology, Frost & Sullivan

Introduction

Specialty Pharmaceutical companies focus on different stages and aspects of drug development and marketing in addition to partnering with large pharmaceutical companies in the life cycle management of their products. The areas of expertise for these companies include drug delivery, clinical development, generic drugs, and sales and marketing. Specialty Pharmaceutical companies typically focus on one or two of these areas, leveraging their expertise and positioning themselves in a niche pharmaceutical market.

Business Models

The business models of Specialty Pharmaceutical companies can be broadly classified into the following four types:

- Strategy 1: Acquire low-sales-generating inline branded products and market them.
- Strategy 2: In-license and develop the market for products.
- Strategy 3: Develop drug delivery technologies for existing and new products.
- Strategy 4: Develop and market generic pharmaceuticals.

Most Specialty Pharmaceutical companies adopt a mix of these business development strategies in a specific field, or a range of related therapeutic areas, and have portfolios that consist of a range of products that have revenues of a few hundred million dollars a year. Core R&D, which begins from screening and preclinical trials, is an expensive and challenging area and is typically carried out by universities, start-up companies, as well as large pharmaceutical and biotechnology companies, which are a partner of choice for Specialty Pharmaceutical companies. By limiting the therapeutic area of focus, Specialty Pharmaceutical companies are able to develop

Table 1. Top Specialty Pharmaceutical Companies: Business Model Adoption (US), 2005-2006.

Company	Model 1	Model 2	Model 3	Model 4
Teva Pharmaceutical Industries Ltd.	Medium	Medium	Low	High
Forest Laboratories Inc	High	High	Low	Low
Allergan Inc	Low	High	Medium	Low
Watson Pharmaceuticals Inc	High	High	Low	High
King Pharmaceuticals Inc		High	High	High Low
Barr Laboratories Inc	Low	High	Medium	High
Cephalon Inc	Medium	Medium	Low	Low
Endo Pharmaceuticals	Low	Medium	Medium	Medium

Key:
Model 1: Acquire "low sales generating" inline branded products and market them
Model 2: In-license and develop the market for products
Model 3: Develop drug delivery technologies for existing and new products
Model 4: Develop and market generic pharmaceuticals

Source: Frost & Sullivan

specialized sales and marketing forces as well as minimize expenditures. Specialty Pharmaceutical companies also focus on generics to a large extent, as this is a lucrative low-margin, high-volume business that suits the companies' broad-level strategy and often complements their therapeutic areas of focus.

Licensing Strategies

Traditionally, Specialty Pharma companies have partnered successfully with Big Pharma companies to acquire/in-license late-stage product candidates with limited market potential, while Big Pharma tends to focus on larger therapeutic areas with multi-billion dollar revenue potential. Several large mergers and acquisitions amongst Big Pharma have also resulted in products being out-licensed or sold off to Specialty Pharma companies, as they did not fit into the strategic direction of the larger company.

Specialty Pharma companies adopt a combination of licensing and acquisition strategies that include single-product acquisition/licensing, franchise acquisition, or corporate acquisition. The top Specialty Pharma companies have been successful in implementing these strategies in a robust manner.

Consolidation to Continue

Big Pharma has been facing increasing pressure with thinning potential blockbuster pipelines, the pull out of several key products and falling margins. Hence, it is expected that 2007 is likely to witness significant market consolidation with several niche biotech, Specialty Pharma, and drug discovery companies likely to be acquired by Big Pharma companies.

Licensing or acquisition of product(s) involves understanding the clinical and market potential in order to have an understanding of the company's theoretical return on investment. The rapid growth of tier 1 and 2 pharmaceutical and biotech companies has resulted in increased competition from several companies targeting corporate and product acquisition. Hence, there is significant pressure on companies to pay a premium, which often results in dependence on a single product, and subsequently increased risk in the case of failure.

The mix of business models and licensing strategies adopted by Specialty Pharma companies enables them to limit clinical risk and absorb commercial risk to a greater extent. In-licensing and out-licensing are likely to remain important concepts in determining the future direction of the industry based on current trends.

Life Cycle Management & Outsourcing

As Specialty Pharma companies continue to exhibit rapid growth, they tend to compete more directly with Big Pharma companies. However, the Specialty Pharma business offers the advantage of carrying lesser risk owing to its preference for late-stage pipeline candidates.

With several major products reaching the end of their patent life recently, there is an increased interest in product life cycle management (LCM). LCM has always been a buzz word in the pharmaceutical industry, but seems to have found increasing focus amongst the Specialty Pharma group. Drug delivery technology platforms are widely used by Specialty Pharma companies for LCM of their products.

Specialty Pharma companies also work closely with contract manufacturing organizations (CMOs) and clinical research organizations (CROs) as these are two key functional areas where there is an increasing trend of outsourcing to achieve cost efficiency and quicker turnaround. There is a large complementary potential between biotechs, which are typically innovation engines, and Specialty Pharma, which focuses on sales and marketing. The combination of the two could create an integrated company that could leverage the strengths on both sides, and complement it further with outsourced activities. This could achieve critical mass at a significantly lower cost compared to the Big Pharma business model.

Conclusions

Overall, Specialty Pharma funding continues to be driven predominantly by investor interest in the robustness of the business model and the business development strategies adopted by companies. With the industry moving forward into a phase of intense competition and consolidation, we are likely to witness a more synergistic and proactive approach by Specialty Pharma companies, which is likely to augur well for the market. ■

Barath Shankar

Research Analyst, Pharmaceuticals & Biotechnology, Frost & Sullivan

Mr. Barath Shankar is a Research Analyst with the Frost & Sullivan North American Healthcare Practice. He focuses on monitoring and analyzing emerging trends, technologies, and market behavior in the pharmaceuticals and biotechnology industries in North America. Since joining Frost & Sullivan in October 2004, Mr. Shankar has completed several research studies and consulting projects on Pharmaceuticals and Biotechnology. Prior to this, Mr. Shankar was a Research & Development intern at IPCA Laboratories Ltd., Mumbai, India. He brings with him considerable analytical and quantitative experience, giving him a keen perception into the functioning of technology in the healthcare industry. Mr. Shankar has received acclaim for his research through articles and quotes published in various magazines, including Specialty Pharma and Drug Delivery Technology.

Facts & Figures

Bionumbers: Specialty Pharma Market Indices Through May 31, 2007

Index Trends

The two specialty indexes went in different directions in May. The Commercial Stage Specialty Pharma Index (CSPI) rose an additional 2% for the month and consolidated the strong gains of April. In contrast, the Emerging Stage Specialty Pharma Index (ESPI) dropped almost 4% to end up at the same level seen at the end of 2006. Both indexes through the fourth week of June though were showing a sharp drop with the CSPI still up almost 10% for the year, while the ESPI was down almost 6% for the year.

Commercial Stage Index Trends (CSPI)

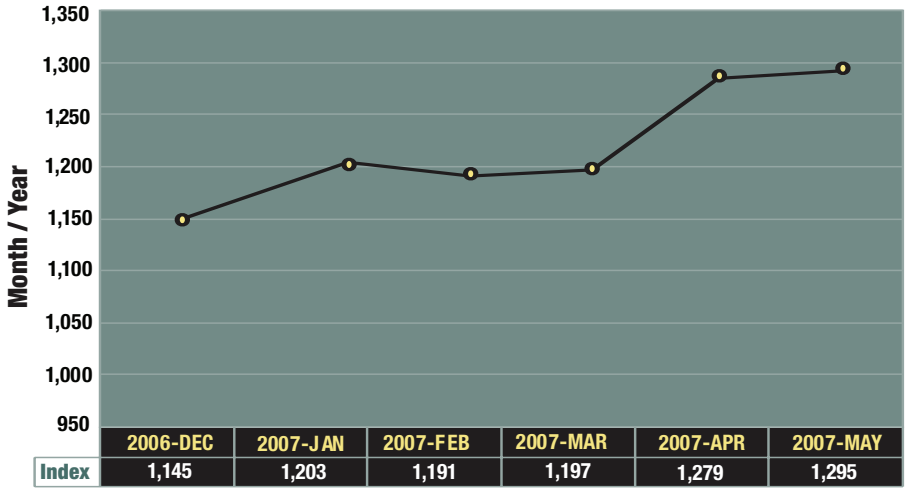
Through the end of May, the top five capitalized companies all were showing double digit gains for the year. King and Warner Chilcott were both up more than 30% for the year. The greatest gainers and laggards once again were found in the small to medium cap companies. Vivus has continued to build on its earlier gains and has almost doubled its valuation. Among the mid-sized companies, Angiotech, The Medicines Company, and Santarus are all down significantly for the year. Index market capitalization rose to almost $65 billion.

Emerging Stage Index Trends (ESPI)

The market was not kind to emerging stage companies in May as the index fell to end of 2006 levels, with things getting even uglier through the third week of June. This loss comes despite the accumulated gain provided by New River earlier in the year. All of the larger cap companies with the exception of Cadence are down for the year. On the bright side, Epicept, Antares, and Javelin were all up significantly, but unable to raise the overall index. Nektar and Penwest, two of the larger companies in the index, were down more than 20% through the end of May. Index market capitalization dropped to $5.4 billion with the earlier loss of New River to acquisition by Shire. ■

Bionumbers Commercial-Stage Specialty Pharma Index

MAY 2007



Key Figures May 2007
Index Value: 1295
Change YTD: +13.1%
Total Index Capitalization: -$64.7 Billion

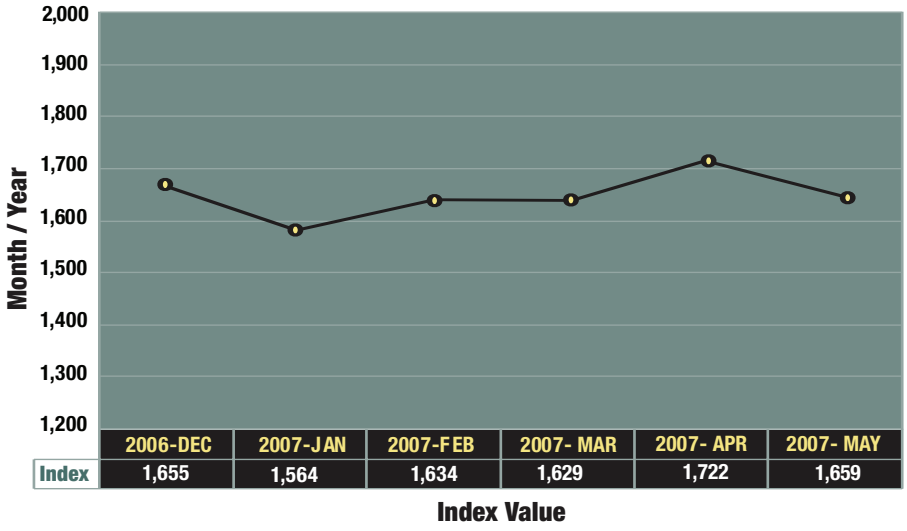
Top 5 Gainers YTD Change	
Vivus	+82%
Avanir	+75%
DepoMed	+44%
Repligen	+38%
Indevus	+38%

Top 5 Laggards YTD Change	
Questcor	-59%
Columbia Labs	-49%
Medicines Co.	-38%
Novavax	-29%
Santarus	-20%

Top 5 Capitalizations YTD Change		
Shire	$12.9 Billion	23%
Hospira	$6.2 Billion	17%
King	$5.2 Billion	34%
Endo	$4.7 Billion	27%
Warner	$4.6 Billion	31%

Bionumbers Emerging-Stage Specialty Pharma Index

MAY 2007



Key Figures May 2007
Index Value: 1659
Change YTD: +0.2%
Total Index Capitalization: $5.4 Billion

Top 5 Gainers YTD Change	
Epicept	+83%
Antares	+60%
Javelin	+40%
Spectrum	+24%
Cadence	+23%

Top 5 Laggards YTD Change	
Scolr	-52%
AP Pharma	-51%
Nektar	-24%
Penwest	-21%
NovaDel	-21%

Top 5 Capitalizations YTD Change		
Nektar	$1040 Million	+24%
Aspreva	$709 Million	-4%
Keryx	$474 Million	-18%
Cadence	$424 Million	+23%
Pain Ther.	$372 Million	-5%

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Azopharma	4	954-433-7480	www.azopharma.com
Baxter BioPharma Solutions	15	800-422-9837	www.baxterbiopharmasolutions.com
BD	2	800-225-3310	www.bdpharma.com
Catalent Pharma Solutions Formerly known as Cardinal Health Pharmaceutical Technologies and Services	85	866-720-3148	www.catalent.com
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The Curse of the Sacred Cows

By: John A. Bermingham

One of the more formidable traps that any person can fall into in their company is to not recognize who the sacred cows are, the danger they represent, and how to treat them. What is a sacred cow you may ask? A sacred cow is a person or policy that is a barrier to success that everyone knows about but no one wants to talk about or confront. Either way, be they people or policies, sacred cows are killer to a company. They keep you stuck in the mud when you are trying to make progress. They jeopardize bright competent executives. They are a common cause of failure.

Let's take the people issue because sacred cow policies and procedures are much easier to deal with. Sacred cows are generally people who lost their effectiveness years ago but are untouchable. They are people who did not grow with the company and are ineffective in their responsibilities. They keep doing the same thing over and over, each time expecting improved results.

My experience throughout the years has shown that almost every company has sacred cows in diverse areas. They are people who have ingratiated themselves with members of the Board, investors, and senior management because they are incompetent people who politic on a consistent basis due to their shortcomings. They can also be people who have been with the company for many years and are, hence, a sacred cow.

When I go into a company to turn it around, I first look at the culture and condition of the company to determine who the sacred cows are and if they can be reprogrammed or moved to a different position in which they can add value. If not, you have to begin the "turn sacred cows into hamburger" process. There are all types of sacred cows, and the following are some examples:

- The people who have their own little fiefdom and no one dares tell them that the world passed them by years ago. They tend to surround themselves with inexperienced or ineffective sacred calves that shout out accolades of the talent of the sacred cow to the Board and follow obediently in the sacred cow's hoof prints.

- The people who continue to adhere to a strategy or methodology from long ago that no longer fits the company.

- The people who are the "yes persons" of the Board or senior management.

Now for the most dangerous sacred cow: the back-channel sacred cow. Back-channel sacred cows are people who continually smile at you and tell you that they are on your team. Then when you are not around, they make negative comments behind your back or look to find ways to cause you problems. What's worse is they take information, modify it to their advantage, and then present the misinformation to the Board, investors, or senior management in a way that is of course advantageous to them and very bad for you. They take the position with the Board or senior management of, "if you really want to know the actual information, then you need me to feed it to you Mr. or Ms. Board member. The CEO is not telling you the whole story." They are very slick and convincing with the Board or management in order to strengthen their sacred cow position at your expense.

I once ran into a back-channel sacred cow. I had to quickly turn this sacred cow into hamburger due to the danger this person presented to me and the company. This person was feeding misinformation to several Board members in an attempt to bond with the Board at my expense. I quickly began developing what I refer to as a "Phoenix File." This is a file in which I place every bit of factual information that pertains to a back-channel sacred cow. E-mails, memos, letters, verbal communications transcribed to written notes, etc. Then when the file is large enough, I meet with the Board to prove that I had presented factual information, and the sacred back-channel cow had presented skewed and misleading information to them. You have to be delicate here as you are also telling the Board that they were suckered by the sacred cow. So whenever you meet a sacred cow, work quickly to turn them into hamburger. Otherwise you may be the one who is put out to pasture! ◆

BIOGRAPHY

John A. Bermingham is currently the President & CEO of Lang Holdings, Inc., an innovative leader in the social sentiment and home décor industries. He was previously the President, Chairman, and CEO of Ampad, a leading manufacturer and distributor of office products. With more than 20 years of turnaround experience, Mr. Bermingham also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona Corporation, and Rolodex Corporation. He turned around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served three 3 in the U.S. Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes, earned his BA in Business Administration from Saint Leo University, and completed the Harvard University Graduate School of Business Advanced Management Program.

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