Drug Delivery Technology®

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Reviewing Colon-Specific Delivery

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

IN THIS ISSUE

INTERVIEW WITH PALATIN TECHNOLOGIES' VP & CTO
SHUBH SHARMA, PHD

Market Evolution 20
Howard S. Wachtler

Particle-Mediated Epidermal Delivery 30
John Beadle, MD, MBA

21st Century pMDIs & DPIs 32
Georgina Fradley

Long-Acting Injection Formulations 36
Roger G. Harrison, PhD

Sweat Gland Delivery 42
Wei Chen, PhD

Buccal Adhesive Systems 51
A.K. Bandyopadhyay, PhD

Clifford M. Davidson, Esq.
Are Inventions Based on Discoveries of Natural Phenomena Patentable?

Mr. Girish Patel
Oral Colon-Specific Drug Delivery: An Overview

Miles Hutchings, PhD
Accelerating Drug Delivery Solutions With Polymer & Analytical Expertise

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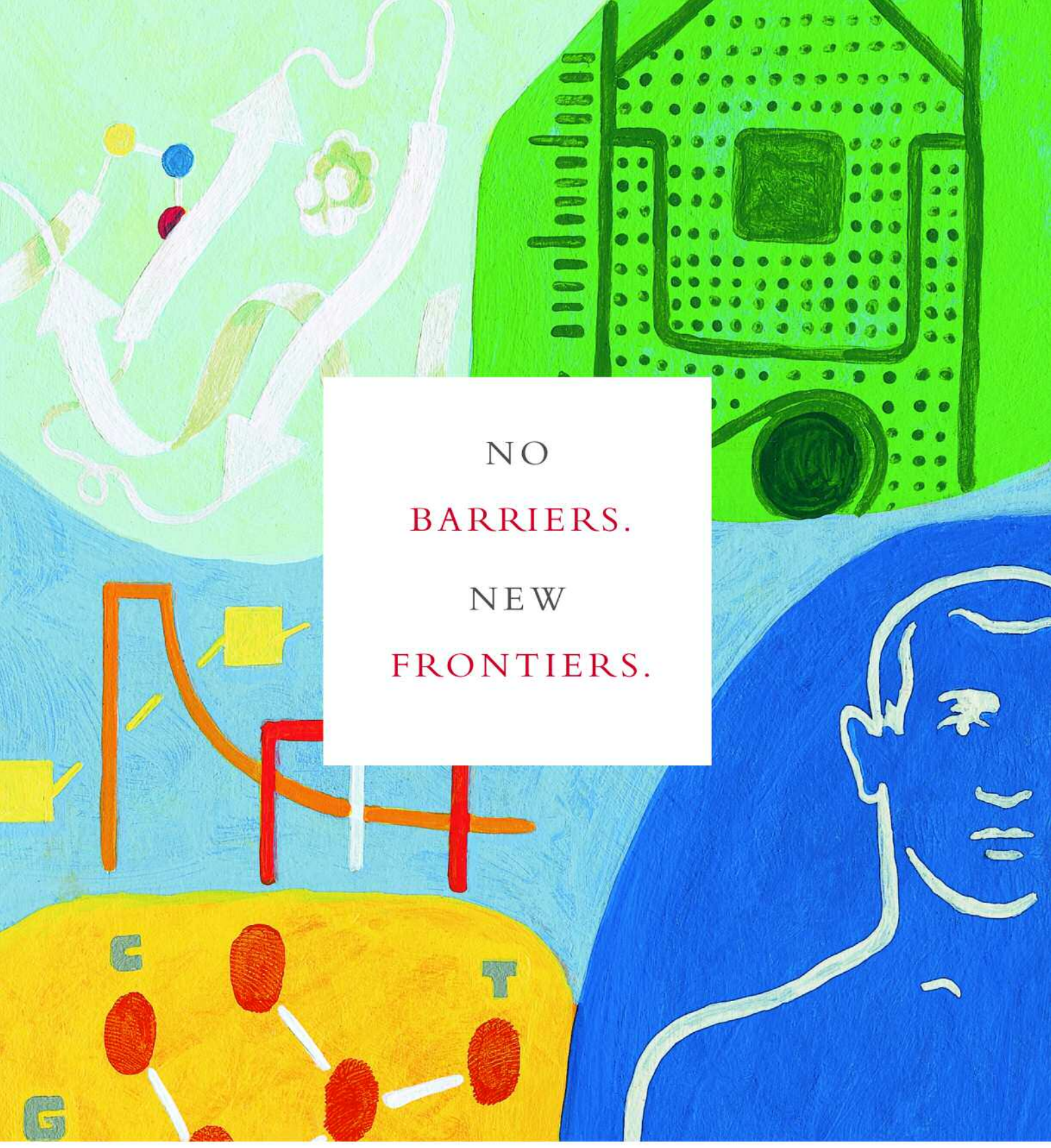

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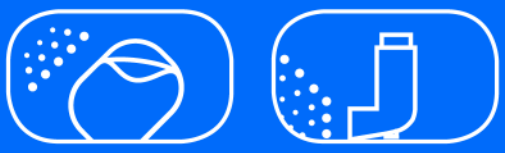

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Oral Colon-Specific Delivery

"Various pharmaceutical approaches that can be exploited for the development of colon-targeted drug delivery systems include the use of prodrugs, pH-sensitive polymers, bacterial degradable polymers, hydrogel and matrices, and multicoating time-dependentdelivery systems."

p.62

Table Of Contents

32 **Living in Harmony – pMDIs & DPIs in the 21st Century**

Ms. Georgina Fradley says that increases in DPI sales have strengthened their position and led to predictions they will increase in popularity across global markets. However, research has shown pMDIs offers many advantages to developers and prescribers and will remain the dominant device in the inhalation market.

36 **Development & Applications of Long-Acting Injection Formulations**

Dr. Roger G. Harrison indicates that the injectable product market, which currently holds 15% of the drug delivery market, could grow thanks to long-acting formulations that offer improved safety/efficacy and patient compliance.

42 **Transdermal Drug Delivery Through the Sweat Glands**

Wei Chen, PhD; Vardan Ter-Antonyan, MS; Heidi Kay, PhD; Michael Salewski (PhD student); and Feiran Huang, PhD; conduct a study that introduces an alternative means of drug transportation through the skin by means of sweat gland activation and reduction of an applied voltage to ensure that the iontophoresis is safe.

48 **Accelerating Drug Delivery Solutions With Polymer & Analytical Expertise**

Miles Hutchings, PhD; Michael Ruberto, PhD; and Dean Hamel explain that the real difference between "partnering" with a consultant practitioner and hiring the standard consultant boils down to extensive, hands-on experience, an intimate knowledge of the materials involved in medical device applications, and an overall vision of and influence on the entire supply chain.

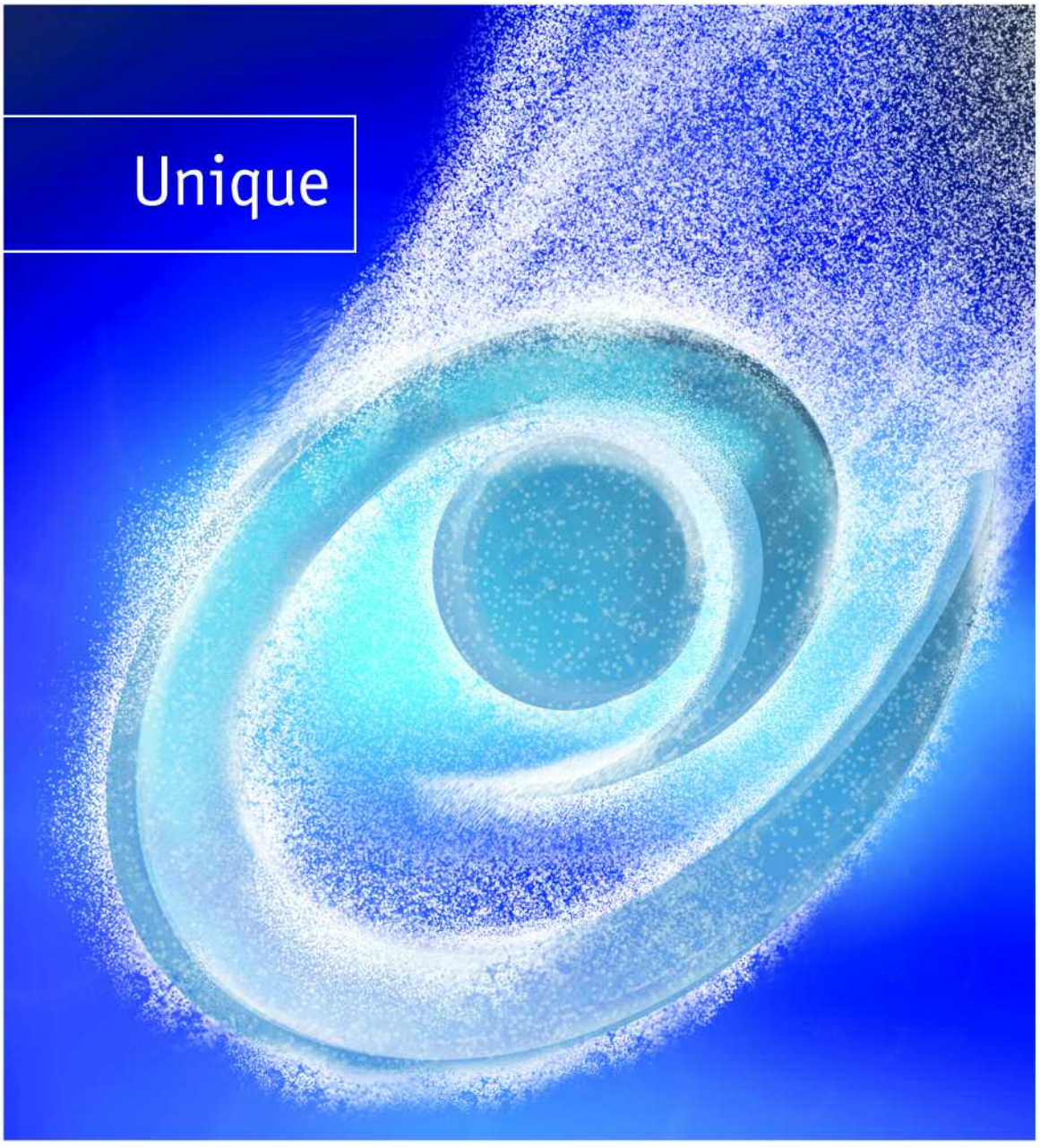

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Table Of Contents

51 *Advances in Buccal Adhesive Drug Delivery*
Drs. A.K. Bandyopadhyay and Yajaman Sudhakar discuss how buccal adhesive systems are well suited for orally inefficient drugs as well as a feasible and attractive route for non-invasive delivery of potent peptide and protein drug molecules.

56 *Palatin Technologies: A Leader in Melanocortin-Based Therapeutics*
Drug Delivery Executive: Shubh Sharma, PhD, Vice President and Chief Technical Officer of Palatin Technologies, discusses his company's MIDAS technology and the melanocortin-based therapeutics in the works.

62 *Oral Colon-Specific Drug Delivery: An Overview*
Girish Patel, MPharm student; Gayatri Patel, MPharm student; Ritesh Patel, MPharm student; Sanjay Patel, MPharm student; Jayavadan Patel, PhD; and Praful Bharadia, PhD; review the considerable amount of research on the development of colon-specific drug delivery systems.

pMDI & DPI Harmony

"Recent increases in dry powder inhaler (DPI) sales have strengthened the position of DPIs and led to predictions in some reports that DPIs will increase in popularity across global markets. However, research has shown the pMDI offers many advantages both to developers and prescribers and will remain the dominant device in the inhalation market."

p.32

Departments

Market News & Trends 12

Business Development 20
Market Evolution & Sector Confusion

Attorney Review 24
Are Inventions Based on Discoveries of Natural Phenomena Patentable?

Advanced Delivery Devices 28
Particle-Mediated Epidermal Delivery of DNA Vacciness

Drug Delivery Showcase 59

External Delivery 74

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Market News and Trends

Fertin Pharma & Generex Biotechnology Announce Collaboration on Diabetes Chewing Gum

Fertin Pharma A/S, a world leader in the development and manufacture of medicinal chewing gum, and Generex Biotechnology Corporation, Canada, a leader in the area of buccal drug delivery, jointly announced they have established a collaboration for the development of a metformin medicinal chewing gum for the treatment of type-2 diabetes mellitus and obesity.

The collaboration will combine Generex's proprietary buccal drug delivery platform technologies with Fertin's know-how related to development and manufacture of medical chewing gum to create a metformin chewing gum that will deliver metformin into the body via the buccal mucosa rather than in its current tablet form.

Metformin is a well-known drug used to regulate blood glucose (sugar) levels. Diabetes is a chronic disease that affects approximately 17 million people in the US alone. Recently compiled data show that approximately 150 million people have diabetes mellitus worldwide. It is estimated that 5% to 10% of diagnosed cases are attributed to type 1 and approximately 90% to 95% to type 2 diabetes. Metformin has been used extensively in Europe without significant adverse effects for more than 50 years but also in the US for many years. However, acute side effects (gastrointestinal side effects) of metformin occur in up to 30% of patients.

The companies expect that this new delivery method, in addition to being much more rapid and providing a much more specific and effective dosing regimen, will avoid some of the adverse side-effects associated with taking metformin in tablet form, such as nausea, vomiting, abdominal pain, diarrhoea, abdominal bloating, and increased gas production. In addition, metformin gum will avoid the bitter taste and large doses associated with the tablet form, thereby improving patient compliance, particularly amongst younger patients.

"We are pleased to have established this collaborative relationship with Fertin Pharma, the industry leader in medicinal gum," said Anna Gluskin, Generex's President & Chief Executive Officer. "Together, we will continue the Generex mission of improving diabetes care and the quality of life of people with diabetes."

Fertin Pharma is a world leader in the development and manufacture of medical chewing gum. Based in Denmark, Fertin Pharma has many years of experience within functional and medical chewing gum, working in partnerships with a wide range of well-respected pharmaceutical companies. The company owns a range of patents within taste modification, release, and development of gum bases that protects its technology brand (MediChew). Fertin Pharma's support to partners includes full product development capabilities, beginning with feasibility studies and leading ultimately to the manufacture and packaging of the MediChew products. It provides its partners with the opportunity to assess an array of prototypes early in the development process in order for the partner to choose the best brand management alternatives. MediChew tablets are sold in 24 countries throughout the world, and MediChew sales in 2004 exceeded $28 million).

BrainLAB AG Opens New Possibilities for Drug Delivery With iPlan Flow

BrainLAB AG, a global leader in image-guided medical technology, recently showcased its new iPlan Flow software at this year's American Society of Clinical Oncology (ASCO) Annual Meeting. This FDA-approved software provides physicians with the ability to accurately locate where and how medications need to be administered in order to precisely treat brain tumors. To date, clinical trials in both Germany and the United States have highlighted the potential of the treatment.

According to the Central Brain Tumor Registry of the United States (2004-5), approximately 40,000 new brain tumors are diagnosed each year in the United States. While surgical technology continues to advance, the accurate treatment of brain tumors and neurodegenerative diseases, such as Parkinson's and Alzheimer's disease remains a challenge. This is largely due to the Blood Brain Barrier (BBB), a tight coating of blood vessels that protects the brain from foreign substances, preventing potentially effective treatments from entering the brain. iPlan Flow enables physicians to effectively circumvent the BBB and supports targeted delivery of larger drug molecules to affected areas in the brain.

Successful treatment of brain tumors through drug delivery directly depends on precision and accurate dosage. Clinical experience, however, has shown that it is extraordinarily difficult to achieve sufficient drug concentration in the correct areas as the fluid dynamics differ throughout different regions of the brain and from patient to patient. Using magnetic resonance imaging to render an individual three-dimensional map of the patient's brain, physicians can calculate the required distribution patterns of the medication. The optimal site for medication delivery in the brain can now be pre-operatively identified, making the process considerably safer and more effective.

"The key to successful treatment of cancer sites in the brain is in precise drug delivery," says Dr. Andrew E. Sloan, Neurosurgeon at the H. Lee Moffitt Cancer Center in Tampa, Florida. "iPlan Flow is the tool that helps us get the drug to wherever we want it to go."

iPlan Flow is the latest module to be added to the BrainLAB iPlan software platform, which is designed with workflow-optimized architecture to guide physicians through the entire planning process. It offers unique diagnostic image handling and processing tools, such as automatic image fusion of all available image data, human atlas-based automatic organ segmentation, and tracking of patients' white matter brain fibers. In addition to iPlan Flow, the iPlan platform offers advanced radiosurgery dose planning and image guided micro-invasive surgery. This enables the integration of three different therapy possibilities, which gives physicians the tools to determine the best possible treatment option for each patient.

"The launch of our iPlan Flow software will revolutionize drug delivery to the brain and create opportunities for both pharmaceutical companies and physicians," said Dr. Christoph Pedain, responsible for pharmaceutical guidance technologies at BrainLAB. "We are confident that this software will improve clinical results by optimizing the benefits of leading-edge medications. The new software is scheduled to be available in summer 2006."

BrainLAB, a privately held company headquartered in Munich, Germany, was founded in 1989 and is specialized in the development, manufacture, and marketing of medical technology for radiosurgery/radiotherapy, orthopedics, neurosurgery, and ENT. Among the products developed by BrainLAB are software and hardware components for image-guided surgery and radiotherapy as well as integrated systems for stereotactic radiosurgery. With around 2,280 systems installed in over 65 countries, BrainLAB is among the market leaders in image-guided medical technology.

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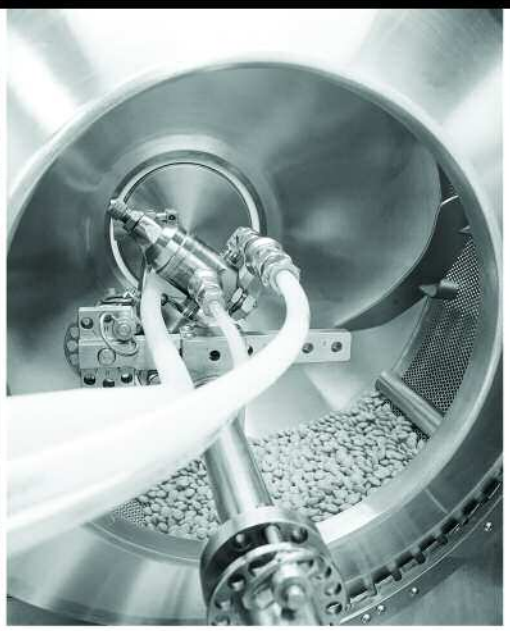

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Market News and Trends

Agile Therapeutics Closes $12-Million Financing for Development of a Low-Estrogen Dose Contraceptive Patch

Agile Therapeutics has completed a $12-million equity financing to further the development of its low-dose transdermal contraceptive patch. The investment was led by ProQuest Investments, a new investor to Agile Therapeutics. All investors from earlier rounds also participated, including the Hillman Company, TL Ventures, and PA Early Stage Partners.

"I'm delighted to welcome ProQuest into our company and to receive the continued support of our current investors," said Dr. Thomas M. Rossi, CEO of Agile Therapeutics. "I'm very gratified that the seasoned entrepreneurs at these firms value our recent progress and outstanding future potential."

Agile Therapeutics, Inc., is a pharmaceutical product development company founded in 1997 based on developing novel pharmaceutical products utilizing its proprietary transdermal drug delivery technology. The company's lead product is a second-generation contraceptive patch, currently in Phase II clinical testing. Agile's technology is making the trusted oral contraceptive hormones, levonorgestrel and ethinyl estradiol, available for the first time in a small, visually appealing 7-day patch. The market demand for transdermal contraception is strong, and this new product will add an attractive choice for women who wish to utilize this method of contraception but prefer a small patch with the same hormone combination found in popular oral contraceptives. The company is backed by a solid management team and committed investors.

Founded in 1998, ProQuest Investments is a healthcare venture capital firm that is managing over $450 million. With a proven superior track record and over 30 investments in such diverse therapeutic categories as oncology, pain, and infectious disease, ProQuest Investments seeks to build long-term, mutually beneficial partnerships with outstanding entrepreneurs.

ProQuest joins Agile's current investors in this round of financing. The Hillman Company and its Affiliates is a diversified investment firm active in venture capital investing for over 25 years. Through its association with Rock Hill Ventures, the Hillman Company was the founding investor in Agile Therapeutics.

TL Ventures, established in 1988, has over $1.4 billion under management. Focused on venture investing in category-defining, early stage companies in information technology, communications, and biotechnology, the Firm provides portfolio companies with operational, entrepreneurial, and financial expertise and a global network of resources and contacts. TL Ventures has offices in Philadelphia, Austin, and Silicon Valley.

PA Early Stage Partners, founded in 1997, is an active and experienced family of venture capital funds that seek portfolio companies located in the corridor from New York to Washington, DC. PA Early Stage invests in early stage Technology and Life Sciences companies, typically as a lead or co-lead investor. PA Early Stage currently has approximately 30 active portfolio companies and more than $235 million under management across three venture funds.

Nastech Receives $7-Million Milestone Payment From Procter & Gamble for Advancement of Parathyroid Hormone (PTH1-34) Nasal Spray Program

Nastech Pharmaceutical Company, Inc., recently announced the receipt of a $7-million payment for attaining a development milestone under the company's collaboration with Procter & Gamble Pharmaceuticals, Inc., a division of The Procter & Gamble Company, for development and commercialization of Parathyroid Hormone (PTH1-34) nasal spray for treatment of osteoporosis. The milestone will be recognized as revenue in the quarter ending June 30, 2006.

"We are pleased with the progress that P&G is making on the PTH1-34 nasal spray program," stated Steven C. Quay, MD, PhD, Chairman, President, and CEO of Nastech. "This milestone represents further validation of Nastech's capabilities in developing well-tolerated, non-invasive delivery alternatives for products that currently require injections."

PTH1-34 is a fragment of the naturally occurring human parathyroid hormone that is an important regulator of calcium and phosphorus metabolism. When given by daily injection, PTH1-34 has been shown to increase bone mineral density and significantly reduce both vertebral and non-vertebral fractures in postmenopausal women. Daily injections of PTH1-34 are approved for the treatment of postmenopausal osteoporosis and had $127 million in sales during the first quarter of 2006. In February 2006, Nastech and P&G entered into a development and commercialization collaboration for PTH1-34 as an investigational nasal spray.

Nastech is a pharmaceutical company developing innovative products based on proprietary molecular biology-based drug delivery technologies. Nastech and its collaboration partners are developing products for multiple therapeutic areas, including osteoporosis, diabetes, obesity, respiratory diseases, and inflammatory conditions

Market News and Trends

Javelin Prepares for Dyloject Launch; Mark Matthews Set as VP of Commercial Affairs

Javelin Pharmaceuticals, Inc., a leading developer of innovative products for pain control, recently announced that Mark Matthews has joined the company as Vice President of Commercial Affairs. Mr. Matthews initial focus will be to prepare for the successful launch of Javelin's lead product, Dyloject, which is currently under review for marketing approval in Europe and in Phase III clinical development in the US. He will also oversee commercial operations and marketing of the company's portfolio of late-stage prescription medications for the treatment of acute moderate-to-severe pain.

Daniel Carr, MD, Chief Executive Officer of Javelin, commented "We are delighted that Mr. Matthews has accepted Javelin's commercial leadership role. His record of achievement in the pharmaceutical industry and his familiarity with older formulations of diclofenac are ideal to support Javelin's transition to commercial success."

Prior to joining Javelin, Mr. Matthews was Vice President, Neurology Marketing at Biogen Idec, where he spent several years in charge of the marketing of Avonex (for multiple sclerosis) and served on the launch team for Tysabri (also for multiple sclerosis). Prior to Biogen Idec, Mr. Matthews served as Vice President, Reproductive Health at Serono, and held numerous positions at Novartis (previously Ciba-Geigy and Sandoz). In the latter roles, Mr. Matthews gained extensive experience in pain management as Brand Director of Voltaren and Cataflam, two earlier formulations of diclofenac. Mr. Matthews also has extensive sales and sales management experience having served as a sales representative in his native England and General Manager for Novartis' Northeast Region.

With corporate headquarters in Cambridge, MA, Javelin applies innovative proprietary technologies to develop new drugs and improved formulations of existing drugs to target unmet and underserved medical needs in the pain management market.

PARI Respiratory Equipment & BOC in Collaboration to Develop Innovative Drug Delivery Systems

PARI, a worldwide leader in aerosol delivery, and BOC, a global provider of medical gases, have signed an agreement to study the effects of gas-enabled drug delivery systems using Heliox. Heliox, the common name for mixtures of helium and oxygen, is three times lighter than air, which makes it easier for patients with compromised lung function to breathe.

It is hoped that the creation of an innovative Heliox delivery device with a customized nebulizer will help critically ill patients by delivering oxygen and aerosol to the lungs with less effort than breathing air. The goal is to improve the delivery range of aerosol therapies used to treat exacerbations of several conditions, such as asthma, COPD, and bronchiolitis.

"Our collaboration with BOC marks an important step toward a commercially available aerosol delivery system that optimizes results using gases other than air or enriched oxygen. We are certain that PARI's 100-year history in developing aerosol delivery systems can improve patient outcomes when using Heliox as well," stated Werner Gutmann, President of PARI Respiratory Equipment.

"We're delighted that PARI shares our vision of novel, easy-to-use drug delivery systems that will enable doctors to safely and reliably provide potentially life-saving therapies," said Brad Walker, Managing Director of BOC's Medical Division.

As study results become available later this year, PARI and BOC will share information with physicians and clinics.

The BOC Group, the world-wide industrial gases, vacuum technologies abatement, and distribution services company, serves 2 million customers in more than 50 countries. It employs some 30,000 people and had annual sales of over 4.6 billion pounds Sterling in 2005.

PARI Respiratory Equipment is the North American arm of PARI GmbH. PARI is a leading worldwide developer and manufacturer of fast and efficient aerosol delivery systems for patients with asthma, chronic lung disease, and cystic fibrosis. PARI's primary focus is to provide patients with innovative products and services that help control disease. Products available include breath-enhanced, reusable nebulizers, including the PARI LC PLUS and PARI LC STAR, masks like Bubbles the Fish II, as well as compressor/nebulizer systems, including the PARI PRONEB Ultra and PARI Trek. PARI is headquartered in Starnberg, Germany, with a major presence in the United States and offices in Japan, United Kingdom, and China.

Market News and Trends

Bioject Medical Technologies Completes Financing & Signs Agreement

Bioject Medical Technologies, Inc., a leading developer of needle-free drug delivery systems, recently announced the completion of its $5.75-million financing with certain affiliates of Sanders Morris Harris (SMH) and shareholder approval of the equity conversion feature of its March 2006 term loan with Partners For Growth (PFG). The company also entered into a development and supply agreement with Merial, Ltd. for the Vitajet 3 needle-free device.

At the annual shareholder meeting, held May 24, 2006, the shareholders approved the issuance of approximately $4.5 million of Series E Preferred Stock to affiliates of SMH. Under the terms of the agreement with the SMH affiliates, upon shareholder approval and satisfaction of other closing conditions, the company received proceeds of $3 million from the issuance of shares of Series E Preferred Stock at a price of $1.37 per share. In addition, $1.5 million of convertible notes issued to certain SMH affiliates in March 2006, plus accrued interest, converted into shares of Series E Preferred Stock, also at a price of $1.37 per share. The Series E Preferred Stock includes an 8% annual payment-in-kind dividend for 24 months following the closing of the Series E Preferred Stock sale.

The shareholders also approved the conversion feature included in the debt financing of $1.25 million entered into with Partners for Growth L.P. in March 2006. The debt is convertible by PFG at any time into Bioject's common stock at a price of $1.37 per share.

In addition, the company signed a development and supply agreement Merial, a world leading animal health company, for the delivery of one of their proprietary vaccines with a modified Vitajet 3 for use in the companion animal market.

"We are pleased with the overwhelming shareholder approval of these transactions. We are also pleased that we have entered into another agreement with Merial," said Jim O'Shea, Chairman, President, and CEO of Bioject. "We believe with the additional funds, the signing of the additional agreement with Merial and future anticipated agreements, we are positioned to continue to execute our strategy and achieve operating profitability within the next 15 to 18 months."

Bioject Medical Technologies, Inc., based in Portland, Oregon, is an innovative developer and manufacturer of needle-free drug delivery systems. Needle-free injection works by forcing medication at high speed through a tiny orifice held against the skin. This creates a fine stream of high-pressure fluid penetrating the skin and depositing medication in the tissue beneath. The company is focused on developing mutually beneficial agreements with leading pharmaceutical, biotechnology, and veterinary companies.

SR Pharma Announces Key Technical Breakthrough With its Lyophilized Liposomal-Based siRNA Formulation

SR Pharma plc, a leader in the development of RNAi Therapeutics, recently announced it has made a technical breakthrough in the formulation of siRNA drugs that enables its proprietary lyophilized (freeze-dried) liposomally formulated siRNA (AtuRNAi) drugs to be stored at room temperature and reconstituted in one simple step, thus providing significant benefits, most notably extended shelf-life and ease of administration.

To date, the AtuRNAi and liposomal components of AtuRNAi drugs have needed to be separately lyophilized (freeze-dried), reconstituted, and then combined, in a multi-step process. The new SR Pharma process enables siRNA drugs preformulated as liposomal nanoparticles to be freeze-dried and then simply reconstituted with water immediately prior to patient administration with no additional preparation steps. such as sonication being required.

"This is a significant breakthrough in the manufacture of siRNA drugs. A dry powder formulation extends the shelf-life and simplifies the distribution chain, with the one-step reconstitution process enhancing ease of administration. We will be applying this technology to the manufacture of our products as we take our siRNA drugs forward toward the clinic." said Dr Klaus Giese, CSO of SR Pharma.

Details of the new process were presented at recent scientific conferences. The presentations showed how this stable and lyophylized dry powder drug formulation only required the addition of water to rehydrate the drug and prepare it for injection.

"This new breakthrough in the manufacturing process of liposomal-based formulations of siRNA-based products underlines the leadership position of SR Pharma in the emerging sector of RNA interference and drug delivery," said Iain Ross, Executive Chairman of SR Pharma.

SR Pharma plc is a European biopharmaceutical company, listed on AIM. The company has two operating subsidiaries Atugen AG, based in Berlin, Germany, and Stanford Rook Ltd, based in London, UK.

CIMA LABS' Drug Delivery Technology Used in Orapred ODT

CIMA LABS INC., a Cephalon company, recently announced that its OraSolv drug delivery technology is being used by BioMarin Pharmaceutical, Inc., and Alliant Pharmaceuticals, Inc., in Orapred ODT (prednisolone sodium phosphate orally disintegrating tablets). The US FDA recently granted marketing approval for Orapred ODT, which is the first orally disintegrating tablet form of prednisolone available in the US.

"We are very pleased to add another product and successful partnership to our growing portfolio," said Todd MacLaughlan, General Manager of CIMA LABS. "Orapred ODT is a good example of the value our innovative taste-masking and orally disintegrating technologies can provide physicians and patients."

Orapred ODT will be prescribed primarily for acute exacerbations of asthma in children. Alliant expects to begin marketing Orapred ODT in the US in the third quarter of 2006. With the addition of Orapred ODT, there are now 11 pharmaceutical products approved for sale in the US and in other countries utilizing orally disintegrating drug delivery technologies developed by CIMA LABS. OraSolv tablets disintegrate on the tongue, without chewing or the need for water, enabling convenient dosing and ease of swallowing.

CIMA LABS INC. is a leading drug delivery technology company that develops and manufactures prescription and over-the-counter pharmaceutical products based on proprietary, orally disintegrating technologies. CIMA LABS' eight prescription and three over-the-counter products are distributed globally by its pharmaceutical partners and are based on OraSolv and DuraSolv orally disintegrating tablet (ODT) technologies. The tablets disintegrate quickly in the mouth without chewing or the need for water, making it easier for patients to take medication. CIMA LABS also developed OraVescent, an oral transmucosal technology. The first product candidate using OraVescent technology currently is under review by the FDA. Located in suburban Minneapolis, Minnesota, CIMA is a wholly owned subsidiary of Cephalon, Inc. Cephalon, headquartered in Frazer, Pennsylvania, is focused on the discovery, development, and marketing of innovative medicines to treat sleep and neurological disorders, cancer, and pain.

Endo Receives FDA Approval for Opana ER Extended-Release & Opana Immediate-Release Tablets CII; Penwest is Development & Commercialization Partner

Endo Pharmaceuticals, Inc., a wholly owned subsidiary of Endo Pharmaceuticals Holdings, Inc., recently announced that the US FDA has granted final approval of the company's NDAs for its extended-release and immediate-release formulations of oxymorphone hydrochloride. These products are now known under the trade names Opana ER tablets and Opana tablets.

A new oral extended-release opioid analgesic option for patients, Opana ER is indicated for the relief of moderate-to-severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time and is not intended to be used on an as-needed basis. This is the first time oxymorphone will be available in an oral, extended-release formulation. Opana ER will be available in 5-, 10-, 20-, and 40-mg tablets. Opana (the immediate-release version) is indicated for the relief of moderate-to-severe acute pain where the use of an opioid is appropriate and will be available in 5- and 10-mg tablets. Both products are expected to be commercially available in the US in the coming weeks. Endo also plans to relaunch its oxymorphone hydrochloride injection under the new trade name in the hospital setting.

Peter A. Lankau, President and Chief Executive Officer, said "We are pleased with the approval of Opana ER and Opana, which represent Endo's first internally developed NDAs to be granted FDA approval. The clinical program for Opana ER and Opana represents one of the most comprehensive ever conducted for an opioid analgesic, with more than 15 clinical trials enrolling over 3,000 patients. Further, Endo is very excited to be able to provide physicians and patients with these important new options for pain management."

Mr. Lankau added, "As a market leader in pain management, Endo is committed to the appropriate use of opioids, and we have worked closely with the FDA and external consultants to develop a program that gives healthcare providers and patients essential information and guidance on responsible opioid use."

Opana ER will compete in the market for long-acting, strong opioid analgesics, a $3.2-billion market in 2005. Its clinical profile demonstrates it can be dosed consistently on a twice-daily basis and is well-tolerated when titrated effectively. Opana ER has also demonstrated maintenance of effective pain control at a stable dose over the 3-month period of the pivotal clinical trials, which the company believes highlights the durability of its analgesic effect. Experts agree that patients suffering from moderate-to-severe chronic pain, which is present much or all of the day, need around-the-clock coverage with an analgesic agent to sustain pain relief. Opana ER utilizes a patented delivery system that was specifically developed to provide continuous delivery of medication over a 12-hour period, helping patients maintain a steady level of pain relief. Opana ER and Opana were both formulated using oxymorphone hydrochloride, which had been available only as an injectable formulation. Both products have been proven to achieve effective relief in multiple moderate-to-severe pain models, in both opioid-naïve and opioid-experienced patients.

Endo is revising its guidance for 2006 and currently expects net sales in 2006 to be approximately $880 to $910 million. Combined net sales of Opana ER and Opana are expected to be approximately $20 to $30 million, substantially composed of Opana ER. Net sales of Lidoderm in 2006 continue to be estimated to be approximately $530 to $540 million. Over the next few weeks, Endo plans to expand its current 370-person sales force by approximately 220 sales representatives to promote all formulations of Opana as well as its existing portfolio of branded products, including Lidoderm and Frova. Additionally, Endo will substantially increase its investment in the Opana franchise and, accordingly, expects to incur a loss for this product franchise in 2006 in connection with this launch. However, the company believes this launch provides another significant growth opportunity to complement its existing portfolio.

At this time, Penwest Pharmaceuticals Co., Endo's development partner, continues to elect not to fund Opana ER; therefore, Endo will recognize 100% of the losses attributable to Opana ER during its launch phase. Endo expects to recover Penwest's share of these losses from the future profits of Opana ER, which will be recognized as an increased share of the profits at that time. As such, the impact of the launch of Opana ER and Opana is expected to reduce Endo's 2006 adjusted diluted earnings per share by approximately $0.20. The company now estimates adjusted diluted earnings per share for 2006 to be approximately $1.55 to $1.60. This excludes estimated upfront and milestone payments to partners, stock compensation charges related to the adoption of SFAS 123 (estimated to be approximately $0.05 per diluted share) and compensation expense and related employer payroll taxes funded by Endo Pharma LLC. Of course, there can be no assurance of Endo achieving these results. These 2006 estimates continue to include net sales of the company's generic OxyContin of approximately $50 to $60 million and earnings attributable to its generic OxyContin sales of approximately $0.20 to $0.24 per diluted share.

Market News and Trends

Abeille Pharmaceuticals In-Licenses Worldwide Exclusive Rights to Technology for Transdermal Patch Applications

Abeille Pharmaceuticals, Inc., recently announced the execution of an agreement granting Abeille worldwide, exclusive rights to a technology platform for all transdermal patch applications. The financial terms were not disclosed. The proprietary technology platform consists of biodegradable ingredients that help overcome the skin's natural barrier properties and enables the rapid penetration of high concentrations of active drug directly through the skin, thereby permitting the formulation and development of new and highly effective transdermal therapies.

"We are extremely pleased to announce the in-licensing of the technology platform. It complements our ongoing product initiatives and allows us to pursue product opportunities that are based on this proprietary platform," stated Suresh Borsadia, President and CEO. "This agreement represents another step forward in the advancement of our strategic plan as a product development company."

"Abeille continues to execute its business plan and recently completed a Phase I study under an US IND Application for a transdermal anti-emetic product, AB-1001. Based on a preliminary review of the data, the company has initiated activities for a Phase II study, which are expected to be completed by August, 2006," continued Mr. Borsadia. "The company's plans call for initiating pivotal Phase III efficacy studies in 4Q, 2006."

Abeille Pharmaceuticals, Inc., is a privately held pharmaceutical company based in Princeton, New Jersey. The company is focused on the formulation of products by applying advanced delivery technologies to existing drugs. These advanced delivery technologies include oral controlled-release and transdermal delivery systems. The new products may benefit patients by requiring a lower dose of medicine, reduced side effects, and easier administration of medication, thereby encouraging a patient to use the medication as prescribed. Abeille is dedicated to the development and commercialization of products that address unmet medical needs and improve the quality of life for patients. The company's initial focus will be on drugs used to treat oncology-related discomforts, diabetes and metabolic disorders, and CNS.

Eli Lilly & Alkermes Complete Patient Enrollment for Phase III Safety Study for Inhaled Insulin

Eli Lilly and Company and Alkermes, Inc., recently announced the completion of patient enrollment in a pivotal safety study required for registration for their AIR Inhaled Insulin System (AIR insulin system), which is being investigated as an innovative treatment option for diabetes. The goal of the study is to more fully define the safety and efficacy of the AIR insulin system in patients with type 1 diabetes. This study is part of a comprehensive Phase III clinical program that began in July 2005, which includes pivotal efficacy studies and additional long-term safety studies in both type 1 and type 2 diabetes patients.

"Diabetes has reached epidemic proportions and is becoming one of the world's most prevalent, costly, and debilitating diseases. There continues to be a significant need for new therapeutic options that can help patients gain control of their blood sugar and achieve better, overall health outcomes," said Dr. Carlos Paya, Vice President of Lilly Research Laboratories and leader of Lilly's pulmonary development platform. "This Phase III study is a vital component of the registration program for our AIR insulin system, and we expect to make continued progress in our Phase III trials throughout the year."

"We are pleased to have completed enrollment in this Phase III study, which is a key step in our progress toward the NDA filing for the AIR insulin system," said Elliot Ehrich, Chief Medical Officer of Alkermes. "We and Lilly are highly encouraged by the clinical data compiled from our AIR insulin system studies conducted to date and are committed to conducting the studies needed to further establish the safety and efficacy of inhaled insulin."

This Phase III open-label, randomized study is designed to evaluate the safety and efficacy of the AIR insulin system compared to injected pre-meal insulin in nearly 400 non-smoking patients with type 1 diabetes. Patients are being treated for 24 months with a 2-month follow-up period. Pulmonary safety tests (PFTs) are used to assess safety. The trial will also evaluate the noninferiority of AIR Insulin (AIR insulin) to injected insulin lispro with respect to A1C levels, the average measure of blood glucose over a 3-month period. At this time, all patients have been enrolled and randomized to receive treatment. The 66-site study began enrolling patients in July 2005 in the United States, Canada, Belgium, Croatia, Hungary, and India.

In addition, the companies recently initiated another study required as part of the Phase III pivotal trial program. This Phase III open-label, noninferiority study is designed to evaluate whether the AIR insulin system is at least as effective in improving glucose control as injected pre-meal insulin over 6 months. Approximately 400 insulin-naive patients with type 2 diabetes who are taking at least one oral antidiabetic medication will be randomized to one of the two treatment groups. The efficacy of the AIR insulin system will be assessed at 6 months, and the safety will be evaluated at 12 and 24 months.

Lilly and Alkermes are conducting Phase III clinical trials for an inhaled insulin system, known as the AIR Inhaled Insulin System, (AIR insulin system) that delivers insulin via inhalation based on Alkermes' AIR pulmonary drug delivery technology. The Lilly/Alkermes program is focused on developing an innovative treatment option that can help address the challenges associated with managing type 1 and type 2 diabetes. The AIR insulin system uses a small, simple inhaler that fits in the palm of a hand.

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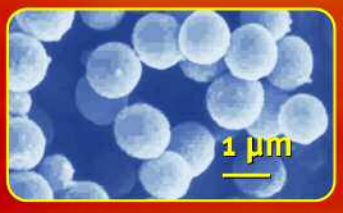

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BUSINESS DEVELOPMENT

Market Evolution & Sector Confusion

By: Howard S. Wachtler

When we look at companies engaged in pharmaceuticals, biotechnology, diagnostics, medical products, specialty pharma, and drug delivery, their fields of work often overlap to the point that it is getting increasingly difficult to define their respective focuses. Of course, these convergences between once fairly well-defined sectors do not emerge randomly. Market characteristics change, which give rise to new markets. New strategic initiatives emerge from new definitions of markets. Successes and failures loom large as barometers for new endeavors. Timing remains omnipotent.

If we take the case of Big Pharma and Biotech, the challenge is to "really differentiate" the two. Once, the difference was clear. Biotech companies were engaged in discovering and developing protein-based drugs that could not be made through chemical synthesis. They had to be produced in genetically engineered living cells. This novel approach lead to a new business model in which biotech companies were focused on developing their drugs only to a certain point and hoped to sell them off to larger pharmaceutical partners. Alternatively, they sought to raise money to finalize their drug development through an IPO not on the strength of revenue, but on the trust in novel science. Other people, who had no interest in biotechnological genetic engineering, seized on that business model, and soon, biotech came to denote the described business model, rather than real biotechnological engineering. So the real question is how well has this business model worked? Being quite cynical, if we look at the biotech sector after many years of existence and billions of dollars of expenditures, what do we really observe? Many executives would admit, maybe not openly, that the biotech sector is really an outgrowth or subset of the pharma sector. Why? Below are some justifications.

- A few decades ago, pharma companies were very traditional. They did not stray too far from their knitting. That strategy has worked for years and satisfied shareholders through significant returns. Well, it works well when the company has significant revenue (to maintain shareholder return) and a vibrant pipeline. Unfortunately for large pharma, the blockbuster era took hold so that for companies to remain economically sound and acceptable to shareholders, they needed "billion dollar" molecules. As we have all come to realize, only a small number of products ever make it to that elite class. Thus, that is not a viable, long- term strategy.

- Biotech came into existence with new technologies, etc. in an effort to start a new industry segment. The segment soon took hold and is today stronger than ever. The segment is composed of many small, early stage companies backed by venture capitalists, etc. and a handful of large companies that have been able to "put it all together" to provide their own acceptable shareholder return.

- The synergies between the two segments became apparent when both entities realized they needed each other. This became obvious due to weak pipelines, patent expirations, etc. Pharma companies became logical partners of biotech enterprises, which helped them with new products, technologies, pipeline additions, sustainable IP, etc. As a matter of fact, many pharma companies have actually established pools of capital to invest in biotechs. This combination has kept both segments together and remains vibrant today.

- Pharma has by necessity come a very long way from its traditional thinking. In addition to licensing,

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partnerships and alliances, which many times can result in acquisitions, have become a staple in their business model. Very significant dollars have been invested in biotech, and we expect that this will continue. It is a necessary component of growth and shareholder satisfaction. Pharma (not having the entrepreneurial bent of biotech) has forged ahead with alliance management teams to interact with and manage alliances. This has been a very prudent move by big pharma as it quickly defines those who have been assigned to the project and key to its success. The smaller biotech company can take advantage of the disciplines available at pharma without all of the beaurocratic red tape. Let us not forget that the biotech sector has been and continues to be entrepreneurial. Tradition would not have spawned this exciting, innovate sector.

Now, let's move our thinking to Drug Delivery and Specialty Pharma. Here, we have two additional sectors that have grown and prospered in today's marketplace. Whether we call these variations on a theme or new businesses doesn't really matter. The market has accepted both and has valued them accordingly, and by the way, they too (in the eyes of some) can be extensions of the pharma and biotech sectors. Below are some thoughts on these sectors.

- The drug delivery sector has evolved as a clever, necessary, and attractive business. This sector stems from serious issues that face pharma companies: How best to deliver a drug? What form should the drug be? Can the required number of doses be reduced while receiving the same amount of drug? Can a medical device be positioned as a delivery device or conduit? These are some of the critical questions this sector has addressed very well.

- As mentioned earlier, pharma companies desperately need to formulate strategies to offset diminished pipelines and loss of IP. Drug delivery to the rescue. Controlled release meds have added a whole new dimension to pharma. Once-a-day or once-a-week formulations from three- or four-times-a-day or several times-a-week drugs have represented very significant patient-accepted advances made by drug delivery companies. Therapeutics have also been priced accordingly to maintain acceptable margins and provide shareholder acceptance.

- Medical devices, implantable or external, have also represented notable advances in the drug delivery sector. The "hassle factor" of a drug/device combo that has riddled regulatory experts is becoming more acceptable. Some examples would include insulin pumps, patient-controlled pain medication, medicated stents, etc.

- Specialty pharma represents yet another successful sector built upon (depending on who you ask) many if not all of the aforementioned sectors. It can incorporate drug delivery, generic, Pharma, and biotech disciplines. It is all in how one defines things.

• Many generic companies now carry the banner of being specialty pharma companies. Some will attempt to command higher prices by identifying themselves as "branded generics." Really, this is nothing more than having a name associated with the generic. In some cases, it really works. As a matter of fact, some mid-tier pharma companies have had success with this. Good companies will have employed GMP practices, and their products will be bioequivalent.

• Specialty pharma has also boasted drug delivery capability to boost its own company and be more attractive to pharma and biotech alike. All of the technologies that are deployed by Drug Delivery companies are quickly being deployed by the Specialty Pharma sector.

As a result of all these new needs and challenges, sector differentiation has become clouded, with all of these sectors working off a common theme. Early on, we mentioned the importance of timing. There is no substitute for proper timing to achieve success. And there are no exceptions in these paradigms. All of the aforementioned segments can be characterized (to a greater or lesser extent) as outgrowths of the pharma and biotech sector. All have their places and have achieved great success. Success does not have to be measured in huge revenues, but rather in extending the life of the product, making it more convenient for a patient (just think of the difference between ingesting one versus several pills a day), selling less expensive (but equivalent) versions of products, and having the ability to work closely through funding and alliances with the key companies in the industry. More today than in the past, Wall Street recognizes real performance versus "promises" that are rarely fulfilled. Some of the best among the life sciences companies have achieved success in building value and infrastructure by positioning themselves as being more synergistic than competitive with their brethren. ◆

Biography

Mr. Howard S. Wachtler is President and CEO of Actinium Pharmaceuticals, Inc., an emerging biotechnology company headquartered in Florham Park, New Jersey. Mr. Wachtler is a senior healthcare industry executive, who brings with him more than 25 years of broad-based and diversified experience in venture capital, business development, strategic planning, general management, and sales and marketing management. Mr. Wachtler joined Actinium Pharmaceuticals from the position of Managing Officer of QED Technologies, Inc., a life science-based strategic consulting and transactional group. Prior to joining QED Technologies, Mr. Wachtler served as Managing Director of Medical Venture Holdings, Inc., an affiliate of Oppenheimer and Co., where he managed a series of globally diversified healthcare venture capital funds. Before joining Oppenheimer,. Mr. Wachtler directed Business Planning and Development for Pfizer, Inc., Hospital Products Group with responsibility for business/strategic planning, acquisitions, strategic alliances, licensing, and venture programs for the division and corporate management worldwide. Prior to his tenure at Pfizer, Mr. Wachtler directed Corporate Development for Organon, Inc., where his responsibilities included the identification, evaluation, and consummation of acquisitions, new ventures, and technologies opportunities for all divisions of the company. He also directed and coordinated the Strategic Planning process for all divisions. Mr. Wachtler also held management positions in sales and marketing research at Sandoz, has served on numerous corporate boards globally, and was a member of the Board of Governors of the Emerging Companies Section of the Biotechnology Industry Organization (BIO). He is a frequent speaker at industry meetings and has lectured and taught undergraduate and graduate level courses. In addition, he currently serves on the Editorial Advisory Board of Drug Delivery Technology magazine and is a regular contributor. Mr. Wachtler has earned his undergraduate and graduate degrees in Business from Pace College and Long Island University, respectively.

ATTORNEY REVIEW

Are Inventions Based on Discoveries of Natural Phenomena Patentable?

By: Clifford M. Davidson, Esq.

INTRODUCTION

Recently, a patent litigation that appeared to mainly involve a dispute over the scope of patent claims for a diagnostic test for detecting vitamin B deficiency spilled over into an apparent dispute over whether the claims (which are based on a naturally occurring relationship between elevated levels of total homocysteine and a deficiency in either cobalamin or folate) are so broad as to cover natural phenomena outside the scope of patentable subject matter as defined in 35 U.S.C. §101. Many patent holders were interested in the future outcome of this case, as it could have implications to broad patent claims in the medical field, where the claims are based on diagnostic tests or treatments that are based on an underlying naturally occurring phenomena.

THE CASE

US Patent No. 4,940,658 (658 patent) is owned by Competitive Technologies and was licensed to Metabolite Laboratories. LabCorp obtained a sublicense from Metabolite, and from 1991 to 1998, LabCorp tested for homocysteine using the specific method encompassed by the claims of the 658 patent and paid royalties to Metabolite and Competitive Technologies. In 1998, LabCorp began utilizing a method developed by Abbott Laboratories and stopped paying the royalties associated with the 658 patent. Metabolite and Competitive Technologies, Inc., sued LabCorp for infringement of the 658 patent. A jury verdict in the US District Court found that LabCorp indirectly infringed the 658 patent and breached its contract with Metabolite, doubled the infringement award based on willful infringement, and issued a permanent injunction. The case was appealed to the Court of Appeals for the Federal Circuit, which reconsidered (i) the proper interpretation of the claims[1]; (ii) whether the specification complied with the written description, enablement,[2] and definiteness[3] requirements of 35 U.S.C. §112; (iii) whether the prior art rendered the claims unpatentable; and (iv) whether the claims were infringed; among other things. The Federal Circuit affirmed the lower court's decision.[4]

In November 2004, LabCorp filed a petition for a writ of certiorari with the Supreme Court posing three questions for review. On October 31, 2005, the US Supreme Court granted certiorari to review only the following question in this matter:

Whether a method patent setting forth an indefinite, undescribed, and non-enabling step directing a party to "correlat[e]" results can validly claim a monopoly over a basic scientific relationship used in medical treatment such that any doctor necessarily infringes the patent merely by thinking about the relationship after looking at a test result.

On March 21, 2006, the Supreme Court heard oral argument in this case. The oral argument went well beyond the issues of indefiniteness, lack of written description and enablement, and ventured into the realm of whether the subject matter of the claim itself is patentable.

A significant part of the oral argument centered around Claim 13 of the 658 patent, which reads as follows:

13. A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of: assaying a body fluid for an elevated level of total homocysteine; and correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

Petitioner LabCorp argued that the correlation between elevated homocysteine levels and vitamin deficiencies stated in Claim 13 does not qualify as a novel invention, but instead is a basic scientific principle or law of nature that cannot be the basis of a valid patent claim under 35 U.S.C. § 101.[5] LabCorp argued that neither the activity of assaying nor the activity of thinking about the scientific correlation transforms Claim 13 into a patentable invention, and further notes the absence of any transformative process in the claim that might otherwise allow the claim to qualify as proper patentable subject matter. LabCorp advanced a general policy argument that upholding the validity of Claim 13 will effectively allow for the patenting of any scientific principle or natural correlation by merely including a "test and correlate" claim similar to Claim 13 into a patent.[6]

A central issue brought to bear by LabCorp was that including scientific principles, such as those set forth in Claim 13 within patentable subject matter, would allow any person who discovers a new correlation a means to demand a royalty from any person or entity who thinks or tells others about the correlation. This in effect would discourage additional researchers from developing new methods or practical applications, which are based on the correlation, thus impeding future discovery and scientific research due to fear of incurring patent infringement liability.[7]

Respondent Metabolite argued that the Supreme

Court should dismiss the writ of certiorari on the grounds that the issue of 35 U.S.C. §101, subject matter patentability, was not raised in the lower court proceedings (although it noted that the LabCorp's answer asserted invalidity based on § 102 (novelty), § 103 (nonobviousness), and §112 paragraph 2 (definiteness). This led to a discussion (and possible disagreement among the Justices) as to whether the issue of subject matter patentability was adequately raised (e.g., by construing LabCorp's arguments broadly).

If the Supreme Court did find that this issue was adequately raised by LabCorp in its papers, then this case could have far-reaching implications not only in this case, but with respect to many patents that have been issued throughout recent years where an inherent or natural phenemona is the "heart" of a granted patent claim.

POSITIONS OF THIRD PARTIES

At the request of the Supreme Court, the Solicitor General filed an amicus brief urging the Supreme Court to deny the writ of certiorari. The Solicitor General believed that the 658 patent appeared to inappropriately claim "all substantial practical applications of the natural relationship," and that the record was not sufficiently developed in the lower court proceedings for the Supreme Court to make a determination on that issue.

An amicus brief was filed by Affymetrix, Inc., a supplier of commercial DNA microarrays. Affymetrix took the position that patent rights should not be granted on basic laws of nature because such rights would directly impede scientific progress. Affymetrix's interest in the matter stems from the fact that its business is primarily in the areas of DNA and gene expression analysis. Similar to the positions set forth by Lab Corp, Affymetrix argues that the correlation between a vitamin deficiency and elevated levels of an amino acid in the blood is a natural phenomenon that is not patentable subject matter under current law.

Similarly, in its amicus brief, the Public Patent Foundation took the position that the Federal Circuit had over-reached the current legal defined boundaries of patentable subject matter by allowing claims similar to Claim 13 of the 658 patent. In addition, the American Medical Association and the American Heart Association filed amicus briefs in favor of the petitioner, Lab Corp, arguing that Claim 13 improperly claims patent rights to a scientific principle and is overly broad because the method stated in Claim 13 is not limited to any particular method of testing homocysteine levels. On the other hand, the American Intellectual Property Law Association and the Federal Circuit Bar Association filed amicus briefs in favor of the positions set forth by respondent, Metabolite.

In its amicus brief, the Intellectual Property Owner's Association (IPO) did not align itself with either party in the underlying matter. Instead, the IPO argued that any ruling in this matter by the Supreme Court should not further limit patentable subject matter under 35 USC § 101. The IPO argues that the requirements of novelty, nonobviousness, and description sufficiently protect against over-reaching patents, thus obviating the need to further restrict the scope of patentable subject matter.

Several members of the financial services industry (including IBM, AMEX, Bear Stearns, and Lehman Brothers) filed amicus briefs arguing that upholding the validity of Claim 13 of the 658 patent allows for the impermissible patenting of abstract ideas and mental thought processes, stemming from their collective concerns regarding the potential impact that affirming the lower court decision in this matter would have on the scope of allowable business method patents. Consequently, these parties advocate that patentable subject matter under 35 USC §101 should be restricted to inventions that involve technological contributions that are both physical and material in nature, thereby excluding abstract ideas from the scope of patentable subject matter.

DISCUSSION

During oral argument, Justice Kennedy noted that the Federal Circuit did not address the subject matter patentability issue, and Justice Scalia noted that it was not mentioned in LabCorp's petition to the Supreme Court. It was pointed out by counsel for LabCorp that this issue was raised in both the district court and Federal Circuit briefs, and that those briefs discussed numerous cases on claiming natural phenomena. On the other hand, Justice Breyer noted that LabCorp thought it obvious from the cases it cited and discussed that it was making a Section 101 subject matter challenge, and both Justice Breyer and Justice Souter noted the intersection between this issue and the definiteness issue (where the claim if construed broadly fails as covering unpatentable subject matter under §101 and if construed narrowly fails because it is indefinite). Under that reasoning, it is possible that Claim 13 could be construed narrowly such that claims are limited by the "assaying" language; it could also possibly be found to be indefinite, e.g., on the basis that the claim is unclear as to what tests outside of the natural phenomena would or wouldn't be covered by the claim.

Is this case similar to previous cases argued to the Supreme Court, such as *O'Reilly v. Morse*, 56 U.S. (15 How.) 62 (1853), where the Supreme Court rejected Samuel Morse's patent claim because it extended a telegraphy invention through the use of electromagnetism to all uses of electromagnetism, or is it more similar to *Dolbear v. Am. Bell Tel. Co.,* 126 U.S. 1 (1888), where a patent claim to voice transmissions using continuous undulating current was held to be not infringed by other uses of that undulating current?

As Justice Alito stated during the oral argument, a finding that Claim 13 was invalid under §101 for covering unpatentable subject matter, would call into question the validity of perhaps "thousands" of other patents. Certainly, one can imagine the

implications to diagnostic claims where a diagnosis is made by assaying a body fluid for the presence or absence of a substance, which indicates, e.g., a disease state. On the other hand, Metabolite was not taking the position that either the homocysteine/vitamin B relationship or the step of "correlating" this natural relationship was independently patentable. Rather, Metabolite took the position that the combination of the two steps ("assaying" and then "correlating") into a practical application with concrete results was the heart of the patentable invention in that claim. The author notes that despite this argument, there is no "practical application" within the terminology of Claim 13 (the concrete result arguably being the determination of an elevated level of homocysteine). Rather, if that were the case, one would have expected to find additional language concerning the step of treating a patient (or not treating a patient) with a therapeutic agent for that disease state as the "practical result."

Underlying many issues in the case is the simple fact that the 658 patent discloses only one particular assay method and is directed for the sole use of detecting vitamin deficiencies. For that reason, the Federal Circuit's holding essentially gave Metabolite a monopoly on all homocysteine testing regardless of intended use of the results or the specific assay employed.

ACTION BY THE SUPREME COURT

On June 22, 2006, without providing any written opinion as to its reasons, the U.S. Supreme Court dismissed the writ as improvidently granted, thereby preserving the decision to uphold the validity of the '658 patent. Although having no precedential value, the dissent by Justice Breyer (joined by Justices Stevens and Souter) provides some insight as to the factors considered by three Justices of the Court: that "this case is not at the boundary" between the realm of patentable subject matter and non-patentable "natural phenomenon" subject matter, but rather "claim 13 as invalid no matter how narrowly one reasonable interprets the doctrine. There can be little doubt that the correlation between homocysteine and vitamin deficiency set forth in claim 13 is a natural phenomenon."

Should the discovery of a single assay method to test for a correlation known in the art prevent others from developing better assay methods for the same test? That is the essence of patent claim draftsmanship, and the eternal fight between the patentee's right to obtain broad patent claim coverage commensurate in scope with his contribution to that art, versus the desire of others to design around that claim and/or to improve the technology. That fight was not solved in the LabCorp litigation, and is unlikely to be resolved in the near future.

ACKNOWLEDGEMENT

Special thanks to Sunil Raval, Esq. of DDK for assisting me with this article. ◆

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1. The proper interpretation of the claims is typically considered in a pre-trial hearing conducted by the court, which is referred to as a "Markman Hearing" and is discussed in an article by this author that appeared in the January '06 issue of Drug Delivery Technology.
2. 35 U.S.C. §112, first paragraph, provides that the specification of a patent "…shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.
3. 35 U.S.C. §112, first paragraph, provides that the specification of a patent "..shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
4. Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings, 370 F.3d 1354 (Fed. Cir. 2004).
5. 35 U.S.C. §101 states that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent thereof, subject to the conditions and requirements of this title."
6. LabCorp also argued that Claim 13 also fails the definiteness, enablement, and written description requirements of 35 U.S.C. §112 paragraph 1 because neither the claim nor the specification of the 658 patent disclose the specific steps a person of ordinary skill in the art would use to "correlate" a particular homocysteine level to a particular vitamin deficiency.
7. LabCorp made the powerful argument that, according to the Federal Circuit's interpretation of Claim 13, the Court finds that every doctor who orders a homocysteine test and looks at the result, regardless of how or why the test is done, automatically engages in the patented "correlating" step by merely thinking of the relationship between homocysteine and vitamin deficiency, and thus would infringe the patent.

BIOGRAPHY

Clifford M. Davidson, Esq. is a founding partner at Davidson, Davidson & Kappel, LLC, an Intellectual Property law firm with offices in New York City and Frankfurt, Germany. He counsels pharmaceutical clients in pharmaceutical patent-related matters, including patent prosecution, freedom to operate and infringement opinions, due diligence and tech-transfer, and litigation (including ex parte and inter partes proceedings worldwide). He has assisted specialty pharma and drug development companies to create significant patent portfolios, and the patents he has written and the patent portfolios he has created have been recognized as creating significant value for his clients. He has written patents covering virtually all areas of drug development, and has pioneered strategic patent focus on the pharmacokinetic profiles and the pharmacologic activity of drug/drug formulations. Mr. Davidson earned his BS in Pharmacy and his JD from Rutgers University and is a member of the New York and New Jersey Intellectual Property Law Associations, the American Pharmaceutical Association, and The Controlled Release Society. His area of expertise includes new chemical entities; new pharmaceutical formulations (including controlled-release oral dosage forms, injectables, transdermals, ophthalmics, inhalation, intranasal, sublingual, suppository, and implantation administration); new combinations of previously known drugs; new modes of administration of previously known drugs; method of treatment; pharmaceutical excipients; and methods of preparation.

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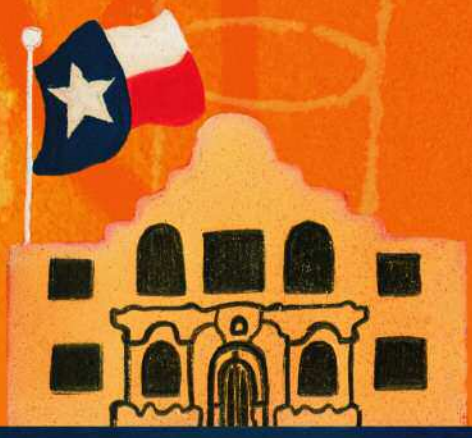

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ADVANCED DELIVERY DEVICES

Particle-Mediated Epidermal Delivery of DNA Vaccines

By: John Beadle, MD, MBA

ABSTRACT

DNA vaccines have been mooted as an important breakthrough in vaccinology since the 1990s. Recently, Dr Anthony Fauci (Director, National Institute of Allergy & Infectious Disease, USA) has listed DNA vaccines as a key component within the future US biodefense and influenza vaccine strategy. Because DNA vaccines are simple to manufacture and have been shown to induce both humoral and cell-mediated immune responses, they present a number of unique possibilities for new vaccine design, development, and commercialization. However, despite the early enthusiasm, the initial exciting data produced by intramuscular administration of DNA in small mammals has not been consistently converted into positive data in humans or even non-human primates, even at very high intramuscular DNA dosages. In stark contrast, Particle-Mediated Epidermal Delivery (PMED™) of DNA vaccines has consistently been shown to produce robust immune responses in humans and primates. This is achieved by delivering microgram amounts of DNA coated onto microscopic gold particles directly into the Antigen Presenting Cells (APC) of the epidermis using a hand-held helium-powered device. In a recent clinical trial, PowderMed has demonstrated that a single dose of PMED DNA influenza vaccine to humans produces a strong and broad immune response. All three single doses tested in this clinical trial (1, 2, and 4 micrograms) were immunogenic with the top dose producing 100% seroprotection with no requirement for boost administrations. At the time of writing, this is the first and only positive published clinical trial using any influenza DNA vaccine. Importantly, in all animals, including humans, protective levels of immunity have been produced using PMED with microgram doses of DNA. This low dosage is unique to PowderMed's PMED vaccine technology, which produces robust immune responses at doses 1000-fold lower than intramuscular DNA, which requires milligram doses.

INTRODUCTION

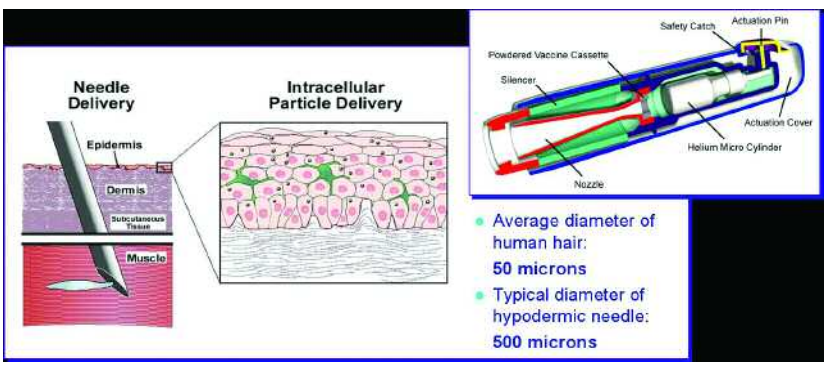
Traditional protein vaccines primarily induce a humoral immune response, which targets extracellular pathogens but is unable to eliminate infected or malignant cells. A vaccine that could elicit both cell-mediated and humoral immune responses may have potential to be used therapeutically as well as prophylactically. Because plasmid DNA vaccines mimic the effect of an intracellular viral infection, without having the risks and side effects of a viral vector, they can induce both humoral and cell-mediated immunity. DNA vaccines can thus have an important role as a prophylaxis against infectious diseases and for the treatment of existing chronic infections and cancers. DNA technology also provides a unique ability to rapidly screen candidate vaccines for their protective capacity in animal models without having to produce large amounts of protein for use as subunit vaccines. This "reverse vaccinology" approach is already revolutionizing vaccine research. Furthermore, because DNA vaccines can now be synthesized and manufactured rapidly and easily, they will also revolutionize vaccine commercialization.

DNA vaccines thus have the ability to revolutionize the entire field of vaccine research, development, and commercialization. The only question that remains is how to unlock that potential.

In 1990, Wolff and colleagues provided compelling evidence that naked DNA can transfect cells *in vivo*.[1] This observation prompted attempts to vaccinate animals using intramuscular DNA vaccination. Despite initial promising results in rodents, intramuscular DNA delivery proved only weakly immunogenic in humans, even when used at milligram doses.[2-10]

There are two principle reasons why intramuscular delivery of DNA vaccines has failed. First, as a non-immunological organ, muscle tissue lacks cells specifically adapted for immunological surveillance. Professional Antigen Presenting cells (APC) are found accumulated at sites where the detection of infection is most likely, but they are virtually absent from muscle tissue and are only recruited in large numbers in the presence of significant local inflammation. Second, in order to work, plasmid DNA vaccines need to be delivered into the nucleus of the cell where the nuclear machinery can transcribe and translate them into proteins that can then be processed and presented by the APC. Unfortunately, the phospholipid bilayer of the cellular plasma membrane presents an efficient hydrophobic barrier to the uptake of large polar DNA molecules, and there are no known efficient mechanisms for the cellular uptake of extracellular DNA.

FIGURE 1



PMED Cutaway (a labeled cross-section of the device compared to IM injection)

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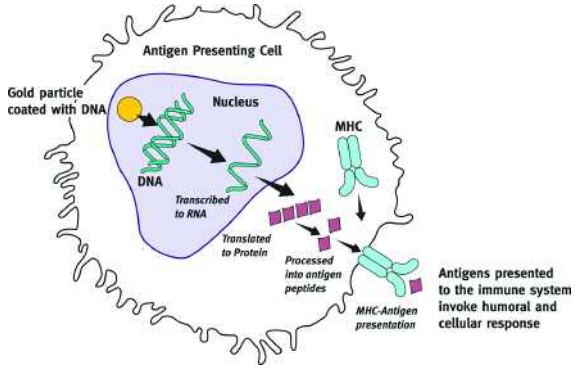

DNA Immunotherapy (the mechanism of action picture - gold particle in cell - DNA - mRNA – protein, etc.)

Needle and syringe injection delivers DNA into the extracellular spaces and is thus exceptionally inefficient. In fact, taking these two factors into consideration, it remains controversial as to exactly how intramuscular DNA vaccines are able to work at all, even in mouse models.[11] The immunogenicity that is seen is thought possibly to be attributable to the inefficient, non-specific uptake of DNA by neighbouring cells possibly augmented by the local trauma and inflammation induced by the intramuscular injection of large fluid volumes. What is now clear is that in order to produce good immune responses in larger mammals, including man, it is necessary to ensure efficient delivery of DNA vaccines directly into the APC.

Because the epidermis sits at the interface between the environment and the body, it has evolved highly efficient immune surveillance capabilities. In particular, it is exceptionally rich in APCs and is thus an ideal site for DNA vaccine delivery. Recent clinical trial results show that PMED of DNA vaccines can overcome the limitations of conventional DNA vaccines by delivering the DNA directly into this rich APC population. PMED reliably induces both cellular and humoral immune responses, and offers new opportunities in the treatment and prophylaxis of chronic diseases, such as AIDS and cancer, as well as offering protection against acute infections, such as influenza.[12-16]

PARTICLE-MEDIATED EPIDERMAL DELIVERY

The core PMED technology comprises two distinct elements: (1)The formulation of DNA therapeutic vaccines as stable, dry powders of DNA precipitated onto the surface of microscopic gold particles contained within a sealed cassette and (2) The helium gas-powered, single-use PMED device (Figure 1).

The DNA plasmid that forms the active component of the therapeutic vaccine is precipitated onto microscopic gold particles (typically 2 micrograms of DNA on 1 mg of gold). Microscopic elemental gold particles (mean particle diameter ~ 2 microns) are used as the plasmid DNA carrier because it is inert and has the appropriate density needed to deliver the vaccine directly into the target epidermal APCs. These microscopic particles are formulated as a stable dry powder. This powder is then filled into sealed cassettes. These cassettes act as the primary drug product container and are inserted into the PMED device during the final product assembly and packaging process.

The PMED device is a single-use, disposable device powered by high-pressure helium. The cassette containing the powdered vaccine is preloaded into the body of the device at the end of the manufacturing process. As the powdered vaccine is stable at ambient temperature and the cassette is sealed, PMED can be stored simply and cheaply. Using the device itself requires minimal training. The nozzle end of the device is placed against the skin at the delivery site where the vaccine is to be delivered, and the actuation button is then pressed to administer the vaccine.

Upon actuation, the release of helium from the self-contained microcylinder ruptures the cassette membrane. The gas stream entrains and accelerates the particles from their stationary state in the cassette through the nozzle and toward the skin surface at high velocity. The helium is vented through the silencer, but the momentum of the gold particles carries them directly into the epidermal cells of the skin. This process is sometimes referred to as biolistic delivery (a combination of biological and ballistic).

Following delivery into the APC, the DNA elutes off the gold particle and is transcribed into RNA. The RNA in turn is translated into the relevant antigen, which is then processed and presented on the cell surface as if it were an intracellular viral protein. An efficient cellular and humoral immune response is thus induced (Figure 2).

CLINICAL RESULTS

A series of clinical trials have been conducted to assess the immunogenicity and safety of a prophylactic hepatitis B virus DNA vaccine.[12-15] These studies have demonstrated that PMED DNA vaccination can elicit antigen-specific humoral and T cell responses. In the study by Roy et al., DNA vaccination with 1 to 4 micrograms of hepatitis B surface antigen elicited measurable cytotoxic T cell responses and Th cell responses in all 12 healthy adults who had not previously been immunized with a hepatitis B vaccine.[13] Furthermore, all 12 previously non-vaccinated subjects also seroconverted with levels of hepatitis B-specific antibody ranging from

FIGURE 3

	Egg-Based Vaccine	Cell-Based Vaccine	PMED™ DNA Vaccine
Manufacture independent of hen flock viability and egg supply	✗	✓	✓
Rapid provision of vaccine (3 - 6 months)	✗	✗	✓
Ease and certainty of manufacture at scale	✗	✗	✓
Manufacture does not involve pathogenic live virus	✗	✗	✓
Room temperature stability & no cold chain distribution	✗	✗	✓
Ability to stockpile vaccine for prolonged periods	✗	✗	✓

POWDERMED

PowderMed Influenza DNA Vaccine (uniquely suited for pandemic preparedness & annual flu vaccine production)

TABLE 1

Serum antibody responses, seroconversion and seroprotection rate

Group	Day	GMT (range)	Seroconversion[a] (%)	Seroprotection[b] (%)	Mean GMT increase (fold)
1	0	16 (5–40)	–	17 (2/12)	–
	14	23 (5–160)	8 (1/12)	42 (5/12)	1.4
	21	28 (10–240)	17 (2/12)	33 (4/12)	1.7
	56	44 (10–320)	33 (4/12)	58 (7/12)	**2.8**
2	0	17 (5–40)	–	33 (4/12)	–
	14	29 (10–60)	17 (2/12)	50 (6/12)	1.7
	21	36 (20–80)	8 (1/12)	58 (7/12)	2.1
	56	65 (20–320)	**67 (8/12)**	**92 (11/12)**	**3.9**
3	0	12 (5–40)	–	8 (1/12)	–
	14	21 (5–80)	17 (2/12)	25 (3/12)	1.8
	21	40 (10–160)	33 (4/12)	67 (8/12)	3.4
	56	97 (40–640)	**64 (7/11)**	**100 (11/11)**	**8.1**

Values meeting CPMP criteria are bold.

[a] Seroconversion is defined as either a negative pre-vaccination titer (≤10) to a post-vaccination titer ≥40, or a significant increase in antibody titer, i.e. at least a 4-fold increase between pre- and post-vaccination titers where the pre-vaccination titer is ≥10.

[b] Seroprotection rate is defined as the proportion of subjects achieving a titer ≥40.

PowderMed Table (table of the clinical study results compared to the CPMP criteria)

10 mIU/ml to more than 5000 mIU/ml. This is of particular significance as intramuscular delivery of DNA with up to 1000-fold more DNA has generated only low or no antibody responses.[2-6, 8-10] The same PMED hepatitis B DNA vaccine was also shown to increase serum antibody titres in 7 of 11 subjects who had previously failed to seroconvert after 3 or more doses of conventional vaccination with licensed recombinant protein vaccine.[14] Finally, this plasmid DNA construct has been used to successfully bridge between the earlier bulky experimental device and the simple, hand-held disposable device that will be used for product commercialization.[15]

A Phase I study has been carried out to investigate the safety and immunogenicity of PMED administration of an influenza prophylactic plasmid, which encodes a single HA antigen of influenza A/Panama/2007/99 (H3N2).[16] A total of 36 healthy subjects with low pre-existing serological responses to this strain received a vaccination of either 1, 2, or 4 micrograms of DNA at a single administration session. The antibody response was then assessed according to the CHMP criteria for the approval of annual flu vaccines in the European Union. Table 1 summarizes these humoral responses, determined as a haemagglutination inhibition titre elicited on Days 0 (predose), 14, 21, and 56. Time points, where responses met the levels required by the CHMP guidelines for licensing of annual influenza vaccine, are shown in bold and red.

The 4-microgram dose group met the CHMP criteria at day 21, demonstrating the ability of PMED DNA vaccination to stimulate serological responses equivalent to those seen in protein-based approaches. Furthermore, the responses in all groups continued to increase up to day 56 (the last day monitored), indicating that responses to PMED vaccination may show a more sustained increase than is typically seen with protein vaccines. By day 56, 100% of those subjects vaccinated with the 4-microgram dose were seroprotected.

The cross reactivity of the serological responses to variant H3 strains was measured by HIA assay and demonstrated that the degree of cross reactivity was very similar to that seen with protein-based vaccines. Cell-mediated immunity was not measured in this trial, although studies with other PMED DNA vaccine indicate that CMI responses to HA may be generated and may further contribute to protection.

Overall, vaccination was very well tolerated with no treatment emergent SAEs reported, and local reactogenicity results were typical of those seen in other PMED studies.

CONCLUSION

By delivering DNA directly into the APCs of the epidermis, PMED DNA vaccines have the potential to revolutionize the discovery, development, and commercialization of DNA vaccines. Figure 3 lists the potential advantages for a PMED influenza vaccine, which is just one of the many applications for which this technology may be applied. Clinical studies are currently being conducted or planned either by PowderMed or its partners in the following fields: hepatitis B, influenza, genital herpes, human papilloma virus (HPV), HIV/AIDS, Hantaan virus, melanoma, and a variety of other cancers. ◆

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BIOGRAPHY

Dr. John Beadle, is Co-founder, CEO, and Chief Medical Officer at PowderMed Ltd. He was previously the Vice President of Medical and Product Development at PowderJect, and before that the Vice President of Global Medical Operations at GlaxoSmithkline. Dr. Beadle gained extensive experience of product development, from preclinical to post-marketing phases, in roles of ascending seniority at The Wellcome Foundation and Glaxo Wellcome. Dr. Beadle graduated as a Medical Doctor at the University of Witwatersrand and earned his MBA from the London Business School with distinction.

MARKET OVERVIEW

Living in Harmony – pMDIs & DPIs in the 21st Century

By: Georgina Fradley

ABSTRACT

2006 marks the 50th anniversary of the pressurized metered dose inhaler (pMDI). First launched in 1956 by Riker Laboratories (now part of 3M), the pMDI has become a favored device in the treatment of asthma and chronic obstructive pulmonary disease (COPD). Recent increases in dry powder inhaler (DPI) sales have strengthened the position of DPIs and led to predictions in some reports that DPIs will increase in popularity across global markets. However, research has shown the pMDI offers many advantages both to developers and prescribers and will remain the dominant device in the inhalation market.

INTRODUCTION

2006 marks the 50th anniversary of the pressurized metered dose inhaler (pMDI). First launched in 1956 by Riker Laboratories (now part of 3M), the pMDI has become a favored device in the treatment of asthma and chronic obstructive pulmonary disease (COPD). The success of Advair™, GSK's dry powder inhaler (DPI) combination of Salmeterol Xinafoate and Fluticasone Propionate in the DiskusTM device, in the US has captured the attention of the industry. This has led to predictions in some reports that DPIs will increase in popularity across global markets and take up to 50% of the MDI/DPI market.[1]

In 2005, 3M Drug Delivery Systems set out to understand the current inhalation market, the changes that have occurred in recent years, and the position of the pMDI going forward through a series of primary and secondary research. Part of the research included interviewing a cross-section of experts from the industry, respiratory clinicians and nurses, and representatives from patient groups. This has provided a thorough understanding of the opinions and needs of pharmaceutical developers, medical professionals, and patients themselves.

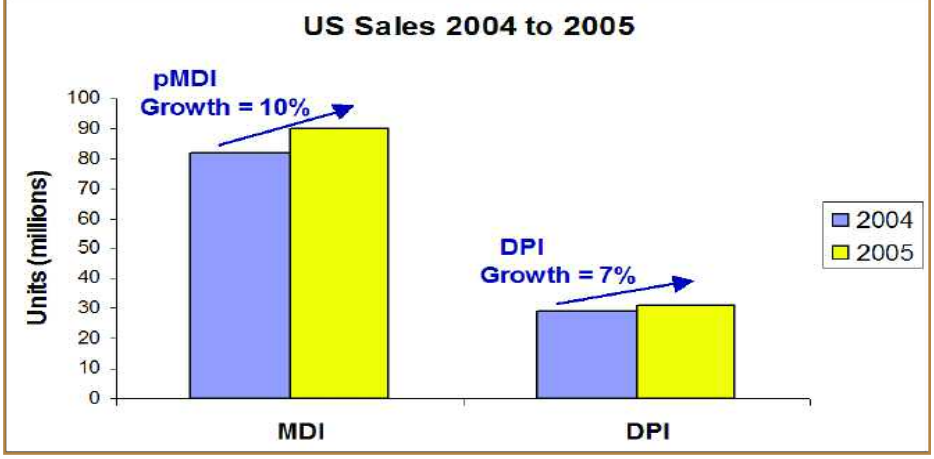
CHANGES IN THE MARKET

Dry powder inhalers were first introduced in the 1970s, but didn't really take a hold on the inhalation market until the signing of the Montreal Protocol in 1987.[2] The challenges of transitioning to CFC-free inhaler devices led many developers to invest in DPIs, and they began to increase in popularity across most of the developed world through the 1990s. The US market was slower to adopt DPIs, and they only accounted for 3% of units in 2000. However, the US inhalation market began to change in 2001, and DPI sales began to grow at significant rates (over 150% growth from 2000 to 2001).[3] The US accounts for approximately 45% of the global inhalation market and, with such growth rates, it is no wonder that analysts took note and predicted such a substantial shift in market preferences.[4] Be that as it may, upon closer inspection, it is clear that the DPI growth observed is due almost entirely to GSK's Advair. Launched in the US in 2001, Advair is the only CFC-free combination product on the US market and has been a tremendously successful product, generating triple figure growth rates in the first 2 years sales. In 2004, 86% of DPI revenues in the US were directly attributable to Advair.

From this evidence, we came to realize that the predicted swing toward DPIs was actually based on the success of a single product within the US market. Although DPIs clearly have a strong role within the inhalation market, it seemed unlikely that they would take the market shares predicted and replace pMDIs in future markets. This opinion was confirmed through our discussions with industry experts and medical professionals. Advances in DPI technologies and the introduction of blockbuster products, such as Advair, have certainly strengthened the position of DPIs in the 21st century. However, there was no question in the minds of industry experts or clinicians that the pMDI will remain the dominant device (by volume) in the market.

Additionally, the US market is once again stabilizing following the introduction of a blockbuster drug. The growth rate of pMDIs and DPIs from 2004 to 2005 can be seen in Figure 1, the trend has now reversed so that, once again, higher growth can be seen for the pMDI. Furthermore, pMDI growth is expected to increase over the next few years with the introduction of new

FIGURE 1 - US Growth Rates 2004-2005



products, such as Sepracor's Xopenex™ pMDI. Xopenex was recently approved in the US, and Altana's Alvesco™, Astrazeneca's Symbicort™, and GSK's Advair pMDIs are currently under review by the FDA. This indicates that the US market has settled into a similar market to that in the rest of the world, where there is a place for both devices in the market and choices can be made according to individual product needs.

WHY CHOOSE A pMDI OR A DPI?

Pharmaceutical companies must consider a number of factors when developing a new inhalation product in order to select between a pMDI or a DPI as the delivery system. The most significant of these is company capability. If a company has the facilities and the experience of developing one device type, then the investment to switch to the other is a substantial barrier, both in terms of cost and time. However, when a selection is to be made, the advantages and limitations of each device type should be considered against company preferences and product requirements. The advantages and limitations of both pMDIs and DPIs can be seen in Figures 2 and 3.

The pMDI is a proven technology, which offers a number of advantages to the pharmaceutical developer. First, technical advances build upon a solid and proven history, thus utilizing vast experience to minimize the time and risk involved in developing new products. For example, 3M Drug Delivery Systems can provide data to support an investigational new drug (IND) or Clinical Trial Application (CTA) within 80 working days.[5] Such experience can also decrease the time approval. The continuity in principle between different pMDIs empowers regulators to apply expectations across all pMDI submissions. When this is combined with a thorough understanding of regulatory requirements, the pain of the approvals process can be eased and the time taken significantly reduced. This is illustrated by the recent single cycle approval of Sepracor's Xopenex, which gained approval in just 304 days.[6]

Other advantages of the long history of pMDI technologies include the well-developed and robust manufacturing processes that can be used across different products, and the ability to source components from a number of different and well-established suppliers. This is a significant advantage in itself, as given the time taken to develop a new product and the life cycle of that product once marketed, financial stability was one of the most critical factors to pharmaceutical companies when selecting a drug delivery partner.

Finally, but possibly of primary importance, is patient acceptability. The

FIGURE 2 - Advantages of pMDIs & DPIs

pMDI	DPI
• Proven technology	• Perceived as modern technology
• Well developed, robust manufacturing process	• Current popularity
• Hardware 'off the shelf' from well known suppliers	• Wide range of dose sizes
• Low cost end product	• Can deliver from one dose upwards
• High efficiency (solution products)	• Breath Actuated
• Patient acceptability	• Dose Indication
• Can outsource development	
• Secure environment	

basic principle of operation of the pMDI has remained effectively unchanged over the past 50 years. Patients and medical professionals are familiar with the devices and view them as easy to use and discreet. The industry has succeeded in making technological advances seamless to the patient, even one so significant as the transition away from CFC propellents.

The rise of the DPI in the US, and the associated press it has gained, is clearly a current advantage for the device type. Added to this is the perception that DPIs are modern devices, often due to the added features that have become standard for DPIs, such as breath actuation and dose indication. Some active DPI devices are able to deliver a wider range of dose sizes than current pMDIs and capsule devices can deliver from one dose upward. These features are key requirements for the emerging inhaled macromolecule market.

The limitations for each device type can be seen in Figure 3. For DPI devices, these tend to be around the relative infancy of the technologies and the distinct differences across the variety of devices available. Therefore, these limitations are difficult for developers to address beyond individual device options. However, there are a number of ways in which limitations for pMDI technologies are currently being addressed.

FIGURE 3 - Limitations of pMDIs and DPIs

pMDI	DPI
• Perceived as old technology • IP Constraints • Need to prime • Co-ordination requirements • Most devices not breath –actuated • Limited range of dose sizes • Minimum number of doses required in a pack • No dose indication (generally)	• High risk if device has not been previously approved • Manufacturing needs to be adjusted to each device • Many different devices linked to originator companies • Limited options for outsourcing • Device specific training

Altering Perceptions

The flip side of patient acceptance and familiarity is that pMDIs may become viewed as old technology, particularly when compared against the new and very different DPI devices. Whilst it is important to maintain the basic operations and appearance of pMDIs to maintain patient familiarity, it is possible to use add-on features, such as breath actuation and dose counting to update devices. Patients associate these features with the "new" DPI devices, and they have been well received, both in terms of improving ease of use (breath actuation) and therapy monitoring (dose counters). Therefore, by using a combination of added features and aesthetic design of actuators, delivery companies can update the look of the pMDI without compromising patient acceptance. In addition, breath actuation and dose counting can improve patients' management of their therapy. Breath actuation removes the need for patient coordination, and dose counting not only indicates when the unit is nearly empty, but an individual count can aid the patient (or parent) and physician to monitor therapy.

Technological Advances

One of the key advances for the pMDI will be technologies that negate the need for a patient to prime the pMDI after periods of storage. This will offer improvement in terms of ease of use for asthma and COPD patients, although current technologies can allow storage periods of up to 14 days before priming is necessary.[7] However, this represents a critical step toward delivering systemic therapies via the pMDI. Such therapies are likely to require intermittent dosing and expensive actives; therefore, developers must make moves to reduce wastage. This can also be achieved through small pack sizes. It is now possible to formulate pack sizes down to 30 doses for pMDIs, and there is potential to reduce this further with packs offering as few as 7 doses.[8] It may ultimately be possible to develop single-shot pMDIs, whereby the dose is contained within a blister that is pierced by the actuator stem and nozzle assembly to create a spray directly.[9]

Gaining Access to Technology

The final limitation highlighted for pMDIs was the intellectual property (IP) landscape, which has traditionally been held by a few key pharmaceutical companies. Although previously it may have been difficult or expensive to obtain the right to use such technologies, it is possible to work with drug delivery companies that are very familiar with the patent landscape to negotiate a way forward.

FUTURE NEEDS FOR THE pMDI

The pMDI has come a long way since its advent in the 1950s. Advances, such as the transition to non ozone-depleting propellents and material selection to reduce extractables have presented significant technical challenges. However, one of the strengths of the pMDI is its familiarity and the fact that, despite the advances made, the basic appearance and principle of operation remains unchanged for the patient.

Looking to the future, the industry foresees advances in two main areas. First, the industry would like to see advances to improve product robustness, thus increasing the chances of success of development programs and decreasing approval times. Technical advances in container closure systems, such as coatings and new valve designs, are making significant progress in the area by enabling reduced deposition and improved dosing uniformity.[10,11] New formulation technologies can also improve robustness, with particle engineering to improve stability and excipients to increase solubility and efficiency of delivery, pushing the boundaries of molecules that can be delivered via inhalation.[12,13]

The second area of interest for both the industry and medical professionals is ease of use for the patient. Pharmaceutical developers are already including technologies to assist patients, such as breath actuation to remove the need for co-ordination and dose counters/indicators to help patients manage their therapies. As container closure systems and formulation technologies develop, pharmaceutical companies can improve product performance in the hands of patients, allowing for better therapy management. However, as these future inhaler technologies are developed, the pMDI devices will need to remain simple and elegant if they are to preserve the familiar appearance and basic operation principles of current devices.

SUMMARY

Recent market predictions that DPI devices will replace the pMDI in many areas and take up to half of global unit sales have been confirmed to be unfounded. A combination of primary and secondary research has shown that whilst the popularity of DPIs has increased in recent years, particularly in the US market, the pMDI remains the most commonly prescribed device, with almost three quarters of global unit sales. The pMDI offers many advantages both to developers and prescribers. For developers, cost benefits, not only in the cost of componentry, but also as both development and manufacturing capabilities for pMDIs are more generic and widespread than are the specific individual capabilities needed for each different DPI, and faster regulatory authority approval times are key drivers. For medical professionals, the pMDI is a respected device that is effective and well accepted by patients. Building on their long successful history, technical advances to increase product robustness, and ease of use for patients, pMDIs will continue to be the chosen delivery system for developers over the next 50 years for both respiratory and systemic therapies.

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BIOGRAPHY

Ms. Georgina Fradley is a Development Specialist in 3M Drug Delivery Systems. A graduate in Chemistry from the University of Nottingham, Ms. Fradley joined 3M HealthCare in 1998 as an Analytical Chemist for inhalation systems development. Having worked across as range of development phases, she is now responsible for aligning new technology development with industry and market needs.

Development & Applications of Long-Acting Injection Formulations

By: Roger G. Harrison, PhD

INTRODUCTION

Injectable products hold approximately 15% of the current drug delivery market. This proportion could continue to grow, relative to other product forms, owing to the increasing proportion of new product approval applications for complex biomolecules, which generally can be given only by injection. While several groups are pursuing alternatives to injection for some of these molecules — for example the well-publicized program by Nektar and Pfizer for inhaled insulin (Exubera), which gained approval in Europe and the US in 2006 — it is unlikely that such approaches can be generalized. Consequently, despite many concerns from patients about receiving injections, and from healthcare staff about needlestick injuries and sharps disposal, injections are going to remain an important part of the future of drug delivery. In recognition of this, there have been approaches to making injections more acceptable, including the development of autoinjectors and needle-free injection devices. These can reduce the psychological concerns that patients have with conventional injection and, for the devices that have no exposed needle before and after injection, reduce the issues associated with inadvertent needlestick. Alternatively, there has been a significant effort to reduce the frequency of injection by development of long-acting injection formulations, and several of these are now being successfully marketed. It is reasonably rationalized that an injection once per week or even less frequently will be more acceptable to patients, encourage compliance, and reduce costs associated with patient management, providing benefits to payors and health professionals.

For the Specialty Pharma company, a focus on technology that enables injectable products to be made more acceptable can provide new life to an old product or ensure optimal acceptance for a new product. The rationale, therefore, for long-acting formulations for injection can be improved safety/efficacy, improved patient compliance and outcomes, cost-of-care reduction, and product life-cycle optimization.

Long-acting injection formulations are not new and have played a key role in the success of several past products. These include penicillin plus probenicid, where the latter was added to block renal tubular secretion of penicillin and prolong its action at a time of short supply; NPH (Neutral Protamine Hagedorn) insulin, introduced in 1946, in which insulin is formulated with protamine derived from herring or salmon milt, in which the precipitated complex provides a longer half-life than insulin alone; benzathine penicillin, an intramuscular pro-drug that releases benzyl penicillin over a 2- to 4-week period; and depot forms of neuroleptics/antipsychotics that were introduced in the 1960s.

Such early work provided a foundation of understanding about the potential for products of this type and, in combination with more advanced formulation options, there has been a resurgence of opportunities in this area in the past decade.

LONG-ACTING INJECTION PRODUCTS

Long-acting injections clearly offer several benefits, but these need to be balanced against the complexity and cost associated with development of such products. Three fundamental methods typically have been used to create long-acting injections. The first requires creating a formulation that delays release of the active drug from the injection site; secondly, covalently changing the chemistry of the parent molecule in order to alter its apparent circulating half-life; or third, generating a non-covalent complex with the drug and a second agent that impacts the release of the drug.

From a formulation perspective, there are several attributes that should be sought in creating a long-acting injection formulations (Table 1). The most significant challenges facing the formulation scientist are: 1) ensuring as near to zero-order release from the formulation as possible, avoiding any dose dumping or burst effect; 2) dealing with the limitations imposed by the relatively

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TABLE 1
Controlled release from a single injection
Biodegradable/biocompatible formulation excipients
Easy to manufacture on conventional equipment
Easy to ship, store, and administer
Compatible with sensitive molecules (e.g. proteins)
Low- or high-loading capacity
Can deliver water soluble of water insoluble products
Provides proprietary protection
Low toxicity
All GRAS materials
Does not require modification of parent drug to achieve desired profile

Formulation goals for a long-acting formulation

few approved excipients that are readily available for this purpose; and 3) ensuring drug stability both during storage and in situ following injection.

Of particular importance has been the use of polylactide/polyglycolide copolymers in developing sustained-release injections. The versatility and safety of these polymers have been well established and proven with several marketed products (Table 2).

While such products may appear to have substantial benefits, this does not always prove to be the case in practice. Nutropin depot was withdrawn from the market after limited commercial success. The benefit of a longer-acting injection appeared not to have overcome disadvantages associated with perceived lessening of efficacy compared with more frequent injections, and increased pain at the injection site, owing to the wider gauge needle required for injection.

The polymers are generally produced by melt polymerization and are primarily linear structures. Racemic DL- and L-polymers are available commercially with L-polymers typically being resorbed more slowly than DL-polymers. Formulations vary in the ratio of lactide to glycolide, with the higher glycolide composition limiting drug release and creating longer-acting formulations. The acceptance of such formulations is based upon their ability to affect drug release over a range of desired profiles, the breakdown of the polymers to innocuous sub-units, and the range of presentations that can be developed. Presentations can be as rods inserted subdermally or subcutaneously, microparticle suspensions in which the polymer is used to coat small particles of the drug, or free-flowing liquids in which the polymer/drug complex is precipitated after injection. Such free-flowing formulations have advantages of ease of delivery by conventional injection. An example of such a product is the sustained release of leuprolide acetate (Eligard) that uses Atrigel technology (QLT Inc.) to create 1-, 3-, 4-, or 6-month dosage forms. The drug is formulated with PLGA and N-methyl-2-pyrollidone, the latter rapidly dispersing after injection, leaving a solid intramuscular depot from which the drug pays out over time.

Liposomes have also proven to have an

TABLE 2			
Product	**Polymer**	**Drug**	**Indication**
Lupron depot	PLA	Leuprolide acetate	Prostate cancer, endometriosis
Nutropin depot	PLGA	Human growth hormone	Growth deficiencies
Sandostatin depot	PLGA-glucose	Octreotide	Acromegaly
Trelstar depot	PLGA	Triptorelin pamoate	Prostate cancer
Zoladex	PLA	Goserelin acetate	Prostate cancer, endometriosis
Arestin	PLGA	Minocycline	Periodontitis
Atridox	PLGA	Doxycycline	Periodontitis
Risperdal Consta	PLGA	Risperidone	Psychoses

Examples of PLA (polylactic acid) and PLGA (polylactic acid/glycolic acid) copolymer formulations

TABLE 3			
Product	**Generic Name**	**Route of Delivery**	**Indication**
Ambisome	Amphotericin B	Intravenous	Antifungal
DepoCyt	Cytarabine	Intrathecal	Antineoplastic
DaunoXome	Daunorubicin	Intravenous	Antineoplastic
Doxil	Doxorubicin	Intravenous	Antineoplastic
Liprostin	Prostaglandin E2	Intravenous	Peripheral vascular disease

Examples of commercially available liposome formulations

important role in creating long-acting injection formulations (Table 3), particularly for anti-infective and antineoplastic agents.

Not only can such approaches produce long-acting formulations, but there can be, as exemplified in the case of amphotericin B, a significant reduction in toxicity associated with the use of the liposomal product compared with the parent drug.

Liposomes can be produced as multi-lamellar or uni-lamellar vesicles, and provide carrying capacity for water-soluble drugs in their aqueous cores, or for lipid-soluble drugs dispersed within their lipid bilayers. Liposomes can now be produced economically, and reproducibly, at large scales offering further opportunity for their application. Particulate injections, including liposomes, given by the intravenous route, are typically recognized as foreign particles by the reticular endothelial system (RES) and consequently disproportionately accumulate in certain organs (liver, spleen, etc). This can be advantageous where a tumor or an infection is located in one of these organs and a high drug concentration is beneficial, but not if prolonged circulating levels of the drug are required. So called "stealth liposomes" are being developed to address this challenge. Such liposomes are described as nanoparticles with a polyethylene glycol coating. The particle size and the coating avoid detection by the RES and can lead to the required longer release of the drug into the circulation.

Chemical modification of the parent drug to create a new entity with a longer half-life has also been an important way of creating longer-acting injections. This can be achieved by creating a pro-drug that releases the active agent over time or by creating a longer-acting form of the drug that has inherent activity in its own right. Early examples of pro-drugs are benzathine penicillin, which releases benzyl penicillin from an intramuscular injection over 2 to 4 weeks, and haloperidol dodecanoate, a lipid soluble ester of haloperidol. The latter is formulated in sesame oil and benzyl alcohol that further delays the release of the active agent from an intramuscular site.

Of particular importance has been the pegylation of proteins. Polyethylene glycols (PEGs) are amphophilic molecules that are generally non-toxic. PEGs chemically bind to proteins, increasing the apparent molecular size and limiting kidney secretion, as well as limiting enzyme recognition and breakdown of the parent structure. In pegylation, covalent links are created between the amino or sufydryl groups of the protein with ester, carbonate, or aldehyde links with the polyethylene glycol. The pegylation reaction is controlled, among other parameters, by PEG/protein type, reaction time, temperature and pH. Products that have been developed from this technology are shown in Table 4.

Additional significant benefits from pegylation include enhanced product solubility, offering formulation benefits, enhanced product stability in storage, and a decrease in potential immunogenicity, as well as the decrease in proteolysis, which leads to the prolonged circulating half-life for such products.

Alternative chemical modification strategies for proteins rely on the power of

TABLE 4		
Product	**Generic Name**	**Indication**
Pegasys	Pegylated · 2a interferon	Neutropenia
Neulasta	PEGfilgrastin	Neutropenia
Adagen	Pegadenosine	Enzyme replacement
Oncospar	Peg l-asparginase	Acute lymphocytic leukemia
Somavert	PEG growth hormone antagonist	Acromegaly

Examples of pegylated products

TABLE 5

Company	Technology	Technology Name	Application Examples
Flamel	Aminoacid polymers	Medusa	Long-acting proteins
Macromed	Thermosetting gels	ReGel	Paclitaxel depot
Alkermes	Cryogenically processed PLGA	Prolease, Medisorb	Human growth hormone, Risperdal consta
SkyePharma	Lipid chambers	Depofoam	Depocyt®
QLT	Thermosetting gels	Atrigel	LHRH
Alza	PEG-coated liposomes	Stealth	Dexil®
Durect	Sucrose acetate isobutyrate	SABER	SABER-bupivacaine

Examples of companies specializing in long-acting injection technology

recombinant technology to create variants of the parent structure that retain the inherent activity, but prolong the half-life of the product. Most work in this regard has focused on insulin. Insulin has been a target for improved convenience of injection for many years with the development of NPH insulin in the 1940s and Lente and Ultralente products in the 1960s. However, the 1990s and 2000s have focused on alternative routes of delivery (eg, inhaled insulin) or protein engineering of the parent molecule to create changes in the primary structure. The first of these to be introduced that conferred a longer-action profile was insulin glargine. This molecule was designed to have low aqueous solubility at neutral pH, but to readily dissolve and have good stability at pH 4. These characteristics allowed for the development of a solution formulation, which is converted into a microcrystalline precipitate when neutralized in the subcutaneous injection site. Insulin glargine is then released at a relative constant rate over 24 hours, providing a patient with their basal insulin requirements. Several specialty companies are now providing long-acting injection technology to the industry (Table 5).

SUMMARY

Several approaches are available to provide long-acting formulations for existing products. These systems can improve safety and/or efficacy, potentially improve patient compliance and hence outcomes, reduce costs (although the drug cost may be substantially increased), and allow for product life-cycle optimization. Additionally, it has become apparent that creation of new active pharmaceutical ingredients, designed to prolong half-life, can provide patient and company benefits. It appears that there will be a continuing demand for such products and a continuing evolution of technologies that can afford solutions to these needs. All of these factors will lead to a willingness to launch optimized dosage forms at the time of product entry or introduce such products after establishing a market position with a parent product form. The latter has the advantage of potential greater speed to market, but needs to be balanced against consideration of non-optimal product performance. Whichever approach is adopted, the patient and healthcare provider requirements for greater product convenience, as well as the need for market competitiveness, will continue to drive this important business sector.

BIOGRAPHY

Dr. Roger G. Harrison is the former CEO and President of Antares Pharma, Inc., and now works as an independent consultant. Prior to joining Antares Pharma, his career had been with Eli Lilly and Company with responsibilities ranging from discovery research, project management, product development, and alliance management. He earned his PhD in Organic Chemistry from the University of Leeds in the United Kingdom and conducted Post-doctoral research at the University of Zurich in Switzerland.

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TRANSDERMAL DELIVERY

Transdermal Drug Delivery Through the Sweat Glands

By: Wei Chen, PhD; Vardan Ter-Antonyan, MS; Heidi Kay, PhD; Matthew Salewski (PhD student); and Feiran Huang, PhD

ABSTRACT

Although iontophoretic transdermal drug delivery is known as an effective means for drug transportation through the human skin, it is not widely used because of the various side effects that come to life due to a high applied voltage (40 to 60 V) and current. This study introduces an alternative means of drug transportation through the skin by means of sweat gland activation and reduction of an applied voltage to ensure that the iontophoresis is safe. The skin-conductance studies (using 50 mM of NaCl solution) on subjects of different gender, physical, and psycho-physiological conditions showed that the activation of sweat glands led to the increase of the skin conductance up to 10 times, which enabled us to use a lower voltage of 2 V in order to achieve noticeable results during the actual drug delivery experiment. In addition, the application of Vaseline on the experimental surface does not allow the decrease of a skin conductance for as long as 24 hrs, which enables drug delivery over a long period of time. Finally, the drug delivery was performed and tested by means of an HPLC method.

INTRODUCTION

Transdermal drug delivery has been a century-old discovery, nevertheless, the topic still attracts new and revolutionary ideas of researchers everywhere in hope to find one transdermal method that would be efficient, practical, safe, and cost effective. One of the leading transdermal drug delivery methods out on the market and still in intense research is iontophoresis. The technique provides a noninvasive method to administer a controlled amount of drugs through the skin by applying an electric current. To simplify its mechanism, iontophoresis is a process of transportation of ionic molecules into the tissues by passing the electric current through the electrolyte solution containing the ionic molecules using a suitable electrode polarity.[1]

There are three main passages through the skin's barrier: the stratum corneum, the sweat duct, and the hair follicles.[2,3] The first passage is used by current iontophoresis methods. Although this method has its advantages, it is not entirely safe. Iontophoresis is carried out using high voltage of up to 60 V in order to overcome the skin barrier that has a resistance of ~1-5 MΩ. Side-effects and reactions, such as itching, erythema, irritation, skin pigmentation, permanent skin diseases, and vascular and non-vascular diseases often occur under the delivery area.[4]

An alternative method would be to avoid the passage across the stratum corneum, where the resistance is so high, by utilizing the porous components of the skin, such as the sweat ducts and the hair follicles, where the resistance is much lower. By doing so, the voltage needed to overcome the resistance can be lower, and side-effects can be eliminated. The areas of the sweat glands and the hair follicles are small compared to the total area of the skin; which is why using these pathways for drug delivery had been ignored; until now.[5] The following method focuses on the efficiency of drug delivery through the sweat glands.

METHOD

The sweat pores provide a pathway from the surface of the skin into the blood vessels. By utilizing the sweat ducts, we can decrease the resistive force of the skin. The conductance of the sweat duct can be maximized by many mechanisms. There are places on a human body where the resistance of the skin is about 500 KΩ, and those are the best places for this experiment.

In addition, the sweat glands must be open to create some passage ways. Sweat can be induced by increasing the body temperature via the following: applying a heating pad to the delivery area or drinking hot tea/water/soup, or by attaching some external object (such as polyethylene) to the skin so that the temperature balance of the skin will be violated and begin inducing sweat by itself, gradually increasing its intensity in order to get rid of the attachment.

The main problem that had to be overcome was sweat gland closure due to the swelling of the stratum corneum.[6] The sweat gland is prevented from closure by applying a thin layer of thick Vaseline on the surface of the skin in the delivery area. The Vaseline not only prevents the pore closure, but also provides a higher conductance because it hydrates the skin and increases its permeability. By

applying Vaseline, we have managed to hold a high conductance reading for a day; this is enough to be convinced that Vaseline solves the problem caused by pore closure. So the objective of the method is to maximize drug delivery transdermally through the sweat glands.

SKIN-CONDUCTANCE STUDY

The systematic components of drug delivery through the sweat glands include a DC power supply, two electrodes, and an ionic solution. Each component must be carefully chosen in order to provide an efficient and safe method.

A DC power supply of 2 V applied to the delivery area gives an average current of 5 μA, which is much safer than the current iontophoresis method that utilizes 60 V. The power supply can be provided by a 2-V battery for portable and practical purpose since the drug delivery period can last up to a day.

The electrodes chosen for the current skin conductance study and the drug delivery are the TransQ-1GS electrodes, manufactured by Pro-Med. These Ag/AgCl electrodes stabilize the pH of the drug and prevent a shift of pH in a drug or in a tissue.[2] Prevention of pH shift eliminates possible skin irritation, stabilizes drugs, and improves drug delivery. Ag/AgCl electrodes are also nonpolarizing. This means the skin and the sweat glands do not get polarized, and so the development of a counter-electromotive force (emf) can be prevented.[2] Also, one of the most important advantages of Ag/AgCl electrodes is that they have a very low junction potential and do not get oxidized (and consequently do not enter the electrolyte).

The electrodes contain a Gel-Sponge element that maximizes a uniform skin contact, and are the best for longer adhesion to prevent leakage of drug solution.

The Gel-Sponge also provides greater conductivity and consistent current and drug distribution. Also, the gel makes sure the drug solution does not make a direct contact with an electrode to prevent the electrolyze phenomenon. These electrodes provide an easy and practical way to inject the drug solution into the electrodes. The larger area of the electrodes covers more area of sweat pores, which maximize the total drug that can be delivered.

Factors that affect drug permeation through the stratum corneum can be distinguished from a simple, steady-state flux equation for a given thickness of the skin (Equation 1).[5]

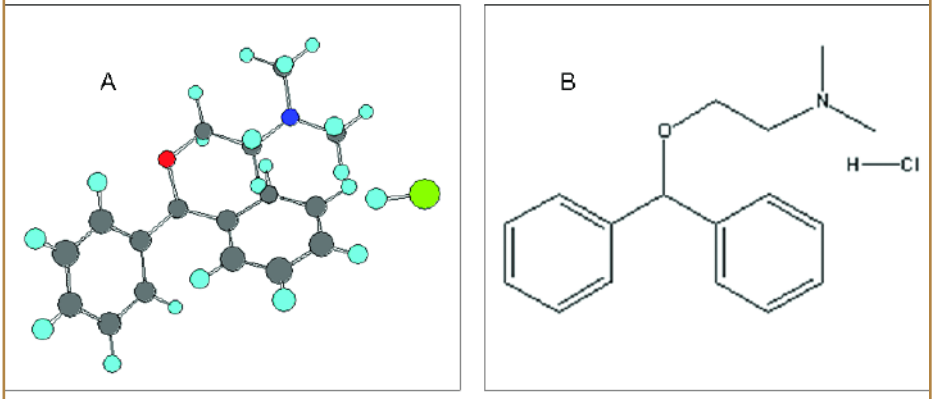
Equation 1. $\Phi \sim CDK$

Where $\Phi = dm/dt$, which is the mass of the drug, m, passing per unit area through the skin, which is also a steady-state flux of the drug. C is the drug concentration in donor solution, K is the partition coefficient of solute between the skin and the solution, and D is the diffusion coefficient .

So factors that affect drug delivery include the ionized state of the drug and its pH range in which the transdermal permission of ionized state is maximum.[1] Other factors, include good solubility in oil/water, low melting point (correlating with good water solubility), low molecular weight (less than 600 Daltons), and a high concentration of the drug.[1,5,7]

The drug solution chosen for delivery is Benadryl (diphenhydramine hydrochloride), which is a known antihistamine (Figure 1). This drug has been chosen for delivery because its solubility in

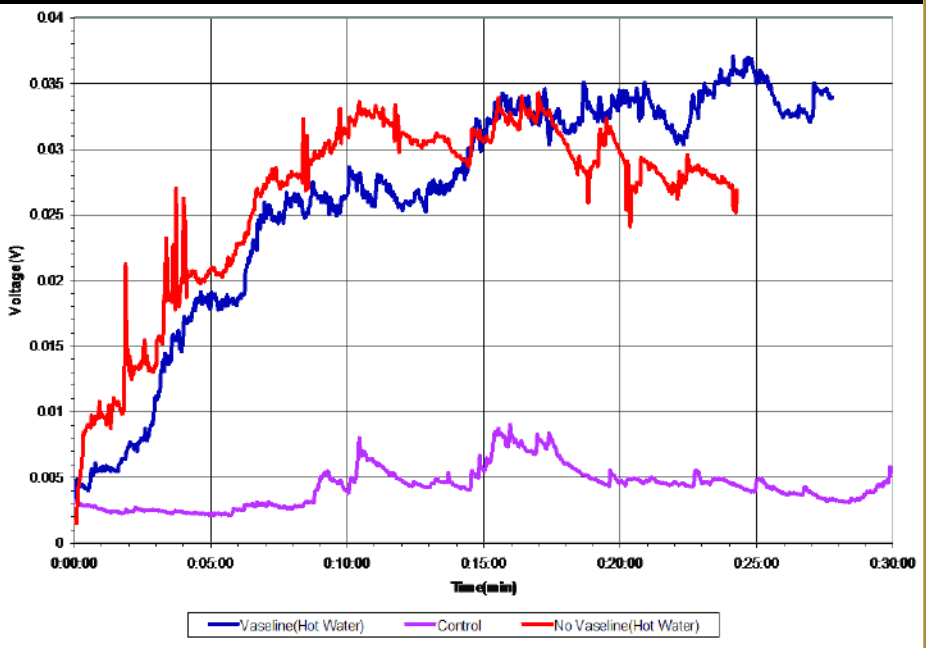
FIGURE 1



The molecule of Diphenhydramine Hydrochloride $C_{17}H_{22}ClNO$ a) in 3-dimensions; b) in 2-dimensions

Location of the Electrodes: Positive electrode is on the internal side of a biceps. Negative electrode is on the external side of a biceps.
Active Area: 7.6 cm²
Fill Volume: 1.5 cc
Drug Concentration: 10 g in 100 mL of water
Resistance of the biceps skin: ~ 0.5 MΩ
Applied Voltage: 2 V
Applied Current: ~ 50 μA
Current Dosage: ~ 7.2 mA-min

FIGURE 2



The average potential versus time graphs for the Control (dry skin, pink line), sweating (red line), and sweating with the Vaseline (blue line)

water is very high (more than 10 g in 100 mL of water), its molecular weight is relatively low (~291.8 Daltons), and its melting point is also low (~166ºC).[8]

The chemical formula of Benadryl is $(C_6H_5)_2CHOCH_2CH_2N(CH_3)_2HCl$, which is the same as $C_{17}H_{22}ClNO$.[9] Benadryl can only be dissolved in water, and it does not enter into a reaction. When dissolved in water, the neutral form of Dimedrol becomes ionized, so we observe the following: $C_{17}H_{22}ClNO + H_2O \Rightarrow R\text{-}H^+ + Cl^-$, which represents a complicated organic radical R with charge (+1) and a remaining non-organic acid with charge (-1).

This is clear because when salts of drugs are dissolved in aqueous solutions, ionized particles are formed, and this process is called dissociation or ionization.[10] Today, almost all the drugs are available in salt form because of great water solubility, and also, the formation of ions is a typical behavior for all the water-soluble drugs and chemicals that have at least one non-organic ion, like salts of non-organic acids, which is the case we have. Under the influence of a 2-V electric field, these ions are transported into the skin through the sweat glands and driven into the bloodstream.

Benadryl can be detected easily by a blood or urine test after 8 hours of experiment,[11] and it has been delivered through the iontophoresis process by many others.[10] Benadryl is also a non-prescription medication that relieves allergy symptoms, hypersensitive reactions, motion sickness, and uncontrollable muscle movements. It also promotes sleepiness and targets the central nervous system.[12]

CONDUCTANCE STUDY RESULTS

Multiple experiments were done on four subjects of different gender, nationality, psycho-physiological condition, and lifestyle. The results presented are the averages of many similar experiments carried out at different times of the day and on different days. In order for an experiment to be successful, a subject has to sweat in the particular areas of the experiment where the electrodes are placed. So once a subject sweats well enough to activate and open the sweat ducts, the potential readings increase significantly.

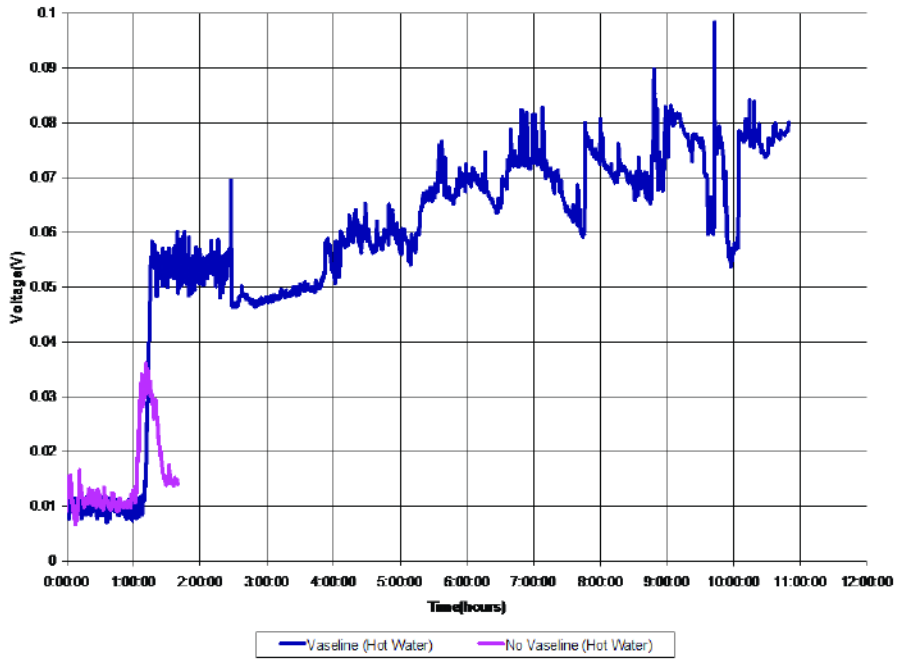
Because the physiological condition of different people is different, their conductance is also different. The human skin conductance studies and all our experiments showed that different people get different readings, but the pattern of the potential versus time graph stays the same.

In order to make sure that the electric field goes through the sweat glands under the positive electrode to the negative electrode through the sweat glands located under it, both electrodes were placed facing each other; positive electrode on one side of a biceps and the negative electrode on the opposite site so that the electric field goes straight from the positive to the negative electrode, which makes sure that the electric field is traveling through the sweat glands and not just through the skin.

The experimental results showed that the conductance of the dry skin was 8 to 10 times less than the conductance of the sweating skin, depending on the individual and his/her psycho-physiological situation, which means that the sweat glands contribute a lot to the conductance of the skin, and the activated sweat glands increase the conductance enough to deliver drugs. The studies of the conductance of the skin were carried out using a 50-mM NaCl solution (due to a low molecular weight of NaCl) and Ag/AgCl electrodes. The average results of the experiments are presented in Figure 2.

The "Control" value of the average skin potential is about 3 mV and after 30 minutes, it increases until about 6 mV. The

FIGURE 3



An 11-hour experiment with Vaseline (blue line) and an approximate 2-hour experiment without Vaseline (pink line), which clearly prove that Vaseline is very efficient in preventing pore closures and holding the conductance constant. The potential of the skin without Vaseline is not as high as that with Vaseline in this case because prior to using any source of heat to the skin, we did a "Control" for an hour, which means that by the time the skin was sweating intensely, the stratum corneum was already swollen, and the sweat glands were closed. In contrast, when we put Vaseline on, the stratum corneum does not swell, and the pores do not close even after an hour of "Control."

potential (therefore the conductance) increased tremendously (with respect to the "Control" value) in the case of the sweating experimental area. Over the course of 10 minutes, the conductance reached its peak value and stayed there for about 5 minutes, then decreased. The decrease of the conductance was due to the closure of the sweat glands. The "Sweating with the Vaseline On" experiments were carried out the same way as the previous ones, but here the experimental area was covered with Vaseline, which prevented the closure of the pores. To prove that the pores remain open for a longer period, we did experiments on different subjects for 2 hours and eventually for 1 day, and the conductance was still holding. One of the results is shown in Figure 3.

In order to make sure the Vaseline still prevents closure of the stratum corneum even if the experiment lasts as long as 24 hours, a series of 5- and 6-hour experiments were conducted and eventually the longest experiment, which lasted 17 hours, in which the electrodes were still on when the subject was sleeping at night, and after the 17 hours, the potential was still holding.

RESULTS OF THE DRUG DELIVERY EXPERIMENT

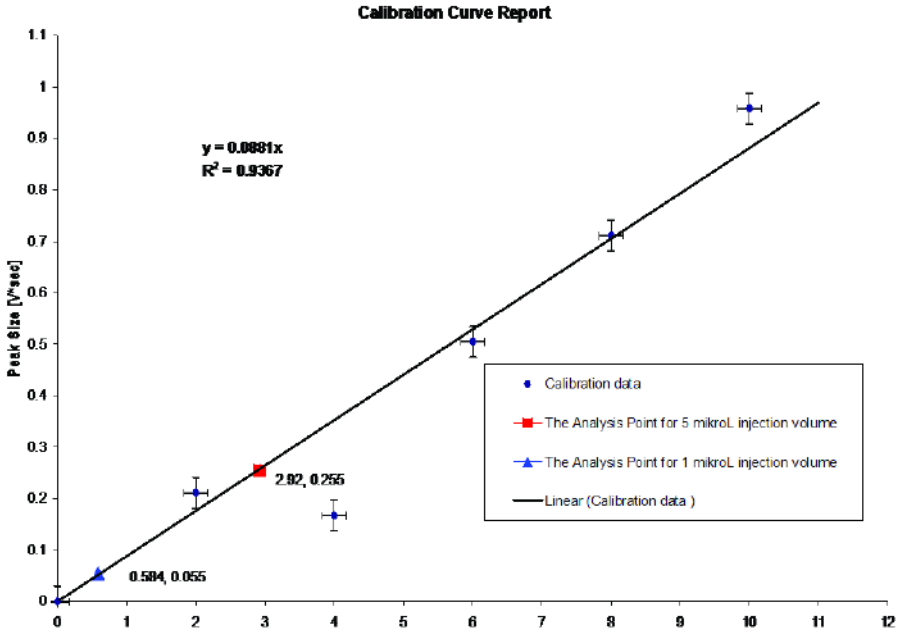
In order to make sure the Benadryl molecule is able to be transported through the sweat glands using our iontophoretic method, some skin-conductance studies were performed using a 10-g solution of Diphenhydramine Hydrochloride $C_{17}H_{22}ClNO$ with 100 mL of deionized water. The results of these experiments showed that the increase in conductance due to the sweat gland activation is about three to four times, which is lower than in the cases of the experiments using NaCl solution with water. That can certainly be explained by the low mobility of the Benadryl molecules due to their large molecular mass and large size. But that increase is enough to get a noticeable result after at least 24 hours of drug delivery.

Finally, transdermal drug delivery was performed on a subject for 8 hours, and the urine was collected to determine the amount of Diphenhydramine Hydrochloride in it. That urine was then worked up under the solid phase extraction (SPE) process. The SPE process eliminates all kinds of contaminants and big particles from the urine so they do not interfere with getting the final urine analysis by means of a special High Performance Liquid Chromatography (HPLC) method. The HPLC method used to separate the Diphenhydramine Hydrochloride was carefully chosen to get the best separation:

Column: ZORBAX Rx/SB-C8 (4.6 x 150 mm)
Eluent: 20 mM of KH2PO4 Phosphoric Acid/Acetonitrile (60/40) (v/v)
Flow Rate: 2 mL/min
Temperature: 25ºC
Detector: UV at λ = 254 nm

The first experiment was done just on the pure sample of 1 mg of Diphenhydramine HCl in 100 mL of HPLC-grade water to find out the retention time of the drug, which turned out to be t_R = 3.655 minutes. After that, 5 consequent experiments were performed at 10-, 8-, 6-,

FIGURE 4



Here, a calibration curve report is presented. Each round point represents experimental data obtained from the HPLC instrument after analysis of 1 mg of pure Diphenhydramine HCl in the 100 mL of HPLC-grade water along with the measurement errors. The big square represents the Diphenhydramine HCl peak with its parameters (amount and peak size) obtained from 5-µL urine injection volume after drug delivery. The big triangle represents the same, but from 1-µL urine injection volume. Also the R^2 coefficient and the calibration function can be seen.

4-, and 2-µL injection volumes for calibration purposes. The constructed calibration curve is presented in the Figure 4. Each experiment was repeated a few times to determine the measurement errors, which can be seen on the curve. The X and Y errors are presented as bars around the points.

After the calibration curve was constructed, drug delivery was performed on the same subject for 8 hours. After the urine was collected, it was passed through the solid phase extraction process, and 5 µL of it was passed though the HPLC instrument using the same aforementioned method. The result is shown in Figure 5.

In Figure 5, it is clear to see the peak of Diphenhydramine HCl having an area of 0.255 V*sec. This point is represented on the calibration curve as a big square having a peak size of 0.255 V*sec and an amount of 2.92 µL. Consequently, for the 1-µL injection volume, a peak having an area of 0.055 V*sec can be seen with an amount of 0.584 µL. This point is presented on the calibration curve as a big triangle.

An analysis of urine without Diphenhydramine Hydrochloride was also performed to determine whether the found peak is the peak sought after or a regular fluctuation. No evidence of any sort of Diphenhydramine peak was found, which shows the results are very reliable because the area under the Diphenhydramine peak is much more than the measurement error, which is about 4%.

To find the contribution of sweat gland activation to the amount of drug found in the urine, the same drug delivery experiment was performed but without an electric field that introduces the drug into the skin by diffusion process. As a result, no Diphenhydramine peak was found in the chromatogram of that urine, which means that the amount of this drug in the urine is smaller than the sensitivity of the instrument, which is about 1 ng, everything else is taken as a noise or a fluctuation. This means that there is no significant contribution to the drug delivery due to the diffusion, and the sweat gland activation is responsible for the delivery of the whole amount of Diphenhydramine Hydrochloride.

SUMMARY

Analysis data shows that we found about 6 +/- 0.24 ng of Diphenhydramine Hydrochloride in 1 µL of injected urine that was obtained from 8 hours of experiment. Consequently, after 24 hours of experiment, we will find about 18 +/- 0.72 ng of Diphenhydramine Hydrochloride in 1 µL of urine injection volume. The average amount of urine after the experiment is about 300 mL, so we find 5.4 +/- 0.2 mg of Diphenhydramine Hydrochloride in the urine after 24 hours of experiment.

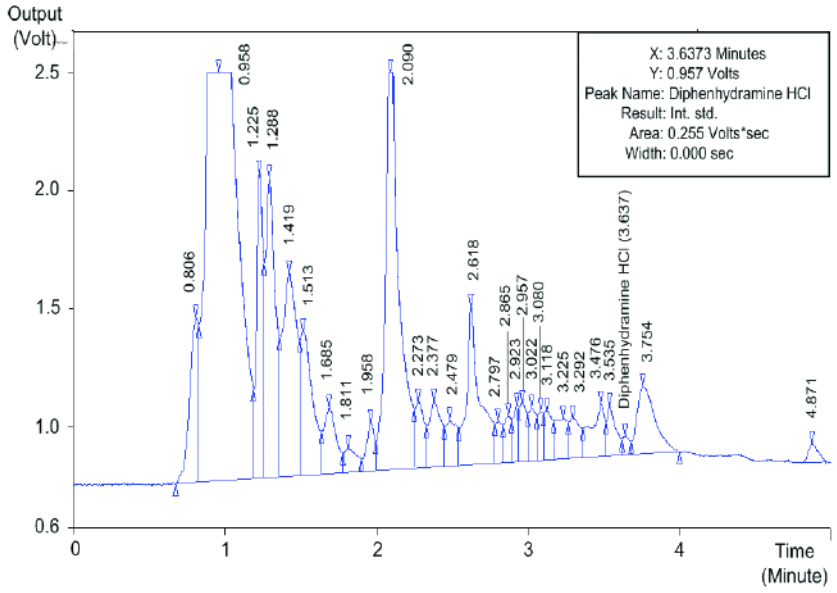
APPLICATIONS

For a drug like Diphenhydramine HCl (Benadryl), the acceptable dosage for adults is 25 mg/day. For children aged 6 to 12 years old, the dosage is about 12 mg/day, and for kids younger than age 6, a dosage lower than 6 mg/day is acceptable, which means that our method could be used for children younger than age 6.

DISCUSSION

The method can be improved if we increase the skin conductance more than 8 to

FIGURE 5



Here, a chromatogram is presented from the urine analysis of a subject who was in the 8-hour drug delivery experiment.

10 times, which would allow more drug to go in through the sweat glands. But we can also change the drug and use a drug with a lower molecular mass. Diphenhydramine Hydrochloride has a molecular mass of almost 300 Daltons, so if we choose to deliver, for example, Vitamin C with a molecular mass of almost twice as less as the Benadryl, then we might find a few times more of it in the urine.

CONCLUSION

The new method of the sweat gland activation enables us to overcome skin resistance. The swelling of the stratum corneum is prevented by applying a thin layer of thick Vaseline to the skin. We deliver about 10 times less amount of drug than the leading methods and instruments, but we deliver drugs up to 30 times safer, which is why this method provides a foundation to deliver drugs more safely and efficiently without any possible side effects.

ACKNOWLEDGEMENTS

The authors would like to thank Prof. Edward Turos, PhD, from the Chemistry Department at USF for his advice on the chemistry of Diphenhydramine Hydrochloride. Also, special thanks to Zhongsheng Zhang, Robin Dando, and Hoang Nguyen for all the help they provided. This study is partially supported by research grants from National Institute of Health, NIH, NIGM50785 (W.C.) and National Science Foundation, NSF0515787 (W.C.)

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BIOGRAPHIES

Dr. Wei Chen (Temple University, 1988) is a Professor of Biophysics at the University of South Florida. He started his professorship at the University of Chicago in 1992 and later moved to the University of Illinois. He is interested in the interaction of electromagnetic fields with living systems, and his research has been continuously funded since 1994 by the NIH and NSF.

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Dr. Heidi Kay (USF, 1999) is an Assistant Professor in the College of Public Health at the University of South Florida. She currently supervises over 5 projects, including cancer treatment, drug delivery systems in supercritical fluid, and Alzheimer's disease treatment.

Mr. Matthew Salewski (USF, 2004) is currently a PhD student in the Department of Biophysics at University of Edinburgh, England.

Dr. Feiran Huang (Rensselaer Polytechnic Institute, 2003) is a Post-doctoral Research Associate in the Center of Cellular and Molecular Biophysics in the Department of Physics at the University of South Florida.

TESTING SERVICES

Accelerating Drug Delivery Solutions With Polymer & Analytical Expertise

By: Miles Hutchings, PhD; Michael Ruberto, PhD; and Dean Hamel

INTRODUCTION

With the high degree of risk involved, consulting in the pharmaceutical and drug delivery industry can and should be a partnership between the specialist and client. The client and consultant should share common goals: less plant downtime, faster time to market, and the most accurate and scientifically documented results possible.

While many consultants will present their test results and leave clients challenged with implementation, those specialized consultants who are also practitioners with extensive knowledge and a wealth of relevant experience will actually help clients put theory into practice in a more efficient manner. Consultant Practitioners will give clients what they demand for their own products, paving the way for a long-term relationship that's built to last.

TRUE STORY

Recently, a new pharmaceutical product involving a plastic inhaler delivery system was poised for an impressive introduction into the marketplace. Expectations were high (clinical trials had already demonstrated the safety and effectiveness of the product), but the pharmaceutical company was unable to seek FDA approval until it could identify the mysterious substance that was leaching out of the polymeric inhaler mouthpiece. This company spent 2 years investigating the substance with its partners to no avail. They finally sought the help of specialized outside consultants from Expert Services, a new business introduced by Ciba Specialty Chemicals Corp. Within a few short months, they had identified not only the substance but its commercial trade name as well. Health and safety evaluations were then possible, and ultimately the FDA approved the product and the drug was finally launched – more than 2 years later than planned. That's a long time in any industry. For pharmaceuticals and drug delivery systems, the repercussions of losing a 2-year head start can have a devastating ripple effect not to mention the significant losses in revenues.

For a variety of reasons, companies are increasingly opting to outsource many, if not all, of the necessary stages in a product's journey to market. Some companies find themselves in the quality control phase of a new product introduction without definitive answers to critical questions. Has the stabilization package added to the plastic components of your drug delivery system changed due to un-notified supplier changes? Are the additives, stabilizers, and colorants leaching out, transforming as a result of interaction with other chemicals, or degrading over time? These questions can be answered and the implications dealt with by Expert Services because of its knowledge and expertise along the polymer supply chain. Many find outsourcing to be both cost effective and efficient, simplifying the way they do business by focusing on what they do best, and outsourcing to specialized experts everything outside of their core competencies.

A PERFECT FIT

This market need, plus its own unique blend of experience and core competencies, encouraged Ciba Specialty Chemicals, a pioneer in polymer stabilization, to create and launch Ciba® Expert Services in 2004. One of Ciba's many core competencies, analytical testing, became the foundation of Ciba® Testing Services, the service arm of Expert Services that offers Leachables and Extractables testing services for the worldwide pharmaceutical industry.

Because transdermal patches, inhalers, IV bags, syringes, and more are all high-risk examples of polymeric delivery systems that can potentially impact consumers, the idea of Ciba's specialized experts consulting with drug delivery manufacturers and pharmaceutical companies appeared to make perfect sense. While some companies were initially reluctant to share confidential information with consultants,

"Because transdermal patches, inhalers, IV bags, syringes, and more are all high-risk examples of polymeric delivery systems that can potentially impact consumers, the idea of Ciba's specialized experts consulting with drug delivery manufacturers and pharmaceutical companies appeared to make perfect sense. "

it became a non-issue when the actual experience of working in tandem with Ciba specialized experts began. Growing a knowledge-based services business relies on cultivating excellent client relationships while maintaining an unblemished reputation. The growing list of clients who now use Ciba Expert Services on a regular basis is the best testament to a trust that has been earned.

THERE'S NOTHING LIKE EXPERIENCE....

Many pharmaceutical and manufacturing companies have already discovered that outsourcing has been proven to be more cost effective and efficient because it enables them to do what they do best (drug research and development, manufacturing, and marketing), while everything outside of their core competencies are assigned to specialty consultants. A company with over 100 years of experience in all areas of the polymer industry (analyzing, testing, and producing) can help bring a client's product to market economically, safely, and quickly. With all the necessary information at its fingertips so to speak, such as comprehensive knowledge of compounds, degradation and transformation profiles, and assessment of health and safety implications, etc., Ciba occupies a unique position in the world of polymers. Ciba Specialty Chemicals had its genesis in two 18th century companies (Ciba and J.R. Geigy). From 1758, when Johann Rudolf Geigy set up a drugs and dyestuffs shop in Basel, Switzerland, until today, Ciba continues to launch breakthrough products. The extensive knowledge of such a long-term practitioner is now being employed to alert pharmaceutical and drug delivery system manufacturers to chemicals that could migrate out of plastic packaging and drug delivery systems, interact with the drugs, and even enter the consumer.

PUTTING THEORY INTO PRACTICE

Pharmaceutical consulting is hardly a new idea. There are as many types of consultants available as there are problems to solve and challenges to be met. Some consultants offer safety auditing and provide safety and compliance recommendations. Others will supply test data. But virtually no other specialized consultant can personally bring to the table actual chemical manufacturing experience. When it's time to implement changes in your manufacturing environment, based on the test data provided by another consultant, you're usually on your own.

Expert Services practices what it preaches. When its safety consultants present test data, they don't leave clients to figure out how this information should be applied. A vital part of their brief is to aid clients in safely introducing a new product into their own manufacturing facility. They're able do this because parent company Ciba Specialty Chemicals has a head start, as an actual practitioner of the art of safe chemical production, it has already introduced many chemical manufacturing processes for a broad variety of chemistries in their own facilities. Chemical manufacturing is Ciba's core competency and, everyday, it must insure that its own chemicals are manufactured to the highest safety standards in its own plants. Armed with this extensive practical experience, Expert Services consultants simply translate their testing data into real-world implementation for clients' manufacturing plants. Only then is a consulting project considered to be successfully completed.

THERE'S ALWAYS MORE!

The relationship that started with client-customized analysis and dedicated

test methods usually continues with client access to many types of drug delivery system-related services and information, for example, tracking down the cause of failure in a component or investigating better stabilization methods. Training might be needed, and sometimes it requires certain flexibility ("your place or ours"), and clients who "want it all" can get information updates on new testing and in-house analytical standards, additional training, and answers to all relevant questions by signing up for a service contract.

Because so many pharmaceutical-related plastic products contain additives, such as antioxidants, antistatic agents, and pigment products similar to those Ciba manufactures, Expert Services personnel can easily carry out the necessary testing studies and can even help to select materials during the design of new medical devices. As members of pharmaceutical industry groups that study extractables and leachables and their toxicological impact, these consultants participate and contribute to solutions. They bring to every project a sophisticated level of chemical and polymer industry knowledge gained from decades of experience that has allowed many clients to significantly cut their testing time. A case in point: one client labored for nearly a year in an attempt to identify an unknown component. Ciba already had standards for that component in its state-of-the-art laboratories, and identification could have been accomplished in less than a day.

The real difference between "partnering" with a consultant practitioner and hiring the standard consultant boils down to extensive, hands-on experience, an intimate knowledge of the materials involved in medical device applications, and an overall vision of and influence on the entire supply chain. Clients get from Expert Services what the chemical leader demands for its own products. And when its clients succeed, so does the consultant.

BIOGRAPHIES

Dr. Miles Hutchings is the head of Expert Services in the NAFTA region. His responsibilities involve the internal provision of services to Ciba as well as the development of external, third-party business. Dr. Hutchings joined Ciba in Basel, Switzerland, in 1987. He has held the positions as Technical Director for Process and Lubricant additives with responsibilities for technical programs to support technical service and new product development in transportation and industrial lubricants. In addition, he gained plastic industry experience as a Product Range Manager for Ciba's specialty line of plastics stabilizers. Prior to joining Ciba, he was a Research Fellow within the department of Bioengineering at the University of Oxford. He has gained Industrial experience with Exxon Chemical Corporation and British Petroleum in the United Kingdom, where he was responsible for oil analysis and base stock response research programs. He holds several patents and has had numerous articles and papers published in industry and scientific publications. Dr. Hutchings earned his PhD in Chemistry and his BSc in Industrial Chemistry from the University Wales in Cardiff. He is a Chartered Chemist and Member of the Royal Society of Chemistry, PDA, ISPE, and ASTM. He can be contacted at 914-785-2533 or miles.hutchings@cibasc.com.

Dr. Michael Ruberto is Head of Regulatory Services for the NAFTA region at Ciba Specialty Chemicals. His group is responsible for worldwide notifications of new products, food contact notifications, and regulatory compliance of Ciba chemicals. He is actively working in the area of designing leachable and extractable studies for the FDA approval of medical devices, packaging, and labels used on drug containers and is a member of the PQRI L&E Working Group. Dr. Ruberto was previously the Director of Analytical Research, where he led a full-service analytical laboratory that specialized in performing testing associated with the development and commercialization of new products, including chemical characterization, migration studies, applications support, and technical service. Dr. Ruberto has been employed by Ciba for 11 years, where he has performed numerous migration studies to support FDA and European Union indirect food contact notification for various additives, pigments, and polymers. He was part of a team commissioned to establish a Good Laboratory Practice (GLP) and Good Manufacturing Practices (GMP) program in Ciba's Analytical Research Department and served as GLP Study Director for many product characterization and Base Set studies needed for global product registration of novel additives. He led the efforts to globally harmonize the Ciba internal analytical protocols for performing migration studies and GLP testing, including a prioritization of tests, experimental procedures, analytical method validation, and report formats. Dr. Ruberto completed this harmonization process by performing a job rotation at Ciba's headquarters in Basel, Switzerland. Dr. Ruberto earned his BS with thesis from Stevens Institute of Technology and his PhD in Analytical Chemistry from Seton Hall University. He can be contacted at 914-785-2892 or michael.ruberto@cibasc.com.

Mr. Dean Hamel is Head of Client Services, NAFTA and Head of EHS Services, Americas. He is responsible for all aspects of the commercial development of environmental, safety, regulatory, laboratory, and educational services in Ciba's Expert Services Organization. Mr. Hamel is a Chemical Engineering graduate from Northeastern University and has over 23 years of experience in the chemical process industry. He has held a variety of positions in process development, engineering, production, resource management, product management, sales, and business management at several Ciba sites around the globe. He is a member of the AIChE, the Society of Plastic Engineers, and the ISPE. He can be contacted at 251-436-2397 or dean.hamel@cibasc.com

BUCCAL DELIVERY

Advances in Buccal Adhesive Drug Delivery

By: A.K. Bandyopadhyay, PhD and Yajaman Sudhakar, PhD

ABSTRACT

Since the early 1980s, delivery of therapeutic agents through various transmucosal routes has gained significant attention, owing to their presystemic metabolism or instability in the acidic environment associated with oral administration. Among the various absorptive mucosae that include nasal, pulmonary, rectal, vaginal, buccal and sublingual, the mucosa of the oral cavity is viewed as a convenient and easily accessible site for the delivery of therapeutic agents. Selecting a suitable route of drug delivery within the oral cavity is mainly based on anatomical and permeability differences that exist across the various oral mucosal routes. Buccal adhesive systems are well suited for orally inefficient drugs as well as a feasible and attractive route for non-invasive delivery of potent peptide and protein drug molecules.

BUCCAL MUCOSA AS A SITE FOR DRUG DELIVERY

Between the two well-established routes of the oral cavity, the buccal is a more preferred route for systemic drug delivery than the sublingual. The buccal mucosa has an expanse of smooth muscle and relatively immobile mucosa that make it a more desirable region for retentive systems. The buccal route avoids hepatic first-pass effect and presystemic elimination of drugs associated with the oral route of administration.[1] Thus, the buccal mucosa is emerging as an alternative for the parenteral route and is more fitted for sustained delivery applications of orally ineffective drugs.

Drug transport across the buccal mucosa occurs by the two permeation pathways that exist for passive diffusion: paracellular and transcellular routes. As the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds have low permeability. The cell membrane is lipophilic in nature; hydrophilic solutes will have difficulty in permeating due to a low partition coefficient. Therefore, the intercellular spaces pose as the major barrier for permeation of lipophilic compounds, and the cell membrane acts as the major transport barrier for hydrophilic compounds. Drug permeation may involve a combination of these two routes.[2]

Advantages of the buccal route include excellent accessibility for application in a painless, precisely located manner to the site of application to get uniform drug release. Moreover, the delivery system can be designed to be unidirectional in drug release so that it can be protected from the local environment of the oral cavity. It has gained direct access to the systemic circulation and is not subject to the hepatic first- pass metabolism. Relative to the nasal and rectal routes, the buccal mucosa has low enzymatic activity and drug inactivation; hence, biochemical degradation is not rapid and extensive. It also permits the inclusion of a permeation enhancer, protease inhibitor, or pH modifier in the formulation to modulate the environment at the application site.

Limitations include involuntary swallowing of saliva containing dissolved drug or swallowing of the delivery system itself that might lead to major loss of drug from the site of absorption. Talking, eating and drinking may affect the retention of the delivery system. Taste and irritancy may also limit the number of drugs. Overhydration may lead to formation of a slippery surface, and this swelling may disrupt structural integrity of the device. Drugs with the potential of changing the physiological condition of the oral cavity may not be suitable for buccal delivery.

MUCO/BIOADHESION

Bioadhesion is the phenomenon in which two materials, at least one being of biological in nature, are held together for extended periods of time

by interfacial forces at the desired site. The term has also been defined as the ability of a synthetic or natural macromolecule to adhere to a biological tissue, which can be either an epithelial surface or the mucus layer covering a tissue. In the first case, it is generally referred to as bioadhesion, and in the later case, the phenomenon is generally referred to as mucoadhesion.[3] The steps involved in the muco/biooadhesion process include (1) spreading, wetting, and swelling of the dosage form at the mucus surface, which initiates contact between the polymer and the mucus/epithelium; (2) interdiffusion and interpenetration between the chains of the mucoadhesive polymer and the mucus gel network; and (3) formation of secondary chemical bonds between the polymer chains and mucin molecules.

Methods for Measuring Muco/Bioadhesion

The majority of the bio/mucoadhesion methods are based on measuring the force required to break the adhesive bond between the model membrane and the adhesive. Depending on the direction in which the adhesive is being separated from the substrate, peel, shear and tensile forces can be measured. The peel adhesion tests are mainly used for buccal adhesive drug delivery devices.

Important Factors for Muco/Bioadhesion

Polymer-related factors (molecular weight, its concentration, flexibility of its chains, spatial conformation etc), environment-related factors (pH, applied strength, initial contact time, swelling, dehydration of the mucosa, interfacial tension, bioadhesive component proportions, carrier solubility, particle size, fracture path, rate and capacity of water absorption etc), and physiological variables (such as mucin turnover, pathological conditions etc) will play a major role on the adhesive interactions.

FORMULATION DESIGN

Generally, a device featuring a maximal duration of delivery of approximately 4 to 6 hrs, 1 to 3cm^2 in size, and a daily dose of 25 mg or less, would be preferable for buccal delivery. The buccal mucosal turnover rate, salivary secretion, composition of mucus, physicochemical parameters (such as solubility, permeability, and stability of drugs), degree of ionization, mechanism of absorption, dose, taste, surface area required for application, additives that interfere with salivary secretion, disease conditions that brings the change in thickness of the buccal mucosa, purpose of the dosage form, and drug interactions with the mucin are to be considered in the formulation design. As the dosage form is to be resident near the tongue, organoleptic factors are also to be considered. For local delivery, the residence time and local concentration of the drug, and for a systemic effect, the amount of drug transported across the mucosa into the circulatory system, are important considerations in designing dosage forms.

Buccal Adhesive Polymers

These are the substances that ensure the attachment of the delivery system at the site of application and release the drug at desired rate. The muco/bioadhesive should possess characteristics, such as the polymer, and its degradation products should possess a wide margin of safety both locally and systemically. It must spread over the substrate to initiate contact and to increase the surface area of contact. It should allow easy incorporation of the drug and must release the drug at the desired rate. The bioadhesive polymers may be polyacrylic acid derivatives (polyamides, polycarbonates, polyalkylenes, polyalkyleneglycols, polyalkyleneoxides, polyalkyleneterephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyglycolides, polysiloxanes, and polyurethanes etc) or cellulose derivatives (alkylcelluloses, hydroxyalkylcelluloses, cellulose ethers, cellulose esters, and nitrocelluloses etc). Substances of natural origin (chitosans, guar gum, xanthum gum, carrageenan, pectin, sodium alginate, dextrans, lectins, aminated gelatin, aminated pectin, hyaluronic acid, inulin), proteins such as zein, serum albumin, or collagen, and mucilaginous substances from edible vegetables can also be used.

Penetration Enhancers

Enhancers are capable of decreasing the penetration barrier of the buccal mucosa by increasing cell membrane

fluidity, extracting the structural intercellular and/or intracellular lipids, altering cellular proteins, or altering mucus structure and rheology. The various penetration enhancers studied exclusively are 23-lauryl ether, Aprotinin, Azone, Benzalkonium chloride, Cetylpyridinium chloride, Cetyltrimethylammonium bromide, Cyclodextrin, Dextran sulfate, Lauric acid, Lysophosphatidylcholine, Menthol, Methoxysalicylate, Methyloleate, Oleic acid, Phosphatidylcholine, Polyoxyethylene, Polysorbate 80, Sodium EDTA, Sodium glycocholate, Sodium glycodeoxycholate, Sodium laurylsulfate, Sodium salicylate, Sodium taurocholate, Sodium taurodeoxycholate, Sulfoxides, and various alkyl glycosides.

Drugs investigated using various enhancers are small molecules like butyric acid and butanol, ionizable low molecular weight drugs like acyclovir, propranolol, and salicylic acid, and peptides such as octreotide, LHRH, insulin, and interferon.

The feasibility of buccal delivery of insulin using various enhancers in different animal models was studied through *in vivo* studies. Enhancers, such as sodium glycocholate, sodium lauryl sulfate, sodium salicylate, sodium EDTA, and aprotinin on rat and dog buccal mucosae, showed an increase in insulin bioavailabilities from about 0.7% to 27% in the presence of sodium glycocholate (5% w/v) and sodium lauryl sulfate (5% w/v).[4] Care must be taken in selecting the permeation enhancer because it will affect the bioadhesive properties of the dosage form.

Permeation Studies

Permeation studies must be conducted to determine the feasibility of the buccal route of administration for the candidate drug. Most of the *in vitro* studies have used buccal tissues from animal models that are collected immediately after sacrificing them. The membranes are then placed and stored in an ice-cold (4°C) Krebs buffer until mounted in diffusion cells. The experiments were generally conducted using simulated saliva in an apparatus consisting of a water jacket and an internal compartment containing 50 ml of dissolution medium. The tablet is to be placed in the metal die sealed at the lower end by paraffin wax to ensure the drug release from one end alone. The medium was stirred with a rotating stirrer at 250 rpm[5]. A buccal perfusion cell apparatus was used that offers larger areas over which drug transfer can take place, has no leakage problem, and provides continuous monitoring of drug loss as a function of time.

Buccal cell cultures have also been suggested as useful *in vitro* models for buccal drug permeation and metabolism. However, to utilize these culture cells for buccal drug transport, the number of differentiated cell layers and the lipid composition of the barrier layers must be well characterized and controlled.

In vivo absorption studies like buccal absorption test involves the swirling of a 25-ml sample of the test solution for up to 15 minutes by human volunteers followed by the expulsion of the solution. The amount of drug remaining in the expelled volume is then determined in order to assess the amount of drug absorbed.[6] An improvement over the traditional buccal absorption test, which involves multiple samples being withdrawn from the mouth using a positive displacement pipette, enables kinetic data to be collected in a single 15-minute trial.[7]

Permeation studies for Salicylic acid, Sulfadimethoxine and Diltiazem were studied using a small perfusion chamber attached to the upper lip of anaesthetized dogs. The perfusion chamber is attached to the tissue by cyanoacrylate cement. The drug solution is circulated through the device for a predetermined period of time, and blood samples are drawn at frequent intervals for estimation of drug.[8]

Researchers have used animals such as rats, hamsters, rabbits, dogs, pigs, and monkeys. The rabbit has a non-keratinized mucosal lining similar to human tissue and has been extensively utilized in experimental studies, whereas the rats and hamsters have keratinized mucosa.[9] Dogs are easier to maintain and considerably less expensive than monkeys, and their buccal mucosa is non-keratinized. Pigs are the best choice because of their non-keratinized buccal mucosa, and they are easy to handle.[10]

DRUG DELIVERY SYSTEMS

Delivery of various drugs via the buccal route using conventional matrix tablets, films, bilayered systems, sprays, non-erodible multiple layer films, and hydrogel systems has been studied and reported.

Buccal Adhesive Tablets

A buccal adhesive double-layered tablet containing Triamcilone acetonide for the treatment of aphthous stomatitis using HPMC and polyacrylic acid for which Nagai has received the award of the Japan National Invention Prize has been reported.[11] Similarly, buccal adhesive tablets of Cetylpyridinium chloride[5], Clotrimazole, Diltiazem, Hydrallazine, Insulin, Isosorbide dinitrate, Miconazole, Morphine, Nimesulide, Nitroglycerin, Nystatin, Omeprazole, Propronolol hydrochloride, Sodium fluoride, Testosterone, Thicolchicoside, Tetracycline, Verapamil, etc were studied by several research groups using different bioadhesives either alone or in combinations.[5,12-28]

Buccal Adhesive Patches

Buccal adhesive patches consisting of two-ply laminates of an impermeable backing layer and a hydrocolloid polymer (HPC, HEC, PVP and PVA) layer containing the drug was developed and evaluated. The integrity of the laminate was based on adhesive bonds between the hydrocolloid layer and an agarose layer grafted to one side of the backing layer sheet and found that among the cellulose ethers studied, HEC and HPC possessed superior mucosal adhesion.[29] A patch consisting of a unidirectional buccal patch comprising three layers (an impermeable backing layer, a rate-limiting center membrane containing the drug, and a mucoadhesive layer containing bioadhesive polymer polycarbophil) was developed. This patch was tested in dog buccal mucosa and was shown to remain in place for up to 17 hrs without any obvious discomfort. *In vivo* studies in human subjects on the buccal patch device consists of a flexible mucoadhesive matrix composed of a blend of poly (acrylic acid), Carbopol 934P, and poly (isobutylene) with a polyurethane-backing layer have revealed effective bioadhesive characteristics for 12 hrs of application.

Similarly, buccal adhesive patches of Buprenorphine, Isosorbide dinitrate, LHRH, Lidocaine, Miconazole nitrate, Propronolol, and Proterilin were prepared using different bioadhesives polymers either alone or in combinations and evaluated.[30-36]

Buccal Adhesive Ointments

Three different hydrogel-based ointments using sodium CMC, Pectin, and gelatin combination in a polyethylene-paraffin base, Carbapol 934P, and neutralized Poly (MAA-co-methyl methacrylate) was developed and investigated by Electron Paramagnetic Resonance. The study showed that P(MAA-co-methylmethacrylate) was the most appropriate for ointment formulation in terms of stability, transport of molecules, and washing out time from the oral mucosa.[37]

A hydrogel ointment containing absorption enhancers for the buccal delivery of 17 β-estradiol to treat osteoporosis was developed to overcome its low bioavailabilities due to hepatic first-pass effect. *In vivo* studies using hamsters demonstrated that the buccal administration of E2 with this formulation allowed the maintenance of plasma level at over 300 ng/ml per cm^3 for 7 hrs.[38]

A novel mucosal adhesive ointment for treatment of lichen planus containing treninoin (vitamin A acid) and neutralized polymethacrylic acid methyl ester, showed neither any local irritation in human buccal mucosa nor any systemic side effects. On twice daily treatment, the macroscopic lesions disappeared after an average of 3 to 4 weeks in 15 to 18 patients.[39]

Buccal Adhesive Gels

Hydrogels formed by the combination of xantham gum and locust bean gums was studied. The mechanism of gel formation is due to the formation of a three-dimensional network between the double helical structure of xantham gum and the straight molecular chain of locust bean gum. Though it showed only a low mucoadhesion, it can be applied to a buccal mucosa because of its safety, gel strength, sustained-release properties, and good mouth feel.[40]

SUMMARY

The buccal mucosa offers several advantages in delivery of drugs for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage. The first-pass metabolism in the liver and presystemic elimination in the gastrointestinal tract is avoided. The area is well suited for a

retentive device because of its surface roughness and is comfortable to the patient. With the right dosage form design, the local environment of the mucosa can be manipulated in order to adjust the rate of drug permeation. The need for safe and effective buccal permeation/absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery. This form of delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules.

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DRUG DELIVERY Executive

PALATIN TECHNOLOGIES, INC.

PALATIN TECHNOLOGIES: A LEADER IN MELANOCORTIN-BASED THERAPEUTICS

Shubh Sharma, PhD
Vice President & CSO
Palatin Technologies, Inc.

"Based on our success in generating both stabilized peptide-like as well as small molecule candidate drug molecules on different projects, we believe MIDAS is uniquely positioned to bridge the gap between versatility and diversity of peptides as ideal candidates for rapid lead generation on one hand and drug-like characteristics of small molecules on the other."

Palatin Technologies, Inc. (Palatin) is a biopharmaceutical company primarily engaged in the development of melanocortin-based therapeutics. The Company's internal research and development programs, anchored by its proprietary MIDAS™ technology, have provided product candidates for the treatment of sexual dysfunction, obesity, congestive heart failure, cachexia, and diagnosis of sites of infection. Palatin's strategy is to develop products and then form marketing collaborations with industry leaders in order to maximize their commercial potential. To date, the Company has formed partnerships with Tyco Healthcare Mallinckrodt, and King Pharmaceuticals. Drug Delivery Technology recently interviewed Shubh Sharma, PhD, Vice President and Chief Scientific Officer of Palatin to discuss the MIDAS technology and the melanocortin-based therapeutics in the works.

Q: Can you provide a brief history of Palatin Technologies and how you came on board?

A: Palatin Technologies originally started as RhoMed Incorporated, which was a privately held company specializing in radiopharmaceuticals, working on a monoclonal antibody for diagnostic radioimaging of sites of infection and inflammation in the body. Palatin developed this product as Neutrospec® for the detection of equivocal appendicitis. I joined RhoMed to lead its peptide-based radiopharmaceutical program, which was focused on developing radioimaging and radiotherapeutic products. During this process, I invented MIDAS, a new rational drug design system based on metal ion chelation to peptides. After we became Palatin, we sought to broaden this technology base beyond radiopharmaceuticals, and it has since become our drug design engine. We are now using the MIDAS technology to develop and commercialize a variety of therapeutic products in the areas of obesity, sexual dysfunction, and congestive heart failure.

Q: What has been your experience in the areas of peptide research, drug design, and discovery?

A: I was trained in peptide-based drug design and have focused on this throughout my career. Prior to joining Palatin, I have worked on peptide-based

drug design projects at Swiss Federal Institute of Technology, Zurich (ETH-Zurich), Switzerland, and University of Arizona, Tucson. Key concepts that I have developed for using peptides as the basis of drug discovery programs have been embodied in the MIDAS drug design system.

Q: Please describe your MIDAS technology and what makes it unique.

A: Palatin's patented drug design platform, MIDAS, streamlines the drug discovery process with an efficient approach to create lead compounds by identifying and fixing bioactive conformations. Metal ion chelation makes a peptide segment rigid in a defined turn structure, with amino acid side chains in a determined position. This is the first important step in the process. This provides us a 3-D map of spatial alignment of key functional groups that are determined to be critical for bioactivity. This configuration is then translated to a drug-like template. The end product resulting from MIDAS can be either an optimized peptide-like peptidomimetic or a small molecule. The overall attempt in MIDAS is to take the drug discovery process toward industrialization.

As you know, the flexible structure of peptides causes them to fold freely, thereby facilitating their interaction with multiple-receptor types and enzymes. Also, specific turnkey technologies, such as phage display technologies, are routinely applied to generate peptide leads for any target. In fact one can generate peptide leads for any target irrespective of whether the natural ligand for that target happens to be a peptide or non-peptide. Converting these peptides into pharmaceutically useful entities is, however, a challenging job. Based on our success in generating both stabilized peptide-like as well as small molecule candidate drug molecules on different projects, we believe that MIDAS is uniquely positioned to bridge the gap between versatility and diversity of peptides as ideal candidates for rapid lead generation on one hand and drug-like characteristics of small molecules on the other.

Q: Can you describe the development of Palatin's lead product, Bremelanotide (formerly PT-141)?

A: In addition to the MIDAS technology, Palatin has developed an in-depth knowledge of the biology of the melanocortin family of G-coupled receptors. The first product developed from this work is Bremelanotide, a nasally administered drug candidate for the treatment of male and female sexual dysfunction. It is first in a new class of melanocortin agonists for the treatment of sexual dysfunction. Unlike approved treatments with the PDE-5 inhibitor class of drugs, Bremelanotide works through a CNS mechanism of action. It is currently undergoing separate Phase II clinical studies for the treatment of both male and female sexual dysfunction. In our previous four Phase II male erectile dysfunction (ED) efficacy studies with over 300 enrolled men, Bremelanotide showed therapeutic promise without the cardiovascular effects of currently available ED drugs. We also conducted a Phase I study in normal 32 premenopausal women, in which the drug was shown to be safe and well tolerated. A Phase IIa pilot clinical study evaluating bremelanotide in premenopausal women diagnosed with female sexual dysfunction (FSD) has shown encouraging results. Following ongoing Phase II studies in men with erectile dysfunction, we plan to initiate a Phase III trial.

Q: Why was a nasal spray chosen for the delivery of PT-141?

A: More and more data now becoming available suggests that nasal delivery may be a viable approach to deliver therapeutic levels of drugs to the brain. This may present an advantage for delivering CNS drugs because it may minimize problems due to higher systemic exposure of drugs. We have seen clear advantages in

terms of efficacy with Bremelanotide in humans. We also have similar results with some ongoing internal projects in animal models.

Q: What are some of the challenges facing nasal delivery systems today?

A: Certainly there are key prerequisites for commercial and development success of nasally administered drugs. Because nasal formulations are liquid formations, the drug needs to be highly soluble in aqueous formulations. For example, in order to deliver 10 to 15 mg of drug in 100-ml volume, you are talking about solubility higher than 100 to 150 mg/ml. This can pose limitations for a number of new chemical entities. The formulation needs to be simple and compatible with the nasal mucosa. Stability of the drug in liquid formulation to meet intended shelf-life and storage conditions can be problematic for some drugs. Cost of the delivery device contribution toward cost per unit dose also needs careful evaluation, particularly for single-use disposable devices.

Q: What other melanocortin-based therapeutics are in the works for Palatin?

A: Palatin is in the process of finalizing lead optimization of small molecule candidate drugs for the treatment of obesity. We are evaluating drug-like characteristics as we move toward development. The progress is very good and based on current data, we believe that our molecules have the right pharmacology. Our molecules are efficacious in decreasing both food intake and associated body weight without causing penile erections. This is a major challenge in the melanocortin-based obesity target. You need to separate these two effects, and we have done that for our obesity molecules. Throughout this process, we have learned a lot about CNS melanocortin receptors and have developed a good understanding of their mechanisms. Industry wide, this is a highly competitive area, and we believe we have an edge. We are also exploring use of melanocortin receptor-4 antagonists for the treatment of cachexia. We have developed potential lead molecules and are profiling these in animal models.

Q: Can you touch upon Palatin's alliance with King Pharmaceutical and the strategic importance?

A: We formed a collaboration with King Pharmaceuticals in August 2004 to jointly develop and commercialize Bremelanotide in North America for both male and female sexual dysfunction. Palatin and King will jointly seek a partner for Bremelanotide for territories outside of North America. We are jointly sharing development and marketing costs and will split all revenues generated from those territories. This is a win-win collaboration for both partners, serving their respective strategic needs. King's large primary care/cardiovascular-focused sales force makes King an ideal partner for Palatin and Bremelanotide. In King, we have a partner that is well energized and focused to move quickly in realizing the full potential of Bremelanotide.

Q: What are the company's long-term goals?

A: Palatin is moving forward with development of its first therapeutic product. This is a good example of what we are capable of accomplishing. We took Bremelanotide from discovery to its current extensive clinical trial stage, moving on a development path toward commercialization. We have built highly effective teams and an infrastructure in the areas of drug discovery, preclinical and clinical research, and product development. We have leveraged our proprietary MIDAS drug design system to garner organic growth by discovering new chemical entities to continually feed into a pipeline of product opportunities. We strive to be an efficient drug discovery and development company developing and managing a pipeline of new therapeutic products. ◆

Drug Delivery Showcase

Ophthalmic Delivery

InSite Vision is an ophthalmic products company focused on ocular infection, glaucoma, and retinal disease. The company specializes in three platform technologies: topical drug delivery (DuraSite), genomics, and retinal drug delivery. The company has a portfolio of both diagnostic and therapeutic products in early and late-stage development. DuraSite, a patented eyedrop formulation, can be customized to deliver a wide variety of potential drug candidates. Importantly, whereas conventional eyedrops typically only last a few minutes and are unable to sustain therapeutic drug levels, DuraSite remains in the eye for up to several hours, during which the active drug is gradually released. The increased time DuraSite remains in the eye allows lower concentrations of a drug to be administered over a longer period of time. For more information, contact InSite Vision at 510.865.8800 or visit **www.insitevision.com.**

Multiple Platforms & Products

Novosis AG is a pharmaceutical company dedicated to development and manufacturing of dermal, transdermal, and implantable drug delivery systems. Novosis has developed proprietary and patented technologies for actively controlled and non-continuous drug release. Big international pharmaceutical customers rely on the partnership with Novosis based on creative solutions and the successful integration of pharmaceutical development and GMP-manufacturing. Novosis AG is also developing own proprietary products and thus providing licensing opportunities for partners interested in transdermal and implantable application systems. For more information, visit Novosis at **www.novosis.com.**

Needle-Free Epidermal Delivery

PowderMed's ground-breaking approach employs a proprietary technology platform called PMED (Particle Mediated Epidermal Delivery), which relies on pressurized helium to shoot DNA-coated gold microparticles at 1,500 miles per hour into the immune network of the skin, which is impossible to access using a needle and syringe. The targeting of this immune cell rich tissue means that immune responses are seen with very small (microgram) doses of DNA; 1,000-fold less than with intramuscular DNA injection. The PMED "gene gun" requires minimal medical training, allows self-administration,and requires no refrigeration for stockpiling. PowderMed's lead product is a DNA-based prophylactic vaccine to target annual and pandemic influenza, which has successfully completed Phase I trials. For more information, visit PowedrMed at **www.powdermed.com.**

Polymer Delivery System

Controlled Therapeutics has developed a patented hydrogel polymer delivery system for the precise administration of drugs over an extended period of time. This controlled release technology has demonstrated an ability to maintain therapeutic levels of a drug when given by different routes of administration. For example, the hydrogel may be administered buccally or vaginally for local or systemic treatments. Specifically designed for pharmaceutical use, the polymer is capable of delivering drugs at a highly predictable and reproducible rate when exposed to body moisture. For more information, visit Controlled Therapeutics at **www.ctscotland.com.**

Drug Delivery Showcase

Solubility Solutions

Phares has developed in depth know-how and patents related to the formulation of poorly soluble compounds. Solubilization and bioavailability improvement are key goals of the formulation techniques. Phares has expertise and solutions for oral, parenteral, and topical delivery. The company delivers the right level of service for each stage of pharmaceutical development, ranging from lead compound selection, through preclinical development, to the scaling up and manufacturing of cGMP supplies for human clinical trials. Its formulators are experienced industrial pharmacists, with decades of cumulative experience working on insoluble compounds. This translates into an expert understanding of the real requirements of preclinical and clinical development, as well as cGMP and the importance of regulatory acceptability of excipients and manufacturing processes. For more information, visit **www.phares.biz.**

Sub-Q Protein Delivery

Would you like to convert your drugs from IV to subcutaneous (Sub-Q) delivery or enhance the dispersion of your existing Sub-Q compounds? With Enhanze™ Technology, microgram quantities of a fully human recombinant enzyme act as a "molecular machete" to clear the subcutaneous "jungle." Based upon this mechanism of action, co-delivery with Enhanze is anticipated to permit the Sub-Q administration of large volumes (up to 10 cc) of antibody drugs, speed onset of action relative to Sub-Q delivery without Enhanze, and improve patient comfort. For more information, contact Mark Wilson, Vice President of Business Development (Halozyme Therapeutics) at mwilson@halozyme.com or (858) 794-8889; or visit **www.halozyme.com.**

Silicone-Coated Papers & Films

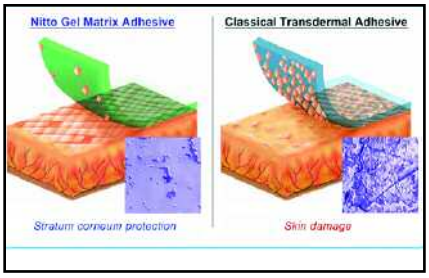
Loparex specializes in thin coatings on flexible webs in the manufacture of release liners for medical pressure sensitive adhesive (PSA) products. The major categories that define the medical PSA market include: Transdermal Drug Delivery Systems, EKG/ECG Electrodes and Electro-Medical Devices, and Wound Dressings. Key performance characteristics of release liners for medical PSA products include: complete traceability, cleanliness, moisture resistance, and die-cutability. Manufacturing release liners that satisfy the requirements of both manufacturer and end user is critical. Because of our continuing commitment to leading-edge technologies in chemistry and substrate development, Loparex is uniquely qualified to develop a release liner designed for your unique application. Look to Loparex for all your medical device release liner needs. For more information, contact Loparex, Inc., at (888) 327-5454, ext. 2671 or visit **www.loparex.com.**

Advanced Spray Technology

Spray Analysis and Research Services offers ways to improve and expedite drug delivery and manufacturing if you're looking for a new way to spray or have an existing coating, drying, or microencapsulation process that could benefit from optimization. A service of Spraying Systems Co., Spray Analysis uses advanced spray technology to help customers improve process efficiency and product quality, shorten development and testing time, and solve spray-related problems. Typical projects include tablet and device coating optimization, spray dry nozzle development and testing, atomizer prototyping, proof-of-concept tests, and spray characterization studies. For more information, contact Spray Analysis and Research Services at (800) 95 SPRAY or visit **www.sprayconsultants.com.**

Drug Delivery Showcase

Gel Matrix Adhesive Technology



Conventional transdermal technology has relied upon traditional pressure-sensitive adhesives, which include primarily acrylate-, silicone-, and rubber- or polyisobutylene- based polymers, as the primary matrix to adhere the patch to the skin. With these traditional adhesive types, a significant amount of stratum corneum cells are removed and transferred to the adhesive surface, resulting in damage and irritation to the skin. The technology employed by Aveva and Nitto Denko is based upon a proprietary adhesive composition, which addresses these problems. This Gel-Matrix adhesive has unusual properties that allow for exceptional adhesion and wear to the skin without the removal of a significant amount of stratum corneum cells. This allows for unique properties, including the ability to reapply patches while reducing skin damage and irritation. For more information, visit Aveva Drug Delivery Systems at **www.avevadds.com.**

Controlled Release Technologies

Egalet a/s is a drug delivery company focusing on formulation and development of oral controlled-release products using its proprietary drug delivery Egalet® and Parvulet® technologies. The company has four products in clinical development, two of which are entering into late-stage pivotal studies. The Egalet tablet incorporates almost any pharmaceutical into a polymeric matrix eroded by body fluids at a constant rate. The tablet, made by a simple, unique injection-moulding technique, can be used for virtually any type of medicine and provides controlled release with precision and reliability. The Parvulet technology is a novel approach for pediatric drug delivery combining improved consumer acceptance with highly competitive development and production costs. Egalet aims to become a preferred partner for the pharmaceutical industry with its strategy for controlling drug development efforts from product formulation to clinical testing, regulatory submissions, and manufacturing. For more information visit Egalet a/s at **www.egalet.com.**

Contract Manufacturer/Supplier

Buender Glas GmbH is a business unit of the Gerresheimer Group headquartered in Duesseldorf, Germany. As a specialist in pharmaceutical glass systems, Buender Glas concentrates primarily on problem solutions relating to all aspects of injections. The company is an international technology leader in the growth market of prefillable syringes and cartridges. Its particular specialities include sterile all-glass syringe systems under the trademark RTF® (Ready-to-Fill). For the production of sterile syringes, Buender Glas has a unique technology center in which state-of-the-art ultrapure water-processing plants and clean-room systems in the 10,000 class set the basic standards. The company's products comply at least with the European, US, and Japanese pharmacopoeia requirements and are FDA registered. For more information, contact Buender Glas North America, Chris King, at (267) 895-1722 or visit **www.buenderglas.com.**

Macromolecule Delivery

Emisphere Technologies' broad-based oral drug delivery technology platform, known as the eligen technology, is based on the use of proprietary, synthetic chemical compounds, known as EMISPHERE delivery agents, or "carriers." These delivery agents facilitate or enable transport of therapeutic macromolecules across biological membranes, such as those of the gastrointestinal tract, allowing the therapeutic molecules to exert their desired pharmacological effect. The delivery agents have no known pharmacological activity themselves at the intended clinical dose levels. Emisphere's eligen technology makes it possible to orally deliver a therapeutic molecule without altering its chemical form or biological integrity. For more information, contact Emisphere Technologies at (914) 347-2220 or visit **www.emispehere.com.**

COLON-SPECIFIC DELIVERY

Oral Colon-Specific Drug Delivery: An Overview

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INTRODUCTION

Oral administration has been the most convenient and commonly used method for drug delivery. For novel controlled drug-release systems, the oral route of administration has received the most attention. Many protein and peptide drugs like insulin cannot be administered through the oral route because of their degradation by the digestive enzymes of the stomach and the small intestine.

Colon- specific drug delivery systems offer several potential therapeutic advantages. Medical rationales for the development of orally administered colonic drug platforms include: (a) the opportunity to reduce adverse effects in the treatment of colonic diseases (eg, ulcerative colitis, colorectal cancer, Chorn's diseases, and amoebiasis) by topical application of drugs, active at the mucosal level; (b) the elucidation of the mode of action of some nonsteroidal anti-inflammatory drugs (NSAIDs), such as sulindac (metabolized in the colon to the active moiety, sulindac sulfide) that were found to interfere with the proliferation of colon polyps (first stage in colon carcinoma), possibly in a local manner; (c) the recognition that in some cases, the colon is capable of absorbing drugs efficiently; (d) accumulated evidence that drug absorption enhancement works better in the colon than in the small intestine; (e) the anticipation that protein drugs can be absorbed better from the large bowel owing to hypothetic reduced proteolytic activity in this organ; and (f) the unique metabolic activity of the colon, which makes it an attractive organ for drug delivery systems designers.[1-4]

Colonic drug delivery can be achieved by oral or by rectal administration. With regard to the rectal route, the drugs do not always reach the specific sites of the colonic diseases and the sites of colonic absorption.[5,6] To reach the colon and to be able to specifically deliver and absorb the drug there, the dosage form must be formulated tacking into account the obstacles of the gastrointestinal tract. The various strategies developed to achieve this goal have used the specific characteristics of this organ, ie, pH, microflora, enzymes, reducing medium, and transit time. Neverthless, these parameters can vary from one individual to the next, and also according to pathological conditions and diet.

Various pharmaceutical approaches that can be exploited for the development of colon-targeted drug delivery systems include the use of prodrugs, pH-sensitive polymers, bacterial degradable polymers, hydrogel and matrices, and multicoating time-dependent delivery systems.

EVOLUTION OF COLON-SPECIFIC DELIVERY TECHNOLOGY

Ongoing research in the area of oral delivery of drugs, a discipline that has basked in the spotlight of pharmaceutical sciences for the past 70 years, has led to improved and profound insights into the physiology, biology, and physical chemistry (pharmacokinetics, partitioning phenomenon) of organs, compartments, cells, membranes, cellular organelles, and functional proteins (eg, transporters) associated with absorption processes of xenobiotics in the alimentary canal. The predominance of this comprehensive research has led to improvements in the design of drug products aimed at performing in the lumen of the small bowel. The large bowel, however, because of its remoteness, different physiology, and relatively poor absorption capacity acquired the status of an outcast. The advent of slow-release technologies increases the chances for a drug to be released in the colon and thus this organ has an important role to play in drug absorption from oral sustained-release formulations. Its unique luminal metabolic activity makes it possible to direct prodrugs for topical treatment of inflammation processes confined to its epithelium. Nonetheless, colonic delivery is far from fully exploited as it still awaits appropriate medical targets and physiologically driven rational drug delivery designs. Smart engineering might not be sufficient, and new creative approaches are most probably needed. For example, it is improbable that a single dosage form, taken orally, will be able to make the long road to the large bowel and allow precise regional treatment or cellular targeting within the colon.

In 1942, Svartz discovered that

COLON-SPECIFIC DELIVERY

Sulfasalazine, the sulfanilamide prodrug of 5-aminosalicylic acid (5-ASA) (Figure 1) is effective in the treatment of rheumatoid arthritis and anti-inflammatory disease.[7] The exact mode by which the drug targets itself to the colon was elucidated much later in 1970: colon-specific azoreduction splits sulfasalazine causing the release of the active moiety, 5-ASA, in a local manner.[8] Once this was understood, several other azo-bond-containing compounds, designed to locally release 5-ASA, were synthesized: bensalazine (Intestinol 1), balsalazide, and the newer prodrug olsalazine (Dipentum 1), which spares the superfluous systemic appearance of the carrier molecule.[9]

An exciting study, which was published in 1986 by Saffran and co-workers, described the use of azo-containing acrylic polymers for the delivery of protein drugs (insulin, lysine–vasopressin) to the colon. The uniqueness of this approach, which was tested in rats and later in dogs, was its suggestion to use a biodegradable polymer not as a polymeric backbone of a particular drug but rather as a general platform to ferry a variety of molecules without the need to invest in efforts to design a carrier for each drug separately.[10] The major concern was that the delayed drug release observed was a result of the delayed polymer hydration, similar to that occurring with enteric coated polymers, which already existed commercially, rather than a specific cleavage phenomenon.

FACTORS TO BE AFFECTED IN THE DESIGN OF COLON-TARGETED DRUG DELIVERY SYSTEMS

Anatomy & Physiology of Colon

The large intestine extends from the distal end of the ileum to the anus. The human large intestine is about 1.5 m long (Table 1). Its caliber is higher near the cecum and gradually diminishes to the rectum, where as it enlarges just above the anal canal. The colon is the upper 5 feet of the large intestine and mainly situated in the abdomen. The colon is a cylindrical tube lined by a moist, soft pink lining called mucosa, the pathway is called the lumen and is approximately 2 to 3 inches in diameter.[13] The cecum forms the first part of the colon and leads to the right colon or the ascending colon (just under the liver) followed by the transverse colon, the descending colon, sigmoidal colon, rectum, and the anal canal (Figure 2).[12] Unlike the small intestine, the colon does not have any villi. However, because of the presence of plicae semilunares, which are crescentic folds, the intestinal surface of the colon is increased

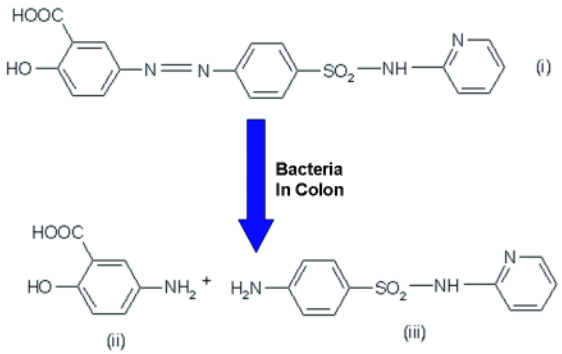
TABLE 1

Region of GI Tract	Characteristics
Length (cm)	
Entire GI Tract	500-700
Small Intestine	
-Duodenum	20-30
-Jejunum	150-250
-Ileum	200-350
Large Intestine	
-Cecum	6-7
-Ascending colon	20
-Transverse colon	45
-Descending colon	30
-Sigmoid colon	40
-Rectum	12
-Anal canal	3
Internal Diamater (cm)	
Small Intestine	3-4
Large Intestine	6
pH	
Stomach	
-Fasted	1.5-3
-Fed	2-5
Small Intestine	
-Duodenum (fasted)	≈6.1
-Duodenum (fed)	≈5.4
- Ileum	≈7-8
Large Intestine	
-Cecum & Colon	≈5.5-7
-Rectum	7

Summary of anatomical and physiological features of small intestine and colon. (Adapted From Reference 45)

COLON-SPECIFIC DELIVERY

FIGURE 1



Hydrolysis of sulfasalazine(i) into 5-aminosalysilic acid (ii) and sulfapyridine (iii). Upon colonic azoreduction, one molecule of sulfasalazine releases a single molecule of 5-ASA. (Adapted From Reference 11)

to approximately 1300 cm^2.[14] The physiology of the proximal and distal colon differs in several respects that can have an effect on drug absorption at each site. The physical properties of the luminal content of the colon also change, from liquid in the cecum to semisolid in the distal colon. The major functions of the colon are: 1) The consolidation of the intestinal contents into feces by the absorption of the water and electrolytes and to store the feces until excretion. The absorptive capacity is very high, each day about 2000 ml of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed. 2) Creation of a suitable environment for the growth of colonic microorganisms, such as Bacteroides, Eubacterium, and Enterobacteriaceae. 3) Expulsion of the contents of the colon at a suitable time. 4) Absorption of water and Na^+ from the lumen, concentrating the fecal content, and secretion of K^+ and HCO_3^-.[12]

pH in The Colon

The pH of the gastrointestinal tract is subject to both inter- and intrasubject variations. Diet, diseased state, and food intake influence the pH of the gastrointestinal fluid. The change in pH along the gastrointestinal tract has been used as a means for targeted colon drug delivery.[16] There is a pH gradient in the gastrointestinal tract with value ranging from 1.2 in the stomach through 6.6 in the proximal small intestine to a peak of about 7.5 in the distal small intestine (Table 1).[17] The right, mid, and left colon have pH values of approximately 6.4, 6.6, and 7.0, respectively.[17] The pH of the colon is often lower than the pH of the small intestine, which can be as high as 8 or 9.[17] The pH difference between the stomach and small intestine has historically been exploited to deliver the drug to the small intestine by way of pH-sensitive enteric coatings. There is a fall in pH on the entry into the colon due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides. For example, lactose is fermented by colonic bacteria to produce large amounts of lactic acid, resulting in a drop in the pH to about 5.0.[18]

Colonic Microflora & Their Enzymes

Intestinal enzymes are used to trigger drug release in various parts of the GI tract. Usually, these enzymes are derived from gut microflora residing in high numbers in the colon. These enzymes are used to degrade coatings/matrices as well as to break bonds between an inert carrier and an active agent (ie, release of a drug from a prodrug). Over 400 distinct bacterial species have been found, 20% to 30% of which are of the genus Bacteroides.[19] The upper region of the GI tract has a very small number of bacteria and predominantly consists of Gram-positive facultative bacteria. The concentration of

TABLE 2

Enzymes	Microorganism	Metabolic Reaction Catalyzed
Nitroreductase	E. coli, Bacteroids	Reduce aromatic and heterocyclic nitro compounds
Azoreductase	Clostridia, Lactobacilli, E. Coli	Reductive cleavage of azo compounds
N-Oxide reductase, sulfoxide reductase	E. coli	Reduce N-Oxides and sulfoxides
Hydrogenase	Clostridia, Lactobacilli	Reduce carbonyl groups and aliphatic double bonds
Esterases and amidases	E. coli, P. vulgaris, B. subtilis, B. mycoides	Cleavage of esters or amidases of carboxylic acids
Glucosidase	Clostridia, Eubacteria	Cleavage of , β-glycosidases of alcohols and phenols
Glucuronidase	E. coli, A. aerogenes	Cleavage of , β-glucuronidases of alcohols and phenols
Sulfatase	Eubacteria, Clostridia, Streptococci	Cleavage of O-sulfates and sulfamates

Drug metabolizing enzymes in the colon that catalyze reactions (Adapted From Reference 46)

COLON-SPECIFIC DELIVERY

bacteria in the human colon is 1011 to 1012 CFU/ml. The most important anaerobic bacteria are Bacteroides, Bifidobacterium, Eubacterium, Peptococcus, Peptostreptococcus, Ruminococcus, Propionibacterium, and Clostridium.[20] A summary of the most important metabolic reactions carried out by intestinal bacteria is provided in Table 2.

Transit of Material in the Colon

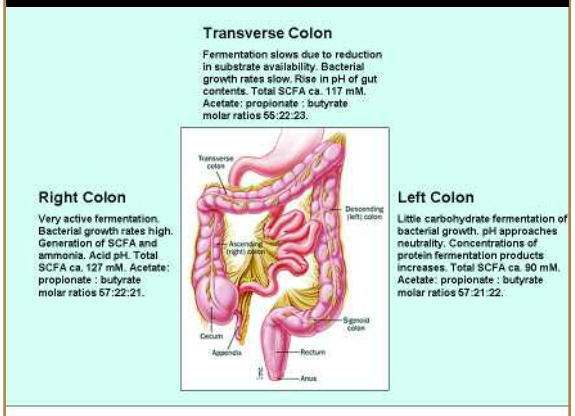
Gastric emptying of dosage forms is highly variable and depends primarily on whether the subject is fed or fasted and on the properties of the dosage form, such as size and density. The transit times of different dosage forms in the GI tract are provided in Table 3.

The effect of transit abnormalities has been examined using gamma scintigraphy. Transit data following oral administration of a radiolabelled liquid meal to UC patients during active and quiescent disease are shown in Table 4.[22] Gastric half-emptying time and mouth-to-cecum transit times of the radiolabelled meal were about the same regardless of disease site or activity. Whole gut transit times were relatively long, ranging from 56 to 78 hours. Colonic transit times (estimated from the difference in mouth to cecum and whole gut transit times) ranged from 50 to 70 hours. Stool weights increased significantly with active disease presumably due to exudates from inflamed epithelium, increased mucus secretion, and reduction in reabsorption of fluid and electrolytes.[22]

DRUGS SUITABLE FOR COLONIC DRUG DELIVERY

Drug delivery selectively to the colon through the oral route is becoming increasingly popular for the treatment of large intestinal diseases and for systemic absorption of peptide and protein drugs. It is well recognized that peptides and proteins are well absorbed intact from the GI tract, but the bioavailability is invariably extremely low, with exceptions, such as dipeptide and tripeptide analogues, cyclosporine.[23,24] A variety of protein and peptide drugs like calcitonin, interferon, interleukins, erythropoietin, growth hormones, and even insulin are being investigated for their systemic absorption using colon-specific delivery.[25] Inflammatory bowel disease (IBD), such as ulcerative colitis and Crohn's disease, require selective local delivery of the drug to the colon. Sulfasalazine is the most commonly prescribed medication for such diseases. The other drugs used in IBD are steroids, such as dexamethasone, prednisolone, and hydrocortisone. In Colonic cancer, anticancer drugs like 5-flurouracil, doxorubicin, and nimustine are to be delivered specifically to the colon. The site-specific delivery of drugs like, metronidazole, medendazole, albendazole are used in the treatment of infectious diseases, such as amoebiasis and helmenthiasis.[26-28] Because of the small extent of paracellular transplant, the colon is a more selective site for drug absorption at the small intestine. Drugs shown to be well absorbed include glibenclamide, diclofenac, theophylline, ibuprofen, metoprolol, and oxprenolol.[29-34]

FIGURE 2



Anatomy of the Colon

STRATEGIES FOR COLON-SPECIFIC DRUG DELIVERY

Prodrugs

A prodrug is pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in vivo to release the active drug. For colonic delivery of drugs, prodrugs are designed to undergo minimal absorption and hydrolysis in the tracts of the upper GI tract and undergo enzymatic hydrolysis in the colon, thereby releasing the active drug moiety from the carrier. A number of other linkages susceptible to bacterial hydrolysis specifically in the colon have been prepared where the drug is attached to hydrophilic moieties like amino acid, glucuronic acid, glucose, galactose, cellulose, coating materials over drug cores, etc (Table 5).

Polysaccharides are used as glucuronic prodrugs, which are specifically degraded by Colonic-glucuronidases, and glycosidic prodrugs, which are specifically degraded by Colonic glycosidases.[35,36] The most widely used polysaccharide of this type is dextran.[37] The action of bacterial glycosidase enzymes on the glycosidic bond permits the release of the attached drug, then triggers its pharmacological activity.[38] The metabolism of azo compounds by the intestinal bacteria is one of the most extensively studied bacterial metabolic processes. Both intracellular and extracellular reduction has been observed. Back in 1942, it was realized that sulphasalazine given for the treatment of rheumatoid arthritis was also useful in patients with IBD. Furthermore, Khan et al found that the active moiety effective in IBD was 5-amino-3 salicylic acid (5-ASA), and sulphapyridine (SP) only acted as a carrier.[39] The high-site specificity of prodrugs clearly indicates the involvement of the colon for the prodrug to drug conversion.

For colonic delivery of drugs, prodrugs are designed to conversion is strengthened by the studies carried out on germ-free animals

TABLE 3			
	Transit Time (h)		
Dosage Form	Stomach	Small Intestine	Total
Tablets	2.7 ± 1.5	3.1 ± 0.4	5.8
Pellets	1.2 ± 1.3	3.4 ± 1.0	4.6
Capsules	0.8 ± 1.2	3.2 ± 0.8	4.0
Solution	0.3 ± 0.07	4.1 ± 0.57	4.4

Transit times of various dosage forms across the segments of the GI tract. (Adapted From Reference 47)

or animals pretreated with antibiotics like kanamycin. These studies have shown that the hydrolysis of the prodrug to active drug moiety was significantly inhibited under such conditions.[40,41]

Anti-inflammatory glucocorticoids do not possess carboxylic acid groups and must be chemically transformed in order to react with dextran. Dexamethasone and methyl prednisolone were attached to dextran using succinic acid as a spacer, and the resultant prodrug were incubated with rat GI tract contents, but were rapidly degraded in caecal and colonic contents.[42,43] This illustrates the usefulness of the conjugates for selective delivery of glucocorticoids to the large intestine.

pH-Dependent System

The pH-dependent systems exploit the generally accepted view that pH of the human GI tract increases progressively from the stomach (pH 1 to 2, which increases to 4 during digestion), small intestine (pH 6 to 7) at the site of digestion, and increases to 7 to 8 in the distal ileum. The coating of pH-sensitive polymers to the tablets, capsules, or pellets provide delayed release and protect the active drug from gastric fluid. The polymers (Table 6) used for colon targeting, however, should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine and also be able to disintegrate at the neutral of slightly alkaline pH of the terminal ileum and preferably at the ileocecal junction. Widely used polymers are methacrylic resins (Eudragits), which are available in water-soluble and water-insoluble forms. Eudragit L and S are copolymers of methacrylic acid and methyl methacrylate. Eudragit L is soluble at pH 6 or above and is used as an enteric coating polymer, while Eudragit S is soluble at pH 7 or above and is used to deliver drugs to the end of the small bowel and large intestine. Colon-targeted drug delivery systems based on methacrylic resins have been used for insulin, prednisolone, quinolones, salsalazine, cyclosporine, beclomethasone dipropionate, and naproxane.[48-58]

In a study performed by Khan et al, lactose placebo tablets were coated using different combinations of Eudragit L and Eudragit S.[59] The Eudragit L-Eudragit S combinations (w/w) studied were 1:0, 4:1, 3:2, 1:1, 2:3, 1:4, 1:5, and 0:1. The disintegration data obtained from the placebo tablets demonstrate that disintegration rate of the tablets is dependent on 1) the polymer combination used to coat the tablets, 2) the pH of the disintegration media, and 3) the coating level of the tablets. It has been shown that polymers with nonesterified phthalic acid groups dissolve much faster and at a lower pH than those with acrylic or methacrylic groups. The presence of plasticizer and the nature of the salts in the dissolution medium influence the dissolution rate.[60]

In a recent study by Peeters and Kinget, the free carboxylic groups of Eudragit-S were partially methylated.[61] The product was found to dissolve in water at a slightly higher pH compared with the original polymer. The effectiveness of this product as a colon-specific coating material had been established with human volunteers using in vivo scintigraphic studies.[62] In a study by Gazzaniga and co-workers, an oral dosage form was developed consisting of a core with two polymeric layers.[63] The outer layer, which was an enteric coating, dissolved at a pH level above 5. The inner layer, made up of Hydroxypropyl methylcellulose, acted as a retarding agent to delay drug release for a predetermined period. The thickness of the inner layer determined the lag time. This system was found to release drug in the colon of the rat between the fifth and tenth hour. Markus et al developed a multi-unit dosage form containing 5-ASA for the treatment of ulcerative colitis.[64] Pellets were prepared by a granulation and spheronization process and then coated with a new pH-sensitive poly(meth)acrylate copolymer (Eudragit FS 30D) to achieve site-specific drug release close to the ileocaecal valve. From the dissolution studies, it was concluded that pellets released rapidly at pH values above 7.5. Between 6.8 and 7.2, drug release was found to be zero-order, while at pH 6.5 and below, no release occurred. In a biorelevant medium, which simulates the fasting proximal small intestine fluid, it was shown that neither surfactants (sodium taurocholate and lecithin) nor changes in ionic strength trigger drug release. Compared to 5-ASA pellets coated with the well-established Eudragit S, and to currently marketed products licensed for the treatment of ulcerative colitis, the multi-unit dosage form coated with the new polymer exhibited an *in vitro* dissolution profile more appropriate to the pH profile of the ileum and the colon observed in ulcerative colitis patients.

TABLE 4

	Total Colitis (n=6)			Distal Colitis (n=8)		
	Active	Quiescent	p	Active	Quiescent	p
Half-time for gastric emptying (min)	46 ± 22[b]	41 ± 6	N.S.[c]	51 ± 23	78 ± 33	<0.005
Mouth-to-cecum transit (min)	298 ± 62	310 ± 60	N.S.	313 ± 87	78 ± 33	N.S.
Whole gut transit (h)	64 ± 22	56 ± 29	N.S.	68 ± 49	293 ± 82	N.S.
Mean daily stool weight (g)	253 ± 72	159 ± 62	<0.02	192 ± 99	144 ± 79	<0.005
Mean daily stool frequency	4.1 ± 1.0	1.9 ± 1.0	<0.002	3.0 ± 0.8	1.2 ± 0.7	<0.001

[a] From Reference 22; [b] Data Are Means F.S.D.; [c] N.S.= Not Significant

Time-Dependent Systems

Time-dependent dosage forms are formulated to release their drug load after a predetermined lag time. While not a site-specific drug delivery system per se, it has been suggested that colonic targeting can be achieved by incorporating a lag time into the formulation equivalent to the mouth-to-colon transit time. A nominal lag time of 5 hours is usually considered sufficient, since small intestinal transit has been considered relatively constant at 3 to 4 hours. A number of systems have been developed based on this principle, with one of the earliest being the somewhat complex Pulsincap device (Figure 3).[66] This device consists of a non-disintegrating half capsule shell sealed at the open end with a hydrogel plug. The plug hydrates on contact with gastrointestinal fluid, and swells to an extent that it is expelled from the capsule body, thus releasing the drug. Usually, the time it takes the hydrogel plug to hydrate and eject from the capsule shell defined the lag time prior to drug release, and hence, by altering the composition and size of the hydrogel plug, it is possible to achieve drug release after varying lag times.

A pulsed system, called the Time-Clock System, has been developed. The system comprises a solid dosage form coated with a hydrophobic surfactant layer to which a water-soluble polymer is attached to improve adhesion to the core.[67] The thickness of the outer layer determines the time required to disperse in an aqueous environment. After the dispersion of the outer layer, the core becomes available for dispersion. An advantage is that common pharmaceutical excipients can be used to manufacture the system. Studies performed in human volunteers showed that the lag time was not affected by gastric residence time. Also, the dispersion of the hydrophobic film was not influenced either by the presence of intestinal digestive enzymes or by the mechanical action of the stomach.

Microflora-Activated Systems

The bioenvironment inside the human GI tract is characterized by the presence of complex microflora, especially the colon that is rich in microorganisms that are involved in the process of reduction of dietary components or other materials. Drugs that are coated with the polymers, which are showing degradability due to the influence of colonic microorganisms, can be exploited in designing drugs for colon targeting. These bacterial-degradable polymers, especially azo polymers, have been explored in order to release an orally administered drug in the colon. Actually, upon passage of the dosage form through the GI tract, it remains intact in the stomach and small intestine where very little microbially degradable activity is present that is quite insufficient for cleavage of the polymer coating.

Chavan et al synthesised a urethane-based analogue containing an azo aromatic linkage in the backbone for use in colon-specific delivery systems by reacting toluene-2, 6-diisocyanate with a mixture of an aromatic azo diol, (bis-4-hydroxyphenyl)-4, 4'-diazobiphenyl, poly (ethylene glycol) and 1, 2-propanediol (propylene glycol).[68] The

TABLE 5

Design Strategy	Drug-Release Triggering Mechanisms	Comments
Prodrugs	Cleavage of the linkage bond between drug and carrier via reduction and hydrolysis by enzymes from colon bacteria. Typical enzymes include azoreductase, glycosidase, and glucuronidase.	Prodrug is able to achieve site specificity. However, it will be considered as a new chemical entity. So far, this approach has been primarily constricted to actives related to the treatment of IBD.
pH-Dependent Systems	Combination of polymers with pH-dependent solubility to take advantage of the pH changes along the GI tract.	Unpredictable site specificity of drug release because of inter/intra subject variation and similarity of pH between small intestine and the colon.
Time-Dependent Systems	The onset of drug release is aligned with positioning the delivery system in the colon by incorporating time factor, simulating the system transit in the upper GI tract.	Even though the transit times in small intestine are rather consistent, high variation of gastric retention times makes this approach complicated in predicting the accurate location of drug release.
Microflora-Activated Systems	Primarily fermentation of non-starch polysaccharides by colon anaerobic bacteria. The polysaccharides have been incorporated into the delivery system via film-coating and matrix formation.	This strategy is highly promising because non-starch polysaccharides can only be degraded in the colon. It should be pointed out that enzymatic degradation of a polysaccharide matrix is a slow process, usually requiring over 12 hrs for complete degradation.

Summary of colon-specific drug delivery strategies. (Adapted From Reference 44)

compounds exhibited low molecular weight, lacked film-forming properties, and had crystallinity in the structure. An *in vitro* bacterial-degradation test to demonstrate the susceptibility of azo bond to bacterial enzymes was performed using media inoculated with lactobacillus culture. The results indicated degradation of films by azoreductase.

A system was developed by Saffran and coworkers in which insulin or vasopressin was encapsulated in a gelatin capsule coated with an impermeable polymer.[69] The coat, prepared by using azo functional cross-linking agents based on divinylazobenzene, was resistant to degradation in the stomach and the small intestine. However, problems were encountered attributable to variability in absorption, which may be because of intra- and intersubject differences in microbial degradation of the coating that may not be hydrophilic enough.

Polysaccharides offer an alternative substrate for the bacterial enzymes present in the colon. Many of these polymers are already used as excipients in drug formulations or are constituents of the human diet and are therefore generally regarded as safe. A large number of polysaccharides have already been studied for their potential as colon-specific drug carrier systems, such as chitosan, pectin, chondroitin sulphate, cyclodextrin, dextrans, guar gum, inulin, amylose, sodium alginate, and locust bean gum.

Chitosan capsules enteric coated with a layer of Hydroxypropyl methylcellulose (HPMC) phthalate have been evaluated for colon delivery of drugs.[70] *In vitro* studies showed that the capsules loaded with a soluble dye, 5-(6)-carboxyfluorescein (CF) showed little release in simulated gastric juice for 2 hours (transit time in stomach) and in artificial intestinal juice (next 4 hours), but the presence of rat cecal contents (33%) in the dissolution fluid increased the release rate of the drug; CF from the capsules from 20 to 100% in the next 4 hours. This suggests that the flora present in the rat cecal content may have produced enzymes for the degradation of chitosan or alternatively, the bacterial fermentation in the cecal contents may have decreased the pH of its contents, and chitosan may have easily dissolved under acidic condition.

TABLE 6	
Polymers	**Threshold pH**
Eudragit® L 100	6.0
Eudragit® S 100	7.0
Eudragit® L-30D	5.6
Eudragit® FS 30D	6.8
Eudragit® L 100-55	5.5
Polyvinyl Acetate Phthalate	5
Hydroxypropyl Methylcellulose Phthalate	4.5- 4.8
Hydroxypropyl Methylcellulose Phthalate 50	5.2
Hydroxypropyl Methylcellulose Phthalate 55	5.4
Cellulose Acetate Phthalate	4.8
Cellulose Acetate Trimellate	5.0

Threshold pH of commonly used polymers. (Adapted From Reference 48)

Macleod et al have studied the potential of pectin:chitosan:Hydroxypropyl methylcellulose films for colonic drug delivery.[71] The results showed that in all cases, the tablets were able to pass through the stomach and small intestine intact. The tablets started to break up once they were in the colon, as a result of degradation of the coating by colonic bacteria.

Cross-linked chondroitin sulphate was used to form a matrix tablet with indomethacin.[72,73] Release of indomethacin from this tablet was studied in the presence of rat cecal contents as compared to the release in phosphate buffer saline. A significant difference in drug release was observed after 14 hours in the two dissolution media.

A series of studies were carried out on chicory inulin.[74] Methacrylated inulin was synthesized, and aqueous solutions of Methacrylated inulin upon free radical polymerization were converted to cross-linked hydrogels.[74] These hydrogels were then studied for their swelling properties.[75,76] Degradation studies carried out in the presence of inulinase showed that increasing enzyme concentration and incubation time degraded inulin faster.

Alginate beads coated with dextran acetate were prepared. These beads showed minimal drug release in the absence of dextranase, but significant drug release was seen in presence of dextranases *in vitro*.[77]

Compression-coated tablets of 5-ASA and matrix tablets of mebendazole have been prepared using guar gum as a carrier.[78] Matrix tablets containing various proportions of guar gum were prepared using a wet granulation technique using starch paste as a binder. The tablets were evaluated for drug content uniformity and were subjected to *in vitro* drug-release studies. The results of the study revealed that matrix tablets containing either 20% or 30% of guar gum are most likely to provide targeting of mebendazole for local action in the colon.

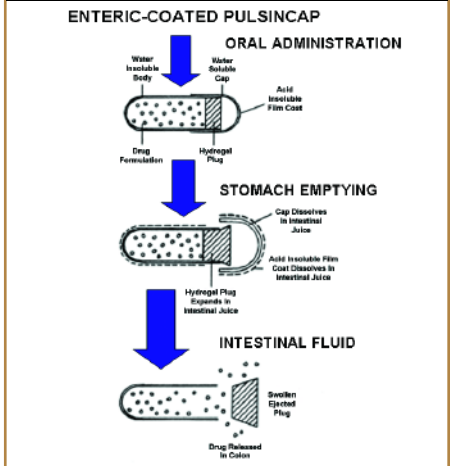
Amylose-Ethocel coating systems, resistant to gastric acid and small intestinal enzymes, but degradable by colonic bacteria, were prepared and evaluated *in vitro* for their potential as a colon drug carrier. Varying concentrations of Amylose and Ethocel in the form of aqueous dispersions were used to coat 5-ASA pellets. A coating formulation comprising Amylose and Ethocel in the ratio of 1:4 w/w showed optimum drug-release-retarding properties in gastric and intestinal fluids.[79,80]

IN VITRO EVALUATION OF COLON-SPECIFIC DRUG DELIVERY SYSTEMS

A successful colon-specific drug delivery system is one that remains intact in the physiological environment of stomach and small intestine, but releases the drug in the colon. Different *in vitro* methods are used to evaluate the colonic drug delivery systems.

The ability of the coats/carriers to

FIGURE 3



Schematic Representation of Pulsincap® System (Adapted From Reference 66)

remain intact in the physiological environment of the stomach and small intestine is generally assessed by conducting drug-release studies in 0.1N HCl for 2 hours (mean gastric-emptying time) and in pH 7.4 Sorensen's phosphate buffer for 3 hours (mean small intestinal transit time) using a USP dissolution rate test apparatus or flow through dissolution apparatus. Currently, four dissolution apparatus are recommended in the USP to accommodate different actives and dosage forms: basket method, paddle method, Bio-Dis method, and flow-through cell method.

Tablets covered with compression coats of pectin were evaluated by this method, and it was found that drug was not released during the period of testing. The ability of the delivery system to release the drug in the colon is tested *in vitro* by incubating it in a buffer medium in the presence of either enzymes (eg, pectinase, dextranase) or rat/guinea pig/rabbit caecal contents.[81-85] The amount of drug released at different time intervals during the incubation is estimated to find out the degradation of the carrier under study.

Rama Prasad et al, while reporting the usefulness of guar gum as a carrier for colon-specific delivery, established that a buffer medium with rat caecal contents (4% w/v) obtained after 7 days of enzyme induction provides the best conditions for *in vitro* evaluation. Another *in vitro* method involves incubation of the drug delivery system in a fermentor with commonly found human colonic bacteria like Streptococcus faecium or Bacteroide ovatus in a suitable medium under anaerobic conditions and the amount of drug released at different time intervals is found out. This method is considered more specific because it involves the use of commonly found human colon bacteria.

USP Dissolution Apparatus III (reciprocating cylinder) was employed to assess *in vitro* the performance of guar-based colonic formulations.[86] Because of the unique set-up of dissolution apparatus III (ie, the dissolution tubes can be programmed to move along successive rows of vessels), drug release can be evaluated in different medium successively. Wong et al evaluated several guar-based colonic formulations using Apparatus III in simulated gastric fluid (pH 1.2), simulated intestinal fluid (pH 7.5), and simulated colonic fluids containing galactomannanase. As expected, when compared with drug release in simulated gastric and intestinal fluids, results showed that drug release was accelerated in the colonic fluid due to the presence of the galactomannanase that could hydrolyze the guar gum.

SUMMARY

A considerable amount of research work has been carried out on the development of colon-specific drug delivery systems. The large inter- and intrasubject variation in the GI pH makes the approach of delivery systems based upon pH-dependent polymers less suitable. The preferred colon-specific delivery systems are those that rely on conditions that are only encountered in the colon, since such systems will give true site-specificity. Of the colon-specific carriers tested to date, the natural polymers, such as dextran, pectin, guar gum, etc, are more favorable with respect to safety. A lot of research remains to be conducted to find out to what extent these molecules can be absorbed after oral administration. It is probable that such formulations will reach the market in the coming years.

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COLON-SPECIFIC DELIVERY

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Cardinal Health	76	866-720-3148		www.cardinal.com/pts
Ciba Expert Services	4	800-242-2669 x2397		www.cibasc.com/cxs
CIMA	5	952-947-8700		www.cimalabs.com
Degussa	13	732-981-5383		www.pharma-polymers.com
Drug Delivery & Deal Making Summit	41	800-599-4950		www.srinstitute.com/cs375
Eurand	7	937-898-9669		www.eurand.com
Filtertek Inc.	37	1-800-648-0791		www.filtertek.com
Genzyme Pharmaceuticals	21	800-868-8208		www.genzymepharmaceuticals.com
Hovione	15	609-918-2600		www.hovione.com
NOF Corporation	75	914-6819790		www.nof.co.jp/dds
Scolr Pharma, Inc	9	425-373-0171		www.scolr.com
SST	73	215-979-1506		
Weiler Engineering	11	847-697-4900		www.weilerengineering.com

SECURED PARTY PUBLIC SALE

PLEASE BE ADVISED THAT National Paintball Supply, Inc. ("Lender") will sell all or a portion of the personal property described below (the "Collateral"), pledged by Blue Arc Holding, LLC (the "Debtor") to Lender pursuant various agreements and documents including, but not limited to, that certain Security Agreement dated as of April 5, 2005 by and between the Lender, as the secured party, and the Debtor, as the debtor, to the highest qualified bidder in public as follows:

Day and Date: Thursday, August 10, 2006
Time: 2:00 p.m. to 4:00 p.m. (prevailing Eastern time)
Place: National Paintball Supply, Inc., 570 Mantua Boulevard, Sewell, NJ 08080

The debtor is entitled to an accounting of the unpaid indebtedness secured by the Collateral. For such an accounting or if you have any questions regarding this notification, please contact Rudolph J. DiMassa, Esquire, counsel for the Lender, at 215-979-1506.

Description of Collateral

All Equipment and Fixtures, including without limitation all machinery, furniture, systems or apparatus, office equipment, computers, appliances, and, with respect to all of the foregoing, all accessions, parts, substitutions, improvements, accessories, replacements, additions, renewals, filings, components, tools, dies, patterns, molds, attachments, and appurtenances in any way used with, attached or related to, or installed in, or intended to be so used, attached, related to or installed in, any of the foregoing;

All Goods, Inventory and Documents, including, without limitation (and whether or not the same constitute Goods, Inventory or Documents), the items referred to in the paragraph above, warehouse receipts, bills of lading, together with all deeds, bills of sale, manuals of operations, maintenance or repair, computer records, printouts, drawings, blueprints and other documents and written materials related thereto; and

All Proceeds of any of the foregoing.

The Collateral includes, but is not limited to, the following:

Inspection and Packing

Qty.	*Manufacturer*	*Description*
1	NESTAFLEX	Accordian Roller Conveyor
1	NESTAFLEX	Accordian Roller Conveyor
1	NESTAFLEX	Accordian Roller Conveyor
1	NESTAFLEX	Accordian Roller Conveyor
4		Inspection Tubs 26x18x9"
1		Hardness Tester
1	Metler/Toledo	Viper D Gram Scale
1	Metler/Toledo	Viper D Gram Scale
1	Metler/Toledo	Viper D Gram Scale
1	Metler/Toledo	Viper D Gram Scale
1		Manual Pallet Jack
1	XPEDX	AUTO TAPE MACHINE+Freight
1	XPEDX	AUTO TAPE MACHINE+Freight
1	XPEDX	AUTO TAPE MACHINE+Freight
1	XPEDX	AUTO TAPE MACHINE+Freight
45	Technapher	Tray Dollies
2232	Technaphar	Shallow Drying Trays
2520	Molded Fiberglass Tray Co.	NEW TRAYS
2248		OLD TRAYS
53	Molded Fiberglass Tray Co.	NEW DOLLIES
45		OLD DOLLIES
4	Xpedx	Stainless Infeed Tables/w castors
1	Technophar	Hardness Tester
1	Pacific Chloride	Forklift & Charger
10	Advance Tabco	Stainless Tables 30"X60"
1		Stainless Platform Truck
2	Meco	Drum Truck 1000 lbs (2)
1		AUTO SHRINK WRAPPER
1		Taping Machine - Expedx
1		Taping Machine - Expedx
1		Tooling for box printing
1		Pallet racks for Warsehouse-Ross Mixing
1		Cutting Dies for Dusobox White Boxes
600		Drying trays from Cardinal
1	Melco	Melco packaging line
3900	Cardinal Health	Used deep drying trays for tunnels

Compounding Equipment

Qty.	*Description*
1	Top Entry Mixers w/Speed Reducers
1	Top Entry Mixers w/Speed Reducers
1	Top Entry Mixers w/Speed Reducers
1	Top Entry Mixers w/Speed Reducers
1	Top Entry Mixers w/Speed Reducers
1	Material Totes
7	Stainless Material Tanks 80 Gal
1	Floor Scale w/Ramp and Controls
1	Floor Scale w/Ramp and Controls
1	Thermal Printer
1	Thermal Printer
1	Speed Weigh Gram Scale
1	Gram Scale
1	Gram Scale
1	Mettler Toledo Panther plus terminal
1	Gelatin Melting / Prep System 270 Gal
2	Heating Kettles
1	Jackson Washer
20	Gelatin Receivers
9	Gel Rcvr Temp Control Boxes
1	Viscometer
1	SS 3 SECTION SINK
1	60" Dew Stainless Steel Table
1	Mixer with Stand
1	Walkie Lift 4000 lbs
1	ROSS MIXER
1	Pump Motor
12	Drum Dolly (12)
3	Rotary Drum Pumps (3)
1	Fork Mounted Drum Grab
1	Water Boss Spray Nozzle
1	Air/Water Washer Spray Nozzle
1	Digital Contoller & receivers-St Louis SG
1	Mixing Tank 2nd pmt & Freight
3	Sandpiper pumps for mixing
3	Heater Control boxes for Gel dispatch
2	Heater Control boxes for Gel dispatch
1	1,000 gallon paint tank & Mixer
4	Heater Controll Boxes for Gel dispatch
1	McCullough Model DS-3000 Dye Mixer

Encapsulation Equipment

Qty.	*Manufacturer*	*Description*	*Serial Number*
4	Ribbon Snap Guage		N/A
12	Lift Bars For Gel Receivers		N/A
1	Cotterman	Roll About Stairs	606 01
12	Mitutoyo	Dial Indicator	N/A
1	Hund Wetzler	Seal Scope	1013782
3		Shutoff Valve & lead assy.	N/A
3		Plexi bounce guards for conveyor	N/A
6		Divider Chute	N/A
6		Spreader Box assy.	N/A
2		Spreader Box	N/A
4		Maxi Medicine Pump	N/A
4		Medicine Hopper w/pneumatic	N/A
4		Pump distributor plate	N/A
1	Technophar	wCaps Machine w/Dryer & Cooler	97-02
1	Technophar	Caps Machine w/Dryer & Cooler	97-03
20		Dryer Basket	N/A
1	Technophar	7 1/4" Caps Machine w/Dryer& Cooler	
1	McMaster Carr	Optical Comparator	
1	CM Loadstar	1 Ton Eletric Chain Hoist	L2681PV
1	CM Loadstar	1 Ton Eletric Chain Hoist	L2777PV
1	CM Loadstar	1 Ton Eletric Chain Hoist	L2778PV
1	CM Loadstar	1 Ton Eletric Chain Hoist	L2682PV
1	CM Loadstar	1 Ton Eletric Chain Hoist	L2684PV
1	CM Loadstar	1 Ton Eletric Chain Hoist	L4002PU
1	CM Loadstar	1 Ton Eletric Chain Hoist	L2680PV
1	CM Loadstar	1 Ton Eletric Chain Hoist	L2683PV
1	CM Loadstar	1 Ton Eletric Chain Hoist	L0246PT
1	CM Loadstar	1 Ton Eletric Chain Hoist	L2679PV
1	CM Loadstar	1 Ton Eletric Chain Hoist	L2677PV
1	CM Loadstar	1 Ton Eletric Chain Hoist	L2678PV
1	Sanpiper	Pneumatic Diaphragm Pumps	745632
1	Sanpiper	Pneumatic Diaphragm Pumps	745633
1	Sanpiper	Pneumatic Diaphragm Pumps	745634
1	Sanpiper	Pneumatic Diaphragm Pumps	745635
1	Sanpiper	Pneumatic Diaphragm Pumps	745636
1	Sanpiper	Pneumatic Diaphragm Pumps	745637
3	Advance Tabco	Stainless Tables 30"X48"	N/A
1	AERO MFG	Stainless Table 30"X60"	N/A
1	Sanyko	Spare 7-1/4 Die set for Technophare	
1	Sanyko	Spare 7-1/4 Die set for Technophare	
1	Sanyko	Spare 7-1/4 Die set for Technophare	
1	Sanyko	Spare parts for Sanyko Caps Machine	
1	Technophar	Technophar 1010 Encapsulation Mch	
1	Sanyko	Sankyo Encapsulation Machine	
1	Technophar	New spare die set for Technophar	

Plant Equipment

Qty.	*Description*
1	75 Horse Power Air Compressor and related Equipment s/n CRN H9097.5L
1	75 Horse Power Air Compressor and related Equipment s/n Unknown
1	SP600 Kathapak and Heat Exchanger
1	Kewanee Boiler 150 HP
1	Trane Series R Chiller 120 Ton
1	Trane Series R Chiller 120 Ton
1	Fleck Water Softner
4	Eye & Face Wash Ststions (4)
1	Chart Recorders
1	Chart Recorders
1	Chart Recorders
1	Chart Recorders
1	Chart Recorders
1	Chart Recorders
6	Paper Towel Dispensers
1	FLOOR SCRUBBER

Time to Throw in the Towel

By: John A. Bermingham

I have often said that being a CEO is the best job and the worst job in the world. I noted in a recent CNN survey that, of the top 50 jobs in the United States, being a CEO did not make the list. Pessimistic fools or are they?

When I was Senior Vice President of Sales and Marketing at Sony, I was always treated like one of the guys. The day that I became President of the Magnetic Products Group, everything changed. I was no longer treated like one of the guys by the same people who did so before. And this change was instant, not over time. This was one of the worst parts of becoming a CEO. That's why the expression, "it's lonely at the top" is very true and it can be a drag!

Management styles of CEOs tend to stay the same. They may make minor changes over time, but they do not change very much. When it comes to style, most CEOs think their style never goes out of fashion. This generally causes the work place culture to pass the CEO by, resulting in morale issues for the people.

Being the CEO of a company can be a real grind. They continually face financial problems, revenue problems, product issues, people problems, competitive problems, Board issues, yadda, yadda, yadda. It burns you out fast. This definitely causes CEO performance issues. When you work in the same company, deal with the same customers, the same employees, the same vendors, the same products or services, the same-old-same-old, the CEO gets bored, then goes stale. As a result, there are more CEO performance issues.

Oftentimes, when a CEO is with a company for too long, he or she becomes complacent in their position and responsibility. This is a very dangerous situation for a company and its people. When a CEO begins to march in place satisfied that all is well with the company, look out!!!

The CEO's responsibility to the shareholders or equity sponsors is to maximize the value of their investment. Thus, the CEO must always be moving the company forward. Otherwise the company, in reality, is going backward.

Mediocre-to-poor CEOs are content to mark time in their companies. They remain with their company for many reasons: a place to go everyday; continuation of income and benefits; perks; the social atmosphere; ego; you name it.

Great CEOs know when enough is enough and that new blood needs to be brought into the company. They bow out gracefully on their own with dignity and respect. They know when to throw in the towel.

So what should happen when a CEO is no longer adding value but will not leave the company? The answer is that the Board of Directors, if they are doing their job, should take the step to bring in a new CEO to re-energize the company when the current CEO has retired in place and didn't tell anyone. If the Board won't do anything, then you should look for a new job and, at the appropriate time, you throw in the towel. It makes no sense to fight a losing fight, resulting in a knock out to you.

Finally, you as an employee of your company may be facing the same issues as a CEO when you have been in the same position for too long. Burnout, boredom, complicacy, etc. is killer on your performance. The solution? Throw in the towel and find a new career position that stimulates you and brings your performance level up to your true potential. ◆

Biography

John A. Bermingham joined Ampad as President and CEO in August 2003 when Ampad was acquired by group of investors composed of an affiliate of Crescent Capital Investments, himself, and another private investor. He also serves as Chairman of the company's Board of Directors. Previously at the helm of numerous industry-leading companies, Mr. Bermingham brings more than 20 years' experience in guiding enterprises to new levels of performance. Most recently prior to joining Ampad, Mr. Bermingham held the positions of Chairman, President, and CEO of Centis, Inc., a diverse multinational manufacturer and marketer of office, storage, and human resources products. Prior to joining Centis, Mr. Bermingham successfully leveraged the potentials of two start-up companies, raising capital, forging key relationships, and establishing the structure and direction that would pave the way for future growth and achievement. Among his many career highlights in the role of President and CEO for companies serving the office products industry, Mr. Bermingham successfully reorganized Smith Corona Corporation, restoring the company's stability, profitability, and reputation. At Rolodex Corporation, he refocused operations and a strategic vision for a dramatic turnaround in corporate culture, and phenomenal increases in both revenue growth and cashflow. Mr. Bermingham's expertise in leveraging technology and optimizing resources for the business products/services markets has also been deployed at industry giants, such as AT&T Consumer Products Group, and by having served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served three years in the U.S. Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes. Earning a BA in Business Administration from Saint Leo University in Florida, Mr. Bermingham has also completed the Harvard University Graduate School of Business Advanced Management Program.

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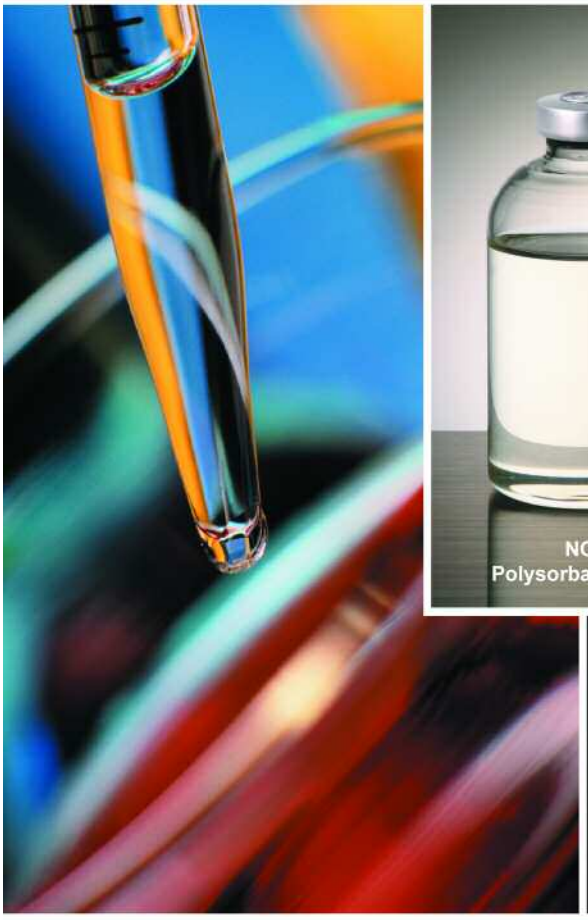

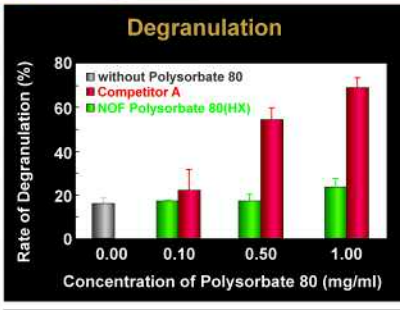

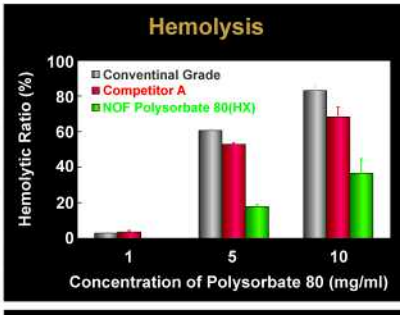

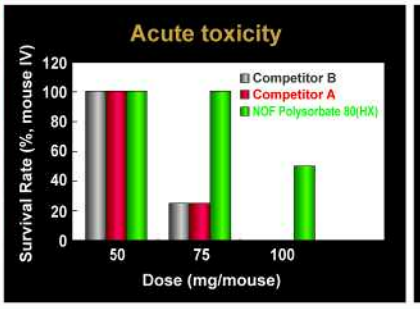

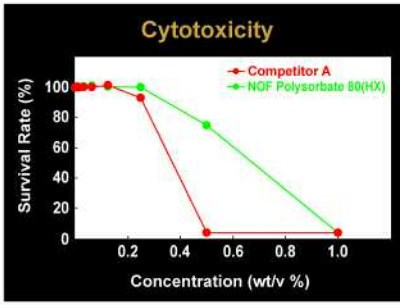

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