Drug Delivery® Technology

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Topical Development's Crystal Ball

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

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TRANSDERMAL TRANSCENDENCE

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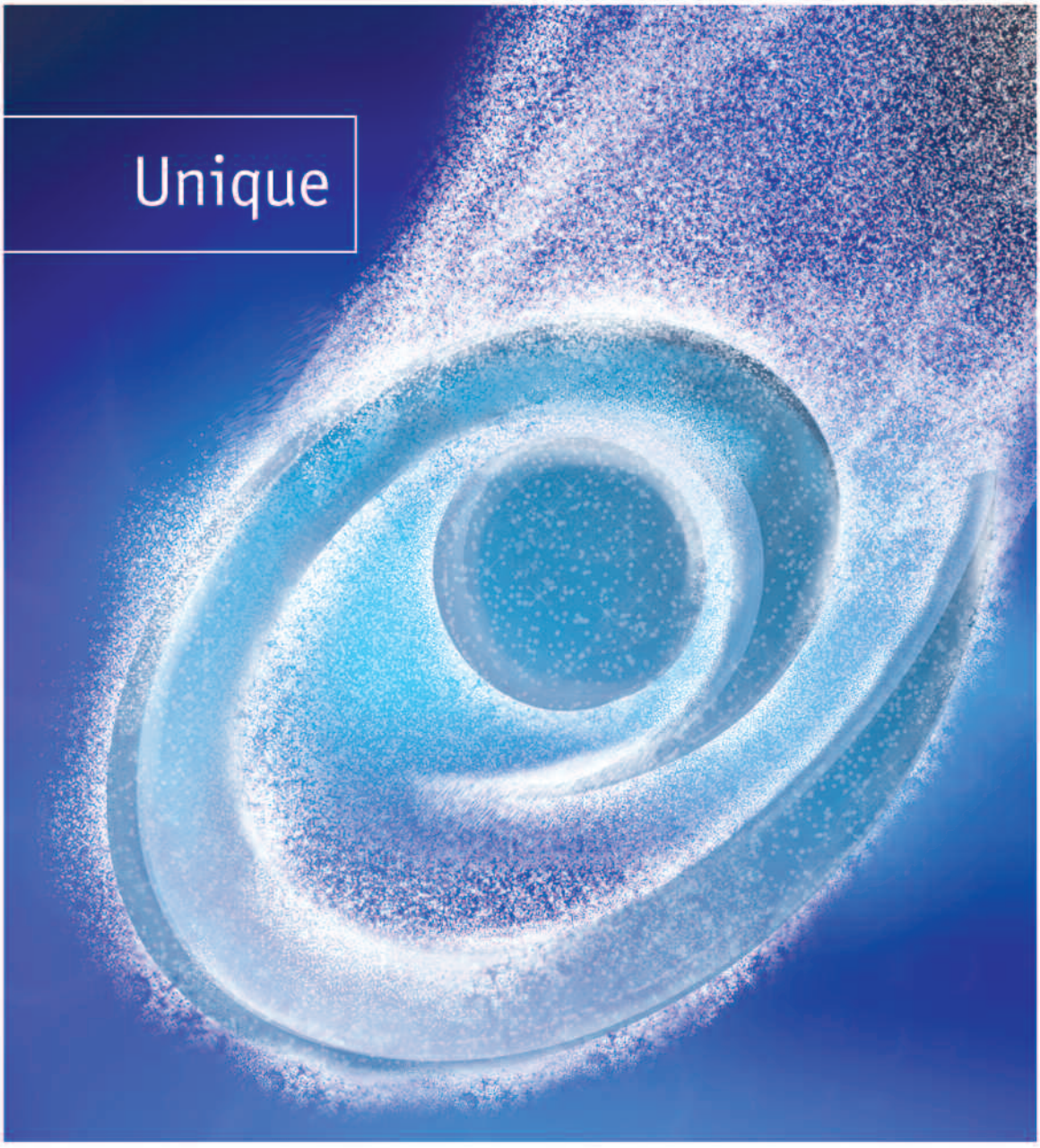

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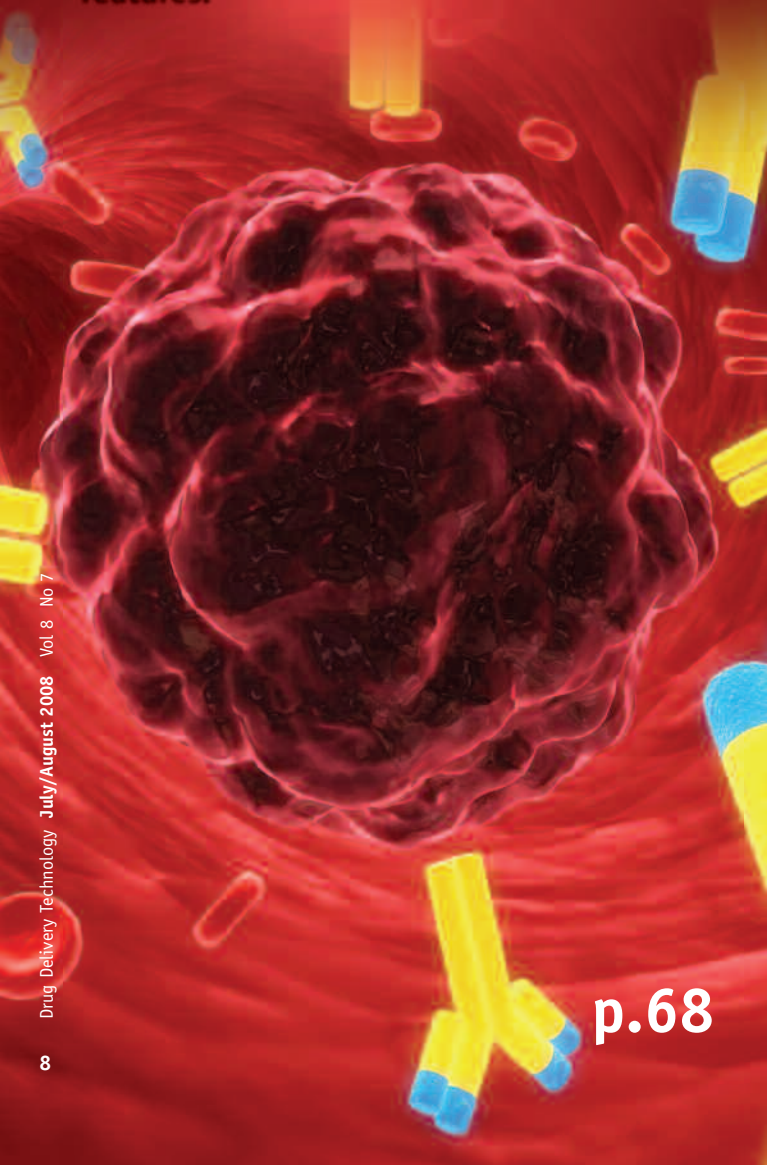

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[1] Graff MR, McClanahan MA. Assessment by patients with diabetes mellitus of two insulin pen delivery systems versus a vial and syringe. Clin Ther. 1998;20(3):486-496.
[2] Weiss, P.M., http://www.femalepatient.com/html/arc/sig/pharma/articles/028_07_031.asp

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Market News and Trends

Roche Signs Cancer Alliance With BioInvent & ThromboGenics Worth up to $775 Million

BioInvent International AB and ThromboGenics NV recently announced they have entered into a license agreement with Roche for their jointly developed anti-cancer agent TB-403. TB-403 is a novel monoclonal antibody that blocks Placental Growth Factor (PIGF), one of the growth factors responsible for the development of new blood vessels.

Under the terms of the agreement effective from June 17, 2008 (or if a US anti-trust clearance is required, from the date of receipt of such clearance), Roche will pay BioInvent and ThromboGenics an up-front payment of $77.5 million. In addition, BioInvent and ThromboGenics could potentially receive up to $700 million over the term of the collaboration based on the successful completion of a series of development and commercial milestones for multiple indications, as well as double-digit royalties on potential product sales, including any back-up antibodies based on inhibition of PlGF.

ThromboGenics, which discovered TB-403, will receive 60%, and BioInvent 40% of the revenue from the deal. Roche will have a worldwide, exclusive license to develop and commercialize TB-403. BioInvent and ThromboGenics will retain co-promotion rights for the product in the Nordic, Baltic, and Benelux regions.

BioInvent and ThromboGenics are responsible for any remaining costs associated with the recently completed Phase Ia trial in healthy volunteers. Roche will assume responsibility for all future development costs for this novel therapy, including the costs of the pending Phase Ib trial in patients to be run by BioInvent and ThromboGenics. BioInvent and ThromboGenics in conjunction with Roche will form a Joint Steering Committee to oversee research and development activities. In addition, Roche will also provide funding to BioInvent and ThromboGenics for research on non-cancer indications and supply of clinical material until transfer of manufacturing.

TB-403 (Anti-PIGF) has completed an initial Phase I clinical trial and recently received approval to enter a Phase Ib dose escalation trial. This Phase Ib trial will be conducted in patients with advanced cancer and is due to commence shortly in Denmark.

TB-403 has the potential to be a major advance in the treatment of cancer. It is a humanized monoclonal antibody that blocks the formation of the new blood vessels that are needed by solid tumors to support their growth. TB-403 has the potential to minimize both the growth and spread of cancer cells.

"We believe that TB-403 has great potential for the treatment of cancer, with its unique mode of action targeting PlGF, and are delighted that Roche has recognized this potential," said Svein Mathisen, CEO of BioInvent. "This agreement demonstrates our ability to identify innovative projects and to realize the clinical potential of a therapeutic antibody. We look forward to seeing the product progress further through clinical development and toward the market."

Professor Désiré Collen, CEO and Chairman of ThromboGenics, added, "TB-403 has generated a great deal of interest from the pharmaceutical community. Therefore, we are delighted that we have signed this major licensing agreement with Roche, given their expertise and success in bringing novel anti-cancer agents to the market. This deal represents a significant milestone in ThromboGenics' development as a company. It also reflects TB-403's potential as a promising treatment for cancer, and is a testament to the hard work and high-quality science on which ThromboGenics' business is based. The funding from this deal also gives us the financial resources to continue to build our strong pipeline. We look forward to working with Roche, and to the successful development of this unique anti-cancer agent."

Dan Zabrowski, Global Head of Pharma Partnering, Roche, added, "We are very pleased to enter this partnership with BioInvent and ThromboGenics. This novel antibody, TB-403 has the potential to play a major role in the treatment of cancer, and we are committed to driving ahead with its development. In addition, we look forward to developing a strong working relationship with BioInvent and ThromboGenics."

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Market News and Trends

MonoSol Rx Licenses Thin Film Formulation of Ondansetron to Strativa

MonoSol Rx, a drug delivery company specializing in dissolving thin film pharmaceutical products, and Strativa Pharmaceuticals, the proprietary products division of a wholly owned subsidiary of Par Pharmaceutical Companies, Inc., recently announced they have entered into an exclusive licensing agreement under which Strativa has acquired the US commercialization rights to the thin film formulation of ondansetron from MonoSol Rx. The ondansetron thin film formulation is a new oral formulation in development for the prevention of chemotherapy-induced nausea and vomiting, prevention of nausea and vomiting associated with radiotherapy, and post-operative nausea and vomiting.

Based on the results of a recently completed pilot bioequivalency study, MonoSol Rx is initiating pivotal trials immediately to enable application for drug approval in the US. Subject to favorable results, it is anticipated that Strativa could file an NDA with the appropriate regulatory authorities within the next 12 months.

Under terms of the agreement, MonoSol Rx will receive milestone payments prior to commercial launch and sales-based milestones that could total $23.5 million as well as payments for purchase of product supply and royalties on net sales.

Anti-emetic therapies constitute one of the largest segments of the supportive care market in the US, with annual sales of over $1.6 billion in 2007. Ondansetron was the prescription leader in the category in 2007, with 2.7 million scripts written.

"We are very excited about the collaboration with Strativa," said A. Mark Schobel, President and CEO of MonoSol Rx. "They are uniquely positioned to market and sell our ondansetron thin film product given their focus on marketing novel prescription drugs. Thin film is particularly well suited for this indication because patients who are prescribed ondansetron often have difficulty swallowing due to extreme nausea caused by chemotherapy and radiation treatments. Following approval, ondansetron would be one of the first prescription drugs to come to market utilizing thin film drug delivery technology."

John A. MacPhee, President of Strativa, added, "We are delighted to collaborate with MonoSol Rx and expand our pipeline of supportive care products. With two unique, yet complementary delivery systems of ondansetron in our portfolio, Zensana oral spray and the oral thin film, we are able to offer patients a better opportunity to find a product that meets their individual needs."

MonoSol Rx is a drug delivery company specializing in proprietary, dissolving thin film pharmaceutical products. The Company's thin film technology, which is similar in size, shape, and thickness to a postage stamp, dissolves rapidly and utilizes a novel process and proprietary encapsulation compositions to mask the taste of the drug contained within the film. The Company's thin film formulations offer significant patient benefits, including convenience, taste, and potentially greater efficacy. MonoSol Rx's strategy is to develop and partner innovative thin film strip products in the prescription, generic, and OTC pharmaceutical markets and to establish a leadership position in thin film drug delivery technology through continued development of its drug delivery technology and intellectual property portfolio.

Strativa Pharmaceuticals is the proprietary products division of Par Pharmaceutical, Inc. Supported by Par's financial and organizational capabilities, including substantial cash resources, Strativa Pharmaceuticals is committed to developing and marketing novel prescription drugs. Its initial focus is on supportive care therapeutics in HIV and oncology. Drawing on the specialty products expertise of its staff, Strativa possesses the resources to prepare products for introduction and to help ensure their success after launch.

3M DDS Collaborates With AVANT on Vaccine Adjuvants

3M Drug Delivery Systems recently announced the signing of a non-exclusive license agreement with Celldex Therapeutics, Inc., a wholly owned subsidiary of AVANT Immunotherapeutics. Under the agreement, 3M will provide its patented toll-like receptor (TLR) agonist compounds to Celldex for an undisclosed licensing fee, milestones, and royalties.

3M's patented TLR immune response modifier compounds, which may be useful as vaccine adjuvants, will be used by Celldex to develop new vaccine products. Once commercialized, Celldex will pay 3M royalty usage fees for IRM compounds.

"The use of TLR agonists topically as well as conjugated to Celldex's vaccines show the broad applicability of our TLR adjuvant platform for use in combination with Celldex's proprietary APC-targeting technology," said Dr. Mark Tomai, PhD, Vaccine Business Development, 3M Drug Delivery Systems.

3M's TLR compounds, also called TLR7 and TLR8 agonists, are small organically synthesized molecules that offer flexibility in formulating and route of delivery, and ease in manufacturing, unlike most other TLR agonists, which are much larger and not as easy to manufacture.

"This license agreement provides a great opportunity to combine synergistic technologies designed to treat various cancers and infectious diseases." said Tibor Keler, PhD, Chief Scientific Officer of Celldex Therapeutics. "We are very pleased to enter into this relationship with 3M and look forward to pursuing our clinical studies using 3M's unique TLR agonists."

Dr. Steven Wick, Technical Director, 3M Drug Delivery Systems, adds, "Our toll-like receptor agonist platform is a major part of our vaccine offering that also includes our Microstructured Transdermal System for needle-free delivery of vaccines. This technology coupled with our TLR compounds can provide both new vaccine adjuvant and delivery technology to further enhance vaccine regimens."

3M Drug Delivery Systems has a portfolio of patent protected toll-like receptor TLR7 and TLR8 agonists that have shown promise as vaccine adjuvants. There are a variety of assets in the portfolio that can be used topically, admixed, or in conjugatable form. The lead candidate, resiquimod (TLR7/8 agonist), has shown promising results in a number of animal models and has an extensive toxicology and clinical data package to support further development as a vaccine adjuvant. In addition, 3M offers other TLR7 and TLR8 agonists, some of which can be attached to various proteins that enhances vaccine efficacy in a number of models. As small molecules, 3M's TLR7 and TLR8 agonists offer unique advantages over other TLR agonists with regard to delivery and manufacturing. 3M is actively seeking partners to license these assets on a non-exclusive basis. In addition, 3M Drug Delivery Systems has a variety of immune response modifier compounds that may be useful in oncology and dermatology.

Celldex is an innovative biotechnology company focused on the discovery, development, and commercialization of targeted immunotherapies. Its core focus includes the use of tumor-specific targets and human monoclonal antibodies as precision-delivered therapeutic agents for the treatment of cancer, infectious diseases, and immune system disorders through its novel active immunization approach.

Emisphere Announces License Agreement With Novo Nordisk to Develop Oral Formulation of GLP-1 Receptor Agonists for Diabetes

Emisphere Technologies, Inc. and Novo Nordisk A/S have entered into an exclusive Development and License Agreement to develop and commercialize oral formulations of Novo Nordisk's proprietary GLP-1 receptor agonists, which have the potential of treating type 2 diabetes, using Emisphere's eligen technology. The agreement includes at least $87 million in product development and sales milestone payments to Emisphere, of which $10 million will be the minimum first-year payment, as well as royalties on sales. The agreement also provides Novo Nordisk with the option to develop oral formulations of Novo Nordisk compounds other than GLP-1 receptor agonists using Emisphere's proprietary carrier technology. Further financial details of the agreement were not made public.

Under the new agreement, Novo Nordisk is responsible for the development and commercialization of the product candidates. Novo Nordisk and Emisphere have collaborated since 2007 on early stage preclinical research that has preliminarily confirmed the utility of Emisphere's carriers to provide bioavailable oral formulations of GLP-1 receptor agonists.

"This partnership with Novo Nordisk is important for Emisphere for several reasons," said Michael V. Novinski, President and Chief Executive Officer of Emisphere. "First, it couples Emisphere with Novo Nordisk, the worldwide leader in the field of diabetes research. Second, it places our technology with a treatment for diabetes that we hope will be able to improve upon the healthcare of millions of patients with this disease. Finally, it also positions our eligen technology in such a way that helps to bring innovative solutions to the pharmaceutical development arena."

"This is an encouraging agreement on a promising technology for oral administration of proteins. It fits very well with Novo Nordisk's strategy within diabetes research," added Peter Kurtzhals, Senior Vice President, Diabetes Research Unit.

Emisphere's broad-based drug delivery technology platform, known as the eligen technology, uses proprietary, synthetic chemical compounds, known as Emisphere delivery agents, sometimes called carriers. Emisphere's eligen technology makes it possible to deliver a therapeutic molecule without altering its chemical form or biological integrity.

Emisphere Technologies, Inc. is a biopharmaceutical company that focuses on a unique and improved delivery of therapeutic molecules and pharmaceutical compounds using its eligen technology. Some of these molecules or compounds can only be given by injection; however, when combined with its technology, convenient oral versions may be safe, effective, and provide significant advantages. The benefits of other compounds are limited due to poor bioavailability, slow on-set of action, or variable absorption. In those cases, use of Emisphere's technology can improve the therapeutic effectiveness of the compounds. The eligen technology can be applied to the oral route of administration as well other delivery pathways.

Fontus Pharmaceuticals Acquires Nephrology & Endocrinology Drug From Roche Laboratories

Fontus Pharmaceuticals, Inc., a specialty pharmaceutical company focused on nephrology and endocrinology, recently announced it has acquired ROCALTROL (calcitriol) from Roche Laboratories Inc. ROCALTROL is a vitamin D analog prescribed by nephrologists for the management of hyperparathyroidism and resultant metabolic bone disease in patients with moderate-to-severe chronic renal failure (CRF) and by endocrinologists for the management of hypocalcemia in patients with post-surgical hypoparathyroidism, idiopathic hypoparathyroidism, and pseudohypoparathyroidism.

ROCALTROL, available as capsules and as an oral solution, is the most potent metabolite of vitamin D available and is active in regulating the absorption of calcium from the gastrointestinal tract and its utilization in the body. The calcitriol in ROCALTROL is believed to be the active hormone that exerts vitamin D activity in the body. ROCALTROL improves calcium absorption in patients who have severe vitamin D deficiencies commonly associated with CRF, chronic kidney disease (CKD), end-stage renal disease (ESRD) or primary hypothyroidism.

ROCALTROL therapy should always be started at the lowest possible dose and should not be increased without careful monitoring of serum calcium. In order to avoid hypercalcemia and related conditions, the optimal daily dose of ROCALTROL must be carefully determined for each patient. The safety and effectiveness of ROCALTROL in pediatric predialysis patients is based on evidence from adequate and well-controlled studies of ROCALTROL in adults with predialysis chronic renal failure and additional supportive data from non-placebo controlled studies in pediatric patients. Specific doses of ROCALTROL are recommended for pediatric predialysis patients. These and other precautions and warnings may be found in the package insert for ROCALTROL.

Fontus Pharmaceuticals, Inc. is a specialty pharmaceutical company distinguished by its strategy to acquire and market FDA-approved products used in the fields of nephrology and endocrinology. Fontus focuses on mature products with widely accepted clinical value and brand loyalty. Fontus re-invigorates promotion and in some cases reformulates products to optimize clinical benefit.

Market News and Trends

Eurand Receives Approvable Letter From FDA for EUR-1008 (Zentase)

Eurand N.V., a specialty pharmaceutical company that develops, manufactures, and commercializes enhanced pharmaceutical and biopharmaceutical products based on its proprietary drug formulation technologies, recently announced it has received an approvable letter from the US FDA for the company's NDA for EUR-1008 (pancrealipase capsules) for the treatment of exocrine pancreatic insufficiency (EPI). The letter marks notable progress toward gaining approval and does not require Eurand to conduct additional clinical trials prior to approving EUR-1008. In addition, the FDA recently completed a successful pre-approval inspection (PAI) of the company's manufacturing facilities. Eurand is working with the FDA to provide a full and timely response to the agency's requests, and based on current information, the company still anticipates that it will be in a position to launch EUR-1008 in the second half of 2008.

"We are pleased with the FDA's conclusion that EUR-1008's NDA is approvable and look forward to cooperating with the agency's requests," said Gearoid Faherty, Chief Executive Officer of Eurand. "We expect that we will be able to respond to and satisfy the FDA's remaining questions on EUR-1008 in an expeditious manner."

Exocrine Pancreatic Insufficiency (EPI) is a deficiency of digestive enzymes normally produced and secreted by the pancreas. EPI can result from a number of diseases, including Cystic Fibrosis and chronic pancreatitis, which causes malnutrition, which can lead to impaired growth, impaired immune response, and shortened life expectancy. EPI is treated by porcine-derived pancreatic enzyme products (PEPs), which have been used by patients for over 70 years. PEPs are inherently unstable and to compensate for enzyme degradation over time, most manufacturers currently include an overfill of enzymes in the finished product. As a result, patients may receive PEPs with variable and uncertain levels of potency, resulting in an inconsistent therapeutic effect. Existing PEPs have been marketed in the US since before the passage of the Federal Food, Drug, and Cosmetic Act in 1938, and none is marketed under an NDA approved by the FDA.

In April 2004, the FDA mandated that all manufacturers of EPI drug products file an NDA and receive approval for their products by April 2008 or be subject to regulatory action. In October 2007, the FDA published a notice in the Federal Register extending the deadline for obtaining marketing approval for EPI drug products until April 28, 2010, for those companies who were marketing unapproved pancreatic enzyme products as of April 28, 2004, have submitted NDAs on or before April 28, 2009, and who continue diligent pursuit of regulatory approval.

Eurand's lead product candidate, EUR-1008 (Zentase), is an innovative pancreatic enzyme replacement therapy being developed to treat pancreatic insufficiency, a condition associated with cystic fibrosis, chronic pancreatitis, and other diseases. The product was developed in response to the 2004 FDA guidance on pancreatic enzyme products, which outlined the need to reduce the unpredictable nature of currently marketed enzyme therapies. The product is a highly stable formulation that includes eight key enzymes and a number of coenzymes and cofactors and is biologically similar to the endogenous human pancreatic secretions necessary for proper human digestion. Eurand completed its NDA submission for EUR-1008 in December 2007, which was granted priority review status. The company plans to market the product in the US and out-license the product outside of the US.

Vyteris to Pursue Strategy for Transdermal Drug Delivery Technology

Vyteris, Inc., manufacturer of the first FDA-approved active patch transdermal drug delivery system, informed its shareholders of important plans to pursue an aggressive partnership and licensing strategy for its transdermal drug delivery technology, as well as restructuring of its board, management, and capitalization.

"With the recent changes made to strengthen the company's management and strategic plan, we believe we are in a stronger position to pursue our key objectives for development of our Smart Patch technology in additional pharma product lines," said Donald F. Farley, Executive Chairman for Vyteris, Inc. "The development program with Ferring has shown successful demonstration of peptide molecule delivery and attempts to forge partnerships with other peptide drug developers is a roadmap we will aggressively pursue."

In a letter to Vyteris shareholders, which was made public by the Company yesterday in an 8-K filed with the SEC, Mr. Farley outlined the company's strategic focus moving forward in the following three key areas:

ASSURE TECHNICAL SUCCESS OF THE FERRING PROJECT: Basic Phase I clinical testing goals have been completed and optimization studies to determine best dosage and related variables are in progress. Vyteris is progressing in manufacturing planning for Phase II clinical supplies and is poised to meet needs when Ferring makes the decision to initiate Phase II. Under the current agreement with Ferring, a $2.5-million milestone payment will be earned when Ferring elects to initiate Phase II clinical trials, and a $3-million milestone will be earned at commencement of Phase III.

PEPTIDE DEVELOPMENT PROGRAM: Based on Vyteris' prior experience with peptide feasibility work and progress-to-date with the Ferring project, a comprehensive program is being launched to identify and secure another peptide development program in 2008, to manage a biotech outreach initiative to secure additional peptide collaborations for 2009, and finally, to establish a licensing initiative for new peptides.

BIOPHARMACEUTICAL DEVELOPMENT PROGRAM: A number of biopharmaceuticals have been qualified as ideal candidates for Vyteris' Smart Patch technology. In some cases, preliminary feasibility work has already been completed. Vyteris now plans to undertake a much more active role in generating collaborative development programs in this area. This includes targeting pharma companies' proprietary molecular candidates and seek to engage them in a collaboration aimed at extending patent life, improving therapeutic outcomes, and/or creating a generic specialty, and selecting specific generic molecules or those approaching the end of their patent lives, and initiate proposals for a development program. Vyteris will take a leadership role and recruit pharma partners.

Vyteris, Inc., a wholly owned subsidiary of Vyteris Holdings (Nevada), Inc., is the maker of the first active drug delivery patch to receive marketing clearance from the US FDA. Vyteris' proprietary active transdermal drug delivery (iontophoresis) technology delivers drugs comfortably through the skin using low-level electrical energy. This active patch technology allows for the potential of precise dosing, giving physicians and patients control in the rate, dosage, and pattern of drug delivery that may result in considerable therapeutic, economical, and lifestyle advantages over existing methods of drug administration.

Merck Serono & Bionomics Limited Announce Multiple Sclerosis Development & Licensing Agreement

Merck Serono, a division of Merck KGaA, Darmstadt, Germany, recently announced that a Development and Licensing Agreement with Bionomics was signed, under which Merck Serono would develop new treatments for multiple sclerosis (MS) and other autoimmune conditions based on compounds from Bionomics Kv1.3 program.

Under the agreement, Bionomics will receive an up-front payment of $2 million and committed research funding. Merck Serono will fund all development activities, including clinical development. Merck Serono intends to select compounds from Bionomics pool of compounds, and for each compound selected, Bionomics may receive milestone payments of up to $47 million, based on successful development and commercialization. In addition, Bionomics will be eligible to receive undisclosed royalties on the net sales of licensed products.

"This partnership with Bionomics reflects our long-term commitment to patients with MS as Kv1.3 inhibition represents an innovative approach for the discovery of oral compounds in the field of MS," said Dr. Bernhard Kirschbaum, Executive Vice President of Research at Merck Serono. "This R&D collaboration brings together Bionomics' expertise in Kv1.3 biology and Merck Serono's expertise in MS pharmacology in a combination that could speed up progress in the identification of novel drug candidates for the treatment of MS."

"As a world leader and pioneer in treatments for MS, Merck Serono is the ideal partner for Bionomics in this Kv1.3 program," added Dr. Deborah Rathjen, CEO and Managing Director of Bionomics. "The agreement with Merck Serono is an important milestone for our company. It validates Bionomics' discovery approach, which has brought the program to this stage. We look forward to working with Merck Serono in the next stage to bring innovative treatment options for patients with MS to the clinic."

The compounds discovered by Bionomics, around which the collaboration will focus, target the potassium ion channel Kv1.3. Kv1.3 is a key modulator of the immune system and it is a target found on human immune cells, which are associated with nerve cell damage in patients with MS. Inhibitors of Kv1.3 have been shown to inhibit the proliferation of these immune cells, suggesting that they have application in the treatment of MS and potentially other autoimmune conditions, including arthritis.

Bionomics discovers and develops innovative therapeutics for cancer and diseases of the central nervous system. Bionomics has small molecule product development programs in the areas of cancer, anxiety, epilepsy, and MS. Bionomics' most advanced program, BNC105 for the treatment of cancer, is based upon the identification of a novel compound that potently and selectively restricts blood flow within tumors. Bionomics' discovery and development activities are driven by its three technology platforms: Angene, the company's angiogenesis target and drug discovery platform, incorporates a variety of genomics tools to identify and validate novel angiogenesis targets. MultiCore is Bionomics' proprietary, diversity-orientated chemistry platform for the discovery of small molecule drugs. ionX is a set of novel technologies for the identification of drugs targeting ion channels for diseases of the central nervous system.

Alnylam Ties Up With Kyowa Hakko Kogyo on Respiratory Drug in Asia

Alnylam Pharmaceuticals, Inc. and Kyowa Hakko Kogyo Co., Ltd. recently announced they have formed an exclusive alliance to develop and commercialize ALN-RSV01, an RNAi therapeutic in Phase II clinical development by Alnylam for the treatment of respiratory syncytial virus (RSV) infection, in Japan and other major markets in Asia.

Under the terms of the collaboration, Kyowa Hakko will pay Alnylam $15 million in an up-front cash payment and up to an additional $78 million in development and sales milestone payments. Upon commercialization, Alnylam will receive double-digit royalties from Kyowa Hakko based on the sales of ALN-RSV01 in this territory. The partnership also includes additional RSV-specific RNAi therapeutic compounds that comprise the ALN-RSV program. Alnylam retains all development and commercialization rights worldwide, excluding Asia.

"We are excited to have formed this new alliance with Kyowa Hakko, a Japanese biotechnology company with a strong commitment to bringing innovative new drugs to the marketplace," said John Maraganore, PhD, CEO at Alnylam. "This new collaboration is yet another example of Alnylam's commitment to work with leading biotechnology and pharmaceutical companies to advance RNAi therapeutics to patients on a global basis. This is an important partnership on our company's lead clinical program in an important pharmaceutical market, and also our third significant alliance formed this year. We will provide an update on our near-term partnership goals and revised financial guidance at our upcoming second-quarter conference call."

"We have been watching the progress Alnylam has made with their ALN-RSV01 program since last year and are very excited to partner with this program at this time. We are looking forward to working with Alnylam, the most scientifically advanced company in the field of RNAi, in the development and commercialization of ALN-RSV01 in Japan and other major markets in Asia," added Yuzuru Matsuda, PhD, CEO at Kyowa Hakko. "There is a significant need for novel medicines to effectively treat patients with RSV, a leading cause of serious infections in both pediatric and adult patients. We are excited to have the opportunity in delivering the benefit of this novel medicine to patients in Asia through the partnership with Alnylam."

Earlier this year, Alnylam achieved human proof-of-concept for ALN-RSV01 in the Phase II GEMINI study, where intranasally administered ALN-RSV01 demonstrated statistically significant anti-viral efficacy with a 38% relative reduction in RSV infection rate and a 95% increase in the number of infection-free subjects as compared with placebo. In addition, Alnylam has initiated a Phase II clinical trial to assess the safety and tolerability of aerosolized ALN-RSV01 versus placebo in adult lung transplant patients naturally infected with RSV. As a secondary objective, this trial will also aim to evaluate the anti-viral activity of ALN-RSV01. The data from this study, in combination with the previous Phase II GEMINI trial and multiple Phase I trials, will comprise a comprehensive safety and efficacy data set with which Alnylam expects to further advance its overall ALN-RSV development program.

Generex Biotechnology Commences Patient Dosing for Pivotal Phase III Trial of Generex Oral-lyn

Generex Biotechnology Corporation, a leader in drug delivery for metabolic diseases through the inner lining of the mouth, has commenced dosing of patients in a Phase III clinical trial of the Company's flagship product, Generex Oral-lyn, an oral insulin spray.

The 6-month Phase III study will involve up to 750 patients with type 1 Diabetes Mellitus in 36 centers located in the US, Canada, Russia, and Eastern Europe. The objective of the study is to compare the efficacy of Generex Oral-lyn and the Company's RapidMist Diabetes Management System with prandial injections of regular human insulin as measured by HbA1c.

Generex Oral-lyn, a liquid formulation of human regular insulin, is sprayed into the mouth with a simple device similar to inhalers used for the treatment of asthma. The oral insulin is buccally absorbed, with the size of the particles precluding entry into the lungs. The Company believes that Generex Oral-lyn will offer a safe, simple, fast, effective, and pain-free alternative to prandial insulin injections, which will improve patient compliance with therapeutic regimes, thereby delaying the progress of diabetes and the onset of its myriad complications

"Diabetes Mellitus is an overwhelming worldwide problem. Many people do not achieve their treatment goals because of failure to use insulin. Buccal delivery affords an opportunity to correct that. As a Principal Investigator, I am pleased to announce that the international Phase III non-inferiority study of 750 patients has dosed its first patient," said Professor Philip Raskin, MD, of The University of Texas Southwestern Medical Center at Dallas, one of the clinical trial sites.

Generex Oral-lyn is presently approved for commercial sale in India and Ecuador. The delivery of Generex Oral-lyn clinical supplies to global sites and centers, including Ukraine and Russia, is ongoing with other regional roll-out to follow.

Generex is engaged in the research, development, and commercialization of drug delivery systems and technologies. Generex has developed a proprietary platform technology for the delivery of drugs into the human body through the oral cavity (with no deposit in the lungs). The Company's proprietary liquid formulations allow drugs typically administered by injection to be absorbed into the body by the lining of the inner mouth using the Company's proprietary RapidMist device. The Company's flagship product, oral insulin (Generex Oral-lyn), which is available for sale in Ecuador for the treatment of patients with type 1 and type 2 diabetes and which was approved for sale in India in October 2007, is in Phase III clinical trials at several sites around the world.

Eli Lilly & TransPharma Medical Announce Licensing & Development Agreement

Eli Lilly and Company and TransPharma Medical Ltd. recently announced that the two companies have entered into a licensing and development agreement related to TransPharma's ViaDerm-hPTH (1-34) product for the treatment of osteoporosis. The product, which is administered transdermally using TransPharma's proprietary technology, is currently in Phase II clinical testing.

Under the terms of the agreement, Lilly will obtain exclusive worldwide rights to TransPharma's ViaDerm-hPTH (1-34) and will also gain non-exclusive access to TransPharma's ViaDerm drug delivery system. TransPharma will receive a $35-million up-front payment, and may also receive development and sales milestones, as well as royalties on sales if a transdermal PTH product is successfully commercialized. TransPharma and Lilly will both fund and participate in Phase II clinical development activities. Thereafter, Lilly will be responsible for further development activities and the potential commercialization of any transdermal PTH products. Other terms of the deal were not disclosed. The transaction is expected to become effective in June or July 2008, contingent upon clearance under the Hart-Scott-Rodino Anti-Trust Improvements Act. At closing, Lilly would expect a $0.02 per share charge to earnings for acquired in-process research and development.

"This agreement expands the scope of our osteoporosis program with a novel, patient-centered approach that builds upon our success with Evista and Forteo," commented Dr. Gwen Krivi, Vice President of Lilly Research Labs and Global Brand Development Platform Leader for Musculoskeletal and Cialis platform. "As we focus on developing a transdermal PTH product with TransPharma, we will leverage our combined expertise, with the goal of providing patients with a product that meets their desire for an alternative to injection for PTH."

"We are extremely pleased to partner with Lilly, a leading player in the osteoporosis market," said Dr. Daphna Heffetz, CEO of TransPharma Medical. "This collaboration is an excellent example for how our transdermal ViaDerm-based products may deliver added value to promising drug compounds. We are confident that Lilly's experience and outstanding drug development capabilities together with our innovative technology could propel our joint ViaDerm-hPTH (1-34) product as an improved therapy for people suffering from osteoporosis."

TransPharma's ViaDerm drug delivery system incorporates a hand-held electronic control unit, which creates microscopic passageways through the outer layer of the skin, allowing for transdermal delivery of a wide variety of drugs from a patch. The system provides a cost-effective, easy-to-use, self-administered solution that enables the safe, reproducible, and accurate delivery of a broad range of product candidates, including hydrophilic small molecules, peptides, and proteins.

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

MBO Discussion Series

Living the Dream!

Part VI of The Born-Again Entrepreneur (February 2008)

By: Derek G. Hennecke, MBA

As the birth of Xcelience grew near, the fun part began. Until now, we'd been chasing financing and building confidence among employees, customers, and the management team. Now for the cool stuff. We needed to shape this organization; decide how it would be different; craft it; and choose a name, marketing strategy, and some really slick business cards. First and foremost, we chose our focus. This must come before all else because everything else must reflect it.

We started by thinking about our clients. Our clients are sophisticated and know where to get the best service and quality. They cherry pick. That's why consolidated roll-ups haven't worked in our industry. After much deliberation, our vision was nothing more sophisticated than getting back to the basics of why our clients come to us. We saw two attractions.

The first is the quality of our drug product research. When a company gives us a product to formulate, it's their baby they're giving us. Chances are it's been years in the making, and they have one shot at getting it to market. This is not a time for taking risks or cutting corners. Our customers need to know that our science is the best you can find, and every product we use, every piece of equipment we run their baby through, and every analyst who touches it is top of the line – not just in terms of knowing their periodic tables; we're talking about people with the smarts to find solutions with the most challenging formulations. Second, it's about agility. Our sponsors need to get to their clinical trials fast to beat the competition so their product can start paying for itself as soon as possible.

This dual objective of quality and agility, we decided, would become our unique selling point. We would live it. It would dominate every aspect of everything we do. It would be the message on our website, our brochures and magazine ads, our sales presentations, and our telephone reception. And so it has been.

We chose the name Xcelience (pronounced X-sell-ee-en(t)s) as a mixture of Excelling and Accelerating, with the word Science. Our ad campaigns feature the slogan *Send Us Your Greatest Challenge*. To distance ourselves from the traditions in our industry of names with acronyms and ad campaigns with pictures of lab assistants in white coats, our ads are a mix of extreme sports and scientific challenge – like the surfer riding a colossal wave inside a huge test tube. We pride ourselves on being able to do what others won't attempt.

In addition to a shiny new marketing plan, we also continued something we had started before the management buyout (MBO), and that was a pre-emptive marketing plan. One of our first innovations was to purchase the Xcelodose technology by Capsugel to fill API in capsules. We had a jump on the competition by at least 3 years because we knew it was the future, and it is that good. We used those 3 years to gain a lot of experience on the Xcelodose and have now produced over 60 batches. Now we are the first and only company in our industry to offer an unqualified guarantee of good results on the Xcelodose. No one knows this machine better than Xcelience.

The next thing we did was identify what our competition was NOT doing, so we could fill a need. We found that most of our competition was meeting only basic customer needs. This was reflected in any number of things – from not being available when the sponsor needed them, to double-booking their facilities so sponsors would have to shift

their clinical dates at the last minute.

Our project-based team structure solved the availability problem. Our teams literally make our lab an extension of the sponsor's lab. We structure teams that include both members of their organization and our own organization in one cohesive group. As a result, availability is not a problem, and our processes are completely transparent to the sponsor. The more heads the better.

Secondly, we pledged never to double book. This has never been a problem. When we do have a cancellation, sponsors booked for later dates rarely mind being scheduled earlier.

Finally, to be able to offer services beyond the basics, we saw the need for a wide selection of equipment to meet almost every manufacturing and analytical formulation need, from DSC to XRD. We began a campaign to significantly expand our capabilities through the purchase of new equipment.

Breaking off on our own would lead to other opportunities beyond the strategic level. Freed from the mother company's systems, we took full advantage of the decreasing cost of computer hardware to install a virtual server with VMware from EMC.

The virtual server has been great for us, making maintaining a compliant, "always up" IT infrastructure a reality in a small company. We have all the data continuously backed up on a separate server offsite so our clients' data is safe and we don't need to rely on an antiquated system of tape back-ups. I believe it would be safe to say that our system is more advanced than many companies 10 times bigger than ourselves.

We were also able to implement numerous cost-cutting measures that aren't possible when your choices are constrained by a corporate head office. We saved money in human resources, IT, photocopying, accounting, and more. I do think it's a mistake many new entrepreneurs make to put undue focus on the cost-cutting end of things. It's easy to get excited about the immediate gratification of saving $10,000 on your air conditioning service contracts, or some other thing, and lose sight of the bigger picture – the dream.

I am reminded of a story I read recently in Jay Abraham's book, *Getting Everything You Can Out of All You've Got*. He tells of a young boy who looked down and spotted a shiny quarter. He was thrilled and picked it up. He'd earned a quarter and it had cost him nothing. He dedicated the rest of his life to the search for more such treasure. In the ensuing years, he would be rewarded with 387 pennies, 62 nickels, 49 dimes, 16 quarters, 2 half-dollars, and 6 one-dollar bills, for a total of $22.87. It cost him nothing – except the 28,745 sunsets he missed, the rainbows, the babies growing, the birds flying, and the opportunity to be part of the lives that passed by him everyday.

We've got to keep our head up and eyes open, as Abraham says. Focus on the bigger picture. Finding a penny here and there is great, but not if you're missing out on those momentous, life-changing opportunities that you really should be looking for personally and professionally. Look at our industry – it's constantly coming up with breakthroughs in all areas. Opportunities abound!

What's more, the Pharma industry tends to be very insular. For those who look beyond industry boundaries, there are even more opportunities to be spotted. Are other industries relying heavily on Internet advertising? Maybe we should try that too! What can we learn from manufacturing practices in the auto industry that might apply to our industry? You get the idea. This type of creativity – the ability to spot opportunities – is the second most important thing I look for when hiring for Xcelience, after teamworking skills.

This has the very positive consequence that we spend a lot of time weighing and testing new ideas. I can't stress the testing part enough. Henry Ford used to take all his important hires out for lunch before offering a position. If they salted their food before testing it, he wouldn't hire them. Why? He felt that if they salted their food without first tasting it, they would implement a plan without first testing it.

Even this article is an example of testing. This is my first time writing a series like this in an industry magazine. Obviously I'm writing this for people considering an MBO, but I'd also like to know if our target market reads it too. So if you're reading this and have any questions about the Xcelodose or anything else about Xcelience, please email me at Xcelodose@Xcelience.com.

We've had successes – but also plenty of great ideas that collapsed utterly in the testing phase. It happens. Take for example our telephone answering service. We are in the outsourcing business, so it's natural for us to outsource the things we don't focus on. Why not outsource our phone service then? For a fraction of the price of a receptionist, we found a company that would answer the phones 24/7. Better customer service, less cost! In theory.

In reality, the operators kept mispronouncing our name. They welcomed our sponsors to Excellence, or Sellience. They couldn't connect people to the person they wanted to speak to, they just took messages that we received by computer. This can be very frustrating for people who need someone NOW. Other times, people would call up asking for me and have the operator ask "Could you spell the name please? What department is he in?" That makes it pretty hard to believe the operator is sitting there in the front office.
It just didn't work.

While many of the changes we were able to bring in were cost savers and quality enhancers, there were, of course, changes brought on by the MBO that cost more money than they had under the previous regime. Our marketing expenses and legal costs definitely went up. And setting things up financially took a bit of trial and error. We had to learn things along the way, but after 2 years on our own, we are well on our way. Living the dream! ◆

BIOGRAPHY

Derek G. Hennecke, MBA
President & CEO
Xcelience

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

ATTORNEY REVIEW

An Update on Intellectual Property News

By: Clifford M. Davidson, Esq.

There is much going on in the world of patents. In the US, certain pending legislation may lead to some of the most extensive changes to patent law in more than 50 years. Particular aspects of these bills include: (1) conversion to a first-inventor-to-file system, (2) adoption of opposition proceedings, (3) reformation of infringement damages calculations, and (4) addition of an abbreviated pathway for FDA approval of biopharmaceuticals. If approved, these bills would greatly alter the landscape of patent procurement and patent litigation. No less significant, the *Tafas/Smithkline Beecham Corp. v. Dudas* summary judgment ruling was a cause of celebration for patent practitioners. US District Court for the Eastern District of Virginia Senior Judge James C. Cacheris granted Tafas' and Smithkline Beecham Corp's (GSK) motions for summary judgment and voided the USPTO's new claims and continuation rules (the Final Rules) as not in accordance with law and in excess of statutory jurisdictional authority.

PENDING LEGISLATION

Change to First to File

Unlike the rest of the world, the US utilizes a first-to-invent patent system. In the case of two patent applications claiming the same invention, the USPTO will determine the first inventor(s) through what is called an interference proceeding. An interference proceeding is a quasi-judicial system used by the USPTO to determine the first inventor, and typically involves proving invention dates through evidentiary proceedings and production of supporting documents (eg, lab notes, memos, etc). In contrast, the rest of the world follows a first-to-file patent system wherein the first person/entity to file a patent application receives the filing date and opportunity to obtain a patent.

The Patent Reform Act of 2007 was passed by the House of Representatives this past September and is awaiting a vote in the Senate. This act, if approved, would change the US to the first-to-file system, which eliminates interference proceedings. Proponents, such as the biotech industry, argue that this will save time from the lengthy and expensive years of proceedings, improve fairness, result in greater legal certainty, and move toward a more harmonized international patent system. Opponents maintain that such a system would favor those with deep pockets and disadvantage small and independent inventors who lack the resources to race to the patent office.

Opposition Proceedings in the US?

Under the current US patent system, after a patent is granted, a third party may file for an ex parte or inter partes reexamination challenging the patent's validity with arguments and evidence based on prior art not considered by the examiner in the initial patent issuance. The arguments within the examination request are limited to anticipation rejections under 35 U.S.C. § 102 and obviousness rejections under 35 U.S.C. § 103. If the USPTO agrees to reexamine the application, it is then up to the patent holder to correspond with the USPTO to prove the validity of the patent, likely faced with new prior art that hadn't been considered previously. The patent holder may make amendments to the claims to preserve the patent in light of the prior art.

Congress is currently reviewing foreign opposition systems in an effort to establish a patent opposition system in the US. In Europe, anyone can file for an opposition with the European Patent Office (EPO) challenging the patent's validity within 9 months from the publication of the mention of the grant. During an opposition, the patent holder contends with the opponent. The case is presented during Oral Proceedings at the

EPO in Munich, where a decision is reached. Afterward, both parties can file an appeal that may lead to another Oral Proceeding. Oppositions permit a greater depth of evidence to be presented to challenge a patent. The proposed bill states that the USPTO shall treat any ex parte or inter partes reexamination request during the 9 months following the patent grant as a request for an opposition proceeding. A request made after the 9-month opposition period and during the pendency of an opposition proceeding will be stayed by the USPTO. It is hoped that this new procedure will increase the quality of US patents by making it simple, speedy, and less expensive to review patents after allowance. The problem with this bill is that it leads to overlap and redundancy between the proposed and existing systems. The experience of Japan and China shows that multiple systems for challenging a patent have the potential to complicate matters by creating undue harassment and consuming valuable and limited patent office resources. Further, the relatively short 9-month opposition period is a disadvantage to small companies who do not have the resources to constantly monitor competitors' patents. In 2003, Japan abolished its post-grant opposition limited window in favor of an invalidation proceeding that allows a challenger to bring a request at anytime during the patent life.

Changes in Damages

Generally, in the US, a patentee is entitled to the lost profits damages it would have made based on the infringer's sales. However, in no way can damages be less than a reasonable royalty. Either the judge or jury makes the calculation for reasonable royalty as guided by the *Georgia Pacific* 15-factor test. This analysis involves envisioning the parties in a hypothetical negotiation for patent licensure. An amount is estimated for what the infringer would have paid and what the inventor would have accepted at the beginning of the infringement.

The proposed rule would ensure damages as the economic value attributable to the invention minus the value attributable to the incorporation of "process of features or improvements, whether or not themselves patented, that contribute economic value to the infringing product." In other words, courts would apportion damages to the patented innovation only. Under this proposal, the court must first look at the relationship of damages to contributions over prior art. Damages may be based on the entire market value of the product if the patented invention is deemed to be the driving force behind market demand for the product. Once there is an appropriate showing that the patentee's specific contribution over the prior art is the predominant basis for market demand, then damages may be based upon other factors, such as the terms of any non-exclusive marketplace licensing of the invention, an established royalty rate based on past licensing, and any other relevant factors. The bill would require the patent holder to establish that the economic value is due to the patent's specific improvement and not from any other features added by the infringer.

Section 5(a) of the bill is set to ensure clarity in the application of damages, which is often an open-ended guessing game as applied by the entire-market-value rule. The current standard bases damage calculations on the value of an entire product, patented and unpatented features, and significant and insignificant components. The damages awards may be inflated to many times the true market value of the innovation.

Proponents say this measure brings the excessive royalty awards more in line with economic realities. Large technology companies that have complex products containing an insignificant patented component are often dragged into frivolous litigations in which patentees base their damage calculations on the value of an entire end product.

Opponents to the proposed bill worry the opposite may happen: artificially low damage awards, unpredictable royalty rates, undermined licenses, voluminous increases in litigation resulting in lengthening damages phases of trials, high cost, and delays to the patent litigation system. The value of patents could be greatly diminished in fields that build upon incremental advances and prior technologies, for example, biotech and pharmaceuticals. An infringing company could reduce damages by limiting an infringed patent to a miniscule part of its product's overall functionality.

Many believe that apportioning damages based on the economic value gained from specific contributions over prior art weakens patent protection by making it easier to infringe, and is viewed as highly favoring infringers who may find it cheaper to copy a patent than to license it.

HATCH-WAXMAN - BIOSIMILARS

The *Hatch-Waxman Act of 1984* created an abbreviated pathway for FDA approval of small molecule drugs, but not generic biopharmaceuticals. Each New Drug Application (NDA) holder is required to list its patent information in the Approved Drug Products with Therapeutic Equivalence Evaluations, known as the *Orange Book*. If the NDA holder has listed patents in the Orange Book, the generic drug company can submit an Abbreviated New Drug Application (ANDA) to the FDA. The generic drug companies may obtain marketing approval without conducting expensive clinical trials to demonstrate safety and efficacy. Instead, generic applicants are required to show that their products are bioequivalent, ie, similar in dosage form, strength, route of administration, quality, performance characteristics, and intended use. An ANDA applicant is required to notify an NDA holder of any Paragraph IV certification stating that the status of the drug for which it seeks approval does not infringe in any way. If the patent holder decides to bring suit within 45 days of receiving the notice, then the FDA may stay the final approval of the ANDA for 30 months. The new bills in Congress seek to eliminate the automatic 30-month stay.

On February 14, 2007, Rep. Henry Waxman introduced the first of the four biosimilars bills, the *Access to Life-Saving Medicine Act*. Instead of filing a patent certification with the FDA, the biosimilar applicant may, at any time, send notice to the patent holder exchanging patent information and giving full details, facts, and legal basis for its belief that the patent may be invalid, unenforceable, or not infringed. The patentee may sue for infringement based only on the patent in the notice and only in a judicial district court of its choosing. In certain cases, the proposed Waxman bill would limit infringement damages to only reasonable royalty as the sole and exclusive remedy.

Rep. Jay Inslee introduced the second biosimilar bill, *Patient Protection and Innovative Biologic Medicines Act of 2007 on April 19, 2007*. The Inslee bill, favored by brandname companies, does not begin patent litigation until after the generic company starts to market its biosimilar drug product.

The third bill, *Biologics Price Competition and Innovation Act of 2007* introduced by Sen. Edward Kennedy on June 26, 2007, is the most complex of the four biosimilars bills. Unlike the voluntary patent exchange under the *Waxman Act*, the Kennedy bill mandates participation in the exchange. The generic drug company is required to send notice to the patent holder either (1) to exchange patent information giving full details, facts, and legal basis for its belief that the patent may be invalid, unenforceable, or not infringed or (2) to promise that there be no commercial marketing of generic products before patent expiration.

Lastly, the bill introduced by Rep. Anna Eshoo on March 13, 2008, is the *Pathway for Biosimilars Act*. The biosimilar applicant provides a copy of its FDA application to the brandname company. The brand company would then reply with listed reasons why it believes there may be patent infringement. The generic company would also send the same notice as under the Kennedy bill. The biosimilar applicant must wait until at least 120 days after it provides a detailed written detailed explanation before it can bring an action for declaratory judgment of invalidity, unenforceability, or non-infringement. Other components of the bill would give the innovator company 12-year exclusivity after initial licensure or 14 years if a medically significant new indication is filed during the 8-year period following licensure of the reference product. Another 6 months will be added to the 12-year or 14-year exclusivity periods for pediatric-indicated products. In addition, the user fees would be the same for biosimilar and brandname product applicants.

The interactions between brand and generic biologics involving patent challengers during the approval process will likely be different from the small molecule drugs under the *Hatch-Waxman Act*. Any new biosimilar legislation will probably have bits of elements from each of the proposed bills.

NEW USPTO RULES: TAFAS V. DUDAS

The USPTO promulgated a set of new rules culminating in final rules that were to go into effect in November 2007. The final rules permitted an applicant to file two continuation applications plus one request for continued examiniation (RCE) after the initial application (the 2 + 1 rule), with an

additional application or RCE upon the filing of a petition and explaining why the amendment/argument could not have been previously presented; and permitted an applicant to present a total of 5 independent claims or 25 total claims for examination without providing any further information about those claims (the 5/25 rule). If the total claims exceeded either amount, the applicant would be required to submit an examination support document (ESD) containing detailed information about the claims to assist the examiner in determining patentability.

Following publication of these final rules, plaintiffs Tafas and GSK separately filed complaints seeking preliminary and permanent injunctions prohibiting the USPTO from implementing the Final Rules and a declaratory judgment that the Rules violated the US Constitution, the Patent Act, etc. On October 31, 2007, the court granted GSK's motion for a temporary restraining order and preliminary injunction. The plaintiffs then moved for summary judgment. On April 1, 2008, the US District Court for the Eastern District of Virginia granted summary judgment in favor of the plaintiffs. The court ruled that the USPTO's proposed limitations to the number of continuation applications and claims per patent were substantive in nature and exceeded the scope of the USPTO's rulemaking authority under 35 U.S.C.S. § 2 (b) (2), and therefore voided the Final Rules. 35 U.S.C.S. § 2 (b) (2) does not give the USPTO the statutory basis for fixing an arbitrary limit to the number of continuing applications that may be filed and that retain the benefit of the priority date.

It is noteworthy that the court held that the USPTO's 2 + 1 continuation rule placed a limit that "deprives applicants of their valuable rights under 35 U.S.C. § 120 to an unlimited number of continuation and continuation-in-part applications as a matter of right." The court also ruled that the 5/25 rule limiting the number of claims was also substantive because the law prevents any strict limit on the number of claims.

The court further took note of the fact that the Federal Circuit has read 35 U.S.C.S. §§ 102, 103, and 131 as placing the burden of proof on the USPTO to make a prima facie case of unpatentability. The Court found that the ESD requirement would change the law by shifting the examination burden onto the applicants. Final Rule 265 would have required that applicants conduct a broad search of patents, patent applications, and literature, and provide, among other things, a detailed explanation of how each of the independent claims is patentable over the cited references. The Court held that such would constitute a drastic departure form the terms of the Patent Act as they are presently understood effecting changes in GSK's and Tafas's existing rights and obligations.

The USPTO filed an appeal on May 7, 2008. It is widely believed that this decision will be upheld. It is unlikely that the matter will be resolved in the coming months and quite possibly not until the end of the Bush administration. ◆

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.

BUCCAL BILAYERED TABLETS

Mucoadhesive Bilayer Buccal Tablets of Propranolol Hydrochloride: Pharmacodynamic Study in Rabbits

By: Vishnu M. Patel, PhD; Rashwin J. Patel, PhD; Jayvadan K. Patel, PhD; Bhupendra G. Prajapati, MPharm

ABSTRACT

The present study was designed to study mucoadhesive bilayered buccal tablets of propranolol hydrochloride (PRO-HCL) using a combination of the bioadhesive polymers sodium alginate (Na-alginate) and Carbopol-934 (CP). Ethyl cellulose (EC) was used as an impermeable backing layer. The tablets were evaluated by weight variation, thickness, hardness, friability, surface pH, mucoadhesive strength, swelling-index, in vitro drug release, ex vivo drug permeation, and in vivo pharmacodynamic study in rabbits. Tablets containing Na-alginate and CP in the ratio of 5:1 gave the maximum percentage of in vitro drug release without disintegration in 12 hours. The mechanism of drug release was found to be by non-Fickian diffusion and followed zero-order kinetics. The ex vivo mucoadhesion test was performed using sheep buccal mucosa on modified physical balance. The optimized tablet (batch F4) showed good bioadhesive strength (28.9 ± 0.99 g) and good in vitro drug permeation (68.65 ± 3.69% for 12 hrs). Stability study of optimized tablets was determined in natural human saliva, and it was found that both drug and buccal tablet were stable in human saliva. Swelling index was proportional to Na-alginate and inversely proportional to CP content. The surface pH of all tablets was within satisfactory limit (7.0 ± 1.5) and hence, these tablets should not cause irritation in the buccal cavity. The optimized tablet (batch F4) was applied to rabbit oral mucosa, and inhibition of isoprenaline-induced tachycardia was achieved. The studies conducted in rabbits confirmed the sustained release as compared to intravenous administration.

INTRODUCTION

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration.[1] It provides direct entry into the systemic circulation, thus avoiding the hepatic first-pass effect, ease of administration, and ability to terminate delivery when required.[2] Attempts have been made to formulate various buccal mucoadhesive dosage forms, including tablets, films, patches, disks, and gels.[3-7] A suitable buccal drug delivery system should possess good bioadhesive properties so that it can be retained in the oral cavity for the desired duration. In addition, it should release the drug in a unidirectional way toward the mucosa, in a controlled and predictable manner to elicit the required therapeutic response. This can be obtained using bilayered devices.[6,8]

PRO-HCL, a non-selective beta-adrenergic blocking agent, has been widely used in the treatment of hypertension, angina pectoris, and many other cardiovascular disorders. PRO-HCL is subjected to an extensive and highly variable hepatic first-pass metabolism following oral administration, with a reported systemic bioavailability between 15% and 23%.[9,10] The physicochemical properties of PRO-HCL, its suitable half life (3 to 5 hrs), and low molecular weight (295.81) make it a suitable candidate for administration by the buccal route.

The present study was designed to study the mucoadhesive bilayered buccal tablets of PRO-HCL, using CP and Na-alginate as the mucoadhesive polymers and EC as an impermeable backing layer. The buccal tablets were characterized by measuring the ex vivo mucoadhesive strength, swelling study, in-vitro drug release, in vitro buccal permeation, and in vivo study to examine the usefulness of the device in suppressing isoprenaline-induced tachycardia in rabbits.

MATERIALS

Propranolol hydrochloride (99% purity), Carbopol-934, and Ethyl cellulose were generously gifted by Sarabhai Chemicals Ltd., Baroda, India. Sodium alginate (300-400 cps), Polyethyleneglycol-4000 (PEG-4000), Polyvinyl pyrrolidone K-30 (PVP K-30), and D-mannitol (S.D. Fine Chemicals, Mumbai, India) were obtained from commercial sources. Isoprenaline sulphate, (Unichem Laboratories Limited, Mumbai, India), Phenobarbitone sodium (Rhone-Poulenc Ltd, Mumbai, India), and heparin injections (Biological E. Limited, Hydrabad, India) were obtained from commercial sources. All other reagents and chemicals used were of analytical reagent grade.

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METHODS

Preparation of Mucoadhesive Bilayered Buccal Tablets

Bilayered buccal tablets were prepared by a direct compressing procedure involving two consecutive steps. The mucoadhesive drug/polymer mixture was prepared by homogeneously mixing the drug with a varying ratio of CP and Na-alginate in a glass mortar for 15 mins. The mixture (100 mg) was then compressed using an 11-mm diameter die in a single stroke multi-station tablet machine (Dhiman, Jalandhar, India). The upper punch was raised, the backing layer of EC was then placed on the above compact, and the two layers were compressed to a mucoadhesive bilayered tablet. Various batches (Table 1) were prepared by varying the ratio of CP and Na-alginate to choose the effective formulation. Each tablet weighed approximately 150 mg with a thickness of 1.5 to 1.6 mm.

Ex Vivo Mucoadhesive Strength

A modified balance method was used for ex vivo mucoadhesion strength.[11] The fresh sheep buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer pH 6.8. The glass vial was placed and tightly fitted in a glass beaker filled with phosphate buffer (pH 6.8, 37ºC ± 1ºC) just touching the mucosal surface. The tablet was stuck to the lower side of the rubber stopper with cyanoacrylate adhesive. Two sides of the balance were balanced with a 5-g weight on the right-hand side pan. A weight of 5 g was removed from the right-hand side pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for different contact times (1, 3, and 5 mins). The water (equivalent to weight) was added slowly with infusion (100 drops/min) set to the right-hand side pan until the tablet detached from the mucosal surface. This detachment force gave the mucoadhesive strength of the tablets in grams.

Swelling Study

Buccal tablets were weighed individually (designated as W1) and placed separately in 2% agar gel plates with the core facing the gel surface and incubated at 37ºC ± 1ºC. At regular 1-hr time intervals until 8 hrs, the tablets were removed from the petri dishes, and the excess surface water was removed carefully using the filter paper. The swollen tablets were then re-weighed (W2), and swelling index (SI) was calculated using the following formula SI = (W2 – W1)/W1 X 100.[6]

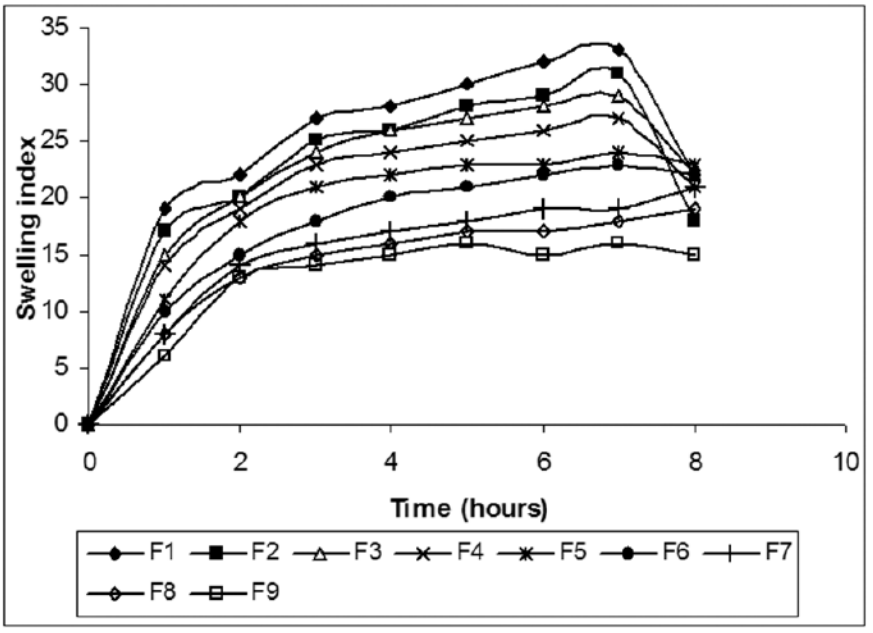
Surface pH Study

The method used to determine the surface pH of the tablets was similar to that described by Bottenberg et al.[12] A combined glass electrode was used for this purpose. The tablets were allowed to swell by keeping them in contact with 1 ml of distilled water (pH 6.5 ± 0.05) for 2 hrs at room temperature, and the pH was noted by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 min.

In Vitro Drug Release

The USP XXIII rotating paddle method (assay conditions: 37ºC ± 0.5ºC, 50 rpm, 200 ml of phosphate buffer pH 6.8, n = 3) was used to study drug release from the bilayered buccal tablets. The back surface of the buccal tablet was attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disks were allocated in the bottom of the dissolution vessels. Samples (5

FIGURE 1



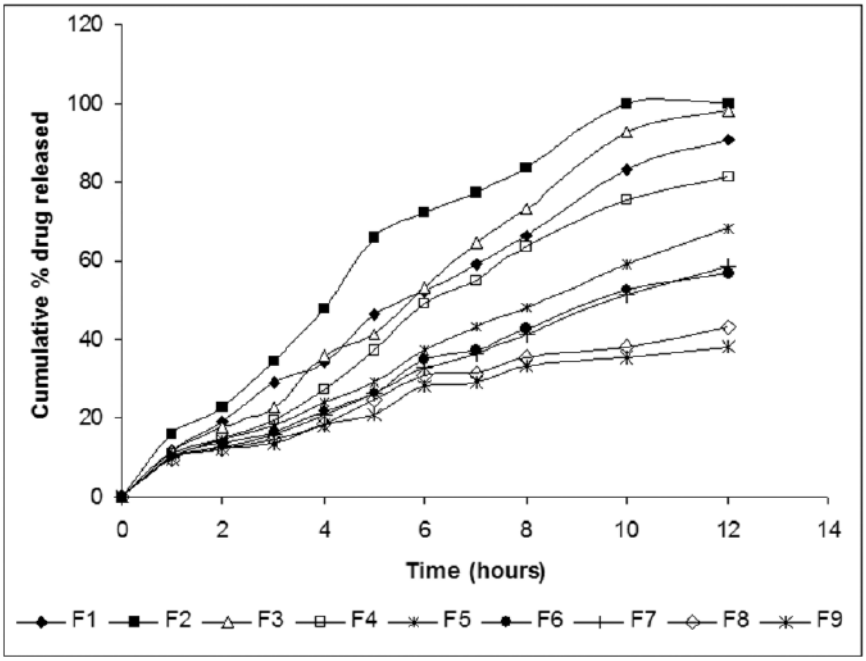
Swelling index of bilayered buccal tablets of batches F1 to F9.

TABLE 1

Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Adhesive Layer									
PRO-HCL	20	20	20	20	20	20	20	20	20
Na-alginate	34.3	33.3	32	30	26.7	20	13.3	10	8
CP-934	5.7	6.7	8	10	13.3	20	26.7	30	32
PVP K-30	30	30	30	30	30	30	30	30	30
D-mannitol	8	8	8	8	8	8	8	8	8
PEG-4000	2	2	2	2	2	2	2	2	2
Backing Layer									
Ethylcellulose	50	50	50	50	50	50	50	50	50
Total	150	150	150	150	150	150	150	150	150

Composition of bilayered buccal tablets of propranolol hydrochloride.

FIGURE 2



Cumulative % drug released from batches F1 to F9.

TABLE 2

Batch	% Weight Variation	Thickness (mm)	Hardness (kg/cm^2)	% Friability	% Drug Content	Surface pH
F1	0.82 ± 0.15	1.5 ± 0.05	4.41 ± 0.16	0.62 ± 0.05	100.73 ± 0.4	6.41 ± 0.02
F2	0.75 ± 0.21	1.5 ± 0.04	4.22 ± 0.17	0.82 ± 0.05	100.26 ± 0.7	6.29 ±0.09
F3	0.89 ± 0.17	1.5 ± 0.10	4.0 ± 0.24	0.81 ± 0.06	99.16 ± 0.5	6.36 ± 0.05
F4	0.69 ± 0.11	1.6 ± 0.05	4.12 ± 0.19	0.72 ± 0.03	100.35 ± 0.6	6.13 ± 0.03
F5	0.71 ± 0.09	1.6 ± 0.03	3.9 ± 0.25	0.79 ± 0.02	99.28 ± 0.4	5.89 ± 0.05
F6	0.78 ± 0.20	1.5 ± 0.04	3.77 ± 0.30	0.82 ± 0.05	100.65 ± 0.8	5.82 ± 0.01
F7	0.84 ± 0.13	1.6 ± 0.05	3.6 ± 0.21	0.65 ± 0.04	100.48 ± 0.5	5.79 ± 0.08
F8	0.88 ± 0.16	1.5 ± 0.12	3.5 ± 0.19	0.81 ± 0.03	99.54 ± 0.4	5.65 ± 0.04
F9	0.74 ± 0.14	1.5 ± 0.26	3.4 ± 0.23	0.79 ± 0.07	99.83 ± 0.7	5.7 ± 0.09

Each value represents the mean ± SD of three determinations.

Physico-chemical properties of bilayered buccal tablets of propranolol hydrochloride.

TABLE 3

Contact Time (Minutes)	Mucoadhesive Strength (g)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	7.5 ± 0.85	7.5 ± 0.75	6.3 ± 1.3	8.9 ± 2.3	8.1 ± 2.44	7.1 ± 3.1	3.7 ± 2.1	3.8 ± 2.22	3 ± 1.5
3	8.5 ± 2.4	8.9 ± 1.7	11.1 ± 0.8	12.3 ± 0.85	15.5 ± 1.9	19.1 ± 3.4	21.3 ± 2.1	20.4 ± 1.8	19 ± 2.9
5	11.65 ± 3.3	13.32 ± 2.1	16.84 ± 2.7	22.30 ± 0.99	23.31 ± 1.3	25.25 ± 1.11	24.55 ± 1.5	27.88 ± 1.7	28.9 ± 2.1

Each value represents the mean ± SD. of three determinations.

In vitro mucoadhesive study of bilayered buccal tablets.

ml) were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through a 0.2-micrometer whatman filter paper and assayed spectrophotometrically at 290 nm. (Shimazdu, SPD-10 A VP, Japan).

In Vitro Buccal Permeation Study

The in vitro drug permeation studies of PRO-HCL through the sheep buccal mucosa were performed using Keshary-Chien type glass diffusion cells at 37ºC ± 0.2ºC. Freshly obtained sheep buccal mucosa was mounted between the donor and receptor compartments. The tablet was placed on the mucosa, and the compartments were clamped together. The donor compartment was filled with 1 ml of phosphate buffer pH 6.8. The receptor compartment (12.5-ml capacity) was filled with phosphate buffer pH 7.4, and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 100 rpm. A 1-ml sample was withdrawn at predetermined time intervals and analyzed for drug content at 290 nm using a UV-spectrophotometer (Shimazdu, SPD-10 A VP, Japan).

Stability Study in Human Saliva

The stability studies of optimized tablets (batch F4) were performed in normal human saliva. The human saliva was collected from humans (ages 18 to 50) and filtered. Tablets were placed in separate petri dishes containing 5 ml of human saliva and maintained at 37ºC ± 2ºC for 6 hrs. At regular time intervals (0, 1, 2, 3, and 6 hrs), the tablet was examined for change in color and shape, collapse of the tablet, and drug content.

Pharmacodynamic Study

The optimized tablet (batch F4) was evaluated by measuring the isoprenaline-induced tachycardia in rabbits.[13,14] Healthy albino rabbits of either sex (1.75 to 2.25 kg) were selected for the study and acclimatized to the laboratory environment for 1 week prior to the experiment. Overnight-fasted rabbits were anesthetized by intravenous administration of 50 mg/kg of phenobarbitone in sterile normal saline. A catheter (scalp vein needle gauge 26) was placed in the marginal ear vein for administration of the drug. Anesthesia was maintained by hourly administration of 6 mg/kg of phenobarbitone sodium. Heparinized saline (20 IU/ml) was filled in the catheter patent and to overcome its dead

volume. The front paws of the rabbits were cleaned by removal of hair. The pulse transducer (MP 100) was placed on the paws and connected to the Power lab 8SP (multi-channel data acquisition system, AD Instruments, Australia). Pulses were recorded in the first channel, and heart rate in beats per minute (BPM) was recorded in the second channel.

Normal heart rate (250 to 280) was recorded for 5 mins. Isoprenaline (3 µg/kg) was given intravenously, and heart rate (330 to 370) was again recorded for 15 mins until it became normal. PRO-HCL in sterile normal saline at a dose of 2.5 mg/kg was administered intravenously for 30 seconds through a catheter and flushed with 1 ml of heparinized saline. Isoprenaline (3 µg/kg) was administered at intervals of 30 mins. for 8 hrs after PRO-HCL dosing, and heart rate was recorded for 10 mins before and after isoprenaline administration. In the case of the pharmacodynamic study of the buccal tablet, the tablet was wetted with a drop of normal saline and stuck on the upper left oral mucosa after wiping the site with a cotton swab. Isoprenaline (3 µg/kg) was administered at predetermined time intervals, and the heart rate was recorded continuously for 10 mins. Care was taken to prevent the rabbit from disturbing the buccal tablet. Heart rate was analyzed by the power lab HRV (heart rate variability) software.

RESULTS & DISCUSSION

The aim of the present work was to prepare mucoadhesive bilayered buccal tablets of PRO-HCL as an antihypertensive drug. The bilayered structural design was expected to provide the prolong release of drug in a unidirectional fashion to the buccal mucosa and to avoid loss of drug due to washout by saliva in the oral cavity. CP and Na-alginate were selected as the bioadhesive polymers due to their excellent bioadhesive properties.[6,15-17] EC, being hydrophobic, has recently been reported to be an excellent backing material given its low water permeability and moderate flexibility, was chosen as an impermeable backing layer.[18]

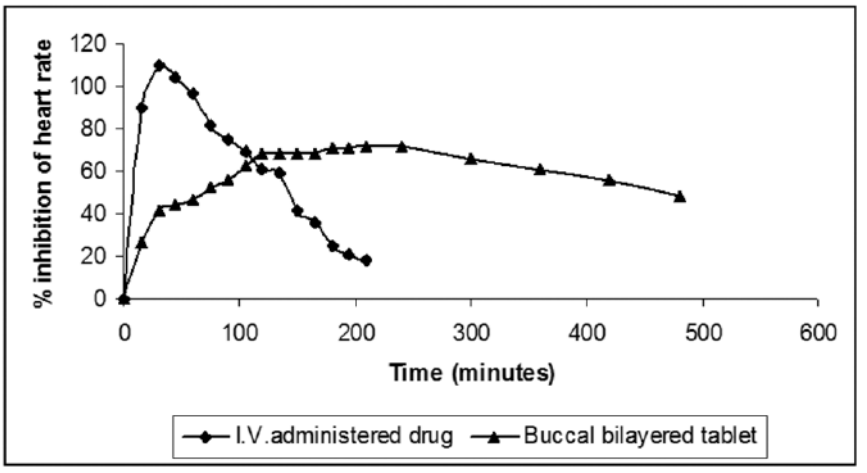
Tablets were found to be satisfactory when evaluated for weight variation (0.78% ± 0.15%), thickness (1.5 ± 0.18 mm), hardness (4.005 ± 0.41 kg/cm^2), friability (0.72% ± 0.04%), and drug content (99.79% ± 0.62%). The surface pH of all the tablets was within satisfactory limit (7.0 ± 1.5 units) (Table 2) and hence, these tablets should not cause any irritation in the buccal cavity.

Appropriate swelling behavior of a buccal adhesive system is an essential property for uniform and prolonged release of drug and effective mucoadhesion.[19] The swelling study indicated that the rate of swelling was proportional to Na-alginate and inversely proportional to CP content of the tablets (Figure 1). The maximum swelling index was found in batch F1 (33.3 ± 1.7) containing higher proportion of Na-alginate. Tablets did not show any appreciable change in their shape and form during the 8 hrs, they were kept on a 2% agar gel plate.

The ex vivo mucoadhesive strength of the tablets was determined for different contact time, using sheep buccal mucosa. Tablets containing higher proportion of Na-alginate showed higher mucoadhesion at 1-min contact time (Table 3). This is due to the hydrophilic nature of Na-alginate; it gets hydrated easily with less contact time and forms a sufficient strong gel that entangles tightly with the mucin molecules. A linear increase in mucoadhesion was observed with increase in contact time for 3 mins. The studies further indicated that tablets containing a higher ratio of CP/Na-alginate showed higher mucoadhesion for 5 mins. contact time. This high mucoadhesive strength of CP may be due to formation of secondary mucoadhesive bonds with mucin due to formation of their rapid swelling and interpenetration of the polymer chains in the interfacial region while the other polymers only undergo superficial bioadhesion.[20] The aforementioned results indicated that the contact time is a more critical factor for mucoadhesion. Optimized tablets (batch F4) showed good mucoadhesion (22.30 ± 0.99 g) for 5 mins contact time.

In vitro drug release studies indicated that the drug release was proportional to Na-alginate and inversely proportional to CP content (Figure 2). The higher uptake of water by the polymer, the more the amount of drug diffused out from the polymer matrix. Thus, this high amount of water uptake by Na-alginate may lead to considerable swelling of the polymer matrix, allowing drug to diffuse out at a faster rate.[21] The progressive decrease in the amount of drug released from batches F1 to F9 may be attributed to the increase in proportion of CP, which is a water-swellable polymer. At higher concentrations, a decrease in the release rate is obtained most likely due to its higher swelling property. All tablets (batches F1 to F9) remained intact during the 12-hr period.

FIGURE 3



% inhibition of isoprenaline-induced heart rate in rabbits (batch F4).

TABLE 4

Sampling Time (hours)	Color Change*	Thickness **(mm)	Change in Shape Diameter (mm)**	Collapsing*	Drug Recovered (%)**
0	No	1.58	11.04	-	99.86
1	No	1.62	11.12	No	99.22
2	No	1.65	11.36	No	99.21
3	No	1.66	12.20	No	99.46
6	No	1.7	12.30	No	99.12

* Visual observation ** Mean of three readings

Stability study of optimized bilayered buccal tablet (batch F4) in normal human saliva.

The drug release data were analyzed using a simple power equation $Mt/M\infty = Kt^n$.[22] For all the batches, the values of n were between 0.5 to 1.0, indicating non-Fickian release. The release data further showed in favor of zero-order release kinetics (for optimized tablet F4, $R^2 = 0.9816$).

The optimization of the tablets was carried out on the basis of in vitro drug release, swelling study, and ex vivo mucoadhesive strength. The optimized tablet (batch F4) was selected for a further in vitro buccal permeation study, stability study in human saliva, and pharmacodynamic study.

The optimized tablet (batch F4) was subjected to an in vitro buccal permeation study using a diffusion cell and showed drug permeation of 68.65% ± 3.69% in 12 hrs. The correlation between in vitro drug release rate and in vitro drug permeation across the sheep buccal mucosa was found to be positive with a correlation coefficient (r^2) of 0.9886.

The stability of optimized tablet (batch F4) was examined in natural human saliva, and the obtained data are presented in Table 4. Tablets did not exhibit change in color or shape, suggesting the satisfactory stability of both the drug and device in the human saliva.

Physical properties of the tablets, such as thickness and diameter, increased slightly owing to swelling of the system in human saliva, but the tablets did not collapse in the human saliva until the end of the study, confirming the sufficient strength of the device.

The optimized tablet (batch F4) showed a gradual increase (up to 2 hrs) in percentage inhibition of heart rate in rabbits and maintained it for longer periods (2 hrs), then slowly decreased in inhibition, suggesting good sustained release for 7 hrs (Figure 3). The tablet showed maximum inhibitory effect of 71.61% at around 3.75 hrs, with a steady state for 2 hrs, and then declined in the inhibitory effects. The time for 50% inhibition (T50%) of the heart rate for the optimized buccal tablet (batch F4) and intravenous administered drug were 7.5 and 2.4 hrs, respectively, while 70% inhibition (T70%) of heart rate was 4.15 and 1.7 hrs, respectively.

CONCLUSION

The new buccal bilayered tablets showed significant mucoadhesive characteristics in contact with sheep buccal mucosa, with good swelling characteristics and drug release. The non-Fickian release behavior obtained suggested that the release of PRO-HCL is controlled by a combination of diffusion of drug in the matrix and swelling of the matrix followed by water penetration into the tablet. In vivo study in rabbits confirmed the evidence for sustained release of drug from the tablet. As a conclusion, the mucoadhesive buccal tablets of PRO-HCL can be a good way to bypass the extensive hepatic first-pass metabolism.

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BIOGRAPHIES

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30th Anniversary of the Franz Cell Finite Dose Model: The Crystal Ball of Topical Drug Development

By: Sam Raney, PhD; Paul Lehman, MSc; and Thomas Franz, MD

ABSTRACT

This article commemorates the 30th Anniversary of the Franz Cell and the in vitro Finite Dose Model, which revolutionized strategic drug development for topical formulations.[1,2] Even after 3 decades, this elegant diffusion cell is still regarded as the single most powerful in vitro model for advancing dermatologic and transdermal product development. Its ability to accurately predict a drug's topical delivery and pharmacokinetics underpins numerous key product development decisions, mitigates costly failures, and accelerates navigation throughout development. Its enormous impact has been not only as a key strategic asset for drug developers, but ultimately, in helping to ensure that safe and optimally effective medications have become available to patients.

INTRODUCTION

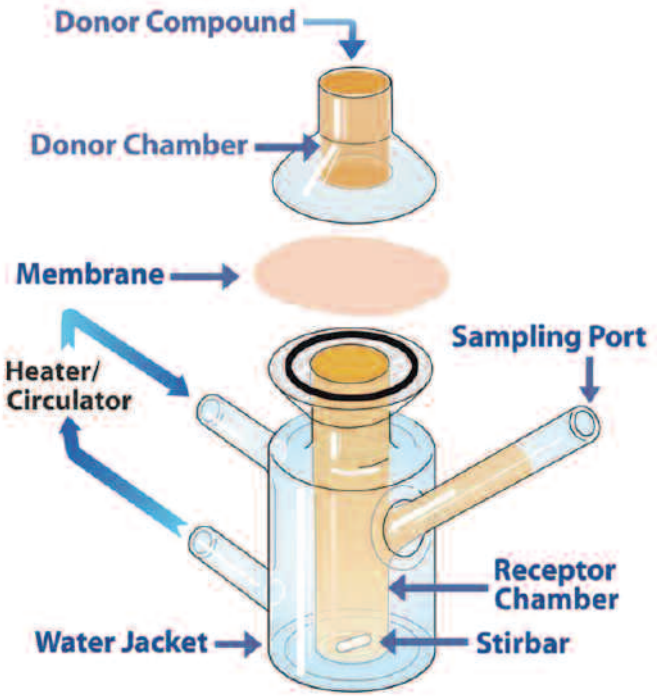
Topicals & Transdermals

Topicals and transdermals are multi-billion dollar drug delivery technologies widely utilized throughout the world. These terms refer to dosage forms administered onto the skin, but the intended site of action for topicals is the skin itself, whereas the site of action for transdermal drugs is systemic. It is expedient to refer to both collectively as topicals, and these include creams, lotions, gels, ointments, foams, shampoos, solutions, lacquers, patches, and several other novel technologies, including medical devices. Topical formulations are convenient and familiar for users, but can be extremely challenging to develop for delivering drugs effectively across the formidable skin barrier.

The Skin Barrier

The outermost layer of the skin is called the stratum corneum (SC). The impressive barrier function of skin resides primarily in this very thin, dead outer layer. The SC is composed of non-viable cells called corneocytes, and its structure and composition have evolved to form an extremely durable and effective barrier for keeping water in, and concurrently, keeping exogenous substances out. Fortunately for drug developers, because the barrier function of skin resides in this non-viable layer, and because the properties of the SC are retained when removed from the body, the absorption of topical compounds

FIGURE 1



The Components of the Franz Cell Set-up
Skin is mounted atop the base of the Franz Cell and bathed from beneath by a physiological solution within the Receptor Chamber, which is maintained at physiological temperature by a Water Jacket connected to an external Circulating Water Bath. A magnetic stirrer below the Franz Cell rotates a miniature Stir bar keeping it well-mixed. The skin is clamped between the base and an upper Donor Chamber, typically with an O-ring seal. The dose is administered from above onto the skin surface. At selected time points, the Receptor Chamber solution is collected from the Sampling Port (and the volume replaced) to measure the amount of drug that has penetrated through the skin. Following the final sampling time point, the skin can be surface-washed and recovered to evaluate drug content in the SC, epidermis, and dermis, thereby to determine distribution of the compound within the skin as well as to calculate mass balance accountability of the dose. (Adapted from an image courtesy of PermeGear – www.PermeGear.com)

through the skin barrier can be accurately evaluated in vitro, by using human skin mounted on a Franz Diffusion Cell.

Delivering Compounds Through Skin

Designing formulations to deliver drugs effectively through the skin is as much an art as a science. It is surprisingly difficult to anticipate the impact of alterations in formulation design on dermal absorption of the drug. Neither animal models nor mathematical simulations are consistent, or accurate, at predicting either dermal absorption or product performance in humans. There are numerous physicochemical characteristics of the penetrating compound, combined with significant contribution of the formulation matrix, that together influence absorption of the compound through human skin. Ultimately, this absorption can only be accurately predicted when evaluated using human skin.

THE FRANZ CELL FINITE DOSE MODEL

Franz & Lehman – The Men Behind the Model

The Franz Cell Finite Dose Model utilizes human skin obtained from surgical procedures or organ donors. The skin is mounted onto glass chambers called Franz Diffusion Cells (Figure 1), so named for Thomas J. Franz, MD. During a scientific partnership spanning 3 decades, Dr. Franz and Paul Lehman innovated many of the key methodologies for utilizing the Franz Diffusion Cell to accurately model clinical situations for the dermal absorption of drugs.

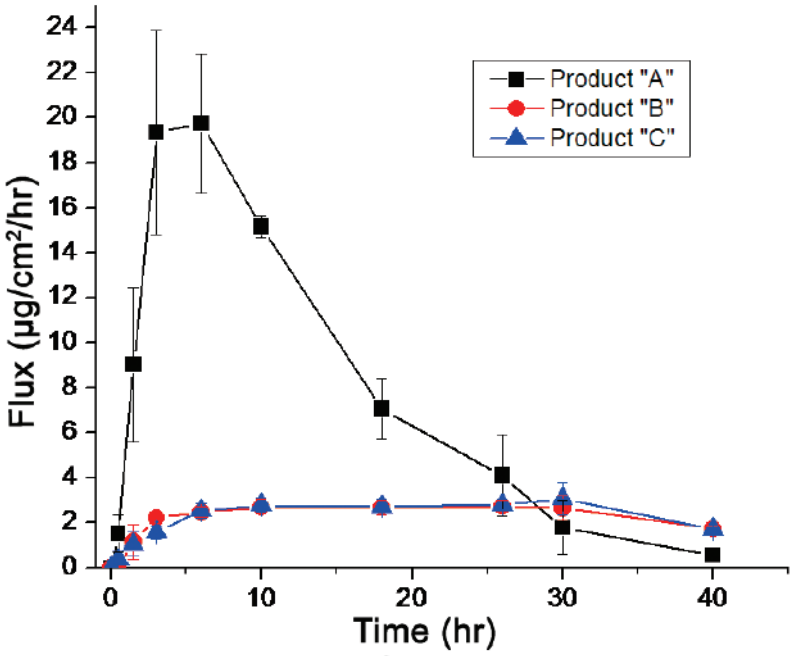
Adaptations & Variations of the Design

The fundamental design of the static Franz Cell is widely accepted and remains the most popular and versatile diffusion cell design. In addition, several adaptations have been made to the basic design. Some examples include the Bronaugh Cell, which has a flow-through reservoir compartment, the Hanson Cell, which is designed as part of an automated sampling system, and a modified Franz Cell, which is adapted for toe and finger nails.[3,4]

The Finite Dose Model & Predictive Modeling

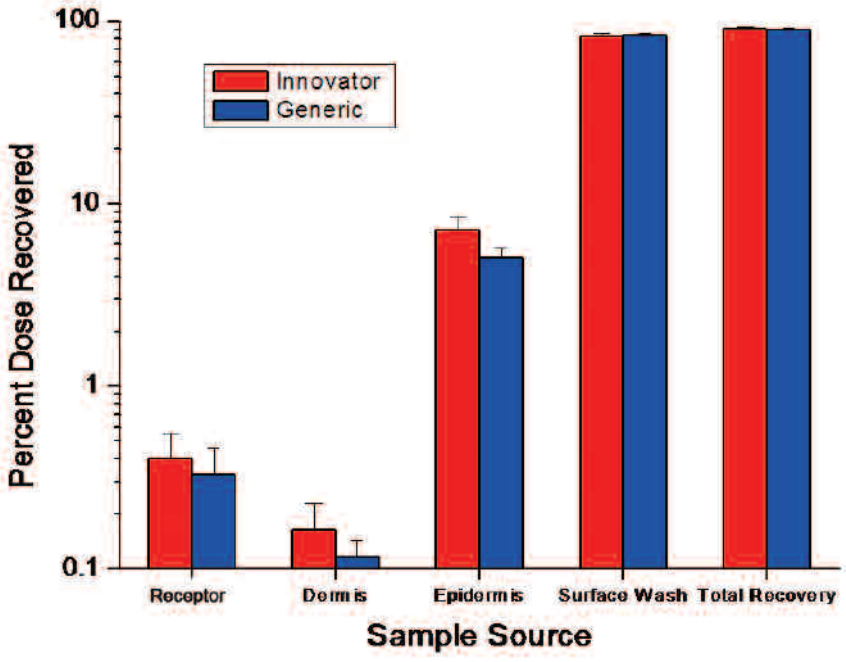
The Franz Cell provided the foundation for in vitro percutaneous absorption studies. However, beyond the cell or any of its adaptations, it was necessary to develop

FIGURE 2



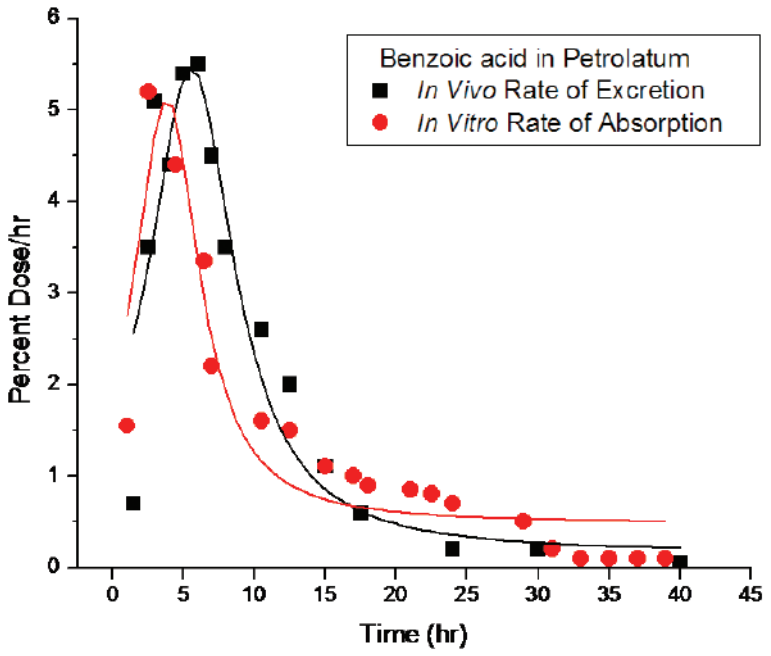
Predicting Product Performance Among Prototypes
This figure demonstrates typical absorption profiles of a single drug in three different formulations. The time course of absorption is characterized by the Flux (rate of absorption) of the compound across the skin as a function of Time, which also shows the total amount absorbed, as the area under the curve. This is utilized to evaluate equivalent performance of generics and innovators or to evaluate significantly different performance among comparator formulations.

FIGURE 3



Dermal Distribution & Mass Balance Accountability
When dose mass balance studies are conducted, residual surface dose, and the distributed content within the epidermis and dermis can also be determined.

FIGURE 4



In Vitro - In Vivo Correlation
The rate of absorption of topically administered Benzoic Acid measured in vitro correlates precisely with the rate of excretion measured in vivo. This is one of many different ways in which the agreement between in vitro and in vivo data has been demonstrated.

insightful methodologies to accurately model the clinical situation. One of the most important examples of this was the Finite Dose technique; the use of a clinically relevant finite dose administered to the skin (~ 3 to 5 mg/cm^2).[2] This new methodology was essential to accurately model the clinical scenario, and was a critical step forward from the prior practice of using an infinite dose to evaluate the percutaneous absorption of topical formulations. An infinite dose can artificially alter the skin barrier, leading to an elevated rate of absorption of the drug across the skin, and an artificial representation of steady state kinetics. By contrast, a finite dose accurately models the pharmacokinetic rise to a maximum peak rate of absorption, followed by a declination phase as the applied surface dose becomes depleted of drug (Figure 2).

Measuring Rate of Release & Skin Metabolism

Other investigators have added to the wealth of knowledge that can be obtained from the Finite Dose Model. One particularly noteworthy example is the use of freshly excised surgical skin, in which metabolic activity can be maintained and from which drug metabolism can be assessed during its percutaneous absorption.[5] Another example is the use of inert membranes to assess the rate of release of drug from the vehicle matrix.[6] The latter instance, using the FDA SUPAC-SS Guidance for semi-solid dosage forms, is commonly utilized throughout stages of topical formulation development to evaluate alterations in the vehicle matrix, which may change the equivalent rates of release among batches.[6]

THE CRYSTAL BALL: IN VITRO - IN VIVO CORRELATION

Building a Topical Product

There are numerous common variables that tend to impact the performance of topical formulations throughout development. The in vitro Franz Cell Finite Dose Model has played a central role facilitating both the efficiency and sophistication of modern topical drug development by providing an accurate and predictive in vitro tool to assess clinical bioavailability and bioequivalence. Topical drug development involves a process of selecting the compound or analogue with the best inherent absorption characteristics through human skin, selecting the most appropriate topical formulation type (cream, gel, etc), selecting the optimum formulation composition, as well as selecting the appropriate concentration of the active ingredient in the formulation, all to ultimately achieve the desired magnitude, profile, and duration of dermal absorption.

Delivery of the compound into the skin can also be very sensitive to changes in the formulation matrix. These include changing sources of the excipients or actives, as well as scale-up, changes in manufacturing processes, changes in manufacturing sites, or even inherent lot-to-lot variability. Consistency in product performance throughout development is essential to compare data across the successive stages, and is particularly important before utilizing a batch in multi-million dollar clinical trials. Similarly, during the process of generic product development, it is essential to engineer formulations from which the absorption of the active(s) through human skin is equivalent to the innovator in magnitude, profile, and duration.

Predicting Drug Delivery for Pharmaceuticals

Percutaneous absorption represents the A in ADME (Absorption - Distribution - Metabolism - Excretion), and it has been consistently demonstrated that in properly modeled and well-conceived studies, which are conducted under identical conditions (matched dose, body site, duration, etc), the in vitro results correlate with and predict in vivo results (Figure 4). Using basic pharmacokinetic principles, this input-function (the absorption phase) thereafter allows for prediction of systemic blood levels, particularly if the clearance and excretion have been well characterized for the drug of interest.[7] Experienced implementation of this model has shown it to be the single best surrogate model for the assessment of bioavailability and bioequivalence for topically administered compounds. As such, because of its predictive power, the model has become the gold standard used by experienced pharmaceutical, biotech, and specialty companies (Figure 5).

When using the Franz Cell and the Finite Dose Model for predicting in vivo bioavailability and percutaneous absorption pharmacokinetics, one must be cognizant of the following three key criteria to ensure success:

1. Be consistent in study design between the in vitro and in vivo methods (eg, same dose amounts, formulations, exposure durations, target body site, etc);

2. Be fully trained in the use of the Franz Cell and the Finite Dose Model; and

3. Have a complete understanding of the penetrant's chemical characteristics in

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relation to skin physiology, formulation design, and the diffusion process.

Predicting Systemic Risk Via Dermal Absorption for Toxicology

In addition to predicting drug delivery for pharmaceuticals, this model is also used to assess the potential systemic exposure from toxic compounds that may come in contact with human skin, such as pesticides and herbicides. This approach is particularly valuable for manufacturers of cosmetic excipients and industrial chemicals, and for government agencies needing to evaluate dermal exposure and toxicity, while minimizing the use of live animal research.

Predicting Equivalent Dermal Absorption for Generics

Another common application of the in vitro Franz Cell Finite Dose Model using human skin is during the development of generic topical products. Given the recognized difficulty to exactly match the manufacturing processes of an innovator, multiple variations of generic formulations can be tested in vitro to determine which one most closely matches the innovator (Figure 2). Clinical trials are the basis for approval of most generic topicals, so it is critical to confirm equivalent product performance between test and reference lots prior to conducting the pivotal clinical dermatology bioequivalence study. Demonstrating equivalent rate and extent of absorption in vitro using the Franz Cell provides a high degree of assurance that bioequivalence will be demonstrated in the clinical trial, where the consequences of failure in a clinical study are dire.

REVOLUTIONIZING DECISION-MAKING THROUGHOUT TOPICAL DEVELOPMENT

The in vitro Franz Cell Finite Dose Model has revolutionized topical product development throughout the past 30 years, and has served as a powerful and sensitive tool by which to accurately quantitate a drug's rate of percutaneous absorption. This in vitro model has become much more than simply a preclinical tool and has grown to be utilized within multiple stages of the drug development process. Preclinically, it is used principally to screen and select the optimum formulation for further development. However, as data continually emerges into the public domain supporting the validity of the model as a surrogate for in vivo measurements of bioavailability and bioequivalence, its application within other phases of the drug development process have become increasingly evident, including the following:

- Evaluating reformulation changes during Phases I-III;
- Development of line extensions and products with altered or enhanced delivery;
- Scale-up changes; and
- Post-approval manufacturing changes

FIGURE 5

Franz Cell Studies are a standard part of development for topicals and transdermals, from preclinical candidate screening and formulation optimization to evaluation of manufacturing specifications and lot-to-lot comparison, as well as for verification of clinical batch performance and equivalence, prior to multi-million dollar clinical trials.

THE FUTURE

Harmonization of Percutaneous Absorption Testing

International initiatives are currently underway to harmonize and standardize the methodologies for conducting studies with the in vitro Franz Cell Finite Dose Model. This standardization will facilitate the comparison of datasets across laboratories and within the literature. This, in turn, will be important to support greater utility by regulatory agencies.

Artificially Cultured Human Skin

The barrier properties of cultured skin models are currently inadequate for absorption studies, and they tend to over-predict absorption. But if they are eventually able to develop a normal SC and competent barrier function, they will be of particular value with Franz Cells in countries where moral or cultural roadblocks preclude the use of natural human skin. Currently, their value is limited to modeling such things as metabolism or cellular responses to penetrating drugs or chemicals.

Substituting Live Animal Research

European initiatives are currently shifting product development paradigms away from in vivo live animal models. Furthermore, the absorption of topically applied compounds in vivo is often at very low levels, and then become even further diluted when monitoring the drug in blood. Sensitive modern analytical techniques, such as LC/MS and LC/MS/MS, or even ligand binding assays, in combination with the in vitro Franz Cell Finite Dose Model, provides an ideal way to provide optimal sensitivity for characterizing percutaneous absorption. Also, in concert with the science, improved documentation and QC/QA oversight as a standard part of these studies is imperative to ensure confidence in the objective quality of the results. In the foreseeable future, data from the in vitro Franz Cell Finite Dose Model could become a part of the basis for approval by international regulatory bodies, as a replacement for more costly, more time consuming, and poorly predictive animal tests.

Franz & Lehman - The Future Happens With Each New Day

Tom Franz, MD, and Paul Lehman, MSc, have worked together for 3 decades, within academia, at the FDA, as consultants, and now, within a contract research organization, to advance the science and practical methodologies for topical product development. Their laboratory started at the University of Washington in Seattle with a handful of cells and a few small experiments each month. Now, as part of the Cetero Research facility in Fargo, North Dakota, they evaluate several thousand skin sections each year with sophisticated analytical capabilities for radiolabel and LC/UV/MS methods, and with industry-standard quality control and quality assurance infrastructure. Throughout the years, they have continually innovated new methodologies for novel situations, collaborated with other experts in the field, contributed to industrial consortium projects, and systematically advanced the development of a large portion of the topical compounds currently on the pharmacy shelves. In addition to conducting both in vivo and in vitro contract work for the industry, they continue to perform independent research to further refine and advance the Franz Cell Finite Dose Model, contribute to national and international symposia, and maintain active dialogue with regulatory agencies related to topical pharmacokinetics.

The Franz Cell has not only survived the test of time, it continues to prove its value to the industry for product development, predicting bioavailability and bioequivalence, and assessing systemic risk for potential toxins. No other model has been developed that can provide so much valuable in vitro information as this simple, but elegant, glass chamber. Throughout the past 30 years, the Franz Cell has become the crystal ball used by topical and transdermal developers to navigate and streamline their critical paths for drug development, and the coming decades will likely see even more utility for this model in topical drug development.

For more information or to contact the authors, please e-mail FranzCell@Cetero.com or call 701-356-2480.

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BIOGRAPHIES

Dr. Sam Raney is the Associate Director of Pre-Clinical Dermatology at Cetero Research. He has over 15 years of experience in skin research and drug development. He is an authority on regulatory aspects, including FDA, EPA, and OECD GLP, as well as International Guidelines pertaining to the conduct of in vitro percutaneous absorption studies. His experience as an industrial scientist, a topical drug development consultant, and a scientific due diligence analyst encompasses strategic pharmaceutical candidate development, scale-up and manufacturing, intellectual property development, and management of drug development projects. Dr. Raney earned his BA in Molecular Biophysics & Biochemistry from Yale University, his MSc in Biology from Marshall University, and his PhD in Biochemistry & Molecular Biology from the University of British Columbia (UBC) in Canada. He was a Research Fellow within the UBC Faculty of Medicine, Division of Dermatology, conducting research in skin barrier function, model membrane systems, barrier replacement therapy, and skin barrier protection technologies for the Department of Defense. Dr. Raney's research has included work in skin tissue regeneration for burn patients, and the development of vaccines and adjuvants using liposomal formulations. His credentials include several each of manuscript publications, poster and lecture presentations, copyrights, and patents.

Mr. Paul Lehman is the Director of the Clinical & Pre-Clinical Dermatology at Cetero Research. He has conducted internationally recognized research in the field of topical pharmacokinetics and topical bioequivalence for 30 years. He earned his BA in Biology, and BBA from Incarnate Word College in San Antonio, Texas. Mr. Lehman later earned his MS in Pharmaceutics at the University of Washington in Seattle. His prior appointment was as Executive Vice President of Clinical and Pre-Clinical Dermatology at DermTech International in San Diego, California. Mr. Lehman has also held faculty appointments at both the University of Arkansas for Medical Sciences and at the University of Washington. In addition, he worked for 2 years at the National Center for Toxicological Research (FDA) in Jefferson, Arkansas, and is currently an Adjunct Professor at North Dakota State University in Fargo. Mr. Lehman has been an integral partner with Dr. Thomas Franz in the conduct of in vitro and in vivo topical pharmacokinetics and the development and validation of dermato-pharmacokinetic bioequivalence methods for topical formulations.

Dr. Thomas Franz is the Executive Medical Director of Clinical Dermatology at Cetero Research. He has over 30 years of academic and industry experience in dermatologic research. Dr. Franz earned his BS from the University of Portland, his MS in Biochemistry, and his MD from the University of Oregon Medical School. His prior appointments include Consulting Medical Officer at the FDA's Division of Topical Drug Products at the Center for Drug Evaluation and Research (CDER), Professor at the Department of Dermatology, University of Arkansas for Medical Sciences, and Associate Professor, Department of Medicine, Division of Dermatology at the University of Washington School of Medicine. Dr. Franz was previously Vice President, Clinical Research in Dermatology at Connetics Corporation, Vice President, Research and Development at Hercon Laboratories, and held management positions at Hoffmann LaRoche, Johnson & Johnson, and Procter and Gamble.

SPECIAL FEATURE

Transdermal Delivery Becoming More Active

By: Cindy H. Dubin, Contributor

Compliance concerns have driven and continue to drive investment in new drug delivery technologies, and the transdermal patch is a prominent example of this impact. Since the FDA approved the first transdermal patch in 1981, it has grown into a $2-billion market in the US with 35 approved products, according to Adhesives Research, Inc., a drug delivery company based in Glen Rock, PA.

Advances in synthetic materials and skin patch designs have led to transdermal drug delivery products that are more aesthetically acceptable and capable of delivering sustained dosing of active compounds for several days in a smaller package. Transdermal patches offer many advantages, including ease of use, pain-free delivery, disposability, controlled delivery, and avoidance of first-pass metabolism by the liver. Growth is being driven by several factors — factors with strong demographic and population trend underpinnings. New technologies are expanding the type and number of prescription and OTC therapies and treatments that can be effectively administered to patients and consumers. Fueled by Rx-to-OTC switching, OTC patches are proliferating as companies move to capture a share of this multibillion dollar market. Non-medicated patches are creating new and significant markets for skin patches.

As work with passive transdermal systems has progressed, so too has the realization of the true extent of the barrier to drug delivery presented by the stratum corneum. Passive permeation of compounds through the skin became a major problem and very soon restricted the choice of compounds that were eligible for delivery in that manner. To expand the limits of transdermal drug delivery, developers are employing microporation techniques and energy sources, such as ultrasound, heat, and electrical current, to affect active transport through the skin. These techniques can increase the upper

molecular size limit significantly, opening up a host of opportunities for transdermal delivery.

To take full advantage of these evolving dynamics, active transdermal delivery participants must deal with a number of economic and market forces influencing the way drug companies develop and commercialize their products. Success will favor those sector participants willing to incorporate patient-centric design features and drug-device combination engineering paradigms into their product development programs.

According to Greystone Associates, combination microporation products will dominate the active transdermal delivery for the next 3 years, representing almost two-thirds of the sector and becoming a $675-million market in 2009. Other important active transdermal segments include iontophoresis and heat-assisted transdermal products. Products based on electroporation, ultrasound ,and lasers will also compete for market share.

ADHESIVES RESEARCH USES INDUSTRIAL PLATFORM FOR PASSIVE TECHNOLOGY

Having gotten its start in the 1960s as an adhesive supplier for industrial labels, it was only a natural progression to offering adhesives to the pharmaceutical industry beginning in the 1980s. "The healthcare industry, including drug delivery, is our fastest growing segment," states Scott A. Knorr, Pharmaceutical Business Manager for Adhesives Research, Inc.

Focused on both active and passive transdermal systems, Adhesives Research (AR) has targeted its technologies (Figure 1) for use in smoking cessation, pain management, hormone therapy, diabetes, and biopharmaceutical compound delivery. "We are able to tailor performance for wear times ranging from minutes to a week (and beyond) in various dermatological environments," says Mr. Knorr.

AR, whose background is in acrylic, rubber, silicone, and multi-chemistry adhesive systems, began to develop additional technologies to meet the needs of the active transdermal delivery market including:

- Conductive adhesives, which overcome the traditional insulative properties of an adhesive to allow current or ion transport (z-direction);
- High-moisture vapor transmission rate (MVTR) polymer coatings, which absorb moisture and/or allow moisture to pass through the coatings and thus away from the surface of the skin;
- Porous adhesives, which are coated systems with tailored pore size/density to allow controlled fluid transfer or doping to create biphasic formulations (like an adhesive "membrane" with chemically and mechanically stable pore geometry);
- Hydrogels, which are high-fluid content coatings to form an interface between skin and sensing element (typically conductive); and
- Molecularly imprinted polymers that are synthesized with the unique chemical and physical "imprint" of a target molecule. MIP compounds can be formulated into adhesive coatings to capture or release target molecules in diagnostic or drug delivery applications.

FIGURE 1

AR's skin-friendly pressure-sensitive adhesives for transdermal applications.

These technologies are used in either existing commercial products or programs in various stages of clinical development. "We continue to innovate to meet the evolving needs of the market," says Mr. Knorr. "For instance, we are currently developing a next-generation transdermal adhesive that will redefine the performance expectations of adhesives used in transdermal drug delivery. This technology will be available in 2009."

ISIS BIOPOLYMER MAKES DELIVERY PERSONAL

Isis Biopolymer, Inc. is an early stage, medical device company that has developed a non-invasive drug delivery system, the Isis Patch™ (Figure 2). This personalized, single-use, flexible, ultra-thin, transdermal drug delivery patch will allow medical professionals to accurately control transdermal drug delivery, ensuring reliable and effective drug administration over an extended period of time, says Michael Jordan, Director of Product Development for Isis. The Isis Patch will deliver the clinical benefits of iontophoresis with the convenience and cost effectiveness of a drug patch.

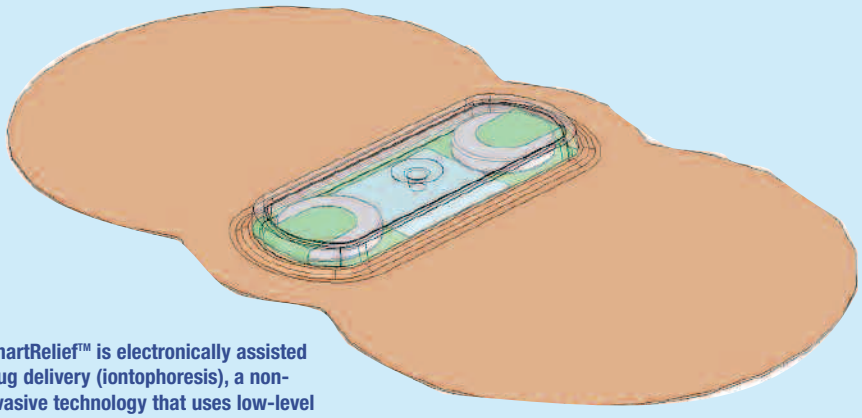
The compact, wireless, active patch uses a patented design that implements advances in microprocessors, thin film batteries, biopolymers, and proprietary adhesives that allow for widespread use. The device also employs patented drug delivery techniques that will enable multiple drugs, as well as a variety of drugs, to be delivered.

Isis Patch is supported by a proprietary, software-based, patient-care management system for physicians and pharmacists to manage and monitor drug delivery through the Isis Patch. "In many cases, it is critical

FIGURE 2

Advances in microprocessors, thin film batteries, biopolymers, and proprietary adhesives will allow more widespread use as well as a wider variety of drugs to be delivered via the Isis iontophoretic patch.

FIGURE 3



SmartRelief™ is electronically assisted drug delivery (iontophoresis), a non-invasive technology that uses low-level electrical current to transport drugs through the skin.

to have modulated delivery over a 24-hour period," says Mr. Jordan. "With this fully programmable patch, the system can be turned on to deliver a dose before the patient even wakes up in the morning and the system can be turned off before bed because some medications can cause insomnia. As a matter of fact, we have spent a lot of time fine-turning the Patch so that when it is off, it is really off. Some other products continue to diffuse drug into the skin when in the off mode."

Mr. Jordan says that Isis is focused on three core therapeutic focus areas right now with the Isis Patch: ADHD, diabetes, and motion disorders. The Patch is currently in preclinical testing and will then enter clinical trials. Mr. Jordan expects the Patch to be released on the market at the end of 2009 or early 2010.

NUPATHE'S ACTIVE MIGRAINE TECHNOLOGY

Numerous unmet medical needs exist in the field of neuroscience. To build its portfolio, NuPathe licenses or acquires innovative drug candidates and drug delivery technologies from universities and other companies.

One of NuPathe's primary focus areas is migraine. Existing products for this condition provide suboptimal solutions for many patients — either inconsistent efficacy or adverse effects, says NuPathe Chief Scientific Officer Mark Pierce, MD, PhD.

NuPathe believes that many medical needs can be addressed by applying novel delivery or formulation technology to existing compounds. Consider NP101 — Migraine SmartRelief™. Migraine is an episodic headache disorder associated with various combinations of neurologic, gastrointestinal, and autonomic symptoms that affects approximately 36 million Americans, mostly women. Gastrointestinal disturbances, including nausea and vomiting, are common associated symptoms of migraine, affecting more than 90% of those experiencing migraine. These GI symptoms can be incapacitating and for 30% of sufferers, migraine-associated nausea or vomiting interferes with their ability to take oral medications. Moreover, many patients suffer from gastric stasis, which can adversely impact drug absorption and pharmacokinetics, resulting in delayed, inconsistent, or incomplete relief.

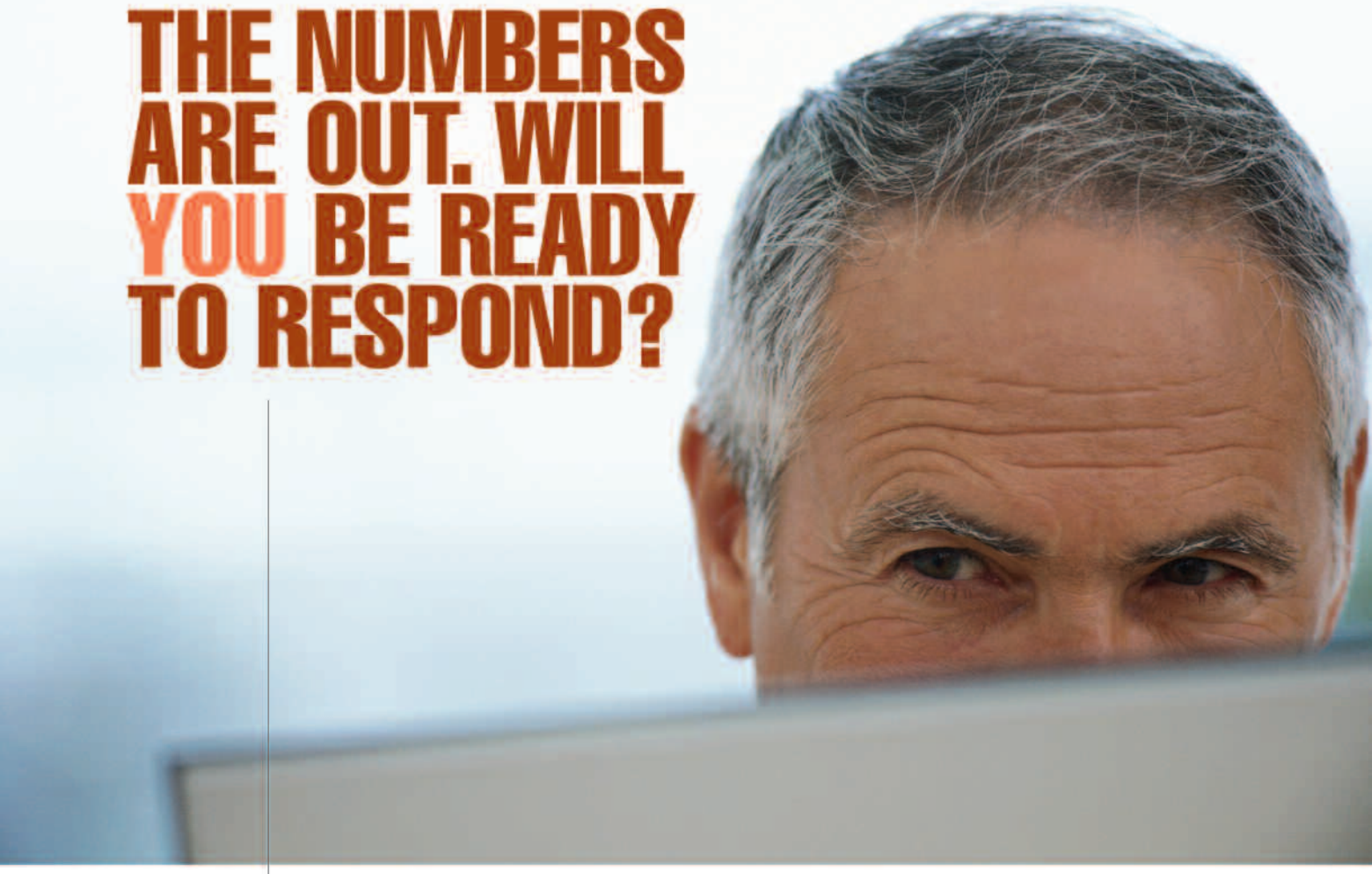
While non-oral formulations are available, only sumatriptan injection does not depend on GI absorption. Both nasal and oral formulations are absorbed primarily through the GI tract. Moreover, few patients elect to use current non-oral formulations due to discomfort, inconvenience, and adverse effects. "We are developing a drug-device combination that delivers sumatriptan transdermally," says Dr. Pierce.

NP101 Migraine SmartRelief is a potentially empowering alternative for migraine sufferers — convenient, consistent, and controlled delivery of their migraine medication regardless of nausea, vomiting, or other gastric symptoms associated with migraine.

SmartRelief is electronically assisted drug delivery (iontophoresis), a non-invasive technology that uses low-level electrical current to transport drugs through the skin (Figure 3). The rate and amount of drug delivered is controlled electronically, with the intent that the patient receives consistent therapy each and every time.

Each SmartRelief patch is preprogrammed, disposable, and convenient to use. "The patch contains a power supply (similar to a watch battery) and a microprocessor to regulate current and timing," explains Dr. Pierce. The current is delivered to electrodes in the patch. Under the electrodes are non-woven pads containing the drug. At the onset of migraine pain, the patient will apply NP101 to the upper arm, back or thigh, and push a

THE NUMBERS ARE OUT. WILL YOU BE READY TO RESPOND?



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button to initiate drug delivery. The system automatically turns off after 4 hours.

NuPathe has completed Phase I studies, demonstrating that therapeutic blood levels can be obtained rapidly, consistently, and tolerably. Phase III trials will commence this summer at multiple centers in the US.

As far as future drug candidates using SmartRelief technology, Dr. Pierce says various forms of pain are ideal as are therapies requiring intermittent dosing. He adds that the drug must be a charged molecule for active delivery and be effective in relatively small doses.

PANTEC BIOSOLUTIONS CONTROLS DOSING INTO PORES

Pantec Biosolutions AG has developed a laser microporation device P.L.E.A.S.E.® (Painless Laser Epidermal System) for large molecular weight drug delivery, such as In Vitro Fertilization (IVF) hormones (Figure 4). According to CEO Christof Böhler, this places the company in a strong position for later-stage licensing or its own commercialization.

P.L.E.A.S.E. is a hand-held laser device that creates controlled aqueous micropores in the epidermis. Due to the features of the device, the micropores do not reach the dermis where nerves and blood vessels reside. An intelligent graphical user interface guarantees simple and safe use by the medical personnel or the patient, who can use the device without supervision.

A special laser source ablates outer skin tissue painlessly in a highly controlled and accurate fashion, and very short pulses practically eliminate thermal damage, says Mr. Böhler. The P.L.E.A.S.E. system allows fine tuning of pore properties (number and depth) to a therapeutic need for a specific drug dose. The laser scanner allows formation of a selected number and depth of pores, thereby controlling the dose by application of a fixed amount of drug over a defined time range. P.L.E.A.S.E. also has a built-in skin layer detection, which checks accurate pore formation through the stratum corneum, the key requirement for drug flux into the skin. Pantec Biosolutions has also developed a preclinical pipeline of identified biopharmaceutical therapies for P.L.E.A.S.E. transdermal application to

FIGURE 4

Pantec Biosolutions' P.L.E.A.S.E.® (Painless Laser Epidermal System)
(A) The module without housing
(B) The device as it stands today
(C) Application on the inner arm

FIGURE 5

resolve unmet medical needs in selected therapeutic areas.

Having received a Series A equity investment of $6 million in December 2007 has enabled Pantec to further develop its device and drug patch technology with the aim of replacing the required hormone treatment regime of daily injections made over a period of several weeks during IVF, with a simpler regime of epidermal preparation and IVF hormone patches. The company's current business model is focused on developing a variety of therapeutic treatments that encompass the IVF therapy regime.

"Building a hand-held laser microporation device is very complex; however, our brilliant team managed to build the most efficient 3-micrometer laser scanner of this small (hand-held) size," says Mr. Böhler. "The combination of a device that pretreats the skin safely and painlessly and a transdermal system, such as a patch, is not very well known with regulatory authorities. The fact that several technologies are screened and approved by authorities during the course of clinical programs helps the entire increasing number of companies trying to develop novel active transdermal systems to deliver large molecular weight drugs, thus avoiding injections."

Pantec's first P.L.E.A.S.E. target application is the multi-week hormone therapy for IVF, and the company is aiming to reach the market as soon as the hormone-containing patches are developed and approved. In addition to IVF, Mr. Böhler says Pantec is currently negotiating with pharmaceutical and biotech companies on several other opportunities in laser-assisted drug delivery.

TRANSPHARMA MEDICAL ANNOUNCES LICENSING & DEVELOPMENT AGREEMENT WITH ELI LILLY

TransPharma Medical Ltd. and Eli Lilly and Company recently announced that the two companies have entered into a licensing and development agreement related to TransPharma's ViaDerm-hPTH (1-34) product for the treatment of osteoporosis. The product, which is administered transdermally using TransPharma's proprietary technology, is currently in Phase II clinical testing.

Under the terms of the agreement, Lilly will obtain exclusive worldwide rights to TransPharma's ViaDerm-hPTH (1-34) and will also gain non-exclusive access to TransPharma's ViaDerm drug delivery system.

TransPharma will receive a $35-million up-front payment, and may also receive development and sales milestones, as well as royalties on sales if a transdermal PTH product is successfully commercialized. TransPharma and Lilly will both fund and participate in Phase II clinical development activities. Thereafter, Lilly will be responsible for further development activities and the potential commercialization of any transdermal PTH products. Other terms of the deal were not disclosed.

"We are extremely pleased to partner with Lilly, a leading player in the osteoporosis market," said Dr. Daphna Heffetz, CEO of TransPharma Medical. "This collaboration is an excellent example for how our transdermal ViaDerm-based products may deliver added value to promising drug compounds. We are confident that Lilly's experience and outstanding drug development capabilities together with our innovative technology could propel our joint ViaDerm-hPTH (1-34) product as an improved therapy for people suffering from osteoporosis."

TransPharma's ViaDerm drug delivery system incorporates a hand-held electronic control unit, which creates microscopic passageways through the outer layer of the skin, allowing for transdermal delivery of a wide variety of drugs from a patch. The system provides a cost-effective, easy-to-use, self-administered solution that enables the safe, reproducible, and accurate delivery of a broad range of product candidates, including hydrophilic small molecules, peptides, and proteins.

SUMMARY

Looking ahead, these industry insiders obviously agree that active transdermal technology will make great strides in delivering larger molecules, dosing on demand, delivering at alternative sites, and in becoming more sophisticated.

"Whether active or passive, a patch can be extraordinary," says Mr. Pierce of NuPathe.

Mr. Knorr of AR references a quote from J. Herbert Waite, a Professor of Biochemistry at the University of California, "All living things in nature are exquisitely assembled from adhesively bonded parts." Mr. Knorr continues, "I believe this quote eloquently depicts the limitless potential of using adhesives in healthcare applications. In transdermals, we are merely scratching the surface of adhesive applications in drug delivery." ◆

BIOGRAPHY

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

GASTRO-RETENTIVE DELIVERY

Gastro-Retentive Drug Delivery: A Technical Note

By: Atishkumar S. Mundada, Natasha V. Bhola, and J.G. Avari, PhD

ABSTRACT

Oral controlled drug delivery forms a crucial facet among novel drug delivery systems. A rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamic profiles is to retain the drug reservoir above its absorption area, ie, in the stomach and to release the drug in a controlled manner, so as to achieve zero-order kinetics (oral infusion) for a prolonged period of time. One such approach is gastro-retentive drug delivery systems (GRDDS). The focus of this article is to highlight various criteria required by a drug to be suitable for gastric retention, the process of gastric emptying, and different approaches (along with their advantages and shortcomings) to formulate GRDDS. Formulation approaches for GRDDS include delayed gastric emptying, high-density systems, floating systems, mucoadhesive systems, magnetic systems, expandable systems, super porous hydrogels, and combinations of different concepts of gastric retention.

INTRODUCTION

Technological advancements have developed several novel approaches for the delivery of various types of drugs that could revolutionize methods of medication and provide a number of therapeutic benefits. The single dose of the dosage form should release the drug over an extended period of time along with delivering the active moiety directly to the site of action to minimize the side effects. Drug biodisponibility is a crucial facet in therapeutic effectiveness. One such approach of oral sustained delivery of drug that has gained the attention of academic and industrial research groups is GRDDS.

GRDDS prolongs the gastric-emptying time, which has been reported to be from 2 to 6 hours in humans in fed state. The therapeutic interest to prolong the gastric residence time of a pharmaceutical dosage form with time-controlled release kinetics can be significant, especially in the case of drugs that:

- degrade in intestine (eg, Captopril),
- act locally in the stomach and require an acidic environment for effective bioavailability (eg, Misoprostol, antacids, and antibiotics active against helicobacter pylori),
- alter normal flora of the colon (eg, antibiotics),
- degraded by intestinal enzymes (eg, Doxifluridine),
- absorbed by a transporter mechanism (eg, Paclitaxel, Ciprofloxacin),
- having narrow absorption window (eg, L-DOPA, p-Aminobenzoic acid, Furosemide, and Riboflavin), and
- exhibit low solubility at high pH values (eg, diazepam, chlordiazepoxide, and verapamil HCl).[1-18]

Contradictorily, retention in the stomach is not desirable for drugs that cause gastric lesions (eg, NSAIDs), are degraded in acidic environments, or undergo a significant first-pass metabolism (eg, Nifedipine).[19]

Gastric Emptying

The process of gastric emptying occurs both during the fasting and fed state. In the fasted state, the process of gastric emptying is characterized by an interdigestive motility pattern that is commonly called migrating motor complex (MMC).[20,21] This is a series of events that cycle through the stomach and small intestine every 1.5 to 2 hours and is divided into the following four consecutive phases:

- Phase I (45 to 60 minutes), develops few or no contractions, the most quiescent.
- Phase II (30 to 45 minutes), consists of intermittent action potentials and contractions, which gradually increase in intensity and frequency as the phase progresses.
- Phase III (5 to 15 minutes), regular contractions with high amplitude, which push indigestible solids distally. It is also termed the housekeeper wave.
- Phase IV (0 to 5 minutes) is a transition period of decreasing activity until the next cycle begins.

In the fed state, the gastric-emptying rate slowed down because the onset of MMC is delayed, ie, the feeding state results in a lag time prior to the onset of gastric emptying.[7,22] Prolonging the gastric residence time (GRT) may widen the

GASTRO-RETENTIVE DELIVERY

stomach potential as a drug-absorbing organ. To achieve gastric retention, the dosage form must satisfy certain requirements; mainly the dosage form should be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions, grinding, and churning mechanisms. It must also be able to resist premature gastric emptying, and once its purpose has been served, the device must be emptied from the stomach with ease. Various methods have been applied to study the parameters affecting the process of gastric emptying via radiography, gamma scintigraphy, endoscopy, radiotelemetry, and magnetic marker monitoring.[7,23-25] Factors affecting gastric emptying for oral dosage forms includes:

- density, size, and shape of dosage form,
- concomitant ingestion of food and its nature, caloric content, and frequency of intake,
- concomitant drug administration (eg, anticholinergics, opiates, and prokinetic agents), and
- biological factors, such as gender, posture, age, sleep, body mass index, physical activity, and disease state (eg, diabetes, Crohn's disease).[26-42]

APPROACHES TO GASTRIC RETENTION

Throughout the past 3 decades, the pursuit and exploration of devices designed to be retained in the upper part of gastrointestinal tract has advanced consistently in terms of technology and diversity. To retain an oral dosage form in the stomach, several approaches have been followed, which are discussed in detail in the following sections.

Delayed Gastric Emptying

Incorporation of various indigestible polymers[43-45] or fatty acids[35,46,47] in food changes the motility pattern of the stomach to a fed state, decreasing the gastric-emptying rate and permitting considerable prolongation of drug release.[35,43-47] Russel et al reported the gastric emptying of polycarbophil, an indigestible particulate substance and also of fiber meals.[43,44] They reported influence of meal viscosity and antroduodenal motility.

High-Density Systems

High-density devices use their weight as a retention mechanism. In such formulations, drug can be coated on a heavy core or mixed with heavy inert materials, such as titanium dioxide, barium sulfate, zinc oxide, iron powder, etc so that the density of system is greater than that of gastric content (1.004 g/cm^3), possibly close to 2.5 g/cm^3.[48] In this system, the coated pellets get entrapped in the folds of antrum and withstand the peristaltic waves of the stomach wall. However, so far, no successful approach has been described for a gastric-retention system being based on high density. In contrast, it has been reported that such devices did not significantly extended the gastric-retention time.[49]

Floating Systems

Floating drug delivery systems are the major approach used in GRDDS, and below we describe several different ways of formulating such systems.

LOW-DENSITY SYSTEMS: These systems have a density lower than gastric contents so that they have immediate buoyancy. They remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug.[50-71] The residual system is emptied from the stomach. Gastric emptying is much more rapid in the fasting state, and the floating system relies heavily on the presence of food to retard emptying and provide sufficient liquid for effective buoyancy.

HYDRODYNAMICALLY BALANCED SYSTEM: These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. The hydration and swelling of surface polymer produces a floating mass. Drug release is controlled by the formation of a hydrated boundary at the surface.[72] Continuous erosion at the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy.[73] Examples of hydrophilic polymers include hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, sodium carboxymethylcellulose, agar, carragenans, alginic acid, etc.[73,74]

GAS-GENERATING SYSTEM: In this system, gas is generated in situ by incorporation of carbonates or bicarbonates, which react with acid – either the natural gastric acid or co-formulated with citric acid or tartaric acid. An alternative is to incorporate a matrix with entrapped liquid that forms gas at body temperature (eg, cyclopentane, diethyl ether).[75-77] However, this approach may only be of theoretical interest. Gas removal from this system and manufacturing of the complex devices may cause significant difficulties. Generally, effervescent systems do not float immediately after swallowing because gas generation takes some time. Therefore, they could be cleared from the stomach before becoming effective. Floating drug delivery systems basically rely on the filling state of the stomach. However, these approaches can be successfully used to prolong the gastric-retention time and have already led to the production of pharmaceutical products that are commercially available in the market.[78,79]

Rough et al have developed floating mini tablets based on HPMC and sodium bicarbonate as a gas-generating agent.[80] The floating properties of these systems containing either piretanide or atenolol as model drugs were improved by introducing a wet granulation step. The generated carbon dioxide was entrapped for longer time periods within the tablet matrix when the latter was prepared via granulation compared with direct compression. The observed floating lag times ranged from 1 to 27 minutes; the floating period partially exceeds 6 hours.

RAFT-FORMING SYSTEMS: In this approach, gel-forming solutions swell and form viscous cohesive gels containing entrapped carbon dioxide bubbles on contact with gastric fluid. Raft-forming systems produce a layer on the top of gastric fluid. These formulations are often used for gastro-esophageal reflux treatment.[81-84] They usually contain aluminum hydroxide or calcium carbonate. Marketed products are Liquid Gaviscon® by GlaxoSmithKline, India, and Topalkan® by Pierre Fabre Drug, France.

Mucoadhesive Systems

Mucoadhesive systems are used to localize drug delivery within the lumen of the body in order to enhance bioavailability. This dosage form sticks to the mucosal surface by different

mechanisms (electronic theory, adsorption theory, wetting theory, and diffusion theory). Materials commonly used for bioadhesion are poly (acrylic acid), chitosan, cholestyramine, tragacanth, sodium alginate, hydroxyl propyl methyl cellulose, sephadex, sucralfate, dextran, poly lactic acid, etc. Though some of these polymers are effective as producing bioadhesion, it is very difficult to maintain it effectively because of no rapid turnover of mucus in the gastrointestinal tract. Moreover, the bioadhesiveness of polymers is decreased as the stomach content is highly hydrated.[48]

Magnetic Systems

In this approach of GRDDS, the dosage form contains a small internal magnet and a magnet placed on the abdomen over the the stomach. Ito et al used this technique in rabbits with bioadhesive granules containing ultrafine ferrite (Fe_20_3). They guided them to the esophagus with an external magnet (~1700 G) for the initial 2 minutes, and almost all the granules were retained in the region after 2 hours.[85] A method for determining gastrointestinal transit of magnetic dosage forms under the influence of an extracorporeal magnet was developed by Groning et al using a pH-telemetring capsule (Heidelberg capsule). Small magnets were attached to the capsule and administered to humans, using an extracorporeal magnet; the gastric residence time of dosage form was > 6 hours compared with 2.5 hours for the control.[86] Although these systems seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.

Expandable Systems

A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter. The dosage form must be small enough to be swallowed, expand in the stomach for gastric retention, and must be finally small enough to enable evacuation after drug release.[87] The expansion can be achieved by swelling or by unfolding in the stomach. Swelling usually occurs by osmosis and unfolding by mechanical shape memory, ie, the GRDF is fabricated in a large size and is folded into a pharmaceutical carrier like a gelatin capsule for convenient intake. The carrier is dissolved in the stomach, and the GRDF unfolds or opens out to achieve extended configuration. Different geometric forms of bioerodible polymer, such as tetrahedron, ring, or planar membrane {4-lobed, disc or 4-limbed cross form} compressed within a capsule were proposed by Caldwell et al.[88,89]

Though expandable systems have interesting characteristics, they have drawbacks. The mechanical shape memory of unfoldable systems is relatively short lived.[90] It is very problematic to store such easily hydrolysable, degradable polymers. Moreover, this kind of dosage form is probably the most difficult to industrialize and may not be cost effective.[74] Finally, these systems must be easily biodegradable, must not have sharp edges so that they cause damage to the mucosa of the gastrointestinal tract, and they must not interfere with gastric motility.

Superporous Hydrogels

Superporous hydrogels have an average pore size of more than 100 microns and swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores.[91] They have a tendency to swell to a large size with a swelling ratio ~100 or more and must have sufficient mechanical strength to withstand pressure by gastric contractions. This is achieved by co formulations with a hydrophilic particulate material, Ac-Di-Sol® (cross carmellose sodium).[92]

Combinations of Different Concepts of Gastric Retention

Various systems use a combination of different gastro-retentive concepts. For example, a gas-generating system is used for lowering the density of a system and enabling it to float. It is also used to formulate expandable systems. A drug containing a carbon dioxide-generating, expandable system surrounded by a hydrophilic membrane has been patented by Sinnreich.[93] Usually, gas generation and entrapment not only increases the size of the drug delivery system but also decreases its density and provides floatation properties; therefore, presenting a combination of two principles to prolong gastro-retentive time. A synergism between bioadhesive systems and floatation systems has also explored.[94] Nur et al prepared tablets consisting of blends of hydroxyl propylmethyl cellulose and carbopol containing 4% to 5% of drug [Captopril]. Jimenez- Castellanos et al also explored this concept by preparing tablets containing sotalol hydrochloride, sodium caboxy methyl cellulose [as bioadhesive polymer], hydroxy propyl cellulose [as matrix forming polymer], and carbonate [as gas generator].

SUMMARY

Thus it can be concluded from the aforementioned various approaches used to formulate a gastro-retentive drug delivery system that there is an adequate control of gastric residence time as well as time controlled drug release that can improve the efficiency of pharmacotherapy. Moreover, it helps in replacing parentral administration of drugs to oral administration, which would help improve patient treatment. In the future, combinations of different gastro-retentive concepts, such as bioadhesion and low-density floating, can be expected to become particularly promising.

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OCULAR DELIVERY

New Controlled Release Technologies Broaden Opportunities for Ophthalmic Therapies

By: Daniel J. Haders II, PhD

INTRODUCTION

In 2007, the total worldwide ophthalmic pharmaceutical sector was valued at approximately $11.52 billion.[1] Due to the increasing age of many populations, financial experts forecast average yearly expansion in the sector to be greater than 10% over the near term.[1] Nonetheless, the sustained delivery of therapeutically effective concentrations of drug to treat diseases of the eye, particularly diseases of the posterior segment of the eye, remains a significant technological challenge. The corresponding problem of patient compliance with existing therapies is a critical issue as well. Thus, substantial market opportunities exist for companies in the ophthalmic pharmaceutical sector that pursue novel molecules, innovative drug delivery systems, or both.

DRUG DELIVERY TO THE EYE

Drugs may be delivered to the eye through the application of four primary modes of administration: systemic, topical, intravitreal, and periocular.[2] For completeness, it is noted that additional modes of administration have been researched, including intrascleral, although a review of such modes is beyond the scope of this article.[3,4]

The efficacy of systemically administered ocular drugs is limited by a number of interdependent factors. For example, the blood-aqueous-barrier and the blood-retinal-barrier (BRB) regulate the transport of molecules from the systemic circulation to anterior and posterior ocular tissue, respectively.[2,5] These barriers are reported to limit the intravitreal drug levels of poorly lipid soluble antibiotics to ~10% of serum levels.[2] As a consequence, frequent dosing is required to maintain therapeutic levels of the drug in the target tissue.[2] However, frequent administration may lead to non-specific absorption and undesirable systemic side effects (toxicity), especially when low therapeutic index drugs are utilized.[2,5] Thus, the treatment of ocular indications via systemic drug administration should be utilized only with well-tolerated drugs with large therapeutic indices and limited systemic side effects, and only when other more localized delivery options are not available.

Topical administration is generally considered the preferred route for the administration of ocular drugs due to its convenience and affordability.[2] Drugs applied in this manner can be packaged in multiple forms, including solutions, ointments, and suspensions.[6] Drug absorption occurs through corneal and non-corneal pathways.[2,5] Most non-corneal absorption occurs via the nasolacrimal duct and leads to non-productive systemic uptake, while most drug transported through the cornea is taken up by the targeted intraocular tissue.[2,5] Unfortunately, corneal absorption is limited by drainage of the instilled solutions, lacrimation, tear turnover, metabolism, tear evaporation, non-productive absorption/adsorption, limited corneal area, poor corneal permeability, binding by the lacrimal proteins, enzymatic degradation, and the corneal epithelium itself.[2,5,6] These limitations confine the absorption window to a few minutes after administration and reduce corneal absorption to < 5%.[2,5] Consequently, multiple daily dosings are often required, leading to decreased patient compliance.

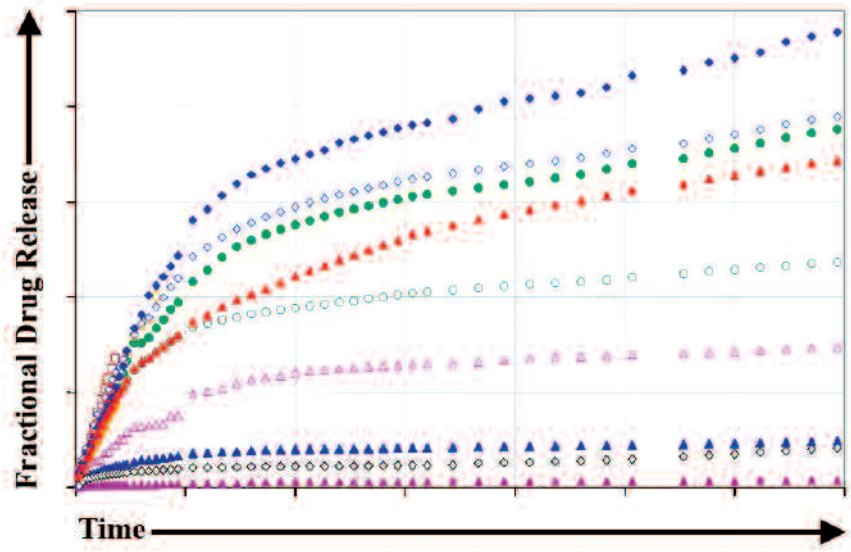
To increase both retention time on the surface of the eye and corneal absorption, novel topical systems have been developed, including ones that utilize in situ gelling polymers, mucoadhesive polymers, inserts, and ocular penetration enhancers.[5,6] However, these formulations only modestly increase the duration of activity and bioavailability as they are still limited by corneal and conjunctival epithelial barriers.[5] High concentrations of penetration enhancers may cause mucosal irritation and corneal abrasion, leading to toxicological complications.[2,6] Thus, topical administration is best suited to the treat diseases localized to the anterior segment of the eye (cornea, conjunctiva, sclera, anterior uvea).[5]

Intravitreal treatment of ocular indications refers to the direct injection of drug into the vitreous cavity through the pars plana.[2,5,7] Although the method has existed for nearly a century, interest in this route of drug administration has grown recently for the treatment of disorders of the posterior segment of the eye.[2,7] However, the pharmacokinetic properties of molecules administered by this route are complex and not completely understood.[2,7] In addition, drug retention in the vitreous is reportedly a function of molecular weight.[2,5,7] Models demonstrate that small molecules tend to be cleared relatively quickly by absorption through the retina or by release into the aqueous humor via the anterior hyaloid membrane, while large molecules move slowly through the vitreous via bulk transport and tend to be cleared primarily through the retina.[7] Patient compliance can be an issue for intravitreal treatment regimens, which typically require patients, many of whom are elderly, to make regular visits to their ophthalmologist to undergo repeated injections. Finally, significant adverse side effects have been reported, including retinal detachment from repeated injections, retinal hemorrhage, endophthalmitis (sterile or infectious), uveitis, and other retinal toxicities, due to high concentrations upon bolus dose administration.[2] The limitations of this technique, namely small molecule retention, complications and poor compliance due to repeated injections, and high concentrations upon bolus dose administration may be overcome through the deployment of controlled/sustained-release formulations.

Nonetheless, periocular injection is considered the least painful and most efficient method for drug delivery to the posterior segment of the eye.[2] Drug administration via this route refers to four unique injections namely retrobulbar, peribulbar, sub-tenon's, and subconjunctival.[2] Drug delivered by this method interfaces directly or nearly directly with the sclera.[2,5] The sclera is more permeable than the cornea, and its permeability is not dependent on drug lipophilicity.[2,5] For example, researchers have demonstrated that prostaglandins are more permeable across the sclera than the cornea.[2] Unfortunately, drug intended for ocular tissues other than the choroid must permeate across the choroid and the BRB, leading to drug clearance and a shortened duration of action.[2,5] Like intravitreal administration, these concerns may be overcome through the utilization of controlled/sustained-release formulations. Thus, the periocular administration of controlled-release formulations presents a potential path to alleviate ocular indications associated with the posterior of the eye, with minimal patient discomfort and without intravitreal-like side effects.

The aforementioned discussion demonstrates that any future paradigm treatment of ocular conditions localized to the posterior segment of the eye or chronic conditions localized to the anterior segment of the eye will likely utilize minimally invasive, periocularly administered, sustained-release formulations. Furthermore, an ideal sustained release vehicle should be biodegradable, biocompatible, and versatile, enabling material properties to be tailored and suited to the compound of interest and its intended therapeutic application. Not surprisingly, forecasts indicate that drugs targeted to diseases of

FIGURE 1



Rutgers University's 10,000+ library of tyrosine-derived polymers offers greater flexibility and value than typical polymer platforms in which only a few polymers are available. The large number of polymers enables characteristics, such as drug release rate, to be tailored to the targeted disease and anatomical location.

FIGURE 2

LX212 is small, about the size of a rice grain, and implanted using a minimally invasive procedure. Source: Rutgers, The State University of New Jersey, and the Center for Biomaterials.

the posterior of the eye and ocular drug delivery systems represent two of the most promising growth drivers in ophthalmic pharmaceuticals.[1]

FIRST GENERATION CONTROLLED RELEASE POLYMER TECHNOLOGY: PLGA

Polyesters such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and their copolymers poly(lactic acid-co-glycolic acid) (PLGA) are some of the most widely investigated biodegradable polymers.[8,9] PLGA is often considered the gold standard of biocompatible biodegradable polymers.[8,9] Numerous papers and patents describe the use of this polymer in controlled drug release applications in the form of implants or injectable micro/nanospheres. The National Institute of Health's PubMed database includes at least 53 references related to use of PLGA for sustained drug delivery to the eye. In addition, PLA, PGA, or PLGA sustained drug delivery products have been or are being commercialized by several companies in the ophthalmic sector, including QLT (Atrigel®), PR Pharmaceuticals (TheraPhase®), and Allergan (Posurdex®).

The biodegradability and non-toxicity of PLGA are a consequence of its inherent chemical structure and its degradation products. Biodegradation of polyesters is considered to occur primarily through a bulk hydrolytic cleavage of ester bonds.[9,10] Degradation may be tailored by controlling factors, including chemical composition, matrix morphology, additives, device dimensions, and molecular weight.[10,11] The non-toxicity of PLGA is due to the fact that its main degradation products are lactic acid and glycolic acid, which occur naturally in the body. Upon erosion, lactic acid and glycolic acid are incorporated into the Krebs cycle and secreted as carbon dioxide and water.

The limitations of PLGA as a vehicle for sustained drug delivery are also a consequence of its inherent chemical structure and its degradation products. Oligomers are formed inside the PLGA matrix upon contact with water via bulk degradation, leading to molecular weight loss in the sample.[10] The initially formed oligomers are insoluble in water and unable to diffuse out of the polymer matrix, preventing any mass loss during the initial stages of degradation.[10] At the same time, the hydrolytic cleavage of ester bonds forms a carboxylic acid end group, which catalyzes the hydrolysis of other PLGA ester bonds (autocatalysis).[10] This, in turn, leads to a more acidic matrix core and accelerated molecular weight loss.[10] Langer and co-workers have observed pH values as low as 1.5 in PLGA microspheres.[12] The PLGA oligomers become water soluble once they are degraded below a molecular weight of about 5000. At this point, rapid mass loss can occur, resulting not only in the fast erosion of the polymer matrix but also in the release of a bolus of acidic degradation products.[13] The consequences of this process are multifold. First, the low internal pH of PLGA matrices may degrade acid-sensitive drugs. Second, the potential decrease in the pH of the surrounding media has been identified as the source of cell or tissue injury in a number of studies.[13] This issue is especially critical in the eye and specifically the vitreous, which has a limited volume of only 3 to 4 mL.[7] Third, the process of autocatalysis, predominantly in the interior of the polymeric matrix, can lead to the formation of hollow implants, which may contribute to the undesirable final burst release observed in single-composition PLGA samples.[4,10] Thus, there is a need to develop next-generation biodegradable,

biocompatible polymers for sustained/controlled ocular drug delivery, which overcome the inherent limitations of the PLGA platform.

NEXT-GENERATION BIODEGRADABLE POLYMER TECHNOLOGIES GREATLY EXPAND OPPORTUNITIES

Competitive Landscape

A number of next-generation biodegradable polymers, which have the potential to serve as sustained-release drug delivery vehicles, are reported in the literature.[8,9] Most of these polymers may be classified into one of seven groups: polyesters, poly(ortho esters), polyanhydrides, polyamides, phosphate-containing polymers, protein-based polymers, and polysaccharides.[8,9] In addition, a number of combination polymers, such as poly(anhydride-imides) and poly(anhydride-esters), have also been reported.[9] A subset of these next-generation polymers are currently under announced development as drug delivery vehicles at companies involved in the ophthalmic sector, including SurModics' SynBiosys™ - poly(ether esters), Eureka™ - polysaccharides, Cameo™ - poly(ester-amides), and PolyActive™ - poly(ether esters) and QLT's Atrigel® - various polymers.

Rutgers University Polymer Technology

Joachim Kohn and co-workers at the New Jersey Center for Biomaterials at Rutgers University have developed a promising proprietary combinatorial polymer library of tyrosine-derived polycarbonates, polyarylates, and copolymers with poly(ethylene glycol), which represent a new drug delivery platform.[14] The polymers are derived from L-tyrosine, a naturally occurring amino acid that contains an aromatic hydroxyl group.[14] The combinatorial library for polyarylates consists of 112 polymers, and that of the second-generation polycarbonates of over 10,000 polymers. The large number of available polymers enables various properties, such as glass transition temperature, surface free energy, mechanical properties, crystallinity, hydrophobicity/hydrophilicity, water uptake, degradation rate, drug-polymer interaction, and cellular adhesion to be varied widely.[14]

The biodegradability, non-toxicity, and biocompatibility of these polymers are a consequence of their chemical structure and their degradation products. Biodegradation, which may be tailored, occurs through the hydrolytic cleavage of "aryl" ester linkages and carbonate bonds in polyarylates and polycarbonates, respectively.[14] The initial hydrolytic degradation products of tyrosine-derived polycarbonates are reported to be desaminotyrosyl-tyrosine and the alcohol used to protect the carboxylic acid group.[14] *in vivo* enzymatic degradation of desaminotyrosyl-tyrosine is then expected to result in the formation of desaminotyrosine and L-tyrosine.[14] *in vitro* and *in vivo* responses indicate that all tested polycarbonates and polyarylates are both non-toxic and biocompatible.[14] The disposition of the polymers *in vivo* has also been studied and documented in the context of several products, which have received FDA 510(k) clearance or are currently in clinical trials (as described below).

The properties of these polymers also make them amenable to a wide variety of fabrication techniques. The low glass transition temperatures and thermal properties of some polyarylates and polycarbonates make it possible to select specific polymer compositions that can be processed by conventional thermal fabrication techniques, such as extrusion, injection molding, and compression molding, at low temperatures.[14] Other members of the polyarylate and polycarbonate libraries are highly soluble in a wide range of organic solvents, facilitating the use of solvent casting, fiber-spinning, electrospinning, and spray-coating to fabricate films, fibers, sponges, and coatings.[14] Fabrication of microparticles and nanoparticles is also possible.

The libraries of tyrosine-derived polyarylates and polycarbonates offer several significant advantages over PLA, PGA, and PLGA. One important difference between tyrosine-derived polymers and these polymers is the amount of acid-released during erosion. The amount of acidic degradation products produced per gram of device for PGA, PLA, tyrosine-derived polyarylate, and tyrosine-derived polycarbonate are 15.5, 11.4, 6.4, and 2.6 meq of acid per gram of polymer, respectively. The significant reduction of the amount of acidic degradation products being formed in tyrosine-derived polymers relative to the commonly used PGA and PLA may contribute to their better tissue compatibility.[14] This was demonstrated by a comparison of subcutaneously implanted disks made of tyrosine-derived polycarbonates, polyarylates, and PLA. The PLA disks elicited an elevated tissue inflammation as compared to polycarbonate and polyarylate disks.[14,15]

PLA disks were found to have a thicker tissue capsule, which contained a greater number of macrophage-like cells.[15] The reduction in acid degradation products also reduces the likelihood of degrading pH-sensitive drugs. In terms of sterilization, the aromatic backbone of the tyrosine-derived polymers makes them significantly more resistant to degradation from gamma irradiation than PGA, PLA, or PLGA, which enables the utilization of cost-effective sterilization methods.[14]

Rutgers' 10,000+ library of tyrosine-derived polymers enables the selection of the most appropriate polymer for a given drug and application and provides significant advantages to PGA, PLA, and PLGA polymers. This approach offers greater flexibility and value than typical drug delivery polymer platforms in which only a few polymers are available and characteristics, such as drug-polymer interactions and fabrication method, cannot be effectively optimized (Figure 1).

Ophthalmic Application of Tyrosine-Derived Bioerodible Polymer Technology: Sustained Ocular Delivery of a Next-Generation Calcineurin Inhibitor

Lux Biosciences, Inc. (Lux) is a clinical-stage biotechnology company specializing in the field of ophthalmic diseases. Lux has exclusively licensed the libraries of tyrosine-derived polyarylates and polycarbonates for worldwide ophthalmic use from Rutgers University. Lux is actively collaborating with a research team led by Professor Kohn, the inventor of the tyrosine-derived polymers, to develop new drug delivery systems for various ocular diseases.

For example, LX212 is a controlled-release, implantable formulation composed of a tyrosine-derived polymer capable of releasing voclosporin, Lux's new calcineurin inhibitor (voclosporin was licensed by Lux for worldwide ophthalmic use from Isotechnika, Inc.). This implantable drug-release system is being developed for the treatment of inflammatory conditions, such as severe dry eye syndrome (DES) and blepharitis. Like other calcineurin inhibitors, voclosporin reversibly inhibits immunocompetent lymphocytes, particularly T-lymphocytes, and also inhibits lymphokine production and release. Both DES and blepharitis are diseases that are characterized by chronic inflammation of the ocular surface and tear-producing lacrimal gland or the meibomian glands, and involve T-cell activation. Hence, calcineurin inhibition is a potent mechanistic approach for the treatment of these conditions. The voclosporin-eluting ocular implant is small (approximately the size of a rice grain) and implanted in a minimally invasive procedure (Figure 2). The implant should enable sustained local delivery of therapeutically effective concentrations of the drug while producing very low systemic levels. The sustained local delivery of therapeutically effective concentrations will likely translate into enhanced efficacy, patient compliance, and comfort.

Currently, it is estimated that the worldwide prevalence of DES is 30 million.[1] Further estimates indicated that 4.6 million patients are afflicted with the severe form of DES and blepharitis in North America and Europe alone.[16] However, there is no cure for either of these chronic, debilitating inflammatory diseases, and currently available treatment options leave substantial room for more effective, better-tolerated products that increase patient compliance. Irrespective of under-diagnosis and these concerns, the current DES market is valued at almost $1.6 billion with near-term growth in excess of 10% annually.[1] The ocular infection drug market to which blepharitis belongs is currently valued at over $1.1 billion.[1] Thus, the sheer number of patients, coupled with the dearth of effective, patient compliant treatment options, suggests that there is an excellent market opportunity for a therapeutically effective pharmaceutical formulation.

Additional Applications of Tyrosine-Derived Bioerodible Polymer Technology

<u>Bioresorbable/Drug-Eluting Surgical Meshes & Implant Device Envelopes:</u>
Applications for Rutgers' polymer libraries extend well beyond the treatment of ocular diseases. Using the same polyarylate library licensed to Lux, TyRx Pharma, Inc. has received 510(k) clearance from the FDA for several implantable devices that utilize bioresorbable polyarylates.[17] PIVIT™, approved in December 2005, is a surgical mesh coated with a bioresorbable polyarylate indicated for the repair of hernias and other abdominal fascial or muscular deficiencies requiring the addition of a reinforcing or bridging material to obtain the desired surgical result. The second approved device, PIVIT AB, is a similarly indicated antimicrobial surgical mesh. In the PIVIT AB mesh, the polyarylate coating releases the antimicrobial agents rifampin and minocycline while degrading. The coating provides protection from microbial colonization of the device during surgical implantation. The most recent approved device is AIGIS$_{RX}$™, a cardiac rhythm medical device (CRMD), anti-bacterial

envelope designed to immobilize and reduce bacterial infection of a Pacemaker or Implantable Cardioverter Defibrillator (ICD) after implantation. Similar to PIVIT AB, the AIGIS$_{RX}$ envelope is composed of a mesh coated with a bioresorbable polyarylate that releases the antimicrobial agents rifampin and minocycline while degrading.

Bioerodible Cardiovascular Stent: REVA Medical, Inc. (REVA) is utilizing the library of tyrosine-derived polycarbonates to develop the first x-ray radiography/fluoroscopy opaque bioresorbable polymer coronary stent, which would support the vessel during healing but resorb afterward.[18] Preclinical studies of stents that utilize Reva's slide-and-lock design and a carefully optimized composition selected from the library of tyrosine-derived polycarbonates demonstrated mechanical performance similar to metal stents and sustained biocompatibility. Patients are currently being recruited for the Phase I RESORB (REVA Endovascular Study of a Bioresorbable Coronary Stent) clinical trial, a non-randomized study of up to 30 patients in Brazil and Germany with an initial assessment of major adverse cardiac events (MACE) at 30 days and a follow-up period of 5 years. REVA intends to develop a drug-eluting bioresorbable stent using the same polymer platform as well.

The commercialization efforts of Lux, TyRx Pharma, and REVA in fields as diverse as ophthalmology and cardiology demonstrate the versatility of the tyrosine-derived polycarbonate and polyarylate libraries developed by Joachim Kohn and co-workers. It is expected that these polymer libraries will be used to develop a wide range of FDA-approved products with numerous biomedical applications from drug delivery to orthopaedics to tissue engineering throughout the next decade and beyond.

SUMMARY

Rutgers University's proprietary combinatorial library of 10,000+ tyrosine-derived biocompatible, biodegradable polymers represents one of the most advanced technology platforms in the field of drug delivery. The wide range of polymers assembled in the library reverses the screening paradigm: the active compound is screened against the library and the delivery system optimized against a target profile, as opposed to adapting the active ingredient to a polymer platform with limited versatility. The highly versatile Rutgers' polymer library provides Lux with exceptional market opportunity to add value to its portfolio compounds through both the expansion of its development pipeline with additional proprietary products, and potentially through partnering to treat diseases outside of the company's focus.

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MATRIX-FORMING AGENT

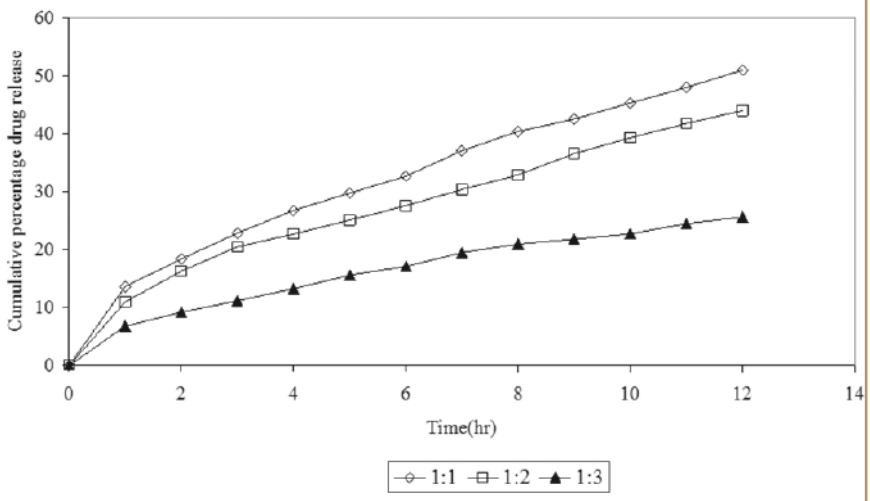
Controlled Release of Dipyridamole From Floating Matrices Prepared Using Glyceryl Behenate

By: V.F. Patel, PhD, MPharm, and N.M. Patel, PhD

ABSTRACT

Inert floating matrices to control the release of dipyridamole were prepared using glyceryl behenate as a matrix-forming material. Dipyridamole has pH-dependent solubility and requires low pH for optimum absorption, making it an ideal candidate for floating drug delivery. The matrices were prepared by direct compression of a physical mixture of drug and polymer or by compression of granules prepared by hot fusion of drug and polymer. The drug release from prepared matrices was carried out on a USP type II paddle apparatus using 0.1 N HCl at paddle rotation of 100 rpm at 37°C ± 0.5°C. The hot-fusion method was found to be more effective than compression of the physical mixture in retarding the release of the drug from the matrix. Compressed matrices were able to control the drug release with floating ability compared to granules. It was observed that as the drug-to-polymer ratio increased, the retardation of drug release was more pronounced. The effect of various release enhancers were studied by incorporating microcrystalline cellulose, lactose, and PEG 4000. The results showed that higher release rates were obtained by all release enhancers tried compared to matrices containing only drug and polymer. It was observed that the floating ability of compressed matrices was dependent upon the hardness of matrices, which had an insignificant effect on release rate. The drug was released via a diffusion mechanism from hydrophobic matrices. The present study revealed that gylceryl behenate can be used as a matrix-forming agent to control the release of poorly water-soluble drugs, such as dipyridamole.

FIGURE 1



Influence of drug-to-glyceryl behenate ratio on drug release from compressed matrices prepared using the hot-fusion method.

INTRODUCTION

Glycerides are a family of excipients that have generated considerable interest for the preparation of oral dosage forms. Gelucires represent a wide range of meltable excipients, which are composed of mixtures of glycerides and fatty acid esters of polyethylene glycol. The nature and proportion of these components determine the hydrophilic lipophilic characteristics (HLB value) of these excipients and the drug-release properties from corresponding drug delivery systems.[1] Matrix drug delivery systems utilizing waxy materials usually employ a core of drug embedded in the wax or a compressed blend of drug and matrix-forming agent. The waxy materials are water insoluble and non-swellable and have been introduced to eliminate the effects of the food present in the GI tract on the matrix integrity of tablets.[2]

Glyceryl behenate (Compritol® 888 ATO) can be used as a glyceride base for the preparation of sustained-release dosage forms. Indeed, the esterification of glycerol by long

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MATRIX-FORMING AGENT

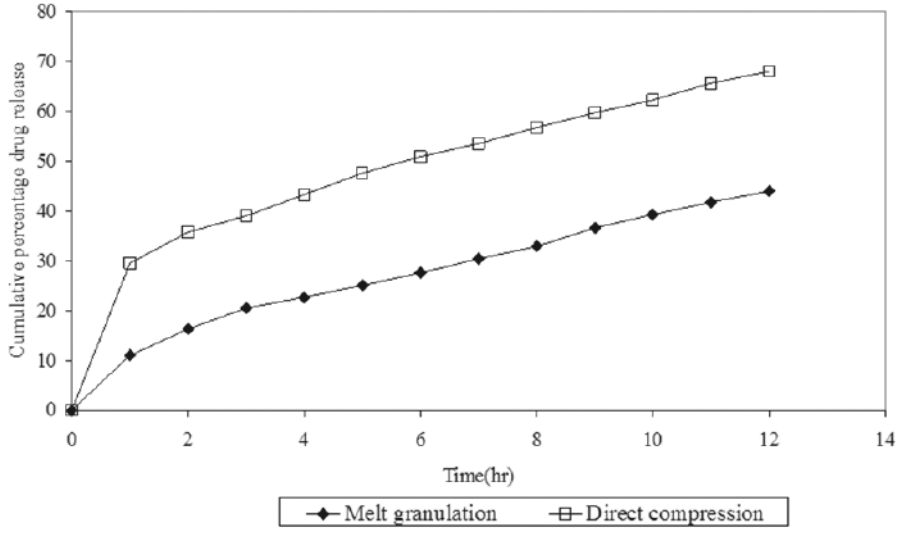
chain fatty acids and the absence of polyethylene glycol esters give them a pronounced hydrophobic character expressed by a low HLB value of 2. The extreme hydrophobicity of glyceryl behenate is responsible for its floating property. It is a waxy material originally introduced as a lubricant in compressing tablets and recently experienced wide application as a sustained-release agent. It is commonly used as a lubricant and binding agent for tablets in 1% to 3% concentrations and sustained-release excipients in 10% concentrations.[3]

Barthelemy and co-workers investigated the use of Compritol as a hot-melt coating agent to prolong the release of theophylline.[4] Their study confirmed a satisfactory coating potential by this agent and a potential in sustaining the release of theophylline over an extended period of time.

Dipyridamole, a poorly soluble weak base with a reported pKa of 6.4, was reported to be altered to a considerable extent by the pH of different digestive fluid; that is dipyridamole dissolves readily in the stomach but incompletely in the intestine. The solubility of dipyridamole at 37°C is as follows: 29.2 mg/ml (pH 2.5), 0.015 mg/ml (phosphate buffer, pH 6.0), and 0.012 mg/ml (phosphate buffer, pH 6.5).[5] A study by Miyazaki and co-workers reported that the extent of absorption of dipyridamole was remarkably lower when gastric pH was continuously elevated to 6.0, whereas it was increased when gastric pH temporarily decreased to 1.8. This finding may be due to the contribution of the precipitation potential of the drug when pH changes from acidic to neutral.[6]

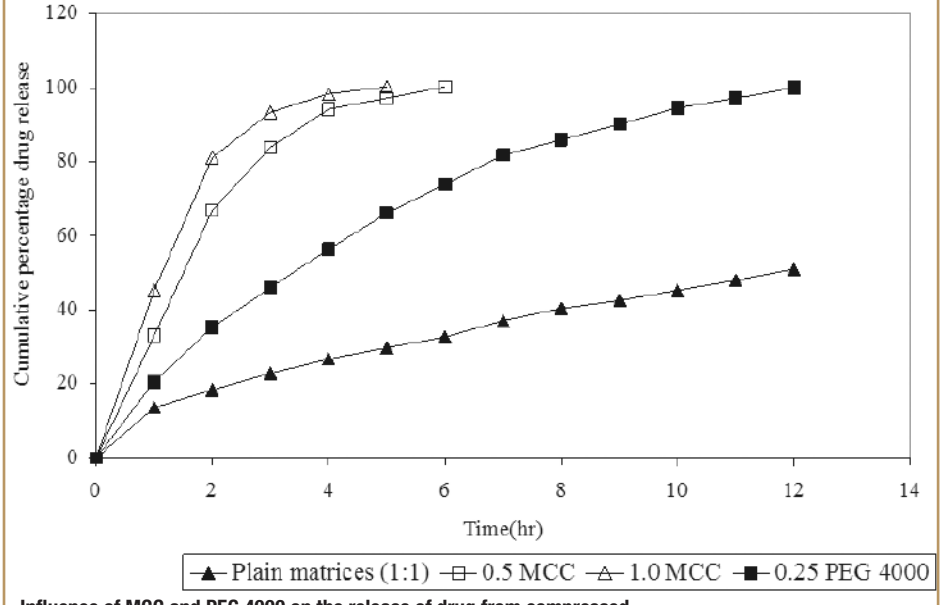
Rapid GI transit could result in incomplete drug release above the absorption zone of the drug delivery system, leading to diminished efficacy of the administered dose. Therefore, different approaches have been proposed to retain the dosage form in the stomach. Among them includes floating drug delivery systems, which are a logical and practical approach to prolong gastric residence time.[7] Due to aforementioned reported facts about dipyridamole bioavailability, it would be beneficial to

FIGURE 2



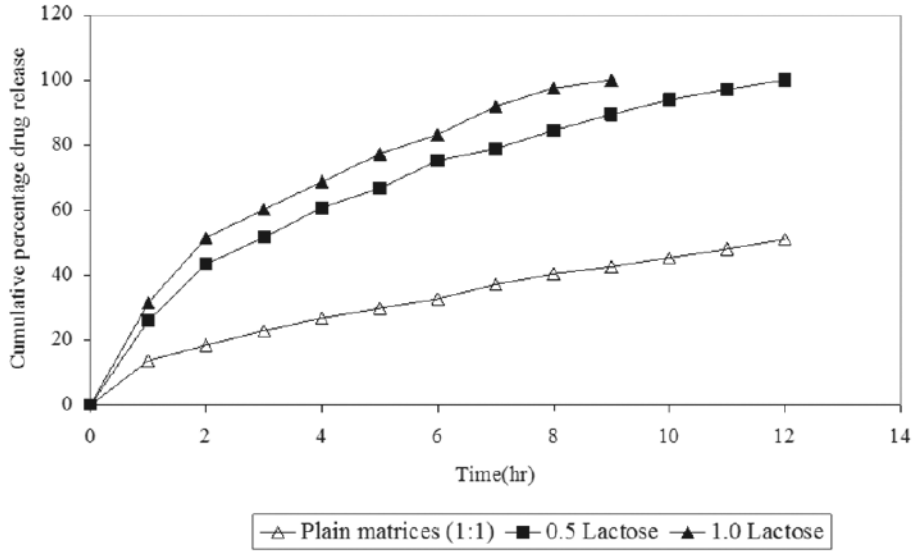
Influence of method of preparation of compressed matrices on dipyridamole release at a drug-to-glyceryl behenate ratio of 1:2.

FIGURE 3



Influence of MCC and PEG 4000 on the release of drug from compressed matrices prepared at a drug-to-glyceryl behenate ratio of 1:1.

FIGURE 4



Influence of lactose on drug release from compressed matrices prepared at drug-to-glyceryl behenate ratio of 1:1.

develop floating drug delivery systems that prolong gastric residence time and release drug in the proximal GI tract where absorption of dipyridamole is more confined. The objective of the present study was to prepare oral controlled release dipyridamole floating matrix tablets utilizing glyceryl behenate as a lipid matrix-forming polymer.

MATERIALS & METHODS

Materials

Dipyridamole was a generous gift from Sun Pharmaceutical Ltd (Vadodara, India). Compritol 888 ATO was a generous gift from Gattefosse (St Priest, Cedex, France). Avicel® PH 102 was a generous gift from FMC Biopolymer (Ireland, US). Tablettose 80 was a generous gift from Meggle GMBH (Germany). PEG 4000 was procured from Lesar Chemicals (Vadodara, India).

Preparation of Floating Matrix Tablet

Glyceryl behenate was melted with continuous stirring in a porcelein dish in a water bath maintained at 75°C. The drug was added with continuous stirring. The molten mass was allowed to cool down and pass through 520-micrometer sieve. The drug was present in its solid form within the molten mass. These granules were compressed into 10-mm flat faced tablets using a Rotary tablet machine (Rimek, Ahmedabad, India). In order to study the effect of microcystalline cellulose (MCC) and lactose on the release of drug from such matrices, other granules were mixed with either MCC or lactose at a specified ratio and compressed into flat faced tablets. To study the effect of polyethylene glycol (PEG) 4000, it was added into the melt granulation stage, and the resulted granules were compressed into flat faced tablets. To compare direct compression and melt granulation techniques, tablets were also prepared by direct compression of a physical mixture of drug and glyceryl behnate. For direct compression, drug and polymer at a ratio of 1:2 was physically blended for 10 minutes and compressed using 10-mm flat faced tablet tooling.

In Vitro Buoyancy Study

The in vitro buoyancy was characterized by floating lag time and total floating time. The test was performed using a USP XXIV type II paddle apparatus using 900 ml of 0.1 N HCl at paddle rotation of 100 rpm at 37°C ± 0.5°C. The time required for the tablet to rise to the surface of the dissolution medium and the duration of time the tablet constantly floated on the dissolution medium were noted as floating lag time and total floating time, respectively (n=3).

In Vitro Drug-Release Study

The in vitro drug release was performed using a USP XXIV type II paddle apparatus using 900 ml of 0.1 N HCl at paddle rotation of 100 rpm at 37°C ± 0.5°C. The samples were withdrawn at a predetermine time interval for a period of 12 hours and replaced with the fresh medium. The samples were filtered through a 0.45-micrometer membrane filter, suitably diluted, and analyzed at 283 nm using a double beam UV/Vis spectrophotometer (Shimadzu Corporation, UV-1601, Japan). The content of drug was calculated using an equation generated from the standard calibration curve. The test was performed in triplicate. The standard deviation was found to be less than 3%, so only the average value was considered.

RESULT & DISCUSSION

Granules prepared with different ratios of drug-to-glyceryl behenate were studied to examine the effect of increasing the amount of glyceryl behante on the release of dipyridamole. The drug release from granules was rapid in all the ratios studied, and the granules were not floated for more than 30 minutes. The drug release was faster, which might be due to non-uniform coating of the drug particles by the polymer. A similar observation was also reported by Bolton and co-workers.[8] They reported faster drug release from glyceryl palmitosterate granules irrespective of the content of the polymer. Fast dissolution of the drug particles from the surface of the granules is expected, and this was relatively similar in all ratios of polymer studied. Hence, it was decided to compress the granules prepared using different levels of glyceryl behenate.

Figure 1 displays the influence of glyceryl behenate ratios on drug release from compressed matrices prepared using the hot-fusion method. It was found that the compression of granules prepared using the hot-fusion method had a significant and marked effect on decreasing the release of the drug in comparision with the drug release from uncompressed granules. It was observed that as the level of polymer increases, drug release rate decreases, which might be due to a more uniform covering of drug particles. Variations in the compression force did not alter the release profile of dipyridamole from the matrices, but it affected the floating capability of the matrices. It was observed in tablets having a hardness of more than 7 kg that the floating ability of matrices was lost. Therefore, throughout the study, the tablets were compressed below a hardness of 7 kg to retain floating ability.

The effect of preparation of matrices on the release of the drug was also examined. This effect was examined in tablets prepared by compression of the physical mixture of drug and glyceryl behenate and in tablets prepared by compression of granules prepared by the hot-fusion method. There was a significant influence regarding the method employed for the preparation of compressed tablets. Figure 2 shows release profiles from matrices made by direct compression of physical mixtures and from matrices made by compression of granules made by the hot-fusion method at a drug-to-polymer ratio of 1:2. Although the release is low and sustained from these matrices, it was higher from the tablets prepared by compression of physical mixtures than from the tablets prepared by compression of granules. The effect observed might be due to complete coating of the drug particles by the polymer melt in the case of hot fusion. It is expected that the penetration of dissolution medium to the matrix will be low in the case of matrices prepared by the hot-fusion method, leading to a slower drug release rate. In either case, both of these matrices will be highly hydrophobic and would be expected to release the drug at a very slow rate as indeed was found to be the case (Figure 2). However, in the case of matrices prepared by direct compression of physical mixtures, it seems that the dissolution of drug particles at the surface of the matrices allowed the establishment of channels throughout which the drug was released. Therefore, the release rate was higher compared with matrices containing granules prepared by the hot-fusion method.

Because the drug release from compressed matrices was too low, the effect of some release enhancers was investigated. The release enhancers studied were MCC, lactose, and PEG 4000. MCC and lactose were used in ratio of 0.5 and 1.0 to the polymer while PEG 4000 was used at a ratio of 0.25 to the polymer. Figure 3 shows the effect of MCC and PEG 4000 on dipyridamole release from compressed matrices. It was observed that the addition of MCC increased the drug release, and it was increased with an increase in content of MCC in matrices. MCC works via a rapid swelling and eventually disintegration of the matrices. The observed effect was explained by the fact that the swellable excipients create channels for drug to release and loosen the matrix integrity, resulting in an increased drug-release rate. The immiscibility between the hydrophobic wax and hydrophilic component resulted in interruption of continuity of the hydrophobic domain of wax due to the swelling of cellulose polymer, leading to faster drug release from matrices. A similar observation was also reported by Lin and co-workers.[9] They reported an increased release rate of phenylpropanolamine hydrochloride upon the addition of cellulose polymer from matrices prepared using glyceryl palmitostearte by the hot-melt extrusion technique.

PEG 4000 also increased the drug release from matrices. PEG 4000, being a water-soluble component, leached rapidly from hydrophobic matrices and resulted in increased drug release by creating pores and channels through which the drug was released (Figure 3). A similar observation was also reported by Paradkar and co-workers.[10] They reported that PEG 4000 leached rapidly from the single-unit matrices prepared from

glyceryl monooleate, resulting in the formation of pores and channels through which dissolution fluid entered, thus accounting for an increase in overall drug-release rate.

The addition of water-soluble filler lactose also resulted in an increased release rate of drug from hydrophobic matrices. Lactose was evaluated at a ratio of 0.5 and 1.0 with granules prepared using a drug-to-glyceryl behante ratio of 1:2. Figure 4 displays the effect of lactose on release of drug from compressed matrices. It was found that using lactose as a release enhancer, the drug release from matrices was increased, but it was low compared to MCC. The result was expected due to the high swelling property of MCC, which opened the channel for drug to get released, compared to lactose, which is soluble but non-swellable.

The mechanism of release of drug from glyceryl behenate appeared to be diffusion controlled release. The data of drug release were well fitted to Higuchi's square root of time model. The good fitness was obtained irrespective of the amount and type of different release-enhancer added. Visual observation of tablets during the dissolution study revealed that the tablet remained intact without any significant change in their shape, indicating dominance of diffusion-based drug release through the channel formed in the matrices. These channels are formed due to rapid dissolution of drug particles on the surface of the matrix and the presence of release enhancers, leading to increased penetration of dissolution medium and allowing more dissolution of drug present in the deeper site of the matrix.

CONCLUSION

In conclusion, this study showed that glyceryl behenate is an appropriate waxy material that can be used as a matrix forming agent to control drug release. Controlling the hardness of compressed matrices, one can explore the hydrophobic properties of glyceryl behante in development of floating drug delivery systems. Preparation of the matrices by compression of granules prepared using the hot-fusion method was found to be more effective for controlling drug release than compression of physical mixture. However, it was also possible to adjust the drug release from such hydrophobic matrices by incorporating release enhancers, such as MCC, lactose, and PEG 4000 at appropriate levels.

ACKNOWLEDGEMENT

The authors are thankful to Sun Pharmaceutical,Vadodara (India) for providing gift samples of dipyridamole and Gattefosse (Cedex, France), FMC Biopolymer (Ireland, US), and Meggle GMBH (Germany) for providing gift samples of excipients.

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BIOGRAPHY

Dr. Viral F. Patel is a Research Scientist in Formulation Development department at Alembic Research Centre, Alembic Limited, Vadodara (India). He has ten publications to his credit in various national and international journals. Dr. Patel has done his PhD in Pharmaceutical Sciences at Hemchandracharya North Gujarat University, Patan (India).

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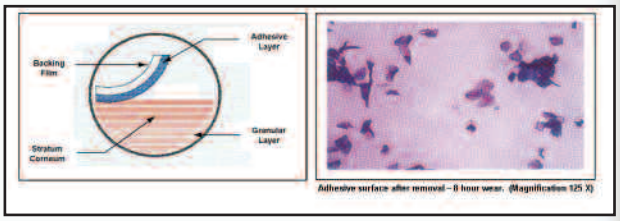

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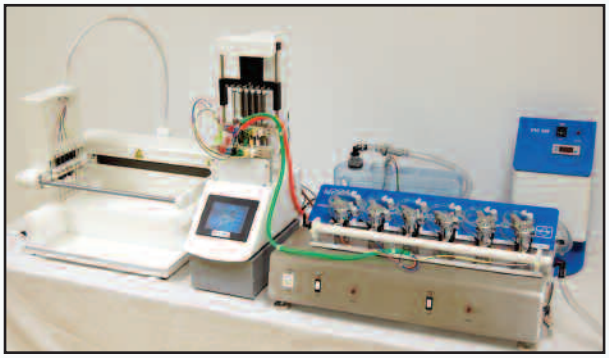

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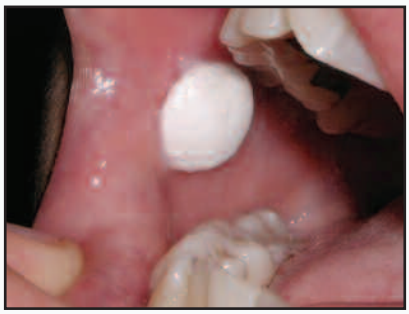

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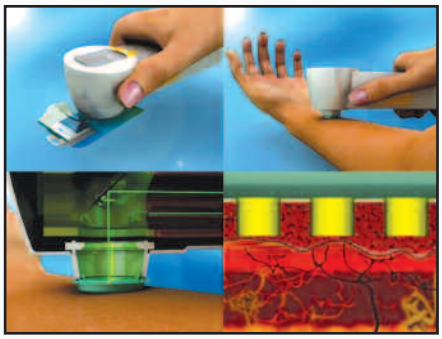

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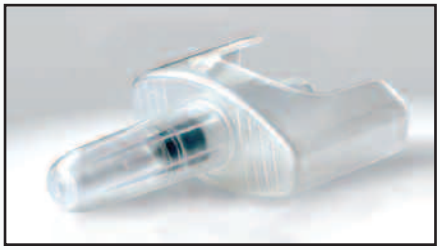

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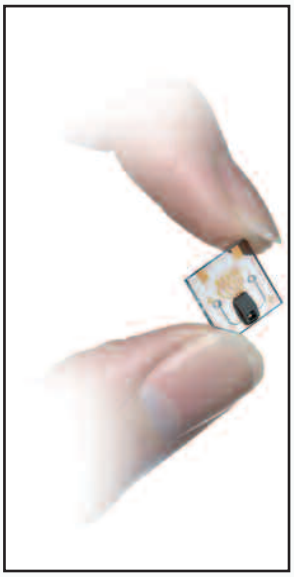


Sensirion AG is expanding its technology portfolio for liquid flow sensor solutions, announcing a new level of miniaturization for non-invasive liquid flow sensors based on planar microfluidic substrates. Innovative packaging enables Sensirion's highly sensitive thermal flow sensor microchips to measure non-invasively through the wall of a flow channel inside a microfluidic substrate. This design provides unique sensitivity for liquid flow measurement and bubble detection in the microliter range. A small digital CMOSens® microchip (2.2 x 3.5 mm) is bonded to the microfluidic channel substrate. Beside the sensor element, it houses the complete digital intelligence as well as the memory necessary for signal linearization, temperature compensation, and self-test algorithms. The sensor boasts a short-flow sensing response time of around 30 ms, and sensor resolutions down to 0.5 nl/min are feasible. For more information, visit Sensirion AG at **www.sensirion.com**.

Benchtop Tube Printer

The TubeWriter is the first direct printer for clinical and laboratory media and vials, including glass or plastic vials, micro-centrifuge tubes, cryogenic vials, cluster tubes, plates, and slides. Information is entered in an Excel spreadsheet on a PC or Mac and printed by the TubeWriter with the same water-proof and alcohol-resistant ink currently used in diagnostic and clinical laboratories. Up to 50 samples may be printed at a time in as little as 3 mins. Because no adhesive labels are used, tubes may be placed in liquid nitrogen, -80ºC freezers, boiling water, and micro-centrifuges without the printing coming off. Printing may be made on the tops or sides of media. For more information, contact Tubewriter at (650) 906-5600 or visit **www.tubewriter.com**.

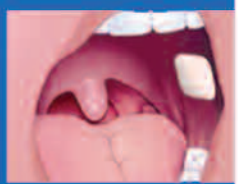
DRUG DELIVERY Executive

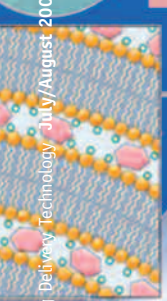
BioDelivery Sciences International

BioDelivery Sciences International: Improving Existing Therapeutics Using Novel Technologies

Mark A. Sirgo, PharmD
President & CEO
BioDelivery Sciences International, Inc.

"We believe the BEMA™ and Bioral® technologies offer promise for broad application across a number of therapeutic areas and drugs to improve the administration and delivery of currently marketed products to meet market opportunities."





BioDelivery Sciences International, Inc., headquartered in Raleigh, North Carolina, is a specialty pharmaceutical company that is using its novel and patent-protected drug delivery technologies to both develop and commercialize new uses or routes of delivery for drugs that are currently available, yet have usage and delivery limitations due to their formulations. The company has two novel drug delivery platforms and is currently focusing its efforts on new therapeutics to treat pain and infections. BioDelivery Sciences is currently approaching the potential approval of its first drug, BEMA™ Fentanyl, for the treatment of breakthrough pain in opioid-tolerant cancer patients. Drug Delivery Technology recently interviewed Mark A. Sirgo, President and Chief Executive Officer of BioDelivery Sciences, to discuss the company's proprietary technologies, product pipeline, and strategic corporate vision.

Q: For those readers not familiar with the company, please provide some background on BioDelivery Sciences.

A: BioDelivery Sciences was founded in 1995 and is focused on using its proprietary, patented drug delivery technologies to develop and commercialize, on our own or in partnerships, new application and delivery methods for proven therapeutics. Our product development strategy utilizes the FDA's 505(b)(2) approval process to potentially obtain timely and efficient approval of new formulations of previously approved therapeutics that incorporate our patented drug delivery technologies, BioErodible MucoAdhesive (BEMA) and Bioral®. This approval process allows us to reference the originator's approval and can significantly reduce the cost of development and expedite the time to market.

Our primary focus is on the formulation of pharmaceuticals largely aimed at treatment opportunities in areas such as pain and infections. We have a number of products in our pipeline, including our lead product, BEMA Fentanyl, which is currently under review at the FDA with a PDUFA data of August 31, 2008. BEMA Fentanyl has been licensed to Meda AB and will be commercialized by its affiliate in the US, Meda Pharmaceuticals (formerly known as Medpointe). We are also conducting clinical trials on our second pain product, BEMA Buprenorphine, and our first product using the Bioral technology, Bioral Amphotericin B.

Q: What are some of the benefits associated with BioDelivery Sciences' drug delivery platforms? How do these technologies compare with other technologies currently on or approaching the market?

A: We developed the BEMA drug delivery technology with the goal of rapidly and reliably delivering therapeutic doses of drug into the

bloodstream via blood vessels in the cheek (transmucosal delivery). The technology consists of a bi-layered polymer film that adheres to the inside of the cheek within seconds and – within 15 to 30 minutes – dissolves and completely disappears.

We believe BEMA is a novel technology with the ability to alleviate some of the most common issues encountered with drugs that cannot be readily and orally absorbed. For example, many of the drugs that fall into this category can be administered only intravenously, and it is our goal to maximize the effect of such drugs through a convenient transmucosal formulation. We further believe transmucosal delivery provides opportunities for such drugs to be utilized in outpatient settings, or to provide greater drug absorption rates than oral formulations, with the intent to maximize their effects.

Unlike other delivery technologies, the BEMA technology is also well-suited for conditions in which rapid and reliable dosing is critical. Additionally, the delivery system was designed to be easy for patients to use. It is for these reasons we believe the BEMA technology represents the next step forward in the evolution of transmucosal drug delivery and addresses some of the limitations and issues with other delivery technologies.

As I previously mentioned, we have a second drug delivery platform called Bioral. Bioral encapsulates – or entraps – and protects a drug within a crystal matrix without forming a chemical bond. We are pursuing the Bioral technology to enable oral dosing of a broad spectrum of compounds that are difficult to administer orally for a number of reasons, such as poor absorption by the body or the tendency to be broken down in the stomach or gastrointestinal tract, thereby reducing potency and effect. Our first product under development using this technology is Bioral Amphotericin B. If successful in clinical trials, Bioral Amphotericin B could be the first orally administered fungicidal treatment available.

Q: Looking ahead 5 to 10 years, what impact do you see BioDelivery Sciences' technologies having in the market?

A: We believe the BEMA and Bioral technologies offer promise for broad application across a number of therapeutic areas and drugs to improve the administration and delivery of currently marketed products to meet market opportunities.

The results we have seen with BEMA Fentanyl for breakthrough pain (BTP) in cancer patients demonstrate the ability of the BEMA technology to deliver therapeutic concentrations of drug quickly and reliably. We have also initiated development of our second product, BEMA Buprenorphine, for the treatment of both acute and chronic pain conditions. And again, our first product using the Bioral platform – Bioral Amphotericin B – could become the first oral fungicidal available in the world.

Overall, our ultimate goal is to pursue alternative treatment options that address important unmet therapeutic needs, and we will do this through identifying external partners and leveraging our own capabilities to advance such products through the development process and into the market.

Q: Describe your licensing and development agreements. What characteristics do you look for in a potential partner?

A: In August 2006, we announced a collaboration with Meda AB for the development and commercialization of BEMA Fentanyl in Europe. Following the acquisition of Medpointe Pharmaceuticals (now known as Meda Pharmaceuticals) by Meda AB, we entered into a licensing agreement covering the US, Canada, and Mexico for the commercial rights to BEMA Fentanyl in those regions. We received an upfront payment of $30 million with the potential for an additional $60 million in milestone payments and a significant double-digit royalty.

Overall, we look for therapeutic area experience, a solid commercial infrastructure, and a clear commitment to our product in potential partners. We believe Meda has been an ideal partner given the company's experiences in the pain category and a strong global

commitment to BEMA Fentanyl. We are also working collaboratively with a number of other large and small pharmaceutical companies to address some of the delivery challenges they are encountering with their pipeline products.

Q: You mentioned BEMA Fentanyl was developed to treat breakthrough cancer pain. Why have you developed your first product to treat this particular condition?

A: Our first product, BEMA Fentanyl, was developed specifically for the treatment of BTP in opioid-tolerant cancer patients. We chose to pursue BTP in cancer patients because we believe there remains a significant need for a potent, rapid-acting product that can transverse the buccal mucosa. While it is estimated that more than a half-million people with cancer suffer from breakthrough pain, only a small number of these patients (less than 20,000) are actually treated with a product specifically indicated to treat the condition. The BEMA technology seemed to be potentially well suited to meet the needs of patients with this condition and so we pursued it as the first application of our BEMA drug delivery technology.

We have applied our BEMA technology to advance the treatment options for cancer patients who experience BTP, which is described as a common, debilitating feature of chronic pain, particularly in patients with cancer. It is a transitory, severe, or excruciating pain flare-up that "breaks through" the relief provided by around-the-clock analgesics. Unlike persistent cancer pain, BTP is generally rapid in onset (within 3 minutes) and lasts for approximately 30 minutes. Patients with cancer may experience several episodes of BTP a day, and this can have a significant impact on their ability to function in daily settings. It is our goal to prove that BEMA Fentanyl is an important treatment option for opioid tolerant cancer patients with BTP. And finally, it is our hope to not only treat the significant number of cancer patients experiencing BTP, but also to make a difference in the lives of those patients and their families.

Q: In what ways, and why, is BioDelivery Sciences an attractive business partner?

A: We are fortunate to have two novel, proprietary drug delivery platforms with wide application potential across a broad range of compounds. The value of our BEMA delivery technology has been demonstrated in the development program for BEMA Fentanyl, and our first product using the Bioral technology is currently in clinical development. We believe that having two broad-based delivery technologies leaves us well positioned for future growth. We have also demonstrated our drug development and clinical capabilities through completion of the development program and FDA submission for BEMA Fentanyl. We also have in place a strong management team with extensive experience in both drug development and commercialization, which also positions us for future success.

Q: What is BioDelivery Sciences' growth strategy?

A: At this point, the potential approval of BEMA Fentanyl represents one of the most significant steps in the evolution of our company. Approval would provide us with a significant additional milestone payment and royalties from eventual sales. This revenue will support the acceleration of our ongoing clinical development programs for BEMA Buprenorphine and Bioral Amphotericin B, as well as our goal of applying our technologies to other drugs and therapeutic areas. Additionally, approval would open the door to other strategic options, including exploring additional potential future technologies and products and the ability to build BioDelivery Sciences into a fully integrated pharmaceutical company where we may eventually sell our own product. We plan to achieve these goals through the diligent pursuit and approval of BEMA Fentanyl, our strong commercialization and research partnerships, robust pipeline, and experienced staff. ◆

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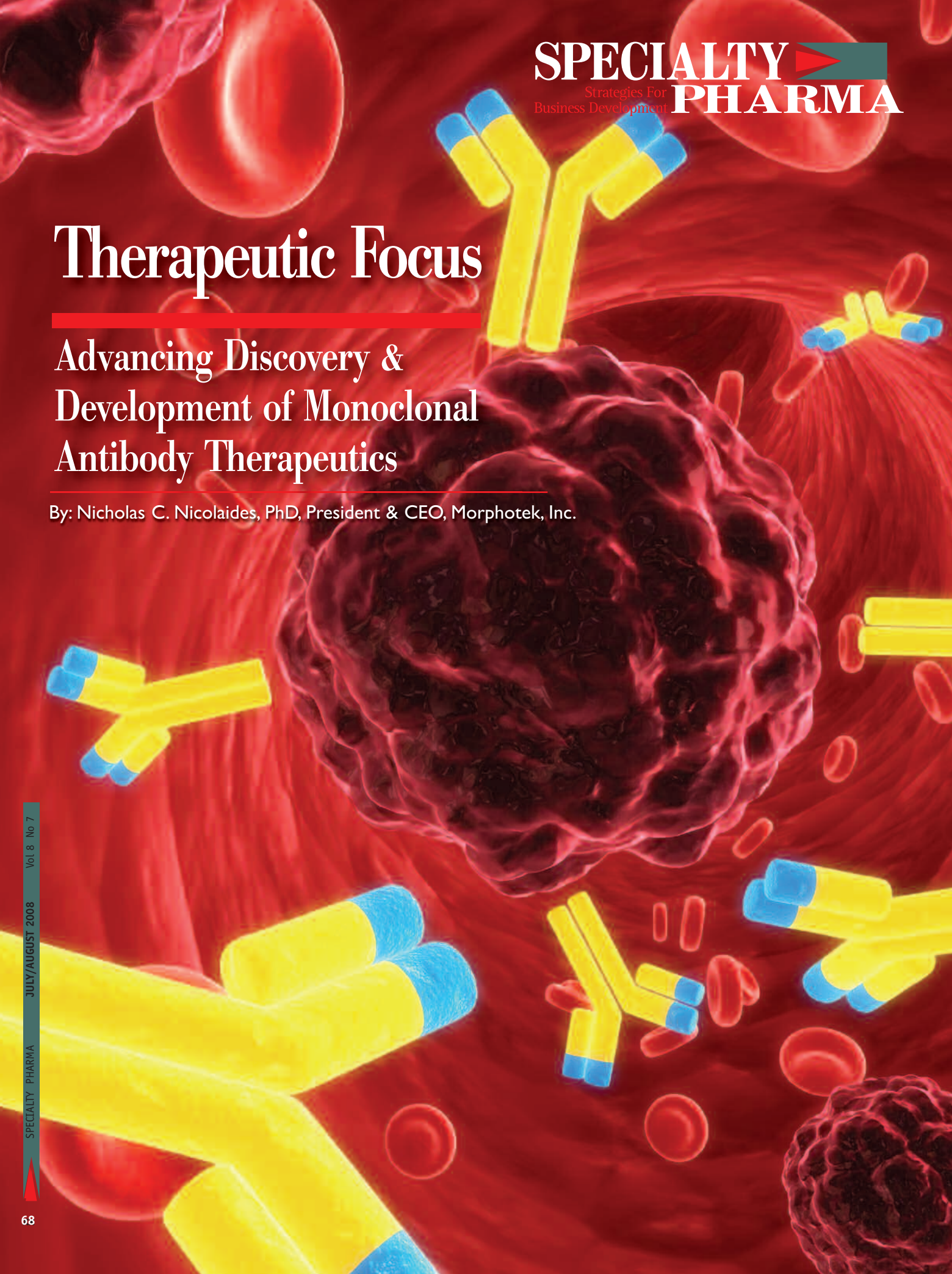
SPECIALTY PHARMA
Strategies For Business Development

Therapeutic Focus

Advancing Discovery & Development of Monoclonal Antibody Therapeutics

By: Nicholas C. Nicolaides, PhD, President & CEO, Morphotek, Inc.



Monoclonal antibodies (mAbs) represent the fastest growing segment of the biopharmaceutical market with current sales upward of $29 billion and a projected growth to exceed $40 billion by the year 2012. One advantage of mAbs is their ability to specifically bind to a disease-associated target. Furthermore, the safety and therapeutic efficacy of antibodies has been reinforced by more than 20 years of established research.

The continued discovery and development of mAbs is expected to grow through advancements in technology and close collaborations with world-renowned leading researchers in biologics, general science, and clinical research. Ultimately, technology and strategic partnerships will play key roles in establishing the future of mAb therapies for treating disease.

One company that has successfully utilized this is Morphotek®, Inc. A wholly owned subsidiary of Eisai Corporation of North America, Morphotek develops novel classes of biological-based products to treat cancer, inflammation, and infectious diseases. The company has made significant advancements in mAb discovery through its proprietary morphogenics and MORPHODOMA® technologies.

These technologies optimize features of biological therapeutics, such as monoclonal antibodies and the cells that produce them. Morphogenics is a broad-based proprietary platform technology that regulates the ability of a host organism to repair mutations that occur during DNA replication. During DNA replication, thousands of mutations occur that are usually corrected prior to cell division by DNA repair mechanisms. One of the most robust repair mechanisms is the process called mismatch repair (MMR), which proofreads newly replicated DNA for mutations. The MMR process is similar to a computer spell-check function. Once the MMR process is completed and mutations in the new genome have been corrected, the cell divides into two genetically identical daughter cells. Cells with dysfunctional MMR accumulate mutations that yield daughter cells with traits different from those of the parent. Regulation of MMR by morphogenics can be used to create variants with desirable features.

In its ongoing research and development program, Morphotek leverages morphogenics to improve antibody therapeutics created through the application of Human MORPHODOMA technology (Figure 1), a process that generates fully human antibodies targeted against disease-associated antigens.

Targeting Disease-Associated Molecules

Currently, Morphotek has two antibodies in clinical development that were made using morphogenics technology (MORAb-003 for the treatment of relapsed ovarian cancer and MORAb-009 for first-line treatment of pancreatic cancer). The MORAb-003 antibody binds to a protein called folate receptor alpha (FRA) that is over-expressed on the surface of a variety of cancers, including ovarian, breast, colorectal, lung, and renal carcinoma. The binding of MORAb-003 to FRA has been shown in preclinical studies to block the biological signaling that is involved in cells being transformed. Preclinical studies indicate that this blockage prevents the cell from being able to grow out of control. A Phase I clinical study showed the drug to be well tolerated.

Morphotek initiated a Phase II efficacy study for MORAb-003. The Phase II clinical trial includes patients with ovarian cancer who are experiencing their first relapse after primary surgery and chemotherapy, and are still sensitive to platinum chemotherapy. The trial is evaluating the efficacy of MORAb-003 both as a single agent and in combination therapy with carboplatin and taxane.

The MORAb-009 antibody binds to mesothelin, a protein that is expressed in a variety of conditions, including pancreatic cancer, mesothelioma, ovarian cancer, and non-small cell lung cancer. The binding of MORAb-009 to mesothelin has been shown in preclinical studies to stop the cells from dividing. A Phase I clinical study showed the drug to be well tolerated.

Earlier this year, Morphotek commenced a global multi-centered Phase II clinical study of its MORAb-009 monoclonal antibody. The study is evaluating MORAb-009, plus the chemotherapy drug gemcitabine, as a first-line treatment for patients with locally advanced or metastatic pancreatic cancer.

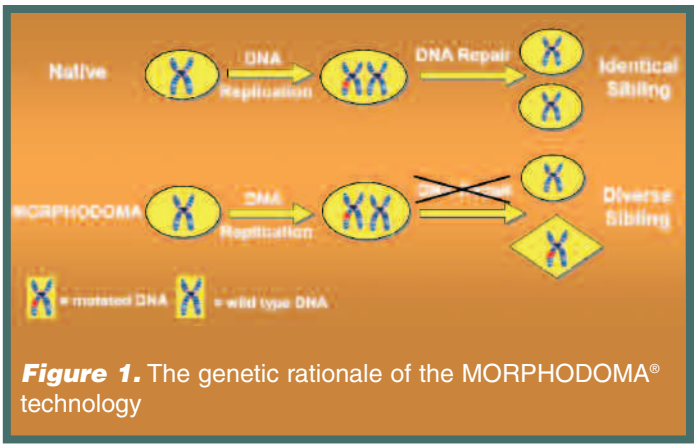


Figure 1. The genetic rationale of the MORPHODOMA® technology

Discovery & Collaboration

Morphotek engages in a collaborative approach to monoclonal antibody discovery and development with academic groups, including leading clinical researchers and disease discovery labs. The company is providing novel antibodies to targets identified by collaborations and Eisai's global research and development efforts, and through in-licensing opportunities to co-develop biological therapies for disease-specific targets.

Morphotek forges strong alliances with academic research groups that have extensively studied the molecular origin of diseases and have uncovered proteins and/or pathways that are unique to the disease states. For example, the targets for MORAb-003 and MORAb-009 were both found in the labs of researchers internationally renowned for studies focused on the molecular basis of cancer.

MORAb-003's target, FRA, was discovered by Lloyd Old, MD, and his colleagues at Memorial Sloan-Kettering (MSK) and the Ludwig Institute for Cancer Research (LICR). Dr. Old is a pioneer in using immunological-based methods to detect and discover cancer-associated targets (antigens) and compounds. His findings that FRA was over-expressed in a number of cancers as compared to normal cells led to the hypothesis that FRA is associated with the underlying pathogenesis of the disease. This hypothesis was validated by several independent studies by Morphotek scientists that showed aberrantly expressed FRA could transform a normal cell into a malignant cell type.

In preclinical studies, the precursor for MORAb-003 was developed by Dr. Old's team, which discovered antibodies that could recognize proteins over-expressed by human tumor cells. Morphotek exclusively licensed the rights to LICR's and MSK's intellectual property and formed a strategic collaboration with Dr. Old's lab. Morphotek used morphogenics to optimize the antibody and generated MORAb-003.

Ira Pastan, MD, Chief of the Laboratory of Molecular Biology at the National Cancer Institute (NCI), National Institutes of Health (NIH) (an agency of the US Public Health Service), and his colleagues at NCI discovered MORAb-009's target, mesothelin. The mesothelin target was identified by similar immunological approaches used to discover FRA. Dr. Pastan found mesothelin to be one of the most prominently over-expressed genes in certain cancer types. Pancreatic adenocarcinomas were found to over-express mesothelin, while its expression in normal pancreatic tissue was undetectable. Dr. Pastan's lab generated lead antibodies to mesothelin. Morphotek in-licensed the rights from PHS, and then generated the MORAb-009 antibody.

Summary

The rapidly growing monoclonal therapeutic antibody market has created significant value and demand for antibody development companies. Morphotek has a unique platform technology to generate and optimize monoclonal antibodies and specifically target a disease-associated antigen. The company leverages its technology with strong collaborative relationships among leading research institutes throughout the world. Morphotek, in conjunction with the global network of its parent, Eisai, has the capability to discover, develop, and market products. Morphotek's proprietary technologies and promising therapeutic antibodies, coupled with Eisai's commitment to this area, allow the companies to continue to address the unmet medical needs of cancer patients around the world.◆

Nicholas C. Nicolaides, PhD

President & CEO
Morphotek, Inc.

Dr. Nicholas C. Nicolaides is one of the country's foremost molecular geneticists and has authored more than 50 scientific papers on the molecular and genetic basis of cancer and respiratory diseases, antibody engineering, and cellular evolution. During his post-graduate studies at Johns Hopkins, his research resulted in the discovery of the genetic cause of Hereditary Non-Polyposis Colon Cancer (HNPCC) and the development of a whole genome evolution technology called morphogenics. Morphotek®, a wholly owned subsidiary of Eisai Co., Ltd., develops novel classes of biological-based products to treat cancer, inflammation, and infectious diseases. Currently, the company has two molecules in clinical development: MORAb-003 for the treatment of relapsed ovarian cancer, and MORAb-009 for first-line treatment of pancreatic cancer. Dr. Nicolaides earned his undergraduate degree in Biology from St Joseph's University and his PhD in Genetics from Thomas Jefferson University in 1992.

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Outsourcing Trends

Outsourcing Trends in Specialty Pharma – Challenges & Future Outlook

By: Barath Shankar Subramanian, Industry Analyst, Pharmaceutical & Biotechnology Practice, Frost & Sullivan

Introduction

The global CRO market has grown considerably due to a variety of factors. Despite this growth, the pharmaceutical industry has yet to catch up with other technology-based industries that have "mastered" outsourcing and have moved from using it as just a cost advantage to leveraging several key benefits. Outsourcing within the pharmaceutical industry is starkly different from other industries mainly because of the level of regulation that exists and the complex nature of business processes. CROs cater to the most important segment of business processes that produce products and candidates for companies to sell/out-license/co-promote.

The number of Phase I-III trials has grown significantly from 40,000 in 2000 to more than 59,000 in 2006[1], indicating the underlying potential for CROs and contract manufacturing organizations (CMOs), which provide manufacturing support for pharmaceutical and biotechnology companies to take their drug through testing into the market.

Shift From Cost-Driven Outsourcing

Technology-based industries like information technology (IT) began driving the outsourcing wave by off-shoring business functions like data processing, data mining, and tech-support to low-cost destinations. However, with time, companies began to move higher-value business functions like design and development to leverage the low-cost, quality workforce in those off-shore destinations. These destinations are now emerging as the hotbed for growth and driving consumption of goods and services. Countries like China and India are growing between 8% and 10% consistently, spurred by a consumer-driven economy.

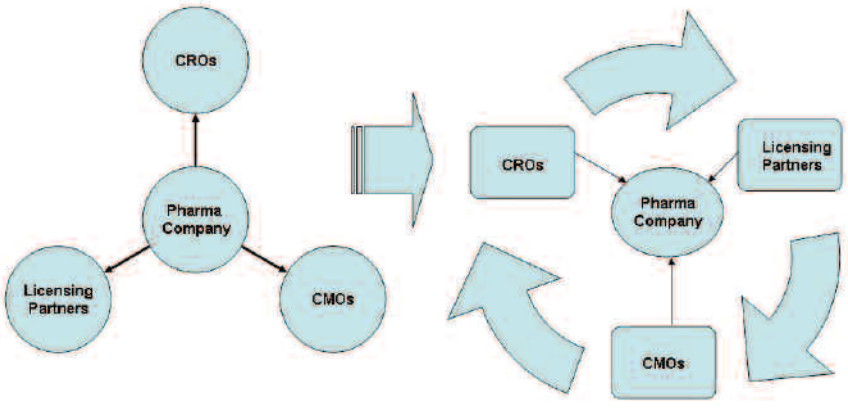
For companies that outsource functions and operations to these destinations, there is a double advantage: their established presence gives them an opportunity to cater to these rapidly growing markets, and they are better able to support other markets. The pharmaceutical industry, however, has not been able to replicate the success of integrated outsourcing in industries like IT. This could be attributed to the highly regulated nature of the market, as well as significantly different local regulations. Unlike IT, it is virtually impossible to open a manufacturing plant in Asia and export finished dosage formulations to the US, all within a few months.

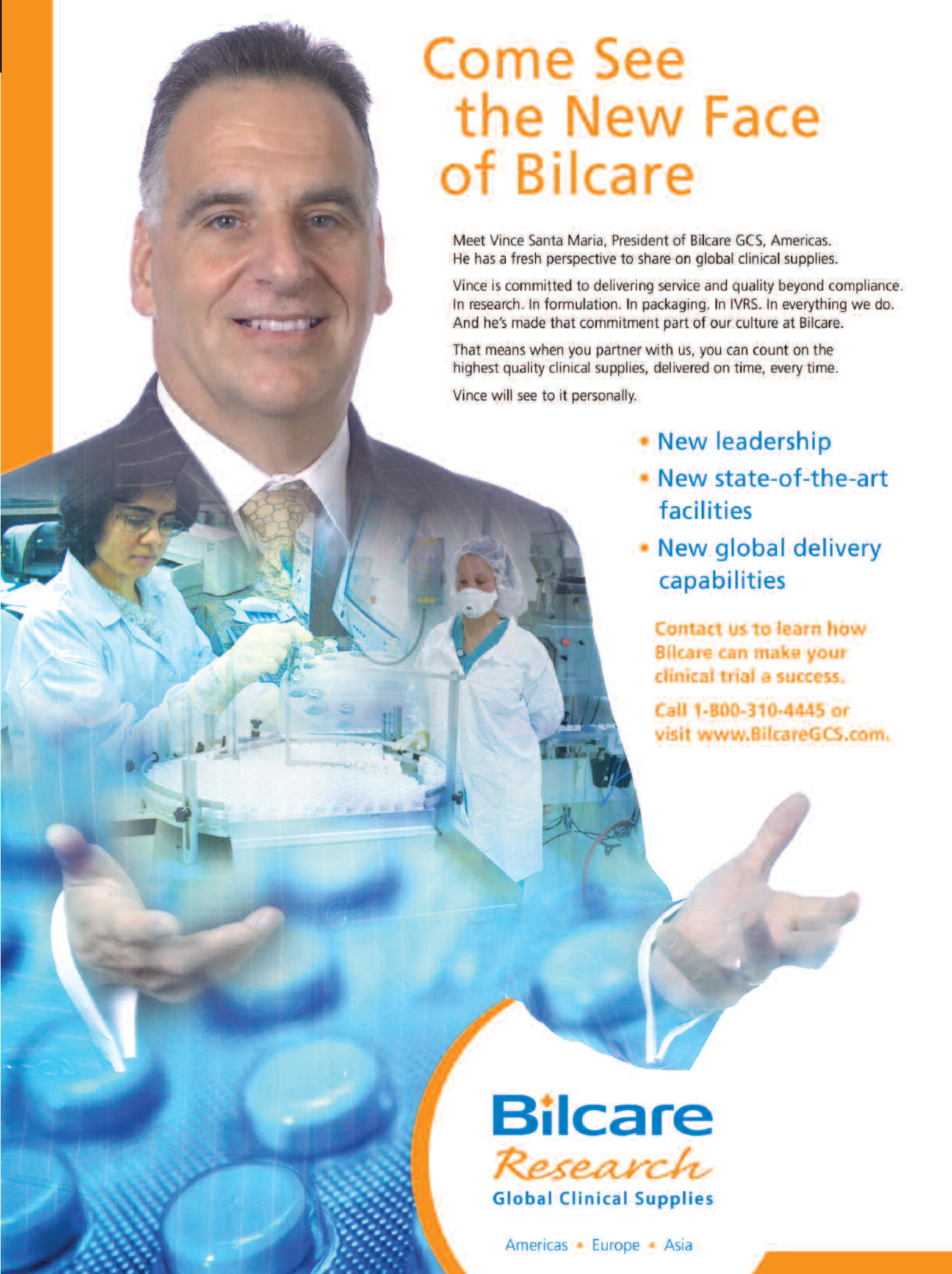
It is interesting to note that although functions like manufacturing, sourcing of APIs, and clinical trials are already being outsourced, most is driven by the cost advantage that the location offers, as opposed to an integrated value-added model.

Challenges & Trends in Emerging Markets

The large number of drug-naïve patients and the diverse population of popular off-shore/outsourcing destinations have resulted

Figure 1. Shift From Transactional to Fully Integrated Risk-Sharing Relationships





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in global clinical trials. There have also been significant changes to regulations that are favorable toward conducting clinical trials in emerging markets like India, China, and Latin America.

Most major drug companies and CROs have a presence in these regions, and the most successful ones are those that have significant built-up infrastructure, access to local centers and investigators, and have had the experience of working closely with regulators. In regions like Asia and Latin America, patients are motivated to participate in clinical trials as a potential route for receiving treatment.

Intellectual property threats are one of the most common risks for companies seeking to do business in emerging markets. Regulatory and bureaucratic delays, lack of awareness amongst patients, inadequate resources, and lack of training on international trial protocols and guidelines are some of the other major challenges CROs face in these regions. Asia has an edge over Latin America in clinical trials due to its established role in the pharmaceutical value chain as the key API supplier (India and China) and better understanding and ability to work within guidelines and protocols. The access to patients and recruitment is faster, thus resulting in quicker turnaround times.

Shift From Transactional to Strategic Relationship Model

The challenge to compete in the global pharmaceutical industry has never been greater for most major pharmaceutical companies. Generic drugs, thinning pipelines, and lack of blockbuster candidates are all posing a great threat to Big Pharma. However, Specialty Pharma, generic, and biotechnology companies are continuing to exhibit strong and consistent growth.

The service provider segment that consists of CROs and CMOs has benefited most by deriving business from Big Pharma that are looking to increase efficiency, productivity, and drive growth through life-cycle management and in licensing/acquisition deals. Specialty Pharma and biotech companies are also continuing to rely increasingly on CROs and CMOs to drive their business, which in this case, could be attributed to the lack of sufficient built-up infrastructure and scale-up ability.

Despite the increasing role of CROs and CMOs in the pharmaceutical value chain, there is a pressing need to shift from a purely transactional relationship to a strategic relationship model. The major restraining factor for this shift has been reluctance on the part of pharmaceutical and biotechnology companies toward entering into risk-sharing partnerships with service providers. Partly, the reasoning behind transactional relationships lies in the mismatch of short- and long-term priorities and goals of pharmaceutical, biotechnology companies, and service providers. However, as companies work more closely with service providers and begin to realize that service providers can actually add more value to business functions and help them better achieve their growth objectives, there is likely to be more synergy between them.

At a corporate level, the key objectives of pharmaceutical companies can be classified in the following ways:

- increased innovation
- increased revenues
- reduced cost

These three primary objectives can be achieved through strategic outsourcing at a global level.

Taking Steps Toward Integration

The next step for pharmaceutical companies could be to integrate the different strategic sourcing components through structured management of these functions. Most service providers are located in different regions of the world, with significant differences in culture, economics, politics, and regulations. These differences have often resulted in high failure rates amongst service providers and sponsor companies. Integrating these different service providers into a partnership/risk-sharing model and driving global business capabilities is possible.

The emergence of companies that provide integration services is a clear indicator of the market demand/potential. The future of the pharmaceutical industry and its continued success and growth depends on this, and it is important that companies take the lead in ensuring that the infrastructure to support integration is robust and in place.

The industry trend is clear. We are likely to see a more synergistic, risk-shared approach in the future, which would augur well for the Specialty Pharma industry and its service providers. ◆

Reference

1. Thomson CenterWatch Analysis; 2006.

Mr. Barath Shankar Subramanian

Industry Analyst
Frost & Sullivan North American Healthcare Practice

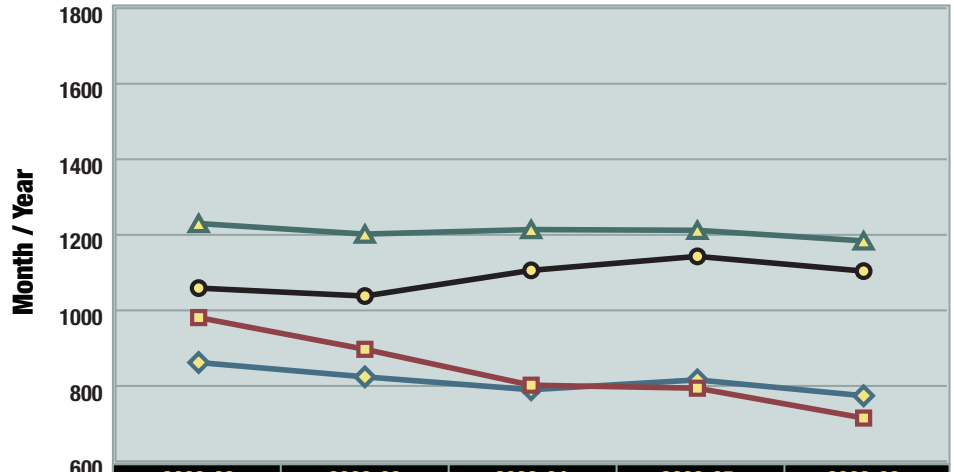
Mr. Barath Shankar Subramanian is a Industry Analyst with the Frost & Sullivan North American Healthcare Practice. He focuses on monitoring and analyzing emerging trends, technologies, and market behavior in the pharmaceuticals and biotechnology industries in North America. Since joining Frost & Sullivan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

For additional information, please contact Johanna Haynes at johanna.haynes@frost.com.

Facts & Figures

For index methodology and more detailed analysis please visit www.bionumbers.com

Bionumbers Composite Index



*The indexes refer to Market Capitalization rather than Share Price

	2008-02	2008-03	2008-04	2008-05	2008-06
CSPI	1,230	1,202	1,214	1,212	1,184
ESPI	981	897	802	794	715
DDI	862	824	790	816	774
NASDAQ	059	1,038	1,106	1,143	1,104

Index Value

CSP Index Value: 1184 | Change YTD: -8.2% | Change M/M: -2.3% | Total Index Capitalization: $48.9 Billion

Top 5 Capitalizations YTD Change		
Shire	$9.3 Billion	-27%
Hospira	$6.3 Billion	-6%
Warner	$4.3 Billion	-4%
Perrigo	$3.1 Billion	-6%
Endo	$2.9 Billion	-19%

Top 5 Gainers YTD Change	
Millbrook	+278%
APP	+63%
Columbia	+53%
Valeant	+40%
Avanir	+34%

Top 5 Laggards YTD Change	
Indevus	-75%
Ista	-63%
KV	-42%
Shire	-27%
Repligen	-26%

ESP Index Value: 715 | Change YTD: -43.0% | Change M/M: -9.9% | Total Index Capitalization: $2.0 Billion

Top 5 Capitalizations YTD Change		
Nektar	$342 Million	-45%
Durect	$327 Million	-31%
Pain Therapeutics	$317 Million	-32%
Cadence	$232 Million	-46%
Javelin	$143 Million	-22%

Top 5 Gainers YTD Change	
NovaDel	+6%

Top 5 Laggards YTD Change	
Keryx	-94%
Epicept	-77%
Elite	-76%
Cadence	-46%
Spectrum	-45%

DD Index Value: 774 | Change YTD: -20.0% | Change M/M: -4.5% | Total Index Capitalization: $8.7 Billion

Top 5 Capitalizations YTD Change		
Biovail	$1.7 Billion	-21%
Alkermes	$1.2 Billion	-24%
Surmodics	$824 Million	-18%
Eurand	$666 Million	-4%
Momenta	$490 Million	+88%

Top 5 Gainers YTD Change	
Momenta	+88%
Acura	+43%
Delcath	+35%
Labopharm	+22%
NovaDel	+6%

Top 5 Laggards YTD Change	
Vyteris	-81%
CytRx	-76%
Elite	-76%
Uluru	-69%
Aradigm	-55%

Marketing Strategies

Silo-Marketing is a Waste

By: Malcolm A. Teasdale, Big Idea Catalyst, Teasdale Worldwide

Introduction

In case you haven't figured it out yet, you're wasting your money on a silo-driven marketing plan. While I'm not advocating that you don't do anything, I am suggesting that you do not fall into some agency trap. Spending your corporate dollars in the wrong media is something most companies do. Spending your corporate dollars in just one medium is something an agency will do for you. It's no coincidence that a public relations agency will put the emphasis on public relations. It's also no coincidence that a web and interactive agency will put the emphasis on web and interactive. Advertising agencies will put the emphasis on advertising, and so on — you get the point. When you focus your plan on one specific medium, this channel-focused approach will prevent you from a truly successful marketing campaign.

Silo-driven-marketing can only benefit the silo-agencies and/or the single-source media outlets that run your message. Please don't yell when your ad or story doesn't produce the desired results that you anticipated. It's not their fault, they are just doing their job. When your public relations firm over-promises what that feature story can deliver, don't blame the magazine because you chose not to advertise in it. When your advertising agency overestimates the power of one medium, don't blame the publication because you chose not to supplement the buy.

So the question is: where do you put the emphasis? The answer can only be found in an integrated marketing plan. The best way to bring in new customers and drive your bottom line is to mix it up. Develop a strong message that is derived from fact-based research and then use it to engage your potential customers with all the media and channels that they tune into.

Integrated Marketing

One recent study, conducted by the Association of National Advertisers, indicates that achieving an effective integrated marketing campaign is the primary concern of marketers. Even though the concept of integrated marketing was first articulated more than 30 years ago, the uncertainty about how to design, communicate, and measure the success of a marketing program is still widespread. Less than 25% of marketers surveyed rated the quality of their integrated marketing campaign as excellent or very good. This underscores the need to identify best practices that will address the barriers that impede integrated marketing. The following are the main hurdles in developing an effective integrated marketing plan:

A LACK OF STRATEGIC CONSISTENCY ACROSS COMMUNICATIONS DISCIPLINES: The starting point should be strong customer insight, which is the foundation for meaningful messaging. That messaging can then be translated into a variety of media and channels. However, more often than not, each channel is developed and executed separately, whether performed internally or by an agency.

THE ABSENCE OF A COMMON MEASUREMENT PROCESS: Although data collection and data analysis have come a long way in supporting marketing efforts, there are still no single, consistent set of metrics that can be applied to all efforts.

THE EXISTENCE OF ENTRENCHED FUNCTIONAL SILOS INSIDE MARKETING ORGANIZTIONS, AS WELL AS WITHIN THEIR AGENCY PARTNERS: While most business people are well aware of the silo that often exists between marketing and other areas, such as operations, finance, or sales, most would be surprised at the level of disconnect within the marketing organization. Marketing functions are vertically organized: research, creative, media, or web marketing all have their own staff, goals, and processes developed and managed separately. This only increases among regional marketing teams. This is also mirrored on the agency side, as marketing managers engage agencies and request medium-based deliverables, and reward them with incentive models specific to their discipline.

Market conditions in 2008 are more difficult than ever: top-line growth is harder to get, budgets are being scrutinized, and the marketing landscape is shifting daily. So what's a marketer to do? Go back to basics and reexamine what it means for your marketing communications to be integrated. Integrated marketing communications should ensure that all communications emanating from a single strategic platform will generate a significantly greater return on your marketing investment than would be the case with traditional independent media executions. Make sure that your internal marketing system is optimized. Are your digital and off-line capabilities fully integrated? How is your brand message developed and deployed? Have you established a clear process to ensure that all your internal marketing channels (executive management, marketing department, and sales force), and external marketing channels (creative agency, media agency, public relations agency, digital agency, etc) are fully collaborating? Going through an internal assessment process will be a worthwhile investment in time and resources.

Integrated marketing can include marketing research, marketing planning, creative services, issues management and advocacy, event planning and marketing, web and mobile marketing, media planning, advertising, sales promotion, public relations, branding, direct marketing, and media relations. It is a common belief that integrated marketing should always use more than one channel; however, multichannel marketing is not integrated marketing. Integration must be consumer-driven, whether you are using few or many channels, with the goal of acquiring and retaining customers.

These five points will help you focus your integrated marketing plan:

1. Identify your key target audiences and their Unique Buying Advantages. The foundation of this process is discovering consumer insight through primary market research.

2. Develop your Big Idea based on your target market's Unique Buying Advantages. A Big Idea satisfies a few criteria: it is relevant to the audience; it stands apart from competitors' messages, it is believable, and it can grow with your business as it evolves.

3. Build your message: a unique, engaging, and differentiated message that you can tailor to the right delivery vehicles. Use the diversity of options available to your advantage, as it allows you to capitalize on each medium's unique strengths.

4. Pick your most appropriate delivery vehicles. A basic rule is that each progressive stage of customer involvement (from initial discovery, making a purchase decision to building solid brand loyalty) requires more individualized communications. However, make sure you consider the entire marketing spectrum.

5. Track and measure your return on investment; it will be important to keep your eye on the ball and not be afraid to make adjustments. Keep the foundation of your message solid, but don't hesitate to instigate change and be noticed.

Summary

There are certain fundamentals used toward achieving the benefits of a truly integrated marketing plan. I speak to corporate executives every day who become so frustrated with their inability to build their brand name in the marketplace. These executives really believe in their companies, they believe they have the best product, they believe they have the best service, they believe they have the best employees, but they can't understand their lack of success in building their brand and their business. Integration may require that you completely reinvent your marketing organization and how all your marketing partners interact. Using a customer-centric and holistic approach is your key to success. I encourage you to make innovation and reinvention your obsession. ◆

Malcolm A. Teasdale

Big Idea Catalyst
Teasdale Worldwide

Mr. Malcolm A. Teasdale leads the creative force and is the marketing expert behind Teasdale Worldwide, the Agency of Innovation that's creating edgy, effectual messaging while continuously applying his Marketing of Distinction™ — a revolutionary process that goes beyond the flawed nature of advertising. For more than 20 years, Mr. Teasdale has elevated the core practice of research combined with vivid creativity and planning As a sought-after speaker, his energetic style invigorates and brings a creative and motivational excitement to conferences, seminars, and results-driven workshops. He shares his expertise based on his extreme aversion to the fact that billions of dollars are wasted annually on advertising messaging that is completely ineffective. Methods to break through and overcome these pitfalls became the foundation for creating BRANDFiltration®, ChanneINSIGHTS™, and Intragrate-M®. He has written many insightful articles and white papers and is currently *completing his first book, Your Opinion Really Doesn't Matter (Your Customer's Does).*

Malcolm A. Teasdale is the founder and "Big Idea Catalyst" of Teasdale Worldwide, a strategic marketing firm headquartered in Tampa, Fla. Reach him at Malcolm@TeasdaleWorldwide.com. To obtain a new direction, and the expertise to empower your marketing call, Sanaa Belfekih at (813) 868-1520 or e-mail Sanaa@TeasdaleWorldwide.com. To view additional articles, register at www.MalcolmOutLoud.com.

Executive Summary

Mr. Simon Wilkinson
CEO
Virionyx

Virionyx: Partnering With the Immune System to Fight a Range of Diseases

Virionyx is a New Zealand-based company with two distinct and unusual drug development platforms. The company has a novel microparticle immune stimulator (MIS), which is a late-stage, preclinical candidate for programs in oncology, infectious disease, autoimmunity, and vaccine development. The company's second platform develops polyclonal antibodies to treat certain life-threatening conditions. The lead candidate from this platform is an AIDS therapy currently in US-based Phase II trials. The drug kills the HIV virus and the HIV-infected cells responsible for ongoing viral production. CEO Simon Wilkinson tells *Specialty Pharma* that the challenge is to overcome the tyranny of distance and to get these programs to the point at which they are ready for partnering in international markets.

Q: ***What is the background on the MIS technology? How was it discovered?***

A: In the mid-90s, Virionyx's founding scientist, Frank B. Gelder, PhD, needed a better adjuvant to help develop non-human, mammalian-derived antibodies to HIV. He was intrigued by the immunogenic properties of muramyl dipeptide (MDP), an NOD-2 signaling pathway ligand. Dr. Gelder screened a range of bacteria as a potential source of MDP and settled on a particular isolate of Propionibacterium acnes. He devised a method to build a microparticle composed of repeated MDP sequences covalently attached to a poly-amino-acid back bone principally composed of lysine and glycine amino acid repeats. The resulting cage-structured, 0.2- to 2.0-micron microparticle retained all the immunostimulating properties of MDP, but with absolutely none of the toxicity associated with the soluble form of the MDP molecule. Hence, Dr. Gelder called it a microparticle immune stimulator or MIS. A major benefit of MIS is its particulate structure, which allows one to covalently attach vaccine immunogens and have the whole adjuvant and antigen payload delivered to the correct cells in the immune system for antibody production.

Q: ***So MIS is principally an Adjuvant?***

A: Well, yes and no. The unusual part of the story is that Dr. Gelder observed strong innate immune system responses to MIS when the microparticle was used as a stand-alone agent; that is with no antigen onboard. Soon

after these observations, Dr. Gelder was diagnosed with polyarteritis nodosa, a serious autoimmune disease and in which the medium term prognosis is normally poor. Based on strong animal safety data and a fair degree of desperation, Dr. Gelder took the highly unusual step of self-medicating with the microparticle. His treatment premise was that up-regulation of innate immunity would re-regulate the aberrant humoral activity responsible for the auto-antibodies. And it worked.

Q: *What further scientific results do you have to support this?*

A: MIS, as an adjuvant, has been the platform that has enabled Virionyx to produce high titers of goat-derived polyclonal antibodies to HIV. The resulting passive immunotherapeutic, called PEHRG214, is currently in Phase II trial in the United States. PEHRG214 has multiple mechanisms of action quite distinct from the current small molecule anti-retrovirals used to treat HIV. These mechanisms include lysis of circulating HIV, inhibition of cell-to-cell infectivity, and discriminative lysis of HIV infected/replicating immune cells. The therapy may also be mediating antibody-dependent cellular cytotoxicity.

We have also used MIS as the adjuvant to induce antibodies to many poorly immunogenic antigens or antigens of interest, such as SARS and WNV. In the biodefense arena, we have made a protective experimental anthrax vaccine comprising recombinant protective antigen (rPA) covalently attached to MIS. The vaccine provided 100% protection in a mouse 2LD100 lethal anthrax toxin challenge after three immunizations over a 20-day period.

Used as a stand-alone agent to upregulate innate immunity, we are showing significant protection in plague, influenza, and anthrax models. The first-stage influenza data is particularly exciting, as we achieved very significant improvements in both mortality and morbidity treating with MIS from 14 days before infection or 1 day post infection. These data may have important implications in the pandemic setting, and our collaborators at the Trudeau Institute (Saranac Lake, NY) are currently running larger studies to test this further.

In the case of Dr. Gelder treating his own autoimmune condition, we have several years of data that document the course of his disease, which include laboratory and clinical evaluation, which demonstrate resolution of pain, peripheral neuropathy, rash and fever, and normalization of auto antibodies.

Q: *What are the opportunities, and how do you plan to develop these?*

A: In essence, Virionyx has two quite separate platforms. The first is the use of MIS to induce safe, potent, and synergistic stimulation and/or modulation of innate and adaptive immunity to potentially treat a range of indications. As an adjuvant, MIS is truly an enabling technology. The microparticle not only targets the NOD2 immune-signaling pathway (MDP is the ligand), but it also contains a highly protected bacterial nucleic acid that is a potent toll-like receptor ligand (a TLR9 ligand). In addition, we can remove the TLR9 ligand, if not desired, and attach other ligands as might be required by the vaccine candidate developer. This flexibility to drive a particular immune-signaling pathway, plus have the vaccine immunogen covalently attached to the microparticle, is unique and could play an important role in several vaccine programs. Our company is not in the vaccine development business, so we are making MIS available to others who are working in this important public health area.

As a stand-alone agent for inducing potent up-regulation of innate immunity, there are several diseases that could benefit. These include oncology, in which the tumors are susceptible to NK and NKT activity. Examples include bladder, liver, melanoma, and metastatic disease. The treatment of certain chronic viral diseases, such as hepatitis B and C, HIV, and influenza, might also be appropriate indications for its use. Obviously, certain autoimmune diseases would be potential indications as illustrated by Dr. Gelder's personal experience. Lastly, we are keen to explore the ability of MIS to protect the immune system from the side effects associated with chemo and radiation therapy or accidental radiation exposure. We are actively collaborating with a number of US-based institutions to advance these preclinical programs, and new collaborations are very welcome.

Underpinning these multiple MIS-related preclinical programs is strong safety data and very cost-effective manufacturing. We hold a cGMP license to manufacture MIS for human clinical trials, so we are on top of the major IND issues around chemistry, manufacturing, and control. MIS is also extremely stable and has an almost indefinite shelf-life frozen or greater than 3 years at ambient temperatures.

Virionyx's second platform capitalizes on New Zealand's unique live stock disease-free status and our technologies to produce passive immunotherapeutics derived from caprine (goat) polyclonal antibodies capable of treating a range of treat life-threatening infectious and/or toxin-based diseases.

Q: *Do you have the resources to support this number of programs?*

A: The short answer is no. Being located in New Zealand severely restricts our ability to access capital and business development expertise. New Zealand has significant advantages in terms of discovery and proof-of-concept research, both from an innovation "can-do" standpoint and very low overhead. But when it comes to the resources to take drugs into the clinic, our 4 million people and 40 million sheep can't produce the size of bankroll needed. We have recently begun aggressively seeking international partnerships for each of our programs, including our HIV clinical program, and so far, we are very pleased with the responses and the feedback. Others have suggested that MIS in particular, because it could support several different clinical programs, might make Virionyx an acquisition target. This could well be the case and would certainly speed up the time to market for MIS. ■

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EXTERNAL DELIVERY

Take Me to Your Leader…….

By: Dan Marino, MSc

I'm filling in for regular columnist John Bermingham this month as he is currently focusing on becoming CEO of a new company. When he returns, I am sure he will tell you all about it because like most CEOs, they like to talk a lot (just kidding Johnny).

I want to talk about an experience I had when I was in the Medical Education business. The owner of the company I was working for was a little eccentric and quite honestly…weird, or even goofy. That being said, he was the leader, he was respected professionally by his employees, and the company was somewhat successful. However, like most companies, some quarters were better than others. And I always wondered how much business the company actually lost after a prospective client had met our leader!

I can remember the VP of Business Development working 6 months to get a Big Pharma company to agree to a lunch meeting. The look on his face when he returned to the office said it all. The potential client had finally agreed to come on-site and sit for a never-ending PowerPoint presentation on the company's capabilities, highly trained staff, facilities, etc. You all know the drill.

The office was spotless and the stage was set. Past educational programs were strategically placed, guaranteed to catch the prospect's eye. The prior staff meeting drafted a game plan dictating just actually who would be allowed to speak and on what topic. The office manager ordered food and drinks from the best caterer in town, making sure to accommodate the pickiest of eaters. And everyone was told to dress in their Sunday best!

I'm going to digress here a little, but I promise it relates. One of my childhood friends and I have managed to remain best friends to this day. There is nothing about him I would change, and I could use every positive adjective one would use in describing a best friend. However, throughout all of our years of friendship, anytime I would introduce him to family members or other friends, more often than not, they were "turned off" by him. This never bothered me as whatever it was that irked them certainly did not me. But then again, he never cost me any money….

Okay, back to the story. The day had arrived for the potential client to come to the office, and I must say, the event was glorious. He did not fall asleep during the PowerPoint presentation, even when the VP of Logistics & Meetings gave her torturous speech. The client seemed very engaged and asked a lot of questions for which everyone had just the right answer. The food was delivered precisely, and wouldn't you know, we even had the right menu for a Vegan! People politely joked throughout the lunch, the tensions seemed to lessen, and the client even hinted at the size of the budget and that he felt very comfortable with us. I was very impressed.

The owner, who aside from making some introductions, had not really been a part of the meeting. Then it hit me. Everyone involved in setting up the meeting had planned it exactly that way! At first I was a little confused. However, right after lunch, I noticed he was determined for some one-on-one time with the prospect. I am not the type of person to point out personality flaws, but whatever flaws he had, they were all showing in the very short conversation he had with the client on the way out the front door.

This story does not have a happy ending, and I personally never heard a specific reason why we did not secure the account, and I don't believe I needed to. After the meeting, I became much more aware of the fact that whenever possible, Account Executives made sure that clients had as little contact as possible with our owner.

So the following question is what I would like to ask all my loyal readers: what will happen when one of your current or potential clients asks to see your leader? That experience could be a deciding factor between secured future business and lost opportunity! ◆

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